Individualising the use of radiotherapy for the treatment of people with Hodgkin lymphoma

Rebecca Shakir
Green Templeton College, University of Oxford

Thesis submitted for the degree of Doctor of Philosophy
Trinity term 2022

Supported by a National Institute of Health and Care Research Doctoral Fellowship

FUNDED BY
NIHR | National Institute for Health and Care Research

Abstract

Hodgkin lymphoma is a cancer of the lymphatic system that typically affects young adults. Chemotherapy and radiotherapy are both highly effective treatments, and 80-90% of patients now become long-term survivors, living long enough to experience late toxicities. Radiotherapy in particular has been shown to increase the long-term risk of cardiovascular disease and second malignancies, and recent trials have attempted to identify patients in whom radiotherapy can be omitted. Omission of radiotherapy has, however, been shown to substantially increase the chance of Hodgkin lymphoma recurrence. The decision about whether or not to use radiotherapy for an individual patient therefore involves weighing up the proven benefit against the potential risks of late toxicity.

The aim of this thesis is to understand the decision-making process about radiotherapy, and provide data that can be used to inform patients and clinicians at various steps. I explore patients' and clinicians' experience of radiotherapy decision-making, and propose a new decision-making model that fits this context. I present a comprehensive summary of the late toxicities of radiotherapy, including the dose-response relationships that can be used to estimate risks from modern radiotherapy. I report the radiation dose received by abdominopelvic organs in a historic cohort of Hodgkin lymphoma survivors, and show how the data has been used to estimate the dose-response relationship for the risk of colorectal cancer. Finally, I present a multivariable linear regression model that estimates the dose a patient's heart would receive from radiotherapy using measures available at the time of their diagnosis. I use the model to estimate individual patient's risk of ischaemic heart disease, and show its accuracy is greatest in the medium heart dose range, where the balance of the benefits and risks of radiotherapy are most uncertain.

Overall, this thesis helps inform individualised decision-making about radiotherapy by highlighting how clinicians can support patient involvement in decisions and providing methods to help individualise risk estimates of radiotherapy late toxicity.

Acknowledgements

I would first like to thank my supervisors, David Cutter, George Ntentas, Michele Peters and Johanna Ramroth, for their invaluable advice, guidance and support during this work. Doing the majority of my DPhil during a global pandemic has been challenging, and I'm grateful for their encouragement to keep going. They have introduced me to the worlds of radiotherapy late-effects, health services research, and cancer epidemiology, and have sparked a passion in me to improve the care of people living beyond cancer. I am also grateful to Usama Ali, Sarah Darby, David Dodwell, Francesca Holt, David Jones, Amanda Kerr, Gurdeep Mannu, Paul McGale, Jake Probert, Nia Roberts, Carolyn Taylor, and Zhe Wang, for their statistical and methodological advice, clinical insight and Stata expertise. I am deeply grateful to Catriona Gilmour-Hamilton for showing me the importance of working with people with lived experience of lymphoma, and am indebted to Craig Bakin, Isabelle Gent, Adam Holloway, and Alison Meeson for showing me what's most important for people who have been treated for lymphoma. It's been a huge privilege to work with them, and I'm hugely grateful for their support, and insightful comments and suggestions.

Much of this work would not have been possible without my collaborators from the UK (Urmila Barthakur, Carolyn Bedi, Victoria Butterworth, Philippa Closier, Caroline Dobeson, Lisa Durrant, Lorna Hawley, Helen Howard, John Frew, Joannne Lewis, George Mikhaeel, Eleanor James, Emily Renninson, Fiona Smith, Lesley Speed, Marie Tiffany, Sam Tudor, Wallis Urquhart, Tom Vasey, and France Yuille), Ireland (Frances Duane and Orla McArdle) the Czech Republic (Vladimír Rak) and the Netherlands (Yvonne Geurts, Berthe Aleman, Flora van Leeuwen, and Michael Schaapveld). My studies use data provided by patients and collected by the NHS and other healthcare systems as part of their care and support, and I am grateful to patients for allowing researchers like myself to use their data, and healthcare staff for their work collecting it. Thank you also to the National Institute for Health and Care Research for funding my research.

I am incredibly grateful to all the patients and clinicians who gave up their time to be interviewed, especially at such a challenging time during the pandemic. And to all those who helped me recruit patients and clinicians to the study, particularly Anne Hook and Stephen Scrowcroft at Lymphoma Action. Thank you to Sarah Lewington, Tim Maughan, and Sara Shaw for their comments at transfer and confirmation assessments that have helped to improve my final thesis.

Finally, to Mum, Dad, Rich, and Isla, thank you for your ongoing love and support, and for always believing in me, even when I don't believe in myself.

Abbreviations

3D-CRT	3D-conformal radiotherapy
AAA	Anisotropic analytical algorithm
ABVD	Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine
AEM	Absolute excess mortality
AER	Absolute excess risk
BCC	Basal cell carcinoma
BETER	Better care after HL: Evaluation of long-term Treatment Effects and screening Recommendations
BMI	Body mass index
B-VMAT	Butterfly volumetric modulated arc therapy
CI	Confidence interval
CMT	Combined-modality therapy
CNS	Clinical nurse specialist
CT	Computed tomography
CTV	Clinical target volume
CVD	Cardiovascular disease
CRC	Colorectal cancer
DIBH	Deep inspiration breath hold
eBEACOPP	Escalated-dose bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, vincristine, procarbazine, and prednisolone
ECG	Electrocardiogram
EFRT	Extended field-radiotherapy
EOR	Excess odds ratio
ERR	Excess relative risk
ERR	Excess rate ratio
FDG	^{18}F-fluorodeoxygenase
GTV	Gross tumour volume
Gy	Gray
HF	Heart failure
HL	Hodgkin lymphoma
HR	Hazard ratio
IFRT	Involved-field radiotherapy
IHD	Ischaemic heart disease
ILROG	International Lymphoma Radiation Oncology Group
IMRT	Intensity-modulated radiotherapy

INRT	Involved-node radiotherapy
IPD	Individual patient data
ISRT	Involved-site radiotherapy
LA-V_{25}	Percentage of left atrium receiving over 25 Gy
LMCA	Left main coronary artery
LV-V_{30}	Percentage of left ventricle receiving over 30 Gy
MHD	Mean heart dose
MDT	Multidisciplinary team
MI	Myocardial infarction
MLVD	Mean left ventricular dose
MV	Megavoltage
NCRI	National Cancer Research Institute
NHL	Non-Hodgkin lymphoma
NICE	National Institute for Health and Care Excellence
NKI	Netherlands Cancer Institute
NMSC	Non-melanoma skin cancer
OARs	Organs-at-risk
OCP	Oral contraceptive pill
OR	Odds ratio
PBC	Pencil beam convolution
PBT	Proton beam therapy
PET-CT	Positon emission tomography integrated with computed tomography
PIS	Participant information sheet
PTV	Planning target volume
py	Person-years
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk
SCC	Squamous cell carcinoma
SIR	Standardised incidence ratio
SMR	Standardised mortality ratio
SSD	Source-to-skin distance
STNI	Subtotal nodal irradiation
SUV	Standard uptake value
TIA	Transient ischaemic attack
TNI	Total nodal irradiation
TPS	Treatment planning system

VEBEP	Etoposide, epirubicin, bleomycin, cyclophosphamide, and prednisolone
VHD	Valvular heart disease
VMAT	Volumetric modulated arc therapy

Contents

1 General introduction

1.1 Hodgkin lymphoma 14
1.2 Radiotherapy 17
1.2.1 Evolution of radiotherapy techniques 19
1.3 Treatment of Hodgkin lymphoma 22
1.3.1 Early-stage Hodgkin lymphoma 22
1.3.2 Advanced-stage Hodgkin lymphoma 25
1.4 Risks of radiotherapy used to treat Hodgkin lymphoma 26
1.4.1 Studying the late-effects of radiotherapy 27
1.4.2 Dose-response relationships 28
1.5 Preferences with regard to Hodgkin lymphoma treatment 30
1.6 Motivation for thesis 31
1.7 Thesis aims and overview 34
1.8 References 36

2 Sharing decisions about radiotherapy for Hodgkin lymphoma: a qualitative study of the experiences of patients and clinicians in the UK

2.1 Background 43
2.1.1 Treatment decisions in Hodgkin lymphoma 43
2.1.2 Decision-making models 44
2.1.3 Decision-making policy in the NHS 47
2.1.4 Study aims 48
2.2 Methods 49
2.2.1 Study approach 49
2.2.2 Sampling and recruitment of participants 50
2.2.3 Interviews 53
2.2.4 Data analysis 54
2.2.5 Ethical considerations 56
2.3 Results 57
2.3.1 Participant characteristics 57
2.3.2 Themes 58
2.3.2.1 Theme 1: Patient involvement in discussions about radiotherapy 59
2.3.2.2 Theme 2: Individual factors in the decision about radiotherapy 65

2.3.2.3 Theme 3: Responsibility for decisions about radiotherapy 72
2.3.2.4 Theme 4: Shared decision-making and decision aids 78
2.3.3 Summary 82
2.4 Discussion 83
2.4.1 Comparison with published data 86
2.4.2 Relevance to current clinical practice 89
2.4.3 Strengths and limitations 92
2.4.4 Future work 93
2.5 Conclusions 94
2.6 References 95

3 Systematic review of the risks of radiotherapy used to treat Hodgkin lymphoma

3.1 Background 100
3.1.1 Radiotherapy late-effects 100
3.1.2 Rationale and study aims 100
3.2 Methods 101
3.2.1 Search questions 101
3.2.2 Study identification 102
3.2.3 Data abstraction 102
3.3 Results 104
3.3.1 All late-effects 106
3.3.2 Cardiovascular disease 107
3.3.2.1 Quantification of risk 107
3.3.2.2 Quantification of radiotherapy treatment factors that modify risk 112
3.3.2.3 Quantification of cardiovascular risk factors that modify risk 115
3.3.2.4 Quantification of dose-response relationships 121
3.3.2.5 Summary of CVD risk data 123
3.3.3 Second malignancies 124
3.3.3.1 Quantification of risk 124
3.3.3.2 Quantification of radiotherapy treatment factors that modify risk 133
3.3.3.3 Quantification of other risk factors that modify risk 138
3.3.3.4 Quantification of dose-response relationships 146
3.3.2.5 Summary of second malignancy risk data 152
3.3.4 Other conditions 153

3.3.4.1 Thyroid disease 153
3.3.4.2 Lung disease 154
3.3.4.3 Other conditions 154
3.4 Discussion 156
3.4.1 Strengths and limitations 159
3.4.2 Data uses 160
3.4.3 Future work 161
3.5 Conclusions 162
3.6 References 163

4 Doses to infradiaphragmatic organs from historic radiotherapy for Hodgkin lymphoma
4.1 Background 181
4.1.1 Radiotherapy techniques for Hodgkin lymphoma 181
4.1.2 Radiation dose-response estimates 182
4.1.3 Study aims 182
4.2 Methods 183
4.2.1 Cohort characteristics 183
4.2.2 Developing a representative CT library 184
4.2.2.1 Contouring of organs-at-risk 189
4.2.3 Radiotherapy treatment reconstruction 190
4.2.4 Estimation of organ-at-risk doses 192
4.3 Results 194
4.3.1 Doses to abdominopelvic organs-at-risk, split by radiotherapy field type 194
4.3.2 Doses to organs-at-risk in individuals who develop colorectal cancer compared to controls 204
4.4 Discussion 207
4.4.1 Relevance in the context of modern radiotherapy 207
4.4.2 Comparison with published data 210
4.4.3 Relevance to the late-effects of radiotherapy 213
4.4.4 Dose-response relationship for colorectal cancer 215
4.4.5 Strengths and limitations 218
4.4.6 Future work 219
4.5 Conclusions 222
4.6 References 223

5 Development of a multivariable model to predict mean heart dose using pre-chemotherapy PET-CT scans
5.1 Background ... 228
5.1.1 Use of PET-CT scans in the management of Hodgkin lymphoma ... 228
5.1.2 Estimating the risks of radiation late-effects ... 230
5.1.2 Rationale and study aims ... 232
5.2 Methods ... 234
5.2.1 Study subjects ... 234
5.2.2 Data collection ... 235
5.2.2.1 Candidate predictors ... 235
5.2.2.2 Outcome measures ... 237
5.2.3 Statistical analysis ... 237
5.2.4 Ethical considerations ... 239
5.3 Results ... 239
5.3.1 Participant characteristics ... 239
5.3.2 Univariable analysis ... 241
5.3.3 Multivariable model development ... 243
5.3.3.1 Checking model assumptions ... 245
5.3.3.2 Model performance ... 245
5.3.3.2 Cardiovascular risk prediction ... 248
5.4 Discussion ... 250
5.4.1 Relevance to current clinical practice ... 252
5.4.2 Strengths and limitations ... 253
5.4.3 Future work ... 254
5.5 Conclusions ... 256
5.6 References ... 256
6 General summary and future perspectives
6.1 Summary of findings ... 261
6.2 Future perspectives ... 264
6.2.1 Decision aid ... 264
6.2.2 Radiotherapy plan optimisation ... 265
6.2.3 Additional clinical impacts ... 266
6.3 Concluding remarks ... 267
6.4 References ... 268

Appendices

Appendix A. Glossary.....269
Appendix B. Supplementary material to Chapter 2.....272
Appendix C. Supplementary material to Chapter 3.....312
Appendix D. Supplementary material to Chapter 4.....535
Appendix E. Supplementary material to Chapter 5.....542

Figures

Figure 1.1: Cotswold modification of the Ann Arbor staging of Hodgkin lymphoma 15
Figure 1.2: Classification of Hodgkin lymphoma..... 16
Figure 1.3: Annotated photo of a linear accelerator, used to deliver radiotherapy 19
Figure 1.4: Radiotherapy field techniques used to treat Hodgkin lymphoma 19
Figure 1.5: Comparison of dose-distribution between two radiotherapy techniques 22
Figure 1.6: Cumulative mortality from major disease categories following treatment for Hodgkin lymphoma 27
Figure 1.7: The dose-response relationship for heart dose and ischaemic (coronary) heart disease risk..... 29
Figure 1.8: Overview of the clinical pathway for making decisions about radiotherapy used to treat patients with Hodgkin lymphoma, highlighting the steps informed by data presented in this thesis 34

Figure 2.1: Models of decision-making..... 45
Figure 2.2: Overview of the clinical pathway for making decisions about radiotherapy used to treat patients with Hodgkin lymphoma, highlighting the steps informed by data presented in this chapter 49
Figure 2.3: The radiotherapy decision-making process in current clinical practice, as described by patients and clinicians.....83
Figure 2.4: Updated models of decision-making.....85

Figure 3.1: Overview of the clinical pathway for making decisions about radiotherapy used to treat patients with Hodgkin lymphoma, highlighting the steps informed by data presented in this chapter 101
Figure 3.2: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram illustrating the studies assessed for inclusion in the review 105
Figure 3.3: Summary of the quality of the evidence for an increased risk of CVD following radiotherapy for HL 123
Figure 3.4: Summary of the quality of the evidence for an increased risk of second malignancies following radiotherapy for HL..... 152

Figure 4.1: Overview of the clinical pathway for making decisions about radiotherapy used to treat patients with Hodgkin lymphoma, highlighting the steps informed by data presented in this chapter 183
Figure 4.2: Correlation between body mass index and mediastinal (A) and para-aortic (B) separation in a cohort of Hodgkin lymphoma survivors 187
Figure 4.3: Measurement of separation for the contemporary cohort 188

Figure 4.4: An example of a (a) radiotherapy prescription, (b) simulation films and (c) reconstructed radiotherapy plan 191
Figure 4.5: Position of the colon segments in relation to the reconstructed radiotherapy fields 195
Figure 4.6: Position of the gastrointestinal organs (excluding the colon) in relation to the reconstructed radiotherapy fields 196
Figure 4.7: Position of the urinary organs in relation to the reconstructed radiotherapy fields 197
Figure 4.8: Position of the male genital organs in relation to the reconstructed radiotherapy fields 198
Figure 4.9: Position of the female genital organs in relation to the reconstructed radiotherapy fields 199
Figure 4.10: Box and whisker plot of mean doses to the colon segments, split by whether the individual subsequently developed colorectal cancer (case) or not (control) 206
Figure 4.11: The modelled radiation dose-response relationship for colorectal cancer following Hodgkin lymphoma 217
Figure 4.12: Linear-quadratic model of cell survival following radiotherapy 221

Figure 5.1: Use of PET-CT to guide radiotherapy treatment volumes 229
Figure 5.2: Dose-response relationship for mean heart dose and ischaemic (coronary) heart disease risk 230
Figure 5.3: Use of the radiotherapy treatment planning system to determine the mean heart dose received during radiotherapy 231
Figure 5.4: Current practice with regard to evaluation of risk of radiotherapy late-effects, compared to the pathway possible if estimates of risk of late-effects were available at the time of diagnosis of Hodgkin lymphoma 233
Figure 5.5: Overview of the clinical pathway for making decisions about radiotherapy used to treat patients with Hodgkin lymphoma, highlighting the steps informed by data presented in this chapter 233
Figure 5.6: Model equation and worked example 244
Figure 5.7: Assessment of model residuals using a) a histogram of residuals, b) a Q-Q plot of residuals, and c) a plot of residuals versus fitted values 245
Figure 5.8: Prediction error between mean heart dose predicted by the model and mean heart dose measured on the radiotherapy treatment plan 246
Figure 5.9: Scatter plot of the mean heart dose predicted by the model versus the mean heart dose measured on the radiotherapy treatment plan 247
Figure 5.10: Scatter plot of the 30-year cumulative absolute excess risk of ischaemic heart disease calculated using the mean heart dose predicted by the model and that calculated using the mean heart dose measured on the radiotherapy treatment plan 249

Figure 6.1: Overview of the clinical pathway for making decisions about radiotherapy used to treat patients with HL, highlighting the steps informed by data presented in this thesis 264

Tables

Table 2.1: Inclusion criteria 51
Table 2.2: Partner organisations in study recruitment 52
Table 2.3: Phases of Braun and Clarke's thematic analysis 55
Table 2.4: Participant characteristics 58

Table 3.1: Study inclusion criteria 102
Table 3.2: Levels of evidence quality 104
Table 3.3: Categories of late-effects reported by included studies 106
Table 3.4: Dose-response relationships for the risk of CVD following radiotherapy 122
Table 3.5: Dose-response relationships for the risk of breast cancer following radiotherapy 148
Table 3.6: Dose-response relationships for the risk of lung cancer following radiotherapy 150
Table 3.7: Dose-response relationships for the risk of gastrointestinal malignancies following radiotherapy 151

Table 4.1: Selection of representative CT library 189
Table 4.2: Categories of radiotherapy fields 194
Table 4.3: Mean organ-at-risk dose, as percentage of total prescribed dose, split by radiotherapy field type 202
Table 4.4: Mean organ-at-risk dose, split by whether an individual subsequently developed colorectal cancer (case) or not (control) 205
Table 4.5: Comparison of the median mean doses to organs-at-risk in this study with published dose constraints 209
Table 4.6: Comparison of median mean abdominal organ-at-risk doses, in gray, between the current and previously published studies 210
Table 4.7: Comparison of mean mean pelvic organ-at-risk doses, in gray, between the current and previously published studies 211
Table 4.8: Comparison of mean doses to abdominal organs-at-risk, expressed as a percentage of prescribed dose, between the current and previously published studies. 212

Table 5.1: Participating centres, and the method of their recruitment to the study 234
Table 5.2: Candidate predictors and outcome measures 236
Table 5.3: Characteristics of 169 participants treated with radiotherapy for mediastinal Hodgkin lymphoma 240
Table 5.4: Variables examined for a relationship with mean heart dose 241
Table 5.5: Candidate predictors for multivariable model development 243
Table 5.6: Multivariable linear regression model specification 244
Table 5.7: Modelled mean heart dose and 30-year risk of ischaemic heart disease compared to those measured on the radiotherapy treatment plan 247
Table 5.8: Differences between the mean heart dose from the radiotherapy plan and that predicted by the model, split by quartiles of mean heart dose 248
Table 5.9: Differences between the 30-year cumulative absolute excess risk of ischaemic heart disease calculated using the mean heart dose from the radiotherapy plan and that predicted by the model, split by quartiles of mean heart dose 249

Chapter 1

General introduction

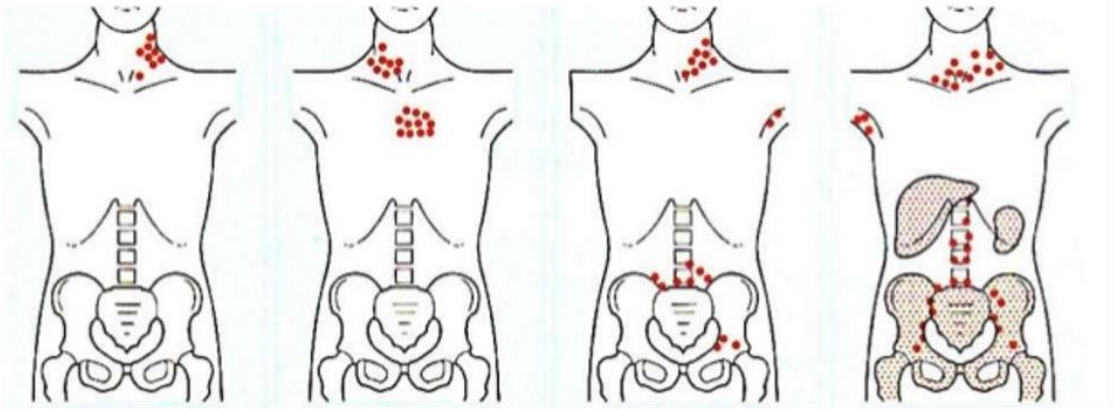
1.1 Hodgkin lymphoma

Hodgkin lymphoma (HL) is a cancer of the lymphatic system, in which the malignant cells are derived from B-lymphocytes [1,2]. The majority (90%) of cases are classical HL, characterised by malignant cells which carry the CD30 antigen on their cell surface, scattered throughout a microenvironment of inflammatory cells, lymphocytes and macrophages [1,2]. The remaining 10% of cases are nodular lymphocyte predominant HL, which is a distinct disease entity that will be reclassified in future editions of the World Health Organisation classification of haematological tumours [1–3]. For the remainder of this thesis, HL will be used to mean classical HL.

The overall incidence of HL is low, with a UK annual age-standardised incidence of 3.3 per 100,000 population [4]. In the UK the incidence is slightly higher in men, and bimodal with regard to age, with a peak in adolescents and young adults, and a second peak in the elderly [4]. Patients commonly present with otherwise asymptomatic lymphadenopathy [1,5]. Additional symptoms may be present due to compression of nearby structures (e.g. cough, chest pain, back pain), or systematic upset (‘B’ symptoms: night sweats, unexplained weight loss and persistent or recurring fever; or less commonly itch or alcohol-induced pain) [1,5]. Diagnosis is based on histological and immunohistochemical analysis of malignant tissue from a biopsy [1].

HL can affect any part of the body, and the areas affected are very variable between individuals. At presentation, lymph nodes above the diaphragm (‘supradiaphragmatic’) are most commonly involved. Spread is often lymphatic to contiguous nodes, and may be haematogenous to the spleen and extranodal regions such as the bone marrow, bones, lungs and liver [1,6]. Disease extent is assessed on imaging [2,7], and used to group HL into one of four stages according to the modified Ann Arbor classification (Figure 1.1) [8]. HL is highly metabolically active, and therefore positon emission tomography, using

radioactive glucose (^{18}F-fluorodeoxygenase (FDG)), integrated with computed tomography (PET-CT) is used to identify affected areas, and is recommended as a routine investigation at HL diagnosis [2].



Stage I:
Single nodal region, or single extranodal site (I_E)

Stage II:
≥2 nodal regions on the same side of the diaphragm, or ≥1 nodal region(s) with local extranodal spread (II_E)

Stage III:
Nodal regions on both sides of the diaphragm, +/- local extranodal extension (III_E)

Stage IV:
Diffuse extranodal disease (e.g. liver, bone marrow, lung, skin)

Additional variables:
A: Free from any B symptoms
B: Presence of any B symptoms (persistent unexplained fever, night sweats, weight loss of >10% body weight over 6 months)
X: Bulky nodal disease (≥10 cm diameter, or ≥⅓ intrathoracic diameter)

Figure 1.1: Cotswold modification of the Ann Arbor staging of Hodgkin lymphoma
Adapted with permission from https://www.slideshare.net/Siddz0312/hodgkins-lymphoma-72629944, accessed 8th May 2019, and Connors et al, 2020 [1]

When considering treatment, there are two approaches to subdividing patients with HL into staging subgroups. One divides them into early- (limited-) or advanced-stage, and another further subdivides those with early-stage disease into two subgroups. The three-stage classification is commonly used in the UK [2], with early-stage disease split into favourable and unfavourable (or intermediate) based on specific risk factors, which differ slightly in different classifications (Figure 1.2).

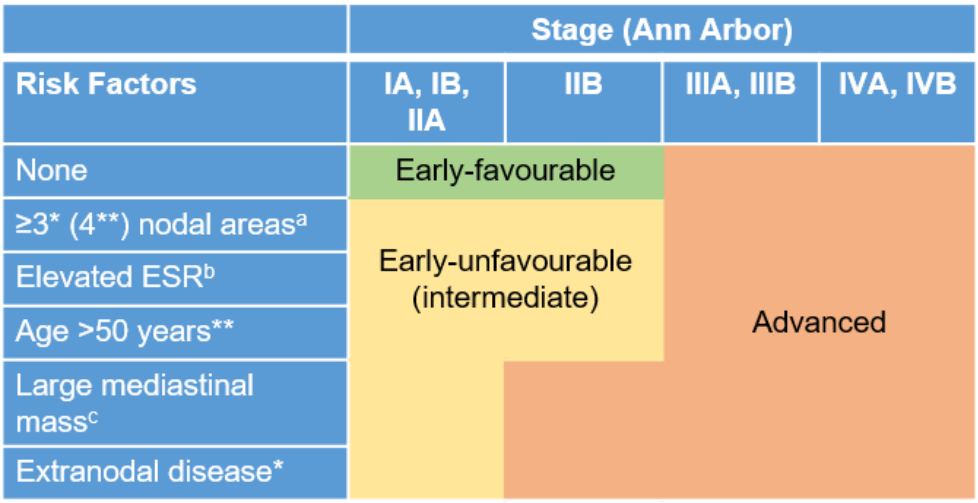


Figure 1.2: Classification of Hodgkin lymphoma
*German Hodgkin Study Group (GHSG) criteria
**European Organisation for Research and Treatment of Cancer (EORTC) criteria
[a]Involvement of ≥3 out of 11 nodal areas on both sides of the diaphragm (GHSG); involvement of >4 out of 5 nodal areas above the diaphragm (EORTC)
[b]Erythrocyte sedimentation rate >50 mm/h without B symptoms, >30 mm/h with B symptoms
[c]Mediastinal mass larger than one third of the maximum thoracic width (GHSG); mediastinum-to-thorax ratio ≥0.35 (EORTC)
Adapted, with permission, from ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of Hodgkin lymphoma [7] and Prognostic factors in Hodgkin lymphoma, Cuccaro et al [9]

Chemotherapy and radiotherapy are highly effective treatments for HL. More recently immunotherapy has proven effective in treating HL that is refractory to chemotherapy [10,11]. As a result of the excellent long-term survival rates, recent research has focused on refining treatment strategies to minimise toxicity whilst maintaining efficacy. There has been a trend towards smaller radiotherapy treatment volumes, lower radiotherapy doses, and fewer chemotherapy cycles. In the UK, radiotherapy is given by clinical oncologists, and chemotherapy for HL is commonly given by haematologists, but sometimes also medical oncologists. Treatment approaches are discussed in detail in section 1.3.

The prognosis of patients with HL has substantially improved over recent decades, meaning it is now one of the most curable adult cancers [12]. In the UK, 10-year survival increased from 47% in 1971 to 80% in 2011 [4]. Consequently, many HL patients become long-term survivors. Expected cure rates exceed 90% for early-stage disease [1,4,13], and 80% for

advanced disease [1]. Even when HL is refractory to first-line treatment, or recurs following treatment, it can still be cured in at least 50% of patients with high-dose chemotherapy and stem cell transplantation [1].

1.2 Radiotherapy

Radiotherapy is the use of radiation from photons (x-rays), electrons, gamma rays, protons, neutrons, or other particles, to kill cancer cells [14]. Radiotherapy used to treat HL is typically delivered using high-energy (megavoltage) photons generated in a machine called a linear accelerator. This type of radiotherapy is most fully termed ‘external-beam radiotherapy’, which I have shortened to ‘radiotherapy’ for the remainder of my thesis.

Radiotherapy must be carefully planned to ensure that it is delivered accurately to the intended target, whilst minimising irradiation of surrounding normal tissue. Clinicians identify macroscopic tumour on a computed tomography (CT) scan, and outline this as a gross tumour volume (GTV). Sequential volume expansions are subsequently applied to account for microscopic spread (clinical target volume, CTV), and patient movement and other variations in day-to-day set-up (planning target volume, PTV) [15]. Where possible, diagnostic images (such as PET-CT scans) are imported into the treatment planning system (TPS) to provide greater certainty of tumour location. Once clinicians have outlined the target volumes, specialist physicists plan how the radiation can be delivered, using complex computer algorithms embedded within the TPS to simulate the deposition of dose by a radiation beam passing through the body [15]. The subsequent radiotherapy plan is reviewed by clinicians to ensure that an adequate dose is received by the tumour, with minimal dose to adjacent normal tissue.

Radiotherapy is delivered to patients by a linear accelerator (Figure 1.3) in a series of daily treatments, termed ‘fractions’. Photons are produced within the linear accelerator as follows: electrons are emitted from a heated gun filament, and their energy is gradually increased as they move through a magnetised waveguide [15]. The beam of electrons is focused and steered to hit a high atomic number (tungsten) target, which produces a photon beam [15]. This beam is shaped using metal plates (‘jaws’) and small metal leaves (‘multi-leaf collimators’) as it passes out of the linear accelerator into the patient [15]. Photons in the beam deposit energy (‘dose’) by interacting with matter within the patient and transferring energy to electrons, which then deposit their energy in the body’s tissues [15]. The unit of dose used for radiotherapy is the gray (Gy); one Gy is defined as one Joule of energy absorbed by one kilogram of matter [16]. In order to ensure that radiotherapy is delivered accurately to the target location, patients are treated in a reproducible position, facilitated by immobilisation devices (such as masks that clip into the treatment couch) and permanent tattoos which line up with lasers in the treatment room.

Historically, radiotherapy was also delivered using cobalt units. These contain a radioactive ^{60}Cobalt source housed in a shielded safe, with a shutter mechanism that can be opened to allow a beam of gamma rays to deliver radiation to a patient lying on a couch beneath [16]. These units are no longer used clinically in the UK, but are relevant for the study I present in Chapter 4.

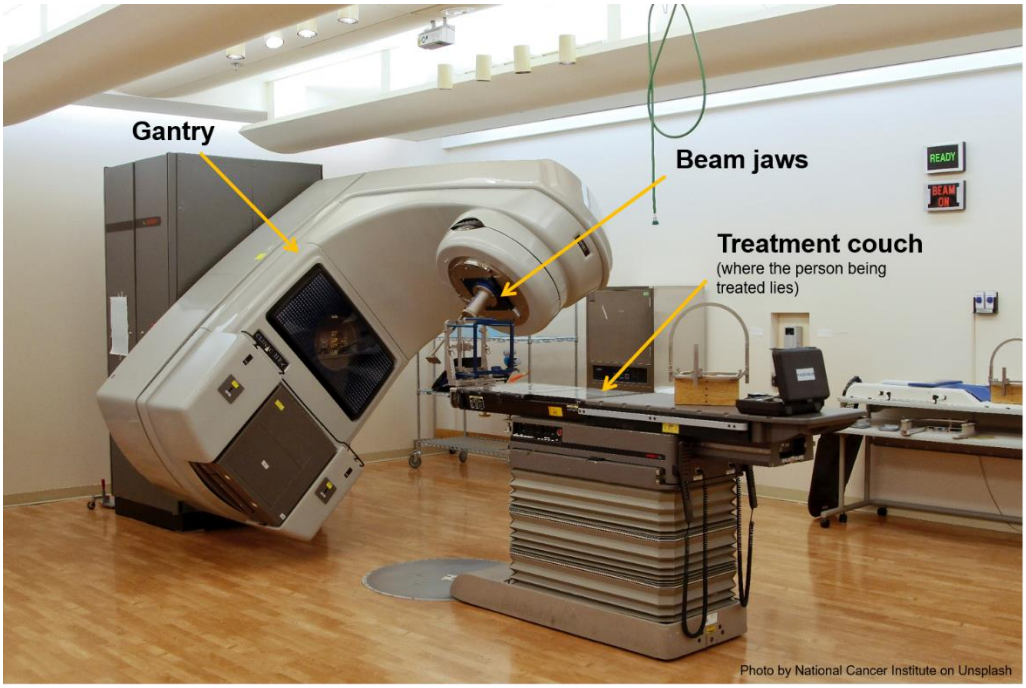


Figure 1.3: Annotated photo of a linear accelerator, used to deliver radiotherapy
Photo used with permission from the National Cancer Institute, on unsplash.com

1.2.1 Evolution of radiotherapy techniques

Radiotherapy techniques used to treat patients with HL have evolved over time, with a reduction in the size of field used. Different field techniques are displayed in Figure 1.4, and described in more detail below.

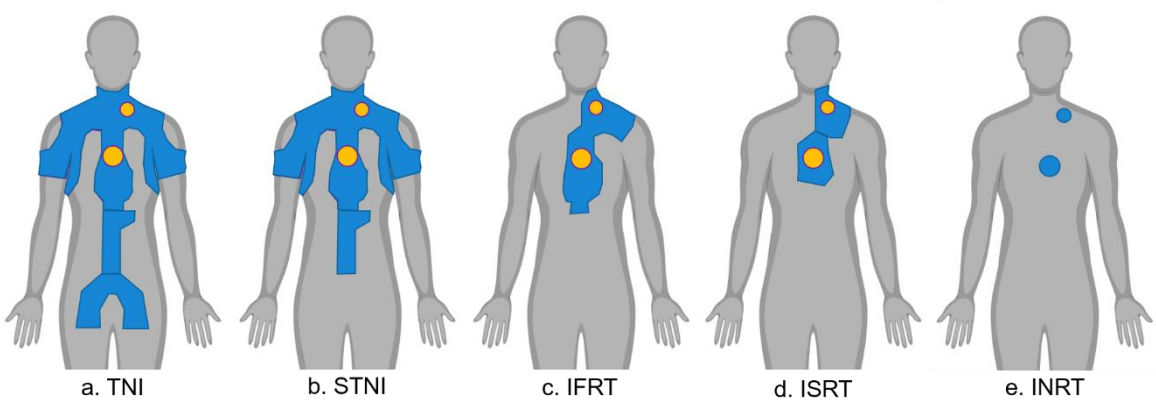


Figure 1.4: Radiotherapy field techniques used to treat Hodgkin lymphoma
The lymph nodes containing Hodgkin lymphoma at diagnosis are represented by the yellow circles, and the shape of the radiotherapy field represented by the blue shaded regions.
Abbreviations - TNI: total nodal irradiation; STNI: subtotal nodal irradiation; IFRT: involved-field radiotherapy; ISRT: involved-site radiotherapy; INRT: involved-node radiotherapy

Historically, the lymph node regions defined by the Ann Arbor staging classification were used to define the borders of radiotherapy fields [17]. A large field called a ‘mantle’ was used to treat the nodes above the diaphragm, and an ‘inverted-Y’ field treated the nodes in the abdomen, pelvis and groins [18–21]. The mantle field covered the mediastinal, hilar, supraclavicular, cervical, infraclavicular and axillary nodes, and the inverted-Y covered the para-aortic, inguinal and iliac nodes, in addition to the spleen (unless the patient had undergone a splenectomy, in which case only the splenic hilar region was included). ‘Total nodal irradiation’ (TNI) (Figure 1.4a) was the combination of mantle and inverted-Y fields, and if the pelvic nodes (iliac and inguinal) were excluded this was termed ‘subtotal nodal irradiation’ (STNI) (Figure 1.4b) [18,22]. ‘Extended-field radiotherapy’ (EFRT) was the term used to encompass these large-field radiotherapy techniques.

It was subsequently recognised that the dominant pattern of relapse after treatment for early-stage HL was in previously involved nodal regions, meaning that ‘elective’ irradiation of uninvolved areas could be reduced if patients were also being treated with chemotherapy. ‘Involved-field radiotherapy’ (IFRT) developed from EFRT, treating just the nodal region(s) that contained HL at diagnosis (Figure 1.4c). IFRT delivered substantially less radiation to normal tissues than historical EFRT [23,24]. Again, relapse tended to be seen predominantly in initially involved nodes, leading to some advocating that only the initially involved node(s) (rather than region) should be irradiated, termed ‘involved-node radiotherapy’ (INRT) (Figure 1.4e) [25]. This however requires specialist pre-treatment imaging to be done exactly in the radiotherapy treatment position, and so a more pragmatic technique has been developed which adds a small margin to initially-involved nodes, termed ‘involved-site radiotherapy’ (ISRT) (Figure 1.4d). ISRT has never been randomly compared with IFRT in a prospective trial, but there is substantial evidence of excellent tumour control [26–28], and it is now the internationally accepted standard of care [2].

Alongside reduction in target volumes for radiotherapy, modern radiotherapy techniques have been developed that can further reduce irradiation of critical organs. Organs that are

within or near radiotherapy fields, whose irradiation could cause damage that results in morbidity, are termed organs-at-risk (OARs) [29,30]. Historically, radiotherapy was delivered using a 2D-conformal technique ('conventional' radiotherapy). This is planned by defining a limited number of beams with the boundaries delineated on orthogonal x-rays of the patient [31]. Beam shaping is limited, resulting in substantial irradiation of adjacent tissues. 3D-conformal radiotherapy (3D-CRT) was subsequently developed that uses CT scans to define the target volume and OARs. TPSs are used to design complicated beam arrangements, and simulate dose-distributions. OAR doses are typically lower from 3D-CRT compared to conventional radiotherapy. More recently, intensity-modulated radiotherapy (IMRT) has been developed, where treatment beams are divided into 'beamlets' of varying intensity, to build up dose in the treatment volume while avoiding adjacent OARs [32,33]. Compared with conventional radiotherapy, IMRT facilitates more conformal shaping of the high-dose volume [32]. Volumetric modulated arc therapy (VMAT) is a further development that delivers radiotherapy with varying beam intensity, but instead of multiple beamlets the dose is delivered continuously as the linear accelerator rotates with variable dose-rate and speed through one or more arcs [32,33]. A further refinement has been made to the VMAT technique to treat mediastinal lymphoma, termed 'butterfly-VMAT' (B-VMAT) [34]. This delivers radiation through multiple partial arcs, avoiding the breasts and the lateral part of the lungs [35,36].

The major limitation of both IMRT and VMAT is the exposure of larger volumes of normal tissue to low-dose radiation (Figure 1.5), which may increase the risk of second malignancy compared to conventional radiotherapy [32,33]. However, radiobiological estimates suggest the risk associated with this low-dose exposure is very small [37–40].

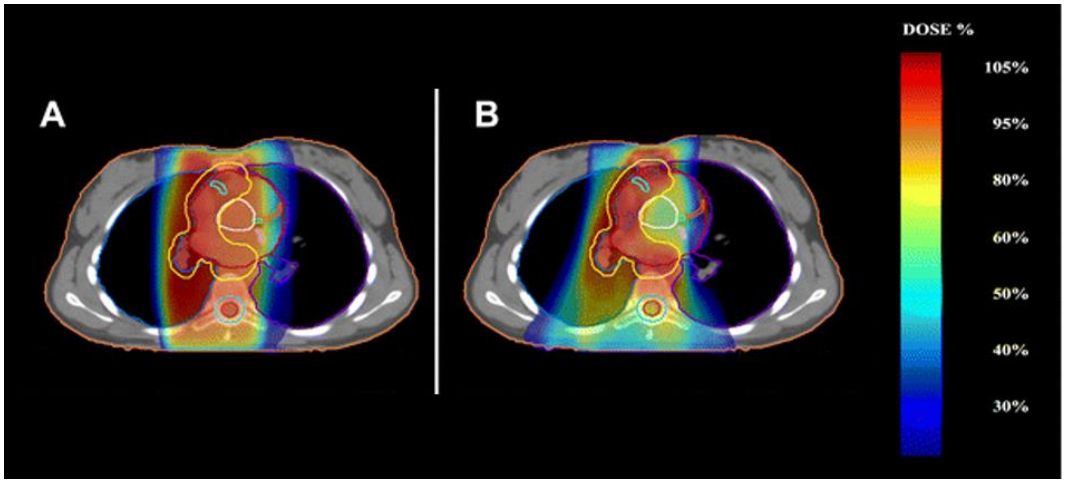


Figure 1.5: Comparison of dose-distribution between two radiotherapy techniques
Panel A: 3D-conformal radiotherapy
Panel B: volumetric modulated arc therapy
The target volume in the superior mediastinum is outlined in yellow, and the organs-at-risk contoured in red (heart); cyan, green, orange, and pink (coronary arteries); and white (aortic root). The radiotherapy dose distribution is shown in colour wash, as a percentage of prescribed dose, with the key to the right of the two panels.
Adapted with permission from Filippi et al, 2017 [28]

More recently, breathing control techniques have been developed that allow radiotherapy to be delivered whilst the patient holds their breath in deep-inspiration [41,42]. This moves the heart down away from the superior mediastinum and expands the lungs, thereby reducing dose to these organs [35,43]. The removal of respiratory movement also allows reduction of the margin added to the CTV, further reducing the amount of normal tissue irradiated [35].

1.3 Treatment of Hodgkin lymphoma

1.3.1 Early-stage Hodgkin lymphoma

Historically, treatment for early-stage HL was with EFRT alone, to doses of 35 to 40 Gy. With the advent of multi-agent chemotherapy, trials such as HD7 and H8 compared EFRT

alone with the combination of chemotherapy and radiotherapy (combined-modality therapy, CMT), and demonstrated significantly better outcomes with CMT, which became the standard of care for early-stage HL [44,45]. However, alongside evidence of better HL control with such approaches came data of the resultant late toxicity. Cohorts treated with radiotherapy were found to have long-term excess mortality, particularly from cardiovascular disease and second malignancies [46]. Anthracycline- and alkylating agent-containing chemotherapy were also shown to result in cardiotoxicity [47,48] and second malignancies [49–52] respectively. Subsequent trials therefore focused on treatment de-escalation, to minimise toxicity whilst maintaining efficacy.

The HD10 trial compared four cycles of Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine (ABVD) with two cycles, and 20 Gy IFRT to 30 Gy [13]. Two cycles of ABVD followed by 20 Gy IFRT was as effective and less toxic than four cycles and 30 Gy, and therefore became the standard of care for early-stage favourable HL [13]. The HD11 and HD14 trials established four cycles of ABVD, or two cycles escalated-dose bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisolone (eBEACOPP) followed by two cycles of ABVD, and 30 Gy IFRT as standards of care for early-stage unfavourable HL [53,54].

With the widespread adoption of routine PET-CT scanning for HL patients came evidence that complete resolution of FDG-activity after 1-2 cycles of chemotherapy was prognostic for achieving long-term cure [55]. More recent trials have therefore utilised early-response by PET-CT as a predictive tool to de-escalate therapy by omitting radiotherapy in early-stage HL. The H10 trial used PET-CT response after two cycles of ABVD to guide further therapy. The standard arm was a total of three (if favourable) or four (unfavourable) cycles of ABVD with INRT, regardless of PET-CT response [56]. In the experimental arms, patients with a negative PET-CT had a further two (favourable) or four (unfavourable) cycles of ABVD with no consolidation radiotherapy. Those with favourable early-stage HL who did

not receive radiotherapy had an 11.9% increased rate of recurrence (hazard ratio (HR) 15.8; 95% confidence interval (CI) 3.8-66.1), and those with unfavourable early-stage HL a 2.5% increase (HR 1.45; 95% CI 0.8-2.5) [56]. The RAPID trial randomised patients with a negative PET-CT scan after three cycles of ABVD to receive IFRT or no further treatment [57]. Omission of radiotherapy led to a 6.3% increase in recurrence, with a HR of 2.36 (95% CI 1.13-4.95) in favour of radiotherapy [57]. The HD16 trial randomised patients with early-stage favourable HL to standard treatment (two cycles ABVD and 20 Gy radiotherapy) or PET-guided therapy [12]. Patients in the PET-guided arm received two cycles of ABVD followed by a PET-CT. Those who were PET-negative had radiotherapy omitted, whereas those who were PET-positive had 20 Gy radiotherapy. Omission of radiotherapy led to a 7.3% increase in recurrence at five years (HR 1.78; 95% CI 1.02-3.12) [12]. Most recurrences were in locations that would have been included in the radiotherapy field, confirming they could most likely have been prevented by radiotherapy [12]. A smaller Italian study of patients with bulky HL randomised those with negative PET-CTs after two cycles of etoposide, epirubicin, bleomycin, cyclophosphamide, and prednisolone (VEBEP) to receive either 32 Gy to the area of bulky disease at diagnosis, or no further treatment. Omission of radiotherapy resulted in a 10% increase in recurrence at a median follow-up of 40 months [58]. A meta-analysis of H10, RAPID, HD16 and updated Italian data confirmed an increased risk of recurrence with the omission of radiotherapy, even in patients with a complete metabolic response on PET-CT scan (HR for recurrence 2.08; 95% CI 1.27-3.43) [55].

Only one trial (HD17) has tested a PET-adapted strategy in early-stage unfavourable HL. Patients received two cycles each of ABVD and eBEACOPP followed by a PET-CT scan, and those with a negative PET-CT were randomised to receive radiotherapy or not [59]. Omission of radiotherapy was non-inferior, with a non-statistically significant increase in recurrence of 2.2% in those not treated with radiotherapy [59].

Despite consistent data demonstrating superior tumour control with radiotherapy, its role in the treatment of early-stage favourable HL continues to be debated. Some maintain that CMT remains standard of care [12,56,58], whereas others argue that increased recurrence does not translate into reduced survival, and therefore a chemotherapy-alone approach is acceptable [57]. Current UK and European guidelines acknowledge that all patient groups experience an increased risk of recurrence when radiotherapy is omitted, but that this doesn't appear to impact on overall prognosis (due to the success of treatment for relapsed disease) [2,7]. They therefore recommend an individualised approach, omitting radiotherapy for individual patients where the late risk is thought to outweigh the benefit of improved disease control [2,5,7].

The next generation of trials is investigating the use of newer drugs upfront, such as brentuximab vedotin immunotherapy (an anti-CD30 antibody conjugated to a chemotherapeutic agent), with the aim of achieving a lower relapse rate compared to ABVD alone [60].

1.3.2 Advanced-stage Hodgkin lymphoma

Multi-agent chemotherapy is considered standard of care for patients with advanced-stage HL [1,2,5,7]. ABVD is the most widely-used regimen internationally, with eBEACOPP used more in Europe. The latter is not recommended for patients over the age of 60 years, due to its increased toxicity profile [2,5]. In the UK, patients are often treated with ABVD upfront, intensified to eBEACOPP if they have a positive PET-CT scan after two cycles, based on data from the RATHL and SWOG S0816 trials [61,62]. However, some clinicians use a risk-adapted approach and offer eBEACOPP upfront to high-risk patients [2].

The GITL/FIL HD0607 trial investigated the role of radiotherapy for patients with advanced-stage HL. It randomised those with a negative PET-CT scan after two cycles of ABVD, who had initial nodal masses over five centimetres in size, to receive radiotherapy or not [63].

There was no statistically significant difference in recurrence rate at six years when radiotherapy was omitted (9% versus 5%) [63]. Radiotherapy is generally therefore only recommended for patients with advanced-stage HL if they have localised residual PET-positive disease after chemotherapy [1,2,7,64]. Since the role of radiotherapy is much clearer in the setting of advanced-stage HL, the remainder of my thesis focuses on the decision about radiotherapy for patients with early-stage HL.

1.4 Risks of radiotherapy used to treat Hodgkin lymphoma

The side-effects of radiotherapy depend on which organs are irradiated. HL commonly involves lymph nodes in the mediastinum (the central compartment of the thorax) [46]. Mediastinal radiotherapy results in the heart, lungs, oesophagus, carotid arteries, and breasts being exposed to radiation, which can result in toxicity due to the short- and long-term effects of radiation damage to these organs. Short-term side-effects include oesophageal inflammation and cough. These are usually mild compared to those caused by chemotherapy, and settle quickly after completion of radiotherapy. Longer-term complications can manifest many years later, and are termed ‘late-effects’, officially defined as side-effects that occur over three months after completion of radiotherapy. The high likelihood of long-term survival following treatment for HL allows sufficient time for these late-effects to manifest and affect quality of life and, in some cases, life expectancy. The first late-effects of HL treatment to be recognised were second malignancies, which were first described in 1972 [65]. A diverse spectrum of late-effects is now recognised, including cardiovascular disease, second malignancies, cerebrovascular disease, respiratory disease, infections and endocrinopathies [46,66]. Mortality from these late-effects exceeds that from HL 15 to 20 years following treatment (Figure 1.6).

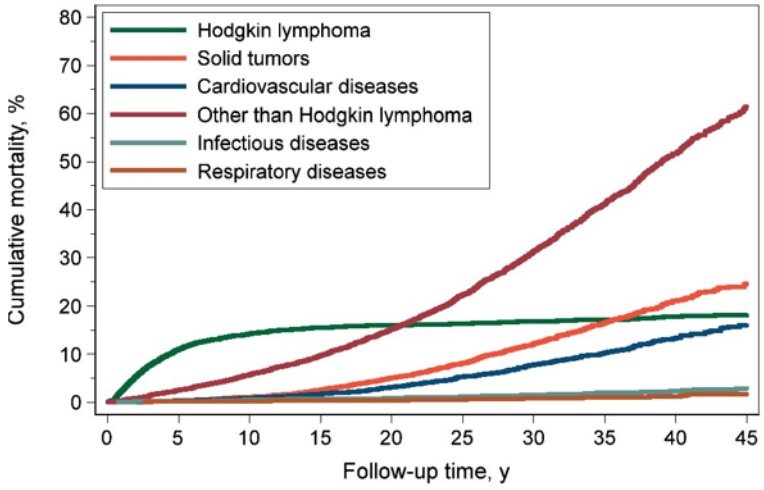


Figure 1.6: Cumulative mortality from major disease categories following treatment for Hodgkin lymphoma
Reused with permission from de Vries et al, 2021 [67]

1.4.1 Studying the late-effects of radiotherapy

A major difficulty in accurately predicting risk from modern radiotherapy arises from the latency of late-effects. This latency means that is it not practical to study late-effects within randomised controlled trials, and instead retrospective observational studies are necessary to understand the risks of late toxicity following radiotherapy. An understanding of basic epidemiological concepts is critical to interpret the results of such studies, and I will explain some of these here to define the terminology I use throughout this thesis.

'Incidence rate' is the number of new cases of disease occurring in a population in a specified time interval, divided by the total time individuals in the population were observed (measured in person-years (py): one py is one person observed for one year) [68]. 'Mortality rate' is the same, but for deaths rather than cases of disease. 'Risk' is the probability of an individual in a defined population developing an event (typically disease or death) [69], and 'cumulative risk' is the probability that an individual develops an event at any time during a specified time interval. The 'rate ratio' is the incidence or mortality rate in a group exposed to a risk factor divided by the rate in those not exposed [70]. A type of rate ratio is the

'hazard ratio', which measures the rate ratio at a given instant in time. The rate ratio can be converted to an 'excess rate ratio' by subtracting one from it. 'Relative risk' is the risk among a group exposed to a risk factor divided by the risk in those not exposed, and the 'excess relative risk' is the relative risk minus one [70]. 'Background' is commonly used to refer to rates and risks in the population not exposed to a risk factor.

Case-control studies enrol a group of people with a disease ('cases') and a comparable group without disease ('controls'). Often the size of the population that the cases originated from is unknown, and risks and rates therefore cannot be calculated [70]. Instead, 'odds ratios' are used that represent the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome in those not exposed [70]. 'Odds' is the probability that an event will occur divided by the probability that it will not. When the probability of an event occurring is low, the odds ratio provides a reasonable approximation of the rate ratio [70].

The 'standardised incidence ratio' is the incidence rate in a population divided by that in a 'reference' population with the same age and sex structure, observed over the same calendar period [71]. The 'standardised mortality ratio' is the same, but for death rather than incidence of disease.

1.4.2 Dose-response relationships

Another important epidemiological concept is the 'dose-response relationship'. This describes the relationship between the probability of a pre-defined outcome and a specified exposure. In the context of the late-effects of radiotherapy, dose-response relationships describe the relationship between the probability of a late-effect developing and the degree of exposure to radiation (i.e. the dose). These relationships can be derived using

information from patients treated in the past, as long as there is sufficient information about the radiation dose they received and the subsequent development of the disease under investigation. Once derived, radiation dose-response relationships can be used to estimate the risks from modern radiotherapy, by multiplying the risk per Gy with the dose that the patient receives.

One example of a dose-response relationship is shown in Figure 1.7. This describes the relationship between the dose received by the heart during radiotherapy and the patient's subsequent risk of ischaemic heart disease, and shows a 7.4% excess rate ratio for each Gy increase in dose received by the heart.

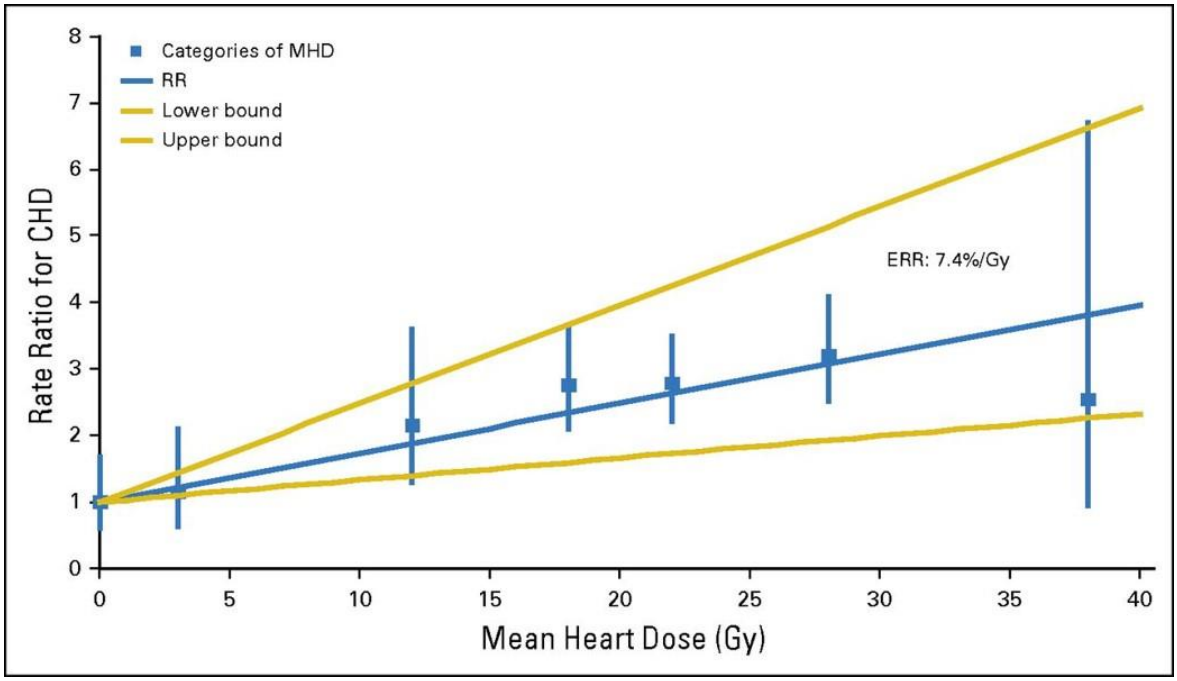


Figure 1.7: The dose-response relationship for heart dose and ischaemic (coronary) heart disease risk

Squares indicate estimates for dose categories and are plotted at the median dose in each category, vertical lines are 95% confidence intervals. The regression line is the best-fitting dose-response relationship (RR = 1 + 0.07402*MHD).

Abbreviations - CHD: coronary heart disease; MHD: mean heart dose; RR: rate ratio

Reused with permission from van Nimwegen et al, 2015 [72]

1.5 Preferences with regard to Hodgkin lymphoma treatment

There is growing advocacy and awareness that patients should be more involved in decisions about their health and healthcare. In 2017, the Lymphoma Coalition demonstrated that when a person has knowledge about their health, they are more likely to take an active role in decisions, ask more questions, and have a better experience of healthcare [73]. In 2018, the Global Patient Survey on Lymphomas found that respondents who felt adequately informed were more confident in accessing medical care, had better doctor-patient communication, and a more positive healthcare experience [73].

As described in section 1.3, there are various treatment options for HL with different outcome probabilities and risk profiles. Understanding patients' preferences and the trade-offs they are willing to make is important when balancing the chance of cure against the risk of late-effects. Despite this, there is a paucity of preference data specific to HL patients. One study, which surveyed HL patients and clinicians specialising in HL, found that both preferred treatments that offered the highest rates of cure [74]. HL patients were willing to accept a treatment with a higher risk of toxicity if it was associated with an increased chance of cure [74]. Clinicians were also willing to accept higher levels of risk in exchange for higher cure rates, but their preferences differed based on hypothetical patient characteristics, such as age, fertility preferences, and lifestyle choices such as smoking [74]. The vast majority of patients treated in German Hodgkin Study Group trials also considered cure from HL as the most important aspect of treatment [75]. Only 2% of patients reported they would rather choose a less effective therapy with fewer acute or late side-effects [75]. A survey of people treated for HL in the UK demonstrated that the majority considered short-term side-effects more important than the risk of late-effects when choosing between treatments with the same chance of cure [76].

Involvement of patients in decisions about their healthcare is particularly pertinent in early-stage HL where there are often significant choices to be made between different treatment options. Shared decision-making has been suggested as the only way that the uncertainty about the benefit-to-risk ratio of radiotherapy for individual patients can be addressed [12]. However, in a study by the British National Lymphoma Investigation Group in 1996, the majority of HL patients reported no involvement in treatment decision-making, half felt they had not been given enough information to participate in decisions, and a quarter felt there had been no real treatment choices available to them [76]. Irrespective of the degree to which they felt involved in decision-making, patients who were satisfied with the amount of information they received were more likely to be content with their level of participation [76].

1.6 Motivation for thesis

By 2030, four million people in the UK will be living with the long-term consequences of cancer and its treatment, but there is a lack of focused research on the problems they face and how these can be reduced [77]. My research corresponds closely with the National Cancer Research Institute 'living with and beyond cancer' research priorities that were identified in partnership with the James Lind Alliance [77]. The decision whether or not to use radiotherapy to treat patients with early-stage HL has huge implications with regard to their risk of late-effects, as well as the probability of requiring further treatment for recurrence. Weighing up the benefits and risks is extremely complex: radiotherapy has a proven benefit in reducing recurrence, but patients are still at risk of late-effects despite the smaller volumes and lower doses adopted by modern techniques. Due to the continual evolution of treatments it can be difficult to estimate the risks of radiotherapy for an individual patient with HL. An additional layer of uncertainty are the patient's preferences and views about treatment. Clinical guidelines recommend an individualised approach to

the decision about radiotherapy, but it is unclear how to practically achieve this. The use of radiotherapy varies regionally in the UK [78], suggesting variation in how decisions are made across the country. Clinicians need to be able to estimate the risks of radiotherapy for an individual patient with HL, and incorporate these risks, together with the patient's values and preferences, into treatment decision-making.

These issues around weighing up the benefits and risks of radiotherapy for individual patients is what I intend to address in my thesis. Such issues are particularly pertinent in the context of HL, because treatments result in cure for the majority, and a substantial proportion of patients are diagnosed at a young age, so the long-term risks of treatment have time to manifest. Numerous cohort studies have demonstrated increased rates of cardiovascular disease and second malignancies in patients who have been treated for HL, a substantial proportion of which can be attributed to the long-term side-effects of radiotherapy. In the past couple of decades, the haemato-oncological community has moved towards wanting to omit radiotherapy, where possible, to avoid these late-effects. Trials have aimed to maximise cure using a chemotherapy-only approach, and in more recent years novel agents such as immunotherapies have been added to further improve cure and reduce the role of radiotherapy. However, randomised trials have demonstrated that there is a substantial reduction in cure rates after primary treatment when radiotherapy is not used, indicating radiotherapy does still have an important role in the treatment of patients with HL. However, it is also clear that for some patients the benefit of radiotherapy, in terms of reducing recurrence of HL, is outweighed by the increased risks of long-term toxicities. Therefore there is a need to be able to weigh the benefits and risks of radiotherapy for each individual patient.

My research group, which is led by Professor Sarah Darby, is one of the leading groups in the field of radiation epidemiology. The group's work focuses on quantifying the benefits and risks of cancer treatments, particularly radiotherapy. Professor Darby's paper

quantifying the risk of ischaemic heart disease in women after radiotherapy for breast cancer is one of the most widely cited papers in our field, and paved the way for our group and others to use data from patients treated in the past to estimate the risks of radiotherapy for those treated today. My main supervisor, Associate Professor David Cutter, joined Professor Darby's group in 2008 and he leads a programme of work investigating the benefits and risks of lymphoma treatments. I joined Dr Cutter's team in 2019, to work on projects investigating the balance of benefits and risks of radiotherapy used to treat people with HL. I subsequently designed my own package of work, based on some of those project ideas, and was successful in obtaining an NIHR Doctoral Research Fellowship, which started in 2020. The data I present in this thesis are the results of studies from my fellowship package of work. For Chapters 4 and 5 some data was provided by other researchers or clinicians, so that I could obtain sufficiently large datasets, but all of the analysis and results, and subsequent interpretation, I present is my own work.

Throughout my research I have worked with a project advisory group made up of four people previously treated for HL. I set this group up with the help of Dr Catriona Gilmour-Hamilton, who is the Haematology Quality Manager for Patient Experience and Engagement at Oxford University Hospitals NHS Foundation Trust. As part of her role, she curates the Oxford Blood Group, which is a group made up of people treated for blood disorders in Oxford who are interested in being involved in research. I first approached Dr Gilmour-Hamilton when I was designing my package of work for my NIHR Fellowship. I wanted to involve people with lived experience from the outset of my research, to ensure that I began with a good understanding of patient experience, and addressed research questions that were relevant to patients. Dr Gilmour-Hamilton advertised my research to the group, and four people expressed an interest in being involved (Mr Craig Bakin, Ms Isabelle Gent, Mr Adam Holloway, and Ms Alison Meeson). I have met with the group regularly during my research, and they have helped refine my research questions and shape the design of my studies. Their perspective has brought new insight, ensured that I

focus on the issues most important to survivors, and gives credibility to the relevance of the research.

1.7 Thesis aims and overview

The aim of this thesis is to understand the decision-making process about radiotherapy, and provide data that can be used to inform patients and clinicians at various steps during decision-making (Figure 1.8).

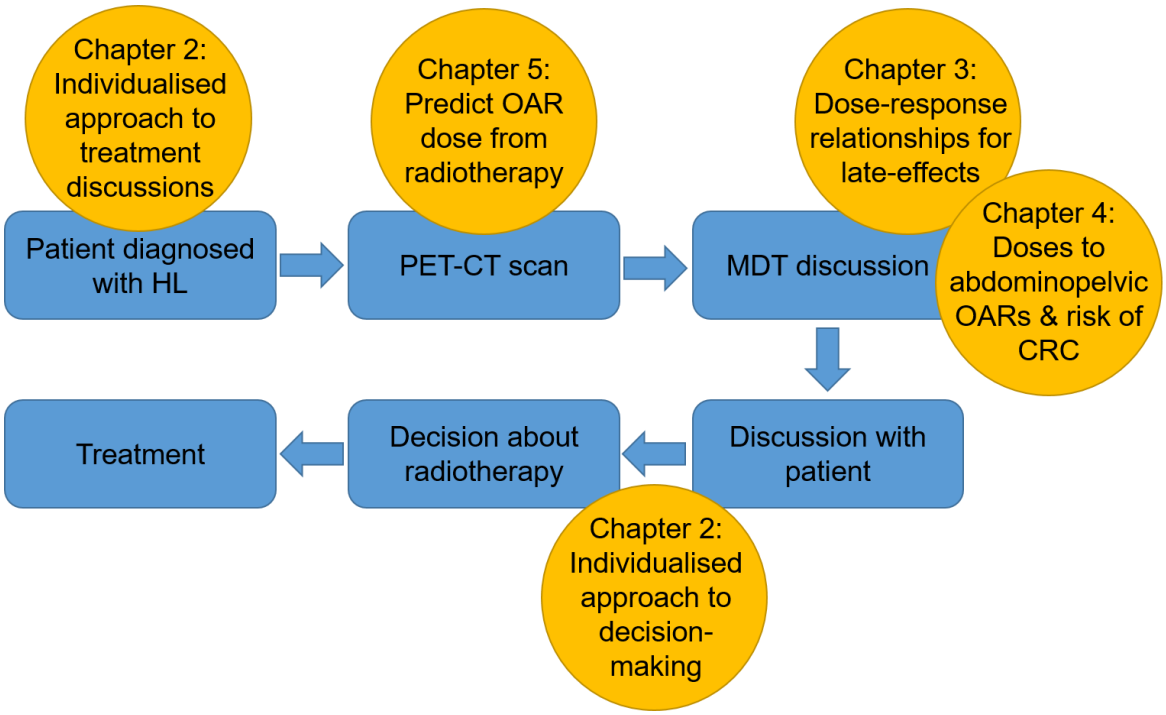


Figure 1.8: Overview of the clinical pathway for making decisions about radiotherapy used to treat patients with Hodgkin lymphoma, highlighting the steps informed by data presented in this thesis

Abbreviations - HL: Hodgkin lymphoma; OAR: organ-at-risk; PET-CT: Positon emission tomography integrated with computed tomography; MDT: multidisciplinary team; CRC: colorectal cancer

In Chapter 2 I report the results of a study that explored patients' and clinicians' experience of the radiotherapy decision-making process. This is a qualitative study, using semi-

structured interviews to gain a deeper understanding of how decisions are made, and the factors influencing patient and clinician preferences with regard to treatment options and decision-making. It gives emphasis to the experiences and views of patients and clinicians and highlights areas where additional data could help guide radiotherapy treatment decisions, and improve patient participation in these decisions. These data gaps shaped three quantitative studies that make up three further results chapters in my thesis.

Chapter 3 is a systematic review aimed at quantifying the risks of radiotherapy used to treat HL, and determining the individual patient factors that affect the magnitude of this risk. I present collated estimates of the risks of late-effects of radiotherapy used to treat HL, and estimates of how the risks vary by factors specific to an individual patient, such as their age and sex, or their treatment, for example radiation dose and field. I identify which late-effects have published dose-response relationships that can be used to estimate the risks from modern radiotherapy, and highlight gaps in the literature that should be addressed to provide more comprehensive data to inform radiotherapy decision-making.

The majority of the data reported in Chapter 3 relates to the risk of radiotherapy delivered to supradiaphragmatic regions, with less data available discussing the risks of infradiaphragmatic radiotherapy. In Chapter 4 I begin to address that gap by reporting the doses received by abdominopelvic organs from historic radiotherapy. Using a cohort of Dutch patients treated for HL between 1965 and 2000, I reconstruct individual patient's radiotherapy fields on representative CT scans, and report mean doses to abdominopelvic OARs. I demonstrate how these doses can be used, and report the results of a nested case-control study where I collaborated with researchers from the Netherlands Cancer Institute to develop a dose-response relationship for the risk of colorectal cancer following treatment for HL.

Currently, it is not possible to calculate the risks of modern radiotherapy for an individual patient until a radiotherapy treatment plan has been produced and the dose to OARs is

known. Risks can therefore only be accurately estimated once the decision to use radiotherapy has already been made, which prevents these estimates informing treatment discussions and decisions. In Chapter 5 I report the results of a study I conducted to address this issue. Using data from seven UK hospitals, and two international centres, I developed a model that uses information available at the time of patient's diagnosis with HL to predict the dose that their heart would receive if they were to receive radiotherapy. I demonstrate that it is feasible to predict dose to the heart, and associated risk of IHD, using data available at diagnosis of HL. Further refinement of the model is required, but it is an important first-step in integrating individualised risk-estimation into treatment decisions about radiotherapy.

My final chapter, Chapter 6, is an overall discussion chapter. In this, I explain how the results of each of my studies contribute to our understanding of how to individualise the use of radiotherapy for patients with HL. I end by discussing future work needed to refine and develop my data into a decision aid that could be used to facilitate individualised decision-making about radiotherapy in clinical practice.

1.8 References

[1] Connors JM, Cozen W, Steidl C, Carbone A, Hoppe RT, Flechtner HH, et al. Hodgkin lymphoma. Nat Rev Dis Prim 2020;6:1–25. doi:10.1038/s41572-020-0189-6.

[2] Follows GA, Barrington SF, Bhuller KS, Culligan DJ, Cutter DJ, Gallop- Evans E, et al. Guideline for the first- line management of classical Hodgkin lymphoma — A British Society for Haematology guideline. Br J Haematol 2022. doi:10.1111/bjh.18083.

[3] Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IB de O, Berti E, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia 2022;36:1720–48. doi:10.1038/s41375-022-01620-2.

[4] Hodgkin lymphoma survival statistics | Cancer Research UK n.d. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/hodgkin-lymphoma/survival (accessed December 24, 2018).

[5] Bröckelmann PJ, Eichenauer DA, Jakob T, Follmann M, Engert A, Skoetz N. Clinical practice guideline: Hodgkin lymphoma in adults—diagnosis, treatment, and follow-up. Dtsch Arztebl Int 2018;115:535–40. doi:10.3238/arztebl.2018.0535.

[6] Kaplan HS. Continuity and progression in Hodgkin's disease. Cancer Res 1971;31:1811–3.
[7] Eichenauer DA, Aleman BMP, André M, Federico M, Hutchings M, Illidge T, et al. Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29:iv19–29. doi:10.1093/annonc/mdy080.
[8] Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989;7:1630–6. doi:10.1200/JCO.1989.7.11.1630.
[9] Cuccaro A, Bartolomei F, Cupelli E, Galli E, Giachelia M, Hohaus S. Prognostic Factors in Hodgkin Lymphoma. Open J Syst Mediterr J Hematol Infect Dis Cit Mediterr J Hematol Infect Dis 2014;6:2014053. doi:10.4084/MJHID.2014.053.
[10] Vassilakopoulos TP, Chatzidimitriou C, Asimakopoulos J V., Arapaki M, Tzoras E, Angelopoulou MK, et al. Immunotherapy in Hodgkin lymphoma: Present status and future strategies. Cancers (Basel) 2019;11:1071. doi:10.3390/cancers11081071.
[11] Houot R, Merryman RW, Morschhauser F. Total immunotherapy for Hodgkin lymphoma. Lancet Haematol 2020;7:e629–30. doi:10.1016/S2352-3026(20)30220-9.
[12] Fuchs M, Goergen H, Kobe C, Kuhnert G, Lohri A, Greil R, et al. Positron emission tomography-guided treatment in early-stage favorable Hodgkin lymphoma: Final results of the international, randomized phase III HD16 trial by the German Hodgkin Study Group. J Clin Oncol 2019;37:2835–45. doi:10.1200/JCO.19.00964.
[13] Engert A, Plütschow A, Eich HT, Lohri A, Dörken B, Borchmann P, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med 2010;363:640–52. doi:10.1056/NEJMoa1000067.
[14] National Cancer Institute. Definition of radiotherapy - NCI Dictionary of Cancer Terms 2022. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/radiotherapy (accessed July 14, 2022).
[15] Hoskin PJ, editor. External Beam Therapy (Radiotherapy in Practice). Third. Oxford University Press; 2019.
[16] Sibtain A, Morgan A, MacDougall N. Physics for Clinical Oncology. First. Oxford University Press; 2012. doi:https://doi.org/10.1093/med/9780199573356.001.0001.
[17] Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the committee on Hodgkin's disease staging classification. Cancer Res 1971;31:1860–1.
[18] Yahalom J, Mauch P. The involved field is back: issues in delineating the radiation field in Hodgkin's disease. Ann Oncol 2002;13:79–83. doi:10.1093/ANNONC/13.S1.79.
[19] Page V, Gardner A, Karzmark CJ. Physical and dosimetric aspects of the radiotherapy of malignant lymphomas. I. The mantle technique. Radiology 1970;96:609–18. doi:10.1148/96.3.609.
[20] Page V, Gardner A, Karzmark CJ. Physical and dosimetric aspects of the radiotherapy of malignant lymphomas. II. The inverted-Y technique. Radiology 1970;96:619–26. doi:10.1148/96.3.619.
[21] Carmel RJ, Kaplan HS. Mantle irradiation in Hodgkin's disease. An analysis of technique, tumor eradication, and complications. Cancer 1976;37:2813–25. doi:10.1002/1097-0142(197606)37:6<2813::AID-CNCR2820370637>3.0.CO;2-S.
[22] Bar V, Paltiel O, Glatstein E. Radiotherapy for early-stage Hodgkin's lymphoma: A 21st century perspective and review of multiple randomized clinical trials. Int J Radiat Oncol 2008;72:1472–9. doi:10.1016/j.ijrobp.2008.08.026.
[23] Hodgson DC, Koh ES, Tu HT, Heydarian M, Tsang R, Pintilie M, et al. Individualized estimates of second cancer risks after contemporary radiation therapy for Hodgkin lymphoma. Cancer 2007;110:2576–86. doi:10.1002/cncr.23081.
[24] Koh ES, Tran TH, Heydarian M, Sachs RK, Tsang RW, Brenner DJ, et al. A comparison of mantle versus involved-field radiotherapy for Hodgkin's lymphoma:

Reduction in normal tissue dose and second cancer risk. Radiat Oncol 2007;2:1–11. doi:10.1186/1748-717X-2-13.

[25] Girinsky T, van der Maazen R, Specht L, Aleman B, Poortmans P, Lievens Y, et al. Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: concepts and guidelines. Radiother Oncol 2006;79:270–7. doi:10.1016/J.RADONC.2006.05.015.

[26] Specht L, Yahalom J, Illidge T, Berthelsen AK, Constine LS, Eich HT, et al. Modern radiation therapy for Hodgkin lymphoma: Field and dose guidelines from the international lymphoma radiation oncology group (ILROG). Int J Radiat Oncol Biol Phys 2014;89:854–62. doi:10.1016/j.ijrobp.2013.05.005.

[27] Wirth A, Mikhaeel NG, Aleman BMP, Pinnix CC, Constine LS, Ricardi U, et al. Involved site radiation therapy in adult lymphomas: an overview of International Lymphoma Radiation Oncology Group guidelines. Int J Radiat Oncol 2020;107:909–33. doi:10.1016/J.IJROBP.2020.03.019.

[28] Filippi AR, Levis M, Parikh R, Hoppe B. Optimal therapy for early-stage Hodgkin's lymphoma: Risk adapting, response adapting, and role of radiotherapy. Curr Oncol Rep 2017;19. doi:10.1007/s11912-017-0592-7.

[29] Sciacca F. Organs at risk. Reference article. Radiopaedia.org. Radiopaedia 2020. doi:10.53347/RID-80650.

[30] Bilić LG, Šantek F. Infradiaphragmal radiotherapy in patients with lymphoma: Volume definition and side effects. Acta Clin Croat 2018;57:554–60. doi:10.20471/acc.2018.57.03.19.

[31] Knipe H, Di Muzio B. Conventional radiation therapy | Radiology Reference Article | Radiopaedia.org n.d. doi:https://doi.org/10.53347/rID-67492.

[32] Hodgson DC. Late effects in the era of modern therapy for Hodgkin lymphoma. Hematol Am Soc Hematol Educ Progr 2011;2011:323–9. doi:10.1182/asheducation-2011.1.323.

[33] Buglione M, Guerini AE, Filippi AR, Spiazzi L, Pasinetti N, Magli A, et al. A systematic review on Intensity Modulated Radiation Therapy for mediastinal Hodgkin's lymphoma. Crit Rev Oncol Hematol 2021;167:103437. doi:10.1016/j.critrevonc.2021.103437.

[34] Fiandra C, Filippi AR, Catuzzo P, Botticella A, Ciammella P, Franco P, et al. Different IMRT solutions vs. 3D-Conformal Radiotherapy in early stage Hodgkin's lymphoma: dosimetric comparison and clinical considerations. Radiat Oncol 2012;7:1–9. doi:10.1186/1748-717X-7-186.

[35] Starke A, Bowden J, Lynn R, Hall K, Hudson K, Rato A, et al. Comparison of butterfly volumetric modulated arc therapy to full arc with or without deep inspiration breath hold for the treatment of mediastinal lymphoma. Radiother Oncol 2018:4–10. doi:10.1016/j.radonc.2018.08.017.

[36] Voong KR, McSpadden K, Pinnix CC, Shihadeh F, Reed V, Salehpour MR, et al. Dosimetric advantages of a " butterfly" technique for intensity-modulated radiation therapy for young female patients with mediastinal Hodgkin's lymphoma. Radiat Oncol 2014;9:1–9. doi:10.1186/1748-717X-9-94.

[37] Maraldo M V., Brodin NP, Aznar MC, Vogelius IR, Munck af Rosenschöld P, Petersen PM, et al. Estimated risk of cardiovascular disease and secondary cancers with modern highly conformal radiotherapy for early-stage mediastinal Hodgkin lymphoma. Ann Oncol 2013;24:2113–8. doi:10.1093/annonc/mdt156.

[38] Weber DC, Johanson S, Peguret N, Cozzi L, Olsen DR. Predicted risk of radiation-induced cancers after involved field and involved node radiotherapy with or without intensity modulation for early-stage Hodgkin lymphoma in female patients. Int J Radiat Oncol Biol Phys 2011;81:490–7. doi:10.1016/j.ijrobp.2010.05.035.

[39] Cella L, Conson M, Pressello MC, Molinelli S, Schneider U, Donato V, et al. Hodgkin's lymphoma emerging radiation treatment techniques: Trade-offs between late radio-induced toxicities and secondary malignant neoplasms. Radiat Oncol 2013;8:1–10. doi:10.1186/1748-717X-8-22.

[40] Filippi AR, Ragona R, Fusella M, Botticella A, Fiandra C, Ricardi U. Changes in breast cancer risk associated with different volumes, doses, and techniques in female Hodgkin lymphoma patients treated with supra-diaphragmatic radiation therapy. Pract Radiat Oncol 2013;3:216–22. doi:10.1016/j.prro.2012.12.006.
[41] Petersen PM, Aznar MC, Berthelsen AK, Loft A, Schut DA, Maraldo M, et al. Prospective phase II trial of image-guided radiotherapy in Hodgkin lymphoma: Benefit of deep inspiration breath-hold. Acta Oncol (Madr) 2015;54:60–6. doi:10.3109/0284186X.2014.932435.
[42] Paumier A, Ghalibafian M, Gilmore J, Beaudre A, Blanchard P, El Nemr M, et al. Dosimetric benefits of intensity-modulated radiotherapy combined with the deep-inspiration breath-hold technique in patients with mediastinal Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 2012;82:1522–7. doi:10.1016/j.ijrobp.2011.05.015.
[43] Aznar MC, Maraldo M V., Schut DA, Lundemann M, Brodin NP, Vogelius IR, et al. Minimizing late effects for patients with mediastinal Hodgkin lymphoma: Deep inspiration breath-hold, IMRT, or both? Int J Radiat Oncol Biol Phys 2015;92:169–74. doi:10.1016/j.ijrobp.2015.01.013.
[44] Engert A, Franklin J, Eich HT, Brillant C, Sehlen S, Cartoni C, et al. Two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine plus extended-field radiotherapy is superior to radiotherapy alone in early favorable Hodgkin's lymphoma: Final results of the GHSG HD7 trial. J Clin Oncol 2007;25:3495–502. doi:10.1200/JCO.2006.07.0482.
[45] Fermé C, Eghbali H, Meerwaldt JH, Rieux C, Bosq J, Berger F, et al. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. N Engl J Med 2007;357:1916–27. doi:10.1056/nejmoa064601.
[46] Aleman BMP, van den Belt-Dusebout AW, Klokman WJ, Van't Veer MB, Bartelink H, van Leeuwen FE. Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol 2003;21:3431–9. doi:10.1200/JCO.2003.07.131.
[47] Myrehaug S, Pintilie M, Tsang R, Mackenzie R, Crump M, Chen Z, et al. Cardiac morbidity following modern treatment for Hodgkin lymphoma: Supra-additive cardiotoxicity of doxorubicin and radiation therapy. Leuk Lymphoma 2008;49:1486–93. doi:10.1080/10428190802140873.
[48] Hodgson DC. Long-term toxicity of chemotherapy and radiotherapy in lymphoma survivors: Optimizing treatment for individual patients. Clin Adv Hematol Oncol 2015;13:103–12.
[49] van Leeuwen FE, Chorus AM, van den Belt-Dusebout AW, Hagenbeek A, Noyon R, van Kerkhoff EH, et al. Leukemia risk following Hodgkin's disease: relation to cumulative dose of alkylating agents, treatment with teniposide combinations, number of episodes of chemotherapy, and bone marrow damage. J Clin Oncol 1994;12:1063–73. doi:10.1200/JCO.1994.12.5.1063.
[50] Valagussa P, Santoro A, Kenda R, Bellani FF, Franchi F, Banfi A, et al. Second malignancies in Hodgkin's disease: A complication of certain forms of treatment. Br Med J 1980;280:216–9. doi:10.1136/bmj.280.6209.216.
[51] Morton LM, Dores GM, Curtis RE, Lynch CF, Stovall M, Hall P, et al. Stomach cancer risk after treatment for Hodgkin lymphoma. J Clin Oncol 2013;31:3369–77. doi:10.1200/JCO.2013.50.6832.
[52] van Eggermond AM, Schaapveld M, Janus CPM, De Boer JP, Krol AD, Zijlstra JM, et al. Infradiaphragmatic irradiation and high procarbazine doses increase colorectal cancer risk in Hodgkin lymphoma survivors. Br J Cancer 2017;117:306–14. doi:10.1038/bjc.2017.177.
[53] Eich HT, Diehl V, Görgen H, Pabst T, Markova J, Debus J, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: Final analysis of the german hodgkin study group HD11 trial. J Clin Oncol 2010;28:4199–206. doi:10.1200/JCO.2010.29.8018.
[54] Von Tresckow B, Plütschow A, Fuchs M, Klimm B, Markova J, Lohri A, et al. Dose-intensification in early unfavorable Hodgkin's lymphoma: Final analysis of the

German Hodgkin study group HD14 trial. J Clin Oncol 2012;30:907–13. doi:10.1200/JCO.2011.38.5807.
[55] Shaikh MP, Alite F, Pugliese N, Picardi M, Vargo JA. Consolidation radiotherapy following positron emission tomography complete response in early-stage Hodgkin lymphoma: a meta-analysis. Leuk Lymphoma 2020;0:1–8. doi:10.1080/10428194.2020.1725506.
[56] André MPE, Girinsky T, Federico M, Reman O, Fortpied C, Gotti M, et al. Early positron emission tomography response-adapted treatment in stage I and II hodgkin lymphoma: Final results of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol 2017;35:1786–96. doi:10.1200/JCO.2016.68.6394.
[57] Radford J, Illidge T, Counsell N, Hancock B, Pettengell R, Johnson P, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med 2015;372:1598–607. doi:10.1056/NEJMoa1408648.
[58] Picardi M, De Renzo A, Pane F, Nicolai E, Pacelli R, Salvatore M, et al. Randomized comparison of consolidation radiation versus observation in bulky Hodgkin's lymphoma with post-chemotherapy negative positron emission tomography scans. Leuk Lymphoma 2007;48:1721–7. doi:10.1080/10428190701559140.
[59] Borchmann P, Plütschow A, Kobe C, Greil R, Meissner J, Topp MS, et al. PET-guided omission of radiotherapy in early-stage unfavourable Hodgkin lymphoma (GHSG HD17): A multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2021;22:223–34. doi:10.1016/S1470-2045(20)30601-X.
[60] Kumar A, Casulo C, Advani RH, Budde E, Barr PM, Batlevi CL, et al. Brentuximab vedotin combined with chemotherapy in patients with newly diagnosed early-stage, unfavorable-risk Hodgkin lymphoma. J Clin Oncol 2021;39:2257–65. doi:10.1200/JCO.21.00108.
[61] Johnson P, Federico M, Kirkwood A, Fosså A, Berkahn L, Carella A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. N Engl J Med 2016;374:2419–29. doi:10.1056/nejmoa1510093.
[62] Stephens DM, Li H, Scho¨der H, Straus DJ, Moskowitz CH, LeBlanc M, et al. Five-year follow-up of SWOG S0816: Limitations and values of a PET-adapted approach with stage III/IV Hodgkin lymphoma. Blood 2019;134:1238–46. doi:10.1182/blood.2019000719.
[63] Gallamini A, Rossi A, Patti C, Picardi M, Romano A, Cantonetti M, et al. Consolidation radiotherapy could be safely omitted in advanced Hodgkin lymphoma with large nodal mass in complete metabolic response after ABVD: Final analysis of the randomized GITIL/FIL HD0607 trial. J Clin Oncol 2020;38:3905–13. doi:10.1200/JCO.20.00935.
[64] Lockney NA, Yang JC. Radiation therapy for advanced-stage Hodgkin lymphoma. Adv Radiat Oncol 2020;5:809–16. doi:10.1016/j.adro.2020.06.001.
[65] Arseneau JC, Sponzo RW, Levin DL, Schnipper LE, Bonner H, Young RC, et al. Nonlymphomatous malignant tumors complicating Hodgkin's disease. N Engl J Med 1972;287:1119–22. doi:10.1056/nejm197211302872204.
[66] Ng AK. Late complications after treatment for Hodgkin lymphoma. Curr Hematol Malig Rep 2008;3:119–25. doi:10.1007/s11899-008-0018-6.
[67] de Vries S, Schaapveld M, Janus CPM, Daniëls LA, Petersen EJ, van der Maazen RWM, et al. Long-term cause-specific mortality in Hodgkin lymphoma patients. J Natl Cancer Inst 2021;113:760–9. doi:10.1093/jnci/djaa194.
[68] Centers for Disease Control and Prevention. Principles of Epidemiology | Lesson 3 - Section 2 2012:1. https://www.cdc.gov/csels/dsepd/ss1978/lesson3/section2.html (accessed July 15, 2022).
[69] Bhopal RS. The concept of risk and fundamental measures of disease frequency: Incidence and prevalence. Concepts Epidemiol. Integr. ideas, Theor. Princ. methods Epidemiol. Third, n.d. doi:10.1093/med/9780198739685.003.0007.
[70] Centers for Disease Control and Prevention. Principles of Epidemiology | Lesson 3 - Section 6 2012:1.

[71] Centers for Disease Control and Prevention. APPENDIX C: Statistical and Epidemiologic Approaches 2013:1. https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6208a4.htm (accessed July 15, 2022).
[72] van Nimwegen FA, Schaapveld M, Cutter DJ, Janus CPM, Krol ADG, Hauptmann M, et al. Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. J Clin Oncol 2016;34:235–43. doi:10.1200/JCO.2015.63.4444.
[73] Dren N, Warwick L, Rassel K Van, Moysiadis T, Karamanidou C, Xochelli A. Correlation of Lymphoma Patient Information Level with Healthcare Experience. Blood 2018;132:4782–4782. doi:10.1182/BLOOD-2018-99-115392.
[74] Bröckelmann PJ, McMullen S, Wilson J Ben, Mueller K, Goring S, Stamatoullas A, et al. Patient and physician preferences for first-line treatment of classical Hodgkin lymphoma in Germany, France and the United Kingdom. Br J Haematol 2019;184:202–14. doi:10.1111/bjh.15566.
[75] Kreissl S, Goergen H, Müller H, Meissner J, Mehnert A, Bürkle C, et al. Survivors' perspectives on risks and benefits of Hodgkin lymphoma treatment: results of a survey by the German Hodgkin Study Group. Leuk Lymphoma 2019;60:1389–98. doi:10.1080/10428194.2018.1540781.
[76] Turner S, Maher EJ, Young T, Young J, Hudson GV. What are the information priorities for cancer patients involved in treatment decisions? An experienced surrogate study in Hodgkin's disease. Br J Cancer 1996;73:222–7. doi:10.1038/bjc.1996.39.
[77] LWBC Home - The National Cancer Research Institute n.d. https://www.ncri.org.uk/lwbc/ (accessed May 30, 2019).
[78] Public Health England, Haematological Malignancy Site-Specific Clinical Reference Group. National Cancer Intelligence Network Working paper on variation in delivery of radiotherapy for patients with lymphoma About Public Health England 2015.

Chapter 2

Sharing decisions about radiotherapy for Hodgkin lymphoma: a qualitative study of the experiences of patients and clinicians in the UK

2.1 Background

2.1.1 Treatment decisions in Hodgkin lymphoma

As discussed in Chapter 1, standard treatment for Hodgkin lymphoma (HL) is risk-adapted chemotherapy, which may or may not be followed by radiotherapy. Radiotherapy is associated with long-term risks, including cardiovascular disease and subsequent malignancy, but its omission results in a higher risk of relapse in the first three to five years after treatment. Whilst there are data from randomised trials and guidelines in relation to which patients may benefit from radiotherapy, there are individual factors (including the patient's sex, age, and distribution of disease) that affect the balance of benefit and risk. These are difficult to quantify on an individual level, and therefore difficult to integrate into clinical decision-making.

The different outcomes and risk profiles associated with the use or omission of radiotherapy mean that patient and clinician preferences are likely to be important when making treatment decisions, but evidence to support this assumption is sparse. Little is known about how decisions are made about radiotherapy in current clinical practice, or patients' preferences for engaging in decision-making [1]. In the UK, there is regional variation in the use of radiotherapy for HL [2], suggesting regional differences in treatment decision-making. This is supported by data demonstrating that individual clinicians differ in their views on the relative merit and disadvantage of radiotherapy [1].

The balance of benefits and risks of radiotherapy differs between patients, and what is acceptable to one patient may be rejected by another. The 'right' treatment decision will therefore depend on the patient's values and goals, and can therefore be considered to be preference-sensitive. Shared decision-making is therefore likely to be key, to allow patients to make a decision that is right for them, informed by the available evidence and their

wishes, needs and preferences. Despite the preference-sensitive nature of radiotherapy decisions, there has been very little research into decision-making specific to HL. People with lymphoma often report not being offered a choice of treatment [3] or not being involved in treatment decisions [4]. Lymphoma is a highly heterogeneous group of malignancies, and so it is difficult to draw conclusions about decision-making in HL from these data. There is some evidence that people with HL have less desire for shared decision-making than patients with other cancers, and are satisfied with a more passive role [5–8], but no studies to date have specifically looked at decision-making about radiotherapy.

2.1.2 Decision-making models

There are four frequently described models of treatment decision-making: paternalistic, interpretative, shared and informed (Figure 2.1) [9,10]. These differ in terms of the type and direction of information exchange, patients' and clinicians' roles in deliberating about different treatment options, and who has ultimate responsibility for treatment decisions [9,11,12].

Decision-stages		Paternalistic	Interpretative	Shared	Informed
Information exchange	Flow	One-way (largely)	One-way (largely)	Two-way	One-way (largely)
	Direction	Clinician ↓ Patient	Clinician ↑ Patient	Clinician ↓ ↑ Patient	Clinician ↓ Patient
	Type	Medical	Personal, values, preferences & beliefs	Medical, personal, values, preferences & beliefs	Medical
	Minimum amount	Legal requirement	Anything relevant to discussion	Anything relevant to discussion	Anything relevant to discussion
Deliberation		Clinician alone (+/- other clinicians)	Clinician alone (integrating medical information)	Clinician & patient (+/- others)	Patient (+/- others)
Ultimate responsibility for decision		Clinician	Clinician	Clinician & patient	Patient

Figure 2.1: Models of decision-making
Adapted, with permission, from Charles et al, 1999 [12], with additional information from Wirtz et al, 2006 [9]

In the paternalistic model, the clinician decides on treatment after evaluation of information about the patient's disease, the treatment options and likely outcomes [9]. In the interpretative model, the clinician also makes the treatment decision, but only after considering the patient's values and preferences [9,10]. Shared decision-making is interactional, where clinicians and patients exchange information, discuss preferences and agree on a treatment decision [9,12,13]. In informed decision-making, the clinician informs the patient of the alternative treatment options, including their benefits and risks, to allow the patient to make their own treatment decision [9,12,13]. The paternalistic model assumes that the clinician can determine what's in the patient's best interest with limited patient participation, and without sharing any of the decision-making steps [10,12]. Interpretative decision-making also assumes that the clinician is best placed to ultimately make a treatment decision, but in contrast to the paternalistic model the clinician integrates the patient's values and preferences into that decision [9,13]. The shared decision-making

model assumes a patient relies on a clinician's support, and both parties participate to make a decision they agree on [9]. In contrast, informed decision-making assumes only the patient can decide on the treatment they receive [9]. Shared and interpretative decision-making emphasise the clinicians' responsibility to elicit patients' values, preferences and beliefs, relevant to the decision, whereas the clinician is exempt from this in the paternalistic and informed models [9]. Only in the shared model is decision-making interactive with both the clinician and patient leading certain discussions depending on who has more expertise to contribute [9,11]. This two-way information exchange, deliberation and decision-making mean that the shared model is often thought to be the most time-consuming [11]. In the other models, the decision can be taken outside of the consultation [9].

More recently, adaptations to these models have been suggested. The concept of concordance has emerged that describes treatment decisions (predominantly about medications) that respect the beliefs and wishes of the patient, reached after negotiation between a patient and clinician [9,14]. Concordance promotes a whole approach to the clinician patient encounter, rather than merely to decision-making, but it does describe a distinct model of decision-making [9]. In contrast to shared decision-making, it asserts that the patient's view should have precedence, and allows the patient to delegate the decision-making responsibility to the clinician [14], which falls outside of shared decision-making models [9]. Integrated decision-making has been suggested as a broad term to encompass an approach where evidence and patient preferences are integrated to make treatment decisions [13]. This term recognises that the locus of decision-making shifts depending on the context of that decision, and there is flexibility in the 'balance of power' between clinician and patient [9,13]. The model proposes that the appropriate approach to decision-making varies depending on the nature of the health issue; patient preferences, values and beliefs; clinician responsibilities; research evidence; and clinical evidence, with the nature of the health issue determining the relative weighting of each of the other four dimensions [13].

2.1.3 Decision-making policy in the NHS

Evidence suggests that patients in the UK wish to be more involved in treatment decisions [15,16]. Patients who are active participants in managing their health have been shown to have better outcomes than those who are passive recipients of care [17]. In light of this, the government's aspiration is that shared decision-making becomes the norm in the NHS [18], as part of the NHS Long Term Plan's commitment to personalised care [19]. Principle four of the NHS Constitution states that "patients will be involved in and consulted on all decisions about their care and treatment" [20].

The National Institute for Health and Care Excellence (NICE) define shared decision-making as "a collaborative process that involves a person and their healthcare professional working together to reach a joint decision about care" [21]. This definition is in general agreement with other definitions in the literature [11,13]. NHS England's definition is broadly similar, but puts the emphasis on the patient being the decision maker: "a collaborative process through which a clinician supports a patient to reach a decision about their treatment" [22]. Policy documents highlight that patients have the right to make fully-informed decisions about their care, and bring their own expertise to the decision-making process [16–21]. In particular, they stress the need to commit to sharing information and decision-making responsibility, and to integrate the patient's personal attitudes to risk, values and preferences into decisions [17]. NICE recommend that shared decision-making is embedded within organisations, and actively promoted to patients [21]. Healthcare professionals are encouraged to ensure that people understand the choices available to them, including a choice about how much they participate in decisions, and are given a chance to discuss what's important to them. The guidelines recommend sharing personalised information on the aims, risks, benefits and consequences of each treatment option, using decision aids where available [17,21].

Commissioners see shared decision-making as a mechanism of reducing unwarranted variation in clinical practice, and essential for patient-centred care [17]. Professional regulatory authorities view it as an ethical imperative that clinicians work in partnership with patients, eliciting their preferences and discussing treatment options, including the risks and uncertainties [23].

Proponents of shared decision-making stress its benefits in terms of patient satisfaction, reduced stress and increased compliance with treatment [17]. They highlight that whilst clinicians have knowledge of the disease and toxicities of treatment, their perception of these and relative priorities may differ from those of patients. The 'right' decision for a patient can therefore only be made through their active participation. Support for shared decision-making is not universal however. Some clinicians argue that it is not realistic given the time pressures within consultations. Others are concerned about the potential for causing patients anxiety by giving them responsibility for decisions, and regret for perceived 'wrong' decisions. There is debate about which clinical decisions should be shared. Some have argued that shared decision-making is best suited to decisions in which no single best alternative can be identified and clinicians are in a state of equipoise. Such decisions have been termed 'preference sensitive' [24]. Others argue it should be applied more broadly, as there is always an option to 'do nothing' [17].

2.1.4 Study aims

The aims of this study were to explore patients' and clinicians' experience of the radiotherapy decision-making process, and better understand how patients' information needs and preferences are taken into account. The intention was to examine how decisions are made, and to gain a deeper understanding of the factors influencing patient and clinician

preferences regarding treatment options. Figure 2.2 illustrates how this study fits into the aims of the thesis as a whole.

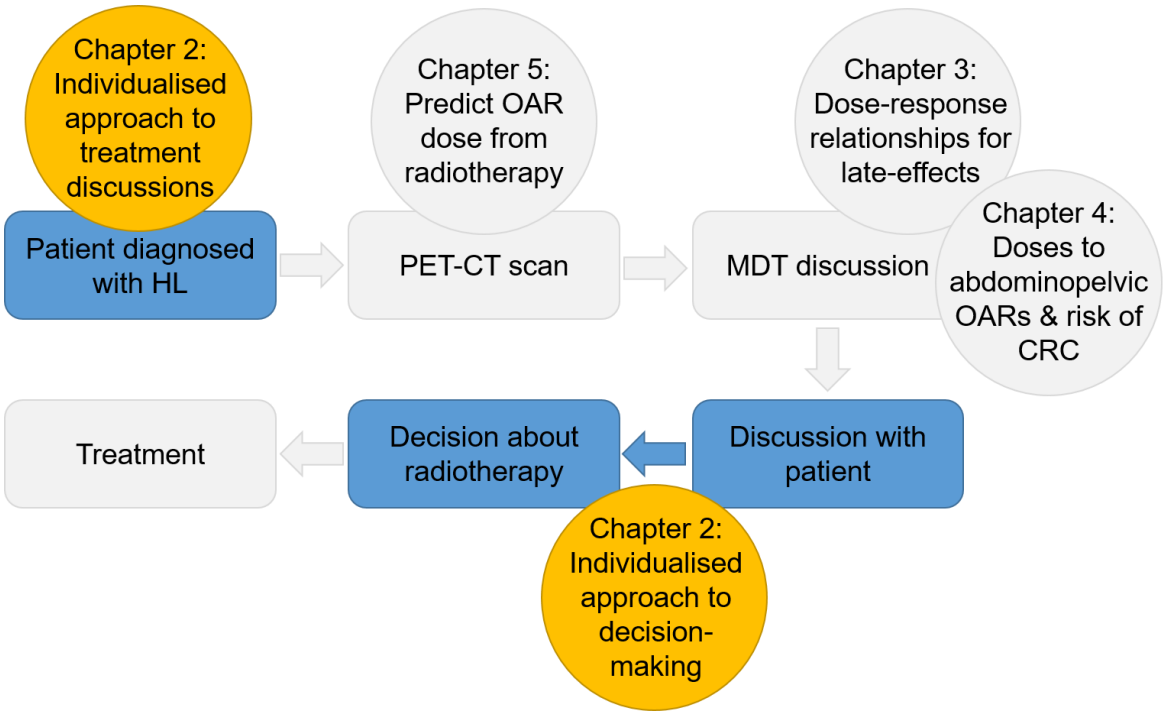


Figure 2.2: Overview of the clinical pathway for making decisions about radiotherapy used to treat patients with Hodgkin lymphoma, highlighting the steps informed by data presented in this chapter

Abbreviations - HL: Hodgkin lymphoma; OAR: organ-at-risk; PET-CT: Positon emission tomography integrated with computed tomography; MDT: multidisciplinary team; CRC: colorectal cancer

2.2 Methods

2.2.1 Study approach

The study involved in-depth interviews with patients and clinicians. A qualitative approach allowed focusing on meaning and experiences articulated by participants, and enabled deeper exploration of the decision-making process. By using a semi-structured approach to interviewing I was able to guide the conversation, but also had the flexibility to alter each

interview depending on the individual's own experiences and opinions. I co-produced the study with a project advisory group that met three to four times a year, initially in person but online since the start of the Covid-19 pandemic. The group consists of four people who have previously been treated for HL (all in the Thames Valley region), and the Patient Experience and Engagement Lead from the local NHS Trust. The group advised on research design and conduct, helped interpret interview data, and is due to support with dissemination of results.

2.2.2 Sampling and recruitment of participants

Participants were people previously treated for HL and healthcare professionals who specialise in the treatment of HL. The inclusion criteria are shown in Table 2.1. At the advice of the project advisory group, only people treated between one and five years previously were invited for interview. This was to allow people time to process their emotions, which are often still raw in the first 12 months following treatment, but still ensure they were able to recall details of their treatment experiences. People also had to have been treated when aged 18 or over, as treatment protocols for children differ, and parents and guardians typically play a major role in decision-making. Along with others [25–27], I prefer not to refer to people being treated for cancer as patients, as I feel this is dehumanising, but for ease of reading here I refer to people previously treated for HL as 'patients' from now on. For the professional interviews, I planned to interview haematologists, medical and clinical oncologists, and clinical nurse specialists (CNSs). In most UK centres, haematologists (and sometimes medical oncologists) deliver chemotherapy and take overall responsibility for the treatment of people with HL, and clinical oncologists deliver radiotherapy. CNSs provide physical and emotional support, coordinate care services, and inform and advise patients on clinical and practical issues [28]. Therefore, these were the professionals that the project advisory group and I identified as being central to treatment discussions. However, during

my interviews with patients, CNSs were described as a key source of support, but not central to the treatment decision-making process. I therefore spoke informally to two CNSs about their involvement in the treatment decision-making process. Neither reported any involvement, and I therefore chose to only interview haematologists and oncologists (collectively referred to as 'clinicians' from now on).

Table 2.1: Inclusion criteria

Patients	Clinicians
Male or female, treated for Hodgkin lymphoma when aged 18 years or above	Working in the UK in the NHS, specialising in the treatment of lymphoma
Treated for Hodgkin lymphoma between 12 and 60 months ago	Clinical experience of treating people with Hodgkin lymphoma
Patients & clinicians	
Able to participate in an interview conducted in English	
Willing and able to give informed consent for participation in the study	

I aimed for a maximum variation, purposive sample, to include men and women, of different ages, and from different parts of the UK, to capture a diverse range of experiences. I advertised the study to patients via the Lymphoma Action website, newsletter and magazine, the National Cancer Research Institute (NCRI) consumer forum and the Oxford Blood Group mailing list (Table 2.2). I sent invitation letters to clinicians via the UK Lymphoma Radiotherapy Group, and the NCRI Lymphoma Research Group and Hodgkin Lymphoma Study Group. I also emailed clinicians who had previously provided their consent to be contacted by my research group about studies. I advertised the study to both patients and clinicians on Twitter.

Table 2.2: Partner organisations in study recruitment

Patients	Clinicians
Lymphoma Action [29]: The UK's only dedicated lymphoma charity	UK Lymphoma Radiotherapy Group: Professional network of clinicians who specialise in radiotherapy for lymphoma
NCRI consumer forum: Patients who are members of NCRI research groups that facilitate collaboration between clinicians, researchers and the public [30]	NCRI lymphoma research group and Hodgkin lymphoma study group: Groups that coordinate UK research within the field of lymphoma
Oxford Blood Group: Patient and public involvement in research group for anyone treated for blood disorders in the Thames Valley and their carers [31]	

The study advert and invitation (Appendix A1) gave details of the study and encouraged potential participants to email me for further details. I sent the participant information sheet (PIS, Appendix A2) to those who contacted me. I initially interviewed the first three consecutive eligible patients. Once it became clear that I would have more potential participants than I could interview, I emailed eligible participants to ask what treatments they had for their HL, and to what extent they were involved in discussions to decide about having radiotherapy. This allowed me to select patients for subsequent interviews who had both been treated with radiotherapy and not, and who had and had not been involved in discussions about radiotherapy. During recruitment it became clear that the majority of patients were white British, despite there being no significant variation in HL incidence by ethnicity in the UK [32]. To attempt to reach a wider ethnic minority population I re-advertised the study via Lymphoma Action, Twitter and BME Cancer Communities [33], specifically asking for patients from ethnic minorities.

2.2.3 Interviews

Interviews were one-to-one and semi-structured. I conducted them on Microsoft Teams, except for one that was done over the phone, and all were recorded. One interview was interrupted by technical difficulties but I was able to reconnect and complete the interview.

I wrote flexible interview guides (Appendix A3) comprising of an opening non-leading question, with more specific follow-on and clarifying questions and prompts. The questions were informed by NICE guidance on shared decision-making [21], the literature surrounding decision-making in HL [1,5–7,17,34], and discussion with my supervisors and project advisory group. In the first, narrative, section of the interview patients were asked to relate, in their own words and at whatever length they chose, what had happened to them from the time when they first noticed symptoms. This enabled them to tell their story briefly, and helped me understand the experience of each participant, and build a rapport, so that I could subsequently ask more insightful questions adapted to their specific context. The narrative section generally took less than five minutes. Additional questions focused on how decisions were made about treatment, whether radiotherapy was discussed and their experience of treatment decisions. In three early interviews it emerged that patients had little involvement in decision-making, and therefore the interview guide was revised to give me greater flexibility to explore patient's experiences around treatment discussions. I started clinician interviews with an open question on treatment decisions in the context of HL, with follow-up questions focusing on treatment discussions and how clinicians adapted the process for individual patients. I ended clinician and patient interviews with specific questions about shared decision-making and the use of decision aids.

Prior to interviewing any study participants, I conducted a pilot interview with an experienced qualitative researcher working at the Nuffield Department of Population Health, University of Oxford. The aim was to test the interview guide, become familiar with using

Microsoft Teams, and get feedback on my interview technique. Following the pilot, I edited the prompt questions to be shorter, with less jargon.

I conducted all the interviews myself, and made participants aware that I am a clinical oncologist, but that for the interviews my primary role was a researcher. I interviewed patients between 23rd February and 29th July 2021, and clinicians between 1st July and 19th October 2021. Interviews were conducted at the participant's convenience from their home or place of work. All but one participant was alone during the interview; one patient's wife was also present. I consented participants prior to starting recording, and gave them a chance to ask any questions they had about the study. Participants could pause or end the interview at any time. Following the interview I emailed a copy of the consent form to the participant. All participants were interviewed once. I transcribed the interviews verbatim, added punctuation to increase readability, and noted important non-verbal communication. I offered participants a copy of their interview transcript, which the majority declined.

2.2.4 Data analysis

I analysed the data using reflexive thematic analysis following the process outlined by Braun and Clarke [35]. This follows six phases (Table 2.3) that are distinct but recursive, with forward and backward movement through the different phases throughout analysis. I conducted recruitment, data collection and analysis simultaneously, to allow subsequent interviews to focus on developing themes.

Table 2.3: Phases of Braun and Clarke's thematic analysis [35]

Phase	Description
1: Data familiarisation	Familiarising yourself with the dataset
2: Data coding	Applying code labels systematically to the dataset
3: Theme generation	Identifying shared patterned meaning across the dataset
4: Theme development	Assessing initial fit of provisional candidate themes to the data
5: Theme refinement	Fine-tuning of the analysis
6: Writing up	Presenting a coherent report, to address the research question

Transcribing the interviews myself allowed me to become extremely familiar with the data, but I also re-read the transcripts at each stage of the analysis. I coded the transcripts line by line using a Qualitative Data Analysis Software package (NVivo Version 12, QSR International Pty Ltd, 2018) and refined the coding and code labels through the analysis, based on fresh perspective and analytic thoughts. When coding the clinician interviews, I found that they were often talking about the same concepts as patients, but they used different language to articulate these. Where this was the case, I coded the clinicians' comments in a new code, but added a note that it was linked to the corresponding code from the patient interviews. Dr Cutter and Dr Peters also read a sample of the interviews and coded them independently. We met regularly to discuss ongoing data collection and analysis, and to agree on theme generation and data interpretation. Braun and Clarke question whether data saturation is a useful concept for thematic analysis [36], and I therefore did not use any quantitative measures of saturation. I did however track my coding, to assess when new concepts were being brought up in interviews (Appendix A4). I did not require any new codes after the tenth patient interview and sixth clinician interview. To generate themes, I compiled clusters of codes that shared a core idea, using the 'one sheet of paper' method [37] (Appendix A5). I grouped codes into subthemes and then themes (Appendix A6), and reviewed the candidate themes and definitions with my supervisors and project advisory group. I revised the themes to ensure they highlighted the most important patterns across the data and were clearly demarcated, and renamed them

to capture their central core concept. Finally, I combined my analytic narrative with transcript extracts, to evidence the themes generated in the data. The overarching patterns presented in the themes apply to both patients and clinicians, but differences in language and meaning are a feature of the data and are discussed as the themes are presented. When writing my results, I used the term 'almost all' to mean over 90%, 'majority' over 75%, 'most' over 50%, 'some' over 30%, and 'a few' over 15%. Where phrases were repeated within a quote, I replaced them with […]. I have included additional illustrative quotes in Appendix A7.

2.2.5 Ethical considerations

I obtained ethical approval for the study from the North of Scotland Research Ethics Committee, 20/NS/0118. All participants gave informed consent before their interview, including consent for their interview data and direct quotes to be used in publications. I anonymised data by removing participants' names, names of others mentioned in the data, and names of hospitals where participants were treated or worked.

One concern when designing the study was that the interviews would lead to patients having questions about their treatment, or being distressed by discussing their experiences of having cancer. With patients' consent, I sent a letter to their GP to highlight that they may have questions about their treatment that would be best answered by their own haematology or oncology team (which may require referral back to them). Patients were given the contact details of the Lymphoma Action helpline, and the team there were informed about the study so that they could support anyone who contacted them.

2.3 Results

2.3.1 Participant characteristics

Between February and August 2021, I was contacted by 48 patients, 15 of whom were not eligible for the study. I sent the remaining 33 the PIS, and 15 took part in an interview. I was contacted by, and sent the PIS, to 16 clinicians, 12 of whom I subsequently interviewed. Patient interviews lasted up to two hours (average 58 minutes, range 38-93) and clinician interviews up to an hour (average 39 minutes, range 23-54). The characteristics of those interviewed are described in Table 2.4. Patients had been treated, and clinicians worked, in centres in England, Scotland and Wales. Ten of the 15 patients, six of the seven oncologists, and two of the five haematologists were female. Clinicians had worked as consultants for a mean of 17 years (range 1-30). Eight patients had received radiotherapy, and only two described treatment decisions as shared.

Table 2.4: Participant characteristics

Patients

ID	Age	Sex	Ethnicity	Time since Rx	RT	Shared decision*
1	54 y	Female	White British	4 y	No	No
2	75 y	Male	White British	1 y	Yes	No
3	70 y	Female	White British	5 y	Yes	No
4	68 y	Female	White other	2 y	No	No
5	28 y	Male	Not disclosed	2 y	No	No
6	33 y	Female	White British	2 y	Yes	No
7	57 y	Female	White British	3 y	Yes	Yes
8	49 y	Male	White British	2 y	Yes	Yes
9	35 y	Female	Not disclosed	2 y	Yes	No
10	31 y	Female	White British	3 y	No	No
11	74 y	Male	White British	3 y	No	No
12	49 y	Female	White British	2 y	Yes	No
13	62 y	Female	White British	2 y	Yes	No
14	36 y	Female	White British	2 y	No	No
15	26 y	Male	White British	4 y	No	No

Clinicians

ID	Job role
H1	Clinical oncologist
H2	Haematologist
H3	Clinical oncologist
H4	Clinical oncologist
H5	Haematologist
H6	Clinical oncologist
H7	Haematologist
H8	Medical oncologist
H9	Clinical oncologist
H10	Haematologist
H11	Haematologist
H12	Clinical oncologist

*Patient's perception of whether the decision about radiotherapy was shared with the clinician
Abbreviations - Rx: treatment; RT: radiotherapy; y: years

2.3.2 Themes

I generated four themes from the interview data, which reflected how people made decisions about radiotherapy as a treatment for HL. These were 1) patient involvement in discussions about radiotherapy, 2) individual factors in the decision about radiotherapy, 3)

responsibility for decisions about radiotherapy, and 4) shared decision-making and decision aids in the context of radiotherapy decisions.

2.3.2.1 Theme 1: Patient involvement in discussions about radiotherapy

This first theme discusses the information requirements and preferences of people with HL, and how information was presented to patients by clinicians. It also covers the timing of treatment discussions, and patients' reflections of their involvement in those discussions.

Information requirements

It was clear from the interviews that people with HL are an engaged group of patients, who questioned their medical team, and had a desire to know more about their illness and treatment. The majority of patients felt they were given adequate information by their medical team, which they complemented with extensive self-directed research. When patients had questions about their cancer or treatment, they found their clinical team was readily available to answer these. This two-way flow of information is characteristic of shared-decision making, and is not seen in any of the other decision-making models (Figure 2.1). A couple of patients reflected that their questioning might have been annoying to the medical team, but none of the clinicians reported feeling this.

> *"and then probably quite annoyingly, went to my consultant then saying well I read this, but what do you think that says?"*
> *Patient 5, 28-year-old male*

Both patients and clinicians spoke about the potential for people to become overwhelmed by the amount of information they were given regarding treatment. One patient explained that this was the reason that she hadn't done any research initially:

> *"I think you're always like looking for as much information as possible at that point to be honest, although there's definitely a line, and it can like I say, at the start it's overwhelming"*
> *Patient 10, 31-year-old female*

Patients spoke about their lack of knowledge about lymphoma and radiotherapy prior to their diagnosis, meaning they did not feel equipped to participate in treatment discussions. This limited their ability to undertake informed decision-making, which requires the patient to deliberate about treatment options (Figure 2.1). Clinicians recognised this, and talked about how the complexity of the information about treatment options impacted on a patient's ability to direct decision-making. They recognised their role in making information accessible to patients, but acknowledged that even experienced clinicians could become overwhelmed with the data around the relative pros and cons of radiotherapy.

> *"I think it's unusual to have a patient who is able to handle the information, which is extremely complex, and has clear enough views that they clearly direct the decision making"*
> *Clinician 11, haematologist*

> *"I've never even heard of this lymphoma up until you told me that I had it. So how can I make a decision that potentially will impact the rest of my life when I don't even really know anything about it? I don't know what radiotherapy is"*
> *Patient 1, 54-year-old female*

Information preferences

Both patients and clinicians discussed that people have individual preferences about the level of information they want about treatment options. Some clinicians explicitly asked patients their preference for information, but none of the patients recalled being specifically asked how much information they wanted, or how they wanted information presented.

> *"I very much tailor the way I talk to patients and the information I give to patients to the individual patient in terms of the way that I give the information, and the amount of information that I give up."*
> *Clinician 5, haematologist*

Both patients and clinicians discussed that more information was not necessarily beneficial. Patients reflected that sometimes the more information they received, the less they actually understood. Clinicians agreed that too much information could inhibit patients' ability to make decisions.

> *"I did actually think that wasn't helpful, and I think if I had not given him so much information, it might have been easier to deal with"*
> *Clinician 7, haematologist*

One patient disagreed that you could ever have too much information, as long as it was explained clearly by the medical team.

> *"Obviously sometimes too much information can mess with the brain, but I think if it's set out now, you know, so by the time you finish the conversation the person's asked all their questions, you know, they fully understand, I think the more information that person gets the better"*
> *Patient 8, 49-year-old male*

Presentation of information about treatment options

The majority of patients reported that their treatment plan was presented as a conclusion, rather than there being a discussion of options, suggesting clinicians had adopted a paternalistic decision-making style (Figure 2.1). Most patients felt that the treatment they were being offered was a package, with no options within that, and that once they were on the "treatment path" there were no decisions to be made. They perceived the only choice was between treatment and no treatment, and since the likely outcome of no treatment was death, there was no real choice. Most patients were reassured by this standard approach to treatment.

> *"obviously it was my decision as to whether I wanted the treatment, but to be honest I didn't have much choice, you know. […] I wanted to give every possible chance I had to fight the cancer so therefore I went with what I was told."*
> *Patient 12, 49-year-old female*

One patient, who was particularly keen to understand the decision-making process, did subsequently have an open discussion about different treatment options, but only once she had "unpicked" the decision that had already been made.

> *"it was very much kind of, almost dealt with kind of in reverse, this is the decision we've made and then it was me unpicking it to say, ok, well can we go back to that shared decision bit about how we've got to that decision, rather than actually sitting down from the outset and having that open discussion"*
> *Patient 6, 33-year-old female*

Most clinicians felt that there was a clear decision about radiotherapy, based on patient's risk stratification from their diagnostic investigations, and genuine equipoise was rare. However, the way that this decision was then relayed to patients differed between clinicians.

Some reported minimal discussion with patients about radiotherapy, whereas others had more in-depth conversations. Almost all acknowledged that these conversations were "shaped" by the multidisciplinary team's (MDT's) view on the favoured treatment option. Only the paternalistic model of decision-making refers to deliberations with other clinicians, such as occurs during an MDT meeting (Figure 2.1). A couple of clinicians highlighted the importance of being open about treatment options, both to maintain the patient's trust and also to ensure they understood the implications of each option on their future health. It was rare for clinicians to encounter situations where they disagreed with the patient about the best option for treatment. Almost all clinicians acknowledged that the way they presented information influenced the decisions that patients made about treatment.

> *"I think we have to recognise that as clinicians we have a lot of influence over the decisions patients make, and we all know that the way in which you discuss the information, and the way in which you portray the pros and cons of things will introduce a preference in a patient for making decisions one way or the other. So we are highly influential in how they decide, and it's really important to be conscious of that even in the situation where it feels to the patient like they're making the decision, we all know that we were capable of influencing that."*
> *Clinician 8, medical oncologist*

It was evident from both the patient and clinician interviews that there were different approaches to discussing the benefits and risks of radiotherapy. Some patients did not recall them being discussed, whereas others remembered extensive discussions and felt more informed about radiotherapy than they had for chemotherapy. Some patients and clinicians commented in particular on the difficulty of discussing the late-effects of radiotherapy. A couple of clinicians were reluctant to emphasise them due to concerns that they were "frightening patients", and stopping them from "moving on", whereas others felt discussions were hampered by a lack of clear data on the magnitude of risk from modern radiotherapy.

> *"I don't think the longer term is really explained to be honest. I think they touch on it, but it is, I think it is quite brushed over. I don't think, because I suppose because it's unknown, and not everybody is gonna get it or get that issue."*
> *Patient 1, 54-year-old female*

> *"And I think once we've got a proper, a better understanding of actual risk then that would be easier to involve, so if you can say that there's a one in whatever chance of this and a one in so, for example"*
> *Clinician 2, haematologist*

Timing of treatment discussions

Patients and clinicians spoke of the importance of the timing of treatment discussions. This is an important aspect of information exchange that often does not feature in models of decision-making. Patients often felt overwhelmed at initial diagnosis, and were keen to defer decisions about radiotherapy until they'd had time to adjust. However, they later found that the side-effects of chemotherapy affected their ability to make decisions, and the decisions they made. Clinicians acknowledged that patients often needed time after diagnosis to consider treatment options, but also recognised that HL treatment was relatively quick, and it was usually important for patients to have a clear treatment plan from the outset.

> *"I think I might have felt quite differently […], if you'd asked me at, different points, and even after different chemo cycles"*
> *Patient 6, 33-year-old female*

Most clinicians preferred to make the decision about radiotherapy at the time of the initial diagnosis, but others left it more open, signposting to patients that there would be a decision to be made later. Some felt it was unrealistic to be able to involve a patient in a decision at the start of their treatment pathway, as explained by one haematologist:

> *"asking somebody […] that you've just told that they've got Hodgkin's disease and you're just about to start on treatment to think about, you know a small percentage difference in relapse risk versus potential long-term complications when you probably haven't even had a conversation about the risk of secondary malignancies at that stage, 'cause you often leave that to somewhat later on in the pathway […], you know it's a really difficult thing to think about doing"*
> *Clinician 5, haematologist*

Some patients found it helpful to have processing time immediately following their diagnosis, whereas others were keen to have all the information upfront. Almost all wanted

the information repeated at various time points, to give them chance to digest and reflect on it. Some expressed a preference for having treatment discussions in a stepwise fashion.

> *"I felt I was better to break it into chunks. Let me get to that hurdle, once I get to that, it's like a marker. Once you get to that marker, that positive marker it gives you hope and that treatment you've had is sort of behind you then, which makes you feel a little bit clearer to then think about another potential stage that might follow."*
> *Patient 1, 54-year-old female*

Reflection on involvement in decision-making

Most patients were happy with their treatment, even if they hadn't been involved in the decision-making about radiotherapy. Those who'd had minimal discussion did feel that they would have wanted to know the information about the benefits and risks of radiotherapy, even if they were happy not to make the decision. This suggests the models of decision-making as presented in Figure 2.1 do not work in this context: patients wanted a two-way flow of information (consistent with the shared decision-making model), but wanted decisions to be made by clinicians, which is seen in the paternalistic and interpretative models. When asked how decision-making could be improved, patients spoke of wanting open discussions of treatment options, where clinicians were open to their thoughts and perspectives. This suggests a preference for the type of information exchange seen in interpretative decision-making (Figure 2.1), in which patients inform clinicians of their personal values, preferences, and beliefs. Some patients felt it was important to discuss emotional as well as physical impacts, and that the practicalities of radiotherapy needed to be explained in more detail. The majority of patients wanted information tailored to them, and discussions tailored to their preferred level of detail and timing. Most patients felt that having individualised information quantifying the benefits and risks of radiotherapy would make them more able to participate in discussions about treatment options. They also wanted information on what they could do to manage, or be more aware of, the risks of radiotherapy.

> *"I think just having a bit more of an open kind of collaborative discussion about it. Maybe a bit more transparency in the rationale."*
> *Patient 6, 33-year-old female*

Patients felt it was critical that clinicians spent time understanding them as an individual, including their social roles, job, experience of being diagnosed, and mental state, to judge how able they were to participate in treatment discussions. This type of information exchange is consistent with the interpretative model of decision-making (Figure 2.1).

> *"I think the more that your medical team know about you, the better, in some ways, in that sense, and particularly with something as life altering as cancer treatment, I think you know there is probably something to be said for you can't, you can't know too much about your patient."*
> *Patient 6, 33-year-old female*

Only one patient felt unhappy with the way that they'd been treated. She felt her treatment plan was "generic" and she wasn't listened to when she tried to "weave in bits" about herself, leading her to lose confidence in her medical team and the treatments they offered.

> *"it felt like they hadn't really looked at how **my** cancer was behaving. So […] that's why it kind of felt quite kind of like disappointing and almost offensive when they just printed off generic kind of check sheets"*
> *Patient 9, 35-year-old female*

2.3.2.2 Theme 2: Individual factors in the decision about radiotherapy

There were individual factors that influenced patients' and clinicians' decisions about radiotherapy, which are encompassed in this second theme. These were a) patients' priorities, b) driving factors, c) the primary concern, and d) perceptions of radiotherapy.

Patients' priorities

Both clinicians and patients recognised there were aspects of their personality that influenced their decisions about treatment. Patients felt the role of the clinician was to understand their personal circumstances and decide on the treatment that best suited them, which fits with the interpretative decision-making model (Figure 2.1). Most clinicians

discussed the importance of understanding a patient's priorities when making decisions about radiotherapy. However, they found that patient's priorities were rarely well-defined, and patients found it difficult to articulate their preference in terms of treatment options. When asked directly, the majority of patients reported they hadn't had the chance to discuss their priorities explicitly, suggesting if they had been given more opportunity to discuss their preferences, it may have been possible to integrate them into treatment decisions.

> *"it's quite unusual to meet someone who is able to think 20 years into the future and consider what their priorities and preferences are in terms of their risks at that time"*
> *Clinician 9, clinical oncologist*

The one patient who was unhappy with their treatment felt that the major problem was that her individual circumstances had not been taken into account.

> *"there were other elements of my lifestyle that were never really taken into consideration. So if they had kind of asked those questions and built that case and then presented me with the risks considering with those, perhaps you know my decisions might have been a bit different, or even theirs as well, perhaps a bit different"*
> *Patient 9, 35-year-old female*

Driving factors

The anatomical area affected by HL was the commonest reason discussed by both patients and clinicians for either using or omitting radiotherapy. Clinicians discussed that disease location influenced radiotherapy fields, and therefore the organs that would receive radiation. They were particularly concerned with radiation dose to the breasts, heart and lungs. Patients reported that disease location was often the main reason why they had or hadn't been offered radiotherapy, particularly for women where proximity of the HL to their breasts was commonly cited as a reason not to use radiotherapy. Some clinicians did not discuss radiotherapy with patients if they felt the disease location meant that the risks were too high, suggesting a paternalistic approach, whereas others used it to inform treatment discussions, in a more shared decision-making approach. For a couple of patients, the lack of proximity to major organs was the deciding factor in them accepting radiotherapy.

> *"the consultant basically said he would not do it. He would not, because of the proximity to the other organs and that, to do with it being so close to my breast and being a woman that risks potential other cancers, he wouldn't, he wouldn't do it."*
> *Patient 9, 35-year-old female*

> *"I think if it been in say on my chest or somewhere which might have affected my heart and lungs a lot more, I don't know if I would have gone for the extra five or six percent, yeah that obviously the radiotherapy gives you"*
> *Patient 8, 49-year-old male*

Sex was also an important factor for clinicians deciding about radiotherapy, linked to disease location and concern regarding the risk of breast cancer. Patients discussed that they may have made a different decision about radiotherapy, or been less likely to have been offered it, if they were the opposite sex.

> *"if I were a woman, obviously my probably, risks of some kind of secondary breast cancer would be higher because it was here with so I, probably if I were then was a female that in my position, I might have been more certain still that they would be going for not having radiotherapy because of that unknown"*
> *Patient 5, 28-year-old male*

Age was also a key factor. Clinicians were less concerned about the risk of radiotherapy late-effects for older patients, and more concerned about their ability to tolerate further chemotherapy if they were to relapse. Some discussed that the risk of second malignancies was higher the younger the patient was at the time of radiotherapy. Both patients and clinicians recognised that people might consider radiotherapy differently based on their age, although clinicians varied in their opinion as to whether younger patients preferred to have radiotherapy or not. This highlights the importance of explicitly asking patients their preferences, and having a bidirectional flow of information (which is only seen in the shared decision-making model, Figure 2.1).

> *"had I been 20 years old, that would have been a different conversation because they say this manifests 30 years down the line potentially, so I'm, I was 55 at the time so 30 years down the line makes me 80 odd, you know. Had I been 20 that would have had a different impact on my life potentially"*
> *Patient 7, 57-year-old female*

> *"Interestingly, younger people tend to be more likely to go for things, I think. Some of my older people prefer to let it be"*
> *Clinician 3, clinical oncologist*

There were other individual circumstances that clinicians and patients felt influenced the decision-making process, such as the patient's medical history (e.g. cardiovascular disease), lifestyle (e.g. smoking), family history, job (e.g. health professional) or having a friend or relative who had been treated for cancer. These factors influenced patients' approach to treatment, and helped clinicians to judge the relative benefits and risks of radiotherapy. None of the factors were deciders in their own right, but all played a role in decisions about radiotherapy.

> *"if you're a smoker and you're determined that you're going to carry on smoking, then I don't really want to irradiate your mediastinum."*
> *Clinician 9, clinical oncologist*

> *"I'm interested if females have breast cancer, strong history, it makes me nervous to agree to radiotherapy, depending on age, of course."*
> *Clinician 4, clinical oncologist*

The practicalities of treatment also influenced treatment decisions. Radiotherapy can prolong the treatment course, and this seemed to dissuade some patients. Clinicians particularly remarked that younger people often wanted their treatment "done and dusted". The immobilisation mask was highlighted by a couple of patients as something that put them off radiotherapy. Patient's experience of chemotherapy also seemed to influence them, especially if radiotherapy was perceived as an option for reducing the number of cycles of chemotherapy. Some patients stated that the different side-effects and hassle of travelling made radiotherapy less attractive.

> *"It's easier to take the route at that moment in time when you're thinking, I'm glad it's gone, I just want to walk away now and get my breath back. I just don't […] want anything, I said don't prod me anymore, I've had enough. It would be the easier option just to walk away and say no [to the radiotherapy], I'll take my chances"*
> *Patient 1, 54-year-old female*

> *"with the radiotherapy I had to go to a different hospital and that hospital was an hour and a half drive away and having to do that every, and obviously I couldn't drive because I, I was too ill to, you know, drive, I couldn't trust myself, having chemo brain as they say. So it was more of a, it was more of an inconvenience if that makes sense. Because it was added, additional, I know it sounds really strange, but it was additional stress"*
> *Patient 12, 49-year-old female*

There were other personal circumstances that influenced a patient's approach to treatment. One patient was diagnosed when pregnant, and that influenced her decision to accept radiotherapy.

> *"actually that present time for me was much more precious than my average lifetime. Kind of, you know, average point in my lifetime, so to speak. So it felt like I wanted to protect that I guess as much as possible and to get that back as quickly as possible."*
> *Patient 6, 33-year-old female*

Primary concern when considering treatment options

HL relapse often occurs in the first few years after treatment, whereas late-effects occur decades later. This difference in timing made balancing the benefits and risks difficult for patients. All patients reported that their primary focus was cure, so if radiotherapy was offered as an option which reduced their chance of relapse they were likely to accept it.

> *"this cancer, this could kill me so I have to take, I have to have everything that, that is given to me in order to fight this. Because you can't see beyond the cancer at that time. Because, you know, you don't know if there is a beyond the cancer at that time. Do you know what I mean? So all these little risks of what, of what the treatment can do it's almost like, well I haven't got a choice, I've got to have this to beat the cancer - so I'll deal with all these other things if they happen, when they happen."*
> *Patient 12, 49-year-old female*

Most clinicians did not explicitly ask patients what their primary concern was, but felt that they were able to elicit what was important to patients during a consultation. This lack of explicit discussion of patient's values suggests a paternalistic approach, but clinicians' suggestion that they did elicit patient's preferences indirectly implies this information was exchanged, potentially fitting the interpretative model (Figure 2.1). Clinicians recognised two groups of patient - those focused on the next few years and doing everything possible

to avoid their cancer coming back (which made up the majority), and those focused on the long-term and keen to avoid anything which worsened their long-term health (the minority).

> *"there are some patients, it's a very small number, who will choose to take the extra risk of relapse. But I would say it's much more like 80:20 the other way round, where patients will choose not to take the extra risk of relapse and accept the treatment"*
> *Clinician 4, clinical oncologist*

Despite recognising that relapse was usually patients' primary concern, clinicians' treatment decisions were often driven by the perceived risks of radiotherapy. The decision about whether the risk of late-effects outweighed the benefits tended to be made in MDTs by clinical oncologists, and radiotherapy only presented as an option to patients if the risk of late-effects was considered small enough by clinicians. In contrast, most patients reported that late-effects weren't at the forefront of their mind when considering radiotherapy. However, there were some exceptions where late-effects were a driving factor in some patients' decision-making.

> *"you can't say, well, I don't want the treatment because I don't want the long term effects, 'cause if the treatment is the only way of getting you better it, you have to just live with whatever you get thrown later on"*
> *Patient 1, 54-year-old female*

> *"some of the more serious long-term effects were definitely weighing on my mind when, in terms of going forward with that decision"*
> *Patient 6, 33-year-old female*

Patients reported that their own preference in terms of considering the short- or long-term influenced their view of radiotherapy. Clinicians did not explicitly explore patients' time preferences, but found this sometimes became clear during consultations when the risk of relapse and the risks of late-effects were being discussed.

> *"probably that because I was that kind of bit more person that was worried a bit more about that longer-term, probably that led me to fall on the side of well, I'll just yeah hope for the best with the next round of chemotherapy"*
> *Patient 5, 28-year-old male*

A couple of patients were reassured that modern radiotherapy techniques are more targeted and are therefore likely to be associated with fewer late-effects than historic

radiotherapy. A few were also reassured by the progress in medicine, and therefore that if they were to experience a late-effect, it was more likely to be treatable by then.

Perceptions of radiotherapy

Both patients and clinicians had pre-existing perceptions of radiotherapy that influenced their decisions. Patients were less familiar with radiotherapy than chemotherapy, which made them less keen to receive it. Clinicians recognised that some patients were anxious about radiotherapy, either because of their relatives' experiences, or fear of the process itself. Other patients, particularly those who had done research into the benefits, were keen to have radiotherapy.

> *"We try and make sure that we dig out any unreasonable fears, particularly about late toxicity because you come across that from time to time that people have a sort of, not irrational, but disproportionate fear of things like radiotherapy and you have to tackle them, make sure that isn't behind their decision-making, if they're taking that route."*
> *Clinician 8, medical oncologist*

Patients often recalled there being vague discussions about radiotherapy, where it was mentioned as a possibility, but not in a way that suggested that it directly applied to them. Detailed radiotherapy discussions were often deferred until patients saw clinical oncologists, at the point of consent, especially when patients received radiotherapy in a different hospital from their chemotherapy treatment. Both patients and clinicians discussed radiotherapy being framed as an option if other treatments did not work, an option if "things don't go to plan". Patients and clinicians often spoke of being able to "get away without radiotherapy", rather than discussions being focused on its potential benefits.

> *"if something went drastically wrong and you didn't respond to the chemo, radiotherapy might be a resort later on down the line, but it wasn't something that they really were considering"*
> *Patient 1, 54-year-old female*

Clinicians spoke openly of their own biases about radiotherapy, and how these influenced their decision-making and the way they presented treatment options to patients. Those who

had seen patients with late-effects questioned the use of radiotherapy; and conversely others who had seen patients die of relapsed HL after not receiving radiotherapy were more likely to recommend it.

> *"all of us are prone to sort of prejudice and experience and, speaking personally, I've seen too many young women with accelerated aortic valve disease and terrible coronary disease as a consequence of mediastinal radiotherapy, which inevitably clouds your judgment."*
> *Clinician 8, medical oncologist*

2.3.2.3 Theme 3: Responsibility for decisions about radiotherapy

The third theme is about responsibility for decisions, and encompasses a) patient preferences for involvement in decisions, b) the roles patients and clinicians played in making decisions about radiotherapy, c) who had responsibility for making decisions, and d) how preferences and roles were affected by the specific context of HL.

Decision-making preferences

Patients' preferences for being involved in decision-making were rarely explicitly explored. Some clinicians actively did not ask patients because they did not perceive that there were many decisions to be made. Others felt they were able to gauge a patient's preference from a consultation, without asking directly. Only a few had explicit discussions with patients about their preferences for involvement in decisions.

> *"I think it's really quite obvious […] if you follow a sort of patient-centred agenda consultation, and so you're sort of asking the patient and getting them to explain what's happening to them and what they're feeling about and everything else; you know whether or not they want to be involved in the decisions, […] you don't need to ask them."*
> *Clinician 5, haematologist*

> *"often you do need to ask explicitly and again, that's something we do pretty routinely, you know - would you like us to tell you what we think is best, or would, do you want us to lay out all the options?"*
> *Clinician 8, medical oncologist*

Clinicians reported that preference for involvement in decision-making varied among patients, with some commenting that younger patients were more likely to want to be involved. They also thought there were regional differences, which they felt might be related to patients' socio-economic backgrounds.

> *"That's quite often, I think, population based as well, or knowing your patients because some of them just don't like that kind of depth of discussion or decision-making."*
> *Clinician 7, haematologist*

Decision roles

Patients perceived clinicians as experts, and therefore best placed to make decisions about radiotherapy. Clinicians recognised the complexity of the decision, and considered it their responsibility to know the data, discuss it in a manageable way, and give an opinion of the best treatment option for that patient. Clinicians reflected on their own experiences of being patients, and felt in those situations they were seeking the advice of experts, and expected to be guided by them.

> *"my job as a professional is to try and guide people not, I mean if all they wanted was neutral information they could look it up on Google. The reason for having a conversation with somebody who has an expertise in this area is for them to help you with their expertise come to the right decision, or come to a decision which is right for you as it were"*
> *Clinician 8, medical oncologist*

> *"I think for me, having that slight steer is definitely something that; it just, I think it just takes away some of the anxiety and the pressure that you feel if you're completely in charge of your own care without the medical knowledge or, you know, of something that's actually really complex."*
> *Patient 6, 33-year-old female*

Patients reported having trust and confidence in their medical team which meant they were confident to let them take the lead in decision-making. They used phrases such as "trust their judgement", "in safe hands", "let them take care of me" and "trust they're doing what's

best for me". This feeling was particularly present when patients had had a prolonged pathway to diagnosis, when they reported feeling "oddly reassured" to be told they had cancer, and relieved they had found a clinician who could offer treatment.

One patient had a contrasting experience. Whilst the majority of patients had the decision about radiotherapy made for them, he was given the sole responsibility. His experience fitted best with the informed decision-making model (Figure 2.1). Like other patients, his preference was for the medical team to make the decision, and he spoke of his anxiety and frustration at not being able to get a steer from his medical team, describing it as a "lonely process" that was "overwhelming at times". He was the only patient to involve anyone else in the decision-making, having lengthy conversations with his partner and two people who'd had treatment for HL, before deciding not to have radiotherapy.

> *"I wanted someone to do the decision for me […], I always wanted a kind of second discussion with one of the other consultants. But yeah, […] they were both; I don't know if it was a kind of a policy they had or anything, but they were both kind of quite hands off in that sense, obviously both giving all the information I needed and yeah, responding to all my questions that I had, but still kind of unwavering in that sense of not telling me what to do."*
> *Patient 5, 28-year-old male*

Clinicians reported the MDT had the central role in decision-making. This involvement of other clinicians in deliberating about decisions is only seen in the paternalistic model of decision-making (Figure 2.1). Clinicians described MDT meetings as an opportunity to decide about radiotherapy for each patient based on the stage of their disease, their age and co-morbidities, and the current evidence. It was the MDT's decision that was presented to the patient as the recommended treatment option. All clinicians agreed that clinical oncologists were central to the MDT, and were best placed to have nuanced discussions with patients about the role of radiotherapy. Haematologists often worked separately to clinical oncologists, often in different locations, although a couple did share clinics. Most clinical oncologists only saw patients once a decision to use radiotherapy had already been made, but some preferred to see patients earlier in the treatment pathway, particularly if

there was equipoise about radiotherapy. A couple of haematologists felt it would be beneficial to see patients jointly with clinical oncologists, but usually this wasn't practical, and only one clinician reported this happening at their centre. Clinical oncologists often found that patients' minds were made up about radiotherapy by the time they saw them, so it was difficult to have discussions about the relative benefits and risks at that point. Some clinicians noticed a difference between centres' use of radiotherapy, based on whether clinical oncologists worked locally.

> *"if the patient's already made that decision then unpicking it is not necessarily at that point, necessarily very constructive, whereas if the patient has still got uncertainty and is asking very justifiable questions about the role of radiotherapy, then you obviously have a much more involved conversation"*
> *Clinician 9, clinical oncologist*

Whilst patients were happy for clinicians to make decisions about radiotherapy, most wanted the decision-making process explained clearly to them, and a chance to influence discussions. None of the models of decision-making presented in Figure 2.1 fits this, as it has elements of the paternalistic (responsibility lying with the clinician), interpretative (integration of values and preferences into the decision), and shared (two-way flow of information) models. Only a couple of patients, who tended to be older, did not feel that patients should play any role in treatment discussions.

> *"I think I felt for me that it was really important that I was fully informed about those decisions and that I understood the clinical rationale that my team had"*
> *Patient 6, 33-year-old female*

Responsibility for decisions

Both patients and clinicians discussed the responsibility for the decision about radiotherapy. Almost all patients felt being given responsibility for the decision would have resulted in anxiety and confusion, suggesting they did not want an informed model of decision-making. They explained the difficulties processing information in a short period of time, and feeling responsible for the long-term implications of their decision. Only one patient reported being

happy to make the decision; so that if he developed a late-effect, he knew it was his choice to accept that risk.

> *"it's scary as well that like the decisions you're making in that moment to get yourself well right now, can like come back, particularly when you're told it's like a curable lymphoma and you're responding well to treatment."*
> *Patient 10, 31-year-old female*

> *"you know if something happens, at least I know that I made those choices so I, not that I'd want to blame someone but, you know, I made that decision knowing that in 20 years' time, 15 years, I may get something else and that's my choice because I knew the risks when I went into it. And I, you know, I would rather have that knowing that I made that choice than just sitting there and someone telling you you're having radiotherapy"*
> *Patient 8, 49-year-old male*

Clinicians recognised that it was often unrealistic to expect patients to make the decision about radiotherapy. They recognised the emotional impact of being diagnosed with HL, as well as the side-effects of chemotherapy, meaning that it was extremely difficult for patients to make a decision. They perceived it to be their job to take responsibility for the decision, to take the burden off patients, so that if patients experienced a relapse, or late-effect from radiotherapy, they did not blame themselves.

> *"I don't think we should make people feel they have to be part of that process. I'm very happy to make decisions on patients' behalf if they're very clear that they don't want that responsibility. Doesn't mean you don't talk openly about pros and cons, it's just some people can, some people can't. That's ok."*
> *Clinician 4, clinical oncologist*

When asked who had the ultimate responsibility for treatment decisions, both patients and clinicians felt it was clinicians, which does not fit with shared decision-making. Some clinicians went further and said it was clinical oncologists, and not haematologists, who made the decision about radiotherapy. Clinicians were keen to point out, however, that they integrated the patient's values and preferences into these decisions. Patients acknowledged that they could challenge clinician's decisions, and decline treatments being offered to them, but most were happy to accept decisions made by their medical team.

> *"when I tell you I make the decision, I make the decision based on all of the feedback that I'm getting from the patient about what their feelings are, so it's sort of, I hesitate to use the phrase shared decision, but I genuinely think it probably is. I'm receiving information from the patient about their priorities, I'm integrating that in with what I know about the treatments, feeding that back to the patient and, and we end up reaching consensus that I have guided heavily, but that nonetheless reflect their priorities as well, I hope."*
> *Clinician 9, clinical oncologist*

Only two patients described the decision as shared, and one other reported they made the decision alone.

> *"I think it was my, ultimately my decision, but I was guided by their expertise and as I said that what they were telling me about the studies and the evidence, and you know, all of that."*
> *Patient 7, 57-year-old female*

One clinician reflected that the patients' perception of the decision-making process may be different from hers. She felt that since patients have to actively participate in having radiotherapy, they must have made the decision to have it. But she acknowledged that consenting to radiotherapy when it was offered was different to making the decision to receive it.

The specific context of HL

Patients discussed the fact that HL is a specific context, with its own practical and emotional considerations, and this impacted on their ability to participate in treatment decisions. Cancer made patients feel vulnerable, so they were more inclined to have clinicians make decisions for them than they would have been if treatment was for a benign condition. They reflected that the emotional shock of being diagnosed meant they did not question clinicians in the way they would in other situations. Some reported that the fact that there was no explanation for why they had developed HL made them feel even more out of control, and less able to participate in decision-making. Clinicians also recognised the impact that a cancer diagnosis had on a patient's ability to participate in treatment decisions.

> *"it is a totally different mind-set when you're faced with cancer you are, well, I've got to have it, I've got no choice, well I do have a choice - if I don't have it I'm going to die, you know, so yes, basically it's totally different mind-set when you've got the cancer and, you know, you have whatever treatment they give you"*
> *Patient 12, 49-year-old female*

Patients noted that treatment discussions were presented in the context of HL being a very treatable cancer, with good odds of a favourable outcome, which made them more inclined to hand over autonomy, as they would be able to regain this following treatment.

