INFORMING THE TREATMENT OF HODGKIN LYMPHOMA THROUGH HEALTH ECONOMIC DECISION ANALYTIC MODELLING AND ANALYSIS OF NATIONAL CANCER REGISTRY DATA



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Abstract

Hodgkin lymphoma, a cancer of the lymphatic system, is highly sensitive to chemotherapy and radiotherapy. >90% of early-stage patients remain disease free ten years after treatment when treated with chemotherapy and adjuvant radiotherapy, typically termed combined modality treatment (CMT).

Radiotherapy, however, confers risks of 'late effects', including increased risks of second cancers and cardiovascular disease. Concern of such late effects has led to the introduction of chemotherapy alone approaches, in which adjuvant radiotherapy is omitted upon evidence of complete response to chemotherapy at interim positron emission tomography/computer tomography (PET-CT) scan. Clinical trials comparing chemotherapy alone approaches versus CMT for all have demonstrated superior disease control with CMT. However, follow-up is insufficient and study sizes too small to observe the benefit of reduced late effects, leading to evidential uncertainty.

In this thesis, individual patient data from the National Cancer Registration Dataset was used to identify whether English NHS trusts differ in their propensity to use radiotherapy alongside chemotherapy (CMT) due to this uncertainty. To better inform treatment decision making, a modelling study was performed to extrapolate the impact, in terms of quality-adjusted survival, of the two treatment approaches across a patient's full life course. This model was subsequently used to determine the quality-adjusted survival benefit and cost-effectiveness of using proton beam therapy over existing conventional techniques within CMT. Finally, this thesis explored the geographic extent of research active lymphoma clinical trial centres in England and repercussions in terms of distances patients need to travel to access trials.

Significant variation was found in the likelihood an NHS trust treated a patient with consolidative radiotherapy. Smoking status was found to predict that chemotherapy-only would be the optimal treatment approach, irrespective of anatomic disease presentation, age, and sex. Never and former smokers benefited the most from a CMT approach. Proton beam therapy provided a small increase in quality-adjusted survival for many patient presentations; however, it is unlikely to be considered cost-effective in the English healthcare setting. Finally, the geographical analysis of precedent location of research active lymphoma clinical trial centres suggested older patients faced larger distances to participate in trials, which may contribute to their historic underrepresentation in lymphoma clinical trials.

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List of abbreviations

3D-CRT	3D-conformal radiotherapy
ABVD	Doxorubicin, bleomycin, vinblastine and dacarbazine
ASCT	Autologous stem cell transplantation
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone
BV	Brentuximab vendotin
CHD	Coronary heart disease
cHL	Classical Hodgkin lymphoma
CI	Confidence interval
CMT	Combined modality treatment
CRN	Clinical Research Network
CTV	Clinical target volume
CWT	Cancer Waiting Times (dataset)
DIBH	Deep inspiration breath hold
DID	Diagnostic Imaging Dataset
DLBCL	Diffuse large B-cell lymphoma
ERR	Excess relative risk
ESHL	Early-stage Hodgkin lymphoma
FL	Follicular lymphoma
GHSG	German Hodgkin Study Group
Gy	Gray; unit of ionising radiation dose
HES	Hospital Episode Statistics (dataset)
HRQoL	Health-related quality of life

HL	Hodgkin lymphoma
ICER	Incremental cost-effectiveness ratio
ICD	International Classification of Disease
IFRT/INRT/ISRT	Involved field/involved node/involved site radiotherapy
IMD	Index of Multiple Deprivation
IMRT	Intensity-modulated radiotherapy
ISHL	Intermediate-stage Hodgkin lymohoma
LMSCA	Left main stem coronary artery
LSOA	Lower layer super output areas
MBD	Mean breast dose
MCL	Mantle cell lymphoma
MDCCA	Mean dose to the common carotid arteries
MHD	Mean heart dose
MLD	Mean lung dose
MOR	Median odds ratio
NCRAS	National Cancer Registration and Analysis Service
NDRS	National Disease Registration Service
NHS	National Health Service
NHL	Non-Hodgkin lymphoma
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NLPHL	Nodular lymphocyte-predominant Hodgkin lymphoma
OAR	Organs-at-risk
ODP	Open Data Platform
ONS	Office for National Statistics

OR	Odds ratio
PET-CT	^{18}F-fluorodeoxyglucose positron emission tomography/computer tomography
PFS	Progression-free survival
PMBCL	Primary mediastinal B-Cell lymphoma
PTCL	Peripheral T-cell lymphoma
PTV	Planning target volume
QALY	Quality-adjusted life year
R-CHOP	Rituximab, cyclophosphamide, vincristine, doxorubicin, prednisolone
RR	Relative risk
RT	Radiotherapy
RTDS	National Radiotherapy Dataset
SACT	Systemic Anti-Cancer Therapy (dataset)
SD	Standard deviation
VMAT	Volumetric-arc therapy
VPC	Variance partition coefficient

1 General introduction

1.1 Introduction

The overarching aim of this thesis is to perform thematically linked analyses which will help to inform current and future decision making for the treatment of lymphomas in the UK. These analyses take various forms, from the interrogation of routinely collected individual patient data to the construction of a decision analytical model to extrapolate treatment outcomes.

In this general introduction, I begin by providing an overview of the epidemiology of lymphomas and detail aspects of the evolution of treatment and the current treatment paradigm. These topics will help frame the importance of the research questions I am aiming to answers, which are outlined at the end of this general introduction. Other relevant background topics, such as an overview of health economic decision modelling have been placed in their related chapters for the purpose of narrative cohesion.

1.2 Hodgkin and non-Hodgkin lymphomas

Lymphoma is the broad name given to a large collection of haematological cancers, all of which commonly arise through the tumorigenesis of lymphocytes. Despite the similar cell of origin, the different types of lymphomas can have markedly different routes to malignancy, genetic mutation profiles, and patterns of presentation and natural histories.

Historic nomenclature, as opposed to pathological categorisation, divided lymphoid neoplasms firstly by the terms Hodgkin or non-Hodgkin lymphoma. This classification is named after Thomas Hodgkin, a British pathologist who first described Hodgkin lymphoma

in his seminal 1832 report titled “On Some Morbid Appearances of the Absorbent Glands and Spleen”.[1]

A minority of content in this thesis relates to non-Hodgkin lymphoma (NHL), therefore only a brief summary is given here. NHL is far more common than Hodgkin lymphoma (HL) with a 2018 UK age-standardised incidence rate of 22.8 cases per 100,000 persons compared to 3.3 cases per 100,000 persons for HL.[2] NHL consists of a large number of subtypes that differ greatly in their disease course, with some aggressive (high grade) in nature requiring immediate treatment, whilst others are more indolent (low grade) and may by best initially managed simply by observation with no active treatment.

The majority of this thesis focuses on Hodgkin lymphoma (HL). HL can be subdivided into five subtypes. The four subtypes nodular sclerosing, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted Hodgkin lymphoma are typically grouped together and are termed classical Hodgkin lymphoma (cHL). These make up between 90% and 95% of all cases.[3] cHL is commonly characterised by the sparse presence of large, mononucleated Hodgkin and multinucleated Reed/Sternberg (HRS) cells which comprise a very small proportion (less than 1%) of the total tumour cell mass. The remainder being composed of inflammatory and reactive healthy cells.

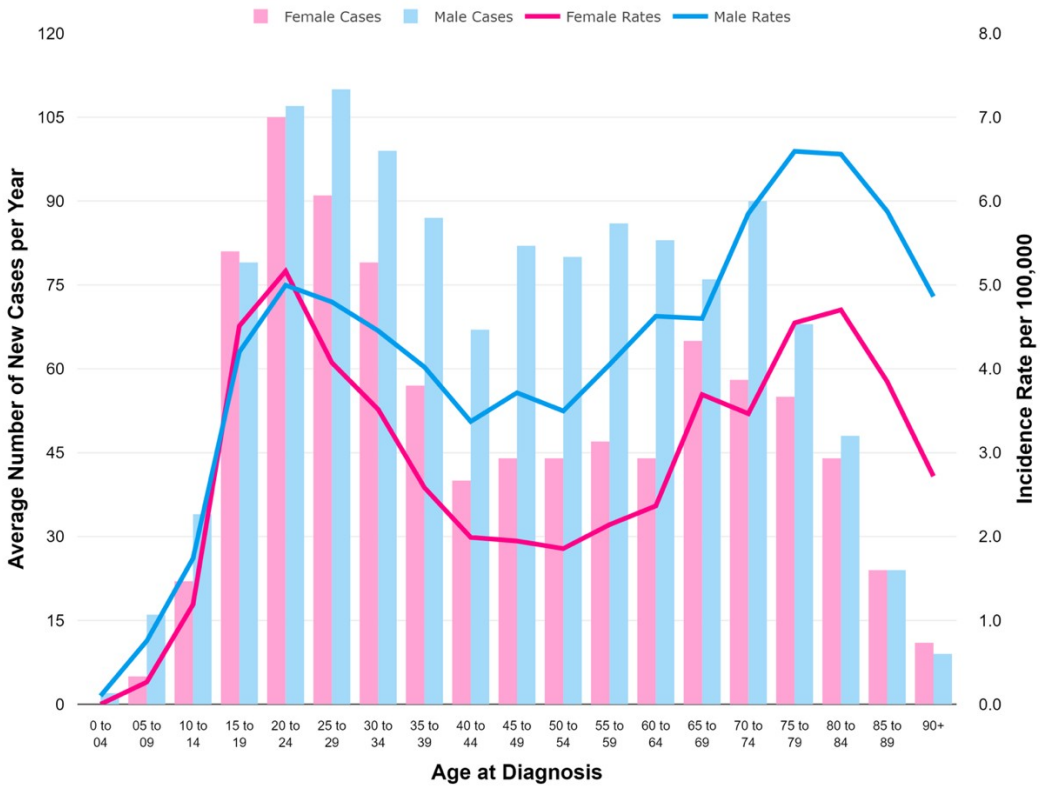
The fifth and less common subtype is nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), which affects the remaining 5% to 10% of HL patients. It is characterized by the presence of lymphocyte predominant (LP) cells rather than HRS cells. Based on research on the differences between HRS and LP cells, the World Health Organization has recently renamed NLPHL to Nodular Lymphocyte Predominant B-cell Lymphoma and reclassified it as a subtype of non-Hodgkin Lymphoma in its 5th edition of the World Health Organization Classification of Haematolymphoid Tumors report, published in 2022.[4] NLPHL has

historically been treated the same as classical HL. Throughout the thesis, HL will denote the grouping of both classical HL and NLPHL.

1.2.1 Epidemiology of Hodgkin lymphoma

Hodgkin lymphoma displays a unique distribution of incidence across attained age, following a bimodal pattern with a first peak occurring in adolescents and young adults (Figure 1 .1). As such, despite not being in the 20 most common malignancies in the overall UK population, it is the one of the most common cancers in the 15-24 age group.[5] This early peak in age-specific incidence is attributable to the nodular sclerosing histological subtype which is less commonly associated with the Epstein-Barr virus than other subtypes of cHL.[6] Interestingly, this peak is of far smaller magnitude in developing countries implying variations in the underlying pathogensis.[7] Incidence in males is greater than that in females, with a male to female rate ratio of 1.5.[8] In particular, the sex gap in incidence is most apparent at ages >25 to 29 years of age (Figure 1 .1).

Figure 1.1 Hodgkin Lymphoma (C81), Average Number of New Cases per Year and Age-Specific Incidence Rates per 100,000 Population, UK, 2017-2019. CRUK Cancer Statistics



1.2.2 Diagnosis and staging

HL often presents in the primary care setting through the painless enlargement of affected lymph nodes, although the anatomical distribution of the disease is highly individual.[9] Most commonly, lymph nodes above the diaphragm, such as the cervical, supraclavicular, and axillary lymph nodes are affected. Progression may be marked by contiguous spread from lymph node of origin to adjacent lymph nodes and lymph node systems.[7] Less commonly people with HL may experience more generalised symptoms such as unintentional weight loss, night sweats and fever. If severe enough these symptoms may be designated as “B symptoms” and are a marker of more advanced disease. Advanced disease may also spread more widely beyond the lymphatic system, e.g. into the bones or other organs, termed extra-nodal disease, causing a variety of possible symptoms.

Excisional or percutaneous core needle biopsy of potentially involved lymph nodes is required for the diagnosis of HL with morphological and immunohistochemical analysis performed on the resultant sample of malignant tissue.[3] Once HL has been diagnosed based on histopathological results from the biopsy, staging is typically undertaken using ^{18}F-fluorodeoxyglucose positron emission tomography/computer tomography (PET-CT). Staging for Hodgkin lymphoma is based on the Lugano classification and comprises of four stages based on the anatomical disease extent and location as given in Table 1 .1. Additionally, the letter suffixes A and B are used to mark the absence or presence of B symptoms. Different research groups have produced risk classification systems based on these stages and the presence of other risk factors. The German Hodgkin Study Groups (GHSG) classification system is widely used, referring to patients as being early, intermediate (previously referred to as early-stage unfavourable), or advanced stage as defined in Table 1 .1.

Table 1.1: Staging of lymphoma

Lugano staging system	
Stage I	HL cells found in a single lymph node region, OR HL cells found in one organ or site outside the lymphatic system.
Stage II	HL cells found in two or more lymph node regions on the same side of the diaphragm, OR
	HL cells found in a lymph node area and a nearby organ outside the lymphatic system, on the same side of the diaphragm
Stage III	HL cells found in lymph node regions on both sides of the diaphragm (above and below), possibly with localised involvement of an organ outside the lymphatic system or the spleen
Stage IV	HL cells have spread widely into one or more organs outside the lymphatic system
A	The patient does not have B symptoms (fever, weight loss or night sweats)
B	The patient has B symptoms
German Hodgkin Study Group risk group classification	
Early stage	Stage IA or IB and IIA or IIB without risk factors

Intermediate stage (previously early stage unfavourable)	Stage IA or IB and stage IIA with one or more risk factors Stage IIB if a high ESR and/or ≥ 3 involved lymph node areas are present as risk factors
Advanced stage	Stage IIB if extranodal disease (E-lesions) and/or large mediastinal mass are present as risk factors Stage IIIA or IIIB Stage IVA or IVB
Risk factors	Presence of a large mediastinal mass, measured by means of a chest X-ray image; the mediastinal mass is considered as large if it measures at least one third of the transverse diameter of the thorax. Extranodal disease, i.e. any tumor spread involving other tissues than those of the lymph nodes, spleen, thymus, Waldeyer's tonsillar ring, appendix and Peyer's patches. High erythrocyte sedimentation rate (ESR) of 50mm/h if A-symptoms are present, and 30mm/h if B-symptoms are present. Involvement of three or more lymph node areas. Lymph node areas do not correspond to the lymph node regions according to the Ann Arbor classification system (a lymph node area may include several lymph node regions)

1.2.3 Selective history of the evolution of treatment

Chapters 2 to 4 of this thesis seek to inform current and future treatment decisions, and therefore it is useful to provide context by outlining the historical development which has led to currently used treatment approaches. The evolution of treatment for HL closely parallels the most important developments in cancer as a whole. HL was among the first neoplasms shown to be curable with external beam radiotherapy through the pioneering work of Vera Peters in the 1950s.[10] Furthermore, the treatment of HL patients with chemotherapy agents started with nitrogen mustard during WWII, and it was the first advanced malignancy of a major organ system in adults to be cured by multi-agent chemotherapy, using a regimen known as MOPP (nitrogen mustard, vincristine, procarbazine and prednisone).[11] In the 1960s, these two modalities were brought together by Henry Kaplan and Saul Rosenberg, with consolidation radiotherapy (as an adjuvant) after chemotherapy.[12]

In the mid-1970s, the chemotherapy regimen known as ABVD (doxurubicin, bleomycin, vinblastine and dacarbazine) was developed at the Istituto Nazionale Tumori in Milan, Italy,

and the subsequent decades saw a series of randomised trials comparing its efficacy in relation to MOPP and alternating MOPP/ABVD. Over this period, ABVD cemented itself as the regimen of choice.[12] In the late 1990s and early 2000s a more intensive regimen, BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone) was developed by the German Hodgkin Study Group (GHSG). The group has comprehensively shown that treatment with BEACOPP is more efficacious than ABVD in terms of event-free survival (EFS).[13] However, BEACOPP's higher acute toxicity burden means that both regimens are commonly used in advanced-stage disease, and ABVD is often still preferred at earlier stages.[3,14]

In parallel, the delivery of consolidative radiotherapy has also undergone considerable evolution. In particular, the size of field has been greatly reduced. Historically, an extensive field called a mantle field was used to irradiate the lymphatic system above the diagram, and an inverted-Y field used to treat nodes beneath in the abdomen, pelvis and groins (plus or minus the spleen or splenic hilum). Such large fields were necessary when radiotherapy was the sole treatment modality, as although the majority of relapses in HL occur in areas of observable disease at diagnosis, relapse can occur in areas of unobservable subclinical disease. With the aforementioned advent of combined modality treatment (CMT), sub-clinical disease could be largely controlled through the systemic component. As a results, involved field radiotherapy (IFRT), in which the field is restricted to nodal region(s) that contained HL at diagnosis, was shown to provide equivalent disease control to extensive fields and became the standard approach to radiotherapy.[15] Importantly, it significantly decreased the volume of healthy tissue being irradiated.

More recently, the techniques of "involved node" (INRT) and "involved site" (ISRT) irradiation have been introduced. The former involving the precise irradiation of initially involved nodes, as opposed to the regional irradiation given in IFRT.[16] This however, requires

stringent pre-treatment imaging in the radiotherapy treatment position, therefore the later was introduced, allowing greater margins around the involved nodes.[17]

Typically, HL patients treated with consolidative radiotherapy receive multiple "fractions" of radiotherapy at a typical dose of 2 Gray (Gy) per fraction. A total prescribed dose of 30 Gy given in 15 fractions has commonly been used. For early-stage patients with favourable prognosis, a 20 Gy in 10 fractions regimen is also commonly prescribed alternative, with the GHSG HD10 trial finding non-inferiority to a 30 Gy regimen.[18]

As well as field size, new technologies have improved the conformality of irradiation given. Historically, the delivery of radiotherapy was guided based on the delineation of the target volume based on orthogonal x-rays of the patient, termed 2D radiotherapy (2D-RT), with shaping limited to simple square or rectangular beams.[15] This has been widely supplanted by the development of 3-dimensional imaging and treatment, termed 3D-conformal radiotherapy (3D-CRT). Here, imaging is performed using CT scans, allowing for "3-dimensional" delineation and contouring of the target volume and organs-at-risk (OAR). Treatment planning systems (themselves under continual development and improvement) enable the optimisation of beam arrangements and simulation of the expected dose distribution to generate an optimised radiotherapy plan. Intensity modulated radiotherapy (IMRT) is a recent extension of 3D-CRT, where many small beams are used at varying intensities to deliver irradiation of the target volume. This technique, and variants such as volumetric arc therapy (VMAT), can reduce the radiation dose received by organs-at-risk OAR, but may increase the volume of healthy tissue receiving a low dose.[19]

Finally, deep inspiration breath hold (DIBH) has been widely introduced as a means of controlling respiratory movement. Here, patients receive pre-radiotherapy coaching on the required breathing technique, typically involving a deep inhalation followed by a 20 second

breath hold, as well as imaging in this hold to plan the delivery of RT. It is during these 20 second periods that the RT is delivered. The control of respiratory motion allows for the reduction of margins to the target volume. Additionally, inhalation expands the lungs and moves the heart downwards, increasing its distance away from lymph nodes in the mediastinum.[20] In sum, these advancements mean that contemporary patients undergoing CMT receive much smaller radiation doses to OAR than similar patients treated historically.[21]

1.2.4 Late effects of treatment

The evolution of radiotherapy towards more conformal techniques reflects concern regarding the impact of collateral irradiation on normal healthy cells - The same process by which irradiation effects tumour cells, through DNA breakages, also occurs in irradiated healthy cells, and such damage may subsequently manifest into radiation-related sequelae, often termed short and late effects. Follow-up of historically treated cohorts suggested a high burden of late effects, with increased risks of cardiovascular disease and second primary cancer occurring in a dose-response manner.[22,23]

Similarly, systemic treatment with cytotoxic chemotherapy not only induces acute treatment-related side such as nausea, and neutropenia, but is also associated with late effects manifesting in the years and decades after treatment. Different families of chemotherapies induce cell apoptosis through a myriad of routes and therefore affect different organ systems. Selective examples include; increased risk of cardiovascular disease and second primary breast cancer in a dose-dependent manner with anthracycline (such as doxorubicin) treatment,[22,23] gonadal dysfunction and increased risks of colorectal cancer with the use of procarbazine,[24] and pulmonary fibrosis with the use of bleomycin.[25]

1.2.5 Recent trials and outcomes in early- and intermediate-stage disease

With high levels of cure broadly achieved with the widespread adoption of combined modality treatment (CMT) involving ABVD or BEACOPP chemotherapy and radiotherapy, but concern regarding the late effects of such treatment, clinical investigation has shifted towards the personalisation of treatment. Developments in imaging have been critical in facilitation this transition, in particular the advancement and increased accessibility of ^{18}F-fluorodeoxyglucose PET-CT scanning. Briefly, this technology involves imaging the distribution of uptake of the radioactive tracer ^{18}F-fluorodeoxyglucose which is delivered intravenously into the blood stream. In lymphoma and many other cancers, this tracer is preferentially taken up by cancerous cells. Measures of uptake have been developed into scores such as the Deauville score, a semi-quantitative method of assessing uptake in relation to background body uptake.[26]

This advance in imaging has allowed the investigation of PET-response adaptive strategies. The high historical burden of radiation-related sequalae motivated the investigation of de-escalation approaches using interim PET scans to identify patients with a complete response to chemotherapy who may not require consolidative radiotherapy. Similarly, those achieving only partial or worse response could receive treatment escalation.

PET-response adaptive strategies for early and intermediate stage Hodgkin lymphoma were investigated in three phase III trials, RAPID, H10, and HD16 starting in the mid 2000s.[27–29]

RAPID

The UK multicenter RAPID trial focused on patients with stage I/IIA cHL without the presence of a mediastinal bulk. Patients received three cycles of ABVD chemotherapy before undergoing PET scanning to assess response. Those with negative PET findings were randomized between receiving consolidative RT or no further treatment. Patients with

positive PET findings received a fourth cycle of ABVD and RT. The per-protocol 3-year progression-free survival (PFS) rate in the RT group and no further therapy arms were 97.1% (95% CI: 94.7% to 99.6%) and 90.8% (95% CI: 86.8% to 94.7%) respectively. Given the pre-specified PFS non-inferiority margin (7%), the study concluded that chemotherapy alone was not proven to be non-inferior to consolidative RT. In terms of overall survival, however, was >97% in both arms and had a non-significant rate ratio of 0.51 (95% CI, 0.15 to 1.68).