> *"it was made clear to me that hopefully within six months this would be done, and then I'd be in remission, but it was, you know, fairly curable and statistics were good, etc. so it was almost like, that it was a short time in my life I'd have to put up with whatever was going to happen to me."*
> *Patient 14, 36-year-old female*

2.3.2.4 Theme 4: Shared decision-making and decision aids

At the end of the interview, I introduced the concept of shared decision-making and decision aids, and asked patients and clinicians how they fitted into the radiotherapy decision-making process.

Shared decision-making

Most patients hadn't heard the term shared decision-making, but when asked assumed it meant clinicians involving patients in making decisions about their treatment. Two had heard the term professionally, rather than as patients, and felt it represented a process of collaboration between the medical team and the patient, bringing all opinions and experience together, and having an open discussion about treatment options. Clinicians perceived shared decision-making to mean involving patients in discussions about their treatment, but not giving the burden of decision-making to the patient, which is not the widely accepted definition of shared decision-making that gives clinicians and patients joint responsibility for decisions. Clinicians felt shared decision-making was achieved by tailoring

the information they gave to an individual patient, building a partnership, respecting their autonomy and individualising treatment to their needs, which actually encompasses a lot of the aspects of interpretative decision-making, rather than shared. Most described the process of shared decision-making as setting out the treatment options, being guided by patients' responses to those, giving an opinion as to the best option for that patient, allowing the patient to consider alternative options, and then coming to a joint decision about the right treatment option for that patient.

> *"to my mind shared decision-making is not asking somebody to take an equal part in making complicated decisions. It's about making sure that the patient's interests and needs are represented in in that decision-making process, and it's not, you don't just make a decision without any thought to the patient."*
> *Clinician 5, haematologist*

Clinicians differed in their views of how shared decision-making fitted with making decisions about radiotherapy in the context of HL. Some felt that the decision was always shared, as it was impossible to decide about radiotherapy without understanding a patient's priorities. Others argued that the complexity of the decision meant that it couldn't be shared, as ultimately patients were reliant on clinicians' expertise and advice. Some clinicians discussed using more 'active' shared decision-making when treating patients whose cancer couldn't be cured. Others found that shared decision-making sat easier with some patients than others, with younger patients more willing to take an active role than older ones.

> *"I think you have to give them the option to comment and be part of the decision-making, but I don't think this kind of really nice ultimate 50:50 sharing is ever going to work for the majority."*
> *Clinician 7, haematologist*

Some clinicians felt that there was an increasing culture of clinicians not feeling comfortable to make decisions. They felt this was reasonable in some situations, where patients wanted it, but in the majority of circumstances it wasn't right to expect patients to take the responsibility for decisions alone.

> *"it looks great on paper, but the reality is that 99.9% of these decisions are being made by the clinician because […] that's actually the way it has to be. Because it's actually not fair to ask somebody in that situation to try and balance and information. Because, you know, clinicians find it difficult, you know, don't we?"*
> *Clinician 5, haematologist*

Patients who had the decision-making process described to them felt decisions were more shared, because they had the opportunity to question things which did not seem "right". The patient who made his own decision about radiotherapy did not perceive the process to be shared, describing it as his decision alone, rather than it being collaborative. Some patients reported their preference for decisions being shared was situation-specific, and had they needed longer-term treatment for HL then they would have wanted to participate in shared decision-making.

> *"Had they have said like, you like, for example, with the diabetes as you say, where you've gotta live your life with this, so you know a cancer where it's not gonna go, and you've got to change your lifestyle or meds or whatever it is to keep fighting it, then I would want more of a shared decision."*
> *Patient 14, 36-year-old female*

Both patients and clinicians acknowledged that time pressures often prevented in-depth discussion of treatment options, which was a barrier to shared decision-making.

> *"the challenge is it takes so long. You know, it really does you know, and the time pressures in a clinic sometimes are a barrier."*
> *Clinician 11, haematologist*

Decision aids

Most patients hadn't heard of decision aids, and most clinicians were aware of them but hadn't used them. I explained to them my research team's proposal to build an online decision aid that would provide individualised estimates of the risks of radiotherapy for patients with HL, using information available to clinicians at the time of a patient's diagnosis. Both patients and clinicians felt that having quantitative, individualised information about the risks would result in more clarity in discussions about radiotherapy. Both felt it might help standardise decisions about radiotherapy, and reduce variations in its use. Clinicians

said they were likely to use a decision aid both in MDTs and during patient consultations, to facilitate a more nuanced discussion of an individual patient's risk. They agreed that graphics were a useful way to present the risks, commenting that visual information is often easier to compute than numerical. Patients would have appreciated receiving quantitative data on the risks of radiotherapy, and they saw a decision-aid as a way of improving their understanding of the decision-making process. However, almost all felt that even with individualised estimates of the risk of radiotherapy, they wouldn't have wanted to make the decision about its use.

> *"to have a tool that would objectify in the MDT, quickly, this would be the risk, you know, would really refine what we're doing at the moment and make it, yeah, much more consistent as well. Standardisation as well I suppose isn't it."*
> *Clinician 11, haematologist*

> *"just have something to structure those discussions on, or questions or something to, if you're just feeling completely overwhelmed, something to actually hang onto rather than just being like, I really don't know what I feel about any of this, but actually, if you had something now, you could say, ok, well, how do I feel about, you know, this specific risk factor. Or what does it mean. And you can start to unpick it a little bit more. I think it would probably help make that decision-making process a little bit clearer."*
> *Patient 6, 33-year-old female*

Some clinicians were concerned that the proposed decision aid did not include estimates of the risk of chemotherapy, and therefore did not give patients the full picture of their risks from HL treatment, and unfairly "singled-out" radiotherapy. Others disagreed, discussing that there was value in having data solely about radiotherapy, as the clinical question is typically whether or not to use radiotherapy after chemotherapy, rather than there being a choice between the two. Some clinicians pointed out the importance of putting the risks of radiotherapy in context of what the patient's risk would have been if they hadn't had treatment for HL.

> *"one of the things that's important is contextual, is how you contextualise that if you're going to use it for patients. Because most patients will not have an appreciation of what their lifetime risk of heart disease and cancer and everything else is"*
> *Clinician 5, haematologist*

Some clinicians discussed that the decision aid could also be used to address some preconceptions about radiotherapy, and determine if their perception of the risks are similar to the reality. A few clinical oncologists felt it would be particularly beneficial for haematologists to use the decision aid, to empower them to have conversations about radiotherapy with patients.

> *"it might be quite enlightening for the MDT as well to sort of get a better feel for where the, where the numbers actually fall out"*
> *Clinician 9, clinical oncologist*

However, support for the decision aid was not universal. Some clinicians reflected that more information often made decisions more difficult. Others were concerned about the errors involved in the predictions, and felt that experienced clinical oncologists would be able to estimate the risks to a similar level of precision. Both clinicians and patients were concerned that having such detailed information would be burdensome and overwhelming for patients. Clinicians concluded they would have to carefully choose the patients that they used the decision aid with.

> *"I'm not sure knowing by what percentage it would increase my risk whether that would be helpful or whether it would just scare the living daylights out of me and then make me a little bit more, less likely to make a decision in a timely manner, I don't know."*
> *Patient 7, 57-year-old male*

> *"Whether in an individual discussion the concept of something like a 30% increase in the risk of ischaemic heart disease is a, is a realistic consideration for people there, it will vary enormously from person to person"*
> *Clinician 8, medical oncologist*

2.3.3 Summary

Figure 2.3 is a graphical representation of the radiotherapy decision-making process as described by my study participants.

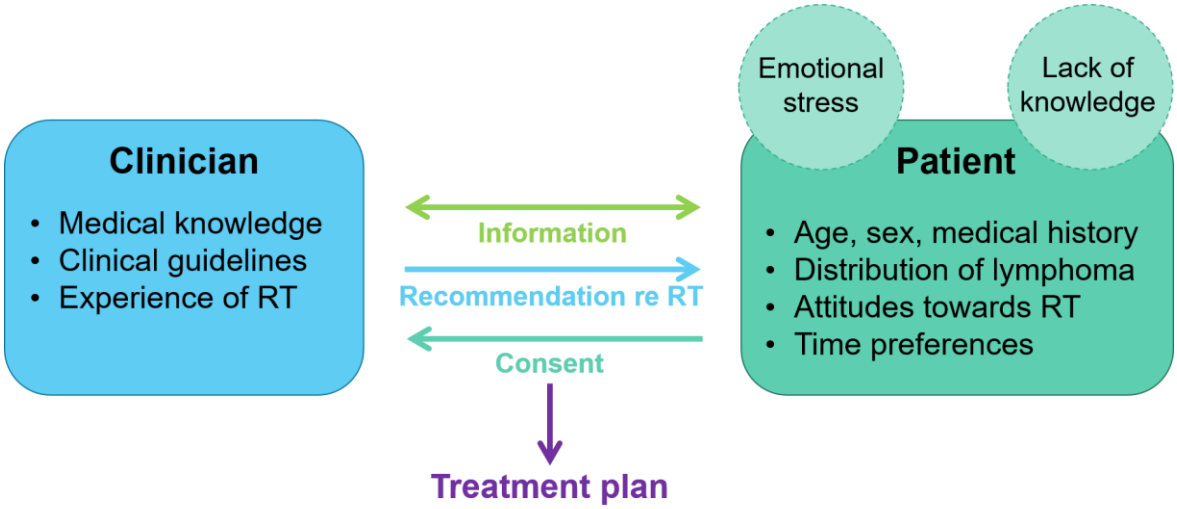


Figure 2.3: The radiotherapy decision-making process in current clinical practice, as described by patients and clinicians
Clinicians used their medical knowledge, experience of radiotherapy, and clinical guidelines, integrated with the patient's age, sex, distribution of lymphoma, attitudes to radiotherapy and focus on short-term benefits rather than long-term risks to make a treatment recommendation for patients to consent to, resulting in a treatment plan. Patients' ability to participate in decision-making was influenced by the emotional stress associated with a cancer diagnosis, and the lack of knowledge about Hodgkin lymphoma and radiotherapy.
Abbreviations – RT: radiotherapy; re: regarding

2.4 Discussion

This study has explored the experience of patients and clinicians in making decisions about radiotherapy used to treat HL. It is one of the first studies to integrate clinicians' and patients' perspectives, and as such gives valuable insights into the complexity of the clinician-patient relationship in this context. The themes that developed from the interviews were around information and discussion of treatment options, individual factors in radiotherapy decisions, where responsibility lay for decision-making, and how shared decision-making fits into this context. These data have shown that the majority of radiotherapy decisions are made by clinicians, which patients are comfortable with, although they would appreciate greater explanation of the decision-making process.

The interviews demonstrated that there are many factors that play into the decision about radiotherapy. Based on these factors, clinicians often feel that there is a 'right' decision about radiotherapy, and treatment discussions are typically framed in a way that means patients don't perceive any choice. Both clinicians and patients expect clinicians to have a dominant role in decision-making about radiotherapy for treating HL. Most patients were not comfortable taking responsibility for treatment decisions, and were happy to accept clinicians' recommendations. Clinicians preferred to take on the role of decision-maker, to remove the burden from patients, and avoid them feeling responsible for the consequences of a 'wrong' decision. Trust in the clinician as the expert had especially high value, and led to patients feeling comfortable to hand over autonomy for decision-making.

This process of decision-making does not fit any of the models of decision-making presented in Figure 2.1 well, and instead combines different elements of a few of the models. The model it fits most is an interpretative model, but there is a two-way flow of information (seen only in the shared model), and clinician deliberation with other clinicians is a key aspect (seen only in the paternalistic model). I therefore propose a different model which fits the context of treatment decisions for people with HL better - the person-centred decision-making model, which has a two-way flow of information between patient and clinician, with discussion of medical information as well as personal values, preferences, and beliefs (Figure 2.4). This information exchange should also include explicit discussion of the patient's preference for involvement in decision-making. The clinician deliberates about the decision with other clinicians (in an MDT meeting), and with the patient (and their relatives if they wish) to ensure the MDT's decision is in line with the patient's values and preferences. The ultimate responsibility for the decision lies with the clinician, although patients retain the ability to disagree with a clinician's decision. This process also has aspects of Drolet and White's proposed concept of "selective paternalism", which describes the obligation of clinicians to use their expertise to facilitate decision-making [38].

Decision-stages		**Paternalistic**	**Interpretative**	**Shared**	**Informed**	**Person-centred**
Information exchange	Flow	One-way (largely)	One-way (largely)	Two-way	One-way (largely)	Two-way
	Direction	Clinician ↓ Patient	Clinician ↑ Patient	Clinician ↓ ↑ Patient	Clinician ↓ Patient	Clinician ↓ ↑ Patient
	Type	Medical	Personal, values, preferences & beliefs	Medical, personal, values, preferences & beliefs	Medical	Medical, personal, values, preferences & beliefs
	Minimum amount	Legal requirement	Anything relevant to discussion	Anything relevant to discussion	Anything relevant to discussion	Anything relevant to discussion; with explicit discussion of preferences for involvement in decision-making
Deliberation		Clinician alone (+/- other clinicians)	Clinician alone (integrating medical information)	Clinician & patient (+/- others)	Patient (+/- others)	Clinician, with other clinicians & patient (+/- others)
Ultimate responsibility for decision		Clinician	Clinician	Clinician & patient	Patient	Clinician

Figure 2.4: Updated models of decision-making
Adapted, with permission, from Charles et al, 1999 [12], with additional information from Wirtz et al, 2006 [9]

It is unrealistic to expect that all medical decisions will follow the same model of decision-making, even within the context of HL. As highlighted by my study participants, patients will have different preferences for decision-making, as will different clinicians. Some clinicians also discussed how they adapted their style depending on the specific circumstances of the consultation. For example, where treatment was not likely to be curative they adopted more of a shared decision-making style. And within the context of curative treatment for HL, where there was a clear recommendation from the MDT about the optimal treatment, their

style was more paternalistic than when there was more debate about treatment options. This suggests that different models of decision-making may be applied in different circumstances.

2.4.1 Comparison with published data

My findings are consistent with those of previous studies. A British National Lymphoma Investigation Group study of patients with HL found that 62% of patients did not participate in decision-making, reporting that clinicians made decisions on their behalf [8]. Twenty-five percent felt that there were no real treatment choices available to them, and 32% wanted more involvement in decision-making. Ernst et al found that fewer than 25% of people with haematological malignancies wanted a shared treatment decision [6] and over 60% wanted clinicians to make all decisions about their care [7]. This is in contrast to patients with solid tumours, 53% of whom wanted shared-decisions [6].

To the best of my knowledge there is only one other qualitative study that explores lymphoma patients' participation in treatment decision-making [5]. They only interviewed patients, but the resultant themes were very similar to mine. They found that patients were overwhelmed by the complexity of their illness and therapy, and did not want to assume any responsibility in decision-making [5]. Patients had very paternalistic role expectations, and described being passive recipients of treatment, like "passengers on a train" [5]. Trust in clinicians was central to decision-making preferences [5]. Interviews on Healthtalk.org with people treated for HL also highlight similar themes: many patients don't feel there are treatment choices to make, and if they do they report being unqualified to make decisions, preferring to defer to clinicians' expertise, particularly if told cure is likely [3]. Even clinicians who developed lymphoma were relieved not to have to make treatment decisions, and were concerned about the emotional stress such responsibility would bring [3]. My study adds to

this data in that it explores how treatment decisions about radiotherapy are made, specifically in the context of HL, and why patients prefer to defer responsibility for these to clinicians. By exploring both the patient and clinician perspective, I have been able to obtain a deeper understanding of the decision-making process, and what aspects patients and clinicians agree on, as well as aspects where patients would appreciate greater involvement.

The primary focus of the patients I interviewed was cure, but clinicians often focussed on avoiding the late-effects on radiotherapy, rather than its ability to reduce recurrence. The patient's focus is consistent with studies of women with breast cancer [39], and HL survivors [40], where the majority considered cure with first-line treatment the most important aspect of treatment. Only 2% of HL survivors, surveyed a median of eight years after treatment within interventional trials, reported that they would have chosen a slightly less effective therapy to avoid side-effects, and the majority were more concerned about relapse risk rather than late-effects [34,40]. Even those who experienced late-effects reported cure as the most important treatment goal [34,40]. A study considering HL patients' preferences for different chemotherapy options also found that people preferred treatments with improved chances of survival [1]. Patients were willing to accept a treatment with a higher risk of long-term toxicity, including infertility and lung disease, if it reduced their chance of recurrence or improved their chances of survival [1]. The perception of the clinician as the expert, and therefore best placed to make treatment decisions, was key. Patients expected clinicians to make these decisions, which is consistent with a previous study where patients with cancer struggled to understand why they were being asked to make important treatment decisions [47].

There is literature which disagrees with the findings of my study. A systematic review of preferred decision-roles concluded that patients want more involvement in decision-making about cancer treatment [41]. However, studies included patients with various cancer types,

and the majority used quantitative measures, such as the Control Preference Scale [42], precluding exploration of the nuances of decision-making. Ziebland et al interviewed patients with pancreatic cancer, which has a much poorer prognosis than HL, and found that only the minority of patients wanted clinicians to take a lead in decision-making [43]. In contrast to my findings, families of patients with pancreatic cancer had a larger role in decision-making, often 'pressurising' patients to accept treatment [43]. Only one patient in Ziebland's study described clinicians as the experts and unquestioningly followed their recommendations [43]. The difference in decision-making here is likely explained by treatments having a much lower chance of cure, with many patients spending most of the rest of their life on treatment, in contrast to the patients with HL who expected to get back to 'normal life' following their treatment.

Studies exploring clinicians' decision-making preferences in the context of HL are scarce. One study explored decision-making as a trade-off between toxicity and cure, and clinicians were willing to accept higher risks of toxicity in exchange for higher survival rates, although UK clinicians were less willing than their French and German counterparts [1]. This seems at odds with the clinicians interviewed in the study, who seemed unwilling to accept the risks of radiotherapy in exchange for reduced recurrence. This may be due to the well-researched direct causal links and easier attribution to toxicities developing within radiation fields leading to a bias against radiotherapy. Most clinicians felt that there was rarely true equipoise in the decision to offer radiotherapy. If the MDT perceived the risks were too high, then radiotherapy was typically not discussed as an option with the patient. This is consistent with previous studies where clinicians only gave information about the treatments they preferred without discussing alternative options [46].

Interpreting my data in the context of the published literature highlights that decision-making preferences appear to be context-specific [44], so broad-brush statements about how much

involvement patients want in decision-making are unlikely to be accurate or appropriate. It is important to obtain data specific to the context of decision-making under investigation.

There are a number of reasons why shared decision-making models may not fit the decision about radiotherapy in HL. It is possible that patients' desire for less participation in decision-making is due to HL affecting their ability to rationally understand information, and their capacity to judge options. Feelings of helplessness and powerlessness are exacerbated by poor knowledge of lymphoma and radiotherapy prior to diagnosis [5], and the complexity of information about treatment, resulting in a greater dependence on medical expertise. Participation may be further limited by a short time-frame for decisions. For there to be shared decision-making, patients have to perceive there to be a choice about treatments [45]. The use or omission of radiotherapy was most commonly presented as part of a package of treatment, with chemotherapy, rather than a separate decision point. For the majority of patients I interviewed, the only options they perceived were treatment or no treatment, which they did not consider as a choice as no treatment would inevitably result in their death. This is consistent with other studies that have found in a life-threatening situation, such as cancer, people don't perceive there to be a real choice about treatment if one option is associated with a lower risk of dying [39,43]. All these factors are consistent with the barriers to shared decision-making identified in Joseph-Williams et al's systematic review [45].

2.4.2 Relevance to current clinical practice

The results of this study challenge the policy that all patients should be actively involved in making treatment decisions. Decisions in medicine are diverse, and it is unlikely that one model fits all of those. My interviews have shown that people have different views on the role they want to take depending on the context of the decision. What is key is ensuring that people know when there is a decision to be made, and are given the opportunity to

discuss their preference for being involved in that decision. Clinicians should recognise the difference between patients being informed of different treatment options, and being involved in making those decisions. In a systematic review of the preferences of people with cancer, almost all wanted full information, even when they did not want to participate actively in decision-making [48]. In this study, patients reported that consultations lacked an explicit discussion of treatment options, and for many our interview was the first time they had realised that radiotherapy could be used to treat HL. If offered, radiotherapy was usually seen as a package with chemotherapy, without the recognition that there was a separate decision made about the addition of radiotherapy. Whilst most patients were happy to take a passive role in decision-making, they would have appreciated greater transparency in the discussion about treatment options. When clinicians explain treatment options, people feel more involved in decisions [3] and are more likely to feel happy with their level of participation [8]. Priority should therefore be given to having an open discussion of the options, tailored to that patient. Preference for involvement in decision-making is individual, so clinicians should ask patients their role preference to support them to achieve their desired level of participation during decision-making [49] . Role preferences are dynamic [48], so there needs to be ongoing appraisal of preference for participation [12], and encouragement to be involved in decision-making where this fits with a patient's preference [45]. Ultimately clinicians should tailor their approach to decision-making to the individual, rather than adhering to one particular model.

Patients bear the consequences of treatment decisions and is therefore critical that their values, priorities and preferences are known and respected. There is no accepted threshold at which the risk of radiotherapy outweighs the benefits, so clinicians cannot make decisions about whether risks are acceptable or too high without some understanding of the patient's priorities. People's interpretation of risks, benefits and consequences is fundamentally embedded in their values and priorities, and so the balance will be different between individuals [21]. Patients diagnosed with HL are likely to feel vulnerable, and may

not initiate discussion of their values and priorities [12], so it is the clinician's responsibility to ensure that this occurs. Time can act as a disincentive to initiate such discussions, and both our interviews and the literature [24,45] confirm that lack of time is a barrier to shared decision-making. However, investing time to build a partnership may save time in subsequent consultations with the same clinician, and continuity of such relationships is associated with more participation in decision-making [24].

Although knowledge alone is not enough for shared decision-making [45], it is a necessary part of it [21]. Patient's poor prior knowledge of lymphoma and radiotherapy made participating in treatment decisions more difficult. Patients with breast and prostate cancer have the highest reported percentage of shared and active role preferences [41], which may be due to a higher level of knowledge and awareness of these cancers in the general public. In 2017, the Lymphoma Coalition demonstrated that when a patient has knowledge surrounding their condition they are more likely to have an active role in treatment discussions, ask more questions, and their patient experience is improved [50]. Turner et al found that patients who felt satisfied with the adequacy of information given were significantly more likely to be happy with their level of participation in decision-making, irrespective of the degree to which they felt involved [8]. Improving the general public's understanding of radiotherapy and lymphoma is likely to help patients feel less overwhelmed at diagnosis, and may facilitate greater participation in treatment decisions.
Clinicians should recognise that the information discussed during a consultation, and the way that it is communicated, influences a patient's participation in, and the outcome of, treatment decisions. The way that radiotherapy is framed will influence patient's perception of its role. Given patients' focus on cure, if radiotherapy is presented as the best way to reduce recurrence, radiotherapy is likely to be seen more positively than if the emphasis is only on the risks to future health.

In the absence of a decision aid that provides personalised estimates of the risks and benefits of radiotherapy, most patients would appreciate a discussion about the relative pros and cons of radiotherapy. On the whole, clinicians agreed that clinical oncologists were best placed to have this discussion with patients, ideally early in the treatment pathway so patients have time to consider their own preferences. If there are clear reasons against radiotherapy that haematologists are comfortable to explain, it may be reasonable for patients not to have a clinical oncology consultation, but only seeing those who have agreed to have radiotherapy may be missing a group who would benefit from a nuanced discussion of the relative benefits and risks.

2.4.3 Strengths and limitations

This study has offered valuable insights into how decisions about radiotherapy are made in current clinical practice. By interviewing both patients and clinicians I have been able to compare and contrast the two points of view throughout, and draw an overall conclusion on decision-making approaches and the extent to which patients' and clinicians' preferences align. I have interviewed patients and clinicians from different regions, ensuring that I am exploring broader decision-making approaches rather than region-specific nuances.

Face-to-face interviews are usually considered 'gold standard' within qualitative research, but the Covid-19 pandemic and social distancing requirements (including shielding of people previously treated for cancer) meant this was not possible. I chose video, rather than phone, calls as they still allow synchronous interaction between the interviewer and interviewee, and maintain the visual and interpersonal aspects [51,52]. These calls maintained a 'face-to-face' experience whilst preserving the participant's safety, and had the added advantage of not being limited by geography in terms of the feasibility of travelling to interviews.

In initial interviews I slipped into clinician-patient interactions, which limited the depth of discussions. In subsequent interviews I changed my interview style and more strongly emphasised my role as a researcher, and was able to have much deeper, less medicalised, conversations. Despite continued efforts I found it hard to recruit people from minority ethnic groups, and their perspectives may be less represented in these data. Another possible limitation of this study is that it is based on patients' accounts, often a few years after the events described. The patients themselves acknowledged that it was difficult to recall the details of the decision-making process. I do not have recordings or observations of the clinical encounters, nor do I have the perspectives of the clinicians involved in those particular consultations. Patients may have forgotten what they were told, or misinterpreted invitations to engage in shared decision-making as directive advice. I have no 'objective' view of treatment discussions, and patients and clinicians may have different perceptions of those conversations. Patients answered based on their own case, where clinicians answered more broadly, and their approach may differ with different patients. However there were many common findings between interviews, between patients and clinicians, and between my results and those in the literature, giving confidence in the data.

2.4.4 Future work

These data support greater discussions with patients about their personal preference for involvement in treatment decisions, and a greater transparency about how decisions are made about radiotherapy in the context of HL. Patient experience is likely to be improved by clinicians taking an individualised approach to decisions about the use of radiotherapy. Using data from this study, it might be possible to outline some questions that clinicians could include in early consultations to tailor discussions of alternative treatment options, and guide later individualisation. For example, clinicians could ask patients their expectations about treatment, their priorities with regard to present and future time, and

their preferred information format. It might also be possible to develop some prompts for patients to use to consider their own priorities, and to question their medical team about how decisions are being made.

Both patients and clinicians discussed that a lack of individualised information about the risks of radiotherapy hampered shared decision-making, and patients discussed finding average treatment outcomes difficult to make personally meaningful. A decision aid which included individualised estimates of the benefits and risks of radiotherapy may be helpful to both patients and clinicians, and could improve patient participation in decision-making [17,44]. It would also fit with NICE's recommendation that clinicians provide patients with numerical personalised risk calculations when discussing treatment options [21].

The remainder of my thesis will focus on obtaining the data necessary to develop such a decision aid. However, before it could be embedded into clinical practice, further research is needed to assess people's preferences for radiotherapy decision-making, with a specific focus on how such data would integrate into the process.

2.5 Conclusions

These data suggest that patients want to be involved in discussions about radiotherapy when being treated for HL, but the majority prefer clinicians to make treatment decisions. Factors enabling patients to participate in decision-making include having adequate information and being involved in discussions regarding choice of therapy. Involvement may be hampered by emotional stress associated with a cancer diagnosis, and the lack of knowledge about lymphoma and radiotherapy.

There are individual differences in preference for involvement in decision-making, and clinicians should recognise this variation, explore it specifically during early consultations, and adapt the content of future discussions to support patients to achieve their preferred level of involvement. Patients should be given the opportunity to choose their degree of engagement, and the extent to which decisions are discussed. This approach could empower those who lack confidence to become more involved in decision-making, whilst allowing those who prefer a more passive role to obtain the clinician's recommendation. Clinicians should ensure that there is a discussion of options and personal priorities even if a passive role is preferred. The availability of data to understand the specific risks of radiotherapy for an individual could enhance the decision-making process. Policymakers should recognise that not all patients want to take an active role in decision-making, and deferring to a clinician's recommendation is a valid approach to person-centred care if it fits with the patient's wishes. Ultimately, there should be flexibility in the way that clinicians structure the decision-making process for radiotherapy, so that individual patient preferences are respected.

2.6 References

[1] Bröckelmann PJ, McMullen S, Wilson J Ben, Mueller K, Goring S, Stamatoullas A, et al. Patient and physician preferences for first-line treatment of classical Hodgkin lymphoma in Germany, France and the United Kingdom. Br J Haematol 2019;184:202–14. doi:10.1111/bjh.15566.

[2] Public Health England, Haematological Malignancy Site-Specific Clinical Reference Group. National Cancer Intelligence Network Working paper on variation in delivery of radiotherapy for patients with lymphoma About Public Health England 2015.

[3] healthtalk.org. Lymphoma - Treatment decisions n.d. https://healthtalk.org/lymphoma/treatment-decisions (accessed May 7, 2020).

[4] Non-Hodgkin's lymphoma: diagnosis and management NICE guideline: methods, evidence and recommendations. 2016.

[5] Ernst J, Berger S, Weißflog G, Schröder C, Körner A, Niederwieser D, et al. Patient participation in the medical decision-making process in haemato-oncology - a qualitative study. Eur J Cancer Care (Engl) 2013;22:684–90. doi:10.1111/ecc.12077.

[6] Ernst J, Kuhnt S, Schwarzer A, Aldaoud A, Niederwieser D, Mantovani-Löffler L, et al. The desire for shared decision making among patients with solid and

hematological cancer. Psychooncology 2011;20:186–93. doi:10.1002/pon.1723.
[7] Ernst J, Brähler E, Aldaoud A, Schwarzer A, Niederwieser D, Mantovani-Löffler L, et al. Desired and perceived participation in medical decision-making in patients with haemato-oncological diseases. Leuk Res 2010;34:390–2. doi:10.1016/j.leukres.2009.06.024.
[8] Turner S, Maher EJ, Young T, Young J, Hudson GV. What are the information priorities for cancer patients involved in treatment decisions? An experienced surrogate study in Hodgkin's disease. Br J Cancer 1996;73:222–7. doi:10.1038/bjc.1996.39.
[9] Wirtz V, Cribb A, Barber N. Patient-doctor decision-making about treatment within the consultation - A critical analysis of models. Soc Sci Med 2006;62:116–24. doi:10.1016/j.socscimed.2005.05.017.
[10] Emanuel EJ, Emanuel LL. Four models of the physician-patient relationship. JAMA J Am Med Assoc 1992;267:2221–6. doi:10.1001/jama.1992.03480160079038.
[11] Charles C, Gafni A, Whelan T. Decision-making in the physician-patient encounter: Revisiting the shared treatment decision-making model. Soc Sci Med 1999;49:651–61. doi:10.1016/S0277-9536(99)00145-8.
[12] Charles C, Gafni A, Whelan T. What do we mean by partnership in making decisions about treatment? BMJ 1999;319:780. doi:10.1136/bmj.319.7212.780.
[13] Trevena L, Barratt A. Integrated decision making: Definitions for a new discipline. Patient Educ Couns 2003;50:265–8. doi:10.1016/S0738-3991(03)00047-8.
[14] Jordan JL, Ellis SJ, Chambers R. Defining shared decision making and concordance: Are they one and the same? Postgrad Med J 2002;78:383–4. doi:10.1136/pmj.78.921.383.
[15] Coulter A. Do patients want a choice and does it work? Br Med J 2010;341:973–5. doi:10.1136/bmj.c4989.
[16] Care Quality Commission. Better care in my hands. 2016.
[17] Coulter A, Collins A. Making shared decision making a reality. No decision about me, without me. 2011.
[18] NHS England and NHS Improvement. Personalised Care | Shared Decision Making Summary guide. 2019.
[19] Department of Health and Social Care. Equity and excellence: Liberating the NHS. 2010.
[20] Department of Health and Social Care. The NHS Constitution for England. 2015.
[21] Shared decision making. NICE Guideline NG197. 2021.
[22] NHS England. NHS England » Shared Decision Making. NHS Engl - Shar Decis Mak 2016:n/a. https://www.england.nhs.uk/shared-decision-making/ (accessed July 27, 2022).
[23] General Medical Council. Good medical practice. 2013. doi:10.1136/bmj.327.7425.1213.
[24] Kaplan RM, Frosch DL. Decision making in medicine and health care. Annu Rev Clin Psychol 2005;1:525–56. doi:10.1146/annurev.clinpsy.1.102803.144118.
[25] Nair BR, Treloar CJ, Harris G. Do we need a new word for patients? Aust N Z J Med 2000;30:716–7. doi:10.1111/J.1445-5994.2000.TB04367.X.
[26] Shevell MI. What do we call 'them'?: the 'patient' versus 'client' dichotomy. Dev Med Child Neurol 2009;51:770–2. doi:10.1111/J.1469-8749.2009.03304.X.
[27] Neuberger J, Tallis R. Education and debate - Do we need a new word for patients? Let's do away with "patients" Commentary: Leave well alone. BMJ 1999;318:1756–8. doi:10.1136/BMJ.318.7200.1756.
[28] Impact Briefs: Cancer Clinical Nurse Specialists. 2015.
[29] Lymphoma Action n.d. https://lymphoma-action.org.uk/ (accessed February 25, 2022).
[30] NCRI Consumer Forum n.d. https://www.ncri.org.uk/how-we-work/patients-carers/ncri-consumer-forum/ (accessed February 25, 2022).
[31] Oxford Blood Group - NIHR Oxford Biomedical Research Centre n.d.

https://oxfordbrc.nihr.ac.uk/research-themes-overview/haematology-and-stem-cells/oxford-blood-group/ (accessed February 25, 2022).
[32] Hodgkin lymphoma incidence statistics | Cancer Research UK n.d. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/hodgkin-lymphoma/incidence#heading-Five (accessed February 25, 2022).
[33] About Us - BMECC n.d. https://www.bmecancer.com/index.php/about-us (accessed February 25, 2022).
[34] Buerkle C, Goergen H, Muller H, Brockelmann P, Kreissl S, Fuchs M, et al. Patient preference - Survey of HL survivors on treatment-associated burdens and side effects. Haematologica 2016;101 (suppl:T025.
[35] Braun V, Clarke V. Thematic Analysis: A Practical Guide. SAGE Publications, London; 2022.
[36] Braun V, Clarke V. To saturate or not to saturate? Questioning data saturation as a useful concept for thematic analysis and sample-size rationales. Qual Res Sport Exerc Heal 2019;13:201–16. doi:10.1080/2159676X.2019.1704846.
[37] Ziebland S, McPherson A. Making sense of qualitative data analysis: an introduction with illustrations from DIPEx (personal experiences of health and illness). Med Educ 2006;40:405–14. doi:10.1111/J.1365-2929.2006.02467.X.
[38] Drolet BC, White CL. Selective paternalism. Virtual Mentor 2012;14:582–8. doi:10.1001/virtualmentor.2012.14.7.oped2-1207.
[39] Charles C, Redko C, Whelan T, Gafni A, Reyno L. Doing nothing is no choice: Lay constructions of treatment decision-making among women with early-stage breast cancer. Sociol Heal Illn 1998;20:71–95. doi:10.1111/1467-9566.00081.
[40] Kreissl S, Goergen H, Müller H, Meissner J, Mehnert A, Bürkle C, et al. Survivors' perspectives on risks and benefits of Hodgkin lymphoma treatment: results of a survey by the German Hodgkin Study Group. Leuk Lymphoma 2019;60:1389–98. doi:10.1080/10428194.2018.1540781.
[41] Tariman JD, Berry DL, Cochrane B, Schepp AD. Preferred and actual participation roles during health care decision making in persons with cancer: a systematic review. Ann Oncol 2010;21:1145–51. doi:10.1093/ANNONC/MDP534.
[42] Degner LF, Sloan JA, Venkatesh P. The Control Preferences Scale. Can J Nurs Res 1997;29:21–43.
[43] Ziebland S, Chapple A, Evans J. Barriers to shared decisions in the most serious of cancers: A qualitative study of patients with pancreatic cancer treated in the UK. Heal Expect 2015;18:3302–12. doi:10.1111/hex.12319.
[44] Say R, Murtagh M, Thomson R. Patients' preference for involvement in medical decision making: A narrative review. Patient Educ Couns 2006;60:102–14. doi:10.1016/j.pec.2005.02.003.
[45] Joseph-Williams N, Elwyn G, Edwards A. Knowledge is not power for patients: A systematic review and thematic synthesis of patient-reported barriers and facilitators to shared decision making. Patient Educ Couns 2014;94:291–309. doi:10.1016/j.pec.2013.10.031.
[46] Evans N, Pasman HRW, Payne SA, Seymour J, Pleschberger S, Deschepper R, et al. Older patients' attitudes towards and experiences of patient-physician end-of-life communication: A secondary analysis of interviews from British, Dutch and Belgian patients. BMC Palliat Care 2012;11:1–10. doi:10.1186/1472-684X-11-24.
[47] Ziebland S, Evans J, McPherson A. The choice is yours? How women with ovarian cancer make sense of treatment choices. Patient Educ Couns 2006;62:361–7. doi:10.1016/J.PEC.2006.06.014.
[48] Gaston CM, Mitchell G. Information giving and decision-making in patients with advanced cancer: A systematic review. Soc Sci Med 2005;61:2252–64. doi:10.1016/j.socscimed.2005.04.015.
[49] Coulter A. Paternalism or partnership? Br Med J 1999;319:719–20. doi:10.1136/bmj.319.7212.719.

[50] Dren N, Warwick L, Rassel K Van, Moysiadis T, Karamanidou C, Xochelli A. Correlation of Lymphoma Patient Information Level with Healthcare Experience. Blood 2018;132:4782–4782. doi:10.1182/BLOOD-2018-99-115392.
[51] Evans A, Elford J, Wiggins D. Using the internet for qualitative research. In: Willig C, Stainton-Rogers W, editors. SAGE Handb. Qual. Res. Psychol., Sage Publications, London; 2008, p. 315–33.
[52] Hanna P. Using internet technologies (such as Skype) as a research medium: A research note. Qual Res 2012;12:239–42. doi:10.1177/1468794111426607.

Chapter 3

Systematic review of the risks of radiotherapy used to treat Hodgkin lymphoma

3.1 Background

3.1.1 Radiotherapy late-effects

There is a well-established link between radiotherapy and several long-term toxicities ('late-effects'), including cardiovascular disease (CVD) and second malignancies. Such late-effects are particularly relevant when radiotherapy is used to treat a cancer that occurs in young people, and where cure rates are high. Hodgkin lymphoma (HL) fits both of these criteria, and epidemiological studies have demonstrated that HL survivors have substantially higher death rates compared to the general population, a proportion of which is attributable to radiation exposure [1]. Due to the latency of development of radiotherapy late-effects, clinicians and people with HL rely on information from historical cohorts to inform them about the risks of modern radiotherapy. The increased risks in these patients must be interpreted in the context of the continual evolution of HL treatment over time, in particular the reduction in radiation dose and field size. The literature is extensive and, as highlighted in Chapter 2, it can be difficult to estimate risk for an individual patient with HL. In particular, it can be difficult to understand how individual patient factors, such as age, sex, and family history, impact on their risk of radiotherapy late-effects.

3.1.2 Rationale and study aims

The aim of this review is to collate estimates of the risks of the late-effects of radiotherapy used to treat HL, particularly how these risks vary by treatment, for example radiation dose and field, and factors specific to an individual, for example their age and sex. After describing the methods, I summarise the risk estimates in the results, separated by type of late-effect, highlighting the treatment and patient factors that affect these risk estimates. I give full details of the results in the appendices (Appendices B2-4), with summaries of radiation dose-response relationships in the main text. Finally, I discuss how the data can

be used, and future work that is needed for this data to be used in estimating the risks of radiotherapy for a person with HL. Figure 3.1 illustrates how this study fits into the aims of the thesis as a whole.

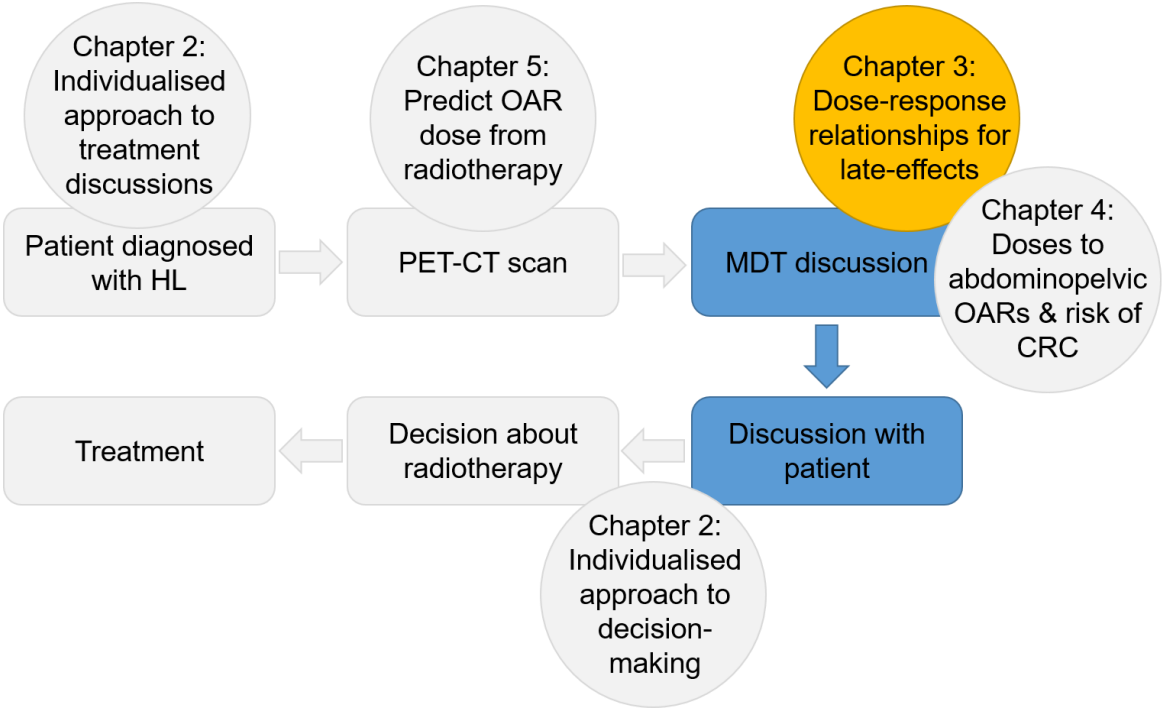


Figure 3.1: Overview of the clinical pathway for making decisions about radiotherapy used to treat patients with Hodgkin lymphoma, highlighting the steps informed by data presented in this chapter

Abbreviations - HL: Hodgkin lymphoma; OAR: organ-at-risk; PET-CT: Positon emission tomography integrated with computed tomography; MDT: multidisciplinary team; CRC: colorectal cancer

3.2 Methods

3.2.1 Search questions

I devised a search strategy with the help of Nia Roberts, outreach librarian, Bodleian Health Care Libraries. We performed searches of MEDLINE, EMBASE and the Cochrane library from database conception until 7th June 2019. The search strategy comprised five major themes related to my research question: a) HL, b) radiotherapy, c) toxicities d)

cardiovascular disease, e) second malignancies. I did not restrict the searches based on study type, geographical region, date or language. I hand-searched reference lists of included studies to identify additional studies for inclusion. The search was rerun on 3rd August 2021 to ensure my results were up-to-date at the time of writing my thesis. The search terms are presented in Appendix B1.

3.2.2 Study identification

In the first stage of screening, I screened the title and abstract of each study and considered studies for full-text assessment if they were relevant to the objectives of this review. In the second stage, I assessed full-texts to determine if they met the inclusion criteria shown in Table 3.1. I discussed papers with my supervisors where I had any doubt about their inclusion.

Table 3.1: Study inclusion criteria

Patients	Adults aged ≥18 years with histologically confirmed HL
Intervention	Radiotherapy
Comparator	Omission of radiotherapy
Outcomes	Future risk, including (but not exclusively) CVD, second malignancy and thyroid disease
Studies	All

Abbreviations - HL: Hodgkin lymphoma; CVD: cardiovascular disease

3.2.3 Data abstraction

I created a table to extract the relevant data from each article, including the first authors' name, publication year, study design, country, patient eligibility, sample size, comparator population and risk estimates. Due to the heterogenous nature of the studies, it was not possible to extract all relevant data into one standardised table. Instead I grouped the

relevant risk estimates into the relevant late-effect (CVD, second malignancies or other conditions), and the factors that influenced risk (treatment- or patient-specific), into separate tables. As the review aimed to determine the risks specifically from radiotherapy, I did not extract chemotherapy risk estimates. Some studies reported on rates of late-effects in cohorts that had been screened, whereas most reported rates of clinically apparent disease. I analysed screening studies separately as their inclusion of asymptomatic disease resulted in substantially different risk estimates to those studies reporting symptomatic disease. Rates of symptomatic disease are most meaningful when estimating risks for patients treated today, and so I primarily focused on those studies, but have included salient points from the screening studies where relevant.

Due to the heterogeneity of the data, meta-analysis was not possible. Instead, I synthesised the available data to quantify the risks of radiotherapy, focusing on identifying data that could be used to predict risk from modern radiotherapy. Not all studies reported confidence intervals and p-values for statistical significance. But where these were given they are included in the tables in the appendices, and only statistically significant values included in the main text, unless otherwise stated. I assessed the amount, consistency and quality of evidence available for each late-effect using the method developed by the International Late-Effects of Childhood Cancer Guideline Harmonization Group (Table 3.2) [2]. This is an adapted version of the Grading of Recommendations Assessment Development and Evaluation criteria, and is an accepted tool for grading the quality of evidence in late-effects research.

Table 3.2: Levels of evidence quality, adapted with permission from Mulder et al 2013 [2]

Level	Description
A	High level of evidence i.e. consistent evidence from well-performed and high-quality studies or systematic reviews with a low risk of bias, and direct, consistent, and precise results
B	Moderate to low level of evidence i.e. evidence from studies or systematic reviews with a few important limitations
C	Very low level of evidence i.e. evidence from studies with serious flaws, only expert opinion, or standards of care

3.3 Results

Figure 3.2 documents the study screening process. I identified 4418 studies from original searches, and 79 from updated searches and citation analysis. I screened 431 full texts, and 244 articles met the inclusion criteria and were included in the review. Reasons for exclusion are given in Figure 3.2, but broadly I excluded articles if they did not quantify the risks specific to radiotherapy, were not specific to HL, presented data only on the outcome of the late-effect, or only quantified the short-term effects of radiotherapy. Table 3.3 shows the included papers grouped into category of late-effect. The majority (167) were cohort studies, with 25 screening studies, 17 nested case-control studies, 16 long-term follow-up of randomised clinical trials, 10 meta-analyses, and nine cross-sectional studies.

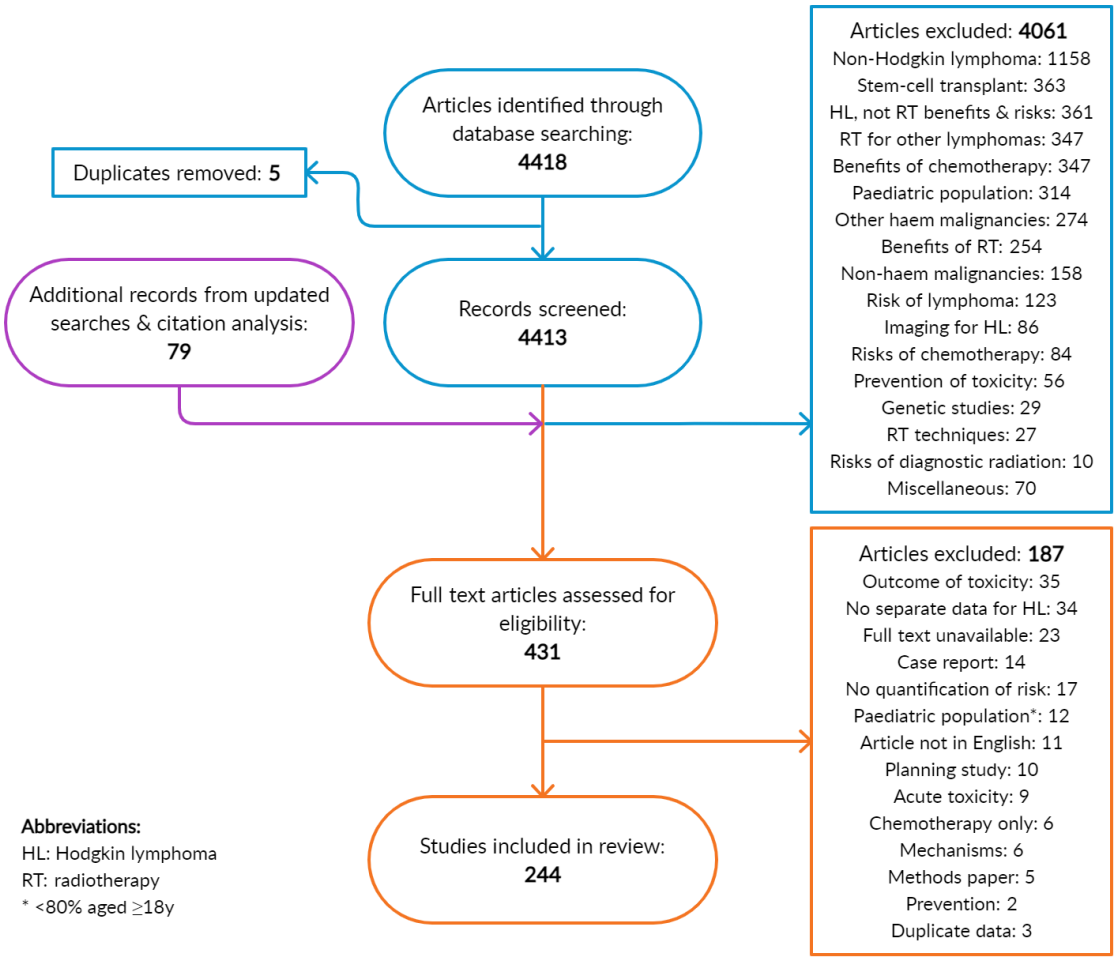


Figure 3.2: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram illustrating the studies assessed for inclusion in the review

Table 3.3: Categories of late-effects reported by included studies

Category	Number of studies
Multiple outcomes	29
Cardiovascular disease	50
Ischaemic heart disease	7
Heart failure	1
Valvular heart disease	5
Pericardial disease & conduction abnormalities	4
Cerebrovascular disease	2
Multiple cardiovascular diseases	31
Second malignancies	134
Breast	22
Lung	11
Gastrointestinal	10
Cutaneous	3
Other solid tumours	2
Haematological	23
Multiple second malignancies	63
Other conditions	32
Thyroid disease	9
Lung disease	2
Other	21
Total	**244**

The data from the included studies is presented below, and in tables in Appendix B, split into CVD, second malignancies and other conditions. For each category I present the data quantifying the risk, how this risk is modified by radiotherapy treatment factors, and other factors that modify the risk.

3.3.1 All late-effects

The studies showed that after 15- 20 years HL survivors experience higher rates of disease than the general population, dominated by CVD and second malignancies, but also thyroid dysfunction, respiratory and gastrointestinal disease and infections [3–12]. Infectious diseases appear to develop first, followed by CVD and then second malignancies. One study found HL survivors had higher mortality rates than the general population for more

than 40 years after treatment [12]. In studies with long-term follow-up, second malignancies accounted for a greater proportion of excess deaths than CVD [1,13,14].

3.3.2 Cardiovascular disease

Studies reported increased risks of ischaemic heart disease (IHD), heart failure (HF), valvular heart disease (VHD), pericardial disease, conduction abnormalities, and cerebrovascular disease.

3.3.2.1 Quantification of risk

Table B2.1 in Appendix B2 summarises the findings of studies that quantified the risk of CVD associated with radiotherapy.

3.3.2.1.1 All cardiovascular disease

Cumulative incidences of CVD ranged from 2-6% at five years [5,15], 5% at 10 years [15], 9-15% at 12-15 years [5,15–17], 14-16% at 20 years [15,17], 23-25% at 25 years [15,17], and 50-55% at 40 years [18,19]. The cumulative mortality from CVD ranged from 2-4% at 10-15 years [13,20] to 16% at 22 years [21] and 13% at 40 [12]. Reported relative risks (RR) ranged from 1.8-3.8 [8,13,21–23], hazard ratios (HR) from 1.5-4.9 [14,24–26], and standardised mortality ratios (SMRs) from 5.5-7.31 [12,27,28]. One study reported an odds ratio (OR) of 4.48 (95% confidence interval [CI] 2.26-8.88) for development of CVD [29], and one a standardised incidence ratio (SIR) of 2.37 (95% CI 1.43-3.91) [30]. Reported absolute excess risks (AERs) ranged from 9-208 per 10,000 person-years (py) [8,12,13,21–23,25,27]. Studies that screened HL survivors for CVD reported higher cumulative incidences (ranging from 11-96% [31–34]), and a RR of 4.7 (95% CI 3.4-5.9) [35].

Patterns of disease

Patients who developed CVD frequently experienced multiple events [18,19], and the frequently observed combinations were HF with VHD or IHD, and conduction abnormalities with IHD or VHD [19]. De Vries et al found that, of all CVD, myocardial infarction (MI) contributed most to excess mortality [12].

Time since treatment

The median interval between treatment for HL and development of CVD ranged from 5-26 years [19,21,24,27,29,36]. A Swedish cohort study found that IHD and HF developed earlier after HL treatment than stroke or VHD [16], but this was not replicated in the other studies. Six studies failed to show a significant difference in RR of CVD by duration of follow-up [1,13,26,28,37,38]. AER increased with duration of follow-up, due to increasing background rates [1,13,37,38], and remained elevated for at least 25 years after treatment [1,19,21,39]. Screening studies found that there was no relationship between time since radiotherapy and arterial stiffness or endothelial dysfunction [40,41], whereas the HR of inducible ischaemia increased with time since treatment [35].

3.3.2.1.2 Ischaemic heart disease

The 10-year cumulative incidence of IHD ranged from 2-6% [15,36,37,42,43], rising to 8-21% at 20 years [15,36,37,43], 13% at 30 years, and 23% at 40 years [18,19]. Reported RRs for MI ranged from 0.9-10.0 [10,17,21,23,37,44–47], HRs from 2.4-4.4 [18,19,29], SIRs from 2.5-5.5 [16,18,19,30], and SMRs from 4.7-6.7 [12,37,48,49]. One study reported an OR of 4.41 (95% CI 1.54-12.7) [29]. Reported AERs ranged from 7-87 per 10,000 py [12,15,18,19,21,23,37,48]. Screening studies reported rates of 4-26% for ischaemia [31,33,34,50–53], 83% for coronary artery calcification [52], 30-32% for stenosis [35,53] and 48-85% for other perfusion deficits [50,54,55].

Time since treatment

The interval to development of IHD ranged from 6-21 years [5,15,18,19,37,43,44,46,49]. Two studies found an increased SMR with increasing time since radiotherapy [37,48], whereas five others found no difference in the SIR or RR with time since treatment [16,18,35,38,45]. One study found an increase in RR 20 years following radiotherapy [21], whereas two others found a decrease in the SMRs after 15-20 years [37]. Van Nimwegen et al found that SIRs of IHD remained significantly increased beyond 35 years after treatment [18].

3.3.2.1.3 Heart failure

Reported RRs of HF ranged from 6.2-8.7 [8,23,56], SIRs from 3.95-6.8 [18,19,30], and HRs from 2.7-7.4 [18,19]. AERs ranged from 20-58 per 10,000 py [8,18,19]. Studies that screened for HF reported that 4-23% had left ventricular systolic dysfunction [31,33,50,51,57], and reduced chamber volumes and abnormal diastolic function were common [55,57].

Time since treatment

The average latent interval ranged from 18-21 years [18,19,58]. Andersson et al found the SIR of HF increased with time since radiotherapy [16], whereas van Nimwegen et al found the SIR was stable over time (and remained increased beyond 35 years after treatment) [18]. In screening studies, echocardiograms were typically normal in the first decade after radiotherapy [59], with left ventricular remodelling occurring subsequent to this [60].

3.3.2.1.4 Valvular heart disease

Cumulative incidence of VHD increased from 1% at 10 years [15,43], to 3-4% at 15 [15,43], 5-6% at 20 [15,43], 8% at 30 [61] and 26% at 40 years [18]. Reported RRs ranged from 18-31 for aortic VHD, and 10-12 for mitral VHD [8,23]. HRs ranged from 6.6-7.0 [18,19], ORs

from 3.5-6.1 [29,62], and one study reported an SIR of 13.1 (95% CI 7.41-23.16) [30]. Reported AERs ranged from 3-34 per 10,000 py [8,15,23]. The aortic valve was the most commonly affected [8,23,43,61,62]. Screening studies demonstrated a high incidence of VHD, ranging from 25-68% [31,50,57,59,62,63].

Time since treatment

The average latent interval from radiotherapy to VHD ranged from 16-24 years [15,18,19,21,43]. Two studies demonstrated that the development of VHD accelerated beyond ten years from radiotherapy [29,62]. In screening studies, the prevalence of VHD increased in the second decade following radiotherapy [57,60], particularly for aortic VHD [57,64]. In Heidenreich et al's screened cohort, the OR of aortic stenosis increased 13.9-fold (95% CI 12.2-15.8) each decade following radiotherapy [64].

3.3.2.1.5 Pericardial disease and conduction defects

The incidence of pericardial effusion after mediastinal radiotherapy ranged from 7-31% [42,65–67], and 11% of an American cohort developed chronic pericardial disease [68]. One study reported an SIR for pericardial disease of 10.7 (95% CI 7.8-14.7) [30], and another reported a RR of 8.5 (95% CI 5.0-14.5), and an AER of 8 per 10,000 py [8]. Pericardial disease was common in screened cohorts, with rates ranging from 3-23% for constrictive pericarditis [33,34,55], 4-43% for pericardial thickening [33,51,55,59,64], and 3% for effusions [64].

Galper et al reported a 25-year cumulative incidence of arrhythmia of 11% [15]. One study reported an SIR of conduction abnormalities of 3.2 (95% CI 2.2-4.7) [30], and another reported a RR of 4.1-5.5, and an AER of 4 (all arrhythmias) to 17 (conduction abnormalities) per 10,000 py [8]. In Heidenreich et al's screened cohort, 2% had electrocardiogram (ECG) abnormalities [64], whereas in Adams' cohort 75% had a conduction abnormality or

arrhythmia [57]. Only one study reported the latent interval to development of conduction defects, at a median of 18 years [19]. The latent interval for the development of pericardial disease was shorter, with a median interval of six months to the development of effusion (with 90% occurring within 12 months) [65], and 13 years for chronic pericardial disease [19]. Heidenreich et al reported the OR of developing right bundle branch block increased 7.3-fold (95% CI 1.2-45.0) each decade following radiotherapy [64].

3.3.2.1.6 Cerebrovascular disease

Cumulative incidence of carotid or subclavian artery stenosis, transient ischaemic attack (TIA) or stroke in an American cohort was 2% at five years, 3% at 10 and 7% at 20 years [43]. In a Dutch cohort there was a 7% cumulative incidence of stoke or TIA 30 years after treatment, with separate incidences of 5% and 3% respectively [39]. Two studies reported raised SIRs of cerebrovascular disease of 2.0 (95% CI 1.6-2.6) and 2.2 (stroke, 95% CI 1.7-2.8) and 3.1 (TIA, 95% CI 2.2-4.2) respectively [30,39], and one an SMR of 2.9 (95% CI 1.5-3.3) [12]. In a Dutch cohort, the HR of cerebrovascular disease was 2.5 (95% CI 1.1-5.6), with an AER of 9 (TIA) to 12 (stroke) per 10,000 py [39].

Time since treatment

De Bruin found the median interval to development of TIA or stroke was 17.4 years [39], which was consistent with the median latent interval to development of subclavian or carotid stenosis in Hull's cohort (21 years) [43]. The median latent interval to TIA or stroke in Hull's study was shorter (5.6 years), and these events appeared to occur in those with pre-existing vascular disease [43]. Andersson et al found that the SIR of being hospitalised with stroke increased with time since diagnosis [16], whereas de Bruin et al found that there was no change in SIR with longer follow-up [39].

3.3.2.1.7 Autonomic dysfunction

One study reported an increased OR of autonomic dysfunction following radiotherapy for HL, manifesting as an elevated resting heart rate (OR 3.96; 95% CI 2.52-6.23) and abnormal heart rate recovery after exercise (OR 5.32; 95% CI 2.94-9.65) [69].

3.3.2.2 Quantification of radiotherapy treatment factors that modify risk

Table B2.2 in Appendix B2 summarises the studies that quantified the effect of radiotherapy treatment factors on the subsequent risk of CVD.

3.3.2.2.1 All cardiovascular disease

Radiotherapy fields

There was conflicting data about how radiotherapy technique affected the subsequent risk of CVD. Hoskin et al found that there was no difference in rates of fatal CVD between extended- (EFRT) and involved-field radiotherapy (IFRT) [70], and in Glanzmann et al's cohort the volume of heart irradiated was not associated with the RR of MI or sudden death [17]. In an American cohort, however, reducing cardiac irradiation by blocking the left ventricular and subcarinal regions was associated with a decrease in the RR of cardiac death [21]. In one cohort, the HR was highest in those treated with supradiaphragmatic radiotherapy [12].

Radiotherapy dose

Three studies found the RR, HR and SIR of CVD increased with increasing prescribed dose of radiation [15,18,21]. In contrast, Lund et al found that radiation dose was not associated with the OR of CVD, but doses in that study varied only within a very narrow range (40-42 gray (Gy)) [32]. Hahn et al built a multivariable model that used dose parameters, in combination with the patient's age and sex, to predict rates of late cardiotoxicity [71]. They

found that the HR of CVD was 0.0109 per Gy mean heart dose (MHD), and homogeneity of dose across the whole heart was associated with a reduced HR of CVD [71]. In one screened cohort, the cumulative incidence of CVD increased according to radiation dose to the mediastinum [34]. Three other screening studies found no relationship between radiotherapy dose and arterial stiffness, endothelial dysfunction [40,41] or inducible ischaemia [35].

3.3.2.2.2 Ischaemic heart disease

Radiotherapy fields

Hull et al found that techniques that increased the chance of overlap between mantle and infradiaphragmatic fields increased the HR of IHD [43], and in a British cohort those treated with total nodal irradiation had the highest SMRs of MI [38]. In the Stanford cohort, reducing cardiac exposure to radiation by blocking the left ventricular and subcarinal regions did not significantly reduce the RR of IHD [21].

Radiotherapy dose

Five studies failed to demonstrate that dose [18,43,46,50] or fractionation [42] significantly affected the HR, RR or cumulative incidence of IHD, but in two of these, patients who developed IHD were prescribed higher doses than those who did not [43,46]. In one Dutch cohort, the cumulative incidence and RR of IHD increased with both prescribed radiation dose, and MHD [44]. Hahn et al found that the HR of IHD was related to the volume of left anterior descending artery receiving 5 Gy and the volume of left circumflex artery receiving 20 Gy [71].

3.3.2.2.3 Heart failure

In two Dutch studies the HR and RR of HF increased with prescribed dose [18,58], and dose received by the heart and left ventricle [58], with the highest RR seen in those treated

with both mediastinal and para-aortic radiotherapy [58]. In a screened cohort, there was no association between radiation dose and the likelihood of systolic dysfunction on echocardiogram [57].

3.3.2.2.4 Valvular heart disease

Hull et al found that patients developing VHD were prescribed a higher dose compared to those who did not [43]. Cella et reported a higher OR of VHD with increasing radiation dose received by the heart, and a higher OR for aortic and mitral VHD with increasing left atrium doses, and a higher OR for tricuspid VHD with increasing right ventricular doses [63]. Two Dutch studies reported that the RR of VHD increased with increased prescribed radiation dose [18,61], and increased dose received by the affected heart valve [61].

3.3.2.2.5 Pericardial disease

One study found that radiation dose had no effect on the incidence of pericardial effusion [65], whereas another reported an increased incidence of symptomatic pericarditis with increasing prescribed dose, but not with increasing volume of heart irradiated [66]. After adjusting for age, sex, mediastinal involvement, and chemotherapy type, Cosset et al found that the RR of pericarditis increased with higher prescribed dose and dose per fraction [42].

3.3.2.2.6 Cerebrovascular disease

In one study, the HR of stroke or TIA was highest in those treated with mediastinal and neck radiotherapy, followed by supraclavicular and / or neck radiotherapy; and lowest for those treated with mediastinal radiotherapy which omitted the neck [39].

3.3.2.2.7 Autonomic dysfunction

In one study, neck irradiation was associated with an increased OR of autonomic dysfunction compared to those treated with mediastinal radiotherapy alone [69]. The

prevalence of abnormal heart rate recovery was significantly higher in those who received more than the median prescribed dose (38 Gy) of radiotherapy compared to those who were treated with a lower dose [69].

3.3.2.3 Quantification of cardiovascular risk factors that modify risk

The results of studies that reported how traditional cardiovascular risk factors modified the risk of CVD following radiotherapy are summarised in Table B2.3 of Appendix B2.

3.3.2.3.1 All cardiovascular disease

In two cohorts, all those that developed CVD after radiotherapy had at least one traditional risk factor (hypertension, diabetes, hypercholesterolaemia, family history of CVD, smoking, or hypothyroidism) [43,46]. In King et al's cohort the average number of risk factors in those who experienced CVD was 2.9, and 39% of the patients had at least four risk factors [46]. Screening studies demonstrated that traditional cardiovascular risk factors were common in HL survivors, with 81% having at least one, and 46% having two or more [31]. One study found that patients with screen-detected CVD had more risk factors compared to those without CVD [31], whereas in another traditional cardiovascular risk factors were no more prevalent in the group which experienced CVD compared with those that did not [32]. In another study, traditional cardiovascular risk factors were more strongly associated with arterial stiffness in controls than in HL survivors [40].

Sex

There was conflicting data about how risk of CVD differed between sexes. Two studies showed that men and women had almost equally increased RRs [21,72], but men had higher AERs because of higher general population rates [1,12,21,73]. A meta-analysis found no significant difference in SMR by sex [28], and one study [32] and a meta-analysis

[72] found a significantly increased OR in women compared to men. In one screened cohort cardiac abnormalities, particularly valvular regurgitation, were more common in women [32], whereas in another there was no significant difference by sex [34], and in another inducible ischaemia was more common in men [35].

Age

Studies reporting cumulative incidence reported higher rates of CVD in those who were older at the time of treatment [21,24,38]. RRs of CVD decreased with increasing age at treatment [1,3,38,43,46,8,12,15,16,19,21,28,37], and in two cohorts RRs were not significantly elevated for those treated over the age of 50 [15,21]. AERs increased with increasing age at treatment, due to increased background rates [19,25,73]. In one study, this increase with age was higher for women, with a substantial increase in OR above the age of 50 years [72]. Screening studies demonstrated no associations between age at treatment and CVD [34] or endothelial dysfunction [41].

Smoking

Significant proportions of those developing CVD within cohort studies smoked: 40.7% in a Turkish cohort [74], and 72% in an American cohort [46]. In a Dutch cohort the effects of smoking were additive to the HR of CVD from mediastinal radiotherapy [18], whereas in a Swedish study smoking did not increase the OR of cardiac events [29].

Other risk factors

In a Swedish cohort, hypertension and hypercholesterolaemia increased the OR of CVD, whereas diabetes did not [29]. In contrast, another study found that diabetes increased the HR for hospitalisation with CVD [24]. In an American cohort, the majority (78%) of those who developed CVD had hypercholesterolaemia, but only 33% had hypertension, and 6% diabetes [46]. Hypertension was associated with an increased OR of IHD or VHD on screening [31].

Pre-existing CVD

Most studies excluded HL survivors who had pre-existing CVD. In contrast, Myrehaug et al studied cardiac morbidity specifically in survivors with pre-existing heart disease and found it was significantly associated with the HR of cardiovascular hospitalisation (HR 3.98; 95% CI 2.26-7.01) [25]. Among those with pre-existing cardiac disease, the median time from HL treatment to cardiovascular hospitalisation was shorter, and the cumulative incidence of CVD higher [25].

Family history

In a Swedish cohort, family history of CVD increased the SIR of cardiac hospitalisation [16]; but in a later study from the same cohort family history did not increase the OR of cardiac events [29]. In an American cohort, 28% of those experiencing a cardiac event had a family history of CVD [46].

3.3.2.3.2 Ischaemic heart disease

In Glanzmann's study those with traditional cardiovascular risk factors had an increased risk of IHD (RR 2.36 [95% CI 1.42-3.68] compared to 0.96 [95% CI 0.20-2.77] for those without risk factors, reference Swiss population) [17]. In a Dutch cohort, the presence of at least one cardiac risk factor was associated with an increased RR of IHD (1.54; 95% CI 1.13-2.10) [44].

Sex and age

In most studies, relative (RR, SMR and HR) and absolute (AER) risks of IHD were higher in men than women [17,21,35,37,38,43,46]. One study found a higher RR in women [45]. RRs and SIRs decreased with increasing age at treatment [16,18,19,21,37,38,43,46], whereas AERs increased due to increasing background rates [18,19,21,37,38].

Other risk factors

Three studies found that smoking increased the HR or RR of IHD [18,19,44], whereas in an American cohort there was no association between smoking and the HR of IHD [43]. In an American cohort, 53% of those who experienced a fatal MI smoked [21]. Four studies found that hypertension increased the HR [19,43], OR [31] or RR [44] of IHD, whereas in a large Dutch cohort there was no association between hypertension and the HR of IHD [19]. Three studies found an increased HR or RR of IHD in those with hypercholesterolaemia [19,43,44]. In a large Dutch cohort, diabetes increased the HR of IHD [19], whereas in two other cohorts there was no association between the two [43,44]. In two cohorts, a family history of CVD increased the SIR or RR of IHD [16,44], whereas in an American cohort there was no association between a positive family history and the HR of IHD [43]. In a Dutch cohort pre-existing cardiac disease was a significant predictor for development of IHD [37]. Only one study investigated obesity and exercise, and found that a BMI over 30 increased the RR of IHD, whilst doing more than three hours exercise per week reduced the RR compared to exercising for one hour [44].

3.3.2.3.3 Heart failure

Sex and age

No studies reported significant differences in risk of HF between sexes. Three studies demonstrated increased SIRs of HF in those treated at younger ages [16,18,19]. In one screened cohort, younger age at treatment was associated with higher risk of diastolic dysfunction on echocardiogram [57].

Other risk factors

Van Nimwegen et al found an increased HR of HF in those who smoked at the time of HL diagnosis [18]. In a large Dutch cohort, smoking, hypercholesterolaemia and diabetes increased the HR of HF, whereas hypertension did not [19]. In another study within the

same cohort, none of the traditional cardiovascular risk factors affected HF rates, but only risk factors definitely identified prior to HF were included, possibly resulting in an underestimation [58]. Andersson et al found a substantially increased SIR of HF in those with a family history of CVD [16].

3.3.2.3.4 Valvular heart disease

Sex and age

Lund et al found that valvular regurgitation was more common in women, and in this and another study, women had an increased OR of left-sided valvular regurgitation compared to men [59,64]. Three studies found that age at treatment did not affect the OR of VHD [29,59,62].

Other risk factors

In Hull et al's cohort, none of the traditional cardiovascular risk factors were significantly associated with the OR of VHD [43]. In contrast, Cutter et al found that the total number of cardiovascular risk factors was associated with an increased RR of VHD [61]. Three studies found that hypertension increased the OR or HR of VHD [19,31,62]. Cutter et al found that hypertension at the end of follow-up was associated with an increase in the RR of VHD, although its effect disappeared when considered simultaneously with other cardiovascular risk factors [61]. Two studies reported increased HRs of VHD in those who smoked [18,19]. Hypercholesterolaemia increased the HR, OR or RR of VHD in three cohorts [19,29,61]. One study reported an increased HR of VHD in patients with diabetes, and another reported that obesity (measured at the end of study follow-up) was associated with an increased RR of VHD [61].

3.3.2.3.5 Pericardial disease and conduction abnormalities

Sex [65,66] and age [39,65,66] did not appear to have an effect on the relative risks of pericardial effusion. One study reported on ethnicity, and found no signficiant difference in ethnic makeup between the groups who did and did not go on to develop pericardial effusions [65]. In one screened cohort, younger age at treatment was associated with increased likelihood of persistent bradycardia following radiotherapy [57].

3.3.2.3.6 Cerebrovascular disease

Sex and age

None of the studies reported significant differences in relative risks of cerebrovascular disease between sexes. Both Andersson and de Bruin found increasing SIRs of stroke with younger age at first treatment [16,39]. In Hull et al's study those developing symptomatic cerebrovascular disease were older at the time of radiotherapy than those with asymptomatic arterial stenosis (median 51 versus 20 years), which was thought to be due to pre-existing arterial disease in the older group [43].

Other risk factors

Hypertension was associated with an increased HR of cerebrovascular disease in two studies [39,43], and in one of these hypercholesterolaemia was also associated with an increased HR [39]. Hull et al found an increased HR of carotid or subclavian stenosis in those with diabetes [43]. In de Bruin's cohort, developing heart disease following treatment for HL significantly increased the risk of ischaemic stroke or TIA. In those treated with mediastinal radiotherapy, the risk of ischaemic stroke or TIA was two-fold higher after cardiac disease than before (HR 2.1; 95% CI 1.2-3.7) [39].

3.3.2.3.7 Autonomic dysfunction

The association of thoracic radiotherapy with elevated resting heart rate was significantly higher in women than men (OR 6.22 [95% CI 4.00-9.67] versus 1.90 [95% CI 1.10-3.27]) [69].

3.3.2.4 Quantification of dose-response relationships

Three studies reported dose-response relationships for the risk of CVD, summarised in Table 3.4. Van Nimwegen et al found a linear dose-response relationship between MHD and risk of subsequent IHD, with a 7.4% increase in excess relative risk (ERR) per Gy, and no threshold dose [44]. This effect was not modified by chemotherapy, sex or traditional cardiovascular risk factors [44]. ERRs were highest in the lowest tertile of age at HL diagnosis, and decreased for middle and highest tertiles, but this difference was not statistically significant [44]. The same group found a non-linear dose-response relationship between MHD and risk of subsequent HF, and linear relationships for mean left ventricular dose (MLVD) and the volume of left ventricle receiving either 20 or 30 Gy [58]. For MHD, there was little evidence of an increase for doses up to 25 Gy, but risk increased steeply thereafter [58]. For MLVD there was a 9% increase in ERR per Gy [58]. The dose-response relationships were modified by the receipt of anthracycline chemotherapy [58]. Cutter et al found the VHD rate was more closely related to the dose to the affected valve than to the prescribed mediastinal dose [61]. There was a non-linear dose-response relationship between dose to the affected valve and risk of VHD, with little increase at doses below 30 Gy, whilst for doses above 30 Gy the percentage increase in VHD rate per Gy increased with increasing dose [61]. The dose-response relationship was not modified by chemotherapy [61].

Table 3.4: Dose-response relationships for the risk of CVD following radiotherapy

Reference	Study population	Disease	Dose-response model
van Nimwegen 2015 [44]	Nested case-control study in cohort of Dutch 5-year survivors treated when aged <51 y 1965-1995	IHD	**RR = 1+(1.074*dose)** **ERR 7.4% / Gy** (95% CI 3.3-14.8%) (mean heart dose)
van Nimwegen 2017 [58]	Nested case-control study in cohort of Dutch 5-year survivors treated when aged <51 y 1965-1995	HF	**RR = 1+(1.09*MLVD)** **ERR 9.0% / Gy** (*P* = .006) (linear, $P_{curvature}$ = .09) (mean LV dose) **RR = 1+β_{radio1}*dose*exp (β_{radio2}*dose)** (non-linear, $P_{curvature}$ = .029) (mean heart dose)
Cutter 2015 [61]	Nested case-control study in cohort of Dutch 5-year survivors treated when aged 15-41 y 1965-1995	VHD	**RR = 1+exp(-5.02)dose* exp(0.075*dose)** (non-linear, $P_{curvature}$ = .03) (dose to affected valve)

Abbreviations - y: years; IHD: ischaemic heart disease; ERR: excess relative risk; Gy: gray; HF: heart failure; RR: relative risk; MLVD: mean left ventricular dose; LV: left ventricle; VHD: valvular heart disease

An Italian group analysed risk of asymptomatic VHD in relation to doses delivered to cardiac substructures. They found that the maximum dose delivered to the heart independently predicted the risk of developing VHD, and using a cut-off of 33 Gy increased the OR 6.4-fold (*P* .003) [63]. The percentage of left atrium receiving over 25 Gy (LA-V_{25}) and the percentage of left ventricle receiving over 30 Gy (LV-V_{30}) correlated with mitral and aortic VHD, and the percentage of right ventricle receiving over 30 Gy correlated with tricuspid VHD [63]. The risk of developing left-sided VHD was higher when both the LA-V_{25} exceeded 63% and the LV-V_{30} exceeded 25%, compared to when only one constraint was exceeded [63].

3.3.2.5 Summary of CVD risk data

Figure 3.3 summarises the CVDs where there is evidence of an increased risk from radiotherapy, and the factors that modify this risk.

Cardiovascular disease following radiotherapy for Hodgkin lymphoma			
Conditions with evidence for an increased risk from radiotherapy			
Ischaemic heart disease	Evidence level A*		
Heart failure	Evidence level A*		
Valvular heart disease	Evidence level A*		
Pericardial disease	Evidence level B†		
Conduction abnormalities	Evidence level C‡		
Cerebrovascular disease	Evidence level B†		
Factors which modify the risk of cardiovascular disease following radiotherapy			
Exposure of heart or substructures to irradiation		Cardiovascular risk factors	
Ischaemic heart disease	Level A*	Sex	
Heart failure	Level A*	Ischaemic heart disease	Level B†
Valvular heart disease	Level A*	Valvular heart disease	Level C‡
Pericardial disease	Level C‡	Age	
		Ischaemic heart disease	Level B†
		Heart failure	Level B†
		Cerebrovascular disease	Level B†
		Hypertension	
		Ischaemic heart disease	Level B†
		Valvular heart disease	Level B†
		Cerebrovascular disease	Level C‡
		Hypercholesterolaemia	
		Ischaemic heart disease	Level B†
		Heart failure	Level C‡
		Valvular heart disease	Level B†
		Cerebrovascular disease	Level C‡
		Diabetes mellitus	
		Ischaemic heart disease	Level C‡
		Heart failure	Level C‡
		Valvular heart disease	Level C‡
		Cerebrovascular disease	Level C‡
		Family history	
		Ischaemic heart disease	Level C‡
		Heart failure	Level C‡
		Pre-existing heart disease	
		Ischaemic heart disease	Level C‡
		Cerebrovascular disease	Level C‡
		Obesity & exercise	
		Ischaemic heart disease	Level C‡
		Valvular heart disease	Level C‡
		Smoking	
		Heart failure	Level C‡
		Valvular heart disease	Level C‡

*level A: high level of evidence; from Mulder et al 2013 [2]
†level B: moderate to low level of evidence; from Mulder et al 2013 [2]
‡level C: very low level of evidence; from Mulder et al 2013 [2]

Figure 3.3: Summary of the quality of the evidence for an increased risk of CVD following radiotherapy for HL

3.3.3 Second malignancies

Studies reported increased risks of the major solid tumours (breast, lung, gastrointestinal, and cutaneous), other solid tumours (thyroid, renal, head and neck, bone and soft-tissue, genitourinary tract and nervous system), and haematological malignancies after radiotherapy.

3.3.3.1 Quantification of risk

Table B3.1 in Appendix B3 summarises the findings of studies that quantified the risk of second malignancies.

3.3.3.1.1 All second malignancies

The reported incidence of second malignancies ranged from 2-23% depending on the length of follow-up of the study, and whether non-melanoma skin cancers were included or not [9,74–88]. A meta-analysis using individual patient data (IPD) from randomised trials reported a 7.6% incidence of second malignancies, after a median of 7.8 years [89]. Reported cumulative incidences increased with time since treatment: 0.3-4% at five years [5,81,90–98], 2-18% at ten years [11,36,98–104,90–97], 7-21% at 15 years [10,78,100,102,103,105–109,81,85,86,90,91,93,96,97], 12-31% at 20 years [36,84,86,91,100,102,103,106,110–112], 14-41% at 25-28 years [75,81,100,111,113,114], 30-33% at 30 years [88,115] and 48.5% at 40 years [88]. An IPD meta-analysis from randomised trials reported cumulative incidences of 2.4%, 5.8%, 13% and 23% at five, 10, 15 and 20 years respectively [116]. Studies with longer follow-up reported 1-5% of patients developed third malignancies [75,86,88,115], and 0.4-0.7% fourth malignancies [75,88]. Median time between second and third malignancies ranged from three to four years [86,115]. Third malignancies were often in the same organ as second malignancies [115].

Studies reported SIRs of 1.6-6.0 [5,27,81,84,88,91,106,112,113,115,117–119] and SMRs 5.1-10.3 [5,12,27]. RRs of second malignancy ranged from 1.5-7.0 [8,10,85,86,93,95–97,108,120–122,22,123–126,23,47,56,75,78,79,84]. HRs ranged from 1.5-2.6 for development of second malignancy [26,115], and one study reported a HR of 5.2 (95% CI 1.6-16.8) for development of a third malignancy [115]. In one Norwegian cohort the HR for death from second malignancy was 6.6 (95% CI 4.7-9.2) [14]. AERs ranged from 34-364 per 10,000 py [10,23,88,108,112,115,117,118,120,124–126,27,75,77,78,81,84–86]. Studies with the lowest estimates tended to exclude non-melanoma skin cancers (NMSCs) from their analyses. One study reported an absolute excess mortality (AEM) from second cancers of 61.5 per 10,000 py [12].

Patterns of malignancy

Studies found increased rates of cancer at most body sites [75,78,84,86,88,92,113,117], with the exception of prostate cancer [88,127]. Solid tumours contributed the most to the excess risk in studies with longer follow-up [75,91,113], whereas those with shorter follow-up found the excess risk of haematological malignancies was more marked [92,117]. Patterns of solid tumours often mirrored those in the general population, with breast and lung cancer [74,81,115,117,118,128,84,86,88,99,101,106,111,114] the commonest, although there were also increased rates of malignancies that are rarer within the general population such as thyroid cancer [8,75,118,119,125,126,129,81,84,86,88,91,93,112,117], sarcoma [8,75,120,124,125,127,129,130,78,84,86,88,91,93,112,118], salivary gland tumours [56,126], and mesothelioma [8,12,23,88,127,131]. Gastrointestinal malignancies were also common [1,8,12,23,56,75,78,81,83–86,88,91,93,101,108,112–114,117,118,120,124–130,132–135]. In Franklin et al's IPD meta-analysis, the most common second malignancies were non-Hodgkin lymphoma (NHL), acute leukaemia, and cancers of the lung, skin, breast, and gastrointestinal tract [89]. This pattern was confirmed in a later meta-analysis, where commonest second malignancies were breast, lung, skin and bowel [116].

Time since treatment

The median latency to second malignancy ranged from 4-24 years [5,27,108,109,111,114,115,123,136,137,36,74,79,93,95,99,104,107]. Seven studies found stable RRs [13,86,93,102,120,126,138] and eight stable SIRs [81,84,88,91,112,117,118] with time since treatment, whereas three found increasing RRs [85,100,123] and one increasing SIRs [113] with longer follow-up. One reported a stable HR with time since treatment [26]. AERs increased with follow-up duration [13,84,88,93,112,113,120], and two studies reported this increase was more pronounced in men than women [9,102]. SIRs remained increased for more than 35 years after treatment [88].

3.3.3.1.2 Solid tumours

The cumulative incidence of solid tumours increased with longer follow-up: 0.5-2.5% at five years [93,96,97,124], 2-11% at 10 [11,20,124,128,138,139,93,96–98,100–102,108], 2-17% at 12-15 [10,85,124,128,140,141,91,93,96,100–102,108,119], 5-24% at 20 [75,91,100–102,128], 14-34% at 24-28 [75,100,113,114,126] and 28.5% at 30 years [88]. In de Vries et al's cohort, the cumulative mortality was 5% at 20 years, and 21% at 40 years [12]. Reported SIRs ranged from 1.7-4.2 [56,88,91,117,119] and RRs ranged from 1.8-11.3 [75,78,103,108,110,120,124–127,129,130,79,138–141,83,86,90,92,93,96,97]. AERs ranged from 36-101 per 10,000 py [75,78,86,88,90,108,120,124–126], and one study reported an AEM of 47.4 per 10,000 py [12].

Time since treatment

The latent interval ranged from 5-14 years [86,92,101,106,108,120,128,137,141]. Seven studies found increasing RRs [75,78,84,86,102,103,120] and one an increasing SIR [117] with longer follow-up, whereas six found stable RRs [1,85,126,127,129] and two stable SIRs [88,91] over time. Five studies reported AERs, all of which increased with follow-up duration [1,75,84,88,120]. The relative proportion of solid tumours to haematological

malignancies increased over time, particularly beyond 10 years [86,120]. In three cohorts, RRs plateaued [1] or decreased [75,126] after 20-25 years. One study found that the cumulative hazard of second solid tumours increased with increasing rate over time [139].

3.3.3.1.3 Breast cancer

In most studies, breast cancer was the commonest second malignancy seen. In a Dutch cohort it contributed 20% of the AER of any second malignancy, and 40.5% of the AER in women [88]. Cumulative incidences increased with longer follow-up: 0.3% at five years [81], 0-6% at 10 [138,142], 1.5-10% at 15 [81,106,142], 4-6% at 20 [106,143], 3-16% at 25 [75,81,126], 12-25% at 30 [88,143,144] and 20-27% at 40 [145]. RRs ranged from 1.3-10.5 [10,21,23,75,78,81,83,85,86,92,93,102,103,108,120,121,124–127,129,142,143,145–149], SIRs from 1.8-5.6 [81,84,88,91,106,112,113,115,117–119,144,150,151], and SMRs from 2.9-9.8 [12,152,153]. Only one study, a pooled analysis of seven cohorts, failed to demonstrate an increased RR of breast cancer [130]. One study reported a RR of 158, but their expected rates were extremely low, with observed rates similar to the other papers, so it's likely there was an error in their calculations [136]. They made the same error with their calculations for all tumour sites, and so I do not report any of their estimates in subsequent sections. Reported AERs ranged from 0.2-57 per 10,000 py [10,23,112,118,120,124–126,143,144,146,150,75,78,81,84–86,88,108]. De Vries et al reported an AEM of 4.4 per 10,000 py [12].

Time since treatment

The latent period ranged from 8-22 years [10,92,106,142,143,146,148,152–160]. Four studies reported increasing SIRs [81,113,117,118], and three increasing RRs [75,86,92], with longer follow-up, whereas three reported stable SIRs [88,144,145], and one stable RRs [126], with time. In six studies, RRs were not increased until after 10-15 years of follow-up [78,102,146,147,150,153]. In a large international cohort, RRs peaked at 10-19 years after

treatment and subsequently fell [127]. Two studies found no diminution of RR with time, after 25 [148] and 30 [144] years. A meta-analysis reported that the highest RR was seen at 15-19 years of follow-up, with a decrease after 20-24 years, then a further rise after 25-29 years, but they did not report a statistical test for trend [143]. AERs increased with longer follow-up [27,75,86,88,144,145].

3.3.3.1.4 Lung cancer

Lung cancer accounted for a large proportion of the excess risk of solid tumours in most studies [84,88,117,161,162]. In a Dutch cohort, it was the second commonest after breast cancer, representing 20.2% of the AER [88]. In an American cohort it was the commonest, contributing most to the overall AER [117]. The cumulative incidence of lung cancer increased with length of follow-up, and estimates ranged from 0.2-0.5% at five years [81,91], 1-3% at 10 [91,92], 1-6% at 15 [81,91,92,106], 3-6% at 20 [84,91,106] and 6% at 30 [88]. SIRs ranged from 2.9-6.8 [56,81,84,88,91,106,112,113,115,117–119], and RRs from 1.3-10.8 [1,8,10,18,23,75,78,81,83,85,86,92,93,103,108,120,121,124–127,129,130,136,163,164]. One study reported an SMR of 6.7 (95% CI 5.9-7.6) for all respiratory malignancies, 6.4 (95% CI 5.6-7.4) for lung cancer and 15.5 (95% CI 9.6-23.8) for mesothelioma [12]. AERs ranged from 1-25 per 10,000 py [1,8,88,108,112,118,120,124–126,10,23,75,78,81,84–86]. In a meta-analysis, the pooled RR was 4.62 (95% CI 3.18-6.70), and AER 10.4 per 10,000 py [165]. Seven studies also reported an increased risk of mesothelioma following radiotherapy. Schaapveld et al reported a cumulative incidence of 0.6% at 30 years [88]. Reported SIRs for mesothelioma ranged from 5.8-15.1 [84,88,131]. In a Danish cohort, the RR of hospitalisation with mesothelioma was 4.9 (95% CI 1.2-19.9) [23], and RRs of pleural malignancy ranged from 19.5 (95% CI 7.3-40.3) in an international cohort [127], to 200 (95% CI 24-722) in a French cohort treated between 1960 and 1984 [108]. Despite high RRs, reported AERs (0.7-2.6

per 10,000 py) [23,88,131] and AEM (2.0 per 10,000 py) [12] were low due to the low background incidence of mesothelioma.

Time since treatment

The median time to development of lung cancer ranged from 7-17 years [79,164–167]. Only one study reported the latent interval to the development of mesothelioma, at a median of 27.7 years [131]. Nine studies reported no increase in RR [75,78,85,102,129,164] or SIR [81,88,91] with duration of follow-up, whereas five reported increased RRs [84,86] or SIRs [113,117,118] over time. Three reported AERs, all showing increase over time [75,88,113]. A meta-analysis found RR increased with follow-up, peaking at 10-14 years, with no increase beyond this [165]. One study reported RRs plateaued beyond 15 years of follow-up [78], and another found a downturn in risk 25 years after treatment [126]. Two studies reported increased SIRs of mesothelioma with longer follow-up [117,131], with cases predominantly seen over 25 years after treatment [131].

3.3.3.1.5 Gastrointestinal malignancies

Gastrointestinal malignancies were the third most common solid tumours in both Dutch [88] and American cohorts [117]. Increased risks were reported for cancers of the oesophagus, stomach, pancreas, liver, small intestine, colon and rectum. Compared to breast and lung cancer, cumulative incidences of gastrointestinal malignancies were lower: 0.1% at five years [81], 0.6-0.9% at 15-20 years [81,135], 1.7% at 25 years [81] and 2-6% at 30 years [88,135]. Colorectal cancer (CRC) was the dominant gastrointestinal malignancy in most studies, with cumulative incidences of 0.3% at 20 [135] and 1.2-1.5% at 30 years [135]. In a large Dutch cohort, 30-year cumulative incidence of oesophageal, gastric and pancreatic cancers were 1.5%, 1.6% and 1.0% respectively [88], which are higher than studies that focused on those cancers individually: Morton et al reported a 30-year cumulative incidence of oesophageal cancer of 0.38% [168], and 0.92% for gastric cancer [169] and Dores et al

reported a 30-year cumulative incidence of pancreatic cancer of 0.54% [170]. After screening colonoscopy, 25% of HL survivors treated with abdominal radiotherapy were found to have advanced pre-invasive colorectal neoplasms [171,172]. SIRs for gastrointestinal malignancies overall ranged from 2.0-4.6 [81,84,88,112,135]. When considering the specific cancer types, SIRs were highest for oesophageal cancer (2.0-9.5) [84,88,112,117,118], followed by gastric (1.6-7.4) [81,84,88,91,112,113,117,118,134], colon (1.6-2.9) [84,88,91,113,117,118,135], pancreatic (1.0-5.7) [84,88,113,118] and rectal (0.9-2.7) [84,88,91,113,117,118,135] cancers. Only two studies reported SIRs of hepatobiliary (1.5 and 4.4) [84,118] and small intestinal tumours (8.8 and 16.2) [84,112]. RRs of gastrointestinal malignancy overall ranged from 1.7-7.7 [1,75,133,78,81,86,120,124,126,129,130], and were 1.3-9.0 for gastric [75,81,85,108,125–127,132,133], 3.5-4.7 for pancreatic [125–127,133], 2.5-4.3 for colon [75,78,83,85,93,125–127], 1.1-7.0 for rectal [75,78,85,126,127,133] and 1.6-40.1 for hepatic tumours [75,126]. There was substantial variation in reported RRs for oesophageal cancer, ranging from 1.7-30.6 [75,85,127,133]. AERs of gastrointestinal malignancy overall ranged from 2.4-24 per 10,000 py [1,12,133,135,75,78,86,88,112,120,124,126]. Those for oesophageal cancer ranged from 0.2-5.6 [12,75,84,85,88,112,118,126,133], 0.9-6.2 for gastric [12,75,126,133,134,78,81,84,85,88,108,112,118], 0.0-3.1 for pancreatic [12,84,88,118,126,133], 1.2-4.7 for colon [12,75,78,84,85,88,118,126,133,135], and 0.1-2.6 for rectal cancer [12,75,78,84,85,88,118,126,133,135].

Time since treatment

In one study, the median interval to development of any gastrointestinal malignancy was 12 years [133]. Latent intervals for individual cancer types were 16 years for oesophageal [168], 15-17 years for gastric [134,169], 19 years for pancreatic [170] and 23 years for colorectal [135]. Five studies reported RRs [86,102,133] or SIRs [84,117] of gastrointestinal malignancy increased with follow-up, whereas two reported stable RRs [75] or SIRs [88] over time. Four studies found increasing AERs with longer follow-up [75,86,88,133]. All six

studies that reported the magnitude of CRC risk over time found increased SIRs [81,84,117,118,135] or RRs [126] with longer follow-up. Two studies found that SIRs of CRC were increased for more than 30 years after radiotherapy [88,135]. Five studies found increased SIRs [84,113,117,118] or RRs [126] of gastric cancer with longer follow-up, whereas two reported stable SIRs [81,134] over time. One study reported increased AERs of gastric cancer over time [113]. Three studies reported increasing SIRs [117,118] or RRs [126] of oesophageal and pancreatic cancer with time since treatment. A screening study found that the OR of advanced neoplasia increased with longer follow-up [172].

3.3.3.1.6 Cutaneous malignancies

Studies reported increased risk of basal cell carcinomas (BCC), squamous cell carcinomas (SCC) (collectively termed NMSC), and melanoma. Patients often developed multiple skin cancers [173,174], with a mean of four per patient in a Dutch cohort (maximum 44) [173]. Daniëls et al reported a 30-year cumulative incidence of all cutaneous malignancies of 15% [173], whereas studies reporting tumour types separately reported lower incidences of 0.7-1.9% for NMSC and 0.4-1.1% for melanoma [81,88]. Tucker et al reported a cumulative incidence for melanoma of 3.3% at 14 years [174]. SIRs ranged from 1.4-3.9 for NMSC [81,84,88,91,112], and from 2.3-4.0 for melanoma [81,84,88,91,112,113,118,173]. Only one study reported a RR of NMSC (2.3, 95% CI not reported) [121]. RRs of melanoma ranged from 1.6-11.8 [75,78,129,130,174,81,86,93,108,120,124,125,127]. AERs of NMSC ranged from 1.4-8.8 per 10,000 py [81,84,88,112], and from 0.7-11.6 for melanoma [75,78,124–126,173,81,84,86,88,108,112,118,120]. Two studies reported SIRs for SCC, of 4.44 (95% CI 3.65-5.41) and 5.0 (95% CI 2.4-9.2) [118,173], and only one for BCC (5.2; 95% CI 4.0-6.6) [173], resulting in AERs of 8.1 and 7.9 per 10,000 py for SCC [118,173] and 53.3 per 10,000 py for BCC [173]. Only Daniëls et al reported the latent period to development of skin cancer, at a median of 18 years [173]. One study each reported stable SIRs of cutaneous malignancies [175] and SCC [118] over time. Two studies reported

increasing SIRs with longer follow-up for NMSC [81] and BCC [173]. Four studies reported increasing SIRs of melanoma with longer follow-up [84,113,117,118], whereas one reported stable SIRs [81].

3.3.3.1.7 Other solid tumours

Studies also reported increased risks of tumours of the thyroid, kidney, head and neck, bone and soft-tissues, genitourinary tract and nervous system. Details of the risk estimates, including variation over follow-up, from these studies can be found in Table B3.1 in Appendix B3.

3.3.3.1.8 Haematological malignancies

Most studies reported that the increased risk of leukaemia observed in HL survivors was mainly attributable to chemotherapy, particularly alkylating agents [20,78,85,91,101,176–185]. The risk of NHL was often equal for all treatment categories [78,84,85,113,186]. Details of the reported risk estimates are presented in Table B3.1 of Appendix B3, and in this and subsequent sections I will discuss the data that relates specifically to the risk from radiotherapy. Omer et al reported an SIR of 0.88 (95% CI 0.02-4.89) for haematological malignancies overall [119]. Reported SIRs for acute leukaemia ranged from 1.2-4.0 [84,113], and those for NHL ranged from 11.9-26.1 [84,113]. RRs for leukaemia ranged from 0.0-5.5 [92,141], and those for NHL ranged from 0.6-6.7 [92,129,141].

Time since treatment

In studies that reported both, haematological malignancies typically occurred after much shorter latent periods than solid tumours. The median time to development of leukaemia ranged from 1-6 years [86,92,101,106–108,139,182,183,187–191], and 4-13 years for NHL [86,92,108,190,192]. Fourteen studies reported that RRs [1,75,78,85,86,92,102,120], SIRs [81,113], and AERs [1,75,86,120] for acute leukaemia were highest during the first 10-15

years of follow-up. Five studies reported the RRs [78,85,120], SIRs [113] and AERs [120] for NHL were also highest during the first 10-15 years of follow-up, whereas two others reported the RRs [75] [92] and AERs [75] for NHL were only raised after the first 10 years.

3.3.3.2 Quantification of radiotherapy treatment factors that modify risk

3.3.3.2.1 All second malignancies

Radiotherapy fields

Studies that reported the location of second malignancies in relation to radiotherapy fields found that the majority developed within or at the margins [5,8,11,27,36,93,95,106,111,193]. Nyandoto et al reported a slightly longer median time to development of second tumours that occurred outside of radiation fields compared to those developing within field borders (16 versus 12 years) [111]. Five studies reported that the rates or RRs of second malignancy increased with larger radiation field size [86,107,108,194,195]. However in four cohorts, a long-term follow-up study of RCTs, and a meta-analysis of RCTs, there were no significant differences in the rates or RR of second malignancy between EFRT and IFRT [70,76,85,111,123,196]. One study found an increased SIR of second malignancy in patients treated with one field per day, rather than two [27].

Radiotherapy dose

Four studies found increased HR, RR or ORs of second malignancies with increasing prescribed radiation dose [79,109,111,137]. However, the cumulative incidence and SIRs did not differ with radiotherapy dose in the cohort treated in the H10 trial [76]; and a meta-analysis found there was insufficient evidence to determine the effect of dose on second malignancy risk [196].

3.3.3.2.2 Solid tumours

Radiotherapy fields

Most studies reported that the majority of second solid tumours developed within or at the margin of radiation fields [78,79,85,90,96,108,113,139,141]. Solid tumours did not exclusively develop in irradiated areas however, and four studies found more than half occurred outside of radiation fields [97,101,123,138]. In van Leeuwen et al's cohort, the proportions of second tumours in irradiated areas was highest for melanoma and soft-tissue sarcoma (100%) and lung cancer (84%); and lower for colorectal (45%), gastric (50%), gynaecological (44%) and genitourinary (50%) cancers [78]. Schaapveld et al found higher SIRs of supradiaphragmatic solid tumours in those treated with supradiaphragmatic radiotherapy, and higher SIRs of infradiaphragmatic tumours in those treated with infradiaphragmatic radiotherapy [88]. They also found that patients who received supradiaphragmatic radiotherapy that did not include the axilla had a much lower risk than those who received mantle-field radiotherapy, largely due to a lower risk of breast cancer [88]. Two studies found that patients treated with supradiaphragmatic radiotherapy had a higher HR or RR of developing second solid tumours compared to those treated with infradiaphragmatic radiotherapy [115,127], but the risk was highest in those treated with both supra- and infra-diaphragmatic fields [115]. Eight studies reported higher cumulative incidences, RRs, HRs or SIRs of second solid tumours in those treated with EFRT rather than IFRT or regional radiotherapy [56,83,85,90,102,107,124,194]. In Franklin et al's meta-analysis, however, there were no significant differences in solid tumour risks between EFRT and IFRT [89]. This may be due to the relatively short follow-up (less than a decade) of patients in the largest included trials, and therefore small numbers of second malignancies seen.

3.3.3.2.3 Breast cancer

Radiotherapy fields

Where reported, most secondary breast cancers arose within or at the margin of the radiotherapy field [113,143,146,148]. Studies reported a higher risk of breast cancer in those who received supradiaphragmatic radiotherapy [88,152], particularly mantle fields [144,145,158]. Schaapveld et al found a reduction in risk from supradiaphragmatic fields that did not include the axilla compared to mantle radiotherapy (HR 0.37; 95% CI 0.19-0.72) [88]. In Franklin et al's meta-analysis, there was a significantly greater risk of breast cancer with EFRT compared to IFRT [89]. Six studies found a lower RR, HR or SIR of breast cancer among those women who received pelvic radiotherapy [144,145,148,156,157,197], likely due to ovarian irradiation inducing early menopause, and therefore reducing breast exposure to oestrogen.

Radiotherapy dose

Six studies reported increased RRs, SIRs or ORs of breast cancer with increasing prescribed radiotherapy dose [145,146,154,156,157,197]. In Travis et al's cohort, RR increased with increasing dose to the location where the subsequent breast tumour developed [148]. Tinger et al found that dose to the axilla was associated with the RR of breast cancer after mantle radiotherapy [198]. Two studies found no association between radiation dose and breast cancer risk [152,160]. The median dose received by the location of a subsequent breast tumour ranged from 24.8-31.7 Gy [148,156,157,197].

3.3.3.2.4 Lung cancer

Radiotherapy fields

Where reported, most lung cancers developed within or at the margin of irradiated fields [79,92,103,113,164,167]. In de Bruin et al's cohort 92.3% of mesotheliomas occurred within radiation fields [131]. In a Dutch cohort, supradiaphragmatic radiotherapy increased the SIR

of subsequent lung cancer, particularly if the axilla was included in the field [88]. Swerdlow et al found an increased OR of lung cancer with increasing volume of lung irradiated [161]. However, in Franklin et al's meta-analysis there were no significant differences in the OR of lung cancer between EFRT and IFRT [89].

Radiotherapy dose

Studies reported increased RRs or HRs of lung cancer with increasing dose to the lung [79,162,164,166,199]. One study suggested a possible downturn in RR for doses greater than 9 Gy to the site of subsequent tumour development [166]. The reported mean dose of radiation to the location of subsequent lung tumour ranged from 7.2-27.2 Gy [164,166,199], and Gilbert et al reported a mean dose of 15.8 Gy to the lobe in which the subsequent tumour developed [199].

3.3.3.2.5 Gastrointestinal malignancies

Radiation fields

Where reported, 60-75% of gastrointestinal cancers arose within radiation fields [81,133]. In an American cohort, all oesophageal, small intestine and pancreatic tumours were within the field and 88% of gastric cancers, but only 10% of CRCs [133]. In contrast, in a Dutch cohort, half of CRCs developed within the radiation field [135]. Studies reported that infradiaphragmatic radiotherapy increased RRs, ORs or SIRs of gastric [88,132,169], pancreatic [88] and colorectal [88,135] cancer, whereas supradiaphragmatic radiotherapy increased the OR of oesophageal cancer [168]. Swerdlow et al reported an increased RR of gastrointestinal malignancies following IFRT, compared to smaller fields [85]. In a Dutch cohort, para-aortic fields increased the SIR of CRC overall, and inverted-Y fields substantially increased the SIR of tumours in the transverse colon and rectum [135].

Radiation dose

Three studies found the RR or OR of gastric cancer increased with increasing radiation dose to the stomach [134,169,200]. Morton et al found that the OR was not significantly increased with gastric doses of less than 25 Gy, and the increase in OR with increasing dose was higher in those diagnosed with gastric cancer before the age of 30 [169]. The mean dose to gastric tumour location in Gilbert et al's cohort was 15.3 Gy [200]. One study found an increased OR of oesophageal cancer with increasing radiation dose to the oesophagus, particularly above 30 Gy [168]. One other study found that pancreatic cancer risk increased with increasing radiation dose above 5 Gy to the pancreatic tumour location [170].

3.3.3.2.6 Cutaneous malignancies

Where reported, the majority of skin cancers developed within or at the margin of radiation fields [81,173]. In Daniëls et al's cohort, skin cancers developing after longer latent intervals were more likely to be located within radiation fields, and patients who received mantle or mediastinal radiotherapy were most likely to develop cancers in the skin of the chest or trunk [173].

3.3.3.2.7 Other solid tumours

Thyroid and renal cancers [81], and sarcomas [201], were reported to most commonly arise within radiation fields. Schaapveld et al found an increased SIR of thyroid cancer in those treated with supradiaphragmatic radiotherapy [88].

3.3.3.2.8 Haematological malignancies

Radiotherapy fields

Three studies reported an increased cumulative incidence or RR of haematological malignancies in those treated with total nodal irradiation compared to more localised

radiotherapy [107,181,188], and an additional five found an increased cumulative incidence, HR or RR of leukaemia with more extensive radiotherapy [191,194,202–204]. In a Dutch cohort, supradiaphragmatic radiotherapy including the axilla was associated with a higher HR of haematological malignancies [88]. The data for an association between radiotherapy field and NHL was mixed. Sasse et al found no difference in cumulative incidence after extensive or localised radiotherapy [194], and in Enrici et al's cohort, the majority of NHL developed outside the irradiated field [205]. Swerdlow et al found higher RRs of leukaemia and NHL in those who received local, rather than extensive, radiotherapy [85]. In a meta-analysis, the radiotherapy fields did not affect leukaemia or NHL risk [89].

Radiotherapy dose

One study found an increased RR of leukaemia in patients who received more 20 Gy to the bone marrow [177].

3.3.3.3 Quantification of other risk factors that modify risk

3.3.3.3.1 All second malignancies

Sex

Seven studies reported increased RRs or SIRs of second malignancy in women compared to men [5,27,95,115–117,120], largely due to breast cancers being included in calculations. In an American cohort, the SIRs of most other cancers were similar in men and women, apart from oropharyngeal cancer where the SIR was higher in women [117]. In 11 other cohorts and a meta-analysis RRs, SIRs and HRs did not differ significantly between sexes [10,79,112,126,206,84,86,88,91,93,97,102,111].

Age at treatment

Most studies reported increased RRs, SIRs and HRs of second malignancy in those treated when young [8,9,12,27,75,84,86,88,91,93,97,112,113,118,120,126]. AERs were greater for patients treated at an older age, due to increased background rates [9,12,27,75,84,86,88,91,97,98,107,112,113,118,120,126]. Tester et al found that there was no difference in time to development of second tumours based on age at treatment of HL [139], whereas Biti et al reported a shorter latent period in patients who were older at treatment [107]. A meta-analysis did not find any significant differences in the OR of second malignancies according to age at treatment [206].

Other factors

One study found an increased SIR of second cancers in those who had a first-degree relative with cancer, which increased further in those who had two or more affected relatives [118]. A meta-analysis of second malignancy risk was underpowered to detect differences according to age and sex, and had no data on other potential risk factors (e.g. smoking) [89].

3.3.3.3.2 Solid tumours

Sex

Four studies found higher RRs or SIRs of second solid tumours in women, again due to the inclusion of breast cancer in calculations [88,100,117,120]. In five other cohorts, there was no difference in RRs, SIRs or HRs of solid tumours between sexes [1,84,91,112,126]. When sex-specific cancers were excluded, Dores et al found similar RRs of solid tumours in men and women, but AERs were higher in men due to a greater number of lung cancers [126]. They also found that RRs of melanoma and cancers of the tongue, liver, gallbladder and brain were only increased in men, whereas bone tumours were only increased in women

[126]. Hodgson et al found increased RRs of solid supradiaphragmatic tumours in women, but no sex differences in the RR of infradiaphragmatic tumours [127].

Age at treatment

Seven studies reported the RRs, SIRs or HRs for second solid cancers decreased with increasing age at the time of treatment [1,75,84,88,91,112,126]. AERs increased with age due to increasing background incidence [1,75,84,91,126]. Studies that modelled cumulative risk of developing second solid tumours found older age at treatment was predictive of increased risk [56,97,102,108,128,137]. In a British cohort, the temporal pattern of risk varied considerably by age [84]. In young adults, solid cancer RRs increased consistently throughout follow-up, whereas in older adults RRs were lower and did not increase with follow-up beyond five years [84]. One study reported that the pattern of malignancy varied by age at treatment [126]. For patients treated aged under 30, the highest RR was for breast cancer; compared to lung cancer for those treated aged 31-60, and lung cancer and NHL for those treated aged over 60 [126].

Smoking

One study found an increased HR of solid tumours in those who were recent or former smokers at the end of study follow-up [88].

3.3.3.3.3 Breast cancer

Age at treatment

Most studies reported that the RR or SIR of breast cancer was higher with younger age at treatment [10,75,84,86,88,91,112,113,118,120,126,143–145,149,150,152,153,159,207]. Five studies (including one meta-analysis) found that RRs were not significantly increased for those treated when aged over 30 [106], 35 [86], 40 [143,144], or 50 [113]. In contrast, two studies reported the SIR or RR was still raised for women treated when aged 35-50

[88,127]. AERs decreased less steeply with increasing age at first treatment than RRs [75,86,113,118,120,144–146,207], due to increasing rates of breast cancer with age in the general population. The temporal trends in RR or SIR varied with age at treatment, but patterns differed between studies. In one British cohort, RR peaked earlier in women treated when aged below 20, with a more marked decrease with longer follow-up compared to women treated at older ages [145]. In another British cohort, SIRs were only significantly increased after more than 10 years of follow-up in patients who were treated before age 25 [84]. Conversely, in a Dutch cohort, the SIRs for women treated before age 30 did not change with longer follow-up, whereas they significantly increased among women treated aged 31-40 [144].

Hormonal factors

Ovarian function significantly affected a women's risk of breast cancer after radiotherapy. Five studies found that premature menopause (when aged under 40) was associated with a significantly decreased RR, HR or OR of breast cancer, and the RR, HR or OR increased with longer intervals between radiotherapy and menopause [144,156,157,208,209]. In contrast, Conway et al found that premature menopause was not associated with an altered risk of breast cancer, but this was based on assumptions about those at risk of ovarian failure rather than confirmed early menopause [158]. Cooke et al found that breast cancer risk increased significantly with proximity of supradiaphragmatic radiotherapy to menarche, particularly in those with late menarche [208]. Krul et al found that the 35-year cumulative incidence of breast cancer increased by 6.4% per additional year of ovarian function [157]. In their cohort, hormone replacement therapy was not associated with breast cancer incidence, but women who used oral contraceptives (OCPs) for more than 15 years had significantly higher rates [157]. Two other studies found that OCPs did not have an effect of breast cancer HR or OR [144,197]. The reported effect of pregnancy on risk of breast cancer varied between studies. Cooke et al found reduced ORs in those who had experienced a full-term pregnancy before receiving radiotherapy, and increased ORs in

those who became pregnant following radiotherapy, but neither of these trends were statistically significant [208]. De Bruin et al found that nulliparity did not have an effect on the HR of breast cancer [144]. Hill et al found an elevated OR in those who became pregnant within five years of radiotherapy, compared to those with a longer interval between radiotherapy and pregnancy [197].

Other factors

Two studies reported that women with a family history of breast cancer had a higher SIR or OR of breast cancer than those without a family history [118,197]. Hill et al found that women with a family history had a lower increase in risk per Gy received by the breast [197], suggesting their family history had a greater impact on their subsequent risk of breast cancer than radiotherapy. Two studies found that BMI had no effect on the HR or OR of breast cancer [144,197], and de Bruin et al found that smoking also had no effect on the HR [144].

3.3.3.3.4 Lung cancer

Sex

Six studies, including one meta-analysis, found no effect of sex on the RR or SIR of lung cancer [10,79,84,88,163,165], whereas four found higher RRs or SIRs in women [91,102,112,126], and one found a higher RR in men [164]. AERs were higher for men compared to women in all [79,84,88,126,163] but one cohort [91], due to higher background rates of lung cancer in men. Two studies found that the RR or SIR of mesothelioma was higher among women than men [102,131].

Age at treatment

Most studies reported that RRs or SIRs of lung cancer decreased with increasing age at treatment [75,84,88,91,112,113,118,126,165,166]. In contrast, one study found age at

treatment had no effect on RR of lung cancer [164]. Another study found no increase in SIRs for patients treated over the age of 60 [113]. AERs increased with age in line with general population rates of lung cancer [75,84,91,113,118,163]. De Bruin et al found a reduction in RR and an increase in AER of mesothelioma with increasing age at treatment [131].

Smoking

Most studies found the majority of patients who developed lung cancer were smokers [78,79,85,88,92,98,103,120,141,161–166,199]. Four studies found increased HRs or RRs of lung cancer in smokers [88,161,162,164]. Two cohorts found increased RRs with increasing amount of smoking after diagnosis of HL (measured in pack-years) [161,166]. Gilbert et al found that the ERR per pack-year was significantly higher for current compared to former smokers [199]. Two studies reported a reduction in RR with increasing time since a patient stopped smoking [161,166]. In two cohorts, there was an interaction between smoking and radiotherapy dose, so that the RR of lung cancer was highest in smokers who received over 5 Gy to the lung [161,164].

Other factors

Sud et al reported a significantly increased SIR in those with a family history of lung cancer [118]. De Bruin et al found that 54% of their patients who had developed mesothelioma had been exposed to asbestos, which is higher than the general population rate and may suggest an interaction between asbestos and radiation in the pathogenesis of mesothelioma [131].

3.3.3.3.5 Gastrointestinal malignancies

Sex

Where reported, the SIRs, RRs and AERs of gastrointestinal malignancies overall did not vary significantly by sex [88,126,133,170]. In two cohorts, the RR or SIR of CRC was slightly higher in men than women [102,135], and a Dutch study found a significantly higher SIR of gastric cancer in women [134]. In a screening study, the OR of advanced colorectal neoplasia was not significantly different between the sexes [172].

Age at treatment

SIRs and RRs of gastrointestinal malignancies were highest in those treated at a young age [75,84,88,118,126,133], and AERs increased with age [75,84,88,118,126,133], due to the greater prevalence of gastrointestinal malignancies with age. Swerdlow et al found the SIRs of gastric and colon cancer were highest in those treated when under the age of 25 [84]. In two cohorts, the SIRs of gastric cancer were only increased in those aged under 40 when treated [113,134]. In van Eggermond et al's cohort the SIRs for colon cancer decreased with older age at treatment, but remained stable for rectal cancer [135]. Dores et al found that the OR of pancreatic cancer did not vary by age at treatment [170].

Other factors

Birdwell et al reported the prevalence of other risk factors in those who developed gastrointestinal cancer. Forty percent reported more than 30 pack-year smoking histories, 20% consumed "excessive amounts" of alcohol, 12% used aspirin "frequently" and had had peptic ulcers, 16% had a history of hepatitis, and 8% each had a history of pancreatitis, obesity, a family history of gastrointestinal cancer or occupational exposure to carcinogens [133]. Sud et al found a significantly increased SIR of CRC in those with a family history of CRC [118].

3.3.3.3.6 Cutaneous malignancies

Sex

RRs or SIRs of skin cancer overall [175], and of NMSC [102] and BCC [173] separately, were not significantly different between sexes. One study showed an increased RR of melanoma in men [126], whereas another showed no difference between sexes [102].

Age at treatment

In Herr et al's cohort, SIRs of cutaneous malignancies were fairly consistent among age categories [175]. In studies looking at specific skin cancers, the SIR of SCC [118] was not affected by age at treatment, whereas the SIR of BCC decreased with older age at treatment [173]. In one cohort, the SIR of melanoma was highest in those treated over the age of 55 [84], whereas in another the SIR was only raised in those treated when aged below 40 [113].

3.3.3.3.7 Other solid tumours

Sex

Two studies found higher RRs of thyroid cancer in women [126,210], whereas another found a higher RR in men [102]. In an international cohort, the RR of salivary gland tumours was substantially higher in women, with no difference in the RR of bone tumours between sexes [102]. Dores et al found no significant differences in RR of other solid tumours between sexes [126].

Age at treatment

The SIR or RR of thyroid [84,126,127,210], bone and soft-tissue [84,126], cervical and buccal [126] cancers decreased with increasing age at treatment. In an American cohort there were no cases of thyroid cancer in people who had radiotherapy when aged over 35 [210].

3.3.3.3.8 Haematological malignancies

Sex

There was mixed data regarding the risk of haematological malignancies between sexes. In a British cohort, the SIR of leukaemia was higher in women [112], whereas in another cohort the RR was highest in men [204], and in six others there was no difference in SIR or RR between sexes [126,177,182,184,203,211]. In two cohorts, the RR [102] and SIR [112] were higher in men.

Age at treatment

Six studies found the SIR [84,97,113,118] or RR [1,126] of leukaemia decreased with increasing age at treatment, whereas in five other cohorts there was no relationship between age at treatment and SIR or RR of leukaemia [75,112,120,182,204]. In one large international cohort, RR increased with age [102], and in a Norwegian cohort the SIR was not increased in those treated over the age of 60 [113]. AERs were highest in those treated at older ages [1,84,106,113,118,120,126,202]. The data on the risk of NHL based on age at treatment was more varied. In three cohorts, there was no significant variation in SIR or RR by age at treatment [112,113,126] , whereas in three others RR [56,102] or SIR [97] increased with older age at treatment. In one cohort, the SIR increased with age in men, but remained stable in women [118].

3.3.3.4 Quantification of dose-response relationships

3.3.3.4.1 Breast cancer

Five studies reported a dose-response relationship for the risk of breast cancer [146,148,156,157,197] (Table 3.5). Van Leeuwen et al found a linear relationship between radiation dose received by the breast and the subsequent risk of breast cancer, with an

ERR of 0.03 per Gy (95% CI 0.002-0.06) [156]. The effect of radiation was modified by chemotherapy. In patients treated with radiotherapy alone, the risk of breast cancer increased significantly with increasing radiation dose, whereas this trend was not seen in those treated with chemotherapy and radiotherapy [156]. The ERR of breast cancer was 0.06 per Gy (95% CI 0.01-0.13) in those treated with radiotherapy alone [156]. Krul et al found a linear relationship, with a crude excess odds ratio (EOR) of 7.9% per Gy (95% CI 3.1-19.8) [157]. When adjusted for duration of post-radiotherapy ovarian function, the EOR per Gy was 6.1% (95% 2.1-15.4) [157]. The relationship was not modified by parity, age at first birth, or BMI [157]. Using dose to the location of the subsequent tumour, Travis et al estimated an ERR of 0.15 per Gy (95% CI 0.04-0.73) for those who received chest radiotherapy only [148]. This relationship was attenuated by treatment with alkylating agents, or radiation doses of 5 Gy or more delivered to the ovaries, and in these women the ERR per Gy was 0.049 (95% CI 0.004-0.34) [148]. Hill et al found that the dose-response relationship differed in women with a family history of breast or ovarian cancer [197]. Those who had no family history had an EOR per Gy of 1.04 (95% CI 1.00-1.07); those with a first- or second-degree relative with breast or ovarian cancer had a lower EOR per Gy [197]. When family history was limited to first-degree relatives, the EOR per Gy above 5 Gy decreased in those with a family history, and increased in those without a family history, suggesting that the relative risk associated with radiation exposure was not higher among women with a family history, and might be lower [197]. This is in contrast to common perception among clinicians, who tend to think that women with a family history of breast cancer have a higher risk from radiotherapy (and use this as a reason to avoid radiotherapy in this group). Women who had had a live birth had a higher EOR per Gy that those who had not [197]. One other study was unable to derive an overall dose-response relationship, due to a narrow distribution of doses, but found that the ERR per Gy decreased with age, but rose with longer follow-up within each age group [146].

Table 3.5: Dose-response relationships for the risk of breast cancer following radiotherapy

Reference	Study population	Dose-response model
Van Leeuwen 2003 [156]	Nested case-control study in Dutch cohort of ≥5 y HL survivors, treated aged <41 y 1965-1988	Patients receiving RT alone **ERR / Gy 0.06** (95% CI 0.01-0.13) Whole cohort **ERR / Gy 0.03** (95% CI 0.002-0.06) (dose to the breast)
Krul 2017 [157]	Retrospective cohort of ≥5 y survivors, treated aged <41 y in the Netherlands 1965-2000	**EOR / Gy 7.9%** (95% CI 3.1-19.8%) Adjusted for duration of post-RT ovarian function **EOR / Gy 6.1%** (95% CI 2.1-15.4%) (dose to breast tumour location)
Travis 2003 [148]	Nested case-control study in international cohort of ≥1 y survivors, treated aged ≤30 y 1965-1994	Patients receiving chest RT alone **ERR / Gy 0.15** (95% CI 0.04-0.73) Alkylating agents & ≥5 Gy to ovaries **ERR / Gy 0.049** (95% CI 0.004-0.34) (dose to breast tumour location)
Hill 2005 [197]	Nested case-control study in international cohort of ≥1 y survivors, treated aged ≤30 y 1965-1994 (same cohort as [148])	**EOR / Gy 1.04** (95% CI 1.0-1.07) (dose to breast tumour location) **Interactions** 1st or 2nd degree relative with breast or ovarian cancer **interaction OR per Gy 0.93** (95% CI 0.89-0.99) Live birth **interaction OR 1.06** (95% CI 1.01-1.12) **ERR / Gy above 5 Gy** 1st degree relative with breast or ovarian cancer **-0.16** (95% CI -0.40-+0.23) No family history **0.17** (95% CI 0.05-0.51)
Hancock 1993 [146]	Retrospective cohort treated 1961-1989 in the USA	**ERR / Gy** <15 y since RT ≥15 y since RT Age <20 y **0.67** Age <20 y **0.87** 20-29 y **0.16** 20-29 y **0.38** ≥30 y **-0.018** ≥30 y **0.08** (prescribed dose to mantle field) (95% CIs not given)

Abbreviations - y: years; HL: Hodgkin lymphoma; RT: radiotherapy; ERR: excess relative risk; Gy: gray; CI: confidence interval; EOR: excess odds ratio

3.3.3.4.2 Lung cancer

One study derived a dose-response relationship for the risk of lung cancer [199] (Table 3.6). Using the dose to the location of the subsequent lung tumour, they found a linear relationship, with an ERR of 0.12 per Gy (95% CI 0.04-0.35) [199]. The ERR per Gy for males was about four times that of females, although the difference was not statistically significant [199]. There was little evidence of modification of the ERR per Gy by follow-up duration (after a five-year minimum latent period), age at radiotherapy, receipt of alkylating agents, attained age, or subsequent histological subtype of lung cancer [199]. Smoking had a multiplicative effect on risk [199]. Analyses using dose to the affected lobe did not fit as well as using doses to the specific tumour location (ERR per Gy 0.19; 95% CI 0.05-0.60) [199].

Table 3.6: Dose-response relationships for the risk of lung cancer following radiotherapy

Reference	Study population	Dose-response model
Gilbert 2003 [199]	Nested case-control in international cohort of ≥1-year survivors, treated 1965-1994	**ERR / Gy 0.12** (95% CI 0.04-0.35) (dose to specific tumour site) **ERR / Gy 0.19** (95% CI 0.05-0.60) (dose to affected lobe)
Interactions: **ERR / Gy** (95% CI)		
Smoking		Number of cycles of alkylating agents
Never / unknown **0.042** (-0.003-0.29)		0 **0.15** (0.056-0.39)
Current, < 32 py **0.095** (0.019-0.33)		1-6 **0.15** (0.001-0.57)
Current, ≥ 32 py **0.35** (0.0095-1.19)		> 6 **0.17** (-0.09-1.05)
Former **0.021** (-0.017-0.27)		
Cigar / pipe only **0.42** (0.018-11.0)		Time of treatment with alkylating agents
		No AA **0.15** (0.057-0.040)
Sex		< 1 y from diagnosis **0.10** (-0.04-0.51)
Male **0.18** (0.063-0.52)		≥ 1 y from diagnosis **0.24** (0.005-0.98)
Female **0.044** (-0.009-0.53)		
		Time since radiotherapy
Age at HL diagnosis		1-5 y **0.006** (-0.019-0.11)
< 37 y **0.33** (0.02->100)		5-10 y **0.18** (0.036-0.81)
37-47.9 y **0.051** (-0.007-0.48)		10-15 y **0.15** (0.029-0.69)
48-55.9 y **0.088** (0.005-0.42)		15-20 y **0.13** (0.006-1.09)
≥ 56 y **0.36** (0.073-1.93)		≥ 20 y **0.07** (<0-0.85)
Age at lung cancer diagnosis		Histopathological type of lung cancer
< 51 y **1.15** (0.030->100)		Squamous cell **0.13** (0.027-0.57)
51-58.9 y **0.062** (0.000-0.32)		Small cell **0.12** (-0.001-1.60)
59-66.9 y **0.13** (0.011-1.05)		Adenocarcinoma **0.47** (0.054->100)
≥ 67 y **0.61** (0.086-6.4)		Large cell **2.00** (0.061->100)
		Other **0.0032** (-0.022-0.41)
(dose to the site of subsequent lung cancer)		

Abbreviations - y: years; HL: Hodgkin lymphoma; Gy: gray; CI: confidence interval; py: pack-years; AA: alkylating agent

3.3.3.4.3 Gastrointestinal malignancies

Three studies derived dose-response relationships for the risk of gastric cancer [134,169,200], one for oesophageal cancer [168] and one for pancreatic cancer [170] (Table 3.7). Using dose to the subsequent tumour location, Morton et al found an EOR for oesophageal cancer of 0.38 per Gy (95% CI 0.04-8.17) [168]. Using the dose to the

subsequent tumour location, Gilbert et al estimated an EOR for gastric cancer of 0.049 per Gy (95% CI 0.007-0.16) [200]. Also using dose to tumour location, Morton et al found a higher EOR of 0.09 per Gy (95% CI 0.04-0.21) [169]. Another Dutch study found an EOR of 0.84 per Gy (95% CI 0.12-15.6), using mean stomach dose [134]. Using dose to subsequent tumour location, Dores et al found an EOR for pancreatic cancer of 0.098 per Gy (95% CI 0.015-0.42) [170].

Table 3.7: Dose-response relationships for the risk of gastrointestinal malignancies following radiotherapy

Reference	Study population	Dose-response model
Oesophageal cancer		
Morton 2014 [168]	Nested case-control study in international cohort of ≥5-year HL survivors, treated 1943-1992	**EOR / Gy 0.38** (95% CI 0.04-8.17) (dose to oesophageal tumour location)
Gastric cancer		
Gilbert 2017 [200]	Nested case-control study in international cohort of ≥ 5-year HL, testicular and cervical cancer survivors	**EOR / Gy 0.049** (95% CI 0.007-0.16) (dose to stomach tumour location) Interaction with sex, **EOR / Gy** (95% CI) Men **0.078** (0.011-0.29) Women **0.032** (-0.010-0.14)
Morton 2013 [169]	Nested case-control in international cohort of ≥ 5-year HL survivors, treated 1943-2003	**EOR / Gy 0.09** (95% CI 0.04-0.21) (dose to stomach tumour location)
van den Belt-Dusebout 2009 [134]	Nested case-control study in a cohort of 5142 5-year survivors of HL or testicular cancer treated in the Netherlands 1965-1995	**ERR / Gy 0.84** (95% CI 0.12-15.6) (mean stomach dose)
Pancreatic cancer		
Dores, 2014 [170]	Nested case-control study in international cohort of ≥ 5-year HL survivors, treated 1953-2003	**EOR / Gy 0.098** (95% CI 0.015-0.42) (dose to pancreatic tumour location)

Abbreviations - y: years; HL: Hodgkin lymphoma; EOR: excess odds ratio; Gy: gray; CI: confidence interval

3.3.2.5 Summary of second malignancy risk data

Figure 3.4 summarises the second malignancies where there is evidence of an increased risk from radiotherapy, and the factors that modify this risk.

Second malignancies following radiotherapy for Hodgkin lymphoma			
Conditions with evidence for an increased risk from radiotherapy			
Breast cancer	Evidence level A*		
Lung cancer	Evidence level A*		
Gastrointestinal malignancies	Evidence level A*		
Cutaneous malignancies	Evidence level B†		
Thyroid cancer	Evidence level C†		
Urogenital cancers	Evidence level C‡		
Head and neck cancers	Evidence level C‡		
Bone and soft-tissue sarcomas	Evidence level C‡		
Haematological malignancies	Evidence level B†		
Factors which influence the risk of second malignancies following radiotherapy			
Exposure of organs-at-risk to irradiation		Other risk factors	
Breast cancer	Level A*	Sex	
Lung cancer	Level A*	Lung cancer	Level C‡
Gastrointestinal malignancies	Level A*	Gastrointestinal malignancies	Level C‡
Cutaneous malignancies	Level C‡	Age	
		Breast cancer	Level A*
		Lung cancer	Level B†
		Gastrointestinal malignancies	Level A*
		Cutaneous malignancies	Level C‡
		Hormonal factors	
		Breast cancer	Level B†
		Family history	
		Breast cancer	Level C‡
		Lung cancer	Level C‡
		Gastrointestinal malignancies	Level C‡
		Smoking	
		Lung cancer	Level A*

*level A: high level of evidence; from Mulder et al 2013 [2]
†level B: moderate to low level of evidence; from Mulder et al 2013 [2]
‡level C: very low level of evidence; from Mulder et al 2013 [2]

Figure 3.4: Summary of the quality of the evidence for an increased risk of second malignancies following radiotherapy for HL

3.3.4 Other conditions

Thirty-one studies reported the risk of conditions other than CVD and second malignancies following radiotherapy for HL. These studies reported increased risks of thyroid disease (predominantly hypothyroidism), lung disease, premature menopause, gastrointestinal disease and infections, and impacts on quality of life. Their results are summarised in Tables B4.1-4.3 of Appendix B4.

3.3.4.1 Thyroid disease

Cumulative incidences ranged from 1.5-56% for hypothyroidism and 2-69% for asymptomatic abnormal thyroid function tests [5,74,212–217]. One study reported an increased RR of hyperthyroidism [218]. Radiation-related hypothyroidism was reported earlier than other late-effects, with median latent intervals of 13-74 months [5,49,212,218]. One study reported incidence reduced after three years [218] whereas another reported rates increased beyond six years [215]. ORs and RRs of hypothyroidism were highest for patients who received higher radiation doses to the thyroid [212,218], and in those treated with intensity modulated radiotherapy (IMRT) compared to 3D conformal radiotherapy (3D-CRT) [212]. Five studies did not show any association between hypothyroidism and age at time of radiotherapy [213,214,216,217,219], whereas one other found RRs decreased with increasing age at treatment [218]. Two studies found elevated RRs in women compared to men [215,218], whereas four others found no difference between sexes [214,216,217,219]. Hancock et al found the RR of hypothyroidism increased by 1.02 per Gy (CI not given) received by the thyroid [218], and three others modelled the risk using dosimetric measures [212,213,218]. In Pinnix's sub-cohort treated with IMRT, the percentage of the thyroid receiving over 25 Gy and the absolute volume spared from 25 Gy were the strongest predictors of hypothyroidism [212]. In Cella's cohort, treated with 3D-CRT, the percentage of the thyroid receiving over 30 Gy was the only predictor [213].

3.3.4.2 Lung disease

Studies reported cumulative incidences of pulmonary fibrosis of 9-13% [74,220]. The latent interval was short (10-17 months) [5,220], so although technically a late-effect (defined as occurring more than three months after radiotherapy), lung disease is perhaps better classified as a subacute effect. One study reported an increased RR of abnormal lung function [221], and three increased RRs, HRs and SMRs of lung disease [12,23,26]. The majority of patients screened had imaging abnormalities [222,223] and reduced lung function during the first year after mediastinal radiotherapy, which recovered beyond three years [223,224]. In Cella et al's cohort, the volume of lung receiving 30 Gy was a predictor of subsequent development of pulmonary fibrosis [220]. In a Turkish cohort, 31% of those developing late pulmonary toxicity were current or previous smokers [74], and in a Danish cohort a higher proportion of smokers treated with mantle radiotherapy had impaired lung function compared to non-smokers exposed to the same radiotherapy [225] .

3.3.4.3 Other conditions

Fertility

Five studies reported the risk of premature menopause following radiotherapy. Two found no increase in incidence in women treated with subtotal nodal irradiation compared to the general population [226,227]. Two studies found an increased incidence and HR of premature menopause in women whose ovaries were included in the radiation field [226,228]. Rosenbrock et al found that involved-site radiotherapy (ISRT) resulted in lower ovarian (and uterine) doses than IFRT, resulting in a longer interval to menopause [229]. Women who were younger at the time of radiotherapy had a longer absolute time gain if treated with ISRT rather than IFRT, with no difference in time to menopause between the two techniques in women treated over the age of 44 [229]. Two other studies found that a greater proportion of women treated at a younger age had regular menses following radiotherapy, compared to those treated when older [228,230]. One study reported a low

rate of spontaneous abortions following radiotherapy, and no difference in foetal abnormalities compared to sibling controls [231].

Gastrointestinal disease

Three studies found increased RRs and SMRs of gastrointestinal disease [8,12,23]. One reported an increased RR of gastric ulcers, with a relatively short median time to development (14 months) [232]. There was no association between radiotherapy dose and the RR of gastric ulcers, but a greater proportion of those treated with large fraction sizes (3.3 Gy) developed ulcers compared to those treated with 2-2.5 Gy per fraction [232].

Infections

Four studies found increased RRs, HRs and SMRs of infection following radiotherapy for HL [8,12,22,23]. In one, mortality from infectious diseases was significantly increased after splenic irradiation [12]. One study reported splenic atrophy following splenic irradiation for HL, which they suggested may be a risk factor for subsequent infection [233].

Diabetes mellitus

One study reported the risk of diabetes following radiotherapy for HL, with a cumulative incidence of 8.3% after 30 years [234]. Patients who received para-aortic radiotherapy had a significantly higher risk than those who did not receive radiotherapy (HR 1.87; 95% CI 1.12-3.13), and those who had both their para-aortic nodes and spleen irradiated had an even higher risk (HR 2.28; 95% CI 1.53-3.38) [234]. Patients treated when aged over 25 had higher SIRs than those treated when younger (SIR 1.56; 95% CI 1.07-2.20) [234]. Mean pancreatic tail doses of over 36 Gy were associated with significantly increased risk of diabetes (HR 2.43; 95% CI 1.22-4.85), and the risk increased with increasing mean dose to the pancreatic tail (HR 1.017 per Gy; P <.001)) [234].

Quality of life

Two studies found that people treated with radiotherapy alone had higher quality of life (QoL) scores six months [235] and nine years [236] after treatment compared to those treated with combined-modality therapy, whereas another found no difference between treatment modalities [237,238] and one found higher rates of fatigue in those treated with radiotherapy compared to chemotherapy [239]. One study found men had worse fatigue and lower QoL scores compared to women [237]. QoL returned to HL patient's individual baseline by two years after treatment [236], but scores remained lower than the general population [57,235].

Other conditions

There were single studies that reported increased rates of myopathy [240], renal tubular damage [241], dental caries [242] and reductions in salivary flow [243] following radiotherapy for HL. Two studies screened HL survivors for parathyroid disease, and failed to show any increased risk, even when the neck had been irradiated [244,245].

3.4 Discussion

This review provides a comprehensive summary of the range of late-effects following radiotherapy for HL, collates the dose-response relationships that relate the risk of specific late-effects to the radiation dose received by organs-at-risk (OARs), highlights the conditions where dose-response relationships are still needed, and identifies the factors that may modifiy the dose-response relationship. There is high-quality evidence that radiotherapy used to treat HL can increase the risk of subsequent IHD, HF, VHD, breast cancer, lung cancer and gastrointestinal malignancies, and moderate-quality evidence to suggest an increased risk of pericardial disease, cerebrovascular disease, cutaneous

malignancies, thyroid cancer, and hypothyroidism. There is lower-quality evidence suggesting there may be an increased risk of cardiac conduction abnormalities, urogenital cancers, head and neck cancers, bone and soft-tissue sarcomas, and diabetes. The increased risk of leukaemia following treatment for HL seems more linked to chemotherapy, and the raised risk of NHL is difficult to interpret, but may be due to shared aetiological factors with HL. The magnitudes of the risk estimates vary substantially depending on the characteristics of the cohort (such as the age and sex profile), the underlying background risk, the combination of treatments used, the duration and completeness of follow-up, and the definitions of endpoints. For many late-effects, this heterogeneity hinders any meaningful meta-analysis, and the meta-analyses that have been published are generally restricted to specific subgroups of patients.

Of all CVDs, IHD contributes the most to mortality. Radiotherapy fields, techniques and doses that deliver a higher dose to the heart or its substructures increase the risk of IHD, HF and VHD. The relative risks of IHD, HF, and cerebrovascular disease appear to be higher in those treated at younger ages, with conflicting data on whether relative risks differ between sexes. There is minimal data quantifying how traditional cardiovascular risk factors affect the magnitude of CVD risk, but there is some data to suggest that both hypertension and hypercholesterolaemia increase the risk of IHD and VHD. The majority of data comes from retrospective cohorts, however, and these risks factors were measured at different time points in different studies (for example at HL diagnosis, or at the end of study follow-up). It is therefore possible that studies are inadequately designed to detect an effect of traditional risk factors, rather than there being an absence of effect. There is a lack of data to suggest the effect of reducing traditional risk factors, and maintaining a healthly lifestyle, on the subsequent risk of cardiovascular disease after radiotherapy for HL.

Of all second malignancies, lung and gastrointestinal cancers contribute the most to mortality. Comparatively more research has been done into the risk of second breast

cancers however, which contribute substantially less to the excess mortality observed in HL survivors. The relative risk of breast, lung and gastrointestinal cancers are highest in those treated at younger ages, with some data to suggest a difference in risk of lung and gastrointestinal cancers between the sexes (although this may be confounded by different exposure to other risk factors, such as smoking). Hormonal factors appear to affect the magnitude of risk of breast cancer following radiotherapy, with a higher risk seen in those with a longer duration of ovarian function. Smoking modifies the dose-response relationship for the risk of lung cancer, and has a multiplicative effect on risk. Only a few studies have attempted to quantify the effect of a family history of cancer on the risk of second malignancies from radiotherapy. However, there are some data to suggest that women with a family history of breast cancer have a lower increase in risk per Gy compared to those without a family history. No studies have quantified the impact of ethnicity on the magnitude of risk of either second malignancies or CVD.

Dose-response relationships exist to quantify how the risk of IHD, HF, VHD, and cancers of the breast, lung, oesophagus, stomach and pancreas vary with dose received by OARs during radiotherapy. These are the most relevant data for estimating the risks for patients treated in the modern era, i.e. those treated with highly conformal radiotherapy to smaller volumes and lower doses than previously. The ERR per Gy for IHD and HF are 7.4% and 9.0% respectively, using MHD for IHD and mean left-ventricular dose for HF. The risk of VHD is best estimated by a non-linear relationship, using dose to the affected valve. There are four estimates of the dose-response relationship for breast cancer. The ERR per Gy using whole breast dose is 6% per Gy, and estimates using dose to breast tumour location range from 4-15%. The dose-response relationship appears to be modified by chemotherapy, ovarian radiotherapy and birth history (probably due to hormonal influence), and differs in those with and without a family history of breast cancer. The ERR per Gy for lung cancer is 12% per Gy, using dose to subsequent tumour location. For gastrointestinal malignancies, the EOR per Gy for oesophageal cancer is 38% (using dose to subsequent

tumour location), 5-9% for gastric cancer using dose to subsequent tumour location, and 84% (ERR) using mean stomach dose, and 9.8% for pancreatic cancer (using dose to subsequent tumour location).

3.4.1 Strengths and limitations

This is a systematic and comprehensive review of the literature quantifying the magnitude of risk associated with radiotherapy used to treat HL. To the best of my knowledge, no previous studies have attempted such a broad synthesis of the data. This is also the first time all the radiation dose-response relationships describing risks following radiotherapy for HL have been presented together.

The broadness of the review is also one of its limitations. In attempting to collate risk estimates I will have lost some of the nuances of the data presented in each individual study. By including studies published since database conception many of the risk estimates presented here originate from cohorts of patients treated with historical treatments, which are expected to carry a higher risk of late-effects than modern treatment approaches. Due to the latency of late-effects, many of the studies used historical chemotherapy regimens, and data quantifying the risks from chemotherapy was therefore not extracted. Considering how radiotherapy and modern chemotherapeutic agents interact to affect risk will be important when estimating the risks for an individual undergoing treatment for HL in the modern era. The data is extremely heterogenous, due to different patient and treatment characteristics, as well as statistical methods used to derive risk estimates. This heterogeneity means that meta-analysis would only be possible if it were restricted to a specific subgroup of patients with a specific outcome. Such an analysis would only quantify specific risks to a specific group, limiting its utility in clinical practice.

3.4.2 Data uses

The aim of this review was to address the problem that patients and clinicians identified in the study in Chapter 2: i.e. the lack of data to estimate the risks of radiotherapy for an individual patient. I have systematically identified the range of late-effects that occur after radiotherapy for HL, and have extracted information on the factors that affect the magnitude of risk. However, this review has not yet been able to provide accessible information that is useable in clinical practice to estimate the magnitude of risk for an individual. The breadth of information and the differences in risk estimates depending on cohort characteristics mean that it is not possible to present summary statistics for the risk of each late-effect. But, with additional work, there are ways that this data could be used to provide information to patients and clinicians about the magnitude of risk from modern radiotherapy. For example, it could be used as the basis of fact sheets to better inform patients of the risks of radiotherapy, similar to those recently developed by the Children's Cancer and Leukaemia Group [246]. I used the range of late-effects identified in this review to write the Royal College of Radiologists lymphoma radiotherapy consent form, which standardises the information given to patients about the toxicities of modern radiotherapy [247].

The dose-response relationship data collated in this review could be used to build models to estimate risk of late-effects for individual patients, based on the dose that their OARs would receive from radiotherapy. There is a Danish team who are incorporating dose-response data into radiotherapy treatment planning systems to optimise radiotherapy plans based on risk estimates of late-effects rather than on dose metrics [248]. Our research group uses dose-response data to compare the risk profiles of different treatment strategies for patients with HL [249–252], and this review provides additional data to refine the models used for this work. We also plan to use the dose-response data to build models that could be used as the basis of a decision aid to inform treatment discussions when a patient first presents with HL. The data could also be used to inform targeted screening programmes

for those treated with radiotherapy in the past, similar to those being implemented in the Netherlands [253].

These data, as well as demonstrating what is known regarding late-effects of radiotherapy for HL, also highlight the areas where less is known and further research studies could be targeted to produce the knowledge required to improve data for the uses summarised above.

3.4.3 Future work

The latency of the late-effects I have described shows that we cannot rely on data from randomised trials alone to show differences in risk from various treatment approaches. Instead, research should focus on developing dose-response relationships that can be used across multiple treatment strategies to estimate risks for patients treated in the modern era. Dose-response relationships are needed for the risk of stroke and TIA, pericardial disease and conduction defects after radiotherapy for HL, and also for the risk of cancers of the skin and thyroid. More work is needed to determine if there is a relationship between radiation dose and the risk of cancers of the pleura, liver, small intestine, bone and soft tissues, genitourinary system, and head and neck. Data is also needed on the risk of haematological malignancies, isolating the effect of radiotherapy from that seen with chemotherapeutic agents. The majority of the data I have presented relates to the risk of supradiaphragmatic radiotherapy, with less data available discussing the risks of infradiaphragmatic radiation, which should be addressed by future studies. Prior to my research, there was no dose-response relationship for the risk of CRC, but we have now derived this and it is presented in Chapter 4. New dose-response relationships should use dose metrics that are known at the time of a patient's diagnosis. The dose-response relationships for the risk of lung, oesophageal and pancreatic cancer describe risk based on the radiation dose to the site of

development of a second cancer, which cannot be used to estimate the magnitude of risk at the time of a patient's diagnosis. Work is needed to estimate the risk of these cancers based on radiation dose received by the whole organ. Future studies should also investigate whether organ substructures, particularly in the heart, are more sensitive to radiation, and therefore are more important to avoid during radiotherapy. For example, models using dose to the left ventricle and heart valve fitted better than MHD in dose-response relationships for HF and VHD respectively.