HD16

HD16 was a similar trial performed by the German Hodgkin Study Group (GHSG), focusing on early-stage favorable HL patients (i.e. including NLPHL) according to their staging criteria. Patients were randomly assigned 1:1 between two cycles of ABVD and 20-Gy involved-field RT or PET-guided treatment where RT was omitted after negative interim PET. Again, the trial looked at non-inferiority. 5-year PFS was 93.4% (95% CI: 90.4% to 96.5%) with CMT and 86.1% (95% CI, 81.4% to 90.9%) with ABVD alone, which was not non-inferior given the pre-specified margins. 5-year OS was again equivalent.

H10

In H10, two parallel studies were performed, one in early-stage favorable and one in early-stage unfavorable cHL. In the early-stage favorable study, patients who were PET negative after two cycles of ABVD chemotherapy were randomized between receiving two more ABVD cycles alone or with the addition of consolidative RT. 5-year PFS rates were 99.0% versus 87.1% (HR, 15.8; 95% CI, 3.8 to 66.1) in favor of CMT. In the early stage unfavorable study, patients after negative interim PET were instead randomized between four more cycles of ABVD alone or two more cycles with RT. Again there was a statistically significant difference in PFS, 92.1% versus 89.6% (HR, 1.45; 95% CI, 0.8 to 2.5) in favor of CMT.

Unsurprisingly however, there was no difference in 5-year OS outcomes. Details on each trial are provided in Table 1 .2.

Table 1.2: Summary of each PET-response adaptive trial

	RAPID	**HD16**	**H10 favourable**	**H10 unfavourable**
Population	cHL stage IA or IIA, n = 602	cHL stage I and II or NLPHL stage IB, IIA, or IIB, n = 1150	cHL stage I and II with no unfavourable* characteristics, n = 754	cHL stage I and II with at least one unfavourable* characteristic, n = 1196
Control arm	3x ABVD + 30Gy RT if PET negative	2x ABVD + 20Gy RT if PET negative	3x ABVD + 30Gy RT if PET negative	4x ABVD + 30Gy RT if PET negative
Experimental arm	3x ABVD if PET negative	2x ABVD if PET negative	4x ABVD if PET negative	6x ABVD if PET negative
PFS outcome	3-year: 94.6% (95% CI, 91.5 to 97.7) vs 90.8% (86.9 to 94.8)	5-year: 93.4% (90.4% to 96.5%) vs 86.1% (81.4% to 90.9%)	5-year: 99.0% (95.9 to 99.7) and 87.1% (82.1 to 90.8)	5-year: 92.1% (88.0 to 94.8) and 89.6% (85.5 to 92.6)
OS outcome	3-year: 97.1% (94.8 to 99.4 vs 99.0% (97.6 to 100)	5-year: 98.1% (96.5% to 99.8%) vs 98.4% (96.5% to 100.0%)	5 year: 100% vs 99.6% (96.9 to 99.9)	5 year: 96.7% (92.9 to 97.8) vs 98.3% (96.0 to 99.3)

* Unfavourable characteristics: age ≥ 50 years or more than three nodal areas or mediastinal-thoracic ratio ≥ 0.35 or no B symptoms and erythrocyte sedimentation rate [ESR] ≥ 50 or B symptoms and ESR ≥ 30

1.2.6 Long term disease outcomes

In the aforementioned trials, 3- and 5- year progression free survival were used as primary endpoints, and such timeframes are frequently used in HL. Long-term estimates of relapse risk after modern treatment from population-based studies suggest a significant tapering of the hazard of relapse with each year of attained remission. For instance, analysis by the Nordic Lymphoma Epidemiology Group Study suggest patients reaching the 2-year and 5-year relapse free milestones have a respective subsequent 5-year relapse risks of 4.2% (95% CI, 3.8% to 4.6%) and 1.3% (95% CI, 1.0% to 1.6%).[30] Over a median follow-up of 16 years, analysis of the same Nordic registries suggests limited-stage patients receiving modern CMT (2-4 cycles of ABVD and 30 Gy limited-field) and achieving 5 years of attained remission had no difference in mortality to the general population. With only those progressing within five years showing significant excess mortality. This finding of no excess mortality in the medium term after modern CMT is notable given long-term follow up of historically

irradiated HL patients suggesting a high burden of second primary cancers and cardiovascular disease up to 40 years after treatment.[22,23]

1.2.7 Relapse

The treatment of patients either refractory to initial therapy or who relapse is influenced by their condition such as age and co-morbidities. For generally healthy patients who are not elderly, autologous stem cell transplantation (ASCT) is considered the standard of care and can provide long-term cure in approximately half of cases.[3,7] This involves the delivery of relapse chemotherapy with the aim or reaching complete response, followed by the mobilisation and collection of patient stem cells with are infused back into the patient after the delivery of high-dose (myeloablative) chemotherapy.

There are myriad options for relapse therapy. Chemotherapy based salvage options include platinum-based regimens such as ICE (ifosfamide, carboplatin, etoposide), DHAP (dexamethasone, cytarabine, cisplatin), and ESHAP (etoposide, cytarabine, cisplatin, methylprednisolone) and gemcitabine-based regimens such as IGEV (ifosfamide, gemcitabine, etoposide), GDP (gemcitabine, dexamethasone, cisplatin), and GVD (gemcitabine, vinorelbine, doxil). Such regimens are chosen with the intention of being non-cross resistant to frontline therapy. Combinations of chemotherapy with novel therapeutics such as targeted antibody-drug conjugates (ADCs) and/or immunotherapy, and even non-chemotherapy monotherapy have also become available.[31]

1.2.8 Novel therapeutics for Hodgkin lymphoma

Lymphomas, being of lymphocyte origin, are particularly amenable to the development of ADCs due to the presence of specific cell-surface antigens termed cluster of differentiation (CD) proteins. cHL ubiquitously expresses CD30, which has been successfully targeted with

the ADC Brentuximab Vendotin (BV) (Adcetris®), Seattle Genetics).[32] Since BVs introduction, various clinical trials have been performed, showing strong efficacy across the relapsed/refractory setting.[31,33]

Following the trialling of radiotherapy omission to reduce the burden of radiotherapy late effects, more recently trials have begun to explore the replacement of cytotoxic chemotherapy agents to reduce chemotherapy related short and late effects. In the frontline setting, US-led trials have focused on the replacement of bleomycin in the ABVD regimen, due to its rare but serious lung toxicity, with BV. In the ECHELON-1 trial, A-AVD (A for Adcetris) has shown superiority to ABVD in terms of progression-free and overall-survival in stage III or IV HL, although this trial was not PET-response adaptive.[34,35] The GHSG have recently reported efficacy and tolerability results of their HD21 randomised phase 3 trial of PET-guided BrECADD versus eBEACOPP in advanced-stage cHL lymphoma. Here BrECADD was developed as a less toxic but similarly efficacious alternative to eBEACOPP, involving a combination of BV, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone. Treatment-related morbidity was significantly lower with BrECADD and at a median follow-up of 48 months, BrECADD improved progression-free survival; 94·3% (95% CI 92·6–96·1) for BrECADD and 90·9% (88·7–93·1) for eBEACOPP, at a statistically significance level.[36]

At present the National Institute for Health and Care Excellence (NICE), the English body which recommends technologies for reimbursement in the NHS, only recommends BV for patients who are refractory or who suffer a relapse after ASCT, for patients after at least 2 prior therapies when ASCT or multi-agent chemotherapy is not a treatment option, or for patients at increased risk of relapse or progression after ASCT.[37] The routine commissioning of BV in the frontline setting will depend on UK-based evidence of efficacy and cost-effectiveness. To this end the RADAR trial, a multicentre trials in the UK, Europe, Australia,

New Zealand, Canada and the USA, has recently opened for recruitment.[38] This trial comprises of a parallel design. Previously untreated early-stage (IA/IIA cHL above the diaphragm, any mediastinal mass ≤0.33 of internal thoracic diameter) will be randomised to receive either ABVD or BV+AVD. An interim PET-CT scan after cycle 2 will determine further treatment. Patients with Deauville score 1-3 will have one further cycle of ABVD/ BV+AVD and only a minority of pre-designated patients (e.g. those with lymph node masses ≥ 5 cm and those over 60 years of age) will receive radiotherapy. Patients with Deauville score 4 will have two further cycles of ABVD/ BV+AVD followed by another PET-CT scan. As long as the patient does not have progressive disease, they will have involved site radiotherapy (ISRT). Patients with Deauville score 5 will stop trial treatment, enter follow up and they will have further treatment for cHL off trial, at their treating clinician's discretion.

Immune checkpoint inhibitors, specifically anti-programmed cell death protein 1 (PD-1) inhibitors such as nivolumab, pembrolizumab, and avelumab have also shown substantial efficacy in HL in the relapsed and refractory setting.[39,40] Nivolumab is currently authorised in the UK for adults relapsing after or refractory to autologous stem cell transplant and treatment with BV. As with BV, anti-PD-1 inhibitors are currently being trialled in the frontline setting in the place of bleomycin. For instance, the German Hodgkin Study Group Phase II NIVAHL Trial recently reported results which compared sequential or concomitant nivolumab+AVD both consolidated with 30 Gy (ISRT) in intermediate stage patients. With a median follow-up of 41 months, no PFS or OS event after completion of study treatment was recorded.[41] A UK based trial, RATiFY of the anti-PD-1 inhibitor tislelizumab is also now under way for the frontline treatment of older patients.[42]

1.2.9 Proton beam therapy for Hodgkin lymphoma

Whilst novel systemic therapies show great promise in Hodgkin lymphoma, there remains a focus on further improving the therapeutic ratio of consolidative radiotherapy. In particular there is great interest in the use of proton beam therapy (PBT) as an alternative to traditional photon-based RT. PBT confers a dosimetric advantage over conventional photon-based radiotherapy (RT) due to differences in their intrinsic tissue depth-dose distribution. Beams of photons deliver irradiation in a gradually declining manner over the depth of the beam, causing unavoidable collateral irradiation to normal tissue structures such as organs-at-risk (OAR) both anterior and posterior to the tumour target. Conversely, charged particles such as protons exhibit a sharp increase in irradiation dose at the end of their trajectory, known as the Bragg peak. By focusing the Bragg peak on the tumour volume, irradiation of adjacent normal tissue structures can be reduced or the dose to the tumour can be escalated for a given accepted level of OAR irradiation.

To compare new radiotherapy technologies and techniques, comparative planning studies are often performed. Here, for a cohort of patients, each undergoes a CT scan on which their radiotherapy treatment is planned through the contouring target volumes and surrounding organs, and subsequent optimisation of radiotherapy beam angles and modulation within a computer planning system to simulate the radiation dose to be delivered. Alternative plans based on the technologies and techniques under comparison (e.g. PBT versus photons) are also created. These plans allow for the comparison of dosimetry, i.e. the calculation and assessment of the planned ionizing radiation dose absorbed by patient. And various dose metrics to organs and tissues can be calculated such as mean heart dose. Such comparative planning studies have consistently shown improved dosimetry with the use of PBT, although there is large variation in dosimetry benefit across HL patients due to heterogeneity in

anatomy and disease location[43–45] and the dosimetric improvements do not necessarily translate into large predictions of clinical benefit.[46] This is the case for many different cancers.[47]

Despite a lack of long-term clinical evidence for the benefit of PBT there has been rapid growth in the number of countries building PBT facilities.[48] Many of these countries, have developed national PBT policies and position papers on the selection and indication of patients to PBT with explicit commitment to the growth of clinical research to improve the acknowledged weak the evidence base for protons.[49–52] In the UK, the Department of Health and Social Care invested £250 million in the construction of two PBT centres at The Christies NHS Foundation Trust, Manchester, and The University College London Hospitals NHS Foundation Trust, London. Since the start of domestic PBT services in England in 2018, four phase III randomised control trials have so far been initiated in head and neck cancer, breast cancer, oligodendroglioma, and mesothelioma .[53] There is interest in the clinical community for a clinical trial in Hodgkin lymphoma.

1.3 Thesis motivation and structure

1.3.1 Informing optimal treatment in early-stage Hodgkin lymphoma

The general overview of lymphoma introduces a number of contemporary topics which will be explored in this thesis. Firstly, section 1.2.5 outlines recent PET-response adaptive clinical trials in Hodgkin lymphoma, demonstrating the current decision uncertainty in the optimal strategy for the treatment of early-stage Hodgkin lymphoma. In interim PET-negative patients, CMT provides an increase in disease control, however, despite medium-term evidence from population-based studies of improved survival,[54] the long-term trade off in

terms of the risk of radiation-related sequelae remains unconfirmed. This same decision problem is also pertinent to the case of DLBCL, where chemotherapy alone or CMT are alternatives.

Therefore, in the first analysis chapter, **Chapter 2,** individual patient data on all Hodgkin lymphoma and DLBCL patients diagnosed in England between 2014 and 2019 is used to assess variation in the use of consolidative radiotherapy across English healthcare providers. Case-mix adjustment and decomposition of this variation is performed to understand the extent to which it can be attributed to the healthcare provider and their clinical biases towards or against the use of consolidative radiotherapy in light of the uncertain evidence.

Chapter 3 follows by directly informing the choice between CMT and chemotherapy alone in interim PET-negative early-stage classical Hodgkin lymphoma patients. Here, an individual-patient level state transition model is developed to extrapolate the outcomes of the RAPID trial over a full patient's life course. The model translates the trade-offs between the risks and benefits of omitting RT into an estimate of life expectancy under the two different treatment scenarios, as well as expected quality-adjusted life years (QALYs) which is an extension incorporating health-related quality of life (HRQoL).

1.3.2 Informing the commissioning of Proton Beam Therapy for Hodgkin lymphoma

In section 1.2.9 the rationale and interest in using consolidative PBT instead of standard photon-RT was introduced. Limited clinical evidence is currently available to inform the decision to use PBT, with most evidence of its benefit restricted to dose comparison studies. Therefore in **Chapter 4**, the aforementioned individual-patient level state transition model is again utilised to translate, for a cohort of 61 comparatively planned intermediate-stage classical HL patients, the dosimetric benefit of consolidative PBT into estimates of life

expectancy and QALYs gained over standard photon-RT consolidation. Furthermore, the cost-effectiveness of consolidative PBT is assessed.

1.3.3 Informing future clinical trials in lymphoma

Finally, in section 1.2.8 the amenability of lymphomas to targeted therapies was presented, as well as the current direction of clinical trials in Hodgkin lymphoma. Building on this, **Chapter 6** seeks to provide novel analysis of the landscape of past lymphoma clinical trials across England. The chapter provides an overview of the characteristics of previously performed clinical trials before focusing on the issue of patient representation, specifically whether the characteristics of enrolled patients aligns with that of the patient population at large.

A contemporary issue for clinical trials, highlighted in the recent Department of Health and Social Care's Future of Clinical Research policy paper, is accessibility and equality of access.[55–57] As such, the chapter then focuses on geographic accessibility to lymphoma clinical trial centres from the patient perspective focusing on the domains of distance, travel times, and catchment before assessing whether the current spatial arrangement of clinical trials centres creates inequalities in access.

2 Variation in use of frontline curative radiotherapy for classical Hodgkin and diffuse large B-cell lymphoma across healthcare providers in England

2.1 Introduction

2.1.1 Recapping the uncertain role of consolidative radiotherapy in Hodgkin lymphoma

This first analytical chapter is concerned with assessing how Hodgkin lymphoma patients are currently treated in clinical practice across England. In section 1.2.3 a history of the evolution of treatment for Hodgkin lymphoma was provided, highlighting the emergence of combined modality treatment (CMT), involving multi-agent chemotherapy followed by consolidative radiotherapy, as the standard of care.[18,27,28] However, the use of RT leads to unavoidable collateral irradiation of organs-at-risk (OAR) close to the tumour volume, which over time may progress into radiation-induced sequelae.[22,58] Based on concerns of such risks, FDG–PET guided omission of RT in chemo-responsive early-stage patients is an option.[3,59–61]

Three randomised phase III trials in early-stage HL reported results on whether such treatment de-escalation was non-inferior to CMT. As summarised in section 1.2.5, each demonstrated omitting RT was not non-inferior to CMT in terms of progression-free survival.[27–29] However, due to the usual latency of radiation-related sequelae, the current length of follow-up is insufficient to determine whether superior disease control with CMT outweighs the risks of late effects occurring 10-40 years after treatment in terms of overall survival probability. Even with sufficient follow-up, trials are unlikely to have sufficient sample sizes to demonstrate differences in late effects.

2.1.2 The uncertain role of consolidative radiotherapy in diffuse large B-cell lymphoma

This same decision problem is also pertinent to the case of diffuse large B-cell lymphoma (DLBCL). Diffuse large B-cell lymphoma is the most common aggressive form of NHL,

accounting for 40% of all lymphoma diagnoses in England.[62] Like HL, DLBCL is aggressive (high grade) in nature, and staging is similarly based on the Lugano classification as given in Table 1 .1. The chemotherapy regimen R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, prednisolone) has long been the standard of treatment, and until very recently has not been surpassed, in terms of overall survival outcomes, despite many clinical trials of alternative regimens.[63] As with cHL, consolidative radiotherapy may be given for patients with limited-stage disease, or in advanced stage disease for extranodal sites or sites of initial bulk.[61] The same rationale for PET-response adaptive omission of RT exists for DLBCL, however clinical trials are still on going.[61]

2.1.3 Treatment decision making in the clinic and chapter objective

The decision to use consolidative RT reflects a multitude of considerations. At a patient-level, relevant factors include the specific anatomical presentation of the disease such as mediastinal bulk and patient characteristics such as co-morbidities. Healthcare professionals will also play a key role in the decision to use RT. Clinicians will possess an underlying propensity towards or against its use which will be based on the specialities of the treating team, access to RT, and crucially, the underlying proclivity of the treating clinicians towards RT based on their individual interpretation of the uncertain evidence, personal clinical experience and their latent preferences, prejudices and biases.

In the English National Health Service (NHS), Trusts are responsible for the provision of secondary care including most oncological and haematological services. Patients, either through referral pathways or emergency presentation, fall under the care of a consulting team at their geographically relevant NHS Trust, and it is through a shared-decision process that a treatment is chosen. It is in this hierarchy, patients nested in NHS Trusts, that treatment decision are made, and within this hierarchy that preferences towards the use of RT exist.

Data from the US suggests there has been a long term declining trend in the use of consolidative RT for both lymphomas despite the results of the three trials, which likely stems from concern of potential late effects.[54,64,65] The analyses controlled for potential changes in patient clinical and sociodemographic factors over time, suggesting that this change may reflect changing clinician preferences away from the use of consolidative RT. Importantly, such preferences may not be homogenous, and this temporal trend at a country level may be underpinned by heterogeneous practices across a country. This chapter's aim, therefore, is to assess variation in the use of consolidative RT utilisation within a country - England, looking at patient and provider factors associated with RT use and the residual heterogeneity which includes differing treatment team preferences.

Previously, a working paper published by the National Cancer Intelligence Network (NCIN) Haematological Malignancy Site-Specific Clinical Reference Group (HMSSCRG) utilised English cancer registry data and linked National Radiotherapy Dataset (RTDS) to perform a similar analysis.[66] In the working paper, all English patients diagnosed during 2009 and 2010 with HL or non-Hodgkin lymphoma (NHL) were analysed for receipt of RT.

Multilevel multivariablee hierarchical (mixed effects) logistic regression models were specified with a hierarchy of patients clustered within hospital trusts, Strategic Clinical Networks (SCNs) and former Cancer Networks. Funnel plots of the observed versus expected rates of RT delivery were then derived and used to compare RT utilisation between Strategic Clinical Networks (SCNs) and to compare the proportion of patients receiving curative/palliative treatment by NHS trust. The working paper found significant variation in the delivery of RT, especially across SCNs. There are many limitations to this work, however, which the authors note. The most serious limitation is the use of RTDS data from its very infancy, before consistent reporting was established. It sets out a number of points for further investigation, including the use of further linked datasets which gives greater patient

information such as stage of disease at diagnosis and greater granularity of treatment intent. This chapter expands upon this earlier work, utilising more recent English cancer registry data and linked datasets from 2014 to 2020.

2.2 Methods

2.2.1 National Cancer Registry and Analysis Service data for lymphoma

For a broader package work, data on every adult diagnosed with lymphoma in England between 1st Jan 1997 and 31st Dec 2017 was obtained from the National Cancer Registry and Analysis Service (NCRAS). A further amendment to the data request provided diagnoses through to 31st December 2020. NCRAS collects, quality assures and analyses data on all people living in England who are diagnosed with cancer.[67] The data consisted of the core National Cancer Registration Dataset, as well as a number of linked datasets which are linked in the data extract through pseudonymised patient and tumour specific codes. A summary of the National Cancer Registration Dataset and linked datasets relevant to this study is given in Table 2 .3

The data was transferred to the Nuffield Department of Population Health based on a data request and study proposal lead by Dr David Cutter and submitted through Public Health England's Office for Data Release. The data request and this study was proportionately reviewed by the NHS Health Research Authority (HRA) and received approval (19/SC/0227). A minor amendment to the ethics document was made adding Mr David Jones to the named researchers was accepted.

Table 2.3 Description of National Cancer Registration Dataset linked datasets

Dataset	Description
National Cancer Registration	The National Cancer Registration Dataset brings together data from

Dataset	more than 500 local and regional datasets to create a table including information about the patient, their diagnosis, tumour, and treatment events.
Systemic Anti-Cancer Therapy Dataset (SACT)	The SACT dataset is derived from mandatory information submitted by NHS Trusts in England on patients receiving cancer chemotherapy. The dataset has been designed to collect information on all drug treatments with an anti-cancer effect, in all treatment settings, including traditional cytotoxic chemotherapy and all newer agents.
National Radiotherapy Data set (RTDS)	The RTDS consists of information from a data standard that requires all NHS Acute Trust providers of radiotherapy services in England to collect and submit standardised data monthly against a nationally defined data set since 2009.
Hospital episode statistics (HES) – Inpatient, outpatient and A&E	HES is a database containing details about admissions, A&E attendances and outpatient appointments at NHS hospitals in England. This data is collected during a patient's time at hospital and is submitted to allow hospitals to be paid for the care they deliver.
National Cancer Waiting Times Monitoring Data Set (CWT)	The CWT dataset is designed to support the continued management and monitoring of English NHS cancer waiting times standards. It contains diagnosis and treatment information on cancer patients who were offered treatment within the NHS, including those who refused treatment or were assigned to active monitoring
Diagnostic Imaging Dataset (DID)	DID is a central collection of detailed information about diagnostic imaging tests carried out on NHS patients, extracted from local radiology information systems and submitted monthly. The DID captures information about referral source, details of the test (type of test and body site), date of imaging request, date of imaging, date of reporting.