Researchers should also focus on improving the quality of evidence quantifying how factors such as sex, ethnicity, family history, smoking etc., affect the risk seen following radiotherapy. Such data is difficult to obtain from retrospective sources, so we must consider how to collect such information from patients treated today, for example by setting up prospective cohorts linked to electronic health records.

The diversity of endpoint definitions reported by studies limits comparison between them, and future studies should consider using a set of agreed outcomes (a core outcome set) to reduce heterogeneity. Although typically used in randomised trials [254,255], adapting this concept to have a set of agreed definitions for radiation late-effects studies would make it more feasible to conduct meta-analyses. Agreeing on a set of definitions would be challenging, as late-effects research spans many disciplines, however having a core outcome set could increase the quality and useability of future research data.

3.5 Conclusions

I have systematically reviewed the literature and collated data quantifying the risk of late-effects from radiotherapy used to treat people with HL, and have shown the range of late-

effects which can be experienced by HL survivors. I have detailed the cardiovascular diseases and second malignancies which are seen after radiotherapy, and have shown that some conditions that are given most prominence (e.g. breast cancer) are actually less of a risk than others which are not as widely recognised (e.g. lung cancer, ischaemic heart disease). Due to the heterogeneity of the studies and their reported outcomes, the risk estimates are not useable in their current form to estimate the risk for individual patients treated with modern radiotherapy. However, this study helps identify the gaps that need to be addressed to allow this. I have presented radiation dose-response relationships that can be used to estimate risks based on radiation dose to OARs, and have identified the factors that might modify these relationships. Future studies should focus on producing dose-response relationships, and modelling the effect of individual patient factors (such as age, sex, ethnicity and family history) on these relationships. Work is also needed to collate such relationships into a form that is useable in the clinic, for example as a decision aid.

3.6 References

[1] Aleman BMP, van den Belt-Dusebout AW, Klokman WJ, Van't Veer MB, Bartelink H, van Leeuwen FE. Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol 2003;21:3431–9. doi:10.1200/JCO.2003.07.131.

[2] Mulder RL, Kremer LCM, Hudson MM, Bhatia S, Landier W, Levitt G, et al. Recommendations for breast cancer surveillance for female survivors of childhood, adolescent, and young adult cancer given chest radiation: A report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol 2013;14:e621–9. doi:10.1016/S1470-2045(13)70303-6.

[3] Gustavsson A, Osterman B, Cavallin-ståhl E. A systematic overview of radiation therapy effects in Hodgkin's lymphoma. Acta Oncol (Madr) 2003;42:589–604. doi:10.1080/02841860310013346.

[4] Hoppe RT. Hodgkin's disease: Complications of therapy and excess mortality. Ann Oncol 1997;8:S115–8. doi:10.1093/annonc/8.suppl_1.S115.

[5] Brusamolino E, Baio A, Orlandi E, Arcaini L, Passamonti F, Griva V, et al. Long-term events in adult patients with clinical stage IA-IIA nonbulky Hodgkin's lymphoma treated with four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine and adjuvant radiotherapy: A single-institution 15-year follow-up. Clin Cancer Res 2006;12:6487–93. doi:10.1158/1078-0432.CCR-06-1420.

[6] Nickson JJ, Fuller LM, Hutchison GB, Kaplan HS, Karnofsky D, Lee BJ, et al. Survival and complications of radiotherapy following involved and extended field therapy of

Hodgkin's disease, stages I and II. A collaborative study. Cancer 1976;38:288–305.
[7] Nickson JJ, Hutchison GB. Extensions of disease, complications of therapy, and deaths in localized Hodgkin's disease; preliminary report of a clinical trial. Am J Roentgenol Radium Ther Nucl Med 1972;114:564–73. doi:10.2214/AJR.114.3.564.
[8] Rugbjerg K, Olsen JH. Radiation therapy for treatment of adolescent and young adult Hodgkin lymphoma and risk for cardiovascular disease and cancer. J Adolesc Young Adult Oncol 2019;8:1–8. doi:10.1089/JAYAO.2018.0060.
[9] Favier O, Heutte N, Stamatoullas-Bastard A, Carde P, Veer MB van't, Aleman BMP, et al. Survival after Hodgkin lymphoma. Cancer 2009;115:1680–91. doi:10.1002/CNCR.24178.
[10] Brierley JD, Rathmell AJ, Gospodarowicz MK, Sutcliffe SB, Munro A, Tsang R, et al. Late effects of treatment for early stage Hodgkin's disease. Br J Cancer 1998;77:1300–10. doi:10.1038/bjc.1998.217.
[11] van Spronsen DJ, Post PN, Crommelin MA, Breed WPM, Coebergh JWW. Modest decline in late mortality following Hodgkin's disease in the southeastern Netherlands since 1972. Ann Hematol 1998;76:205–9. doi:10.1007/s002770050390.
[12] de Vries S, Schaapveld M, Janus CPM, Daniëls LA, Petersen EJ, van der Maazen RWM, et al. Long-term cause-specific mortality in Hodgkin lymphoma patients. J Natl Cancer Inst 2021;113:760–9. doi:10.1093/jnci/djaa194.
[13] Ng AK, Bernardo MP, Weller E, Backstrand KH, Silver B, Marcus KC, et al. Long-term survival and competing causes of death in patients with early-stage Hodgkin's disease treated at age 50 or younger. J Clin Oncol 2002;20:2101–8. doi:10.1200/JCO.2002.08.021.
[14] Kiserud CE, Loge JH, Fosså A, Holte H, Cvancarova M, Fosså SD. Mortality is persistently increased in Hodgkin's lymphoma survivors. Eur J Cancer 2010;46:1632–9. doi:10.1016/j.ejca.2010.02.010.
[15] Galper SL, Yu JB, Mauch PM, Strasser JF, Silver B, LaCasce A, et al. Clinically significant cardiac disease in patients with Hodgkin lymphoma treated with mediastinal irradiation. Blood 2011;117:412–8. doi:10.1182/blood-2010-06-291328.
[16] Andersson A, Näslund U, Tavelin B, Enblad G, Gustavsson A, Malmer B. Long-term risk of cardiovascular disease in Hodgkin lymphoma survivors - Retrospective cohort analyses and a concept for prospective intervention. Int J Cancer 2009;124:1914–7. doi:10.1002/ijc.24147.
[17] Glanzmann C, Kaufmann P, Jenni R, Hess OM, Huguenin P. Cardiac risk after mediastinal irradiation for Hodgkin's disease. Radiother Oncol 1998;46:51–62. doi:10.1016/s0167-8140(97)00125-4.
[18] van Nimwegen FA, Schaapveld M, Janus CPM, Krol ADG, Petersen EJ, Raemaekers JMM, et al. Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. JAMA Intern Med 2015;175:1007–17. doi:10.1001/jamainternmed.2015.1180.
[19] Aleman BMP, van den Belt-Dusebout AW, De Bruin ML, van 't Veer MB, Baaijens MHA, Boer JP de, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood 2007;109:1878–86. doi:10.1182/blood-2006-07-034405.
[20] van Rijswijk RE, Verbeek J, Haanen C, Dekker AW, van Daal WA, van Peperzeel HA. Major complications and causes of death in patients treated for Hodgkin's disease. J Clin Oncol 1987;5:1624–33. doi:10.1200/JCO.1987.5.10.1624.
[21] Hancock SL, Tucker MA, Hoppe RT. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. JAMA J Am Med Assoc 1993;270:1949. doi:10.1001/jama.1993.03510160067031.
[22] Mauch PM, Kalish LA, Marcus KC, Shulman LN, Krill E, Tarbell NJ, et al. Long-term survival in Hodgkin's disease relative impact of mortality, second tumors, infection, and cardiovascular disease. Cancer J Sci Am 1995;1:33–42.
[23] Rugbjerg K, Maraldo M, Aznar MC, Cutter DJ, Darby SC, Specht L, et al. Long-term hospitalisation rates among 5-year survivors of Hodgkin lymphoma in adolescence or young adulthood: A nationwide cohort study. Int J Cancer 2017;140:2232–45.

doi:10.1002/ijc.30655.
[24] Myrehaug S, Pintilie M, Tsang R, Mackenzie R, Crump M, Chen Z, et al. Cardiac morbidity following modern treatment for Hodgkin lymphoma: Supra-additive cardiotoxicity of doxorubicin and radiation therapy. Leuk Lymphoma 2008;49:1486–93. doi:10.1080/10428190802140873.
[25] Myrehaug S, Pintilie M, Yun L, Crump M, Tsang RW, Meyer RM, et al. A population-based study of cardiac morbidity among Hodgkin lymphoma patients with preexisting heart disease. Blood 2010;116:2237–40. doi:10.1182/blood-2010-01-263764.
[26] Lagerlöf I, Fohlin H, Enblad G, Glimelius B, Goldkuhl C, Palma M, et al. Limited, but not eliminated, excess long-term morbidity in stage I-IIA Hodgkin lymphoma treated with doxorubicin, bleomycin, vinblastine, and dacarbazine and limited-field radiotherapy. J Clin Oncol 2022;40:1487–96. doi:10.1200/jco.21.02407.
[27] Lee CKK, Aeppli D, Nierengarten ME. The need for long-term surveillance for patients treated with curative radiotherapy for Hodgkin's disease: University of Minnesota experience. Int J Radiat Oncol 2000;48:169–79. doi:10.1016/S0360-3016(00)00647-7.
[28] Boyne DJ, Mickle AT, Brenner DR, Friedenreich CM, Cheung WY, Tang KL, et al. Long-term risk of cardiovascular mortality in lymphoma survivors: A systematic review and meta-analysis. Cancer Med 2018;7:4801–13. doi:10.1002/cam4.1572.
[29] Andersson A, Enblad G, Erlanson M, Johansson AS, Molin D, Tavelin B, et al. High risk of cardiovascular side effects after treatment of Hodgkin's lymphoma – Is there a need for intervention in long-term survivors? Ups J Med Sci 2021;126:6117. doi:10.48101/ujms.v126.6117.
[30] Stone CR, Mickle AT, Boyne DJ, Mohamed A, Rabi DM, Brenner DR, et al. Treatment for lymphoma and late cardiovascular disease risk: A systematic review and meta-analysis. Heal Sci Reports 2019;2. doi:10.1002/hsr2.135.
[31] Chen MH, Blackington LH, Zhou J, Chu TF, Gauvreau K, Marcus KJ, et al. Blood pressure is associated with occult cardiovascular disease in prospectively studied Hodgkin lymphoma survivors after chest radiation. Leuk Lymphoma 2014;55:2477–83. doi:10.3109/10428194.2013.879716.
[32] Lund MB, Kongerud J, Boe J, Nome O, Abrahamsen AF, Ihlen H, et al. Cardiopulmonary sequelae after treatment for Hodgkin's disease: Increased risk in females? Ann Oncol 1996;7:257–64. doi:10.1093/oxfordjournals.annonc.a010569.
[33] Applefeld MM, Wiernik PH. Cardiac disease after radiation therapy for Hodgkin's disease: Analysis of 48 patients. Am J Cardiol 1983;51:1679–81.
[34] Zinzani PL, Gherlinzoni F, Piovaccari G, Frezza G, Bendandi M, Ferretti RM, et al. Cardiac injury as late toxicity of mediastinal radiation therapy for Hodgkin's disease patients. Haematologica 1996;81:132–7.
[35] Heidenreich PA, Schnittger I, Strauss HW, Vagelos RH, Lee BK, Mariscal CS, et al. Screening for coronary artery disease after mediastinal irradiation for Hodgkin's disease. J Clin Oncol 2007;25:43–9. doi:10.1200/JCO.2006.07.0805.
[36] Vlachaki MT, Ha CS, Hagemeister FB, Fuller LM, Rodriguez MA, Besa PC, et al. Long-term outcome of treatment for Ann Arbor Stage 1 Hodgkin's disease: Patterns of failure, late toxicity and second malignancies. Int J Radiat Oncol 1997;39:609–16. doi:10.1016/S0360-3016(97)00371-4.
[37] Reinders JG, Heijmen BJ, Olofsen-van Acht MJ, van Putten WL, Levendag PC. Ischemic heart disease after mantlefield irradiation for Hodgkin's disease in long-term follow-up. Radiother Oncol 1999;51:35–42. doi:10.1016/s0167-8140(99)00026-2.
[38] Swerdlow AJ, Higgins CD, Smith P, Cunningham D, Hancock BW, Horwich A, et al. Myocardial infarction mortality risk after treatment for Hodgkin disease: A collaborative British cohort study. J Natl Cancer Inst 2007;99:206–14. doi:10.1093/jnci/djk029.
[39] De Bruin ML, Dorresteijn LDA, Van't Veer MB, Krol ADG, Van Der Pal HJ, Kappelle AC, et al. Increased risk of stroke and transient ischemic attack in 5-year survivors

of hodgkin lymphoma. J Natl Cancer Inst 2009;101:928–37. doi:10.1093/jnci/djp147.
[40] Van Leeuwen-Segarceanu EM, Dorresteijn LDA, Vogels OJM, Biesma DH, Bos W-JW, Van Leeuwen-Segarceanu E. Arterial stiffness is increased in Hodgkin lymphoma survivors treated with radiotherapy. Leuk Lymphoma 2013;54:1734–41. doi:10.3109/10428194.2012.748906.
[41] Zelcer S, Chen B, Mangel J, Vujovic O, Thiessen-Philbrook HR, Reider M, et al. Impaired vascular function in asymptomatic young adult survivors of Hodgkin lymphoma following mediastinal radiation. J Cancer Surviv 2010;4:218–24. doi:10.1007/s11764-010-0138-6.
[42] Cosset JM, Henry-Amar M, Pellae-Cosset B, Carde P, Girinski T, Tubiana M, et al. Pericarditis and myocardial infarctions after Hodgkin's disease therapy. Int J Radiat Oncol 1991;21:447–9. doi:10.1016/0360-3016(91)90794-5.
[43] Hull MC, Morris CG, Pepine CJ, Mendenhall NP. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin lymphoma treated with radiation therapy. JAMA 2003;290:2831. doi:10.1001/jama.290.21.2831.
[44] van Nimwegen FA, Schaapveld M, Cutter DJ, Janus CPM, Krol ADG, Hauptmann M, et al. Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. J Clin Oncol 2015;34:235–43. doi:10.1200/jco.2015.63.4444.
[45] Boivin J-F, Hutchison GB, Lubin JH, Mauch P. Coronary artery disease mortality in patients treated for Hodgkin's disease. Cancer 1992;69:1241–7. doi:10.1002/cncr.2820690528.
[46] King V, Constine LS, Clark D, Schwartz RG, Muhs AG, Henzler M, et al. Symptomatic coronary artery disease after mantle irradiation for Hodgkin's disease. Int J Radiat Oncol 1996;36:881–9. doi:10.1016/s0360-3016(96)00295-7.
[47] Hancock SL, Hoppe RT, Horning SJ, Rosenberg SA. Intercurrent death after Hodgkin disease therapy in radiotherapy and adjuvant MOPP trials. Ann Intern Med 1988;109:183–9. doi:10.7326/0003-4819-109-3-183.
[48] Eriksson F, Gagliardi G, Liedberg A, Lax I, Lee C, Levitt S, et al. Long-term cardiac mortality following radiation therapy for Hodgkin's disease: Analysis with the relative seriality model. Radiother Oncol 2000;55:153–62. doi:10.1016/S0167-8140(00)00166-3.
[49] Tarbell NJ, Thompson L, Mauch P. Thoracic irradiation in Hodgkin's disease: Disease control and long-term complications. Int J Radiat Oncol Biol Phys 1990;18:275–81. doi:10.1016/0360-3016(90)90089-3.
[50] Machann W, Beer M, Breunig M, Störk S, Angermann C, Seufert I, et al. Cardiac magnetic resonance imaging findings in 20-year survivors of mediastinal radiotherapy for Hodgkin's disease. Int J Radiat Oncol Biol Phys 2011;79:1117–23. doi:10.1016/j.ijrobp.2009.12.054.
[51] Pohjola-Sintonen S, Tötterman K -J, Salmo M, Siltanen P. Late cardiac effects of mediastinal radiotherapy in patients with Hodgkin's disease. Cancer 1987;60:31–7. doi:10.1002/1097-0142(19870701)60:1<31::AID-CNCR2820600107>3.0.CO;2-D.
[52] Andersen R, Wethal T, Günther A, Fosså A, Edvardsen T, Fosså SD, et al. Relation of coronary artery calcium score to premature coronary artery disease in survivors >15 years of Hodgkin's lymphoma. Am J Cardiol 2010;105:149–52. doi:10.1016/J.AMJCARD.2009.09.005.
[53] Elerding SC, Fernandez RN, Grotta JC, Lindberg RD, Causay LC, McMurtrey MJ. Carotid artery disease following external cervical irradiation. Ann Surg 1981;194:609–15.
[54] Pierga J-Y, Maunoury C, Valette H, Socie G, Girinski T, Tchernia G, et al. Follow-up thallium-201 scintigraphy after mantle field radiotherapy for Hodgkin's disease. Int J Radiat Oncol 1993;25:871–6. doi:10.1016/0360-3016(93)90317-O.
[55] Gustavsson A, Eskilsson J, Landberg T, Svahn-Tapper G, White T, Wollmer P, et al. Late cardiac effects after mantle radiotherapy in patients with Hodgkin's disease. Ann Oncol 1990;1:355–63. doi:10.1093/oxfordjournals.annonc.A057774.

[56] Cosset JM, Henry-Amar M, Meerwaldt JH. Long-term toxicity of early stages of Hodgkin's disease therapy: The EORTC experience. Ann Oncol 1991;2:77–82. doi:10.1093/annonc/2.suppl_2.77.
[57] Adams MJ, Lipsitz SR, Colan SD, Tarbell NJ, Treves ST, Diller L, et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. J Clin Oncol 2004;22:3139–48. doi:10.1200/JCO.2004.09.109.
[58] van Nimwegen FA, Ntentas G, Darby SC, Schaapveld M, Hauptmann M, Lugtenburg PJ, et al. Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines. Blood 2017;129:2257–65. doi:10.1182/blood-2016-09-740332.
[59] Lund MB, Ihlen H, Voss BM, Abrahamsen AF, Nome O, Kongerud J, et al. Increased risk of heart valve regurgitation after mediastinal radiation for Hodgkin's disease: an echocardiographic study. Heart 1996;75:591–5. doi:10.1136/hrt.75.6.591.
[60] Wethal T, Lund M-B, Edvardsen T, Fosså SD, Pripp AH, Holte H, et al. Valvular dysfunction and left ventricular changes in Hodgkin's lymphoma survivors. A longitudinal study. Br J Cancer 2009;101:575–81. doi:10.1038/sj.bjc.6605191.
[61] Cutter DJ, Schaapveld M, Darby SC, Hauptmann M, van Nimwegen FA, Krol ADG, et al. Risk for valvular heart disease after treatment for Hodgkin lymphoma. JNCI J Natl Cancer Inst 2015;107. doi:10.1093/jnci/djv008.
[62] Bijl JM, Roos MM, van Leeuwen-Segarceanu EM, Vos JM, Bos W-JW, Biesma DH, et al. Assessment of valvular disorders in survivors of Hodgkin's lymphoma treated by mediastinal radiotherapy ± chemotherapy. Am J Cardiol 2016;117:691–6. doi:10.1016/j.amjcard.2015.11.027.
[63] Cella L, Liuzzi R, Conson M, Torre G, Caterino M, De Rosa N, et al. Dosimetric predictors of asymptomatic heart valvular dysfunction following mediastinal irradiation for Hodgkin's lymphoma. Radiother Oncol 2011;101:316–21. doi:10.1016/j.radonc.2011.08.040.
[64] Heidenreich PA, Hancock SL, Lee BK, Mariscal CS, Schnittger I. Asymptomatic cardiac disease following mediastinal irradiation. J Am Coll Cardiol 2003;42:743–9. doi:10.1016/S0735-1097(03)00759-9.
[65] Ruckdeschel JC, Chang P, Martin RG, Byhardt RW, O'Connell MJ, Sutherland JC, et al. Radiation-related pericardial effusions in patients with Hodgkin's disease. Medicine (Baltimore) 1975;54:245–59.
[66] Byhardt R, Brace K, Ruckdeschel J, Chang P, Martin R, Wiernik P. Dose and treatment factors in radiation related pericardial effusion associated with the mantle technique for Hodgkin's disease. Cancer 1975;35:795–802. doi:10.1002/1097-0142(197503)35:3<795::AID-CNCR2820350335>3.0.CO;2-M.
[67] Mill WB, Baglan RJ, Kurichety P, Prasad S, Lee JY, Moller R. Symptomatic radiation-induced pericarditis in Hodgkin's disease. Int J Radiat Oncol Biol Phys 1984;10:2061–5. doi:10.1016/0360-3016(84)90203-7.
[68] Applefeld MM, Cole JF, Pollock SH, Sutton FJ, Slawson RG, Singleton RT, et al. The late appearance of chronic pericardial disease in patients treated by radiotherapy for Hodgkin's disease. Ann Intern Med 1981;94:338–41. doi:10.7326/0003-4819-94-3-338.
[69] Groarke JD, Tanguturi VK, Hainer J, Klein J, Moslehi JJ, Ng A, et al. Abnormal exercise response in long-term survivors of Hodgkin lymphoma treated with thoracic irradiation: Evidence of cardiac autonomic dysfunction and impact on outcomes. J Am Coll Cardiol 2015;65:573–83. doi:10.1016/J.JACC.2014.11.035.
[70] Hoskin PJ, Smith P, Linch DC. Late morbidity and survival in early stage Hodgkins disease treated with involved field or wide field radiotherapy alone. Ann Oncol 2002;13:65.
[71] Hahn E, Jiang H, Ng A, Bashir S, Ahmed S, Tsang R, et al. Late cardiac toxicity after mediastinal radiation therapy for Hodgkin lymphoma: Contributions of coronary artery and whole heart dose-volume variables to risk prediction. Int J Radiat Oncol 2017;98:1116–23. doi:10.1016/j.ijrobp.2017.03.026.

[72] Khalid Y, Fradley M, Dasu N, Dasu K, Shah A, Levine A. Gender disparity in cardiovascular mortality following radiation therapy for Hodgkin's lymphoma: A systematic review. Cardio-Oncology 2020;6:1–8. doi:10.1186/S40959-020-00067-7/FIGURES/4.

[73] Eloranta S, Lambert PC, Sjoberg J, Andersson TML, Bjorkholm M, Dickman PW. Temporal trends in mortality from diseases of the circulatory system after treatment for Hodgkin lymphoma: A population-based cohort study in Sweden (1973 to 2006). J Clin Oncol 2013;31:1435–41. doi:10.1200/JCO.2012.45.2714.

[74] Kilickap S, Barista I, Ulger S, Celik I, Selek U, Gullu I, et al. Long-term complications in Hodgkin's lymphoma survivors. Tumori 2012;98:601–6. doi:10.1177/030089161209800510.

[75] van Leeuwen FE, Klokman WJ, van't Veer MB, Hagenbeek A, Krol ADG, Vetter UAO, et al. Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. J Clin Oncol 2000;18:487–97. doi:10.1200/jco.2000.18.3.487.

[76] Sasse S, Bröckelmann PJ, Goergen H, Plütschow A, Müller H, Kreissl S, et al. Long-term follow-up of contemporary treatment in early-stage Hodgkin lymphoma: Updated analyses of the German Hodgkin Study Group HD7, HD8, HD10, and HD11 trials. J Clin Oncol 2017;35:1999–2007. doi:10.1200/JCO.2016.70.9410.

[77] Cutuli B, Petit T, Hoffstetter S, Velten M, Dufour P, Giron C, et al. Treatment of subdiaphragmatic Hodgkin's disease: long-term results and side effects. Oncol Rep 1998;5:1513–21. doi:10.3892/OR.5.6.1513.

[78] Van Leeuwen FE, Klokman WJ, Hagenbeek A, Noyon R, Van Den Belt-Dusebout AW, Van Kerkhoff EHM, et al. Second cancer risk following Hodgkin's disease: A 20-year follow-up study. J Clin Oncol 1994;12:312–25. doi:10.1200/JCO.1994.12.2.312.

[79] Almagro-Casado E, Sánchez A, Cantos B, Salas C, Pérez-Callejo D, Provencio M. Lung cancer and other second neoplasms after treatment of Hodgkin lymphoma. Clin Transl Oncol 2016;18:99–106. doi:10.1007/s12094-015-1342-7.

[80] Rodriguez MA, Fuller LM, Zimmerman SO, Allen PK, Brown BW, Munsell MF, et al. Hodgkin's disease: Study of treatment intensities and incidences of second malignancies. Ann Oncol 1993;4:125–31. doi:10.1093/oxfordjournals.annonc.a058414.

[81] Petrakova K, Vyskocil J, Grell P, Majek O, Soumarova R, Novak J, et al. Second cancers in Hodgkin's lymphoma long-term survivals: A 60-year single institutional experience with real-life cohort of 871 patients. Int J Clin Pract 2018;72:e13235. doi:10.1111/ijcp.13235.

[82] Bessell EM, Bouliotis G, Armstrong S, Baddeley J, Haynes AP, O'Connor S, et al. Long-term survival after treatment for Hodgkins disease (1973-2002): Improved survival with successive 10-year cohorts. Br J Cancer 2012;107:531–6. doi:10.1038/bjc.2012.228.

[83] Behringer K, Josting A, Schiller P, Eich HT, Bredenfeld H, Diehl V, et al. Solid tumors in patients treated for Hodgkin's disease: A report from the German Hodgkins lymphoma Study Group. Ann Oncol 2004;15:1079–85. doi:10.1093/annonc/mdh273.

[84] Swerdlow AJ, Barber JA, Hudson GV, Cunningham D, Gupta RK, Hancock BW, et al. Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: The relation to age at treatment. J Clin Oncol 2000;18:498–509. doi:10.1200/jco.2000.18.3.498.

[85] Swerdlow AJ, Douglas AJ, Vaughan Hudson G, Bennett MH, MacLennan KA. Risk of second primary cancers after Hodgkin's disease by type of treatment: Analysis of 2846 patients in the British National Lymphoma Investigation. Br Med J 1992;304:1137–43. doi:10.1136/bmj.304.6835.1137.

[86] Ng AK, Patricia Bernardo M V., Weller E, Backstrand K, Silver B, Marcus KC, et al. Second malignancy after Hodgkin disease treated with radiation therapy with or without chemotherapy: Long-term risks and risk factors. Blood 2002;100:1989–96. doi:10.1182/blood-2002-02-0634.

[87] Okines A, Thomson CS, Radstone CR, Horsman JM, Hancock BW. Second primary malignancies after treatment for malignant lymphoma. Br J Cancer 2005;93:418–24. doi:10.1038/sj.bjc.6602731.
[88] Schaapveld M, Aleman BMP, van Eggermond AM, Janus CPM, Krol ADG, van der Maazen RWM, et al. Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. N Engl J Med 2015;373:2499–511. doi:10.1056/nejmoa1505949.
[89] Franklin J, Pluetschow A, Paus M, Specht L, Anselmo AP, Aviles A, et al. Second malignancy risk associated with treatment of Hodgkin's lymphoma: Meta-analysis of the randomised trials. Ann Oncol 2006;17:1749–60. doi:10.1093/annonc/mdl302.
[90] Chronowski GM, Wilder RB, Tucker SL, Ha CS, Younes A, Fayad L, et al. Analysis of in-field control and late toxicity for adults with early-stage Hodgkin's disease treated with chemotherapy followed by radiotherapy. Int J Radiat Oncol Biol Phys 2003;55:36–43. doi:10.1016/S0360-3016(02)03915-9.
[91] Swerdlow AJ, Barber JA, Horwich A, Cunningham D, Milan S, Omar RZ. Second malignancy in patients with Hodgkin's disease treated at the Royal Marsden Hospital. Br J Cancer 1997;75:116–23. doi:10.1038/bjc.1997.19.
[92] Van Leeuwen FE, Somers R, Taal BG, Van Heerde P, Coster B, Dozeman T, et al. Increased risk of lung cancer, non-Hodgkin's lymphoma, and leukemia following Hodgkin's disease. J Clin Oncol 1989;7:1046–58. doi:10.1200/JCO.1989.7.8.1046.
[93] Munker R, Grützner S, Hiller E, Aydemir Ü, Enne W, Dietzfelbinger H, et al. Second malignancies after Hodgkin's disease: the Munich experience. Ann Hematol 1999;78:544–54. doi:10.1007/s002770050556.
[94] Valagussa P, Santoro A, Kenda R, Bellani FF, Franchi F, Banfi A, et al. Second malignancies in Hodgkin's disease: A complication of certain forms of treatment. Br Med J 1980;280:216–9. doi:10.1136/bmj.280.6209.216.
[95] Rubin P, Zagars G, Chuang C, Thomas EM. Hodgkin's disease: Is there a price for successful treatment? A 25-year experience. Int J Radiat Oncol Biol Phys 1986;12:153–66. doi:10.1016/0360-3016(86)90088-X.
[96] Henry Amar M. Second cancers after radiotherapy and chemotherapy for early stages of Hodgkin's disease. JNCI J Natl Cancer Inst 1983;71:911–6. doi:10.1093/jnci/71.5.911.
[97] Sont JK, van Stiphout WAHJ, Noordijk EM, Molenaar J, Zwetsloot-Schonk JHM, Willemze R, et al. Increased risk of second cancers in managing Hodgkin's disease: the 20-year Leiden experience. Ann Hematol 1992;65:213–8. doi:10.1007/BF01703947.
[98] Economoupoulos T, Stathakis N, Alexopoulos C, Pavlidis N, Constantinidou M, Briassoulis E, et al. Second malignancies following treatment for Hodgkin's disease: A Greek experience. Haematologica 1994;79:273–6.
[99] Lemieux MH, Solanki AA, Mahmood U, Chmura SJ, Koshy M. Risk of second malignancies in patients with early-stage classical Hodgkin's lymphoma treated in a modern era. Cancer Med 2015;4:513–8. doi:10.1002/cam4.405.
[100] Glanzmann C, Veraguth A, Lutolf U. Incidence of second solid cancer in patients after treatment of Hodgkin's disease. Strahlentherapie Und Onkol 1994;170:140–6.
[101] Cimino G, Papa G, Tura S, Mazza P, Rossi Ferrini PL, Bosi A, et al. Second primary cancer following Hodgkin's disease: Updated results of an Italian multicentric study. J Clin Oncol 1991;9:432–7. doi:10.1200/JCO.1991.9.3.432.
[102] Henry-Amar M. Second cancer after the treatment for Hodgkin's disease: A report from the International Database on Hodgkin's Disease. Ann. Oncol., vol. 3, Kluwer Academic Publishers; 1992, p. S117–28. doi:10.1093/annonc/3.suppl_4.S117.
[103] Salloum E, Doria R, Schubert W, Zelterman D, Holford T, Roberts KB, et al. Second solid tumors in patients with Hodgkin's disease cured after radiation or chemotherapy plus adjuvant low-dose radiation. J Clin Oncol 1996;14:2435–43. doi:10.1200/JCO.1996.14.9.2435.
[104] Zulian GB, Mirimanoff RO. Ten-year nodular sclerosis Hodgkin's disease and second malignancies. Eur J Cancer Clin Oncol 1989;25:659–65. doi:10.1016/0277-

5379(89)90202-2.
[105] Koshy M, Rich SE, Mahmood U, Kwok Y. Declining use of radiotherapy in stage I and II Hodgkin's disease and its effect on survival and secondary malignancies. Int J Radiat Oncol Biol Phys 2012;82:619–25. doi:10.1016/j.ijrobp.2010.10.069.
[106] Cellai E, Magrini SM, Masala G, Alterini R, Costantini AS, Rigacci L, et al. The risk of second malignant tumors and its consequences for the overall survival of Hodgkin's disease patients and for the choice of their treatment at presentation: Analysis of a series of 1524 cases consecutively treated at the Florence University Hosp. Int J Radiat Oncol Biol Phys 2001;49:1327–37. doi:10.1016/S0360-3016(00)01513-3.
[107] Biti G, Cellai E, Magrini SM, Papi MG, Ponticelli P, Boddi V. Second solid tumors and leukemia after treatment for Hodgkin's disease: An analysis of 1121 patients from a single institution. Int J Radiat Oncol Biol Phys 1994;29:25–31. doi:10.1016/0360-3016(94)90222-4.
[108] Dietrich P-Y, Henry-Arnar M, Cosset J-M, Bodis S, Bosq J, Hayat M. Second primary cancers in patients continuously disease-free from Hodgkin's disease: A protective role for the spleen? Blood 1994;84:1209–15.
[109] Abou-Antoun T, Mikhael R, Massoud M, Chahine G, Saad A. Effects of radiotherapy on the risk of developing secondary malignant neoplasms in Hodgkin's lymphoma survivors. Asia Pac J Clin Oncol 2016;17:749–54. doi:http://dx.doi.org/10.7314/APJCP.2016.17.2.749.
[110] Doria R, Holford T, Farber LR, Prosnitz LR, Cooper DL. Second solid malignancies after combined modality therapy for Hodgkin's disease. J Clin Oncol 1995;13:2016–22. doi:10.1200/JCO.1995.13.8.2016.
[111] Nyandoto P, Muhonen T, Joensuu H. Second cancer among long-term survivors for Hodgkin's disease. Int J Radiat Oncol Biol Phys 1998;42:373–8. doi:10.1016/S0360-3016(98)00217-X.
[112] Swerdlow AJ, Higgins CD, Smith P, Cunningham D, Hancock BW, Horwich A, et al. Second cancer risk after chemotherapy for Hodgkin's lymphoma: A collaborative British cohort study. J Clin Oncol 2011;29:4096–104. doi:10.1200/JCO.2011.34.8268.
[113] Foss Abrahamsen A, Andersen A, Nome O, Jacobsen AB, Holte H, Foss Abrahamsen J, et al. Long-term risk of second malignancy after treatment of Hodgkin's disease: The influence of treatment, age and follow-up time. Ann Oncol 2002;13:1786–91. doi:10.1093/annonc/mdf289.
[114] Bonadonna G, Viviani S, Bonfante V, Gianni AM, Valagussa P. Survival in Hodgkin's disease patients – Report of 25 years of experience at the Milan Cancer Institute. Eur J Cancer 2005;41:998–1006. doi:10.1016/J.EJCA.2005.01.006.
[115] van Eggermond AM, Schaapveld M, Lugtenburg PJ, Krol ADG, De Boer JP, Zijlstra JM, et al. Risk of multiple primary malignancies following treatment of Hodgkin lymphoma. Blood 2014;124:319–27. doi:10.1182/blood-2013-10-532184.
[116] Eichenauer DA, Becker I, Monsef I, Chadwick N, De Sanctis V, Federico M, et al. Secondary malignant neoplasms, progression-free survival and overall survival in patients treated for Hodgkin lymphoma: A systematic review and meta-analysis of randomized clinical trials. Haematologica 2017;102:1748–57. doi:10.3324/haematol.2017.167478.
[117] Kumar V, Garg M, Chandra AB, Mayorga VS, Ahmed S, Ailawadhi S. Trends in the risks of secondary cancers in patients with Hodgkin lymphoma. Clin Lymphoma, Myeloma Leuk 2018;18:576–89. doi:10.1016/j.clml.2018.05.021.
[118] Sud A, Thomsen H, Sundquist K, Houlston RS, Hemminki K. Risk of second cancer in Hodgkin lymphoma survivors and influence of family history. J Clin Oncol 2017;35:1584–90. doi:10.1200/JCO.2016.70.9709.
[119] Omer B, Kadan-Lottick NS, Roberts KB, Wang R, Demsky C, Kupfer GM, et al. Patterns of subsequent malignancies after Hodgkin lymphoma in children and adults. Br J Haematol 2012;158:615–25. doi:10.1111/j.1365-2141.2012.09211.x.

[120] Mauch PM, Kalish LA, Marcus KC, Coleman N, Shulman LN, Krill E, et al. Second malignancies after treatment for laparotomy staged IA-IIIB Hodgkin's disease: Long-term analysis of risk factors and outcome. Blood 1996;87:3625–32.
[121] Prior P, Pope DJ. Hodgkin's disease: Subsequent primary cancers in relation to treatment. Br J Cancer 1988;58:512–7. doi:10.1038/bjc.1988.253.
[122] Arseneau JC, Sponzo RW, Levin DL, Schnipper LE, Bonner H, Young RC, et al. Nonlymphomatous malignant tumors complicating Hodgkin's disease. N Engl J Med 1972;287:1119–22. doi:10.1056/nejm197211302872204.
[123] Nelson DF, Cooper S, Weston MG, Rubin P. Second malignant neoplasms in patients treated for Hodgkin's disease with radiotherapy or radiotherapy and chemotherapy. Cancer 1981;48:2386–93. doi:10.1002/1097-0142(19811201)48:11<2386::AID-CNCR2820481109>3.0.CO;2-B.
[124] Chronowski GM, Wilder RB, Levy LB, Atkinson EN, Ha CS, Hagemeister FB, et al. Second malignancies after chemotherapy and radiotherapy for Hodgkin disease. Am J Clin Oncol 2004;27:73–80. doi:10.1097/01.coc.0000045853.73233.42.
[125] Hancock SL, Hoppe RT. Long-term complications of treatment and causes of mortality after Hodgkin's disease. Semin Radiat Oncol 1996;6:225–42. doi:10.1016/S1053-4296(96)80018-X.
[126] Dores GM, Metayer C, Curtis RE, Lynch CF, Clarke EA, Glimelius B, et al. Second malignant neoplasms among long-term survivors of Hodgkin's disease: A population-based evaluation over 25 years. J Clin Oncol 2002;20:3484–94. doi:10.1200/JCO.2002.09.038.
[127] Hodgson DC, Gilbert ES, Dores GM, Schonfeld SJ, Lynch CF, Storm H, et al. Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. J Clin Oncol 2007;25:1489–97. doi:10.1200/JCO.2006.09.0936.
[128] Enrici RM, Anselmo A, Osti M, Santoro M, Tombolini V, Mandelli F, et al. Analysis of the risk of solid tumour following Hodgkin's disease. Haematologica 1997;82:57–63. doi:10.3324/%X.
[129] Boivin JF, Hutchison GB, Zauber AG, Bernstein L, Davis FG, Michel RP, et al. Incidence of second cancers in patients treated for Hodgkin's disease. J Natl Cancer Inst 1995;87:732–41. doi:10.1093/jnci/87.10.732.
[130] Boivin J -F, O'Brien K. Solid cancer risk after treatment of Hodgkin's disease. Cancer 1988;61:2541–6. doi:10.1002/1097-0142(19880615)61:12<2541::AID-CNCR2820611225>3.0.CO;2-G.
[131] De Bruin ML, Burgers JA, Baas P, Van't Veer MB, Noordijk EM, Louwman MWJ, et al. Malignant mesothelioma after radiation treatment for Hodgkin lymphoma. Blood 2009;113:3679–81. doi:10.1182/blood-2008-10-184705.
[132] Dietrich PY, Bellefqih S, Henry-Amar M, Cosset JM, Hayat M. Linitis plastica after Hodgkin's disease. Lancet 1993;342:57–8. doi:10.1016/0140-6736(93)91926-D.
[133] Birdwell SH, Hancock SL, Varghese A, Cox RS, Hoppe RT. Gastrointestinal cancer after treatment of Hodgkin's disease. Int J Radiat Oncol Biol Phys 1997;37:67–73. doi:10.1016/S0360-3016(96)00489-0.
[134] van den Belt-Dusebout AW, Aleman BMP, Besseling G, de Bruin ML, Hauptmann M, van 't Veer MB, et al. Roles of radiation dose and chemotherapy in the etiology of stomach cancer as a second malignancy. Int J Radiat Oncol 2009;75:1420–9. doi:10.1016/J.IJROBP.2009.01.073.
[135] van Eggermond AM, Schaapveld M, Janus CPM, De Boer JP, Krol AD, Zijlstra JM, et al. Infradiaphragmatic irradiation and high procarbazine doses increase colorectal cancer risk in Hodgkin lymphoma survivors. Br J Cancer 2017;117:306–14. doi:10.1038/bjc.2017.177.
[136] Várady E, Deák B, Molnár ZS, Rosta A, Schneider T, Ésik O, et al. Second malignancies after treatment for Hodgkin's disease. Leuk Lymphoma 2001;42:1275–81. doi:10.3109/10428190109097752.
[137] Shbib Dabaja B, Boyce-Fappiano D, Dong W, Damron E, Fang P, Gunther J, et al. Second malignancies in patients with Hodgkin's Lymphoma: Half a century of

experience. Clin Transl Radiat Oncol 2022;35:64–9. doi:10.1016/J.CTRO.2022.04.011.
[138] Lavey RS, Eby NL, Prosnitz LR. Impact on second malignancy risk of the combined use of radiation and chemotherapy for lymphomas. Cancer 1990;66:80–8. doi:10.1002/1097-0142(19900701)66:1<80::AID-CNCR2820660116>3.0.CO;2-9.
[139] Tester WJ, Kinsella TJ, Waller B, Makuch RW, Kelley PA, Glatstein E, et al. Second malignant neoplasms complicating Hodgkin's disease: The National Cancer Institute experience. J Clin Oncol 1984;2:762–9. doi:10.1200/JCO.1984.2.7.762.
[140] Tucker MA, Coleman CN, Cox RS, Varghese A, Rosenberg SA. Risk of second cancers after treatment for Hodgkin's disease. N Engl J Med 1988;318:76–81. doi:10.1056/nejm198801143180203.
[141] Valagussa P, Santoro A, Fossati-Bellani F, Banfi A, Bonadonna G. Second acute leukemia and other malignancies following treatment for Hodgkin's disease. J Clin Oncol 1986;4:830–7. doi:10.1200/JCO.1986.4.6.830.
[142] Gervais-Fagnou DD, Girouard C, Laperriere N, Pintillie M, Goss PE. Breast cancer in women following supradiaphragmatic irradiation for Hodgkin's disease. Oncology 1999;57:224–31. doi:10.1159/000012035.
[143] Ibrahim EM, Abouelkhair KM, Kazkaz GA, Elmasri OA, Al-Foheidi M. Risk of second breast cancer in female Hodgkin's lymphoma survivors: a meta-analysis. BMC Cancer 2012;12:197–215. doi:10.1186/1471-2407-12-197.
[144] De Bruin ML, Sparidans J, Veer MB van't, Noordijk EM, Louwman MWJ, Zijlstra JM, et al. Breast cancer risk in female survivors of Hodgkin's lymphoma: Lower risk after smaller radiation volumes. J Clin Oncol 2009;27:4239–46. doi:10.1200/JCO.2008.19.9174.
[145] Swerdlow AJ, Cooke R, Bates A, Cunningham D, Falk SJ, Gilson D, et al. Breast cancer risk after supradiaphragmatic radiotherapy for Hodgkin's lymphoma in England and Wales: A national cohort study. J Clin Oncol 2012;30:2745–52. doi:10.1200/JCO.2011.38.8835.
[146] Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin's disease. JNCI J Natl Cancer Inst 1993;85:25–31. doi:10.1093/JNCI/85.1.25.
[147] Curtis RE, Boice JD. Second cancers after radiotherapy for Hodgkin's disease. N Engl J Med 1988;319:244–5.
[148] Travis LB, Hill DA, Dores GM, Gospodarowicz M, Leeuwen FE van, Holowaty E, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA 2003;290:465–75. doi:10.1001/JAMA.290.4.465.
[149] O'Brien P, Barton M, Fisher R. Breast cancer following treatment for Hodgkin's disease: The need for screening in a young population. Australas Radiol 1995;39:271–6. doi:10.1111/J.1440-1673.1995.TB00291.X.
[150] Veit-Rubin N, Rapiti E, Usel M, Benhamou S, Vinh-Hung V, Vlastos G, et al. Risk, characteristics, and prognosis of breast cancer after Hodgkin's lymphoma. Oncologist 2012;17:783–91. doi:10.1634/theoncologist.2011-0451.
[151] Wendland MMM, Tsodikov A, Glenn MJ, Gaffney DK. Time interval to the development of breast carcinoma after treatment for Hodgkin disease. Cancer 2004;101:1275–82. doi:10.1002/cncr.20516.
[152] El-Din MAA, Hughes KS, Finkelstein DM, Betts KA, Yock TI, Tarbell NJ, et al. Breast cancer after treatment of Hodgkin's lymphoma: Risk factors that really matter. Int J Radiat Oncol Biol Phys 2009;73:69–74. doi:10.1016/J.IJROBP.2008.03.066.
[153] Wahner-Roedler DL, Nelson DF, Croghan IT, Achenbach SJ, Crowson CS, Hartmann LC, et al. Risk of breast cancer and breast cancer characteristics in women treated with supradiaphragmatic radiation for Hodgkin lymphoma: Mayo Clinic experience. Mayo Clin Proc 2003;78:708–15. doi:10.4065/78.6.708.
[154] Travis LB, Hill D, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, et al. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. JNCI J Natl Cancer Inst 2005;97:1428–37. doi:10.1093/JNCI/DJI290.
[155] Cutuli B, Borel C, Dhermain F, Magrini SM, Wasserman TH, Bogart JA, et al. Breast

cancer occurred after treatment for Hodgkin's disease: Analysis of 133 cases. Radiother Oncol 2001;59:247–55. doi:10.1016/S0167-8140(01)00337-1.
[156] van Leeuwen FE, Klokman WJ, Stovall M, Dahler EC, van't Veer MB, Noordijk EM, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. JNCI J Natl Cancer Inst 2003;95:971–80. doi:10.1093/JNCI/95.13.971.
[157] Krul IM, Opstal-van Winden AWJ, Aleman BMP, Janus CPM, van Eggermond AM, De Bruin ML, et al. Breast cancer risk after radiation therapy for Hodgkin lymphoma: Influence of gonadal hormone exposure. Int J Radiat Oncol 2017;99:843–53. doi:10.1016/j.ijrobp.2017.07.016.
[158] Conway JL, Connors JM, Tyldesley S, Savage KJ, Campbell BA, Zheng YY, et al. Secondary breast cancer risk by radiation volume in women with Hodgkin lymphoma. Int J Radiat Oncol 2017;97:35–41. doi:10.1016/j.ijrobp.2016.10.004.
[159] Meattini I, Livi L, Saieva C, Marrazzo L, Rampini A, Iermano C, et al. Breast cancer following Hodgkin's disease: The experience of the University of Florence. Breast J 2010;16:290–6. doi:10.1111/j.1524-4741.2010.00904.x.
[160] Diller L, Nancarrow CM, Shaffer K, Matulonis U, Mauch P, Neuberg D, et al. Breast cancer screening in women previously treated for Hodgkin's disease: A prospective cohort study. J Clin Oncol 2002;20:2085–91. doi:10.1200/JCO.2002.08.031.
[161] Swerdlow AJ, Schoemaker MJ, Allerton R, Horwich A, Barber JA, Cunningham D, et al. Lung cancer after Hodgkin's disease: A nested case-control study of the relation to treatment. J Clin Oncol 2001;19:1610–8. doi:10.1200/JCO.2001.19.6.1610.
[162] Kaldor JM, Day NE, Bell J, Clarke EA, Landmark F, Karjalainen S, et al. Lung cancer following Hodgkin′s disease: A case-control study. Int J Cancer 1992;52:677–81. doi:10.1002/ijc.2910520502.
[163] Lorigan P, Radford J, Howell A, Thatcher N. Lung cancer after treatment for Hodgkin's lymphoma: a systematic review. Lancet Oncol 2005;6:773–9. doi:10.1016/S1470-2045(05)70387-9.
[164] Travis LB, Gospodarowicz M, Curtis RE, Clarke A, Andersson M, Glimelius B, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst 2002;94:182–92. doi:10.1093/jnci/94.3.182.
[165] Ibrahim EM, Kazkaz GA, Abouelkhair KM, Al-Mansour MM, Al-Fayea TM, Al-Foheidi M, et al. Increased risk of second lung cancer in Hodgkin's lymphoma survivors: A meta-analysis. Lung 2013;191:117–34. doi:10.1007/s00408-012-9418-4.
[166] van Leeuwen FE, Klokman WJ, Stovall M, Hagenbeek A, van den Belt-Dusebout AW, Noyon R, et al. Roles of radiotherapy and smoking in lung cancer following Hodgkin's disease. J Natl Cancer Inst 1995;87:1530–7. doi:10.1093/jnci/87.20.1530.
[167] List AF, Doll DC, Greco FA. Lung cancer in Hodgkin's disease: Association with previous radiotherapy. J Clin Oncol 1985;3:215–21. doi:10.1200/JCO.1985.3.2.215.
[168] Morton LM, Gilbert ES, Stovall M, van Leeuwen FE, Dores GM, Lynch CF, et al. Risk of esophageal cancer following radiotherapy for Hodgkin lymphoma. Haematologica 2014;99:e193–6.
[169] Morton LM, Dores GM, Curtis RE, Lynch CF, Stovall M, Hall P, et al. Stomach cancer risk after treatment for Hodgkin lymphoma. J Clin Oncol 2013;31:3369–77. doi:10.1200/JCO.2013.50.6832.
[170] Dores GM, Curtis RE, van Leeuwen FE, Stovall M, Hall P, Lynch CF, et al. Pancreatic cancer risk after treatment of Hodgkin lymphoma. Ann Oncol 2014;25:2073–9. doi:10.1093/annonc/mdu287.
[171] Rigter LS, Spaander MCW, Aleman BMP, Bisseling TM, Moons LM, Cats A, et al. High prevalence of advanced colorectal neoplasia and serrated polyposis syndrome in Hodgkin lymphoma survivors. Cancer 2019;125:990–9. doi:10.1002/cncr.31903.
[172] Ykema BLM, Rigter LS, Spaander MCW, Moons LMG, Bisseling TM, Aleman BMP, et al. Clinicopathological features and risk factors for developing colorectal neoplasia in Hodgkin's lymphoma survivors. Dig Endosc 2022;34:163–70. doi:10.1111/den.14004.

[173] Daniëls LA, Krol ADG, Schaapveld M, Putter H, Jansen PM, Marijt EWA, et al. Long-term risk of secondary skin cancers after radiation therapy for Hodgkin's lymphoma. Radiother Oncol 2013;109:140–5. doi:10.1016/J.RADONC.2013.06.041.
[174] Tucker MA, Misfeldt D, Coleman CN, Clark WH, Rosenberg SA. Cutaneous malignant melanoma after Hodgkin's disease. Ann Intern Med 1985;102:37–41. doi:10.7326/0003-4819-102-1-37.
[175] Herr MM, Schonfeld SJ, Dores GM, Withrow DR, Tucker MA, Curtis RE, et al. Mutual risks of cutaneous melanoma and specific lymphoid neoplasms: Second cancer occurrence and survival. J Natl Cancer Inst 2018;11:1248–58. doi:10.1093/jnci/djy052.
[176] Salvagno L, Simonato L, Sorarù M, Bianco A, Chiarion-Sileni V, Aversa SML, et al. Secondary leukemia following treatment for Hodgkin's disease. Tumori J 1993;79:103–7. doi:10.1177/030089169307900204.
[177] Kaldor JM, Day NE, Clarke EA, Van Leeuwen FE, Henry-Amar M, Fiorentino M V., et al. Leukemia Following Hodgkin's disease. N Engl J Med 1990;322:7–13. doi:10.1056/NEJM199001043220102.
[178] Blayney DW, Longo DL, Young RC, Greene MH, Hubbard SM, Postal MG, et al. Decreasing risk of leukemia with prolonged follow-up after chemotherapy and radiotherapy for Hodgkin's disease. N Engl J Med 1987;316:710–4. doi:10.1056/NEJM198703193161203.
[179] Gomez GA, Friedman M, Reese P. Occurrence of acute nonlymphocytic leukemia in a prospective randomized study of treatment for Hodgkin's disease. Am J Clin Oncol 1983;6:319–23. doi:10.1097/00000421-198306000-00011.
[180] Larsen J, Brincker H. The incidence and characteristics of acute myeloid leukaemia arising in Hodgkin's disease. Scand J Haematol 1977;18:197–206.
[181] van Leeuwen FE, Chorus AM, van den Belt-Dusebout AW, Hagenbeek A, Noyon R, van Kerkhoff EH, et al. Leukemia risk following Hodgkin's disease: relation to cumulative dose of alkylating agents, treatment with teniposide combinations, number of episodes of chemotherapy, and bone marrow damage. J Clin Oncol 1994;12:1063–73. doi:10.1200/JCO.1994.12.5.1063.
[182] Zinzani PL, Fiacchini M, Mazza P, Gherlinzoni F, Bocchia M, Tura S. Fifteen-year experience in Hodgkin's disease: role of combined modality treatment and splenectomy in the incidence of secondary acute leukemia. Haematologica 1991;76:305–10.
[183] Devereux S, Selassie TG, Vaughan Hudson G, Vaughan Hudson B, Linch DC. Leukaemia complicating treatment for Hodgkin's disease: the experience of the British National Lymphoma Investigation. BMJ 1990;301:1077–80. doi:10.1136/bmj.301.6760.1077.
[184] Pedersen-Bjergaard J, Larsen SO. Incidence of acute nonlymphocytic leukemia, preleukemia, and acute myeloproliferative syndrome up to 10 years after treatment of Hodgkin's disease. N Engl J Med 1982;307:965–71. doi:10.1056/NEJM198210143071601.
[185] Scholz M, Engert A, Franklin J, Josting A, Diehl V, Hasenclever D, et al. Impact of first- and second-line treatment for Hodgkin's lymphoma on the incidence of AML/MDS and NHL—experience of the German Hodgkin's Lymphoma Study Group analyzed by a parametric model of carcinogenesis. Ann Oncol 2011;22:681–8. doi:10.1093/ANNONC/MDQ408.
[186] Rueffer U, Josting A, Franklin J, May M, Sieber M, Breuer K, et al. Non-Hodgkin's lymphoma after primary Hodgkin's disease in the German Hodgkin's Lymphoma Study Group: Incidence, treatment, and prognosis. J Clin Oncol 2001;19:2026–32. doi:10.1200/JCO.2001.19.7.2026.
[187] Schonfeld SJ, Gilbert ES, Dores GM, Lynch CF, Hodgson DC, Hall P, et al. Acute myeloid leukemia following Hodgkin lymphoma: A population-based study of 35511 patients. J Natl Cancer Inst 2006;98:215–8. doi:10.1093/jnci/djj017.
[188] Brusamolino E, Anselmo AP, Klersy C, Santoro M, Orlandi E, Pagnucco G, et al. The

risk of acute leukemia in patients treated for Hodgkin's disease is significantly higher after combined modality programs than after chemotherapy alone and is correlated with the extent of radiotherapy and type and duration of chemotherapy: a case-con. Haematologica 1998;83:812–23.

[189] Coleman CN, Williams CJ, Flint A, Glatstein EJ, Rosenberg SA, Kaplan HS. Hematologic neoplasia in patients treated for Hodgkin's disease. N Engl J Med 1977;297:1249–52. doi:10.1056/nejm197712082972303.

[190] Krikorian JG, Burke JS, Rosenberg SA, Kaplan HS. Occurrence of non-Hodgkin's lymphoma after therapy for Hodgkin's disease. N Engl J Med 1979;300:452–8. doi:10.1056/nejm197903013000902.

[191] Josting A, Wiedenmann S, Franklin J, May M, Sieber M, Wolf J, et al. Secondary myeloid leukemia and myelodysplastic syndromes in patients treated for Hodgkin's disease: A report from the German Hodgkin's Lymphoma Study Group. J Clin Oncol 2003;21:3440–6. doi:10.1200/JCO.2003.07.160.

[192] Xavier AC, Armeson KE, Hill EG, Costa LJ. Risk and outcome of non-Hodgkin lymphoma among classical Hodgkin lymphoma survivors. Cancer 2013;119:3385–92. doi:10.1002/cncr.28194.

[193] Mendenhall NP, Shuster JJ, Million RR. The impact of stage and treatment modality on the likelihood of second malignancies and hematopoietic disorders in Hodgkin's disease. Radiother Oncol 1989;14:219–29. doi:10.1016/0167-8140(89)90170-9.

[194] Sasse S, Klimm B, Görgen H, Fuchs M, Heyden-Honerkamp A, Lohri A, et al. Comparing long-term toxicity and efficacy of combined modality treatment including extended- or involved-field radiotherapy in early-stage Hodgkin's lymphoma. Ann Oncol 2012;23:2953–9. doi:10.1093/annonc/mds110.

[195] Canellos GP, Arseneau JC, Devita VT, Whang-Peng J, Johnson REC. Second malignancies complicating Hodgkin's disease in remission. Lancet 1975;305:947–9. doi:10.1016/S0140-6736(75)92007-3.

[196] Franklin J, Eichenauer DA, Becker I, Monsef I, Engert A. Optimisation of chemotherapy and radiotherapy for untreated Hodgkin lymphoma patients with respect to second malignant neoplasms, overall and progression-free survival: Individual participant data analysis. Cochrane Database Syst Rev 2017;2017. doi:10.1002/14651858.CD008814.PUB2.

[197] Hill DA, Gilbert E, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, et al. Breast cancer risk following radiotherapy for Hodgkin lymphoma: modification by other risk factors. Blood 2005;106:3358–65. doi:10.1182/BLOOD-2005-04-1535.

[198] Tinger A, Wasserman TH, Klein EE, Miller EA, Roberts T, Piephoff J V., et al. The incidence of breast cancer following mantle field radiation therapy as a function of dose and technique. Int J Radiat Oncol 1997;37:865–70. doi:10.1016/S0360-3016(97)00026-6.

[199] Gilbert ES, Stovall M, Gospodarowicz M, Leeuwen FE Van, Andersson M, Glimelius B, et al. Lung cancer after treatment for Hodgkin's disease : Focus on radiation effects. Radiat Res 2003;159:161–73.

[200] Gilbert ES, Curtis RE, Hauptmann M, Kleinerman RA, Lynch CF, Stovall M, et al. Stomach cancer following Hodgkin lymphoma, testicular cancer and cervical cancer: a pooled analysis of three international studies with a focus on radiation effects. Radiat Res 2017;187:186–95. doi:10.1667/RR14453.1.

[201] Zanini M, Zucali R, Banfi A. Bone and soft tissue sarcomas in the follow-up of Hodgkin's disease. Tumori 1983;69:473–6.

[202] Delwail V, Jais JP, Colonna P, Andrieu JM. Fifteen-year secondary leukaemia risk observed in 761 patients with Hodgkin's disease prospectively treated by MOPP or ABVD chemotherapy plus high-dose irradiation. Br J Haematol 2002;118:189–94. doi:10.1046/J.1365-2141.2002.03564.X.

[203] Andrieu JM, Ifrah N, Payen C, Fermanian J, Coscas Y, Flandrin G. Increased risk of secondary acute nonlymphocytic leukemia after extended-field radiation therapy combined with MOPP chemotherapy for Hodgkin's disease. J Clin Oncol

1990;8:1148–54. doi:10.1200/JCO.1990.8.7.1148.
[204] van der Velden JW, van Putten WLJ, Guinee VF, Pfeiffer R, van Leeuwen FE, van der Linden EAM, et al. Subsequent development of acute non-lymphocytic leukemia in patients treated for Hodgkin's disease. Int J Cancer 1988;42:252–5. doi:10.1002/ijc.2910420218.
[205] Enrici RM, Anselmo AP, Iacari V, Osti MF, Santoro M, Tombolini V, et al. The risk of non-Hodgkin's lymphoma after Hodgkin's disease, with special reference to splenic treatment. Haematologica 1998;83:636–44.
[206] Franklin J, Paus MD, Pluetschow A, Specht L. Chemotherapy, radiotherapy and combined modality for Hodgkin's disease, with emphasis on second cancer risk. Cochrane Database Syst Rev 2005;2005. doi:10.1002/14651858.CD003187.PUB2.
[207] Aisenberg AC, Finkelstein DM, Doppke KP, Koerner FC, Boivin JF, Willett CG. High risk of breast carcinoma after irradiation of young women with Hodgkin's disease. Cancer 1997;79:1203–10. doi:10.1002/(SICI)1097-0142(19970315)79:6.
[208] Cooke R, Jones ME, Cunningham D, Falk SJ, Gilson D, Hancock BW, et al. Breast cancer risk following Hodgkin lymphoma radiotherapy in relation to menstrual and reproductive factors. Br J Cancer 2013;108:2399–406. doi:10.1038/bjc.2013.219.
[209] Travis LB, Hill DA, Gospodarowicz M, Leeuwen FE Van, Holowaty E, Glimelius B, et al. Breast Cancer Following Radiotherapy and Chemotherapy Among Young Women With Hodgkin Disease. J Am Med Assoc 2003;290:465–76. doi:10.1001/jama.290.4.465.
[210] Michaelson EM, Chen YH, Silver B, Tishler RB, Marcus KJ, Stevenson MA, et al. Thyroid malignancies in survivors of Hodgkin lymphoma. Int J Radiat Oncol 2014;88:636–41. doi:10.1016/J.IJROBP.2013.11.237.
[211] Prósper F, Robledo C, Cuesta B, Rifón J, Borbolla JR, Pardo J, et al. Incidence of non-Hodgkin's lymphoma in patients treated for Hodgkin's disease. Leuk Lymphoma 1994;12:457–62. doi:10.3109/10428199409073788.
[212] Pinnix CC, Cella L, Andraos TY, Ayoub Z, Milgrom SA, Gunther J, et al. Predictors of hypothyroidism in Hodgkin lymphoma survivors after intensity modulated versus 3-dimensional radiation therapy. Int J Radiat Oncol 2018;101:530–40. doi:10.1016/J.IJROBP.2018.03.003.
[213] Cella L, Conson M, Caterino M, De Rosa N, Liuzzi R, Picardi M, et al. Thyroid V30 predicts radiation-induced hypothyroidism in patients treated with sequential chemo-radiotherapy for Hodgkin's lymphoma. Int J Radiat Oncol 2012;82:1802–8. doi:10.1016/J.IJROBP.2010.09.054.
[214] Khoo V, Liew K, Crennan E, D'Costa I, Quong G. Thyroid dysfunction after mantle irradiation of Hodgkin's disease patients. Australas Radiol 1998;42:52–7. doi:10.1111/J.1440-1673.1998.TB00565.X.
[215] Illés Á, Bíró E, Miltényi Z, Keresztes K, Váróczy L, András C, et al. Hypothyroidism and thyroiditis after therapy for Hodgkin's disease. Acta Haematol 2003;109:11–7. doi:10.1159/000067269.
[216] Bethge W, Guggenberger D, Bamberg M, Kanz L, Bokemeyer C. Thyroid toxicity of treatment for Hodgkin's disease. Ann Hematol 2000;79:114–8. doi:10.1007/s002770050565.
[217] Smith RE, Adler RA, Clark P, Brinck-Johnsen T, Tulloh ME, Colton T. Thyroid function after mantle irradiation in Hodgkin's disease. JAMA J Am Med Assoc 1981;245:46–9. doi:10.1001/jama.1981.03310260024022.
[218] Hancock SL, Cox RS, McDougall IR. Thyroid diseases after treatment of Hodgkin's disease. N Engl J Med 1991;325:599–605. doi:10.1056/nejm199108293250902.
[219] Peerboom PF, Hassink EAM, Melkert R, DeWit L, Nooijen WJ, Bruning PF. Thyroid function 10-18 years after mantle field irradiation for Hodgkin's disease. Eur J Cancer 1992;28:1716–8. doi:10.1016/0959-8049(92)90075-D.
[220] Cella L, Liuzzi R, D'Avino V, Conson M, Biase A Di, Picardi M, et al. Pulmonary damage in Hodgkin's lymphoma patients treated with sequential chemo-radiotherapy: Predictors of radiation-induced lung injury. Acta Oncol (Madr)

2014;53:613–9. doi:10.3109/0284186X.2013.850739.
[221] Avivi I, Hardak E, Shaham B, Igla M, Rowe JM, Dann EJ. Low incidence of long-term respiratory impairment in Hodgkin lymphoma survivors. Ann Hematol 2012;91:215–21. doi:10.1007/S00277-011-1255-7.
[222] Mah K, Keane TJ, Dyk J Van, Braban LE, Poon PY, Hao Y. Quantitative effect of combined chemotherapy and fractionated radiotherapy on the incidence of radiation-induced lung damage: A prospective clinical study. Int J Radiat Oncol Biol Phys 1994;28:563–74. doi:10.1016/0360-3016(94)90180-5.
[223] Shapiro SJ, Shapiro SD, Mill WB, Campbell EJ. Prospective study of long-term pulmonary manifestations of mantle irradiation. Int J Radiat Oncol Biol Phys 1990;19:707–14. doi:10.1016/0360-3016(90)90500-J.
[224] Horning SJ, Adhikari A, Rizk N, Hoppe RT, Olshen RA. Effect of treatment for Hodgkin's disease on pulmonary function: Results of a prospective study. J Clin Oncol 1994;12:297–305. doi:10.1200/JCO.1994.12.2.297.
[225] Jensen B V., Carlsen NLT, Groth S, Nissen NI. Late effects on pulmonary function of mantle-field irradiation, chemotherapy or combined modality therapy for Hodgkin's disease. Eur J Haematol 1990;44:165–71. doi:10.1111/j.1600-0609.1990.tb00371.x.
[226] De Bruin ML, Huisbrink J, Hauptmann M, Kuenen MA, Ouwens GM, van't Veer MB, et al. Treatment-related risk factors for premature menopause following Hodgkin lymphoma. Blood 2008;111:101–8. doi:10.1182/BLOOD-2007-05-090225.
[227] Madsen BL, Giudice L, Donaldson SS. Radiation-induced premature menopause: A misconception. Int J Radiat Oncol 1995;32:1461–4. doi:10.1016/0360-3016(95)00025-T.
[228] Fisher B, Cheung AYC. Delayed effect of radiation therapy with or without chemotherapy on ovarian function in women with Hodgkin's disease. Acta Oncol (Madr) 1984;23:43–8. doi:10.3109/02841868409135984.
[229] Rosenbrock J, Vásquez-Torres A, Mueller H, Behringer K, Zerth M, Celik E, et al. Involved site radiotherapy extends time to premature menopause in infra-diaphragmatic female Hodgkin lymphoma patients – An analysis of GHSG HD14- and HD17-patients. Front Oncol 2021;11:1933. doi:10.3389/fonc.2021.658358.
[230] Horning SJ, Hoppe RT, Kaplan HS, Rosenberg SA. Female reproductive potential after treatment for Hodgkin's disease. N Engl J Med 1981;304:1377–82. doi:10.1056/nejm198106043042301.
[231] Holmes GE, Holmes FF. Pregnancy outcome of patients treated for Hodgkin's disease. A controlled study. Cancer 1978;41:1317–22.
[232] Cosset JM, Henry-Amar M, Burgers JMV, Noordijk EM, Van der Werf-Messing B, Meerwaldt JH, et al. Late radiation injuries of the gastrointestinal tract in the H2 and H5 EORTC Hodgkin's disease trials: Emphasis on the role of exploratory laparotomy and fractionation. Radiother Oncol 1988;13:61–8. doi:10.1016/0167-8140(88)90299-X.
[233] Dailey MO, Coleman CN, Kaplan HS. Radiation-induced splenic atrophy in patients with Hodgkin's disease and non-Hodgkin's lymphomas. N Engl J Med 1980;302:215–7. doi:10.1056/nejm198001243020406.
[234] van Nimwegen FA, Schaapveld M, Janus CPM, Krol ADG, Raemaekers JMM, Kremer LCM, et al. Risk of diabetes mellitus in long-term survivors of Hodgkin lymphoma. J Clin Oncol 2014;32:3257–63. doi:10.1200/JCO.2013.54.4379.
[235] Ganz PA, Moinpour CM, Pauler DK, Kornblith AB, Gaynor ER, Balcerzak SP, et al. Health status and quality of life in patients with early-stage Hodgkin's disease treated on Southwest Oncology Group Study 9133. J Clin Oncol 2003;21:3512–9. doi:10.1200/JCO.2003.01.044.
[236] Greil R, Holzner B, Kemmler G, Kopp M, Buchowski A, Oberaigner W, et al. Retrospective assessment of quality of life and treatment outcome in patients with Hodgkin's disease from 1969 to 1994. Eur J Cancer 1999;35:698–706. doi:10.1016/S0959-8049(99)00025-8.
[237] Norum J, Wist EA. Quality of life in survivors of Hodgkin's disease. Qual Life Res

1996;5:367–74. doi:10.1007/BF00433921.
[238] Daniëls LA, Oerlemans S, Krol ADG, Creutzberg CL, Van De Poll-Franse L V. Chronic fatigue in Hodgkin lymphoma survivors and associations with anxiety, depression and comorbidity. Br J Cancer 2014;110:868–74. doi:10.1038/bjc.2013.779.
[239] Trachtenberg E, Gurion R, Mashiach T, Tadmor T, Kedmi M, Dann EJ. Recognizing severe fatigue and decline in quality of life in Hodgkin lymphoma survivors. Leuk Lymphoma 2019;60:3449–54. doi:10.1080/10428194.2019.1641803.
[240] Ghosh PS, Milone M. Clinical and laboratory findings of 21 patients with radiation-induced myopathy. J Neurol Neurosurg Psychiatry 2015;86:152–8. doi:10.1136/JNNP-2013-307447.
[241] Fels LM, Bokemeyer C, Rhee J van, Schmoll H-J, Stolte H. Evaluation of late nephrotoxicity in long-term survivors of Hodgkin's disease. Oncology 1996;53:73–8. doi:10.1159/000227539.
[242] Keene HJ, Fleming TJ, Toth BB. Cariogenic microflora in patients with Hodgkin's disease before and after mantle field radiotherapy. Oral Surgery, Oral Med Oral Pathol 1994;78:577–82. doi:10.1016/0030-4220(94)90167-8.
[243] Bucher JA, Fleming TJ, Fuller LM, Keene HJ. Preliminary observations on the effect of mantle field radiotherapy on salivary flow rates in patients with Hodgkin's disease. J Dent Res 1988;67:518–21. doi:10.1177/00220345880670021801.
[244] Miltényi Z, Keresztes K, Lakos G, Váróczy L, Miltényi L, Illés Á. Is the treatment of Hodgkin's disease detrimental to the parathyroid gland? Acta Haematol 2004;112:148–51. doi:10.1159/000079726.
[245] Nader S, Schultz PN, Fuller LM, Samaan NA. Calcium status following neck radiation therapy in Hodgkin's disease. Arch Intern Med 1984;144:1577–8. doi:10.1001/ARCHINTE.1984.00350200069010.
[246] Group CC and L. Aftercure late effects factsheets n.d. https://www.cclg.org.uk/Aftercurefactsheets (accessed June 20, 2022).
[247] National radiotherapy consent forms | The Royal College of Radiologists n.d. https://www.rcr.ac.uk/clinical-oncology/service-delivery/national-radiotherapy-consent-forms (accessed July 30, 2022).
[248] Brodin NP, Maraldo M V., Aznar MC, Vogelius IR, Petersen PM, Bentzen SM, et al. Interactive decision-support tool for risk-based radiation therapy plan comparison for Hodgkin lymphoma. Int J Radiat Oncol Biol Phys 2014;88:433–45. doi:10.1016/j.ijrobp.2013.10.028.
[249] Jones DA, Candio P, Shakir R, Ntentas G, Ramroth J, Gray AM, et al. Informing radiotherapy decisions in stage I/IIa Hodgkin lymphoma: modeling life expectancy using radiation dosimetry. Blood Adv 2022;6:909–19. doi:10.1182/bloodadvances.2021006254.
[250] Ntentas G, Dedeckova K, Andrlik M, Aznar MC, George B, Kubeš J, et al. Clinical intensity modulated proton therapy for Hodgkin lymphoma: Which patients benefit the most? Pract Radiat Oncol 2019;9:179–87. doi:10.1016/j.prro.2019.01.006.
[251] Ntentas G, Dedeckova K, Andrlik M, Aznar MC, Shakir R, Ramroth J, et al. Proton therapy in supradiaphragmatic lymphoma: Predicting treatment-related mortality to help optimize patient selection. Int J Radiat Oncol Biol Phys 2022;112:913–25. doi:10.1016/j.ijrobp.2021.10.151.
[252] Cutter DJ, Ramroth J, Diez P, Buckle A, Ntentas G, Popova B, et al. Predicted risks of cardiovascular disease following chemotherapy and radiotherapy in the UK NCRI RAPID trial of positron emission tomography-directed therapy for early-stage Hodgkin lymphoma. J Clin Oncol 2021;39:3591–601. doi:10.1200/JCO.21.00408.
[253] Nijdam A, Dekker N, Aleman BMP, van 't Veer MB, Daniels LA, van der Maazen RW, et al. Setting up a national infrastructure for survivorship care after treatment for Hodgkin lymphoma. Br J Haematol 2019. doi:10.1111/bjh.15936.
[254] Harji D. COMET Initiative Home. Http://WwwComet-InitiativeOrg/ 2011. https://www.comet-initiative.org/ (accessed July 30, 2022).

[255] Webbe J, Sinha I, Gale C. Core outcome sets. Arch Dis Child Educ Pract Ed 2018;103:163–6. doi:10.1136/archdischild-2016-312117.

Chapter 4

Doses to infradiaphragmatic organs from historic radiotherapy for Hodgkin lymphoma

4.1 Background

4.1.1 Radiotherapy techniques for Hodgkin lymphoma

As described in Chapter 1, historically large radiation fields termed 'extended-field radiotherapy' (EFRT) were used to treat patients with Hodgkin lymphoma (HL): a mantle field for supradiaphragmatic nodal regions, and an inverted-Y for infradiaphragmatic nodes [1,2]. More recently, involved-field (IFRT) and then involved-site (ISRT) radiotherapy were adopted, which treat only the nodal regions that contain HL at diagnosis [3,4]. Numerous studies have reported doses received by thoracic organs from mantle radiotherapy [5–9], but very few have studied doses received by abdominopelvic organs from infradiaphragmatic radiotherapy [10,11].

HL confined to the infradiaphragmatic nodes is an uncommon presentation, making up less than 10% of early-stage diagnoses [12,13]. The incidence of infradiaphragmatic involvement is between 4-13% in those with early-stage disease [12]. However, historically, EFRT commonly included infradiaphragmatic fields. The organs irradiated by infradiaphragmatic EFRT include the stomach, small bowel, large bowel, kidneys, pancreas, liver and bladder. Adults treated with such radiotherapy have been shown to be at increased risk of multiple abdominopelvic malignancies, including gastric [14–17], pancreatic [17,18], colorectal [19], small bowel [17], renal [20], bladder and endometrial [21] cancer. Infradiaphragmatic radiotherapy also increases the risk of non-malignant conditions, such as renal dysfunction [22,23] and diabetes [24–26].

4.1.2 Radiation dose-response estimates

As described in Chapter 1, the dose to organs-at-risk (OARs) from modern radiotherapy is lower than from historic techniques, and therefore the risk of late-effects seen in most published cohorts cannot be directly applied to people treated today. Instead, radiation dose-response relationships have been published that investigate the rate of late-effects in relation to exposure to radiotherapy, as presented in Chapter 3. Such relationships can be used to estimate risks from modern treatment, using the dose delivered to an OAR. Modern radiotherapy treatment planning systems (TPSs) allow the dose delivered to OARs to be estimated using an individual patient's computerised tomography (CT) scan to simulate the treatment. However, these methods only came into routine use in the 1990s, meaning that data on the radiation doses to OARs are not available for the majority of individuals included in observational studies. Retrospective estimation of the radiation doses, termed 'retrospective dosimetry', must therefore be done to derive radiation dose-response relationships. Once available, dose-response relationships can be used by clinicians to provide people with HL estimates of the risks of radiotherapy specific to them. This individualised information can help inform conversations about the relative benefits and risks of radiotherapy, thereby facilitating shared decision-making about its use.

4.1.3 Study aims

The aim of this study was to determine the radiation doses delivered to abdominopelvic OARs from historic radiotherapy for HL, compare them to those expected from modern radiotherapy, and consider the implications for patients treated in the modern era. An additional aim was to provide data that could be used to determine the dose-response relationship for the risk of CRC following treatment for HL. Figure 4.1 illustrates how this study fits into the aims of the thesis as a whole.

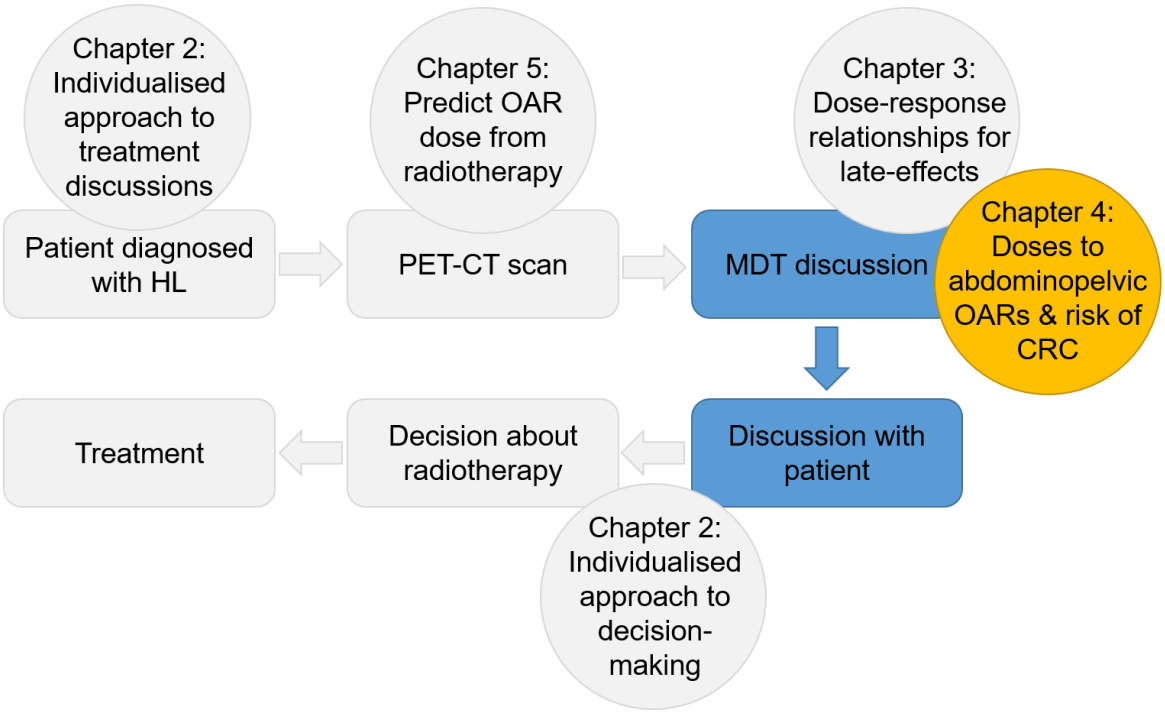


Figure 4.1: Overview of the clinical pathway for making decisions about radiotherapy used to treat patients with Hodgkin lymphoma, highlighting the steps informed by data presented in this chapter

Abbreviations - HL: Hodgkin lymphoma; OAR: organ-at-risk; PET-CT: Positon emission tomography integrated with computed tomography; MDT: multidisciplinary team; CRC: colorectal cancer

4.2 Methods

4.2.1 Cohort characteristics

This study is part of a collaborative nested case-control study conducted within an existing multicentre hospital-based cohort of people treated for HL in the Netherlands between 1965 and 2000 (N=2996). The epidemiological data collection was performed by collaborators at the Netherlands Cancer Institute (NKI). Patients were eligible for this study if:

a) they survived at least five years after HL diagnosis,

b) they were diagnosed with HL before the age of 51 years,

c) HL was their first primary malignancy (except for non-melanoma skin cancer or carcinoma in situ of the cervix or breast), and

d) they had not had any additional radiotherapy, apart from that for HL.

A total of 83 possible cases of CRC were identified, but five were subsequently excluded based on the eligibility criteria. Medical records were available for all 78 remaining confirmed cases, but only 65 had sufficient information about their radiotherapy to be included in this analysis. For each case with CRC, three control patients were selected from the cohort, individually matched on sex, age at diagnosis of HL (within one year) and date of diagnosis of HL (within three years). If fewer than three control patients were found for a case, the matching criteria were relaxed until three were found, up to a maximum difference of three years for age at diagnosis of HL, and four years for date of diagnosis of HL. Control patients were selected with replacement; individuals could be a control for more than one case, and cases could also be controls if matched with a case at a time point prior to their CRC diagnosis. A total of 151 control patients were selected, but only 124 (111 unique individuals) had sufficient information about their radiotherapy to be included in this analysis.

The data I required to perform retrospective dosimetry for all cases and controls was provided by researchers at NKI. This consisted of radiotherapy prescription charts and treatment positioning x-rays ('simulation fields'). The data did not identify whether the individual was a case or control. The study was exempt from institutional review board approval according to Dutch law as it used existing data from medical files.

4.2.2 Developing a representative CT library

Modern radiotherapy treatment planning uses CT scans of an individual patient to simulate the radiotherapy fields and estimate the dose that will be delivered to the tumour and OARs. Routine use of CT planning was only established in the late 1990s, and therefore this data

was not available for the individuals included in this study. Instead, I received a treatment positioning x-ray which demonstrated the size and shape of the radiotherapy fields in relation to bony landmarks. In order to estimate what dose was delivered to OARs from these fields, I needed to reconstruct them on a representative CT scan within a modern radiotherapy TPS. For the OAR dose estimates to be accurate, the representative CT used should match the individual's body as closely as possible. It is not practical to have a different representative CT for each individual, and my research group's previous studies [27–29] have used two (one male, one female). To allow closer matching based on body size as well as sex, and increase the accuracy of dose estimation, I conducted a study to expand the CT library.

I selected CT scans from a cohort of 66 patients (30 female and 36 male) treated for HL within the Thames Valley between 2010 and 2018 who had given permission for their images to be used for research. These CTs were taken after two or three cycles of chemotherapy, and therefore were closest in time sequence to the measurements taken for radiotherapy planning in the historic cohort. To determine the range of body sizes required for the representative CT library, I received weight, height and separation data for a sample of the historic cohort (n=111). Separation is the distance between the anterior and posterior body surfaces, and is one of the main factors that determines radiation distribution through the body. Historically, separation was used when calculating what energy and dose of radiation should be prescribed in order to deliver the intended dose to the tumour. Before digital treatment planning was available using CT scans, radiotherapy was prescribed as a 'midplane dose'. The 'midplane' refers to the midpoint between the anterior and posterior body surfaces, and is therefore at a depth of half the separation distance. The radiation beam begins to deposit dose as soon as it enters the body, so if 30 Gy is prescribed as a midplane dose, the dose delivered needs to be high enough to account for this attenuation of the beam as it passes through the body. The further into the body that the beam has to travel to reach the midplane (i.e. the larger the separation), the higher the dose that has to

be delivered in order to ensure that 30 Gy is delivered to the midplane. Separation is therefore crucial in determining what dose is prescribed to an individual patient, and how that dose is distributed in their body. The historic cohort had separation measured at four supradiaphragmatic and two infradiaphragmatic locations:

- Upper neck
- Lower neck
- Mid-mediastinum
- Lower-mediastinum
- Para-aortic
- Ileocaecal

Computer TPSs have replaced manual dose calculations, so measurement of separation is no longer needed when prescribing radiotherapy. Separation data was therefore not documented for the contemporary cohort. Body mass index (BMI) was however available, and was also available for the historic cohort. As BMI is also a measure of body size, I hypothesised that it could be used as a surrogate of separation when selecting representative CTs. I therefore investigated the correlation between the BMI of the individuals in the historic cohort, and their separation distances measured at the time of radiotherapy. Matching at the mid-mediastinal and para-aortic level was most relevant for the radiotherapy fields used in the historic cohort. As demonstrated in Figure 4.2, there was unsatisfactory correlation between BMI and separation at both these points in males, and low correlation in females. It was therefore more appropriate to use separation to select representative CTs, rather than BMI.

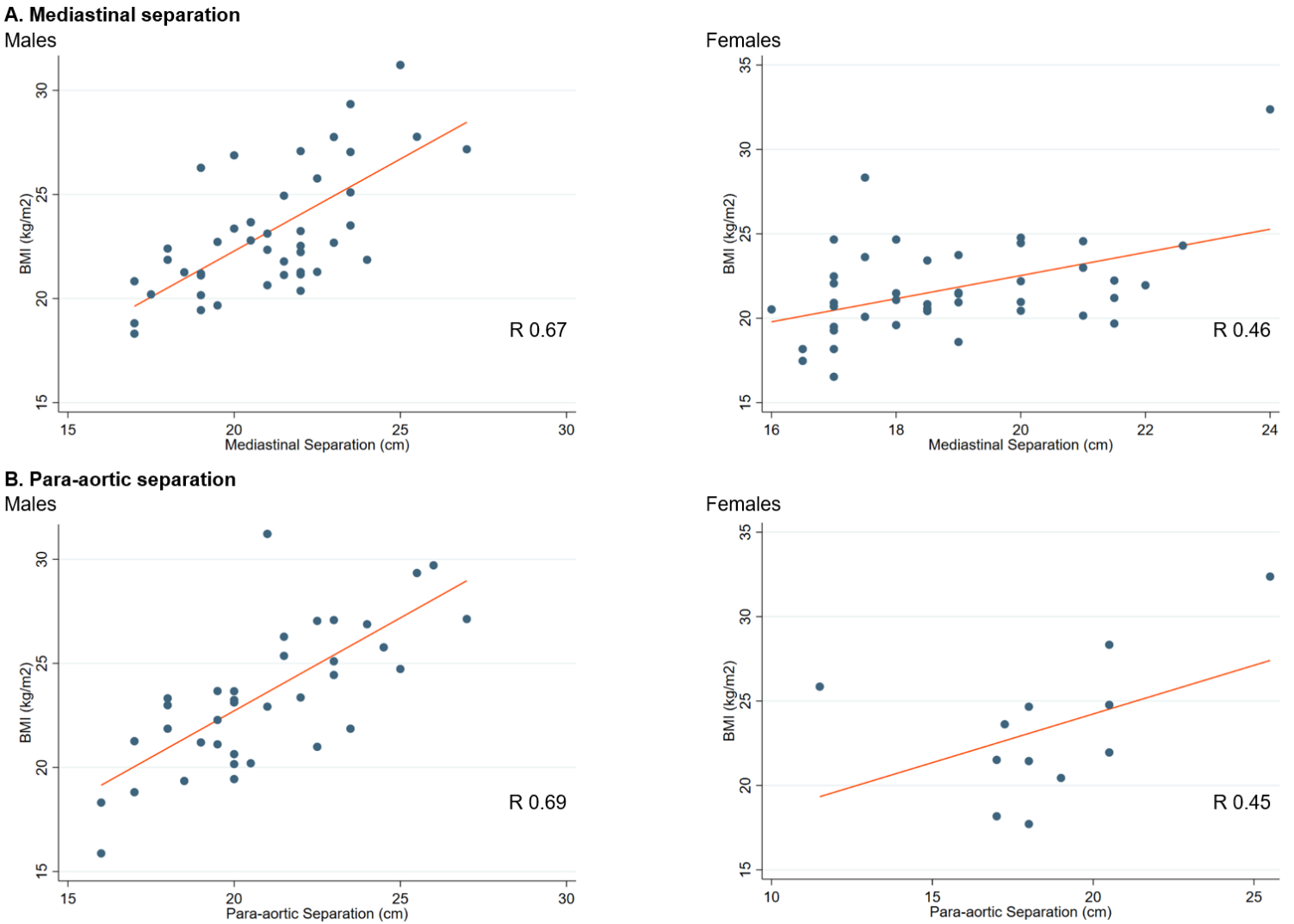


Figure 4.2: Correlation between body mass index and mediastinal (A) and para-aortic (B) separation in a cohort of Hodgkin lymphoma survivors

Abbreviations - BMI: body mass index

I obtained data on separation for the contemporary cohort by measuring the distance between their anterior and posterior body surfaces on axial CT slices at points that matched the anatomical landmarks used in the historic cohort, as shown in Figure 4.3.

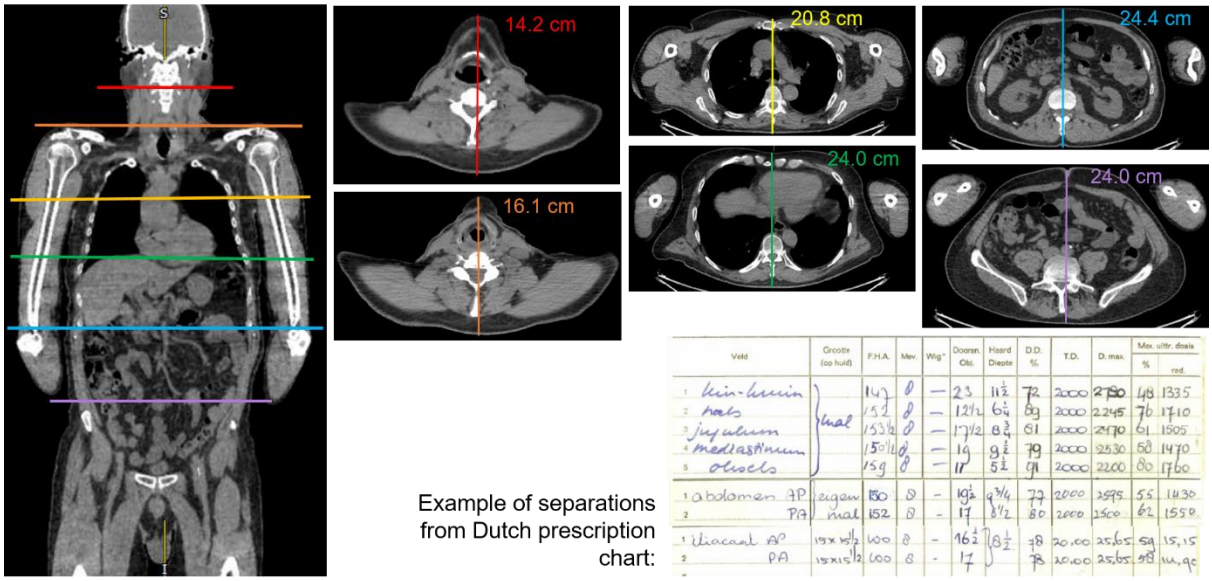


Figure 4.3: Measurement of separation for the contemporary cohort

I initially planned to select CTs from eight female and eight male patients: four to use for supradiaphragmatic field reconstruction (based on mediastinal separation), and four for infradiaphragmatic (based on para-aortic separation). However, the contemporary cohort had larger separations than patients in the historic cohort, meaning it was not possible to select a CT scan to represent the smallest historic quartile. I therefore split the historic cohort into tertiles based on their mediastinal separation, and again based on their para-aortic separation, and chose CTs from the contemporary cohort that most-closely matched the median separation for each tertile (Table 4.1). I reviewed the chosen CT to ensure acceptable image quality, and absence of major anatomical variations or persistent large-volume lymphoma. The final representative CT library contained 12 full-body CT scans: three each for supradiaphragmatic dose-reconstruction for females and males, and three each for infradiaphragmatic dose-reconstruction for females and males. These scans were fully anonymised and loaded into the research TPS.

Table 4.1: Selection of representative CT library

	Range of mediastinal separation in historic cohort (cm)	Median mediastinal separation in historic cohort (cm)	Separation of chosen representative CT from modern cohort (cm)
Supradiaphragmatic			
Males			
Group 1	17.0 – 20.3	18.65	20.1 (lowest suitable)
Group 2	20.4 – 23.7	22.05	22.0
Group 3	23.8 – 27.1	25.45	25.5
Females			
Group 1	16.0 – 18.6	17.30	18.3 (lowest suitable)
Group 2	18.7 – 21.3	20.00	21.0*
Group 3	21.4 – 24.0	22.70	23.5
Infradiaphragmatic			
Males			
Group 1	16.0 – 19.6	17.80	19.1 (lowest suitable)
Group 2	19.7 – 23.3	21.50	21.4
Group 3	23.4 – 27.1	25.25	25.3
Females			
Group 1	11.5 – 16.1	13.80	14.6 (lowest suitable)
Group 2	16.2 – 20.8	18.50	18.6
Group 3	20.9 – 25.5	23.20	23.8

*chosen to ensure that the 'small' and 'medium' representative CTs were not too close in separation
Abbreviations - cm: centimetre; CT: computerised tomography

4.2.2.1 Contouring of organs-at-risk

I contoured abdominopelvic OARs using published radiotherapy consensus guidelines [30,31]. The colon is typically contoured as a single structure for the purpose of routine radiotherapy planning in the clinic, rather than being split into segments. I therefore used consensus anatomical divisions of the large intestine, used to describe primary colorectal tumour location, to define the segments of the colon [32]. The contours were checked by my supervisor, Dr David Cutter, a senior clinical oncologist, and where there was any doubt I sought assistance from a diagnostic radiologist.

4.2.3 Radiotherapy treatment reconstruction

I used the Eclipse TPS (Version 13.0.28, Varian Medical Systems, Palo Alto, CA) to retrospectively reconstruct the radiotherapy fields delivered to the 189 patients sent to me by researchers at NKI. I chose a representative CT for each individual in the cohort, based on their separation at either the para-aortic or mid-mediastinal level. For individuals treated with both supra- and infra-diaphragmatic fields, I chose the representative CT that most closely matched the separation at the para-aortic level, as the primary focus of this study was dose to abdominopelvic OARs. For individuals treated with only supra- or infradiaphragmatic radiotherapy, I chose the representative CT based on only the mid-mediastinal or para-aortic separation respectively.

I extracted treatment planning variables from the patients' original radiotherapy prescription, including prescribed dose, fractionation regime, beam arrangement, beam energy, source-to-skin distance (SSD), field size and field shielding. I then used this information and the original simulation films to reconstruct each patient's radiotherapy treatment, blinded to whether the individual was a case or control. I used the patient's original simulation film to reconstruct the radiotherapy fields on a digitally reconstructed radiograph from the representative CT data set, and matched block borders to anatomic landmarks, as shown in Figure 4.4.

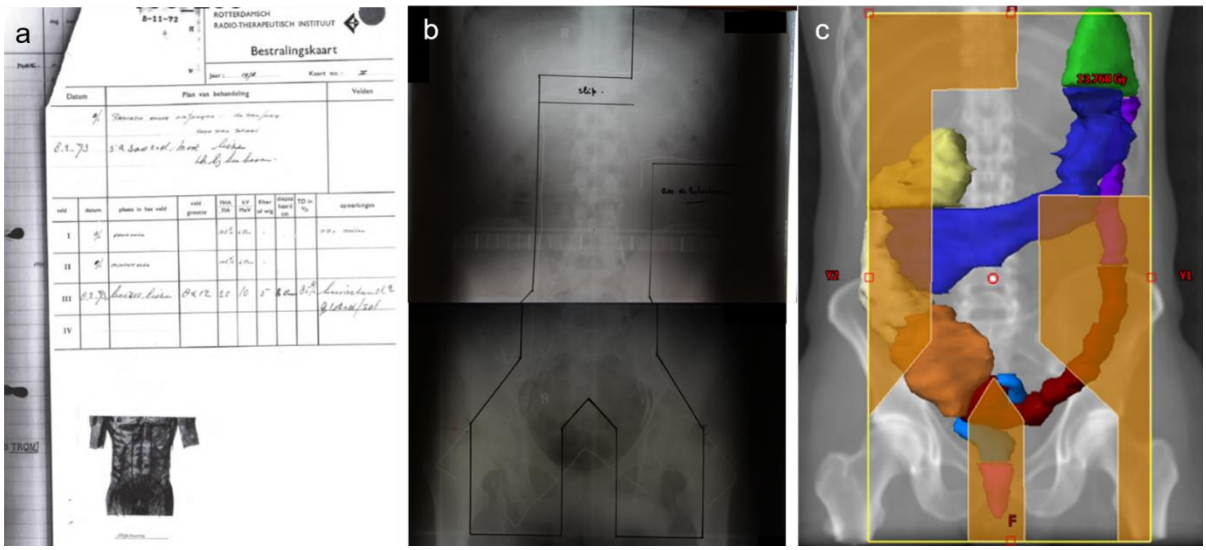


Figure 4.4: An example of a (a) radiotherapy prescription, (b) simulation films and (c) reconstructed radiotherapy plan
The original simulation films (b) were used to reconstruct the radiotherapy fields on a digitally reconstructed radiograph from the representative CT data set (c), and block borders (black in b, orange in c) matched to anatomic landmarks.

For patients who were treated with a combination of mediastinal and infradiaphragmatic fields, common practice was to include a slip zone between the inferior border of the mediastinal field and the superior border of the infradiaphragmatic field (typically an inverted-Y or para-aortic field) [33,34]. These borders therefore moved up or down during treatment, typically with the inferior vertebrae of the mediastinal field and the superior vertebrae of the infradiaphragmatic field being blocked or unblocked for one half of treatment. The aim of this was to minimise areas of over- and under-dosing at the junction of the two fields. Where this technique was used, I incorporated it into the individual reconstruction. When treating people with bulky mediastinal disease, common practice was to start radiotherapy with a wide mediastinal field and then narrow it once the disease started to respond and shrink [35]. Where this was the case, and the simulation fields indicated the borders of the wide and narrow fields, I also incorporated this narrowing into the individual reconstruction.

Patients were treated with between one and 19 fields each (median four). I reconstructed a total of 1053 fields for 189 unique patients. Simulation films were not available for 172 fields from 53 patients (16.3% fields, 28.0% patients). For these, I reconstructed the radiotherapy fields using multiple other information sources. I extracted the field type and size from the radiotherapy prescription, along with information from any diagrams or dose calculations contained within the prescription. I used this information in combination with the fields used in other patients treated at the same treatment centre at a similar time to the individual in question. There was no information on beam energy for 15 patients (7.9%). For these, I imputed the energy from other individuals with similar separation treated at the same centre with the same field type in the same time period. For two patients (1.1%) there was no information on prescribed dose or fractionation, and for an additional eight patients (4.2%) only the total dose was documented. In these cases I imputed the dose and fractionation from other individuals treated at the same centre with the same fields types in the same treatment period. Five patients were treated with orthovoltage fields (27 fields, 2.6% patients, 2.6% fields) that are not available within the TPS. However, these fields were typically used as a superficial boost to the groins or axilla, for example, following megavoltage or cobalt-60 radiotherapy and as such the dose to abdominopelvic OARs would have been negligible. I therefore omitted the orthovoltage fields.

4.2.4 Estimation of organ-at-risk doses

I used the anisotropic analytical algorithm (AAA) photon dose calculation model in the TPS to calculate the dose distributions for patients who received radiotherapy using a linear accelerator (172 patients [91.0%], 965 fields [91.6%]). I used the pencil beam convolution (PBC) algorithm for those patients who received radiotherapy using a cobalt-60 machine (23 patients [12.2%], 61 fields [5.8%]). AAA results in more accurate dose distributions compared to PBC, because it accounts for lateral electron transfer, which is especially

relevant in heterogeneous and low density tissue (such as lung) [36]. However, as cobalt-60 is a historic treatment, there is no AAA model available to use in combination with a cobalt-60 beam in the TPS. As only a small number of fields were delivered using cobalt-60, the overall effect of using PBC rather than AAA is negligible.

Once I had calculated the dose from each field, I summed the dose distribution from all fields for each individual participant, and extracted the mean doses to each of the abdominopelvic OARs and segments of the colon. I report the doses as a percentage of the total prescribed dose when discussing the differences between the radiotherapy field types, and as absolute doses when discussing the differences between cases and controls. The total prescribed dose was the combined maximal prescribed dose for any fields that included the OAR in question. For example, if a patient was prescribed 30 Gy to a mantle field (which did not include the colon), 40 Gy to an inverted-Y (which included the colon), and a groin boost of 5 Gy (which also included the colon), then the total prescribed dose was 45 Gy. Expressing the doses as percentages of the total prescribed dose allows clinicians to estimate what dose OARs are likely to have received from a specific radiotherapy field. For example, if a patient was treated with 40 Gy delivered to an inverted-Y field, their colon would be expected to have received 61% of this dose, i.e. 24.4 Gy. When considering the difference between patients who went on to develop CRC and those who did not, it is more useful to consider the absolute dose delivered to OARs.

I assessed differences in mean OAR doses between cases and controls, and between the different radiotherapy field types, using the Wilcoxon rank sum test. I used this test rather than the two-sample t-test as the doses were not normally distributed, and the sample size small.

4.3 Results

4.3.1 Doses to abdominopelvic organs-at-risk, split by radiotherapy field type

The radiotherapy fields used could be broadly grouped into seven categories (Table 4.2). Sixty-eight patients were treated with a mantle field only, and 22 with an inverted-Y. Forty-three were treated with subtotal nodal irradiation (STNI), i.e. the combination of mantle and para-aortic fields, including the spleen. Twenty-five were treated with both mantle and inverted-Y fields, i.e. total nodal irradiation (TNI). Twenty-six patients had IFRT, 19 to supradiaphragmatic regions, and seven to infradiaphragmatic. Five had subtotal or total nodal irradiation for primary treatment, with additional infradiaphragmatic fields on relapse.

Table 4.2: Categories of radiotherapy fields

Radiotherapy field	Number (% of cohort)
Mantle	68 (36.0)
Inverted-Y	22 (11.6)
Subtotal nodal irradiation	43 (22.8)
Total nodal irradiation	25 (13.2)
Supradiaphragmatic IFRT	19 (10.1)
Mediastinum	8
Unilateral neck	4
Mediastinum and axilla or SCF	3
Unilateral SCF or axilla	2
Bilateral neck and SCF or axilla	2
Infradiaphragmatic IFRT	7 (3.7)
Unilateral pelvis	2
Pelvis and unilateral groin	2
Para-aortic nodes	1
Pelvis	1
Para-aortic nodes and pelvis	1
(S)TNI & infradiaphragmatic*	5 (2.6)

*These patients had subtotal or total nodal irradiation for primary treatment, with additional infradiaphragmatic fields on relapse
Abbreviations - IFRT: involved field radiotherapy; SCF: supraclavicular fossa; (S)TNI: (sub)total nodal irradiation

Figures 4.5, 4.6, 4.7, 4.8, and 4.9 show the position of the abdominopelvic OARs in relation to the main radiotherapy field types.

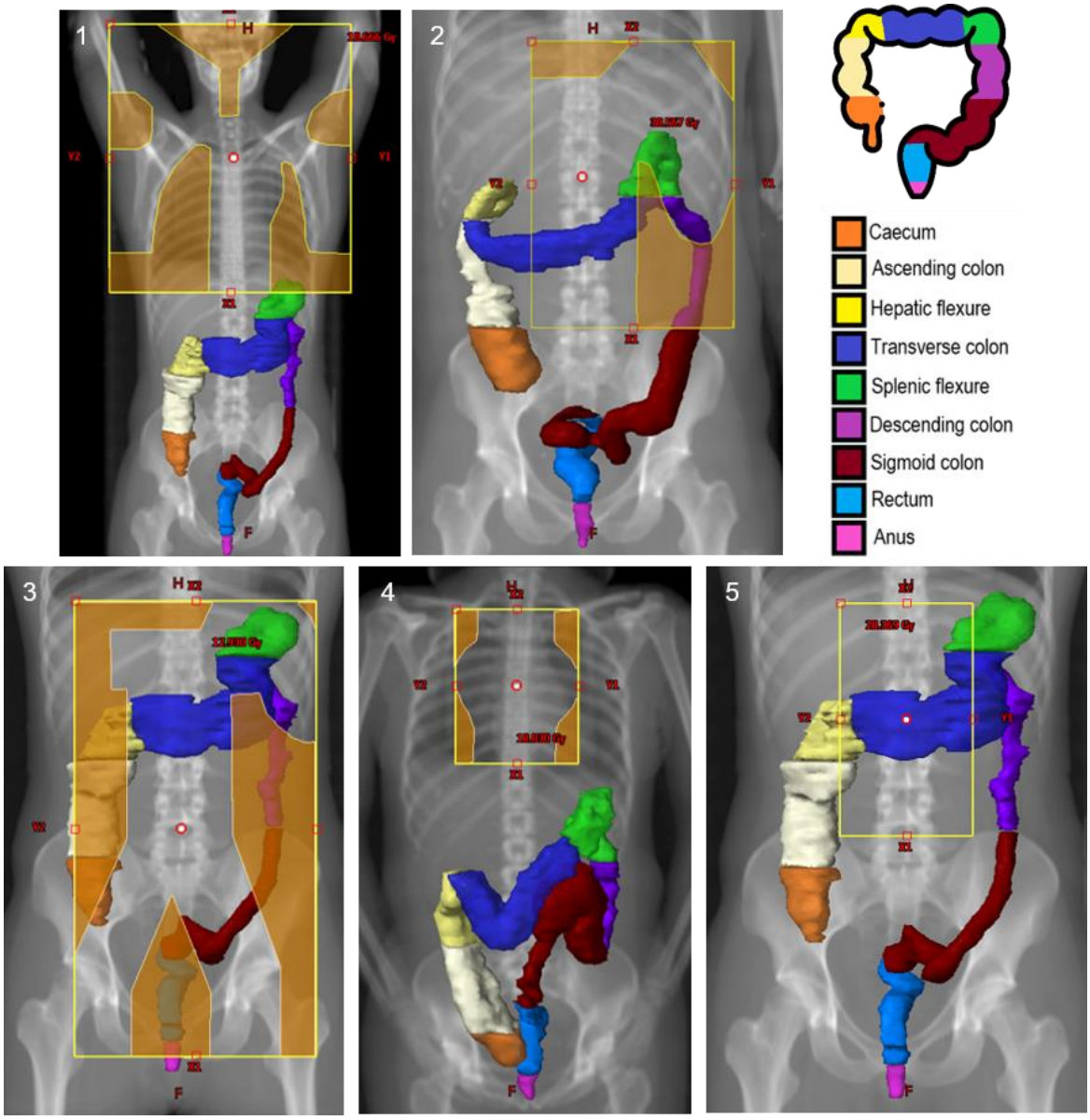


Figure 4.5: Position of the colon segments in relation to the reconstructed radiotherapy fields

1. Mantle
2. Para-aortic field with spleen
3. Inverted-Y
4. Supradiaphragmatic involved field radiotherapy (mediastinum in this example)
5. Infradiaphragmatic involved field radiotherapy (para-aortic nodes in this example)

Subtotal nodal irradiation (STNI) is the combination of mantle and para-aortic with spleen fields
Total nodal irradiation (TNI) is the combination of mantle and inverted-Y fields

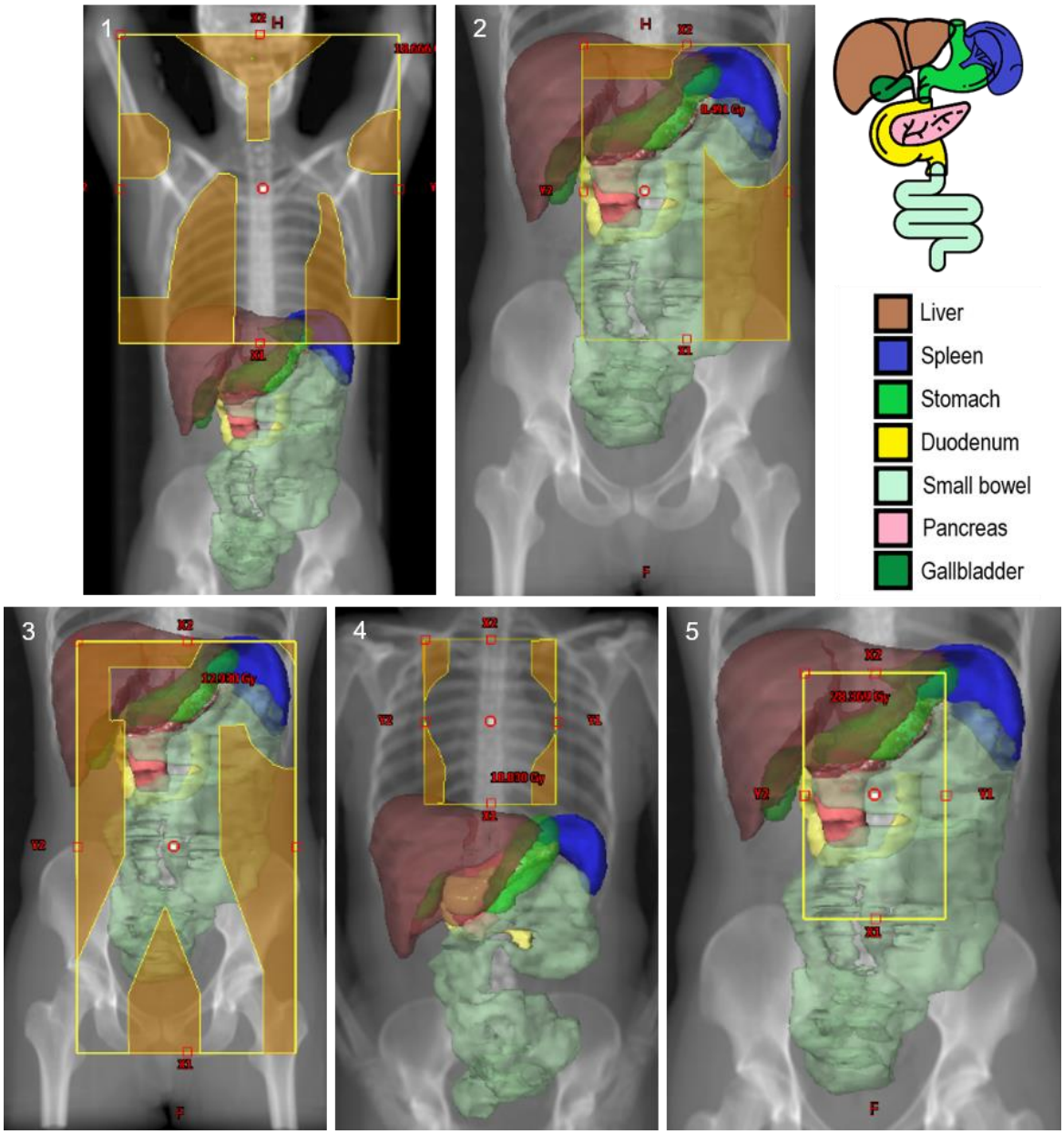


Figure 4.6: Position of the gastrointestinal organs (excluding the colon) in relation to the reconstructed radiotherapy fields

1. Mantle
2. Para-aortic field with spleen
3. Inverted-Y
4. Supradiaphragmatic involved field radiotherapy (mediastinum in this example)
5. Infradiaphragmatic involved field radiotherapy (para-aortic nodes in this example)

Subtotal nodal irradiation (STNI) is the combination of mantle and para-aortic with spleen fields

Total nodal irradiation (TNI) is the combination of mantle and inverted-Y fields

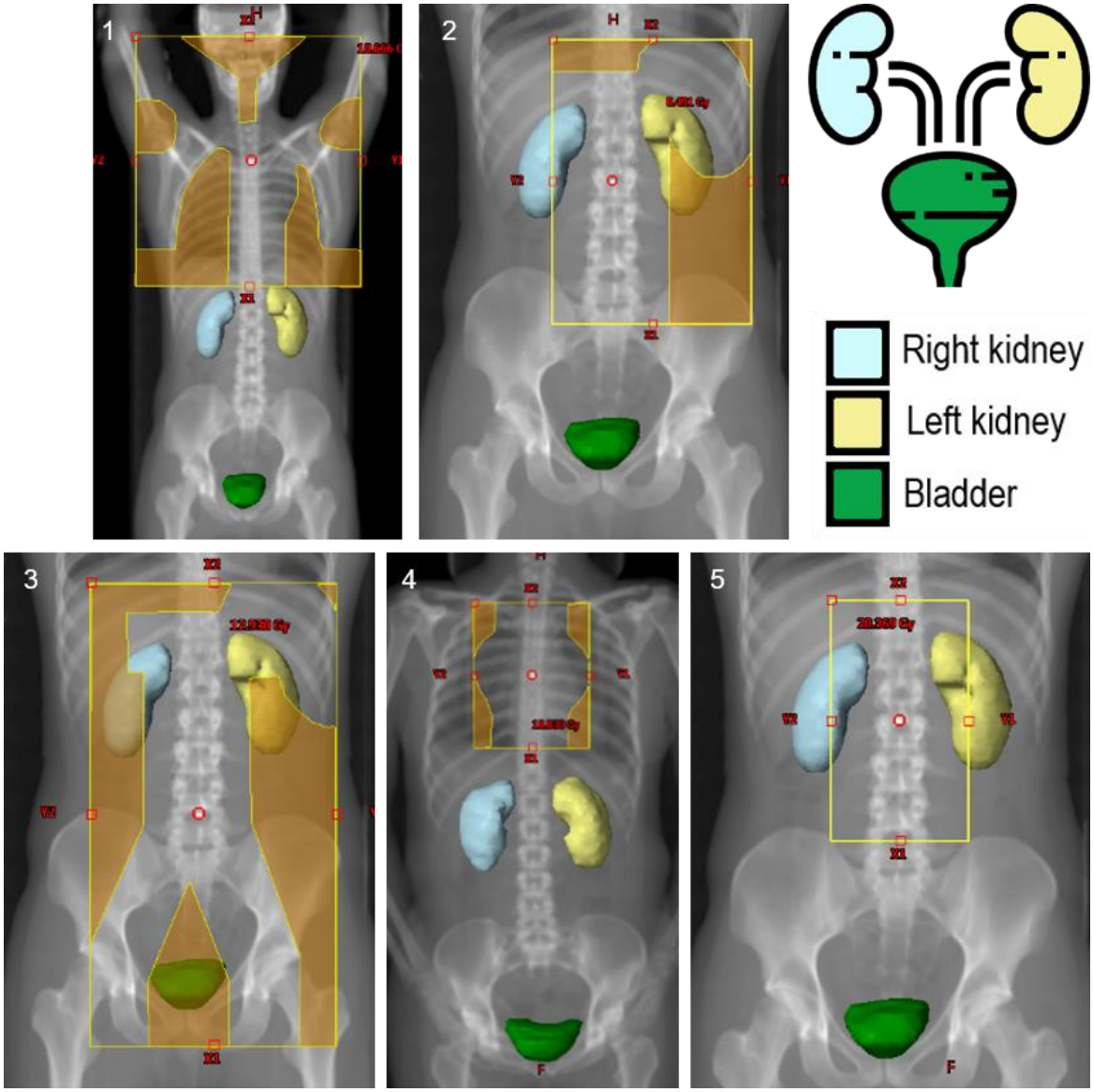


Figure 4.7: Position of the urinary organs in relation to the reconstructed radiotherapy fields

1. Mantle
2. Para-aortic field with spleen
3. Inverted-Y
4. Supradiaphragmatic involved field radiotherapy (mediastinum in this example)
5. Infradiaphragmatic involved field radiotherapy (para-aortic nodes in this example)

Subtotal nodal irradiation (STNI) is the combination of mantle and para-aortic with spleen fields
Total nodal irradiation (TNI) is the combination of mantle and inverted-Y fields

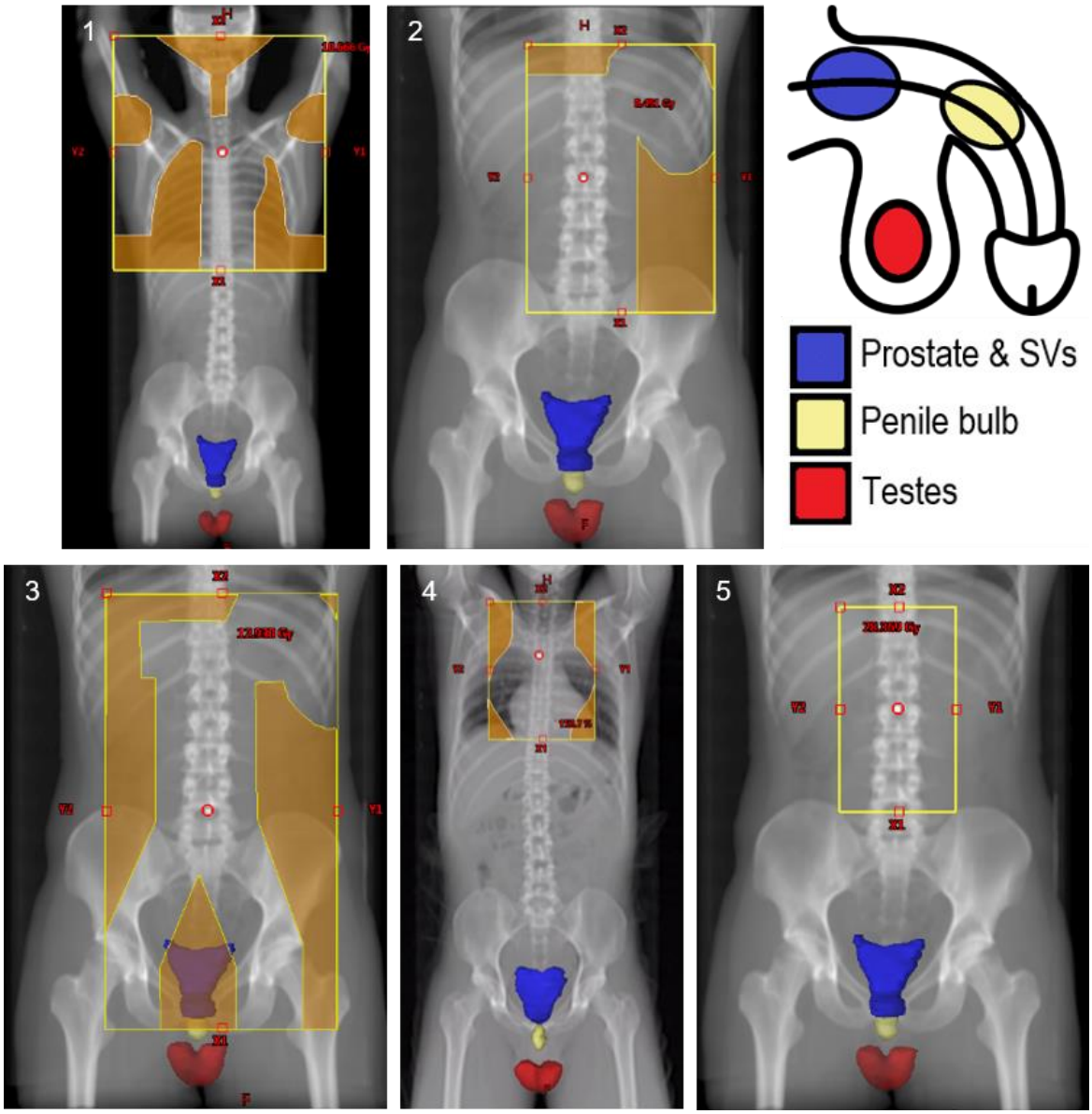


Figure 4.8: Position of the male genital organs in relation to the reconstructed radiotherapy fields

1. Mantle
2. Para-aortic field with spleen
3. Inverted-Y
4. Supradiaphragmatic involved field radiotherapy (mediastinum in this example)
5. Infradiaphragmatic involved field radiotherapy (para-aortic nodes in this example)

Subtotal nodal irradiation (STNI) is the combination of mantle and para-aortic with spleen fields

Total nodal irradiation (TNI) is the combination of mantle and inverted-Y fields

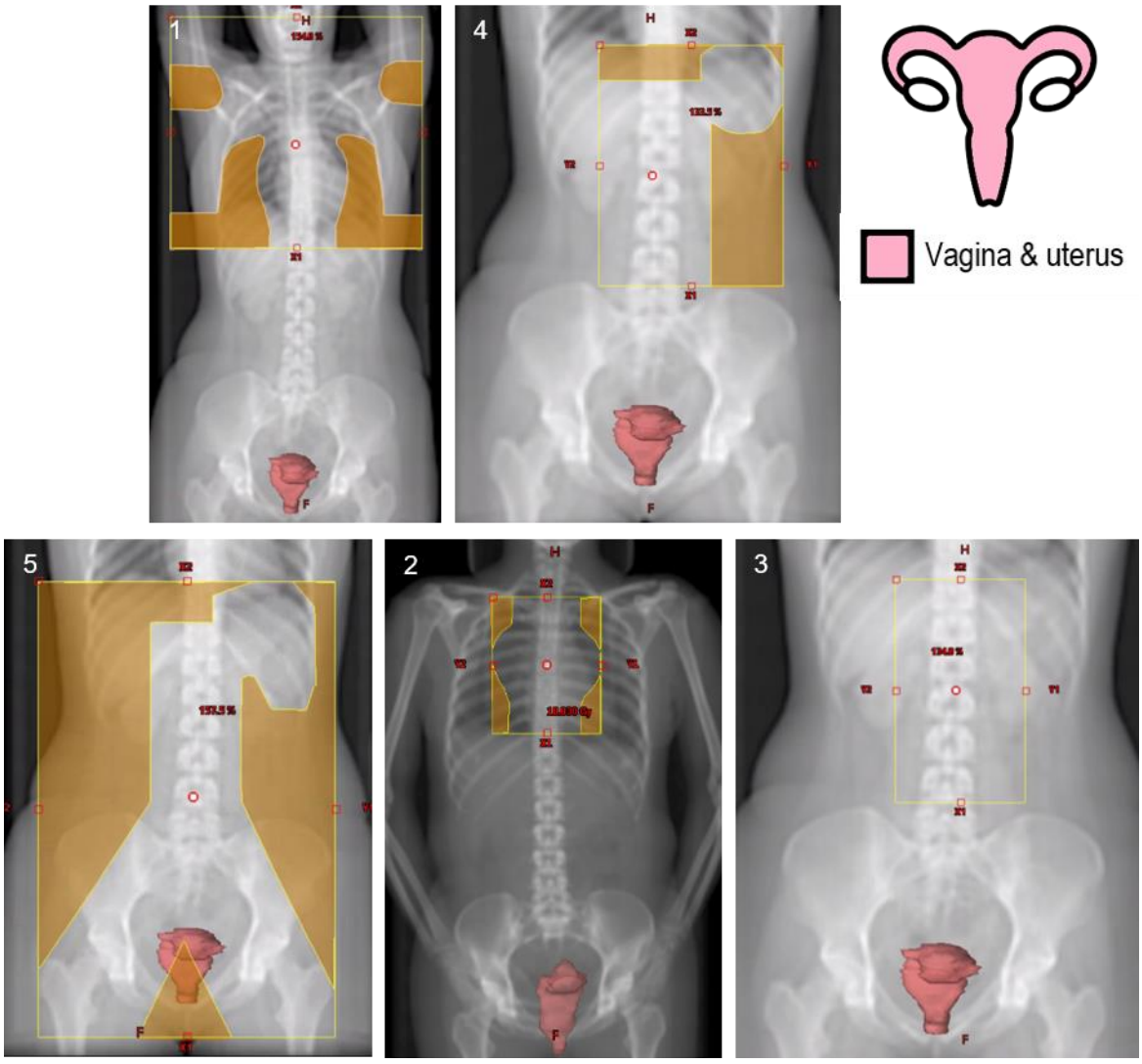


Figure 4.9: Position of the female genital organs in relation to the reconstructed radiotherapy fields

1. Mantle
2. Para-aortic field with spleen
3. Inverted-Y
4. Supradiaphragmatic involved field radiotherapy (mediastinum in this example)
5. Infradiaphragmatic involved field radiotherapy (para-aortic nodes in this example)

Subtotal nodal irradiation (STNI) is the combination of mantle and para-aortic with spleen fields

Total nodal irradiation (TNI) is the combination of mantle and inverted-Y fields

The median values of the mean doses to OARs from the radiotherapy fields, as a percentage of the total prescribed dose, are shown in Table 4.3. Patients who received infradiaphragmatic fields on relapse, following subtotal or total nodal irradiation for primary treatment, were excluded from this analysis (n=5). The same data is presented as absolute dose in Table C1, and displayed graphically in Figures C1-C4, in Appendix C.

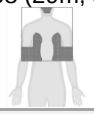
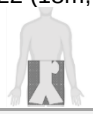
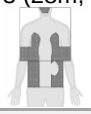
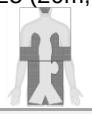
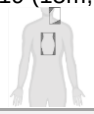
The colon received the highest doses from inverted-Y fields, but a greater proportion was outside the field or under more shielding during STNI. The transverse colon, which lies in the central abdomen, was present in the unshielded portion for the majority of infradiaphragmatic field types, and therefore received relatively high doses from all fields. The median mean dose ranged from 60.6% of prescribed dose for STNI to 71.4% of prescribed dose for inverted-Y fields. When the spleen was irradiated, the splenic flexure was also in the unshielded portion of the field and received significant radiation doses. The median mean dose ranged from 96.1% of prescribed dose for inverted-Y fields to 66.0% for TNI. Radiotherapy fields that included the iliac lymph nodes were the biggest contributor of dose to the caecum. The median mean dose ranged from 88.2% of prescribed dose for TNI to 2.0% for STNI. TNI resulted in the highest whole colon doses (median mean dose 61.8% prescribed dose). In some cases, the splenic flexure received a radiation dose from mantle field irradiation (median mean dose 2.9% of prescribed dose). This was dependent on the inferior border of the mantle field, the width of the lung shielding and the individual colonic anatomy of the representative CT used.

The pancreas, duodenum and stomach, which are central abdominal organs, received high doses from all infradiaphragmatic field types (median mean dose ranges 92.2-95.3%, 83.9-92.1% and 80.9-90.1% of prescribed dose respectively). The stomach and liver also received relatively high doses from mantle fields (median mean dose of 12.5% and 16.4% of prescribed dose respectively). The left kidney received higher doses than the right, due to its proximity to the unshielded portion of infradiaphragmatic fields designed to treat the

spleen. The bladder, prostate and seminal vesicles and vagina and uterus received high doses from inverted-Y fields (median mean dose of 70.3%, 52.9%, and 63.5% of prescribed dose respectively).

The IFRT categories included patients treated with a wide range of field shapes and sizes, making it difficult to draw any conclusions about the OAR doses in these groups. The majority of patients in the infradiaphragmatic IFRT category had radiotherapy to the pelvis, rather than abdomen (Table 4.2).

Table 4.3: Mean organ-at-risk dose, as percentage of total prescribed dose, split by radiotherapy field type

	Mantle n=68 (29m, 39f)	**Inverted-Y** n=22 (18m, 4f)	**STNI** n=43 (28m, 15f)	**TNI** n=25 (20m, 5f)	**IFRT SD** n=19 (15m, 4f)	**IFRT ID** n=7 (6m, 1f)
						
Mean OAR dose: Median (interquartile range) (as % of total prescribed dose*)						
Whole colon	**<1.0** (-)	**61.0** (51.9-66.3)	**25.5** (16.3-38.9)	**61.8** (49.6-65.3)	**<1.0** (-)	**22.1** (19.4-29.2)
Caecum	**<1.0** (-)	**82.0** (47.8-100.7)	**2.0** (0.9-3.5)	**88.2** (60.1-100.3)	**<1.0** (-)	**49.2** (3.1-78.5)
Ascending colon	**<1.0** (-)	**18.8** (12.5-32.6)	**5.8** (3.6-7.9)	**16.0** (11.1-37.4)	**<1.0** (-)	**5.6** (1.6-24.6)
Hepatic flexure	**1.3** (0.9-1.9)	**37.5** (18.6-51.0)	**20.4** (12.0-42.0)	**46.5** (24.8-52.9)	**<1.0** (-)	**2.0** (0.5-21.1)
Transverse colon	**<1.0** (-)	**71.4** (54.6-75.0)	**60.6** (50.4-76.0)	**63.9** (52.8-78.5)	**<1.0** (-)	**4.4** (1.2-34.8)
Splenic flexure	**2.9** (1.8-5.1)	**96.1** (42.6-102.0)	**85.6** (16.2-102.9)	**66.0** (15.2-100.1)	**<1.0** (-)	**1.2** (0.2-9.1)
Descending colon	**<1.0** (-)	**25.6** (12.1-43.8)	**15.9** (7.1-29.6)	**16.0** (11.8-41.4)	**<1.0** (-)	**3.2** (1.0-6.6)
Whole sigmoid	**<1.0** (-)	**85.2** (77.9-92.9)	**1.9** (1.3-2.5)	**86.0** (70.0-88.4)	**<1.0** (-)	**61.5** (10.0-77.3)
Sigmoid	**<1.0** (-)	**28.3** (21.0-65.8)	**3.0** (2.1-4.4)	**29.7** (19.2-46.1)	**<1.0** (-)	**13.5** (2.7-55.7)
Rectosigmoid	**<1.0** (-)	**102.0** (94.8-104.1)	**1.5** (1.0-2.2)	**99.7** (87.4-101.2)	**<1.0** (-)	**63.2** (11.1-89.5)
Rectum	**<1.0** (-)	**75.9** (45.1-90.5)	**<1.0** (-)	**69.1** (46.8-84.6)	**<1.0** (-)	**23.0** (15.2-55.7)
Anal canal	**<1.0** (-)	**14.7** (6.9-26.1)	**<1.0** (-)	**10.0** (7.6-12.5)	**<1.0** (-)	**7.8** (1.6-13.4)
Stomach	**12.5** (7.5-20.2)	**90.1** (71.8-95.8)	**96.4** (75.4-108.8)	**80.9** (55.6-98.2)	**1.6** (0.0-4.6)	**2.1** (0.9-40.2)

Duodenum	**2.0** (1.5-3.2)	**89.2** (83.3-96.7)	**83.9** (72.3-92.6)	**92.1** (82.8-97.4)	**<1.0** (-)	**4.4** (0.7-75.4)
Small bowel	**<1.0** (-)	**69.4** (65.1-83.0)	**30.4** (24.7-35.8)	**66.3** (61.7-74.6)	**<1.0** (-)	**31.9** (13.6-52.8)
Liver	**16.4** (12.3-22.4)	**31.5** (24.0-41.6)	**41.6** (32.4-47.3)	**44.7** (32.9-49.8)	**3.0** (0.0-8.1)	**4.0** (0.2-29.3)
Gallbladder	**2.1** (1.6-3.3)	**19.5** (13.4-32.3)	**19.1** (10.7-38.7)	**19.4** (15.5-30.9)	**<1.0** (-)	**1.6** (0.1-7.4)
Pancreas	**3.4** (2.7-5.8)	**95.3** (86.4-99.3)	**94.9** (86.1-101.2)	**92.2** (83.8-99.4)	**1.0** (0.0-1.9)	**2.2** (0.2-62.5)
Pancreatic tail	**4.2** (3.3-6.7)	**95.3** (81.2-99.9)	**94.8** (78.7-102.1)	**88.6** (71.4-99.2)	**1.1** (0.0-2.3)	**1.8** (0.1-44.3)
Spleen	**7.4** (4.7-9.8)	**97.0** (37.2-103.7)	**87.3** (39.2-109.0)	**42.7** (27.2-100.7)	**2.1** (0.0-2.6)	**1.7** (0.1-12.3)
Kidneys	**2.4** (1.8-3.6)	**47.5** (41.4-56.5)	**42.2** (35.0-52.7)	**41.2** (38.3-53.2)	**0.7** (0.0-1.3)	**3.1** (0.3-17.1)
Left kidney	**2.8** (2.0-5.0)	**57.6** (40.8-69.7)	**51.0** (36.1-69.1)	**47.4** (40.2-60.4)	**<1.0** (-)	**2.5** (0.2-16.0)
Right kidney	**1.7** (1.1-2.9)	**38.5** (25.0-50.8)	**31.4** (25.9-38.9)	**34.9** (24.5-51.4)	**<1.0** (-)	**3.9** (0.5-18.3)
Bladder	**<1.0** (-)	**70.3** (55.9-99.7)	**<1.0** (-)	**67.2** (58.4-81.1)	**<1.0** (-)	**31.8** (30.0-57.7)
Prostate & SVs	**<1.0** (-)	**52.9** (36.7-76.6)	**<1.0** (-)	**47.4** (38.0-67.7)	**<1.0** (-)	**22.7** (17.1-31.2)
Penile bulb	**<1.0** (-)	**7.1** (5.7-10.9)	**<1.0** (-)	**5.8** (4.4-9.6)	**<1.0** (-)	**4.1** (1.7-12.7)
Testes	**<1.0** (-)	**8.5** (3.3-16.3)	**<1.0** (-)	**7.9** (4.1-17.7)	**<1.0** (-)	**1.1** (1.0-5.1)
Vagina / uterus	**<1.0** **(-)**	**63.5** (61.5-83.4)	**<1.0** (-)	**60.7** (37.9-60.7)	**<1.0** (-)	**31.6** (-[§])

*Total prescribed dose = combined maximal prescribed dose for any fields that include the OAR in question. Patients who received infradiaphragmatic fields on relapse, following subtotal or total nodal irradiation for primary treatment, were excluded from this analysis (n=5).
[§]Only one dose in this category
Abbreviations - STNI: subtotal nodal irradiation; TNI: total nodal irradiation; IFRT: involved field radiotherapy; SD: supradiaphragmatic; ID: infradiaphragmatic; SVs: seminal vesicles; OAR: organ-at-risk

4.3.2 Doses to organs-at-risk in individuals who develop colorectal cancer compared to controls

The median mean doses to OARs, as absolute dose, for cases and controls are shown in Table 4.4. The biggest absolute differences in dose to colon segments were seen for the transverse colon (median mean dose 18.1 Gy in cases versus (vs) 1.0 Gy in controls) and the whole colon (11 Gy vs 0.9 Gy). Smaller, but statistically significant, differences were also seen for the hepatic flexure (6.8 Gy vs 0.8 Gy), ascending colon (2.8 Gy vs <0.5 Gy), sigmoid colon (1.3 Gy vs 0.5 Gy) and caecum (1.0 Gy vs <0.5 Gy). The median mean doses to the splenic flexure and descending colon were also higher for cases than controls, but these differences were not statistically significant (Table 4.4).

Both the duodenum and small bowel received higher doses in cases compared to controls (duodenum 26.4 Gy vs 1.8 Gy, small bowel 12.2 Gy vs 0.7 Gy). The gallbladder also received a higher dose in cases (5.3 Gy vs 1.5 Gy in controls). The right kidney received a higher dose in cases (9.8 Gy vs 2.0 Gy in controls), but there was no statistically significant difference in the dose received by the left kidney, or the kidneys overall. There was also no statistically significant difference in the median mean doses to the stomach, liver, pancreas, or spleen between cases and controls. Pelvic OARs all received extremely low doses, as they were outside of the majority of radiotherapy fields.

Figure 4.10 shows that the ranges of mean doses to each of the colon segments were similar in cases and controls. However, for most segments, the median and interquartile range was lower in controls. There were significantly more outliers in controls compared to cases.

Table 4.4: Mean organ-at-risk dose, split by whether an individual subsequently developed colorectal cancer (case) or not (control)

	Whole cohort	**Cases**	**Controls**	**Difference**	
	N=189 (118m, 71f)	n=65 (44m, 21f)	n=124 (74m, 50f)	Abs	$P_{difference}$
	Mean OAR dose: Median (interquartile range) (Gy)				
Whole colon	**5.7** (<0.5-16.0)	**11.0** (<0.5-21.0)	**0.9** (<0.5-14.3)	**10.1**	**0.003***
Caecum	**<0.5** (<0.5-13.8)	**1.0** (<0.5-29.4)	**<0.5** (<0.5-2.5)	**0.8**	**0.001***
Ascending colon	**1.3** (<0.5-4.0)	**2.8** (<0.5-8.9)	**<0.5** (<0.5-3.0)	**2.4**	**0.0003***
Hepatic flexure	**2.6** (<0.5-11.3)	**6.8** (0.9-17.4)	**0.8** (<0.5-8.0)	**6.0**	**0.001***
Transverse colon	**7.3** (<0.5-24.2)	**18.1** (0.7-26.6)	**1.0** (<0.5-23.9)	**17.1**	**0.04***
Splenic flexure	**2.9** (<0.5-28.9)	**3.5** (1.3-27.0)	**2.2** (0.8-31.6)	1.3	0.3
Descending colon	**1.7** (<0.5-7.2)	**2.7** (<0.5-7.5)	**0.7** (<0.5-6.9)	2.0	0.08
Whole sigmoid	**0.5** (<0.5-21.5)	**0.8** (<0.5-28.6)	**<0.5** (<0.5-3.1)	**<0.5**	**0.01***
Sigmoid	**0.8** (<0.5-4.6)	**1.3** (<0.5-13.1)	**0.5** (<0.5-2.6)	**0.8**	**0.003***
Rectosigmoid	**<0.5** (<0.5-25.3)	**0.6** (<0.5-33.8)	**<0.5** (<0.5-2.2)	**<0.5**	**0.02***
Rectum	**<0.5** (<0.5-9.5)	**<0.5** (<0.5-19.1)	**<0.5** (<0.5-2.5)	**<0.5**	**0.02***
Anal canal	**<0.5** (<0.5-2.0)	**<0.5** (<0.5-4.5)	**<0.5** (<0.5-0.5)	-	-
Stomach	**15.5** (4.0-34.7)	**18.7** (4.6-31.8)	**11.5** (3.4-34.8)	7.2	0.3
Duodenum	**12.1** (0.7-33.1)	**26.4** (1.4-33.9)	**1.8** (0.6-31.7)	**24.6**	**0.02***
Small bowel	**5.8** (<0.5-18.1)	**12.2** (0.4-25.4)	**0.7** (0.2-15.4)	**11.5**	**0.005***
Liver	**9.6** (5.2-15.9)	**11.5** (6.2-16.0)	**7.7** (4.8-15.5)	3.8	0.06
Gallbladder	**2.6** (0.7-17.0)	**5.3** (1.4-9.7)	**1.5** (0.7-6.3)	**3.8**	**0.003***
Pancreas	**18.2** (1.2-35.8)	**25.0** (2.2-36.3)	**4.9** (1.1-35.7)	20.1	0.2
Pancreatic tail	**15.6** (1.5-35.2)	**23.0** (2.2-35.2)	**7.3** (1.4-35.1)	15.7	0.3
Spleen	**5.4** (2.0-29.9)	**7.3** (2.7-27.0)	**4.5** (1.9-30.9)	2.8	0.6
Kidneys	**7.4** (0.9-16.5)	**11.2** (1.2-17.1)	**2.4** (0.7-15.7)	8.8	0.09
L kidney	**6.6** (0.9-19.8)	**10.8** (1.2-19.8)	**2.5** (0.8-19.7)	8.3	0.3
R kidney	**5.4** (0.6-12.0)	**9.8** (1.0-15.7)	**2.0** (0.5-10.8)	**7.8**	**0.003***
Bladder	**<0.5** (<0.5-9.5)	**<0.5** (<0.5-24.2)	**<0.5** (<0.5-1.3)	-	-
Prostate & SVs	**<0.5** (<0.5-14.9)	**<0.5** (<0.5-18.0)	**<0.5** (<0.5-9.9)	-	-
Penile bulb	**<0.5** (<0.5-2.2)	**<0.5** (<0.5-2.9)	**<0.5** (<0.5-1.8)	-	-
Testes	**<0.5** (<0.5-1.7)	**<0.5** (<0.5-4.8)	**<0.5** (<0.5-1.1)	-	-
Vagina / uterus	**<0.5** (<0.5-<0.5)	**<0.5** (<0.5-17.4)	**<0.5** (<0.5-<0.5)	-	-

Lower limit capped at 0.5 Gy as beyond this the accuracy of the TPS is poor [37]

*Statistically significant (P<0.05) difference between the median mean OAR dose in two groups, as tested using a Wilcoxon rank sum test

Abbreviations - m: male; f: female; Abs: absolute; P: probability value; OAR: organ-at-risk; Gy: gray; L: left; R: right; TPS: treatment planning system

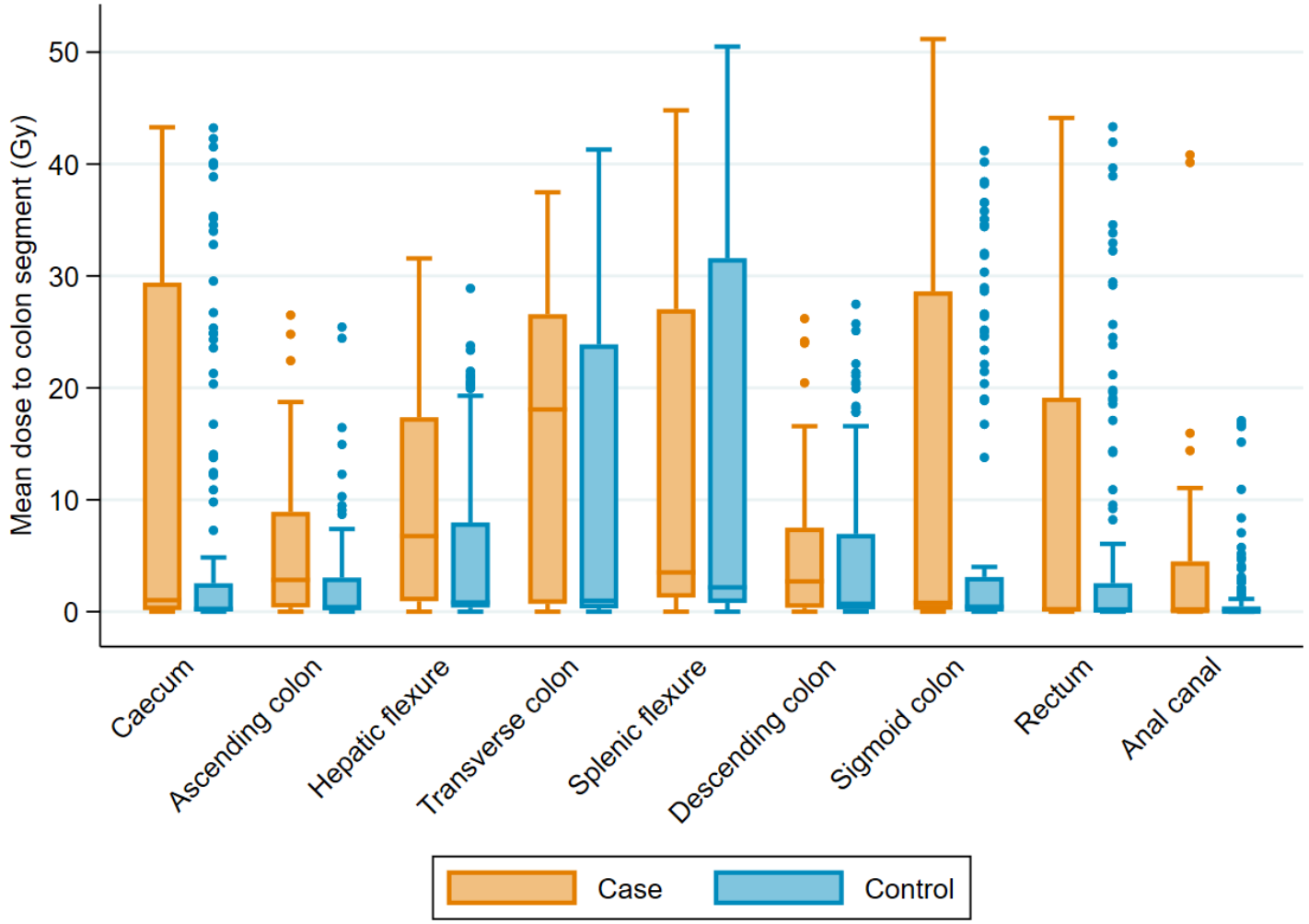


Figure 4.10: Box and whisker plot of mean doses to the colon segments, split by whether the individual subsequently developed colorectal cancer (case) or not (control)
Abbreviation - Gy: gray

4.4 Discussion

This study is the first to systematically and comprehensively derive estimates of radiation doses to abdominopelvic OARs from historic radiotherapy for HL. I have reported doses as percentages of prescribed dose for the main radiotherapy field types, and as absolute dose for the cohort as a whole, and separately for patients who went on to develop CRC or not. The highest OAR doses overall were seen in those treated with inverted-Y fields, and the highest doses to upper abdominal OARs seen in those treated with TNI. Patients who developed CRC received higher doses to the colon compared to those who did not develop CRC, and also higher doses to the duodenum, small bowel, gallbladder and right kidney. Doses to the stomach, liver, pancreas, spleen and left and bilateral kidneys were not statistically significantly different between cases and controls. The range of doses delivered to the colon segments was similar between those who went on to develop CRC and those who did not, indicating that, for an individual, receiving a high radiation dose alone is not sufficient to guarantee cancer induction.