2.2.2 Cohort identification, receipt of frontline curative intent radiotherapy, and assigning patients to their decision-making NHS Trust of care

The National Cancer Registration Dataset and linked datasets, hereafter referred to as the NCRAS lymphoma data, in its raw form required various steps of processing and cleaning. For this study, it was necessary to; (1) restrict the dataset to those with an index diagnosis of cHL or DLBCL, (2) identify which of these patients received frontline curative intent radiotherapy, and (3) identify for each patient the NHS Trust at which decision regarding treatment approach was made.

2.2.2.1 Restrict the dataset to those with an index diagnosis of cHL or DLBCL

Starting with restricting the dataset to index diagnoses of cHL or DLBCL, the cancer registry dataset contains many diagnostic variables including ICD-10 code(s), ICD-O-3 code(s), tumour histology and morphology which may not necessarily align. The NCRAS lymphoma data is being used in a number of different studies within NDPH as well as this thesis chapter. Data preparation work therefore had been undertaken by colleagues, Dr Johanna Ramroth, Jake Probert, and Andrew Challenger to categorise lymphomas into seven broad diagnosis categories, including cHL (NLPHL is not included in this category) and DLBCL, based on a decision hierarchy involving the information from the various diagnostic variables. The decision rules were developed alongside a clinical oncologist (David Cutter) and a specialist haematological pathologist (Daniel Royston). This categorisation was used to identify patients for this study. Patients were defined as having cHL if they had an ICD-10 (ICD-O-3) coding of C811 (9663, 9664, 9665, 9667), C812 (9652), C813 (9653, 9654, 9655), C814 (9651), and C819 (9650). DLBCL patients were identified through ICD-10 (ICD-0-3) codes; C832 (9675), C833 (9680, 9688, 9735), C834 (9684), C835, and C836. All stages of disease were considered with stage given as per the Ann Arbour staging system (I, II, III, IV) described in section 1.2.2.

2.2.2.2 Identify which patients received frontline curative intent radiotherapy

Secondly, for each cHL and DLBCL patient it needed to be determined whether they received radiotherapy, and whether this was in the frontline curative setting or later settings such as for relapse treatment or palliation. Two sources of information were available in the NCRAS lymphoma data for this purpose. Most simply, the cancer registry dataset contains a yes/no binary indicator of whether the patient received radiotherapy. This is derived from the raw data flows received by NCRAS, and is based on their identification of a first radiotherapy episode. The exact method used by NCRAS is not published.

The more extensive source of information is the National Radiotherapy Dataset (RTDS). Here, beginning in 2009, all NHS Trust providers of radiotherapy services in England have been required to collect and submit monthly data against a nationally defined data standard to NCRAS. The data collected undergoes a process of checks and validation, before being added to existing patient records within the cancer registry, or where a patient does not exist one is created. The RTDS is the culmination of this process.

Based on communication with Dr Katie Spencer, NHS Digital's National Clinical Lead for Radiotherapy Data, the RTDS was chosen as the basis for the identification of radiotherapy as it is generally thought to be more accurate. Furthermore, different standards of the RTDS have come into being over the index diagnosis period. In 2014, the fourth version (V4) of the RTDS standard was introduced which greatly improved ascertainment and quality of the data inputted. On this basis, the study cohort was restricted to cHL and DLBCL patients diagnosed after 1st Jan 2014.

The RTDS provides information on all radiotherapy attendances for each patient after index diagnosis, including for relapsed/refractory disease, palliation, or treatment of other primary malignancies. Each attendance sits within a radiotherapy episode, defined as a continuous period of care for radiotherapy including preparation, planning and delivery of radiotherapy. Patients may have multiple episodes of care, for instance where a patient is later diagnosed with a subsequent primary tumour or metastasis, then related radiotherapy will form part of a different episode. Each episode will contain at least one prescription of a total radiotherapy dose (Gy) and number of fractions.[68] Attendances, however, do not perfectly nest within prescriptions, as a patient can have treatment from more than one prescription within one attendance.

The RTDS includes a flag variable as to whether a radiotherapy episode was of curative or palliative intent. However, this variable does not distinguish between lines of curative intent radiotherapy or whether the episode was for the treatment of second primary cancers. Its accuracy when cross referenced with other variables such as prescribed dose and fractions suggested it could not be taken as singularly accurate.

It was, therefore, necessary to define the intention of each radiotherapy episode utilising the different variables given in the RTDS such as the date difference between diagnosis and receipt of RT (must be given in one year to be considered potentially first line), prescribed dose and prescribed fractions dose (must be considered a clinically possible curative regimen), and number of attendances (as a proxy measure of fractions). Sequential decision rules were created to determine whether a patient had received frontline curative intent radiotherapy based on the data with clinical support provided by clinical oncologist colleagues Dr David Cutter and Dr Rebecca Shakir. A sequential process was required as although dose and fractionation guidance are clear in medical guidelines, many patients had non-typical dose and fraction prescriptions. This could be due, for instance, to the fact patients may be replanned during treatment, tolerability/toxicities/patient condition necessitated deviations, or a clinical decision made to hypofractionate (i.e. deliver the same biological dose in fewer fractions than standard). The decision rules for cHL and DLBCL are shown respectively in Figure 2 .2 and Figure 2 .3

2.2.2.3 Identify for each patient the NHS Trust at which decisions regarding treatment approach were made

Finally for the analysis it was necessary to define for each patient their NHS Trust of care where it was most likely their treatment decision was made. Several candidate variables across the dataset indicating location of treatment were available. The linked CWT dataset included a field giving the NHS Trust code of “the health care provider (NHS Trust) where

the decision to treat the patient was made". For most patients, this variable was used, however for ~25% of patients this data field was missing. Next, the decision-making NHS trust was inferred from the cancer registry 'NHS trust of diagnosis' field. Where both CWT and cancer registry code were available (87% of all patients), there was 72% agreement between them. Only 5% of patients had both missing CWT and cancer registry codes. Assignment for the 5% was then inferred from other organisational records in the linked treatment datasets again using a sequential decision tree informed with clinical input again from Dr David Cutter and Dr Rebecca Shakir. The sequence is provided in Figure 2 .4.With NHS Trusts being transient over time, the naming configuration of NHS Trusts as of 2022 was used. NHS Trusts which had been merged or split were mapped to their most appropriate 2022 Trust.

Figure 2.2 Decision rules for the identification of patients who received frontline curative intent radiotherapy: classical Hodgkin lymphoma

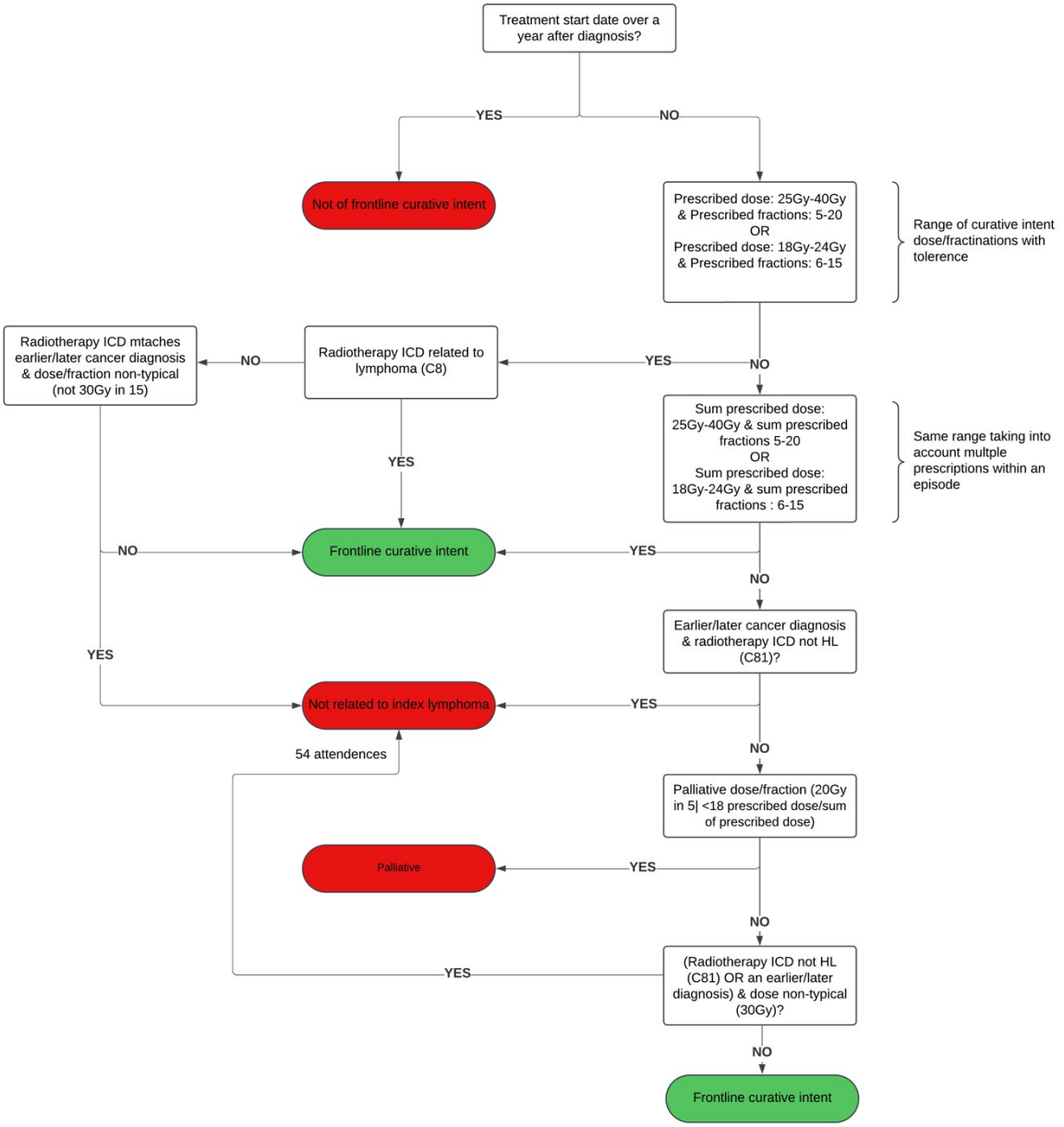


Figure 2.3 Decision rules for the identification of patients who received frontline curative intent radiotherapy: Diffuse large B-cell lymphoma

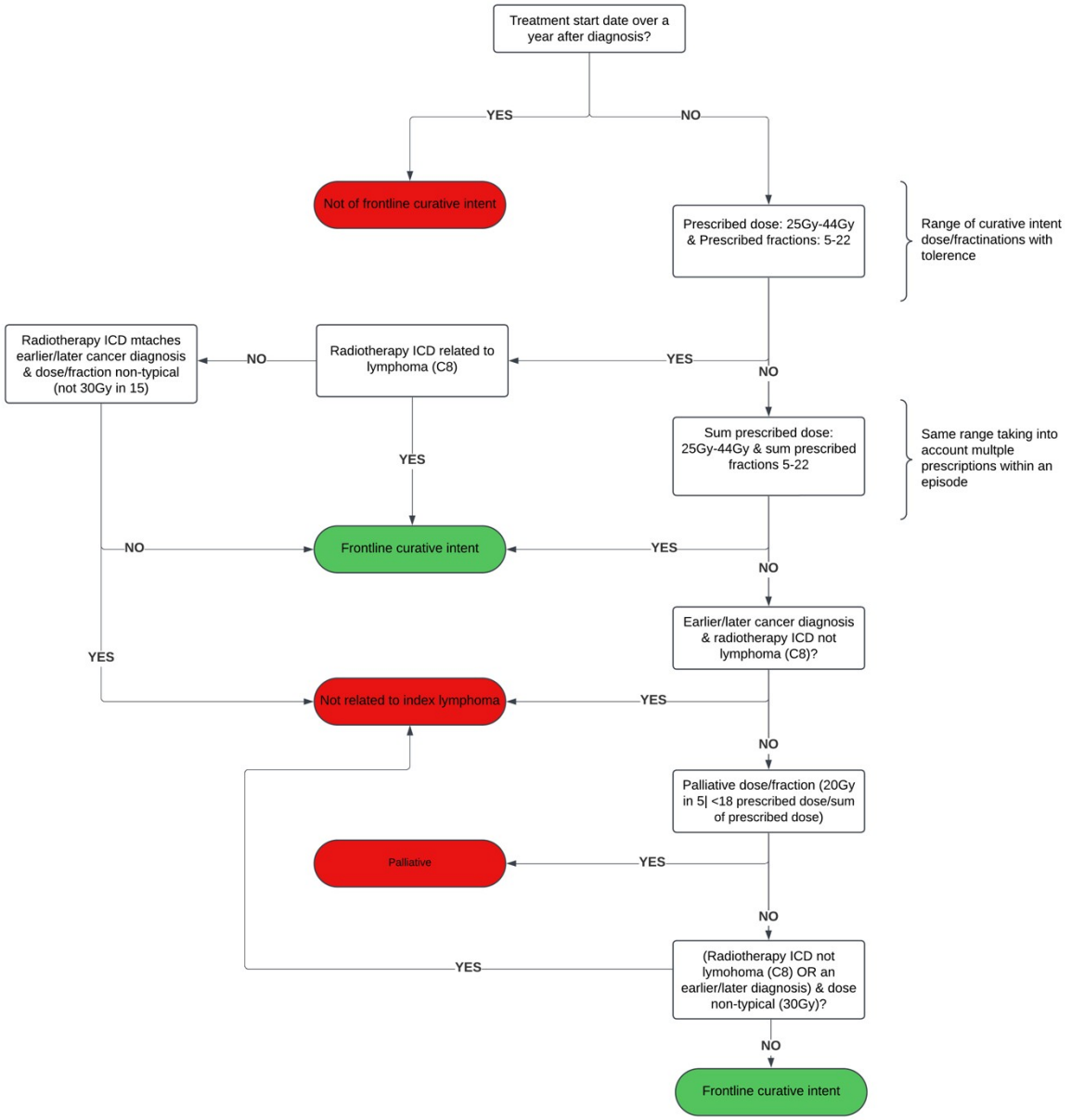
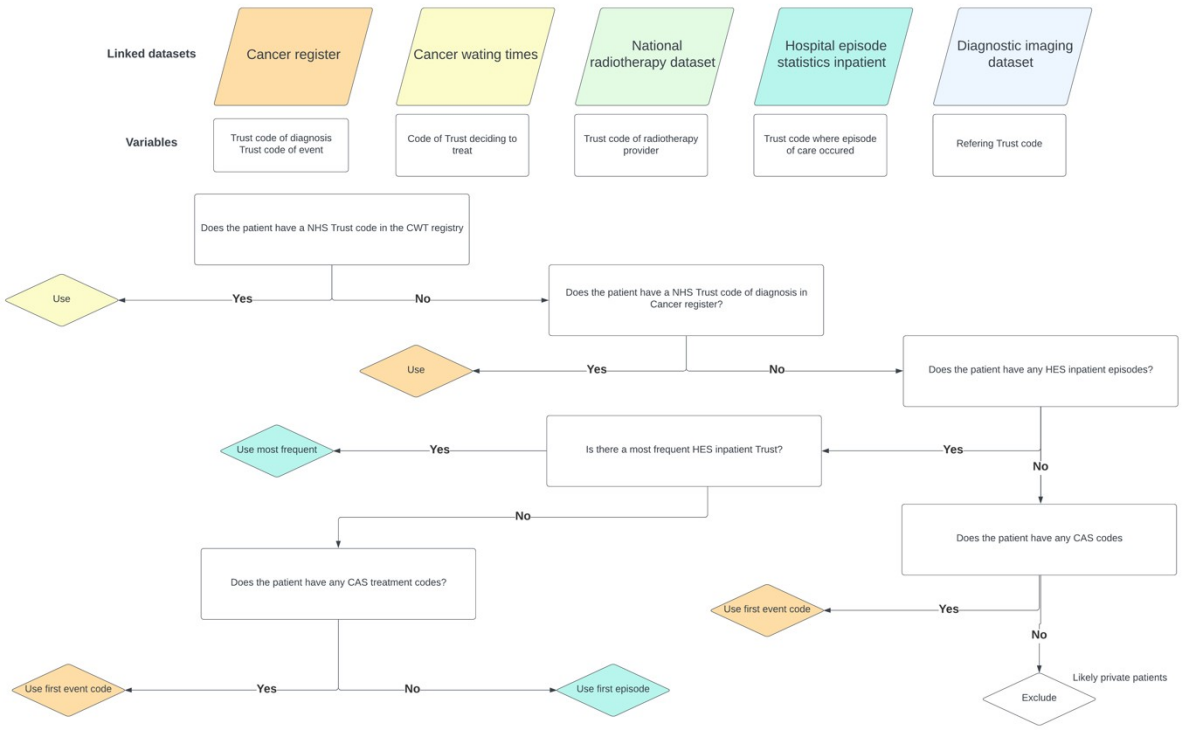


Figure 2.4 Decision rules for the identification of a patient's decision-making NHS Trust



2.3 Statistical analysis and study outcomes

2.3.1 Descriptive statistics of the patient cohort

Descriptive statistics of the cHL and DLBCL patient cohorts were derived separately. The temporal trend in the annual unadjusted proportion of patients receiving frontline RT over this the diagnosis period was also evaluated.

2.3.2 Funnel plots for institutional comparison

Risk-adjusted funnel plots were produced separately for cHL and DLBCL to investigate whether variation in the utilisation of RT across NHS Trusts is beyond that which would be expected through random variation given an assumed common underlying distribution.[69] Such plots typically consist of either, on the y axis, the ratio of the observed over the expected

outcomes for each NHS Trust or the covariate adjusted proportion, with specified control limits forming a funnel shape along the x-axis (the expected number of patients) which marks the limits of the expected outcome for each NHS Trust.

The expected utilisation rate of RT at each NHS Trust was estimated by summing the patient expectations from a logistic regression model. In the model, receipt of frontline consolidative RT, a binary yes/no as defined previously, was regressed against a set of covariates. This set consisted of patient factors in the National Cancer Registration Dataset which would be expected, a priori, to influence the decision to deliver frontline curative intent radiotherapy;

- the patient's age at diagnosis. Categorised into bands: 18-29y, 30-39y, 40-49y, 50-59y, 60-69y, 70-79y, and 80+y for cHL with 18-29y as reference category, and 18-49y, 50-59y, 60-69y, 70-79y, 80+y for DLBCL with 18-49y as reference category. These categorisations reflect the even distribution of cHL across ages, whereas DLBCL is rare in those <50y (table 2.2). Categorisation was considered due to the potential for non-linear effects and the ease of interpretation.
- Sex (dummy variable, male as reference category),
- Index of Multiple Deprivation (IMD) quintile (IMD quintile 1 (most deprived) as reference category),
- Stage at diagnosis (I-IV and missing) (Stage I as reference category, stage III and IV were pooled together as they are similarly considered advanced stage).
- Charlson Comorbidity Index (CCI) score derived 76-6 months before diagnosis (0, 1, 2, 3, and 4+ with 0 as reference category)
- Route to diagnosis. A patient's route to diagnosis could be one of six categories; GP referral, urgent suspected cancer pathway, other outpatient, inpatient elective, emergency presentation, and unknown. GP referral, urgent suspected cancer pathway,

other outpatient and inpatient elective were grouped into one category, which acted as the reference.

- Additionally, a patient's distance in kilometres (km) to their nearest radiotherapy centre was included as a covariate (considered continuous) in the logistic regression model. This was approximately estimated by using the Lower Layer Super Output Areas (LSOA) code of residence for each patient as given in the National Cancer Registration Dataset. LSOAs are small geographically defined area units of England which contain on average 1500 people. Distance in km was calculated from the centroid of the LSOA area to the point location of each of the 52 NHS Trusts with a radiotherapy centre, with the lowest distance taken.

The logistic regression model specification for the cHL model is as follows, with the same being employed for DLBCL although with less age categories:

$$logit\left(P\left(Y_i=1\right)\right)=\beta_0+\beta_1\,Age18¿29¿_i\ldots+\beta_6\,Age80\,plus_i+\beta_7\,SexFemale_i+\beta_8\,IMD2_i\ldots+\beta_{11}\,IMD5_i+\beta_{12}\,StageI$$

Upper and lower control limits were constructed at 2δ and 3δ (corresponding to 95% and 99.8% confidence intervals) around the overall mean observed to expected utlisation ratio, using the exact binomial method, interpretable as a two-sided statistical test comparing a specific NHS Trust to the hypothesis that their result does not differ from the overall rate at a two-sided 5% or 0.02% significance level.[70,71]

Greater than expected variability may suggest true differences between NHS Trust in their preference towards/against giving RT, but may also reflect, to an extent, incomplete case-mix adjustment.[72] Ideally, tumour characteristics such as bulk and location would be included in the regression model, however, such information is not available in the National Cancer Registration Dataset. Nonetheless, it is unlikely that tumour characteristics would vary substantially nor systematically between NHS Trusts. As an exploratory check that any excess

variation relates, at least in part, to centre contextual effects, the correlation between the case-mix adjusted utilisation rate for HL and DLBCL was assessed.

2.3.3 Hierarchical regression specification and contextual effects

To further assess variables associated with RT utilization and assess the extent of residual contextual effects, a hierarchical (mixed effect) specification of the previous logistic regression model was utilised. In the hierarchical specification, an NHS Trust level was added via a random intercept term. Such a model assumes in this case that the patient characteristics influence the choice to irradiate similarly across the NHS Trusts, but the random intercepts term allows each NHS trust's regression intercept to deviate (following a normal distribution with mean zero) from the overall intercept. This fits with our hypothesis of an underlying propensity to give or omit radiotherapy at the NHS trust-level. The mixed effects logistic regression model specification is as follows:

$$logit\left(P\left(Y_{ij}=1\right)\right)=\beta_0+\beta_1 Age18¿29¿_i\ldots+\beta_6 Age80\ plus_i+\beta_7 SexFemale_i+\beta_8 IMD2_i\ldots+\beta_{11} IMD5_i+\beta_{12} StageI$$

Where $\alpha_j \sim N\left(0,\sigma_\alpha^2\right)$, is an NHS trust-specific deviation from the overall intercept, assumed to follow a normal distribution

A likelihood ratio test was performed comparing the non-hierarchical and hierarchical specifications to formally assess whether the odds of receiving radiotherapy for a given patient varies because of the treating NHS Trusts (due to unobserved factors such as latent preferences towards RT).Furthermore the variance partition coefficient (VPC), using the latent threshold method, and median odds ratio (MOR) were estimated for the hierarchical model.[73] The VPC provides an estimate of the of proportion of total variability attributable to the different model levels (patient and NHS Trust levels), and the MOR reflecting the ratio between the odds that the same patient (as defined by the patient covariate set) would receive

frontline RT in any two randomly selected NHS Trusts – the ratio of the median odds of receiving frontline curative intent radiotherapy between an NHS Trust with high utilisation and one with low utilisation. The MOR, as an odd ratio, can be compared with the effect sizes of fixed effects covariates (patient characteristics). Intercepts and coefficients of fixed effects were assessed for statistical significance at a 95% level.