4.4.1 Relevance in the context of modern radiotherapy

Table 4.5 compares the median mean doses from the individuals in the cohort who received infradiaphragmatic radiotherapy to the generally accepted constraints for late toxicity in otherwise normal organs, when standard fractionation is used. The doses used to treat lymphoma (typically 20-40 Gy) are much lower than some other tumours (e.g. prostate cancer treated to 74 Gy). Therefore, the universal dose constraints (Emami and QUANTEC [38–45]) applied to treating all tumour sites are typically higher than OAR doses seen with even historical radiotherapy techniques. The International Lymphoma Radiation Oncology Group (ILROG) provide lymphoma-specific dose constraints, but these currently only exist for thoracic OARs, and not abdominopelvic [4]. However, radiotherapy centres are able to adapt

guidelines from other tumour sites for their own practice. Our local Oxford protocol dose constraints are given in Table 4.5. Modern radiotherapy techniques allow more rapid fall-off of radiation dose, and potentially result in a greater volume of OARs receiving low-dose radiation. Volumetric dose constraints are therefore now favoured, rather than mean organ doses which are used when reporting doses from historical two-dimensional radiotherapy. Direct comparison with the doses obtained during this study is therefore difficult. However, where comparison is possible, the mean OAR doses observed in this study are higher than would be expected from modern HL radiotherapy. In particular, a mean spleen dose of 28.1 Gy is very high, and above the 10 Gy modern limit, beyond which patients are recommended to receive prophylactic vaccination and antibiotics [46]. Renal doses are also higher than would typically be accepted today, with the left kidney on average receiving 19 Gy. Current recommendations are that if one kidney receives over 18 Gy, the dose to the contralateral kidney should be kept to an absolute minimum. However, in this cohort, doses to the right kidney were also relatively high (median mean dose 11.6 Gy). The median mean dose to the testes was 0.9 Gy, which is extremely close to the current 1 Gy constraint. However, the testes are typically strapped away from the radiation field where possible during radiotherapy treatment, which was not replicated in the representative CTs. Also, for the majority of reconstructions the testes were out of the radiation field, where the dose is generally underestimated by the TPS [47]. The dose estimates reported here are therefore unlikely to be accurate.

Table 4.5: Comparison of the median mean doses to organs-at-risk in this study with published dose constraints

Organ-at-risk	Dose constraints		
	Emami / QUANTEC*	**OUH HL protocol**	**Current study (IDRT only)**
Stomach	D100 <50 Gy	D100 <45 Gy	Mean 32.3 Gy
Liver	Mean ≤30 Gy	Mean <32 Gy V40 30-35% D100 ≤25 Gy D66 ≤28 Gy D33 ≤38 Gy	Mean 14.0 Gy
Small bowel	V50 <5%	V45 <195 cm^3 (bowel bag)	Mean 17.3 Gy
Spleen		If mean dose ≥10 Gy consent for risk of overwhelming infection	Mean 28.1 Gy
Kidneys	Mean dose to one kidney <18 Gy	Mean ≤18 Gy V28 <20% V23 <30% V20 <32% V12 <55% (If mean >18 Gy to one kidney, V6 for contralateral <30%)	Mean 16.1 Gy Left mean 19.0 Gy Right mean 11.6 Gy
Colon	D100 <45 Gy		Mean 15.4 Gy
Rectum	V50 <50% V60 <35% V65 <25% V70 <20% V75 <15%		Mean 7.7 Gy
Bladder	D100 <65 Gy		Mean 8.0 Gy
Penile bulb	Mean <50 Gy		Mean 1.5 Gy
Testes		Mean <1 Gy Dmax ≤2 Gy to any part outside PTV	Mean 0.9 Gy

Abbreviations - QUANTEC: Quantitative analyses of normal tissue effects in the clinic; OUH: Oxford University Hospitals; HL: Hodgkin lymphoma; IDRT: infradiaphragmatic radiotherapy; Gy: gray; D100: dose that covers 100% of the organ; V40: % organ volume that receives ≥40 Gy; D66: dose that covers 66% of the organ; D33: dose that covers 33% of the organ; V50: % organ volume that receives ≥50 Gy; V45: % organ volume that receives ≥45 Gy; V28: % organ volume that receives ≥28 Gy; V23: % organ volume that receives ≥23 Gy; V20: % organ volume that receives ≥20 Gy; V12: % organ volume that receives ≥12 Gy; V6: % organ volume that receives ≥6 Gy: V60: % organ volume that receives ≥60 Gy; V65: % organ volume that receives ≥65 Gy; V70: % organ volume that receives ≥70 Gy; V75:% organ volume that receives ≥75 Gy; Dmax: maximum dose; PTV: planning target volume

*References [38–45]

4.4.2 Comparison with published data

To the best of my knowledge, there are only two other studies that report infradiaphragmatic OAR doses from modern radiotherapy techniques used to treat patients with HL. One is a planning study that compared abdominal OAR doses from three different techniques: three-dimensional conformal radiotherapy (3D-CRT), intensity modulated radiotherapy (IMRT) and proton beam therapy (PBT) [10]. The second is a study investigating risk of premature menopause that compared pelvic OAR doses in those treated with IFRT and ISRT in the HD17 trial [11]. The second study also analysed sex hormone levels in patients treated with either infradiaphragmatic or supradiaphragmatic radiotherapy in the HD14 trial, but they did not have OAR dose data for that cohort, and therefore only the data from the HD17 patients is discussed below.

Table 4.6 shows how abdominal OAR doses from the planning study compare to those from our cohort.

Table 4.6: Comparison of median mean abdominal organ-at-risk doses, in gray, between the current and previously published studies

Organ-at-risk	**Sachsman et al** [10]		**Current study**	
	3D-CRT	IMRT	All	IDRT only
	Median mean OAR dose (Gy)			
Stomach	21	14	15.5	32.3
Liver	5	8	9.6	14.0
Pancreas	19	17	18.2	35.4
Small bowel	8	8	5.8	17.3
Kidneys			7.4	16.1
Right kidney	1	4	5.4	11.6
Left kidney	16	15	6.6	19.0

Abbreviations - 3D-CRT: 3D conformal radiotherapy, IMRT: intensity modulated radiotherapy; IDRT: infradiaphragmatic radiotherapy; OAR: organ-at-risk; Gy: gray

The patients in our cohort were treated with two-dimensional radiotherapy. This is similar to 3D-CRT, but the radiation beam is only matched to the height and width of the target area,

rather than in three dimensions. IMRT is similar to modern radiotherapy techniques, and allows more conformal shaping of the treatment volume. PBT is not routinely available for the treatment of patients with HL in the UK, so I focus here on comparing the doses from 3D-CRT and IMRT with our cohort. Doses to the stomach, liver and pancreas are comparable between our study and those seen with 3D-CRT and IMRT. Doses to the small bowel and left kidney are lower, and those to the right kidney are higher. Most of these differences will be because our cohort includes some patients who had only supradiaphragmatic radiotherapy, whereas Sachsman et al's cohort is only those who had infradiaphragmatic radiotherapy [10]. When only those treated with infradiaphragmatic radiotherapy were included, the doses from our cohort were substantially higher for all OARs.

Table 4.7 shows how pelvic OAR doses from patients treated in HD17 compare to those from our cohort. The mean pelvic OAR doses from our cohort are comparable to those from patients treated with IFRT, apart from uterine doses which are lower for our cohort. This is likely due to random chance, as there are a small number of female patients in our cohort (all were female in the HD17 cohort) [11].

Table 4.7: Comparison of mean mean pelvic organ-at-risk doses, in gray, between the current and previously published studies

Organ-at-risk	**Rosenbrock et al** [11]		**Current study**	
	IFRT	ISRT	All	IDRT only
	Mean mean OAR dose (Gy)			
Small bowel	13.29	7.88	10.2	18.8
Bladder	11.67	8.74	7.4	13.6
Rectum	10.03	6.44	7.1	13.1
Uterus	14.51	8.94	3.7	9.4

Abbreviations - IFRT: involved-field radiotherapy; ISRT: involved-site radiotherapy; IDRT: infradiaphragmatic radiotherapy; OAR: organ-at-risk; Gy: gray

Maraldo et al also report doses to the spleen and stomach, as part of a study modelling doses from historic radiotherapy [7]. Table 4.8 shows how their doses compare to those from our cohort.

Table 4.8: Comparison of mean doses to abdominal organs-at-risk, expressed as a percentage of prescribed dose, between the current and previously published studies

Organ-at-risk	Maraldo et al [7]	Current study
	Mean OAR dose, as % of prescribed dose	
Mantle		
Spleen	5.7	6.6
Stomach	8.1	12.3
Mediastinal IFRT		
Spleen	5.7	1.12
Stomach	8.1	<1
Mantle & spleen		
Spleen	97.9 (+/- 12)	42.6
Stomach	75.7 (+/- 18)	46.6

Abbreviations - OAR: organ-at-risk; IFRT: involved field radiotherapy

Their estimates for spleen and stomach dose from mantle fields were relatively similar to ours (5.7% vs 6.6% and 8.1% vs 12.3% respectively). Their doses from mediastinal IFRT were higher than ours for both the spleen (5.7% vs 1.12%) and stomach (8.1% vs <1%). Doses for both the spleen and stomach were substantially higher for the mantle and spleen radiotherapy group in Maraldo's study compared to ours (97.9% vs 42.6% and 75.7% vs 46.6% respectively). There are a number of reasons why the doses reported by Maraldo et al differ from those found in the current study. They used a fixed SSD of 100 cm, whereas in our study this varied from 50 to 175.5 cm. Altering the SSD has significant effects on the absorbed dose deposited by a radiation beam, as absorbed dose is inversely proportional to the square of the distance from the source of radiation [48]. Using a fixed SSD of 100 cm, when this doesn't reflect the SSD at which patients were historically treated, will therefore affect the estimated absorbed dose to OARs. They also reconstructed all fields using six megavoltage (MV) photons [7], whereas our patients were treated with a range of energies (4-25 MV), and some with cobalt-60 machines. Finally, they did not account for inter-patient variability, which leads

to significant uncertainty in the accuracy of dose estimations for OARs located at the edge of radiotherapy fields [7]. A previous study of the accuracy of dose-reconstruction methods confirmed that this method performed poorly, particularly in lower dose regions [49]. There are also some differences in field reconstructions that probably account for the majority of differences between Maraldo's doses [7] and those from this study. Our group of supradiaphragmatic IFRT includes some patients treated with only neck, supraclavicular or axillary radiotherapy, where spleen and stomach doses would be expected to be much lower than that seen with mediastinal IFRT. I have used our STNI group to compare to Maraldo's mantle and spleen group, which includes some patients who did not have their spleen irradiated [7], therefore accounting for the lower spleen and stomach doses seen in our study compared to Maraldo's.

4.4.3 Relevance to the late-effects of radiotherapy

A study analysing the risk of gastric cancer in HL survivors found that the mean dose to the stomach, in cases and controls, was 15.3 Gy [15]. The excess odds ratio (EOR) for developing gastric cancer was 0.049 (95% confidence interval [CI] 0.007-0.16) per Gy delivered to the stomach [15]. A second study analysing risk of gastric cancer also found an increased risk with increasing radiation dose to the stomach [14]. Compared to patients who did not receive radiotherapy, the risk was significantly increased for those who received more than 25 Gy to the stomach (odds ratio [OR] 5.8, 95% CI 3.0-12.3) [14]. The median mean dose to the stomach for my whole cohort was 15.5 Gy, 18.7 Gy in cases, and 32.3 Gy in those treated with infradiaphragmatic radiotherapy. Risk of pancreatic cancer has been shown to increase with increasing radiation dose to the pancreas [18]. The EOR of pancreatic cancer was 0.098 (95% CI 0.015-0.42) per Gy delivered to the pancreas. This resulted in an OR of 9.1 (95% CI 1.7-77) at doses of 40 Gy or higher, and 4.3 (95% CI 1.7-15) for those receiving more than 10 Gy compared to less than 10 Gy. The median mean dose to the pancreas in my study was

18.2 Gy, but was higher in cases (25.0 Gy), and in those who received infradiaphragmatic radiotherapy (35.4 Gy). These data suggest that the cohort in my study is at a significantly increased risk of developing gastric and pancreatic cancer as late-effects of radiotherapy.

Yavas et al found there was an increased risk of impaired renal function a year after radiotherapy if the mean kidney dose exceeded 15 Gy [23]. As a whole, our cohort received doses lower than that, but the mean kidney dose for those who received infradiaphragmatic radiotherapy was higher (16.1 Gy).

Data from childhood cancer survivors suggests that the risk of diabetes is related to the radiation dose received by the tail of the pancreas, where the islets of Langerhans are concentrated [24]. In a cohort of French and British childhood cancer survivors, those who received 10 Gy or more to the pancreatic tail had a relative risk of diabetes of 11.5 (95% CI 3.9-34.0) compared to those who did not receive radiotherapy [24]. There was a linear-exponential dose-response relationship between dose to the pancreatic tail and subsequent risk of diabetes, with an excess relative risk of 0.66 (95% CI 0.23-1.71) per Gy [24]. On average, patients in our cohort received 15.6 Gy to the pancreatic tail, and those who went on to develop CRC received on average 23 Gy. An increased risk of diabetes mellitus has been observed in this cohort, particularly in those who received over 36 Gy to the para-aortic nodes and spleen [25]. Consistent with data from childhood cancer survivors, the risk of diabetes significantly increased with higher mean radiation doses to the pancreatic tail, with a hazard ratio of 1.017 per Gy (P <.001) [25]. However, overall, the rates of diabetes are lower in our cohort than would be predicted from the childhood cancer cohort. This may be due to a decrease in the radiosensitivity of the pancreas with age. De Vathaire found that the increase in relative risk of diabetes per Gy was higher in children younger than two years at the time of radiotherapy compared to those that were older [24]. In our cohort, the risk was highest for those treated before the age of 25 [25]. If the pancreas does become less sensitive with age,

one would expect the excess relative risk per Gy to be lower for adults than children. It would be interesting to determine if this is the case in our cohort.

4.4.4 Dose-response relationship for colorectal cancer

Data from this study have been used in collaboration with NKI to quantify the CRC rate following treatment for HL, in relation to radiation dose to the large bowel and procarbazine dose. Our analyses have shown that overall, CRC rate increased linearly with increasing mean radiation dose to the whole large bowel (overall excess rate ratio per gray (ERR/Gy) 9.2%, 95% CI 2.5-23.0), and with mean dose to the bowel segment in which the tumour subsequently developed ('affected segment', overall ERR/Gy 7.5%, 95% CI 2.2-17.8%). The radiation dose-effect was modified by cumulative procarbazine dose. For radiation dose to the whole large bowel, the ERR/Gy was 3.5% (95% CI 0.4-12.6%) for patients who did not receive procarbazine, and for each gram per metre-squared (g/m^2) increase in procarbazine dose the ERR/Gy increased 1.19-fold (95% CI 1.06-1.33) (Figure 4.11, panels A and C). For radiation dose to the affected segment, the ERR/Gy was 2.2% (95% CI 0.2-8.6%) for patients who did not receive procarbazine, and increased 1.17-fold (95% CI 1.03-1.33) for each g/m^2 increase in procarbazine dose (Figure 4.11, panels B and D). For radiation dose to the whole large bowel, sex, age at HL diagnosis, time since first HL treatment, and receipt of anthracyclines did not modify the dose-response relationship. The dose-response for radiation dose to the affected segment was modified by sex, with a higher ERR/Gy for women (39.1% versus 3.5% for men). This interaction was possibly driven by the receipt of pelvic radiotherapy (no pelvic radiotherapy versus pelvic radiotherapy: rate ratio (RR) in men 1.6, 95% CI 0.8-3.0; RR in women 12.0, 95% CI 2.6-56.4), and was no longer present when patients who received pelvic radiotherapy were excluded.

This is the first time a dose-response relationship between therapeutic radiation to the large bowel and CRC has been derived. The ERR/Gy is much lower than that from the Life Span Study in Japanese atomic bomb survivors (excess relative risk per Sievert 39.5%, 90% CI 11.3-72.5%). This is consistent with dose-response findings for other second solid cancers where the ERR/Gy is typically five to ten times higher among atomic bomb survivors than after therapeutic radiation [50,51]. This is likely due to different radiobiological effects from a single whole body dose of radiation compared to more targeted, higher-dose, fractionated exposures [50]. The finding that procarbazine modifies the radiation dose-response relationship is consistent with previous studies of gastrointestinal malignancies in HL survivors [19,52]. The exact biological mechanisms of interaction between radiation and procarbazine in carcinogenesis are not completely understood, but in vitro studies suggest a number of plausible mechanisms for synergistic effects in disrupting normal DNA repair and cell-cycle progression [53,54].

Although HL treatments have evolved considerably over recent decades, with fewer patients receiving infradiaphragmatic radiotherapy or high-dose procarbazine, our results remain relevant and important for clinicians treating patients for HL in the modern era. Our dose-response relationship enables individualised estimation of CRC risk, and selection of the optimal treatment strategy, for patients who are treated with infradiaphragmatic radiotherapy or procarbazine. They also emphasise the need for clinicians to identify HL survivors treated in the past in whom screening is warranted given their high-risk of developing CRC [55].

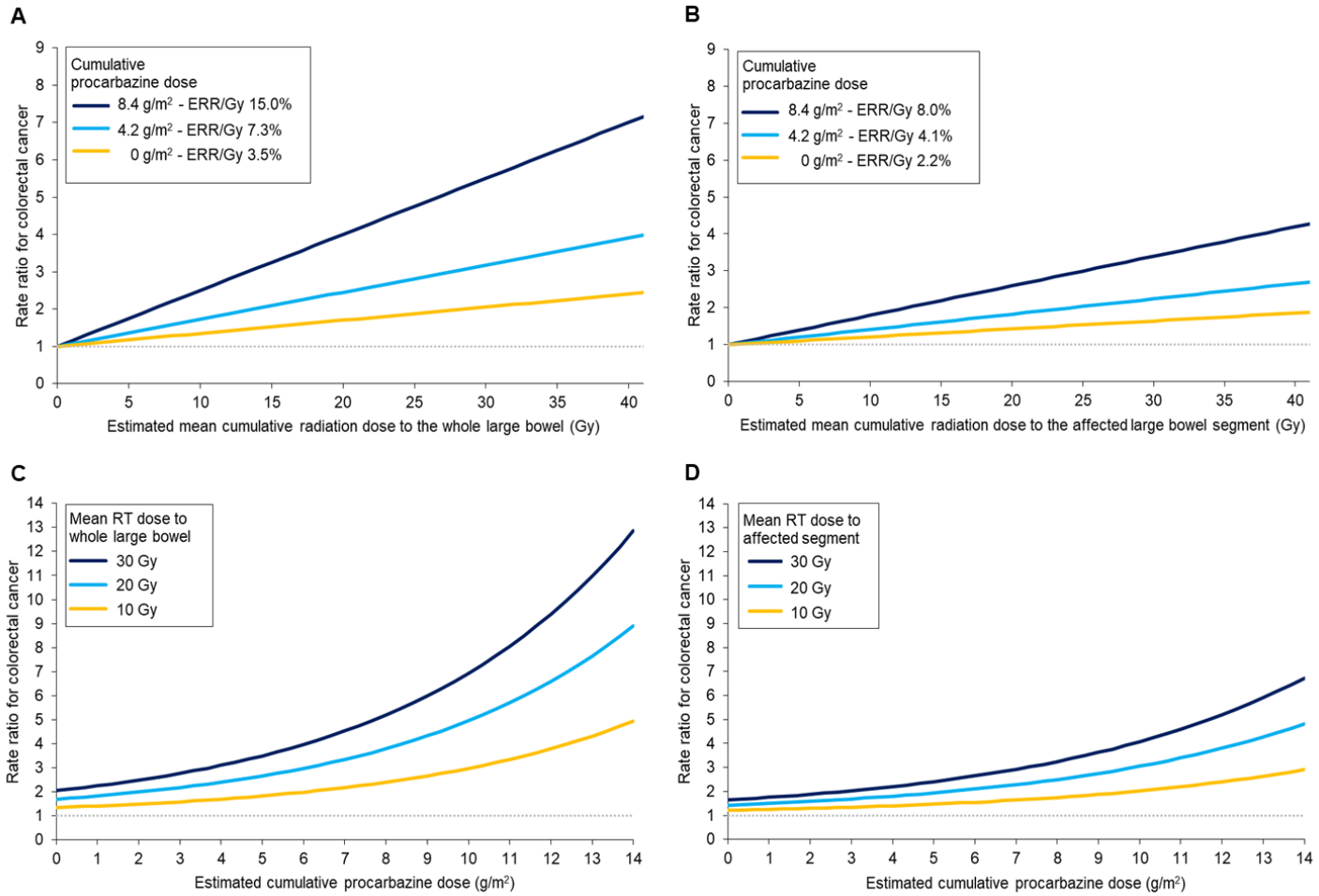


Figure 4.11: The modelled radiation dose-response relationship for colorectal cancer following Hodgkin lymphoma

A. Radiation dose-response for radiation dose to the whole large bowel for incremental procarbazine doses
B. Radiation dose-response for radiation dose to the affected bowel segment (matched segment for controls) for incremental procarbazine doses
C. Procarbazine dose-response for incremental radiation doses to the whole large bowel
D. Procarbazine dose-response for incremental radiation doses to the affected bowel segment (matched segment for controls)

Abbreviations - g/m^2: grams per metre-squared; ERR/Gy: excess rate ratio per gray; Gy: gray; RT: radiotherapy

4.4.5 Strengths and limitations

The doses reported here have been obtained by reconstructing individual patient's radiotherapy fields, using their treatment data to produce personalised estimates of the doses received by their OARs. Twelve representative CTs were used to match each patient's separation as closely as possible, to improve the accuracy of dose reconstruction. Although this wider range of representative CTs is expected to have increased the accuracy of OAR dose estimates compared to previous studies done by my research group using similar methods [27–29], there will still be residual inaccuracies associated with this method. Abdominal organ size and position varies significantly between patients, and within the same individual over time [56]. The gastrointestinal organs in particular (stomach, small bowel, colon, and rectum) are highly variable in size, shape and position between patients, and in the same patient on different days. It was not possible to account for these patient-specific variations in abdominal anatomy, which will have resulted in inaccuracies in the OAR doses calculated. In addition, some individuals in the cohort had a splenectomy prior to radiotherapy that would have resulted in shifts in the position of the remaining abdominal organs compared to those seen in the representative CTs. It is no longer common practice for people with lymphoma to undergo splenectomy, so it was not possible to obtain a representative CT from an individual without a spleen. The representative CTs used for the reconstructions were taken in the supine position, and none were available in the prone position. Therefore, it was not possible to account for the fact that the original posterior fields were delivered with the patient prone, and the posterior fields had to be simulated by gantry rotation. Organ position shifts when the patient is prone compared to supine [56], so there will have been some inaccuracies in dose estimation when only the supine position was simulated.

In addition, it is not possible to account for changes in anatomy and positioning errors during the course of an individual's radiotherapy, as these were not recorded on the prescription

charts we received. This introduces additional uncertainty between the planned dose and the reconstructed doses. This is particularly relevant because this cohort were treated in an era when patient immobilisation and image-guidance were not as sophisticated as they are today. Daily variation in patient set-up during historic radiotherapy has been shown to result in up to 15% tumour coverage error, suggesting there may be similar variation in the doses to OARs [57,58].

Despite these limitations, dose reconstruction using representative CTs has been shown to estimate mean heart dose to within 4% of the dose calculated using the individual's own CT scan, with errors having only small effects on the subsequent dose-response relationships obtained [49]. The methods I have used mirror those used in that paper, and so the uncertainties in the abdominopelvic OAR doses I have estimated can be expected to have similar accuracy overall.

4.4.6 Future work

As described above, the OAR doses reported here suggest that this cohort will be at increased risk of additional gastrointestinal malignancies, as well as non-malignant conditions such as renal impairment and diabetes. It will therefore be important to determine whether there is a dose-response relationship between the dose delivered to the abdominopelvic OARs and the subsequent risk of these late-effects. It is clear that currently published dose-constraints are not hugely relevant to treatment of HL, due to lower prescribed doses. Most published dose-response relationships are linear with no threshold, and therefore it is prudent to aim for as low a dose as possible to OARs when treating patients with HL. It would therefore be helpful for ILROG to publish guidelines on the doses which should be achieved. The counter-argument to this is that some may see such doses as thresholds below which you can stop trying to optimise the radiotherapy plan. Perhaps

a better approach is to encourage clinical oncologists to focus on the magnitude of risk for an individual patient, rather than just the dose to their organs. Danish researchers have suggested a method of risk-optimised radiotherapy planning, using a tool that graphically displays late-effects risk estimates based on the dose to OARs from a radiotherapy plan [59]. Such a tool could be embedded into TPSs, to optimise radiotherapy plans based on risk rather than OAR dose. For some OARs, risk of late toxicity may be related to the volume of tissue receiving a certain radiotherapy dose, rather than the mean dose to the whole organ. For example, the risk of renal dysfunction increases with increasing volume of renal tissue receiving five, 10 and 20 Gy [22]. Future studies could report volumetric doses and investigate whether dose-response relationships using these describe the risk of late-effects more accurately. The ranges of OAR dose were often similar between those patients who went on to develop CRC and those who did not, which is in keeping with the stochastic nature of carcinogenesis [60]. But it is also possible that there are additional factors which affect the risk of late-effects following radiotherapy. Future research should consider interactions with other specific chemotherapy agents, as well as patient-specific factors such as smoking and family history, to determine whether there are individual determinants of the dose-response relationship.

In line with other studies investigating risk of second malignancies following radiotherapy, we have used the physical doses to determine the dose-response relationship for the risk of CRC. This is in contrast to studies investigating cardiovascular late-effects of radiotherapy that have converted physical dose to equivalent dose in 2 Gy per fraction, taking the alpha/beta (α/β) ratio of the heart into account [28,29,61]. The α/β ratio is derived from the linear-quadratic model that describes the relationship between cell survival and delivered dose of radiotherapy [62]. When survival is plotted on a log scale, the dose-response curve is ‘shouldered’ with an initial linear region (α) at low doses, followed by increasing curvature (quadratic region, β). The degree of curvature is defined in terms of the α/β ratio, which corresponds to the dose (in gray) at which the linear and quadratic

contributions are equal [62]. Cells with a high α/β ratio are killed at a relatively constant rate with increasing radiation dose, whereas those with a low α/β ratio are killed at a higher rate with increasing dose (Figure 4.12) [62].

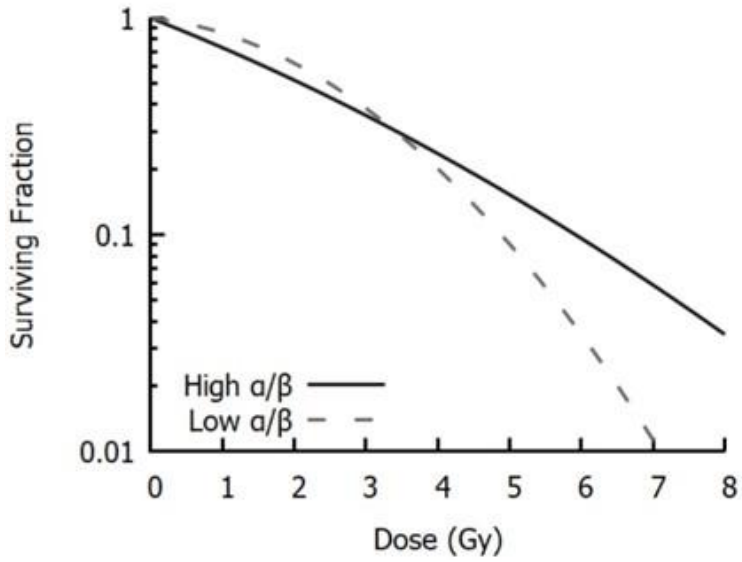


Figure 4.12: Linear-quadratic model of cell survival following radiotherapy
Cells with a high α/β ratio have near-constant rates of cell survival with increasing dose (solid line), whilst cells with a low α/β ratio experience lower survival per unit dose (in gray) at higher doses (dotted line).
Adapted from McMahon, 2018 [62] in line with the terms of the Creative Commons Attribution 3.0 licence

The linear-quadratic model was validated by single dose killing and isoeffective tissue responses, to predict effects from varying fractionation regimes, and therefore there is concern that it cannot be applied to second cancer induction. The α/β ratio for second cancer development has not been defined, and it is difficult to obtain data to measure it due to its latency and the lack of data for radiotherapy exposures with suitably variable fraction sizes. Therefore, it is reasonable to use physical dose currently, but future studies should consider whether an α/β ratio is relevant for the risk of second cancers and if it could be defined.

4.5 Conclusions

This study's results demonstrate that patients who received infradiaphragmatic radiotherapy for HL in the past received high radiation doses to OARs. Radiation doses to the colon were, on average, higher in those who developed CRC compared to those who did not, and there is a linear dose-response relationship between dose received by the large bowel and CRC risk. Such dose-response relationships allow the risks of modern radiotherapy to be estimated, which can facilitate informed and shared decision-making about radiotherapy for the treatment of HL. As doses from modern radiotherapy are much lower than those reported here, patients treated for HL currently are likely to be at a lower risk of late-effects.

The high OAR doses seen in this cohort mean that consideration should be given to screening people previously treated with infradiaphragmatic radiotherapy. Surveillance guidelines for childhood cancer survivors recommend that people exposed to more than 30 Gy of abdominal radiation should undergo colonoscopy a minimum of every five years, beginning at 10 years after radiation, or at age 35 years, whichever is later [63]. As yet, there is no screening programme for gastrointestinal cancer, diabetes or renal dysfunction for adult HL survivors, but this may be warranted to reduce premature mortality from the late-effects of radiotherapy.

4.6 References

[1] Yahalom J, Mauch P. The involved field is back: issues in delineating the radiation field in Hodgkin's disease. Ann Oncol 2002;13:79–83. doi:10.1093/ANNONC/13.S1.79.

[2] Bar V, Paltiel O, Glatstein E. Radiotherapy for early-stage Hodgkin's lymphoma: A 21st century perspective and review of multiple randomized clinical trials. Int J Radiat Oncol 2008;72:1472–9. doi:10.1016/j.ijrobp.2008.08.026.

[3] Girinsky T, van der Maazen R, Specht L, Aleman B, Poortmans P, Lievens Y, et al. Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: concepts and guidelines. Radiother Oncol 2006;79:270–7. doi:10.1016/J.RADONC.2006.05.015.

[4] Wirth A, Mikhaeel NG, Aleman BMP, Pinnix CC, Constine LS, Ricardi U, et al. Involved site radiation therapy in adult lymphomas: an overview of International Lymphoma Radiation Oncology Group guidelines. Int J Radiat Oncol 2020;107:909–33. doi:10.1016/J.IJROBP.2020.03.019.

[5] Pinnix CC, Gunther JR, Fang P, Bankston ME, Milgrom SA, Boyce D, et al. Assessment of radiation doses delivered to organs at risk among patients with early-stage favorable Hodgkin lymphoma treated with contemporary radiation therapy. JAMA Netw Open 2020;3:e2013935–e2013935. doi:10.1001/JAMANETWORKOPEN.2020.13935.

[6] Maraldo M V., Brodin P, Aznar MC, Vogelius IR, Munck af Rosenschöld P, Petersen PM, et al. Doses to carotid arteries after modern radiation therapy for Hodgkin lymphoma: Is stroke still a late effect of treatment? Int J Radiat Oncol 2013;87:297–303. doi:10.1016/J.IJROBP.2013.06.004.

[7] Maraldo M V., Lundemann M, Vogelius IR, Specht L. A new method to estimate doses to the normal tissues after past extended and involved field radiotherapy for Hodgkin lymphoma. Radiother Oncol 2015;114:206–11. doi:10.1016/j.radonc.2015.01.008.

[8] Maraldo M V, Brodin NP, Aznar MC, Vogelius IR, Munck Af Rosenschöld P, Petersen PM, et al. Doses to head and neck normal tissues for early stage Hodgkin lymphoma after involved node radiotherapy. Radiother Oncol 2014;110:441–7. doi:10.1016/j.radonc.2013.09.027.

[9] Maraldo M V., Jørgensen M, Brodin NP, Aznar MC, Vogelius IR, Petersen PM, et al. The impact of involved node, involved field and mantle field radiotherapy on estimated radiation doses and risk of late effects for pediatric patients with Hodgkin lymphoma. Pediatr Blood Cancer 2014;61:717–22. doi:10.1002/PBC.24861.

[10] Sachsman S, Hoppe BS, Mendenhall NP, Holtzman A, Li Z, Slayton W, et al. Proton therapy to the subdiaphragmatic region in the management of patients with Hodgkin lymphoma. Leuk Lymphoma 2015;56:2019–24. doi:10.3109/10428194.2014.975802/SUPPL_FILE/ILAL_A_975802_SM1574.ZIP.

[11] Rosenbrock J, Vásquez-Torres A, Mueller H, Behringer K, Zerth M, Celik E, et al. Involved site radiotherapy extends time to premature menopause in infra-diaphragmatic female Hodgkin lymphoma patients – An analysis of GHSG HD14- and HD17-patients. Front Oncol 2021;11:1933. doi:10.3389/fonc.2021.658358.

[12] Hull MC, Price Mendenhall N, Colgan ME. Subdiaphragmatic Hodgkin's disease: The University of Florida experience. Int J Radiat Oncol 2002;52:161–6. doi:10.1016/S0360-3016(01)01813-2.

[13] Harris MA, Radford JA, Deakin DP, James RD, Swindell R, Cowan RA. Limited field radiotherapy for early stage, infra-diaphragmatic Hodgkin's lymphoma. Clin Oncol 2004;16:53–7. doi:10.1016/J.CLON.2003.08.007.

[14] Morton LM, Dores GM, Curtis RE, Lynch CF, Stovall M, Hall P, et al. Stomach cancer risk after treatment for Hodgkin lymphoma. J Clin Oncol 2013;31:3369–77. doi:10.1200/JCO.2013.50.6832.

[15] Gilbert ES, Curtis RE, Hauptmann M, Kleinerman RA, Lynch CF, Stovall M, et al. Stomach cancer following Hodgkin lymphoma, testicular cancer and cervical cancer: a pooled analysis of three international studies with a focus on radiation effects. Radiat Res 2017;187:186–95. doi:10.1667/RR14453.1.
[16] van den Belt-Dusebout AW, Aleman BMP, Besseling G, de Bruin ML, Hauptmann M, van 't Veer MB, et al. Roles of radiation dose and chemotherapy in the etiology of stomach cancer as a second malignancy. Int J Radiat Oncol 2009;75:1420–9. doi:10.1016/J.IJROBP.2009.01.073.
[17] Birdwell SH, Hancock SL, Varghese A, Cox RS, Hoppe RT. Gastrointestinal cancer after treatment of Hodgkin's disease. Int J Radiat Oncol Biol Phys 1997;37:67–73. doi:10.1016/S0360-3016(96)00489-0.
[18] Dores GM, Curtis RE, van Leeuwen FE, Stovall M, Hall P, Lynch CF, et al. Pancreatic cancer risk after treatment of Hodgkin lymphoma. Ann Oncol 2014;25:2073–9. doi:10.1093/annonc/mdu287.
[19] van Eggermond AM, Schaapveld M, Janus CPM, De Boer JP, Krol AD, Zijlstra JM, et al. Infradiaphragmatic irradiation and high procarbazine doses increase colorectal cancer risk in Hodgkin lymphoma survivors. Br J Cancer 2017;117:306–14. doi:10.1038/bjc.2017.177.
[20] Hodgson DC, Gilbert ES, Dores GM, Schonfeld SJ, Lynch CF, Storm H, et al. Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. J Clin Oncol 2007;25:1489–97. doi:10.1200/JCO.2006.09.0936.
[21] Schaapveld M, Aleman BMP, van Eggermond AM, Janus CPM, Krol ADG, van der Maazen RWM, et al. Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. N Engl J Med 2015;373:2499–511. doi:10.1056/NEJMoa1505949.
[22] Diavolitsis VM, Rademaker A, Boyle J, Kang Z, Kiel K, Mulcahy M, et al. Change in creatinine clearance over time following upper abdominal irradiation: a dose-volume histogram multivariate analysis. Am J Clin Oncol Cancer Clin Trials 2011;34:53–7. doi:10.1097/COC.0B013E3181D27080.
[23] Yavas G, Elsurer R, Yavas C, Ata O. Basal renal function reserve and mean kidney dose predict future radiation-induced kidney injury in stomach cancer patients. Support Care Cancer 2014;22:445–51. doi:10.1007/S00520-013-1996-Z/TABLES/4.
[24] de Vathaire F, El-Fayech C, Ben Ayed FF, Haddy N, Guibout C, Winter D, et al. Radiation dose to the pancreas and risk of diabetes mellitus in childhood cancer survivors: a retrospective cohort study. Lancet Oncol 2012;13:1002–10. doi:10.1016/S1470-2045(12)70323-6.
[25] van Nimwegen FA, Schaapveld M, Janus CPM, Krol ADG, Raemaekers JMM, Kremer LCM, et al. Risk of diabetes mellitus in long-term survivors of Hodgkin lymphoma. J Clin Oncol 2014;32:3257–63. doi:10.1200/JCO.2013.54.4379.
[26] Meacham LR, Sklar CA, Li S, Liu Q, Gimpel N, Yasui Y, et al. Diabetes mellitus in long-term survivors of childhood cancer: increased risk associated with radiation therapy: a report for the Childhood Cancer Survivor Study. Arch Intern Med 2009;169:1381–8. doi:10.1001/ARCHINTERNMED.2009.209.
[27] van Nimwegen FA, Ntentas G, Darby SC, Schaapveld M, Hauptmann M, Lugtenburg PJ, et al. Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines. Blood 2017;129:2257–65. doi:10.1182/blood-2016-09-740332.
[28] Cutter DJ, Schaapveld M, Darby SC, Hauptmann M, Van Nimwegen FA, Krol ADG, et al. Risk for valvular heart disease after treatment for Hodgkin lymphoma. J Natl Cancer Inst 2015;107:1–9. doi:10.1093/jnci/djv008.
[29] van Nimwegen FA, Schaapveld M, Cutter DJ, Janus CPM, Krol ADG, Hauptmann M, et al. Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. J Clin Oncol 2015;34:235–43. doi:10.1200/jco.2015.63.4444.
[30] Gay HA, Barthold HJ, O'Meara E, Bosch WR, El Naqa I, Al-Lozi R, et al. Pelvic normal tissue contouring guidelines for radiation therapy: a Radiation Therapy

Oncology Group consensus panel atlas. Int J Radiat Oncol 2012;83:e353–62. doi:10.1016/J.IJROBP.2012.01.023.
[31] Jabbour SK, Hashem SA, Bosch W, Kim TK, Finkelstein SE, Anderson BM, et al. Upper abdominal normal organ contouring guidelines and atlas: a Radiation Therapy Oncology Group consensus. Pract Radiat Oncol 2014;4:82–9. doi:10.1016/J.PRRO.2013.06.004.
[32] Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma: the 3d English Edition [Secondary Publication]. J Anus, Rectum Colon 2019;3:175–95. doi:10.23922/jarc.2019-018.
[33] Kumar PP, Good RR, Jones EO, Somers JE, McAnulty BE, McCaul GF, et al. Extended-field isocentric irradiation for Hodgkin's disease. J Natl Med Assoc 1987;79:969–80.
[34] Prosnitz LR, Brizel DM, Light KL. Radiation techniques for the treatment of Hodgkin's disease with combined modality therapy or radiation alone. Int J Radiat Oncol Biol Phys 1997;39:885–95. doi:10.1016/S0360-3016(97)00463-X.
[35] Svahn-Tapper & G, Landberg T. Mantle treatment of Hodgkin's disease with cobalt 60: technique and dosimetry. Acta Radiol Ther Phys Biol 1971;10:33–55. doi:10.3109/02841867109129744.
[36] Rønde HS, Hoffmann L. Validation of Varian's AAA algorithm with focus on lung treatments. Acta Oncol (Madr) 2009;48:209–15. doi:10.1080/02841860802287108.
[37] Huang JY, Followill DS, Wang XA, Kry SF. Accuracy and sources of error of out-of field dose calculations by a commercial treatment planning system for intensity-modulated radiation therapy treatments. J Appl Clin Med Phys 2013;14:186–97. doi:10.1120/JACMP.V14I2.4139.
[38] Emami B. Tolerance of normal tissue to therapeutic radiation. Reports Radiother Oncol 2013;1:123–7.
[39] Emami B, Lyman J, Brown A, Cola L, Goitein M, Munzenrider JE, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol 1991;21:109–22. doi:10.1016/0360-3016(91)90171-Y.
[40] Pan CC, Kavanagh BD, Dawson LA, Li XA, Das SK, Miften M, et al. Radiation-associated liver injury. Int J Radiat Oncol 2010;76:S94–100. doi:10.1016/J.IJROBP.2009.06.092.
[41] Kavanagh BD, Pan CC, Dawson LA, Das SK, Li XA, Ten Haken RK, et al. Radiation dose–volume effects in the stomach and small bowel. Int J Radiat Oncol 2010;76:S101–7. doi:10.1016/J.IJROBP.2009.05.071.
[42] Dawson LA, Kavanagh BD, Paulino AC, Das SK, Miften M, Li XA, et al. Radiation-associated kidney injury. Int J Radiat Oncol 2010;76:S108–15. doi:10.1016/J.IJROBP.2009.02.089.
[43] Viswanathan AN, Yorke ED, Marks LB, Eifel PJ, Shipley WU. Radiation dose–volume effects of the urinary bladder. Int J Radiat Oncol 2010;76:S116–22. doi:10.1016/J.IJROBP.2009.02.090.
[44] Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose–volume effects in radiation-induced rectal injury. Int J Radiat Oncol 2010;76:S123–9. doi:10.1016/J.IJROBP.2009.03.078.
[45] Roach M, Nam J, Gagliardi G, El Naqa I, Deasy JO, Marks LB. Radiation dose–volume effects and the penile bulb. Int J Radiat Oncol 2010;76:S130–4. doi:10.1016/J.IJROBP.2009.04.094.
[46] The Royal College of Radiologists. Incidental irradiation of the spleen. RCR guidance. 2021.
[47] Sánchez-Nieto B, Medina-Ascanio KN, Rodríguez-Mongua JL, Doerner E, Espinoza I. Study of out-of-field dose in photon radiotherapy: a commercial treatment planning system versus measurements and Monte Carlo simulations. Med Phys 2020;47:4616–25. doi:10.1002/MP.14356.
[48] Podgorsak EB. sponsored by I. Radiation oncology physics: a handbook for teachers and students. International Atomic Energy Agency; 2005. doi:http://www-

naweb.iaea.org/nahu/DMRP/syllabus.html.
[49] Ntentas G, Darby SC, Aznar MC, Hodgson DC, Howell RM, Maraldo M V, et al. Dose-response relationships for radiation-related heart disease: impact of uncertainties in cardiac dose reconstruction. Radiother Oncol 2020;153:155–62. doi:10.1016/j.radonc.2020.08.022.
[50] Berrington De Gonzalez A, Gilbert E, Curtis R, Inskip P, Kleinerman R, Morton L, et al. Second solid cancers after radiation therapy: a systematic review of the epidemiologic studies of the radiation dose-response relationship. Int J Radiat Oncol 2013;86:224–33. doi:10.1016/J.IJROBP.2012.09.001.
[51] Little MP. Comparison of the risks of cancer incidence and mortality following radiation therapy for benign and malignant disease with the cancer risks observed in the Japanese A-bomb survivors. Int J Radiat Biol 2009;77:431–64. doi:10.1080/09553000010022634.
[52] Morton LM, Dores GM, Curtis RE, Lynch CF, Stovall M, Hall P, et al. Stomach cancer risk after treatment for Hodgkin lymphoma. J Clin Oncol 2013;31:3369–77. doi:10.1200/JCO.2013.50.6832.
[53] Wilson GD, Bentzen SM, Harari PM. Biologic basis for combining drugs with radiation. Semin Radiat Oncol 2006;16:2–9. doi:10.1016/j.semradonc.2005.08.001.
[54] Lawrence TS, Blackstock AW, McGinn C. The mechanism of action of radiosensitization of conventional chemotherapeutic agents. Semin Radiat Oncol 2003;13:13–21. doi:10.1053/srao.2003.50002.
[55] Rigter LS, Spaander MCW, Aleman BMP, Bisseling TM, Moons LM, Cats A, et al. High prevalence of advanced colorectal neoplasia and serrated polyposis syndrome in Hodgkin lymphoma survivors. Cancer 2019;125:990–9. doi:10.1002/cncr.31903.
[56] Langen KM, Jones DTL. Organ motion and its management. Int J Radiat Oncol Biol Phys 2001;50:265–78. doi:10.1016/S0360-3016(01)01453-5.
[57] Marks JE, Haus AG, Sutton HG, Griem ML. Localization error in the radiotherapy of Hodgkin's disease and malignant lymphoma with extended mantle fields. Cancer 1974;34:83–90.
[58] Marks JE, Haus AG, Sutton HG, Griem ML. The value of frequent treatment verification films in reducing localization error in the irradiation of complex fields. Cancer 1976;37:2755–61.
[59] Brodin NP, Maraldo M V., Aznar MC, Vogelius IR, Petersen PM, Bentzen SM, et al. Interactive decision-support tool for risk-based radiation therapy plan comparison for Hodgkin lymphoma. Int J Radiat Oncol Biol Phys 2014;88:433–45. doi:10.1016/j.ijrobp.2013.10.028.
[60] Moolgavkar SH. Stochastic models of carcinogensis. In: Rao CR, Chakraborty R, editors. Handb. Stat. Vol. 8. Stat. Methods Biol. Med. Sci., Elsevier; 1991, p. 373–93. doi:https://doi.org/10.1016/S0169-7161(05)80168-3.
[61] van Nimwegen FA, Ntentas G, Darby SC, Schaapveld M, Hauptmann M, Lugtenburg PJ, et al. Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines. Blood 2017;129:2257–65. doi:10.1182/blood-2016-09-740332.
[62] McMahon SJ. The linear quadratic model: Usage, interpretation and challenges. Phys Med Biol 2019;64. doi:10.1088/1361-6560/aaf26a.
[63] Landier W, Bhatia S, Eshelman DA, Forte KJ, Sweeney T, Hester AL, et al. Development of risk-based guidelines for pediatric cancer survivors: The Children's Oncology Group Long-Term Follow-Up Guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. J Clin Oncol 2004;22:4979–90. doi:10.1200/JCO.2004.11.032.

Chapter 5

Development of a multivariable model to predict mean heart dose using pre-chemotherapy PET-CT scans

5.1 Background

5.1.1 Use of PET-CT scans in the management of Hodgkin lymphoma

Positron emission tomography with computed tomography (PET-CT) imaging is used routinely in the management of Hodgkin lymphoma (HL), to accurately stage disease, and evaluate response to treatment. These scans are taken after a patient is given an intravenous radioactive glucose analogue, ^{18}F-fluorodeoxyglucose (FDG). Malignant cells, such as HL, have higher rates of aerobic glycolysis, and therefore glucose uptake, than normal tissues [1]. They therefore accumulate FDG, and as the ^{18}F radionuclide decays it emits a positron that travels a few millimetres in tissue before undergoing an 'annihilation reaction' with an electron [2]. This reaction results in the release of two 511-keV photons that are detected by the PET scanner [2]. These images are then fused with CT images, to allow the anatomical location of FDG-avid tissues to be determined.

Patients with HL are staged at diagnosis with a PET-CT scan and this result provides important information to help determine the first-line treatment strategy [3]. Patients also often have an interim PET-CT scan, typically after two or three cycles of chemotherapy, to assess response, which may lead to adaptation of treatment [3]. Residual FDG-avidity on interim-PET is associated with a higher risk of relapse than a negative scan (no FDG-avidity) [4–6], and is reassessed using subsequent PET-CTs after further treatment [3]. Where radiotherapy is used after chemotherapy, PET-CTs are used to guide treatment volumes (Figure 5.1). In early-stage HL, the aim is to cover all the pre-chemotherapy PET-avid areas, whereas in advanced stages typically only areas that remain PET-avid after chemotherapy are irradiated [3,7,8].

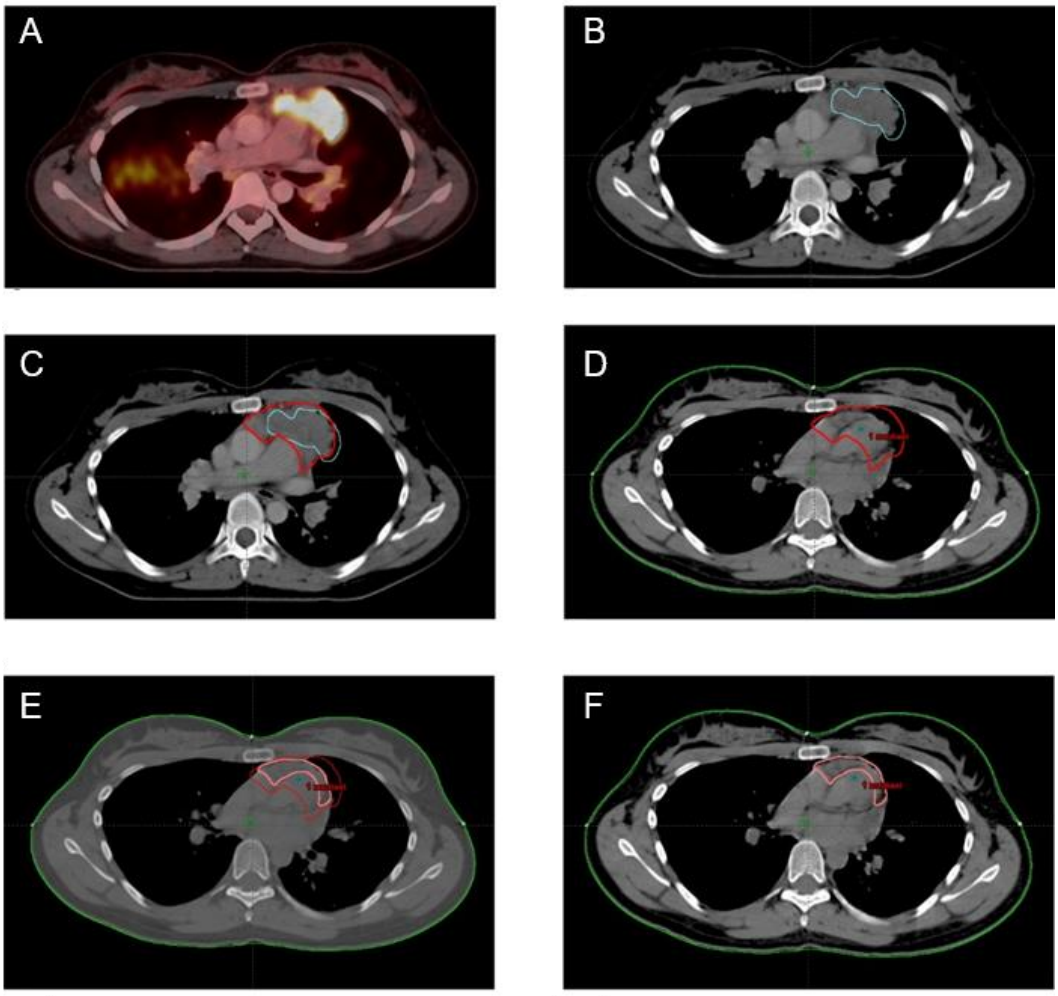


Figure 5.1: Use of PET-CT to guide radiotherapy treatment volumes

A. Pre-chemotherapy PET-CT scan showing the initially PET-positive disease (bright yellow) in the upper mediastinum
B. PET-positive disease volume contoured (blue) on the CT component of the pre-chemotherapy PET-CT scan
C. Anatomical disease volume contoured (red) on the CT component of the pre-chemotherapy PET-CT scan
D. Post-chemotherapy radiotherapy planning CT scan with the pre-chemotherapy disease volume (red) transferred by image fusion
E. Clinical target volume (pink) contoured on the radiotherapy planning CT scan. This volume represents the tissue that contained lymphoma initially, and is created by modifying the pre-chemotherapy disease volume to take into account tumour shrinkage and anatomic boundaries to spread that have not been breached
F. Post-chemotherapy radiotherapy planning CT scan with the final clinical target volume ('treatment volume'), which encompasses all of the initial lymphoma volume whilst avoiding normal structures that were never involved by lymphoma

Abbreviations - PET: positron emission tomography; CT: computed tomography
Adapted, with permission, from Illidge et al, 2014 [9]

5.1.2 Estimating the risks of radiation late-effects

The risk of radiation late-effects is related to the dose that organs-at-risk (OARs) receive from radiotherapy. Researchers have quantified this in the form of dose-response relationships, which give estimates of the risk of a late-effect based on the radiation dose that an OAR receives. To date, relationships have been determined for the risk of ischaemic heart disease (IHD) [10], heart failure [11], valvular heart disease [12], and breast [13–16], lung [17,18], gastric [19–21], oesophageal [22], pancreatic [23], and colorectal (unpublished data, Chapter 4) cancers following treatment for HL. The dose-response relationship for the risk of IHD is shown in Figure 5.2. This describes the relationship between the mean dose received by the heart during radiotherapy (MHD) and the patient's subsequent risk of IHD. The regression line is the best-fitting relationship, and indicates a 7.4% excess rate ratio for each gray (Gy) increase in MHD.

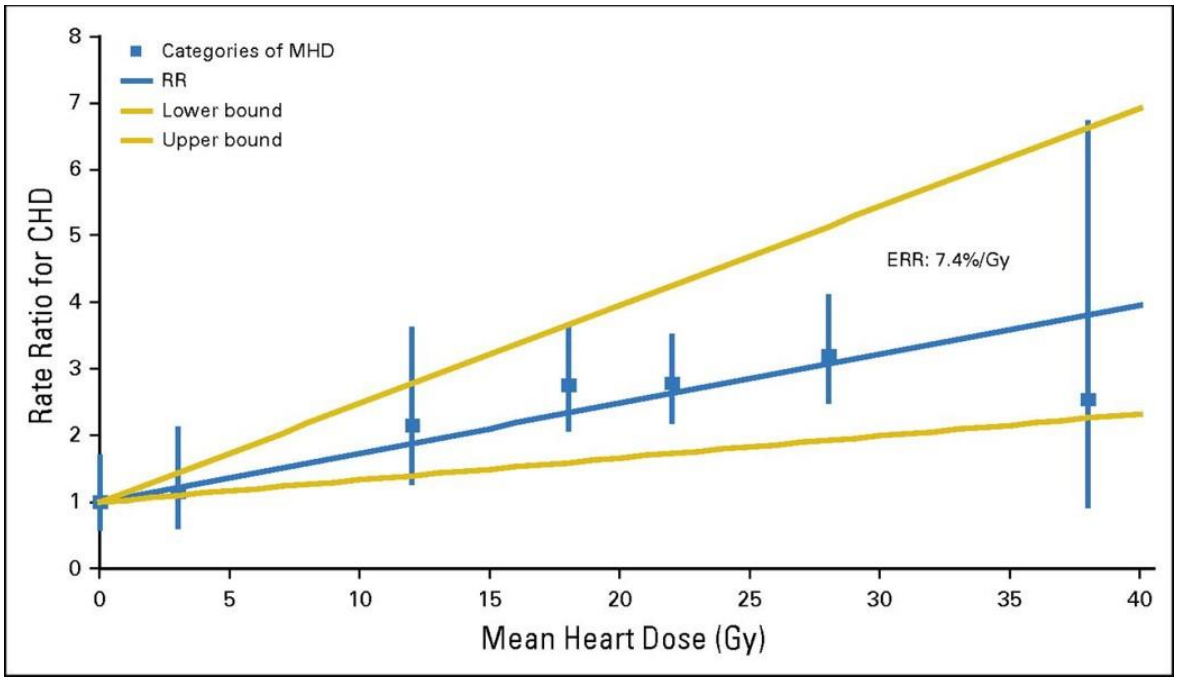


Figure 5.2: Dose-response relationship for mean heart dose and ischaemic (coronary) heart disease risk

Squares indicate estimates for dose categories and are plotted at the median dose in each category, vertical lines are 95% confidence intervals. The regression line is the best-fitting dose-response relationship (RR = 1 + 0.07402*MHD).

Abbreviations - CHD: coronary heart disease; MHD: mean heart dose; RR: rate ratio

Reused, with permission, from van Nimwegen et al, 2015 [10]

The MHD can be precisely estimated on a patient's radiotherapy treatment planning CT. This is a CT done once a decision has been made to treat a patient with radiotherapy. It is uploaded into a radiotherapy treatment planning system (TPS), where a clinician is able to outline the anatomical locations that require treatment with radiotherapy, and the OARs that should be avoided (Figure 5.1). The TPS is then used to simulate different radiotherapy fields and techniques, and select the treatment method that best delivers radiation to the treatment volume whilst minimising dose to OARs. This method is represented by a radiotherapy treatment plan, that estimates the radiation dose that will be received by the treatment volume and OARs. The TPS produces dose-volume histograms and statistical measures of radiation dose (Figure 5.3) that provide detailed measures of the radiation received by the treatment volume and OARs.



Figure 5.3: Use of the radiotherapy treatment planning system to determine the mean heart dose received during radiotherapy

The heart is contoured on the patient's radiotherapy planning CT (pink outline in panel a). Once a radiotherapy plan is produced a dose-volume histogram is available (panel b) and the mean dose determined (panel c).

Once the MHD is known, this can be used in combination with published dose-response relationships to estimate an individual's relative risk of radiation late-effects. For example, using the dose-response for IHD, a MHD of 4.3 Gy would give an excess rate ratio (ERR) of IHD of 31.82% (4.3*7.4), i.e. a risk of 1.32 times that without radiation exposure.

5.1.2 Rationale and study aims

Current practice is that patients have a PET-CT scan at diagnosis of HL, and then receive chemotherapy (which lasts between two to six months, depending on the stage of their disease). Where radiotherapy has been chosen as part of their treatment, patients then have a radiotherapy planning CT scan, a radiotherapy plan is made, and the radiation dose to OARs evaluated. Only then can the risk of late-effects be estimated precisely, which means treatment decisions cannot be informed by individualised estimates of the relative benefits and risks of radiotherapy.

This study aimed to build a model that could be used to predict the MHD expected from radiotherapy, using measures from a patient's pre-chemotherapy PET-CT scan. Such a model could then be used at the beginning of a patient's treatment pathway to estimate what their risk of cardiovascular disease (CVD) would be. This information could be used to inform discussions about radiotherapy at a much earlier stage than is currently possible (Figure 5.4). Figure 5.5 illustrates how this study fits into the aims of the thesis as a whole.

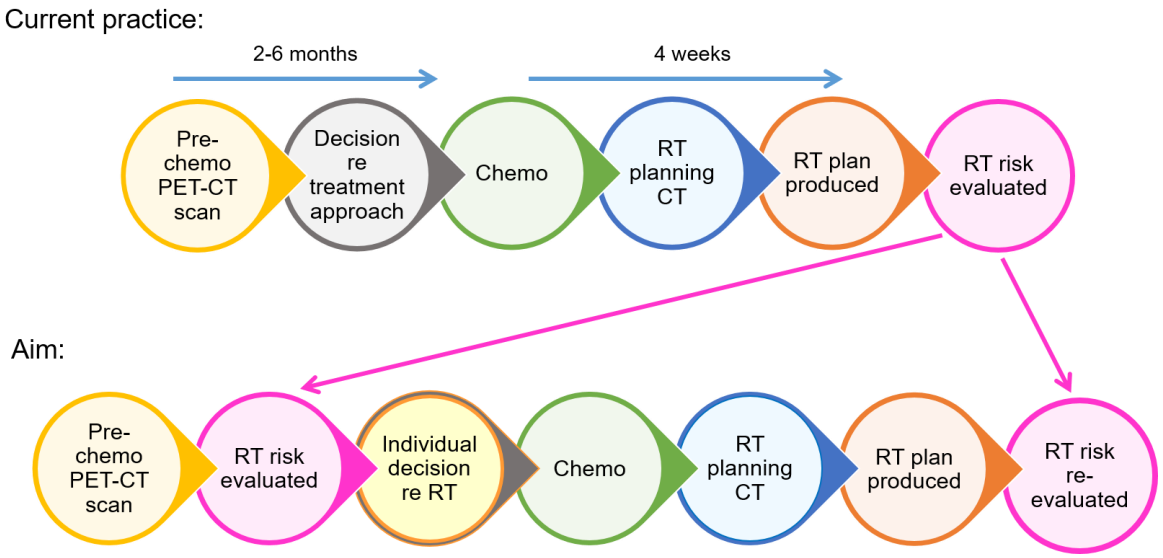


Figure 5.4: Current practice with regard to evaluation of risk of radiotherapy late-effects, compared to the pathway possible if estimates of risk of late-effects were available at the time of diagnosis of Hodgkin lymphoma

Abbreviations - chemo: chemotherapy; PET: positron emission tomography; CT: computed tomography; re: regarding; RT: radiotherapy

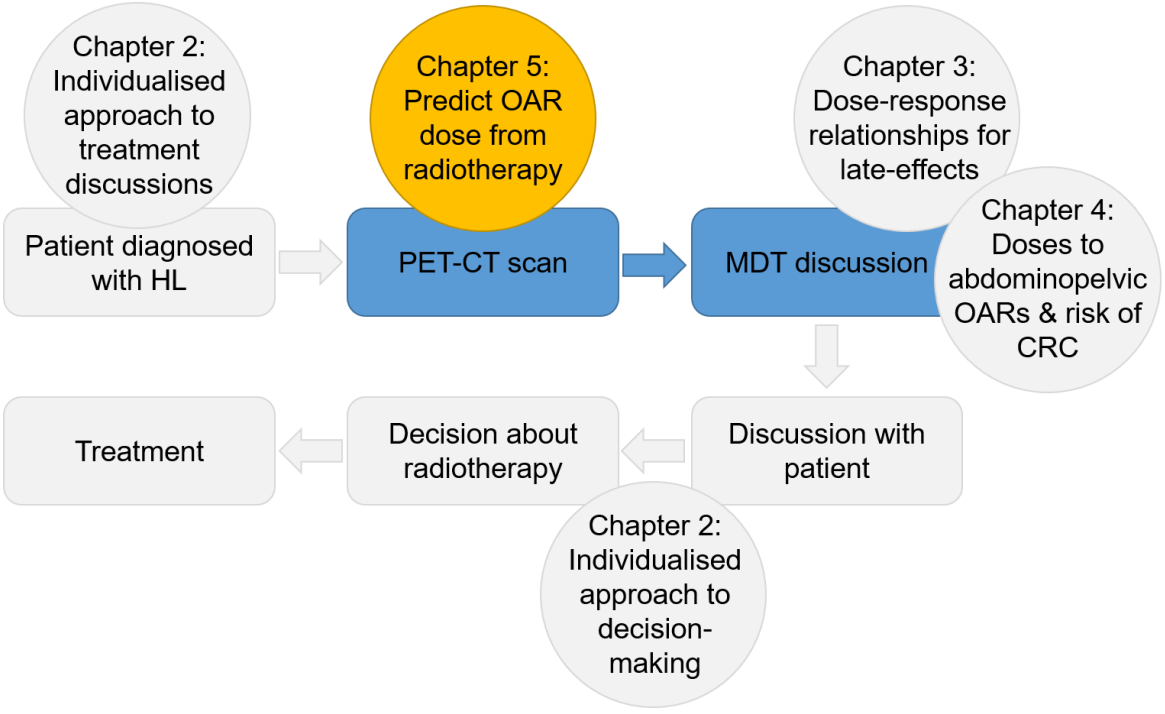


Figure 5.5: Overview of the clinical pathway for making decisions about radiotherapy used to treat patients with Hodgkin lymphoma, highlighting the steps informed by data presented in this chapter

Abbreviations - HL: Hodgkin lymphoma; OAR: organ-at-risk; PET-CT: Positon emission tomography integrated with computed tomography; MDT: multidisciplinary team; CRC: colorectal cancer

5.2 Methods

5.2.1 Study subjects

This is a retrospective cohort study, using routine clinical data. I collaborated with eight other centres to obtain data on patients treated for classical HL with chemotherapy and radiotherapy, when aged 18 or over, between 2010 and 2021 (inclusive). 2010 is when most centres started to perform PET-CT scans on all patients with HL prior to chemotherapy. For centres where routine PET-CT scanning was adopted later than this, the start of accrual was the year when pre-chemotherapy PET-CT scans became available. The participating centres, and methods of recruitment, are listed in Table 5.1. Each centre identified eligible study participants using their hospital's electronic records.

Table 5.1: Participating centres, and the method of their recruitment to the study

Treatment centre	Method of recruitment
Oxford University Hospitals NHS Foundation Trust	My host institution
Guy's and St Thomas' NHS Foundation Trust	Established collaboration, and host institution of one of my supervisors
Masaryk Memorial Cancer Institute, Czech Republic	New research collaboration
St James's Hospital, Dublin, Ireland	Established collaboration
University Hospitals Bristol NHS Foundation Trust	Email to members of the UK Lymphoma Radiotherapy Group (UKLRG)
NHS Lothian, Edinburgh	
NHS University Hospitals of Leicester	
Nottingham University Hospitals NHS Trust	
Newcastle Hospitals NHS Foundation Trust	

I did not conduct sample size calculations as I was limited by the number of patients treated with radiotherapy at each of the collaborating centres. Also, there are no generally accepted approaches to estimate the sample size requirements for prediction models [24,25]. Instead, I attempted to build as large a dataset as possible to maximise the power and generalisability of the results. Once I had obtained the data, I used the number of events

(i.e. outcome measures) per candidate predictor as a crude estimate of the study's statistical power.

5.2.2 Data collection

The data was extracted by collaborators at each of the participating centres, from their hospital's electronic records. I collected data from the Oxford cohort and developed a guide, based on my approach, to outline the methods to be used. This ensured a consistent approach to variable measurement between centres (Appendix D1). I sent each centre a data collection spreadsheet, to ensure standardised reporting. The collaborating centres gave each of their study participants a unique pseudonymised ID number to enable queries to be resolved.

5.2.2.1 Candidate predictors

The candidate predictors are listed in Table 5.2. I chose these variables as those that could affect MHD, based on literature review, clinical knowledge, discussion with my supervisors, and the results of a pilot study conducted by an MSc student I co-supervised. I also considered ease of measurement in a clinical setting. The predictors were measured on the patient's pre-chemotherapy PET-CT scan. If radiotherapy was given for a disease relapse, the PET-CT scan related to that episode was used, rather than one from their first diagnosis. Additional information was recorded from the patient's radiotherapy treatment plan, including the areas treated, prescribed dose, and treatment techniques.

Table 5.2: Candidate predictors and outcome measures

Variable	Description
Demographics	
Study ID	Unique participant ID (pseudonymised)
Treatment centre	Unique ID for each centre
Sex	Participant sex
Age	Participant age at diagnosis, in years
Disease stage	Stage of HL at diagnosis (I-IV)
Relapse	Indicator of whether RT was given for relapsed disease
PET date	Date of the PET-CT scan used for measurements
Pre-chemotherapy PET-CT variables	
Mediastinal disease	Disease in the mediastinum at diagnosis (yes/no)
Axillary disease	Disease in the axilla at diagnosis (yes/no)
Neck disease	Disease in the neck at diagnosis (yes/no)
SCF disease	Disease in the SCF at diagnosis (yes/no)
Hilar disease	Disease in thoracic nodal station 10 at diagnosis (yes/no)
Subcarinal disease	Disease in thoracic nodal station 7 at diagnosis (yes/no)
Width mediastinal disease	Maximum width of contiguous mediastinal disease (cm)
Disease thoracic width ratio	Maximum disease width (cm) / maximum thoracic cavity width (cm)
Length mediastinal disease	Maximum length of contiguous mediastinal disease (including contiguous neck disease if present) (cm)
Inferior vertebral level	Vertebral level at inferior extent of disease
Above or below T7	Inferior extent of disease above or below T7
Above or below LMS	Inferior extent of disease above or below the origin of the left main stem coronary artery
Length heart overlap	Length of disease overlapping the heart (cm)
Percentage heart overlap	Length of heart overlap, as a percentage of heart length
Radiotherapy plan variables	
Mediastinal RT	Radiotherapy fields included the mediastinum (yes/no)
Neck RT	Radiotherapy fields included the neck (yes/no)
SCF RT	Radiotherapy fields included the SCF
Axillary RT	Radiotherapy fields included the axilla
Dose	Prescribed radiotherapy dose (Gy)
Fractions	Number of fractions of radiotherapy
Delivery technique	Radiotherapy delivery technique (3D-conformal, hybrid, IMRT, VMAT, butterfly-VMAT)
Breathing mode	Radiotherapy done as free-breathing or in DIBH
PTV margin	PTV margin added during radiotherapy planning (mm)
Outcome	
MHD	MHD, as a percentage of the prescribed dose

Abbreviations - HL: Hodgkin lymphoma; PET-CT: positron emission tomography with computed tomography; SCF: supraclavicular fossa; cm: centimetres; T7: 7th thoracic vertebra; LMS: left main stem; RT: radiotherapy; Gy: gray; IMRT: intensity modulated radiotherapy; VMAT: volumetric modulated arc therapy; DIBH: deep inspiration breath hold; PTV: planning target volume; mm: millimetres MHD: mean heart dose. Disease refers to FDG-avid disease.

5.2.2.2 Outcome measures

The outcome measure was MHD, expressed as a percentage of the prescribed radiotherapy dose (Gy) to account for variation in the dose used to treat HL. MHD was recorded from the participant's individual radiotherapy treatment plan. The heart had already been outlined as part of the participant's treatment in most cases. If it hadn't, I or the researcher at that centre contoured the heart in line with published atlases used for radiotherapy planning [26–28]. Hearts that had already been contoured were checked at the time of data collection to ensure the borders were defined as per these guidelines.

5.2.3 Statistical analysis

I carried out statistical analyses using Stata statistical software (Version 17, StataCorp. 2021, College Station, Texas). I limited analyses to those patients who had received radiotherapy to the mediastinum, as this is the group in whom predicting MHD is most relevant. I did not anticipate any missing data, as only patients who had both a pre-chemotherapy PET-CT scan and a radiotherapy treatment plan were eligible for inclusion. However, in case of any missing information, I planned to only use those participants with complete data, as long as the data was missing at random. I characterised the relationship between each candidate predictor and MHD by univariable analysis. For continuous variables, I checked the distribution of the data, and whether the relationship with MHD was linear. I retained the original scale for all. Some predictors were alternative ways of looking at the same measure of disease ('analogous'), for example length and percentage heart overlap. In those cases, I chose the variable with the strongest relationship with MHD (highest R^2), or the one which could be measured most reliably in clinical practice if there was no substantial difference in the R^2 value. I used a correlation matrix to determine whether any of the remaining predictors were highly correlated (defined as a variance inflation factor of over five to 10). I used multivariable linear regression with backward

stepwise selection, with a *P* value greater than 0.157 for removal of variables (as a proxy for Akaike's information criteria) [29,30]. This allowed me to judge the effects of candidate predictors simultaneously. I used the multiple correlation coefficient squared (R^2), adjusted for the number of variables in the model, to assess the percentage of total variance in the MHD explained by the final model. In order to check model assumptions for linear regression, I checked the distribution and variance of the residuals, using QQ-plots and histograms to assess for normality and residual plots to confirm homoscedasticity. I calculated variance inflation factors to assess the relationship between the variables included in the model.

I assessed the ability of the model to predict MHD for new patients who had not been included in deriving it. I did this by fitting the model to data on all the participants but one, and then using the fitted model to predict MHD for the excluded participant. I calculated the prediction error as the difference between the omitted participant's actual MHD, derived from their radiotherapy treatment plan, and the MHD predicted by the model. I repeated this procedure for each study participant, and analysed the in-patient differences. This method has previously been used by my research group to predict cardiac dose for women treated for breast cancer [31]. The MHD predicted by the model is expressed as a percentage of the prescribed dose, which makes interpretation of the magnitude of the prediction error complex. I therefore converted the MHD predicted by the model into absolute dose by multiplying the dose from the model by that participant's prescribed radiotherapy dose.

I used the MHD predicted by the model to estimate the 30-year cumulative absolute excess risk (AER) of ischaemic heart disease (IHD) for each participant, and compared this to the AER estimated using the MHD from their radiotherapy plan. This method has previously been used by my research group to predict risks of CVD for the cohort treated in the RAPID trial [32]. The detailed method is given in Appendix D2, but briefly: estimating each individual's AER of IHD first involved calculating their background risk of developing IHD if

they did not receive radiotherapy, using general population incidence rates that I obtained from a study I co-led that used primary care data to derive rates of CVD (Table D1, Appendix D2; manuscript under review). Next, their ERR of IHD from radiotherapy was calculated by multiplying their MHD (in Gy) by the ERR/Gy for their age category, published by van Nimwegen et al [33], then adding one. These ERRs were multiplied by their background risk, to determine their probability of developing IHD if they were to receive radiotherapy. Finally, their 30-year cumulative AER of IHD was calculated as the sum of the difference between their background risk and risk if treated with radiotherapy, for each year after treatment, up to 30 years.

5.2.4 Ethical considerations

I obtained ethical approval for the study from the Health Regulatory Authority and Health and Care Research Wales, 280718, and from the Public Benefit and Privacy Panel for Health and Social Care, 2122-0142 Shakir. Inclusion of the two international centres was covered by data-sharing agreements.

5.3 Results

5.3.1 Participant characteristics

I obtained data on 227 patients, 169 of whom received mediastinal radiotherapy and were included in the analysis. The median age at the time of treatment was 32 years (range 18-83), and 57% of patients were female. Eighty-three percent of patients had stage II disease (Table 5.3). The median MHD was 6.17 Gy (range 0.08-21.21).

Table 5.3: Characteristics of 169 participants treated with radiotherapy for mediastinal Hodgkin lymphoma

Characteristic		Number	(%)
Demographics			
Sex	Female	96	(56.8)
	Male	73	(43.2)
Age at treatment	18-20 y	5	(3.0)
	21-30 y	70	(41.4)
	31-40 y	43	(25.4)
	41-50 y	22	(13.0)
	51-60 y	13	(7.7)
	>60 y	16	(9.5)
Year of treatment	2010-2014	13	(7.7)
	2015-2019	134	(79.3)
	2020-2021	22	(13.0)
Treating centre	Oxford	38	(22.49)
	Guys	34	(20.12)
	Czech Republic	28	(16.57)
	Dublin	23	(13.61)
	Bristol	11	(6.51)
	Edinburgh	11	(6.51)
	Leicester	9	(5.33)
	Nottingham	9	(5.33)
	Newcastle	6	(3.55)
Disease characteristics			
Disease stage	I	7	(4.1)
	II	140	(82.8)
	III	6	(3.6)
	IV	16	(9.5)
Relapsed disease	Yes	16	(9.5)
	No	153	(90.5)
Radiotherapy			
Prescription	30 Gy in 15#	106	(62.7)
	30.6 Gy in 17#	32	(18.9)
	20 Gy in 10#	14	(8.3)
	40 Gy in 20#	9	(5.3)
	Other*	8	(4.7)
Delivery technique	3D-CRT	29	(17.2)
	Hybrid	9	(5.3)
	IMRT	22	(13.0)
	VMAT	82	(48.5)
	Butterfly-VMAT	27	(16.0)
Breathing technique	Free-breathing	110	(65.1)
	DIBH	59	(34.9)

* 24 Gy 12#, 27 Gy 9#, 30 Gy 20#, 35 Gy 15#, 38 Gy 18#, 46 Gy 23#, 30 Gy 15# + 6 Gy 3# boost (2)
Abbreviations - y: years; Gy: gray; #: fractions; 3D-CRT: 3D conformal radiotherapy; IMRT: intensity-modulated radiotherapy; VMAT: volumetric modulated arc therapy; DIBH: deep inspiration breath hold

5.3.2 Univariable analysis

Prior to analysis, I grouped the data into variables that were likely predictors of MHD (based on clinical knowledge and literature review), ones that were analogous where a decision was needed as to which to use, and ones where there was no indication that they should affect MHD (Table 5.4).

Table 5.4: Variables examined for a relationship with mean heart dose

Predictor variables	Delivery technique Breathing mode PTV margin Hilar disease	
Analogous predictors	Length heart overlap Percentage heart overlap Length mediastinal disease Inferior vertebral level Above or below T7 Above or below LMS	All relating to disease length
	Width mediastinal disease Disease thoracic width ratio	Both relating to disease width
Variables not considered to be related to MHD	Sex Age HL stage Relapse PET date	Treatment centre Axillary, neck & SCF disease Subcarinal disease Axillary, neck & SCF RT

Abbreviations - PTV: planning target volume; T7: 7th thoracic vertebra; LMS: left main stem; PET: positron emission tomography; SCF: supraclavicular fossa; RT: radiotherapy

Six participants had the outcome measure (MHD) missing, and seven others had data for the predictors missing (PTV margin in six, and width and length of mediastinal disease in one). The seven participants with missing predictor data were not used for model development but they remained in the dataset and were used to assess model performance. Those with missing MHDs could not be used for model development or performance assessment.

I undertook univariable analyses to confirm my assumptions that the variables not considered related did not have a significant relationship with MHD, and to determine which of the analogous predictors should be included in multivariable model development. The results of these analyses are in Appendix D3. Of the variables not considered related, only treatment centre and PET date had significant relationships with MHD, but this was accounted for by difference in delivery techniques between centre and treatment period. Of the six length variables, the two measures of heart overlap (absolute and percentage) had the strongest relationship with MHD. Percentage heart overlap was chosen to be included in subsequent analyses as it also accounts for variation in heart size between patients. Length of mediastinal disease did not have a significant relationship with MHD on univariable analysis, but during exploratory analyses its inclusion in multivariable models had a significant effect and I therefore included it in subsequent model development. I chose the width of mediastinal disease over the disease thoracic width ratio as it had a slightly stronger relationship with MHD and is simpler to measure.

The candidate predictors I took forward for model development are shown in Table 5.5. There was no significant correlation between any of these predictors using a correlation matrix. The events per variable was 23.3 (calculated as the number of participants with the outcome (163) divided by the number of candidate variables (7)).

Table 5.5: Candidate predictors for multivariable model development

Continuous predictors	**Median**	**(IQR)**
Percentage heart overlap	15.9%	(0-36.1%)
Width of mediastinal disease	7.6 cm	(5.0-9.8 cm)
Length of mediastinal disease	14.6 cm	(10.0-19.6 cm)
PTV margin	9.0 mm	(5.0-10.0 mm)
Categorical predictors	**Category**	**n** (%)
Hilar disease	Yes	59 (34.9)
	No	110 (65.1)
Delivery technique	3DCRT	29 (17.2)
	Hybrid	9 (5.3)
	IMRT	22 (13.0)
	VMAT	82 (48.5)
	Butterfly-VMAT	27 (16.0)
Breathing mode	Free-breathing	110 (65.1)
	DIBH	59 (34.9)

Abbreviations - IQR: interquartile range; PTV: planning target volume; 3DCRT: 3D conformal radiotherapy; IMRT: intensity-modulated radiotherapy; VMAT: volumetric modulated arc therapy; DIBH: deep inspiration breath hold

5.3.3 Multivariable model development

Using backward stepwise selection, the length of mediastinal disease and PTV margin were removed, leaving five variables in the final model (Table 5.6). A hybrid, VMAT or butterfly-VMAT radiotherapy technique reduced MHD compared to 3D-conformal radiotherapy by 3.58%, 4.56% and 9.45% respectively, whereas IMRT increased the MHD by 8.19%. The presence of hilar disease increased the MHD by 8.52%. Delivering radiotherapy with the patient in breath-hold, compared to free-breathing, reduced the MHD by 8.22%. For every 1% increase in disease overlapping the heart (relative to heart length), the MHD increased by 0.2%. For every one centimetre increase in mediastinal disease width the MHD increased by 0.72%. The model can be expressed as the formula in Figure 5.6, which can be used to predict the MHD for a patient with HL.

Table 5.6: Multivariable linear regression model specification

	Coefficient	SE	t	P>|t|	95% CI	
Delivery						
3D-CRT	Ref					
Hybrid	-3.58	5.18	-0.69	0.491	-13.83	6.67
IMRT	8.19	3.81	2.15	0.034	0.64	15.74
VMAT	-4.56	3.48	-1.31	0.193	-11.46	2.34
Butterfly-VMAT	-9.45	4.43	-2.13	0.035	-18.21	-0.68
Percentage heart overlap (%)	0.20	0.05	4.17	0.000	0.11	0.30
Hilar disease						
No	Ref					
Yes	8.52	2.45	3.48	0.001	3.67	13.37
Width mediastinal disease (cm)	0.72	0.39	1.81	0.072	-0.07	1.49
Breathing mode						
Free-breathing	Ref					
DIBH	-8.22	2.90	-2.84	0.005	-13.95	-2.48
Constant	18.11	4.00	4.53	0.000	10.20	26.03

Abbreviations - SE: standard error; t: t-statistic; P: probability; CI: confidence interval; 3DCRT: 3D-conformal radiotherapy; IMRT: intensity modulated radiotherapy; VMAT: volumetric modulated arc therapy; cm: centimetres; DIBH: deep inspiration breath hold

$$\mathbf{MHD\ (as\ \%\ prescribed\ dose)} = \mathbf{18.11} + \mathbf{0.2} * \%\boldsymbol{heart\ overlap} + \mathbf{0.72} * \boldsymbol{width\ mediastinal\ disease} + \boldsymbol{hilar\ disease} + \boldsymbol{delivery} + \boldsymbol{breathing}$$

Where:

% heart overlap = length disease overlapping heart / length heart * 100

width mediastinal disease = maximum width of mediastinal disease in cm

hilar disease = 8.52 where hilar disease is present, 0 if not

delivery depends on radiotherapy delivery technique proposed:

3D-CRT: 0 VMAT: -4.56
Hybrid: -3.58 Butterfly-VMAT: -9.45
IMRT: 8.19

breathing = -8.22 if radiotherapy would be given in DIBH, 0 if not

So, for a patient being considered for VMAT radiotherapy in breath-hold, who has mediastinal disease that includes the hilum, is 7 cm wide and overlaps the heart by 40% of its length:

MHD (as %prescribed) = 18.11 + (0.2*40) + (0.72*7) + -4.56 + 8.52 + -8.22
= 26.89%

i.e. for a prescription dose of 30 Gy, the estimated MHD would be 8.07 Gy

Figure 5.6: Model equation and worked example

Abbreviations - MHD: mean heart dose; cm: centimetres; 3D-CRT: 3D-conformal radiotherapy; IMRT: intensity-modulated radiotherapy; VMAT: volumetric modulated arc therapy; DIBH: deep inspiration breath hold

5.3.3.1 Checking model assumptions

I examined the model's residuals to confirm that they fit with the assumptions required for linear modelling. As shown in Figure 5.7, the residuals were approximately normally distributed, and there was no evidence that either the linearity or homoscedasticity assumptions were violated.

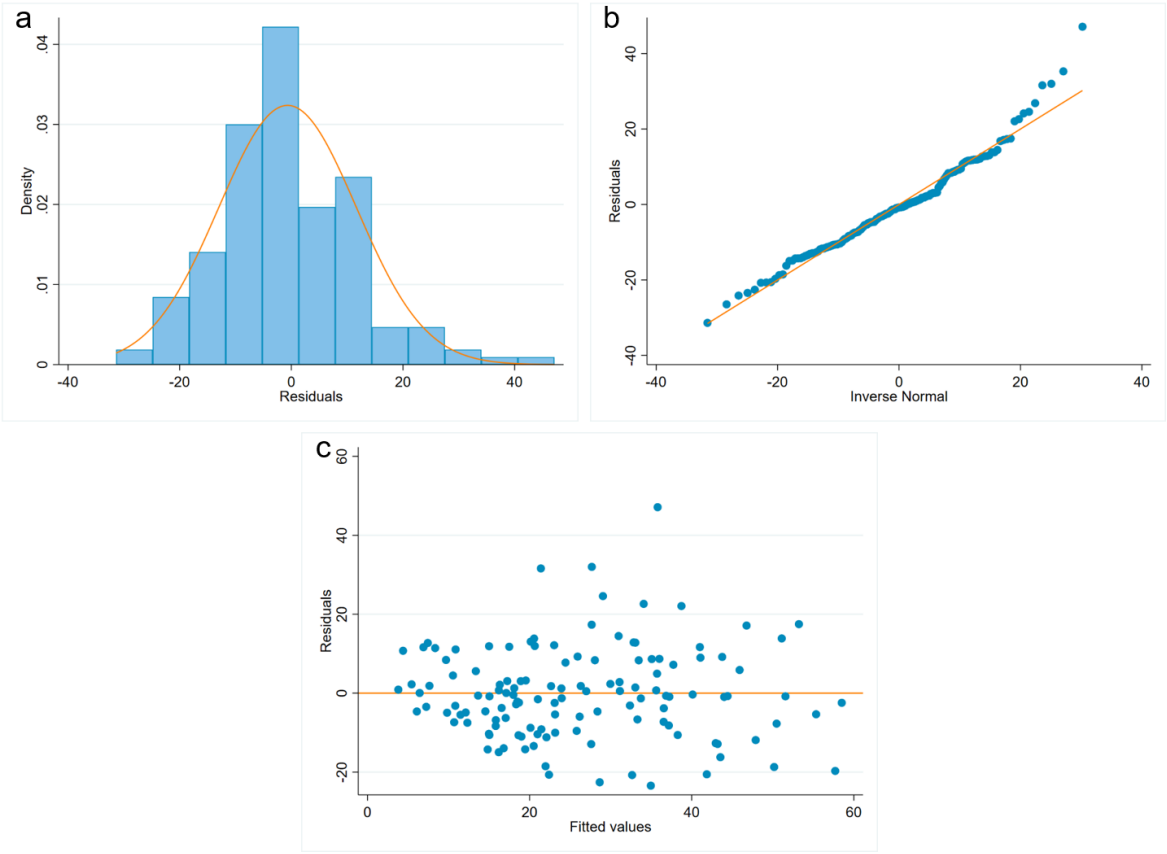
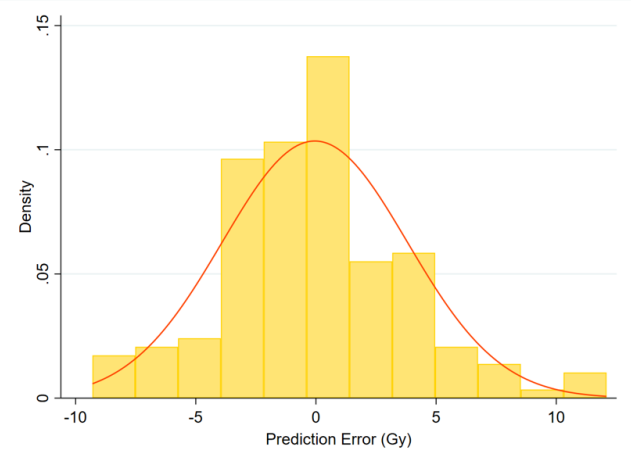


Figure 5.7: Assessment of model residuals using a) a histogram of residuals, b) a Q-Q plot of residuals, and c) a plot of residuals versus fitted values

5.3.3.2 Model performance

The differences between each individual's MHD from their radiotherapy plan, and that predicted by the model ('prediction error') were relatively normally distributed, although there was a tendency of the model to overestimate MHD (Figure 5.8). The mean prediction error was 2.9 Gy, with a range of 0.2 to 12.1 Gy.



	Difference (Gy)
Mean	2.9
Range	0.2-12.1
75% predictions within 3.87 Gy	
90% predictions within 6.65 Gy	
95% predictions within 7.86 Gy	

Figure 5.8: Prediction error between mean heart dose predicted by the model and mean heart dose measured on the radiotherapy treatment plan
Abbreviations - Gy: gray

The MHDs predicted by the model were relatively closely correlated with the MHDs from the radiotherapy plan (R 0.68) (Figure 5.9). The mean within-patient differences in MHD were not statistically significant (Table 5.7). However, the within-patient difference varied substantially for individual patients (Appendix D4). When results were considered for quartiles of MHD (from the radiotherapy plan), within-patient differences were smaller for patients in the second and third quartiles compared to those with the lowest or highest MHDs (Table 5.8). The model tended to overestimate MHD for patients in the lowest quartile, and underestimate MHD for patients in the highest (Figure D1, Appendix D4).

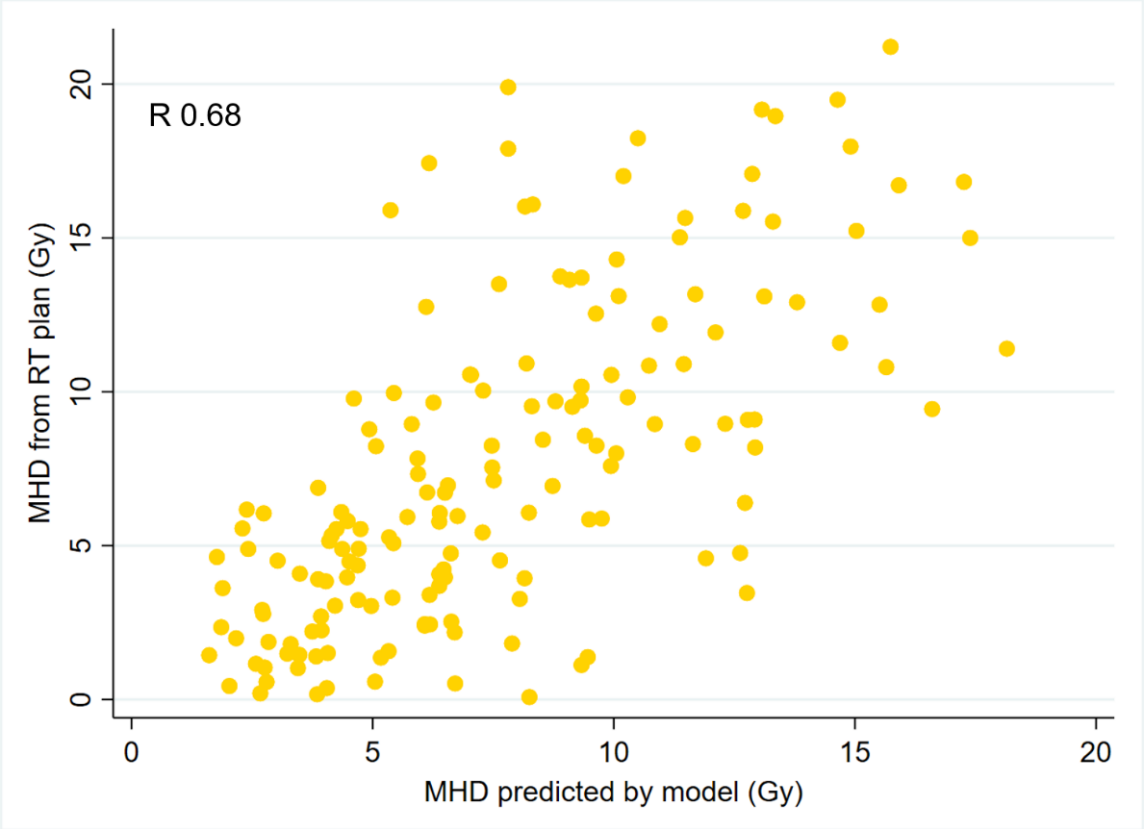


Figure 5.9: Scatter plot of the mean heart dose predicted by the model versus the mean heart dose measured on the radiotherapy treatment plan
Abbreviations - R: correlation coefficient; MHD: mean heart dose; RT: radiotherapy; Gy: gray

Table 5.7: Modelled mean heart dose and 30-year risk of ischaemic heart disease compared to those measured on the radiotherapy treatment plan

	MHD (Gy)		30 y cumulative AER of IHD (%)	
	Median	**(IQR)**	**Median**	**(IQR)**
Radiotherapy plan	6.2	(3.4-10.9)	1.79	(0.81-3.14)
Model	6.7	(4.5-10.1)	1.93	(1.06-3.30)
P_{diff}*	0.88		0.51	

*Calculated with a paired t-test, testing the difference between the MHD from the model compared to the MHD taken from the radiotherapy treatment plan; and separately for the difference between the 30-year cumulative AER calculated using the MHD taken from the radiotherapy treatment plan compared to that calculated using the MHD from the model
Abbreviations - MHD: mean heart dose; Gy: gray; AER: absolute excess risk; IHD: ischaemic heart disease; IQR: interquartile range

Table 5.8: Differences between the mean heart dose from the radiotherapy plan and that predicted by the model, split by quartiles of mean heart dose

		Mean heart dose			
		RT plan	Model	Mean difference	
Quartile	n	Range (mean) (Gy)	Range (mean) (Gy)	(Gy)	As % of mean RT plan MHD
1	67	0.08-5.33 (2.80)	1.61-12.76 (5.04)	-2.24	-79.96
2	54	5.43-10.56 (7.87)	2.30-16.60 (7.78)	0.08	1.06
3	27	10.80-15.90 (13.26)	5.37-18.15 (11.61)	1.65	12.47
4	15	16.02-21.21 (18.00)	6.17-17.26 (11.78)	6.22	34.55

Abbreviations - RT: radiotherapy; Gy: gray; MHD: mean heart dose

5.3.3.2 Cardiovascular risk prediction

The 30-year AERs of IHD using the MHD predicted by the model were closely correlated with those calculated using the MHD from the radiotherapy plan (R 0.81) (Figure 5.10). The mean in-patient difference in AER was 0.9%, with a range of 0.1 to 5.5%. Ninety percent of participants had their AER predicted to within 2.2% of the estimate using the MHD from the radiotherapy plan. The mean within-patient differences in AERs were not statistically significant (Table 5.7). However, the within-patient difference varied substantially for individual study participants (Appendix D4). When results were considered for quartiles of MHD (from the radiotherapy plan), within-patient differences were smaller for patients in the first, second and third quartiles compared to those with the highest MHDs (Table 5.9).

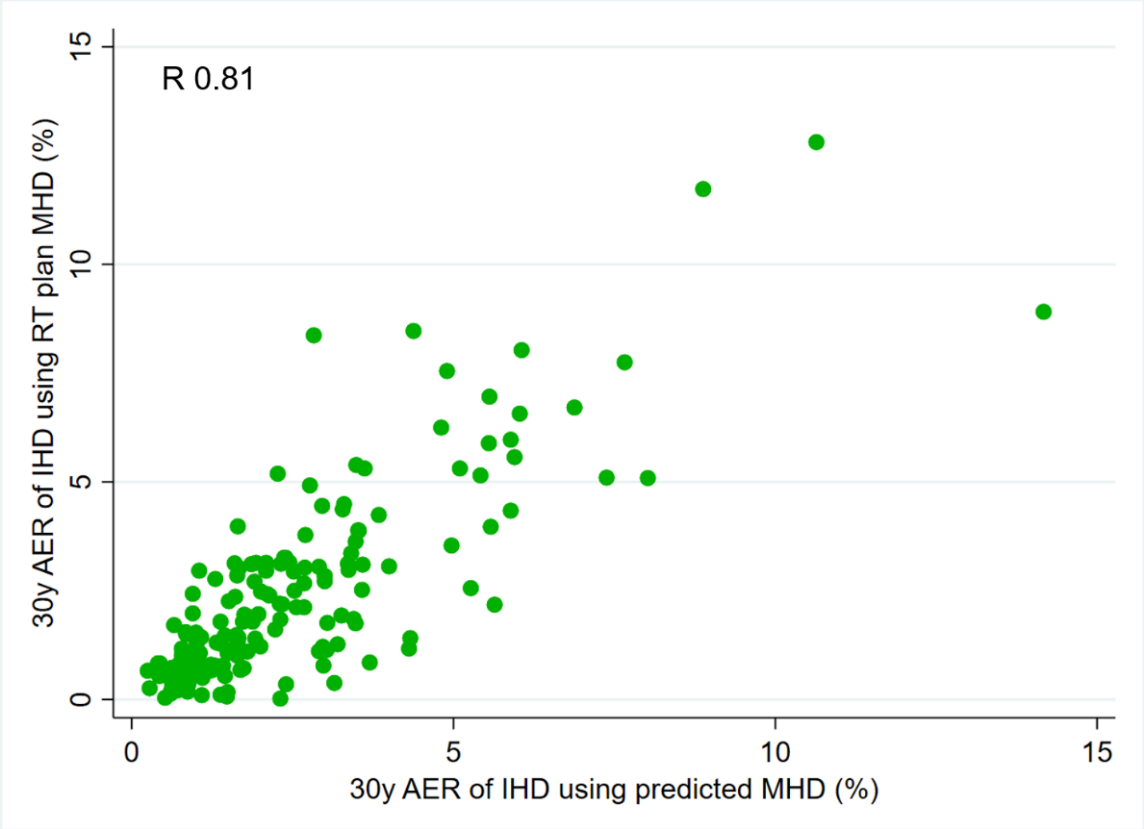


Figure 5.10: Scatter plot of the 30-year cumulative absolute excess risk of ischaemic heart disease calculated using the mean heart dose predicted by the model and that calculated using the mean heart dose measured on the radiotherapy treatment plan
Abbreviations - R: correlation coefficient; y: year; AER: absolute excess risk; IHD: ischaemic heart disease; RT: radiotherapy; MHD: mean heart dose

Table 5.9: Differences between the 30-year cumulative absolute excess risk of ischaemic heart disease calculated using the mean heart dose from the radiotherapy plan and that predicted by the model, split by quartiles of mean heart dose

		30-year cumulative AER of IHD			
		RT plan	Model	Mean difference	
Quartile	n	Range (mean) (%)	Range (mean) (%)	(%)	As % of mean AER from plan
1	125	0.02-3.15 (1.47)	0.25-5.64 (1.77)	-0.30	-20.45
2	27	3.26-6.25 (4.58)	1.65-8.02 (4.19)	0.39	8.44
3	9	6.57-8.91 (7.70)	2.83-14.17 (6.50)	1.21	15.66
4	2	11.73-12.81 (12.27)	8.88-10.64 (9.76)	2.51	20.46

Abbreviations - AER: absolute excess risk; IHD: ischaemic heart disease; MHD: mean heart dose; RT: radiotherapy

5.4 Discussion

This study has demonstrated, for this first time, that it is possible to estimate the cardiac dose from radiotherapy, and the associated AER of IHD, using data available at the time of a patient's diagnosis with HL. The variables that best predict MHD are the extent to which mediastinal disease overlaps the heart, width of mediastinal disease, presence of hilar disease, and radiotherapy delivery and breathing techniques. A multivariable linear regression model containing these variables results in an estimation of MHD with a mean prediction error of 2.9 Gy. MHDs predicted by the model are moderately correlated with, and not statistically significantly different from, those measured on a radiotherapy treatment plan. When these estimates are converted into AERs of IHD at 30-years, risk estimates are accurate to within 2.2% for 90% of individuals. However, the magnitude of the prediction error varies substantially between individuals. When participants are grouped by ascending radiotherapy plan MHD, the model performs best in the second and third quartiles (5-15 Gy). Poorer performance in the lowest quartile may be due to more rapid fall off of dose at the edge of radiotherapy volumes, which are more individual and therefore difficult to predict. Performance in the highest quartile is hampered by a lack of data. Further work is needed before this model provides individualised estimates of the risks of radiotherapy that are accurate enough to inform clinical discussions about its use. However, this study demonstrates that it is feasible to develop models that are able to predict OAR dose from information available at the time of a patient's diagnosis. The fact that the model performs best in the middle quartiles of MHD is reassuring, as it is within this dose range where there is the greatest debate about the relative benefits and risks of radiotherapy.

The variables shown to be predictive of MHD in the final model make clinical sense, and are consistent with data from planning studies that have assessed the disease factors that increase cardiac dose from radiotherapy for HL. Ntentas et al showed that for patients with mediastinal disease below the origin of the left main coronary artery (LMCA), proton beam

therapy (PBT) reduced MHD, particularly if the disease overlapped longitudinally with the heart for more than 40% of heart length [34]. In an earlier study, they showed that PBT reduced MHD if disease extended below the seventh thoracic vertebra [35]. This is consistent with my model, built using data from an independent patient cohort, which shows that the extent to which mediastinal disease overlaps the heart is a strong predictor of MHD. Inclusion of variables describing disease extent in relation to the LMCA or seventh thoracic vertebra did not improve model performance however, and both variables were removed during backward stepwise selection (data not shown).

The model demonstrates that the radiotherapy delivery and breathing technique used alter the MHD substantially. One of the most advanced delivery techniques, butterfly-VMAT, reduced the MHD by 9.45% compared to 3D-conformal radiotherapy. Delivering radiotherapy with the patient in breath-hold, compared to free-breathing, reduced the MHD by 8.22%. This indicates that using optimal technology can substantially reduce the dose a patient's heart receives from radiotherapy (essentially cancelling out the constant of 18.11%), regardless of the anatomical measures of their disease. It also suggests that if everyone were to be treated with optimal technology, there may be different anatomical parameters that would predict MHD.

To the best of my knowledge, no other studies have attempted to predict OAR dose received during radiotherapy from pre-treatment imaging in this way. There has been one other paper that used linear regression modelling to predict cardiac dose from breast radiotherapy [31]. Their model used one measure, maximum heart distance on axial slices of the radiotherapy planning CT, to predict MHD, with an average prediction error of 0.8% [31]. They used data from the radiotherapy treatment plans, rather than diagnostic scans, and all participants received the same radiation fields meaning their data was much more homogeneous than in this study.

5.4.1 Relevance to current clinical practice

This model has been developed using real-world clinical data, from patients treated at a variety of centres from 2010-2022, using a variety of radiotherapy delivery techniques. Variation in radiotherapy practice is accounted for in the model, and as such it is relevant to any centre treating patients with HL. The model uses measures that are routinely collected during the treatment of patients with HL, and so could be implemented in clinical practice relatively easily. The risk-estimates made possible by the model could be used in multidisciplinary team meetings to guide discussions about the use of radiotherapy, and with patients to help them understand their individual risks from radiotherapy. However, it requires further refinement and validation before it is accurate enough to be used to guide treatment decisions. Performance of the model is lacking at the extremes of MHD, highlighting an ongoing need for clinical oncology expertise to make individual judgements about likely OAR doses. This may be particularly relevant when MHD is expected to be low, where a clinical oncologist may be able to estimate the likelihood of cardiac exposure more accurately than predicted by the model. It is possible, however, that model performance will improve with more data.

Some readers may question the choice of MHD as the outcome measure. Modern imaging and radiotherapy planning techniques have allowed the radiation dose to cardiac substructures to be estimated, and some researchers believe that the risk of late-effects is related to the dose received by those substructures rather than the dose received by the whole heart [36]. Modern radiotherapy techniques allow more conformal shaping of the treatment volumes, with higher heterogeneity of dose over the treatment volume. This means that some areas of the heart may receive much higher doses than others, and so the MHD (which averages these doses out over the whole heart) may not be a good reflection of the dose received by some of the cardiac substructures. Some researchers and clinicians recommend estimating the dose received by cardiac substructures such as

the left ventricle and the left anterior descending coronary artery [36]. They feel these doses are better suited to estimating the risks from modern radiotherapy owing to the greater variation in dose delivered to these substructures, compared to historic radiotherapy techniques [36]. However, two of the four dose-response relationships we have for estimation of risk of cardiovascular disease use MHD (Table 3.4), hence I chose MHD as the outcome measure. In the future, it would be possible to apply the approach outlined in this chapter to develop a model to predict dose to cardiac substructures.

5.4.2 Strengths and limitations

This study is the first to demonstrate that it is possible to estimate individualised risks of radiotherapy prior to radiotherapy treatment planning taking place. It therefore provides a means to incorporate individualised risk estimates into treatment decisions at the time of HL diagnosis and staging, when patients and clinicians need as much information as possible to make informed decisions. For this study, the pre-chemotherapy disease measures were taken by healthcare professionals familiar with identification of HL on PET-CT scans. Defining the extent of disease can be subjective, and there may have been slight differences in the way that disease was defined between the centres. However, I held virtual meetings with each centre where we reviewed example scans to minimise systematic differences in variable measurement. I chose to develop a model to predict MHD, as this is the dosimetric measure used in published dose-response relationships of cardiovascular risk after radiotherapy, and the most commonly used measure in clinical practice. However, contemporary radiotherapy techniques result in less homogenous dose distribution across OARs meaning that dose to cardiac substructures may be more critical for the development of late-effects than MHD [36]. There are recent data from patients treated for lung cancer to suggest that cardiovascular risk is best predicted using coronary artery dose, for example [37]. HL is rare, so my cohort is relatively large in comparison to some. However, my

analyses lack statistical power, resulting in uncertainties in the model, and more data is needed to improve performance, particularly at the extremes of MHD. A larger sample size is also required to explore interactions between variables. There may be other variables that predict MHD that I did not investigate. As this is the first study of its kind, the choice of candidate predictors was mainly guided by clinical knowledge and was relatively subjective. If additional variables are identified in the future, the model should be updated to investigate the effect of these. Finally, the AER estimates presented here do not take other cardiovascular risk factors into account, such as smoking, which may have a larger effect on a patient's risk of IHD than their radiotherapy [34].

5.4.3 Future work

Having now demonstrated that MHD can be predicted using a patient's pre-chemotherapy PET-CT, this approach could be used to develop models to predict dose to other OARs, such as the breasts and lungs. These doses could then be used in conjunction with published dose-response relationships to estimate a patient's risk of breast and lung cancer. In the future, if additional dose-response relationships become available to predict risk of late-effects, for example stroke risk from carotid dose, my modelling approach could also be applied to predicting dose to those OARs. Use of automatic segmentation of FDG-avid disease would minimise inter-researcher variation in variable measurement. Several studies have investigated the use of thresholding PET-CT images at a set standard uptake value (SUV), to define the extent of FDG-avid disease in lymphoma [38–41]. Suggestions include using a percentage of the maximum SUV in a tumour (e.g. 25% or 41%) [42,43], an absolute SUV (e.g. 2.5 or 4.0) [40,43,44], an SUV above mean liver uptake [45], or including voxels detected by at least two methods [40]. Such approaches are time-consuming [38,40], subject to inter-observer variation [46], rely on standardised PET-CT scanning

protocols [39,40], either under- or over-estimate FDG-avid disease [38–40,47], and are not yet in routine clinical use. However, in the future it may be that such approaches could be used to standardise measures of FDG-avid disease to further refine the models used to predict OAR dose.

The model requires further work before it can be used in clinical practice. This requires a larger development dataset, and I plan to continue to expand my collaborations to facilitate this. This dataset should include more patients with low and high MHDs, to improve model performance in those quartiles. I would also like to investigate the variables that are predictive of MHD when the development dataset is restricted to those treated using specific radiotherapy techniques. It may be that different models can be developed for when the patient is treated in breath-hold, and for the different radiotherapy delivery techniques. Such models would also show the difference in predicted MHD between these different techniques, and may encourage people to adopt optimal technologies to minimise cardiac exposure to radiation. It may be possible to use machine learning approaches to develop a model to predict MHD, but such techniques usually require very large datasets to provide accurate predictions [48].

External validation of the MHD model will also be critical before it can be used in clinical practice. This will require additional datasets, which could be obtained from international collaborations, for example through the International Lymphoma Radiation Oncology Group.

5.5 Conclusions

This is the first study that has shown it is possible to predict MHD, and associated risk of IHD, using data available at diagnosis of HL. Further refinement of the model is required, and it will need to be externally validated before it can be used in clinical practice. However, it is an important first-step in bringing individualised estimates of the risks of radiotherapy into early treatment discussions for patients with HL.

5.6 References

[1] Warburg O, Wind F, Negelein E. The metabolism of tumors in the body. J Gen Physiol 1927;8:519–30. doi:10.1085/jgp.8.6.519.

[2] Griffeth LK. Use of PET/CT scanning in cancer patients: Technical and practical considerations. Baylor Univ Med Cent Proc 2005;18:321–30. doi:10.1080/08998280.2005.11928089.

[3] Follows GA, Barrington SF, Bhuller KS, Culligan DJ, Cutter DJ, Gallop- Evans E, et al. Guideline for the first- line management of classical Hodgkin lymphoma — A British Society for Haematology guideline. Br J Haematol 2022. doi:10.1111/bjh.18083.

[4] Radford J, Illidge T, Counsell N, Hancock B, Pettengell R, Johnson P, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med 2015;372:1598–607. doi:10.1056/NEJMoa1408648.

[5] André MPE, Girinsky T, Federico M, Reman O, Fortpied C, Gotti M, et al. Early positron emission tomography response-adapted treatment in stage I and II hodgkin lymphoma: Final results of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol 2017;35:1786–96. doi:10.1200/JCO.2016.68.6394.

[6] Fuchs M, Goergen H, Kobe C, Kuhnert G, Lohri A, Greil R, et al. Positron emission tomography-guided treatment in early-stage favorable Hodgkin lymphoma: Final results of the international, randomized phase III HD16 trial by the German Hodgkin Study Group. J Clin Oncol 2019;37:2835–45. doi:10.1200/JCO.19.00964.

[7] Wirth A, Mikhaeel NG, Aleman BMP, Pinnix CC, Constine LS, Ricardi U, et al. Involved site radiation therapy in adult lymphomas: an overview of International Lymphoma Radiation Oncology Group guidelines. Int J Radiat Oncol 2020;107:909–33. doi:10.1016/J.IJROBP.2020.03.019.

[8] Specht L, Yahalom J, Illidge T, Berthelsen AK, Constine LS, Eich HT, et al. Modern radiation therapy for Hodgkin lymphoma: Field and dose guidelines from the international lymphoma radiation oncology group (ILROG). Int J Radiat Oncol Biol Phys 2014;89:854–62. doi:10.1016/j.ijrobp.2013.05.005.

[9] Illidge T, Specht L, Yahalom J, Aleman B, Berthelsen AK, Constine L, et al. Modern radiation therapy for nodal non-Hodgkin lymphoma - Target definition and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys 2014;89:49–58. doi:10.1016/j.ijrobp.2014.01.006.

[10] van Nimwegen FA, Schaapveld M, Cutter DJ, Janus CPM, Krol ADG, Hauptmann

M, et al. Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. J Clin Oncol 2016;34:235–43. doi:10.1200/JCO.2015.63.4444.

[11] van Nimwegen FA, Ntentas G, Darby SC, Schaapveld M, Hauptmann M, Lugtenburg PJ, et al. Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines. Blood 2017;129:2257–65. doi:10.1182/blood-2016-09-740332.

[12] Cutter DJ, Schaapveld M, Darby SC, Hauptmann M, Van Nimwegen FA, Krol ADG, et al. Risk for valvular heart disease after treatment for Hodgkin lymphoma. J Natl Cancer Inst 2015;107:1–9. doi:10.1093/jnci/djv008.

[13] Travis LB, Hill DA, Dores GM, Gospodarowicz M, Leeuwen FE van, Holowaty E, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA 2003;290:465–75. doi:10.1001/JAMA.290.4.465.

[14] Hill DA, Gilbert E, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, et al. Breast cancer risk following radiotherapy for Hodgkin lymphoma: modification by other risk factors. Blood 2005;106:3358–65. doi:10.1182/BLOOD-2005-04-1535.

[15] van Leeuwen FE, Klokman WJ, Stovall M, Dahler EC, van't Veer MB, Noordijk EM, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. JNCI J Natl Cancer Inst 2003;95:971–80. doi:10.1093/JNCI/95.13.971.

[16] Krul IM, Opstal-van Winden AWJ, Aleman BMP, Janus CPM, van Eggermond AM, De Bruin ML, et al. Breast cancer risk after radiation therapy for Hodgkin lymphoma: Influence of gonadal hormone exposure. Int J Radiat Oncol 2017;99:843–53. doi:10.1016/j.ijrobp.2017.07.016.

[17] Gilbert ES, Stovall M, Gospodarowicz M, Leeuwen FE Van, Andersson M, Glimelius B, et al. Lung cancer after treatment for Hodgkin's disease : Focus on radiation effects. Radiat Res 2003;159:161–73.

[18] Travis LB, Gospodarowicz M, Curtis RE, Clarke A, Andersson M, Glimelius B, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst 2002;94:182–92. doi:10.1093/jnci/94.3.182.

[19] van den Belt-Dusebout AW, Aleman BMP, Besseling G, de Bruin ML, Hauptmann M, van 't Veer MB, et al. Roles of radiation dose and chemotherapy in the etiology of stomach cancer as a second malignancy. Int J Radiat Oncol 2009;75:1420–9. doi:10.1016/J.IJROBP.2009.01.073.

[20] Morton LM, Dores GM, Curtis RE, Lynch CF, Stovall M, Hall P, et al. Stomach cancer risk after treatment for Hodgkin lymphoma. J Clin Oncol 2013;31:3369–77. doi:10.1200/JCO.2013.50.6832.

[21] Gilbert ES, Curtis RE, Hauptmann M, Kleinerman RA, Lynch CF, Stovall M, et al. Stomach cancer following Hodgkin lymphoma, testicular cancer and cervical cancer: a pooled analysis of three international studies with a focus on radiation effects. Radiat Res 2017;187:186–95. doi:10.1667/RR14453.1.

[22] Morton LM, Gilbert ES, Stovall M, van Leeuwen FE, Dores GM, Lynch CF, et al. Risk of esophageal cancer following radiotherapy for Hodgkin lymphoma. Haematologica 2014;99:e193–6. doi:10.3324/haematol.2014.108258.

[23] Dores GM, Curtis RE, van Leeuwen FE, Stovall M, Hall P, Lynch CF, et al. Pancreatic cancer risk after treatment of Hodgkin lymphoma. Ann Oncol 2014;25:2073–9. doi:10.1093/annonc/mdu287.

[24] Riley RD, Ensor J, Snell KIE, Harrell FE, Martin GP, Reitsma JB, et al. Calculating the sample size required for developing a clinical prediction model. BMJ 2020;368:m441. doi:10.1136/bmj.m441.

[25] Moons KGM, Altman DG, Reitsma JB, Ioannidis JPA, Macaskill P, Steyerberg EW, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): Explanation and elaboration. Ann Intern Med 2015;162:W1–73. doi:10.7326/M14-0698.

[26] Feng M, Moran JM, Koelling T, Chughtai A, Chan JL, Freedman L, et al.

Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. Int J Radiat Oncol Biol Phys 2011;79:10–8. doi:10.1016/j.ijrobp.2009.10.058.

[27] Duane F, Aznar MC, Bartlett F, Cutter DJ, Darby SC, Jagsi R, et al. A cardiac contouring atlas for radiotherapy. Radiother Oncol 2017;122:416–22. doi:10.1016/j.radonc.2017.01.008.

[28] Kong F-M, Quint L, Mitchell M, Bradley J. Atlases for Organs at Risk (OARs) in Thoracic Radiation Therapy. Radiat Ther Oncol Gr 2018.

[29] Heinze G, Wallisch C, Dunkler D. Variable selection – A review and recommendations for the practicing statistician. Biometrical J 2018;60:431–49. doi:10.1002/bimj.201700067.

[30] Sauerbrei W. The use of resampling methods to simplify regression models in medical statistics. J R Stat Soc 1999;48:313–29. doi:10.1111/1467-9876.00155.

[31] Taylor CW, McGale P, Povall JM, Thomas E, Kumar S, Dodwell D, et al. Estimating cardiac exposure from breast cancer radiotherapy in clinical practice. Int J Radiat Oncol Biol Phys 2009;73:1061–8. doi:10.1016/j.ijrobp.2008.05.066.

[32] Cutter DJ, Ramroth J, Diez P, Buckle A, Ntentas G, Popova B, et al. Predicted risks of cardiovascular disease following chemotherapy and radiotherapy in the UK NCRI RAPID trial of positron emission tomography-directed therapy for early-stage Hodgkin lymphoma. J Clin Oncol 2021;39:3591–601. doi:10.1200/JCO.21.00408.

[33] van Nimwegen FA, Schaapveld M, Cutter DJ, Janus CPM, Krol ADG, Hauptmann M, et al. Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. J Clin Oncol 2015;34:235–43. doi:10.1200/jco.2015.63.4444.

[34] Ntentas G, Dedeckova K, Andrlik M, Aznar MC, Shakir R, Ramroth J, et al. Proton therapy in supradiaphragmatic lymphoma: Predicting treatment-related mortality to help optimize patient selection. Int J Radiat Oncol Biol Phys 2022;112:913–25. doi:10.1016/j.ijrobp.2021.10.151.

[35] Ntentas G, Dedeckova K, Andrlik M, Aznar MC, George B, Kubeš J, et al. Clinical intensity modulated proton therapy for Hodgkin lymphoma: Which patients benefit the most? Pract Radiat Oncol 2019;9:179–87. doi:10.1016/j.prro.2019.01.006.

[36] Hoppe BS, Bates JE, Mendenhall NP, Morris CG, Louis D, Ho MW, et al. The meaningless meaning of mean heart dose in mediastinal lymphoma in the modern radiation therapy era. Pract Radiat Oncol 2020;10:e147–54. doi:10.1016/j.prro.2019.09.015.

[37] Atkins KM, Bitterman DS, Chaunzwa TL, Kozono DE, Baldini EH, Aerts HJWL, et al. Mean heart dose is an inadequate surrogate for left anterior descending coronary artery dose and the risk of major adverse cardiac events in lung cancer radiation therapy. Int J Radiat Oncol Biol Phys 2021;110:1473–9. doi:10.1016/j.ijrobp.2021.03.005.

[38] Ilyas H, Mikhaeel NG, Dunn JT, Rahman F, Møller H, Smith D, et al. Defining the optimal method for measuring baseline metabolic tumour volume in diffuse large B cell lymphoma. Eur J Nucl Med Mol Imaging 2018;45:1142–54. doi:10.1007/s00259-018-3953-z.

[39] Kanoun S, Tal I, Berriolo-Riedinger A, Rossi C, Riedinger JM, Vrigneaud JM, et al. Influence of software tool and methodological aspects of total metabolic tumor volume calculation on baseline [18F] FDG PET to predict survival in Hodgkin lymphoma. PLoS One 2015;10:1–15. doi:10.1371/journal.pone.0140830.

[40] Barrington SF, Zwezerijnen BGJC, de Vet HCW, Heymans MW, Mikhaeel NG, Burggraaff CN, et al. Automated segmentation of baseline metabolic total tumor burden in diffuse large B-cell lymphoma: Which method is most successful? A study on behalf of the PETRA consortium. J Nucl Med 2021;62:332–7. doi:10.2967/jnumed.119.238923.

[41] Cottereau AS, Hapdey S, Chartier L, Modzelewski R, Casasnovas O, Itti E, et al. Baseline total metabolic tumor volume measured with fixed or different adaptive

thresholding methods equally predicts outcome in peripheral T cell lymphoma. J Nucl Med 2017;58:276–81. doi:10.2967/jnumed.116.180406.

[42] Meignan M, Sasanelli M, Casasnovas RO, Luminari S, Fioroni F, Coriani C, et al. Metabolic tumour volumes measured at staging in lymphoma: Methodological evaluation on phantom experiments and patients. Eur J Nucl Med Mol Imaging 2014;41:1113–22. doi:10.1007/s00259-014-2705-y.

[43] Nestle U, Kremp S, Schaefer-Schuler A, Sebastian-Welsch C, Hellwig D, Rübe C, et al. Comparison of different methods for delineation of18F-FDG PET-positive tissue for target volume definition in radiotherapy of patients with non-small cell lung cancer. J Nucl Med 2005;46:1342–8.

[44] Mikhaeel NG, Smith D, Dunn JT, Phillips M, Møller H, Fields PA, et al. Combination of baseline metabolic tumour volume and early response on PET/CT improves progression-free survival prediction in DLBCL. Eur J Nucl Med Mol Imaging 2016;43:1209–19. doi:10.1007/s00259-016-3315-7.

[45] Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving considerations for PET response criteria in solid tumors. J Nucl Med 2009;50:122S-150S. doi:10.2967/jnumed.108.057307.

[46] Barrington SF, Meignan M. Time to prepare for risk adaptation in lymphoma by standardizing measurement of metabolic tumor burden. J Nucl Med 2019;60:1096–102. doi:10.2967/jnumed.119.227249.

[47] Tylski P, Stute S, Grotus N, Doyeux K, Hapdey S, Gardin I, et al. Comparative assessment of methods for estimating tumor volume and standardized uptake value in18F-FDG PET. J Nucl Med 2010;51:268–76. doi:10.2967/jnumed.109.066241.

[48] Van Der Ploeg T, Austin PC, Steyerberg EW. Modern modelling techniques are data hungry: A simulation study for predicting dichotomous endpoints. BMC Med Res Methodol 2014;14:1–13. doi:10.1186/1471-2288-14-137/FIGURES/13.

Chapter 6

General summary and future perspectives

6.1 Summary of findings

This thesis has provided data to help individualise the use of radiotherapy when treating people with Hodgkin lymphoma (HL).

In Chapter 2 I explored the experiences of patients and clinicians in making decisions about using radiotherapy to treat people with HL. The decision about radiotherapy was commonly made by clinicians and presented to patients as a conclusion. Patients often perceived themselves to be in a life-threatening situation with no real choice about treatment. They were highly engaged and keen to receive information, but the majority felt too overwhelmed by the complexity of their illness to participate in treatment decisions. Patients and clinicians agreed that the ultimate responsibility for radiotherapy decisions lay with clinicians, and that it was too challenging to lay the burden of this decision solely on the patient. Clinicians considered individual patient factors when deciding about radiotherapy, and recognised the importance of ensuring that decisions were in line with a patient's values and preferences. Both patients and clinicians felt that decision-making about radiotherapy would be improved by easily accessible information estimating the risks of radiotherapy for an individual. This process of decision-making does not fit any models of decision-making well, and instead I proposed a new model: person-centred decision-making. The key aspects of this model are bidirectional flow of information (medical and personal), and deliberation about decisions between clinicians (in MDT meetings), with the ultimate responsibility for decisions lying with clinicians.

In Chapter 3 I showed there is high-quality data to suggest that radiotherapy can increase rates of ischaemic heart disease (IHD), heart failure (HF), valvular heart disease (VHD), breast cancer, lung cancer, and gastrointestinal malignancies in HL survivors, and moderate-level evidence to suggest an increased risk of pericardial disease, cerebrovascular disease, cutaneous malignancies, thyroid cancer, and thyroid dysfunction.

There is lower-quality evidence suggesting there may be an increased risk of cardiac conduction abnormalities, urogenital cancers, head and neck cancers, bone and soft-tissue sarcomas, and diabetes. I characterised how these risks are affected by a large number of factors that vary between individuals. Risks are related to organ-at-risk (OAR) exposure to radiation, and rates are higher with radiation fields that included OARs, and at higher prescribed radiation doses. The risks of both cardiovascular disease and second malignancies are higher in those treated at younger ages, with conflicting data on whether relative risks differ between sexes. I presented the dose-response relationships that exist to quantify how the risk of IHD, HF, VHD, and cancers of the breast, lung, oesophagus, stomach, and pancreas vary with radiation dose received by OARs.

In Chapter 4 I presented estimates of radiation doses to abdominopelvic OARs from historic radiotherapy for HL, split by the main radiotherapy field types, and separately for patients who went on to develop colorectal cancer (CRC) or not. The highest OAR doses were seen with inverted-Y fields, and the highest doses to upper abdominal OARs were from total-nodal irradiation. Patients who went on to develop CRC received higher doses to the colon compared to those who did not develop CRC. I demonstrated how I used these data in collaboration with researchers from the Netherlands Cancer Institute to determine the dose-response relationship between the radiation dose received by the colon and the patient's subsequent risk of CRC. Overall, CRC rate increased linearly with mean radiation dose to the bowel. The effect was modified by cumulative procarbazine dose: the excess rate ratio per gray to the whole bowel was 3.5% (95% CI 0.4-12.6) for patients who did not receive procarbazine, and increased 1.19-fold (95% CI 1.06-1.33) for each gram per metre-squared increase in procarbazine dose.

In Chapter 5 I demonstrated that it is possible to estimate the cardiac dose from radiotherapy using data available at the time of a patient's diagnosis with HL. The variables that best predicted mean heart dose (MHD) were the extent to which mediastinal disease

overlapped the heart, width of mediastinal disease, presence of hilar disease, and radiotherapy delivery and breathing techniques. The model predicted MHD to within 12% for patients in the middle two quartiles of MHD, but it performed poorly for patients with MHDs at the extremes of the cohort (an 80% underestimate for those in the lowest quartile, and a 35% overestimate for those in the highest quartile). When MHDs predicted by the model were converted into absolute excess risks of IHD at 30-years, risk estimates were accurate to within 16% for the middle two quartiles, and to within 20% for the lowest and highest quartiles. The patients for whom the decision to treat with radiotherapy is most complex are those who lie in the mid-range for predicted MHD. Therefore, this model works best for those patients who need it most.

Taken together, these data help inform various steps of decision-making about radiotherapy, supporting clinicians to consider a more individualised approach to its use (Figure 6.1). Chapter 2 highlights that shared decision-making is not always appropriate for every healthcare decision. Instead, clinicians should be encouraged to explore each patient's preference for involvement in decision-making, and adapt their approach accordingly. I have proposed a new model of decision-making that clinicians should consider to ensure a person-centred approach to treatment decisions. Chapter 5 demonstrates that it is feasible to predict OAR doses from radiotherapy at the beginning of a patient's treatment pathway. Chapter 3 presents the published data that can be used to translate these OAR doses into risks of radiotherapy, to inform MDT discussions, and identifies the areas where more data are needed. Chapter 4 adds to the data by reporting doses to abdominopelvic OARs, and determining the dose-response relationship for the risk of CRC. Chapter 2 explores how clinicians integrate information about benefits and risks of radiotherapy into treatment discussions, and illustrates how they can tailor their approach to decision-making to support patients to achieve their preferred level of involvement.

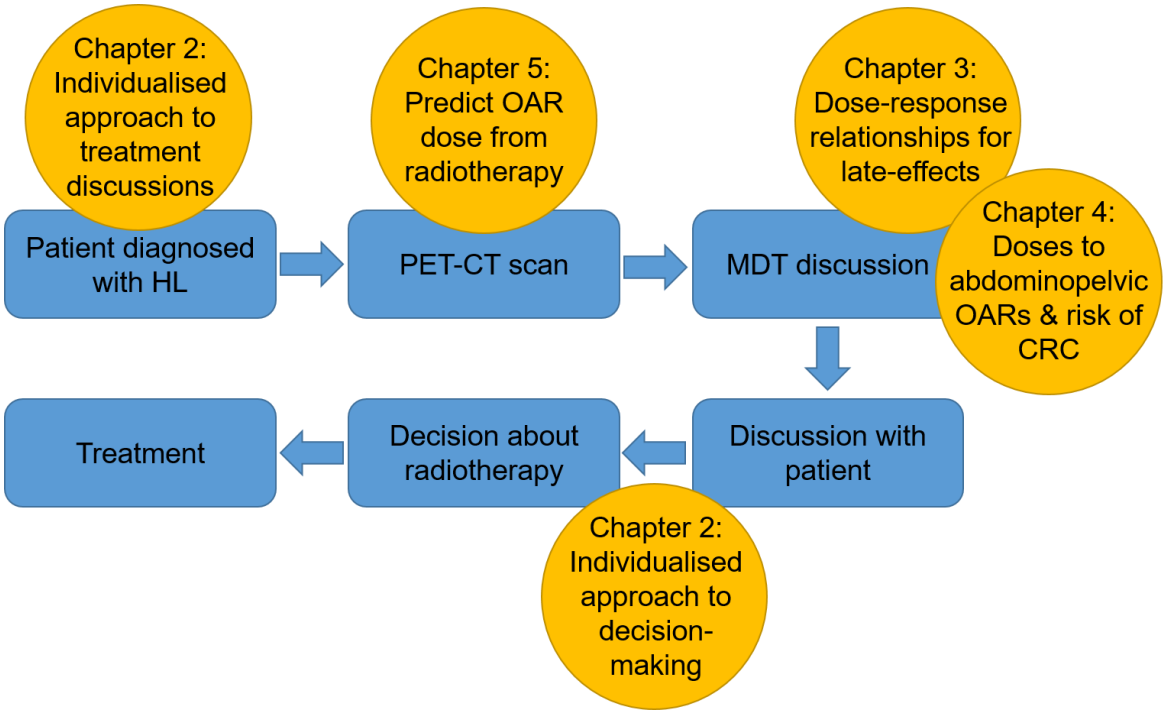


Figure 6.1: Overview of the clinical pathway for making decisions about radiotherapy used to treat patients with HL, highlighting the steps informed by data presented in this thesis

Abbreviations - HL: Hodgkin lymphoma; OAR: organ-at-risk; PET-CT: Positon emission tomography integrated with computed tomography; MDT: multidisciplinary team; CRC: colorectal cancer

6.2 Future perspectives

6.2.1 Decision aid

A key element in developing an individualised approach to decisions about radiotherapy in the context of HL is the need to individually assess whether a 6-12% difference in the rate of relapse is worth the added potential risk [1]. Addressing this requires both individualised estimates of the risks of radiotherapy, and a means to discuss these with patients to allow them to express their preferences in terms of future risk of relapse or late-effects. The studies presented in this thesis address both of these points. Chapter 2 suggests an alternative approach to decision-making that would support patients to achieve their preferred level of involvement, and demonstrates that individualised risk estimates would

facilitate greater discussion of treatment options. Data in Chapters 3, 4 and 5 could be used to build models to estimate individualised risks of late-effects according to the age of the patient, the site(s) of disease, and the radiotherapy dose to OARs. Such models could be developed into a decision aid that could provide patients and clinicians with evidence-based quantitative estimates of the risks of radiotherapy for an individual patient.

Decision aids, such as that proposed above, can improve patients' knowledge of treatment options, facilitate discussion between patient and clinician, and increase the accuracy of risk perceptions [2,3]. They can also support patients to value their own contribution to decision-making, and define their own priorities [2]. Patients and clinicians should be involved in developing a radiotherapy decision aid, and it would need to be tested in prospective studies, and refined based on the results and any new data on the benefits and risks of radiotherapy. My project advisory group, and the patients and clinicians I spoke to in Chapter 2, think that the clarity a decision aid could offer would be invaluable in terms of treatment discussions.

6.2.2 Radiotherapy plan optimisation

Data presented in this thesis could also be used to optimise radiotherapy plans. Currently, the optimal radiotherapy plan is chosen based on which delivers the prescribed dose to the tumour whilst minimising dose to OARs. A Danish group is working on embedding risk estimation into radiotherapy treatment planning systems (TPSs) so that OAR doses can be converted into risk estimates of late-effects for individual patients [4]. This requires dose-response relationships to be programmed into TPSs. They have currently attempted this to estimate patients' subsequent risk of cardiovascular disease (unpublished work, presented at ILROG meeting May 2022 and personal correspondence), but are yet to do so for second

malignancies. The first step is identification of published dose-response relationships, and I have discussed sharing the data presented in Chapter 3 to contribute to this work.

6.2.3 Additional clinical impacts

There is a lack of structured long-term follow-up programmes for people treated for HL in the UK. In the Netherlands, the BETER consortium (Better care after HL: Evaluation of long-term Treatment Effects and screening Recommendations) developed a national structured survivorship programme for 5-year HL survivors with the aim of reducing morbidity and mortality from late-effects [5]. They have published guidelines on follow-up based on sex, age at HL diagnosis, and treatments received [6]. Screening is delivered in BETER clinics, staffed by haematologists, clinical oncologists, and specialist nurses [5]. They develop a tailored survivorship care plan that can be shared with the patient's GP, summarising treatment, toxicities, and recommendations for screening and treatment of late-effects.

In the UK, the only comprehensive long-term follow-up programme that I am aware of is ADAPT in Manchester [7,8]. Patients have a consultation five years after completing treatment for HL, during which the potential late-effects of treatment are discussed and a late toxicity management plan produced [7]. They then have open access to the ADAPT service, and complete an annual questionnaire about quality of life, new diagnoses and medication. I would like to use the knowledge I have gained from my research to develop a long-term follow-up programme for patients treated for HL in Oxford. This programme would be a means to access support and up-to-date reliable information about late-effects and existing surveillance programmes, and data suggests it might help people to adjust positively to life beyond their cancer treatment [9–11].

An additional clinical impact of this thesis would be the development of information about the role of radiotherapy in the treatment of HL. Whilst such information currently exists [12],

in Chapter 2 patients cited lack of understanding about radiotherapy as a barrier to being involved in treatment discussions; and many lacked knowledge of its late-effects. Having informational needs met at an appropriate level is a key enabler of patient involvement in decisions [3]. The data presented in this thesis could be used to develop more detailed information for patients about the relative benefits and risks of radiotherapy specific to the treatment of HL.

6.3 Concluding remarks

HL is a highly curable malignancy, meaning life beyond cure is a key consideration for patients and clinicians. The use of radiotherapy requires an individualised approach to assess the risk of late-effects versus the risk and subsequent consequences of HL relapse. This thesis helps to inform decision-making about radiotherapy by highlighting how clinicians can support patient involvement in decisions, and providing methods to individualise risk estimates of radiotherapy late-effects.

Alongside the academic and clinical implications of this research, this thesis has had a huge impact personally on my future career plans. I have gained a deep understanding of the late-effects of radiotherapy, and have become passionate about the ongoing care of people living beyond cancer. Working with people treated for HL, as members of the project advisory group, and talking to patients during the decisions study, has given me a fresh perspective on cancer treatment, and a greater ability to provide high-quality person-centred care.

6.4 References

[1] Illidge T. Balancing risks in developing a personalised approach to the treatment of early Hodgkin lymphoma: Have we got the balance right? Clin Oncol 2015;27:454–6. doi:10.1016/j.clon.2015.05.007.

[2] Stacey D, Légaré F, Lewis K, Barry MJ, Bennett CL, Eden KB, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2017;2017. doi:10.1002/14651858.CD001431.pub5.

[3] Joseph-Williams N, Elwyn G, Edwards A. Knowledge is not power for patients: A systematic review and thematic synthesis of patient-reported barriers and facilitators to shared decision making. Patient Educ Couns 2014;94:291–309. doi:10.1016/j.pec.2013.10.031.

[4] Brodin NP, Maraldo M V., Aznar MC, Vogelius IR, Petersen PM, Bentzen SM, et al. Interactive decision-support tool for risk-based radiation therapy plan comparison for Hodgkin lymphoma. Int J Radiat Oncol Biol Phys 2014;88:433–45. doi:10.1016/j.ijrobp.2013.10.028.

[5] Nijdam A, Dekker N, Aleman BMP, van 't Veer MB, Daniels LA, van der Maazen RW, et al. Setting up a national infrastructure for survivorship care after treatment for Hodgkin lymphoma. Br J Haematol 2019. doi:10.1111/bjh.15936.

[6] Homepage - Beter Na Hodgkin n.d. https://www.beternahodgkin.nl/ (accessed July 18, 2022).

[7] Radford J, Goode V, White E, Monkhouse R, Cowan R. Managed local follow-up of long term lymphoma survivors – the ADAPT programme. NCRI Cancer Conf., 2016.

[8] Adept ADAPTations - ADAPT - University of Manchester - Innovation Factory n.d. https://www.uominnovationfactory.com/projects/adept-adaptations/ (accessed July 26, 2022).

[9] Matheson L, Boulton M, Lavender V, Collins G, Mitchell-Floyd T, Watson E. The experiences of young adults with Hodgkin lymphoma transitioning to survivorship: a grounded theory study. Oncol Nurs Forum 2016;43:E195–2014. doi:10.1188/16.onf.e195-e2014.

[10] Bober SL, Park ER, Schmookler T, Medeiros Nancarrow C, Diller L. Perceptions of breast cancer risk and cancer screening: A qualitative study of young, female Hodgkin's disease survivors. J Cancer Educ 2007;22:42–6.

[11] Grinyer A. The late effects of mantle field radiotherapy: The information and support needs of women survivors of Hodgkin's disease. Eur J Oncol Nurs 2010;14:183–9. doi:10.1016/j.ejon.2009.12.006.

[12] Lymphoma Action. Lymphoma Action | Radiotherapy 2020. https://lymphoma-action.org.uk/about-lymphoma-treatment-lymphoma/radiotherapy (accessed July 26, 2022).

Appendix A

Glossary

CD30 – a member of the tumour necrosis factor receptor superfamily that is expressed as an antigen on the surface of activated white blood cells (lymphocytes) and certain haematological malignancies, including Hodgkin lymphoma

Chemotherapy – a type of cancer treatment that uses one or more anti-cancer drugs as part of a standardised regimen

Complete metabolic response – the resolution of all areas of abnormality on a PET-CT scan during or following cancer treatment

Decision aid – a tool or intervention designed to facilitate people's participation in decision-making

Electrons – a small particle with a negative charge that is found in all atoms

Gamma ray – penetrating electromagnetic radiation that arises from the radioactive decay of an atomic nucleus

Haematogenous – spread via the bloodstream

Histological – the study of tissues and cells under a microscope

Immunohistochemical – the use of antibodies to check for specific antigens (markers) in tissues or cells

Immunotherapy – a type of cancer treatment that uses substances to stimulate or supress the immune system

Irradiated – treated with radiation

Late-effects – side-effects that occur over three months after completion of radiotherapy

Latency – the time that passes between being exposed to something that can cause a disease and having symptoms

Lymphatic system – the tissues and organs that produce, store, and circulate the body's white blood cells; namely the bone marrow, spleen, thymus, lymph nodes, and lymph vessels.

Mediastinum – the central compartment of the thorax (chest), between the lungs, that contains the heart and its large blood vessels, the trachea, the oesophagus, the thymus, and lymph nodes

Neutrons – a subatomic particle with no electrical charge that is found in the nucleus of all atoms apart from hydrogen

Organs-at-risk – organs that are within or near radiotherapy fields, whose irradiation could cause damage that results in morbidity

Photons – a particle of electromagnetic radiation

Protons – a subatomic particle with positive charge that is found in all atomic nuclei

Radiotherapy – the use of radiation to kill cancer cells

Radiotherapy field – the area covered by a radiation beam

Radiotherapy treatment plan – a simulation of a course of radiotherapy, used to estimate the doses delivered to the target volume and organs-at-risk

Recurrence – cancer that has come back after a period of time when it was undetectable

Relapse – the return of a disease, or its signs and symptoms, after a period of improvement

Second malignancy – a new cancer that develops in someone who has previously been treated for cancer

Splenectomy – an operation to remove the spleen

Target volume – the area of tissue intended to be treated with radiotherapy

Appendix B

Supplementary material to Chapter 2

Appendix B1: Study advertisements



UNIVERSITY OF OXFORD

Nuffield Department of Population Health

Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF
Email: rebecca.shakir@ndph.ox.ac.uk

We would like to invite you to participate in a research study being carried out by researchers from the University of Oxford.

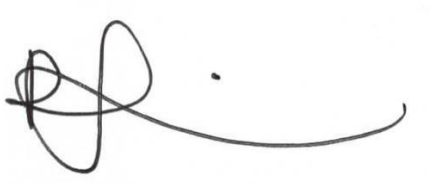
The study is called '**Decisions regarding radiotherapy used to treat Hodgkin lymphoma: patients' and healthcare professionals' perspectives'**. We are trying to understand more about how decisions are made regarding radiotherapy used after chemotherapy for the treatment of Hodgkin lymphoma, with a focus on early-stage disease. We are interested in the views of health care professionals who are involved in the care of people with Hodgkin lymphoma, including Haematologists, Clinical Nurse Specialists and Clinical Oncologists.

We have enclosed an information sheet for you to read and consider whether you would like to takepart. Taking part or not is entirely up to you.

If you would like to take part in this study, please email us on rebecca.shakir@ndph.ox.ac.uk. Oncewe receive your email we will contact you to arrange an interview at a time most convenient to you.It is likely that this interview will take place over video call given the current social distancing guidelines.

If you would like to find out more about the study before deciding whether or not to take part please contact the Chief Investigator, Dr Rebecca Shakir, on rebecca.shakir@ndph.ox.ac.uk.

Yours sincerely,



Dr Rebecca Shakir
Clinical Research Fellow & Clinical Oncology SpR

Appendix B2: Participant information sheets

Nuffield Department of POPULATION HEALTH
UNIVERSITY OF OXFORD

Nuffield Department of Population Health
University of Oxford • Richard Doll Building •
Old Road Campus • Roosevelt Drive •
Oxford • OX3 7LF • www.ndph.ox.ac.uk •

Decisions About Radiotherapy Used to Treat Hodgkin Lymphoma: Patients' & Healthcare Professionals' Perspectives Can you help?

Summary:

- **This information sheet is for people who have been treated for Hodgkin lymphoma.**
- **We would like to interview people to discuss how treatment decisions are made. This study will focus on discussions about radiotherapy, but anyone who has been treated for Hodgkin lymphoma can take part.**
- **The interview will be conducted on video call or over the phone. You can choose what would be better for you, and the time. It should not take more than an hour of your time.**
- **The results of these interviews will be used to help improve future decision making about Hodgkin lymphoma treatment.**

For more information, please contact the researcher:
Contact name: Dr Rebecca Shakir
Email address: rebecca.shakir@ndph.ox.ac.uk

The rest of this leaflet tells you more detail about the study.

Invitation to participate in the study

- We are inviting you to take part in a research project.
- Before you decide, it is important you understand why the research is being done and what it would involve for you.
- Please take time to read the following information carefully. Talk to others about the study if you wish.
- Ask us if there is anything that is not clear or if you would like more information.
- Take time to decide whether or not you wish to take part.

What is the purpose of the study?

- The aim of this study is to understand more about how decisions about radiotherapy are made by people who are being treated for Hodgkin lymphoma, as well as the involvement of their friends and relatives, and health care professionals in those decisions.

- We will conduct interviews to find out what is important to people faced with decisions about radiotherapy.
- We will ask questions about your treatment for Hodgkin lymphoma, positive and negative aspects of your treatment, how you made decisions about your treatment, whether radiotherapy was discussed with you, and what could have helped you to make decisions. We will also talk to you about whether a decision support tool would have helped you.
- The study is part of a larger project which is developing a support tool to improve shared decision making about radiotherapy between health care professionals and people with Hodgkin lymphoma in the future.

Why have I been invited?

- You have been invited because you have been treated for Hodgkin lymphoma in the last five years.
- We would like to hear about whether you had any discussions about radiotherapy as part of the treatment for your lymphoma, and how your treatment decisions were made.
- We would also like to talk to you about the information people with Hodgkin lymphoma might need to help them make their decisions about radiotherapy.
- We are interested in talking to people who did not have radiotherapy, as well as those that did.
- We know that close family members, or friends, are also involved in decisions about treatment. If you are comfortable we will discuss these issues during the interview and will ask you whether you would be happy for your relative or friend to be interviewed at a later date. If so, we would ask you to share study information with them, so they can be contact us if they are interested.
- We hope to interview 15-20 people who have been treated for Hodgkin lymphoma, the relative or friend they nominate, and 10-15 health care professionals.

Do I have to take part?

- No. It is up to you to decide. Taking part in this study is entirely voluntary. If you do not want to take part, you do not have to and you do not have to give a reason.
- If you decide to take part but later change your mind, you can withdraw from the study at any time and do not have to give a reason. No one will be upset if you do this, and it would not affect any current or future treatment you receive.
  There may be opportunities to take part in future research projects run by this group. If you do not want to be interviewed but are interested in taking part in future research projects then please let us know via email. You will then be sent further information at a later date. You will only be contacted about participating in future research projects if you have agreed to this.

What will I have to do if I take part?

- If you wish to take part in the study, then please email us on the address below and provide your contact details.
- Once we receive the email, a member of the research team will contact you to arrange an interview at a time most convenient to you. Given the current guidelines

regarding social distancing, the interview will take part over a video call. If this is not possible, it could take place over the phone.

- If the guidelines allow in the future, and you wanted to meet in person, it may be possible to conduct face-to-face interviews, at a place most convenient to you. If taking part in an interview meant you had to travel to meet us, we would reimburse your travel costs.
- The interview will last for about an hour, and we will audio record it with your consent.
- If you agree, your GP will be informed that you are taking part in the study. They will not be told about any of your answers.

What are the possible risks and disadvantages of taking part?

- The main disadvantage is the inconvenience in terms of the time taken to be interviewed. The interviews will take approximately an hour to conduct.
- You may find some of the questions difficult to answer. If you find any of the questions upsetting the interview can be stopped at your request at any time. We will also provide you sources of support if the interview brings up any difficult feelings or questions.

What are the possible benefits of taking part?