2.4 Results

2.4.1 Study cohort and NHS Trusts

The National Cancer Registration Dataset contained 39,977 patients diagnosed with HL (9,789 patients) or DLBCL (30,188 patients) between 1st Jan 2014 and 31st December 2020. Subsequently, the decision-making healthcare provider was identified for 39,955 patients, of which 39,760 were included after the exclusion of patients treated at a private provider or who were assigned an NHS Trust of care outside of England or to a specialist NHS Trust (Mental, children's or women's). Patients were also excluded if their route to diagnosis was by death certificate only (n = 6), or if their Charlson Comorbidity Index (CCI) score (n = 42) or LSOA was missing (n = 176). Finally, 39,536 patients (9656 and 29,880 respectively for cHL and DLBCL respectively) were included in the final analysis set after the exclusion of patients with invalid LSOA codes.

The included patients spanned 126 English decision-making NHS Trusts. The number of HL patients under the care of each NHS Trust ranged from 3 to 344 (median 64) and the number of DLBCL patients ranged from 15 to 788 (median 200). Patient characteristics by lymphoma subtype are presented in Table 2 .4. Across the time range of diagnosis, 2014 to 2020, the

(unadjusted) percentage of patients receiving radiotherapy delivery remained relatively stable (), averaging 20% and 22% across all stages for HL and DLBCL, respectively**.**

Table 2.4: Characteristics of patient cohort

		HL	DLBCL
Total patients: n		9656	29880
Age at diagnosis: Median (IQR)		45 (29 to 66)	71 (60 to 79)
	18-29	2595 (26.9%)	549 (1.8%)
	30-39	1587 (16.4%)	878 (2.9%)
	40-49	1108 (11.5%)	1764 (5.9%)
	50-59	1147 (11.9%)	3765 (12.6%)
	60-69	1221 (12.6%)	6750 (22.6%)
	70-79	1208 (12.5%)	9345 (31.3%)
	80+	790 (8.2%)	6829 (22.9%)
Sex: n (%)	Female	4258 (44.1%)	13200 (44.2%)
	Male	5398(55.9%)	16680 (55.8%)
Stage: n (%)	I	920 (9.5%)	4806 (16.1%)
	II	3082 (31.9%)	4233 (14.2%)
	III	1826 (18.9%)	4318 (14.5%)
	IV	2869 (29.7%)	13019 (43.6%)
	Unknown/ Missing	959 (9.9%)	3504(11.7%)
IMD quintile: n (%)	1 (most deprived)	1925 (19.8%)	5030 (16.8%)
	2	1962 (20.1%)	5614 (18.8%)
	3	2060 (21.4%)	6213 (20.8%)
	4	1896 (19.7%)	6521 (21.8 %)
	5 (least deprived)	1813 (19.0%)	6502 (22.8%)
Charlson Comorbidity Index 76 to 6 month before diagnosis: n (%)	0	7793 (80.7%)	20189 (67.6%)
	1	941 (9.8%)	4316 (14.4%)
	2	473 (4.9%)	2682 (9.0%)
	3	241 (2.5%)	1348 (4.5%)
	4+	208 (2.2%)	1345 (4.5%)
Route to diagnosis	Emergency presentation	1272 (13.2%)	7129 (23.9%)

	GP referral	1674 (17.3%	4679 (15.7%)
	Inpatient elective	89 (0.9%)	368 (1.2%)
	Other outpatient	655 (6.8%)	1974 (6.6%)
	Urgent Suspected Symptom	2969 (30.7%)	6801 (22.8%)
	Unknown	2997 (31.0%)	8929 (29.9%)
Distance to nearest RT centre (Median; IQR)		13.3 km (6.1 km to 21.9 km)	14.4 km (7.1 km to 23.4 km)
	0-10 km	3846 (39.8%)	10668 (35.7%)
	10-20 km	2943 (30.5%)	9061 (30.3%)
	20-30 km	1844 (19.1%)	6305 (21.1%)
	30-40 km	620 (6.4%)	2324 (7.8%)
	40+km	403 (4.2%)	1522 (5.1%)

Figure 2.5: Percentage of Hodgkin and diffuse large B-cell lymphoma patients receiving frontline curative radiotherapy by year of diagnosis and stage

and Figure 2 .7 provide the patient case-mix adjusted funnel plots for HL and DLBCL, respectively. Results from the logistic regression model of the association between patient case-mix variables and the odds of receiving frontline curative intent radiotherapy are given in Table 2 .5. For both HL and DLBCL, female sex (HL: OR 0.88, p <0.001) (DLBCL: OR 0.83, p <0.001) lead to a statistically significant decrease in the odds of receiving RT compared to being of male sex. Similarly, a diagnosis of stage II (HL: OR 0.24, p <0.001) (DLBCL: OR 0.43, p <0.001) or III/IV (HL: OR 0.04, p <0.001) (DLBCL: OR 0.21, p <0.001) disease led to a statistically significant decrease compared to diagnosis of stage I disease. Here notably, the odds ratio was closer to 1 than 0 for DLBCL compared to HL. This is likely due to the proportion of patients at stage I receiving radiotherapy being less in DLBCL than HL, whilst the proportion is similar for stage II, III and IV as shown in Figure 2.4.

For CCI score there was a trend towards an incrementally decreasing odds ratio of receiving radiotherapy as the score increased, with a CCI score of 3 or 4+ having a statistically significant effect compared to the reference category of 0 for both lymphomas. In cHL, a non-linear effect of age is apparent; the 40-49y, 50-59y and 60-69y age categories had a statistically significant greater odds ratio of receiving radiotherapy compared to the age 18-29y reference which became insignificant and close to 1 in the 70-79y and 85y+ age categories. For DLBCL, there was a trend towards a decreasing odds ratio of receiving radiotherapy with increasing age category compared to the 19-49 reference group. Emergency presentation was associated with a decreased odds of receiving radiotherapy for both cHL and DLBCL. There was no statistically significant effect with respect to distance, however in DLBCL, there is a monotonic trend towards increasing odds of receiving radiotherapy as distance increases.

Figure 2.6 Funnel plot of the covariate-adjusted proportionof radiotherapy utlisation for each NHS Trust with 95% and 99.8% control limits: Hodgkin lymphoma

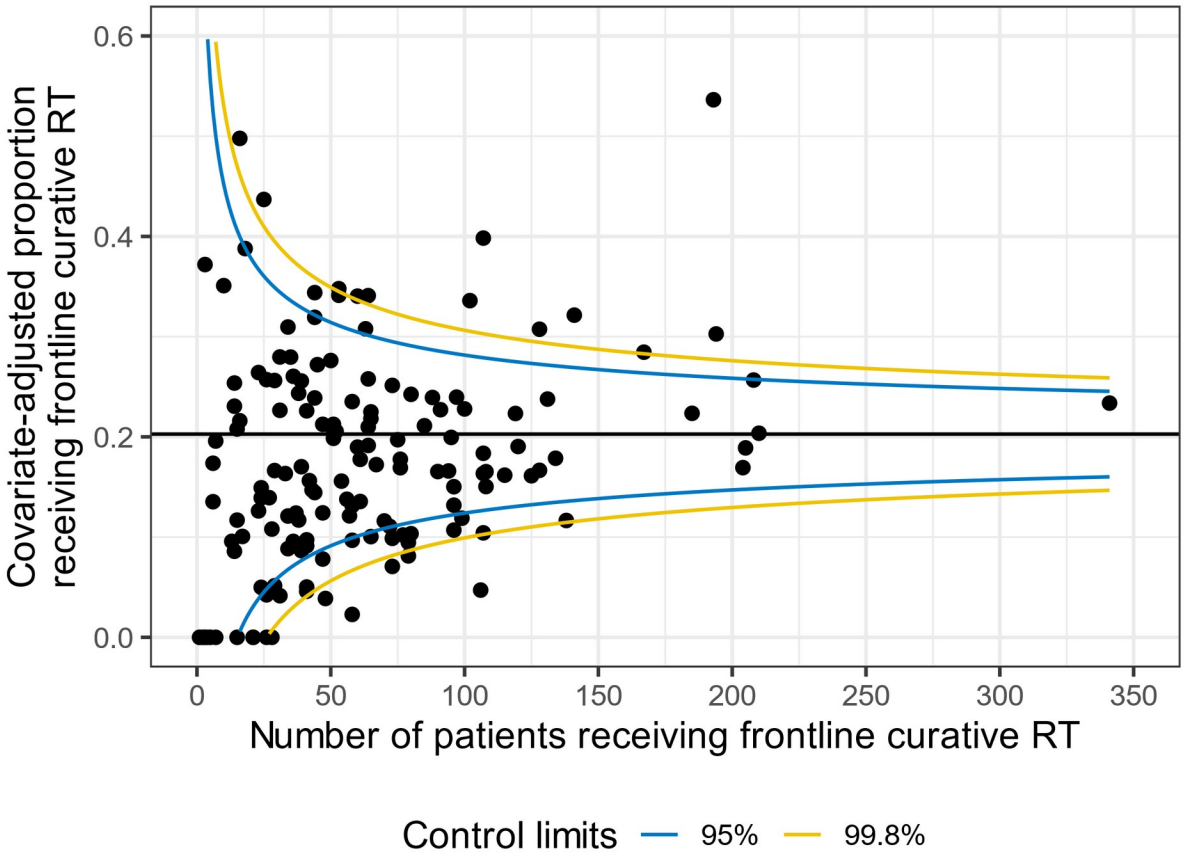
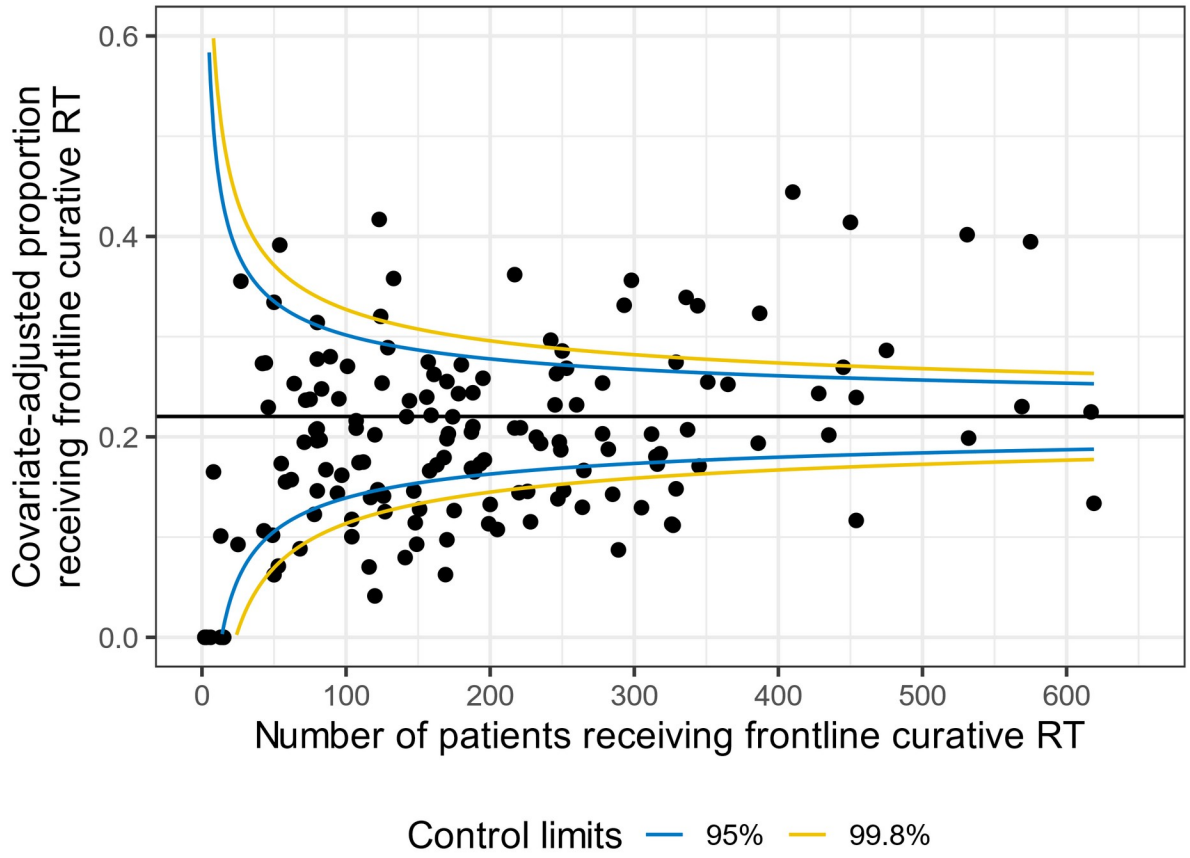
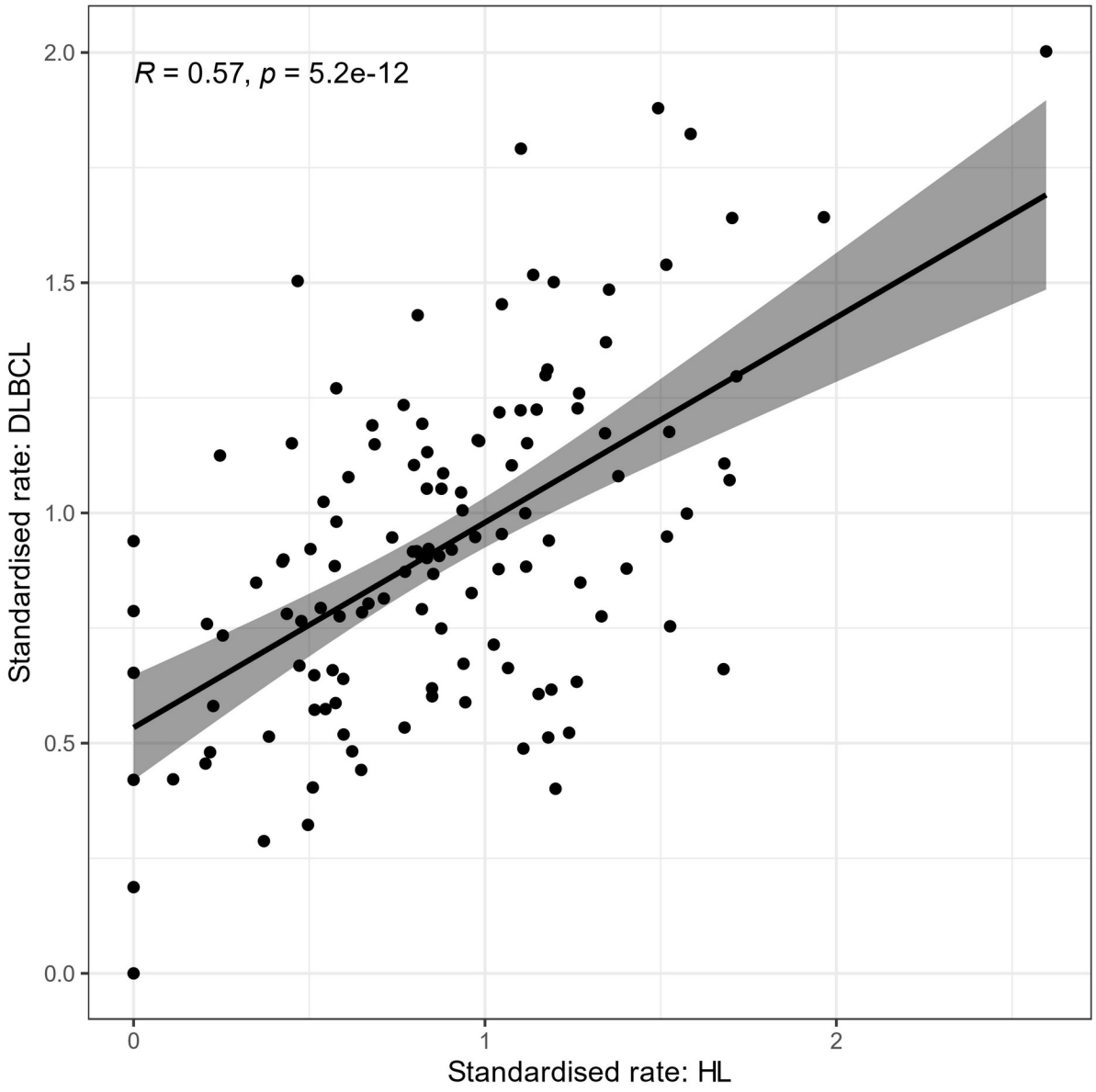

Covariate-adjusted proportion receiving frontline curative RT
0.6
0.4
0.2
0.0
0
50
100
150
200
250
300
350
Number of patients receiving frontline curative RT
Control limits
95%
99.8%

Figure 2.7 Funnel plot of the the covariate-adjusted proportion of radiotherapy utlisation for each NHS Trust with 95% and 99.8% control limits: Diffuse large B-cell lymphoma



For HL and DLBCL respectively, 40 and 63 NHS Trusts (of 126) were outside of the 95% control limits, indicated excess variation over what would be expected due to random variation. Furthermore, there was a positive and statistically significant association between the ratio of observed over expected utilisation rate for HL and DLBCL (Figure 2 .8). Therefore, NHS Trusts who had a higher radiotherapy delivery rate for HL patients were more likely to have a higher RT delivery rate for DLBCL.

Figure 2.8 Comparison of the standard rate of radiotherapy utlisation for HL and DLBCL at each NHS Trust



2.4.3 NHS Trust level associations and variation attribution

Outcomes from the hierarchical logistic regression models are also provided in Table 2 .5 for both HL and DLBCL. The likelihood ratio test found for both lymphomas that the addition of a random intercept for the NHS trust provided a statistically significant improvement in model fit. Patient characteristics had similar associations as the non-hierarchical logistic model.

Table 2.5: Regression results for the non-hierarchical and hierarchical logistic regression model

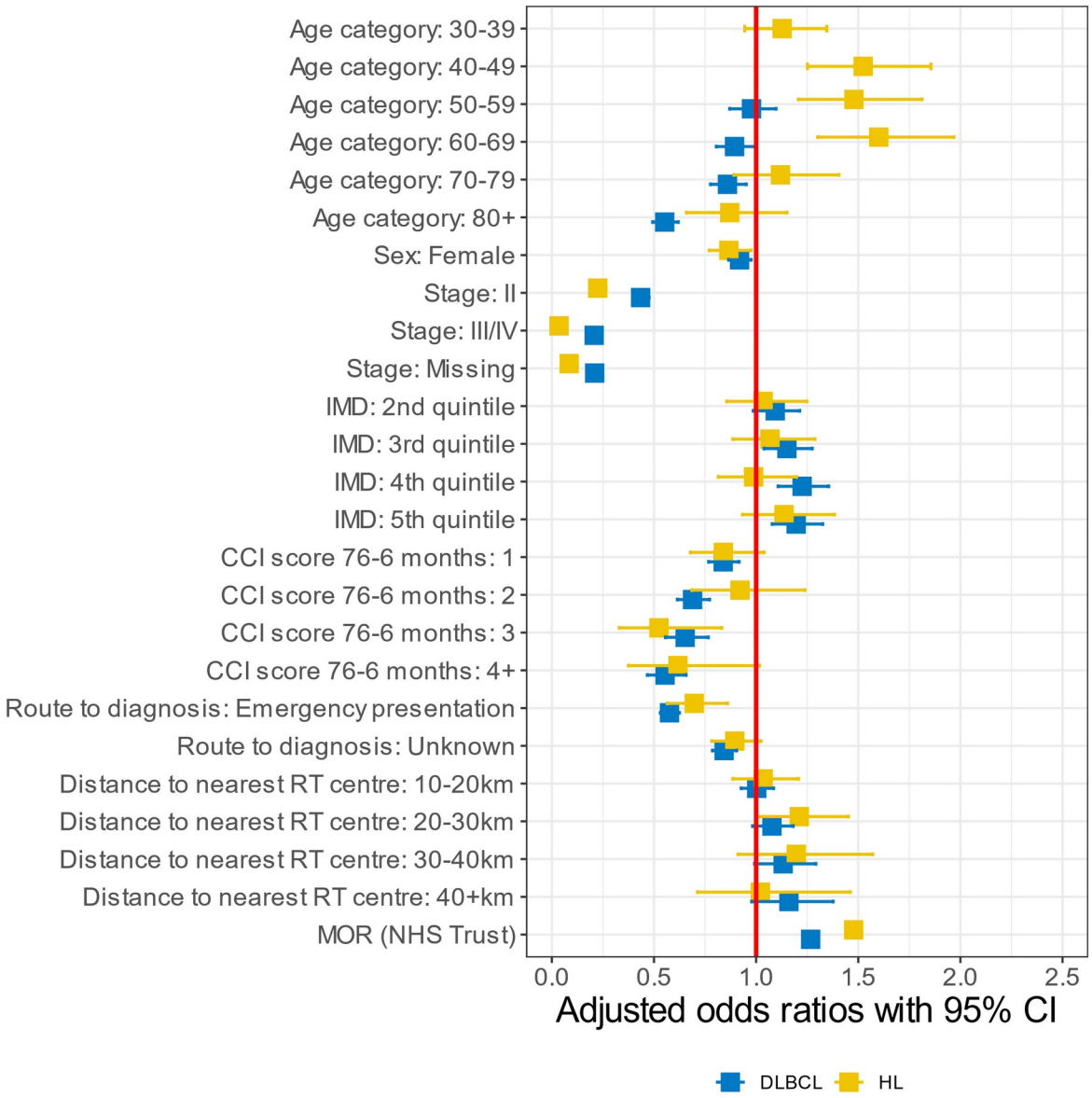
		cHL (n = 9656)		DLBCL (n = 29880)	
		Logistic model OR (95% CI, p value)	**Hierarchical model OR (95% CI, p value)**	**Logistic model OR (95% CI, p value)**	**Hierarchical model OR (95% CI, p value)**
Age at diagnosis: cHL reference category; 18-29y, DLBCL reference category; 18-49y	30-39	1.1 (0.93 to 1.3, 0.268)	1.13 (0.94 to 1.35, 0.185)	-	-
	40-49	1.34 (1.11 to 1.62, 0.002)	1.52 (1.25 to 1.86, <0.001)	-	-
	50-59	1.3 (1.07 to 1.57, 0.008)	1.48 (1.21 to 1.81, <0.001)	0.99 (0.88 to 1.11, 0.838)	0.98 (0.87 to 1.1, 0.699)
	60-69	1.42 (1.16 to 1.72, 0.001)	1.6 (1.3 to 1.97, <0.001)	0.89 (0.8 to 0.99, 0.027)	0.89 (0.81 to 0.99, 0.037)
	70-79	1.01 (0.81 to 1.25, 0.96)	1.12 (0.89 to 1.41, 0.333)	0.85 (0.77 to 0.94, 0.001)	0.86 (0.78 to 0.95, 0.004)
	80+	0.77 (0.59 to 1, 0.057)	0.87 (0.66 to 1.15, 0.332)	0.55 (0.49 to 0.61, <0.001)	0.55 (0.49 to 0.62, <0.001)
Sex: male as reference category	Female	0.88 (0.78 to 0.98, 0.021)	0.87 (0.77 to 0.97, 0.017)	0.93 (0.88 to 0.99, 0.016)	0.92 (0.87 to 0.98, 0.006)
Stage: I as reference category	II	0.24 (0.21 to 0.29, <0.001)	0.22 (0.19 to 0.27, <0.001)	0.43 (0.39 to 0.47, <0.001)	0.43 (0.4 to 0.48, <0.001)
	III/IV	0.04 (0.03 to 0.05, <0.001)	0.04 (0.03 to 0.04, <0.001)	0.21 (0.2 to 0.23, <0.001)	0.21 (0.19 to 0.22, <0.001)
	Unknown/Missing	0.1 (0.08 to 0.12, <0.001)	0.08 (0.07 to 0.11, <0.001)	0.2 (0.18 to 0.22, <0.001)	0.21 (0.19 to 0.24, <0.001)
IMD quintile: 1 (most deprived) as reference category	2	1.04 (0.87 to 1.24, 0.649)	1.03 (0.86 to 1.25, 0.728)	1.01 (0.91 to 1.11, 0.871)	1.09 (0.99 to 1.21, 0.091)
	3	1.01 (0.85 to 1.2, 0.92)	1.07 (0.89 to 1.29, 0.492)	1.08 (0.98 to 1.19, 0.133)	1.15 (1.04 to 1.27, 0.007)
	4	0.97 (0.81 to 1.16, 0.711)	0.99 (0.81 to 1.2, 0.9)	1.18 (1.08 to 1.3, 0.001)	1.23 (1.11 to 1.36, <0.001)
	5 (least deprived)	1.1 (0.92 to 1.32, 0.292)	1.14 (0.93 to 1.38, 0.203)	1.16 (1.05 to 1.27, 0.003)	1.2 (1.08 to 1.33, 0.001)
Charlson Comorbidity Index 76 to 6 month before diagnosis: 0 as reference category	1	0.87 (0.71 to 1.06, 0.179)	0.84 (0.68 to 1.04, 0.108)	0.85 (0.77 to 0.92, <0.001)	0.84 (0.77 to 0.92, <0.001)
	2	0.94 (0.7 to 1.24, 0.649)	0.92 (0.69 to 1.24, 0.587)	0.71 (0.63 to 0.79, <0.001)	0.69 (0.61 to 0.77, <0.001)
	3	0.54 (0.34 to 0.82, 0.006)	0.52 (0.33 to 0.83, 0.006)	0.67 (0.57 to 0.79, <0.001)	0.65 (0.56 to 0.77, <0.001)
	4+	0.61 (0.37 to 0.97, 0.046)	0.62 (0.37 to 1.02, 0.058)	0.59 (0.5 to 0.69, <0.001)	0.55 (0.47 to 0.66, <0.001)
Route to diagnosis:	Emergency	0.67 (0.55 to	0.7 (0.56 to 0.	0.58 (0.54 to	0.58 (0.53 to 0.

TWW/inpatient/outpatient/GP referral as reference category		0.82, <0.001)	86, 0.001)	0.63, <0.001)	62, <0.001)
	Unknown	0.91 (0.8 to 1. 04, 0.162)	0.9 (0.78 to 1. 02, 0.107)	0.84 (0.78 to 0.9, <0.001)	0.84 (0.79 to 0. 9, <0.001)
Distance to nearest RT centre: 0-10km as reference category	10-20km	0.96 (0.83 to 1.1, 0.537)	1.03 (0.89 to 1.21, 0.668)	0.96 (0.89 to 1.03, 0.261)	1 (0.93 to 1.09, 0.943)
	20-30km	1.1 (0.94 to 1. 28, 0.227)	1.21 (1.01 to 1.45, 0.037)	0.99 (0.91 to 1.07, 0.788)	1.08 (0.98 to 1. 18, 0.112)
	30-40km	1.16 (0.91 to 1.46, 0.217)	1.2 (0.91 to 1. 57, 0.196)	1.02 (0.91 to 1.15, 0.686)	1.13 (0.99 to 1. 29, 0.065)
	40+km	1.06 (0.79 to 1.4, 0.715)	1.02 (0.71 to 1.46, 0.911)	1 (0.87 to 1.1 5, 0.993)	1.16 (0.98 to 1. 38, 0.088)

For HL and DBCL respectively, the variance partition coefficient (VPC) estimate, the estimated proportion of total variation attributable to the NHS Trust level, was 11.0% and 7.0%. The median odds ratios (MORs), the median increase in odds of receiving curative intent radiotherapy were the same patient to switch from a cluster with lower odds to a cluster with higher odds of using radiotherapy, was 1.47 and 1.27 respectively (Figure 2.8).

Figure 2.9: Estimated adjusted odds ratios of receiving radiotherapy with 95% confidence intervals from the hierarchical logistic regression model, and the median odds ratio

between NHS Trusts.



2.5 Discussion

In this study it was hypothesised that uncertainty surrounding the long-term effects of frontline curative radiotherapy for HL and DBCL may result in variation in its use across a country, and this hypothesis was explored using English National Cancer Registration data. The results of the analysis suggest a high degree of variability in RT delivery for both HL and DBCL outside of what would be expected due to observed patient case-mix variables. The estimated MOR ratios from the hierarchical regression analysis can be interpreted as for a given HL (DLBCL) patient the odds of receiving frontline curative radiotherapy would be

1.47 (1.27) times greater were the patient to be treated at high delivery NHS Trust (i.e. one with a higher than the average. delivery rate) versus a low delivery NHS Trust. These effect sizes are greater than patient factors such as sex (inverse odds ratio (1/OR), i.e. flipping the reference categories from male to female, for HL; 1.15 and DLBCL; 1.08)), where established perception of the added risk of second primary breast cancer is commonly used as a rationale for radiotherapy avoidance in women. Although the effect size was not as great as stage, with stage II to IV disease greatly reducing the odds of receiving radiotherapy (e.g. Stage II Hodgkin lymphoma has an odds ratio of 0.22 compared to stage I reference with the inverse odds ratio being 4.55). As such, the location at which a patient is treated is a significant determinant of whether or not frontline curative radiotherapy will be used in their treatment. This is likely reflective, at least in part, of clinician predilection regarding the use of radiotherapy.

The linked NCRAS dataset enabled the inclusion of many patient-case mix characteristics which were a priori hypothesised to affect the choice to irradiate or not. However, it was not possible to incorporate some patient-level variables which may influence the decision to irradiate, such involvement of the mediastinum, performance status, and other radiological features, as they are not recorded in the routine datasets used. Additionally, patient choice could not be observed. Such unobserved characteristic may contribute to the overdispersion observed. However, it is reasonable to assume such variables, once conditioned for factors included such as age and sex, to be evenly distributed across geographies and years of incidence. Furthermore, we found that NHS Trusts who had a higher radiotherapy delivery rate for HL patients were similarly more likely to have a higher RT delivery rate for DLBCL, supporting the interpretation that treating teams exhibit differing preferences towards or against the use of frontline curative radiotherapy. It should be noted though that the variation observed at the NHS trust-level may also reflect other specific characteristics of the NHS-

Trust which were not incorporated into the model due to the difficulty in capturing them. For instance, over these periods certain trusts may be enrolling patients into clinical trials which prespecify a given treatment approach. Additionally, our analysis did not include further hierarchical components which may contribute to variation, which were instead assigned to NHS Trusts effects. For instance, clinicians from geographic related NHS Trusts form multidisciplinary teams (MDT) who review cases and collaborate on treatment decisions. It is plausible that NHS Trusts within the same MDT may have more similar utilisation rates. Inclusion of such a level was precluded by the lack data to enable the mapping of these MDTs.

The analysis relies on two allocation steps using the dataset variables available; the assignment of individuals to their decision-making NHS trust and the intent of any radiotherapy received. Neither of these variables are uniquely and completely given, therefore decision rules guided by clinical colleagues were created. External validation of these decision rules was not possible due to the lack of such external data. Analysis comparing agreement between the 'NHS trust where the decision to treat the patient was made' as given in the CWT and the cancer registry's 'NHS trust of diagnosis' found modest agreement (agreement in 72% of patients). The variables do however measure different events, the decision to treat versus diagnosis. It was thought that the latter variable provides the closest approximation of the desired variable, the 'decision making' NHS trust, hence the sequential approach to allocation was used. A limitation of this analysis is that no sensitivity analyses were performed which looked at the effect on outcomes of changes to the NHS trust and the intent of any radiotherapy assignment rules. The presence of such variation in clinical treatment practice, due in part to the uncertainty in clinic evidence, is suboptimal from the perspective of maximising patient outcomes – although it is not known what the 'correct' utilisation of RT is, the variation implies some NHS trusts must be giving either too much or

too little RT, resulting in suboptimal patient outcomes. Even with sufficient follow-up, clinical trials of RT omission may not have sufficient sample sizes to demonstrate differences in late effects, therefore the development and clinical adoption of patient risk models can be an aid for making more informed treatment decision making with respect to omitting radiotherapy. Analysis of PET features such a standardized uptake value (SUV), a measure of radioactivity in a specific area of interest relative to an idealized even distribution of radioactive, suggest such radiological features may be used to identify individuals at a high risk of relapse for whom omission of radiotherapy may not be beneficial. Similarly, nested case-control studies of historically treated patients relating the dose of irradiation received by specific organs to the risk of subsequence disease may enable the identification of patients most of risk of the late effects radiotherapy such as cardiovascular disease and new primary cancers. Ideally such disparate risks should be brought together to give predictions of outcomes over the life course of the patient.[74] This premise is taken forward into the next chapter.

3 Informing radiotherapy decisions in stage I/IIa classical Hodgkin lymphoma through lifetime microsimulation modelling

3.1 Background

3.1.1 Study rationale

As outlined in section 1.2.3 and in the previous chapter, there is uncertainty surrounding the use of RT in the frontline treatment of Hodgkin lymphoma. It is recommended in various treatment guidelines, in particular for those patients with early stage classical Hodgkin lymphoma (ESHL),[3,59] and is highly efficacious, contributing to freedom from progression of >90% ten years after treatment.[75] These excellent outcomes combined with a young median age of incidence, however, allow time for latent collateral radiation injury to organs-at-risk (OAR) to manifest into radiation-induced disease. Therefore, long-term survivors are at an increased risk of developing radiation-induced late effects including heart disease, ischemic stroke and second cancers that can substantially affect quality of life and lead to early mortality.[76–80] Currently, trial evidence from the RAPID, H10 and HD16 trials concordantly show a reduction in progression-free survival with PET-response adaptive omission of RT. The combined PFS events from the three trials in early-stage patients (the 'favorable cohort of the H10 trial) demonstrates this statistically significantly difference (HR=2.77; 95% CI 1.08–7.11, p=.03), with only 3.7% (28/764) of patients in the RT group having a progressive event compared with 10.8% (81/749) in the group without RT.[81]

None of the three trials, however, found a statistically significant difference in overall survival. This reflects both the success of treatment for relapsed HL leading to a limited number of events (deaths) and a limited amount of follow-up time (between 3-5 years). Many important radiation-related late effects occur between 10 and 40 years after RT, therefore, it is potentially decades before follow-up in these trials is mature enough to observe the manifestation of radiation-induced disease. It may be the case that for some patients, a greater initial risk of early HL relapse might be offset by the benefit of lower incidence and mortality

from late effects or vice versa. In practice, and as discussed in the previous chapter, persistent concerns regarding the risk of late effects seen following historical radiotherapy techniques, combined with this contemporary uncertainty, has resulted in geographic variation in radiotherapy use. This may be to the detriment of some patients where the radiation-related risks may in fact be minimal with modern radiotherapy techniques and the avoidance of RT to reduce these risks unnecessary.[82]

3.1.2 Chapter objectives

Ideally, the choice to omit radiotherapy should be made through shared decision making by the patient and clinicians, with access to all relevant evidence. This should include not only progression free survival results from clinical trials, but longer-term estimations of the full set of benefits and risks. Therefore, to better inform such choices, individualized modelling of the patient outcomes of this decision over the life course of the patient is necessary.[74]

To summarize the trade-offs between the risks and benefits of omitting RT, translation is required into a composite and readily understandable measure. An overall survival probability expressed as expected life years, or an extension to this incorporating health-related quality of life (HRQoL), generally referred to as expected quality-adjusted life years (QALYs). To this end, the objective of this chapter is to develop a decision analytic model capable of simulating in detail the life course of a classical HL patient after treatment with CMT or chemotherapy alone, and apply the model to a number of illustrative early-stage patients to determine which treatment strategy maximizes life expectancy and QALYs

3.1.3 Chapter structure

This chapter is structured to provide information on the model developed and also the thought process behind the components of the model at each stage. I begin in section 3.2 with

methodological development, which includes conceptualization of the model and its requirements to appropriately address the research question. I then go on to outline the final model developed (section 3.3.1), before elaborating further on the separate components of the model and the considerations and choices which were taken. Thereafter, results from the application of the model are provided, and discussed.

3.2 Model conceptualisation and requirements

Mathematical models are a ubiquitous way of representing and simulating patient health.[83] The process of creating the model can be helpfully separated into two distinct processes.[84] Firstly the conceptualisation of the decision problem itself, in which knowledge of the health care process or decision is formalised into a representation of the problem. This then leads into the second process, model conceptualisation.[84]

3.2.1 Conceptualisation of the decision problem and model requirements

Conceptually, the decision problem this chapter aims to address is as follows: A patient presents with early-stage classical Hodgkin lymphoma (noting that NLPHL is now considered a non-Hodgkin lymphoma and a transition in treatment approach is occurring) and begins multi-agent chemotherapy. The patient undergoes interim PET imaging to assess response, finding a complete response to initial chemotherapy. The patient and their clinician must then make a final choice between radiotherapy (therefore receiving CMT), or treatment with chemotherapy alone.

This choice is dependent on the expected outcomes of the two different strategies, and the weight the patient and clinician places on these outcomes. For the option of chemotherapy alone this includes the increased risk of relapse and the consequences of relapse. For CMT it

includes reduced risk of relapse and, in addition, the risks of late effects. Currently, the three randomised trials of radiotherapy omission provide clear evidence of a greater risk of relapse in the 3 to 5 years following treatment if radiotherapy is omitted. However, there is limited evidence regarding the expected increased risk of late effects, which may not occur for many years or even decades following treatment, with what evidence we do have predominantly coming from historical studies in which patient received outdated radiotherapy techniques. To further complicate the decision problem, the patient and clinician must then explicitly trade-off these distinct risks/benefits profiles.

To aid this decision problem, ideally there should be clearer elucidation of the risks of modern radiotherapy, given the patient's anatomical location of their disease, and their baseline risks relating to their age, sex, and health behaviours. Additionally, the decision problem would be aided by the translation of the multiple outcomes - risk of relapse and risk of late effects - into a unified outcome, such as life expectancy and quality of life.

Given this conceptualised decision problem, the model designed for this study should take a lifetime perspective, providing a singular outcome measure such as life expectancy or quality-adjusted life expectancy. Life expectancy estimation must take into account the long term expected outcome of Hodgkin lymphoma after treatment, and for the CMT scenario, the potential lifetime outcome of late effects from radiotherapy. The model should also provide individualised estimation based on patient age, sex, health behaviours and anatomy of disease presentation.

3.2.2 Type of decision analytic model

Many forms of modelling approaches exist with inherent capabilities and limitations. In health economic evaluation, state-transition models are widely used in the evaluation of treatment strategies, and are particularly useful where time dependency is required such as in

the case of our decision problem.[85] State-transition models emulate patient progression over time through the natural history of disease using a series of health states. Movement over time between health states is defined by allowable transitions which are assigned transition probabilities governing the likelihood of such movement. Whilst time can be treated continuously, most often it is discretised into cycles with a length appropriate to the disease modelled, for oncology this is typically months or years.

Discrete state transition models can be programmed as a cohort ("Markov") model in which the cohort, of arbitrary size, is divided between the states as determined by the transition probabilities over time. These typically have a memoryless (or Markovian) property whereby past events do not affect the transition probability. Alternatively, individual-patient level state-transition (microsimulation) models can be programmed which explicitly simulate a singular patient who can only be in one state during each cycle. Microsimulation models are advantageous when characterizing a disease, or disease combinations, requiring a large number of health states and when there are a large number transition probabilities that depend on model time and prior health events.[85] Given the need to model a large number of late effects and likely dependency of transition probabilities on past event, a microsimulation modelling approach was taken for this decision problem.

3.3 Model development

With the model conceptualisation and the requirements formalised, this section provides exposition of the model developed and insight into considerations and the various choices taken over the period of development. In general, the model was created and parameterised in a systematic manner with continual clinical input throughout. The model's structure was created through this clinical input dialog, considering the most important features of the

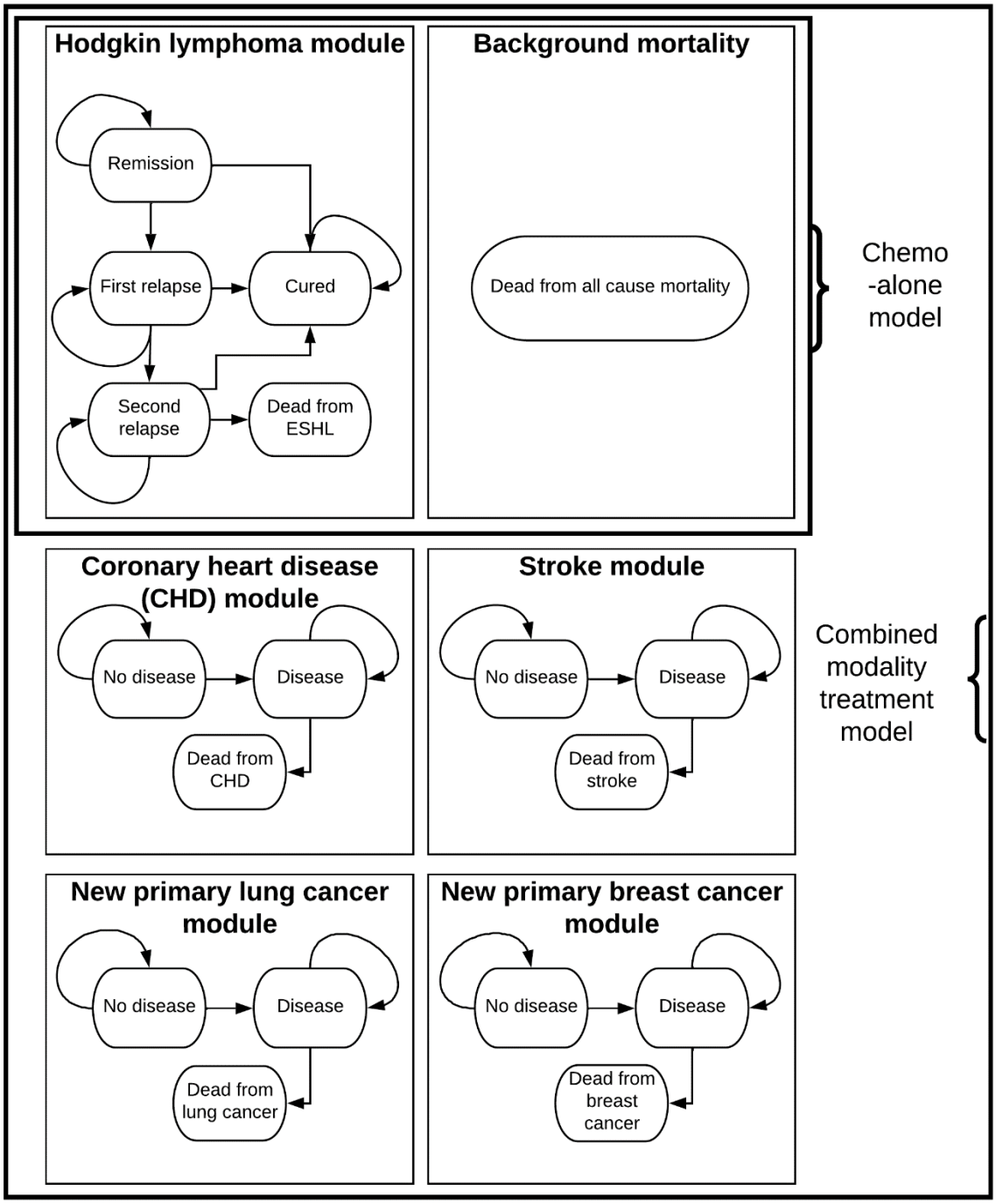
Hodgkin lymphoma disease progression pathway (and the availability of data to inform it), and the most clinically significant late-effects of radiotherapy. Parameters were sourced either through the use of systematic reviews (late-effects and in the next chapter costs), or where infeasible focused searches with clinical input. I begin by outlining the final model before then going into greater detail on the different components of the model. Reasoning and justification for the choices made are given throughout in line with NICE DSU Technical Support Document 13 (NICE DSU 13: Identifying and reviewing evidence to inform the conceptualisation and population of cost-effectiveness models).

3.3.1 Overview of the final developed model

The microsimulation model developed was designed as a series of sub-models which separately model the course of cHL and, when evaluating the CMT scenario, four late effects of radiotherapy, namely breast cancer, lung cancer, coronary heart disease (CHD) and ischaemic stroke. These four late effects were chosen as they are the most common and burdensome late effects experienced, and will be discussed further in section 3.3.3.1. An outline of the states and transitions in the model is given in Figure 3.1.