- This research study will not directly benefit you, but what you tell us will give us a much better understanding of the views of and choices made by people treated for Hodgkin lymphoma.
- This will help us provide better information and guidance for people facing similar decisions in the future.

Will my information be kept confidential?

- Yes, all information that is collected about you during the course of the research will be kept strictly confidential.
- With your permission, the interview will be recorded to make an accurate record of what is said and then transcribed by the research team, with personal details removed so it is not identifiable. Recordings and transcriptions will be stored separately, in digital format and will only be available to research staff working on the study. When the study is complete the recordings will be destroyed.
- Everyone who takes part in the study will be assigned a case number, and all of the data relating to each person will be held on a database and will only be linked to that code number, and not to your name or address so that you cannot be recognised.
- All interview documents will be stored in a locked room in the University. Any information stored on computers will be protected with passwords.
- If you decide to withdraw from the study at any time you will not be asked for any further information. Any interviews that you have completed will be kept confidential, or can be destroyed if you wish. The records will be kept for 3 years after the end of the study and then destroyed.
- Responsible members of the University of Oxford may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

What will happen to my data?

- Data protection regulation requires that we state the legal basis for processing information about you. For research, this is 'a task in the public interest.' The University of Oxford is the data controller and is responsible for looking after your information and using it properly.
- We will be using information from you in order to undertake this study and will use the minimum personally-identifiable information possible. We will keep identifiable information about you for 6 months after the study has finished. This excludes any research documents with personal information, such as consent forms, which will be held securely at the University of Oxford for up to 3 years after the end of the study. If you want to receive a copy of the research findings, we will retain your contact details for 3 years.
- If you agree to your details being held to be contacted regarding future research, we will retain a copy of your consent form until such time as your details are removed from our database (maximum 10 years). Any contact would come from our department and we would not share your details with any third parties without your permission. Agreement to be contacted does not create any obligation to participate and we can remove your details at any time, upon request. We will keep the consent form and your details separate.
- It may be necessary to keep your information for longer to complete our study, or to fulfil any legal, accounting or reporting requirements. This will always be done in accordance with data protection laws and we will inform you should such an extension be required.
- Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at https://compliance.web.ox.ac.uk/individual-rights
- You can find out more about how we use your information by contacting rebecca.shakir@ndph.ox.ac.uk

What will happen to the results of the study?

- The results of the study will be included in Dr Shakir's DPhil thesis, presented at conferences and published in scientific journals, and will be made available to you if you wish.
- You will not be identifiable in any of the presented or published reports. Quotes from interviews may be used when presenting results; these will be fully anonymised so that you could not be identified.
- Please indicate on the consent form if you would like to receive a copy of the research findings.

Who is organising the study?

- The study is being carried out ('sponsored') by the University of Oxford.
- The research is funded by the National Institute for Health Research.

Who has approved the study?

- All research is looked at by an independent group of people, called a Research Ethics Committee, to protect your safety, rights, well-being and dignity.
- This study has been approved by the North of Scotland 2 Research Ethics Committee.

What if there is a problem?

- If you wish to complain about any aspect of the way in which you have been approached or treated, or how your information is handled during the course of this study, you should contact Rebecca Shakir on rebecca.shakir@ndph.ox.ac.uk.
- Alternatively, you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 616480, or the head of CTRG, email ctrg@admin.ox.ac.uk.
- The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study.
- In respect to how your personal data is processed, you can also contact the University of Oxford's Data Protection Office via data.protection@admin.ox.ac.uk. You also have the right to lodge a complaint with a supervisory authority. In the UK, this is the Information Commissioner's Office (ICO). A complaint to the ICO can be made by visiting their website https://ico.org.uk/make-a-complaint/ or by calling their helpline on 0303 123 1113.

How can I find out more?

- If you would like any further information, or have any questions concerning this study, please contact the researcher:

Contact name: Dr Rebecca Shakir
Email address: rebecca.shakir@ndph.ox.ac.uk

What do I need to do now?

If you would like to take part in this study, please email us at rebecca.shakir@ndph.ox.ukwith your contact details. Once we receive your email, a member of our research team will contact you. We will arrange an interview at a time most convenient to you. Feel free to email us with any queries you may have and/or talk the study over with anyone else.
If you don't want to take part at the moment, but would be happy to be contacted by us at a later date, please let us know. We will also ask if you would be interested in being contacted about other parts of the study at a later date. We completely understand if you would rather not be contacted again.

Please keep this information leaflet for future reference.
Thank you for reading this information sheet and for taking an interest in the research study.

Nuffield Department of POPULATION HEALTH
UNIVERSITY OF OXFORD

Nuffield Department of Population Health
University of Oxford • Richard Doll Building •
Old Road Campus • Roosevelt Drive •
Oxford • OX3 7LF • www.ndph.ox.ac.uk •

Decisions About Radiotherapy Used to Treat Hodgkin Lymphoma: Patients' & Healthcare Professionals' Perspectives Information Sheet for Health Care Professionals

Summary:

- **This information sheet is for health care professionals involved in the care of people with Hodgkin lymphoma.**
- **We would like to interview you about how you make decisions about radiotherapy used after chemotherapy to treat patients with early-stage Hodgkin lymphoma.**
- **The interview will be conducted on video call or over the phone. It should not take more than an hour of your time.**
- **The results of these interviews will be used to help improve future decision making about Hodgkin lymphoma treatment.**

For more information, you can contact the researcher:
Contact name: Dr Rebecca Shakir
Email address: rebecca.shakir@ndph.ox.ac.uk

The rest of this leaflet tells you more detail about the study.

Invitation to participate in the study

We would like to invite you to take part in a research study.
Before you decide, it is important that you understand why the research is being done and what it would involve for you.
Please take time to read the following information carefully.
Ask us if there is anything that is not clear or if you would like more information.

What is the purpose of the study?

Decisions about the use of radiotherapy after chemotherapy for Hodgkin lymphoma are complex, and patients often rely on the advice they are given by professionals providing their care.

Information discussed during a consultation and the way it is communicated may influence patients' decisions about treatment choices.
We would like to talk to you about how you and your patients make decisions regarding radiotherapy.
We will ask questions about the issues you discuss during a consultation with a patient with Hodgkin lymphoma about radiotherapy, and the factors which you feel are important to consider, as well as your views on radiotherapy and other management options.

Why have I been invited?

If you are involved in the management of people with Hodgkin lymphoma we are interested in interviewing you.
We will be interviewing 15-20 people previously treated for Hodgkin lymphoma, the relative or friend they identify as being involved in their treatment decisions, and 10-15 healthcare professionals including Haematologists, Clinical Nurse Specialists and Clinical Oncologists.

Do I have to take part?

No, it is entirely up to you to decide. Your taking part in this study is entirely voluntary.
If you do not want to take part, you do not have to and you do not have to give a reason.
If you decide to take part but later change your mind, you can withdraw from the study at any time and do not have to give a reason.

What will happen if I take part?

If you wish to take part in the study, then please email us on rebecca.shakir@ndph.ox.ac.uk with your contact details.
Once we receive the email, a member of the research team will contact you to arrange an interview at a time more convenient to you.
It is likely that the interview will be conducted over a video call, but in the future it may be possible to hold face-to-face interviews depending on social distancing guidelines at the time.
Interviews will take about an hour and will be audio recorded with your consent.

What are the possible risks and disadvantages of taking part?

There are no specific risks associated with taking part in this study, but you may suffer some inconvenience in terms of the time taken to be interviewed.

What are the possible benefits of taking part?

This research study will not directly benefit you, but what you tell us will give us a much better understanding of the decisions surrounding radiotherapy used to treat Hodgkin lymphoma. It will feed into a larger project with the aim of producing a decision support tool, which we hope will benefit your clinical practice in the future.

Will my information be kept confidential?

Yes, all information that is collected about you during the course of the research will be kept strictly confidential.
With your permission, the interview will be recorded to make an accurate record of what is said and then transcribed by the research team, with personal details removed so it is not identifiable. Recordings and transcriptions will be stored separately, in digital format, and will only be available to research staff working on the study. When the study is complete the recordings will be destroyed.

Everyone who takes part in the study will be assigned a case number, and all of the data relating to each person will be held on a database and will only be linked to that code number, and not to your name or address so that you cannot be recognised.
All interview documents will be stored in a locked room in the University. Any information stored on computers will be protected with passwords
If you decide to withdraw from the study at any time you will not be asked for any further information. Any interviews that you have completed will be kept confidential, or can be destroyed if you wish.
Responsible members of the University of Oxford may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

What will happen to my data?

Data protection regulation requires that we state the legal basis for processing information about you. For research, this is 'a task in the public interest', GDPR Article 6(1)(e). The University of Oxford is the data controller and is responsible for looking after your information and using it properly.
We will be using information from you in order to undertake this study and will use the minimum personally-identifiable information possible. We will keep identifiable information about you for 6 months after the study has finished. This excludes any research documents with personal information, such as consent forms, which will be held securely at the University of Oxford for up to 3 years after the end of the study. If you want to receive a copy of the research findings, we will retain your contact details for 3 years.
If you agree to your details being held to be contacted regarding future research, we will retain a copy of your consent form until such time as your details are removed from our database (maximum 10 years). Any contact would come from our department and we would not share your details with any third parties without your permission. Agreement to be contacted does not create any obligation to participate and we can remove your details at any time, upon request. We will keep the consent form and your details separate.
Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at https://compliance.web.ox.ac.uk/individual-rights
You can find out more about how we use your information by contacting rebecca.shakir@ndph.ox.ac.uk

Who is organising the study?

The study is being carried out ('sponsored') by the University of Oxford.
The research is funded by the National Institute for Health Research.

Who has approved the study?

This study has been approved by the North of Scotland 2 Research Ethics Committee.

What will happen to the results of the study?

The results of the study will be included in Dr Shakir's DPhil thesis, presented at conferences and published in scientific journals, and will be made available to you if you wish.

You will not be identifiable in any of the presented or published reports. Quotes from interviews may be used when presenting results; these will be fully anonymised so that you could not be identified.
Please indicate on the consent form if you would like to receive a copy of the research findings.

What if there is a problem?

If you wish to complain about any aspect of the way in which you have been approached or treated, or how your information is handled during the course of this study, you should contact Rebecca Shakir on rebecca.shakir@ndph.ox.ac.uk.
Alternatively, you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 616480, or the head of CTRG, email ctrg@admin.ox.ac.uk.
The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study.
In respect to how your personal data is processed, you can also contact the University of Oxford's Data Protection Office via data.protection@admin.ox.ac.uk. You also have the right to lodge a complaint with a supervisory authority. In the UK, this is the Information Commissioner's Office (ICO). A complaint to the ICO can be made by visiting their website https://ico.org.uk/make-a-complaint/ or by calling their helpline on 0303 123 1113.

How can I find out more?

If you would like any further information, or have any questions concerning this study, please contact the researcher:
Contact name: Dr Rebecca Shakir
Email address: rebecca.shakir@ndph.ox.ac.uk

What do I need to do now?

If you would like to take part in this study, please email us at rebecca.shakir@ndph.ox.ac.uk with your contact details. Once we receive your email, a member of our research team will contact you. We will arrange an interview at a time most convenient to you. Feel free to email us with any queries you may have and/or talk the study over with anyone else.

If you wish to take part in the study, please provide us with your contact details.

Please keep this information leaflet for future reference.

Thank you for reading this information sheet and for taking an interest in the research study.

Appendix B3: Interview guides

Decisions Regarding Radiotherapy in HL: Interview Guide Version 2: 4th March 2021

People previously treated for HL

Prior to the interview (email):

- When treated for HL
- Stage of HL (if known), what treatment they had
- Whether they were involved in a decision about radiotherapy

At start:

- Introductions
- Brief overview of study
- Explain purpose of interview
- Check had time to read information leaflet
- Answer any questions
- Sign consent form
- Confidentiality and anonymity issues
- Check ok to record interview
- Ensure participants feel free to stop the interview at any point
- Demographics
    - Occupation (working, retired, at home etc)
    - Marital status

1. Can you tell me about when you had Hodgkin lymphoma

How exactly did that happen that you ended up having chemotherapy?
How happy were you with that treatment plan?
How much was it explained why you needed that treatment?
Were you happy with that?

2. After you were diagnosed, what decisions were made about your treatment?

Can you explain who was involved in deciding what your treatment was going to be?
Who did you want involved?
To what extent were you involved in the decisions made?
How were alternative treatment options discussed?
What opportunities were there for you to influence the treatment plan?
How important was it for you to participate in the process of making decisions about your treatment?
To what extent did the medical team explore this / discuss this with you?
To what extent were you given the chance to express your opinions about the (different) treatments available?
To what extent do you think the plan was made by the doctor / you / jointly?
How did you feel about that?
How would you have wanted it to be different?

What could have been improved about the discussions you had regarding treatment?

One of the other possible treatments is radiotherapy.

3.1. Do you remember that being discussed?

What explanations were given about why radiotherapy was needed, or not?

Were you happy with that?

Would you have like the opportunity to discuss it more?

3.2. To what extent did you feel there was a decision to make about radiotherapy?

It's not always clear what option is right or wrong, and ideally doctors should discuss the pros and cons of any treatment options you have.

Thinking about radiotherapy, to what extent was that done?

How much would you have liked that to be discussed?

A. If they made a decision about radiotherapy

4.1. What was your experience with your decision about radiotherapy?

What information were you given about radiotherapy?

To what extent was the role of radiotherapy, and it's relative pros and cons, discussed with you?

How did you feel about the way that the benefits and risks were communicated?

How did you come to a decision about radiotherapy?

What kinds of issues were important to you as you made your decision?

Which of these issues were most important to you?

How much time were you given?

(When was radiotherapy first mentioned?)

What was the hardest part about deciding?

Who was involved in making this decision?

To what extent did you have the opportunity to ask the doctor questions?

To what extent did you feel like you told the doctor everything you needed to say?

How did you talk about your concerns with your doctors?

What helped you talk about the decision with your doctor?

What made it hard to talk about the decision with your doctor?

4.2. How do you feel about your decision now?

To what extent did you feel that you got the chance to talk through your decision with your doctors?

What, if anything, do you know now that you wish you had known when you were making your decision?

B. If they didn't make a decision about radiotherapy

Even when a scan after chemotherapy shows the lymphoma has all gone, there is still a debate about whether radiotherapy is useful. A small number of people can still benefit in terms of reducing the chance of the cancer coming back.

4.1. Would you have appreciated the chance to discuss this more?

How would you have wanted that to be discussed?

It is good to take personal preferences into account when deciding about whether radiotherapy is likely to benefit someone with HL.

4.2. What things would you have liked the medical team to know about you to help them make a decision?

What information did the medical team give you about why they made the decision they did?

What questions did they ask you to help them make decisions?

What information did they base their decision on?

5. How did you feel / would you have felt if you had been asked to make the decision about radiotherapy?

How appropriate do you think it is for doctors to ask you if you want radiotherapy?

How would you want the medical team to approach having that discussion?

What information would you have wanted?

Why do you think it's better for the doctors to make the decision?

What aspects about your treatment did you feel you made decisions about?

Are there situations where you think it would be appropriate for you to make a decision about your treatment?

6. Was there any information you needed or which would have helped you to become more involved in making the decision about radiotherapy?

One of the things that makes a difference to some people when they're considering whether or not to have radiotherapy is how much they focus on things that happen in the short-term compared to the long-term.

Radiotherapy can have some short-term advantages in terms of reducing the chance of the cancer coming back. But it has some long-term disadvantages in terms of increasing the chance of getting different cancers or heart disease. If you're someone who thinks more about things that happen in the short-term compared to the long-term, radiotherapy may look more attractive than if you were someone who worries a lot about the long-term risks.

7. To what extent was this explored with you?

To what extent do you know whether you're someone who thinks more about short-term or long-term possibilities?

How would you have felt discussing these with your medical team?

8. What factors influenced whether you were involved in decisions about your treatment?

To what extent was your preference about being involved in decisions explored?

To what extent were you given the opportunity to discuss what was important to you?

To what extent was the way you wanted information explored?

What helped you be more involved in decisions about your own treatment?

What prevented you from being more involved in decisions about your treatment?

What could healthcare professionals do to help you be more involved?

What could you do to help you be involved?

9. We're interested in a concept called shared-decision making. It's absolutely fine if you've never heard of it before, but if you have what does that term mean to you?

Shared decision making is a way for patients and their clinicians to work together to reach agreement about a health decision. Often, there is no clear 'best' option for a patient's health condition. Instead, the choice depends on patient values and preferences.

10. What would sharing a decision about radiotherapy look like?

What does it mean for you 'to be involved in the decision-making process'?

Which elements of such participation are essential from your perspective?

What do you think is the importance of engaging a patient in shared decision making?

What do you think are the challenges that limit patients' participation in shared decision making?

To what extent would you want to be involved in making a decision about radiotherapy?

Who do you think should make the final decision?

How would you have felt if the decision had been completely up to you?

What information would you want for this?

How would you have felt if your doctor had shared the uncertainty of the decision with you?

How do you think patient participation in decision making could be improved?

11. We are also interested in the use of patient decision aids. What, if anything, have you heard about these?

Decision aids are tools that help people think about their health choices. They provide information about options, help people think about what matters to them, and help them make a step by step decision. They come in various formats, for example on paper, online, or video. Some allow patients or clinicians to personalise information and add their own thoughts or any relevant health information.

How would you feel about using a patient decision aid to help make a decision about radiotherapy?

When would you have liked to use a decision aid during your decision process?

What do you think would be the best format for these tools?

Closing

Is there anything we haven't spoken about that you'd like to tell me?

At end

- What will happen with the data, including timescale
- Ensure participant has my contact details, to discuss anything related to the interview
- Ask if they wish to receive the transcript, or a summary of the findings
- Check if they have any questions
- Let them know about the support available, should they need it
- Ask if they would be happy to share some study information with their 'support person' who was involved in the decision-making process
- Thank the participant for their time and support with the study

Decisions Regarding Radiotherapy in HL: Interview Guide Version 2: 10th June 2021, updated 1st July 2021

Clinicians

At start:

- Introductions
- Brief overview of study
- Explain purpose of interview
- Check had time to read information leaflet
- Answer any questions
- Sign consent form
- Confidentiality and anonymity issues
- Check ok to record interview
- Ensure participants feel free to stop the interview at any point
- Demographics
    - Job title
    - Years worked in that role
    - Ethnicity

1. Can you describe how decisions are made about radiotherapy in the context of HL in your centre?

Can you tell me about the last patient that you talked about radiotherapy to?
What factors do you consider?
How do you weight the various factors?
And does this differ between patients?
If so, based on what (gender, age etc).

2. Can you describe how you discuss radiotherapy with patients?

What do you discuss?
How is that received by patients?
When do you discuss radiotherapy?

3. To what extent does you approach differ between patients?

What is it that guides you on what approach you should take?
Is there a reason that you don't involve patients more in the decision?
What is your approach to someone who doesn't want to be involved in the decision?
What is your approach to someone who disagrees with your recommendation?

4. To what extent do you discuss a patient's preference to be involved in the decision about radiotherapy?

5. What factors do you think are important for patients to consider when deciding about radiotherapy?

May not be relevant if patients aren't involved in the decision

6. Who do you feel tends to ultimately makes the decision about radiotherapy?

You or the patient?
How much influence does the patient have on the decision?

7. Are you familiar with the term shared-decision making?
Explain if they are not familiar with it
Do you think that the decision about radiotherapy for HL is shared decision making?

8. This work is part of a bigger project aiming to develop a decision support tool. Are you familiar with any such tools?
Explain if they aren't aware of any (use Predict as an example)
Do you think a decision support tool would help with decisions about radiotherapy?
When do you think it should be used?
By whom?
In what format?
What data do you think it should present?

Closing

Is there anything we haven't spoken about that you think is important to discuss?

At end

- What will happen with the data, including timescale
- Ensure participant has my contact details, to discuss anything related to the interview
- Ask if they wish to receive the transcript, or a summary of the findings
- Check if they have any questions
- Thank the participant for their time and support with the study

After the interview

- Email consent form ☐
- Transcribe ☐
- Send transcript if have requested ☐

Appendix B4: Codes

Code	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12
Able to question the medical team		☑	☑			☑	☑		☑	☑	☑	☑	☑	☑	☑												
Age		☑	☑		☑			☑	☑	☑	☑					☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑
Appreciated chance to influence treatment								☑																			
Barriers to shared decision making									☑	☑								☑	☑							☑	
Balancing benefits & risks	☑					☑	☑	☑		☑						☑	☑	☑	☑	☑	☑			☑		☑	☑
Central role of MDT																☑	☑	☑		☑	☑	☑	☑	☑	☑	☑	☑
Concern re treatment side-effects	☑				☑	☑		☑								☑					☑						
Confused by information	☑					☑			☑																		
Decision aid - definition					☑	☑		☑	☑												☑				☑		
Decision aid - usefulness					☑	☑	☑	☑	☑	☑	☑	☑	☑	☑		☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑
Diagnosis	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑			☑									
Didn't feel need to do own research		☑																									
Didn't perceive role as decision-maker		☑									☑		☑														
Different opinions on best option																		☑	☑			☑	☑		☑		☑
Difficulties of making treatment decision	☑				☑	☑				☑								☑		☑		☑		☑			

Difficulty applying statistics to individuals		☑			☑		☑			☑						☑	☑			☑		☑		☑			☑
Discussion of primary concern																☑		☑		☑	☑						
Discussion of treatment options				☑	☑		☑	☑				☑			☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑
Discussions about benefits of radiotherapy			☑		☑	☑		☑	☑			☑				☑	☑	☑	☑			☑				☑	☑
Discussions about risks of radiotherapy			☑		☑	☑	☑	☑	☑	☑		☑	☑			☑	☑	☑			☑	☑		☑			☑
Disease location	☑				☑	☑		☑		☑		☑				☑	☑	☑	☑	☑	☑	☑	☑	☑	☑		☑
Engaged patient	☑		☑	☑	☑	☑			☑	☑		☑	☑		☑								☑				
Expected more of a discussion						☑		☑																			
Family history																☑	☑	☑	☑							☑	
Felt treatment decision their responsibility					☑																						
Follow-up	☑	☑	☑	☑								☑			☑												
Gave up autonomy to make decisions		☑					☑																				
Given adequate information	☑	☑	☑	☑			☑				☑	☑		☑	☑												
Given statistics of success		☑	☑	☑	☑	☑	☑	☑						☑													
Had influence over decision							☑					☑															
Happy not to be involved	☑						☑			☑	☑		☑														
HCP bias																☑		☑	☑	☑	☑		☑	☑		☑	

HCP decision, but aware could refuse		☑	☑			☑					☑				☑		☑	☑	☑	☑							
HCP expertise	☑	☑	☑		☑	☑	☑	☑		☑	☑		☑	☑			☑	☑	☑	☑		☑	☑			☑	☑
Helpful to have stepwise discussions	☑				☑	☑				☑	☑	☑	☑	☑		☑							☑				
How information is presented																					☑		☑			☑	
Implications of discussing late-effects	☑															☑	☑	☑	☑			☑			☑		
Individual preferences re information	☑				☑	☑	☑	☑	☑			☑	☑		☑	☑	☑			☑	☑	☑	☑				
Information preferences			☑		☑	☑	☑	☑	☑	☑		☑	☑	☑	☑		☑			☑		☑					
Information vs decision	☑					☑									☑												
Important to know how decision made	☑					☑	☑			☑								☑	☑		☑					☑	
Importance of considering individual factors							☑		☑	☑		☑				☑	☑	☑	☑	☑	☑			☑	☑	☑	
Importance of quantifying risk or benefit										☑		☑															
Knew how to get questions answered		☑	☑	☑							☑			☑													
Knowing is different to understanding		☑																				☑					
Lack of knowledge re lymphoma	☑													☑	☑												☑

Lack of steer from medical team					☑																					
Late-effects not primary concern	☑	☑	☑	☑								☑		☑						☑		☑			☑		
Lucky to avoid radiotherapy				☑																							
Neutral presentation of information					☑		☑			☑		☑	☑	☑	☑	☑		☑	☑	☑		☑	☑	☑		☑	☑
No choice	☑	☑						☑			☑	☑		☑	☑										☑		☑
No role in treatment decision	☑	☑						☑					☑	☑	☑												
Not enough knowledge to make decision	☑	☑								☑	☑			☑	☑				☑			☑					
Option if things go wrong	☑			☑				☑	☑					☑	☑	☑		☑									
Overwhelmed with information	☑	☑	☑	☑		☑	☑			☑		☑		☑	☑						☑	☑				☑	
Partnership, but not equal		☑																									
Experience of loved one with cancer	☑	☑					☑	☑				☑	☑			☑		☑	☑								
Job		☑	☑			☑	☑						☑									☑					
Other personal circumstances		☑	☑	☑		☑		☑										☑					☑				
Previous health issues		☑		☑		☑	☑			☑		☑	☑				☑	☑						☑	☑	☑	
Personality			☑				☑						☑	☑				☑					☑		☑	☑	
Practical considerations	☑	☑	☑		☑	☑	☑	☑		☑	☑	☑			☑	☑		☑								☑	☑
Pre-existing perceptions of radiotherapy																☑		☑					☑				☑

Preference for HCP to steer decision	☑	☑				☑	☑			☑	☑		☑			☑	☑		☑		☑	☑	☑	☑	☑	☑	☑
Preference for involvement in decision																☑		☑	☑	☑	☑	☑	☑	☑	☑	☑	☑
Presented as very treatable	☑			☑	☑	☑				☑	☑			☑	☑			☑		☑	☑		☑	☑			
Pressing medical team to give opinion					☑																						
Primary focus on cure	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑		☑	☑	☑		☑	☑	☑	☑	☑	☑	☑				☑	
Primary focus on avoiding late-effects																				☑		☑		☑		☑	☑
Radiotherapy process			☑						☑			☑		☑													
Radiotherapy separate to rest of treatment									☑			☑															
Reassured by lack of choice	☑	☑																									
Reassured by modern radiotherapy					☑																						
Reassured that it was a team decision	☑														☑												
Reassured that late-effects treatable		☑																									
Reassured that no right or wrong answer					☑																☑						
Recall difficult		☑		☑	☑		☑		☑	☑	☑																
Reflection on decision							☑	☑			☑	☑	☑				☑	☑	☑								

Reliant on medical team for information		☑					☑			☑	☑															
Responsibility for decision																☑	☑	☑	☑	☑	☑	☑	☑	☑		☑
Role of PET scans																☑	☑	☑		☑		☑				
Role of clinical oncology																☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑
Satisfied despite lack of involvement	☑	☑	☑			☑					☑			☑												
Self-directed research	☑		☑	☑	☑	☑	☑	☑		☑			☑		☑						☑			☑		☑
Sex					☑			☑	☑							☑	☑	☑	☑		☑	☑	☑		☑		☑
Shared decision-making: definition				☑	☑	☑	☑	☑		☑		☑	☑	☑	☑	☑		☑	☑	☑	☑	☑	☑		☑	☑	☑
Shared decision-making: HL treatment				☑	☑	☑	☑	☑	☑			☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑		☑	☑	☑
Shared decision-making: problems																			☑	☑		☑					☑
Sharing uncertainty			☑					☑										☑	☑		☑						
Side-effects of chemotherapy			☑	☑		☑		☑	☑			☑		☑	☑		☑	☑	☑	☑	☑	☑					
Side-effects of radiotherapy			☑									☑									☑						
Smoking																		☑	☑		☑		☑	☑			
Specific context of cancer	☑	☑				☑	☑		☑	☑		☑	☑	☑		☑		☑		☑							☑
Standard pathway	☑	☑				☑	☑	☑	☑	☑			☑		☑	☑	☑	☑		☑	☑	☑	☑	☑	☑		☑
Support from family & friends	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑			☑	☑	☑												
Support from other people with cancer	☑	☑	☑	☑	☑		☑							☑													
Time preferences					☑	☑	☑	☑		☑				☑		☑	☑		☑		☑		☑			☑	

Timing of late-effects discussion	☑							☑						☑										☑	☑		
Timing of treatment discussions	☑			☑		☑		☑		☑				☑	☑			☑	☑	☑	☑		☑	☑	☑		☑
Told it was a team decision	☑		☑								☑				☑												
Too much information not helpful		☑		☑			☑			☑	☑		☑	☑								☑			☑		
Treatment	☑	☑	☑	☑	☑	☑	☑	☑	☑		☑				☑												
Treatment presented as a conclusion	☑	☑	☑	☑		☑		☑	☑	☑	☑	☑	☑	☑	☑												
Trust an important factor	☑	☑					☑		☑	☑	☑	☑	☑	☑	☑												
Ultimate decision			☑	☑	☑	☑	☑	☑	☑			☑															
Uncertainty not shared	☑					☑		☑					☑														
Uncomfortable questioning medical team					☑	☑							☑														
Unhappy with treatment plan or team									☑																		
Unknowns surrounding late-effects	☑				☑			☑																			
Unknowns surrounding radiotherapy	☑					☑						☑	☑														
Vague discussions about radiotherapy	☑	☑	☑	☑		☑	☑	☑	☑	☑				☑													

View of decision linked to treatment success	☑	☑			☑					☑	☑	☑	☑														
Wanted more information	☑	☑			☑	☑			☑	☑			☑														
Ways to improve decision making					☑	☑	☑	☑	☑	☑		☑	☑														

Key
New code

Appendix B5: Theme generation - 'one sheet of paper'



Appendix B6: Codes and themes

Theme	Subtheme	Codes (number of participants / extracts)
Information and discussion of treatment options	Information requirements	Self-directed research (14 / 24) Overwhelmed with information (13 / 30) Engaged patient (13 / 19) Able to question the medical team (11 / 21) Given adequate information (9 / 19) Wanted more information (8 / 13) Not enough knowledge to make decision (8 / 11) Knew how to get questions answered (5 / 14) Lack of knowledge re lymphoma (4 / 7) Confused by information (3 / 4) Uncomfortable questioning medical team (3 / 4)
	Information preferences	Individual preferences for information (15 / 30) Information preferences (14 / 30) Too much information not helpful (9 / 13)
	Presentation of information about treatment options	Standard pathway (20 / 62) Treatment presented as conclusion (20 / 60) Discussion of treatment options (19 / 53) Neutral presentation of information (17 / 32) Discussion about risks of radiotherapy (16 / 31) Balancing benefits & risks (14 / 22) Discussion about benefits of radiotherapy (13 / 25) Difficulty applying statistics to individuals (10 / 16) No choice (9 / 24) Given statistics of success (8 / 9) Implications of discussing late-effects (7 / 13) Unknowns surrounding late-effects (6 / 13) *Different opinions on best option (6 / 11) Sharing uncertainty (5 / 9) *Role of PET scans (5 / 9) Uncertainty not shared (4 / 9) *How information is presented (3 / 6) Expected more of a discussion (2 / 4) Importance of quantifying risk or benefit (2 / 3) Reassured by lack of choice (2 / 2)
	Timing of treatment discussions	Timing of treatment discussions (15 / 43) Helpful to have stepwise discussions (10 / 16) Timing of late-effects discussions (5 / 8)
	Reflection on involvement in decision-making	Ways to improve decision-making (11 / 29) Reflection on decision (8 / 15) View of decision linked to treatment success (7 / 8) Satisfied despite lack of involvement (6 / 8) Happy not to be involved (5 / 7) Unhappy with treatment plan or team (1 / 4)

Individual factors in the decision about radiotherapy	Patient's priorities	Importance of considering individual factors (13 / 33) Personality (8 / 12)
	Driving factors	Age (20 / 52) Disease location (17 / 34) Practical considerations (15 / 43) Sex (12 / 17) Experience of friend or relative with cancer (10 / 22) Previous health issues (10 / 23) Other personal circumstances (9 / 17) Job (6 / 12) *Family history (5 / 7) *Smoking (5 / 8) Side-effects of radiotherapy (3 / 6)
	Primary concern when considering treatment options	Primary focus on cure (21 / 77) Time preferences (12 / 19) Late-effects not primary concern (10 / 15) Concern re treatment side-effects (6 / 14) *Primary focus on avoiding late-effects (5 / 11) Discussion of primary concern (4 / 14) Reassured by modern radiotherapy (2 / 5) Reassured that late-effects treatable (2 / 4)
	Perceptions of radiotherapy	Vague discussions about radiotherapy (11 / 22) Option if things go wrong (8 / 12) *HCP bias (8 / 10) *Pre-existing perceptions of radiotherapy (4 / 8) Radiotherapy process (4 / 8) Radiotherapy separate to rest of treatment (2 / 3) Lucky to avoid radiotherapy (1 / 1)
Responsibility for decisions about radiotherapy	Decision-making preferences	*Preference for involvement in decision (11 / 27)
	Decision roles	HCP expertise (19 / 32) Preference for HCP to steer decision (17 / 30) Support from family & friends (13 / 33) Trust an important factor (13 / 27) *Role of clinical oncology (12 / 45) *Central role of MDT (11 / 30) Important to know how decision made (8 / 16) Support from other people with cancer (7 / 27) No role in treatment decision (6 / 6) Reliant on medical team for information (4 / 5) Told was a team decision (4 / 5) Didn't perceive role as decision-maker (3 / 4) Information vs decision (3 / 3) Gave up autonomy to make decisions (2 / 2) Had influence over decision (2 / 2) Reassured that it was a team decision (2 / 2) Knowing is different to understanding (2 / 2)

		Appreciated chance to influence treatment (1 / 3) Pressing medical team to give opinion (1 / 2) Lack of steer from medical team (1 / 1) Partnership, but not equal (1 / 1)
	Responsibility for decisions	Ultimate decision (20 / 36) *Responsibility for decision (9 / 24) HCP decision, but aware could refuse (9 / 14) Difficulties of making treatment decision (8 / 22) Felt treatment decision their responsibility (1 / 2)
	The specific context of HL	Specific context of cancer (13 / 56) Presented as very treatable (13 / 19)
Shared decision-making and decision aids	Shared decision-making	Shared decision-making: definition (20 / 23) Shared decision-making: HL treatment (21 / 41) Shared decision-making: barriers (5 / 8) *Shared decision-making: problems (4 / 5)
	Decision aid	Decision aid: definition (6 / 6) Decision aid: usefulness (22 / 74)
*New code in HCP interviews Within each subtheme, codes are listed in order of frequency Abbreviations - PET: positron-emission tomography; HCP: healthcare professional; MDT: multidisciplinary team; HL: Hodgkin lymphoma		

Appendix B7: Additional illustrative quotes

Theme 1: Patient involvement in decisions about radiotherapy
Information requirements
"I'm a very analytical person and I want to know absolutely everything about everything, so I just Googled it, I read the book, I spoke to the lymphoma nurses, I went online" *Patient 1, 54-year-old female*
"it's a lot of information for patients, and very complicated. But we should, we should try, we should still try and break it down into an understandable way, that's our job" *Clinician 11, haematologist*
Information preferences
"I guess it's very much guided with what the patients; you know, I'll give them all the information and give them the opportunity to discuss, but I guess quite how detailed it goes partly depends on how that patient is and what they're asking." *Clinician 7, haematologist*
"I'm sure there's lots of patients that love to be told by their medical team what they're doing, and that's all they want to know. But I was perhaps a bit more involved in and kind of wanting to be part of those discussions." *Patient 6, 33-year-old female*
"I sometimes think the more you know, the less; the more you learn, the less you actually know. And then it becomes too confusing" *Patient 13, 62-year-old female*
Presentation of information about treatment options
"it wasn't really a discussion is-as-much. Obviously, I've got a choice whether I choose to have it or not, but there wasn't like all right, there's two treatments on offer for you" *Patient 14, 36-year-old female*
"my consultant just said you're doing that, you're having the treatment, your chemo here and then you go to [name of hospital] to have the radiotherapy. There wasn't even a discussion then that I didn't have to have it if I didn't want to." *Patient 8, 49-year-old male*
"the only bit that I felt, as I say, I felt like I had much choice over, was actually choosing where I go for the treatment, not what the treatment was." *Patient 15, 26-year-old male*
"when I signed up to have the treatment, I just saw it comes as a package and you had to have it." *Patient 8, 49-year-old male*
"I often start off very neutrally […..] And then see if they come back with key priorities or views, and then of course you can, you know, shape the discussion that, you know, and help them make their choice based on what your clinical perspective is." *Clinician 11, haematologist*
"I like to think that we [the MDT] give it good consideration, and then we do involve the patient as well. So we would decide what we would favour and then we'll discuss the options with the patient." *Clinician 2, haematologist*
"I remember at one point saying to him, what's my alternative and he basically said there is no alternative. So that was it, that was my path." *Patient 1, 54-year-old female*

"they had just a very standard approach to kind of how they how they treated people and how they kind of came to those […] treatment decisions."
Patient 15, 26-year-old male

"I got reassured there, you're going down that path, so there's not really any negotiation about it"
Patient 1, 54-year-old female

"I think it's important always to have discussed it, you know, because certainly we've had patients, you know, I have certainly treated some patients who've relapsed not having had radiotherapy as first line, you know, so I think it's important to have at least brought it up in that discussion, you know, makes it's almost easier, then if they relapse, that you know that they understand."
Clinician 1, clinical oncologist

"ethically, I think you have to tell them, but also just be practically you know, this group of patients have read everything so it behoves you tell them everything, because otherwise they lose their trust in you, if they know something, and you don't even mention it, that's a difficult position to be in, I think."
Clinician 6, clinical oncologist

"in Hodgkins, […] they're not particularly contentious decisions, you know, they're fairly standard, it's not a whole broad range of, you know, grey areas, or what you could be doing or not"
Clinician 1, clinical oncologist

"we decide at the MDT and then that, that is just relayed to the patient, really, I don't think there, there is any sort of discussion apart from that. I very much doubt that patients hear about the discussion"
Clinician 12, clinical oncologist

"I think I certainly felt like it was presented as this is what we think is the best option. It wasn't presented as a particularly grey decision"
Patient 6, 33-year-old female

"So I sort of spend my time saying look this is, there isn't necessarily right or wrong here, thing here and it very much depends on the person. This is what the radiotherapy involves, this is what it can help with, these are the side-effects of it, and these are the two ways of going"
Clinician 3, clinical oncologist

"I was told that the less chemotherapy, but with localised radiotherapy, would give me a better chance of long term remission"
Patient 6, 33-year-old female

"I think I remember him saying that he felt it was probably like a 5 to 10% difference in terms of long term Hodgkin's remission for the use of radiotherapy"
Patient 6, 33-year-old female

"I sat down with my haematologist, the oncologist at the other hospital, the radiotherapy, and you know sat down with me as well and they both, they both said look yes there is a risk of breast cancer, but you know we need to treat you for Hodgkin lymphoma, and this is the best, the best treatment"
Patient 12, 49-year-old female

"how I generally would phrase it is that we have better disease control if we include radiotherapy, and depending on the patient I would talk about what percentage in terms

of progression free survival […], 'cause some people want to hear that, some people don't.”
Clinician 2, haematologist
“it was literally like, these are your dates, this is what you’ll be having, this many sessions, and read this leaflet and off you go.”
Patient 13, 62-year-old female
“I think it’s quite balanced presentation of risks versus benefits. They were very open about the fact that there were risks, but they were also very open about the fact that there were benefits for remission.”
Patient 6, 33-year-old female
“whilst we're trying to make the best decision we can for the patient, and yes, I try and incorporate the patient’s perspective as far as I can elicit it in that, I'm sort of doing it with one hand tied behind my back because the reality is I don't really know exactly what the risks are going to be, so it's quite hard to.”
Clinician 9, clinical oncologist
“I think probably if you think too much about the long term implications, it would probably stop you being able to move on as easily and get your life back.”
Clinician 1, clinical oncologist
“I think I had a block at times about emphasising elements of long-term risk for, not because anything was important, but I sometimes felt I was frightening patients”
Clinician 4, clinical oncologist
“I certainly don’t emphasise it, taken in long-term risk of heart disease, 'cause I just think God, you know it's bad enough to get through this, you don't actually want to spend your life thinking about what, when's the next thing coming. And, you know, I think they have to be aware it’s there, but I don't go into it in much detail.”
Clinician 7, haematologist
“It certainly does feel from the outside that there’s quite a lot of variation in how quite similar cases are treated.”
Patient 6, 33-year-old female
“when […] we have a steer that we want to avoid radiotherapy, it might not even be presented to the patient as a choice in that way because we have made a decision on their behalf. It’s the least best option”
Clinician 4, clinical oncologist
“So, in my practice that would happen with an explanation to the patient that there are multiple ways of treating them, and that these are the two different options. And then we'd have a conversation about what they could expect from both options in terms of the practicalities, the side effects, both acute and late. And try and get some feeling from them as to a bit about their lifestyle, their priorities”
Clinician 9, clinical oncologist
Timing of treatment discussions
“it all happened very, very quickly, so there wasn't, you know, loads of time to think of all the alternatives”
Patient 14, 36-year-old female
“they need to be done at the beginning so that person knows what the plan is, because it soon goes by, soon whips by does Hodgkin's treatment, and you want to tell that patient from the front, from the beginning what their plans are. You don't want to suddenly scoop in that they're having radiation”

Clinician 3, clinical oncologist
Reflection on involvement in decisions
“I feel that, in hindsight, maybe I could have sat back a little and maybe dallied a while over the decision, but actually, what would be the point? ‘Cause I would’ve just gone down the same treatment route anyway”
Patient 7, 57-year-old female
“it [radiotherapy] was, felt very much a little bolt on at the end, at a bit of an afterthought. Uh, so yeah, so if it could have been a bit more of a transition that would have been much more helpful and would have helped with those discussions”
Patient 9, 35-year-old female

Theme 2: Individual factors in the decision about radiotherapy

Patients’ priorities
“I cannot infer and judge someone sitting across the room’s priorities without questioning and you know, allowing the opportunity for those to come through. And to make these decisions in Hodgkin's lymphoma requires that level of understanding, that input from the patients, so it's the only way to do it actually, you cannot do it without that”
Clinician 11, haematologist
“I've had the odd person who cannot take uncertainty and observation, they want to have everything”
Clinician 3, clinical oncologist
“there's personalities in terms of risk, risk benefit, there's differences in how we, yeah, perceive these risks and that's all personality driven”
Clinician 11, haematologist
Driving factors
“it's generally driven by the extent of disease and the number of sites that would require to be in the field, and quite often the oncologists will say, you know, prefer to go for chemo only”
Clinician 7, haematologist
“because if was being up where the lymph nodes were as well, with some of them kind of getting quite close to the heart”
Patient 5, 28-year-old male
“looking at an upper mediastinum, or somewhere where you’re going to be treating the breast, so for those groups we tend to be shying away from the likely multi-modality treatment”
Clinician 3, clinical oncologist
“female or male is important, and because we assess the degree of breast tissue exposure with a potential plan for radiotherapy”
Clinician 4, clinical oncologist
“I felt like radiotherapy was mentioned at one point and then they sort of explained why we maybe wouldn’t go down that route, yeah, because of my age”
Patient 10, 31-year-old female
“currently I tend to give less radiotherapy for the youngsters and much more for the elderly”
Clinician 3, clinical oncologist

“older patients, they don’t really care so much about the late toxicities. And actually a lot of the younger patients they want to get on with their lives” *Clinician 12, clinical oncologist*
“I think possible because, you know, seeing my brother go through it as well, I think, really made me think, you know, yes this is going to be horrendous but I need to do it. You know, I need to, this is I need, this is what needs to be done” *Patient 12, 49-year-old female*
“I thought, ok, I can go with that because I hadn’t had a bad experience of radiotherapy and the previous treatment, so it wasn’t something that scared me” *Patient 13, 62-year-old female*
“I think he had an aunt who’d had head and neck cancer, and, you know, had the usual terrible toxicity and that just completely skewed his, you know his view of radiotherapy” *Clinician 1, clinical oncologist*
“if you've got someone who you would be say concerned about their cardiac function, for example, and they had localised disease, and you didn't want to give him too much anthracycline, you might be more keen to stress that your preference would be not to give six cycles of ABVD, whatever. You know, give like two or three and then give radiotherapy to reduce the cardiac risk” *Clinician 10, haematologist*
“someone who’s like claustrophobic, being pinned down by a mask mind, might have found that absolutely horrendous, you know, so I think there was that consideration in it as well. It’s not just the treatment, it’s actually what you have to go through to have the treatment” *Patient 7, 57-year-old female*
“they're at the point where actually they’re suffering after the side-effects of chemo, which is still ongoing, they’re completely exhausted, they just want to see the end of that tunnel. That's what they will often describe it as, you know, I just want to get to the end of it so I can move on with my life” *Clinician 12, clinical oncologist*
“I don’t want to undergo any more extra treatment than what I have to ‘cause it’s already hellish” *Patient 10, 31-year-old female*
“it was like the quicker I can just get through treatment, the quicker I can get back to life and that is my like literal like laser focus” *Patient 10, 31-year-old female*
“I think I was more relieved that I wasn’t going to have any more chemotherapy than I was, than I was, that I was having to have the radiotherapy” *Patient 3, 70-year-old female*
Primary concern when considering treatment options
“I needed to have the best treatment to survive the cancer, to fight the lymphoma, and whatever treatment that was I was going to have” *Patient 12, 49-year-old female*
“the natural default is to say that well, you know, I want the thing that’s got the best chance of curing me, because you’re not really thinking about what might happen to you in 20 years’ time” *Clinician 5, haematologist*

“I think late-effects are really important in our decision making. I’m really, you know, I think there is a risk that we cause a lot of harm in a lot of situations in lymphoma” *Clinician 11, haematologist*
“if the late-effects are a higher priority, so you know mediastinal involvement, then we tend to not offer the radiotherapy anyway, so it feels that […] we in the MDT are just discussing the late-effects, whereas […] for the patient it is, you know, if we're offering that combined modality, it might be because we're less concerned about the late-effects” *Clinician 2, haematologist*
“I remember sitting with the radiotherapy consultant and them saying well it could cause long-term problems with your heart, it cause long-term problems with, blah, blah. And you do hear that, and you do go, oh, that might be something I have to worry about in the future, but, as I said, you know, you’re so caught up with that moment in time, that everything around you, everything is, is lymphoma. Nothing else is, not relevant, but nothing else is as life-threatening, at that moment” *Patient 12, 49-year-old female*
“I think there's a lot more in a way slightly a bit more scaremongering about radiotherapy when they probably doesn't need to be that much” *Clinician 12, clinical oncologist*
“I have some kind of, yeah, peace of mind that hopefully whatever comes in the future in terms of secondary cancers and things that I’ve kind of reduced those risks” *Patient 5, 28-year-old male*
“he was very clear he was going to worry more about the late effects of radiotherapy, you know, than his, than that small risk, so for him that that sort of 6 or 7% risk, you know, he could accept” *Clinician 1, clinical oncologist*
“some people worry very much about the lymphoma and they just want to be sure they've got rid of it, other people don't want to live the rest of their lives worried about the possibility of developing say breast cancer, having an increased risk of breast cancer for the rest of their lives and, you know, that's a perfectly good decision. You know, what is it that worried you, what concerns you most, kind of would be how I'd put it” *Clinician 6, clinical oncologist*
“medicine is changing all the time, and yes, you might be at slightly increased risks of these other things, but by the point that happens in your life hopefully those things will be much more treatable and much more will be known about them” *Patient 6, 33-year-old female*
Perceptions of radiotherapy
“I hadn’t heard great things about radiotherapy, anyway, so it would have scared me” *Patient 14, 36-year-old female*
“We have some patients who have fixed ideas about actually wanting or not wanting radiotherapy and it, it’s pretty 50:50 in terms of some are, you know, early doors deciding they won’t have it if they can possibly help it, but surprisingly there are some that are very keen to have it” *Clinician 4, clinical oncologist*

"I think radiotherapy was kind of mentioned as a vague possibility, but it very much wasn't this is likely it was, you know, we might adjust the treatment. It was quite vague terms initially" *Patient 6, 33-year-old female*
Theme 3: Responsibility for decisions about radiotherapy
Decision-making preferences
"it's about signposting where decisions are being made. And so this is a decision point now. And what would you think? Rather than giving the impression that every interaction involves a decision when actually it doesn't." *Clinician 10, haematologist*
I think generally it feels like an older population will be more likely to say, just do what you think is best doc. And I don't want to be involved in this. Whereas for the younger patients who we're normally talking about in this context, that that's quite unusual really" *Clinician 9, clinical oncologist*
Decision roles
"often at the MDT, everyone's put their view and we kind of know what our view is. And unless the patient feels very strongly differently, then we'll probably go with what everybody feels" *Clinician 3, clinical oncologist*
"Many patients will say well, you know, what do you think? What do you think is best? And then that helps you just to go ahead with what the MDT consensus was or, you know, what you think is right" *Clinician 11, haematologist*
"I think I felt confident because I knew that it wasn't just one person's decision and one person's judgement, it was based on a number, a team of people and medical team of people with different specialisms in that room making that decision, that final decision" *Patient 1, 54-year-old female*
"I just thought my care and like the team, it was so hard for me to get a diagnosis and once I got to the right people they were just amazing. So I was very much just like whatever they say, I'll do because I trust them implicitly, you know." *Patient 10, 31-year-old female*
"I'd like to see all the facts and have it laid out and see how the decision was made, but if you were left to be given information, so that do you want this or not, that would be a really tough decision to make" *Patient 1, 54-year-old female*
"if there are patients where the decision is not so clear cut, they'll meet with both teams and then as a clinical oncologist we will go through the pros and cons, you know, the acute and late toxicities, and sort of give a measured view and then the patient can decide on that" *Clinician 12, clinical oncologist*
"in ones where we can see that it's an equivocal discussion and a degree of equipoise, we will meet them earlier, to have those face to face discussions" *Clinician 4, clinical oncologist*
"because we're a centre that has clinical oncology as well, overall, our tendency to consider radiotherapy is probably greater than it is in many centres that don't have access to radiotherapy"

Clinician 5, haematologist
Responsibility for decisions
“it may make it easier for them to come to terms with whatever happens in the future if they know that actually, that was the recommended thing, the right thing, and, you know, it supports that”
Clinician 1, clinical oncologist
“what I don’t want them to do is feel more stressed that they’ve got the onus of this decision, that’s not helping anyone”
Clinician 2, haematologist
“I think that we have to be careful as professionals to make sure that they don’t feel that the responsibility for taking decisions is entirely on them”
Clinician 8, medical oncologist
“I guess there comes a point where you think, well you’re the experts, you tell me what to do”
Patient 6, 33-year-old female
“if I was a patient, I would do the same. I’d be saying to the doctor with the experience, ok, I know what you’re saying, you know, there’s you can’t tell me one way or the other, but what do you think”
Clinician 7, haematologist
“I mean most people, even if they're quite well informed, often don't feel that they want the responsibility for taking the decision entirely on their own, and would like us to give them our advice as to what we think is the best thing to do”
Clinician 8, medical oncologist
“if you were left to be given information, so that do you want this or not, that would be a really tough decision to make”
Patient 1, 54-year-old female
“you're only talking you know 2-3 months after somebody's been diagnosed, and their brains are not in a good place at that stage, no matter what they tell you. They'll often tell you they’re fine, but usually they're actually not, and so it's a really difficult thing to ask somebody to make a decision”
Clinician 5, haematologist
“it was the consultants, they really made the decision of what treatment I was going to have. And that I would be having radiotherapy”
Patient 12, 49-year-old female
“I was aware that I could make the decision not to have it, but it felt very much like this is the medical team and they kind of knew the best, the best thing to do”
Patient 6, 33-year-old female
“I think most of us are lying if we’re saying that the reality is that we don’t basically take to the patient the decision that we think they should have”
Clinician 5, haematologist
“my way of dealing with it is to try and make sure that I understand the patient and what's driving them, what's going on in their life, what their concerns are, to sort of hopefully, then have the best idea about what might be the best treatment for them”
Clinician 5, haematologist
“I suspect for a majority of patients that they will perceive that that decision to go ahead with that […] is the clinician’s, and they then passively go through the process. But I'm not sure that they would, for most patients they wouldn't dream of jumping off the couch

and saying I've done with this. So maybe I'm being, maybe it's not fair to say that they are, they are making the decision there. Whilst they implicitly make the decision, actually they, I suspect from the patient perspective, will feel that the clinicians made the decision” *Clinician 9, clinical oncologist*
The specific context of HL
“'cause at the point that you're having to make the decision, your mind isn't in the right space to be able to focus on it, 'cause you're so stressed by what you're having to go through. The thought of having to make a life decision like that could be a little bit difficult to have to, you know, if you if you were involved in having to make that decision at a time when your mind is not straight, you know, clear enough could be quite hard” *Patient 1, 54-year-old female*

Theme 4: Shared decision-making & decision aids

Shared decision-making
“shared decision-making for me is that, the joining up of the clinical data that I know and hopefully I can break down in an understandable way, the options that come out of that and aligning those with the patient’s views, wishes, priorities, perspectives etc., on the different aspects that are critical to come to a joint treatment plan.” *Clinician 11, haematologist*
“it is shared decision-making because they have the option to say I don’t want the radiotherapy or I do want the radiotherapy, so it is shared, but I still think, you know, we should be influencing it” *Clinician 7, haematologist*
“I think there’s collaboration and cooperation without saying right, you know, you have as much input into this as I have. I don’t think that’s fair to patients, actually, for the majority” *Clinician 7, haematologist*
“I think we did have that because we were, everything was very well explained all along and I think if there had been anything we had felt wasn’t right, we would have said so” *Patient 4, 68-year-old female*
Decision aids
“I think the decision aid is almost, you know, helping or at least giving a kind of construct for that conversation with the patients who are really struggling, you know, and maybe giving a focus to questions and how you work them through that pathway of coming to that decision” *Clinician 1, clinical oncologist*
“I’m that type of person who kind of wants to know we can have in sometimes absolute figure so we can then know well, yeah, what’s my kind of threshold of risk that I’m comfortable with and knowing and then yeah, those kind of figures then would make me feel well, yeah on what which side of radiotherapy or not do I fall on” *Patient 5, 28-year-old male*
“it almost singles out radiotherapy as the problem treatment, so I’d be very wary about saying that, you know, there’s this risk of cancer or heart disease and things, you now, related to your radiotherapy treatment. And, you know, it should be this is your treatment decision tool” *Clinician 1, clinical oncologist*

“I think if you’re, if you’re isolating a radiotherapy question, I think they, there’s still value. You know, if you’re, ‘cause you’re talking about excess risk, you know, you’ll be able to calculate excess risk over and above that from anthracyclines. So that’s still of value if, in the context of, I’ve given chemotherapy, I have a choice now to give radiotherapy or not, and I want to know the excess risk of giving that radiotherapy in addition” *Clinician 11, male haematologist*
“so we need three bits of information in the MDT: we need the risk modelling for radiotherapy, the risk modelling for chemo, and then the relapse risk. Which again could be more accurate, because those figures we throw out for the whole population. So, so I think it would be good, but only, it’s going to be only a value if we’ve got all three of those.” *Clinician 2, haematologist*
“therefore people who are a bit naturally biased against radiotherapy, like I am for reasons I don’t quite understand, but I am, might learn something useful out of that.” *Clinician 5, male haematologist*
“if we could provide the haematologists in [location] with some of the estimated but quantitative data of what do we expect these risks to be. That allows them to have a bit more of a conversation as well, and open that up to a group of patients who maybe are deprived of an opportunity to discuss it.” *Clinician 9, clinical oncologist*

Appendix C

Supplementary material to Chapter 3

Appendices

Appendix C1: Search terms

MEDLINE

# ▲	Searches
1	Hodgkin Disease/rt
2	Lymphoma/rt
3	Hodgkin Disease/ or *Lymphoma/
4	exp Lymphoma/ and (Mediastinal Neoplasms/ or Mediastinum/)
5	lymphoma?.ti.
6	(hodgkin* adj (lymphoma? or disease?)).ti,ab.
7	(lymphoma? adj5 mediastin*).ti,ab.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	exp Radiotherapy/
10	Radiotherapy Dosage/
11	(radiotherap* or radiation therap* or irradiat*).ti,ab.
12	(radiation adj4 (neck? or heart? or mediastin*)).ti,ab.
13	9 or 10 or 11 or 12
14	8 and 13
15	1 or 2 or 14
16	exp Radiotherapy/ae
17	exp Radiation Injuries/
18	Neoplasms, Second Primary/
19	Mediastinum/re or Heart/er or Neck/re
20	cardiovascular diseases/ or heart diseases/ or vascular diseases/ or cerebrovascular disorders/
21	heart failure/ or exp Myocardial Ischemia/
22	ischemic attack, transient/ or stroke/
23	exp Heart Valve Diseases/
24	exp Cardiac Surgical Procedures/
25	mortality/ or "cause of death"/ or fatal outcome/ or survival rate/ or survival analysis/
26	exp Radiotherapy/mo
27	Hodgkin Disease/mo
28	((radiation or radiotherap* or irradiat*) adj5 (late effect? or adverse effect? or adverse event? or toxicit*)).ti,ab.
29	(cardiotoxic* or cardio-toxic* or heart toxic*).ti,ab.
30	((cardiovascular or cardio-vascular or cvd or cerebrovascular or vascular or heart or cardiac or coronary) adj5 (outcome? or event? or mortality)).ti,ab.
31	((cardiovascular or cardio-vascular or cvd or cerebrovascular or vascular or heart or cardiac or coronary) adj disease?).ti,ab.
32	(angina or (myocardial adj (infarct* or isch?emi*)) or acute coronary syndrome or stroke or transient isch?emi* attack? or heart failure).ti,ab.
33	((valv* or aortic or mitral or tricuspid) adj3 (regurg* or insufficienc* or stenosis)).ti,ab.
34	(pericard* adj (disease or fibrosis)).ti,ab.

35 (coronary artery bypass* or angioplast* or ((heart or cardiac) adj (transplant* or surg*)) or revasculari?ation? or (valv* adj3 (replace* or surg*)) or pericardectom*).ti,ab.
36 ((second? or treatment-related or treatment-induced) adj2 (cancer? or neoplas? or malignan*)).ti,ab.
37 (mortality or death? or survival or (fatal adj (event? or outcome? or event?))).ti,ab.
38 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39 Risk/ or Risk Factors/
40 risk?.ti,ab.
41 (standardi?ed adj (incidence ratio or mortality ratio)).ti,ab.
42 event rate?.ti,ab.
43 ((hazard or rate) adj ratio).ti,ab.
44 39 or 40 or 41 or 42 or 43
45 8 and 38
46 limit 45 to "reviews (maximizes specificity)"
47 15 and 38
48 randomized controlled trial.pt.
49 controlled clinical trial.pt.
50 randomized.ab.
51 placebo.ab.
52 clinical trials as topic.sh.
53 randomly.ab.
54 trial.ti.
55 48 or 49 or 50 or 51 or 52 or 53 or 54
56 exp animals/ not humans.sh.
57 55 not 56
58 47 and 57
59 15 and 38 and 44
60 Epidemiologic studies/
61 exp case control studies/
62 exp cohort studies/
63 Case control.tw.
64 (cohort adj (study or studies)).tw.
65 Cohort analy$.tw.
66 (Follow up adj (study or studies)).tw.
67 (observational adj (study or studies)).tw.
68 Longitudinal.tw.
69 Retrospective.tw.
70 prospective.tw.
71 48 or 49 or 50 or 51 or 52 or 53 or 54 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70
72 exp animals/ not humans.sh.
73 71 not 72
74 59 and 73
75 46 or 58 or 74

EMBASE

# ▲	Searches
1	exp Hodgkin Disease/rt
2	Lymphoma/rt
3	exp Hodgkin Disease/ or *Lymphoma/
4	exp Lymphoma/ and (exp mediastinum tumor/ or Mediastinum/)
5	lymphoma?.ti.
6	(hodgkin* adj (lymphoma? or disease?)).ti,ab.
7	(lymphoma? adj5 mediastin*).ti,ab.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	exp Radiotherapy/
10	exp Radiation Dose/
11	(radiotherap* or radiation therap* or irradiat*).ti,ab.
12	(radiation adj4 (neck? or heart? or mediastin*)).ti,ab.
13	9 or 10 or 11 or 12
14	8 and 13
15	1 or 2 or 14
16	exp Radiotherapy/ae
17	exp Radiation Injury/
18	Neoplasms, Second Primary/
19	[Mediastinum/re or Heart/er or Neck/re]
20	cardiovascular disease/ or heart disease/ or vascular disease/
21	heart failure/ or exp ischemic heart disease/
22	transient ischemic attack/ or cerebrovascular disease/ or exp cerebrovascular accident/
23	exp valvular heart disease/
24	exp heart surgery/
25	mortality/ or all cause mortality/ or cancer mortality/ or cardiovascular mortality/ or mortality rate/
26	survival analysis/ or cancer survival/ or survival rate/ or cancer specific survival/ or survival/
27	((radiation or radiotherap* or irradiat*) adj5 (late effect? or adverse effect? or adverse event? or toxicit*)).ti,ab.
28	(cardiotoxic* or cardio-toxic* or heart toxic*).ti,ab.
29	((cardiovascular or cardio-vascular or cvd or cerebrovascular or vascular or heart or cardiac or coronary) adj5 (outcome? or event? or mortality)).ti,ab.
30	((cardiovascular or cardio-vascular or cvd or cerebrovascular or vascular or heart or cardiac or coronary) adj disease?).ti,ab.
31	(angina or (myocardial adj (infarct* or isch?emi*)) or acute coronary syndrome or stroke or transient isch?emi* attack? or heart failure).ti,ab.
32	((valv* or aortic or mitral or tricuspid) adj3 (regurg* or insufficienc* or stenosis)).ti,ab.
33	(pericard* adj (disease or fibrosis)).ti,ab.
34	(coronary artery bypass* or angioplast* or ((heart or cardiac) adj (transplant* or surg*)) or revasculari?ation? or (valv* adj3 (replace* or surg*)) or pericardectom*).ti,ab.
35	((second? or treatment-related or treatment-induced) adj2 (cancer? or neoplas? or malignan*)).ti,ab.
36	(mortality or death? or survival or (fatal adj (event? or outcome? or event?))).ti,ab.

37 16 or 17 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38 risk/ or attributable risk/ or exp cardiovascular risk/ or mortality risk/ or risk factor/
39 risk?.ti,ab.
40 (standardi?ed adj (incidence ratio or mortality ratio)).ti,ab.
41 event rate?.ti,ab.
42 ((hazard or rate) adj ratio).ti,ab.
43 38 or 39 or 40 or 41 or 42
44 8 and 37
45 limit 44 to "reviews (maximizes specificity)"
46 15 and 37
47 randomized controlled trial/
48 single blind procedure/ or double blind procedure/
49 crossover procedure/
50 random*.tw.
51 (trial or ((singl* or doubl*) adj (blind* or mask*)) or crossover or cross over or factorial* or latin square or assign* or allocat* or volunteer*).ti,ab.
52 47 or 48 or 49 or 50 or 51
53 (exp animals/ or nonhuman/) not human/
54 52 not 53
55 46 and 54
56 15 and 37 and 43
57 Clinical Study/
58 Case control study/
59 Family study/ or Longitudinal study/ or Retrospective study/ or Prospective study/ or Cohort analysis/
60 Case control.tw.
61 (cohort adj (study or studies)).tw.
62 Cohort analy$.tw.
63 (Follow up adj (study or studies)).tw.
64 (observational adj (study or studies)).tw.
65 Longitudinal.tw.
66 Retrospective.tw.
67 prospective.tw.
68 47 or 48 or 49 or 50 or 51 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67
69 (exp animals/ or nonhuman/) not human/
70 68 not 69
71 56 and 70
72 45 or 55 or 71

Cochrane

#1 MeSH descriptor: [Hodgkin Disease] explode all trees and with qualifier(s): [radiotherapy - RT]
#2 MeSH descriptor: [Lymphoma] explode all trees and with qualifier(s): [radiotherapy - RT]
#3 MeSH descriptor: [Hodgkin Disease] explode all trees
#4 MeSH descriptor: [Lymphoma] explode all trees
#5 (lymphoma*):ti,ab,kw OR ((hodgkin* NEXT (lymphoma* or disease*))):ti,ab,kw OR ((lymphoma* NEAR mediastin*)):ti,ab,kw
#6 #3 or #4 or #5
#7 MeSH descriptor: [Radiotherapy] explode all trees
#8 MeSH descriptor: [Radiation Dosage] explode all trees
#9 ((radiotherap* or "radiation therap*" or irradiat*)):ti,ab,kw OR ((radiation NEAR (neck* or heart* or mediastin*))):ti,ab,kw
#10 #7 or #8 or #9
#11 #6 and #10
#12 #1 or #2 or #11
#13 MeSH descriptor: [Radiotherapy] explode all trees and with qualifier(s): [adverse effects - AE]
#14 MeSH descriptor: [Radiation Injuries, Experimental] explode all trees
#15 MeSH descriptor: [Neoplasms, Second Primary] explode all trees
#16 MeSH descriptor: [Mediastinum] explode all trees and with qualifier(s): [radiation effects - RE]
#17 MeSH descriptor: [Heart] explode all trees and with qualifier(s): [radiation effects - RE]
#18 MeSH descriptor: [Neck] explode all trees and with qualifier(s): [radiation effects - RE]
#19 MeSH descriptor: [Cardiovascular Diseases] explode all trees
#20 MeSH descriptor: [Mortality] explode all trees
#21 MeSH descriptor: [Radiotherapy] explode all trees and with qualifier(s): [mortality - MO]
#22 MeSH descriptor: [Hodgkin Disease] explode all trees and with qualifier(s): [mortality - MO]
#23 (((radiation or radiotherap* or irradiat*) NEAR ("late effect*" or "adverse effect*" or "adverse event*" or toxicit*))):ti,ab,kw OR ((cardiotoxic* or cardio-toxic* or "heart toxic*")):ti,ab,kw OR (((cardiovascular or cardio-vascular or cvd or cerebrovascular or vascular or heart or cardiac or coronary) NEAR (outcome* or event* or mortality))):ti,ab,kw OR (((cardiovascular or cardio-vascular or cvd or cerebrovascular or vascular or heart or cardiac or coronary) NEXT disease?)):ti,ab,kw OR ((angina or myocardi* or "acute coronary syndrome" or stroke or ischemi* or ischaemi* or "heart failure")):ti,ab,kw
#24 (((valv* or aortic or mitral or tricuspid) NEAR/3 (regurg* or insufficienc* or stenosis))):ti,ab,kw OR ((pericard* NEXT (disease or fibrosis))):ti,ab,kw OR ("coronary artery bypass"* or angioplast* or ((heart or cardiac) NEXT (transplant* or surg*)) or revasculari* or (valv* NEAR/3 (replace* or surg*)) or pericardectom*):ti,ab,kw OR (((second* or treatment-related or treatment-induced) NEAR/2 (cancer* or neoplas* or malignan*))):ti,ab,kw OR ((mortality or death? or survival or (fatal NEXT (event* or outcome* or event*)))):ti,ab,kw

#25	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
#26	#12 and #25

Appendix C2: Risk of cardiovascular disease following radiotherapy for Hodgkin lymphoma

Table C2.1: Estimates of risk of cardiovascular disease following treatment with radiotherapy for Hodgkin lymphoma

a. All cardiovascular disease

Study details	Risk estimate
Cumulative incidence	
Brusamolino 2006 [5] Retrospective cohort with stage 1A-2A HL treated in Italy with ABVD & RT 1990-2003 (n=120); median f/u 120 m	5 y: **5.5%** 12 y: **14%**
van Spronsen 1998 [11] Retrospective cohort of 5 y survivors treated in the Netherlands 1972-1993 (n=345); median f/u not given; comparator general population	Death from CVD **7%**
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	Cumulative mortality 20 y **3.1%** 40 y **13.2%**
Ng 2002 [13] Retrospective cohort of patients with stage IA-IIB HL treated in the USA when aged ≤50 y 1969-1997 (n=1080)	Death from CVD 15 y **2.0%** 20 y **3.1%**
Galper 2011 [15] Retrospective cohort treated with mediastinal RT in the USA 1969-1998 (n=1279); median f/u 14.7 y; comparator American general population	Any CVD 5 y **2.2%** 10 y **4.5%** 15 y **9.6%** 20 y **16.0%** 25 y **23.2%** Any cardiac procedure 5 y **0.7%** 10 y **1.2%** 15 y **3.0%** 20 y **7.1%** 25 y **11.8%**
Glanzmann 1998 [17] Retrospective cohort treated in Switzerland 1964-1992 (n=352), 144 screened for CVD; mean f/u 11.2 y	IHD, SUD & HF: 10 y **2.9%** (all), **3.5%** (screened) 15 y **9.1%** (all; not reported for screened) 20 y **13.7** (all), **13.4%** (screened) 25 y **24.7%** (all), **23.5%** (screened) Grade ≥3 CVD: 10 y **2.9%** (all), **3%** (screened)

	15 y **8.1%** (all), **9.9%** (screened) 20 y **13.7%** (all), **17.4%** (screened) 25 y **24.7%** (all), **23.8%** (screened) No CV RFs: **1.3%** (all) & **2.3%** (screened) after 10, 20, 25 and 30y
van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population	40 y **54.6%** (51.2-57.9)
van Rijswijk 1987 [20] Retrospective cohort treated in the Netherlands 1970-1984 (n=340); mean f/u 76.6 m	Fatal MI or sudden cardiac death, 10 y RT **3.8%** (0.0-8.3)
Hancock 1993 [21] Retrospective cohort treated with mediastinal RT in the USA 1960-1991 (n=2232); average f/u 9.5 y; comparator matched general population	Cardiac death ≥22 y post-RT: **16%**
Chen 2014 [31] Screening of American HL survivors >5 y following mediastinal RT, with no CVD diagnosis (n=182); median f/u 14.8 y	**26%**
Applefeld 1983 [33] Screening of cohort with stage 1-3A HL treated with RT in the USA 1967-1973 (n=81); median f/u 8.1 y	**96%**
Zinzani 1996 [34] Screening of cohort treated with mediastinal RT in Italy 1970-1980 (n=102); mean f/u 17.5 y	**11%**
Kilickap 2012 [74] Prospective cohort treated in Turkey with combined modality therapy 1990-2006 (n=336); median f/u 8.5 y	**16.1%**
Standardised incidence ratio	
Stone 2019 [30] Meta-analysis of studies (n=22) assessing CVD incidence in ≥5 y HL survivors; median f/u of studies ≥10 y	**2.37** (1.43-3.91)
Standardised mortality ratio	

de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**5.5** (5.0-6.1)	
Lee 2000 [27] Retrospective cohort of patients with stage 1-3 HL treated in the USA 1970-1986 (n=210); median f/u 15.6 y; comparator general pop. High-risk: large mediastinal masses and/or hilar disease and/or splenic involvement; remainder low-risk. Radical RT: mantle field & liver & upper periaortic LN chains.	**7.2** (4.3-11.5) High-risk **3.3** (radical RT); **11.7** (standard RT) (95% CI not given) Low-risk **6.7** (95% CI not given)	
Boyne 2018 [28] Meta-analysis of studies (n=27) quantifying long-term risk of CV mortality among lymphoma survivors compared to the general pop.; median f/u of studies ≥10 y	**7.31*** (5.29-10.10)	
Relative risk		
Aleman 2003 [1] Retrospective Dutch cohort treated when aged <41 y 1965-1987 (n=1261); median f/u 17.8y; comparator general Dutch population	Death from CVD **7.2** (4.2-11.6)	Fatal MI **5.4** (2.2-11.1)
Rugbjerg 2019 [8] Retrospective cohort of Danish >5 y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	Hospitalisation: **2.76** (2.54-3.01)	
Ng 2002 [13] Retrospective cohort of patients with stage 1A-2B HL treated in the USA when aged ≤50 y 1969-1997 (n=1080)	Death from CVD **3.2** (1.9-5.2)	
Hancock 1993 [21] Retrospective cohort treated with mediastinal RT in the USA 1960-1991 (n=2232); average f/u 9.5 y; comparator matched general population	Cardiac death **3.8** (2.8-4.8) Cardiac death excluding MI **3.2** (1.9-4.0)	
Mauch 1995 [22] Retrospective cohort with stage 1A-3B HL treated in the USA 1969-1988 (n=794); median f/u of survivors 11 y	Cardiac death: **2.0** (0.9-3.9)	
Rugbjerg 2017 [23]	Hospitalisation: **1.8** (1.8-1.9)	

Retrospective Danish cohort treated when aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population		
Heidenreich 2007 [35] Screening of cohort treated with mediastinal RT ≥35 Gy in the USA 1964-1994 (n=294); median f/u not reported	**4.7** (3.4-5.9)	
Hazard ratio		
Kiserud 2010 [14] Retrospective cohort treated in Norway when aged 15-61y 1971-1991 (n=557); median f/u 13.0 y; comparator age- and sex-matched general population	Death from CVD **4.9** (3.1-7.9)	
Myrehaug 2008 [24] Retrospective cohort of patients treated in Canada 1988-200 (n=615); median f/u 11.8 y; comparator general Canadian population	Hospitalisation: Mediastinal RT, no doxorubicin **1.82** (*P* = .038) Mediastinal RT, doxorubicin **2.77** (*P* < .0001)	
Myrehaug 2010 [25] Randomly selected subcohort of patients treated for HL in Canada 1988-2003 (n=1096); median f/u 10 y	Hospitalisation: Mediastinal RT, no chemotherapy **1.02** (0.56-1.85) (*P* = .945) Mediastinal RT, doxorubicin **1.76** (1.08-2.86) (*P* = .022)	
Lagerlöf 2022 [26] Retrospective cohort of patients treated for HL with 2/4 cycles ABVD and 30 Gy limited-field RT in Sweden 1999-2003; median f/u 16 y	**1.5** (1.1-2.0)	
Odds ratio		
Andersson 2021 [29] Retrospective cohort of patients treated for HL when aged ≤45 y in Sweden 1965-1995 (n=319); median f/u 22.0 y	**4.48** (2.26-8.88)	
Absolute excess risk		
Aleman 2003 [1] Retrospective Dutch cohort treated when aged <41 y 1965-1987 (n=1261); median f/u 17.8y; comparator general Dutch population	Death from CVD (/ 10,000 py) **21.2**	Fatal MI (/ 10,000 py) **8.3**
Rugbjerg 2019 [8] Retrospective cohort of Danish >5 y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	**208** (180-236) / 10,000 py	

de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**AEM 33.4** / 10,000 py			
Ng 2002 [13] Retrospective cohort of patients with stage 1A-2B HL treated in the USA when aged ≤50 y 1969-1997 (n=1080)	Death from CVD **9.0** / 10,000py			
Hancock 1993 [21] Retrospective cohort treated with mediastinal RT in the USA 1960-1991 (n=2232); average f/u 9.5 y; comparator matched general population	Cardiac death: **37.1** / 10,000py Cardiac death exc. MI: **11.4** / 10,000py			
Mauch 1995 [22] Retrospective cohort with stage 1A-3B HL treated in the USA 1969-1988 (n=794); median f/u of survivors 11 y	Cardiac death: **26.4** / 10,000py			
Rugbjerg 2017 [23] Retrospective Danish cohort treated when aged 15-39y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	Hospitalisation **66** (44-88) / 10,000 py			
Lee 2000 [27] Retrospective cohort of patients with stage 1-3 HL treated in the USA 1970-1986 (n=210); median f/u 15.6 y; comparator general pop. High-risk: large mediastinal masses and/or hilar disease and/or splenic involvement; remainder low-risk. Radical RT: mantle field & liver & upper periaortic LN chains.	**4.18** / 1000 py High-risk: **0.66** / 1000 py (radical RT); **7.96** / 1000 py (std RT) Low-risk: **5.11** / 1000 py (std RT)			
Heidenreich 2007 [35] Screening of cohort treated with mediastinal RT ≥35 Gy in the USA 1964-1994 (n=294); median f/u not reported	**33.4** / 10,000py			
Variation in risk with time since radiotherapy				
Aleman 2003 [1] Retrospective Dutch cohort treated when aged <41 y 1965-1987 (n=1261); median f/u 17.8y; comparator general Dutch population (AERs per 10,000 py)	Fatal CVD **RR** 0-5 y **7.6** (2.1-19.4) 6-10 y **7.0** (2.6-15.2) 11-15 y **4.5** (1.6-9.7)	 **AER** 0-5 y **6.1** 6-10 y **10.6**	Fatal MI **RR** 0-5 y **7.1** (0.9-25.8) 6-10 y **1.9** (0.1-10.7) 11-15 y **3.8** (0.8-11.0)	 **AER** 0-5 y **3.0** 6-10 y **1.0** 11-15 y **5.1**

	16-20 y **6.8** (3.4-12.2) 21-25 y **8.3** (4.3-14.5) 26-30 y **4.9** (1.6-11.5) >30 y **2.6** (0.1-14.3)	11-15 y **10.7** 16-20 y **28.7** 21-25 y **53.9** 26-30 y **41.3** >30 y **26.9**	16-20 y **4.4** (1.2-11.1) 21-25 y **6.4** (2.1-14.9) 26-30 y **1.9** (0.1-10.6) >30 y **0.0** (0.0-19.4)	16-20 y **9.4** 21-25 y **21.6** 26-30 y **4.9** >30 y **-8.4**
Ng 2002 [13] Retrospective cohort of patients with stage 1A-2B HL treated in the USA when aged ≤50 y 1969-1997 (n=1080) (AERs per 10,000 py)	Fatal CVD **RR** 0.5 y **4.4** (1.2-11.0) 5-10 y **2.7** (0.6-7.9) 10-15 y **2.5** (0.5-7.0) 15-20 y **2.8** (0.6-8.2) 20^{+} y **4.5** (1.2-11.6)		**AER** 0.5 y **6.3** 5-10 y **5.3** 10-15 y **7.2** 15-20 y **13.9** 20^{+} y **41.1**	
Lagerlöf 2022 [26] Retrospective cohort of patients treated for HL with 2/4 cycles ABVD and 30 Gy limited-field RT in Sweden 1999-2003; median f/u 16 y	**HR** 0-5 y **2.3** (1.50-3.52) (*P* < 0.0001) 5-10 y **1.2** (0.69-2.09) (*P* = .485)		>10 y **1.0** (0.58-1.72) (*P* = .992)	
Reinders 1999 [37] Retrospective cohort treated with RT alone in the Netherlands 1965-1980 (n=258); median f/u 14.2 y; comparator Dutch general population (AER / 100,000 py)	Hospitalisation **RR** 0-5 y **0.94** (0.11-3.4) >5-10 y **3.0** (1.9-6.1) >10-15 y **4.0** (1.9-7.3) >15y **2.6** (1.0-5.8)		**AER** 0-5 y **-10** >5-10 y **484** >10-15 y **1028** >15 y **749**	
Swerdlow 2007 [38] Retrospective cohort treated in the UK between 1967-2000 (n=7033); average f/u 11.1y; comparator general population of England and Wales	**SMR** < 1 y **4.2** (2.7-6.3) 1-4 y **1.7** (1.1-2.4) 5-9 y **2.3** (1.6-3.1) 10-14 y **1.9** (1.2-2.8) 15-19 y **4.1** (2.8-5.8)		**AER** < 1 y **257.1** 1-4 y **46.3** 5-9 y **109.1** 10-14 y **85.3** 15-19 y **288.8**	

	20-24 y **3.1** (1.6-5.4) ≥ 25 y **2.8** (0.6-8.3)	20-24 y **196.8** ≥ 25 y **221.5**
Median time to development		
Galper 2011 [15] Retrospective cohort treated with mediastinal RT in the USA 1969-1998 (n=1279); median f/u 14.7 y; comparator American general population	Cardiac procedure **17.6 y**	
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	**18.8 y**	
Hancock 1993 [21] Retrospective cohort treated with mediastinal RT in the USA 1960-1991 (n=2232); average f/u 9.5 y; comparator matched general population	Death from CVD, excluding acute MI **11.3 y**	
Myrehaug 2008 [24] Retrospective cohort of patients treated in Canada 1988-200 (n=615); median f/u 11.8 y; comparator general Canadian population	**5.6 y**	
Lee 2000 [27] Retrospective cohort of patients with stage 1-3 HL treated in the USA 1970-1986 (n=210); median f/u 15.6y; comparator general pop. High-risk: large mediastinal masses and/or hilar disease and/or splenic involvement; remainder low-risk. Radical RT: mantle field & liver & upper periaortic LN chains.	**13 y**	
Andersson 2021 [29] Retrospective cohort of patients treated for HL when aged ≤45y in Sweden 1965-1995 (n=319); median f/u 22 y	**26 y** (mean)	
Vlachaki 1997 [36] Retrospective cohort of patients with stage 1 HL, treated with RT +/- chemotherapy in the USA between 1967-1987 (n=145); median f/u 16.5 y	**9.8 y**	

*pooled estimate (meta-analysis)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.
Abbreviations – HL; Hodgkin lymphoma; ABVD; doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine; RT: radiotherapy; n: number; f/u: follow-up; m: months; y: years; CVD: cardiovascular disease; IHD: ischaemic heart disease; SUD: sudden unexpected death; HF: heart failure; RFs: risk factors; MI: myocardial infarction; CI: confidence interval; py: person-years; AER; absolute excess risk; AEM: absolute excess mortality; RR: relative risk; SMR: standardised mortality ratio

b. Ischaemic heart disease

Study details	Risk estimate		
Cumulative incidence			
Brierley 1998 [10] Retrospective cohort with stage 1-2 HL treated in Canada 1973-1984 (n=611); median f/u 11 y; comparator age-matched general population	5 y: **11%**		
Galper 2011 [15] Retrospective cohort treated with mediastinal RT in the USA 1969-1998 (n=1279); median f/u 14.7 y; comparator American general population	CAD 5 y **1.1%** 10 y **2.4%** 15 y **5.2%** 20 y **9.4%** 25 y **13.6%**	CABG 5 y **0.1%** 10 y **0.4%** 15 y **0.9%** 20 y **3.0%** 25 y **4.1%**	Angioplasty 5 y **0.4%** 10 y **0.7%** 15 y **1.6%** 20 y **3.0%** 25 y **5.0%**
van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population	CHD as a first event 40 y **22.9%** (20.7-25.1)		
Chen 2014 [31] Screening of American HL survivors >5 y following mediastinal RT, with no CVD diagnosis (n=182); median f/u 14.8y	≥70% coronary artery stenosis: **4.3%**		
Applefeld 1983 [33] Screening of cohort with stage 1-3A HL treated with RT in the USA between 1967-1973 (n=81); median f/u 8.1 y	**12%**		
Zinzani 1996 [34] Screening of cohort treated with mediastinal RT in Italy between 1970-1980 (n=102); mean f/u 17.5 y	**7.9%**		

Heidenreich 2007 [35] Screening of cohort treated with mediastinal RT ≥35 Gy in the USA between 1964-1994 (n=294); median f/u not reported	≥50% stenosis **7.4%** ≤50% stenosis **22.5%**		Prior MI **21.4%** Inducible ischaemia **18%**
Vlachaki 1997 [36] Retrospective cohort of patients with stage 1 HL, treated with RT +/- chemotherapy in the USA between 1967-1987 (n=145); median f/u 16.5 y	Fatal IHD: 10 y **3.4%**, 20 y **8.2%**		
Reinders 1999 [37] Retrospective cohort treated with RT alone in the Netherlands 1965-1980 (n=258); median f/u 14.2 y; comparator Dutch general population	IHD: 10 y **6.4%,** 20-25 y **21.2%** MI: 10 y **3.4%,** 20-25 y **14.2%** Fatal IHD: 10 y **2.6%,** 20-25 y **10.2%**		
Cosset 1991 [42] Retrospective French cohort treated with mediastinal RT 1971-1984 (n=499); median f/u not reported; comparator population no mediastinal RT (n=138)	MI: 10 y **3.9%**		
Hull 2003 [43] Retrospective cohort treated with RT in the USA 1962-1998 (n=415), ≥2y post RT; fields included heart or carotid / subclavian arteries; median f/u 11.2y; comparator matched general population	5 y: **3%**	10 y: **6%**	20 y: **10%**
Eriksson 2000 [48] Retrospective cohort treated in Sweden 1972-1985 (n=157); median f/u not reported; comparator Swedish general population	Fatal IHD: **8.3%**		
Machann 2011 [50] Screening of cohort treated with mediastinal RT in Germany between 1978-1985 (n=53); median follow-up 24 y	Infarctions: **26%** Perfusion deficits: **68%**		
Pohjola-Sintonen 1987 [51] Screening of cohort with stage 1-3A Hodgkin lymphoma, aged <40 y treated with mediastinal RT ≥5 y prior, in Finland (n=28); median f/u 8.6 y	**7%**		
Andersen 2010 [52] Screening of cohort treated Norway 1980-1988 (n=47); mean f/u 22 y	**15%** Coronary artery calcification: **83%**		
Pierga 1993 [54] Screening of cohort treated in France 1978-1988 (n=32); median f/u 7 y	Perfusion defects: **85%**		
Cosset 1991 [56]	MI 10 y **2.4%**		

Pooled analysis of 4 EORTC trials H1, H2, H5, H6), run 1964-1988; 1660 patients; median f/u not reported	15 y **4.6%**
Kilickap 2012 [74] Prospective cohort treated in Turkey 1990-2006 (n=336); median f/u 8.5 y	**8.0%**
Chronowski 2003 [90] Retrospective cohort of patients with stage 1-2 HL treated with RT in the USA between 1980-1996 (n=286); median follow-up 7.4 y	Requiring surgery: 5 y **0.4%**, 10 y **1.6%**, 15 y **4.1%**

Standardised incidence ratio

Galper 2011 [15] Retrospective cohort treated with mediastinal RT in the USA 1969-1998 (n=1279); median f/u 14.7y; comparator American general population	CABG **3.19** (2.83-3.55) Percutaneous angioplasty **1.55** (1.39-1.71)
Andersson 2009 [16] Retrospective cohort treated in Sweden 1965-1995 (n=6946); mean f/u 11.8 y; comparator Swedish general population	**5.53** (3.89-7.62)
Van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population	**3.2** (3.0-3.5)
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	MI **3.6** (2.9-4.4) Angina **4.1** (3.5-4.9) MI as 1st event **3.2** (2.7-3.7) MI or angina as 1st event **4.0** (3.5-4.6)
Stone 2019 [30] Meta-analysis of studies (n=22) assessing CVD incidence in ≥5 y HL survivors; median f/u of studies ≥10 y	**2.54*** (1.95-3.31)

Standardised mortality ratio

de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	MI **3.7** (3.0-4.5) Other IHD **4.7** (3.2-6.7)
Reinders 1999 [37] Retrospective cohort treated with RT alone in the Netherlands 1965-1980 (n=258); median f/u 14.2 y; comparator Dutch general population	Fatal MI or SCD **5.3** (2.7-9.3)

Eriksson 2000 [48] Retrospective cohort treated in Sweden 1972-1985 (n=157); median f/u not reported; comparator Swedish general population	**5.0** (2.7-8.6)
Tarbell 1990 [49] Retrospective cohort with stage IA-IIIB HL treated with mantle RT in the USA 1969-1984 (n=590); median f/u 8.7 y	Acute MI **6.7** (2.91-13.3)
Relative risk	
Brierley 1998 [10] Retrospective cohort with stage 1-2 HL treated in Canada 1973-1984 (n=611); median f/u 11 y; comparator age-matched general population	Fatal MI **1.55** (0.7-3.0)
Glanzmann 1998 [17] Long-term f/u of RCT participants (mantle RT +/- chemotherapy) (n=352), 144 had regular screening for CVD; mean f/u 11.2 y	MI **3.0** (0.6-8.8) MI / SUD **5.0** (1.6-11.7)
Hancock 1993 [21] Retrospective cohort treated with mediastinal RT in the USA 1960-1991 (n=2232); average f/u 9.5 y; comparator matched general population	Fatal MI: RT alone **4.1** (95% CI not given)
Rugbjerg 2017 [23] Retrospective Danish cohort treated when aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	Hospitalisation: Angina **1.8** (0.5-7.4) Acute MI **1.7** (1.0-2.9) Chronic IHD **3.0** (1.7-5.2)
Reinders 1999 [37] Retrospective cohort treated with RT alone in the Netherlands 1965-1980 (n=258); median f/u 14.2 y; comparator Dutch general population	Hospitalisation **2.7** (1.7-4.0)
van Nimwegen 2015 [44] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator general pop	**2.63** (1.74-3.99) (mediastinal RT)
Boivin 1992 [45] Retrospective cohort of patients treated in the USA and Canada 1942-1985 (n=4665); case-cohort to investigate IHD; median f/u 7 y	All IHD: **1.87** (0.92-3.80) (death); **3.31** (1.38-7.96) (direct cause) Acute MI: **2.56** (1.11-5.93) (death); **4.09** (1.54-10.89) (direct cause) Chronic IHD: **1.49** (0.60-3.73) (death); **2.12** (0.56-8.05) (direct cause)
King 1996 [46] Retrospective cohort of ≥3 y HL survivors treated in the USA 1954-1989 (n=326); median f/u 13.3 y; comparator general pop.	Fatal MI **2.8** (0.7-4.9)

Hancock 1988 [47] Combined analysis of patients with stage 1-3 HL treated with RT +/- MOPP RCTs in the USA between 1967-1980 (n=326); median f/u >14 y	Acute MI **0.86** (0.42-1.57)
Hazard ratio	
Van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population	**2.7** (2.0-3.7)
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	MI: **2.42** (1.12-5.24) Angina: **4.85** (1.97-11.9)
Andersson 2021 [29] Retrospective cohort of patients treated for HL when aged ≤45 y in Sweden 1965-1995 (n=319); median f/u 22.0 y	**4.41** (1.54-12.7)
Absolute excess risk	
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**AEM** Myocardial infarction **7.0** / 10,000 py Other ischaemic heart disease **2.5** / 10,000 py
Galper 2011 [15] Retrospective cohort treated with mediastinal RT in the USA 1969-1998 (n=1279); median f/u 14.7 y; comparator American general population	CABG **18.24** / 10,000 py Percutaneous angioplasty **19.29** / 10,000 py
Van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population	**70** / 10,000 py
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	MI **35.7** / 10,000 py (61.7 as 1st event) Angina **49.6** / 10,000 py (87.0 as 1st event)
Hancock 1993 [21] Retrospective cohort treated with mediastinal RT in the USA 1960-1991 (n=2232); average f/u 9.5 y; comparator matched general population	Fatal MI: **25.7** / 10,000 py
Rugbjerg 2017 [23]	Hospitalisation Angina **7** (0-14) / 10,000 py Acute MI **5** (-1-12) / 10,000 py Chronic IHD **8** (1-14) / 10,000 py

Retrospective Danish cohort treated when aged 15-39y 1943-2004 (n=1768); median f/u 14.4y; comparator population age-matched general population			
Reinders 1999 [37] Retrospective cohort treated with RT alone in the Netherlands 1965-1980 (n=258); median f/u 14.2 y; comparator Dutch general population	Hospitalisation **468** / 100,000 py Fatal MI or SCD **281 /** 100,000 py		
Eriksson 2000 [48] Retrospective cohort treated in Sweden 1972-1985 (n=157); median f/u not reported; comparator Swedish general population	**51** / 10,000 py		
Median time to development			
Brusamolino 2006 [5] Retrospective cohort of patients with stage 1A-2A HL treated in Italy with 4 cycles ABVD & limited RT 1990-2003 (n=120); median f/u 10 y	Myocardial infarction **67 m**		
Galper 2011 [15] Retrospective cohort treated with mediastinal RT in the USA 1969-1998 (n=1279); median f/u 14.7 y; comparator American general population	**15.8 y**		
van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population	**18 y**		
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	CHD **20.2 y**	Acute MI **19.5 y**	Angina **20.7 y**
Reinders 1999 [37] Retrospective cohort treated with RT alone in the Netherlands 1965-1980 (n=258); median f/u 14.2 y; comparator Dutch general population	**11.8 y**		
Hull 2003 [43] Retrospective cohort treated with RT in the USA 1962-1998 (n=415), ≥2 y post RT; fields included heart or carotid / subclavian arteries; median f/u 11.2 y; comparator matched general population	**9 y**		
Tarbell 1990 [49] Retrospective cohort with stage 1A-3B HL treated with mantle RT in the USA 1969-1984 (n=590); median f/u 8.7 y	**7.5 y**		

van Nimwegen 2015 [44] Retrospective cohort of >5 y survivors of Hodgkin lymphoma treated with RT when aged <51 y in the Netherlands between 1965-1995 (n=2524); median f/u 20 y; comparator general Dutch population	**19.0 y**		
King 1996 [46] Retrospective cohort of American ≥3 y HL survivors treated 1954-1989 (n=326); median f/u 13.3 y; comparator North American general population	**12.6 y**		
Variation in risk with time since radiotherapy			
Andersson 2009 [16] Retrospective cohort treated in Sweden 1965-1995 (n=6946); mean f/u 11.8 y; comparator Swedish general population	**SIR** 1-9 y **1.13** (1.00-1.28)	10-19 y **1.59** (1.41-1.80)	≥20 y **1.22** (1.01-1.45)
van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population (AER / 10,000 py)	**SIR**, ≥35 y since treatment **5.8** **SIR** 5-9 y **2.3** (1.7-3.0) 10-14 y **2.9** (2.3-3.6) 15-19 y **3.7** (3.0-4.4) 20-24 y **3.6** (2.9-4.4) 25-29 y **3.5** (2.7-4.4) 30-34 y **3.1** (2.2-4.3) ≥35 y **3.9** (2.6-5.6)	**AER** 5-9 y **26** 10-14 y **53** 15-19 y **97** 20-24 y **127** 25-29 y **155** 30-34 y **152** ≥35 y **475**	
Heidenreich 2007 [35] Screening of cohort treated with mediastinal RT ≥35 Gy in the USA between 1964-1994 (n=294); median f/u not reported	**RR**, fatal MI: <10 y **7.3** (4.0-10.5) 10-19 y **8.1** (4.3-12.4)	≥20 y **6.9** (2.5-15.1)	
Reinders 1999 [37] Retrospective cohort treated with RT alone in the Netherlands 1965-1980 (n=258); median f/u 14.2 y; comparator Dutch general population (AER / 100,000 py)	IHD / SCD **SMR**: 0-5 y: **0** (0-5.1) >5-10 y: **6.5** (1.8-16.5) >10-15 y: **9.8** (3.2-23.0) >15 y: **7.0** (1.4-20.5)	**AER**: 0-5 y **-61** >5-10 y **344** >10-15 y **592** >15 y **472**	
Swerdlow 2007 [38]	**SMR**, MI SD RT alone:	All SD RT:	

Retrospective cohort treated in the UK between 1967-2000 (n=7033); average f/u 11.1 y; comparator general population of England and Wales	< 1 y **2.8** (0.9-6.4) 1-9 y **2.1** (1.4-3.1) 10-19 y **3.4** (2.2-5.0) ≥ 20 y **2.7** (1.0-6.0)	< 1 y **1.8** 1-9 y **2.4** 10-19 y **3.6** ≥ 20 y **4.3**
Eriksson 2000 [48] Retrospective cohort treated in Sweden 1972-1985 (n=157); median f/u not reported; comparator Swedish general population	**SMR** 0-5 y **2.8** (0.6-8.2) 5-10 y **7.9** (2.9-17.2)	10-15 y **2.0** (0.0-11.0) >15 y **12.4** (2.5-36.2)
Boivin 1992 [45] Retrospective cohort of patients treated for HL in Canada 1940-1975 (n=4665); average f/u 7 y	**RR,** fatal MI 0-4 y **1.97** (0.78-4.95) 5-9 y **3.57** (0.8-14.50)	≥10y **1.87** (0.39-8.98)

*pooled estimate (meta-analysis)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – HL: Hodgkin lymphoma; n: number; f/u: follow-up; RT: radiotherapy; CAD: coronary artery disease; CABG: coronary artery bypass graft; CHD: coronary heart disease; CVD: cardiovascular disease; IHD: ischaemic heart disease; MI: myocardial infarction; EORTC: European Organisation for Research and Treatment of Cancer; RCT: randomised controlled trial; SCD: sudden cardiac death; SUD: sudden unexpected death; CI: confidence interval; MOPP: mechlorethamine, Oncovin (vincristine), procarbazine, prednisone; AEM:; absolute excess mortality; py: person-years; ABVD: Adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine; SIR: standardised incidence ratio; AER: absolute excess risk; RR: relative risk; SMR: standardised mortality ratio; m: months; y: years; SD: supradiaphragmatic

c. Heart failure

Study details	Risk estimate	
Cumulative incidence		
van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population	Any HF 40 y **24.8%** (21.4-28.4)	HF as a 1st event 40 y **8.1%** (6.7-9.7)
Chen 2014 [31] Screening of American HL survivors >5 y following mediastinal RT, with no CVD diagnosis (n=182); median f/u 14.8 y	Ejection fraction ≤55% **14%**	
Applefeld 1983 [33] Screening of cohort with stage 1-3A HL treated with RT in the USA between 1967-1973 (n=81); median f/u 8.1 y	LV dysfunction **4%**	
Machann 2011 [50] Screening of cohort treated with mediastinal RT in Germany between 1978-1985 (n=53); median f/u 24 y	Reduced ejection fraction **23%**	
Pohjola-Sintonen 1987 [51] Screening of cohort with stage 1-3A HL, aged <40 y treated with mediastinal RT ≥5 y prior, in Finland (n=28); median f/u 8.6 y	Reduced ejection fraction **7%**	
Cosset 1991 [56] Pooled analysis of 4 EORTC trials H1, H2, H5, H6, run 1964-1988; 1660 patients; median f/u not reported	Fatal 20 y **6.7%**	
Adams 2004 [57] Screening of cohort treated with mediastinal RT in the USA when aged ≤25 y, since 1969 (n=48); median f/u 14.3 y	Systolic dysfunction **11.6%** Diastolic dysfunction **37.2%**	
Kilickap 2012 [74] Prospective cohort treated in Turkey 1990-2006 (n=336); median f/u 8.5 y	**4.2%**	
Standardised incidence ratio		
Van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population	**6.8** (5.9-7.6)	
Aleman 2007 [19]	**4.9** (3.6-6.4)	

Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population		
Stone 2019 [30] Meta-analysis of studies (n=22) assessing CVD incidence in ≥5 y HL survivors; median f/u of studies ≥10 y	Myocardial disease **3.95*** (2.48-6.27)	
Relative risk		
Rugbjerg 2019 [8] Retrospective cohort of Danish >5 y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	Hospitalisation: HF **7.0** (5.1-9.6)	Cardiomyopathy **4.7** (2.4-9.1)
Rugbjerg 2017 [23] Retrospective Danish cohort treated when aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	Hospitalisation **6.2** (3.6-10.5)	
Cosset 1991 [56] Pooled analysis of 4 EORTC trials H1, H2, H5, H6), run 1964-1988; 1660 patients; median f/u not reported	Fatal cardiac failure **8.63** (5.53-12.85)	
Hazard ratio		
Van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population	**2.7** (2.0-3.7)	
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	**7.37** (1.81-30.0)	
Absolute excess risk		
Rugbjerg 2019 [8] Retrospective cohort of Danish >5 y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	Heart failure **20** / 10,000 py (13-27) Cardiomyopathy **4** / 10,000 py (0.6-8)	
Van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population	**58** / 10,000 py	

Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	**25.6** / 10,000 py		
Rugbjerg 2017 [23] Retrospective Danish cohort treated when aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	Hospitalisation **10** (4-17) / 10,000py		
Median time to development			
van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population	**19 y**		
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	Congestive HF **18.5 y**	Cardiomyopathy **18.0 y**	
van Nimwegen 2017 [58] Nested case-control study in cohort of 5 y survivors treated with RT in the Netherlands between 1965-1995 when aged <51 y (325 cases, 1204 matched controls); median f/u not reported	**20.6 y**		
Variation in risk with time since radiotherapy			
Andersson 2009 [16] Retrospective cohort treated in Sweden 1965-1995 (n=6946); mean f/u 11.8 y; comparator Swedish general population	**SIR** 1-9 y **0.45** (0.29-0.67)	10-19 y **1.51** (1.19-1.89)	≥20 y **2.98** (2.48-3.56)
van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population (AER / 10,000 py)	**SIR** 5-9 y **4.8** (2.5-8.3) 10-14 y **6.1** (4.0-8.9) 15-19 y **8.0** (5.9-10.5) 20-24 y **8.7** (6.7-11.0) 25-29 y **6.5** (4.7-8.7) 30-34 y **5.1** (3.3-7.5) ≥35 y **5.8** (3.8-8.5)	**AER** 5-9 y **13** 10-14 y **26** 15-19 y **55** 20-24 y **97** 25-29 y **101** 30-34 y **101** ≥35 y **382**	

*pooled estimate (meta-analysis)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.
Abbreviations – y: years; HL: Hodgkin lymphoma; RT: radiotherapy; n: number; f/u: follow-up; HF: heart failure; CVD: cardiovascular disease; LV: left ventricle; EORTC: European Organisation for Research and Treatment of Cancer; py: person-years; SIR: standardised incidence ratio; AER: absolute excess risk

d. Valvular heart disease

Study details	Risk estimate			
Cumulative incidence				
Galper 2011 [15] Retrospective cohort treated with mediastinal RT in the USA 1969-1998 (n=1279); median f/u 14.7 y; comparator American general population	VHD 5 y **0.5%** 10 y **1.4%** 15 y **3.3%**	 20 y **5.0%** 25 y **8.7%**	Valve repair 5 y **0.1%** 10 y **0.3%** 15 y **0.5%**	 20 y **1.1%** 25 y **1.2%**
van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population	VHD as 1st event 40 y **25.9%** (23.4-28.5)			
Chen 2014 [31] Screening of American HL survivors >5 years following mediastinal RT, with no CVD diagnosis (n=182); median f/u 14.8 y	**8.8%** (≥moderate)			
Hull 2003 [43] Retrospective cohort treated with RT in the USA 1962-1998 (n=415), ≥2 y post RT; fields included heart or carotid / subclavian arteries; median f/u 11.2 y; comparator matched general population	10 y **1%**	15 y **4%**	20 y **6%**	
Machann 2011 [50] Screening of cohort treated with mediastinal RT in Germany 1978-1985 (n=53); median f/u 24 y	**42%**			
Adams 2004 [57] Screening of cohort treated with mediastinal RT in the USA when aged ≤25 y, since 1969 (n=48); median f/u 14.3 y	≥1 valvular abnormality **68%** ≥1 abnormality unexpected in a healthy population **42.6%**			
Cella 2011 [63]	5 y: **28%**			

Screening of patients treated in Italy 2002-2008 (n=56); median f/u 5.9 y	7 y: **44%**	
Kilickap 2012 [74] Prospective cohort treated in Turkey 1990-2006 (n=336); median f/u 8.5 y	Stenotic: **0.6%**	
Standardised incidence ratio		
Rugbjerg 2019 [8] Retrospective cohort of Danish >5 y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	Hospitalisation: Aortic **30.7** (23.4-40.5) Mitral **12.1** (6.9-21.1)	Endocarditis **21.1** (12.0-37.1)
Galper 2011 [15] Retrospective cohort treated with mediastinal RT in the USA 1969-1998 (n=1279); median f/u 14.7 y; comparator American general population	Valve surgery **9.19** (8.07-10.31)	
Stone 2019 [30] Meta-analysis of studies (n=22) assessing CVD incidence in ≥5 y HL survivors; median f/u of studies ≥10 y	**13.10*** (7.41-23.16)	
Hazard ratio		
Van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population	**6.6** (4.0-10.8) (as first event)	
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	**7.01** (2.59-18.9) (mediastinal RT)	
Odds ratio		
Andersson 2021 [29] Retrospective cohort of patients treated for HL when aged ≤45 y in Sweden 1965-1995 (n=319); median f/u 22.0 y	**6.14** (2.30-16.40)	
Bijl 2016 [62] Cross-sectional screening study of Dutch patients treated with RT 1969-2005 (n=82); median f/u 13.4y; comparator survivors not treated with RT	≥ mild AR **8.55** (1.82-40.16) (*P* = .007) ≥mild MR **2.8** (0.91-8.59) (*P* = .074)	≥mild TR **7.37** (0.89-60.95) (*P* = .064) ≥mild AS **2.63** (0.52-13.4) (*P* = .242)
Relative risk		
Rugbjerg 2017 [23]	Hospitalisation:	

Retrospective Danish cohort treated when aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	Aortic valve disorders **18.4** (10.7-31.4)	Mitral valve disorders **9.9** (3.7-26.9)
Absolute excess risk		
Rugbjerg 2019 [8] Retrospective cohort of Danish >5 y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	Aortic **34** / 10,000 py (25-43) Endocarditis **8** / 10,000 py (3-12) Mitral **7** / 10,000 py (3-12)	
Galper 2011 [15] Retrospective cohort treated with mediastinal RT in the USA 1969-1998 (n=1279); median f/u 14.7 y; comparator American general population	Valve surgery **14.07** / 10,000 py	
Rugbjerg 2017 [23] Retrospective Danish cohort treated when aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	Hospitalisation: Aortic valve disorders **12** (5-18) / 10,000 py Mitral valve disorders **3** (0-7) / 10,000 py	
Median time to development		
Galper 2011 [15] Retrospective cohort treated with mediastinal RT in the USA 1969-1998 (n=1279); median f/u 14.7 y; comparator American general population	**16.1 y**	
van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population	**24 y**	
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	**23.3 y**	
Hancock 1993 [21] Retrospective cohort treated with mediastinal RT in the USA 1960-1991 (n=2232); average f/u 9.5 y; comparator matched general population	Asymptomatic VHD **11.5 y**	Symptomatic VHD **16.5 y**
Hull 2003 [43] Retrospective cohort treated with RT in the USA 1962-1998 (n=415), ≥2 y post RT; fields included heart or carotid / subclavian arteries; median f/u 11.2 y; comparator matched general population	**22 y**	

Variation in risk with time since radiotherapy			
Bijl 2016 [62] Cross-sectional screening study of Dutch patients treated with RT 1969-2005 (n=82); median f/u 13.4y; comparator survivors not treated with RT	**OR**, per year AR **1.16** (1.06-1.28) (*P* = .002)	TR **1.11** (1.02-1.21) (*P* = .021)	AS **1.14** (1.03-1.26) (*P* = .010)
Heidenreich 2003 [64] Screening of cohort treated with mediastinal RT ≥35 Gy in the USA 1964-1994 (n=294); median f/u not reported	**Cumulative incidence** ≥mild AR: <20 y **4%** ≥20 y **60%**	≥moderate TR: <20 y **0%** ≥20 y **4%**	AS: <20 y **0%** ≥20 y **16%**
	AS: **OR 13.9** (12.2-15.8) for each 10 y following RT		

*pooled estimate (meta-analysis)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – RT: radiotherapy; n: number; f/u: follow-up; y: years; VHD: valvular heart disease; HL: Hodgkin lymphoma; CVD: cardiovascular disease; AR: aortic regurgitation; MR: mitral regurgitation; TR: tricuspid regurgitation; AS: aortic stenosis; py: person-years; OR: odds ratio; Gy: gray

e. Pericardial disease and conduction abnormalities

Study details	**Risk estimate**		
Cumulative incidence			
Galper 2011 [15] Retrospective cohort treated with mediastinal RT in the USA 1969-1998 (n=1279); median f/u 14.7 y; comparator American general population	Arrhythmia 5 y **1.1%** 10 y **2.1%** 15 y **4.2%** 20 y **6.7%** 25 y **11.3%**	Pacemaker insertion 5 y **0.2%** 10 y **0.3%** 15 y **0.6%** 20 y **0.9%** 25 y **2.2%**	Pericardial surgery 5 y **0.1%** 10 y **0.1%** 15 y **0.4%** 20 y **0.6%** 25 y **1.3%**
	Conduction abnormality **6.6%** ≥1 type rhythm disturbance **2.3%** Atrial fibrillation **1.9%**	SVT **2.0%** Ventricular tachycardia **0.4%**	
Lund 1996 [32]	Pericardial thickening **15%**		

Screening of cohort of 5 y survivors treated in Norway when aged <50 y 1980-1988 (n=116); median f/u not reported	
Applefeld 1983 [33] Screening of cohort with stage 1-3A HL treated with radiotherapy in the USA 1967-1973 (n=81); median f/u 8.1 y	Constrictive pericarditis **23%** Occult constrictive pericarditis **27%**
Zinzani 1996 [34] Screening of cohort treated with mediastinal RT in Italy 1970-1980 (n=102); mean f/u 17.5y	Constrictive pericarditis **2.9%**
Cosset 1991 [42] Retrospective cohort treated in France with mediastinal RT 1971-1984 (n=499); median f/u not reported; comparator pop. no mediastinal RT (n=138)	Pericarditis 10 y **9.5%**
Hull 2003 [43] Retrospective cohort treated with RT in the USA 1962-1998 (n=415), ≥2 y post RT; fields included heart or carotid / subclavian arteries; median f/u 11.2 y; comparator matched general population	Non-coronary atherosclerotic disease 5 y **2%** 10 y **3%** 20 y **7%**
Pohjola-Sintonen 1987 [51] Screening of cohort with stage 1-3A HL, aged <40 y when treated with mediastinal RT ≥5 y prior, in Finland (n=28); median f/u 8.6 y	Pericardial disease **43%**
Adams 2004 [57] Screening of cohort treated with mediastinal RT in the USA when aged ≤25 y, since 1969 (n=48); median f/u 14.3 y	Conduction abnormality or arrhythmia **74.5%**
Wethal 2009 [60] Screening of 5 y survivors aged <50 y at RT in Norway 1980-1988 (n=116); median f/u 10 y; comparator age- & sex-matched survivors (n=25)	**93%**
Heidenreich 2003 [64] Screening of cohort treated with mediastinal RT ≥35 Gy in the USA 1964-1994 (n=294); median f/u not reported	Pericardial thickening **21%** ECG abnormalities **2%** Pericardial effusions **3%**
Byhardt 1975 [66] Retrospective cohort treated in America with mantle RT since 1967 (n=83); mean f/u 30 m	Pericardial effusion **28.9%**
Mill 1984 [67]	Symptomatic pericarditis **6.7%**

Retrospective cohort treated in America 1968-1976 (n=345); median f/u not given	
Kilickap 2012 [74] Prospective cohort treated in Turkey 1990-2006 (n=336); median f/u 8.5 y	Pericarditis **0.3%** Conduction abnormalities **9.5%**
Standardised incidence ratio	
Galper 2011 [15] Retrospective cohort treated with mediastinal RT in the USA 1969-1998 (n=1279); median f/u 14.7 y; comparator American general population	Pacemaker insertion **1.90** (1.70-2.21) Pericardial surgery **12.91** (10.61-15.21)
Stone 2019 [30] Meta-analysis of studies (n=22) assessing CVD incidence in ≥5 y HL survivors; median f/u of studies ≥10 y	Pericardial disease **10.67*** (7.75-14.69) Dysrhythmia **3.23*** (2.23-4.68)
Relative risk	
Rugbjerg 2019 [8] Retrospective cohort of Danish >5y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	Pericardial disease **8.5** (5.0-14.5) AV block & other conduction abnormalities **5.5** (3.9-7.7) Other arrhythmias **4.1** (2.1-8.0)
Absolute excess risk	
Rugbjerg 2019 [8] Retrospective cohort of Danish >5 y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	Pericardial disease **8** / 10,000 py (3-12) AV block & other cardiac arrhythmias **17** / 10,000 py (10-24) Other arrhythmias **4** / 10,000py (0.5-7)
Galper 2011 [15] Retrospective cohort treated with mediastinal RT in the USA 1969-1998 (n=1279); median f/u 14.7 y; comparator American general population	Pacemaker insertion **9.38** / 10,000 py Pericardial surgery **4.69** / 10,000 py
Median time to development	
Galper 2011 [15] Retrospective cohort treated with mediastinal RT in the USA 1969-1998 (n=1279); median f/u 14.7 y; comparator American general population	Pericardial disease **18.3 y** Conduction abnormalities **14.2 y**
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	Pericarditis **13.6 y** Dysrhythymia **18.3 y**
Ruckdeschel 1975 [65]	Pericardial effusion on imaging **6 m**

Randomised trial of treatment-naïve patients with stage 1-2 HL 1968-1972, randomised to RT alone (extended field) vs combination chemotherapy following RT (involved plus adjacent nodal areas only) (n=81)	
Variation in risk with time since radiotherapy	
Heidenreich 2003 [64] Screening of cohort treated with mediastinal RT ≥35 Gy in the USA 1964-1994 (n=294); median f/u not reported	Cumulative incidence of pericardial thickening: 2-10 y **16%** 11-20 y **18%** >20 y **33%** RBBB: **OR 7.3** (1.2-45) for each 10 y following RT

*pooled estimate (meta-analysis)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – RT: radiotherapy; n: number; f/u: follow-up; y: years; SVT: supraventricular tachycardia; HL: Hodgkin lymphoma; Gy: gray; ECG: electrocardiogram; AV: atrioventricular; py: person-years; RBBB: right bundle brance block; OR: odds ratio

f. Cerebrovascular disease

Study details	Risk estimate	
Cumulative incidence		
De Bruin 2009 [39] Nested case-control study of Dutch 5 y HL survivors treated when aged <51 y 1965-1995 (n=2201); median f/u 17.5 y; comparator general pop	30 y: Ischaemic stroke & TIA **7%** Ischaemic stroke **5%**	TIA **3%**
Elerding 1981 [53] Screening of cohort of 5 y survivors treated with neck RT in the USA between 1948-1973 (n=324); mean f/u 9 y	Carotid stenosis **22%**	
Kilickap 2012 [74] Prospective cohort treated in Turkey 1990-2006 (n=336); median f/u 8.5 y	Carotid stenosis **3.9%**	
Standardised incidence ratio		
Stone 2019 [30] Meta-analysis of studies (n=22) assessing CVD incidence in ≥5 y HL survivors; median f/u of studies ≥10 y	**1.99*** (1.56-2.55)	
De Bruin 2009 [39]	Stroke **2.2** (1.7-2.8) RT alone **2.0** (1.2-3.1)	TIA **3.1** (2.2-4.2) RT alone **3.4** (1.9-5.5)

Nested case-control study of Dutch 5 y HL survivors treated when aged <51 y 1965-1995 (n=2201); median f/u 17.5 y; comparator general pop	CMT **2.6** (1.9-3.5)	CMT **3.4** (2.2-5.1)
Standardised mortality ratio		
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**2.9** (1.5-3.3)	
Absolute excess risk		
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**AEM 1.8** / 10,000 py	
De Bruin 2009 [39] Nested case-control study of 5 y HL survivors treated in the Netherlands when aged <51 y 1965-1995 (n=2201); median f/u 17.5 y; comparator general Dutch population	Stroke **12** / 10,000 py (7-18)	TIA **9** / 10,000 py (6-14)
Median time to development		
De Bruin 2009 [39] Nested case-control study of 5 y HL survivors treated in the Netherlands when aged <51 y 1965-1995 (n=2201); median f/u 17.5 y; comparator general Dutch population	**17.4 y**	
Hull 2003 [43] Retrospective cohort treated with RT in the USA 1962-1998 (n=415), ≥2 y post RT; fields included heart or carotid / subclavian arteries; median f/u 11.2 y; comparator matched general population	Stroke / TIA **5.6 y**	Subclavian / carotid stenosis **21 y**
Variation in risk with time since radiotherapy		
Andersson 2009 [16] Retrospective cohort treated in Sweden 1965-1995 (n=6946); mean f/u 11.8 y; comparator Swedish general population	**SIR** 1-9 y **1.07** (0.87-1.30) 10-19 y **1.37** (1.10-1.69)	≥20 y **1.16** (0.53-1.15)

*pooled estimate (meta-analysis)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – y: years; HL ;Hodgkin lymphoma; TIA: transient ischaemic attack; f/u: follow-up; RT: radiotherapy; AEM: absolute excess mortality; py: person-years; SIR: standardised incidence ratio

Table C2.2: Effect of radiotherapy treatment factors on the risk of cardiovascular disease following treatment for Hodgkin lymphoma

a. All cardiovascular disease

Study details	Risk estimate
Radiotherapy fields	
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**HR** Supradiaphragmatic RT **4.36** (vs no [SD] RT) (2.74-6.94) Infradiaphragmatic RT Excluding spleen **1.21** (vs no [ID] RT) (0.90-1.63) Including spleen **1.38** (vs no [ID] RT) (1.06-1.80)
Hancock 1993 [21] Retrospective cohort treated with mediastinal RT in the USA 1960-1991 (n=2232); average f/u 9.5y; comparator matched general population; before 1972 RT higher dose/fraction and no subcarinal blocking	Fatal CVD in those treated before 1972: RR **4.3** (3.1-5.5); **5.3** (3.1-7.5) exc. MI AER **48.9** / 10,000py; **24.2** / 10,000py exc. MI Fatal CVD in those treated after 1972: RR **2.6** (1.7-3.6); **1.4** (0.8-2.9) exc. MI AER **15.3** / 10,000py; **-** exc. MI
Radiotherapy dose	
Galper 2011 [15] Retrospective cohort treated with mediastinal RT in the USA 1969-1998 (n=1279); median f/u 14.7 y; comparator American general population	Mediastinal dose HR diagnosis **0.93** (0.50-1.73) (*P* = .812) HR procedure **1.40** (0.44-4.49) (*P* = .568) (≥36 Gy vs. <36 Gy) SIR procedure <36 Gy **0.91** (0.29-2.83) ≥36 Gy **2.06** (1.66-2.56) RR procedure <36 Gy Ref ≥36 Gy **1.48** (0.46-4.81) (*P* = .51)
van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population	**HR**, prescribed dose 1-29 Gy **2.1** (1.2-3.6) 30-35 Gy **3.1** (2.3-4.2) ≥36 Gy **3.8** (3.0-5.0)
Hancock 1993 [21] Retrospective cohort treated with mediastinal RT in the USA 1960-1991 (n=2232); average f/u 9.5 y; comparator matched general population	Fatal CVD in those prescribed >30 Gy: **RR 3.5** (2.5-4.5); **3.5** (2.2-4.7) exc. MI **AER 29.9** (**11.4** exc. MI)
Zinzani 1996 [34]	**Cumulative incidence** according to RT dose to mediastinum:

Screening of cohort treated with mediastinal RT in Italy between 1970-1980 (n=102); mean f/u 17.5 y	36-44 Gy **0%** 45 Gy **10.2%** 46-50 Gy **66%**
Hahn 2017 [71]	Multivariable model of all CVD: **HR** MHD (cGy) **1.09** (1.02-1.16) (*P* = .0083) Whole heart dose homogeneity **0.94** (0.89-0.98) (*P* = .0034) Male **2.3** (1.18-4.52) (*P* = .014) Age **1.03** (1.01-1.06) (*P* = .049)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.
Abbreviations – RT: radiotherapy; f/u: follow-up; y: years; CVD: cardiovascular disease; RR: relative risk; MI: myocardial infarction; AER: absolute excess risk; py: person-years; HR; hazard ratio; Gy: gray; SIR: standardised incidence ratio; Ref: reference; MHD: mean heart dose; cGy: centigray

b. Ischaemic heart disease

Study details	Risk estimate
Radiotherapy technique	
Hancock 1993 [21] Retrospective cohort treated with mediastinal RT in the USA 1960-1991 (n=2232); average f/u 9.5y; comparator matched general population; before 1972 RT higher dose/fraction and no subcarinal blocking	Fatal MI in those treated before 1972: **RR 3.7** (2.3-5.1) **AER 24.7 / 10,000py** Fatal MI in those treated after 1972: **RR 3.4** (2.0-4.8) **AER 13.9 / 10,000py**
Swerdlow 2007 [38] Retrospective cohort treated in the UK 1967-2000 (n=7033); average f/u 11.1 y; comparator general population of England and Wales	Fatal MI, SMR: TNI **8.9** (5.4-13.8) (*P* < .001) Other SD RT **1.9** (1.2-2.9) (*P* = .01) Mantle RT **3.2** (2.3-4.2) (*P* < .001) Unknown field **2.3** (1.4-3.6) (*P* = .8)
Hull 2003 [43] Retrospective cohort treated with RT in the USA 1962-1998 (n=415), ≥2 y post RT; fields included heart or carotid / subclavian arteries; median f/u 11.2 y; comparator matched general population	SD & ID RT: HR **7.8** (1.1-53.2) (vs SD or ID RT alone)

Radiotherapy dose			
van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population (AER / 10,000 py); CHD as 1st event	**HR**, prescribed dose 1-29 Gy **1.2** (0.6-2.7)	30-35 Gy **2.3** (1.1-3.4)	≥36 Gy **2.2** (1.6-3.1)
Hancock 1993 [21] Retrospective cohort treated with mediastinal RT in the USA 1960-1991 (n=2232); average f/u 9.5 y; comparator matched general population	Fatal MI in those prescribed >30 Gy: RR **3.5** (2.5-4.5) AER **18.6** / 10,000py		
van Nimwegen 2015 [44] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator general Dutch pop **25y cumulative incidence** MHD 0 Gy **4.1%** MHD 15-20 Gy **9.4%** MHD ≥25 Gy **12.6%**	**RR** Prescribed (0 Gy ref): 15-24 Gy **1.51** (0.58-3.96) 25-34 Gy **2.30** (1.49-3.56) 35-39 Gy **2.52** (2.10-3.03) 40-45 Gy **3.03** (2.41-3.82) *P* trend < .001	MHD (0 Gy ref): 1-5 Gy **1.14** (0.62-2.10) 5-14 Gy **2.14** (1.28-3.58) 15-19 Gy **2.76** (2.10-3.59) 20-24 Gy **2.79** (2.23-3.49) 25-34 Gy **3.21** (2.52-4.09) 35-45 Gy **2.54** (0.93-6.69) P_{trend} < .001	

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – RT: radiotherapy; y: years; MI: myocardial infarction; RR: relative risk: AER: absolute excess risk; f/u: follow-up; SMR: standardised mortality ratio; TNI: total nodal irradiation; SD: supradiaphragmatic; ID: infradiaphragmatic; HR: hazard ratio; CHD: coronary heart disease; Gy: gray; MHD: mean heart dose

c. Heart failure

Study details	**Risk estimate**		
Radiotherapy technique			
Van Nimwegen 2017 [58] Nested case-control study in cohort of 5 y survivors treated with RT in the Netherlands between 1965-1995 when aged <51 y (325 cases, 1204 matched controls); median f/u not reported	**RR**: No RT Ref PAN-RT **0.66** (0.15-2.98)	Med RT **1.87** (1.27-2.75) Med & PAN RT **2.59** (1.80-3.72)	

Radiotherapy dose			
van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population; HF as first event	**HR**, prescribed dose 1-29 Gy **1.7** (0.5-5.7)	30-35 Gy **2.4** (1.0-4.8)	≥36 Gy **4.0** (2.3-7.0)
Van Nimwegen 2017 [58] Nested case-control study in cohort of 5 y survivors treated with RT in the Netherlands between 1965-1995 when aged <51 y (325 cases, 1204 matched controls); median f/u not reported **Cumulative incidence**, dose to left ventricle: 0-15 Gy **4.4%** (25 y), **7.5%** (35 y) 16-20 Gy **6.2%** (25 y), **10.2%** (35 y) ≥21 Gy **13.3%** (25 y), **21.8%** (35 y)	**RR of HF as 1st CVD** Prescribed (Gy): 20-34 **2.35** (0.85-6.46) 35-39 **2.10** (0.86-5.13) ≥ 40 **3.02** (1.23-7.40) MHD (Gy): 1-20 **1.43** (0.83-2.50) 21-25 **1.03** (0.63-1.67) 26-30 **2.78** (1.69-4.59) ≥ 31 **4.16** (2.14-8.10)	MLVD (Gy): 1-15 **1.27** (0.86-1.89) 16-20 **1.65** (0.98-2.77) 21-25 **3.84** (1.97-7.47) ≥ 26 **4.39** (2.00-9.65) LV-V_{30} (%): 1-24 **0.95** (0.52-1.71) 25-49 **1.05** (0.70-1.58) 50-74 **1.80** (1.12-2.91) 75-100 **3.22** (1.3-7.86)	LV-V_{20} (%): 1-24 **0.27** (0.06-1.11) 25-49 **1.38** (0.89-2.14) 50-74 **1.51** (0.99-2.28) 75-100 **2.5** (1.33-4.69)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – y: years; RT: radiotherapy; f/u: follow-up; RR: relative risk; RT: radiotherapy; PAN: para-aortic nodes; HF: heart failure; HR: hazard ratio; Gy: gray; CVD: cardiovascular disease; MLVD: mean left ventricular dose; LV-V_{20}: volume of left ventricle receiving 20 gray or more; MHD: mean heart dose; LV-V_{30}: volume of left ventricle receiving 30 gray or more

d. Valvular heart disease

Study details	**Risk estimate**		
Radiotherapy dose			
van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population	**HR**, prescribed dose 1-29 Gy **4.2** (1.8-9.8)	30-35 Gy **4.8** (2.7-8.4)	≥36 Gy **7.2** (4.4-11.8)

Cutter 2015 [61] Nested case-control study of Dutch 5 y survivors treated when aged 15-41 y 1965-1995 (89 cases, 200 matched controls); median f/u 18.8 y	**RR** Prescribed dose (Gy) No RT **1.0** (0.3-3.5) ≤ 30 **0.6** (0.1-4.7) 31-35 **3.1** (1.7-5.7) 36-40 **4.1** (2.9-5.6) > 40 **4.6** (1.2-18.5) (P_{trend} = .005)	 Dose to affected valve (Gy) No RT **1.0** (0.2-4.8) ≤ 30 **1.4** (0.5-3.8) 31-35 **3.1** (1.7-5.7) 36-40 **5.4** (3.9-7.7) > 40 **11.8** (4.9-28.5) (P_{trend} < .001)	**30y cumulative incidence** Dose to affected valve (Gy) No RT **1.6%** ≤ 30 **3.0%** 31-35 **6.4%** 36-40 **9.3%** > 40 **12.4%**
Cella 2011 [63] Screening of patients treatedin Italy 2002-2008 (n=56); median f/u 5.9 y	**OR** All VHD: Heart D_{max} >33 Gy vs ≤33 Gy **6.4** (P = .003) Aortic & mitral: LA-V_{25} >63% vs ≤63% **5.7** (P = .03) LA-V_{30} >25% vs ≤25% **4.4** (P = .02) Tricuspid: RV-V_{30} >65% vs ≤65% **7.2** (P = .02)		

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – y: years; HL: Hodgkin lymphoma; RT: radiotherapy; f/u: follow-up; HR: hazard ratio; Gy: gray; RR: relative risk; Ref: reference; OR: odds ratio; VHD: valvular heart disease; D_{max}: maximum dose; LA-V_{25}: volume of left atrium receiving 25 gray or more; LA-V_{30}: volume of left atrium receiving 30 gray or more; RV-V_{30}: volume of right ventricle receiving 30 gray or more

e. Pericardial disease and conduction abnormalities

Study details	Risk estimate
Radiotherapy dose	
Cosset 1991 [42] Retrospective cohort treated in France with mediastinal RT 1971-1984 (n=499); median f/u not reported	Cumulative incidence pericarditis, dose to pericardium: 35-37 Gy **4.1%** 39-41 Gy **5.8%**

	41-43 Gy **10.4%**

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.
Abbreviations – RT: radiotherapy; n: number: f/u: follow-up; Gy: gray

f. Cerebrovascular disease

Study details	Risk estimate
Radiotherapy technique	
De Bruin 2009 [39] Nested case-control study of 5 y HL survivors treated in the Netherlands when aged <51 y 1965-1995 (n=2201); median f/u 17.5 y; comparator general Dutch population	**HR** (no SD RT ref) Supraclavicular and/or neck RT **2.3** (0.7-7.6) Mediastinal RT **1.2** (0.1-9.8) Mediastinal & neck RT **2.5** (1.1-5.6)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.
Abbreviations – y: years; HL: Hodgkin lymphoma; f/u: follow-up; SD: supradiaphragmatic; RT: radiotherapy; HR: hazard ratio

Table C2.3: Effect of traditional cardiovascular risk factors on the risk of cardiovascular disease following treatment for Hodgkin lymphoma

a. All cardiovascular disease

Study details	Risk estimate			
Sex				
Aleman 2003 [1] Retrospective Dutch cohort treated when aged <41 y 1965-1987 (n=1261); median f/u 17.8 y; comparator general Dutch population	Fatal CVD **RR** Male **6.0** (4.1-8.4) Female **7.3** (3.6-13.0) **AER** (/ 10,000 py) Male **24.4** Female **9.8**		Fatal MI **RR** Male **3.9** (2.1-6.7) Female **4.2** (0.9-12.4) **AER** (/ 10,000 py) Male **8.3** Female **2.4**	
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**HR** Female **0.57** (vs male) (0.46-0.71)			
Galper 2011 [15] Retrospective cohort treated with mediastinal RT in the USA 1969-1998 (n=1279); median f/u 14.7 y; comparator American general population	**HR** diagnosis **1.56** (1.16-2.11) (*P* = .003) (Male vs female)	**HR** procedure **1.84** (1.18-2.86) (*P* = .007)	**SIR** procedure Female **2.12** (1.48-3.03) Male **1.80** (1.37-2.33)	**RR** procedure Female Ref Male **0.83** (0.53-1.30) (*P* = .42)
Hancock 1993 [21] Retrospective cohort treated with mediastinal RT in the USA 1960-1991 (n=2232); average f/u 9.5 y; comparator matched general population	Fatal CVD **RR** Male **3.1** (2.4-3.9) 2.9 (1.7-4.1) exc. MI Female **2.7** (1.6-3.4) 2.8 (1.4-5.1) exc. MI		**AER** (/ 10,000 py) Male **28** (13.0 exc. MI) Female **11.9** (6.4 exc. MI)	
Lund 1996 [32] Screening of cohort of 5 y survivors treated in Norway when aged <50 y 1980-1988 (n=116); median f/u not reported	**OR** Female **6.1** (2.4-15.7)			

Khalid 2020 [72] Systematic review of studies (n=10) comparing cardiovascular mortality by sex following RT	**OR** Female **3.74*** (2.44-5.72) (*P* < .001) (vs male)	
Eloranta 2013 [73] Retrospective cohort aged 19-80 y when treated in Sweden 1973-2006 (n=5462); median f/u not given	**HR**, Excess mortality from CVD Male Ref Female **0.6** (0.38-0.93) (*P* = .02)	
Age at time of radiotherapy		
Aleman 2003 [1] Retrospective Dutch cohort treated when aged <41 y 1965-1987 (n=1261); median f/u 17.8 y; comparator general Dutch population (AER / 10,000 py)	Fatal CVD **RR** ≤ 20 y **13.6** (5.0-29.6) 21-30 y **7.3** (4.3-11.5) 31-40 y **4.9** (3.0-7.5) **AER** ≤ 20 y **9.5** 21-30 y **15.9** 31-40 y **29.6**	Fatal MI **RR** ≤ 20 y **5.1** (0.1-28.4) 21-30 y **3.7** (1.2-8.7) 31-40 y **4.1** (1.9-7.4) **AER** ≤ 20 y **1.4** 21-30 y **3.7** 31-40 y **13.3**
Rugbjerg 2019 [8] Retrospective cohort of Danish >5y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	**RR** 15-19 y **3.3** (2.6-4.2) 20-24 y **3.0** (2.5-3.5) 25-29 y **2.9** (2.5-3.4)	 30-34 y **2.6** (2.2-3.2) 35-39 y **2.2** (1.7-2.7)
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**HR**, vs < 25 y 25-34 y **0.73** (0.55-0.97)	 35-50 y **0.71** (0.53-0.97)
Galper 2011 [15] Retrospective cohort treated with mediastinal RT in the USA 1969-1998 (n=1279); median f/u 14.7 y; comparator American general population	**HR** diagnosis, vs < 20 y 20-29 y **1.48** (0.98-2.24) (*P* = .65) 30-39 y **2.63** (1.64-4.21) (*P* < .001) 40-49 y **7.70** (4.57-12.97) (*P* < .001) > 50 y **13.12** (7.87-21.89) (*P* < .001) **HR** procedure, vs < 20 y	**SIR** procedure < 20 y **7.21** (4.54-11.44) 20-29 y **2.61** (1.79-3.80) 30-39 y **2.07** (1.34-3.22) 40-49 y **1.22** (0.66-2.27) ≥ 50 y **0.87** (0.51-1.46)

	20-29 y **1.29** (3.0-4.5) (*P* = .398) 30-39 y **3.12** (3.0-4.5) (*P* = .001) 40-49 y **6.37** (3.0-4.5) (*P* < .001) > 50 y **12.51** (3.0-4.5) (*P* < .001)	**RR** procedure, vs <20 y 20-29 y **0.35** (0.19-0.64) (*P* = .001) 30-39 y **0.28** (0.15-0.53) (*P* < .001) 40-49 y **0.17** (0.08-0.36) (*P* < .001) ≥ 50 y **0.11** (0.05-0.23) (*P* < .001)
Hancock 1993 [21] Retrospective cohort treated with mediastinal RT in the USA 1960-1991 (n=2232); average f/u 9.5 y; comparator matched general population (AER / 10,000 py)	Deaths, exc. MI **RR** < 20 y **21.5** (6.8-52.0) 20-29 y **8.8** (3.8-17.4) 30-39 y **4.8** (2.1-9.4) 40-49 y **1.9** (0.5-5.1) ≥ 50 y **1.7** (0.8-3.3)	 **AER** < 20 y **7.3** 20-29 y **8.1** 30-39 y **13.4** 40-49 y **1.9** ≥ 50 y **1.7**
Boyne 2018 [28] Meta-analysis of studies (n=27) quantifying long-term risk of CV mortality among lymphoma survivors compared to the general pop.; median f/u of studies ≥10 y	**SMR** ≤ 21 y **13.4*** (9.22-19.57)	 > 21 y **3.3*** (2.54-4.35)
Swerdlow 2007 [38] Retrospective cohort treated in the UK between 1967-2000 (n=7033); average f/u 11.1 y; comparator general population of England and Wales	**SMR** < 35 y **8.5** (4.7-14.0) 35-54 y **2.4** (1.4-3.7)	 ≥ 55 y **2.1** (1.4-3.0)
Eloranta 2013 [73] Retrospective cohort aged 19-80 y when treated in Sweden 1973-2006 (n=5462); median f/u not given	Excess mortality from CVD 19-35y **0.11** (0.05-0.21) 36-50 y **0.42** (0.24-0.74)	 51-65y Ref 66-80 y **2.26** (1.28-4.00)
Smoking		
van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population	**HR**, smoking at HL diagnosis Smoker **5.9** (3.8-9.0)	 Non-smoker **4.3** (2.8-6.6)
Hypertension		
Andersson 2021 [29] Retrospective cohort of patients treated for HL when aged ≤45 y in Sweden between 1965-1995 (n=319); median f/u 22.0 y	OR **3.85** (2.17-6.75)	
Chen 2014 [31]	OR **3.02** (1.08-8.46) (*P* = .03)	

Screening of American HL survivors >5 y following mediastinal RT, with no CVD diagnosis (n=182); median f/u 14.8 y	
Hypercholesterolaemia	
Andersson 2021 [29] Retrospective cohort of patients treated for Hodgkin lymphoma when aged ≤45 y in Sweden between 1965-1995 (n=319); median f/u 22.0 y	OR **8.45** (4.61-15.48)
Diabetes	
Myrehaug 2008 [24] Retrospective cohort of patients treated in Canada 1988-200 (n=615); median f/u 11.8 y; comparator general Canadian population	**HR**, cardiac hospitalisation **2.42** (*P* = .0005)
Pre-existing cardiovascular disease	
Myrehaug 2010 [25] Randomly selected subcohort of patients treated for HL in Canada between 1988-2003 (n=1096); median f/u 10 y	Cardiac hospitalisation: **HR 3.98** (2.26-7.01) Median time to hospitalisation: 1.8 y vs. 3.5 y 10y cumulative incidence (adjusted for age at diagnosis): Male Pre-existing CVD **67%** No CVD **13.5%** Female Pre-existing CVD **43%** No CVD **9.2%**

*pooled estimate (meta-analysis)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.
Abbreviations – HL: Hodgkin lymphoma; f/u: follow-up; y: years; HR: hazard ratio; CVD: cardiovascular disease; AER: absolute excess risk; py: person-years; MI: myocardial infarction; RT: radiotherapy; SIR: standardised incidence ratio; RR: relative risk; Ref: reference; OR: odds ratio; HR: hazard ratio; exc.: excluding; CV: cardiovascular; SMR: standardised mortality ratio

b. Ischaemic heart disease

Study details	Risk estimate	
Multiple risk factors		
Glanzmann 1998 [17] Retrospective cohort of patients treated in Switzerland between 1964-1992 (n=352), 144 had regular screening for CVD; mean f/u 11.2 y	**RR** No RFs **0.96** (0.20-2.77); **0.63** (0.07-2.31) exc. SUD With RFs **2.36** (1.42-3.68); **1.87** (1.05-3.09) exc. SUD	
van Nimwegen 2015 [44] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator general Dutch pop	≥1 of diabetes, hypercholesterolaemia or hypertension: **RR 1.54** (1.13-2.10) (*P* = .006)	
Sex		
Glanzmann 1998 [17] Retrospective cohort of patients treated in Switzerland 1964-1992 (n=352), 144 had regular screening for CVD; mean f/u 11.2 y	**RR** MI: Female **1.72** (0.04-9.6) Male **5.3** (2.1-10.9)	MI or SUD: Male **8.6** (4.5-15.3)
Hancock 1993 [21] Retrospective cohort treated with mediastinal RT in the USA 1960-1991 (n=2232); average f/u 9.5 y; comparator matched general population	Fatal MI **RR** Male **3.3** (2.3-1.4) Female: **2.6** (1.2-5.0)	**AER** (/ 10,000 py) Male **27** Female **5.5**
Heidenreich 2007 [35] Screening of cohort treated with mediastinal RT ≥35 Gy in the USA between 1964-1994 (n=294); median f/u not reported	RR fatal MI Male **7.5** (5.0-10.1) Female **8.2** (5.1-11.2)	
Reinders 1999 [37] Retrospective cohort treated with RT alone in the Netherlands 1965-1980 (n=258); median f/u 14.2 y; comparator Dutch general population	Fatal IHD / SCD **SMR** Male **6.0** (2.8-10.6) Female **3.7** (0.4-13.2)	**AER** (/ 100,000py) Male **465** Female **86**
Swerdlow 2007 [38] Retrospective cohort treated in the UK between 1967-2000 (n=7033); average f/u 11.1 y; comparator general population of England and Wales	**SMR** MI Male: **2.5** (2.1-3.0) (*P* < .001) Female: **2.2** (1.4-3.1) (*P* < .001)	**AER** MI (/ 100,000py) Male: **173.6** Female: **49.7**
Hull 2003 [43]	**HR** male **2.9** (1.4-6.0)	

Retrospective cohort treated with RT in the USA 1962-1998 (n=415), ≥2 y post RT; fields included heart or carotid / subclavian arteries; median f/u 11.2 y; comparator matched general population		
Boivin 1992 [45] Retrospective cohort of patients treated for HL in Canada 1940-1975 (n=4665); average f/u 7 y	**RR**, fatal MI Male **2.11** (0.80-5.53)	Female **3.42** (0.91-12.88) *P* heterogeneity = .52
King 1996 [46] Retrospective cohort of American ≥3 y HL survivors treated 1954-1989 (n=326); median f/u 13.3 y; comparator North American general population	**RR**, fatal MI Male **3.1** (0.7-4.9) Female **1.8** (0.6-5.7)	**RR,** fatal MI, treated <21 y age Male **22.3** (0-65.9) Female **133.8** (0-396.2)
Age at time of radiotherapy		
Andersson 2009 [16] Retrospective cohort treated in Sweden 1965-1995 (n=6946); mean f/u 11.8 y; comparator Swedish general population	**SIR**, time since treatment Age <40 y at treatment 1-9 y **2.94** (1.92-4.30) 10-19 y **3.06** (2.41-3.83) ≥20 y **1.71** (1.36-2.12)	 Age >40 y at treatment 1-9 y **1.61** (1.26-2.02) 10-19 y **1.06** (0.93-1.21) ≥20 y **1.33** (1.14-1.54)
van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population (AER / 10,000 py)	**SIR** <18 y **8.8** (6.3-12.3) 18-24 y **5.4** (4.5-6.5) 25-29 **4.1** (3.3-5.1) 30-39 y **2.8** (2.4-3.3) 40-50 y **2.0** (1.6-2.4)	**AER** <18 y **53** 18-24 y **72** 25-29 y **84** 30-39 y **94** 40-50 y **100**
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	**SIR**, MI ≤20 y **5.4** (2.4-10.3) 21-25 y **5.9** (3.8-8.7) 26-30 y **4.1** (2.6-6.2) 31-35 y **2.7** (1.8-4.1) 36-40 y **2.6** (1.6-4.0) **AER**, MI ≤20 y **15.0** 21-25 y **39.7**	**SIR**, angina ≤20 y **11.6** (7.0-17.9) 21-25 y **6.2** (4.2-8.8) 26-30 y **4.8** (3.2-6.9) 31-35 y **2.6** (1.7-3.9) 36-40 y **2.9** (1.9-4.2) **AER**, angina ≤20 y **37.2** 21-25 y **48.1**

	26-30 y **40.4** 31-35 y **40.7** 36-40 y **51.8**		26-30 y **58.6** 31-35 y **43.5** 36-40 y **70.2**
Hancock 1993 [21] Retrospective cohort treated with mediastinal RT in the USA 1960-1991 (n=2232); average f/u 9.5 y; comparator matched general population (AER / 10,000 py)	Fatal MI **RR**: <20 y **44.1** (17.8-91.8) 20-29 y **7.3** (3.4-13.8) 30-39 y **5.1** (2.9-7.4) 40-49 y **3.0** (1.4-5.5) ≥ 50 y **1.8** (1.0-3.0)		**AER**: <20 y **11.3** 20-29 y **9.0** 30-39 y **27.4** 40-49 y **43.6** ≥ 50 y **-**
Reinders 1999 [37] Retrospective cohort treated with RT alone in the Netherlands 1965-1980 (n=258); median f/u 14.2 y; comparator Dutch general population	**SMR** IHD / SCD < 30 y **11.0** (1.3-40.2) ≥ 30 y **4.8** (2.3-8.8) **SIR** IHD hospitalisation: < 30 y **4.0** (1.6-8.2) ≥ 30 y **2.4** (1.4-3.8)		**AER** (/ 100,000 py) Fatal IHD / SCD: < 30 y **86** ≥ 30 y **591** IHD hospitalisation: < 30 y **249** ≥ 30 y **834**
Swerdlow 2007 [38] Retrospective cohort treated in the UK between 1967-2000 (n=7033); average f/u 11.1 y; comparator general population of England and Wales	Fatal MI **SMR**: < 25 y **18.7** (10.9-20.9) 25-34 y **5.9** (3.7-9.0) 35-44 y **2.6** (1.6-4.0) 45-54 y **2.6** (1.9-3.5) 55-64 y **1.8** (1.3-2.4) ≥ 65 y **1.4** (0.8-2.2)	**AER** (/ 100,000 py): < 25 y **56.5** 25-34 y **76.5** 35-44 y **103.5** 45-54 y **365.7** 55-64 y **411.5** ≥ 65 y **346.9**	**20 y cumulative incidence** < 35 y: **1.8%** 35-54 y: **7.4%** ≥ 55 y: **23.6%**
Hull 2003 [43] Retrospective cohort treated with RT in the USA 1962-1998 (n=415), ≥2 y post RT; fields included heart or carotid / subclavian arteries; median f/u 11.2 y; comparator matched general population	**HR**, older than median age at RT **8.1** (3.2-20.3)		
van Nimwegen 2015 [44]	**ERR / Gy MHD** < 27.5 y **20.0% / Gy** (5.4-70.4)		