Figure 3.10: Overview of the individual-patient level state-transition model used to evaluate combined modality treatment and chemotherapy-alone for early stage classical Hodgkin

lymphoma



A simulated patient begins the model in the “Remission” and four “No disease” states of the sub-models – in effect, there are 5 separate independent models. Transitions between states in each sub-model do not affect those in other sub-models. This is likely to bias the model towards estimating longer life expectancies, as in the real world these disease states are likely to interact, for instance having one of the diseases is likely to increase the risk of another. As

such patients are able to experience multiple late toxicities, e.g. a patient can transition from the “no disease” to the “disease” states of stroke and CHD in the same cycle. Due to the discrete nature of the model with yearly cycles, no ‘ordering’ of events occurs.

Once any death state is reached, the model run is terminated, thereby accounting for competing risks of death. Alternatively, the model ends after the simulated patient reaches 100 years of attained age to provide a stop point in the very rare event a patient has not yet reached death. Background mortality is included, with age- and sex-specific rates derived from Office for National Statistics mortality statistics for England and Wales.[86] Yearly cycles are used for the progression of time. Below, each sub-model is described in further detail.

3.3.2 ESHL sub-model

The ESHL sub-model consists of five health states as shown in

. Generally, to inform the ESHL sub-model, pertinent clinical-trial/cohort studies were identified from the literature using web engine searches and citation searches – this was thought appropriate given the rareness of the disease, the insular nature of the field, and the collaboration of Lymphoma specialists well versed in the literature. This representation of the

natural history of ESHL, with only two relapses explicitly considered (although outcomes post-relapse are informed by data which includes subsequent relapses), was decided upon through holistic assessment of the literature available to inform disease outcomes post-first relapse, which is sparse.

In the model conception, the decision problem is faced by the patient assuming a complete response at the interim PET scan. Furthermore, it was assumed an end of treatment PET scan would remain negative, with a positive scan at this point being very rare.[28] Each of the three randomised controlled trials of radiotherapy omission followed slightly different lengths of chemotherapy, either two, three, of four cycles of ABVD, and in practice there is variation in what is preferred by different clinical teams. With the RAPID trial predominantly recruiting in the UK setting, and also due to having access to dosimetry data from the trial, it was assumed in the model that the patients followed this treatment course (3 cycles of ABVD +/- RT), and as such, the (per protocol) RAPID trial result was used as the basis of risk of first relapse in this analysis, although other studies can be readily used here, including those in other stages of disease.[28] Therefore, the predictions from this model are pertinent to patients meeting the RAPID inclusion criteria: stage I or IIa classical H (one nodal site [stage IA] or two or more nodal sites on the same side of the diaphragm [stage IIA], with no night sweats, unexplained fever [temperature, ≥38°C], or weight loss of ≥10%)A simulated patient, therefore, is assumed to start this sub-model in remission after negative findings on PET after three cycles of ABVD chemotherapy. From this state patients are at risk of first relapse, with the yearly probability of relapse under both the chemotherapy only and CMT scenarios derived through reconstruction of individual patient time-to-event data using the per-protocol Kaplan–Meier (KM) plots of progression-free survival (PFS) from the RAPID trial publication.[28,87] The commonly used Guyot et al (2012)[87] procedure was performed for this reconstruction. Parametric survival curves (Exponential, Weibull, Gamma, log-Normal, log-

Logistic, Generalised gamma, Generalised F and Gompertz distributions) were fitted to the reconstructed data, with yearly transition probabilities derived from the best fitting parametric model, informed by the Akaike and Bayesian information criteria. This procedure was performed using the *survHE* package in R.[88,89] As discussed in section 1.2.6, relapses are particularly rare after 5 years, and patients approach the same mortality rate as that of the general population. Therefore in the ESHL sub-model, a patient still in the remission state was considered cured after 5 years due to the rarity of relapses past this point.[75]

It is assumed in the model that all relapsed patients receive salvage treatment with bridging chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT). This is the common approach to salvage treatment recommended by all treatment guidelines, especially in patients of the ages considered in this study.[3] There is, however, large variation in the types of bridging chemotherapy used and there has and continues to be rapid development in the introduction of targeted treatments and immunotherapy in this treatment line. Based on precedent in other Hodgkin lymphoma models[90], and the opinion of collaborating clinical haematologists that the PFS outcomes were indicative of modern outcomes irrespective of bridging chemotherapy, the yearly probabilities of second relapse were chosen to be estimated from the PFS results of the brentuximab vendotin consolidation arm of AETHERA trial, using the same procedure as above.[33] Patients are assumed to be at risk of second relapse for the following three years, in line with the plateau of the KM curve. If no second relapse occurs, patients then transition into the cured state. Little information exists on long term risk post ASCT, therefore patients are again assumed to return to the population-based risk of mortality.

Very limited information is available on outcomes after second relapse especially after the introduction of modern agents. To capture contemporary outcomes, although this is rapidly evolving , the yearly probability of death from ESHL was derived from the overall survival

KM plot from the only study (single centre) identified providing mortality outcomes after ASCT relapse in the era of Brentuximab Vendotin and immune check point inhibitors.[91] Again using the same methodology as previously described. After 10 years, if a patient has not died, they transition to the cured state, in which they are assumed again to have the same background mortality rate as the general population, as well as any increased risk from late-effects in the CMT scenario. Table 3 .6 provides transition probabilities used in this sub-model.

Table 3.6: Health state transitions in the ESHL sub-model

Transition	Estimate and Description
Remission to First relapse - CMT	Yearly transition probabilities for the first 5 years after initial treatment obtained from an exponential distribution: rate = 0·001061 (95% CI: 0·000603 - 0·001869). Using the point estimate this corresponds to a 1·3% yearly probability of relapse over the 5 years.[28]
Remission to First relapse – Chemotherapy only	Yearly transition probabilities for the first 5 years after initial treatment obtained from a log-normal distribution: log mean = 7·837 (95% CI: 6·350 - 9·324), log SD = 3·55 (95% CI: 2·478 - 4·622). Using the point estimates this corresponds to yearly relapse probabilities of 5·7%, 2·9%, 2·2%, 1·8% and 1·6% over the 5 years.[28]
Remission to Cured	Patients were considered cured after 5 years
First relapse to Second relapse	Yearly transition probabilities for the first 3 years after first relapse obtained from a log-normal distribution: log mean = 3·715 (95% CI: 3·359 - 4·071), log SD = 1·577 (95% CI: 1·291 - 1·928). Using the point estimates this corresponds to yearly relapse probabilities of 21·8%, 19·1% and 15·8% over the 3 years.[33]
First relapse to Cured	Patients were considered cured after 3 years
Second relapse to Dead from HL	Yearly transition probabilities for the first 5 years after second relapse obtained from an exponential distribution: rate = 0·00886 (95% CI: 0·00571 - 0·01373). Using the point estimate this corresponds to a 10·1% yearly probability of death from HL over the 10 years.[91]
Second relapse to Cured	Patients were considered cured after 10 years

3.3.3 Late effects sub-models

3.3.3.1 Choice of late effects

There are many late effects associated with the use of radiotherapy. Starting with a historical perspective, the established curative treatment of Hodgkin lymphoma began with the use of RT in the 1960's, producing 5-year survival for localized disease of more than 70%.[92] At this time, "extended-fields" of RT were used, bathing the torso in radiation. Lymph nodes above the diaphragm were irradiated by a large field called a 'mantle', which covered the mediastinal and hilar nodes in the chest, nodes in the neck, and axillary nodes in the armpit. Furthermore, an 'inverted-Y' field irradiated the nodes and spleen (if not removed) below the diaphragm, in the abdomen, pelvis and groins. Long-term follow-up of patients treated with such historical radiotherapy fields show substantial excess risks of incidence and mortality for many diseases including second malignancies and diseases of circulatory, respiratory, digestive and genitourinary systems.[93–96]

Whilst late effects related to irradiation below the diaphragm are not so relevant in the early-stage setting (where the disease is much more commonly localised above), ideally all relevant radiation-induced late effects would be included in the model to capture the full effects of irradiation. However, this is constrained heavily by the availability of data and complexity of the model. In agreement with clinical colleagues, four late effects were included in the model, constituting those that would most influence morbidity and mortality, and had the necessary data available. These were; breast cancer, lung cancer, coronary heart disease (CHD) and ischaemic stroke: Breast and lung cancers account for the majority of the absolute excess risk (AER) of second cancers in patients with supradiaphragmatic disease, with others such as sarcoma and thyroid contributing <5% of the AER each.[95] Similarly, CHD and stroke have the highest absolute excess risk of mortality of the radiation-related cardiovascular diseases.[97]

3.3.3.2 Risks of late effects

Data on the incidence of such late effects naturally comes from cohorts treated with historical radiotherapy, given decades in the past. With the continual development of techniques and technology, radiotherapy given in these cohorts is vastly different from that given to modern patient who face the present decision problem, irradiating far more healthy normal tissue to higher doses. Given these differences, as well as differences in the background rates of cancers and cardiovascular diseases in more recent eras, direct use of incidence statistics from such studies is not directly transferable.

This historical data has, however, been used to produce dose-response relationships between the amount of irradiation received and the increased relative risk of disease, which may be generalised to modern cohorts. For radiation-induced cancers, a variety of methods and approaches have been utilised to model the dose-response relationship. Much of this work has been produced for the purposes of radiation protection, with early empirical evidence of a dose-response relationship for radiation carcinogenesis coming from the Life Span Study (LSS) of the atomic bomb survivors of Hiroshima and Nagasaki. This study included 90,000 individuals who received a “significant” (1-2Gy) dose of radiation from the event and were carefully followed throughout the years, with many reports published.[98,99] The work established that cancer induction is linearly correlated with radiation dose in the low-dose range of up to about 1-2 Gy. However, this work is specific to risk estimation at a population level, and is not necessarily transferrable to the estimation of specific cancer risk in individuals receiving much higher doses in the medical, fractionated setting.[100]

Previously, the patterns of cancer risk after fractionated high-dose medical radiation was much less well understood than those after lower-dose exposures. In particular, there was uncertainty regarding the continuation of and shape of dose-response curve at such high doses as well as the effect size of the risk per unit dose. Therefore, mechanistic dose-response

models involving the modelling of the cell killing, proliferation, and transformation process have previously been used as an alternative for estimating the risk of second cancers in Hodgkin and breast cancer patient.[101,102] However, robust empirical evidence has now developed indicating a linear no-threshold dose-response relationship for a large number of specific cancers in the medical high dose setting.[103] Similarly, such linear no-threshold dose-response relationships have also been robustly characterised for radiation-related cardiovascular disease.[79,104,105]

Empirical estimates of the dose-response relationship for breast cancer, lung cancer, CHD and stroke were, therefore, used in the model to estimate the incidence of the late effects. The dose response models give the excess relative risk per Gy (ERR per Gy) of mean organ radiation dose. Dose-response relationship publications involving cohorts of previously irradiated Hodgkin Lymphoma patients were identified using a recent systematic review undertaken within Dr David Cutter's group (accessible as part of Dr Rebecca Shakir's thesis: https://ora.ox.ac.uk/objects/uuid:192961fb-d886-4c06-89e8-37a79658be15), The identified and used studies are outlined in Table 3.2, with further detail below.

Table 3.7: Published dose-response relationships used to estimate risks of radiation-related cardiovascular disease, stroke, and second cancers

Reference	Study population	Disease	Risk model
Van Nimwegen et al (2015)[79]	The Netherlands (hospital-based) 325 cases and 1,024 controls Median age_tx:32 y Treated 1965-1995	CHD	ERR =0.20 age_tx <28 y ERR =0.088 28≤ age_tx ≤36 y ERR =0.042 age_tx >36 y RR = 1 + ERR∗MHD
De Bruin et al (2009)[80]*	The Netherlands (hospital-based) 55 cases All patients age_tx <51y Treated 1965-1995	Stroke	ERR = (2.8/31.85)/1.286 age_tx ≤20 y ERR = (2.1/31.85)/1.286 20< age_tx ≤30 y ERR = (1.0/31.85)/1.286 30< age_tx ≤40 y ERR = (0.4/31.85)/1.286 age_tx >40 y RR=1+ ERR x MDCCA

Travis et al (2002)[77] **&** **Gilbert et al (2003)[78]**	International (population- and hospital-based) 222 cases and 444 controls Treated 1965-1994	Lung cancer	ERR = 0.15 (95% CI: 0.06 to 0.39) RR=1+(ERR x MLD x 1.672†)
Travis et al (2003)[76]	International (population- and hospital-based) 105 cases and 206 controls Treated 1965-1994	Breast cancer	ERR = 0.15 (95% CI: 0.04 to 0.73) Age at exposure adjustment (using RRs by age from Swerdlow et al and Schaapveld et al):
Swerdlow et al (2012)[106]	England and Wales (population-based) Cohort study of 5002 women (373 cases) Treated 1956-2003		Age 0-9 years, ERR = 0.097 Age 10-14 years, ERR = 0.395 Age 15-19 years, ERR =0.257 Age 20-24 years, ERR =0.097 Age 25-29 years, ERR =0.057 Age 30-34 years, ERR =0.043 Age 35-50 years, ERR = 0.030
Schaapveld et al (2015)[95]	The Netherlands (hospital-based) Cohort study including 1698 women (183 cases) Treated 1965-2000		RR=1+(ERR x MBD x 1.608†)

Age_tx; age at treatment; ERR; excess relative risk, MHD, mean heart dose to the whole heart; MDCCA, mean dose to the common carotid arteries; MBD, mean breast dose to bilateral breast tissue; MLD, mean lung dose to the whole lungs.

† Adjustment factor between MLD/MBD and spot dose as described below

Typically, radiotherapy dose-response studies involve the use of a nested case-control design. As an example, in their estimation of the radiation dose-response relationship for risk of CHD, Van Nimwegen et al (2015) conducted a nested case-control study in a cohort of 2,617 5-year HL survivors, treated between 1965 and 1995.[79] Patients who had an event ("cases") were compared to those who did not ("controls"), in this example by matching one case patient to four similar controls based on sex, age and time period of diagnosis. Using conditional logistic regression on sets of individual cases and their matched controls, odds ratios were calculated for the association between mean heart dose (MHD) and an event. Such odds ratios, given the dynamic sampling of controls over time, can be interpreted as relative risk (RRs), the proportional increase/decrease in risk over the background absolute risk.[107] The Van Nimwegen et al study provided excess relative risk (ERR) per Gray (Gy) MHD by age at treatment in 3 groups (<28 years, 28 to 36 years and >36 years) and these estimates were incorporated into the model.

Dose-response relationships for the excess risks of breast and lung cancer were again obtained from case-control studies in HL survivors.[76–78] In both cases, the case-control studies

estimated the excess risk in terms of the increase in point dose at the site of the second cancer. However, point dose is not the most appropriate measure for predicting future risk as it is not known exactly where a future cancer may develop. Therefore, to derive the relationship in terms of the mean organ dose in a similar manner to CHD (i.e. ERR per Gy of mean breast/lung dose), an adjustment factor was defined. Here, published dosimetry studies were used to define the ratio between the mean dose at the point the cancer developed (as a percentage of prescribed dose)[76–78] to the mean organ dose (as a percentage of prescribed dose).[108] For breast cancer this adjustment factor was 1.608, and 1.672 for lung cancer.

Additionally for breast cancer, further studies have shown the relative risk of breast cancer to vary by age at treatment, in a pattern similar to the van Nimwegen CHD study. The ERR of 0.15 per Gy estimated in the original Travis et al[76] paper was therefore transformed as follows to account for this - This transformation, as well as the stroke risk model (which was based on cohort data rather than a case-control study), were originally derived by colleagues at NDPH for a different study, however the published paper for which these methods were derived was reduced in scope to examine cardiovascular disease only compared to earlier drafts, and therefore the cancer risk models were not published alongside the study.[97] Firstly, the number of cases and their proportion of total cases for the age groups between 0-29 at treatment were extracted from Swerdlow et al[106], as well as the published relative risks. These relative risks were then scaled relative to the largest group by number of cases (20-24 age group). This process is outlined in Table 3 .8

Table 3.8: Derivation of age-specific excess relative risks for breast cancer (1/2)

Age	Cases	Proportion in that age group	RR of BC	RR Relative to 20-24 (largest group)
0-9	8	0.026	5.4	1
10-14	23	0.075	22.0	4.074
15-	81	0.264	14.3	2.648

19				
20-24	107	0.349	5.4	1
24-29	88	0.287	3.2	0.593

Next, an adjustment factor was calculated such that the relative size of the relative risks, given the proportion in the age group (weight to that age group), summed to the excess relative risk given in Travis et al (0.15). This adjustment factor was found by iteration until the summed value of contributions equalled 0.15. Through this process, an adjustment factor of 0.097 was derived. Age-adjusted ERR were then calculated (last column). Finally, further relative risks from older age groups were added from Schaapveld et al.[95] This part of the process is outlined in Table 3 .9

Table 3.9: Derivation of age-specific excess relative risks for breast cancer (2/2)

Age	**(1) Proportion of age group**	**(2) RR of BC**	**(3) Relative RR to 20-24 (largest group)**	**(4) Contribution to 0.15 ERR to find adjustment factor**	**ERR per Gy (to match Travis 2003)**
Equation				*(1) Proportion * (3) Relative RR * adjustment factor*	*(2) Relative RR * 0.097*
0-9	0.026	5.4	1	0.0025	0.097
10-14	0.075	22.0	4.074	0.0296	0.395
15-19	0.264	14.3	2.648	0.0676	0.257
20-24	0.349	5.4	1	0.0337	0.097
24-29	0.287	3.2	0.593	0.0164	0.057
				Sum = 0.15 when adjustment = *0.097*	
From Schaapveld					
30-34 (RR: 2.4)		2.4	0.444		0.043
35-50 (RR: 1.7)		1.7	0.315		0.030

For stroke, there are currently no published studies estimating the ERR per Gy. The critical structure relating to the risk of stroke from radiotherapy is presumed to be the two common carotid arteries which run on both sides of the neck. Irradiation accelerates atherosclerosis increasing the risk of carotid stenosis.[80] Therefore a dose-response relationship was constructed involving the mean dose to the common carotid arteries (MDCCA) as follows. Age-specific standardised incidence ratios (SIRs) for the risk of stroke in a cohort of HL survivors treated with mantle field radiotherapy, were published by De Bruin et al.[80] Although the MDCCA for each patient in this study was not published, Maraldo et al[108] provide a retrospective dose reconstruction method for estimating MDCCA as a percentage of the prescribed dose for HL patients treated with mantle and involved field radiotherapy.[108] Since the cohort in the De Bruin et al study received predominantly mantle field radiotherapy, this method was used to estimate the average MDCCA for this cohort to derive an ERR per Gy of MDCCA.[80] The SIRs reported in the De Bruin et al study were divided by this estimated MDCCA in order to derive ERR per Gy of MDCCA for the risk of stroke.

Additional adjustment was also necessary as not all cases of stroke reported in the De Bruin et al study were first presentations of cardiovascular disease. Of the 65 stroke cases, 17 had developed prior heart disease. Prior heart disease was reported to increase the risk of stroke by a factor of 2.1 compared to having no prior heart disease. As the focus of our study was the first cardiovascular event, the ERR per Gy for stroke was thus scaled to account for a reduced risk of stroke as a first cardiovascular event. To derive the appropriate scale factor, it was assumed that $0.74X + 0.26 \times 2.1X = Y$, where X is the ERR per Gy for stroke without prior heart disease applicable to the 74% of patients who did not have prior heart disease, 2.1X is the ERR per Gy applicable to the 26% of patients who did have prior heart disease, and Y is the ERR per Gy for all patients in the study. It follows that $X = Y/1.286$, so the observed ERRs per Gy were divided by 1.286.

3.3.3.3 Modelling late effects incidence and outcome

The dose-response models derived in the prior section estimate the excess relative risk per Gy (ERR per Gy) received to the relevant organs. That is, the excess risk over the absolute risk of the matched controls which in each study were sampled from the general population. As such, it follows that the incidence rates of the four late effects in the model would ideally be based on age- and sex- specific incidence rates of the general population, modified by the estimated excess risk.

For modelling the course of late effects, a myriad of approaches could be taken. With the requirement that what happens on average need only be considered, rather than detailed exposition of the course of each event, only a "diseased' state was incorporated into the model, from which a patient was at risk of death from disease (case-fatality). Each late effect therefore was modelled using a simple and generalisable three- state sub-model, consisting of the health states; no disease, diseased, and dead from disease due to the availability of data.

Baseline (without-irradiation) age- and sex-specific yearly incidence and case-fatality rates governing the transition from no disease to diseased and from diseased to dead from disease respectively were taken from the PRIMEtime model previously developed within the Nuffield Department of Population Health. This model was developed for the purpose of evaluating the full life time impact of dietary interventions on dietary-mediated diseases, including the four late effect diseases considered in this model.[109] In this model, age- and sex-specific disease incidence rates were derived from UK cohort studies and/or administrative healthcare datasets and disease-specific mortality rates were taken from ONS cause-specific death registrations.[110,111] Internally consistent age- and sex-specific case-fatality rates were then derived using the World Health Organisation's DISMOD II program. The incidence and case-fatality rates are adjusted for their expected 20-year trend.[110]

Although case-fatality is a simplistic measure of outcome, detailed modelling of such outcomes relies on the availability of data, and such a complex model is not warranted in this scenario given that there is a need only for an estimate of the population "average" outcome of an incidence case. The advantage of using such case-fatality rates is that they are, like the incidence rates, derived from population-level data and therefore provide an "average" estimate of the outcome of an incidence case of disease.

Within the model the annual probability of the incidence of a late effect (transition from no disease to disease) is derived as follows. For a given patient, their ERR for each late effect is calculated based on the mean dose to the organs of relevance and the ERR per Gy equations previously shown. The age- and gender- specific probability of having the late effect is calculated by transforming the population-based age- and gender-specific incidence rates into annual probabilities to give a baseline probability, through the canonical formula $p(t) = 1 - e^{-rt}$, where r is the rate and t is the cycle length, which is then multiplying by the relative risk (RR) (which is given by 1+ERR). The baseline probability is subtracted to account for the normal incidence of the late effect which would occur without irradiation (background rate), as this will be captured in the general population mortality.

3.3.3.4 Incorporating the effect of smoking status into the model

Due to the strong association between smoking and increased risk of lung cancer, coronary heart disease and stroke, and the desire to produce personalized estimates of life expectancy, an extra step was taken to adjust the population-based age- and sex- specific incidence rates to account for smoking status. This step is performed before the modification for the ERR based on patient dosimetry outlined above.

The population-based incidence rates are an aggregation of all individuals who have a range of smoking behaviors. To simplify this range, based on categories for which there is data, The

population-based age- and sex– specific incidence rates were disaggregated into those for current smoker, former smoker, and never smokers. The US CDC's method for estimating smoking-attributable mortality was used for disaggregation:[112]

1. Estimates of the prevalence of never, former, and current smokers in the UK population by age and sex were obtained from the 2012 General Lifestyle Survey.[113] These can be found in Table 3 .10. This survey was chosen for its large size (it was discontinued after 2012). There were no applicable estimates of smoking status proportions amongst individuals with Hodgkin lymphoma. Given the disease is not associated with smoking, the general population estimate was considered appropriate.

2. Estimates of the relative risk of disease for lung cancer CHD and Stroke were identified from the Royal College of Physician's "Hiding in plain sight: Treating tobacco dependency in the NHS" report, which is used by Public Health England.[114] Table 3 .11 provides the estimates and corresponding 95% confidence intervals.

3. The yearly age- and sex-specific population-based incidence rates, relative risks, and prevalence data were used to calculate the incidence rate in non-smokers using the equation:

$$IRnonsmokers_{dsi} = \frac{IRpop_{dsi}}{¿¿}$$

where,

$IRnonsmokers_{dsi}$ = incidence rate for non-smokers in disease d, sex s, and age category *i*

$IRpop_{dsi} = ¿$ Incidence rate for the population (all risk groups combined) in disease d, sex s, and age category *i*

$RR_{dsk} = relative\ risk\ for\ incidence \in disease\ d, sex\ s, \wedge\ smoking\ group\ k \mid k = 1 : former\ smokers, 2 : current\ smoke$

$Prev_{ski} = prevalence\ estimate \in sex\ s, smoking\ group\ k, \wedge age\ category\ i$

4. Finally, the incidence rate for former and current smokers were calculated using the following formula:

$IR_{dski} = IRnonsmokers_{dsi} * RR_{dsk}$

where,

IR_{dski} = incidence rate in disease d, sex s, smoking group k, and age category *i*

Table 3.10: Proportions of people who have never smoked, ex-smokers and smokers from the 2012 General Lifestyle Survey

Age band	Sex	Proportion of never smokers	Proportion of ex-smokers	Proportion of smokers
15-19	Male	0.80669	0.0223	0.171
20-24		0.59302	0.07752	0.32946
25-29		0.53276	0.1339	0.33333
30-34		0.53511	0.13801	0.32688
35-39		0.5426	0.19955	0.25785
40-44		0.53157	0.1833	0.28513
45-49		0.54409	0.22326	0.23265
50-54		0.51454	0.22595	0.25951
55-59		0.46042	0.30833	0.23125
60-64		0.41586	0.38685	0.19729
65-69		0.40319	0.4511	0.14571
70-74		0.40642	0.47326	0.12032
80+		0.42834	0.50082	0.07084
15-19	Female	0.77255	0.01961	0.20784
20-24		0.57713	0.09043	0.33245
25-29		0.59319	0.12425	0.28257
30-34		0.58681	0.17188	0.24132
35-39		0.60304	0.16047	0.23649
40-44		0.59304	0.17913	0.22783
45-49		0.61191	0.14982	0.23827

50-54	0.587	0.19503	0.21797
55-59	0.55028	0.26376	0.18596
60-64	0.60204	0.2466	0.15136
65-69	0.51705	0.30303	0.17992
70-74	0.62697	0.24944	0.1236
80+	0.6629	0.25792	0.07919

Table 3.11: Relative risk and 95% confidence interval for lung cancer, CHD, and stroke used to adjust the population incidence rates

Disease	**Gender**	**Age**	**Relative risk and 95% confidence interval**	
			Current Smokers	**Former Smoker**
Lung cancer[115]	Male and female	All	10.92 (8.28–14.40)	3.85 (2.77–5.34)
CHD[112]	Male	≤64	3.18 (2.34–4.33)	1.59 (1.11–2.27)
	Male	>65	1.96 (1.62–2.37)	1.16 (1.01–1.34)
	Female	≤64	3.93 (2.56–6.05	1.48 (0.82–2.64)
	Female	>65	1.95 (1.60–2.37)	1.37 (1.18–1.58)
Ischemic Stroke[116]	Male	All	1.57 (1.49–1.88)	1.08 (1.03–1.13)
	Female	All	1.83 (1.58–2.12)	1.17 (1.12–1.22)

3.3.3.5 Estimation of model outcomes

Total life years are calculated in the model as the number of yearly cycles (cycles are one year in length) in which the patient remained alive. To calculate QALYs, life years are adjusted for age- and disease-related HRQoL effects using utility values sourced from the catalogue of EuroQol-5D (EQ-5D) Scores for the United Kingdom.[117] This source was chosen based on a search of the literature, focusing on studies that could provide a singular source of utility decrements across the disparate diseases covered by the model, as well as for age increments and by sex. This was desired as opposed to values from different studies that natural then come from different cohorts and analyses. For each cycle in which the patient is alive, a QALY is estimated based on the utility value associated with the patient's age in that cycle, minus any decrements associated with the specific health states they are in (Table 3 .12). For the late effects, their respective decrements were applied to every cycle for which the patient is in the diseased state. For ESHL, the long-term effect of ASCT was considered, with

disutility permanently applied to every cycle lived after first relapse, even if cured. Mean utility values and standard errors are presented in Table 3 .12. Total expected QALYs were taken as the sum of each cycle's QALY.

Table 3.12. EQ-5D values from Sullivan et al (2011)

		Mean utility value/decrement	Standard Error
Age band	10-19	0.913	0.004
	20-29	0.905	0.002
	30-39	0.879	0.002
	40-49	0.837	0.003
	50-59	0.798	0.004
	60-69	0.774	0.004
	70-79	0.723	0.005
	80+	0.657	0.008
Disease decrement	Transplant (Autologous stem-cell transplant)	-0.142	0.077
	Breast cancer	-0.019	0.014
	Lung cancer	-0.119	0.043
	Coronary heart disease	-0.037	0.026
	Ischaemic stroke	-0.073	0.009

3.3.3.6 Uncertainty

Microsimulation models simulate the trajectory of a patient's health over time by transitioning that patient through health states in a stochastic manner. Here, at the end (or beginning) of each cycle the transitions available, given the state the patient is currently in, are evaluated and the state the patient moves to is selected using a random sampling process, weighted according to the transition probabilities. Therefore, the trajectory of health over time and resulting outcomes for the same patient (in terms of patient inputs) simulated twice will likely be different. This "difference" is often called stochastic (or first-order or Monte Carlo) error. To minimise such error, typically a large number of model runs are performed, and the outcomes are then averaged. In the model, each patient is simulated 10,000 times. This number was chosen by testing the stability of estimated outcomes from 1000 simulations upwards in increments of 1000.

Evaluation of parameter uncertainty was also programmed into the model to give not only a central estimate of the outcome but also a corresponding 95% confidence interval reflecting joint known parameter uncertainty. Often termed probabilistic sensitivity analysis (PSA), this involves running the model a given number of times. At each run, model parameters are sampled from their corresponding sampling distribution. The mean outcome is simply the average of all runs, and the 95% confidence interval of joint parameter uncertainty is the corresponding 2.5th and 97.5th outcome when outcomes are ordered from smallest to largest. For this model, the survival curves, most ERR/Gy estimates and EQ-5D values had known uncertainty intervals, and 1000 probabilistic iterations were performed with these parameters sampled from their appropriately parameterized underlying parametric distributions: For the survival curves this was done within the survHE function (Table 3 .6), for ERR/Gy and EQ-5D samples were drawn assuming a lognormal[118] and normal distribution, respectively, parameterized by the mean and standard error/confidence interval (Table 3 .7, Table 3 .12). A summary of parameters, their reference within the chapter, and whether they were fixed or varied in the PSA is provided in table 3.8.

Table 3.13. Summary of model parameters and whether held fixed or varied in probablistic sensitivity analysis

Parameter category	Fixed or varied	Values reference
ESHL sub-model transition probabilities	Varied	Survival curve distribution and parameter values provided in table 3.1 Samples drawn based on the fitted survival curves as given in table 3.1
Late effects dose-response relationships	CHD and stroke fixed, breast and lung cancer varied	ERR/Gy values provided in table 3.2 Samples were drawn based on the reported 95% CI assuming a lognormal[118]
Late effects incidence, case fatality, incidence trend, and care fatality trend	Fixed	Values provided in Appendix A table 1 & 2

Smoking proportions	Fixed	Proportions of never/former/current smokers provided in table 3.5
Relative risk of late effects from smoking	Fixed	Relative risks provided in table 3.6
Health state utilities	Varied	EQ-5D values and standard errors provided in table 3.7 PSA samples drawn assuming a normal distribution

3.3.4 Application of the model

The patient characteristics that influence model outcomes include age at treatment, sex, smoking status, and the set of representative OAR radiation doses, namely mean doses to the breast tissue (MBD), lung (MLD), heart (MHD), and common carotid arteries (MDCCA). To develop a comprehensive set of optimal treatment choices, the model was applied to the decision choice for 90 representative patient presentations who differed in these characteristics; a combination of five sets of OAR dose parameters, three ages (20, 35, 50), three smoking risk categories, and both sexes as follows.

Four sets of OAR mean doses (MBD, MLD, MHD, MDCCA) were chosen to reflect the spectrum of disease and doses seen in patients matching the inclusion criteria for the RAPID trial, thereby representing the clinical range of involved field radiotherapy (IFRT) in a modern era. Doses are given in Table 3 .14 and their derivation outlined below.

1) Unilateral neck IFRT (seen in ~35% of patients recruited to RAPID);

2) Average IFRT doses for the all PET-negative patients in the RAPID cohort;

3) Average IFRT doses for PET-negative patients with mediastinal involvement in the RAPID cohort;

4) Maximal cardiovascular doses seen in patients requiring bilateral neck and whole mediastinal IFRT (<5% of patients recruited to RAPID);

5) Finally, a fifth example corresponding to OAR doses previously seen with mantle radiotherapy was included to add historical perspective.

Table 3.14: Organ-at-risk doses for the five example sets

	1: Unilateral neck only	2: Avg doses for all PET-patients	3: Avg doses with mediastinal involvement	4: Bilateral neck and whole mediastinum	5: Mantle field RT
MBD (0 Gy for males):	1·4 Gy	2·1 Gy	2·7 Gy	4·6 Gy	12·4 Gy
MLD	2·2 Gy	4·2 Gy	6·1 Gy	11·7 Gy	13·6 Gy
MHD	0·3 Gy	4·0 Gy	7·8 Gy	19·5 Gy	19·5 Gy
MDCCA	13·8 Gy	21·5 Gy	28·3 Gy	30·0 Gy	30·0 Gy

Radiotherapy plans for 144 patients from the RAPID trial have been previously obtained by NDPH for a prior study and their expected MHD and MDCCA derived. These prior derivations were used to give the average MHD and MDCCA for the entire group in RAPID (as per example 2) and the average for patients with mediastinal involvement (as per example 3).[97,108] The four OAR doses for examples 1, 4 and 5 were derived differently. MBD, MLD, MHD, and MDCCA were estimated using calculations provided in Maraldo et al (2015), which provides estimates of MBD, MLD, MHD, and MDCCA as the percentage of the prescribed dose (30Gy in this instance) based on the technique (IFRT or mantle) and anatomical locations of disease.[108] Subsequently, MBD and MLD for the average RAPID example (example 2) and average with mediastinal involvement (example 3) were then calculated by interpolating using examples 1 and 4 based on their MHDs.

Each of the five sets of OAR doses were run for three ages at treatment: 20y, 35y, and 50y, three smoking risk categories: never, former, and current smoker, and for both females and males, giving 90 distinct combinations. For each of the 90 patient combinations the model

was run both with and without the addition of a discount rate applied to future health outcomes. In the undiscounted run of the model, life years and QALYs are accrued each cycle (of year length) the patient is alive and summed to give their total life years/QALYs. E.g.

$$\sum_{cycle=1}^{n} QALYs_{cycle}$$

When the model is run with a specified discount rate, this rate is applied to the life years/QALYs accrued in each cycle, with the discount increasing with time. E.g.

$$\frac{\sum_{cycle=1}^{n} QALYs_{cycle} * 1}{¿¿}$$

Discounting future health outcomes is commonly performed in economic evaluations, and reduces the weight given to later health outcomes when summing life years and QALYs across a lifespan; they would therefore be expected to reduce the impact of late toxicities. A 3·5% discount rate was used as recommended by the UK's National Institute for Health and Care Excellence (NICE). As an example, a year of life expectancy 20 years from now has a net present value of 0.50 years in net present terms (1/((1+0.035)^20)).

3.3.5 Model validation

A process of model validation was performed to check that the assumptions and structure of the model are reliable, sensible, and can be explained intuitively. The scope of this exercise consisted of experiments to assess whether changes in model input values generated a logical effect on model output. This included:

- Null and extreme value checks
- Checking that increasing radiation dose, all else held constant, reduces life years and QALY's in the CMT scenario

- Checking that increasing the health discount rate reduces life years and QALY's in both scenarios
- Checking that life expectancy and QALYs decreased with increasing age in each scenario (although this may have variable effects on the difference)

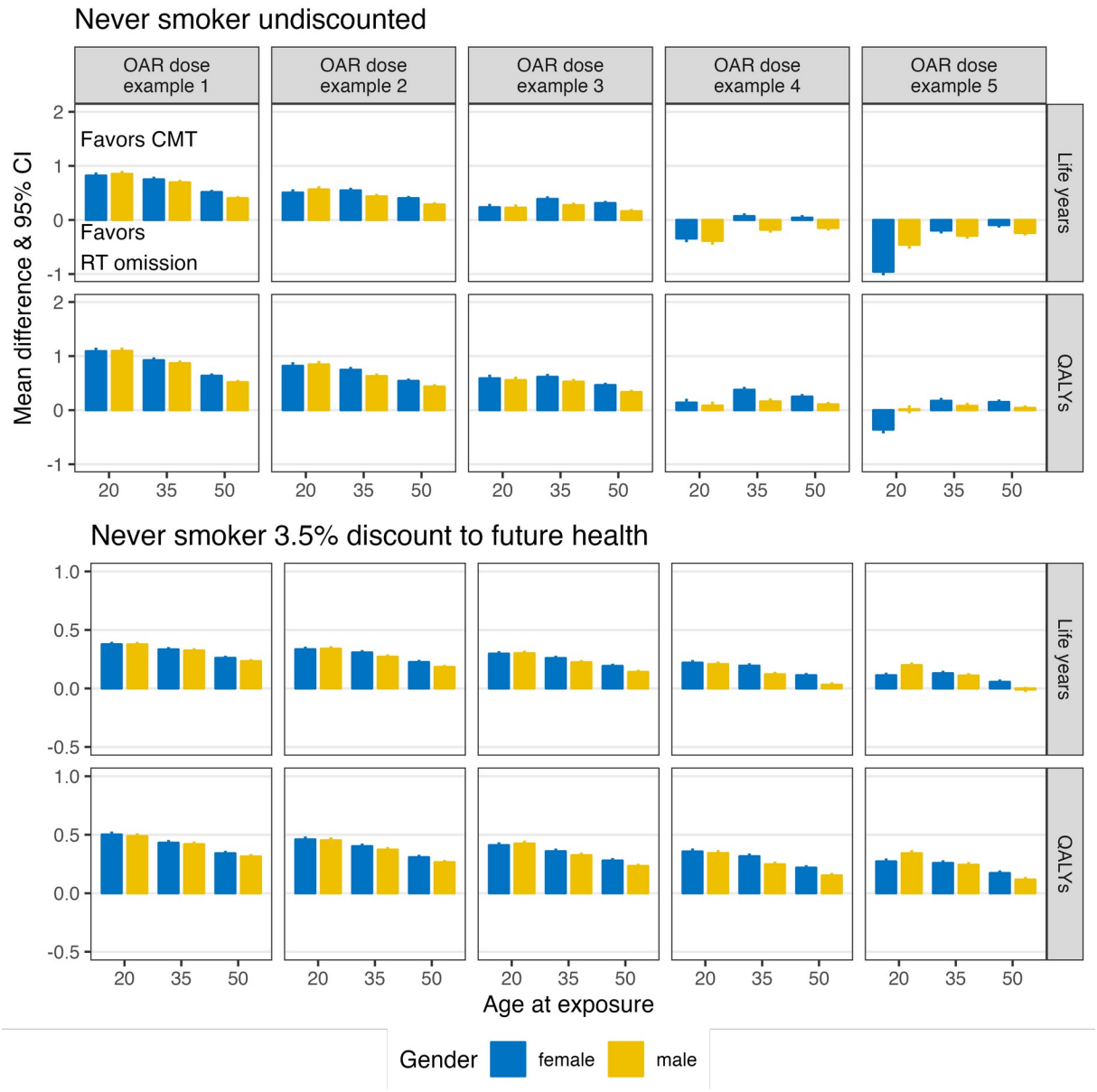
3.4 Results

Tables of results giving the estimated mean differences in expected life years and QALYs between CMT and chemotherapy-alone for the five organ at risk dose examples are given in Appendix A separately for never, former and current smoker example patients and separately by sex and by the application or not of a discount to health.

Never smokers

Smoking status had a significant effect on the choice of optimal treatment. In never smokers, CMT produced more QALYs than chemotherapy-alone for all of the four modern OAR dose strata, irrespective of age at treatment, sex, and the discount rate applied to future health. A 20y female patient with unilateral neck involvement only, for instance, would expect to gain 1.095 (95% CI: 1.054 to 1.137) undiscounted QALYs with the addition of consolidative radiotherapy. With increased MBD, MLD and, MHD doses due to mediastinal involvement the benefit of CMT lessens but remains optimal; For instance, a 20y female patient receiving IFRT to the bilateral neck and whole mediastinum would expect to gain only 0.139 (95% CI: 0.088 to 0.190) undiscounted QALYs.

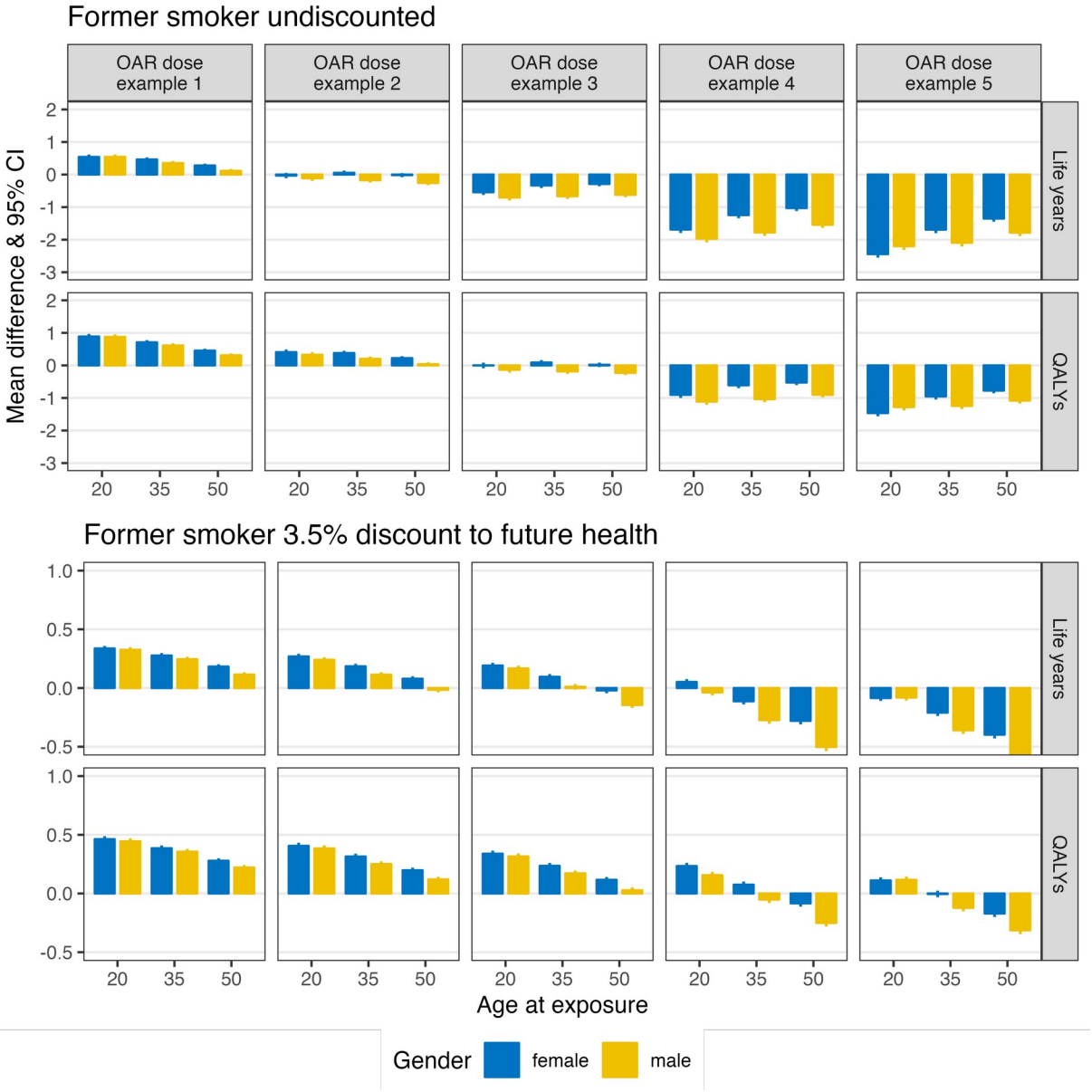
Figure 3.11. Never smokers: Mean difference in life years and QALYs and their 95% confidence intervals between combined modality treatment and chemotherapy-alone



Former smokers

The optimal treatment choice for former smokers was dependent on OAR dose, age, and whether a discount rate was applied to future health. With the application of the 3.5% discount rate, chemotherapy-alone was only beneficial in terms of QALYs to older patients in the highest modern dose stratum.