Retrospective cohort of >5 y survivors of HL treated with RT when aged <51 y in the Netherlands between 1965-1995 (n=2524); median f/u 20 y; comparator general Dutch population	27.5-36.4 y **8.8% / Gy** (2.6-22.9) 36.5-50.9 y **4.2% / Gy** (0.6-11.1)
Boivin 1992 [45] Retrospective cohort of patients treated in the USA and Canada between 1942-1985 (n=4665); case-cohort to investigate IHD; median f/u 7y	**RR**, fatal IHD 0-39 y **1.84** 40-59 y **1.23** ≥60 y **2.16** (95% CIs not given)
King 1996 [46] Retrospective cohort of American ≥3 y HL survivors treated 1954-1989 (n=326); median f/u 13.3 y; comparator North American general population	**RR,** fatal MI: <21 y **38.2** (0-91.1)
Hypertension	
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	**HR** MI **0.52** (0.29-0.94) Angina **0.90** (0.58-1.42)
Chen 2014 [31] Screening of American HL survivors >5 y following mediastinal RT, with no CVD diagnosis (n=182); median f/u 14.8 y	**OR 3.02** (1.08-8.46) (*P* = .03) for screen-detected IHD
Hull 2003 [43] Retrospective cohort treated with RT in the USA 1962-1998 (n=415), ≥2 y post RT; fields included heart or carotid / subclavian arteries; median f/u 11.2 y; comparator matched general population	**HR 3.0** (1.6-5.8)
van Nimwegen 2015 [44] Retrospective cohort of >5 y survivors of HL treated with RT when aged <51 y in the Netherlands between 1965-1995 (n=2524); median f/u 20 y; comparator general Dutch population	**RR 1.86** (1.29-2.68) (*P* = .001)
Smoking	
van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population	**HR**, smoking at HL diagnosis Smoker **4.8** (2.8-2.2) Non-smoker **2.9** (1.7-5.0)
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	**HR**: MI **2.04** (1.29-3.23) Angina **1.35** (0.85-2.16)
van Nimwegen 2015 [44]	**RR 1.56** (1.13-2.15) (*P = .007)*

Retrospective cohort of >5 y survivors of HL treated with RT when aged <51 y in the Netherlands between 1965-1995 (n=2524); median f/u 20 y; comparator general Dutch population	
Hypercholesterolaemia	
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	**HR** MI **4.12** (2.68-6.33) Angina **4.55** (3.10-6.68)
Hull 2003 [43] Retrospective cohort treated with RT in the USA 1962-1998 (n=415), ≥2 y post RT; fields included heart or carotid / subclavian arteries; median f/u 11.2 y; comparator matched general population	**HR 3.0** (1.2-7.4)
van Nimwegen 2015 [44] Retrospective cohort of >5 y survivors of HL treated with RT when aged <51 y in the Netherlands between 1965-1995 (n=2524); median f/u 20 y; comparator general Dutch population	**RR 2.08** (1.60-2.72) (*P* < .001)
Diabetes mellitus	
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	**HR** MI **1.44** (0.73-2.83) Angina **2.43** (1.45-4.09)
van Nimwegen 2015 [44] Retrospective cohort of >5 y survivors of HL treated with RT when aged <51 y in the Netherlands between 1965-1995 (n=2524); median f/u 20 y; comparator general Dutch population	**HR 1.11** (0.55-2.26) (*P* = .764)
Family history	
Andersson 2009 [16] Retrospective cohort treated in Sweden 1965-1995 (n=6946); mean f/u 11.8 y; comparator Swedish general population	**SIR** Family history of CVD **5.53** (3.89-7.62) No family history **2.15** (1.53-2.94) **SIR**, time since treatment Family history of CVD 1-9 y **1.22** (0.73-1.90) No family history of CVD 1-9 y **1.13** (0.99-1.28)

	10-19 y **3.13** (2.39-4.02) ≥20 y **2.15** (1.52-2.97)	10-19 y **1.38** (1.20-1.59) ≥20 y **1.02** (0.81-1.26)
van Nimwegen 2015 [44] Retrospective cohort of >5 y survivors of HL treated with RT when aged <51 y in the Netherlands between 1965-1995 (n=2524); median f/u 20 y; comparator general Dutch population	**RR** Family history of CVD **2.87** (1.41-5.88) (*P* = .004)	
Obesity (BMI ≥30)		
van Nimwegen 2015 [44] Retrospective cohort of >5 y survivors of HL treated with RT when aged <51 y in the Netherlands between 1965-1995 (n=2524); median f/u 20 y; comparator general Dutch population	**RR 1.64** (1.24-2.16) (*P* < .001)	
Exercise		
van Nimwegen 2015 [44] Retrospective cohort of >5 y survivors of HL treated with RT when aged <51 y in the Netherlands between 1965-1995 (n=2524); median f/u 20 y; comparator general Dutch population	≥4 h / wk **RR 0.52** (0.32-0.83) (*P* = .136)	

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – n: number; f/u: follow-up; y: years; RR: relative risk; RFs: risk factors; exc.: excluding; SUD: sudden unexpected death; HL: Hodgkin lymphoma; RT: radiotherapy; MI: myocardial infarction; AER: absolute excess risk; py: person-years; ERR: excess relative risk; Gy; gray; MHD: mean heart dose; IHD: ischaemic heart disease; CI: confidence interval; SCD: sudden cardiac death; SMR: standardised mortality ratio; HR: hazard ratio; OR: odds ratio; SIR: standardised incidence ratio; cumul. inc.: cumulative incidence; CVD: cardiovascular disease

c. Heart failure

Study details	Risk estimate	
Age at time of radiotherapy		
Andersson 2009 [16] Retrospective cohort treated in Sweden 1965-1995 (n=6946); mean f/u 11.8 y; comparator Swedish general population	**SIR**, ≤40 y **10.1** (8.03-12.64) **SIR**, time since treatment Age <40 y at treatment 1-9 y **2.64** (0.53-7.72) 10-19 y **3.45** (1.65-6.34) ≥20 y **10.1** (8.03-12.64)	 Age >40 y at treatment 1-9 y **0.40** (0.25-0.62) 10-19 y **1.39** (1.07-1.77) ≥20 y **1.32** (0.96-1.77)
van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population (AER / 10,000 py)	**SIR** <18 y **38.9** (25.2-57.4) 18-24 y **18.7** (14.5-23.6) 25-29 **10.4** (7.5-14.2) 30-39 y **5.7** (4.4-7.2) 40-50 y **2.7** (2.0-3.7)	**AER** <18 y **48** 18-24 y **59** 25-29 y **56** 30-39 y **61** 40-50 y **67**
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	**SIR** ≤20 y **18.2** (9.0-32.6) 21-25 y **7.0** (3.5-12.5) 26-30 y **6.7** (3.6-11.5) 31-35 y **2.5** (1.1-4.9) 36-40 y **2.7** (1.2-5.1)	**AER** ≤20 y **27.6** 21-25 y **23.1** 26-30 y **34.7** 31-35 y **16.0** 36-40 y **26.4**
Smoking		
van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population	**HR**, smoking at HL diagnosis Smoker **5.4** (2.0-14.9)	 Non-smoker **3.7** (1.4-10.2)
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	**HR 1.96** (1.16-3.30)	
Hypercholesterolaemia		

Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	**HR 1.48** (0.85-2.58)
Diabetes mellitus	
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	**HR 4.45** (2.54-7.81)
Family history	
Andersson 2009 [16] Retrospective cohort treated in Sweden 1965-1995 (n=6946); mean f/u 11.8 y; comparator Swedish general population	**SIR**, family history of congestive HF **25.0** **SIR**, time since treatment Family history of CVD / No family history of CVD 1-9 y **0.92** (0.01-5.10) / 1-9 y **0.44** (0.28-0.66) 10-19 y **7.69** (2.81-16.74) / 10-19 y **1.41** (1.10-1.78) ≥20 y **21.67** (1.53-37.05) / ≥20 y **2.71** (2.23-3.26)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.
Abbreviations – f/u: follow-up; y: years; SIR: standardised incidence ratio; HL: Hodgkin lymphoma; RT: radiotherapy; AER: absolute excess risk; py: person-years; HR: hazard ratio; HF: heart failure; CVD: cardiovascular disease

d. Valvular heart disease

Study details	Risk estimate
Sex	
Lund 1996 [59] Retrospective cohort of Norwegian 5 y survivors treated at <50 y 1980-1988 (n=116); median f/u not given; comparator healthy individuals (n=40)	**OR**, AR & MR Females **4.7** (2.0-11.2)
Heidenreich 2003 [64] Screening of cohort treated with mediastinal RT ≥35 Gy in the USA between 1964-1994 (n=294); median f/u not reported	**OR**, AR Females **2.1** (1.5-3.0)
Hypertension	

Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	**HR 1.28** (0.86-1.92)	
Chen 2014 [31] Screening of American HL survivors >5 y following mediastinal RT, with no CVD diagnosis (n=182); median f/u 14.8 y	**OR 3.02** (1.08-8.46) (*P* = .03) (screen-detected VHD)	
Bijl 2016 [62] Cross-sectional screening study of Dutch patients treated with RT 1969-2005 (n=82); median f/u 13.4y; comparator survivors not treated with RT	**OR** AR **10.00** (2.24-44.57) (*P* = .003) TR **1.11** (1.47-30.00) (*P* = .014)	 PR **11.00** (1.02-118.87) (*P* = .048) AS **14.57** (2.42-87.73) (*P* = .003)
Smoking		
van Nimwegen 2015 [18] Retrospective cohort of Dutch >5 y HL survivors treated with RT when aged <51 y 1965-1995 (n=2524); median f/u 20 y; comparator Dutch population	**HR**, smoking at HL diagnosis Smoker **6.4** (3.2-12.5)	 Non-smoker **6.7** (3.4-13.1)
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	**HR 1.23** (0.80-1.88)	
Hypercholesterolaemia		
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	**HR 1.65** (1.11-2.44)	
Andersson 2021 [29] Retrospective cohort of patients treated for HL when aged ≤45 y in Sweden between 1965-1995 (n=319); median f/u 22.0 y	**OR 3.40** (1.70-6.78)	
Cutter 2015 [61] Nested case-control study of Dutch 5 y survivors treated when aged 15-41 y 1965-1995 (89 cases, 200 matched controls); median f/u 18.8 y	**RR 5.0** (2.6-9.5) (*P* < .001) (at end of follow-up)	
Diabetes mellitus		
Aleman 2007 [19] Nested case-control study in Dutch cohort treated with RT when aged <41 y 1965-1995 (n=1474); median f/u 18.7 y; comparator Dutch population	**HR 1.81** (1.07-3.04)	
Obesity (BMI ≥30)		

Cutter 2015 [61] Nested case-control study of Dutch 5 y survivors treated when aged 15-41 y 1965-1995 (89 cases, 200 matched controls); median f/u 18.8 y	**RR 2.0** (1.0-4.0) (*P* = .05) (at end of follow-up)	
Multiple risk factors		
Cutter 2015 [61] Nested case-control study of Dutch 5 y survivors treated when aged 15-41 y 1965-1995 (89 cases, 200 matched controls); median f/u 18.8 y	**RR**, number of factors 0 **1.0** (0.5-1.9) 1 **1.0** (0.7-1.6) 2 **1.5** (0.9-2.4)	 3 **3.1** (1.5-6.3) 4 **3.7** (1.2-11.5) (P_{trend} = .002)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – y: years; f/u: follow-up; n: number; OR: odds ratio; AR: aortic regurgitation; MR: mitral regurgitation; RT: radiotherapy; Gy: gray; HR: hazard ratio; HL: Hodgkin lymphoma; OR: odds ratio; TR: tricuspid regurgitation; PR: pulmonary regurgitation; RR: relative risk; BMI: body mass index

e. Cerebrovascular disease

Study details	Risk estimate	
Age at time of radiotherapy		
Andersson 2009 [16] Retrospective cohort treated in Sweden 1965-1995 (n=6946); mean f/u 11.8 y; comparator Swedish general population; family history was one or more first degree relatives with CVD	**SIR**, time since treatment Age <40y at treatment 1-9 y **1.23** (0.33-3.14) 10-19 y **1.29** (0.62-2.38) ≥20 y **1.93** (1.32-2.73)	 Age >40 y at treatment 1-9 y **1.07** (0.87-1.30) 10-19 y **1.37** (1.11-1.66) ≥20 y **1.16** (0.88-1.49)
De Bruin 2009 [39] Nested case-control study of 5-year HL survivors treated in the Netherlands when aged <51 y 1965-1995 (n=2201); median f/u 17.5 y; comparator general Dutch population	Stroke **SIR** < 20 y **3.8** (1.6-7.4) 21-30 y **3.1** (1.9-4.6) 31-40 y **2.0** (1.2-3.1) 41-50 y **1.4** (0.7-2.3) **AER** (/ 10,000 py)	TIA **SIR** < 20 y **7.6** (2.4-17) 21-30 y **4.2** (2.1-7.5) 31-40 y **3.1** (1.7-5.2) 41-50 y **2.1** (1.0-3.7) **AER** (/ 10,000 py)

	< 20 y **7** 21-30 y **14** 31-40 y **15** 41-50 y **11**	< 20 y **5** 21-30 y **7** 31-40 y **13** 41-50 y **18**
Hypertension		
De Bruin 2009 [39] Nested case-control study of 5-year HL survivors treated in the Netherlands when aged <51 y 1965-1995 (n=2201); median f/u 17.5 y; comparator general Dutch population	**HR 2.1** (1.3-3.3)	
Hull 2003 [43] Retrospective cohort treated with RT in the USA 1962-1998 (n=415), ≥2 y post RT; fields included heart or carotid / subclavian arteries; median f/u 11.2 y; comparator matched general population	Carotid or subclavian stenosis: **HR 4.0** (1.9-8.3)	
Hypercholesterolaemia		
De Bruin 2009 [39] Nested case-control study of 5-year HL survivors treated in the Netherlands when aged <51 y 1965-1995 (n=2201); median f/u 17.5 y; comparator general Dutch population	**HR 1.6** (1.0-2.6)	
Diabetes mellitus		
Hull 2003 [43] Retrospective cohort treated with RT in the USA 1962-1998 (n=415), ≥2 y post RT; fields included heart or carotid / subclavian arteries; median f/u 11.2 y; comparator matched general population	Carotid or subclavian stenosis: **HR 5.5** (2.0-15.0)	
Family history		
Andersson 2009 [16] Retrospective cohort treated in Sweden 1965-1995 (n=6946); mean f/u 11.8 y; comparator Swedish general population; family history was one or more first degree relatives with CVD	**SIR**, time since treatment Family history of CVD 1-9 y **3.55** (2.03-5.76) 10-19 y **1.57** (0.63-3.23) ≥20 y **0.96** (0.26-2.46)	 No family history of CVD 1-9 y **0.95** (0.76-1.18) 10-19 y **1.35** (1.09-1.66) ≥20 y **1.18** (0.89-1.53)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – f/u: follow-up; y: years; SIR: standardised incidence ratio; HL: Hodgkin lymphoma; py: person-years; HR: hazard ratio

Appendix C3: Risk of second malignancies following radiotherapy for Hodgkin lymphoma

Table C3.1: Estimates of risk of second malignancies following treatment with radiotherapy for Hodgkin lymphoma

a. All second malignancies

Study details	Risk estimate
Cumulative incidence	
Brusamolino 2006 [5] Retrospective cohort of patients with stage 1A-2A HL treated in Italy with 4 cycles ABVD & limited RT 1990-2003 (n=120); median f/u 10 y	5 y: **4%** 12 y: **8%**
Brierley 1998 [10] Retrospective cohort with stage 1-2 HL treated in Canada 1973-184 (n=611); median f/u 11 y; comparator age-matched general population for same period	15 y **9.7%** (excluding NMSC) **13.0** (including NMSC)
van Spronsen 1998 [11] Retrospective cohort of 5 y survivors treated in the Netherlands 1972-1993 (n=345); median f/u not given; comparator general population	10 y All **8%** Death from 2nd malignancy **5%**
Ng 2002 [13] Retrospective cohort of patients with stage 1A-2B HL treated in the USA when aged ≤50 y 1969-1997 (n=1080)	Death from 2nd malignancy 15 y **5.1%** 20 y **9.8%**
Vlachaki 1997 [36] Retrospective cohort of patients with stage 1 HL, treated with RT +/- chemotherapy in the USA between 1967-1987 (n=145); median f/u 16.5 y	10 y **7.4%** 20 y **16.3%**
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	All cancers excluding NMSC 5 y **2.0%** 15 y **7.3%**
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y	20 y **14.7%** (12.9-16.6)
Swerdlow 1992 [85]	15 y **11.5%**

Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given			
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	15 y **14%** 20 y **23%**		
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	Excluding MDS 30 y **32.5%** 40 y **48.5%**		
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y	25 y **27.7%** (23.1-32.8)		
Chronowski 2003 [90] Retrospective cohort of patients with stage 1-2 HL treated with RT in the USA between 1980-1996 (n=286); median follow-up 7.4 y	5 y **1.9%** 10 y **9.3%** 15 y **16.8%**		
Swerdlow 1997 [91] Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1 y	Excluding NMSC 5 y **2.7%** (1.8-4.1) 10 y **6.9%** (5.2-9.2)		15 y **10.3%** (7.9-13.3) 20 y **14.0%** (10.6-18.4)
Van Leeuwen 1989 [92] Retrospective cohort treated for HL in the Netherlands 1966-1986 (n=744); median f/u 6.4 y	5 y **2.6%** (+/- 0.6) 10 y **11.2%** (+/- 1.7)		15 y **20.6%** (+/- 2.9)
Munker 1999 [93] Retrospective cohort treated in Germany 1974-1994 (n=1120); mean f/u 9.1 y	5 y **3.1%**	10 y **7.1%**	15 y **11.7%**
Valagussa 1980 [94] Retrospective cohort treated in Italy 1965-1976 (n=764); median f/u 47 m	3 y **1.1%**	5 y **2.6%**	10 y **14.9%**
Rubin 1986 [95] Retrospective cohort treated in the USA 1957-1982 (n=320); median f/u ~6y	5 y **1.0%**	10 y **1.5%**	
Henry-Amar 1983 [96] Retrospective cohort treated in EORTC trials 1964-1972 (n=334); median f/u 10 y	5 y **0.3%** (+/- 0.3) 10 y **4.3%** (+/- 1.3)		15 y **13.2%** (+/- 3.8)
Sont 1992 [97] Retrospective cohort treated in the Netherlands 1969-1988 (n=482); average f/u 6.05 y	5 y **3.5%**	10 y **10.0%**	15 y **15.9%**

Economoupoulos 1994 [98] Retrospective cohort treated in Greece 1977-1991 (n=217); median f/u 67 m	5 y **3.3%**	10 y **5.4%**		
Glanzmann 1994 [100] Retrospective cohort treated in Germany 1964-1992 (n=340); follow-up ≥1.5 y	10 y **7.0%**	15 y **13.6%**	20 y **30.7%**	24 y **40.5%**
Cimino 1991 [101] Retrospective cohort treated for HL in Italy 1969-1979 (n=947); median f/u 10.5 y	10 y **5.0%** (+/- 0.9)		19 y **23.1%** (+/- 5.8)	
Henry-Amar 1992 [102] Retrospective international cohort of 1 y HL survivors treated 1960-1987 (n=12,411); median f/u not given	10 y **6.4%**	15 y **11.2%**	20 y **18.6%**	
Salloum 1996 [103] Retrospective cohort treated in the USA 1968-1994 (n=313); median f/u 12.8 y	10 y **1.8%**	15 y **9.8%**	20 y **15.3%**	
Zulian 1989 [104] Retrospective cohort treated in Swizerland 1975-1985 (n=72); average f/u 5.3 y	10 y **18.0%**			
Cellai 2001 [106] Retrospective cohort treated in Italy 1960-1991 (n=1524); average f/u 10.7 y	15 y **9.6%** 20 y **15.5%**			
Biti 1994 [107] Retrospective cohort treated in Italy 1960-1988 (n=1121); mean f/u >9 y	15 y **7.8%**			
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	5 y: **8.6%**			
Abou-Antoun 2016 [109] Retrospective cohort treated in Lebanon 1990-2011 (n=112); median f/u 13 y	13 y **9.8%**			
Doria 1995 [110] Retrospective cohort treated in USA 1969-1982 (n=102); median f/u 153-212 m	20 y **12%**			
Nyandoto 1998 [111] Retrospective cohort of >5 y HL survivors treated in Finland 1970-1979 (n=202); median f/u of survivors 22 y	20 y **17%** 25 y **24%**			
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	20 y **18.4%**			
Foss Abrahamsen 2002 [113]	28 y **18.8%**			

Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y				
Bonadonna 2005 [114] Retrospective cohort treated for intermediate or advanced-stage HL in Italy 1973-1990 (n=811); median f/u 16.7-29 y (substudies)	25 y **22.2%** (incidence), **11.6%** (death)			
van Eggermond 2014 [115] Retrospective cohort of 5y survivors treated in the Netherlands when aged <51 y 1965-1995 (n=3122); median f/u 22.6 y	30 y 2nd malignancy **30.7%** 3rd malignancy **4.6%** 10 y cumulative incidence from diagnosis of 2nd malignancy 3rd malignancy **13.3%**		10 y cumulative incidence from diagnosis of breast cancer Another breast cancer **13.8%** Solid non-breast cancer **5.9%** 5 y cumulative incidence of any 3rd malignancy after Lung cancer **3.6%** GI tract **7.5%** NHL **8.0%** Urogenital tract **13.4%**	
Eichenauer 2017 [116] Individual patient data meta-analysis of 9498 patients treated within 16 RCTs 1984-2007; median f/u 7.4 y	5 y **2.4%**	10 y **5.8%**	15 y **13%**	20 y **23%**
Standardised incidence ratio				
Brusamolino 2006 [5] Retrospective cohort of patients with stage 1A-2A HL treated in Italy with 4 cycles ABVD & limited RT 1990-2003 (n=120); median f/u 10 y	**2.6** (*P* = .014)			
Lee 2000 [27] Retrospective cohort of patients with stage 1-3 HL treated in the USA 1970-1986 (n=210); median f/u 15.6y; comparator general pop	**6.0** (95% CI not given)			
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	**2.9** (2.5-3.4) (excluding NMSC)			
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y	**2.3** (1.9-2.8) (excluding NMSC)			
Schaapveld 2015 [88]	**5.1** (4.7-5.4)			

Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1y; comparator Dutch general pop	
Swerdlow 1997 [91] Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1 y	**2.6** (1.6-3.8) (*P* < .001) (excluding NMSC)
Cellai 2001 [106] Retrospective cohort treated in Italy 1960-1991 (n=1524); average f/u 10.7 y	**2.02** (1.5-2.7)
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	**3.9** (3.5-4.4) (excluding NMSC)
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y	**3.5** (3.1-4.1)
van Eggermond 2014 [115] Retrospective cohort of 5y survivors treated in the Netherlands when aged <51 y 1965-1995 (n=3122); median f/u 22.6 y	**4.7** (4.4-5.1) 3rd malignancy after 2nd **5.4** (4.4-6.5)
Kumar 2018 [117] Retrospective cohort treat in the USA 1973-2014 (n=23,864); comparator USA general population; median f/u not given	**1.97** (1.9-2.04)
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6y; comparator general Swedish population	**2.39** (2.29-2.53)
Omer 2012 [119] Retrospective cohort treated in the USA 1970-2004 (n=198); median f/u 21.1; comparator general population	**1.57** (0.97-2.41)
Standardised mortality ratio	
Brusamolino 2006 [5] Retrospective cohort of patients with stage 1A-2A HL treated in Italy with 4 cycles ABVD & limited RT 1990-2003 (n=120); median f/u 10 y	**5.1** (*P* < .001)
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**5.9** (5.5-6.4)
Lee 2000 [27]	**10.3** (6.9-14.1)

Retrospective cohort of patients with stage 1-3 HL treated in the USA 1970-1986 (n=210); median f/u 15.6 y; comparator general pop	
Absolute excess risk	
Rugbjerg 2019 [8] Retrospective cohort of Danish >5 y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	Hospitalisation **108** / 10,000 py (89-127)
Brierley 1998 [10] Retrospective cohort with stage I-II HL treated in Canada 1973-184 (n=611); median f/u 11y; comparator age-matched general population for same period	**34** / 10,000 py
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**AEM 61.5** / 10,000 py
Ng 2002 [13] Retrospective cohort of patients with stage 1A-2B HL treated in the USA when aged ≤50 y 1969-1997 (n=1080)	Death from 2nd malignancy **41.2** / 10,000 py
Mauch 1995 [22] Retrospective cohort with stage 1A-3B HL treated in the USA 1969-1988 (n=794); median f/u of survivors 11 y	Death from second malignancy: **26.4** / 10,000 py
Rugbjerg 2017 [23] Retrospective Danish cohort treated when aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	Hospitalisation **39** (20-57) / 10,000py
Lee 2000 [27] Retrospective cohort of patients with stage 1-3 HL treated in the USA 1970-1986 (n=210); median f/u 15.6 y; comparator general pop.	**8.9** / 1000 py Death **4.18** / 1000 py
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	**80.8** / 10,000 py
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py)	**44.5** / 10,000 py (excluding NMSC)
Swerdlow 1992 [85]	**41.4** / 10,000 py

Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	**79.6** / 10,000 py
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	**121.8** (111.8-132.4) / 10,000 py **134.0** (95% CI not given) / 10,000 py (females)
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y	**72.3** / 10,000 py
van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	**62.5** / 10,000 py
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	**79** / 10,000 py
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	**65.3** / 10,000 py
van Eggermond 2014 [115] Retrospective cohort of 5 y survivors treated in the Netherlands when aged <51 y 1965-1995 (n=3122); median f/u 22.6 y	2nd malignancy **121.2** / 10,000 py 3rd malignancy **309.3** / 10,000 py
Kumar 2018 [117] Retrospective cohort treat in the USA 1973-2014 (n=23,864); comparator USA general population; median f/u not given	**56.56** / 10,000 py
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population	**71.2** / 10,000 py
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	**36.2** / 10,000 py

Prior 1988 [121] Retrospective cohort treated in the UK 1950-1979 (n=2999); median f/u 6.7 y; comparator general population	**1.5** / 1000 py
Chronowski 2004 [124] Retrospective cohort treated for stage 1-2 HL in the USA 1980-1995 (n=286); median f/u of survivors 7.4 y	**58.4** / 10,000 py
Hancock 1996 [125] Retrospective cohort treated in the USA 1960-1990 (n=2162); mean f/u 9.3y	**71** / 10,000 py
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given	**47.2** / 10,000 py
Relative risk	
Rugbjerg 2019 [8] Retrospective cohort of Danish >5 y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	Hospitalisation **3.59** (2.31-5.58)
Brierley 1998 [10] Retrospective cohort with stage 1-2 HL treated in Canada 1973-184 (n=611); median f/u 11y; comparator age-matched general population for same period	**2.2** (1.6-3.1) (*P* < .0001)
Ng 2002 [13] Retrospective cohort of patients with stage 1A-2B HL treated in the USA when aged ≤50 y 1969-1997 (n=1080)	Death from second malignancy **11.2** (8.6-14.4)
Mauch 1995 [22] Retrospective cohort with stage 1A-3B HL treated in the USA 1969-1988 (n=794); median f/u of survivors 11 y	Death from second malignancy: **5.1** (3.0-8.1)
Rugbjerg 2017 [23] Retrospective Danish cohort treated when aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	Hospitalisation **2.5** (2.0-3.1)
Hancock 1988 [47] Combined analysis of patients with stage 1-3 HL treated with RT +/- MOPP RCTs in the USA between 1967-1980 (n=326); median f/u >14 y	**2.35** (1.46-3.24)
Cosset 1991 [56]	**3.84** (2.81-5.12)

Pooled analysis of 4 EORTC trials H1, H2, H5, H6), run 1964-1988; 1660 patients; median f/u not reported	
Swerdlow 1992 [85] Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	**2.7** (2.3-3.3) (*P* < .001)
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	**4.0** (*P* = .015)
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y	**7.0** (5.9-8.3)
van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	**3.5** (2.9-4.1)
Almagro-Casado 2016 [79] Retrospective cohort treated in Spain 1968-2012 (n=604); median f/u not given	**2.8** (1.5-5.1) (*P* = .001)
Munker 1999 [93] Retrospective cohort treated in Germany 1974-1994 (n=1120); mean f/u 9.1y	**3.3** (2.6-4.2)
Rubin 1986 [95] Retrospective cohort treated in the USA 1957-1982 (n=320); median f/u ~6y	**4.76** (2.72-6.80) (*P* < .05)
Henry-Amar 1983 [96] Retrospective cohort treated in EORTC trials 1964-1972 (n=334); median f/u 10 y	**4.55** (*P* < .001)
Sont 1992 [97] Retrospective cohort treated in the Netherlands 1969-1988 (n=482); average f/u 6.05 y	**2.3** (95% CI not given)
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	**4.68** (3.51-6.12) (*P* < .001)
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	**4.1** (0.8-11.9)

Prior 1988 [121] Retrospective cohort treated in the UK 1950-1979 (n=2999); median f/u 6.7 y; comparator general population	**1.5** (95% CI not given)
Arseneau 1972 [122] Retrospective cohort treated in the USA 1953-1971 (n=425); median f/u not given	**3.4** (95% CI not given)
Nelson 1981 [123] Retrospective cohort treated in the USA 1960-1977 (n=248); median f/u 5.8 y	**4.3** (2.90-7.99)
Chronowski 2004 [124] Retrospective cohort treated for stage 1-2 HL in the USA 1980-1995 (n=286); median f/u of survivors 7.4 y	**2.6** (1.6-4.0)
Hancock 1996 [125] Retrospective cohort treated in the USA 1960-1990 (n=2162); mean f/u 9.3 y	**5.2** (4.1-6.3)
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given	**2.3**
Hazard ratio	
Kiserud 2010 [14] Retrospective cohort treated in Norway when aged 15-61 y 1971-1991 (n=557); median f/u 13.0 y; comparator age- and sex-matched general population	Death from 2nd malignancy **6.6** (4.7-9.2)
Lagerlöf 2022 [26] Retrospective cohort of patients treated for HL with 2/4 cycles ABVD and 30 Gy limited-field RT in Sweden 1999-2003; median f/u 16 y	**1.5** (1.0-2.4)
van Eggermond 2014 [115] Retrospective cohort of 5 y survivors treated in the Netherlands when aged <51 y 1965-1995 (n=3122); median f/u 22.6 y (HR for TNI vs no radiotherapy)	2nd malignancy **2.6** (1.9-3.7) 3rd malignancy **5.2** (1.6-16.8)
Odds ratio	
Franklin 2006 [89] Individual patient data meta-analysis from RCTs comparing RT vs CMT, chemo vs CMT, RT vs chemo or IFRT vs EFRT	**0.78*** (0.62-0.98) (*P* = .03) (RT vs CMT) **2.12*** (*P* = .13) (RT vs chemotherapy alone)
Median time to development	
Brusamolino 2006 [5]	**45 m**

Retrospective cohort of patients with stage 1A-2A HL treated in Italy with 4 cycles ABVD & limited RT 1990-2003 (n=120); median f/u 10 y	
Lee 2000 [27] Retrospective cohort of patients with stage 1-3 HL treated in the USA 1970-1986 (n=210); median f/u 15.6 y; comparator general pop	**13 y**
Vlachaki 1997 [36] Retrospective cohort of patients with stage 1 HL, treated with RT +/- chemotherapy in the USA between 1967-1987 (n=145); median f/u 16.5 y	**6.1 y**
Kilickap 2012 [74] Prospective cohort treated in Turkey 1990-2006 when aged >16 y (n=336); median f/u 8.5 y	**8.7 y**
Almagro-Casado 2016 [79] Retrospective cohort treated in Spain 1968-2012 (n=604); median f/u not given	**11.8 y** (excluding lung cancer)
Rubin 1986 [95] Retrospective cohort treated in the USA 1957-1982 (n=320); median f/u ~6 y	**7.0 y** (mean)
Henry-Amar 1983 [96] Retrospective cohort treated in EORTC trials 1964-1972 (n=334); median f/u 10 y	**10 y**
Zulian 1989 [104] Retrospective cohort reated in Swizerland 1975-1985 (n=72); average f/u 5.3 y	**57 m**
Biti 1994 [107] Retrospective cohort treated in Italy 1960-1988 (n=1121); mean f/u >9 y	**12 y**
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	**7.75 y**
Abou-Antoun 2016 [109] Retrospective cohort treated in Lebanon 1990-2011 (n=112); median f/u 13 y	**24 y**
Nyandoto 1998 [111] Retrospective cohort of >5 y HL survivors treated in Finland 1970-1979 (n=202); median f/u of survivors 22 y	**14 y**
Bonadonna 2005 [114]	**9.7 y** (death from second malignancy)

Retrospective cohort treated for intermediate or advanced-stage HL in Italy 1973-1990 (n=811); median f/u 16.7-29 y (substudies)		
van Eggermond 2014 [115] Retrospective cohort of 5 y survivors treated in the Netherlands when aged <51 y 1965-1995 (n=3122); median f/u 22.6 y	**19.4 y** Median interval between 2nd and 3rd malignancy **4.3 y**	
Nelson 1981 [123] Retrospective cohort treated in the USA 1960-1977 (n=248); median f/u 5.8 y	**10 y**	
Shbib Dabaja 2022 [137] Retrospective cohort treated in the USA 1956-2009 (n=1653); median f/u 22 y	**12.8 y**	
Median age at development		
Kilickap 2012 [74] Prospective cohort treated in Turkey 1990-2006 when aged >16 y (n=336); median f/u 8.5 y	**42 y**	
Almagro-Casado 2016 [79] Retrospective cohort treated in Spain 1968-2012 (n=604); median f/u not given	**45.5 y** (excluding lung cancer)	
Abou-Antoun 2016 [109] Retrospective cohort treated in Lebanon 1990-2011 (n=112); median f/u 13 y	**45 y**	
van Eggermond 2014 [115] Retrospective cohort of 5 y survivors treated in the Netherlands when aged <51 y 1965-1995 (n=3122); median f/u 22.6 y	2nd malignancy **50.5 y** 3rd malignancy **53.9 y**	
Variation in risk with time since treatment		
Ng 2002 [13] Retrospective cohort of patients with stage 1A-2B HL treated in the USA when aged ≤50 y 1969-1997 (n=1080)	Death from 2nd malignancy RR 0.5 y **10.9** (5.2-20.0) 5-10 y **14.5** (8.2-23.1) 10-15 y **10.0** (4.9-16.6) 15-20 y **12.7** (7.0-21.5) 20+ y **7.8** (3.2-16.2)	 AER (/ 10,000 py) 0.5 y **18.7** 5-10 y **41.6** 10-15 y **43.7** 15-20 y **92.9** 20+ y **80.6**
Lagerlöf 2022 [26] Retrospective cohort of patients treated for HL with 2/4 cycles ABVD and 30 Gy limited-field RT in Sweden 1999-2003; median f/u 16 y	**HR** 0-5 y **1.8** (0.83-3.95) (*P* = .138) 5-10 y **0.9** (0.38-2.18) (*P* = .826)	 >10 y **2.0** (0.99-3.85) (*P* = .054)

Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	**SIR** 5-9 y **4.5** (3.8-5.3) 10-14 y **4.3** (3.7-5.0) 15-19 y **5.1** (4.4-5.8) 20-24 y **4.5** (3.8-5.3) 25-29 y **4.9** (4.1-5.9) 30-34 y **4.9** (3.8-6.1) ≥ 35 y **3.9** (2.8-5.4) (P_{trend} = .82) **SIR** 35y+ after treatment **3.9**	**AER** 5-9 y **55.6** 10-14 y **83.5** 15-19 y **150** 20-24 y **182** 25-29 y **274** 30-34 y **362** ≥ 35 y **364**
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	**SIR** <5 y **1.8** (1.0-2.9) 5-15 y **2.7** (2.0-3.5)	15-25 y **3.0** (2.2-4.0) >25 y **4.2** (3.1-5.7)
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py)	**SIR**, excluding NMSC 0-4 y **2.0** (1.6-2.4) 5-9 y **3.3** (2.7-4.0) 10-14 y **3.3** (2.6-4.1) ≥15 y **3.7** (2.8-4.8)	**AER**, excluding NMSC 0-4 y **20.3** 5-9 y **55.3** 10-14 y **64.0** ≥15 y **102.6**
Swerdlow 1992 [85] Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	**RR** 0-4 y **2.0** 5-9 y **3.5** ≥10 y **4.0**	**AER** 0.5 y **22.2** 5-10 y **54.2** 10-15 y **82.5** 15-20 y **229.2** >20 y **404.7**
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	**RR** 0-5 y **2.2** (1.4-3.1) 5-10 y **3.4** (2.4-4.7) 10-15 y **4.0** (2.8-5.5)	15-20 y **7.8** (5.8-10.3) >20 y **10.9** (7.8-14.2)
Swerdlow 1997 [91] Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1 y	**SIR** (excluding NMSC) 0-4 y **2.9** (1.9-4.4) (P < .001) 5-9 y **4.6** (3.0-6.6) (P < .001)	10-14 y **3.0** (1.6-5.1) (P < .01) ≥15 y **2.6** (1.3-4.6) (P < .01)
Munker 1999 [93]	**RR**	**AER** (/ 10,000 py)

Retrospective cohort treated in Germany 1974-1994 (n=1120); mean f/u 9.1 y	0-4 y **2.9** (2.1-3.9) 5-9 y **2.5** (1.7-3.6) ≥ 10 y **3.9** (2.9-5.2)	0-4 y **44.6** 5-9 y **37.4** ≥ 10 y **101.3**
Sont 1992 [97] Retrospective cohort treated in the Netherlands 1969-1988 (n=482); average f/u 6.05 y	**RR** (95% CIs not given) 0-4 y **2.9** 5-9 y **6.3**	 10-14 y **2.5** 15-19 y **3.1**
Glanzmann 1994 [100] Retrospective cohort treated in Germany 1964-1992 (n=340); follow-up ≥1.5 y	**RR**, excluding NMSC 1-5 y **0.83** (0.02-4.6) 5-10 y **2.5** (0.3-9.0)	10-15 y **2.5** (0.3-9.0) 15-20 y **10.0** (2.7-25.6) > 20 y **10.0** (1.21-7.2)
Henry-Amar 1992 [102] Retrospective international cohort of 1 y HL survivors treated 1960-1987 (n=12,411); median f/u not given	**RR,** male 1-4 y **2.46** 5-9 y **3.27** 10-14 y **3.35** 15-19 y **4.10** ≥ 20 y **2.27** (95% CIs not given)	**RR**, female 1-4 y **1.90** 5-9 y **3.10** 10-14 y **2.70** 15-19 y **3.00** ≥ 20 y **5.20**
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given (AER / 10,000 py)	**SIR** 0-4 y **3.1** (2.3-4.1) 5-9 y **3.6** (2.8-4.5) 10-14 y **3.7** (2.9-4.8) 15-19 y **4.9** (3.8-6.3) 20-24 y **4.6** (3.2-6.5) ≥25 y **4.9** (3.0-7.5) (*P* = .06)	**AER** 0-4 y **33.3** 5-9 y **50.5** 10-14 y **68.7** 15-19 y **122.1** 20-24 y **128.5** ≥25 y **195.4**
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y	**SIR** 1-4 y **2.2** (1.5-3.2) 5-9 y **3.5** (2.6-4.7) 10-19 y **4.1** (3.3-5.0) ≥20 y **4.5** (3.1-6.4)	**AER** (/ 10,000 py) 1-4 y **80** 5-9 y **133** 10-19 y **184** ≥20 y **277**

Kumar 2018 [117] Retrospective cohort treat in the USA 1973-2014 (n=23,864); comparator USA general population; median f/u not given	**SIR** 2-11 m **1.74** 12-59 m **1.64**	60-119 m **1.78** 120-179 m **1.99**	180-239 m **2.28** ≥240 m **2.34**
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population (AERs / 10,000 py)	**SIR** 1-9 y **2.12** (1.96-2.30) 10-19 y **2.92** (2.61-3.26) (All *P* < .001)		20-30 y **2.55** (2.19-2.98) >30 y **2.65** (2.07-3.39)
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population (AER / 10,000 py)	**RR** <5 y **4.5** (2.7-7.3) 5-9 y **5.0** (30-7.9) 10-14 y **6.1** (3.7-10.0) ≥15 y **7.4** (4.4-11.7)		**AER** <5 y **35.9** 5-9 y **56.0** 10-14 y **104.6** ≥15 y **217.5**
Nelson 1981 [123] Retrospective cohort treated in the USA 1960-1977 (n=248); median f/u 5.8 y	**RR** Patients followed for >5 y **4.8** (0.99-13.99) Patients followed for ≥10 y **16.1** (3.31-49.94)		
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given	**RR** 1-9 y **2.3** 10-14 y **3.2**	15-19 y **3.5** 20-24 y **4.5**	≥25 y **2.3**
Lavey 1990 [138] Retrospective cohort treated in the USA 1970-1981 (n=999); median f/u 10 y; comparator Connecticut general population	**RR** 0.5-4.9 y **5.0** 5.0-9.9 y **10.0**		10.0-17 y **10.0** (95% CIs not given)

*pooled estimate (meta-analysis)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – HL: Hodgkin lymphoma; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, dacarabazine; RT: radiotherapy; n: number; f/u; follow-up; y: years; NMSC: non-melanoma skin cancer; CI: confidence interval; MDS: myelodysplastic syndrome; EORTC: European Organisation for Research and Treatment of Cancer; GI: gastrointestinal; NHL: non-Hodgkin lymphoma; RCT: randomised controlled trial; py: person-years; AEM: absolute excess mortality; MOPP: mustargen, vincristine (Oncovin); procarbazine, prednisone; CMT: combined-modality therapy; m: months; HR: hazard ratio; AER: absolute excess risk; SIR: standardised incidence ratio; RR: relative risk

b. Solid tumours

Study details	Risk estimate
Cumulative incidence	
Brierley 1998 [10] Retrospective cohort with stage 1-2 HL treated in Canada 1973-184 (n=611); median f/u 11y; comparator age-matched general population	15 y **6.93%**
van Spronsen 1998 [11] Retrospective cohort of 5 y survivors treated in the Netherlands 1972-1993 (n=345); median f/u not given; comparator general population	10 y **4%**
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	Cumulative mortaltity 20 y **5.0%** 40 y **21.0%**
van Rijswijk 1987 [20] Retrospective cohort treated in the Netherlands 1970-1984 (n=340); mean f/u 76.6 m	10 y **1.4%** (0.0-7.9
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y	20 y **7.8%** (6.4-9.5) (excluding lung cancer and NMSC)
Swerdlow 1992 [85] Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	15 y **8.5%**
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	30 y **28.5%**
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y	25y **23.3%** (18.9-28.6)
Rodriguez 1993 [80] Retrospective cohort treated for HL in the USA 1966-1987 (n=1013); median f/u >5 y; comparator general population	Including skin cancers **11.0%** Excluding skin cancers **7.6%**
Swerdlow 1997 [91]	Excl. NMSC

Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1 y	5 y **1.9%** (1.1-3.2) 10 y **3.6%** (2.4-5.3)		15 y **5.2%** (3.5-7.6) 20 y **8.3%** (5.5-12.5)	
Munker 1999 [93] Retrospective cohort treated in Germany 1974-1994 (n=1120); mean f/u 9.1 y	5 y **2.0%**	10 y **4.6%**	15 y **7.7%**	
Henry-Amar 1983 [96] Retrospective cohort treated in EORTC trials 1964-1972 (n=334); median f/u 10 y	5 y **0.3%** (SE +/- 0.3) 10 y **3.5%** (SE +/- 1.2)		15 y **10.8%** (SE +/- 3.6)	
Sont 1992 [97] Retrospective cohort treated in the Netherlands 1969-1988 (n=482); average f/u 6.05 y	5 y **2.4%**	10 y **6.4%**		
Economoupoulos 1994 [98] Retrospective cohort treated in Greece 1977-1991 (n=217); median f/u 67 m	10 y **3.2%**			
Glanzmann 1994 [100] Retrospective cohort treated in Germany 1964-1992 (n=340); follow-up ≥1.5 y	10 y **3.1%**	15 y **9.3%**	20 y **23.5%**	24 y **34.3%**
Cimino 1991 [101] Retrospective cohort treated for HL in Italy 1969-1979 (n=947); median f/u 10.5 y	10 y **0.9%** (+/- 0.3) 15 y **0.9%** (+/- 0.3)		19 y **17.0%** (+/- 0.1)	
Henry-Amar 1992 [102] Retrospective international cohort of 1 y HL survivors treated 1960-1987 (n=12,411); median f/u not given	10 y **3.7%**	15 y **7.5%**	20 y **13.6%**	
Biti 1994 [107] Retrospective cohort treated in Italy 1960-1988 (n=1121); mean f/u >9 y	15 y **7.6%**			
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	10 y **4.0%**	15 y **9.9%**		
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y	28 y **14.4%**			
Bonadonna 2005 [114] Retrospective cohort treated for intermediate or advanced-stage HL in Italy 1973-1990 (n=811); median f/u 16.7-29 y (substudies)	25 y **17.7%**			
Omer 2012 [119]	15 y **4%**	25 y **16%**	35 y **20%**	

Retrospective cohort treated in the USA 1970-2004 (n=198); median f/u 21.1 y; comparator general population	
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given	25 y **21.9%** (11.7% when competing causes of death considered)
Enrici 1997 [128] Retrospective cohort treated in Italy 1972-1992; average f/u 72 m	10 y **2.0%** 20 y **13.4%**
Lavey 1990 [138] Retrospective cohort treated in the USA 1970-1981 (n=999); median f/u 10 y; comparator Connecticut general population	10 y **11.2%** (2.5-19.9)
Tester 1984 [139] Retrospective cohort treated in USA 1964-1984 (n=473); median f/u >12 y	10 y **0.07%**
Tucker 1988 [140] Retrospective cohort treated in the USA 1968-1985 (n=1507); mean f/u 5.4 y	15 y **7.0%**
Valagussa 1986 [141] Retrospective cohort treated in Italy 1965-1982 (n=1329); median f/u 9.5 y	12 y: **8.9%**
Standardised incidence ratio	
Cosset 1991 [56] Pooled analysis of 4 EORTC trials H1, H2, H5, H6), run 1964-1988; 1660 patients; median f/u not reported	**1.7** (1.2-2.4) (*P* < .005)
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	**4.2** (3.9-4.5)
Swerdlow 1997 [91] Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1 y	**2.2** (1.2-3.6) (excluding NMSC)
Kumar 2018 [117] Retrospective cohort treat in the USA 1973-2014 (n=23,864); comparator USA general population; median f/u not given	**1.73** (1.53-1.96)
Omer 2012 [119] Retrospective cohort treated in the USA 1970-2004 (n=198); median f/u 21.1; comparator general population	**1.7** (1.04-2.62)
Absolute excess risk	

Aleman 2003 [1] Retrospective Dutch cohort treated when aged <41 y 1965-1987 (n=1261); median f/u 17.8 y; comparator general Dutch population	**26.0** / 10,000 py
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	AEM: **47.4** / 10,000 py
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	**59.1** / 10,000 py
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	**100.5** (91.3-110.2) / 10,000 py
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y	**54.5** / 10,000 py
van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	**32.4** / 10,000 py
Chronowski 2003 [90] Retrospective cohort treated for stage 1-2 HL in the USA 1980-1995 (n=286); median f/u 7.4 y	**42.5** / 10,000 py
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	**50** / 10,000 py
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	**36.2** / 10,000 py
Chronowski 2004 [124] Retrospective cohort treated for stage 1-2 HL in the USA 1980-1995 (n=286); median f/u of survivors 7.4 y	**42.5** / 10,000 py
Hancock 1996 [125] Retrospective cohort treated in the USA 1960-1990 (n=2162); mean f/u 9.3 y	**53** / 10,000 py

Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given	**33.1** / 10,000 py
Relative risk	
Aleman 2003 [1] Retrospective Dutch cohort treated when aged <41 y 1965-1987 (n=1261); median f/u 17.8 y; comparator general Dutch population	**5.4** (3.4-8.2)
Behringer 2004 [83] Retrospective analysis of patients treated in GHSG trials 1983-1998 (n=5367); median f/u 72 m	**2.1** (1.1-2.3)
Swerdlow 1992 [85] Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	**1.5** (1.2-2.1) (excluding lung cancer)
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	**3.5** (3.0-4.2)
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y	**4.9** (3.0-7.4) (excluding breast cancer)
van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	**2.4** (1.9-2.9)
Almagro-Casado 2016 [79] Retrospective cohort treated in Spain 1968-2012 (n=604); median f/u not given	**3.1** (1.6-6.1) (*P* < .001)
Van Leeuwen 1989 [92] Retrospective cohort treated for HL in the Netherlands 1966-1986 (n=744); median f/u 6.4 y	**2.5** (1.7-3.5) **1.8** (1.1-2.9) (excluding lung cancer)
Munker 1999 [93] Retrospective cohort treated in Germany 1974-1994 (n=1120); mean f/u 9.1y	**1.8** (1.4-2.3)
Henry-Amar 1983 [96] Retrospective cohort treated in EORTC trials 1964-1972 (n=334); median f/u 10 y	**3.76** (2.19-6.02) (*P* < .001)

Sont 1992 [97] Retrospective cohort treated in the Netherlands 1969-1988 (n=482); average f/u 6.05 y	**2.4** (95% CI not given)
Chronowski 2003 [90] Retrospective cohort treated for stage 1-2 HL in the USA 1980-1995 (n=286); median f/u 7.4 y	**2.4** (1.3-3.6)
Salloum 1996 [103] Retrospective cohort treated in the USA 1969-1985 1968-1994 (n=313); median f/u 12.8 y)	**3.3** (2.0-5.3) (*P* < .001) (excluding NHL)
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	**3.42** (2.41-4.71) (*P* < .001)
Doria 1995 [110] Retrospective cohort treated in USA 1969-1982 (n=102); median f/u 153-212 m	**1.88** (0.6-4.0)
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	**4.7** (3.6-6.1)
Chronowski 2004 [124] Retrospective cohort treated for stage 1-2 HL in the USA 1980-1995 (n=286); median f/u of survivors 7.4 y	**2.4** (1.3-3.6)
Hancock 1996 [125] Retrospective cohort treated in the USA 1960-1990 (n=2162); mean f/u 9.3 y	**4.3** (3.5-5.0)
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given	**2.0** (95% CI not given)
Hodgson 2007 [127] Retrospective cohort of 5y HL survivors treated in North America & Europe 1970-2001 (n=18,862); median f/u 12.2 y	**4.6** (4.1-5.2)
Boivin 1995 [129] Retrospective cohort treated in the USA and Canada 1940-1987 (n=10,472); average f/u 7.1 y (after discounting the 1st year after diagnosis)	**2.7** (2.5-4.2)
Boivin 1988 [130]	**2.2** (95% CI not given)

Pooled analysis of data from 7 cohorts with incidence rates of second cancers, and details of treatment given for HL; 6513 participants; median f/u 43-71.4 m	
Lavey 1990 [138] Retrospective cohort treated in the USA 1970-1981 (n=999); median f/u 10 y; comparator Connecticut general population	**6.5** (2.4-14.0)
Tester 1984 [139] Retrospective cohort treated in USA 1964-1984 (n=473); median f/u >12 y	**0.60** (+/- 0.045)
Tucker 1988 [140] Retrospective cohort treated in the USA 1968-1985 (n=1507); mean f/u 5.4 y	**2.8** (1.4-4.3)
Valagussa 1986 [141] Retrospective cohort treated in Italy 1965-1982 (n=1329); median f/u 9.5 y	**11.3** (95% CI not given)
Odds ratio	
Franklin 2006 [89] Individual patient data meta-analysis from RCTs comparing RT vs CMT, chemo vs CMT, RT vs chemo or IFRT vs EFRT	**0.78*** (*P* = .05) (CMT vs RT alone)
Median time to development	
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	**13.8 y** (34 m from 2nd to 3rd malignancy)
Van Leeuwen 1989 [92] Retrospective cohort treated for HL in the Netherlands 1966-1986 (n=744); median f/u 6.4 y	**6.8 y**
Cimino 1991 [101] Retrospective cohort treated for HL in Italy 1969-1979 (n=947); median f/u 10.5 y	**76 m**
Cellai 2001 [106] Retrospective cohort treated in Italy 1960-1991 (n=1524); average f/u 10.7 y	**12 y**
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	**9.83 y**
Mauch 1996 [120]	**12.2 y**

Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population		
Enrici 1997 [128] Retrospective cohort treated in Italy 1972-1992; average f/u 72 m	**8.0 y**	
Shbib Dabaja 2022 [137] Retrospective cohort treated in the USA 1956-2009 (n=1653); median f/u 22 y	**13.8 y**	
Valagussa 1986 [141] Retrospective cohort treated in Italy 1965-1982 (n=1329); median f/u 9.5 y	**64 m**	
Variation in risk with time since radiotherapy		
Aleman 2003 [1] Retrospective Dutch cohort treated when aged <41 y 1965-1987 (n=1261); median f/u 17.8 y; comparator general Dutch population (AERs per 10,000 py)	Death from solid tumours **RR** (*P* for trend = .02) 0-5 y **0.0** (0.0-4.8) 6-10 y **4.1** (1.3-9.6) 11-15 y **5.4** (2.7-9.7) 16-20 y **8.6** (5.4-13.0) 21-25 y **7.3** (4.3-11.6) 26-30 y **8.3** (4.7-13.7) >30 y **7.6** (2.5-17.8)	 **AER** 0-5 y **-1.4** 6-10 y **7.8** 11-15 y **20.7** 16-20 y **59.4** 21-25 y **79.4** 26-30 y **136.9** >30 y **191.8**
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py)	**SIR**, non-lung solid tumours 0-4 y **1.2** (0.9-1.6) 5-9 y **1.9** (1.4-2.5) 10-14 y **2.2** (1.5-2.9) ≥15 y **2.9** (2.0-4.0)	**AER**, non-lung solid tumours 0-4 y **3.0** 5-9 y **14.8** 10-14 y **24.0** ≥15 y **54.4**
Swerdlow 1992 [85] Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	**RR**, non-lung solid tumours 0-4 y **1.2** (0.7-1.8) 5-9 y **2.0** (1.2-3.1) ≥10 y **2.1** (1.0-3.9) All **1.6** (1.2-2.1)	**AER** ≥10 y **71.5** / 10,000 py
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y (AER / 10,000 py)	**RR** 0.5 y **0.7** (0.3-1.4) 5-10 y **2.0** (1.2-3.1)	**AER** 0.5 y **-5.9** 5-10 y **20.5**

	10-15 y **3.5** (2.3-4.9) 15-20 y **7.7** (5.7-10.3) >20 y **9.2** (6.5-12.4)		10-15 y **63.9** 15-20 y **213.9** >20 y **317.8**	
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	**SIR** 5-9 y **3.3** (2.7-4.1) 10-14 y **3.7** (3.1-4.4) 15-19 y **4.8** (4.1-5.6) 20-24 y **4.4** (3.7-5.2) 25-29 y **4.6** (3.8-5.6) 30-34 y **4.7** (3.6-5.9) ≥35 y **3.6** (2.5-5.0) (P_{trend} = .06)		**AER** 5-9 y **33.6** 10-14 y **63.5** 15-19 y **132** 20-24 y **165** 25-29 y **241** 30-34 y **324** ≥35 y **302** (P_{trend} < .001)	
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y	**RR** 1-4 y **3.2** (1.2-6.9) 5-9 y **2.6** (1.2-5.0) 10-14 y **6.0** (3.9-8.9) 15-19 y **9.1** (6.4-12.6) ≥20 y **7.6** (5.1-10.8)		**AER** 1-4 y **9.0** 5-9 y **11.5** 10-14 y **60.0** 15-19 y **154** ≥20 y **201**	
van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	**RR** < 1 y **0.9** (0.3-2.4) 1-4 y **1.9** (1.2-2.8) 5-9 y **2.6** (1.7-3.8) 10-14 y **2.8** (1.7-4.4) ≥ 15 y **4.2** (2.5-6.6)			
Swerdlow 1997 [91] Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1 y	**SIR** (excluding NMSC) 0-4 y **2.8** (1.6-4.5) (*P* < .01) 5-9 y **2.3** (1.1-4.2) (*P* < .05)		10-14 y **1.7** (0.6-3.7) ≥15 y **2.7** (1.2-5.1) (*P* < .05)	
Henry-Amar 1992 [102] Retrospective international cohort of 1 y HL survivors treated 1960-1987 (n=12,411); median f/u not given	**RR** Males 1-4 y **1.18** 5-9 y **1.86**	15-19 y **1.73** ≥20 y **1.33**	Females 1-4 y **0.71** 5-9 y **1.99**	15-19 y **3.60** ≥20 y **6.25**

	10-14 y **2.33** (95% CIs not given)		10-14 y **2.33**
Salloum 1996 [103] Retrospective cohort treated in the USA 1969-1985 1968-1994 (n=313); median f/u 12.8 y	**RR** 0-9 y **1.0** (0.4-3.0) (*P* < .323) >10 y **6.5** (3.8-11.1) (*P* < .001)		
Kumar 2018 [117] Retrospective cohort treat in the USA 1973-2014 (n=23,864); comparator USA general population; median f/u not given	**SIR** 2-11 m **1.33** 12-59 m **1.2**	60-119 m **1.47** 120-179 m **1.72**	180-239 m **2.16** ≥240 m **2.29**
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population (AER / 10,000 py)	**RR** <5 y **3.7** (1.9-6.4) 5-9 y **2.8** (1.3-5.4) 10-14 y **5.9** (3.4-9.5) ≥15 y **7.4** (4.4-12.1)	**AER** <5 y **23.7** 5-9 y **22.7** 10-14 y **87.2** ≥15 y **193.3**	
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given	**RR** 1-9 y **1.9** (*P* < .05) 10-14 y **2.7** (*P* < .05) 15-19 y **3.5** (*P* < .05)		20-24 y **4.4** (*P* < .05) ≥25 y **2.4** (*P* < .05)
Hodgson 2007 [127] Retrospective cohort of 5y HL survivors treated in North America & Europe 1970-2001 (n=18,862); median f/u 12.2 y	**RR** SD 1-4 y **3.2** (2.5-4.2) 5-9 y **6.0** (4.8-7.4) 10-19 y **5.3** (4.4-6.3) 20-24 y **5.7** (4.1-7.5) 25 y **5.6** (3.3-8.8)		ID 1-4 y **1.4** (0.9-1.9) 5-9 y **1.9** (1.3-2.5) 10-19 y **3.1** (2.6-3.8) 20-24 y **3.4** (2.4-4.6) 25 y **4.2** (2.7-6.2)
Boivin 1995 [129] Retrospective cohort treated in the USA and Canada 1940-1987 (n=10,472); average f/u 7.1 y (after discounting the 1st year after diagnosis) (adjusted for chemo)	**RR** 0-4 y **0.7** (0.5-1.2) 5-9 y **0.7** (0.4-1.3)		≥10 y **1.6** (0.8-3.2) All **0.9** (0.6-1.4)

*pooled estimate (meta-analysis)
Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – HL: Hodgkin lymphoma; n: number; f/u: follow-up; y: years; m: months; NMSC: non-melanoma skin cancer; excl.: excluding; EORTC: European Organisation for Research and Treatment of Cancer; AEM: absolute excess mortality; py: person-years; CMT: combined-modality therapy; RCTs: randomised controlled trials; IFRT: involved-field radiotherapy; EFRT: extended-field radiotherapy; AER: absolute excess risk; SIR: standardised incidence ratio; RR: relative risk; SD: supradiaphragmatic; ID: infradiaphragmatic

c. Breast cancer

Study details	Risk estimate		
Cumulative incidence			
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	5 y **0.3%**	15 y **1.4%**	25 y **3.3%**
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	30 y **16.6%** (14.1-19.2) (females)		
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y	25 y **16.3%** (10.8-24.0) (women)		
Cellai 2001 [106] Retrospective cohort treated in Italy 1960-1991 (n=1524); average f/u 10.7 y	15 y **3.0%** 20 y **4.6%**		
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given	25 y **9.3%**		
Lavey 1990 [138] Retrospective cohort treated in the USA 1970-1981 (n=999); median f/u 10 y; comparator Connecticut general population	10 y **6.2%** (2.8-9.7)		
Gervais-Fagnou 1999 [142] Retrospective cohort of women treated with supradiaphragmatic RT when aged ≤30 y in Canada 1965-1990 (n=427); mean f/u 12.3 y	10 y **0%**	15 y **10%**	16 y+ **20%**
Ibrahim 2012 [143]	20 y **5.4%*** 30 y **12%***		

Meta-analysis of studies reporting the risk of breast cancer in female HL survivors; total of 24,505 women; median f/u 14.9 y	
de Bruin 2009 [144] Retrospective cohort of female 5 y HL survivors treated when aged <51 y in the Netherlands 1965-1995; median f/u 17.8 y; comparator general population	30 y: **25%** (19% if death included as a competing risk)
Standardised incidence ratio	
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	**4.4** (2.8-6.6)
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y	**2.5** (1.4-4.0)
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1y; comparator Dutch general pop	**4.7** (4.0-5.4) (females)
Swerdlow 1997 [91] Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1 y	**1.8** (0.7-3.9)
Cellai 2001 [106] Retrospective cohort treated in Italy 1960-1991 (n=1524); average f/u 10.7 y	**2.9** (1.5-5.1)
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	**2.4** (1.6-3.4)
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y	**5.0** (2.8-8.0)
van Eggermond 2014 [115] Retrospective cohort of 5 y survivors treated in the Netherlands when aged <51 y 1965-1995 (n=3122); median f/u 22.6 y	2nd malignancy **4.9** (4.2-5.8) 3rd malignancy **8.2** (5.6-11.4)
Kumar 2018 [117] Retrospective cohort treat in the USA 1973-2014 (n=23,864); comparator USA general population; median f/u not given	**1.95** (1.31-2.78)
Sud 2017 [118]	**2.52** (2.15-2.97)

Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population	
Omer 2012 [119] Retrospective cohort treated in the USA 1970-2004 (n=198); median f/u 21.1; comparator general population	**3.4** (1.37-7.01)
de Bruin 2009 [144] Retrospective cohort of female 5 y HL survivors treated when aged <51 y in the Netherlands 1965-1995; median f/u 17.8 y; comparator general population	**5.6** (4.6-6.8)
Veit-Rubin 2012 [150] Retrospective cohort treated in the USA 1973-2007 (n=9620); median f/u 9.83 y; comparator general population	**3.2** (2.8-3.6) (*P* < .01)
Wendland 2004 [151] Retrospective cohort treated in the USA 1973-1999 (n=8036); median f/u 14 y; comparator general population or those treated with chemotherapy alone	**3.17** (*P* < .01) (vs general population) **1.9** (*P* < .01) (vs no RT)
Standardised mortality ratio	
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**4.4** (3.3-5.7)
El-Din 2009 [152] Retrospective cohort of women treated for stage 1-2 HL when aged ≤60 y in the USA 1964-2001 (n=248); median f/u 15.2 y	**9.78** (*P* < .0001)
Wahner-Roedler 2003 [153] Retrospective cohort treated for HL with supradiaphragmatic RT in the USA 1950-1993 (n=649); median f/u 8.7 y	**2.9** (2.0-4.2)
Absolute excess risk	
Brierley 1998 [10] Retrospective cohort with stage 1-2 HL treated in Canada 1973-184 (n=611); median f/u 11 y; comparator age-matched general population for same period	**14.7** / 10,000 py
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**AEM 4.4** / 10,000 py
Rugbjerg 2017 [23]	Hospitalisation **14** (6-22) / 10,000 py

Retrospective Danish cohort treated aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	**30.8** / 10,000 py
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y	**3.1** / 10,000 py
Swerdlow 1992 [85] Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	**1.2** / 10,000 py
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	**20.8** / 10,000 py
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	**24.9** / 10,000 py **54.3** / 10,000 py (females)
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y	**29.4** / 10,000 py (females)
van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	**1.1** / 10,000 py
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	**13** / 10,000 py
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	**5.1** / 10,000 py
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population	**9.2** / 10,000 py
Mauch 1996 [120]	**13.0** / 10,000 py

Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	
Chronowski 2004 [124] Retrospective cohort treated for stage 1-2 HL in the USA 1980-1995 (n=286); median f/u of survivors 7.4 y	**0.2** / 10,000 py
Hancock 1996 [125] Retrospective cohort treated in the USA 1960-1990 (n=2162); mean f/u 9.3 y	**21.5** / 10,000 py
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given	**10.5** / 10,000 py
Ibrahim 2012 [143] Meta-analysis of studies reporting the risk of breast cancer in female HL survivors; total of 24,505 women; median f/u 14.9 y	**22.9*** / 10,000 py
de Bruin 2009 [144] Retrospective cohort of female 5 y HL survivors treated when aged <51 y in the Netherlands 1965-1995; median f/u 17.8 y; comparator general population	**57** / 10,000 py
Hancock 1993 [146] Retrospective cohort of women treated for HL in USA 1961-1990 (n=885); mean f/u 10 y	**18.8** / 10,000 py
Veit-Rubin 2012 [150] Retrospective cohort treated in the USA 1973-2007 (n=9620); median f/u 9.83 y; comparator general population	**18** / 10,000 py
Relative risk	
Brierley 1998 [10] Retrospective cohort with stage 1-2 HL treated in Canada 1973-184 (n=611); median f/u 11 y; comparator age-matched general population for same period	**2.9** (1.1-6.3) (*P* = .006)
Rugbjerg 2017 [23] Retrospective Danish cohort treated when aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	Hospitalisation **3.8** (2.5-5.9)
Behringer 2004 [83] Retrospective analysis of patients treated in GHSG trials 1983-1998 (n=5367); median f/u 72 m	**1.9** (0.7-4.7)

Swerdlow 1992 [85] Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	**1.6** (0.6-3.4)
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	**6.7** (4.8-8.9)
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y	**7.7** (4.3-12.7)
van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	**1.3** (0.6-2.6)
van Leeuwen 1989 [92] Retrospective cohort treated for HL in the Netherlands 1966-1986 (n=744); median f/u 6.4 y	**4.9** (2.7-8.2)
Munker 1999 [93] Retrospective cohort treated in Germany 1974-1994 (n=1120); mean f/u 9.1y	**2.4** (1.3-4.2)
Henry-Amar 1992 [102] Retrospective international cohort of 1 y HL survivors treated 1960-1987 (n=12,411); median f/u not given	**1.5** (*P* < .05)
Salloum 1996 [103] Retrospective cohort treated in the USA 1969-1985 1968-1994 (n=313); median f/u 12.8 y	**2.0** (0.6-7.4) (*P* < .07)
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	**5.93** (2.56-11.67) (*P* < .001)
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	**6.5** (3.5-11.2)
Prior 1988 [121] Retrospective cohort treated in the UK 1950-1979 (n=2999); median f/u 6.7 y; comparator general population	**3.1** (95% CI not given)
Chronowski 2004 [124]	**1.0** (0.0-5.8)

Retrospective cohort treated for stage 1-2 HL in the USA 1980-1995 (n=286); median f/u of survivors 7.4 y	
Hancock 1996 [125] Retrospective cohort treated in the USA 1960-1990 (n=2162); mean f/u 9.3 y	**4.1** (2.4-5.7)
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given	**2.0** (1.9-2.0)
Hodgson 2007 [127] Retrospective cohort of 5 y HL survivors treated in North America & Europe 1970-2001 (n=18,862); median f/u 12.2 y	**3.8** (2.2-6.4)
Boivin 1995 [129] Retrospective cohort treated in the USA and Canada 1940-1987 (n=10,472); average f/u 7.1 y (after discounting the 1st year after diagnosis)	**1.4** (0.9-2.3)
Boivin 1988 [130] Pooled analysis of data from 7 cohorts with incidence rates of second cancers, and details of treatment given for HL; 6513 participants; median f/u 43-71.4 m	**0.9** (95% CI not given)
Varady 2001 [136] Retrospective cohort treated in Hungary 1978-1996 (n=665); median f/u not given Quoted expected incidences of second cancers extremely low, resulting in disproportionally high relative risks, therefore values not included in text	**157.89** (32.58-461.58)
Gervais-Fagnou 1999 [142] Retrospective cohort of women treated with supradiaphragmatic RT when aged ≤30 y in Canada 1965-1990 (n=427); mean f/u 12.3 y; comparator general pop	**10.5** (5.2-18.8)
Ibrahim 2012 [143] Meta-analysis of studies reporting the risk of breast cancer in female HL survivors; total of 24,505 women; median f/u 14.9 y	**4.7*** (3.28-6.75)
Swerdlow 2012 [145] Retrospective cohort of women treated with supradiaphragmatic RT when aged <36 y in England and Wales 1956-2003 (n=5002); median f/u not given	**5.0** (4.5-5.5)
Hancock 1993 [146] Retrospective cohort of women treated for HL in USA 1961-1990 (n=885); mean f/u 10 y	**4.1** (2.5-5.7) (*P* = .0002) Death **5.1** (2.2-10)
Curtis 1988 [147]	**1.9** (95% CIs not given)

Retrospective cohort treated in the USA 1935-1985 (n=2653); median f/u not given	
Travis 2003 [148] Case-control study nested n a cohort of 3817 female 1 y HL survivors treated when aged <30 y 1965-1994 (105 cases, 266 controls); median f/u not given	**3.2** (1.4-8.2)
O'Brien 1995 [149] Retrospective cohort of women treated in the USA 1961-1980 (n=855); mean f/u 10 y	**3.2** (1.2-6.3) (*P* = .012)
Median time to development	
Brierley 1998 [10] Retrospective cohort with stage 1-2 HL treated in Canada 1973-184 (n=611); median f/u 11 y; comparator age-matched general population for same period	**10 y**
Van Leeuwen 1989 [92] Retrospective cohort treated for HL in the Netherlands 1966-1986 (n=744); median f/u 6.4 y	**8.1 y**
Cellai 2001 [106] Retrospective cohort treated in Italy 1960-1991 (n=1524); average f/u 10.7 y	**15 y**
Gervais-Fagnou 1999 [142] Retrospective cohort of women treated with supradiaphragmatic RT when aged ≤30 y in Canada 1965-1990 (n=427); mean f/u 12.3 y	**17.0 y**
Ibrahim 2012 [143] Meta-analysis of studies reporting the risk of breast cancer in female HL survivors; total of 24,505 women; median f/u 14.9 y	**17.7* y**
Hancock 1993 [146] Retrospective cohort of women treated for HL in USA 1961-1990 (n=885); mean f/u 10 y	**15 y** (mean)
Travis 2003 [148] Case-control study nested n a cohort of 3817 female 1 y HL survivors treated when aged <30 y 1965-1994 (105 cases, 266 controls); median f/u not given	**18.0 y**
El-Din 2009 [152] Retrospective cohort of women treated for stage 1-2 HL when aged ≤60 y in the USA 1964-2001 (n=248); median f/u 15.2 y	**18.4 y**

Wahner-Roedler 2003 [153] Retrospective cohort treated for HL with supradiaphragmatic RT in the USA 1950-1993 (n=649); median f/u 8.7 y	**19.9 y**
Diller 2002 [160] Prospective cohort of female HL survivors treated in the USA when aged <30 y since 1995; follow-up ≥8 y	**19.5 y**
Travis 2005 [154] International case-control study of breast cancer in 3817 female >1 y HL survivors treated 1965-1994 (105 cases; 266 matched controls); median f/u not given	**18 y**
Cutuli 2001 [155] Retrospective cohort with stage 1A-2B HL treated in France 1976-1990 (n=55); median f/u 8 y	**16 y**
van Leeuwen 2003 [156] Case-control study nested in a cohort of 770 female patients treated for HL in the Netherlands when aged <41 y (48 cases, 175 matched controls); mean f/u 3.4 y	**18.7 y**
Krul 2017 [157] Case-control study nested in a cohort of female 5 y HL survivors treated when aged <41 y (174 cases, 466 controls); median f/u not given	**21.9 y**
Conway 2017 [158] Retrospective cohort of female patients treated for HL in Canada 1961-2009 (n=734); median f/u 18 y	**20 y**
Meattini 2010 [159] Retrospective cohort treated in Italy 1690-2003 with >6 m f/u (n=1538, 725 women); median f/u not given	**19.5 y** (mean)
Median age at development	
Gervais-Fagnou 1999 [142] Retrospective cohort of women treated with supradiaphragmatic RT when aged ≤30 y in Canada 1965-1990 (n=427); mean f/u 12.3 y	**41 y**
Ibrahim 2012 [143] Meta-analysis of studies reporting the risk of breast cancer in female HL survivors; total of 24,505 women; median f/u 14.9 y	**35.0* y**
Hancock 1993 [146]	**40 y**

Retrospective cohort of women treated for HL in USA 1961-1990 (n=885); mean f/u 10 y	
Travis 2003 [148] Case-control study nested n a cohort of 3817 female 1 y HL survivors treated when aged <30 y 1965-1994 (105 cases, 266 controls); median f/u not given	**41.0 y**
El-Din 2009 [152] Retrospective cohort of women treated for stage 1-2 HL when aged ≤60 y in the USA 1964-2001 (n=248); median f/u 15.2 y	**43.8 y**
Wahner-Roedler 2003 [153] Retrospective cohort treated for HL with supradiaphragmatic RT in the USA 1950-1993 (n=649); median f/u 8.7 y	**44.4 y**
Diller 2002 [160] Prospective cohort of female HL survivors treated in the USA when aged <30 y since 1995; follow-up ≥8 y	**43 y**
Cutuli 2001 [155] Retrospective cohort with stage 1A-2B HL treated in France 1976-1990 (n=55); median f/u 8 y	**42 y**
van Leeuwen 2003 [156] Case-control study nested in a cohort of 770 female patients treated for HL in the Netherlands when aged <41 y (48 cases, 175 matched controls); mean f/u 3.4 y	**44 y**
Krul 2017 [157] Case-control study nested in a cohort of female 5 y HL survivors treated when aged <41 y (174 cases, 466 controls); median f/u not given	**46.1 y**
Conway 2017 [158] Retrospective cohort of female patients treated for HL in Canada 1961-2009 (n=734); median f/u 18 y	**46 y**
Meattini 2010 [159] Retrospective cohort treated in Italy 1690-2003 with >6 m f/u (n=1538, 725 women); median f/u not given	**50.8 y**
Hill 2005 [197] Case-control study nested in an international cohort of 3817 patients treated when aged <30 y (105 patients, 266 controls); median f/u not given	**41 y**

Variation in risk with time since treatment			
Lee 2000 [27] Retrospective cohort of patients with stage 1-3 HL treated in the USA 1970-1986 (n=210); median f/u 15.6 y; comparator general pop	**AER** (/ 1000 py) 0-5 y **2.94** 5-10 y **-0.32**	10-15 y **10.4** 15-20 y **27.3**	20-25 y **5.56**
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	**SIR** <5 y **1.4** (0.0-7.8) 5-15 y **3.0** (1.0-7.0)		15-25 y **2.7** (0.9-6.4) >25 y **10.6** (5.6-18.1)
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y (AER / 10,000 py; women only)	**RR** 0-5 y **0** (0.0-2.6) 5-10 y **2.3** (0.5-6.6) 10-15 y **3.9** (1.3-9.1) 15-20 y **16.1** (9.2-26.1) >20 y **20.1** (11.3-33.2) Women who had mantle, MPA or TNI at age ≤30 y **RR** Overall **15.9** (10.6-22.0) 0-5 y **0.0** (0.0-30.0) 5-10 y **6.8** (0.8-24.7) 10-15 y **4.1** (0.5-14.9) 15-20 y **25.8** (14.1-43.3) 20 y+ **24.5** (13.4-41.1)		**AER** 0.5 y **-5.4** 5-10 y **8.5** 10-15 y **27.7** 15-20 y **198.9** >20 y **338.4** **AER** Overall **57.3** 0-5 y **-0.7** 5-10 y **11.8** 10-15 y **14.8** 15-20 y **225.0** 20 y+ **368.2**
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1y; comparator Dutch general pop	**SIR** 5-9 y **1.6** (0.8-2.9) 10-14 y **3.4** (2.2-4.9) 15-19 y **5.6** (4.1-7.5) 20-24 y **4.8** (3.3-6.8) 25-29 y **8.0** (5.7-11.0) 30-34 y **6.7** (3.9-10.5) ≥35 y **5.3** (2.5-9.7) (*P* < .001)		**AER** 5-9 y **4.5** 10-14 y **28.0** 15-19 y **76.8** 20-24 y **83.0** 25-29 y **186** 30-34 y **170** ≥35 y **140** (*P* < .001)

van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y (AER / 10,000 py)	**RR** 1-4 y **-** 5-9 y **1.0** (0.03-5.5) 10-14 y **2.4** (0.5-7.1) 15-19 y **10.9** (5.8-18.6) ≥20 y **8.0** (3.8-14.7)		**AER** 1-4 y **-** 5-9 y **-** 10-14 y **11.5** 15-19 y **119** ≥20 y **125**
van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	**RR** <1 y **1.9** (0.1-10.8) 1-4 y **0.6** (0.0-3.2) 5-9 y **1.2** (0.1-4.3)		10-14 y **0** (0-3.0) ≥15 y **4.0** (1.1-10.3)
Van Leeuwen 1989 [92] Retrospective cohort treated for HL in the Netherlands 1966-1986 (n=744); median f/u 6.4 y	**RR** <5 y **1.9** (0.4-5.7) 5-10 y **6.7** (2.5-14.6)		≥10 y **11.3** (3.7-26.3)
Henry-Amar 1992 [102] Retrospective international cohort of 1y HL survivors treated 1960-1987 (n=12,411); median f/u not given	**RR** 1-4 y **0.52** 5-9 y **1.38**	10-14 y **1.72** 15-19 y **6.47**	≥ 20 y **0.0** (95% CIs not given)
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y	**SIR** 1-4 y **1.9** (0.2-7.0) 5-9 y **0.8** (0-4.5) 10-19 y **5** (2.7-8.5) ≥ 20 y **6.2** (2.5-12.8)		**AER** 1-4 y **6** 5-9 y **3** 10-19 y **27** ≥ 20 y **59**
Kumar 2018 [117] Retrospective cohort treat in the USA 1973-2014 (n=23,864); comparator USA general population; median f/u not given	**SIR** 2-11 m **0.47** 12-59 m **0.69**	60-119 m **1.31** 120-179 m **2.1**	180-239 m **2.93** ≥240 m **3.03**
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population	**SIR** 1-9 y **1.27** (0.18-9.00) 10-19 y **4.16** (3.25-5.31)		20-30 y **3.92** (2.80-5.48) >30 y **3.01** (1.57-5.78)
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given	**RR** 1-9 y **1.2** (7.91-24.30) 10-14 y **3.2** 15-19 y **5.0**		20-24 y **3.9** ≥25 y **4.1**

Hodgson 2007 [127] Retrospective cohort of 5 y HL survivors treated in North America & Europe 1970-2001 (n=18,862); median f/u 12.2 y	**RR** 1-4 y **0.94** (< 1-1.7) 5-9 y **1.9** (1.3-2.8) 10-19 y **4.6** (3.8-4.6)	 20-24 y **2.9** (2.1-4.0) 25 y **2.4** (1.5-3.8)
Ibrahim 2012 [143] Meta-analysis of studies reporting the risk of breast cancer in female HL survivors; total of 24,505 women; median f/u 14.9 y	**RR** 0-4 y **3.52*** 5-9 y **3.03*** 10-14 y **6.65*** 15-19 y **13.87*** (7.91-24.30)	 20-24 y **8.67*** 25-29 y **11.59*** ≥20 y **6.95*** (4.8-10.1) ≥30 y **7.03*** (5.2-9.5)
de Bruin 2009 [144] Retrospective cohort of female 5 y HL survivors treated when aged <51 y in the Netherlands 1965-1995; median f/u 17.8 y; comparator general population (AER / 10,000 py)	**SIR** 5-9 y **1.7** 10-14 y **4.2** 15-19 y **6.8** 20-24 y **6.3** 25-30 y **9.4** ≥30 y **9.5** (*P* < .0001)	**AER** 5-9 y **5** 10-14 y **33** 15-19 y **86** 20-24 y **103** 25-30 y **205** ≥30 y **249**
Swerdlow 2012 [145] Retrospective cohort of women treated with supradiaphragmatic RT when aged <36 y in England and Wales 1956-2003 (n=5002); median f/u not given (AER / 10,000 py)	**SIR** 0-4 y **0.6** (0.1-2.2) 5-9 y **1.1** (0.5-2.2) 10-14 y **4.8** (3.6-6.2) 15-19 y **6.4** (5.2-7.9) 20-24 y **6.5** (5.3-8.0) 25-29 y **6.2** (4.9-7.8) 30-34 y **5.1** (3.8-6.9) 35-39 y **2.5** (1.3-4.8) ≥40 y **2.2** (0.6-8.8) (*P* < .001)	**AER** 0-4 y **-0.7** (-1.4-1.5) 5-9 y **0.3** (-1.9-4.1) 10-14 y **25.5** (17.4-35.4) 15-19 y **61.3** (46.9-78.1) 20-24 y **96.9** (74.8-122.6) 25-29 y **127.9** (95.5-166.3) 30-34 y **126.7** (82.7-182.0) 35-39 y **51.0** (4.7-127.5) ≥40 y **43.3** (-26.4-250.3) (*P* < .001)
Hancock 1993 [146] Retrospective cohort of women treated for HL in USA 1961-1990 (n=885); mean f/u 10 y	**RR** <15 y **0.8** (0.1-2.5) ≥15 y **13.0** (6.6-23.1)	**AER** (/ 10,000 py) <15y **-** ≥15y **164**

Curtis 1988 [147] Retrospective cohort treated in the USA 1935-1985 (n=2653); median f/u not given	**RR** <1 y **1.5** 1-4 y **1.2**	5-9 y **1.4** ≥10 y **4.3**	(95% CIs not given)
Travis 2003 [148] Case-control study nested n a cohort of 3817 female 1 y HL survivors treated when aged <30 y 1965-1994 (105 cases, 266 controls); median f/u not given	**RR**, ≥4 Gy to breast (vs <4 Gy) 5-9 y **-** (*P* = .04) 10-14 y **1.6** (0.5-6.1) (*P* = .47) 15-19 y **5.8** (1.5-38.9) (*P* = .01)		20-24 y **2.1** (0.6-8.2) (*P* = .24) ≥ 25 y **2.3** (0.5-16.5) (*P* = .30)
Veit-Rubin 2012 [150] Retrospective cohort treated in the USA 1973-2007 (n=9620); median f/u 9.83 y; comparator general population	**SIR** < 2 y **0.7** (0.3-1.3) < 5 y **0.9** (0.5-1.4) < 10 y **1.5** (1.1-2.0) (*P* < .01)		< 15 y **3.2** (2.5-4.0) (*P* < .001) < 20 y **4.5** (3.6-5.6) (*P* < .001) ≥ 20 y **3.7** (2.9-4.6) (*P* < .001)
El-Din 2009 [152] Retrospective cohort of women treated for stage 1-2 HL when aged ≤60 y in the USA 1964-2001 (n=248); median f/u 15.2 y	**SMR** 0-<5 y **2.14** (0.02-11.92) 5-10 y **5.12** (1.03-14.97) 10-15 y **6.70** (2.16-15.65) 15-20 y **18.90** (10.32-31.71) 20-25 y **12.78** (5.50-25.19) >25 y **9.67** (3.54-21.43)		<15 y **5.01** (2.29-9.51) ≥15 y **14.34** (9.45-20.86) (*P* = .033)
Wahner-Roedler 2003 [153] Retrospective cohort treated for HL with supradiaphragmatic RT in the USA 1950-1993 (n=649); median f/u 8.7 y	SMR 0-<5 y **1.33** (0.28-3.87) 5-<10 y **0.55** (0.01-3.05) 10-<15 y **2.34** (0.64-5.99) 15-<20 y **4.56** (1.84-9.39)		20-25 y **5.71** (2.30-11.75) 25-<30 y **5.63** (1.83-13.11) >30 y **3.79** (0.78-11.06)

*pooled estimate (meta-analysis)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – y: years; HL: Hodgkin lymphoma; n: number; f/u: follow-up; RT: radiotherapy; py: person-years; CI: confidence interval; NHL: non-Hodgkin lymphoma; AEM: absolute excess mortality; m: months; AER: absolute excess risk; MPA: mantle and para-aortic radiotherapy; TNI: total nodal irradiation; Gy: gray

d. Lung cancer

Study details	Risk estimate		
Cumulative incidence			
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	5 y **0.5%**	15 y **2.0%**	25 y **3.1%**
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y	20 y **3.6%**		
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	30 y Lower respiratory tract **7.1%** (6.0-8.3) Lung or bronchus **6.4%** (5.4-7.6) Mesothelioma **0.6%** (0.3-1.1)		
Swerdlow 1997 [91] Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1 y	5 y **0.2%** (0.1-0.9) 10 y **1.3%** (0.6-2.6)		15 y **3.0%** (1.7-5.1) 20 y **3.4%** (2.0-5.8)
Van Leeuwen 1989 [92] Retrospective cohort treated for HL in the Netherlands 1966-1986 (n=744); median f/u 6.4 y	10 y **3.0%** (+/- 1.0%) 15 y **6.2%** (+/- 1.9%)		
Cellai 2001 [106] Retrospective cohort treated in Italy 1960-1991 (n=1524); average f/u 10.7 y	15 y **1.0%** 20 y **4.1%**		
Standardised incidence ratio			
Cosset 1991 [56] Pooled analysis of 4 EORTC trials H1, H2, H5, H6), run 1964-1988; 1660 patients; median f/u not reported	Males **3.3** (*P* = .001))		
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	**3.9** (2.1-6.5)		
Swerdlow 2000 [84]	**3.4** (2.7-4.2) Pleura **6.2** (1.6-16.2)		

Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y		
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	Lower respiratory tract **6.7** (5.8-7.8) Lung / bronchus **6.4** (5.5-7.4) Mesothelioma **15.1** (8.8-24.2)	
Swerdlow 1997 [91] Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1 y	**4.2** (1.8-8.1) (*P* < .01)	
Cellai 2001 [106] Retrospective cohort treated in Italy 1960-1991 (n=1524); average f/u 10.7 y	**3.9** (2.1-6.7)	
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	**5.1** (3.8-6.5)	
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y	**6.6** (3.6-11.0)	
van Eggermond 2014 [115] Retrospective cohort of 5 y survivors treated in the Netherlands when aged <51 y 1965-1995 (n=3122); median f/u 22.6 y	2nd malignancy **6.8** (5.7-8.1) 3rd malignancy **6.0** (2.5-9.8)	
Kumar 2018 [117] Retrospective cohort treat in the USA 1973-2014 (n=23,864); comparator USA general population; median f/u not given	**2.84**	
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population	**3.61** (3.05-4.36)	
Omer 2012 [119] Retrospective cohort treated in the USA 1970-2004 (n=198); median f/u 21.1 y; comparator general population	**2.9** (0.93-6.66)	
de Bruin 2009 [131] Retrospective cohort of 5 y HL survivors treated in the Netherlands when aged <51 y 1965-1995; median f/u 18.1 y	Mesothelioma **5.8** (0.2-32.1)	
Standarised mortality ratio		
de Vries 2021 [12]	All respiratory **6.7** (5.9-7.6)	Mesothelioma **15.5** (9.6-23.8)

Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	Lung, bronchus & trachea **6.4** (5.6-7.4)	
Absolute excess risk		
Aleman 2003 [1] Retrospective Dutch cohort treated when aged <41 y 1965-1987 (n=1261); median f/u 17.8 y; comparator general Dutch population	Death from lung cancer **9.4** / 10,000 py	
Rugbjerg 2019 [8] Retrospective cohort of Danish >5 y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	Hospitalisation (/ 10,000 py) Lung, bronchus & trachea **20** (12-28)	Mesothelioma **2.9** (0.2-5.6) Other respiratory **2** (-0.2-5.1)
Brierley 1998 [10] Retrospective cohort with stage I-II HL treated in Canada 1973-184 (n=611); median f/u 11y; comparator age-matched general population for same period	**9.8** / 10,000 py	
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**AEM** (/ 10,000 py) All respiratory **20.3** Lung, bronchus & trachea **17.9**	Mesothelioma **2.0**
Rugbjerg 2017 [23] Retrospective Danish cohort treated when aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	Hospitalisation (/ 10,000 py) All respiratory **5** (0-10) Lung, bronchus, trachea **4** (0-9)	Mesothelioma **1** (-1-4)
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	**14.9** / 10,000 py	
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y	**11.7** / 10,000 py Pleura **0.5** / 10,000 py	
Swerdlow 1992 [85] Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	**13.6** / 10,000 py	
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	**11.0** / 10,000 py	
Schaapveld 2015 [88]	Lower respiratory tract **27.3** (22.9-32.1) / 10,000 py Lung / bronchus **24.6** (20.5-29.3) / 10,000 py	

Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	Mesothelioma **2.6** (1.5-4.3) / 10,000 py
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y	**6.9** / 10,000 py
van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	**13.6** / 10,000 py
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	**15** / 10,000 py Pleura **4** / 10,000 py
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	**14.0** / 10,000 py
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population (AERs / 10,000 py)	**10.3** / 10,000 py
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	**7.3** / 10,000 py
Chronowski 2004 [124] Retrospective cohort treated for stage 1-2 HL in the USA 1980-1995 (n=286); median f/u of survivors 7.4 y	**1.0** / 10,000 py
Hancock 1996 [125] Retrospective cohort treated in the USA 1960-1990 (n=2162); mean f/u 9.3y	**16.2** / 10,000 py
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given	**9.7** / 10,000 py
de Bruin 2009 [131] Retrospective cohort of 5 y HL survivors treated in the Netherlands when aged <51 y 1965-1995; median f/u 18.1 y	Mesothelioma **0.7** (-0.1-4.7) / 10,000 py
Ibrahim 2013 [165]	**10.4*** (4.1-13.6) / 10,000 py

Meta-analysis of papers quantifying risk of second lung cancer in HL survivors; data on 74,831 patients; median f/u 11.5 y		
Relative risk		
Aleman 2003 [1] Retrospective Dutch cohort treated when aged <41 y 1965-1987 (n=1261); median f/u 17.8 y; comparator general Dutch population	Death from lung cancer **8.8** (95% CI not given)	
Rugbjerg 2019 [8] Retrospective cohort of Danish >5 y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	Hospitalisation: Lung, bronchus & trachea **4.8** (3.5-6.5)	Mesothelioma **21.4** (8.6-53.3) Other respiratory **4.9** (3.5-6.5)
Brierley 1998 [10] Retrospective cohort with stage 1-2 HL treated in Canada 1973-184 (n=611); median f/u 11 y; comparator age-matched general population for same period	**3.3** (1.5-7.0)	
Rugbjerg 2017 [23] Retrospective Danish cohort treated when aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	Hospitalisation: All respiratory **2.8** (1.4-5.3) Lung, bronchus, trachea **2.8** (1.4-5.6))	Mesothelioma **4.9** (1.2-19.9)
Behringer 2004 [83] Retrospective analysis of patients treated in GHSG trials 1983-1998 (n=5367); median f/u 72 m	**3.8** (1.7-8.2)	
Swerdlow 1992 [85] Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	**3.8** (2.6-5.4)	
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	**4.9** (3.0-7.1)	
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y	**7.0** (3.7-11.9)	
van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	**3.7** (2.5-5.3)	
van Leeuwen 1989 [92]	**5.4** (2.5-10.2)	

Retrospective cohort treated for HL in the Netherlands 1966-1986 (n=744); median f/u 6.4 y		
Munker 1999 [93] Retrospective cohort treated in Germany 1974-1994 (n=1120); mean f/u 9.1 y	**2.8** (1.5-4.8)	
Salloum 1996 [103] Retrospective cohort treated in the USA 1969-1985 1968-1994 (n=313); median f/u 12.8 y	**10.8** (5.3-22.2) (*P* < .001)	
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	**6.47** (2.96-12.29) (<.001) Pleura **200.00** (24-722) (<.001)	
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	**4.5** (1.9-8.9)	
Prior 1988 [121] Retrospective cohort treated in the UK 1950-1979 (n=2999); median f/u 6.7 y; comparator general population	**2.5** (95% CI not given)	
Chronowski 2004 [124] Retrospective cohort treated for stage 1-2 HL in the USA 1980-1995 (n=286); median f/u of survivors 7.4 y	**1.3** (0.0-7.2)	
Hancock 1996 [125] Retrospective cohort treated in the USA 1960-1990 (n=2162); mean f/u 9.3 y	**10.3** (7.0-13.7)	
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given	**2.9** (2.6-3.2)	
Hodgson 2007 [127] Retrospective cohort of 5 y HL survivors treated in North America & Europe 1970-2001 (n=18,862); median f/u 12.2 y	**6.7** (5.6-7.8) Pleura **19.5** (7.3-40.3)	
Boivin 1995 [129] Retrospective cohort treated in the USA and Canada 1940-1987 (n=10,472); average f/u 7.1 y (after discounting the 1st year after diagnosis)	**2.6** (2.1-4.0)	**1.5** (0.9-2.7) (thoracic RT field)
Boivin 1988 [130] Pooled analysis of data from 7 cohorts with incidence rates of second cancers, and details of treatment given for HL; 6513 participants; median f/u 43-71.4 m	**2.5** (95% CI not given)	

Varady 2001 [136] Retrospective cohort treated in Hungary 1978-1996 (n=665); median f/u not given Quoted expected incidences of second cancers extremely low, resulting in disproportionally high relative risks, therefore values not included in text	**10.57** (3.42-24.67)	
Lorigan 2005 [163] Systematic review of studies reporting risk of lung cancer following treatment for HL published in English since 1985; 20 studies included	**2.6-7.0***	
Travis 2002 [164] Case-control study nested in cohort of 19,046 HL survivors treated in the Netherlands 1965-1994 (222 cases, 444 matched controls); median f/u not given	**5.9** (2.7-13.5)	
Ibrahim 2013 [165] Meta-analysis of papers quantifying risk of second lung cancer in HL survivors; data on 74,831 patients; median f/u 11.5 y	**4.88*** (3.14-7.60)	
van Leeuwen 1995 [166] Retrospective cohort treated in the Netherlands 1966-1983 (n=744); median f/u 6.4 y	**4.1** (vs chemo only) (0.48-36) Crude **5.3** (0.57-49)	Adj. for smoking **4.3** (0.44-43)
Median time to development		
Almagro-Casado 2016 [79] Retrospective cohort treated in Spain 1968-2012 (n=604); median f/u not given	**16.5 y**	
de Bruin 2009 [131] Retrospective cohort of 5 y HL survivors treated in the Netherlands when aged <51 y 1965-1995; median f/u 18.1 y	Mesothelioma **27.7 y**	
Travis 2002 [164] Case-control study nested in cohort of 19,046 HL survivors treated in the Netherlands 1965-1994 (222 cases, 444 matched controls); median f/u not given	**10.0 y**	
Ibrahim 2013 [165] Meta-analysis of papers quantifying risk of second lung cancer in HL survivors; data on 74,831 patients; median f/u 11.5 y	**11.5* y** (mean)	
van Leeuwen 1995 [166]	**9.2 y**	

Retrospective cohort treated in the Netherlands 1966-1983 (n=744); median f/u 6.4 y		
List 1985 [167] Retrospective cohort treated in the USA 1970-1982 (n=260); median f/u not given	**7 y**	
Median age at development		
Almagro-Casado 2016 [79] Retrospective cohort treated in Spain 1968-2012 (n=604); median f/u not given	**54.9 y**	
de Bruin 2009 [131] Retrospective cohort of 5 y HL survivors treated in the Netherlands when aged <51 y 1965-1995; median f/u 18.1 y	Mesothelioma **56.4 y**	
Ibrahim 2013 [165] Meta-analysis of papers quantifying risk of second lung cancer in HL survivors; data on 74,831 patients; median f/u 11.5 y	**45.0* y**	
Variation in risk with time since radiotherapy		
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	**SIR** < 5 y **2.1** (0.6-5.4) 5-15 y **4.6** (2.5-7.7)	 15-25 y **3.3** (1.3-6.7) > 25 y **1.5** (0.2-5.3)
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py)	**SIR** 0-4 y **1.9** (1.1-2.9) 5-9 y **3.8** (2.5-5.5) 10-14 y **4.9** (3.1-7.4) ≥15 y **5.2** (3.0-8.5)	**AER** 0-4 y **3.9** 5-9 y **13.8** 10-14 y **21.5** ≥15 y **28.3**
Swerdlow 1992 [85] Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	**RR** 0-4 y **2.4** (1.2-4.2) 5-9 y **4.3** (2.2-7.8)	 ≥10 y **8.3** (4.0-15.3) All **3.8** (2.6-5.4)
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y (AER / 10,000 py)	**RR** 0-5 y **0** (0.0-3.1) 5-10 y **3.8** (1.0-9.8) 10-15 y **5.2** (1.7-2.2) 15-20 y **8.0** (2.9-17.3)	**AER** 0.5 y **-2.0**/ 5-10 y **6.9** 10-15 y **13.5** 15-20 y **30.0**

	>20 y **11.9** (4.8-24.5)	>20 y **63.5**
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y	**RR** 1-4 y **-** 5-9 y **3.7** (0.1-20.7) 10-14 y **6.9** (1.4-20.0) 15-19 y **9.9** (3.2-23.1) ≥20 y **7.5** (2.0-19.1)	**AER** 1-4 y **-** 5-9 y **1.5** 10-14 y **7.4** 15-19 y **21.6** ≥20 y **26.7**
van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	**RR** < 1 y **2.0** (0.2-7.1) 1-4 y **2.8** (1.2-5.5) 5-9 y **4.8** (2.4-8.6)	10-14 y **5.2** (2.1-10.7) ≥15 y **4.0** (0.8-11.7)
Swerdlow 1997 [91] Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1 y	**SIR** 0-4 y **1.3** (0.2-4.0) 5-9 y **5.7** (2.3-11.6) (*P* < .001)	10-14 y **7.8** (3.1-15.8) (*P* < .001) ≥ 15 y **1.6** (0.1-7.0)
Henry-Amar 1992 [102] Retrospective international cohort of 1 y HL survivors treated 1960-1987 (n=12,411); median f/u not given	**RR** Males 1-4 y **1.22** 5-9 y **2.34** 10-14 y **4.03** (95% CIs not given)	15-19 y **2.38** ≥20 y **5.26** Females 1-4 y **0.89** 5-9 y **7.22** 10-14 y **8.70**
		15-19 y **0.00** ≥20 y **33.33**
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y (AER / 10,000 py)	**SIR** 1-4 y **1.7** (0.2-6.3) 5-9 y **4.8** (1.8-10.5) 10-19 y **6.4** (3.4-11.0) ≥ 20 y **7.3** (2.4-17.1)	**AER** 1-4 y **6** 5-9 y **17** 10-19 y **27** ≥ 20 y **42**
Kumar 2018 [117] Retrospective cohort treat in the USA 1973-2014 (n=23,864); comparator USA general population; median f/u not given	**SIR**, lung cancer 2-11 m **2.21** 12-59 m **1.79**	60-119 m **2.69** 120-179 m **2.67**
		180-239 m **4.04** ≥240 m **3.65**

	SIR, mesothelioma 2-11 m **0** 12-59 m **1.27**	60-119 m **5.3** 120-179 m **0**	180-239 m **4.42** ≥240 m **2.78**
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population (AERs / 10,000 py)	**SIR** 1-9 y **2.65** (2.04-3.44) 10-19 y **4.48** (3.28-6.10)		20-30 y **5.41** (3.80-7.69) >30 y **4.52** (2.50-8.16)
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given (AERs / 10,000py)	**RR** 1-9 y **3.3** 10-14 y **4.1**	15-19 y **4.0** 20-24 y **5.5**	≥25 y **0.7** (*P* < .05)
Boivin 1995 [129] Retrospective cohort treated in the USA and Canada 1940-1987 (n=10,472); average f/u 7.1 y (after discounting the 1st year after diagnosis)	**RR** 0-4 y **1.5** (0.7-3.5) 5-9 y **0.9** (0.4-2.2)		≥10 y **2.7** (1.1-6.8) All **1.5** (0.9-2.7)
de Bruin 2009 [131] Retrospective cohort of 5 y HL survivors treated in the Netherlands when aged <51 y 1965-1995; median f/u 18.1 y	**SIR**, mesothelioma 5-25 y **15.5** (5.7-33.8) ≥2 5 y **58.4** (23.5-120)		**AER**, mesothelioma 5-25 y **1.7** (0.6-3.9) ≥25 y **21.5** (8.4-44.7)
Travis 2002 [164] Case-control study nested in cohort of 19,046 HL survivors treated in the Netherlands 1965-1994 (222 cases, 444 matched controls); median f/u not given	**RR,** RT ≥5 Gy to lungs 1-4 y **1.2** (0.3-4.5) (*P* = .76) 5-9 y **9.2** (2.9-34) (*P* < .001) 10-14 y **1.9** (0.5-7.7) (*P* = .34)		15-19 y **2.4** (0.6-12.9) (*P* = .27) ≥20 y **3.0** (0.7-18.9) (*P* = .24)
Ibrahim 2013 [165] Meta-analysis of papers quantifying risk of second lung cancer in HL survivors; data on 74,831 patients; median f/u 11.5 y	**RR** 10-14 y **4.17*** (3.62-8.81) ≥15 y **4.01*** (2.6-5.98)		

*pooled estimate (meta-analysis)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – y: years; HL: Hodgkin lymphoma; n: number; f/u: follow-up; EORTC: European Organisation for Research and Treatment of Cancer; py: person-years; confidence interval; RT: radiotherapy; m: months; SIR: standardised incidence ratio; AER: absolute excess risk; RR: relative risk; RT: radiotherapy; Gy: gray

e. Gastrointestinal malignancies

Study details	Risk estimate	
Cumulative incidence		
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	All: 5 y **0.1%** 15 y **0.9%** 25 y **1.7%**	Stomach: 15 y **0.5%** 25 y **1.7%**
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	30 y: All **7.0%** (5.9-8.3) Oesophagus **1.5%** (1.0-2.1) Stomach **1.6**% (1.1-2.3) Pancreas **1.0%** (0.6-1.6)	Colon **1.5%** (1.0-2.1) Rectum / rectosigmoid **1.0%** (0.6-1.5)
van Eggermond 2017 [135] Retrospective cohort of Dutch 5 y HL survivors treated 1965-1995 (n=3121); median f/u 22.9 y	20 y: **0.6%** (0.4-1.0) Colon **0.3%** (0.1-0.5) Ascending **0.1%** (0.0-0.2) Transverse **0.1%** (0.0-0.3) Descending **0.1%** (0.0-0.3) Rectum **0.4%** (0.2-0.6)	30 y: **2.1%** (1.4-2.8) Colon **1.2%** (0.8-1.9) Ascending **0.4%** (0.2-0.8) Transverse **0.5%** (0.2-0.9) Descending **0.3%** (0.1-0.6) Rectum **0.8%** (0.5-1.0)
Morton 2014 [168] International nested case-control study in cohort of 19,882 >5 y HL survivors treated 1943-1992 (36 casesd, 71 controls); median f/u not given	Oesophageal: 30 y **0.38%**	
Morton 2013 [169] International case-cohort study nested in a cohort of 19,882 HL survivors treated 1953-2003 (89 cases, 190 matched controls); median f/u not given	Stomach: 15 y **0.39%** (0.28-0.50)	30 y **0.92%** (0.70-1.13)
Dores 2014 [170] Nested case-control study in international cohort of ≥5 y HL survivors, treated 1953-2003 (n=36 cases, 70 controls)	Pancreatic: 15 y **0.16%** (0.09-0.23)	30 y **0.54%** (0.36-0.72)
Standardised incidence ratio		
Cosset 1991 [56]	Stomach (males) **7.1** ($P < .001$)	

Pooled analysis of 4 EORTC trials H1, H2, H5, H6), run 1964-1988; 1660 patients; median f/u not reported		
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	Colon & rectum **2.5** (1.5-3.9) Stomach **4.4** (2.1-8.1)	
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5	All **1.7** Oesophagus **2.0** Stomach **1.6** Liver **4.4** Pancreas **1.0**	Small intestine **8.8** Colon **1.3** Rectum **1.3**
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	**4.6** (3.9-5.3) Oesophagus **9.5** (6.7-13.1) Stomach **7.4** (5.3-10.1)	Colon **2.9** (2.1-3.9) Rectum / rectosigmoid **2.6** (1.7-3.9) Pancreas **5.7** (3.6-8.5)
Swerdlow 1997 [91] Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1y	Stomach **4.0** (1.2-9.3) (*P* < .05) Colon **1.4** (0.2-4.4)	
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	Oesophagus **4.1** (1.6-8.4) Stomach **2.7** (1.2-5.3)	Small intestine **16.2** (3.3-47.3) Colon / rectum **2.0** (1.2-3.2)
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y	Stomach **4.9** (1.8-10.7) Pancreas **1.3** (0.2-4.7)	Colon **1.9** (0.9-3.7) Rectum **2.7** (1.0-5.5)
Kumar 2018 [117] Retrospective cohort treat in the USA 1973-2014 (n=23,864); comparator USA general population; median f/u not given	Oesophagus **2.12** Stomach **2.42**	Colon **1.57** Rectum / recto-sigmoid **0.87** Anus / ano-rectum **4.07**
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population	Oesophagus **2.62** (1.52-4.51) Stomach **1.78** (1.25-2.52) Hepatobiliary **1.47** (0.93-2.34) Pancreas **2.09** (1.44-3.03)	Colon **2.21** (1.78-2.74) Rectum **1.38** (0.97-1.95) Colorectal **1.85** (1.54-2.23)
van den Belt-Dusebout 2009 [134]	Stomach **5.0** (3.0-7.8)	

Nested case-control study in a cohort of 5142 5 y survivors of HL or testicular cancer treated in the Netherlands 1965-1995; only data relating to HL patients extracted (19 cased, 69 controls); median f/u not given		
van Eggermond 2017 [135] Retrospective cohort of Dutch 5 y HL survivors treated 1965-1995 (n=3121); median f/u 22.9 y	**2.4** (1.8-3.2) Colon **2.5** (2.5-2.2) Ascending **2.2** (1.1-3.8) Transverse **6.5** (3.3-11.3)	Descending **1.2** (0.5-2.4) NOS **4.3** (0.5-15.4) Rectum **2.4** (1.5-3.7)
Standardised mortality ratio		
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	All **5.1** (4.4-6.0) Oesophagus **7.8** (5.5-10.7) Stomach **6.8** (4.6-9.6)	Pancreas **5.0** (3.4-7.1) Colon **2.8** (1.8-4.1) Rectum, sigmoid & anus **6.7** (4.1-10.4)
Absolute excess risk		
Aleman 2003 [1] Retrospective Dutch cohort treated when aged <41 y 1965-1987 (n=1261); median f/u 17.8 y; comparator general Dutch population	Death from GI malignancy **10.4** / 10,000py	
Rugbjerg 2019 [8] Retrospective cohort of Danish >5 y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	Hospitalisation (/ 10,000 py) Stomach **4** (0.7-7.5)	 Oesophagus **3** (-0.1-5.2)
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y (AERs / 10,000 py)	All **13.8** Oesophagus **3.4** Stomach **2.7**	Pancreas **1.7** Colon **1.8** Rectum, sigmoid & anus **2.6**
Rugbjerg 2017 [23] Retrospective Danish cohort treated when aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	Hospitalisation: All gastrointestinal **8** (1-14) / 10,000 py Colorectal **3** (-1-7) / 10,000 py	
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	Stomach: **6.2** / 10,000 py	
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py)	Oesophagus **0.5** Stomach **1.5** Small intestine **0.4**	Liver **0.5** Colon **2.2** Rectum **0.3**

	Pancreas **0.0**	
Swerdlow 1992 [85] Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	Oesophagus **0.7** / 10,00 0py Stomach **0.4** / 10,000 py	Colon **3.2** / 10,000 py Rectum **0.1** / 10,000 py
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	**11.3** / 10,000 py	
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1y; comparator Dutch general pop (AERs / 10,000 py)	All **24.0** (19.7-28.7) Oesophagus **5.6** (3.8-8.0) Stomach **5.6** (3.7-8.0)	Pancreas **3.1** (1.7-5.0) Colon **4.6** (2.6-7.0) Rectum / rectosigmoid **2.6** (1.1-4.5)
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y	All **14.1** / 10,000 py Oesophagus **3.0** / 10,000 py Stomach **3.9** / 10,000 py	Liver **1.8** / 10,000 py Colon **1.2** / 10,000 py Rectum **2.6** / 10,000 py
van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	**6.1** / 10,000 py Stomach **0.9** / 10,000 py	Colon **2.8** / 10,000 py Rectum **0.5** / 10,000 py
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	Stomach **3** / 10,000 py Other digestive organs **3** / 10,000 py	
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	**2.4** / 10,000 py Oesophagus **1.5** / 10,000 py	Stomach **1.5** / 10,000 py Small intestine **0.8** / 10,000 py
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6y; comparator general Swedish population	Oesophagus **0.8** / 10,000 py Stomach **1.4** / 10,000 py Hepatobiliary **0.6** / 10,000 py Pancreas **1.5** / 10,000 py	Colon **4.7** / 10,000 py Rectum **0.9** / 10,000 py Colorectal **5.4** / 10,000 py
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	**9.4** / 10,000 py	
Chronowski 2004 [124]	**2.6** / 10,000 py	

Retrospective cohort treated for stage 1-2 HL in the USA 1980-1995 (n=286); median f/u of survivors 7.4 y		
Hancock 1996 [125] Retrospective cohort treated in the USA 1960-1990 (n=2162); mean f/u 9.3y	Stomach **3.2** / 10,000 py	
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given (AERs / 10,000 py)	All **5.9** Oesophagus **0.7** Stomach **1.5** Small intestine **0.1**	Colon **2.0** Rectum **0.4** Liver / gallbladder **0.4** Pancreas **0.5**
Birdwell 1997 [133] Retrospective cohort treated in the USA 1961-1994 (n=2441); average f/u 10.9 y (AERs / 10,000 py)	Incidence **5.8** Oesophagus **0.2** Stomach **2.6** Small intestine **0.7** Pancreas **1.1** Colon **1.1** Rectum **0.4** Colorectal **1.5**	Mortality **5.3** Oesophagus **0.2** Stomach **2.4** Small intestine **0.7** Pancreas **1.2** Colorectal **1.1**
van den Belt-Dusebout 2009 [134] Nested case-control study in a cohort of 5142 5 y survivors of HL or testicular cancer treated in the Netherlands 1965-1995; only data relating to HL patients extracted (19 cased, 69 controls); median f/u not given	Stomach **5.0** / 10,000 py	
van Eggermond 2017 [135] Retrospective cohort of Dutch 5 y HL survivors treated 1965-1995 (n=3121); median f/u 22.9 y (AERs / 10,000 py)	**5.7** (3.3-8.6) Colon **3.5** (1.7-5.9) Ascending **1.1** (0.1-2.7) Transverse **1.8** (0.8-3.4)	Descending **0.3** (-0.5-1.6) NOS **0.3** (0.0-1.2) Rectum **2.1** (0.7-4.1)
Relative risk		
Aleman 2003 [1] Retrospective Dutch cohort treated when aged <41y 1965-1987 (n=1261); median f/u 17.8y; comparator general Dutch population	Death from gastrointestinal malignancies **7.7** (95% CI not given)	
Rugbjerg 2019 [8] Retrospective cohort of Danish >5y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	Hospitalisation Stomach **6.5** (3.2-13.1)	Oesophagus **6.0** (2.5-14.6)

Rugbjerg 2017 [23] Retrospective Danish cohort treated when aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	Hospitalisation: All gastrointestinal **3.1** (1.8-5.3)	Colorectal **2.4** (1.1-5.4)
Behringer 2004 [83] Retrospective analysis of patients treated in GHSG trials 1983-1998 (n=5367); median f/u 72 m	Colon **3.2** (1.3-7.9)	
Swerdlow 1992 [85] Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	Oesophagus **2.5** (0.3-9.0) Stomach **1.3** (0.3-3.9)	Colon **3.2** (1.4-6.2) Rectum **1.1** (0.1-3.9)
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	**4.0** (2.5-8.8)	
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y (individual malignancy data irrespective of treatment)	All **3.7** (1.0-9.5)	Oesophagus **30.6** (9.9-71.4) Stomach **10.9** (4.4-22.6) Colon **2.8** (0.6-8.1) Rectum **7.0** (2.3-16.4) Liver **40.1** (8.3-117)
van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	**2.0** (1.2-3.1) Stomach **1.6** (0.4-4.1)	Colon **2.5** (1.1-4.9) Rectum **1.4** (0.3-4.0)
Munker 1999 [93] Retrospective cohort treated in Germany 1974-1994 (n=1120); mean f/u 9.1 y	Colon **1.6** (0.7-3.2)	
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	Stomach **4.26** (0.52-15.37) (*P* > .20) Other digestive organs **1.68** (0.46-4.30) (> .20)	
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	**4.9** (2.3-9.1)	
Chronowski 2004 [124] Retrospective cohort treated for stage 1-2 HL in the USA 1980-1995 (n=286); median f/u of survivors 7.4 y	**2.4** (1.3-3.6)	
Hancock 1996 [125]	Stomach **4.9** (2.3-9.4)	Pancreas **3.9** (1.0-10.5)

Retrospective cohort treated in the USA 1960-1990 (n=2162); mean f/u 9.3 y	Colon or rectum **1.3** (0.5-2.7)	
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given	All **1.7** (1.5-1.8) Oesophagus **2.8** (1.8-4.0) Stomach **1.9** (1.5-2.4) Small intestine **1.5** (0.5-3.5)	Colon **1.6** (1.4-1.9) Rectum **1.2** (0.9-1.6) Liver / gallbladder **1.6** (1.1-2.3) Pancreas **1.5** (1.1-2.0)
Hodgson 2007 [127] Retrospective cohort of 5 y HL survivors treated in North America & Europe 1970-2001 (n=18,862); median f/u 12.2 y	Oesophagus **4.2** (1.8-7.8) Stomach **9.5** (6.9-12.6) Pancreas **4.7** (2.9-7.1)	Colon **4.3** (3.2-5.6) Rectum & anus **1.8** (1.0-3.0)
Boivin 1995 [129] Retrospective cohort treated in the USA and Canada 1940-1987 (n=10,472); average f/u 7.1 y (after discounting the 1st year after diagnosis)	**1.8** (1.1-3.2)	
Boivin 1988 [130] Pooled analysis of data from 7 cohorts with incidence rates of second cancers, and details of treatment given for HL; 6513 participants; median f/u 43-71.4 m	**1.8** (95% CI not given)	
Birdwell 1997 [133] Retrospective cohort treated in the USA 1961-1994 (n=2441); average f/u 10.9 y	Incidence **2.5** (1.5-3.5) Oesophagus **1.7** (0.0-8.3) Stomach **7.3** (3.4-13.8) Small intestine **11.6** (1.9-38.3) Pancreas **3.5** (1.1-8.5) Colon **1.7** (0.7-3.4) Rectum **1.5** (0.4-4.1) Colorectal **1.7** (0.8-3.0)	Mortality **3.8** (2.4-4.7) Oesophagus **1.9** (0.0-9.5) Stomach **10.8** (4.7-21.4) Small intestine **43.5** (7.2-143.8) Pancreas **4.1** (1.3-9.8) Colorectal **2.3** (0.8-5.0)
Varady 2001 [136] Retrospective cohort treated in Hungary 1978-1996 (n=665); median f/u not given Quoted expected incidences of second cancers extremely low, resulting in disproportionally high relative risks, therefore values not included in text	Oesophagus **18.18** (0.46-101.3) Stomach **9.05** (1.05-32.67) Pancreas **20.41** (0.52-113.67)	Liver **27.03** (0.68-150.54) Colorectal **9.84** (2.03-28.75)
Median time to development		
Birdwell 1997 [133] Retrospective cohort treated in the USA 1961-1994 (n=2441); average f/u 10.9 y	**12 y**	

van den Belt-Dusebout 2009 [134] Nested case-control study in a cohort of 5142 5 y survivors of HL or testicular cancer treated in the Netherlands 1965-1995; only data relating to HL patients extracted (19 cased, 69 controls); median f/u not given	Stomach **17.4 y**
van Eggermond 2017 [135] Retrospective cohort of Dutch 5 y HL survivors treated 1965-1995 (n=3121); median f/u 22.9 y	Colorectal **22.9 y**
Morton 2014 [168] International nested case-control study in cohort of 19,882 >5 y HL survivors treated 1943-1992 (36 cases, 71 controls); median f/u not given	Oesophageal **16 y**
Morton 2013 [169] International case-cohort study nested in a cohort of 19,882 HL survivors treated 1953-2003 (89 cases, 190 matched controls); median f/u not given	Stomach **15 y**
Dores 2014 [170] Nested case-control study in international cohort of ≥5y HL survivors, treated 1953-2003 (n=36 cases, 70 controls)	Pancreas **19 y**
Median age at development	
Dietrich 1993 [132] Retrospective cohort treated in France 1960-194 (n=892); median f/u not given	Stomach **38.8 y** (mean)
Birdwell 1997 [133] Retrospective cohort treated in the USA 1961-1994 (n=2441); average f/u 10.9 y	**49 y**
van den Belt-Dusebout 2009 [134] Nested case-control study in a cohort of 5142 5 y survivors of HL or testicular cancer treated in the Netherlands 1965-1995; only data relating to HL patients extracted (19 cases, 69 controls); median f/u not given	Stomach **41.6 y**
van Eggermond 2017 [135] Retrospective cohort of Dutch 5 y HL survivors treated 1965-1995 (n=3121); median f/u 22.9 y	Colorectal **56.4 y**
Morton 2014 [168] International nested case-control study in cohort of 19,882 >5 y HL survivors treated 1943-1992 (36 casesd, 71 controls); median f/u not given	Oesophageal **54 y**

Morton 2013 [169] International case-cohort study nested in a cohort of 19,882 HL survivors treated 1953-2003 (89 cases, 190 matched controls); median f/u not given	Stomach **50 y**		
Dores 2014 [170] Nested case-control study in international cohort of ≥5 y HL survivors, treated 1953-2003 (n=36 cases, 70 controls)	Pancreatic **60.5 y**		
Variation in risk with time since radiotherapy			
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	**SIR**, colon & rectum <5 y **0.8** (0.0-4.4) 5-15 y **2.3** (0.8-5.0) 15-25 y **2.3** (0.7-5.3) >25 y **4.7** (1.9-9.7)	**SIR**, stomach <5 y **0.0** (0.0-6.2) 5-15 y **4.8** (1.3-12.3) 15-25 y **9.5** (3.1-22.2) >25 y **3.2** (0.1-17.9)	
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y	**SIR**, all <5 y **1.1** (0.6-1.9) 5-9 y **2.3** (1.3-3.5) 10-14 y **1.8** (0.8-3.2) ≥15 y **4.6** (2.7-7.3)	**SIR**, stomach <5 y **0.8** (0.1-2.5) 5-9 y **2.9** (1.0-6.3) 10-14 y **2.7** (0.7-7.0) ≥15 y **4.3** (1.1-11.1)	**SIR**, colon <5 y **1.3** (0.4-3.1) 5-9 y **2.3** (0.8-5.0) 10-14 y **2.7** (0.8-6.2) ≥15 y **4.7** (1.7-10.2)
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y (AER / 10,000 py)	**RR** 0-5 y **2.5** (0.7-6.4) 5-10 y **2.9** (0.8-7.4) 10-15 y **2.4** (0.5-6.9) 15-20 y **7.2** (2.9-14.9) >20 y **8.3** (3.1-18.1)	**AER** 0.5 y **4.1** 5-10 y **6.1** 10-15 y **5.8** 15-20 y **34.4** >20 y **52.3**	
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	**SIR** 5-9 y **2.8** (1.4-5.0) 10-14 y **3.3** (2.0-5.2) 15-19 y **4.4** (2.9-6.3) 20-24 y **4.5** (2.9-6.6) 25-29 y **3.8** (2.3-6.0) 30-34 y **4.0** (2.2-6.6) ≥ 35 y **3.0** (1.3-6.0)	**AER** 5-9 y **3.8** 10-14 y **8.4** 15-19 y **19.1** 20-24 y **29.0** 25-29 y **34.0** 30-34 y **49.3** ≥ 35 y **47.1**	

	(*P* = .68)		(*P* < .001)	
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y	**RR** 1-4 y **3.4** (0.1-18.9) 5-9 y **5.3** (1.1-15.6) 10-14 y **11.1** (4.8-21.8) 15-19 y **6.8** (2.2-15.9) ≥ 20 y **11.5** (5.3-21.9)		**AER** 1-4 y **1.5** 5-9 y **5.0** 10-14 y **20.9** 15-19 y **20.5** ≥ 20 y **63.4**	
Henry-Amar 1992 [102] Retrospective international cohort of 1 y HL survivors treated 1960-1987 (n=12,411); median f/u not given	**RR**, men (no data given for women) (95% CIs not given) 1-4 y **1.12** 5-9 y **2.29**	10-14 y **2.73**	15-19 y **0.0**	≥20 y **0.0**
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y	**SIR**, stomach 1-4 y **1.2** (0-6.4) 5-9 y **1.3** (0-7.5) 10-19 y **8** (3.2-16.4) ≥2 0y **13** (2.7-38.1)		**AER**, stomach (/ 10,000 py) 1-4 y **3** 5-9 y **3** 10-1 9y **14** ≥20 y **25**	
Kumar 2018 [117] Retrospective cohort treat in the USA 1973-2014 (n=23,864); comparator USA general population; median f/u not given (all times in months)	**SIR**, all 2-11 **0.96** 12-59 **0.85** 60-119 **1.12** 120-179 **1.76** 180-239 **1.94** ≥240 **2.75**	Stomach 2-11 **0** 12-59 **1.34** 60-119 **1.09** 120-179 **2.18** 180-239 **3.71** ≥240 **5.31**	Colon 2-11 **1.64** 12-59 **0.74** 60-119 **1.21** 120-179 **1.81** 180-239 **1.91** ≥240 **2.51**	Liver & gb 2-11 **0.64** 12-59 **0.51** 60-119 **0.68** 120-179 **1.44** 180-239 **2.82** ≥240 **2.02**
	Oesophagus 2-11 **0** 12-59 **0.83** 60-119 **1.71** 120-179 **2.48** 180-239 **2.13** ≥240 **3.84**	Small intestine 2-11 **0** 12-59 **1.47** 60-119 **0.71** 120-179 **2.52** 180-239 **0.97** ≥240 **3.0**	Rectum 2-11 **0.33** 12-59 **0.74** 60-119 **0.97** 120-179 **0.62** 180-239 **0.77** ≥240 **1.33**	Pancreas 2-11 **0.44** 12-59 **0.86** 60-119 **0.77** 120-179 **1.95** 180-239 **1.19** ≥240 **3.44**

Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population	**SIR** Oesophagus 1-9 y **0.72** (0.18-2.90) 10-19 y **4.33** (1.80-10.41) 20-30 y **2.71** (0.68-10.83) > 30 y **12.84** (4.82-34.2) Stomach 1-9 y **1.58** (0.99-2.50) 10-19 y **2.53** (1.31-4.85) 20-30 y **1.11** (0.28-4.42) > 30 y **3.06** (0.77-12.24) Hepatobiliary 1-9 y **1.48** (0.82-2.68) 10-19 y **1.09** (0.35-3.37) 20-30 y **2.00** (0.65-6.20) > 30 y **1.08** (0.25-12.77) Pancreas 1-9 y **1.37** (0.76-2.47) 10-19 y **3.68** (2.04-6.64) 20-30 y **2.96** (1.23-7.12) > 30 y **1.51** (0.21-10.69)		Colon 1-9 y **2.00** (1.49-2.70) 10-19 y **2.80** (1.87-4.17) 20-30 y **2.26** (1.28-3.98) > 30 y **1.82** (0.68-4.86) Rectum 1-9 y **1.47** (0.94-2.30) 10-19 y **1.29** (0.61-2.70) 20-30 y **1.17** (0.44-3.12) > 30 y **1.41** (0.35-5.64) Colorectal 1-9 y **1.75** (1.36-2.25) 10-19 y **2.16** (1.51-3.09) 20-30 y **1.85** (1.13-3.02) > 30 y **1.68** (0.76-3.75)	
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given	**RR**, oesophagus 1-9 y **1.3** 10-14 y **6.2** 15-19 y **10.2** 20-24 y **19.5** **RR**, stomach 1-9 y **1.4** 10-14 y **4.4** 20-24 y **5.4** ≥25 y **5.3**		**RR**, colon 1-9 y **1.3** 10-14 y **2.1** 15-19 y **2.2** 20-24 y **2.9** ≥25 y **1.8** **RR**, rectum 1-9 y **1.1** 20-24 y **4.9**	

	15-19 y **3.4**	10-14 y **1.1** ≥25 y **1.1** 15-19 y **4.4**	
Birdwell 1997 [133] Retrospective cohort treated in the USA 1961-1994 (n=2441); average f/u 10.9 y	**RR** <10 y **2.0** (.1-3.5) 10-19 y **2.2** (1.0-4.2) ≥20 y **6.1** (2.5-12.7) <15 y **2.0** ≥15 y **1.8**	**AER** <10 y **3.1** 10-19 y **5.9** ≥20 y **40.0** <15 y **3.7** ≥15 y **5.5**	
van den Belt-Dusebout 2009 [134] Nested case-control study in a cohort of 5142 5 y survivors of HL or testicular cancer treated in the Netherlands 1965-1995; only data relating to HL patients extracted (19 cases, 69 controls); median f/u not given (AER / 10,000 py)	**SIR**, stomach 5-9 y **0.8** (0.0-4.5) 10-14 y **4.4** (1.1-11.2) 15-19 y **11.4** (4.9-22.6) 20-24 y **6.3** (1.2-18.6) ≥25 y **6.7** (1.3-20.0)	**AER**, stomach 5-9 y **-0.3** 10-14 y **3.8** 15-19 y **12.4** 20-24 y **7.2** ≥25 y **10.4**	
van Eggermond 2017 [135] Retrospective cohort of Dutch 5 y HL survivors treated 1965-1995 (n=3121); median f/u 22.9 y	**SIR** All colon sites 5-9 y **1.0** (0.0-5.3) 10-19 y **1.7** (0.7-3.4) 20-29 y **2.8** (1.5-4.7) ≥ 30 y **3.4** (1.7-5.9) Transverse 5-9 y **-** 10-19 y **6.7** (1.8-17.3) 20-29 y **8.1** (2.6-18.9) ≥ 30 y **7.0** (1.4-20.4)	Colon, other 5-9 y **0.9** (0.0-5.2) 10-19 y **0.8** (0.2-2.3) 20-29 y **2.1** (0.9-3.9) ≥ 30 y **2.9** (1.3-5.4) Rectum 5-9 y **1.4** (0.0-7.9) 10-19 y **3.2** (1.5-6.1) 20-29 y **2.2** (0.9-4.6) ≥ 30 y **1.9** (0.5-4.9)	
Morton 2013 [169] International case-cohort study nested in a cohort of 19,882 HL survivors treated 1953-2003 (89 cases, 190 matched controls); median f/u not given	**OR**, stomach <15 y since treatment <25 Gy ≥5600 mg/m^2 proc Ref	≥15 y since treatment <25 ≥5600 Ref	

	≥25 <5600 **1.5** (0.4-5.6) <25 ≥5600 **1.2** (0.4-3.9) ≥25 ≥5600 ∞ (10.0-∞) ($P_{interaction}$ = .003)	≥25 <5600 **4.2** (1.4-14.1) <25 ≥5600 **1.2** (0.3-4.2) ≥25 ≥5600 **67.0** (10.5-1407) ($P_{interaction}$ = .02)

*pooled estimate (meta-analysis)
Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.
Abbreviations – n: number; f/u: follow-up; y: years; HL: Hodgkin lymphoma; EORTC: European Organisation for Research and Treatment of Cancer; NOS: not otherwise specified; CI: confidence interval py: person-years; m: months; SIR: standardised incidence ratio; AER: absolute excess risk; RR; relative risk; Gy: gray; mg/m^2: milligrams per metre-squared

f. Cutaneous malignancies

Study details	Risk estimate			
Cumulative incidence				
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	NMSC: 5 y **0.1%** 15 y **0.5%**	25 y **1.9%**	Melanoma: 15 y **0.3%**	25 y **0.4%**
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	30 y: Melanoma **1.1** (0.7-1.5)	NMSC **0.7** (0.4-1.2)		
Daniëls 2013 [173] Retrospective cohort treated 1965-2005 in the Netherlands (n=889); comparator Dutch general population; median f/u not given	10 y **1.5%**	20 y **5%**	30 y **15%**	
Tucker 1985 [174] Retrospective cohort treated in the USA (n=1405) 1965-1982; average f/u 5.8 y; comparator regional general population	14 y: melanoma **3.3%** (+/-2.6)			
Standardised incidence ratio				
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	NMSC **1.9** (1.2-2.9)		Melanoma **3.5** (1.3-7.7)	

Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y	NMSC **1.4** (0.9-2.1)	Melanoma **2.3** (0.9-4.6)
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	NMSC **3.4** (2.2-5.0)	Melanoma **2.8** (1.9-3.9)
Swerdlow 1997 [91] Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1 y	NMSC **3.9** (1.9-6.8) (*P* < .001)	Melanoma **4.0** (0.7-12.2)
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	NMSC **2.4** (1.6-3.4)	Melanoma **2.7** (1.1-5.5)
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y	Melanoma **2.8** (2.4-5.8)	
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population	SCC **4.44** (3.65-5.41)	Melanoma **2.08** (1.54-2.82)
Daniëls 2013 [173] Retrospective cohort treated 1965-2005 in the Netherlands (n=889); comparator Dutch general population; median f/u not given	Melanoma **2.6** (0.9-5.6) SCC **5.0** (2.4-9.2) 1st BCC **7.9** (5.5-11.2)	BCC **5.2** (4.0-6.6) Head & neck **2.1** (1.2-3.4) Trunk **11.7** (8.2-16.2) Limbs **1.7** (0.3-5.0) Other/NOS **185.6** (92.7-332.1)
Herr 2018 [175] Retrospective cohort of Causasian adults initially diagnosed with lymphoid neoplasms or cutaneous malignancies in the US 2000-2014 when aged 20-83 y (151,949 >1 y survivors of lymphoid neoplasms); only data related to HL extracted	**2.09** (1.37-3.03) Location: Head & neck **1.37** (0.63-2.61) Trunk **1.62** (0.97-2.53) ($P_{heterogeneity}$ = .81)	 Limb **1.92** (1.26-2.79) Other **3.09** (0.84-7.91)
Absolute excess risk		
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	NMSC **8.8** / 10,000 py	Melanoma **3.4** / 10,000 py
Swerdlow 2000 [84]	NMSC **1.4** / 10,000 py	Melanoma **0.7** / 10,000 py

Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y		
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	Melanoma **3.1** / 10,000 py	
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1y; comparator Dutch general pop	NMSC **3.1** (1.6-5.1) / 10,000 py	Melanoma **3.6** (1.9-5.9) / 10,000 py
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y	Melanoma **3.5** / 10,000 py	
van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	Melanoma **2.4** / 10,000 py	
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	Melanoma **4** / 10,000 py	
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	NMSC **5.1** / 10,000 py	Melanoma **1.3** / 10,000 py
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population (AERs / 10,000 py)	SCC **8.1** / 10,000 py	Melanoma **2.3** / 10,000 py
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	Melanoma **2.7** / 10,000 py	
Chronowski 2004 [124] Retrospective cohort treated for stage 1-2 HL in the USA 1980-1995 (n=286); median f/u of survivors 7.4 y	Melanoma **11.6** / 10,000 py	
Hancock 1996 [125] Retrospective cohort treated in the USA 1960-1990 (n=2162); mean f/u 9.3 y	Melanoma **4.1** / 10,000 py	
Dores 2002 [126]	Melanoma **0.9** / 10,000 py	

Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given		
Daniëls 2013 [173] Retrospective cohort treated 1965-2005 in the Netherlands (n=889); comparator Dutch general population; median f/u not given	Melanoma **3.6** / 10,000 py SCC **7.9** / 10,000 py 1st BCC **93.9** / 10,000 py	BCC **53.3** / 10,000 py Head & neck **8.8** / 10,000 py Trunk **32.4** / 10,000 py Limbs **1.2** / 10,000 py Other **10.8** / 10,000 py
Relative risk		
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	Melanoma **3.3** (1.3-6.7)	
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y	Melanoma **5.5** (2.2-11.2)	
van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	Melanoma **4.9** (1.6-11.3)	
Munker 1999 [93] Retrospective cohort treated in Germany 1974-1994 (n=1120); mean f/u 9.1 y	Melanoma **2.5** (0.4-8.2)	
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	Melanoma **11.76** (1.42-43) (*P* < .001)	
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	Melanoma **4.1** (0.8-11.9)	
Prior 1988 [121] Retrospective cohort of 1y HL survivors treated in the UK 1950-1979 (n=1976); mean f/u 6.7 py	Non-melanoma **2.3** (95% CI not given)	
Chronowski 2004 [124] Retrospective cohort treated for stage 1-2 HL in the USA 1980-1995 (n=286); median f/u of survivors 7.4 y	Melanoma **7.3** (1.5-21.3)	
Hancock 1996 [125]	Melanoma **11.6** (5.7-21.3)	

Retrospective cohort treated in the USA 1960-1990 (n=2162); mean f/u 9.3 y		
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given	Melanoma **1.7** (1.3-2.3)	
Hodgson 2007 [127] Retrospective cohort of 5 y HL survivors treated in North America & Europe 1970-2001 (n=18,862); median f/u 12.2 y	Melanoma **1.6** (1.1-2.3)	
Boivin 1995 [129] Retrospective cohort treated in the USA and Canada 1940-1987 (n=10,472); average f/u 7.1 y (after discounting the 1st year after diagnosis)	Melanoma **2.2** (1.2-3.6)	
Boivin 1988 [130] Pooled analysis of data from 7 cohorts with incidence rates of second cancers, and details of treatment given for HL; 6513 participants; median f/u 43-71.4 m	Melanoma **6.7** (95% CI not given)	
Varady 2001 [136] Retrospective cohort treated in Hungary 1978-1996 (n=665); median f/u not given Quoted expected incidences of second cancers extremely low, resulting in disproportionally high relative risks, therefore values not included in text	Melanoma **55.56** (6.44-200.56)	
Tucker 1985 [174] Retrospective cohort treated in the USA (n=1405) 1965-1982; average f/u 5.8 y; comparator regional general population	Melanoma **8.0** (3-17)	
Median time to development		
Daniëls 2013 [173] Retrospective cohort treated 1965-2005 in the Netherlands (n=889); comparator Dutch general population; median f/u not given	**18 y**	
Median age at development		
Daniëls 2013 [173] Retrospective cohort treated 1965-2005 in the Netherlands (n=889); comparator Dutch general population; median f/u not given	**52 y**	
Variation in risk with time since radiotherapy		
Petrakova 2018 [81]	**SIR**, melanoma <5 y **0.0** (0.0-14.7)	**SIR**, NMSC <5 y **0.6** (0.0-3.4)

Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	5-15 y **3.4** (0.4-12.4) 15-25 y **1.8** (0.0-10.2) >25 y **9.3** (1.9-27.3)	5-15 y **1.0** (0.3-2.6) 15-25 y **2.4** (1.1-4.5) >25 y **3.3** (1.5-6.3)
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y	**SIR**, melanoma <5 y **4.2** (1.3-9.9) 5-9 y **1.3** (0.1-5.8)	 10-14 y **1.8** (0.1-7.8) ≥15 y **-**
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y	**SIR**, melanoma 1-4 y **6** (1.2-17.6) 5-9 y **1.5** (0-8.3) 10-19 y **2.3** (0.5-6.9) ≥20 y **2.4** (0.1-13.5)	**AER**, melanoma 1-4 y **9** 5-9 y **3** 10-19 y **6** ≥ 20y **8**
Kumar 2018 [117] Retrospective cohort treat in the USA 1973-2014 (n=23,864); comparator USA general population; median f/u not given	**SIR**, melanoma 2-11 m **1.01** 12-59 m **1.58**	 60-119 m **1.29** 120-179 m **1.47**	 180-239 m **1.78** ≥240 m **0.94**
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6y; comparator general Swedish population	**SIR**, SCC 1-9 y **4.91** (3.80-6.35) (*P* <.001) 10-19 y **4.66** (3.15-6.89) (*P* <.001) 20-30 y **3.52** (1.73-5.64) (*P* <.001) >30 y **3.13** (1.30-7.52) (*P* <.01)	Melanoma 1-9 y **2.34** (1.58-3.46) (*P* <.001) 10-19 y **1.69** (0.88-3.25) (*P* <.001) 20-30 y **2.00** (0.90-4.44) (*P* <.001) >30 y **3.13** (1.30-7.52) (*P* <.01)
Daniëls 2013 [173] Retrospective cohort treated 1965-2005 in the Netherlands (n=889); comparator Dutch general population; median f/u not given	**SIR**, 1st BCC 0-1 y **0** (-) 1-5 y **1.8** (0.2-6.3) 5-10 y **3.0** (0.9-7.0) 10-15 y **2.1** (0.6-5.5) 15-20 y **2.8** (1.0-6.2) 20-25 y **6.7** (3.7-11.3) 25-29 y **6.3** (3.0-11.7) 30-34 y **8.0** (3.8-14.7) >35 y **15.9** (9.1-25.9)	**AER**, 1st BCC 0-1 y **-** 1-5 y **5.1** / 10,000 py 5-10 y **16.0** / 10,000 py 10-15 y **11.7** / 10,000 py 15-20 y **24.7** / 10,000 py 20-25 y **98.1** / 10,000 py 25-29 y **113.0** / 10,000 py 30-34 y **218.7** / 10,000 py >35 y **626.4** / 10,000 py

Tucker 1985 [174] Retrospective cohort treated in the USA (n=1405) 1965-1982; average f/u 5.8 y; comparator regional general population	**AER** Melanoma (/ 1000 py) 1-2 y **0.3** 4-5 y **1.7**
Herr 2018 [175] Retrospective cohort of Causasian adults initially diagnosed with lymphoid neoplasms or cutaneous malignancies in the US 2000-2014 when aged 20-83 y (151,949 >1 y survivors of lymphoid neoplasms); only data related to HL extracted	**SIR** <5 y **1.93** (1.33-2.72) ≥5 y **1.57** (1.02-2.29) ($P_{heterogeneity}$ = .31)

*pooled estimate (meta-analysis)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – y: years; HL: Hodgkin lymphoma; n: number; f/u: follow-up; NMSC: non-melanoma skin cancer; SCC; squamous cell carcinoma; RT: radiotherapy; BCC: basal cell carcinoma; NOS: not otherwise specified; py: person-years; m: months; SIR: standardised incidence ratio; AER: absolute excess risk

g. Other solid tumours

Study details	Risk estimate	
Cumulative incidence		
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	Thyroid: 15 y **0.2%** 25 y **0.8%**	Kidney: 15 y **0.2%** 25 y **0.4%**
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1y; comparator Dutch general pop	30 y Thyroid **0.8%** (0.5-1.2) Kidney **0.4%** (0.2-0.8) Urinary tract **1.3%** (0.9-2.0) Bladder **0.6%** (0.3-1.1) Lip, oral cavity or pharynx **0.5%** (0.3-0.9)	Female genital organ **2.9%** (2.0-4.0) Endometrium **1.6%** (females) (0.9-2.6) Male genital organ **1.8%** (1.1-2.8) Prostate **1.4%** (0.8-2.4) CUP **1.3%** (0.8-1.9)
Michaelson 2014 [210]	Thyroid 10 y **0.26%**	

Retrospective cohort treated in the USA 1969-2008 (n=1981); median f/u 14.3 y		
Standardised incidence ratio		
Cosset 1991 [56] Pooled analysis of 4 EORTC trials H1, H2, H5, H6), run 1964-1988; 1660 patients; median f/u not reported	Salivary glands (parotid) **>50** (*P* <.001)	
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	Thyroid **11.9** (5.1-23.4) Kidney **2.7** (1.1-5.6)	
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y	Thyroid **7.6** (2.7-16.4) Bladder **0.8** (0.3-1.8) Cervix **2.1** (0.9-4.1) Prostate **0.8** (0.2-1.7)	Oropharynx **2.8** (1.1-5.8) Bone **10.7** (3.3-24.8) Soft tissue **3.9** (1.0-10.1) Nervous system **2.5** (1.1-4.8) CUP **2.3** (1.3-3.8)
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1y; comparator Dutch general pop	Thyroid **14.0** (8.9-21.0) Kidney **2.3** (1.2-4.1) Urinary tract **3.5** (2.5-4.7) Bladder **4.1** (2.6-6.2) Male genital organ **1.1** (0.7-1.7) Prostate **1.0** (0.6-1.7)	Lip, oral cavity or pharynx **3.2** (2.0-4.9) Soft-tissue sarcoma **12.0** (7.5-18.2) Female genital organ **2.8** (1.9-3.9) Endometrium: **3.6** (2.1-5.8) CUP **4.9** (3.3-7.0)
Swerdlow 1997 [91] Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1 y	Thyroid **8.2** (0.5-36.0) Prostate **2.1** (0.4-6.5) CUP **3.5** (0.9-9.1)	Oropharynx **5.7** (0.9-17.5) Bone **26.5** (4.4-81.8) Soft tissue **16.9** (2.8-52.3)
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	Thyroid **5.1** (1.1-15.0) Oropharynx **3.5** (1.3-7.7) Bone **9.0** (1.1-32.5)	Soft tissue **8.9** (2.9-20.7) CUP **4.7** (2.7-7.6)
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y	Prostate **1.7** (0.8-3.0)	Cervix **1.5** (0.2-5.4)
Kumar 2018 [117]	Thyroid **2.84**	Kidney **1.61**

Retrospective cohort treat in the USA 1973-2014 (n=23,864); comparator USA general population; median f/u not given	(95% CIs not given)	
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population	Thyroid **5.13** (3.31-7.94) Kidney **1.48** (0.98-2.22) Bladder **1.57** (1.15-2.15) Prostate **1.21** (0.73-2.07)	Pharynx **3.52** (1.95-6.35) Soft tissue **5.73** (3.7-8.89) Brain **2.58** (1.83-3.65) Uterus **1.22** (0.73-2.07)
Omer 2012 [119] Retrospective cohort treated in the USA 1970-2004 (n=198); median f/u 21.1; comparator general population	Thyroid **7.45** (0.9-26.93)	
Standardised mortality ratio		
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	Urogenital tract **2.0** (1.4-2.7) Ill-defined & unspecified site **6.9** (4.9-9.6)	
Absolute excess risk		
Rugbjerg 2019 [8] Retrospective cohort of Danish >5 y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	Hospitalisation (/ 10,000 py) Thyroid **2.2** (-0.2-4.6) Other endocrine **0.6** (-0.6-1.8) Urinary system **7** (2-11) Nervous system **2.2** (-0.2-4.6)	 Connective tissue **3.9** (0.7-7.1) Pharynx **2** (-0.5-4) Buccal cavity **4** (0.7-7.5) Meninges **0.03** (-1-1)
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**AEM** (/ 10,000 py) Urogenital tract **2.0**	 Ill-defined & unspecified site **3.2**
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	Thyroid: **5.9** / 10,000 py	Kidney: **3.5** / 10,000 py
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py)	Thyroid **0.9** Cervix **0.8** Prostate **-0.3** Bladder **-0.2**	Tongue, mouth & pharynx **0.8** Bone **0.8** Soft tissue **0.5** Nervous system **0.9** CUP **1.6**
Swerdlow 1992 [85]	Thyroid **1.0**	Mouth & pharynx **0.9**

Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given (AER / 10,000 py)	Bladder **0.6** Cervix **1.5**	Larynx **0.3** Bone **1.1**
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y (AER / 10,000 py)	Thyroid **2.6** Genitourinary **3.1** Head & neck **3.3**	Sarcoma **6.7** Gynaecological **-2.9** CNS **0.2**
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1y; comparator Dutch general pop (AERs / 10,000 py)	Thyroid **3.5** (2.1-5.5) Kidney **1.1** (0.2-2.6) Bladder **2.8** (1.4-4.6) Urinary tract **4.6** (2.7-7.0) Male genital organ **0.3** (-1.0-2.2) Prostate **0.1** (-1.1-1.9)	Lip, oral cavity or pharynx **2.3** (1.0-4.1) Soft-tissue sarcoma **3.3** (2-5.2) Female genital organ **3.6** (1.9-5.9) Endometrium **1.9** (0.8-3.6) CUP **3.8** (2.2-5.9)
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y (AERs / 10,000 py)	Thyroid **2.3** Urogenital **4.8** Urinary tract **0.7**	Mouth & pharynx **2.8** Connective tissue **1.7** Female genital **7.1** Male genital **1.5**
van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population (AERs / 10,000 py)	Kidney **1.2** Bladder **1.2** Urogenital **6.7** Prostate **1.5**	Head & neck **2.0** Connective tissue **1.6** Cervix **2.0** Ovary **1.9**
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	Head and neck **<1** / 10,000 py	
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given (AER / 10,000 py)	Thyroid **0.7** Oropharynx **1.2**	Bone **0.5** Soft tissue **1.3** CUP **3.7**
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6y; comparator general Swedish population (AERs / 10,000 py)	Thyroid **1.8** Kidney **0.8** Bladder **1.5** Prostate **2.1**	Pharynx **0.8** Connective tissue **1.7** Brain **2.1** Uterus **0.3**
Mauch 1996 [120]	Sarcoma **6.9**	Genitourinary / genitalia **0.1**

Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population (AER / 10,000 py)	Head & neck **3.9**	
Chronowski 2004 [124] Retrospective cohort treated for stage 1-2 HL in the USA 1980-1995 (n=286); median f/u of survivors 7.4 y (AER / 10,000 py)	Female genital system **1.3** Male genital system **-0.5** Urinary system **2.7**	Endocrine system **3.8** Brain **4.0** Soft tissue **4.3**
Hancock 1996 [125] Retrospective cohort treated in the USA 1960-1990 (n=2162); mean f/u 9.3y; all AERs / 10,000 py	Thyroid **2.3** Urogenital **4.1** Salivary gland **2.4**	Soft tissue sarcoma **3.8** Osteosarcoma **0.9**
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given (AERs / 10,000py)	Thyroid **1.4** Kidney **0.6** Bladder **0.8** Testis **0.3** Prostate **-0.1** Female genital, all **3.4** Cervix **1.6** Endometrium **0.8** Ovary **0.5**	Bone **0.3** Connective tissue **1.0** Brain & CNS **0.03** Eye **0.5** Buccal, all **2.7** Lip **0.6** Tongue **0.4** Salivary gland **0.5** Gum, other mouth **0.4** Pharynx **0.7** Larynx **0.3**
Michaelson 2014 [210] Retrospective cohort treated in USA 1969-2008 (n=1981); median f/u 14.3 y	**9.6** / 10,000 py	
Relative risk		
Rugbjerg 2019 [8] Retrospective cohort of Danish >5 y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	Hospitalisation Thyroid **9.4** (3.5-25.4) Other endocrine **34.3** (-) Urinary system **4.2** (2.5-6.9) Nervous system **9.3** (3.4-25.2)	 Soft tissue **10.9** (5.1-23.2) Pharynx **4.1** (1.5-11.1) Buccal cavity **6.2** (3.1-12.5) Meninges **1.1** (-)
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	Thyroid **15.6** (5.1-36.3) Kidney **5.4** (2.0-11.8)	
Swerdlow 1992 [85]	Thyroid **9.4** (1.1-33.9)	Mouth & pharynx **4.4** (0.5-15.7)

Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	Bladder **1.5** (0.3-4.5) Prostate **0.6** (0.02-3.6) Cervix **1.9** (0.2-6.8)	Larynx **2.0** (0.05-10.9) Bone **15.2** (1.8-54.7)
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	Thyroid **5.6** (1.8-13.0) Genitourinary **1.8** (0.9-3.2) Gynaecological **0.5** (0.1-1.2)	Sarcoma **26.6** (13.3-47.6) Head & neck **4.0** (1.6-8.2) CNS **1.4** (0.04-7.5)
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y	Thyroid **15.2** (4.1-39.0) Urinary tract **2.4** (0.3-8.6) Urogenital **3.5** (1.7-6.2) Male genital organs **3.0** (0.4-11)	Mouth & pharynx **9.8** (3.2-22.9) Connective tissue **12.1** (2.5-35.3) Female genital organs **4.1** (1.7-8.5)
van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	Kidney **2.9** (0.6-8.3) Bladder **2.0** (0.6-5.2) Prostate **1.5** (0.3-4.4) Urogenital **2.4** (1.4-3.7)	Head & neck **6.9** (1.9-17.5) Connective tissue **8.8** (1.8-25.8) Cervix **5.9** (1.6-15.2) Ovary **4.4** (1.2-11.3)
Munker 1999 [93] Retrospective cohort treated in Germany 1974-1994 (n=1120); mean f/u 9.1 y	Thyroid **4.0** (0.7-13.1) Genitourinary **1.5** (0.8-2.6)	Head & neck **2.8** (1.0-6.5) Sarcoma **20.0** (6.9-46.8)
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	Head and neck **1.09** (0.23-3.20) (*P* > .20)	
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	Genitourinary / gynaecological **1.0** (0.2-3.1)	Sarcoma **44.5** (16.3-97.3) Head & neck **5.7** (1.4-14.4)
Prior 1988 [121] Retrospective cohort treated in the UK 1950-1979 (n=2999); median f/u 6.7 y; comparator general population	Bone **20.0** (95% CI not given)	
Chronowski 2004 [124] Retrospective cohort treated for stage 1-2 HL in the USA 1980-1995 (n=286); median f/u of survivors 7.4 y	Urinary system **2.5** (0.1-13.9) Male genital **0.9** (0.0-5.0) Female genital **1.2** (0.1-4.2)	Soft tissue **21.5** (0.6-119.9) Brain **9.4** (0.3-52.4) Endocrine **6.3** (0.2-34.9)
Hancock 1996 [125] Retrospective cohort treated in the USA 1960-1990 (n=2162); mean f/u 9.3 y	Thyroid **10.6** (3.9-23.6) Urogenital **2.2** (1.3-2.9)	Bone **12.3** (2.1-41.6) Oral cavity **0.7** (0.0-3.3)

	Salivary gland **37.9** (13.8-84.2) Soft tissue **24.3** (11.3-48.3)	CUP **3.4** (0.8-9.2)
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given	Thyroid **4.1** (3.0-5.5) Kidney **1.5** (1.1-21) Bladder **1.4** (1.1-1.8) Testis **1.4** (0.8-2.4) Prostate **1.0** (0.8-1.2) Female genital **1.6** (1.3-1.9) Cervix **2.0** (1.4-2.7) Endometrium **1.4** (1.0-1.9) Ovary **1.3** (0.8-1.9)	Bone **3.8** (1.7-7.2) Connective tissue **5.1** (3.5-7.2) Brain & CNS **1.5** (1.1-2.1) Eye **1.4** (0.3-4.1) Buccal, all **3.4** (2.8-4.2) Lip **3.9** (2.4-5.9) Tongue **2.8** (1.5-4.7) Salivary gland **6.1** (3.5-9.9) Gum, other mouth **2.5** (1.5-4.0) Pharynx **3.3** (2.2-4.9) Larynx **1.6** (0.9-2.5)
Hodgson 2007 [127] Retrospective cohort of 5y HL survivors treated in North America & Europe 1970-2001 (n=18,862); median f/u 12.2 y	Bladder **1.0** (0.6-1.59) Kidney **3.1** (1.9-4.8) Thyroid **3.1** (1.8-5.2) Prostate **1.0** (0.8-1.3)	Buccal **5.1** (3.5-7.0) Brain **1.8** (1.1-2.7) Soft tissue / bone **11.7** (8.2-16.1) Female genital **2.2** (7.91-24.30) CUP **10.6** (7.91-24.30)
Boivin 1995 [129] Retrospective cohort treated in the USA and Canada 1940-1987 (n=10,472); average f/u 7.1 y (after discounting the 1st year after diagnosis)	Thyroid **4.5** (2.4-7.7) Female genital system **2.8** (2.0-4.2) Lip, oral cavity & pharynx **26.0** (13.8-44.5) Bones & soft tissues **12.0** (7.7-17.9)	
Boivin 1988 [130] Pooled analysis of data from 7 cohorts with incidence rates of second cancers, and details of treatment given for HL; 6513 participants; median f/u 43-71.4 m	Endocrine system **2.7** Urinary system **1.5** Male genital system **1.1** Female genital system **1.2** Eye & orbit **0.0** (95% CIs not given)	Buccal cavity & pharynx **4.1** Bones & joints **20.0** Soft tissues **18.3** Brain & nervous system **3.6** CUP **1.0**
Varady 2001 [136] Retrospective cohort treated in Hungary 1978-1996 (n=665); median f/u not given	Thyroid **100.00** (2.53-557.00) Bladder **21.74** (2.52-78.48)	Head and neck **7.14** (0.18-39.79) Bone **200.00** (5.06-1114.00)

Quoted expected incidences of second cancers extremely low, resulting in disproportionally high relative risks, therefore values not included in text			Soft tissue **105.26** (12.21-380.0)
Hancock 1991 [218] Retrospective cohort of patients treated in the USA with RT 1961-1989 (n=1677); median f/u 9.9 y	Thyroid **15.6** (6.3-32.5)		
Median time to development			
Zanini 1983 [201] Retrospective cohort treated in Italy 1960s-1980s (n=800); median f/u not given	Sarcoma **50 m**		
Michaelson 2014 [210] Retrospective cohort treated in the USA 1969-2008 (n=1981); median f/u 14.3 y	Thyroid **20.3 y**		
Khoo 1998 [214] Screening of cohort treated with mantle RT in Australia 1970-1989 (n=320); median f/u 9 y	Thyroid **11 y**		
Hancock 1991 [218] Retrospective cohort of patients treated in the USA with RT 1961-1989 (n=1677); median f/u 9.9 y	Thyroid **13.3 y**		
Variation in risk with time since radiotherapy			
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	**SIR**, thyroid <5 y **0.0** (0.0-40.8) 5-15 y **9.1** (1.1-32.9) 15-25 y **17.7** (4.8-45.3) >25 y **14.7** (1.8-52.9)	**SIR**, kidney <5 y **0.0** (0.0-10.0) 5-15 y **2.3** (0.3-8.3) 15-25 y **1.2** (0.0-6.9) >25 y **7.5** (2.0-19.1)	
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py)	**SIR** Thyroid <5 y **-** 5-9 y **5.2** (0.3-22.9) 10-14 y **16** (2.7-49.5) ≥15 y **26.7** (4.4-82.4)	Nervous system <5 y **2.6** (0.7-6.8) 5-9 y **-** 10-14 y **3.7** (.6-11.6) ≥15 y **6.1** (1.0-18.8)	Bone & soft tissue <5 y **4.1** (0.7-12.6) 5-9 y **9.3** (2.3-24.3) 10-14y **9.6** (1.6-29.8) ≥15 y **-**
van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	**RR**, urogenital < 1 y **1.1** (0.0-6.4)		10-14 y **3.6** (1.2-8.4)

				1-4 y **2.7** (1.1-5.5) 5-9 y **1.8** (0.5-4.7)		≥ 15 y **2.3** (0.3-8.3)	
Kumar 2018 [117] Retrospective cohort treat in the USA 1973-2014 (n=23,864); comparator USA general population; median f/u not given (times in months)				**SIR**, thyroid 2-11 **8.34** 12-59 **1.28** 60-119 **1.39** 120-179 **2.61** 180-239 **4.76** ≥240 **3.43**	Penis 2-11 **0** 12-59 **0** 60-119 **3.39** 120-179 **8.75** 180-239 **0** ≥240 **6.42**	Vulva 2-11 **0** 12-59 **2.57** 60-119 **1.25** 120-179 **0** 180-239 **5.42** ≥240 **4.51**	Cervix 2-11 **0** 12-59 **2.18** 60-119 **0.78** 120-179 **1.36** 180-239 **0** ≥240 **3.77**
Oropharynx 2-11 **0.39** 12-59 **2.27** 60-119 **3.81** 120-179 **2.24** 180-239 **3.35** ≥240 **1.39**	Lip 2-11 **3.25** 12-59 **2.84** 60-119 **6.54** 120-179 **1.53** 180-239 **4.21** ≥240 **0**	Salivary gland 2-11 **0** 12-59 **4.14** 60-119 **9.48** 120-179 **3.97** 180-239 **6.65** ≥240 **7.39**	Brain 2-11 **0.79** 12-59 **1.42** 60-119 **0.62** 120-179 **0.81** 180-239 **0.35** ≥240 **2.05**	Kidney 2-11 **4.9** 12-59 **1.47** 60-119 **1.08** 120-179 **1.41** 180-239 **1.18** ≥240 **1.89**	Testis 2-11 **0** 12-59 **1.64** 60-119 **0.3** 120-179 **0.46** 180-239 **0.8** ≥240 **1.01**	Ovary 2-11 **0.01** 12-59 **1.29** 60-119 **0.86** 120-179 **0.52** 180-239 **0.95** ≥240 **1.18**	Soft tissue 2-11 **3.54** 12-59 **2.72** 60-119 **4.1** 120-179 **6.31** 180-239 **4.33** ≥240 **7**
Tongue 2-11 **0** 12-59 **2.93** 60-119 **3.65** 120-179 **2.89** 180-239 **4.44** ≥240 **1.18**	Floor of mouth 2-11 **0** 12-59 **2.28** 60-119 **1.47** 120-179 **1.26** 180-239 **3.26** ≥240 **1.03**			Bladder 2-11 **0.67** 12-59 **0.8** 60-119 **1.67** 120-179 **0.99** 180-239 **1.44** ≥240 **1.5**	Prostate 2-11 **0.75** 12-59 **0.92** 60-119 **0.84** 120-179 **0.78** 180-239 **0.8** ≥240 **1.15**	Endometrium 2-11 **0.45** 12-59 **0.98** 60-119 **1.35** 120-179 **2.16** 180-239 **1.32** ≥240 **1.37**	Bones & joints 2-11 **0** 12-59 **3.16** 60-119 **1.7** 120-179 **6.76** 180-239 **2.99** ≥240 **6.42**
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6y; comparator general Swedish population				**SIR** Thyroid 1-9 y **4.18** (2.25-7.76) 10-19 y **8.38** (4.20-16.77) 20-30 y **4.71** (1.17-18.83) >30 y **-**		Pharynx 1-9 y **4.25** (2.03-8.92) 10-19 y **3.79** (1.22-11.74) 20-30 y **2.01** (0.28-14.23) >30 y **-**	

	Kidney 1-9 y **1.09** (0.58-2.02) 10-19 y **2.24** (1.13-4.50) 20-30 y **1.48** (0.48-4.60) >30 y **2.61** (0.65-10.43)		CT 1-9 y **3.50** (1.67-7.35) 10-19 y **8.20** (3.91-17.21) 20-30 y **8.67** (3.25-23.06) >30 y **11.43** (2.86-45.72)	
	Bladder 1-9 y **1.54** (1.00-2.26) 10-19 y **1.36** (0.68-2.72) 20-30 y **2.44** (1.26-4.68) >30 y **0.65** (0.09-4.61)		Brain 1-9 y **2.06** (1.24-3.42) 10-19 y **3.06** (1.59-5.89) 20-30 y **3.29** (1.37-7.91) >30 y **4.60** (1.48-14.27)	
	Prostate 1-9 y **1.20** (0.93-1.55) 10-19 y **1.32** (0.91-1.91) 20-30 y **0.95** (0.57-1.57) >30 y **1.51** (0.84-2.73)		Uterus 1-9 y **1.48** (0.77-2.84) 10-19 y **2.74** (0.35-3.40) 20-30 y **0.55** (0.08-3.90) >30 y **1.27** (0.18-9.00)	
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given (AERs / 10,000 py)	**RR**, thyroid 1-9 y **1.6** 10-14 y **7.3** 15-19 y **4.1** 20-24 y **23.8** ≥ 25 y **7.8**	**RR**, bladder 1-9 y **1.1** 10-14 y **1.8** 15-19 y **3.6** 20-24 y **5.9** ≥ 25 y **1.0**	**RR**, bone / CT 1-9 y **4.2** 10-14 y **15.4** 15-19 y **15.9** 20-24 y **-** ≥ 25 y **-**	**RR**, cervix 1-9 y **1.5** 10-14 y **1.2** 15-19 y **1.1** 20-24 y **4.7** ≥ 25 y **12.4**
Boivin 1995 [129] Retrospective cohort treated in the USA and Canada 1940-1987 (n=10,472); average f/u 7.1 y (discounting the 1st year after diagnosis); after abdominal RT	**RR**, female genital system All **1.5** (0.9-2.6) 0-4 y **1.0** (0.4-2.3)		5-9 y **1.6** (0.6-4.1) ≥ 10 y **2.4** (1.1-5.4)	
Michaelson 2014 [210] Retrospective cohort treated in the USA 1969-2008 (n=1981); median f/u 14.3 y	Thyroid cancer, male aged <20 y at HL treatment **Incidence rate** per 10,000 py <10 y **5.4**	10-15 y **31.1**	15-20 y **61.4**	≥20 y **74.6**

*pooled estimate (meta-analysis)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.
Abbreviations – y: years; HL: Hodgkin lymphoma; n: number: EORTC: European Organisation for Research and Treatment of Cancer; py: person-years; CUP: cancer of unknown primary; CNS: central nervous system; RR: relative risk; SIR: standardised incidence ratio

h. Haematological malignancies

Study details	Risk estimate
Cumulative incidence	
Brierley 1998 [10] Retrospective cohort with stage 1-2 HL treated in Canada 1973-184 (n=611); median f/u 11 y; comparator age-matched general population for same period	15 y Acute leukaemia **1.13%** NHL **1.64%**
van Spronsen 1998 [11] Retrospective cohort of 5 y survivors treated in the Netherlands 1972-1993 (n=345); median f/u not given; comparator general population	10 y Leukaemia **3%** NHL **0.3%**
Cosset 1991 [56] Pooled analysis of 4 EORTC trials H1, H2, H5, H6, run 1964-1988; 1660 patients; median f/u not reported	ANLL 10 y **1.2%** 15 y **2.3%** NHL 10 y **1%** 15 y **1.9%**
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	NHL: 5 y **0.6%** 25 y **2.0%** 15 y **1.1%** Leukaemia: 5 y **0.2%** 25 y **0.9%** 15 y **0.5%**
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y	20 y Leukaemia, excl. CLL **1.7%** NHL **2.3%**
Swerdlow 1992 [85] Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	15 y: Leukaemia **1.4%** NHL **1.5%**
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	30 y: All **5.0%** (4.1-6.0) Leukaemia **1.3%** (0.9-1.7) NHL **3.7%** (3.0-4.6)

van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	Leukaemia, inc. MDS **4.0%**	NHL **4.1%**	
Swerdlow 1997 [91] Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1 y	5 y **0.6%** (0.3-1.5) 10 y **1.9%** (1.1-3.4)		15 y **1.9%** (1.1-3.4) 20 y **2.3%** (1.3-4.2)
Van Leeuwen 1989 [92] Retrospective cohort treated for HL in the Netherlands 1966-1986 (n=744); median f/u 6.4 y	NHL 10 y **0.7%** (+/- 0.5%) 15 y **5.9%** (+/- 2.1%)		Leukaemia & MDS 5 y **1.0%** (+/- 0.4%) 10 y **5.1%** (+/- 1.2%) 15 y **6.3%** (+/- 1.7%)
Munker 1999 [93] Retrospective cohort treated in Germany 1974-1994 (n=1120); mean f/u 9.1 y	Leukaemia 5 y **0.2%** 10 y **0.5%** 15 y **0.95%**		NHL 5 y **0.9%** 10 y **2.0%** 15 y **4.6%**
Henry-Amar 1983 [96] Retrospective cohort treated in EORTC trials 1964-1972 (n=334); median f/u 10 y	Acute leukaemia 5 y **0%** 10 y **0.8%** (SE +/- 0.6)		15 y **2.8%** (SE +/- 1.6)
Sont 1992 [97] Retrospective cohort treated in the Netherlands 1969-1988 (n=482); average f/u 6.05 y	5 y Leukaemia **1.6%**		NHL **15%**
Economoupoulos 1994 [98] Retrospective cohort treated in Greece 1977-1991 (n=217); median f/u 67 m	ANLL & MDS: 6 y **2.4%**		
Chronowski 2003 [90] Retrospective cohort treated for stage 1-2 HL in the USA 1980-1995 (n=286); median f/u 7.4 y	AML 5 y **0.8%**	10 y **1.3%**	15 y **1.3%**
Cimino 1991 [101] Retrospective cohort treated for HL in Italy 1969-1979 (n=947); median f/u 10.5 y	ANLL 10 y **2.8%** (+/- 0.6) 19 y **10.2%** (+/- 5.2)		NHL 10 y **0.9%** (+/- 0.3) 19 y **0.9%** (+/- 0.3)
Henry-Amar 1992 [102] Retrospective international cohort of 1 y HL survivors treated 1960-1987 (n=12,411); median f/u not given	Acute leukaemia 10 y **1.8%** 15 y **2.2%** 20 y **2.4%**		NHL 10 y **1.0%** 15 y **1.8%** 20 y **3.2%**

Cellai 2001 [106] Retrospective cohort treated in Italy 1960-1991 (n=1524); average f/u 10. 7y	Leukaemia 15 y **0.4%** 20 y **0.4%**	NHL 15 y **0.6%** 20 y **1.1%**
Biti 1994 [107] Retrospective cohort treated in Italy 1960-1988 (n=1121); mean f/u >9 y	15 y **0.2%**	
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	ANLL & MDS 10 y **1.7%** 15 y **1.7%**	NHL 10 y **1.2%** 15 y **2.0%**
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y	28 y ANLL **1.5%**	 NHL **3.0%**
Bonadonna 2005 [114] Retrospective cohort treated for intermediate or advanced-stage HL in Italy 1973-1990 (n=811); median f/u 16.7-29 y (substudies)	Leukaemia or MDS 25 y **4.5%**	
Lavey 1990 [138] Retrospective cohort treated in the USA 1970-1981 (n=999); median f/u 10 y; comparator Connecticut general population	Acute leukaemia 10 y **1.2%** ANLL **1.4%**	
Tucker 1988 [140] Retrospective cohort treated in the USA 1968-1985 (n=1507); mean f/u 5.4 y	15 y Leukaemia **0.6%**	 NHL **3.5%**
Valagussa 1986 [141] Retrospective cohort treated in Italy 1965-1982 (n=1329); median f/u 9.5 y	NHL **1.9%** ANLL **0%**	
Zinzani 1991 [182] Retrospective cohort treated in Italy 1970-1984 (n=552); median f/u 12 y	ANLL: 5 y **0.0174%** (+/-.0061) 10 y **0.0365%** (+/-.0105)	
Devereux 1990 [183] Retrospective cohort treated in the UK 1970-1986 (n=2676); median f/u not given	Leukaemia 15 y **1.7%**	
Pedersen-Bjergaard 1982 [184] Retrospective cohort treated in Denmark 1970-1981 (n=391); median f/u not given	ANLL, preleukaemia, acute myeloproliferative syndrome **1.2%** per year 5 y **3.9%** (+/-1.3)	 9 y **9.9%** (+/-2.9)
Blayney 1987 [178]	ANLL, MDS, refractory pancytopenia & aplastic anaemia 5 y **0.03** (+/- 0.015)	

Prospective screening of cohort treated in National Cancer Institute trials in the USA 1964-1975 (n=192); median f/u not given	10 y **0.10** (+/- 0.03)		
Gomez 1983 [179] Prospective randomised study of RT vs CMT for patients with stage 1-3 HL (n=164)	ANLL **0.41%** / year	1.4 y **0.6%** 5.3 y **1.6%**	6 y **2.7%** 7.6 y **4.6%**
Rueffer 2001 [186] Retrospective analysis of patients treated for HL in GHSG trials 1981-1998 (n=5406); median f/u 46 m	NHL 2 y **0.5%** (0.3-0.7) 5 y **0.9%** (0.5-1.3)		8 y **1.5%** (0.9-2.1)
Brusamolino 1998 [188] Retrospective cohort treated in Italy 1975-1992 (n=1659); median f/u 10 y	Leukaemia 15 y **4.2%**		
Coleman, 1977 [189] Retrospective cohort treated in the USA 1968-1975 (n =680); median f/u not given	Leukaemia 5 y **1.5%**		10 y **2.0%**
Krikorian 1979 [190] Prospective cohort of patients treated for HL in the USA 1962-1977 (n=579); median f/u not given	NHL 10 y **4.4%** (1.2-15.0) Leukaemia 10 y **2.0%** (0.3-12.9)		
Xavier 2013 [192] Retrospective cohort treated in the USA 1992-2009 (n=26,826); median f/u 26 m	NHL 5 y **0.41%** (0.32-0.50) 10 y **1.34%** (1.41-1.55)		15 y **2.50%** (2.10-2.89)
Delwail 2002 [202] Retrospective cohort treated in France 1972-1988 (n=462); median f/u 8.5 y	15 y All leukaemia **2.4%** (0.0-4.9)		ANLL **2.1%** (0.7-3.4)
Andrieu 1990 [203] Retrospective cohort treated for stage 1-3 HL in France 1972-1980 (n=462); median 10.5 y	ANLL 15 y **3.5%** (+/- 2.7%)		
van der Velden 1988 [204] Nested case-control study in cohort of 1681 patients with HL treated in the Netherlands 1972-1978; median f/u 66 m (18 cases)	ANLL 10 y **2.3%**		
Enrici 1998 [205] Retrospective cohort treated in Italy 1972-1996 (n=1391); average f/u 84 m	NHL 5 y **0.7%** (0-1.5) 10 y **1.5%** (0.1-2.9)		15 y **1.5%** (0.1-2.9) 20 y **3.4%** (0-43.2)

Prosper 1994 [211] Retrospective cohort treated in Spain 1973-1988 (n=101); median f/u 73 m	NHL 5 y **0%** 10 y **4.6%** (0-11)	15 y **17%** (4-32)
Standardised incidence ratio		
Cosset 1991 [56] Pooled analysis of 4 EORTC trials H1, H2, H5, H6, run 1964-1988; 1660 patients; median f/u not reported	ANLL **36.6** (21.3-58.5) (*P* < .001)	NHL **33.3** (17.8-57) (*P* < .001)
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1y; comparator Dutch general pop	**10.4** (8.8-12.2) Leukaemia **9.5** (6.8-12.9) NHL **13.4** (10.9-16.2)	
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	Leukaemia **5.8** (2.3-12.0) NHL **13.1** (7.3-21.6)	
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py)	Leukaemia **14.6** (10.7-19.2) Excl. CLL **21.1** (15.5-27.9)	NHL **14.0** (10.5-18.3)
Swerdlow 1997 [91] Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1 y	Leukaemia **23.5** (12.9-38.6) (*P* < .001) Excluding CLL **31.3** (16.7-52.4) (*P* < .05)	NHL **4.6** (1.2-12.0) (*P* < .05)
Cellai 2001 [106] Retrospective cohort treated in Italy 1960-1991 (n=1524); average f/u 10. 7y	Leukaemia **3.63** (0.4-13.1)	NHL **3.85** (0.8-11.2)
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	Leukaemia **22.7** (16.3-30.7) Excl. CLL **30.6** (22.1-41.4)	NHL **17.1** (12.7-22.5)
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y	ANLL **4.0** (0.5-14.5) NHL **26.1** (14.6-42.9)	
Kumar 2018 [117] Retrospective cohort treat in the USA 1973-2014 (n=23,864); comparator USA general population; median f/u not given	Leukaemia **4.44**	NHL **5.83**
Sud 2017 [118]	Leukaemia **6.46** (5.19-8.06)	NHL **7.99** (6.70-9.53)

Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population		
Omer 2012 [119] Retrospective cohort treated in the USA 1970-2004 (n=198); median f/u 21.1; comparator general population	**0.88** (0.02-4.89)	
Xavier 2013 [192] Retrospective cohort treated in the USA 1992-2009 (n=26,826); median f/u 26 m	Aggressive B-cell NHL **10.5** (8.9-12.4) Indolent B-cell NHL **4.0** (3.1-5.1) T-cell NHL **14.6** (10.3-20.1)	
Standardised mortality ratio		
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	Leukaemia **15.6** (11.7-20.4) NHL **25.7** (20.6-31.7)	
Absolute excess risk		
Rugbjerg 2019 [8] Retrospective cohort of Danish >5 y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	Hospitalisation (/ 10,000 py): Leukaemia **2** (-0.6-5)	NHL **5** (1-9)
Brierley 1998 [10] Retrospective cohort with stage I-II HL treated in Canada 1973-184 (n=611); median f/u 11 y; comparator age-matched general population for same period	Leukaemia **7.9** / 10,000 py	
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	Absolute excess mortality (/ 10,000 py) Leukaemia **5.2** NHL **8.8**	
Rugbjerg 2017 [23] Retrospective Danish cohort treated when aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	Hospitalisation (/ 10,000 py): All haematological **2** (-2-6) Leukaemia **1**(-1-3)	NHL **1** (-2-3)
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	Leukaemia **4.6** / 10,000 py	NHL **11.1** / 10,000 py
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py)	Leukaemia **8.9** Excl. CLL **8.9**	NHL **9.9**
Swerdlow 1992 [85]	NHL **9.2** / 10,000 py	

Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	Leukaemia **8.7** / 10,000 py	
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1y; comparator Dutch general pop	**22.2** (18.4-26.5) / 10,000 py NHL **16.0** (12.9-19.7) / 10,000 py	Leukaemia **6.1** (4.2-8.5) / 10,000 py
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y (AERs / 10,000 py)	Leukaemia (excl. MDS) **10.8** ANLL **9.1**	NHL **9.4**
van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	Leukaemia **18.1** / 10,000 py ANLL **16.0** / 10,000 py	NHL **13.1** / 10,000 py
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y (AERs / 10,000 py)	Acute leukaemia **14.3** NHL **14.2**	Multiple myeloma **1.7**
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	Acute leukaemia **15** / 10,000 py	NHL **15** / 10,000 py
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given (AERs / 10,000 py)	Leukaemia **11.7** Leukaemia, exc. CLL **11.8**	NHL **13.9**
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population	Leukaemia **6.9** / 10,000 py NHL **11.5** / 10,000 py	
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	Leukaemia **3.6** / 10,000 py	NHL **10.6** / 10,000 py
Chronowski 2004 [124] Retrospective cohort treated for stage 1-2 HL in the USA 1980-1995 (n=286); median f/u of survivors 7.4 y (AERs / 10,000 py)	AML **13.3** NHL **3.2**	
Hancock 1996 [125] Retrospective cohort treated in the USA 1960-1990 (n=2162); mean f/u 9.3 y	Leukaemia **2.4** / 10,000 py	NHL **14** / 10,000 py
Dores 2002 [126]	All leukaemia **8.8**	NHL **5.2**

Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given (AERs / 10,000py)	ALL **0.4** ANLL **6.3** CLL **-0.02** CML **0.1**	Myeloma **0.1** Other lymphohaematopoietic disorders **0.04**
Schonfeld 2006 [187] Retrospective cohort of >1 y HL survivors treated in Nordic countries and the USA 1970-2001 (n=35,511); comparator general population; median f/u not given	AML **6.2** / 10,000 py (5.4-7.1)	
Relative risk		
Rugbjerg 2019 [8] Retrospective cohort of Danish >5 y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	Hospitalisation Leukaemia **2.9** (1.2-7.0)	NHL **4.7** (2.5-8.7)
Brierley 1998 [10] Retrospective cohort with stage I-II HL treated in Canada 1973-184 (n=611); median f/u 11 y; comparator age-matched general population for same period	Leukaemia **10.4** (3.4-24.0) (*P* <.0001)	
Rugbjerg 2017 [23] Retrospective Danish cohort treated when aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	Hospitalisation All haematological **2.0** (0.8-4.9) Leukaemia **1.8** (0.5-7.4)	NHL **2.6** (0.7-10.6)
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	Leukaemia **5.6** (1.2-16.5) NHL **5.9** (1.2-17.1)	
Swerdlow 1992 [85] Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	Leukaemia **2.5** (95% CI not given) NHL **15.0** (95% CI not given)	
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	Acute leukaemia **82.5** (53.5-122.2) NHL **16.5** (10.2-23.8) Multiple myeloma **9.4** (1.9-27.4)	
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y	Leukaemia **37.5** (22.2-59.2) ANLL **66.7** (37.4-110) NHL **21.5** (12.3-34.9)	
van Leeuwen 1994 [78]	Leukaemia **34.7** (23.6-49.3)	

Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	ANLL **82.9** (54.6-121) NHL **20.6** (13.1-30.9)	
Almagro-Casado 2016 [79] Retrospective cohort treated in Spain 1968-2012 (n=604); median f/u not given	Leukaemia **4.1** (0.8-20.1) (*P* = .08)	
Van Leeuwen 1989 [92] Retrospective cohort treated for HL in the Netherlands 1966-1986 (n=744); median f/u 6.4 y	Leukaemia **5.5** (0.14-30.9)	NHL **6.7** (0.17-37.1)
Munker 1999 [93] Retrospective cohort treated in Germany 1974-1994 (n=1120); mean f/u 9.1y	Leukaemia **20.5** (10.3-37.4) NHL **25.9** (17.6-37.2)	Multiple myeloma **7.4** (1.3-24.1)
Henry-Amar 1983 [96] Retrospective cohort treated in EORTC trials 1964-1972 (n=334); median f/u 10 y	Leukaemias **40** (*P* < .001)	
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	Acute leukaemia **27.59** (11.91-54) (*P* < .001) NHL **50.00** (21.59-98) (*P* < .001)	
Doria 1995 [110] Retrospective cohort treated in USA 1969-1982 (n=102); median f/u 153-212 m	NHL **9.91** (5.8-14.9)	
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	Leukaemia **66.2** (28.1-130.7) NHL **18.4** (8.6-33.8) Multiple myeloma **9.0** (0.22-50.3)	
Chronowski 2004 [124] Retrospective cohort treated for stage 1-2 HL in the USA 1980-1995 (n=286); median f/u of survivors 7.4 y	AML **69.3** (14.3-202.6)	NHL **3.4** (0.1-18.8)
Hancock 1996 [125] Retrospective cohort treated in the USA 1960-1990 (n=2162); mean f/u 9.3 y	Leukaemia **5.5** (1.4-15.1) AML **17.5** (2.9-58)	NHL **29.6** (17.2-39.6)
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given	All leukaemia **9.9** (8.7-11.2) ALL **7.1** (3.6-12.8) ANLL **21.5** (18.3-25.0) CLL **0.9** (0.4-1.8) CML **1.3** (0.7-2.2)	NHL **5.5** (4.7-6.4) Myeloma **1.2** (0.7-2.1) Other **2.2** (0.3-7.9)
Boivin 1995 [129]	Leukaemia **23.9** (19.9-36.2)	

Retrospective cohort treated in the USA and Canada 1940-1987 (n=10,472); average f/u 7.1 y (after discounting the 1st year after diagnosis)	NHL **5.6** (3.9-8.5)	
Boivin 1988 [130] Pooled analysis of data from 7 cohorts with incidence rates of second cancers, and details of treatment given for HL; 6513 participants; median f/u 43-71.4 m	NHL **8.1** (95% CIs not given)	Multiple myeloma **0.0**
Lavey 1990 [138] Retrospective cohort treated in the USA 1970-1981 (n=999); median f/u 10 y; comparator Connecticut general population	ANLL **50** (0.7-278)	
Tucker 1988 [140] Retrospective cohort treated in the USA 1968-1985 (n=1507); mean f/u 5.4 y	Leukaemia **11** (1.2-38)	NHL **21** (6.7-48.6)
Blayney 1987 [178] Prospective screening of cohort treated in National Cancer Institute trials in the USA 1964-1975 (n=192); median f/u not given	Leukaemia **95.7** (41.2-188.7)	
Larsen 1977 [180] Retrospective cohort treated in Denmark 1964-1975 (n=201); median f/u not given	AML **75** (95% CI not given) All leukaemia **37.5** (95% CI not given)	
Schonfeld 2006 [187] Retrospective cohort of >1 y HL survivors treated in Nordic countries and the USA 1970-2001 (n=35,511); comparator general population; median f/u not given	AML **20.2** (17.6-23.0)	
van der Velden 1988 [204] Nested case-control study in cohort of 1681 patients with HL treated in the Netherlands 1972-1978; median f/u 66 m (18 cases)	ANLL **64** (38-101)	
Odds ratio		
Franklin 2006 [89] Individual patient data meta-analysis from RCTs comparing RT vs CMT, chemo vs CMT, RT vs chemo or IFRT vs EFRT	NHL **0.46*** (*P* = .03) (CMT vs RT alone)	
Median time to development		
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	Leukaemia **5.3 y** NHL **7.1 y**	
Van Leeuwen 1989 [92]	Leukaemia **5.7 y**	

Retrospective cohort treated for HL in the Netherlands 1966-1986 (n=744); median f/u 6.4 y	NHL **13.3 y**	
Cimino 1991 [101] Retrospective cohort treated for HL in Italy 1969-1979 (n=947); median f/u 10.5 y	ANLL **58 m**	
Cellai 2001 [106] Retrospective cohort treated in Italy 1960-1991 (n=1524); average f/u 10.7 y	Leukaemia **6.6 y** (mean)	
Biti 1994 [107] Retrospective cohort treated in Italy 1960-1988 (n=1121); mean f/u >9y	Acute leukaemia **5.2 y**	
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	ANLL & MDS **3.42 y** NHL **7.50 y**	
Shbib Dabaja 2022 [137] Retrospective cohort treated in the USA 1956-2009 (n=1653); median f/u 22 y	**7.4 y**	
Tester 1984 [139] Retrospective cohort treated in USA 1964-1984 (n=473); median f/u >12 y	Leukaemia **67 m**	
Zinzani 1991 [182] Retrospective cohort treated in Italy 1970-1984 (n=552); median f/u 12 y	ANLL **17 m**	
Devereux 1990 [183] Retrospective cohort treated in the UK 1970-1986 (n=2676); median f/u not given	Leukaemia **79.7 m** (mean)	
Josting 2003 [191] Retrospective analysis of patients treated in GHSG trials 1981-1998 (n=5411); median f/u 55 m	AML / MDS **12.5 m**	
Schonfeld 2006 [187] Retrospective cohort of >1 y HL survivors treated in Nordic countries and the USA 1970-2001 (n=35,511); comparator general population; median f/u not given	AML **5.9 y**	
Brusamolino 1998 [188] Retrospective cohort treated in Italy 1975-1992 (n=1659); median f/u 10 y	Acute leukaemia **60 m**	MDS **54 m**
Coleman 1977 [189]	Leukaemia **22 m**	

Retrospective cohort treated in the USA 1968-1975 (n =680); median f/u not given			
Krikorian 1979 [190] Prospective cohort of patients treated for HL in the USA 1962-1977 (n=579); median f/u not given	AML **52 m**	NHL **94 m**	
Xavier 2013 [192] Retrospective cohort treated in the USA 1992-2009 (n=26,826); median f/u 26 m	NHL **48 m**		
Prosper 1994 [211] Retrospective cohort treated in Spain 1973-1988 (n=101); median f/u 73 m	NHL **106 m** (mean)		
Median age at development			
Rueffer 2001 [186] Retrospective analysis of patients treated for HL in GHSG trials 1981-1998 (n=5406); median f/u 46 m	NHL **49 y**		
Josting 2003 [191] Retrospective analysis of patients treated in GHSG trials 1981-1998 (n=5411); median f/u 55 m	AML / MDS **47 y**		
Xavier 2013 [192] Retrospective cohort treated in the USA 1992-2009 (n=26,826); median f/u 26 m	NHL **56 y**		
Enrici 1998 [205] Retrospective cohort treated in Italy 1972-1996 (n=1391); average f/u 84 m	NHL **41 y**		
Variation in risk with time since radiotherapy			
Aleman 2003 [1] Retrospective Dutch cohort treated when aged <41y 1965-1987 (n=1261); median f/u 17.8y; comparator general Dutch population (AERs per 10,000py)	Death from leukaemia / MDS **RR** 0-5 y **34.4** (9.4-88.0) 6-10 y **137** (75.0-230) 11-15 y **36.8** (10.0-94.2) 16-20 y **19.6** (2.4-70.8) 21-25 y **0** (0.0-46.0) 26-30 y **0** (0.0-68.0) >30 y **0** (0.0-208)	**AER** 0-5 y **6.8** 6-10 y **28.7** 11-15 y **9.0** 16-20 y **5.8**	21-25 y **-0.3** 26-30 y **-0.6** >30 y **-0.8**

Lee 2000 [27] Retrospective cohort of patients with stage 1-3 HL treated in the USA 1970-1986 (n=210); median f/u 15.6y; comparator general pop	**AER** (/ 1000 py) 0-5 y **3.91** 10-15 y **1.19** 20-25 y **-0.26** 5-10 y **1.00** 15-20 y **2.50**	
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	**SIR**, leukaemia <5 y **8.4** (1.0-30.2) 5-15 y **4.7** (0.6-16.9) 15-25 y **9.1** (1.9-26.6) >25 y **0.0** (0.0-17.9)	**SIR**, NHL <5 y **25.5** (8.3-59.5) 5-15 y **10.1** (2.8-25.9) 15-25 y **17.7** (6.5-38.4) >25 y **0.0** (0.0-17.1)
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py)	**SIR**, leukaemia (excl CLL) 0-4 y **17.5** (10.1-27.9) 5-9 y **31.7** (19.5-48.1) 10-14 y **15.3** (6.1-31.1) ≥15 y **16.7** (5.2-38.8) **SIR**, NHL 0-4 y **12.1** 7.1-19.0) 5-9 y **18.8** (11.6-28.6) 10-14 y **13.6** (6.8-23.9) ≥15 y **10.1** (3.6-21.6)	**AER,** leukaemia 0-4 y **6.5** 5-9 y **13.7** 10-14 y **11.9** ≥15 y **11.2** **AER**, NHL 0-4 y **6.7** 5-9 y **13.4** 10-14 y **7.2** ≥15 y **9.4**
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y (AER / 10,000 py)	**RR**, leukaemia 1-4 y **49.5** (13.4-127) 5-9 y **79.3** (36.3-151) 10-14 y **34.7** (9.4-89.0) 15-19 y **-** ≥20 y **12.7** (0.3-70.6) **RR**, NHL 1-4 y **-** 5-9 y **-** 10-14 y **42.9** (18.5-84.6) 15-19 y **24.2** (6.6-62.0)	**AER**, leukaemia 1-4 y **8.6** 5-9 y **18.4** 10-14 y **11.2** 15-19 y **-** ≥20 y **7.1** **AER**, NHL 1-4 y **-** 5-9 y **-** 10-14 y **22.5** 15-19 y **18.5**

	≥20 y **26.7** (7.2-68.3)	≥20 y **29.7**
van Leeuwen 1994 [78] Retrospective cohort treated in the Netherlands 1966-1986 (n=1939); median f/u 9.2 y; comparator general population	**RR**, leukaemia < 1 y **0** (0-36.7) 1-4 y **36.4** (18.2-65.1) 5-9 y **60.4** (33.8-99.5) 10-14 y **19.4** (4.0-56.8) ≥ 15 y **23.0** (2.8-83.2)	**RR**, NHL < 1 y **18.4** (2.2-66.4) 1-4 y **2.8** (0.1-15.8) 5-9 y **22.3** (8.9-45.9) 10-14 y **53.2** (26.6-95.2) ≥ 15 y **14.9** (1.8-54.0)
Swerdlow 1992 [85] Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	**RR,** leukaemia ≥10 y **14.1** 0-4 y **12.6** All **16.0** 5-9 y **23.2** **AER**, leukaemia & NHL: ≥10y **23.8**	**RR**, NHL 0-4 y **13.2** ≥10 y **18.6** 5-9 y **21.9** All **16.8**
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	**RR**, leukaemia 0-5 y **128.0** (63.9-229.0) 5-10 y **100.3** (40.3-206.6) 10-15 y **52.8** (10.9-154.3) 15-20 y **0** (0.0-93.8) >20 y **74.8** (9.0-269.9) **RR**, NHL 0.5 y **12.2** (4.0-28.5) 5-10 y **22.5** (9.7-44.4) 10-15 y **6.4** (0.8-23.3) 15-20 y **8.9** (1.7-32.2) >20 y **44.3** (17.8-91.3)	**AER**, leukaemia (/ 10,000 py) 0.5 y **18.7** 5-10 y **16.1** 10-15 y **9.8** 15-20 y **-0.2** >20 y **19.5** **AER**, NHL 0.5 y **22.2** 5-10 y **54.2** 10-15 y **82.5** 15-20 y **229.2** >20 y **404.7**
Van Leeuwen 1989 [92] Retrospective cohort treated for HL in the Netherlands 1966-1986 (n=744); median f/u 6.4 y	**RR**, leukaemia <5 y **32.0** (11.7-69.5) 5-10 y **75.5** (32.5-149) ≥10 y **35.8** (4.3-129)	**RR**, NHL <5 y **13.2** (1.6-6.6) *95% CI correctly extracted, but clearly incorrect 5-10 y **11.4** (0.29-63.3) ≥10 y **121** (44.9-266)

Henry-Amar 1992 [102] Retrospective international cohort of 1y HL survivors treated 1960-1987 (n=12,411); median f/u not given	**RR**, acute leukaemia		**RR**, NHL	
	Males	Females	Males	Females
	1-4 y **30.82**	1-4 y **31.40**	1-4 y **28.26**	1-4 y **21.43**
	5-9 y **36.67**	5-9 y **32.39**	5-9 y **31.94**	5-9 y **45.46**
	10-14 y **12.96**	10-14 y **14.63**	10-14 y **44.74**	10-14 y **13.64**
	15-19 y **12.50**	15-19 y **0.0**	15-19 y **120.0**	15-19 y **0.0**
	≥ 20 y **0.0**	≥ 20 y **0.0**	≥ 20 y **100.0**	≥ 20 y **0.0**
	(95% CIs not given)			
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y (AERs / 10,000 py)	**SIR**, ANLL		**AER**, ANLL	
	1-4 y **9.9** (2-29)		1-4 y **9**	
	5-9 y **21.1** (7.8-46)		5-9 y **17**	
	10-19 y **13.2** (4.3-30.8)		10-19 y **10**	
	≥20 y **0** (-)		≥20 y **0**	
	SIR, NHL		**AER**, NHL	
	1-4 y **24.4** (7.6-62.5)		1-4 y **11**	
	5-9 y **41.1** (20.5-73.6)		5-9 y **31**	
	10-19 y **20.9** (11.1-35.7)		10-19 y **27**	
	≥20 y **13** (2.7-38.3)		≥20 y **35**	
Kumar 2018 [117] Retrospective cohort treat in the USA 1973-2014 (n=23,864); comparator USA general population; median f/u not given (all times in months)	**SIR**, all haem	NHL	Myeloma	Leukaemia
	2-11 **5.99**	2-11 **11.63**	2-11 **0**	2-11 **1.56**
	12-59 **5.97**	12-59 **7.45**	12-59 **1.19**	12-59 **7.37**
	60-119 **4.56**	60-119 **4.71**	60-119 **0.73**	60-119 **6.98**
	120-179 **4.63**	120-179 **6.57**	120-179 **0.60**	120-179 **4.19**
	180-239 **3.29**	180-239 **5.02**	180-239 **1.09**	180-239 **1.75**
	≥240 **2.86**	≥240 **3.94**	≥240 **1.65**	≥240 **1.68**
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population (AERs / 10,000 py)	**SIR**, leukaemia		**SIR**, NHL	
	1-9 y **8.54** (6.63-11.0)		1-9 y **8.03** (6.33-10.18)	
	10-19 y **3.51** (1.89-6.52)		10-19 y **8.32** (5.88-11.79)	
	20-30 y **4.77** (2.39-9.54)		20-30 y **9.08** (5.92-13.92)	
	>30 y **1.51** (0.21-10.68)		>30 y **3.38** (1.09-10.46)	

Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	**RR**, leukaemia <5 y **96.5** 5-9 y **85.5** **RR**, NHL <5 y **5.8** 5-9 y **38.3**	10-14 y **38.3** ≥15 y **0** 10-14 y **15.9** ≥15 y **11.1**	**AER**, leukaemia (/ 10,000 py) <5 y **10.7** 5-9 y **11.5** **AER**, NHL (/ 10,000 py) <5 y **2.2** 5-9 y **22.7**	10-14 y **6.4** ≥15 y **-0.25** 10-14 y **12.3** ≥15 y **12.7**
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given (AERs / 10,000 py)	**RR**, ANLL 1-9 y **24.7** 10-14 y **18.0**	15-19 y **3.3** 20-24 y **14.6**	**RR**, NHL 1-9 y **5.7** 10-14 y **13.9** 15-19 y **5.4**	20-24 y **13.4** ≥25 y **4.9**
Boivin 1995 [129] Retrospective cohort treated in the USA and Canada 1940-1987 (n=10,472); average f/u 7.1 y (after discounting the 1st year after diagnosis) (adjusted for chemo)	**RR**, leukaemia 0-4 y **1.6** (0.8-3.5) 5-9 y **1.1** (0.5-2.5)		≥10 y **0.7** (0.2-1.7) All **1.2** (0.6-2.1)	

*pooled estimate (meta-analysis)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – HL: Hodgkin lymphoma; n: number; f/u: follow-up; y: years; NHL: non-Hodgkin lymphoma; EORTC: European Organisation for Research and Treatment of Cancer; inc.: including; MDS: myelodysplastic syndrome; ecxl.: excluding; CLL: chronic lymphocytic leukaemia; m: months; CI: confidence interval; ANLL: acute non-lymphocytic leukaemia; GHSG: German Hodgkin Study Group; py: person-years; ALL: acute lymphocytic leukaemia; CML: chronic myeloid leukaemia; AML: acute myeloid leukaemia; RT: radiotherapy; CMT: combined-modality therapy; IFRT: involved-field radiotherapy; EFRT: extended-field radiotherapy; RR: relative risk; AER: absolute excess risk; SIR: standardised incidence ratio; haem: haematological

Table C3.2: Effect of radiotherapy treatment factors on the risk of second malignancies following treatment for Hodgkin lymphoma

a. All second malignancies

Study details	Risk estimate	
Radiotherapy field		
Lee 2000 [27] Retrospective cohort of patients with stage 1-3 HL treated in the USA 1970-1986 (n=210); median f/u 15.6 y; comparator general pop. High-risk: large mediastinal masses and/or hilar disease and/or splenic involvement; remainder low-risk. Radical RT: mantle field & liver & upper periaortic LN chains. **SMR** (95% CIs not given) High-risk patient, radical RT **17.8** High-risk patient, standard RT **12.7** Low-risk patient, standard RT **7.7** **AEM** (/ 1000 py) High-risk, radical RT **6.22** High-risk, standard RT **9.63** Low-risk, standard RT **6.27**	**SIR** (95% CIs not given) Radical RT (high-risk) **7.5** Standard RT **5.6** Low-risk **5.3** High-risk **6.4** 1 field/day **6.7** 2 fields/day **3.5**	**AER** (/ 1000 py) Radical RT (high-risk) **7.5** Standard RT **9.6** Low-risk **9.0** High-risk **11.6** 1 field/day **11.8** 2 fields/day **2.8**
Hoskin 2002 [70] Retrospective analysis of BNLI trial 1970-1979 comparing IFRT to EFRT (n=603); median f/u not given	**25 y cumulative incidence** IFRT **20%** EFRT **19%**	
Swerdlow 1992 [85] Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	**RR** Extensive RT **2.3**	Local RT **2.1**
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y (AER / 10,000 py; MPA / PPA = mantle & paraaortics / paraarotics & pelvic)	**RR** Mantle **2.1** (0.8-4.6) MPA/PPA alone **4.2** (3.4-5.1) TNI alone **5.1** (2.8-8.5)	**AER** Mantle **58.1** MPA/PPA alone **78.9** TNI alone **94.7**
Sasse 2017 [76] Long-term follow-up data from GHSG trials HD7, HD10, HD8, HD11 1993-2003 (n=4276); median f/u 120 m, 98 m, 153 m, 106 m	**15 y cumulative incidence** ES, unfavourable (HD8) COPP/ABVD & EFRT **17%** COPP/ABVD & IFRT **14%**	**SIR** ES, unfavourable (HD8) COPP/ABVD & EFRT **3.6** (2.9-4.5 COPP/ABVD & IFRT **2.6** (2.0-3.3)

Franklin 2006 [89] Individual patient data meta-analysis from RCTs comparing RT vs CMT, chemo vs CMT, RT vs chemo or IFRT vs EFRT	**OR** IFRT vs EFRT **1.17** (*P* = .73)	
Biti 1994 [107] Retrospective cohort treated in Italy 1960-1988 (n=1121); mean f/u >9 y	**15 y cumulative incidence** IFRT / mantle **5.1%** STNI / TNI **12.0%**	
Dietrich 1994 [108] Retrospective cohort treated in France 1960-1984 (n=1003); median f/u not given	**15 y cumulative incidence** Regional RT **8.0%**	Extended RT **18.9%**
Nyandoto 1998 [111] Retrospective cohort of >5 y HL survivors treated in Finland 1970-1979 (n=202); median f/u of survivors 22 y	**Risk ratio** TNI **1.09** (vs <TNI) (*P* = .85)	**Median time to development** Within RT field **12y** Outside RT field **16y**
van Eggermond 2014 [115] Retrospective cohort of 5 y survivors treated in the Netherlands when aged <51y 1965-1995 (n=3122); median f/u 22.6 y	**Hazard ratio** ≥5 y since RT Supradiaphragmatic **2.4** (1.5-3.9) Infradiaphragmatic **1.6** (0.9-2.7)	<5 y since RT Supradiaphragmatic 2nd malignancy **2.1** (1.5-2.9) 3rd malignancy **2.8** (0.9-9.0) Supra & infradiaphragmatic 2nd malignancy **2.6** (1.9-3.7) 3rd malignancy **5.2** (1.6-16.8)
Nelson 1981 [123] Retrospective cohort treated in the USA 1960-1977 (n=248); median f/u 5.8 y	**RR** <EFRT **5.1** (1.8-11.08)	EFRT or TNI **3.6** (0.97-9.14)
Sasse 2012 [194] Retrospective cohort treated in the GHSG HD8 RCT (n=1204), randomised to 4 cycles of chemotherapy followed by 30 Gy EFRT or IFRT; median f/u 133 m	**Cumulative incidence** EFRT **10.9%** (8.4-13.9) (*P* = .2)	IFRT **8.5%** (6.2-11.2)
Canellos 1975 [195] Retrospective cohort treated in the USA (n=452); time period and median follow-up not given	**RR** TNI or EFRT **3.8** (95% CI not given) Less extensive RT **1.6** (95% CI not given)	
Radiotherapy dose		
Sasse 2017 [76]	ES, favourable (HD10) **10y cumulative incidence**	ES, unfavourable (HD11) **10y cumulative incidence**

Long-term follow-up data from GHSG trials HD7, HD10, HD8, HD11 1993-2003 (n=4276); median f/u 120 m, 98 m, 153 m, 106 m	4ABVD & 30 Gy: **8%** 4ABVD & 20 Gy: **6**% 2ABVD & 30 Gy: **8%** 2ABVD & 20 Gy: **9%** **SIR** 4ABVD & 30 Gy **2.1** (1.4-3.1) 4ABVD & 20 Gy **1.5** (0.9-2.3) 2ABVD & 30 Gy **1.6** (1.0-2.5) 2ABVD & 20 Gy **2.1** (1.4-3.2)	ABVD & 30 Gy: **6%** ABVD & 20 Gy: **7%** BEACOPP & 30 Gy: **7%** BEACOPP & 20 Gy: **5%** **SIR** ABVD & 30 Gy **1.4** (0.8-2.3) ABVD & 20 Gy **2.4** (1.5-3.7) BEACOPP & 30 Gy **2.2** (1.4-3.3) BEACOPP & 20 Gy **1.7** (1.0-2.6)
Almagro-Casado 2016 [79] Retrospective cohort treated in Spain 1968-2012 (n=604); median f/u not given	**HR** ≥42 Gy **3.3** (1.6-6.7) (*P* = .001)	
Abou-Antoun 2016 [109] Retrospective cohort treated in Lebanon 1990-2011 (n=112); median f/u 13 y	**13 y cumulative incidence** 31-40 Gy: **13.9%** ≥41 Gy: **33.33%**	**Odds ratio** ≥41 Gy vs 20-30 Gy **1.5** (0.674-3.339) (*P* = .012)
Nyandoto 1998 [111] Retrospective cohort of >5 y HL survivors treated in Finland 1970-1979 (n=202); median f/u of survivors 22 y	**Risk ratio** 20-39 Gy **0.38** 40 Gy **-** (*P* = .0319)	>40 Gy **2.23**
Shbib Dabaja 2022 [137] Retrospective cohort treated in the USA 1956-2009 (n=1653); median f/u 22 y	**HR**, all (vs ≤30 Gy) 30.1-36 Gy **2.03** (1.145-3.587) (*P* = .0153) 36.1-60 Gy **1.53** (0.902-2.580) (*P* = .1152) **HR**, ESHL (vs ≤30 Gy) 30.1-36 Gy **2.45** (1.097-5.480) (*P* = .0288) 36.1-60 Gy **1.57** (0.724-3.417) (*P* = .2531)	**HR**, all (vs 1-2 courses) ≥3 courses **1.89** (1.258-2.837) (*P* = .0022) **HR**, ESHL (vs 1-2 courses) ≥3 courses **3.30** (*P* = .007)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – HL: Hodgkin lymphoma; n: number; f/u: follow-up; y: years; RT: radiotherapy; LN: lymph node: SIR: standardised incidence ratio; AER: absolute excess risk; py: person-years; SMR: standardised mortality ratio; AEM: absolute excess mortality; BNLI: British National Lymphoma Investigation; IFRT: involved-field radiotherapy; EFRT: extended-field radiotherapy; CI: confidence interval; GHSG: German Hodgkin Study Group; m: months; ES: early-stage; COPP: cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine; SIR: standardised incidence ratio;; RR: relative risk; TNI: total nodal irradiation; OR: odds ratio; RCTs: randomised controlled trials; CMT: combined-modality therapy; STNI: subtotal nodal irradiation; Gy: gray; BEACOPP: bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone; HR: hazard ratio: ESHL: early-stage Hodgkin lymphoma

b. Solid tumours

Study details	Risk estimate	
Radiotherapy field		
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**HR** Supradiaphragmatic RT **2.02** (vs no SD RT) (1.54-2.65) Infradiaphragmatic RT Excluding spleen **1.46** (vs no ID RT) (1.16-1.85) Including spleen **1.52** (vs no ID RT) (1.23-1.87)	
Cosset 1991 [56] Pooled analysis of 4 EORTC trials H1, H2, H5, H6, run 1964-1988; 1660 patients; median f/u not reported	Relative risk EFRT (STNI or TNI) **2.0** (*P* = .05)	
Behringer 2004 [83] Retrospective analysis of patients treated in GHSG trials 1983-1998 (n=5367); median f/u 72 m	**RR** CMT with EFRT **3.3** (2.4-4.4)	CMT with local RT **1.6** (1.1-2.3)
Swerdlow 1992 [85] Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	**RR**, non-lung solid tumours Extensive RT **1.9** *By time since treatment* **RR**, extensive RT 0-4 y **1.9** (0.8-3.7) 5-9 y **2.4** (1.0-4.8) ≥10 y **3.1** (1.1-6.7)	Local RT **0.9** **RR**, local RT 0-4 y **1.4** (0.4-3.5) 5-9 y **1.1** (0.1-3.9) ≥10 y **1.0** (0.02-5.4)

Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	**SIR**, SD solid tumours No SD RT **2.1** (1.4-2.9) SD RT **6.3** (5.7-6.9) (*P* < .001) **SIR**, ID solid tumours No ID RT **1.7** (1.3-2.1) ID RT **4.6** (3.9-5.4) (*P* < .001)	**HR** Mantle RT Ref Other SD field with axilla **0.98** (0.78-1.34) Other SD field **0.64** (0.49-0.83) (*P* < .001) No ID RT Ref ID RT with spleen **1.40** (1.16-1.68) Other ID field **1.05** (0.87-1.27) (*P* = .001)
Chronowski 2003 [90] Retrospective cohort treated for stage 1-2 HL in the USA 1980-1995 (n=286); median f/u 7.4 y	**Cumulative risk** EFRT 5 y **2.7%** 10 y **11.1%** 15 y **28.7%** IFRT or regional RT 5 y **0.0%** 10 y **6.9%** 15 y **11.4%**	**RR** SD or ID RT **1.1** (0.4-2.6) SD & ID RT **3.9** (2.0-6.8) **AER** SD or ID RT **6.5** SD & ID RT **65.7**
Biti 1994 [107] Retrospective cohort treated in Italy 1960-1988 (n=1121); mean f/u >9 y	**15 y cumulative incidence** IFRT / mantle **5.1%** STNI / TNI **11.6%**	
van Eggermond 2014 [115] Retrospective cohort of 5 y survivors treated in the Netherlands when aged <51 y 1965-1995 (n=3122); median f/u 22.6 y	**HR** Solid non-breast cancer after solid non-breast ≥5 y since RT Supradiaphragmatic **2.9** Infradiaphragmatic **1.6**	<5 y since RT Supradiaphragmatic 2nd malignancy **2.2** (1.5-3.3) 3rd malignancy **2.0** (0.4-8.5) Supra & infradiaphragmatic 2nd malignancy **2.8** (1.9-4.1)

	3rd malignancy **5.3** (1.3-22.2)
Hodgson 2007 [127] Retrospective cohort of 5y HL survivors treated in North America & Europe 1970-2001 (n=18,862); median f/u 12.2 y	**RR** Supradiaphragmatic **6.8** (5.7-8.2) Infradiaphragmatic **3.6** (2.8-4.5)
Sasse 2012 [194] Retrospective cohort treated in the GHSG HD8 RCT (n=1204), randomised to 4 cycles of chemotherapy followed by 30 Gy EFRT or IFRT; median f/u 133 m	Cumulative incidence EFRT **7.0%** (4.9-9.5) IFRT **5.8%** (4.0-8.2)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – HL: Hodgkin lymphoma; n: number; f/u: follow-up; y: years; HR: hazard ratio; RT: radiotherapy; SD: supradiaphragmatic; ID: infradiaphragmatic; EORTC: European Organisation for Research and Treatment of Cancer; EFRT: extended-field radiotherapy; STNI: subtotal nodal irradiation; TNI: total nodal irradiation; SIR: standardised incidence ratio; GHSG: German Hodgkin Study Group; m: months; RR: relative risk; AER: absolute excess risk; RCT: randomised controlled trial

c. Breast cancer

Study details	**Risk estimate**	
Radiotherapy field		
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	**SIR** No SD RT **1.0** (0.3-2.2) SD RT **5.4** (4.6-6.2) (*P* < .001)	**HR** Mantle RT Ref Other SD field with axilla **0.41** (0.17-1.01) Other SD field **0.37** (0.19-0.72) (*P* < .001)
Franklin 2006 [89] Individual patient data meta-analysis from RCTs comparing RT vs CMT, chemo vs CMT, RT vs chemo or IFRT vs EFRT	**OR** EFRT **3.25*** (*P* = .04) (vs IFRT)	
Boivin 1995 [129] Retrospective cohort treated in the USA and Canada 1940-1987 (n=10,472); average f/u 7.1 y (after discounting the 1st year after diagnosis)	RR - Thoracic field **1.1** (0.5-2.7)	Age <30 y at RT **0.7** (0.2-3.1) ≥15 y following RT **1.2** (0.3-5.7)
de Bruin 2009 [144]	SIR Mantle, no pelvic **8.2** (6.6-10.1)	AER Mantle, no pelvic **87** (68-109)

Retrospective cohort of female 5 y HL survivors treated when aged <51 y in the Netherlands 1965-1995; median f/u 17.8 y; comparator general population	Mantle & pelvic **2.7** (1.0-5.9) Mediast, no pelvic **3.7** (1.2-8.7) Other SD **1.6** (0.3-4.6) RR **2.7** (1.1-6.9) mantle vs mediastinal RT	Mantle & pelvic **25** (0-71) Mediast, no pelvic **31** (2-88) Other SD **8** (-9-49)
Swerdlow 2012 [145] Retrospective cohort of women treated with supradiaphragmatic RT when aged <36 y in England and Wales 1956-2003 (n=5002); median f/u not given	All SD RT **SIR** Mantle **6.0** (5.3-6.7) 2 mantle compts **3.4** (2.4-4.7) 1 mantle compt **2.5** (1.7-3.7) (*P* < .001) **AER** Mantle **41.5** (36.0-47.5) 2 compts **20.7** (11.7-32.4) 1 compt **11.3** (4.8-20.0) **Cumulative risk** Mantle **5.3** (20 y), **12.2** (40 y) 2 mantle components **3.2** (20 y), **16.9** (40 y) 1 mantle components **2.2** (20 y), **11.4** (40 y) **SIR** SD RT alone **6.0** (5.2-7.0) SD & ≥5Gy pelvic **1.4** (0.5-4.4) **AER** SD RT alone **42.9** (35.3-51.4) SD & ≥5 Gy pelvic **4.7** (-8.2-35.8)	SD RT only **Cumulative risk** Mantle **7.4** (20 y), **29.9** (40 y) 2 mantle components **3.1** (20 y), **21.2** (40 y) 1 mantle components **1.0** (20 y), **20.9** (40 y) SD RT & alkylating agents or pelvic RT **Cumulative risk** Mantle **4.4** (20 y), **18.7** (40 y) 2 mantle components **3.7** (20 y), **14.6** (40 y) 1 mantle components **2.7** (20 y), **8.5** (40 y) **Cumulative risk** SD RT alone **6.3** (20 y), **27.9** (30 y) All SD RT **4.5** (20 y), **20.2** (30 y)

El-Din 2009 [152] Retrospective cohort of women treated for stage 1-2 HL when aged ≤60 y in the USA 1964-2001 (n=248); median f/u 15.2 y	**SMR** Supradiaphragmatic RT **9.07** (5.81-18.04)
Krul 2017 [157] Case-control study nested in a cohort of female 5 y HL survivors treated when aged <41 y (174 cases, 466 controls); median f/u not given	**OR**, pelvic RT No Ref Yes **0.33** (0.13-0.84) (adj. for RT dose to breast Ca location, alkylating chemo)
Conway 2017 [158] Retrospective cohort of female patients treated for HL in Canada 1961-2009 (n=734); median f/u 18 y	**20 y cumulative incidence** Mantle RT **7.5%** (4.4-11.5) Smaller field RT **3.1%** (1.0-7.7) **HR**, mantle RT **2.90** (vs chemo) (1.4-6.0) (*P* = .004) **3.34** (vs small-field) (1.33-8.04) (*P* = .01) **HR**, smaller-field RT **0.87** (vs chemo) (0.61-2.27) (*P* = .63)

Radiotherapy dose

Swerdlow 2012 [145]
Retrospective cohort of women treated with supradiaphragmatic RT when aged <36 y in England and Wales 1956-2003 (n=5002); median f/u not given

SD RT only
Cumulative risk
1-34 Gy **8.8** (20 y), **22.8** (40 y)
35 Gy **5.4** (20 y), **29.0** (40 y)
36-39 Gy **4.3** (20 y), **23.2** (40 y)
40 Gy **8.2** (20 y), **39.8** (40 y)
≥41 Gy **7.7** (20 y), **46.3** (40 y)

SD RT & alkylating agent / pelvic RT
Cumulative risk
1-34 Gy **2.1** (20 y), **24.6** (40 y)
35 Gy **5.3** (20 y), **19.5** (4 0y)
36-39 Gy **8.9** (20 y), **26.7** (40 y)
40 Gy **6.8** (20 y), **22.2** (40 y)
≥41 Gy **0.0** (20 y), **12.3** (40 y)

Mantle dose
All SD RT
SIR
1-34 Gy **5.6** (3.5-8.9)
35 Gy **5.8** (4.3-7.8)
36-39 Gy **6.5** (4.3-9.9)
40 Gy **7.2** (5.3-9.7)
≥41 Gy **5.8** (3.0-11.1)
(*P* = .445)
AER
1-34 Gy **43.0** (21.6-73.3)
35 Gy **37.2** (24.8-52.8)
36-39 Gy **45.7** (25.5-73.5)

Pelvic dose
All SD RT
Cumulative risk
0-4 Gy **5.2** (20 y), **22.8** (40 y)
≥5 Gy **1.2** (20 y), **8.9** (40 y)

SD RT only
Cumulative risk
0-4 Gy **6.3** (20 y), **27.9** (40 y)
≥5 Gy **-**

SD RT & alkylating agent / pelvic RT

	40 Gy **50.0** (33.9-70.1) ≥41 Gy **49.6** (17.1-103.4) **Cumulative risk** 1-34 Gy **3.5** (20 y), **24.9** (40y) 35 Gy **4.9** (20 y), **24.4** (40y) 36-39 Gy **6.4** (20 y), **24.6** (40y) 40 Gy **7.3** (20 y), **29.4** (40 y) ≥41 Gy **3.3** (20 y), **29.6** (40 y)	**Cumulative risk** 0-4 Gy **4.6** (20 y), **18.6** (40 y) ≥5 Gy **1.2** (20 y), **8.9** (40 y)
Hancock 1993 [146] Retrospective cohort of women treated for HL in USA 1961-1990 (n=885); mean f/u 10 y (AER / 10,000 py)	RR, mantle dose 7.5-39.6 Gy **3.5** (0.0-17.1) ≥40 Gy **3.5** (1.8-6.0)	AER, mantle dose 7.5-39.6 Gy **32.0** ≥40 Gy **17.5**
Travis 2003 [148] Case-control study nested n a cohort of 3817 female 1 y HL survivors treated when aged <30 y 1965-1994 (105 cases, 266 controls); median f/u not given	RR Dose to site of breast tumour 0-3.9 Gy Ref 4.0-6.9 Gy **1.8** (0.7-4.5) (*P* = .21) 7.0-23.1 Gy **4.1** (1.4-12.3) (*P* = .008) 23.2-27.9 Gy **2.0** (0.7-5.9) (*P* = .22) 28.0-37.1 Gy **6.8** (2.3-22.3) (*P* < .001) 37.2-40.4 Gy **4.0** (1.3-13.4) (*P* = .02) 40.5-61.3 Gy **8.0** (2.6-26.4) (*P* < .001) Dose to ovaries < 3 Gy Ref 3.0-4.9 Gy **1.2** (0.3-3.9) (*P* = .78) ≥ 5 Gy **0.4** (0.1-1.1) (*P* = .07)	22-30 y at RT < 4 Gy Ref 4.0-23.0 Gy **2.9** (0.98-9.8) (*P* = .05) 23.1-37.1 Gy **3.3** (0.98-13.3) (*P* = .05) 37.2-61.3 Gy **4.5** (1.2-20.1) (*P* = .03) No alkylating agents, < 5 Gy ovaries < 4 Gy Ref 4.0-23.0 Gy **2.1** (0.8-6.2) (*P* = .15) 23.1-37.1 Gy **5.0** (1.7-16.4) (*P* = .004) 37.2-61.3 Gy **7.2** (2.2-26.5) (*P* < .001)

	≤ 21 y at RT < 4 Gy Ref 4.0-23.0 Gy **2.2** (0.8-6.7) (*P* = .13) 23.1-37.1 Gy **3.3** (1.0-11.7) (*P* = .046) 37.2-61.3 Gy **5.2** (1.3-23.7) (*P* = .02)	Any alkylating agents or ≥ 5 Gy to ovaries < 4 Gy **0.6** (0.2-2.0) (*P* = .45) 4.0-23.0 Gy **1.7** (0.6-4.9) (*P* = .31) 23.1-37.1 Gy **1.2** (0.3-4.3) (*P* = .80) 37.2-61.3 Gy **1.5** (0.4-5.7) (*P* = .55)
El-Din 2009 [152] Retrospective cohort of women treated for stage 1-2 HL when aged ≤60 y in the USA 1964-2001 (n=248); median f/u 15.2 y	SMR, dose to mediastinum < 40 Gy **10.01** (5.93-21.16)	≥ 40 Gy **9.56** (5.66-20.20)
van Leeuwen 2003 [156] Case-control study nested in a cohort of 770 female patients treated for HL in the Netherlands when aged <41 y (48 cases, 175 matched controls); mean f/u 3.4 y	RR Dose to affected quartile 0.26-3.9 Gy Ref 4-23.2 Gy **1.05** (0.32-3.51) (*P* = .94) 24-38.2 Gy **3.23** (0.90-11.6) (*P* = .07) 38.5-56 Gy **4.47** (1.25-16.0) (*P* = .02) Adj. for ovarian dose & chemo 0.26-3.9 Gy Ref 4-23.2 Gy **1.11** (0.32-3.85) (*P* = .87) 24-38.2 Gy **4.20** (0.99-17.8) (*P* = .05) 38.5-56 Gy **5.16** (1.27-21.0) (*P* = .02) Adj. for menopausal status & age at menopause 0.26-3.9 Gy Ref 4-23.2 Gy **1.20** (0.35-4.19) (*P* = .77) 24-38.2 Gy **4.91** (1.06-22.8) (*P* = .04) 38.5-56 Gy **8.18** (1.64-40.8) (*P* = .01)	

	Dose to ovary <5 Gy Ref ≥5 Gy **0.12** (0.02-0.93) (*P* = .04) Adj for breast RT dose & chemo <5 Gy **Ref** ≥5 Gy **0.13** (0.02-1.08) (*P* = .06)	
Krul 2017 [157] Case-control study nested in a cohort of female 5 y HL survivors treated when aged <41 y (174 cases, 466 controls); median f/u not given (adjusted for post-RT ovarian function)	**OR**, dose to tumour location (median) 0.0-2.9 Gy (1.2) Ref 3.0-7.9 Gy (4.9) **1.33** (0.64-2.77) 8.0-27.9 Gy (17.5) **2.21** (1.09-4.46) 28.0-35.9 Gy (33.9) **2.38** (1.17-4.83) 36.0-61.2 Gy (39.4) **4.70** (2.36-9.38)	
Hill 2005 [197] Case-control study nested in an international cohort of 3817 patients treated when aged <30 y (105 patients, 266 controls); median f/u not given	**OR**, dose to site of breast Ca 0-4.9 Gy Ref	5.0-61.3 Gy **2.7** (1.4-5.2)
Tinger 1997 [198] Retrospective cohort of women treated with mantle field RT in the USA 1966-1985 (n=152); median f/u 13 y	**RR**, anterior d_{max} dose >40 Gy **6.2** (*P* < .05) ≤40 Gy **2.6** (NS)	
Location of second tumour in relation to radiation field		
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	Occurring within RT field **SIR 6.4** (4.0-9.7)	**AER 46.9** / 10,000 py

*pooled estimate (meta-analysis)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – y: years; HL: Hodgkin lymphoma; f/u: follow-up; SIR: standardised incidence ratio; SD: supradiaphragmatic; RT: radiotherapy; HR; hazard ratio; RCT; randomised controlled trial; CMT: combined-modality therapy; IFRT: involved-field radiotherapy; EFRT: extended-field radiotherapy; OR: odds ratio; RR; relative risk; AER: absolute excess risk; py: person-years; Gy: gray; AMR: standardised mortality ratio; Ca: cancer; Adj.: adjusted; Ref: reference; d_{max}: maximum dose

d. Lung cancer

Study details	Risk estimate	
Radiotherapy field		
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	**SIR** No SD RT **2.7** (1.6-4.3) SD RT **7.7** (6.5-9.0) (*P* < .001)	**HR** Mantle RT Ref Other SD field with axilla **1.45** (0.83-2.52) Other SD field **0.85** (0.52-1.39) (*P* < .001)
Swerdlow 2001 [161] Case-control study nested in a cohort of 5519 patients treated for HL in the UK 1963-1993 (88 cases, 176 matched controls); median f/u not given	**OR**, volume of lung irradiated None / small / medium Ref Large **1.90** (0.49-9.16)	
Radiotherapy dose		
Almagro-Casado 2016 [79] Retrospective cohort treated in Spain 1968-2012 (n=604); median f/u not given	**HR** ≥42 Gy **4.0** (1.1-11.6) (*P* = .01)	
Kaldor 1992 [162] International case-control study in >1 y HL survivors (98 cases, 259 matched controls); median f/u not given	**RR**, dose to lung 0-<100 cGy Ref 100-250 cGy **1.4** (0.60-3.55) >250 cGy **1.6** (0.66-4.12) (P_{trend} = .48)	
Travis 2002 [164] Case-control study nested in cohort of 19,046 HL survivors treated in the Netherlands 1965-1994 (222 cases, 444 matched controls); median f/u not given	**RR**, dose to location of subsequent lung tumour 0 Gy Ref > 0-4.9 Gy **1.3** (0.3-4.9) (*P* = .69) 5.0-14.9 Gy **4.1** (0.7-22) (*P* = .12) 15.0-29.9 Gy **2.5** (0.1-16.1) (*P* = .46) 30.0-39.9 Gy **8.6** (2.9-30) (*P* < .001) ≥ 40.0 Gy **7.2** (2.2-28) (*P* = .001)	
van Leeuwen 1995 [166] Retrospective cohort treated in the Netherlands 1966-1983 (n=744); median f/u 6.4 y	**RR**, dose to affected lung area 1-5 Gy **3.5** (0.39-32)	Adjusted for smoking 1-5 Gy **2.9** (0.32-26)

	5-9 Gy **7.1** (0.81-62) ≥9 Gy **9.6** (0.93-98) (P_{trend} = .01)	5-9 Gy **6.3** (0.71-56) ≥9 Gy **8.9** (0.86-91) (P_{trend} = .02)
Gilbert 2003 [199] International case-control study within cohort of 19,046 1 y HL survivors (227 cased, 455 matched controls); median f/u not given	**RR**, adjusted for smoking & no. cycles alkylating agents No RT **1.0** RT <5 y prior **1.0** (95% CIs not given)	RT ≥5 y prior >0-4.9 Gy **1.64** (0.53-5.2) (*P* = .39) 5.0-14.9 Gy **4.18** (0.70-21) (*P* = .11) 15.0-29.9 Gy **2.69** (0.15-15) (*P* = .40) 30.0-39.9 Gy **8.50** (3.3-24) (*P* < .001) ≥40 Gy **6.27** (2.2-19) (*P* < .001)
Location of second tumour in relation to radiation field		
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	Occurring within RT field **SIR 4.1** (2.4-6.6)	 **AER 17.0** / 10,000py

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – y: years; HL: Hodgkin lymphoma; f/u: follow-up; SIR: standardised incidence ratio; SD: supradiaphragmatic; RT: radiotherapy; HR: hazard ratio; OR: odds ratio; Ref: reference; Gy: gray; RR: relative risk; cGy: centigray; AER: absolute excess risk; py: person-years

e. Gastrointestinal malignancies

Study details	Risk estimate	
Radiotherapy field		
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	HR, GI cancer (stomach, pancreas, colorectal) Mantle RT Ref Other SD field with axilla **2.11** (1.12-3.97) Other SD field **0.57** (0.27-1.22) (*P* = .004)	 No ID RT Ref ID RT with spleen **3.11** (1.93-5.00) Other ID field **2.26** (1.40-3.64) (*P* < .001)

	SIR, all gastrointestinal No ID RT **1.9** (1.3-2.6) ID RT **6.2** (5.0-7.7) (*P* < .001)	**SIR**, oesophageal No SD RT **5.1** (1.6-11.8) SD RT **11.2** (7.7-15.9) (*P* = .1)
Swerdlow 1992 [85] Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	**RR** Extensive RT **3.9**	 Local RT **2.3**
Boivin 1995 [129] Retrospective cohort treated in the USA and Canada 1940-1987 (n=10,472); average f/u 7.1 y (after discounting the 1st year after diagnosis)	RR, trunk field **0.9** (0.5-1.7)	
Dietrich 1993 [132] Retrospective cohort treated in France 1960-194 (n=892); median f/u not given	**15 y cumulative incidence**, gastric cancer Para-aortic RT **2.4%** No para-aortic RT **0%**	
van Eggermond 2017 [135] Retrospective cohort of Dutch 5 y HL survivors treated 1965-1995 (n=3121); median f/u 22.9 y	**SIR**, colorectal cancer SD RT **0.9** ID +/- SD RT **1.8** **SIR**, all colon sites SD RT **1.0** ID +/- SD RT **2.2** **SIR**, transverse colon SD RT **3.5** ID +/- SD RT **4.9** **SIR**, other colon sites SD RT **0.5** ID +/- SD RT **1.8** **SIR**, rectum SD RT **0.8**	*Infradiaphragmatic RT* **SIR**, colorectal cancer No ID RT **1.5** PAO **2.2** PAO & spleen **2.2** Inverted Y +/- spleen **6.1** Other ID **6.3** **SIR**, all colon sites No ID RT **1.4** (0.7-2.5) PAO **3.0** (1.0-7.1) PAO & spleen **2.3** (0.8-5.4) Inverted Y +/- spln **6.0** (3.0-10.7) Other ID **5.2** (0.6-18.9) **SIR**, transverse colon No ID RT **1.9** (0.2-7.0) PAO **8.8** (1.0-32.0)

	ID +/- SD RT **1.0** **AER**, all SD RT **-0.4** ID +/- SD RT **3.3** **Cumulative incidence** No ID RT **0.3** (20 y), **1.4** (30 y) PAO RT **0.7** (20 y), **2.2** (30 y) PAO & spleen RT **0.7** (20 y), **1.3** (30 y) Inverted Y +/- spleen **1.6** (20 y), **4.2** (30 y) Other ID **1.0** (20 y), **4.4** (3 0y)	PAO & spleen **14.0** (3.8-35.8) Inv Y +/- spln **15.9** (4.3-40.8) Other ID **-** **SIR**, other colon sites No ID RT **1.3** (0.6-2.5) PAO **2.0** (0.4-5.8) PAO & spleen **0.5** (0.0-2.9) Inverted Y +/- spln **4.2** (1.7-8.7) Other ID **5.7** (0.7-20.7) **SIR**, rectum No ID RT **1.6** (0.7-3.2) PAO **0.9** (0.0-5.2) PAO & spleen **2.1** (0.4-6.1) Inverted Y +/- spln **6.3** (2.5-13.0) Other ID **8.1** (1.0-29.1) **AER** No ID RT **2.0** PAO **4.9** PAO & spleen **4.3** Inverted Y +/- spleen **21.1** Other ID **18.1**
Morton 2014 [168] International nested case-control study in cohort of 19,882 >5 y HL survivors treated 1943-1992 (36 casesd, 71 controls); median f/u not given	**OR**, oesophageal cancer Supradiaphragmatic radiotherapy **10.8** (2.1-199.0)	
Morton 2013 [169] International case-cohort study nested in a cohort of 19,882 HL survivors treated 1953-2003 (89 cases, 190 matched controls); median f/u not given	**OR**, stomach cancer No RT Ref Any subdiaphragmatic fields **6.2** (2.1-21.4) Supradiaphragmatic fields only **1.4** (0.5-4.5)	

Radiotherapy dose

van den Belt-Dusebout 2009 [134] Nested case-control study in a cohort of 5142 5 y survivors of HL or testicular cancer treated in the Netherlands 1965-1995; only data relating to HL patients extracted (19 cased, 69 controls); median f/u not given	**RR**, stomach dose <11 Gy Ref 11-20 Gy **2.9** (1.2-7.2) (*P* = .018)	 >20 Gy **9.9** (3.2-31.2) (*P* < .0001)
Morton 2014 [168] International nested case-control study in cohort of 19,882 >5 y HL survivors treated 1943-1992 (36 casesd, 71 controls); median f/u not given	Oesophageal cancer **OR**, dose to oesophagus ≥ 30 Gy **4.3** (1.5-15.3) (vs < 30 Gy)	 30.0-39.9 Gy **5.0** (1.3-23.6) ≥ 40 Gy **3.9** (1.3-15.0) (P_{trend} < .001)
Morton 2013 [169] International case-cohort study nested in a cohort of 19,882 HL survivors treated 1953-2003 (89 cases, 190 matched controls); median f/u not given (OR adjusted for procarbazine & dacarbazine, and unknown RT dose)	**OR**, gastric cancer 0 Ref 0.1-0.9 Gy **1.3** (0.4-4.1) 1.0-4.9 Gy **1.0** (0.3-3.5) 5.0-24.9 Gy **0.5** (0.1-2.7) 25.0-34.9 Gy **4.6** (1.2-20.5) 35.0-39.9 Gy **8.2** (2.6-29.7) ≥ 40 Gy **4.2** (1.2-15.6)	 < 25 Gy to stomach < 5600 mg/m^2 procarbazine Ref ≥ 25Gy < 5600 mg/m^2 **2.8** (1.3-6.4) < 25Gy ≥ 5600 mg/m^2 **1.2** (0.5-2.7) ≥ 25 Gy ≥ 5600 mg/m^2 **77.5** (14.7-1452)
	OR, gastric cancer, adjusted for chemotherapy & unknown dose Prescribed dose <25 Gy Ref Prescribed dose ≥25 Gy **5.8** (3.0-12.3) (P_{trend} < .001)	
Dores 2014 [170] Nested case-control study in international cohort of ≥5 y HL survivors, treated 1953-2003 (n=36 cases, 70 controls)	**OR**, pancreatic cancer Dose to site of tumour, adj. for alkylating agents 0-< 0.5 Gy Ref 0.5-< 5 Gy **0.5** (0.1-2.0) 10-< 40 Gy **1.8** (0.5-8.1) ≥ 40 Gy **9.1** (1.7-77) (P_{trend} = .005)	 RT dose & number of alkylating agent cycles < 10 Gy & < 6 Ref ≥ 10 Gy & < 6 **3.0** (0.7-17) < 10 Gy & ≥ 6 **1.8** (0.4-9.7) ≥ 10 Gy & ≥ 6 **17.9** (3.5-158) ($P_{multiplicative\ interaction}$ = .29) ($P_{additive\ interaction}$ = .041)
Gilbert 2017 [200]	OR, stomach cancer	

Case-control study nested in a cohort of >5 y HL survivors treated in Norway and the Netherlands (48 cases, 135 controls); median f/u not given	Dose to site of tumour (T), mean stomach dose (M) T 0-0.19 Gy, M 0.07 Gy Ref T 0.2-1.99 Gy, M 0.9 Gy **1.1** (0.27-4.4) T 2-4.99 Gy, M 2.9 Gy **1.6** (0.20-12.0) T 5-24.99 Gy, M 15.0 Gy **1.3** (0.19-8.0) T 25-34.99 Gy, M 31.4 Gy **2.1** (0.35-14.0) T 35-39.99 Gy, M 37.8 Gy **5.1** (1.1-28.0) T 40-59.1 Gy, M 42.7 Gy **2.8** (0.56-15.0)	
Location of second tumour in relation to radiation field		
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	Occurring within RT field **SIR** Colon / rectum **4.9** (2.1-9.6) Stomach **6.1** (2.4-12.5) Liver **7.4** (1.5-21.5)	 **AER** Colon / rectum **22.8** / 10,000 py Stomach **7.5** / 10,000 py Liver **3.8** / 10,000 py

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.
Abbreviations – y: years; HL: Hodgkin lymphoma; f/u: follow-up; HR: hazard ratio; GI: gastrointestinal; RT: radiotherapy; SD: supradiaphragmatic; SIR: standardised incidence ratio; ID: infradiaphragmatic; RR: relative risk; PAO: para-aortic; AER: absolute excess risk; py: person-years; OR: odds ratio; Gy: gray; mg/m^2: milligrams per metre-squared; adj.: adjusted

f. Cutaneous malignancies

Study details	Risk estimate	
Location of second tumour in relation to radiation field		
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	Occurring within RT field **SIR** NMSC **15.5** (3.2-45.4)	 **AER** NMSC **200.3** / 10,000 py

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.
Abbreviations – n: number; y: year; RT: radiotherapy; SIR: standardised incidence ratio; NMSC; non-melanoma skin cancer; AER; absolute excess risk; py: person-years

g. Other solid tumours

Study details	Risk estimate	
Radiotherapy field		
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	**SIR**, thyroid cancer No SD RT **0.0** (0.0-14.0)	SD RT **16.0** (9.9-24.5) (*P* < .001)
Boivin 1995 [129] Retrospective cohort treated in the USA and Canada 1940-1987 (n=10,472); average f/u 7.1 y (after discounting the 1st year after diagnosis)	RR, head & neck field Lip, oral cavity & pharynx **2.7** (xxx) Thyroid **1.3** (0.3-6.1) (2.3 (0.2-21) if ≥10 y f/u) RR any field: Bone & soft tissue **0.9** (0.5-1.7) RR, abdominal field: Female genital system **1.5** (0.9-2.6)	
Location of second tumour in relation to radiation field		
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	Occurring within RT field **SIR** Thyroid **14.1** (5.2-30.8) Kidney **7.1** (1.5-20.8)	**AER** Thyroid **7.1** / 10,000py Kidney **12.3** / 10,000py

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.
Abbreviations – y: years; HL: Hodgkin lymphoma; SIR: standardised incidence ratio; SD: supradiaphragmatic; RT: radiotherapy; n: number; f/u: follow-up; RR: relative risk; AER: absolute excess risk; py: person-years

h. Haematological malignancies

Study details	Risk estimate
Radiotherapy dose	
Kaldor 1990 [177] Case-control study nested in an international retrospective cohort diagnosed with HL since 1960 (n=29,552, cases n=163)	**RR**, leukaemia ≤ 20 Gy to bone marrow Ref > 20 Gy to bone marrow **7.0** (95% CI not given)

Radiotherapy field

Swerdlow 1992 [85] Retrospective cohort treated for HL in the UK 1970-1987 (n=2846); median f/u not given	**RR,** leukaemia Extensive RT **-** Local RT **6.8**	**RR**, NHL Extensive RT **3.9** Local RT **33.8**
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	**HR**, leukaemia / MDS Mantle RT Ref Other SD field with axilla **1.26** (0.48-3.28) Other SD field **0.75** (0.34-1.65) (*P* = .73) No ID RT Ref ID RT with spleen **1.73** (0.86-3.48) Other ID field **2.00** (1.01-3.97) (*P* = .1)	**HR**, NHL Mantle RT Ref Other SD field with axilla **1.39** (0.68-2.85) Other SD field **0.38** (0.17-0.85) (*P* = .02) No ID RT Ref ID RT with spleen **1.13** (0.66-1.92) Other ID field **0.89** (0.53-1.50) (*P* = .77)
Biti 1994 [107] Retrospective cohort treated in Italy 1960-1988 (n=1121); mean f/u >9 y	**15 y cumulative incidence** IFRT / mantle **-**	 STNI / TNI **3.4%**
van Leeuwen 1994 [181] Case-control study nested in a cohort of 1939 patients treated for HL in the Netherlands 1966-1986 (44 cases, 124 matched controls); median f/u not given	RR (vs no RT) Mantle only, inverted Y only or local only **1.1** STNI **0.67** (0.08-6.0) (*P* = .72) TNI **2.5** (0.32-18.8) (*P* = .39)	
Josting 2003 [191] Retrospective analysis of patients treated in GHSG trials 1981-1998 (n=5411); median f/u 55 m	**AER**, AML EFRT **13.04** / 100,000 py (7.5-21)	 IFRT **8.80** / 100,000 py (1.1-32)
Brusamolino 1998 [188] Retrospective cohort treated in Italy 1975-1992 (n=1659); median f/u 10 y	**15 y cumulative risk, all** IFRT **0.9%** Mantle +/- PAN **3.8%** **15 y cumulative risk**, leukaemia RT alone **0.3%** Mantle +/- PA **0%**	 Inverted Y **5.2%** STNI or TNI **8.9%** SD RT or STNI **1.8%** Inverted Y or TNI **6.1%**

	Inverted Y **0%** STNI or TNI **0.6%**	
Sasse 2012 [194] Retrospective cohort treated in the GHSG HD8 RCT (n=1204), randomised to 4 cycles of chemotherapy followed by 30 Gy EFRT or IFRT; median f/u 133 m	Cumulative incidence EFRT AML / MDS **2.1%** (1.0-3.7) NHL **1.7%** (0.8-3.2)	IFRT AML / MDS **0.8%** (0.2-1.9) NHL **1.9%** (0.9-3.4)
Delwail 2002 [202] Retrospective cohort treated in France 1972-1988 (n=462); median f/u 8.5 y	Leukaemia **15 y actuarial risk** SD RT or STNI **2.4%** (0.0-4.9)	Inverted Y or TNI **13.9%** (0.2-25.6)
Andrieu 1990 [203] Retrospective cohort treated for stage 1-3 HL in France 1972-1980 (n=462); median 10.5 y	**15 y actuarial risk** MOPP & SD RT **2.7%** MOPP & ID RT **17.4%**	MOPP & STNI / TNI **8.6%** (*P* < .001)
van der Velden 1988 [204] Nested case-control study in cohort of 1681 patients with HL treated in the Netherlands 1972-1978; median f/u 66 m (18 cases)	**OR,** extensive RT **22** (1.2-417)	
Location of second tumour in relation to radiation field		
Petrakova 2018 [81] Retrospective cohort treated in the Czech Republic 1953-1996 (n=871); median f/u 12 y	Occurring within RT field **SIR** Leukaemia **7.0** (2.3-16.3) NHL **10.1** (4.1-20.8)	**AER** leukaemia **5.1** / 10,000 py NHL **7.5** / 10,000 py

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – HL: Hodgkin lymphoma; n: number; RR: relative risk; Gy: gray; Ref: reference; y: years; f/u: follow-up; HR: hazard ratio; MDS: myelodysplasic syndrome; RT: radiotherapy; SD: supradiaphragmatic; ID: infradiaphragmatic; NHL: non-Hodgkin lymphoma; IFRT: infradiaphragmatic radiotherapy; STNI: subtotal nodal irradiation; TNI: total nodal irradiation; PAN: para-aortic nodes; m: months; AER: absolute excess risk; py: person-years; AML: acute myeloid leukaemia; EFRT: extended field radiotherapy; MDS: myelodysplastic syndrome; OR: odds ratio; SIR: standardised incidence ratio

Table C3.3: Effect of other factors on the risk of second malignancies following treatment for Hodgkin lymphoma

a. All second malignancies

Study details	Risk estimate	
Sex		
Brusamolino 2006 [5] Retrospective cohort of patients with stage 1A-2A HL treated in Italy with 4 cycles ABVD & limited RT 1990-2003 (n=120); median f/u 10 y	**SIR** Male **1.6** (*P* = .530) Female **4** (*P* = .003)	**SMR** Male **2.8** (*P* = .029) Female **9.4** (*P* < .001)
Brierley 1998 [10] Retrospective cohort with stage 1-2 HL treated in Canada 1973-184 (n=611); median f/u 11 y; comparator age-matched general population for same period	**RR** Male **1.9** (1.1-3.0) (*P* = .004) Female **2.7** (1.6-4.1) (*P* <.0001)	
Lee 2000 [27] Retrospective cohort of patients with stage 1-3 HL treated in the USA 1970-1986 (n=210); median f/u 15.6y; comparator general pop	**SIR** (95% CIs not given) Male **5.3** Female **7.1**	**AER** Male **9.2** / 1000 py Female **8.6** / 1000 py
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py)	**SIR** excluding NMSC Male **3.0** (2.6-3.4) Female **2.6** (2.2-3.2) (χ^2 1.0)	**AER** excluding NMSC Male **48.1** Female **38.7**
Ng 2002 [86] Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	**RR** Male **4.5** (3.6-5.6) Female **4.8** (4.0-5.8)	**AER** Male **70.0** / 10,000 py Female **113.4** / 10,000 py
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	**SIR** Male **4.5** (4.1-4.9) Female **4.8** (4.4-5.3) (*P* = .28)	**AER** Male **112** / 1000 py Female **134** / 1000 py (*P* = .038)
Swerdlow 1997 [91] Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1 y	**SIR** excluding NMSC Male **3.5** (2.5-4.7) (*P* < .01) Female **3.0** (2.0-4.4) (*P* < .01)	**AER** excluding NMSC Male **51.5** Female **45.6**
Munker 1999 [93]	**RR**	

Retrospective cohort treated in Germany 1974-1994 (n=1120); mean f/u 9.1 y	Male **3.3** (2.6-4.2)	Female **2.9** (2.1-3.9)
Rubin 1986 [95] Retrospective cohort treated in the USA 1957-1982 (n=320); median f/u ~6 y	**RR** Male **3.66** (1.13-6.19) (*P* < .05)	Female **5.84** (2.66-9.02) (*P* < .05)
Sont 1992 [97] Retrospective cohort treated in the Netherlands 1969-1988 (n=482); average f/u 6.05 y	**RR** Male **4.7** (95% CI not given)	Female **2.7** (95% CI not given)
Henry-Amar 1992 [102] Retrospective international cohort of 1 y HL survivors treated 1960-1987 (n=12,411); median f/u not given	**RR** Male **3.0** (*P* < .001) Female **2.6** (*P* < .001)	
Biti 1994 [107] Retrospective cohort treated in Italy 1960-1988 (n=1121); mean f/u >9 y	**15y cumulative incidence** Male **14.4%**	Female **7.3%**
Nyandoto 1998 [111] Retrospective cohort of >5 y HL survivors treated in Finland 1970-1979 (n=202); median f/u of survivors 22 y	**Median time to development** Female **14 y**	Male **15 y**
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	**SIR** Male **4.1** (3.5-4.8) Female **3.6** (3.0-4.3) (*P* = .26)	**AER** Male **68.0** / 10,000 py Female **61.2** / 10,000 py
van Eggermond 2014 [115] Retrospective cohort of 5y survivors treated in the Netherlands when aged <51y 1965-1995 (n=3122); median f/u 22.6 y	**HR** Female Ref Male 2nd malignancy **0.7** (0.6-0.9) 3rd malignancy **0.4** (0.3-0.6) **10 y cumulative incidence** of 3rd malignancy after 2nd cancer Male **9.2%** Female **17.1%**	**SIR** 3rd malignancy after 2nd Male **4.4** (3.1-5.9) (4.3 (3.0-5.8) with breast Ca exc.) Female **6.2** (4.9-7.9) (5.2 (3.7-7.2) with breast Ca exc.)
Kumar 2018 [117] Retrospective cohort treat in the USA 1973-2014 (n=23,864); comparator USA general population; median f/u not given	**SIR** Male **1.84** (1.75-1.92) Female **2.17** (2.06-2.28)	
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	**RR** Male **5.0** (3.4-6.9) Female **6.4** (4.5-8.8)	**AER** Male **57.2** / 10,000 py Female **86.2** / 10,000 py

Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given	**RR** Male **2.2** (95% CI not given) Female **2.3** (95% CI not given)	**AER** Male **48.4** / 10,000 py Female **45.6** / 10,000 py
Age at treatment		
Rugbjerg 2019 [8] Retrospective cohort of Danish >5y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	**RR** hospitalisation 15-19 y **5.9** (4.2-8.2) 20-24 y **4.2** (3.3-5.4) 25-29 y **2.9** (2.2-3.8)	 30-34 y **3.1** (2.4-4.2) 35-39 y **3.4** (2.5-4.6)
Favier 2009 [9] Retrospective cohort treated for HL in Europe 1964-2000 (n=4401); median f/u 7.8 y; comparator population World Health Organisation Mortality Database	**SMR** 15-39 y **7.5** (5.5-9.9) 40-49 y **3.6** (2.4-5.1) 50-69 y **2.7** (2.0-3.5)	**AER** (/ 10,000py) 15-39 y **15.9** (11.1-21.9) 40-49 y **41.9** (22.3-67.9) 50-69 y **99.6** (60.3-147.7)
Lee 2000 [27] Retrospective cohort of patients with stage 1-3 HL treated in the USA 1970-1986 (n=210); median f/u 15.6y; comparator general pop (AER / 1000 py) (95% CIs not given)	**SIR** ≤18 y **17.9** 19-35 y **6.7** ≥36 y **4.0**	**SMR** ≤18 y **54.8**	**AER** (inciden.) ≤18 y **7.1** 19-35 y **6.8** ≥36 y **21.5**	**AER** (death) ≤18 y **5.02**
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py)	Excluding NMSC **SIR** <15 y **26.1** (12.5-47.0) 15-24 y **7.0** (5.1-9.3) 25-34 y **4.1** (3.1-5.3) 35-44 y **3.0** (2.3-3.9) 45-54 y **2.6** (2.1-3.3) ≥55 y **1.9** (1.6-2.4)	**20 y cumulative incidence** <45 y **9.5%** ≥45 y **37.9%** **AER** <15 y **45.5** 15-24 y **24.1** 25-34 y **27.9** 35-44 y **47.1** 45-54 y **92.1** ≥55 y **119.3**
Ng 2002 [86]	**RR**	**AER**

Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y	<20 y **10.7** (7.8-14.4) 20-50 y **4.9** (4.0-5.9) >50 y **2.4** (1.6-3.4)	<20 y **71.0** 20-50 y **88.5** >50 y **211.0**
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1y; comparator Dutch general pop	**SIR** 15-24 y **8.4** (7.5-9.5) 25-34 y **5.0** (4.4-5.6) 35-50 y **3.1** (2.8-3.5) (*P* < .001)	**AER** 15-24 y **111** 25-34 y **118** 35-50 y **144** (*P* = < .001)
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y (AERs / 10,000 py)	**RR** ≤20 y **13.3** (8.8-19.2) 21-30 y **8.2** (6.3-10.5) 31-39 y **4.9** (3.6-6.4)	**AER** ≤20 y **58.3** 21-30 y **72.2** 31-39 y **86.6**
Swerdlow 1997 [91] Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1 y	**SIR** <25 y **8.9** (4.9-14.7) (*P* < .01) 25-44 y **4.2** (2.7-6.1) (*P* < .01) 45-54 y **3.3** (1.8-5.4) (*P* < .01) ≥55 y **1.9** (1.1-2.9) (*P* < .05)	**AER** <25 y **29.3** 25-44 y **44.1** 45-54 y **126.6** ≥55 y **110.2**
Munker 1999 [93] Retrospective cohort treated in Germany 1974-1994 (n=1120); mean f/u 9.1 y	**RR** <19 y **12.0** (5.3-24.0)	20-39 y **4.9** (3.6-6.5) ≥40 y **2.3** (1.8-3.0)
Sont 1992 [97] Retrospective cohort treated in the Netherlands 1969-1988 (n=482); average f/u 6.05 y	**RR** <40 y **4.9** 40-49 y **4.3** ≥50 y **3.1** (95% CIs not given)	**Cumulative incidence** 5 y: 10 y: 30-39 y **0.9%** 30-39 y **6.1%** 40-49 y **2.4%** 40-49 y **7.9%** >49 y **17.9%** >49 y **22.2%**
Economoupoulos 1994 [98] Retrospective cohort treated in Greece 1977-1991 (n=217); median f/u 67 m	**Cumulative incidence** <40 y 10 y **1.6%** 15 y **14.5%**	 >40 y 10 y **12.0%** 15 y **29.6%**
LeMieux 2015 [99] Retrospective cohort with stage 1-2 HL treated in the USA 1988-2009 (n=8807); median f/u 7.2 y	**HR** < 16 y Ref 16-25 y **1.78** (0.86-3.70) 26-35 y **1.96** (0.95-4.04)	 46-55 y **7.39** (3.56-15.35) 56-65 y **18.86** (9.15-38.86) ≥ 66 y **18.04** (8.69-37.47)

	36-45 y **4.72** (2.30-9.68)	
Biti 1994 [107] Retrospective cohort treated in Italy 1960-1988 (n=1121); mean f/u >9 y	**15 y cumulative risk** <20 y **1.4%** 20-40 y **7.9%**	 41-60 y **22.9%** >60 y **25.2%**
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	**SIR** <25 y **9.4** (7.5-11.7) 25-34 y **4.2** (3.3-5.4) 35-44 y **3.5** (2.6-4.5) 45-54 y **3.3** (2.5-4.4) 55-64 y **2.3** (1.6-3.3) ≥65 y **1.7** (0.9-3.1) (*P* < .001)	**20y cumulative incidence** <25 y **12.9%** 25-34 y **13.5%** 35-44 y **24.4%** 45-54 y **40.2%** ≥55 y **43.2%** **AER** <25 y **52.1** 25-34 y **44.9** 35-44 y **75.7** 45-54 y **159.9** 55-64 y **160.4** ≥65 y **133.5**
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y	**SIR** 0-40 y **6.2** (5.0-7.6) 41-50 y **3.7** (2.6-5.2) 51-60 y **2.5** (1.7-3.5) ≥ 60 y **2.1** (1.5-2.9)	**AER** 0-40 y **10** 41-50 y **209** 51-60 y **265** ≥ 60 y **372**
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population (AERs / 10,000 py)	**SIR**, Male <35 y **4.26** (3.68-4.92) (*P* < .001) ≥35 y **2.08** (1.91-2.28) (*P* < .001) **SIR**, Female <35 y **4.61** (3.99-5.32) (*P* < .001) ≥35 y **1.73** (1.53-1.96) (*P* < .001)	**30 y cumulative incidence** Male <35 y **13.9%** ≥35 y **20.4%** Female <35 y **24.5%** ≥35 y **14.9%**

	AER, Male <35 y **47** ≥35 y **111** **AER**, Female <35 y **64** ≥35 y **67**			
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	**RR** <17 y **33.8** (18.6-56.8) 17-39 y **8.3** (6.0-11.1) >40 y **2.0** (1.1-3.3)		**AER** <17 y **74.6** 17-39 y **67.9** >40 y **69.6**	
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given (AERs / 10,000py)	**RR** <21 y **7.7** 21-30 y **4.3** 31-40 y **2.7**	41-50 y **2.5** 51-60 y **2.0** ≥61 y **1.3**	**AER** <21 y **30.0** 21-30 y **34.9** 31-40 y **42.0**	41-50 y **80.5** 51-60 y **107.5** ≥61 y **51.7**
Hodgson 2007 [127] Retrospective cohort of 5y HL survivors treated in North America & Europe 1970-2001 (n=18,862); median f/u 12.2 y	**30 y cumulative incidence** Male 20 y **10.5%** 30 y **18.3%** 40 y **27.1%**		Female 20 y **24.3%** 30 y **26.1%** 40 y **26.7%**	
Family history				
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population (AERs / 10,000 py)	**SIR** for number of relatives with cancer 0 **2.16** (2.00-2.33) ≥ 1 **2.83** (2.58-3.10) (*P* < .001)		1 **2.67** (2.40-2.97) ≥ 2 **3.40** (2.85-4.09)	

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – HL: Hodgkin lymphoma; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine; RT: radiotherapy; n; number; f/u: follow-up; y: years; SIR: standardised incidence ratio; RR: relative risk; AER: absolute excess risk; py: person-years; NMSC: non-melanoma skin cancer; CI: confidence interval; HR: hazard ratio; Ca: cancer; exc.: excluded; inciden: incidence; m: months; HR: hazard ratio; Ref: reference

b. Solid tumours

Study details	Risk estimate	
Sex		
Aleman 2003 [1] Retrospective Dutch cohort treated when aged <41 y 1965-1987 (n=1261); median f/u 17.8 y; comparator general Dutch population (AERs per 10,000 py)	Death from solid tumours **RR** Male **6.9** (4.9-9.3) Female **6.3** (4.4-8.8)	 **AER** Male **30.1** Female **30.5**
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**HR** Female **0.88** (vs male) (0.75-1.05)	
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py)	**SIR** Male **1.9** (1.5-2.3) Female **1.7** (1.3-2.2) (χ^2 0.3)	**AER** Male **14.2** Female **14.4**
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	**SIR** Male **3.9** (3.5-4.4) Female **4.5** (4.1-5.0) (*P* = .029)	**AER** Male **85.8** Female **119** (*P* = .001)
Swerdlow 1997 [91] Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1y	**SIR** excluding NMSC Male **2.8** (1.8-4.2) (*P* < .01) Female **2.1** (1.2-3.3) (*P* < .05)	**AER** Male **23.7** Female **20.2**
Henry-Amar 1992 [102] Retrospective international cohort of 1y HL survivors treated 1960-1987 (n=12,411); median f/u not given	**RR** Male **1.74** (*P* < .001) Female **1.67** (*P* < .001)	 Male vs female **1.2**
Cellai 2001 [106] Retrospective cohort treated in Italy 1960-1991 (n=1524); average f/u 10.7y	**Cumulative incidence** Male **5.5%** (15 y), **8.9%** (20 y) Female **11.5%** (15 y), **18%** (20 y)	
Biti 1994 [107] Retrospective cohort treated in Italy 1960-1988 (n=1121); mean f/u >9y	**15 y cumulative incidence** Male **12.0%**	 Female **6.1%**
Swerdlow 2011 [112]	**SIR** non-lung solid tumours	

Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	Male **2.3** (1.8-2.9) (*P* = .61)	Female **2.6** (2.0-3.2)
van Eggermond 2014 [115] Retrospective cohort of 5y survivors treated in the Netherlands when aged <51y 1965-1995 (n=3122); median f/u 22.6 y	**HR**, solid non-breast cancer (3rd), after a solid non-breast cancer (2nd) Female Ref Male **1.3** (1.0-1.5)	
Kumar 2018 [117] Retrospective cohort treat in the USA 1973-2014 (n=23,864); comparator USA general population; median f/u not given	**SIR** Male **1.56** (1.48-1.65) Female **1.97** (1.86-2.09)	
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	**AER** (/ 10,000 py) Male **34.9** Female **68.1**	**RR** Male **5.0** (3.4-6.9) Female **6.4** (4.5-8.8)
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given (AERs / 10,000 py)	**RR** Male **1.9** Female **2.0** **25 y actuarial risk** Male **19.3%** Female **24.8%**	**AER** Male **32.4** Female **33.9**
Hodgson 2007 [127] Retrospective cohort of 5y HL survivors treated in North America & Europe 1970-2001 (n=18,862); median f/u 12.2y	**RR** Supradiaphragmatic tumours Male **5.6** (4.7-6.6) Female **6.9** (5.5-8.5)	 Infradiaphragmatic tumours Male **3.8** (3.2-4.6) Female **3.5** (2.6-4.5)
Age at treatment		
Aleman 2003 [1] Retrospective Dutch cohort treated when aged <41y 1965-1987 (n=1261); median f/u 17.8y; comparator general Dutch population (AERs per 10,000py)	Death from solid tumours **RR** (*P* for trend < 0.001) ≤20 y **14.8** (8.1-24.9) 21-30 y **8.6** (6.1-11.9) 31-40 y **4.0** (2.6-5.9)	 **AER** ≤20 y **22.3** 21-30 y **33.5** 31-40 y **33.1**
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**HR**, vs <25 years 25-34 y **0.69** (0.56-0.86) 35-50 y **0.48** (0.38-0.61)	
Cosset 1991 [56]	**RR**	

Pooled analysis of 4 EORTC trials H1, H2, H5, H6, run 1964-1988; 1660 patients; median f/u not reported	>40 y **3.6** (*P* < .001)	
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py)	Non-lung solid tumours, excluding NMSC **SIR** < 15 y **26.4** (11.3-51.0) 15-24 y **4.6** (3.0-6.7) 25-34 y **2.8** (1.9-3.9) 35-44 y **1.6** (1.0-2.4) 45-54 y **1.5** (1.0-2.1) ≥ 55 y **1.2** (0.8-1.6)	**20 y cumulative incidence** <45 y **5.6%** ≥45 y **19.0%** **AER** <15 y **35.4** 15-24 y **12.3** 25-34 y **13.5** 35-44 y **10.8** 45-54 y **19.0** ≥55 y **15.3**
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1y; comparator Dutch general pop (AERs / 1000 py)	**SIR** 15-24 y **8.3** (7.3-9.4) 25-34 y **4.6** (4.0-5.2) 35-50 y **2.6** (2.6-3.0) (*P* < .001)	**AER** 15-24 y **99.8** 25-34 y **97.7** 35-50 y **105** (*P* = .73)
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y (AER / 10,000 py)	All solid tumours **RR** ≤20 y **13.9** (9.0-20.6) 21-30 y **6.5** (4.7-8.8) 31-39 y **4.2** (3.0-5.8) **AER** ≤20 y **52.3** 21-30 y **49.1** 31-39 y **65.9**	Non-breast solid tumours **RR** ≤20 y **12.7** (7.2-20.6) 21-30 y **6.9** (4.7-9.8) 31-39 y **4.9** (3.4-7.0) **AER** ≤20 y **33.2** 21-30 y **35.8** 31-39 y **57.9**

Swerdlow 1997 [91] Retrospective cohort treated in UK 1963-1991 (n=1039); average f/u 9.1 y	**SIR** excluding NMSC <25 y **7.4** (3.5-13.3) (*P* < .01) 25-44 y **2.8** (1.5-4.6) (*P* < .05) 45-54 y **1.8** (0.6-3.8) ≥55 y **1.5** (0.7-2.6)	**AER** excluding NMSC <25 y **19.7** 25-44 y **20.2** 45-54 y **31.0** ≥5 5y **39.6**	
Sont 1992 [97] Retrospective cohort treated in the Netherlands 1969-1988 (n=482); average f/u 6.05 y	Solid tumours <40 y Ref >40 y **10.0** (95% CI not given)		
Glanzmann 1994 [100] Retrospective cohort treated in Germany 1964-1992 (n=340); f/u ≥1.5 y	**RR** Men <30 y at Rx **9.3** (2.5-23.8) Med >30 y at Rx **2.12** (0.85-4.36) Women <30 y at Rx **44** (9.1-129)	**Cumulative incidence** Women <30 y at Rx ≥10 y **0%** ≥20 y **22.1%** ≥15 y **9.1%** ≥24 y **48%**	
Cellai 2001 [106] Retrospective cohort treated in Italy 1960-1991 (n=1524); average f/u 10.7 y	**Cumulative incidence** <28 y **2.1%** (15 y), **5.7%** (20 y) 28-44 y **8.1%** (15 y), **13.6%** (20 y) >44 y **20.8%** (15 y), **25.6%** (20 y)		
Biti 1994 [107] Retrospective cohort treated in Italy 1960-1988 (n=1121); mean f/u >9y	**15 y cumulative incidence** <20 y - 20-40 y **7.2%**	41-60 y **17.0%** >60 y **25.2%**	
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	**SIR** < 25 y **7.0** (5.2-9.2) 25-34 y **2.6** (1.8-3.7)	35-44 y **2.0** (1.3-2.9) 45-54 y **1.4** (0.8-2.3)	≥ 55 y **1.2** (0.8-1.9) (*P* < .001)
van Eggermond 2014 [115] Retrospective cohort of 5y survivors treated in the Netherlands when aged <51y 1965-1995 (n=3122); median f/u 22.6 y	**HR**, solid non-breast cancer (3rd), after a solid non-breast cancer (2nd) <25 y Ref	25-34 y **1.7** (1.3-2.1)	35-50 y **3.4** (2.7-4.3)
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	**AER** / 10,000 py <17 y **69.6**	17-39 y **49.9**	>40 y **5.7**
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given (AERs / 10,000 py)	**RR** <21 y **7.0** (*P* <.05) 21-30 y **3.6** (*P* <.05)	**AER** <21 y **23.8** 21-30 y **25.3**	

	31-40 y **2.1** (*P* <.05) 41-50 y **2.1** (*P* <.05) 51-60 y **1.8** (*P* <.05) ≥61 y **1.2** (P_{trend} < .001)	31-40 y **25.4** 41-50 y **58.7** 51-60 y **79.2** ≥61 y **27.0**
Tester 1984 [139] Retrospective cohort treated in USA 1964-1984 (n=473); median f/u >12 y	**10 y cumulative incidence** <30 y **0.05%** 30-39 y **0.04%**	 40-49 y **0.10%** ≥50 y **0.29%**
Smoking		
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general population	**HR**, smoking at end of f/u Never smoked Ref Former smoker **1.23** (1.02-1.48)	 Recent smoker **1.80** (1.47-2.21) Unknown **1.43** (1.15-1.79) (*P* < .001)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – HL: Hodgkin lymphoma; n: number: f/u: follow-up; y: years; HR: hazard ratio; AER: absolute exess risk; py: person-years; RR: relative risk; SIR: standardised incidence ratio; NMSC: non-melanoma skin cancer; CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; Rx: treatment

c. Breast cancer

Study details	Risk estimate	
Age at treatment		
Brierley 1998 [10] Retrospective cohort with stage 1-2 HL treated in Canada 1973-1984 (n=611); median f/u 11 y; comparator age-matched general population for same period	**RR** <30 y **6.67** (3.55-11.4)	 >30 y **1.65 (**1.1-2.45)
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py)	**SIR** < 25 y **14.4** (5.7-29.3) 25-44 y **1.6** (0.5-3.7) 45-54 y **1.9** (0.3-5.8) ≥ 55 y **1.2** (0.2-3.8)	**20 y cumulative incidence** <25 y **4.2%** ≥25 y **2.9%**
Ng 2002 [86]	**RR**	**AER**

Retrospective cohort treated for stage 1-4 HL in USA 1969-1997 (n=1319); median f/u 12 y (AERs / 10,000 py)	<15 y **111.8** (36.2-261.0) 15-19 y **32.0** (14.6-60.7) 20-25 y **16.6** (8.0-30.6) 26-29 y **8.4** (3.6-16.5) 30-35 y **3.7** (1.0-9.5) 36-40 y **3.4** (0.4-12.1) > 40 y **0.4** (0.01-2.5)	<15 y **82.1** 15-19 y **58.2** 20-25 y **52.8** 26-29 y **57.2** 30-35 y **30.8** 36-40 y **39.6** > 40 y **-17.7**
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	**SIR** 15-24 y **10.2** (8.3-12.5) 25-34 y **4.4** (3.4-5.6) 35-50 y **1.7** (1.1-2.5) (*P* < .001)	**AER** 15-24 y **73.3** 25-34 y **54.1** 35-50 y **18.4** (*P* < .001)
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y	**RR** ≤20 y **16.9** (7.8-32.2) 21-30 y **5.6** (2.9-9.8) 31-39 y **2.4** (0.9-5.2)	**AER** ≤20 y **37.8** 21-30 y **29.6** 31-39 y **18.9**
Swerdlow 1997 [91] Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1 y	**RR** < 25 y **7.8** (1.3-24.2) < 20 y **32.8** (5.5-101.3) ≥ 25 y **1.2** (0.3-3.1)	**20 y cumulative incidence** < 25 y **2.1%** < 20 y **4.1%** ≥ 25 y **2.1%**
Cellai 2001 [106] Retrospective cohort treated in Italy 1960-1991 (n=1524); average f/u 10.7 y	**SIR** <30 y **4.4** (1.2-11)	
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y (AERs / 10,000 py)	**SIR** 16-20 y **30.2** (9.8-70.5) 21-25 y **14.2** (5.2-31) 26-40 y **2.2** (0.7-5.1) 41-50 y **4.4** (1.4-10.3) 51-60 y **0** (-) ≥ 60 y **0** (-)	**AER** 16-20 y **34** 21-25 y **29** 26-40 y **10** 41-50 y **30**
Sud 2017 [118]	**SIR,** Male <35 y **12.60** (1.78-89.43)	**30 y cumulative incidence** Male

Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population (AERs / 10,000 py)	≥35 y **4.58** (1.14-18.29) **SIR**, Female <35 y **6.00** (4.91-7.33) ≥35 y **1.14** (0.85-1.51) **AER**, Male <35 y **0.3** ≥35 y **0.6** **AER**, Female <35 y **34** ≥35 y **3**	<35 y **0.1%** ≥35 y **0.1** Female <35 y **13.8%** ≥35 y **3.3%**
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population (AERs / 10,000 py)	**RR** <15 y **458** (91.7-1345) 15-24 y **23.3** (7.5-54.5) 25-34 y **4.0** (0.8-11.8) ≥35 y **2.0** (0.20-7.1)	**AER** <15 y **24.1** 15-24 y **13.9** 25-34 y **9.3** ≥35 y **7.1**
Ibrahim 2012 [143] Meta-analysis of studies reporting the risk of breast cancer in female HL survivors; total of 24,505 women; median f/u 14.9 y	**RR** ≤15 y **68.70*** (28.8-168.11) 15-19 y **22.32*** (13.4-37.16) 20-24 y **14.43*** (11.65-17.88) 25-29 y **6.60*** (4.24-10.29) **RR**, aged ≤30 y at treatment **14.08***	>20 y **4.26*** >30 y **2.42*** ≥40 y **0.55*** (0.09-3.52)
de Bruin 2009 [144] Retrospective cohort of female 5 y HL survivors treated when aged <51 y in the Netherlands 1965-1995; median f/u 17.8 y; comparator general population	**SIR** ≤20 y **5.6** 21-30 y **17.9** 31-40 y **3.2** 41-50 y **1.4** (*P* < .0001) **SIR**, split by time since treatment	**AER** ≤20 y **79** 21-30 y **62** 31-40 y **42** 41-50 y **11**	**30 y cumulative incidence** ≤21 y **26%**

	5-14 y ≤20 y **20.0** (7.3-43.4) 21-30 y **5.3** (2.5-9.7) 31-40 y **1.8** (0.7-3.9) 41-50 y **0.9** (0.1-3.1) *15-24 y* ≤20 y **20.8** (12.6-32.6) 21-30 y **7.3** (4.5-11.3) 31-40 y **3.2** (1.4-6.3) 41-50 y **2.0** (0.4-5.9)	*≥25 y* ≤20 y **14.2** (7.6-24.3) 21-30 y **9.0** (4.7-15.7) 31-40 y **8.4** (3.4-17.2) 41-50 y **2.4** (0.1-13.2)	
Swerdlow 2012 [145] Retrospective cohort of women treated with supradiaphragmatic RT when aged <36 y in England and Wales 1956-2003 (n=5002); median f/u not given (AERs / 10,000 py)	All SD RT **SIR** 15-19 y **14.3** 20-24 y **5.4** 25-29 y **3.2** 30-35 y **2.4** (*P* < .001) **AER** 15-19 y **58.6** 20-24 y **30.7** 25-29 y **22.1** 30-35 y **19.4** (*P* < .001) **20 y cumulative inc** 15-19 y **5.8** 20-24 y **3.4**	SD RT only **SIR** 15-19 y **14.5** 20-24 y **7.0** 25-29 y **3.9** 30-35 y **3.3** (*P* < .001) **AER** 15-19 y **60.5** 20-24 y **43.2** 25-29 y **29.5** 30-35 y **33.8** (*P* = 0.13) **20 y cumulative inc** 15-19 y **6.4** 20-24 y **3.5**	SD RT & alkylating &/or pelvic RT **SIR** 15-19 y **15.0** 20-24 y **4.2** 25-29 y **3.0** 30-35 y **1.9** (*P* < .001) **AER** 15-19 y **56.8** 20-24 y **20.8** 25-29 y **19.2** 30-35 y **11.5** (*P* < .001) **20 y cumulative inc** 15-19 y **5.4** 20-24 y **3.6**

	25-29 y **4.8** 30-35 y **4.9** **40 y cumulative inc** 15-19 y **29.7** 20-24 y **19.6** 25-29 y **13.1** 30-35 y **17.6**	25-29 y **7.4** 30-35 y **9.8** **40 y cumulative inc** 15-19 y **36.1** 20-24 y **29.2** 25-29 y **17.4** 30-35 y **27.5**	25-29 y **4.3** 30-35 y **2.8** **40 y cumulative inc** 15-19 y **27.7** 20-24 y **11.5** 25-29 y **12.0** 30-35 y **14.4**
Hancock 1993 [146] Retrospective cohort of women treated for HL in USA 1961-1990 (n=885); mean f/u 10 y (AER / 10,000 py)	**RR** <15 y **136** (34-371) 15-19 y **19** (4.7-51) 20-24 y **19** (9.3-35) 25-29 y **7** (3.2-14) 30-39 y **0.6** (0.0-2.8) 40-49 y **0.9** (0.0-4.6) ≥50 y **0.6** (0.0-2.9) **RR breast cancer** <15 y since RT Age <20 y **26** (4.3-85.3) 20-29 y **7.8** (3.4-15.58) ≥30 y **0.2** (0.0-1.2) ≥15y since RT Age <20 y **38** (12.0-92.3) 20-29 y **17** (8.1-30.6) ≥30 y **4.4** (0.7-14.5)	**AER** <15 y **38.4** 15-19 y **16.7** 20-24 y **47.2** 25-29 y **32.6** 30-39 y **-** 40-49 y **-** ≥50 y **-** **AER** death from breast Ca <30 y **10.8** **RR** death from breast Ca <30 y **23** (10.0-45.4) (*P* < .0002)	
Travis 2003 [148] Case-control study nested n a cohort of 3817 female 1 y HL survivors treated when aged <30 y 1965-1994 (105 cases, 266 controls); median f/u not given	**RR** ≥4 Gy to breast (vs <4 Gy) 13-17 y **4.2** (1.1-21.8) (*P* = .04) 18-21 y **2.1** (0.7-8.3) (*P* = .22)	22-25 y **2.0** (0.3-17.2) (*P* = .46) 26-30 y **2.9** (1.0-10.5) (*P* = .05)	

O'Brien 1995 [149] Retrospective cohort of women treated in the USA 1961-1980 (n=855); mean f/u 10 y	**RR** < 30 y **7.0** (1.4-1.7) (*P* = .01)	≥ 30 y **2.1** (0.43-5.0) (*P* = .18)
Veit-Rubin 2012 [150] Retrospective cohort treated in the USA 1973-2007 (n=9620); median f/u 9.83 y; comparator general population	**SIR** ≤ 19 y **13.4** (10.5-17.0) (*P* < .001) 20-29 y **4.4** (3.6-5.3) (*P* < .001) 30-39 y **2.0** (1.5-2.5) (*P* < .001)	40-49 y **1.4** (0.9-2.0) ≥ 50 y **1.03** (0.8-1.4)
El-Din 2009 [152] Retrospective cohort of women treated for stage 1-2 HL when aged ≤60 y in the USA 1964-2001 (n=248); median f/u 15.2 y	**SMR** 15-19 y **74.54** (37.16-178.21) 20-24 y **16.36** (7.04-35.80) 25-29 y **4.51** (0.90-9.42) ≥ 30 y **4.64** (2.31-8.30)	< 30y **19.05** (12.33-28.13) ≥ 30 y **4.64** (2.31-8.30) (*P* < .00003)
	Median time to development 0-< 20 y **18.4 y**	20-< 30y **20.2 y** ≥ 30 y **15.8 y**
Wahner-Roedler 2003 [153] Retrospective cohort treated for HL with supradiaphragmatic RT in the USA 1950-1993 (n=649); median f/u 8.7 y	**SMR** <30 y **8.5** (5.3-13.1) ≥30 y **1.2** (0.5-2.2)	**RR** 15-19 y **12.5** (5.4-24.6) 20-24 y **6.3** (2.0-14.6) 25-29 y **4.4** (1.2-11.3) ≥30 y **1.2** (0.5-2.2)
Meattini 2010 [159] Retrospective cohort treated in Italy 1690-2003 with >6 m f/u (n=1538, 725 women); median f/u not given	Cumulative incidence at end of f/u ≤20 y **50.8%** (19.8-91.3) 20.1-30 y **30.7%** (17.2-50.9) (*P* = .33)	30.1-40 y **8.0%** (3.2-19.5) ≥40 y **17.8%** (8.1-36.4)
Aisenberg 1997 [207] Retrospective cohort of women treated in the USA for stage 1-2 HL when aged <60 y 1964-1984; median f/u 18 y (AER / 10,000 py)	**RR** <20 y **56** (23.3-107) 20-29 y **7.0** (2.3-16.4) ≥30 y **0.9** (0-5.3) **AER** <20 y **118** 20-29 y **46.7**	**25 y cumulative incidence** <20 y **34.0%** (14.2-53.8) 20-29 y **22.3%** (4.1-40.5) ≥30 y **3.5%** (0-10.1)

	≥30 y **-**			
Hormonal factors				
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given (AERs / 10,000 py)	**RR**		**AER**	
	<21 y **14.2**	41-50 y **1.7**	<21 y **18.6**	41-50 y **13.0**
	21-30 y **3.7**	51-60 y **1.0**	21-30 y **12.9**	51-60 y **0.3**
	31-40 y **1.2**	≥61 y **1.1**	31-40 y **2.6**	≥61 y **1.7**
de Bruin 2009 [144] Retrospective cohort of female 5 y HL survivors treated when aged <51 y in the Netherlands 1965-1995; median f/u 17.8 y; comparator general population	**HR**, premature menopause Menopause ≥41 y Ref Menopause <41 y **0.4** (0.2-0.8) Age ≤41 y at end f/u **0.5** (0.2-0.9) **HR**, nulliparity Yes vs no/unknown **0.9** (0.5-1.4)		**HR**, yrs intact ovarian function <10 y **0.3** (0.2-0.6) 10-20 y Ref >20 y **5.3** (2.9-9.9) **HR**, oral contraceptive use Yes vs no/unknown **1.3** (0.8-2.2)	
Travis 2003 [148] Case-control study nested n a cohort of 3817 female 1 y HL survivors treated when aged <30 y 1965-1994 (105 cases, 266 controls); median f/u not given	**RR**, menopausal status at end of f/u Pre & peri-menopausal **3.5** (1.6-8.3) (*P* = .002) Postmenopausal **1.9** (0.5-12.9) (*P* = .38) Unknown **1.6** (0.3-12.4) (*P* = .59)		**RR**, pregnancy status at HL diagnosis Nulliparous **2.9** (1.3-6.9) (*P* = .006) Parous **4.5** (1.2-24.3) (*P* = .02)	
van Leeuwen 2003 [156] Case-control study nested in a cohort of 770 female patients treated for HL in the Netherlands when aged <41 y (48 cases, 175 matched controls); mean f/u 3.4 y (RT dose is dose to the area of the breast where the tumour subsequently developed)	**OR**, interaction btwn no. premenopauseal years & RT dose (Gy) ≥15 y menstruating post-HL, ≥24 breast Ref <15 y menstruating post-HL, <24 breast **0.16** (0.03-1.02) ≥15 y menstruating post-HL, ≥24 breast **13.0** (1.42-120) <15 y menstruating post-HL, <24 breast **0.70** (0.14-3.57)			
Krul 2017 [157] Case-control study nested in a cohort of female 5 y HL survivors treated when aged <41 y (174 cases, 466 controls); median f/u not given	**35 y cumulative incidence** High-dose mediastinal RT **13.5%** Lower-dose mediastinal RT **11.2%** No chest RT **2.1%**			

	Interaction between ovarian function & prescribed RT dose ≥35 Gy mantle RT & ≥20 y ovarian function **27.6%** ≤35 Gy (in)complete mantle RT & ≥20 y ovarian function **22.4%** ≥35 Gy (in)complete mantle RT & 10-19 y ovarian function **19.6%** ≥35 Gy (in)complete mantle RT & <10 y ovarian function **13.8%**	
Conway 2017 [158] Retrospective cohort of female patients treated for HL in Canada 1961-2009 (n=734); median f/u 18 y	**HR**, premature menopause risk Not at risk Ref (*P* = .63)	 At risk **1.18** (0.61-2.27)
Hill 2005 [197] Women diagnosed with HL ≤30 y; ORs adjusted for breast RT dose, ovarian RT dose & number of cycles of alkylating chemotherapy	**OR**, age at menarche >12 y Ref	 ≤1 2y **1.2** (0.40-3.4)
	OR, menopausal status *Pre- / peri-menopausal* No AA & < 5 Gy to ovaries Ref AA or ≥ 5 Gy to ovaries **0.7** (0.3-1.5)	 *Post-menopausal* No AA & < 5 Gy to ovaries Ref AA or ≥ 5 Gy to ovaries **0.2** (0.1-1.3)
	No alkylating agents, <5 Gy to ovaries	
	OR, ever had live birth No Ref Yes **0.9** (0.4-1.9)	**OR**, age at 1st live birth ≤ 22 y Ref 23-26 y **1.0** (0.5-2.2) ≥ 27 y **0.9** (0.4-2.2)
	OR, number of live births 1 Ref 2 **0.8** (0.3-2.1) ≥ 3 **0.7** (0.3-2.1)	**OR**, oral contraceptive use Never Ref Ever **1.0** (0.5-2.2) 1-6y **0.9** (0.3-2.4) ≥ 7y **1.9** (0.7-5.0)

		OR, interaction between history of live birth & RT dose No live birth, ≤ 5 Gy to breast Ref No live birth, > 5 Gy to breast **1.1** (0.3-4.7) Live birth, ≤ 5 Gy to breast **0.4** (0.1-1.6) Live birth, > 5 Gy to breast **1.4** (0.4-4.8) **OR**, effect of ≤ 5 Gy to breast (vs < 5 Gy to breast) No live births **1.1** (0.3-4.7) Live births **3.5** (1.4-8.9)	
Cooke 2013 [208] Case-control data from questionnaires completed by 2497 women from a cohort of 5002 treated with supradiaphragmatic RT when aged <36 y 1956-2003		**OR**, menopause <40 y No Ref Yes **0.65** (0.44-0.94) (*P* = .02) Unknown **1.09** (0.69-1.73) (*P* = .7) **OR**, menopause <5 y from Rx No Ref Yes **0.55** (0.35-0.85) (*P* = .01) Unknown **0.92** (0.61-1.38) (*P* = .68)	**OR**, any full-term pregnancies No Ref Yes **1.17** (0.79-1.73) (*P* = .42) **OR**, FTP before SD RT No Ref Yes **0.77** (0.52-1.12) (*P* = .17) **OR**, FTP after SD RT No Ref Yes **1.33** (0.92-1.92) (*P* = .13)
OR, premen yrs after Rx <1 y Ref 1-4 y **0.96** (0.34-2.69) (*P* = .94) 5-9 y **1.02** (0.36-2.87) (*P* = .97) 10-14 y **1.49** (0.63-3.55) (*P* = .36) 15-24 y **1.62** (0.76-3.44) (*P* = .21) ≥25 y **3.56** (1.50-8.45) (*P* = .004) Unknown **1.74** (0.84-3.64) (*P* = .14)	**OR**, timing of 1st FTP No FTPs Ref >10 y before SD RT **1.52** (0.59-3.88) (*P* = .38) 5-10 y before SD RT **0.64** (0.27-1.55) (*P* = .32) <5 y before SD RT **1.03** (0.57-1.84) (*P* = .93) SD RT during 1st FTP **1.81** (0.35-9.33) (*P* = .48) <5 y after SD RT **1.41** (0.83-2.38) (*P* = .20) 5-10 y after SD RT **1.39** (0.79-2.44) (*P* = .26) >10 y after SD RT **1.25** (0.63-2.49) (*P* = .52) Unknown **1.03** (0.40-2.63) (*P* = .95)		
Family history			
Sud 2017 [118]		**SIR** for number of relatives with breast cancer	

Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population (AERs / 10,000 py)	0 **2.36** (1.98-2.81) (*P* = .04)	≥1 **4.36** (2.60-6.55)
Hill 2005 [197] Case-control study nested in an international cohort of 3817 patients treated when aged <30 y (105 patients, 266 controls); median f/u not given (Fhx = breast and/or ovarian cancer in a 1st or 2nd degree relative)	**OR**, 1st or 2nd degree relative with breast or ovarian cancer No Ref Yes **2.5** Unknown **1.0** **OR**, interaction between family history & RT dose No family history, ≤ 5 Gy to breast Ref No family history, > 5 Gy to breast **5.8** (2.1-16.3) Family history, ≤ 5 Gy to breast **11.5** (2.5-52.6) Family history, > 5 Gy to breast **9.5** (3.0-30.1) **OR**, effect of ≥ 5 Gy to breast (vs <5 Gy to breast) No family history **5.8** (2.1-16.3) Family history **0.8** (0.2-3.4)	
Other factors		
de Bruin 2009 [144] Retrospective cohort of female 5 y HL survivors treated when aged <51 y in the Netherlands 1965-1995; median f/u 17.8 y; comparator general population	**HR** , BMI >30 at end of f/u Yes vs no/unknown **1.2** (0.8-1.9)	**HR**, smoking at end of f/u Yes vs no/unknown **1.0** (0.6-1.6)
Hill 2005 [197] Case-control study nested in an international cohort of 3817 patients treated when aged <30 y (105 patients, 266 controls); median f/u not given	**OR**, BMI at HL diagnosis <19.5 Ref 19.5-21.1 **0.5** (0.2-1.2)	 21.2-23.3 **0.5** (0.2-1.1) ≥23.4 **0.4** (0.2-0.9)

*pooled estimate (meta-analysis)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – HL: Hodgkin lymphoma; n: number; f/u: follow-up; y: years; RR: relative risk; SIR: standardised incidence ratio; AER: absolute excess risk; py: person-years; RT: radiotherapy; SD: supradiaphragmatic; inc: incidence; Gy: gray; m: months; HR: hazard ratio; OR: odds ratio; AA: aIkylating agents; premen: premenopausal; Ref: reference; FTP: full-term pregnancy; BMI: body mass index

d. Lung cancer

Study details	Risk estimate	
Sex		
Brierley 1998 [10] Retrospective cohort with stage 1-2 HL treated in Canada 1973-184 (n=611); median f/u 11 y; comparator age-matched general population for same period	**RR** Male **2.0** (0.6-5.0) (*P* = 0.15) Female **9.0** (2.5-24.0) (*P* < .0001)	
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y	**SIR** Male **3.0** (2.3-3.9) Female **5.2** (3.2-7.8) (χ^2 3.9, *P* <.05)	**AER** Male **13.4** / 10,000 py Female **9.0** / 10,000 py
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	**SIR** Male **6.7** (5.6-7.9) Female **5.8** (4.3-7.7) (*P* = .43)	**AER** Male **32.9** Female **15.0** (*P* < .001)
Swerdlow 1997 [91] Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1 y	**SIR** Male **3.1** (1.6-5.5) (*P* < .01) Female **6.3** (2.3-13.5) (*P* < .01)	**AER** Male **12.0** / 10,000 py Female **11.0** / 10,000 py
Henry-Amar 1992 [102] Retrospective international cohort of 1 y HL survivors treated 1960-1987 (n=12,411); median f/u not given	**RR** (Lung) Male **2.2** (*P* < .001) Female **4.6** (*P* < .001)	**RR** (Pleura) Male **8.3** (*P* < .01) Female **30.8** (*P* < .01)
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	**SIR:** Male **4.5** (3.3-6.1)	 Female **7.0** (4.1-11.0)
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given (AERs / 10,000 py)	**RR** Male **2.7** (*P* <.05) Female **3.4** (*P* <.05) **25y actuarial risk** Male **6.2%** Female **3.2%**	**AER** Male **12.7** Female **5.8**
de Bruin 2009 [131]	**SIR**	**AER**

Retrospective cohort of 5 y HL survivors treated in the Netherlands when aged <51 y 1965-1995; median f/u 18.1 y	Male **17.9** (7.7-35.3) Female **85.2** (27.6-199)	Male **3.9** (1.6-7.9) Female **3.0** (0.9-7.1)
Lorigan 2005 [163] Systematic review of studies reporting risk of lung cancer following treatment for HL published in English since 1985; 20 studies included	**RR** Male **2.7*** (95% CI not given) Female **3.4*** (95% CI not given)	**AER** Male **12.7*** / 10,000 py Female **5.8*** / 10,000 py
Travis 2002 [164] Case-control study nested in cohort of 19,046 HL survivors treated in the Netherlands 1965-1994 (222 cases, 444 matched controls); median f/u not given	**RR** Male **7.2** (3.0-18.6) (*P* < .001) Female **2.1** (0.6-11.5) (*P* = .27)	
Ibrahim 2013 [165] Meta-analysis of papers quantifying risk of second lung cancer in HL survivors; data on 74,831 patients; median f/u 11.5 y	**RR** Male **2.59*** (2.21-3.03) Female **3.25*** (2.22-4.74) (*P* = .28)	
Age at treatment		
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py)	**SIR** <25 y **10.9** (0.6-48.0) 25-44 y **6.2** (3.0-11.2) 45-54 y **3.3** (1.5-6.1) ≥55 y **1.7** (0.8-3.0)	**20 y cumulative incidence** <45 y **1.4%** ≥45 y **14.8%** **AER** <15 y **5.2** 15-24 y **1.8** 25-34 y **3.7** 35-44 y **14.6** 45-54 y **42.3** ≥55 y **39.7**
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1y; comparator Dutch general pop	**SIR** 15-24 y **10.3** (7.1-14.5) 25-34 y **7.4** (5.6-9.6) 35-50 y **5.2** (4.2-6.4) (*P* < .001)	**AER** 15-24 y **12.5** 25-34 y **23.5** 35-50 y **44.9** (*P* < .001)
van Leeuwen 2000 [75]	**RR** ≤20 y **-**	**AER** ≤20 y **-**

Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y (AER / 10,000 py)	21-30 y **11.5** (4.2-25.1) 31-39 y **5.5** (2.2-11.4)	21-30 y **7.4** 31-39 y **13.0**
Swerdlow 1997 [91] Retrospective cohort treated in the UK 1963-1991 (n=1039); average f/u 9.1y	**SIR** <25 y **41.4** (6.9-127.8) (*P* < .01) 25-44 y **6.2** (1.9-14.4) (*P* < .01) 45-54 y **5.3** (1.9-11.4) (*P* < .01) ≥55 y **1.7** (0.5-3.9)	**AER** <25 y **5.0** 25-44 y **8.1** 45-54 y **57.1** ≥55 y **22.6**
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	**SIR** <25 y **23.1** (10.0-45.6) 25-34 y **7.8** (3.7-14.4) 35-44 y **5.6** (2.9-9.8)	 45-54 y **5.8** (3.5-9.0) ≥55 y **2.3** (1.1-4.1) (*P* < .001)
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y	**SIR** <40 y **9.8** (4.5-18.6) 41-50 y **6.6** (2.7-13.6) 51-60 y **4.7** (1.9-9.7) ≥60 y **1.8** (0.4-5.3)	**AER** 0-40 y **20** 41-50 y **43** 51-60 y **56** ≥60 y **30**
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6y; comparator general Swedish population (AERs / 10,000 py)	**SIR**, Male <35 y **6.16** (3.93-9.66) ≥35 y **3.20** (2.56-4.00) **SIR**, Female <35 y **8.84** (5.70-13.70) ≥35 y **2.50** (1.67-3.77) **AER**, Male <35 y **5** ≥35 y **21** **AER**, Female <35 y **7** ≥35 y **8**	**30y cumulative incidence** Male <35 y **2.0** ≥35 y **3.0** Female <35 y **2.6** ≥35 y **1.4**

Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given (AERs / 10,000 py)	**RR** <21 y **5.5** 21-30 y **5.4** 31-40 y **4.0**	41-50 y **3.5** 51-60 y **3.4** ≥61 y **1.5**	**AER** <21 y **0.7** 21-30 y **3.3** 31-40 y **8.2**	41-50 y **21.8** 51-60 y **44.6** ≥61 y **12.3**
de Bruin 2009 [131] Retrospective cohort of 5 y HL survivors treated in the Netherlands when aged <51 y 1965-1995; median f/u 18.1 y	**SIR** ≤30 y **66.8** (26.9-138) 31-50 y **15.0** (5.5-32.5)		**AER** (/ 10,000 py) ≤30 y **3.0** (1.1-6.2) 31-50 y **4.4** (1.4-9.8)	
Lorigan 2005 [163] Systematic review of studies reporting risk of lung cancer following treatment for HL published in English since 1985; 20 studies included	**RR** 15-24 y **15.3** (3.8-39.6) 25-34 y **6.4** (2.5-12.9) 35-44 y **5.3** (2.9-8.8) 45-54 y **4.1** (2.7-5.9) >55 y **2.2** (1.5-3.1)		**AER** (/ 10,000 py) 15-24 y **1.8** 25-34 y **3.7** 35-44 y **14.6** 45-54 y **39.7** >55 y **39.7**	
Travis 2002 [164] Case-control study nested in cohort of 19,046 HL survivors treated in the Netherlands 1965-1994 (222 cases, 444 matched controls); median f/u not given	**RR** <40 y **3.8** (1.2-21) (*P* = .026) 40-54 y **3.5** (1.2-11.8) (*P* = .025) ≥55 y **10.2** (2.9-43) (*P* < .001) **Median time to development** <40 y **17.0 y**	40-54y **10.6 y**	≥55 y **6.7 y**	
Ibrahim 2013 [165] Meta-analysis of papers quantifying risk of second lung cancer in HL survivors; data on 74,831 patients; median f/u 11.5 y	**RR** 15-24 y **8.76*** (4.55-16.89)		≥55 y **2.88*** (2.33-3.56)	
Smoking				
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1y; comparator Dutch general pop	**HR**, smoking at end of f/u Never smoked Ref Former smoker **3.68** (2.19-6.19)		Recent smoker **7.66** (4.51-13.0) Unknown **4.63** (2.60-8.24) (*P* < .001)	
Swerdlow 2001 [161] Case-control study nested in a cohort of 5519 patients treated for HL in the UK 1963-1993 (88 cases, 176	**OR:** Ever smoker **6.16** (vs never) (1.57-42.59) **RR** (per pack-year)	**RR**, amount of smoking after diagnosis of HL (pack-years) *Crude* 0 or <1 Ref 1-10 **3.0**	*Adjusted for RT dose to lung* 0 or <1 Ref 1-10 **2.9**	

matched controls); median f/u not given	Crude **1.017** Adjusted for RT dose **1.016** **RR,** no. packs / week at diagnosis *Crude* 0 or <1 Ref 1-7 **2.2** >7 **2.0** *Adjusted for smoking post-diagnosis & RT dose to lung* 0 or <1 Ref 1.7 **0.6** >7 **0.3**	>10 **7.0** Linear trend/pack-year **1.157** **RR**, number of years since last smoking *Crude* >10 or never smoked Ref 1-10 **2.9** >10 **3.5** **RR**, unmatched *0 or <1 pack-year* <1 Gy **1.0** 1-5 Gy **0.99** ≥5 Gy **2.5**	>10 **6.2** Linear trend/pack-yr **1.141** *Adjusted for smoking post-diagnosis & RT dose to lung* >10 or never smoked Ref 1-10 **2.3** >10 **1.2** *≥1 pack year(s)* <1 Gy **0.48** 1-5 Gy **7.7** ≥5 Gy **9.1**
Kaldor 1992 [162] International case-control study in >1 y HL survivors (98 cases, 259 matched controls); median f/u not given		**RR** Never smoker Ref Ever smoker **13.0** (3.0-59) (*P* = .001) Unknown **4.1** (0.9-18) (*P* = .067)	
Travis 2002 [164] Case-control study nested in cohort of 19,046 HL survivors treated in the Netherlands 1965-1994 (222 cases, 444 matched controls); median f/u not given (RT dose to lung)	**RR**, 5 y before lung cancer diag. Never smoker Ref Current cigarette **22.6** (9.5-65) (*P* < .001) Former cigarette **5.7** (2.2-16.6) (*P* < .001) Cigar or pipe only **8.9** (2.6-32) (*P* < .001) Not stated **5.0** (1.9-15.3) (*P* = .001)	At HL diagnosis Never smoker Ref Current cigarette **21.2** (8.6-62) (*P* < .001) Former cigarette **4.0** (1.4-12.5) (*P* = 0.009) Cigar or pipe only **9.0** (2.5-35) (*P* < .001) Not stated **4.0** (0.53-5.2) (*P* = .005)	RT <5 Gy & no alkylating agents Non/light/other smoker Ref Mod/heavy smoker **6.0** (1.9-20.4) (*P* = .002) RT ≥5 Gy, no alkylating agents Non/light/other smoker **7.2** (2.9-21.2) (*P* < .001) Mod/heavy smoker **20.2** (6.8-68) (*P* = .39) RT ≥5 Gy & alkylating agents Non/light/other smoker **7.2** (2.8-21.6) (*P* < .001)

			Mod/heavy smoker **49.1** (15.1-187) (*P* < .001)
van Leeuwen 1995 [166] Retrospective cohort treated in the Netherlands 1966-1983 (n=744); median f/u 6.4 y	**RR**, smoking after HL diagnosis 0 or <1 pack-years Ref 1-10 pack-y **2.9** (1.1-8.0) (*P* = .04) >10 pack-y **6.2** (1.2-3.1) (*P* = .03)	**RR**, no. of packs per week at HL diagnosis 0 or <1 Ref 1-7 **0.6** (0.10-3.9) (*P* = .60) >7 **0.3** (0.04-3.0) (*P* = .33)	**RR**, no. years since ever last smoked >10 y or never smoked Ref 1-20 y **2.3** (0.46-12) (*P* = .30) <1 y **1.2** (0.20-6.8) (*P* = .87)
	Linear trend per pack-year **1.141** (1.019-1.277) (*P* = .02) **RR**, total amount ever smoked, linear trend, per pack-year **1.016** (0.992-1.041) (*P* = .19)		
Family history			
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish populatio	**SIR** for number of relatives with lung cancer 0 **3.39** (2.85-4.03) (*P* < .001)		≥1 **11.24** (6.38-19.79)

*Pooled estimate (meta-analysis)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – HL: Hodgkin lymphoma; n: number; f/u: follow-up; y: years; RR: relative risk; SIR: standardised incidence ratio; AER: absolute excess risk; py: person-years; Gy: gray; Ref: reference; Mod: moderate

e. Gastrointestinal malignancies

Study details	Risk estimate			
Sex				
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1 y; comparator Dutch general pop	**SIR** Male **3.8** (3.0-4.7) Female **3.8** (2.8-5.0) (*P* = .95)		**AER** Male **17.9** Female **12.2** (*P* = .12)	
Henry-Amar 1992 [102] Retrospective international cohort of 1 y HL survivors treated 1960-1987 (n=12,411); median f/u not given	**RR** (Small intestine) Male **9.6** (*P* < .01) Female **5.6**		**RR** (Colon) Male **1.9** (*P* < .01) Female **0.9**	
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given (AERs / 10,000 py)	**RR** *All* Male **1.7** *Oesophagus* Male **2.1** *Stomach* Male **2.0** *Small bowel* Male **1.4** *Colon* Male **1.6** *Rectum* Male **1.2** *Liver, gb* Male **1.9** *Pancreas* Male **1.5**	Female **1.7** Female **4.7** Female **1.8** Female **1.6** Female **1.7** Female **1.3** Female **1.3** Female **1.5**	**AER** *All* Male **6.4** *Oesophagus* Male **0.6** *Stomach* Male **2.0** *Small bowel* Male **0.1** *Colon* Male **1.9** *Rectum* Male **0.3** *Liver, gb* Male **0.6** *Pancreas* Male **0.5**	Female **5.2** Female **0.8** Female **0.9** Female **0.1** Female **2.1** Female **0.4** Female **0.2** Female **0.5**
Birdwell 1997 [133] Retrospective cohort treated in the USA 1961-1994 (n=2441); average f/u 10.9 y	Incidence **RR**		Mortality **RR**	

(AER / 10,000 py)	Men **2.6** (1.6-32.0) Women **2.2** (1.0-4.4) **AER** Men **7.4** Women **3.4**	Men **3.7** (2.1-5.7) Women **4.1** (1.6-5.7) **AER** Men **6.4** Women **4.0**
van den Belt-Dusebout 2009 [134] Nested case-control study in a cohort of 5142 5 y survivors of HL or testicular cancer treated in the Netherlands 1965-1995; only data relating to HL patients extracted (19 cased, 69 controls); median f/u not given	Stomach **SIR** Men **3.0** (1.3-5.8) Women **10.0** (5.0-18.0)	 **AER** Men **3.2** / 10,000 py Women **7.3** / 10,000 py
van Eggermond 2017 [135] Retrospective cohort of Dutch 5 y HL survivors treated 1965-1995 (n=3121); median f/u 22.9 y	**SIR** All colon sites Men **3.3** (2.1-5.0) Women **1.6** (0.8-2.9) Transverse Men **8.5** (3.7-16.7) Women **4.4** (1.2-11.2) Rectum Men **2.9** (1.5-5.2) Women **2.0** (1.0-3.7) Other colon Men **2.4** (1.4-4.0) Women **1.1** (0.5-2.3)	**AER** Men **7.4** Women **3.6** **Cumulative incidence** Male **0.7** (20 y), **2.0** (30 y) Female **0.6** (20 y), **2.1** (30 y)
Dores 2014 [170] Nested case-control study in international cohort of ≥5y HL survivors, treated 1953-2003 (n=36 cases, 70 controls)	Pancreas **OR** < 10 Gy vs ≥ 10 Gy Male **5.1** (1.3-25) (P_{diff} > 0.5)	 Female **3.2** (0.6-27)

Age at treatment

Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py)	**SIR**, all <25 y **4.1** (0.2-18.3) 25-44 y **2.4** (0.8-5.1) 45-54 y **1.2** (0.3-3.1) ≥55 y **1.5** (0.7-2.7) **AER**, all <25 y **2.6** ≥55 y **21.4**	**SIR**, stomach <25 y **11.3** (0.6-49.6) 25-44 y **3.2** (0.8-8.2) 45-54 y **3.4** (1.2-7.4) ≥55 y **1.1** (0.3-2.6) **SIR**, colon <25 y **5.4** (0.3-23.7) 25-44 y **1.9** (0.5-4.9) 45-54 y **1.6** (0.4-4.3) ≥55 y **2.7** (1.4-4.6)
Schaapveld 2015 [88] Retrospective cohort of >5 y HL survivors treated in the Netherlands 1965-2000 when aged 15-50 y (n=3905); median f/u 19.1y; comparator Dutch general pop	**SIR** 15-24 y **9.8** (7.0-13.3) 25-34 y **3.6** (2.5-5.0) 35-50 y **2.6** (1.9-3.4) (*P* < .001)	**AER** 15-24 y **15.5** 25-34 y **11.7** 35-50 y **19.9** (*P* = .65)
van Leeuwen 2000 [75] Retrospective cohort treated for HL in the Netherlands 1966-1986 when aged <40 y (n=1253); median f/u 14.1 y (AER / 10,000 py)	**RR** ≤20 y **35.7** (14.4-73.6) 21-30 y **10.5** (5.3-18.9) 31-39 y **4.3** (1.9-8.5)	**AER** ≤20 y **15.3** 21-30 y **13.4** 31-39 y **14.0**
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y	Stomach **SIR** 0-40 y **17.7** (6.5-38.5) 41-50 y **2.7** (0.1-15.3) 51-60 y **4.4** (0.9-12.9) ≥ 60 y **1.5** (0.2-5.4)	 **AER** 0-40 y **7** 41-50 y **6** 51-60 y **24** ≥ 60 y **20**
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population (AERs / 10,000 py)	Colorectal **SIR**, Male <35 y **4.07** (2.57-6.46) (*P* < .01) ≥35 y **1.73** (1.33-2.26)	 **30 y cumulative incidence** Male <35 y **1.4%**

			≥35 y **2.2%**	
	SIR, Female <35 y **1.31** (0.49-3.48) ≥35 y **1.65** (1.19-2.30) **AER**, Male <35 y **4** ≥35 y **10** **AER**, Female <35 y **0.4** ≥35 y **8**		Female <35 y **0.6%** ≥35 y **2.1%**	
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given (AERs / 10,000py)	**RR**, all <21 y **10.0** 21-30 y **3.9** 31-40 y **2.1** 41-50 y **2.3** 51-60 y **1.6** ≥61 y **1.0**	**RR**, colon <21 y **4.7** 21-30 y **3.5** 31-40 y **1.3** 41-50 y **2.0** 51-60 y **1.6** ≥61 y **1.4**	**AER**, all <21 y **3.5** 21-30 y **3.9** 31-40 y **4.6** 41-50 y **15.4** 51-60 y **15.1** ≥61 y **1.1**	**AER**, colon <21 y **0.6** 21-30 y **1.2** 31-40 y **0.4** 41-50 y **3.9** 51-60 y **5.1** ≥61 y **6.9**
	RR, stomach <21 y **13.8** 21-30 y **7.1** 31-40 y **3.4** 41-50 y **3.0** 51-60 y **1.5** ≥61 y **0.9**	**RR**, rectum <21 y **12.4** 21-30 y **1.8** 31-40 y **1.9** 41-50 y **1.5** 51-60 y **1.1** ≥61 y **0.7**	**AER**, stomach <21 y **0.8** 21-30 y **1.4** 31-40 y **1.8** 41-50 y **4.4** 51-60 y **2.2** ≥61 y **-1.5**	**AER**, rectum <21 y **0.8** 21-30 y **0.2** 31-40 y **0.8** 41-50 y **1.1** 51-60 y **0.7** ≥61 y**-2.6**
Birdwell 1997 [133] Retrospective cohort treated in the USA 1961-1994 (n=2441); average f/u 10.9 y	**RR** ≤24 y **7.2** (2.3-17.3) 25-34 y **4.5** (2.0-8.4) 35-44 y **3.7** (1.6-7.3)		**AER** ≤24 y **2.8** 25-34 y **6.4** 35-44 y **16.0**	

	45-54 y **1.63** (0.5-3.9) ≥55 y **0.84** (0.2-2.3)	45-54 y **11.0** ≥55 y **-**
van den Belt-Dusebout 2009 [134] Nested case-control study in a cohort of 5142 5 y survivors of HL or testicular cancer treated in the Netherlands 1965-1995; only data relating to HL patients extracted (19 cased, 69 controls); median f/u not given (AER / 10,000 py)	**SIR** stomach <20 y **64.2** (20.3-151) 20-29 y **21.2** (10.1-39.1) 30-39 y **3.3** (0.6-9.8) 40-49 y **0.0** (0.0-4.0) ≥50 y **0.7** (0.0-4.2)	**AER** stomach <20 y **8.5** 20-29 y **8.0** 30-39 y **2.8** 40-49 y **-2.7** ≥50 y **-2.3**
van Eggermond 2017 [135] Retrospective cohort of Dutch 5 y HL survivors treated 1965-1995 (n=3121); median f/u 22.9 y (AER / 10,000 py)	**SIR** All colon sites <25 y **6.8** (3.7-11.3) 25-34 y **2.4** (1.2-4.4) 35-50 y **1.3** (0.6-2.4) Transverse <25 y **19.3** (7.1-42.0) 25-34 y **5.3** (1.1-15.6) 35-50 y **3.1** (0.6-18.9) Colon, other <25 y **4.2** (1.8-8.2) 25-34 y **1.9** (0.7-3.8) 35-50 y **1.0** (0.4-2.2) Rectum <25 y **2.1** (0.4-6.1) 25-34 y **2.2** (0.8-4.7) 35-50 y **2.6** (1.4-4.6)	**SIR** All colorectal <25 y **4.9** 25-34 y **2.3** 35-50 y **1.8** **Cumulative incidence** 20 y <25 y **0.2%** 25-34 y **0.2%** 35-50 y **1.9%**	**AER** <25 y **5.2** 25-34 y **4.9** 35-50 y **7.8** 30 y <25 y **1.1%** 25-34 y **2.5%** 35-50 y **3.3%**
Morton 2013 [169] International case-cohort study nested in a cohort of 19,882 HL survivors treated 1953-2003 (89 cases, 190 matched controls); median f/u not given	**OR** stomach <30 y at treatment: <25 Gy <5600 mg/m^2 proc Ref	≥30 y at treatment: <25 Gy <5600 mg/m^2 proc Ref

	≥25 <5600 **7.1** (1.9-36.8) <25 ≥5600 **1.9** (0.5-7.3) ≥25 ≥5600 **124** (15.8-3169) ($P_{interaction}$ = .06)	≥25 <5600 **1.5** (0.5-4.2) <25 ≥5600 **0.8** (0.3-2.4) ≥25 ≥5600 ∞ (8.8-∞) ($P_{interaction}$ = .002)
Dores 2014 [170] Nested case-control study in international cohort of ≥5y HL survivors, treated 1953-2003 (n=36 cases, 70 controls)	Pancreas **OR** <10 Gy vs ≥10 Gy 12-49 y **11.0** (1.9-219) (*P* = .20)	 50-76 y **2.1** (0.5-10)
Family history		
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6 y; comparator general Swedish population	**SIR** for number of relatives with colorectal cancer 0 **1.76** (1.45-2.14) (*P* <.03)	 ≥1 **3.71** (2.05-6.70)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – y: years; HL: Hodgkin lymphoma; SIR: standardised incidence ratio; AER: absolute excess risk; RR: relative risk; py: person-years; OR: odds ratio; Gy: gray; mg/m^2: milligrams per metre-squared; proc: procarbazine; Ref: reference

f. Cutaneous malignancies

Study details	Risk estimate	
Sex		
Henry-Amar 1992 [102] Retrospective international cohort of 1 y HL survivors treated 1960-1987 (n=12,411); median f/u not given	**RR** melanoma Male **1.9** Female **1.2**	**RR** NMSC Male **3.6** (*P* < .001) Female **3.5** (*P* < .001)
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given (AERs / 10,000 py)	**RR**, melanoma Male **2.2** Female **1.1**	**AER**, melanoma Male **1.5** Female **0.1**
Daniëls 2013 [173] Retrospective cohort treated 1965-2005 in the Netherlands (n=889); comparator Dutch general population; median f/u not given	First BCC **SIR** Male **5.7** (4.0-7.7)	 **AER** Male **59.4** / 10,000 py

	Female **4.6** (3.0-6.7)	Female **46.2** / 10,000 py
Herr 2018 [175] Retrospective cohort of Causasian adults initially diagnosed with lymphoid neoplasms or cutaneous malignancies in the US 2000-2014 when aged 20-83 y (151,949 >1 y survivors of lymphoid neoplasms); only data related to HL extracted	**SIR** Male **1.57** (1.08-2.21) Female **2.05** (1.34-3.01) ($P_{heterogeneity}$ = .41)	
Age at treatment		
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py)	**SIR**, melanoma <25 y **2.0** (0.1-8.7) 25-44 y **1.5** (0.3-4.8)	 45-54 y **-** ≥55 y **6.9** (1.7-18.0)
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y	Melanoma **SIR** 0-40 y **3.7** (1.4-8.0) 41-50 y **2.0** (0.1-11.1) 51-60 y **2.4** (0.1-13.3) ≥60 y **0**	 **AER** 0-40 y **7** 41-50 y **6** 51-60 y **8**
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6y; comparator general Swedish population (AERs / 10,000 py)	SCC **SIR,** Male <35 y **5.89** (2.94-11.77) (*P* < .001) ≥35 y **3.96** (3.03-5.18) (*P* < .001) **SIR**, Female <35 y **6.37** (2.65-15.31) (*P* < .001) ≥35 y **4.87** (3.46-6.85) (*P* <.001) **AER**, Male <35 y **2** ≥35 y **17**	**30 y cumulative incidence** Male <35 y **0.5%** ≥35 y **2.0%** Female <35 y **0.1%** ≥35 y **1.9%**

	AER, Female <35 y **2** ≥35 y **15**	
Daniëls 2013 [173] Retrospective cohort treated 1965-2005 in the Netherlands (n=889); comparator Dutch general population; median f/u not given (AER / 10,000 py)	**SIR**, 1st BCC <35 y **8.0** (5.8-10.7) 35-65 y **3.1** (1.9-4.9) >65 y **1.1** (0-6.2)	**AER** <35 y **54.9** / 10,000 py 35-65 y **51.7** / 10,000 py >65 y **6.8** / 10,000 py
Herr 2018 [175] Retrospective cohort of Causasian adults initially diagnosed with lymphoid neoplasms or cutaneous malignancies in the US 2000-2014 when aged 20-83 y (151,949 >1 y survivors of lymphoid neoplasms); only data related to HL extracted	**SIR** 20-39 y **2.15** (1.29-3.35) 40-49 y **1.26** (0.54-2.48) (P_{trend} = .33)	 50-59 y **2.65** (1.57-4.19) 60-69 y **1.20** (0.65-2.01)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – y: years; HL: Hodgkin lymphoma; RR: relative risk; NMSC: non-melanoma skin cancer; AER: absolute excess risk; py: person-years; BCC: basal cell carcinoma; standardised incidence ratio

g. Other solid tumours

Study details	**Risk estimate**			
Sex				
Henry-Amar 1992 [102] Retrospective international cohort of 1 y HL survivors treated 1960-1987 (n=12,411); median f/u not given	**RR** Thyroid Male **5.1** (*P* < .01) Female **1.5**	**RR** Bone Male **6.2** (*P* < .01) Female **6.5**	**RR** Salivary gland Male **7.8** (*P* < .01) Female **16.4**	
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given (AERs / 10,000 py)	**RR** *Thyroid* Male **3.1** *Kidney* Male **1.6** *Bladder*	 Female **4.6** Female **1.4** 	**AER** *Thyroid* Male **0.5** *Kidney* Male **0.8** *Bladder*	 Female **2.5** Female **0.3**

	Male **1.3** *Bone* Male **2.0** *Conn. tissue* Male **5.1** *Brain, CNS* Male **1.8** *Buccal, all* Male **3.1** *Lip* Male **3.3** *Tongue* Male **3.3** *Salivary gland* Male **5.0** *Gum, other* Male **2.1** *Pharynx* Male **3.1** *Larynx* Male **1.6**	Female **1.9** *Bone* Female **7.1** *Conn. tissue* Female **5.0** *Brain, CNS* Female **1.2** *Buccal, all* Female **4.5** *Lip* Female **9.5** *Tongue* Female **1.6** *Salivary gland* Female **7.7** *Gum, other* Female **3.6** *Pharynx* Female **4.1** *Larynx* Female **1.6**	Male **1.9** *Bone* Male **0.1** *Conn. tissue* Male **1.1** *Brain, CNS* Male **0.8** *Buccal, all* Male **3.2** *Lip* Male **0.8** *Tongue* Male **0.6** *Salivary gland* Male **0.5** *Gum, other* Male **0.4** *Pharynx* Male **1.0** *Larynx* Male **0.4**	Female **0.7** Female **0.5** Female **0.9** Female **0.1** Female **2.0** Female **0.4** Female **0.1** Female **0.6** Female **0.4** Female **0.5** Female **0.1**
Michaelson 2014 [210] Retrospective cohort treated in the USA 1969-2008 (n=1981); median f/u 14.3 y (IR & AER per 10,000 py)	Thyroid **IR** Male **5.7** Female **14.0**	**IR ratio** Male Ref Female **2.45** (*P*= .027)	**RR** Male **12** (5.0-13.0) Female **8.3** (5.0-22.9) **AER** Male **5.3** Female **12.3**	
Age at treatment				

Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py)	**SIR**, thyroid <25 y **13.1** (2.2-40.5) 25-44 y **10.9** (2.7-28.1) 45-54 y **-** ≥55 y **-** **RR**, thyroid <25 y **16.6** (2.0-59.8) 25-44 y **9.6** (1.2-34.5)		**SIR**, nervous systm <25 y **2.2** (0.1-9.9) 25-44 y **2.6** (0.6-6.8) 45-54 y **5.0** (1.2-13.0) ≥55 y **-** **SIR**, bone & soft-tiss <25 y **14.5** (4.5-33.7) 25-44 y **7.1** (1.7-18.3) 45-54 y **-** ≥55 y **-**	
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given (AERs / 10,000 py)	**RR**, thyroid <21 y **13.7** 21-30 y **4.4** 31-40 y **1.4** 41-50 y **0.8** 51-60 y **-** ≥61 y **3.7** **RR**, cervix <21 y **6.1** 21-30 y **2.1** 31-40 y **0.9** 41-50 y **1.4** 51-60 y **2.2** ≥61 y **1.2**	**RR**, bone/CT <21 y **12.6** 21-30 y **5.7** 31-40 y **3.7** 41-50 y **5.1** 51-60 y **2.3** ≥61 y **1.5** **RR**, buccal <21 y **6.1** 21-30 y **6.6** 31-40 y **3.8** 41-50 y **2.2** 51-60 y **3.2** ≥61 y **3.0**	**AER**, thyroid <21 y **3.6** 21-30 y **1.4** 31-40 y **0.2** 41-50 y **-0.1** 51-60 y **-0.6** ≥61 y **2.2** **AER**, cervix <21 y **3.2** 21-30 y **1.5** 31-40 y **-0.1** 41-50 y **1.2** 51-60 y **3.2** ≥61 y **0.5**	**AER**, bone/CT <21 y **2.3** 21-30 y **1.0** 31-40 y **0.8** 41-50 y **1.8** 51-60 y **0.8** ≥61 y **0.5** **AER**, buccal <21 y **0.6** 21-30 y **1.8** 31-40 y **2.3** 41-50 y **2.4** 51-60 y **7.4** ≥61 y **8.4**
Michaelson 2014 [210] Retrospective cohort treated in the USA 1969-2008 (n=1981); median f/u 14.3 y (AER per 10,000 py)	Thyroid **RR** <20 y **31.3** (18.2-50.1)		**IR** / 10,000 py <20 y **19.5**	**IR ratio** <20 y **3.66**

	≥20 y **4.4** (2.2-7.9) **AER** <20 y **18.9** ≥20 y **4.1**	≥20 y **5.3**	≥20 y **1.00** (*P* = .001)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.
Abbreviations – y: years; HL: Hodgkin lymphoma; n: number; f/u: follow-up; RR: relative risk; AER: absolute excess risk; py: person-years; IR: incidence rate; systm: system; CT: connective tissue

h. Haematological malignancies

Study details	Risk estimate	
Sex		
Aleman 2003 [1] Retrospective Dutch cohort treated when aged <41 y 1965-1987 (n=1261); median f/u 17.8 y; comparator general Dutch population (AERs per 10,000 py)	Death from MDS / leukaemia **RR** Male **35.3** (18.2-61.6) Female **49.8** (25.7-86.9)	 **AER** Male **10.0** Female **12.2**
Brierley 1998 [10] Retrospective cohort with stage 1-2 HL treated in Canada 1973-1984 (n=611); median f/u 11 y; comparator age-matched general population for same period	**RR** of leukaemia Male **13.0** (3.5-33.0) (*P* < .0001) Female **5.9** (0.2-33.0) (*P* < 0.5)	
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py)	Leukaemia, excluding CLL **SIR** Male **17.8** (11.8-25.6) Female **28.6** (17.3-43.9) (χ^2 2.3) **AER** Male **8.5** Female **9.6**	NHL **SIR** Male **15.5** (11.1-20.9) Female **10.5** (5.5-18.0) (χ^2 1.4) **AER** Male **12.6** Female **5.5**

Henry-Amar 1992 [102] Retrospective international cohort of 1y HL survivors treated 1960-1987 (n=12,411); median f/u not given	**RR**, leukaemia Male **28.6** (*P* < .001) Female **25.7** (*P* < .001)		**RR** NHL Male **35.6** (*P* < .001) Female **24.2** (*P* < .001)	
Cellai 2001 [106] Retrospective cohort treated in Italy 1960-1991 (n=1524); average f/u 10.7 y	**15 y cumulative incidence** of leukaemia Male **2.1%** Female **1.4%**			
Biti 1994 [107] Retrospective cohort treated in Italy 1960-1988 (n=1121); mean f/u >9 y	**15 y cumulative incidence** Male **2.7%** Female **0.6%**			
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	**SIR**, leukaemia Male **27.3** (17.7-40.3) Female **37.2** (21.7-59.6)		**SIR**, NHL Male **20.4** (14.7-27.6) Female **9.7** (4.5-18.5)	
Mauch 1996 [120] Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population (AER / 10,000 py)	**AER**, leukaemia Male **8.1** (95% CI not given) Female **10.9** (95% CI not given)		**AER**, NHL Male **15.6** Female **5.1**	
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given (AERs / 10,000 py)	**RR**		**AER**	
	Leukaemia, all		*Leukaemia, all*	
	Male **9.7**	Female **10.2**	Male **10.1**	Female **7.2**
	ALL		*ALL*	
	Male **7.9**	Female **5.7**	Male **0.5**	Female **0.2**
	ANLL		*ANLL*	
	Male **23.1**	Female **18.9**	Male **7.5**	Female **4.9**
	CLL		*CLL*	
	Male **1.1**	Female **0.7**	Male **0.02**	Female **-0.1**
	CML		*CML*	
	Male **1.0**	Female **1.7**	Male **0.02**	Female **0.2**
	NHL		*NHL*	
	Male **5.5**	Female **5.6**	Male **5.9**	Female **4.3**
	Myeloma		*Myeloma*	
	Male **1.0**	Female **1.6**	Male **-0.01**	Male **0.2**
Tester 1984 [139]	Leukaemia			

Retrospective cohort treated in USA 1964-1984 (n=473); median f/u >12 y	**RR** <30 y: **0.03** (+/- 0.014) 30-39 y: **0.06** (+/- 0.041) 40-49 y: **0** ≥50 y: **0**	**10 y cumulative incidence** <30 y: **0.03%** 30-39 y: **0.06%** 40-49 y: **0%** ≥50 y: **0%**
Delwail 2002 [202] Retrospective cohort treated in France 1972-1988 (n=462); median f/u 8.5 y	**15 y cumulative incidence** Secondary leukaemia Male **2.3%** (0.7-3.9) Female **2.5**% (0.0-5.1)	 ANLL Male **2.1%** (0.5-3.6) Female **2.2%** (0.0-4.7)
Andrieu 1990 [203] Retrospective cohort treated for stage 1-3 HL in France 1972-1980 (n=462); median 10.5 y	**15 y cumulative incidence** ANLL Male **2.9%** (NS)	 Female **5.7%**
van der Velden 1988 [204] Nested case-control study in cohort of 1681 patients with HL treated in the Netherlands 1972-1978; median f/u 66 m (18 cases)	ANLL, **RR** Male **89** (51-145) Female **20** (2.4-72)	**10 y cumulative incidence** Male **3.2%** (*P* < .01) Female **1.0%** (*P* < .01)
Age at treatment		
Aleman 2003 [1] Retrospective Dutch cohort treated when aged <41y 1965-1987 (n=1261); median f/u 17.8 y; comparator general Dutch population (AERs per 10,000 py)	Death from leukaemia / MDS **RR** ≤20 y **37.7** (10.3-96.6) 21-30 y **57.7** (31.6-96.9) 31-40 y **25.8** (9.5-56.1)	 **AER** ≤20 y **6.7** 21-30 y **14.1** 31-40 y **10.2**
Cosset 1991 [56] Pooled analysis of 4 EORTC trials H1, H2, H5, H6, run 1964-1988; 1660 patients; median f/u not reported	**RR** NHL > 40 y **6.6** (*P* < .01)	
Swerdlow 2000 [84] Retrospective cohort treated for HL in the UK 1963-1993 (n=5519); average f/u 8.5 y (AERs / 10,000 py) NHL **SIR** 15-24 y **8.0** (2.0-20.8)	Leukaemia, excluding CLL **SIR** 15-24 y **53.6** (29.5-88.2) 25-34 y **26.3** (12.7-47.5) 35-44 y **22.4** (9.6-43.3) 45-54 y **17.2** (7.4-33.2) ≥55 y **10.5** (4.8-19.6)	**20 y cumulative risks** <45 y **1.3%** ≥45 y **4.2%** **AER** 15-24 y **8.3**
	20 y cumulative risks <45 y **1.4%** ≥45 y **6.0%**	

25-34 y **9.4** (3.7-19.0) 35-44 y **15.7** (7.9-27.5) 45-54 y **11.9** (5.7-21.5) ≥55 y **18.7** (11.8-27.8)	**AER** 15-24 y **1.7** 25-34 y **3.9** 35-44 y **12.9** 45-54 y **17.8** ≥55 y **49.2**		25-34 y **6.3** 35-44 y **9.2** 45-54 y **14.2** ≥55 y **17.9**
Sont 1992 [97] Retrospective cohort treated in the Netherlands 1969-1988 (n=482); average f/u 6.05 y	Leukaemia <40 y Reference >40 y **0.6** (95% CI not given)		NHL <40 y Reference >40 y **13.2** (95% CI not given)
Henry-Amar 1992 [102] Retrospective international cohort of 1y HL survivors treated 1960-1987 (n=12,411); median f/u not given	**RR**, leukaemia 15-19 y **1.0** 20-29 y **1.3** 30-39 y **1.4** 40-49 y **2.5** 50-59 y **4.0** 60+ y **4.5** (95% CIs not given)		**RR**, NHL 15-19 y **1.0** 20-29 y **0.8** 30-39 y **1.3** 40-49 y **3.1** 50-59 y **8.4** 60+ y **12.0**
Cellai 2001 [106] Retrospective cohort treated in Italy 1960-1991 (n=1524); average f/u 10.7y	**15 y cumulative incidence** of leukaemia <28 y **0.9%** 28-44 y **2.3%** >44y **1.9%**		
Biti 1994 [107] Retrospective cohort treated in Italy 1960-1988 (n=1121); mean f/u >9y	**15 y cumulative incidence** <20 y **1.4%** 20-40 y **0.7%**		41-60 y **4.6%** >60 y -
Swerdlow 2011 [112] Retrospective cohort treated in the UK 1963-2001 (n=5798); comparator general population; median f/u not given	**SIR**, leukaemia, exc. CLL < 25 y **36.9** (19.1-64.4) 25-34 y **26.4** (12.1-50.1) 35-44 y **33.0** (14.2-65.0) 45-54 y **20.5** (5.6-52.4) ≥ 55 y **33.7** (15.4-63.9) (*P* = .75)		**SIR**, NHL < 25 y **18.1** (8.3-34.4) 25-34 y **16.9** (9.0-29.0) 35-44 y **15.0** (7.2-27.6) 45-54 y **23.9** (12.4-41.8) ≥ 55 y **12.7** (5.1-26.1) (*P = .81*)
Foss Abrahamsen 2002 [113] Retrospective cohort treated in Norway 1968-1985 (n=1024); median f/u 14 y	ANLL **SIR**		NHL **SIR**

			0-40 y **24.9** (10-51.2) 41-50 y **20.1** (4.2-58.8) 51-60 y **8.3** (1-29.9) ≥60 y **5** (0.6-17.8) **AER** 0-40 y **8** 41-50 y **18** 51-60 y **16** ≥ 60 y **20**	0-40 y **33.2** (19.7-52.4) 41-50 y **13.2** (2.7-38.7) 51-60 y **14.5** (4-37.2) ≥60 y **25.2** (9.3-55) **AER** 0-40 y **20** 41-50 y **18** 51-60 y **16** ≥ 60 y **60**
Sud 2017 [118] Retrospective cohort treated in Sweden 1965-2013 (n=9522); median f/u 12.6y; comparator general Swedish population (AERs / 10,000 py) NHL **SIR**, Male <35 y **15.9** (11.28-22.32) (*P* < .001) ≥35 y **6.93** (5.32-9.02) (*P* <.001) **SIR**, Female <35 y **6.23** (2.96-13.04) (*P* <.001) ≥35 y **6.55** (4.58-9.37) (*P* <.001) **AER**, Male <35 y **10** ≥35 y **19** **AER**, Female <35 y **3** ≥35 y **15**		**30 y cumulative incidence** Male <35 y **2.9** ≥35 y **2.4** Female <35 y **0.8** ≥35 y **1.6**	Leukaemia **SIR** Male <35 y **12.15** (7.75-19.05) (*P* < .001) ≥35 y **5.57** (4.02-7.72) (*P* < .001) Female <35 y **10.36** (5.39-19.92) (*P* < .001) ≥35 y **4.51** (2.72-7.48) (*P* < .001) **AER** Male <35 y **5** ≥35 y **12** Female <35 y **3** ≥35 y **7**	**30 y cumulative incidence** Male <35 y **1.5%** ≥35 y **1.3%** Female <35 y **0.6%** ≥35 y **0.9%**
Mauch 1996 [120]			**AER**, leukaemia	**AER**, NHL

Retrospective cohort treated in the USA for stage 1A-3B HL 1969-1988 (n=794); median f/u 10.7 y; comparator general USA population	17-39 y **6.9** (no 95% CI)	>40 y **30.1**	17-39 y **11.8**	>40 y **28.1**
Dores 2002 [126] Retrospective cohort treated in the USA and Europe 1935-1994 (n=32,591); median f/u not given (AERs / 10,000py)	**RR**, ANLL <21 y **39.2** 21-30 y **31.7** 31-40 y **35.7** 41-50 y **28.6** 51-60 y **21.2** ≥61 y **5.9**	**RR**, NHL <21 y **6.9** 21-30 y **7.5** 31-40 y **8.7** 41-50 y **5.3** 51-60 y **4.3** ≥61 y **3.8**	**AER**, ANLL <21 y **3.6** 21-30 y **4.2** 31-40 y **7.2** 41-50 y **10.6** 51-60 y **14.5** ≥61 y **6.8**	**AER**, ANLL <21 y **1.5** 21-30 y **3.2** 31-40 y **7.1** 41-50 y **7.1** 51-60 y **9.4** ≥61 y **12.8**
Valagussa 1986 [141] Retrospective cohort treated in Italy 1965-1982 (n=1329); median f/u 9.5 y	**Overall incidence** 17-40 y **2.7%** (*P* < .02)		>40 y **7.0%**	
Pedersen-Bjergaard 1982 [184] Retrospective cohort treated in Denmark 1970-1981 (n=391); median f/u not given	**9 y cumulative incidence** <40 y **8.6%** (+/-5.6) (*P* = .0001)		≥40 y **39.5%** (+/-10.1)	
Schonfeld 2006 [187] Retrospective cohort of >1 y HL survivors treated in Nordic countries and the USA 1970-2001 (n=35,511); comparator general population; median f/u not given	**AER** (/ 10,000 py), AML <35 y **3.2** (1.6-5.7) (1970-1984), **1.6** (0.6-3.6) (1985-2000)		≥3 5 y **14.3** (8.7-22.1), **7.0** (2.9-13.8)	
Xavier 2013 [192] Retrospective cohort treated in the USA 1992-2009 (n=26,826); median f/u 26 m	**15 y cumulative incidence** NHL < 20 y **0.67%** (0.04-1.29) 20-59 y **2.23%** (1.77-2.67)		≥ 60 y **5.59%** (4.21-6.97)	
Delwail 2002 [202] Retrospective cohort treated in France 1972-1988 (n=462); median f/u 8.5 y	**15 y cumulative incidence** Leukaemia <40 y **1.8%** (0.6-3.0) ≥40 y **4.5%** (0.0-20.0)		ANLL <40 y **1.6%** (0.5-2.7) ≥40 y **3.9%** (0.0-19.1)	
Andrieu 1990 [203] Retrospective cohort treated for stage 1-3 HL in France 1972-1980 (n=462); median 10.5 y	**15y cumulative incidence** <20 y **5%** (NS)	>20, <40 y **2%** (NS)	≥40 y **12%** (NS)	
Enrici 1998 [205] Retrospective cohort treated in Italy 1972-1996 (n=1391); average f/u 84 m	**RR** NHL >40 y **3.05** (*P* = .0152)			

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.
Abbreviations – HL: Hodgkin lymphoma; n; number; f/u: follow-up; y: years; RR: relative risk; AER: absolute excess risk; py: person-years; MDS: myelodysplastic syndrome; CLL: chromic lymphocytic leukaemia; NHL: non-Hodgkin lymphoma; SIR: standardised incidence ratio; CI: confidence interval; ANLL: acute non-lymphocytic leukaemia; EORTC: European Organisation for Research and Treatment of Cancer; exc: excluding; AML: acute myeloid leukaemia; m: months

Appendix C4: Risk of other conditions following radiotherapy for Hodgkin lymphoma

Table C4.1: Risk of thyroid disease following radiotherapy for Hodgkin lymphoma

Study details	Risk estimate
Cumulative incidence	
Brusamolino 2006 [5] Retrospective cohort of patients with stage 1A-2A HL treated in Italy with 4 cycles ABVD & limited RT 1990-2003 (n=120); median f/u 10 y	Asymptomatic biochemical abnormalities 5 y **2%** 12 y **7%**
Kilickap 2012 [74] Prospective cohort treated in Turkey 1990-2006 (n=336); median f/u 8.5 y	Hypothyroidism **1.5%** Asymptomatic biochemical abnormalities **17.1%**
Pinnix 2018 [212] Retrospective cohort treated in USA with IMRT to the mediastinum +/- neck 2009-2015 with ≥18 m follow-up (n=90); external validation cohort treated with 3D-CRT in Italy 2001-2009 (n=50, from same cohort as [213]); median f/u 41.1 m (IMRT), 32.0 m (3D-CRT)	3-year freedom from hypothyroidism IMRT **40%** 3D-CRT **56.1%** (*P* = .057)
Cella 2012 [213] Retrospective cohort treated in Italy with RT 2001-2009 (n=61); median f/u 32 m	Hypothyroidism 24 m **43.5%** 60m **49.1%**
Khoo 1998 [214] Screening of cohort treated with mantle RT in Australia 1970-1989 (n=320); median f/u 9 y	Asymptomatic biochemical abnormalities **39%**
Illés 2003 [215] Retrospective cohort treated with RT in Hungary 1970-2000 (n=151); median f/u not given	Subclin hypothyroidism: **17.2%** Hyperthyroidism: **1.3%** Clinical hypothyroidism: **8.0%**
Bethge 2000 [216] Retrospective cohort treated in Germany 1970-1995 (n=177); median f/u 6y	Hypothyroidism: **35%**
Smith 1981 [217] Retrospective cohort treated in USA 1966-1976 (n=64); median f/u not given	Thyroid insufficiency: **69%**
Hancock 1991 [218]	20 y 26 y

Retrospective cohort of patients treated in the USA with RT 1961-1989 (n=1677); median f/u 9.9 y	≥1 abnorm **52%** Hypothyroidism **43%** Graves' disease **3.3%** Silent thyroiditis **0.6%** Hashimoto's **0.7%** Thyroid cancer **1.7%** Benign nodule **3.3%** Benign cyst **0.7%** Multinodular goitre **0.5%**	≥1 abnorm **67%** Hypothyroidism **47%** Graves' disease **3.3%** Silent thyroiditis **0.6%** Hashimoto's **0.7%** Thyroid cancer **1.7%** Benign nodule **5.1%** Benign cyst **0.7%** Multinodular goitre **0.5%**
Median time to development		
Brusamolino 2006 [5] Retrospective cohort of patients with stage 1A-2A Hodgkin lymphoma treated in Italy with 4 cycles ABVD & limited RT 1990-2003 (n=120); median f/u 10 y	Asymptomatic biochemical abnormalities **74 m**	
Tarbell 1990 [49] Retrospective cohort with stage 1A-3B HL treated with mantle RT in the USA 1969-1984 (n=590); median f/u 8.7 y	Biochemical dysfunction **44 m** Clinical hypothyroidism **12 m**	
Pinnix 2018 [212] Retrospective cohort treated in USA with RT to the mediastinum +/- neck 2009-2015 with ≥18 m follow-up; median f/u 41.1m (IMRT), 32.0m (3D-CRT)	Hypothyroidism: IMRT **13 m**	3D-CRT **19.5 m**
Hancock 1991 [218] Retrospective cohort of patients treated in the USA with RT 1961-1989 (n=1677); median f/u 9.9y	≥1 thyroid disease **4.6 y** Hypothyroidism **4.0 y** Graves' disease **4.9 y** Silent thyroiditis **3.7 y** Hashimoto's **7.9 y**	Benign nodule **12.6 y** Benign cyst **8.1 y** Multinodular goitre **13.8 y**
Median age at development		
Brusamolino 2006 [5] Retrospective cohort of patients with stage 1A-2A Hodgkin lymphoma treated in Italy with 4 cycles ABVD & limited RT 1990-2003 (n=120); median f/u 120m	Asymptomatic biochemical abnormalities **27 y**	

Kilickap 2012 [74] Prospective cohort treated in Turkey 1990-2006 (n=336); median f/u 8.5 y	Asymptomatic biochemical abnormalities **30.2 y**	
Radiation dose		
Pinnix 2018 [212] Retrospective cohort treated in USA with RT to the mediastinum +/- neck 2009-2015 with ≥18 m follow-up; median f/u 41.1 m (IMRT), 32.0 m (3D-CRT)	Cut-off points of 63.5% (V_{25}) and 2.2ml (V_{S25}Gy) classified patients as high risk (80-82%) or low risk (37-44%) of hypothyroidism (*P* < .001) **OR 6.9**	
Cella 2012 [213] Retrospective cohort treated in Italy with RT 2001-2009 (n=61); median f/u 32 m	**Cumulative incidence**: V_{30} ≤62.5%: 11.5% V_{25} ≥62.5%: 70.8% (*P* < .0001) **OR 12.6** (95% CI not given)	**Cumulative incidence**: V_{20} ≤82.4%: **13.6%** V_{20} ≥82.4%: **60.7%** (*P* = .001)
Hancock 1991 [218] Retrospective cohort of patients treated in the USA with RT 1961-1989 (n=1677); median f/u 9.9 y	Hypothyroidism: **RR 1.06 / Gy** (*P* = .0000001) **20 y incidence**, thyroid dose: >30 Gy: **44%** (20% excl subclin) 7.5-30 Gy: **27%** (5%) No thyroid RT: **2%** (2%)	Hyperthyroidism: 20 y incidence, thyroid dose: >30 Gy: **3%** 7.5-30 Gy: **1%** No thyroid RT: **2%**
Age at time of radiotherapy		
Hancock 1991 [218] Retrospective cohort of patients treated in the USA with RT 1961-1989 (n=1677); median f/u 9.9 y	**RR**, hypothyroidism: **0.99 / year** age at treatment (*P* = .125)	
Sex		
Illés 2003 [215] Retrospective cohort treated with RT in Hungary 1970-2000 (n=151); median f/u not given	**RR**, hypothyroidism: Female **1.5** (versus male) (95% CI not given)	
Hancock 1991 [218] Retrospective cohort of patients treated in the USA with RT 1961-1989 (n=1677); median f/u 9.9 y	**RR**, hypothyroidism: Female **1.6** (versus male) (*P* = .0000002)	

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – HL: Hodgkin lymphoma; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine; RT: radiotherapy; n: number; f/u: follow-up; y: years; IMRT: intensity modulated radiotherapy; m: months; 3D-CRT: 3-dimensional conformal radiotherapy; V_{25}: volume of thyroid gland receiving 25 Gy; V_{S25}: volume of thyroid gland spared 25 Gy; excl: excluding; V_{30}: volume of thyroid gland receiving 30 Gy; V_{20}: volume of thyroid gland receiving 20 Gy; OR: odds ratio; RR: relative risk; CI: confidence interval

Table C4.2: Risk of lung disease following radiotherapy for Hodgkin lymphoma

Study details	Risk estimate
Cumulative incidence	
Kilickap 2012 [74] Prospective cohort treated in Turkey 1990-2006 (n=336); median f/u 8.5 y	RILF **8.6%** Pulmonary fibrosis **5.3%** Interstitial fibrosis & pneumonia **1.87%**
Cella 2014 [220] Prospective cohort treated in Italy when aged >14 y 2001-2009 (n=80); median f/u 80 m	RILF **13%**
Mah 1994 [222] Prospective cohort treated in Canada 1985-1990 (n=102); followed-up until lung damaged detected or 6 m following RT	Asymptomatic imaging abnormalities **46%**
Shapiro 1990 [223] Prospective monitoring of American cohort treated with mantle RT (n=13); median f/u 56 m	**92%** abnormalities on CXR or ventilation-perfusion scans **62%** abnormalities on CXR (maj. apical fibrosis); mean **9 m** post-RT **73%** decreased perfusion to apices (50% with ventilation deficits)
Horning 2016 [224] Prospective cohort treated in RCTs in the USA 1980-1990 (n=119); followed up for >36 m	FVC <80% predicted **32%**
Relative risk	
Rugbjerg 2017 [23] Retrospective cohort treated in Denmark when aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	Hospitalisation, respiratory disorders **2.0** (1.6-2.4)
Avivi 2012 [221] Prosective cohort treated with RT in Israel 1999-2005 (n=176); median f/u 57 m; comparator population treated with chemotherapy alone	Abnormal lung function tests **2.2** (0.5-9.7)
Standardised hospitalisation ratio	
Rugbjerg 2019 [8]	Diseases of respiratory system **2.99** (2.64-3.39)

Retrospective cohort of Danish >5 y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop		
Hazard ratio		
Lagerlöf 2022 [26] Retrospective cohort of patients treated for HL with 2/4 cycles ABVD and 30 Gy limited-field RT in Sweden 1999-2003; median f/u 16 y	All respiratory disease **2.6** (1.60-4.33) (*P* < .0001) Variation with time since RT 0-5 y **3.0** (1.28-7.23) (*P* = .012) 5-10 y **1.7** (0.65-4.32) (*P* = .286) >10 y **3.4** (1.47-7.66) (*P* = .004)	Asthma **3.5** Variation with time since RT 0-5 y **2.5** 5-10 y **2.5** >10 y **5.7**
Absolute excess risk		
Rugbjerg 2017 [23] Retrospective cohort treated in Denmark when aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	Hospitalisation, respiratory disorders **42** (25-59) / 10,000 py	
Mortality		
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**SMR**, exc pneumonia **3.6** (2.6-5.0) **40y cumulative mortality 1.2%**	**AEM**, exc pneumonia **2.9** / 10,000 py
Median time to development		
Brusamolino 2006 [5] Retrospective cohort with stage 1A-2A HL treated in Italy with ABVD & RT 1990-2003 (n=120); median f/u 120 m	**17.5 m**	
Cella 2014 [220] Prospective cohort treated in Italy when aged >14 y 2001-2009 (n=80); median f/u 80 m	**10 m**	
Radiation dose		
Cella 2014 [220] Prospective cohort treated in Italy when aged >14 y 2001-2009 (n=80); median f/u 80 m	**OR**, symptomatic pulmonary fibrosis Left lung V30 (%) **1.164** (95% CI 1.031-1.312)	

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

Abbreviations – n: number; f/u: follow-up; y: years; RILF: radiation-induced lung fibrosis; m: months: FVC: forced vital capacity; RT: radiotherapy; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine; Gy: gray; py: person-years; SMR: standardised mortality ratio; exc: excluding; AEM: absolute excess mortality

Table C4.3: Risk of other conditions following radiotherapy for Hodgkin lymphoma

Study details	Risk estimate	
Premature menopause		
De Bruin 2008 [226] Retrospective cohort of >5 y HL female survivors treated in the Netherlands when aged 14-40 y 1965-1995 (n=518); median f/u 9.4 y	Cumulative incidence **2%** **HR 24.4** (6.2-95.5) (RT fields inc. ovaries vs supradiaphragmatic RT alone)	
Madsen 1995 [227] Retrospective cohort of women treated for stage 1-2 HL when aged <50y in the USA 1967-1985; mean f/u 14 y	**2.7%** at mean f/u 14 y	
Fisher 1984 [228] Retrospective cohort of women treated in the UK 1964-1981 when aged <50 y; median f/u 7 y	RT fields limited to above pelvic brim: **93%** retain ovarian function	
Rosenbrock 2021 [229] Screening of cohort treated with RT in the HD14 and HD17 trials (n=499; 258 f, 241 m); median f/u 41.4 m	Proportion of surviving non-growing follicles: IFRT **11.87%** ISRT **24.48%**	
Horning 1981 [230] Retrospective cohort of women treated in US 1968-1978 (n=129); median f/u 64 m	Regular menses TLI alone **47%**	TLI & chemo **20%**
Gastrointestinal disease		
Rugbjerg 2019 [8] Retrospective cohort of Danish >5 y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	**SHRR** digestive system disorders **1.35** (1.18-1.54)	
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**SMR** Digestive disorders **2.9** (2.0-4.1)	**AEM** (/ 10,000 py) Digestive disorders **2.2**
Rugbjerg 2017 [23] Retrospective Danish cohort treated when aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	Hospitalisation: **RR 0.9** (0.7-1.1)	**AER -10** (-26-6) / 10,000 py

Cosset 1988 [232] Retrospective cohort with stage 1-2 supradiaphragmatic HL treated in France 1972-1976 (n=235); median f/u not given	**RR** gastroduodenal ulcer **2.18** (1.45-3.16) **Mean time to development** Gastroduodenal ulcer or gastritis **14 m** Small bowel pathology **18 m**	
Infections		
Rugbjerg 2019 [8] Retrospective cohort of Danish >5 y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	**SHRR** infections & parasitic diseases **2.71** (2.22-3.32)	
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**SMR** Infections (inc pneumonia) **8.3** (6.5-10.5) **HR** SD RT **2.17** (vs no [SD] RT) (0.99-4.79) ID RT Exc spn **1.70** (vs no [ID] RT) (0.87-3.30) Inc spn **2.81** (vs no [ID] RT) (1.55-5.07) **Cumulative mortality** 40 y **2.3%**	**AEM** **6.3** / 10,000 py **HR** Female **0.71** (vs male) (0.43-1.18) 25-34 y at treatment **1.47** (vs <25) (0.74-2.93) 35-50 y **1.31** (vs <25 y) (0.61-2.82)
Mauch 1995 [22] Retrospective cohort with stage 1A-3B HL treated in the USA 1969-1988 (n=794); median f/u of survivors 11 y	**RR** fatal infections **14.9** (3.7-38.1) **AER** Fatal infections **6.8** / 10,000py	
Rugbjerg 2017 [23] Retrospective Danish cohort treated when aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	**RR** (hospitalisation) Infections **2.1** (1.6-2.8) Sepsis **5.5** (3.3-9.0)	Bacterial meningitis **16.4** (6.7-40.3) Pneumonia **2.6** (1.9-3.7)

	AERs (hospitalisation) All infections **64** / 10,000py Sepsis **11** / 10,000py	 Bacterial meningitis **4** / 10,000py Pneumonia **19** / 10,000py
Kilickap 2012 [74] Prospective cohort treated in Turkey 1990-2006 when aged >16 y (n=336); median f/u 8.5 y	Viral **3.9%** TB **1.5%**	Viral & TB **5.4%**
Diabetes mellitus		
van Nimwegen 2014 [234] Retrospective cohort of >5 y HL survivors, diagnosed before age 51 y, treated in the Netherlands 1965-1995 (n=2264); median f/u 21.5 y **AER** By PAN RT dose: None **27** 10-35 Gy **21** ≥36 Gy **39** By age at treatment: <25 y All **15** 10-35 Gy PAN **2** ≥36 Gy PAN **98** 25-51 y **38** 10-35 Gy PAN **38** ≥36 Gy PAN **72** By follow-up duration: 5-19 y All **87** 10-35 Gy PAN **55** ≥36 Gy PAN **302** 20-29 y **15** 10-35 Gy PAN **9** ≥36 Gy PAN **102** ≥30 y **168** 10-35 Gy PAN **152** ≥36 Gy PAN **341**	**SIR** By PAN RT dose: None **1.57*** (95% CI 1.14-2.12) 10-35 Gy **1.36** (95% CI 0.65-2.49) ≥36 Gy **2.58*** (95% CI 0.74-3.68) By age at treatment: <25 y All **1.61** (95% CI 0.80-2.88) 10-35 Gy PAN **1.06** (95% CI 0.13-3.82) ≥36 Gy PAN **1.46** (95% CI 0.63-2.87) 25-51 y **1.56*** (95% CI 1.07-2.20) 10-35 Gy PAN **4.22*** (95% CI 2.18-7.36) ≥36 Gy PAN **2.05*** (95% CI 1.22-3.24) By follow-up duration: 5-19 y All **1.81*** (95% CI 1.07-2.86) 10-35 Gy PAN **1.43** (95% CI 0.17-5.15)	**Cumulative incidence** 20 y **4.1%** (95% CI 3.3-5.1) 30 y **8.3%** (95% CI 6.9-9.8) 30y, RT field: No PAN RT **6.1%** (95% CI 4.5-8.0) PAN RT **7.4%** (95% CI 4.8-10.7) PAN+spleen **12.2%** (95% CI 9.3-15.5) 30 y, PAN RT: None **6.1%** (95% CI 4.5-8.0) 10-35 Gy **7.1%** (95% CI 4.2-11.0) ≥36 Gy **14.2%** (95% CI 10.7-18.3) **Hazard ratio** PAN RT vs none **1.87*** (95% CI 1.12-3.13) PAN+spleen RT vs none **2.28*** (95% CI 1.53-3.38) 10-35 Gy PAN RT vs none **1.26** (95% CI 0.74-2.13)

	≥36 Gy PAN **3.27*** (95% CI 1.79-5.49) 20-29 y **1.15** (95% CI 0.58-2.06) 10-35 Gy PAN **1.07** (95% CI 0.41-2.40) ≥36 Gy PAN **1.86** (95% CI 0.89-3.12) ≥30 y **1.79** (95% CI 0.98-3.00) 10-35 Gy PAN **1.79** (95% CI 0.49-4.58) ≥36 Gy PAN **3.06*** (95% CI 1.12-6.65)	≥36 Gy PAN RT vs none **2.28*** (95% CI 1.53-3.38) BMI ≥30 at end of f/u **1.61** (95% CI 0.84-3.08) ≥36 Gy to PAN, based on age at treatment <25 y **4.49*** (95% CI 2.12-9.54) 25-50 y **1.83*** (95% CI 1.15-2.91) Mean pancreatic tail dose ≥36 Gy **2.43*** (95% CI 1.22-4.85) **1.017 per gray***
Quality of life		
Adams 2004 [57] Screening of cohort treated with mediastinal RT in the USA when aged ≤25 y, since 1969 (n=48); median f/u 14.3 y	Mean SF-36 score Physical **52.08** (*P* = .0085 vs general population) Mental **51.01** (*P* = .0835 vs general population)	
Ganz 2003 [235] Prospective cohort treated within an RCT (SWOG 9133) comparing STNI with CMT (n=247), surveyed at 6 m, 1 y and 2 y with multiple standardised questionnaires	Symptom distress scale at 6 months 6m CMT **28.4%** increase STNI **8.4%** increase (*P* < .0001)	
Greil 1999 [236] Retrospective cohort treated in Austria 1969-1994, surveyed by questionnaire (EORTC QLQ-C30) (n=126); mean f/u 9.1 y	RT: mean (SD) Physical functioning 96.32 (10.25) Fatigue **18.21** (21.77) Pain **6.58** (14.78) Dyspnoea **14.91** (20.06)	CMT: mean (SD) Physical functioning **87.37** (22.24) Fatigue **31.11** (30.50) Pain **17.84** (28.84) Dyspnoea **26.32** (33.18)
Norum 1996 [237] Retrospective cohort treated in Norway 1985-1993 (n=42), surveyed by questionnaire (EORTC QTQ-C30)	Mean fatigue score Females 20 (95% CI 8-31) Males 35 (95% 25-45) (*P* = .04)	Mean global quality of life score Females 80 (95% CI 69-92) Male 64 (95% 56-71) (*P* = .016)

Daniëls 2014 [238] Retrospective cohort treated in the Netherlands 1999-2010, surveyed by questionnaire (EORTC QLQ-C30 & FAS) (n=180); comparator general pop	Fatigue (EORTC QLQ-C30) HL survivors **43%** General pop 28% (*P* = .002)	Fatigue (FAS) HL survivors **41%** General pop 23% (*P* < .001)
Trachtenberg 2019 [239] Retrospective cohort treated in Israel when aged 18-65 y, sent questionnaires (EORTC QTQ-C30) 6 m - 15 y post-treatment (n=120)	**OR**, RT vs no RT Mental fatigue **1.55** (*P* = .34) Reduced activity **1.71** (*P* = .25) Physical fatigue **1.10** (*P* = .71)	 General fatigue **1.18** (*P* = .72) Reduced motivation **0.85** (*P* = .84)
Other		
Rugbjerg 2019 [8] Retrospective cohort of Danish >5 y HL survivors treated with RT when aged 15-39 y 1943-2004 (n=1684); median f/u 19.2 y; comparator general pop	**SHHR** Haematological **3.77** (2.75-5.18) Endocrine **2.22** (1.77-2.77) Benign neoplasm **1.69** (1.34-2.11) Nervous system **1.76** (1.38-2.24) Ear **0.79** (0.40-1.59)	 Skin **1.49** (1.10-2.00) Eye **1.53** (0.98-2.40) Urogenital **1.17** (1.00-1.36) Musculoskeletal **0.93** (0.76-1.13)
de Vries 2021 [12] Retrospective cohort of HL survivors treated in the Netherlands 1965-2000 (n=4919); median f/u 20.2 y	**SMR** Haematological **12.1** (5.2-23.9) Endocrine **1.7** (0.9-2.9) Mental **1.1** (0.4-2.6) Nervous system **1.3** (0.6-2.4) Genitourinary **1.6** (0.4-4.2)	**AEM** (/ 10,000 py) Haematological **0.8** Endocrine **0.5** Mental **0.1** Nervous system **0.2** Genitourinary **0.2**
Rugbjerg 2017 [23] Retrospective cohort treated in Denmark when aged 15-39 y 1943-2004 (n=1768); median f/u 14.4 y; comparator population age-matched general population	**RR** (hospitalisation) Urogenital **1.1** (0.9-1.4) Renal failure **1.9** (0.6-6.0) **AERs** (/ 10,000 py) Endocrine **10** (0-20) Benign neoplasms **25** (13-38) Nervous system **10** (0-20) Musculoskeletal **-14** (-27-1) Ear & mastoid **0** (-4-4)	 Haematological **3.1** (1.9-5.0) Nervous system **1.5** (1.1-2..1) Non-malignant haem **10** (3-17) Skin & subcutaneous **6** (-4-15) Urogenital **7** (-9-22) Renal failure **1** (-2-4) Eye **2** (-3-7)

Lagerlöf 2022 [26] Retrospective cohort of patients treated for HL with 2/4 cycles ABVD and 30 Gy limited-field RT in Sweden 1999-2003; median f/u 16 y	**HR**, VTE **3.7** (1.9-7.2) (not significant if events <6 m from HL diagnosis excluded & patients and comparators censored at diagnosis malignancy / HL relapse) Variation in risk by time since treatment: **HR** 0-5 y **15.0** (4.2-53.9) (*P* < .0001) >10 y **2.1** (0.6-7.0) (*P* = .224) 5-10 y **1.1** (0.2-5.0) (*P* = .949)

Numbers given in brackets after risk estimates are 95% confidence intervals. Where no confidence intervals are displayed this is because none were presented in the paper.

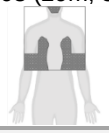
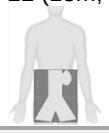
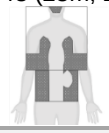
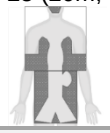
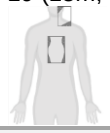
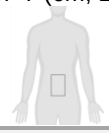
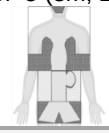
Abbreviations – y: years; HL: Hodgkin lymphoma; n; number; f/u: follow-up; RT: radiotherapy; f: female; m: male; IFRT: involved-field radiotherapy; ISRT: involved-site radiotherapy; TLI: total lymphoid irradiation; PAN: para-aortic node; CMT: combined modality therapy; STNI: subtotal nodal irradiation; SD: standard deviation; SIR: standardised incidence ratio; SHRR: Standardised hospitalisation rate ratio: SMR: standardised mortality ratio; AEM: absolute excess mortality; py: person-years; RR: relative risk; AER: absolute excess risk; SD: supradiaphragmatic; ID: infradiaphragmatic; TB: tuberculosis; ABVD: doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine; VTE: venous thromboembolism

Appendix D

Supplementary material to Chapter 4

Appendix D1. Doses to abdominopelvic organs-at-risk, split by radiotherapy field type

Table D1: Mean organ-at-risk doses, as absolute dose, split by radiotherapy field type

	Mantle n=68 (29m, 39f)	**Inverted-Y** n=22 (18m, 4f)	**STNI** n=43 (28m, 15f)	**TNI** n=25 (20m, 5f)	**IFRT SD** n=19 (15m, 4f)	**IFRT ID** n=7 (6m, 1f)	**(S)TNI + ID*** n=5 (3m, 2f)
							
	Mean OAR dose: Median (interquartile range)						
Whole colon	**<0.5** (-)	**23.0** (18.6-25.3)	**9.9** (6.5-14.1)	**21.9** (19.7-25.7)	**<0.5** (-)	**7.2** (6.6-10.3)	**17.1** (15.4-22.6)
Caecum	**<0.5** (-)	**26.6** (16.7-35.0)	**0.8** (0.3-1.3)	**34.0** (21.3-39.9)	**<0.5** (-)	**12.2** (1.2-23.6)	**14.1** (9.8-28.8)
Ascending colon	**<0.5** (-)	**7.4** (4.3-10.3)	**2.2** (1.4-3.1)	**5.8** (4.1-14.9)	**<0.5** (-)	**1.5** (0.7-7.4)	**12.4** (5.2-13.6)
Hepatic flexure	**0.5** (0.3-0.7)	**14.4** (7.7-18.9)	**7.6** (4.2-15.9)	**14.4** (9.9-20.4)	**<0.5** (-)	**0.5** (0.2-6.3)	**13.3** (8.1-19.4)
Transverse colon	**<0.5** (-)	**25.4** (20.5-28.6)	**23.7** (18.8-28.4)	**26.7** (19.4-30.2)	**<0.5** (-)	**1.1** (0.4-13.7)	**25.8** (18.8-27.0)
Splenic flexure	**1.1** (0.7-1.7)	**31.0** (17.0-39.4)	**33.8** (6.5-38.5)	**21.4** (5.5-37.1)	**<0.5** (-)	**<0.5** (-)	**26.4** (20.2-27.6)
Descending colon	**<0.5** (-)	**9.6** (4.6-14.5)	**5.7** (2.6-12.2)	**5.4** (4.3-16.6)	**<0.5** (-)	**1.2** (0.3-2.4)	**7.9** (5.5-9.0)
Whole sigmoid	**<0.5** (-)	**30.2** (25.0-36.6)	**0.7** (0.5-0.9)	**32.0** (27.0-35.1)	**<0.5** (-)	**20.9** (3.0-24.6)	**28.0** (13.9-35.1)
Sigmoid	**<0.5** (-)	**10.6** (7.7-23.7)	**1.1** (0.8-1.7)	**9.8** (7.7-18.4)	**<0.5** (-)	**4.0** (0.8-21.1)	**20.2** (3.7-23.4)
Rectosigmoid	**<0.5** (-)	**34.5** (27.3-41.8)	**0.6** (0.4-0.9)	**39.5** (29.7-41.2)	**<0.5** (-)	**22.8** (3.3-26.8)	**29.8** (11.8-40.0)
Rectum	**<0.5** (-)	**25.0** (17.2-31.2)	**<0.5** (-)	**21.7** (18.7-32.2)	**<0.5** (-)	**8.4** (4.6-16.7)	**14.2** (10.9-29.3)
Anal canal	**<0.5** (-)	**4.9** (2.8-7.3)	**<0.5** (-)	**3.9** (2.6-5.0)	**<0.5** (-)	**2.9** (0.5-4.0)	**7.0** (5.6-15.2)
Stomach	**4.6**	**32.7**	**36.7**	**28.0**	**0.5**	**0.5**	**35.2**

	(2.9-7.7)	(21.6-36.6)	(24.3-42.8)	(21.6-39.3)	(0.0-1.2)	(0.0-14.5)	(34.9-35.7)
Duodenum	**0.7** (0.6-1.1)	**30.6** (27.4-37.0)	**32.1** (26.9-35.8)	**35.4** (31.8-38.4)	**<0.5** (-)	**1.1** (0.2-22.6)	**31.2** (22.8-38.0)
Small bowel	**<0.5** (-)	**26.1** (21.7-30.1)	**11.8** (8.1-14.3)	**26.5** (23.5-28.6)	**<0.5** (-)	**12.7** (5.2-17.2)	**22.1** (16.2-23.6)
Liver	**6.2** (4.5-8.3)	**11.0** (7.4-16.7)	**16.0** (11.8-18.4)	**16.7** (12.7-19.6)	**0.8** (0.0-3.3)	**1.0** (0.0-8.8)	**13.5** (7.7-19.6)
Gallbladder	**0.8** (0.6-1.3)	**7.0** (5.3-12.5)	**7.0** (3.6-14.2)	**7.5** (5.7-12.4)	**0.3** (0.0-0.6)	**0.4** (0.0-2.2)	**5.6** (4.5-7.9)
Pancreas	**1.3** (1.0-2.2)	**35.5** (26.7-39.2)	**36.0** (29.3-40.4)	**36.3** (31.4-39.5)	**<0.5** (-)	**0.5** (0.0-24.7)	**34.9** (34.3-35.5)
Pancreatic tail	**1.7** (1.3-2.5)	**36.9** (25.2-38.8)	**35.2** (27.2-40.8)	**35.4** (28.2-39.5)	**<0.5** (-)	**0.5** (0.0-17.5)	**34.2** (33.8-34.8)
Spleen	**2.5** (1.7-3.8)	**31.6** (18.1-41.4)	**32.3** (9.2-43.9)	**16.8** (10.9-36.4)	**0.6** (0.0-1.0)	**0.4** (0.0-4.4)	**29.9** (11.6-38.1)
Kidneys	**0.9** (0.6-1.4)	**19.2** (14.4-20.7)	**15.6** (11.8-20.7)	**16.2** (14.1-19.8)	**<0.5** (-)	**0.8** (0.1-6.8)	**15.8** (12.3-20.2)
Left kidney	**1.0** (0.7-1.8)	**21.8** (15.2-28.9)	**19.4** (13.1-27.6)	**19.5** (13.6-22.9)	**<0.5** (-)	**0.6** (0.1-6.3)	**16.5** (16.1-22.0)
Right kidney	**0.6** (0.4-1.0)	**12.9** (9.3-18.2)	**11.7** (9.3-14.5)	**13.2** (8.8-20.8)	**<0.5** (-)	**1.0** (0.1-7.2)	**13.1** (8.1-15.0)
Bladder	**<0.5** (-)	**24.9** (16.6-40.3)	**<0.5** (-)	**26.3** (19.7-30.0)	**<0.5** (-)	**12.0** (9.0-15.3)	**19.8** (13.8-37.7)
Prostate & SVs	**<0.5** (-)	**18.3** (14.7-21.6)	**<0.5** (-)	**17.5** (13.1-24.5)	**<0.5** (-)	**7.9** (5.1-11.2)	**16.7** (14.9-27.0)
Penile bulb	**<0.5** (-)	**2.9** (1.9-4.4)	**<0.5** (-)	**2.3** (1.6-3.8)	**<0.5** (-)	**1.5** (0.5-3.8)	**7.1** (5.7-19.4)
Testes	**<0.5** (-)	**3.3** (1.3-4.9)	**<0.5** (-)	**3.1** (1.3-6.7)	**<0.5** (-)	**<0.5** (-)	**9.4** (6.4-14.5)
Vagina / uterus	**<0.5** **(-)**	**20.1** (18.3-31.6)	**<0.5** (-)	**24.3** (13.7-24.6)	**<0.5** (-)	**7.8** (-[§])	**24.9** (1.0-48.8)

[*]Subtotal or total nodal irradiation given as primary treatment, with additional infradiaphragmatic radiotherapy field(s) at the time of relapse. Para-aortic and spleen field shown here in light grey, as an example of a field given on relapse.
[§]Only one dose in this category
Abbreviations - STNI: subtotal nodal irradiation; TNI: total nodal irradiation; IFRT: involved field radiotherapy; SD: supradiaphragmatic; ID: infradiaphragmatic; OAR: organ-at-risk; SVs: seminal vesicles

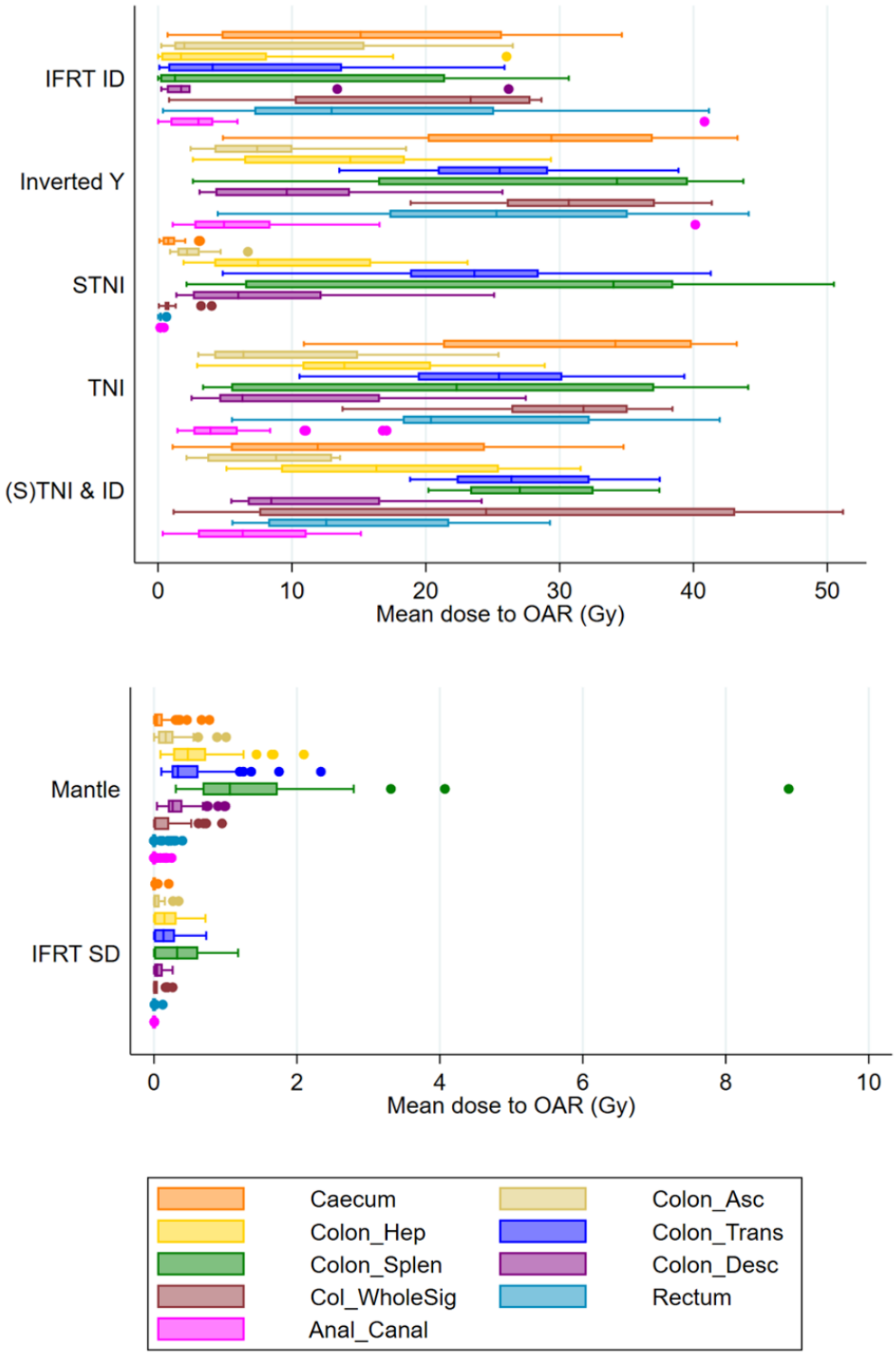


Figure D1: Box and whisker plot displaying doses to large bowel, split by radiotherapy field type

Abbreviations - IFRT: involved field radiotherapy; ID: infradiaphragmatic; STNI: subtotal nodal irradiation; TNI: total nodal irradiation; OAR: organ-at-risk; Gy: gray; SD: supradiaphragmatic; Colon_Hep: hepatic flexure; Colon_Splen: splenic flexure; Col_WholeSig: sigmoid colon; Colon_Asc: ascending colon; Colon_Trans: transverse colon; Colon_Desc: descending colon

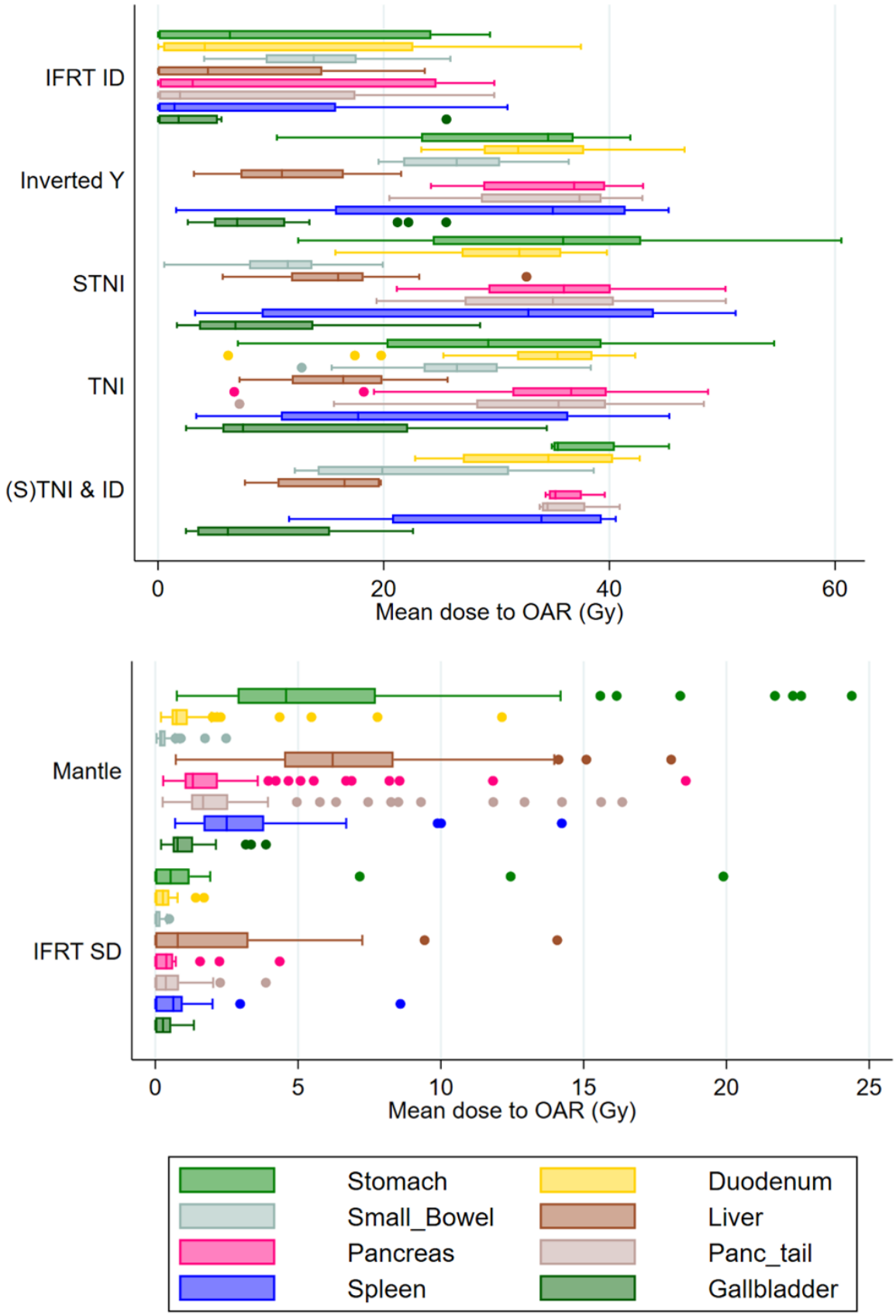


Figure D2: Box and whisker plot displaying doses to gastrointestinal organs-at-risk (excluding large bowel), split by radiotherapy field type

Abbreviations - IFRT: involved field radiotherapy; ID: infradiaphragmatic; STNI: subtotal nodal irradiation; TNI: total nodal irradiation; OAR: organ-at-risk; Gy: gray; SD: supradiaphragmatic; Panc_tail: pancreatic tail

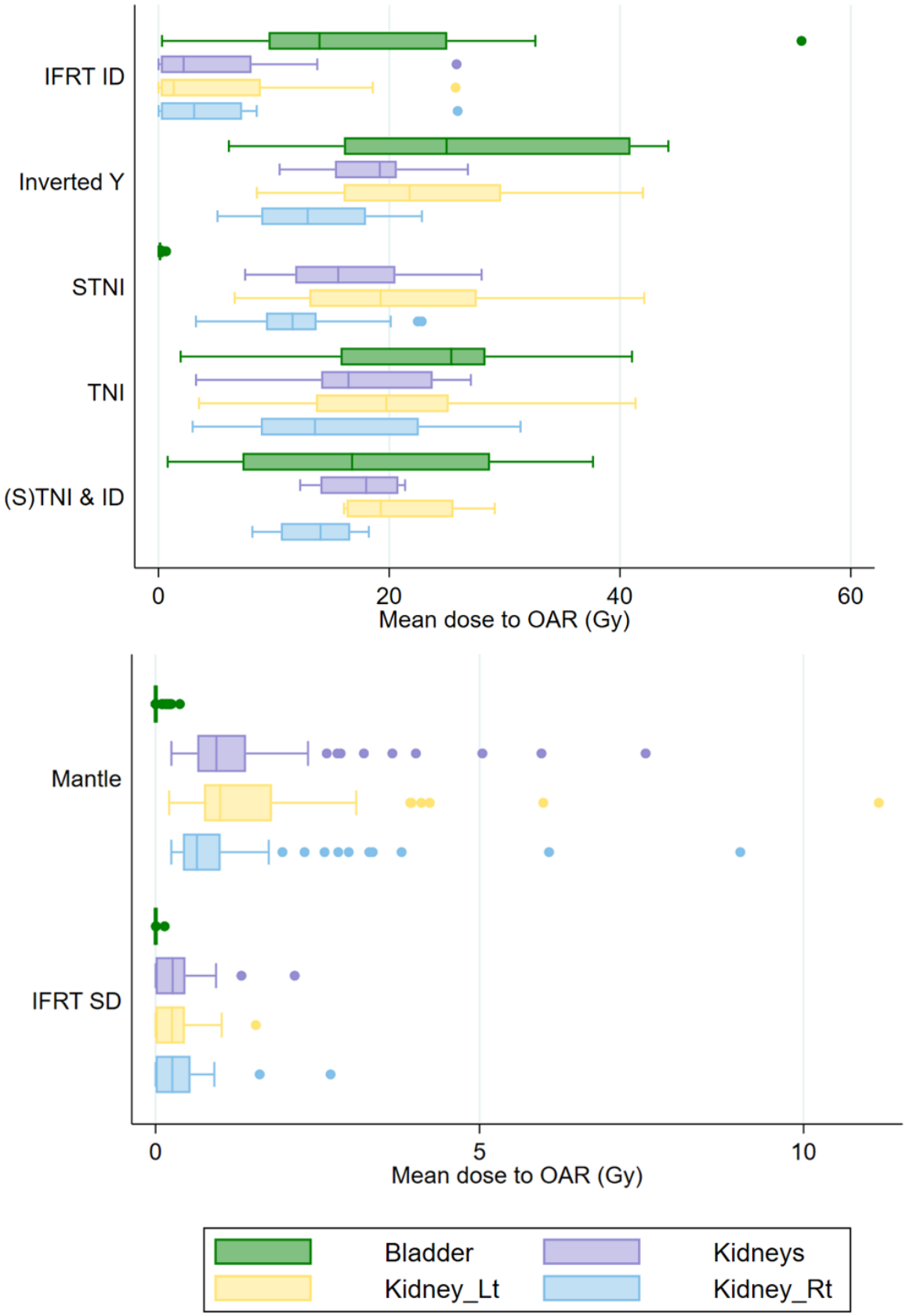


Figure D3: Box and whisker plot displaying doses to urinary organs-at-risk, split by radiotherapy field type

Abbreviations - IFRT: involved field radiotherapy; ID: infradiaphragmatic; STNI: subtotal nodal irradiation; TNI: total nodal irradiation; OAR:organ-at-risk; Gy: gray; SD: supradiaphragmatic; Lt: left; Rt: right

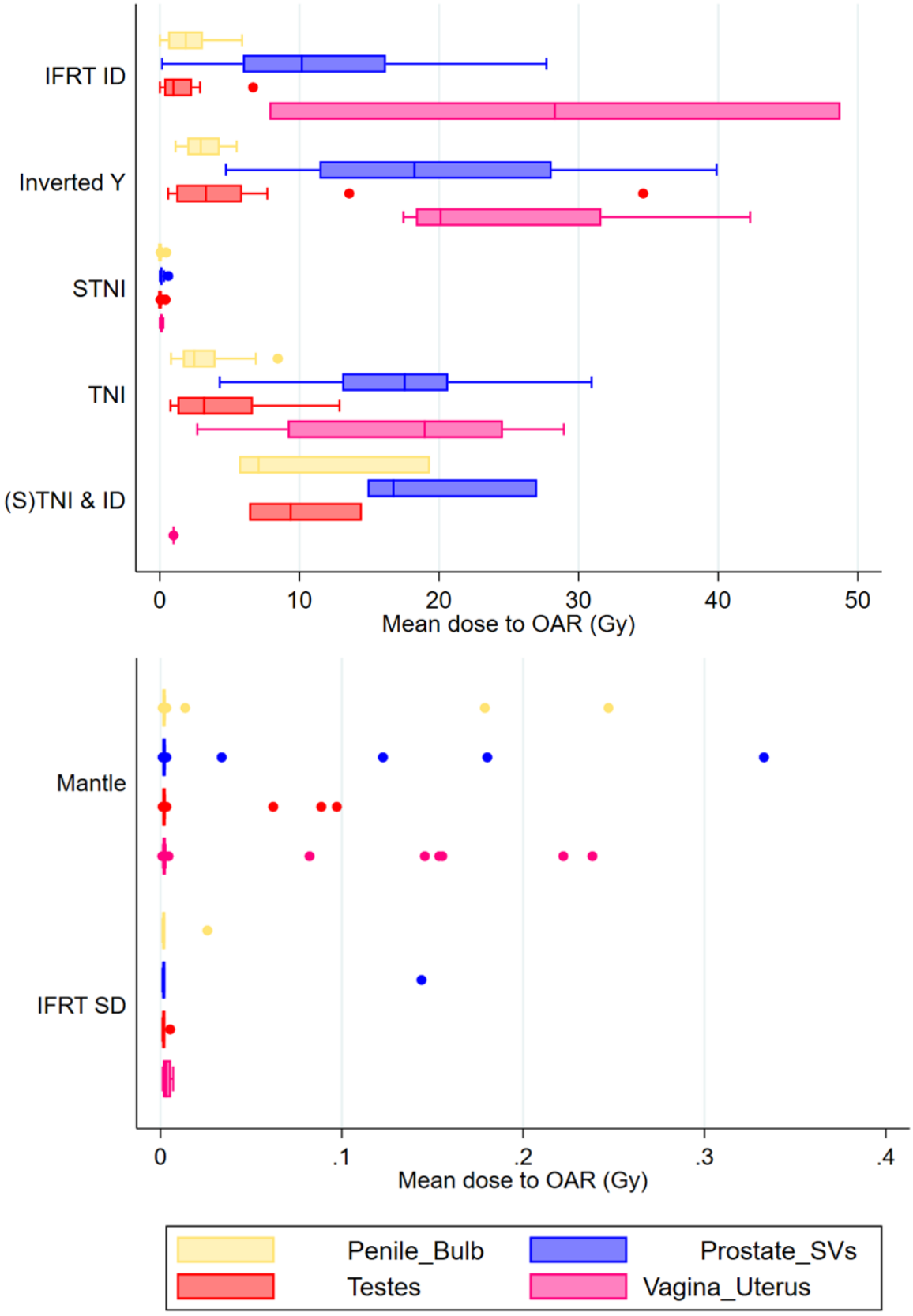


Figure D4: Box and whisker plot displaying doses to genitalia, split by radiotherapy field type

Abbreviations - IFRT: involved field radiotherapy; ID: infradiaphragmatic; STNI: subtotal nodal irradiation; TNI: total nodal irradiation; OAR: organ-at-risk; Gy: gray; SD: supradiaphragmatic; SVs: seminal vesicles

Appendix E

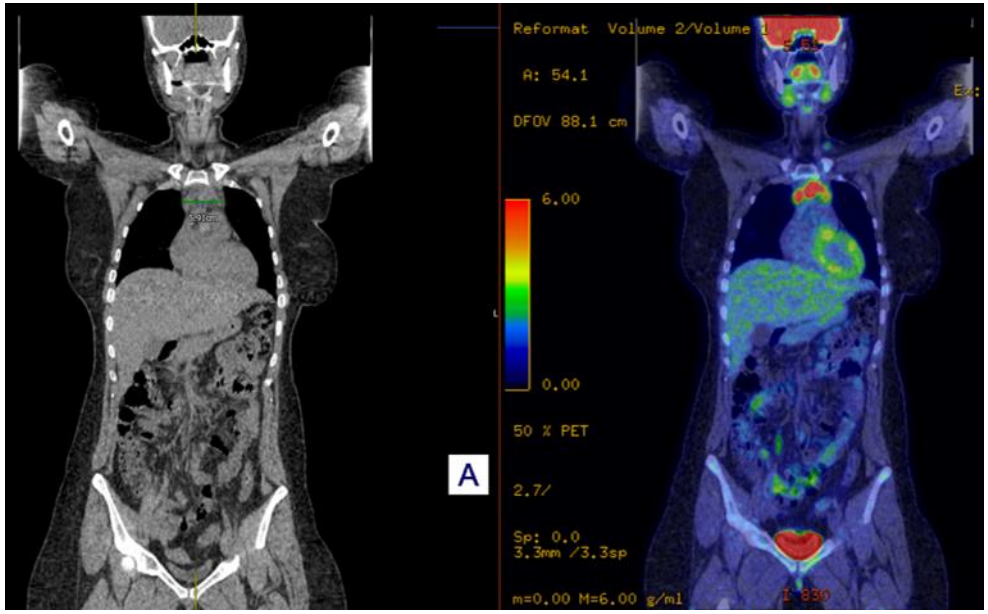
Supplementary material to Chapter 5

Appendix E1: Study guide

PET Study: Instructions for Data Collection from PET-CT

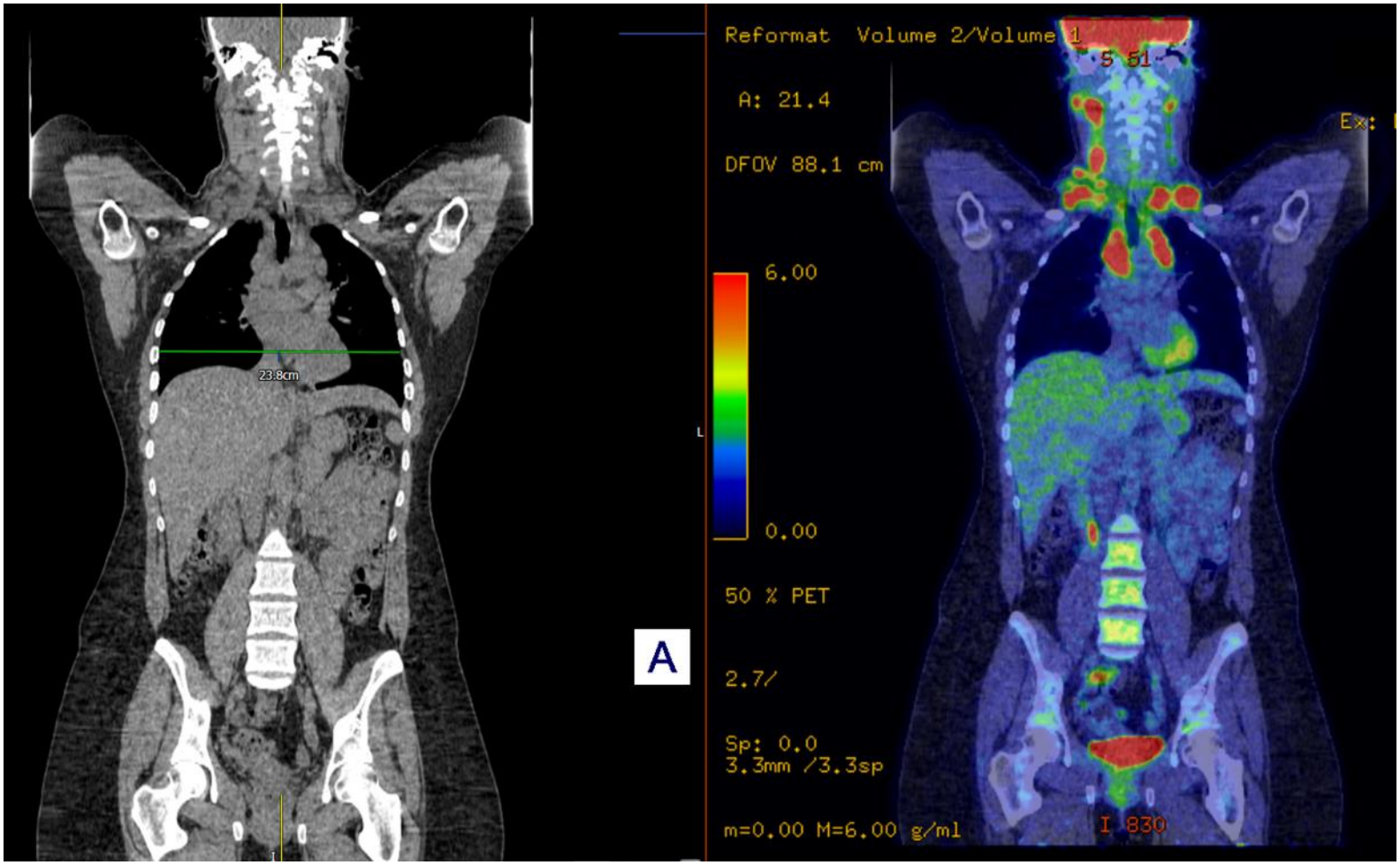
Maximum width of mediastinal disease (cm)

For this study, the superior aspect of the mediastinum is defined as the superior border of T1, and the inferior aspect as the crura of the diaphragm. maximum width of PET-positive mediastinal disease is determined by scrolling through the axial or coronal views of the PET component of the PET-CT. The measurement is then taken in centimetres from the corresponding slice of the CT component. The measurement should be of contiguous disease. However, where the disease wraps around mediastinal structures such as the trachea, the maximum width can include those structures if they would be included in the PTV. This is 5.91 cm in this example:



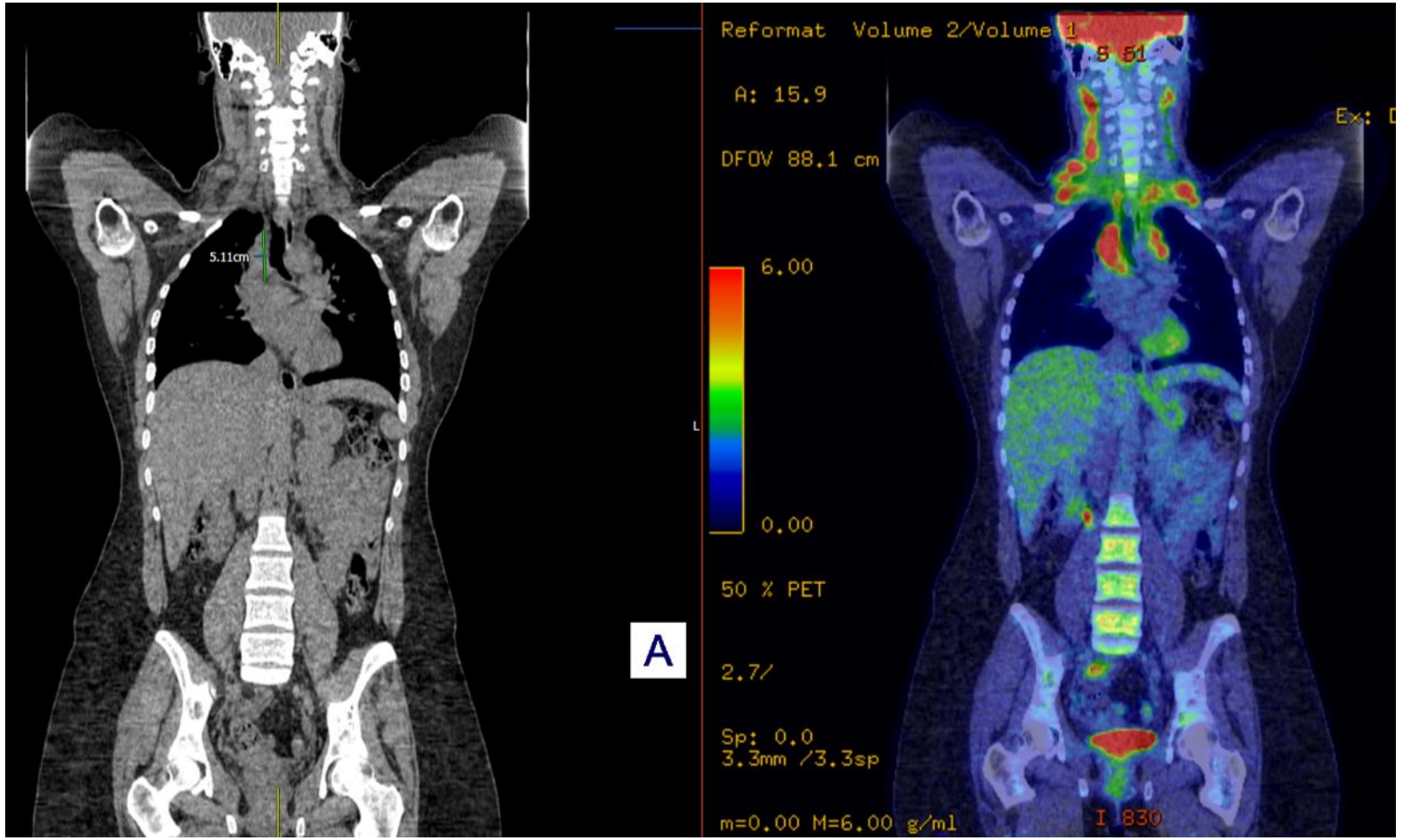
Thoracic cavity width (cm)

The width of the thoracic cavity at its widest point in centimetres, measured from inner rib to inner rib on either the axial or coronal view of the CT component of the PET-CT scan. This is 23.8 cm in this example:



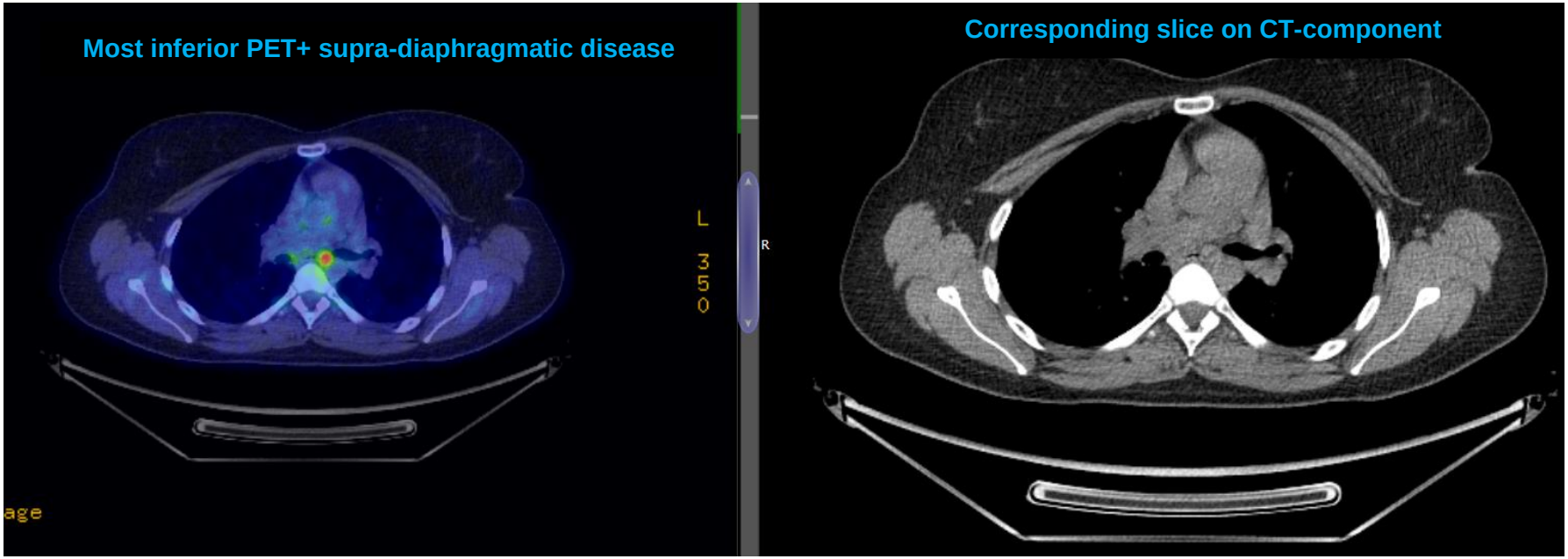
Maximum length of mediastinal disease (cm)

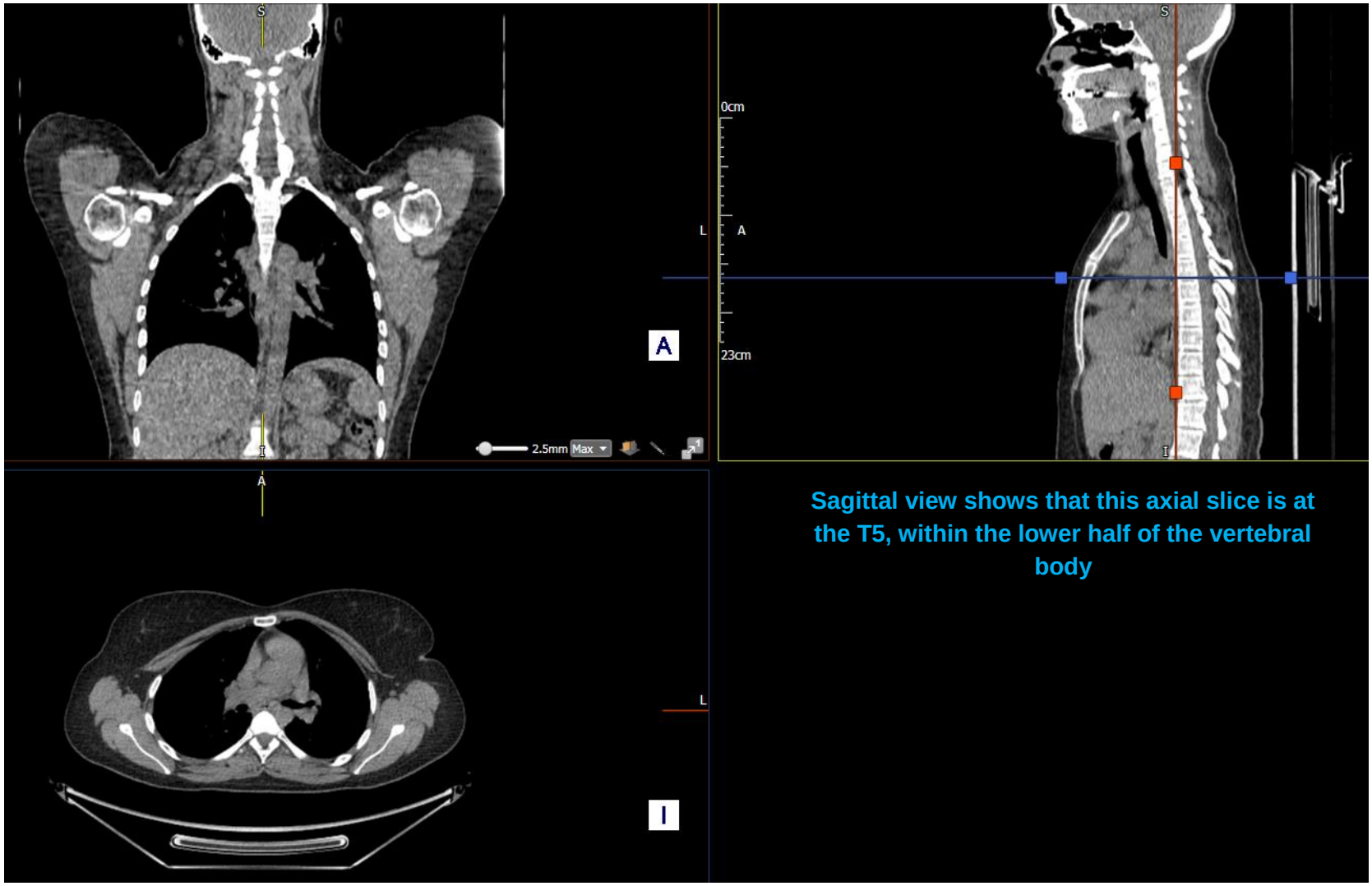
The maximum vertical length of contiguous PET-positive mediastinal disease is determined by scrolling through the coronal views of the PET component of the PET-CT. The measurement is then taken in centimetres from the corresponding slice of the CT component. This is 5.11 cm in this example:



Inferior vertebral level

The most inferior slice containing supradiaphragmatic PET-positive disease is identified on the axial views of the PET component of the PET-CT. The corresponding slice on the axial component of the CT component of the PET-CT is identified, and the saggital view used to determine the vertebral level at this slice. Once the vertebra itself has been determined, T5 in this example, the vertebral level should be reported as “upper” if the most inferior axial slice is within the upper half of the vertebra, “lower” if it is within the lower half, and “mid” if it is halfway (lower T5 in this example). If the axial slice is within a disc space this should be recorded as e.g. T5/6 disc space.

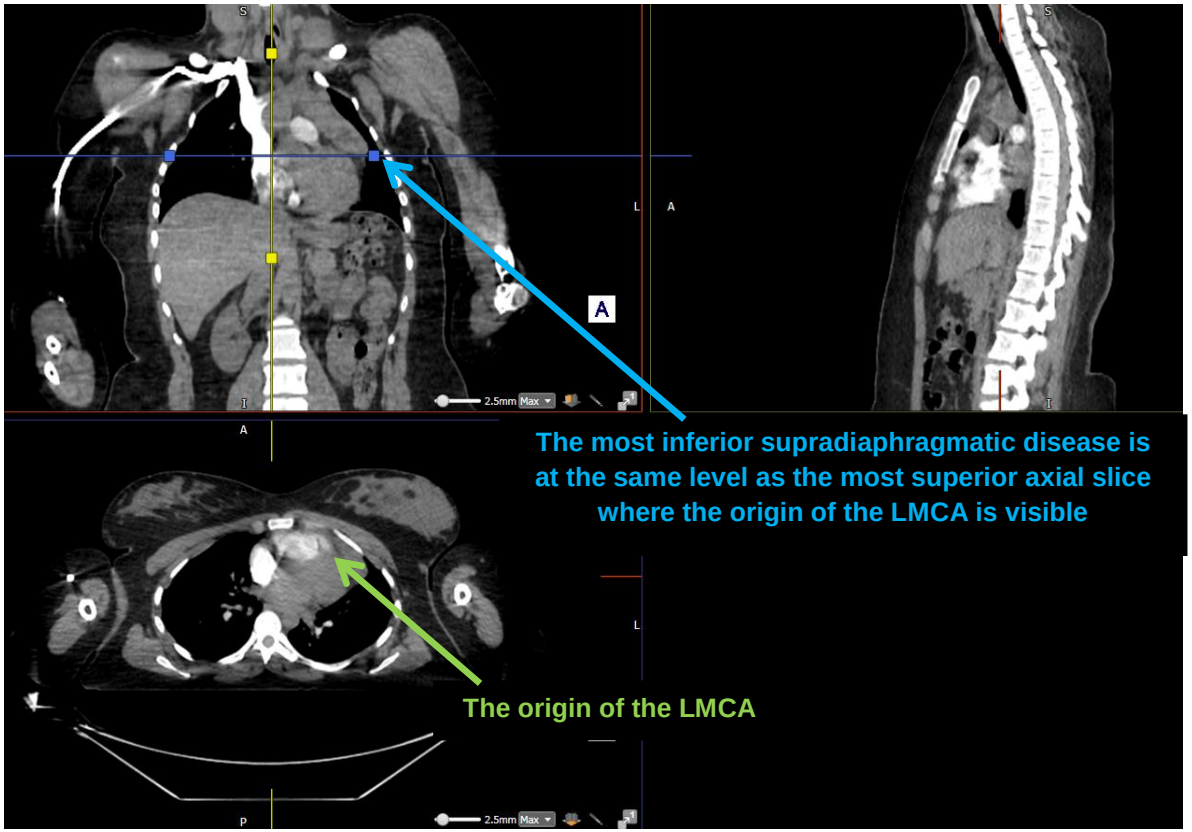




If there is also infradiaphragmatic disease the same assessment should be made for the inferior vertebral level of infra-diaphragmatic disease, and noted down separately in the data collection spreadsheet.

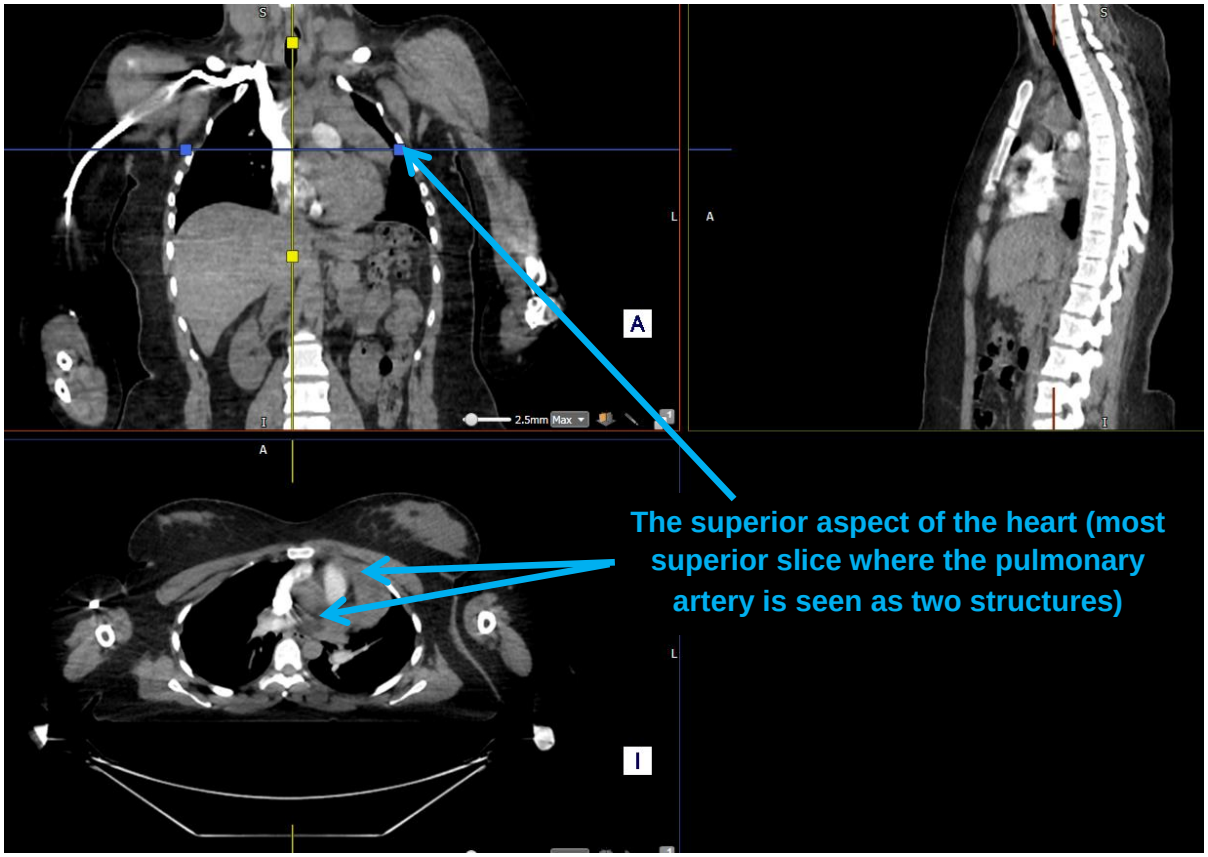
Above or below the origin of the left main coronary artery

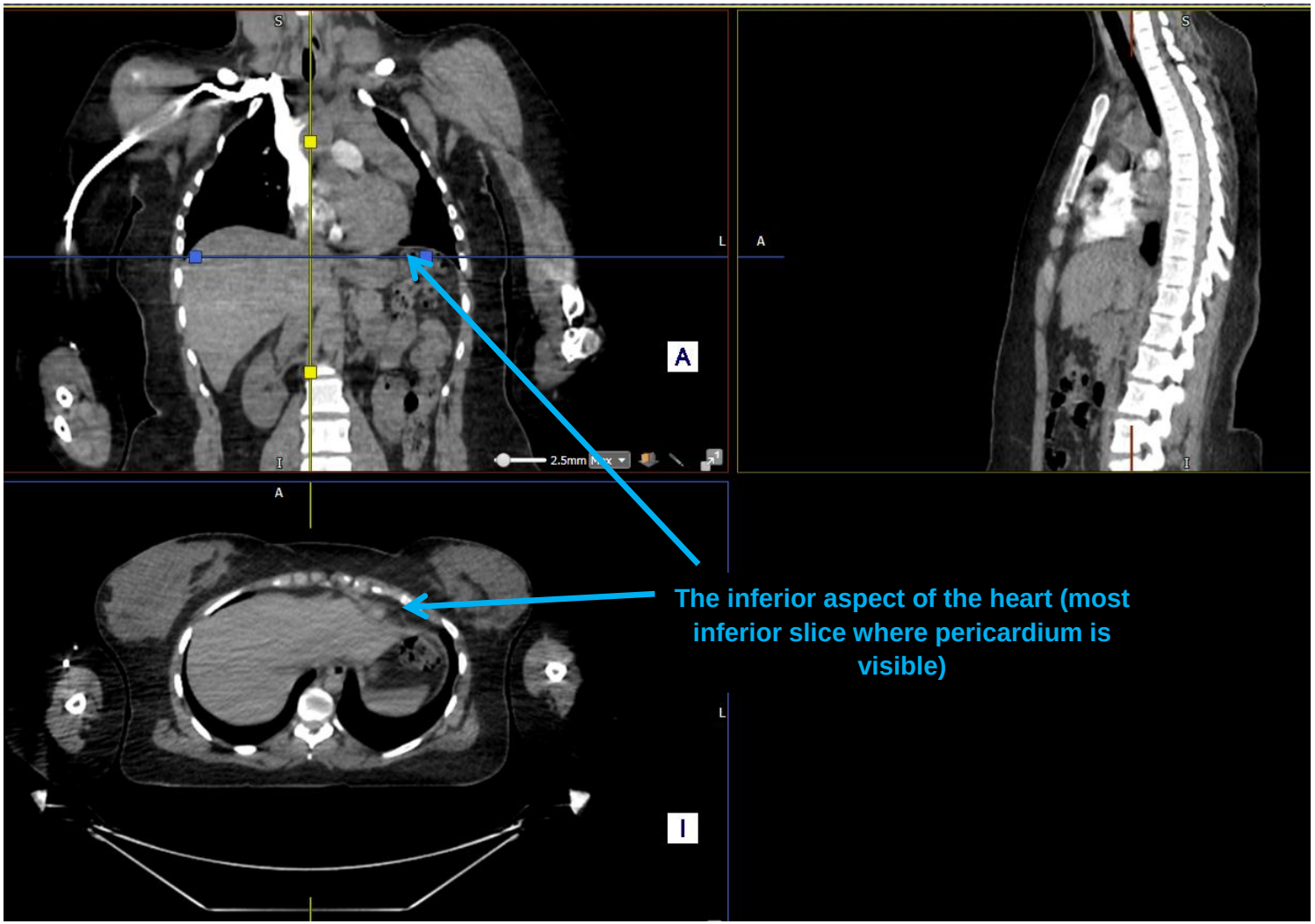
The origin of the left main coronary artery (LMCA) should be identified on the axial slices of the CT component of the PET-CT. The LMCA is a branch of the ascending aorta, with its normal origin in the left aortic sinus, just superior to the aortic valve. It can be difficult to identify on PET-CT scans, so please contact us if you are having difficulty identifying the origin of the LMCA on your scans.
Once the LMCA is identified, determine whether the most superior axial CT slice where it is visible is above or below the axial CT slice which contains the most inferior supradiaphragmatic PET-positive disease.
In the example below, the most inferior supradiaphragmatic PET-positive disease is at the level of the origin of the LMCA, and is recorded as being “at the level” (i.e. this variable can be recorded as either “above”, “below”, or “at the level” of the LMCA).

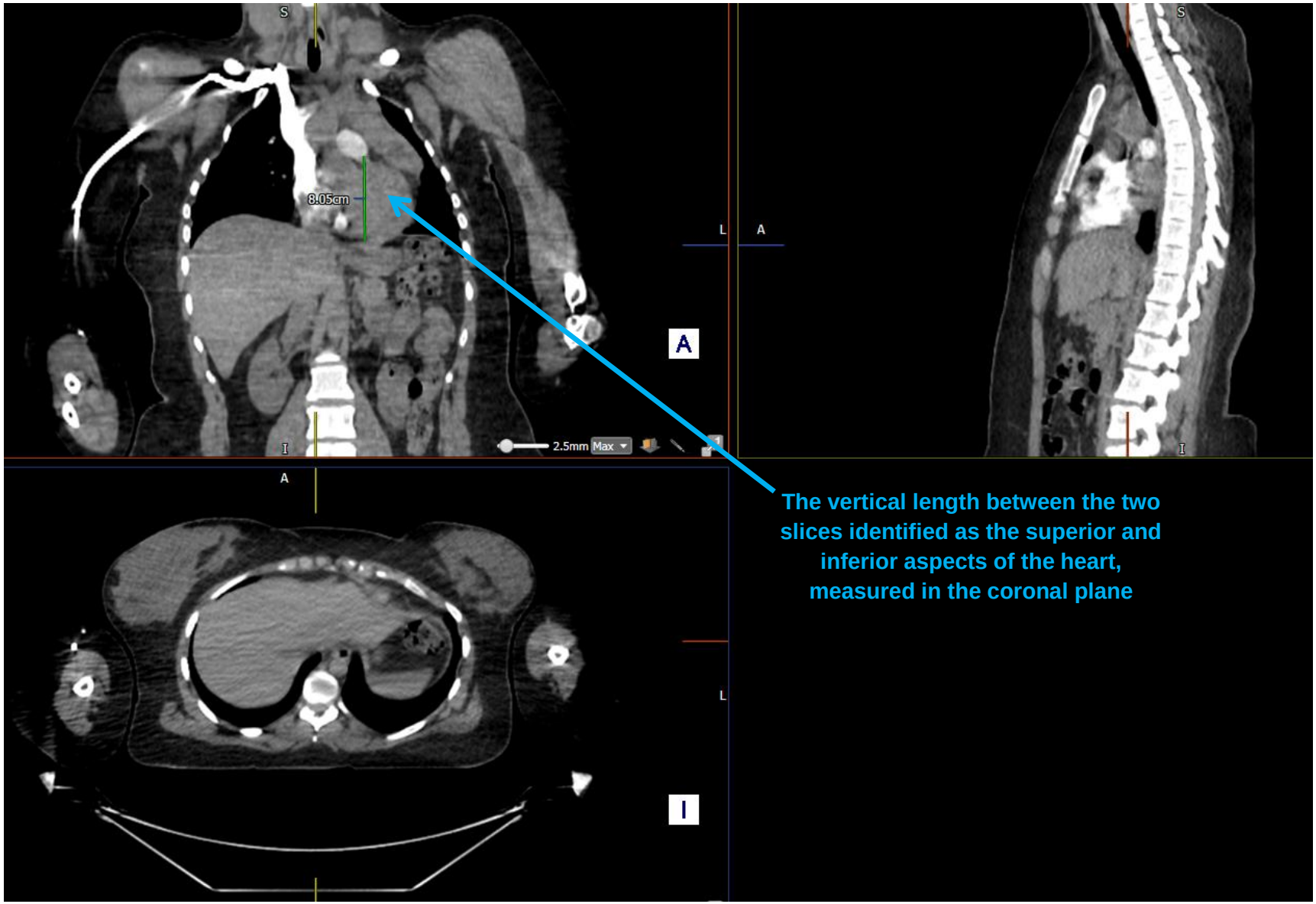


Vertical length of the heart (cm)

The superior aspect of the heart is defined as the most superior axial CT slice where the pulmonary artery is seen as two separate structures, as described in the RTOG heart contouring atlas, https://www.eviq.org.au/getmedia/a4c012a8-d6a7-4d87-93f7-d3f465b49889/RTOG-heart-contouring-atlas.pdf.aspx?ext=.pdf. The inferior aspect is the most inferior axial CT slice where the pericardium is visible, as shown in the RTOG atlas. Once identified, the vertical length between the superior and inferior aspects of the heart can be measured on the coronal slices of the CT component of the PET-CT. This is 8.05 cm in the example below:

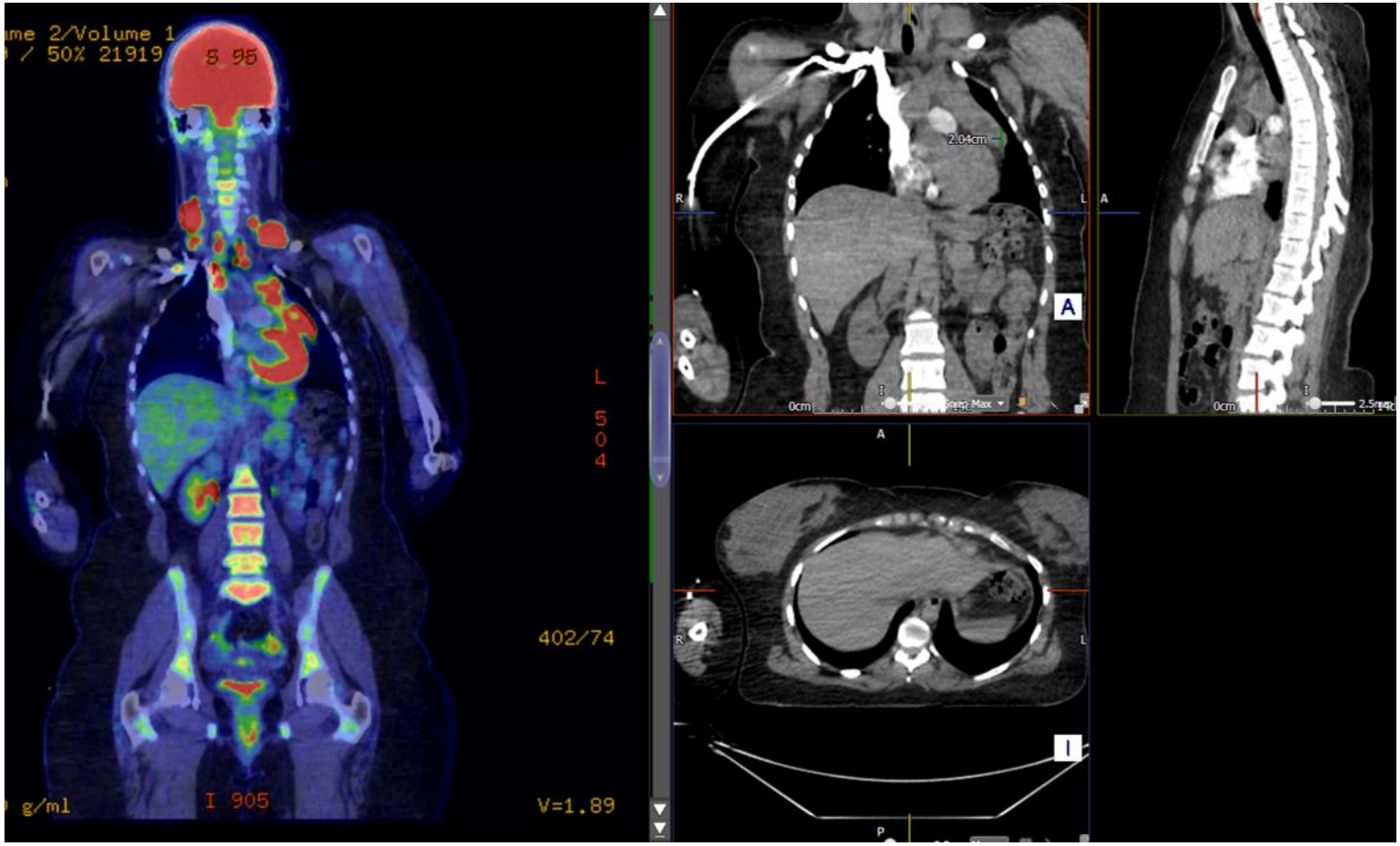



S
L
A
A
2.5mm
I
S
I
A
L
I
The inferior aspect of the heart (most inferior slice where pericardium is visible)


S
8.05cm
L
A
A
I
2.5mm Max
S
I
A
L
I
The vertical length between the two slices identified as the superior and inferior aspects of the heart, measured in the coronal plane

Length of heart overlap (cm)

The maximal vertical length of PET-positive disease overlapping the heart. This is measured in centimetres on the coronal slices of the CT component, as the distance between the superior aspect of the heart (as defined above), and the most inferior slice of contiguous PET-positive disease. This is 2.04 cm in this example:



Length of contiguous neck and mediastinal disease (cm)

The maximum vertical length of contiguous supra-diaphragmatic PET-positive disease is determined by scrolling through the coronal views of the PET component of the PET-CT. The measurement is then taken in centimetres from the corresponding slice of the CT component. This is 17.2 cm in this example:



Appendix E2: Calculation of 30-year cumulative absolute excess risk of ischaemic heart disease

Table E1: Crude and age-standardised rates of ischaemic heart disease, by age and sex

Age (yrs)	Female	Male	Both
	Rate* *95% CI*	Rate* *95% CI*	Rate* *95% CI*
1-9	-- -	-- -	-- -
10-19	-- -	-- -	-- -
20-29	31 *19 - 51*	57 *41 - 81*	45 *34 - 60*
30-39	115 *91-146*	299 *258 - 345*	207 *183 - 235*
40-49	481 *436 - 531*	1374 *1296 - 1457*	928 *883 - 976*
50-54	967 *873 - 1070*	2924 *2758 - 3099*	1947 *1851 - 2048*
55-59	1357 *1238 - 1488*	4178 *3963 - 4406*	2753 *2629 - 2882*
60-64	1923 *1779 - 2078*	5028 *4782 - 5285*	3420 *3279 - 3566*
65-69	2488 *2314 - 2674*	5619 *5338 - 5915*	3955 *3792 - 4124*
70-74	3847 *3596 - 4115*	7771 *7372 - 8191*	5607 *5379 - 5844*
75-79	5754 *5411 - 6118*	9611 *9091 - 10,161*	7382 *7083 - 7692*
80-84	8074 *7599 - 8579*	12,513 *11,765 - 13,308*	9781 *9368 - 10,213*
85+	13,384 *12,746 - 14,054*	17,790 *16,707 - 18,943*	14,762 *14,203 - 15,342*
No. cases	7197	11,464	18,660
Person yrs	4,892,483	4,773,726	9,666,209
Crude rate	1471 *1437 - 1505*	2401 *2358 - 2446*	1930 *1903 - 1958*
Age-std	1454 *1421 - 1488*	2857 *2805 - 2910*	2091 *2061 - 2121*

*Rates are given per 1,000,000 person-years. Cases and person-years are numbers; all other figures are rates.
Abbreviations – yrs: years; CI: confidence interval; No.cases: total number of cases; Person yrs: Total person-years; Age-std: age-standardised

Method for calculating 30-year absolute excess risk of ischaemic heart disease

The estimated 30-year cumulative absolute excess risk (AER) of ischaemic heart disease (IHD) for each participant, taking into account the background incidence of IHD in the population, was calculated as follows.

Step 1: The probability of each individual developing IHD each year, up to 30 years, was calculated from background incidence rates (Table D1), based on their sex and age at time of radiotherapy. This value did not take into account any excess risk from radiotherapy, and was considered as the participant's background risk of developing IHD if they did not receive radiotherapy.

Step 2: Each participant's excess relative risk of IHD from radiotherapy was calculated by multiplying their mean heart dose (MHD) with the excess rate ratio (ERR) per gray from van Nimwegen's study [33]. The ERR/Gy used depended on the patient's age at radiotherapy:

Aged below 28 years: 0.20 / Gy

Aged 28-36 years: 0.088 / Gy

Aged over 36 years: 0.042 / Gy

Step 3: Each participant's absolute risk of IHD was calculated by multiplying their background risk (from step 1) by their excess relative risk (from step 2). This represented the probability of each individual developing IHD each year, up to 30 years, if they were treated with radiotherapy.

Step 4: Each participant's AER of IHD was calculated as the difference between their background risk (step 1) and their risk if they were treated with radiotherapy (step 3), for each year after treatment, up to 30 years.

Step 5: Each participant's cumulative AER of IHD 30 years after radiotherapy was calculated as the sum of the AER for each year after radiotherapy, up to 30 years.

This method has previously been used by my research group to estimate the predicted risks of CVD in patients treated in the RAPID clinical trial [32].

Appendix E3: Results of univariable analyses

Table E2: Univariable analysis of analogous candidate predictors and those considered probably to be unrelated

Variable	Adjusted R^2	Prob >F	Coefficient
Length heart overlap	0.1847	0.0000	2.7913
Percentage heart overlap	0.1925	0.0000	0.2870
Length mediastinal disease	0.0245	0.0264	0.7416
Inferior vertebral level	0.1818	0.0000	Multiple
Above or below T7	0.1374	0.0000	Below 13.9034 At 1.9815
Above or below LMS	0.1562	0.0000	Below 14.5762 At 1.9815
Width mediastinal disease	0.1443	0.0000	1.8771
Disease thoracic width ratio	0.1234	0.0000	45.3073
Sex	-0.0013	0.3763	Female 2.4308
Age	-0.0055	0.7278	-0.0352
Disease stage	0.0121	0.1770	Multiple
Relapse	-0.0045	0.5983	2.4005
PET date	0.1291	0.0007	Multiple
Treatment centre	0.1582	0.0000	Multiple
Axillary disease	-0.0008	0.3540	-2.7742
Neck disease	-0.0052	0.6891	-1.1267
SCF disease	-0.0062	0.9837	0.0717
Subcarinal disease	0.0385	0.0071	-8.4708
Axillary radiotherapy	0.0027	0.2316	-4.2932
Neck radiotherapy	-0.0008	0.87	2.6503
SCF radiotherapy	-0.0011	0.3711	-2.5445

Appendix E4: Comparison of mean heart doses, and 30-year absolute excess risks of ischaemic heart disease, between the radiotherapy plan and the model

Table E3: Mean heart dose from the radiotherapy plan and from the model for each study participant, with subsequent 30-year cumulative absolute excess risk estimates for ischaemic heart disease

Study ID	Mean heart dose			30-year cumulative AER IHD		
	RT plan	Model	Difference	RT plan	Model	Difference
192	0.08	8.25	-8.17	0.02	2.31	-2.29
187	0.17	3.85	3-3.68	0.07	1.48	-1.41
203	0.20	2.67	-2.47	0.04	0.52	-0.48
175	0.37	4.05	-3.68	0.10	1.09	-0.99
105	0.44	2.03	-1.59	0.13	0.60	-0.47
163	0.52	6.71	-6.19	0.11	1.38	-1.27
149	0.57	2.80	-2.23	0.18	0.87	-0.69
206	0.58	5.05	-4.47	0.17	1.49	-1.32
83	1.02	3.45	-2.43	0.20	0.68	-0.48
208	1.04	2.76	-1.72	0.23	0.62	-0.39
166	1.12	9.33	-8.21	0.38	3.15	-2.77
98	1.16	2.58	-1.42	0.50	1.10	-0.60
89	1.36	5.17	-3.81	0.78	2.98	-2.20
178	1.38	9.46	-8.08	0.35	2.40	-2.05
124	1.40	3.83	-2.43	0.24	0.66	-0.42
102	1.44	1.61	-0.17	0.59	0.65	-0.06
108	1.45	3.48	-2.03	0.72	1.74	-1.02
86	1.49	3.23	-1.74	0.31	0.67	-0.36
197	1.51	4.07	-2.56	0.54	1.45	-0.91
101	1.57	5.33	-3.76	0.22	0.74	-0.52
185	1.80	3.30	-1.5	0.67	1.24	-0.57
152	1.82	7.87	-6.07	0.85	3.70	-2.85
226	1.87	2.84	-0.97	0.75	1.14	-0.39
106	1.99	2.17	-0.18	0.26	0.28	-0.02
73	2.18	6.70	-4.52	1.41	4.33	-2.92
75	2.21	3.75	-1.54	0.56	0.95	-0.39
120	2.25	3.94	-1.69	0.46	0.81	-0.35
96	2.35	1.86	0.49	0.54	0.43	0.11
110	2.40	6.08	-3.68	1.27	3.20	-1.93
97	2.44	6.19	-3.75	0.35	0.88	-0.53
224	2.45	6.08	-3.63	0.68	1.69	-1.01
225	2.53	6.63	-4.10	1.11	2.91	-1.80
143	2.70	3.93	-1.23	0.42	0.62	-0.20
222	2.78	2.73	0.05	1.47	1.45	0.02
90	2.91	2.71	0.20	0.81	0.74	0.07
79	3.04	4.97	-1.93	0.42	0.69	-0.27
103	3.05	4.22	-1.17	1.61	2.23	-0.62

64	3.23	4.70	-1.47	0.75	1.09	-0.34
113	3.27	8.05	-4.78	1.21	2.97	-1.76
217	3.31	5.41	-2.10	1.22	2.00	-0.78
121	3.40	6.18	-2.78	0.78	1.42	-0.64
71	3.46	12.76	-9.30	1.17	4.31	-3.14
116	3.62	1.89	1.73	0.83	0.44	0.39
21	3.69	6.38	-2.69	1.76	3.04	-1.28
144	3.84	4.03	-0.19	1.79	1.88	-0.09
107	3.91	3.87	0.04	0.88	0.89	-0.01
117	3.94	8.15	-4.21	2.56	5.27	-2.71
212	3.97	4.47	-0.50	0.62	0.70	-0.08
223	3.97	6.50	-2.53	1.10	1.80	-0.70
201	4.07	6.38	-2.31	0.58	0.91	-0.33
213	4.09	3.49	0.60	0.56	0.48	0.08
168	4.23	6.47	-2.24	0.80	1.23	-0.43
76	4.36	4.69	-0.33	3.12	3.36	-0.24
221	4.48	4.52	-0.04	1.96	1.97	-0.01
172	4.51	3.03	1.48	0.71	0.47	0.24
227	4.52	7.64	-3.12	1.93	3.26	-1.33
164	4.59	11.91	-7.32	2.18	5.64	-3.46
80	4.63	1.77	2.86	0.66	0.25	0.41
84	4.75	6.62	-1.87	1.07	1.49	-0.42
100	4.76	12.62	-7.86	1.14	3.03	-1.89
170	4.89	4.37	0.52	1.95	1.75	0.20
198	4.89	2.42	2.47	0.83	0.41	0.42
142	4.90	4.71	0.19	0.95	0.91	0.04
188	5.08	5.43	-0.35	2.19	2.34	-0.15
122	5.15	4.10	1.05	1.05	0.84	0.21
171	5.27	5.34	-0.07	2.50	2.53	-0.03
215	5.33	4.15	1.18	3.15	2.45	0.70
78	5.43	7.28	-1.85	1.12	1.50	-0.38
63	5.54	4.25	1.29	1.01	0.78	0.23
207	5.54	4.75	0.79	0.73	0.63	0.10
181	5.56	2.30	3.26	3.98	1.65	2.33
218	5.78	6.38	-0.60	2.72	3.00	-0.28
85	5.80	4.48	1.32	1.30	1.01	0.29
14	5.85	9.49	-3.64	1.01	1.64	-0.63
155	5.88	9.75	-3.87	0.78	1.29	-0.51
92	5.93	5.72	0.21	0.82	0.79	0.03
93	5.96	6.76	-0.80	2.98	3.37	-0.39
99	6.05	2.74	3.31	3.02	1.67	1.35
216	6.06	6.39	-0.33	2.84	3.00	-0.16
109	6.07	8.24	-2.17	4.34	5.89	-1.55
27	6.09	4.35	1.74	3.78	2.70	1.08
82	6.17	2.39	3.78	1.71	0.66	1.05
162	6.39	12.72	-6.33	1.75	3.48	-1.73
91	6.72	6.50	0.22	1.79	1.73	0.06

214	6.73	6.13	0.60	3.88	3.53	0.35
37	6.88	3.87	3.01	4.92	2.77	2.15
81	6.94	8.73	-1.79	1.32	1.65	-0.33
87	6.96	5.65	0.40	1.91	1.80	0.11
161	7.12	7.51	-0.39	1.29	1.36	-0.07
173	7.33	5.94	1.39	2.48	2.01	0.47
114	7.54	7.48	0.06	1.07	1.06	0.01
165	7.59	9.94	-2.35	3.06	4.00	-0.94
190	7.83	5.93	1.90	1.43	1.08	0.35
47	8.00	10.05	-2.05	1.84	2.31	-0.47
30	8.19	12.93	-4.74	5.09	8.02	-2.93
94	8.23	5.07	3.16	3.14	1.93	1.21
39	8.25	7.47	0.78	3.89	3.52	0.37
182	8.25	9.64	-1.39	1.42	1.66	-0.24
128	8.30	11.64	-3.34	3.54	4.97	-1.43
111	8.44	8.53	-0.09	1.31	1.32	-0.01
41	8.57	9.40	-0.83	1.48	1.63	-0.15
104	8.78	4.93	3.85	1.51	0.85	0.66
77	8.95	5.81	3.14	1.54	1.00	0.54
95	8.95	10.85	-1.90	4.45	2.96	1.49
88	8.96	12.31	-3.35	1.40	1.92	-0.52
59	9.09	12.78	-3.69	3.97	5.58	-1.61
127	9.10	12.92	-3.82	2.52	3.58	-1.06
43	9.44	16.60	-7.16	1.85	3.45	-1.60
34	9.51	9.14	0.37	5.31	5.10	0.21
1	9.53	8.30	1.23	2.42	2.11	0.31
153	9.65	6.26	3.39	7.55	4.90	2.65
55	9.69	8.79	0.90	4.24	3.84	0.40
186	9.72	9.31	0.41	3.63	3.48	0.15
65	9.78	4.61	5.17	2.77	1.30	1.47
183	9.82	10.29	-0.47	2.20	2.30	-0.10
137	9.96	5.44	4.52	1.55	0.84	0.71
200	10.04	7.29	2.75	3.26	2.37	0.89
169	10.17	9.33	0.84	6.57	6.03	0.54
74	10.55	9.95	0.60	5.89	5.55	0.34
189	10.55	7.04	3.51	2.26	1.51	0.75
140	10.56	7.02	3.54	1.17	0.78	0.39
129	10.80	15.65	-4.85	5.10	7.38	-2.28
57	10.85	10.73	0.12	7.75	7.66	0.09
130	10.90	11.45	-0.55	5.15	5.42	-0.27
141	10.92	8.19	2.73	4.49	3.30	1.19
123	11.40	18.15	-6.75	8.91	14.17	-5.26
157	11.59	14.69	-3.10	2.12	2.68	-0.56
72	11.93	12.11	-0.18	3.36	3.41	-0.05
20	12.20	10.95	1.25	2.39	2.14	0.25
11	12.54	9.63	2.91	6.25	4.81	1.44
191	12.76	6.11	6.65	1.98	0.95	1.03

44	12.83	15.51	-2.68	2.12	2.56	-0.44
32	12.91	13.80	-0.89	5.57	5.95	-0.38
138	13.10	13.12	-0.02	2.67	2.68	-0.01
38	13.11	10.10	3.01	1.79	1.38	0.41
204	13.17	11.69	1.48	3.03	2.39	0.34
139	13.50	7.62	5.88	1.50	0.85	0.65
24	13.64	9.08	4.56	3.14	2.09	1.05
66	13.71	9.33	4.38	2.36	1.61	0.75
31	13.75	8.89	4.86	5.39	3.49	1.90
209	14.30	10.06	4.24	2.71	1.91	0.80
125	15.00	17.39	-2.39	3.10	3.59	-0.49
174	15.02	11.37	3.65	11.73	8.88	2.85
56	15.23	15.03	0.20	5.97	5.89	0.08
42	15.53	13.30	2.23	2.94	2.52	0.42
28	15.65	11.48	4.17	3.26	2.39	0.87
12	15.88	12.68	3.20	6.96	5.56	1.40
177	15.90	5.37	10.53	8.37	2.83	5.54
195	16.02	8.16	7.86	3.12	1.60	1.53
179	16.09	8.32	7.77	8.47	4.38	4.09
167	16.71	15.91	0.80	3.05	2.91	0.14
68	16.82	17.26	-0.44	6.71	6.88	-0.17
180	17.01	10.20	6.81	3.11	1.86	1.25
5	17.08	12.87	4.21	8.03	6.06	1.97
2	17.43	6.17	11.26	2.96	1.05	1.91
131	17.90	7.81	10.09	5.19	2.27	2.9
184	17.97	14.91	3.06	12.81	10.64	2.17
176	18.24	10.50	7.74	2.85	1.64	1.21
17	18.96	13.35	5.61	2.96	2.09	0.87
25	19.17	13.07	6.10	5.31	3.62	1.69
61	19.49	14.64	4.85	4.37	3.28	1.09
160	19.90	7.81	12.09	2.43	0.95	1.48
48	21.21	15.74	5.47	3.12	2.32	0.80

Abbreviations - AER: absolute excess risk; IHD: ischaemic heart disease; RT: radiotherapy

Figure E1: Difference in mean heart dose from the radiotherapy plan and from the model, for each study participant, ordered in ascending order of mean heart dose from the radiotherapy plan

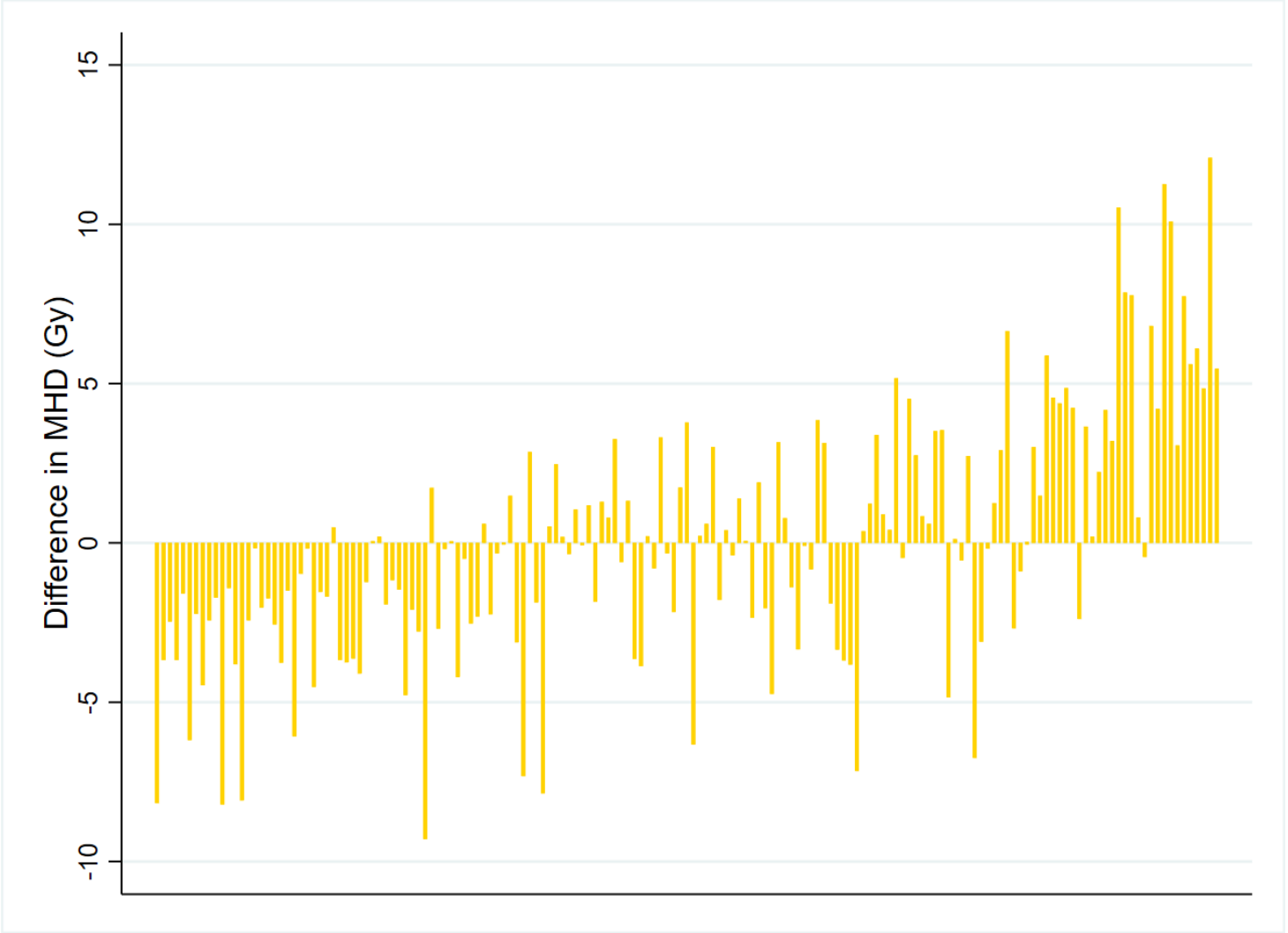


Figure E2: Difference in 30-year cumulative absolute excess risk calculated using the mean heart dose from the radiotherapy plan and from the model, for each study participant, ordered in ascending order of mean heart dose from the radiotherapy plan