Figure 3.12. Former smokers: Mean difference in life years and QALYs and their 95% confidence intervals between combined modality treatment and chemotherapy-alone

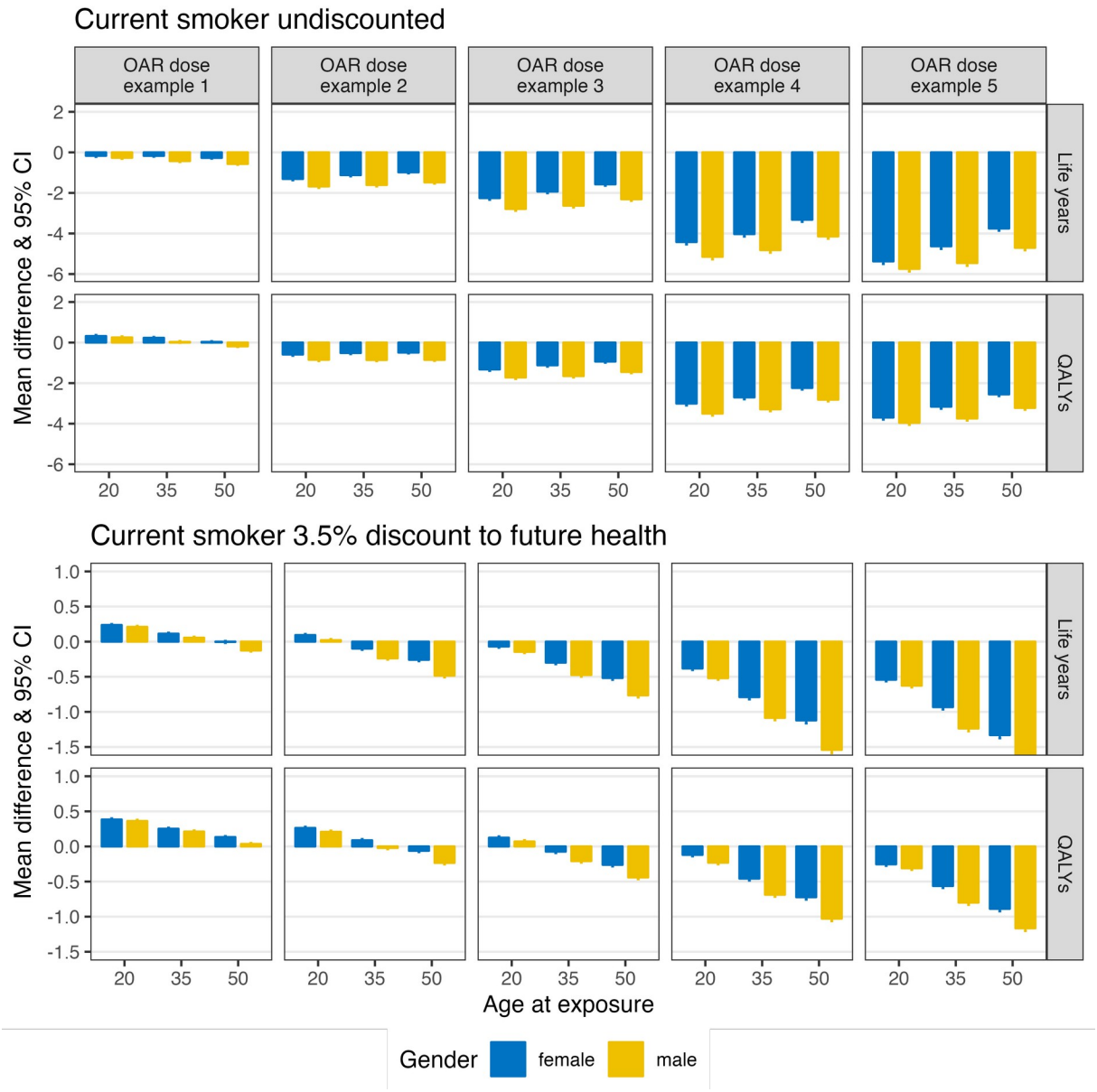


Current smokers

In current smokers, chemotherapy-alone produced greater undiscounted life years and QALYs at average doses for PET-negative RAPID patients, irrespective of age and sex. With discounting CMT remained optimal in the 20y age strata. In the highest OAR dose example, a substantial number of QALYs would be lost by current smokers were they to be treated with

consolidative radiotherapy, for instance, a 20y male would be estimated to lose 3.500 (95% CI: 3.400 to -3.600) undiscounted QALYs.

Figure 3.13. Current smokers: Mean difference in life years and QALYs and their 95% confidence intervals between combined modality treatment and chemotherapy-alone



3.5 Discussion

3.5.1 Results summary

Simulation modelling makes it possible to estimate the long-term outcomes of omitting consolidative radiotherapy for the treatment of ESHL, in the absence of decades of clinical follow-up.[74] Such outcomes must be interpretable by both patients and clinicians, requiring

the translation of individual risks from multiple diseases into a unified estimate of their overall impact, using a metric such as overall survival or quality-adjusted survival.

This is the first model to evaluate this treatment choice using not only individual patient characteristics such as age, sex, and smoking status, but importantly representative radiotherapy dosimetry based on 144 patients treated in a clinical trial.[97] And, crucially, the model estimates the excess risks of late effects based on published dose-response relationships obtained from large cohorts of patients treated for HL. Another key strength of the model is the use of parameter inputs that are informed throughout by real data rather than assumptions or expert opinion. Only one other study has performed a model-based comparison of QALYs in this setting. This exploratory study, however, did not explicitly model specific late effects nor base the probability of experiencing any late effect on radiation dosimetry and dose-response relationships.[119]

3.5.2 Results intuition

In each of figures 3.2 to 3.4, it can be seen that when the life years and QALYs difference is positive, i.e. CMT provides greater benefit, the difference is higher for QALYs. Similarly, the reverse can be seen, when the difference is negative, i.e. chemotherapy-alone provides greater benefit, there is a larger decrease in life years compared to QALYs. This effect is driven by the substantial negative utility decrement attached to ESHL relapse (and the assumed treatment with autologous stem cell transplant). This decrement, as with all the decrements, is applied in all subsequent cycles the event. As this event can only take place within the first five years, the resulting QALY outcome in the chemotherapy-alone arm (where the risk of relapse is greater) can be significantly lower than the CMT estimate, enough so that the difference in QALYs is greater than the difference in life years.

Generally, there is a pattern in each of figures 3.2 to 3.4 showing that as the radiation dose increases (moving across columns from left to right) the QALY benefit of CMT over chemotherapy-alone reduces, and in some cases turns negative. When this pattern is looked at comparing the undiscounted (e.g. top graph of figure 3.2) to the discount differences (e.g. bottom graph of figure 3.2), notably, the point at which the results 'flip' to favouring chemotherapy-alone happens at lower radiotherapy dose example in the undiscounted analysis. Therefore, in some of these patient combination instances, there can be seen a net benefit with CMT in the undiscounted analysis but a net harm when discounted. This can be most easily seen in the never smoker OAR dose set 5 example (far right side of figure 3.2). This pattern manifests as a result of the timings of the toxicities that occur with the different treatment options. In the chemotherapy-alone scenario, as described in the paragraph above, there is a greater risk of relapse which happens early in the time horizon. Whereas the 'harm' caused by radiotherapy, the late-effects, typically happens far later. In the undiscounted analysis the 'harms' of radiotherapy may outweigh the 'harm' of chemotherapy-alone. However, when discounting is applied, these harms from CMT, being much further into the future have minimal impact on life years and QALYs in net present value terms, which can lead to the scenario in which the 'harm' of chemotherapy-alone is greater. And hence in the discounted analysis CMT is preferred.

3.5.3 Results implication

The results highlight, firstly, the excellent outcomes for most patients with stage I/IIa classical HL irrespective of treatment decision. For instance, a 20-year-old never smoking female patient would be expected to live into her early eighties under both choices, even with higher-than-average OAR radiation doses than would usually be received during modern

radiotherapy, such as in OAR dose example 4 (table 3.10). Patients and clinicians can, therefore, be reassured by the high probability of a normal life expectancy.

Table 3.15 Comparison of modeled life expectancy and QALYs for a female 20 year old never smoker to general population (quality-adjusted) life expectancy norms

OAR dose set	**CMT model estimate**		**CMT model estimate**		**2017/19 UK life expectancy**	**Quality-Adjusted Life Expectancy Norms (10.1016/j.jval.2022.07.005)**
	LEs	QALYs	LEs	QALYs	LEs	QALYs
1: Unilateral neck	61.8	49.6	61.0	48.5	63.5	53.2
2: Avg. RAPID	61.5	49.3	-	-	-	-
3: Avg. RAPID w/ medstinm	61.2	49.1	-	-	-	-
4: Bilat neck + whole medstinm	60.6	48.6	-	-	-	-
5: Mantle	60	48.2	-	-	-	-

Secondly, the results highlight the importance of considering a patient's underlying health, health-related behaviours (especially smoking), expected OAR radiation doses, and time preference for health when deciding treatment choice. In the model, a patient's smoking status is accounted for due to its well characterized and significant effect on the incidence of lung cancer, CHD, and stroke. Age-band specific proportions of smokers were obtained from the 2012 General Life Survey. Although this data is over a decade old, it demonstrates a relatively high minority of the population have cigarette exposure. For example, the smoking proportion amongst sampled 20-24 year olds was 33%. More recent survey data, for instance the Health Survey for England, 2021 suggests this is declining but still significant. Comparing the results from the smoking stratified analysis with those from the unadjusted analysis demonstrates the importance of doing so, as the optimal treatment choice differs greatly by smoking status.

Beyond smoking, other underlying factors such as obesity and co-morbid conditions could also have an impact on optimal treatment choice. Increasing the range of risk factors would add significant complexity to the derivation of baseline late effects incidence by subgroup and would greatly increase the possible number of patient presentations, therefore it was not undertaken. Generally however, where such factors increase the baseline risks of the four late effects, as did smoking, the favorability of a chemotherapy-alone strategy would increase. It should also be noted however that older less healthy patients may tolerate relapse therapy less well, and that minimizing the risk of relapse using radiotherapy as part of frontline treatment may have benefits for these patients that are also not currently incorporated into the model. Nonetheless, the results for the never-smoking patient examples suggests CMT provides more benefit over chemotherapy-alone in patients, irrespective of age, sex, and OAR doses, with otherwise good underlying health.

The results also highlight that, based on our model, CMT is comparatively more favorable the younger the patient. This contradicts the commonly held maxim that young patients, especially female, should be spared radiation. Despite younger patients having higher ERR/Gy estimates and a longer period of excess risk, due to the negligible yearly incidence rates of lung cancer, CHD and ischemic stroke before the age of 65, there is only a small excess incidence from radiotherapy before this age. This contrasts to a high morbidity burden for a young patient if they were to relapse soon after frontline treatment. Additionally, the results suggest only small differences in outcomes between the sexes. This is likely due to the size and distribution of age-specific year rates for the four late side-effects. Whilst males do not share the excess risk of breast cancer, below the age of ~70 their baseline incidence and case-fatality rates for lung cancer, CHD and ischemic stroke are higher than those of females of the same age.

The impact on results of discounting future health outcomes is also significant. As described above, it shifts the point at which CMT is favourable. Having a positive time preference, which has the effect of discounting future health, is a common human behavior often observed in discrete choice experiments, and corresponds with surveys in HL survivors indicating that for many patients, primary cure is of most importance.[120,121] Therefore when considering omission of radiotherapy, for instance in those with adverse underlying health factors, this time preference with respect to health should also be considered by the clinician. Smokers for instance, evidenced perhaps by their decision to smoke, may exhibit a strong preference towards current health. It should be noted however that, for non-smokers, CMT is favoured even without discounting future health outcomes for the most commonly experienced modern OAR radiation dose examples (1 to 3).

In sum, the comprehensive set of outcomes suggests that only in patients with significant baseline risks of late effects could the radiation-related excess risks be large enough to warrant radiotherapy omission. It should be strongly emphasized that in the RAPID trial, on which our estimates of first relapse risk and OAR doses are based, fewer than 5% of patients in the trial received OAR doses close to the (4) maximal bilateral neck and whole mediastinum example. Consequently, the proportion of patients with stage I/IIa disease who would benefit from omission of radiotherapy, under the preferred quality- and discount-adjusted analysis, is likely very small. Furthermore, radiotherapy techniques have advanced since the RAPID trial with the introduction of the involved site concept and breath-hold techniques.[108,122] The result is that, for contemporary cohorts, the radiation doses to OARs are substantially lower than those examined here,[21] and the expected favourability of CMT greater.

3.5.4 Further limitations

There are, of course, many caveats to the modelling approach and the assumptions made. The use of population-derived incidence and case-fatality rates assumes baseline equivalence between radiation-induced disease and general population disease. New primary cancers, CHD and ischemic stroke in ESHL survivors may be detected at an earlier stage due to survivor clinical follow-up, screening programs and increased health awareness and self-monitoring. For secondary primary cancers, earlier diagnosis could lower the case-fatality rate, whilst for CHD and ischemic stroke, preventative medication might slow disease progression and reduce the incidence rate of acute events. Therefore, our model may overestimate the quality of life burden and mortality from late effects, making our comparative results less favorable for CMT. However, it is also important to note that the biology of radiation-related late effects may be different from sporadic forms of the same disease and treatment may be made more difficult due to the previous treatments. Additionally, it was assumed that the incidence of one late effect did not change the risks of incidence of the other. However, treatment for breast and lung cancer may for instance increase the risk of CHD.

The model was limited to accounting for the increased risk of breast and lung cancer, CHD and ischemic stroke. However, irradiation increases the risk of a number of other rarer second malignancies, such as esophageal and thyroid cancer, as well as other cardiovascular events such as valvular heart disease and heart failure.[104,105] It was also assumed there was no increased risk of mortality from the use of ABVD chemotherapy, although evidence does suggests an excess risk of heart failure associated with anthracycline (A – Adriamycin (doxorubicin)) use.[105] Given patient's receive the same number of ABVD cycles, this risk was not modelled as the risks were assumed equivalent. This assumption, however, is likely to

inflate the absolute estimates of life years and QALYs. It is also likely to increase, though minimally, the favorability of the chemotherapy-alone strategy, as fewer patients would reach the age where the radiotherapy late effect most often occur. I.e. It introduces a competing mortality risk.

The true relationships between the dose and volume of radiation received by a patient during radiotherapy and their subsequent risk of specific late effects are not known with certainty and can only be modeled based on the best data available from historical cohorts. In this study, published dose-response models of the ERR/Gy were chosen, generated from epidemiological studies involving HL survivors, with mean organ dose acting as the summary metric of radiation dose. Alternative approaches include the use of estimates derived from the follow-up of historic low-dose radiation events such as the Life Span Study Atomic Bomb Survivor Cohort, radiobiological models, and hybrid models as discussed in section 3.3.3.2.[102,123,124] This approach was taken as the ERR/Gy estimates have shown robustness even when derived from survivor cohorts of other primary cancers, and it is widely accepted that, with very few exceptions, dose-response relationships for cancer induction in the treatment range are linear with no threshold.[125,126] Under this relationship, mean organ dose is an adequate measure for prediction as it does not vary according to the distribution of radiation dose. Nonetheless, the transferability of these dose-response models, derived from cohorts treated with historic radiotherapy techniques, to make predictions for contemporary radiotherapy cannot be tested directly due to the inherent latency of late effects. Contemporary radiotherapy techniques such as intensity modulated radiotherapy offer greater conformity, typically reducing the amount of normal tissue exposed to high radiation doses, but can increase the volume of normal tissue receiving low doses.[127] There have been theoretical concerns that the ‘low dose bath’ from IMRT may increase risk more than 3D conformal RT. These predictions are, however, strongly dependent on the radiobiological models chosen and observational data from clinical

series has not, so far, demonstrated any increase in risk with IMRT in adult patients.[128] Nonetheless, as cohorts treated with more modern techniques mature there is a need for further validation of the dose-response models. Future modelling studies may wish to include sensitivity analysis to allow for different assumptions such as this low-bath effect. Lastly, it should be acknowledged that organs are not homogenous entities, with radiation dose to different tissues and substructures potentially being more critical for the pathogenesis of specific late effects. For instance, similar to breast cancer, the best data currently available for Hodgkin lymphoma suggests that the risk of CHD is linear with no threshold when related to mean heart dose.[79,125] However, there are recent suggestions from other thoracic cancers, such as lung cancer, that predictions may be improved in future using additional metrics, such coronary artery doses.[129]

Smoking status was incorporated into the model based on fixed categories of smoking status; current, former, never. Such categorization of smoking simplifies a complex course of cigarette consumption over time in those who have ever smoked, and does not explicitly quantify to degree of tobacco consumption. However, such simplification was necessary to enable linkage with the relative risk data, which is also typically based on these categories, and the subsequent decomposition of the late effects incidence rates. As such a large degree of nuance in the outcomes estimates is lost, which should be taken into account. For instance, an individual may be a current smoker, but may smoke relatively infrequently and have a low number of pack years. The life years and QALY outcomes estimated for current smokers is likely to overestimate the favourability of chemotherapy alone for such a person.

Finally, in our ESHL sub-module, we have made the assumption that all relapsed patients would be eligible and undergo ASCT and that after such salvage therapy, the non-relapse related subsequent all-cause mortality rate for the individual is equal to that of the general population. For the latter, we found no estimates for the standardized mortality rate (SMR)

after stem cell transplant that excluded deaths attributable to subsequent relapse or first line radiotherapy. However, studies suggest ASCT recipients have SMRs reaching that of the population after ten years event-free survival.[130] Furthermore, with the advent of immuno- and targeted therapies, salvage without ASCT is a growing area of research.[31]

Joint estimation of parameter uncertainty through probabilistic sensitivity analysis was incorporated into the model. The resulting confidence intervals around the health outcome means were narrow in nature. Rather than suggesting certainty in the estimate, these narrow confidence intervals should be taken cautiously as an artifact of the limited known uncertainty in the input parameters; partially, this is a function of the natural history of Hodgkin lymphoma (as few people relapse) being derived from population-based mortality and incidence rates which inherently have little to no uncertainty attached. Beyond parameter uncertainty, structural and methodological uncertainty is harder to quantify and incorporate into the outcome estimates. Here for instance, the choice to use population-based incidence rates is a structural choice, as is the use of the dose-response relationships to inform late effects incidence and the assumption that all individuals who relapse receive an autologous stem cell transplant discussed in the previous paragraphs. External validation of parts of the model such as comparison of long-term predicted survival against those seen in trials and late effects incidence is made infeasible due to the lack of any such published data. As such, the results must be taken cautiously with these limitations in mind.

3.5.5 Generalisability

The study results relate to stage I/IIa ESHL with no mediastinal bulk as per the RAPID inclusion criteria. The RAPID trial was chosen as representative dosimetry for OARs for this trial was available, it was UK-based, and significantly and in contrast to the other two trials,

the authors concluded that omission of radiotherapy may be an acceptable treatment option in patients who are PET-negative after initial chemotherapy.

Similar PET response-adaptive omission of radiotherapy was assessed in the GHSG HD16 and EORTC/LYSA/FIL H10 trials albeit with slightly different treatments, patient characteristics, and PET-negativity definitions. The GHSG HD16 trial assessed 2 cycles of ABVD chemotherapy with or without 20Gy IFRT in PET-negative favorable (GHSG criteria) ESHL. The difference in 5-year progression-free survival (PFS) rates, which were 93.4% and 86.1% respectively, were very similar to the 5-year extrapolated PFS estimates for the RAPID trial. Additionally, with the use of 20Gy IFRT as opposed to 30Gy, radiation-related risks would be expected to be reduced by a third. In H10, favorable (EORTC criteria) ESHL patients received 3 cycles of ABVD chemotherapy and 30Gy involved-node radiotherapy (INRT, a lower volume of radiotherapy) in the control arm, and 4 cycles of chemotherapy-alone in the PET-negative experimental arm. The difference in 5-year PFS rates, which were 99.0% and 87.1% respectively, were greater than our 5-year extrapolated PFS estimate for the RAPID trial. Given the better survival rates and lower radiation doses and volumes administered compared to RAPID, it is likely that including HD16 and H10 trial favorable patient data in the model would confirm and possibly increase the already large majority of patients for whom CMT would be preferable.

The role of consolidative radiotherapy in the H10 unfavorable (EORTC criteria) group is less clear due to smaller differences in PFS. Additionally, the role of radiotherapy has been challenged by the results of the RATHL trial[25] in advanced HL, which included stage IIA patients with adverse features, and recent findings of non-inferiority of chemotherapy-alone with 2 + 2 intensified treatment in GHSG HD14.[131]

Within classifications of disease stage there may still remain variation in disease and patient factors which could influence relapse risk. For instance, in post-hoc analysis of the RAPID trial, baseline maximum tumor diameter (MTD) was prognostic of subsequent relapse in patients who had achieved complete metabolic response.[132] Notably, there was an approximate 19% increase in HL relapse risk per centimeter increase in MTD (P=0.02). For patients with MTD of ≥5 cm, five-year event-free survival (EFS) in those assigned to chemotherapy-alone was 79.3% compared to 94.9% in those assigned to CMT (P = .03). This result may indicate that the benefit of consolidative radiotherapy varies with MTD. These results are based on a small number of events in the CMT group, as such, MTD was not included in the model. However, such factors could be incorporated in future, when additional supporting data become available, and may impact optimal treatment choice. For instance, were MTD to be incorporated into the model based on the above findings,[132] the difference in QALYs gained from CMT for never smokers with smaller MTDs would diminish or even favor chemotherapy-alone. Conversely, the benefit of CMT for never smokers with larger MTDs would increase. This highlights the need for identification of robust baseline prognostic biomarkers which would allow for even greater personalization of predicted outcomes.

3.5.6 Conclusion

In the previous chapter, chapter 2, excess variation in the use of frontline curative intent radiotherapy was observed across NHS trusts in England, likely due in part to the uncertainty in clinic evidence. To address this uncertainty and better inform this treatment choice, this chapter outlines and applies a microsimulation model developed to provide individualized prediction of benefit from receiving or omitting consolidative radiotherapy, incorporating both patient characteristics and radiotherapy dosimetry.

Due to the structure of the model, it may be readily extended to compare outcomes from the other PET response-adaptive radiotherapy omission trials, to incorporate prognostic biomarkers such as MTD, or for assessing the benefit of identifying patients who might benefit most from advanced organ-sparing radiotherapy techniques such as deep inspiration breath hold and proton beam therapy.[44,122,133] In the next chapter, the microsimulation model is used again for this later purpose.

4 Individualised estimation of quality-adjusted survival benefit and cost-effectiveness of proton beam therapy in intermediate-stage classical Hodgkin lymphoma

4.1 Background

In section 2.1.1, the rationale for the use of consolidative radiotherapy (RT) after chemotherapy in early-stage classical Hodgkin Lymphoma (ESHL) was discussed with various phase III RCTs showing that the addition of RT leads to a statistically significant increase in relapse-free survival, even in chemo-responsive patients. Nonetheless, although such combined modality treatment (CMT) provides long-term freedom from recurrence, approaching 95%,[27,28] it can come at the cost of increased risk of late toxicities such as new primary cancers and cardiovascular disease.[95] Due to the unknown trade-off between the immediate benefits of consolidative radiotherapy and future risks of late toxicities, often occurring 20-40 years in the future, the question of whether the benefits outweigh the risks cannot be answered by the RCTs.

A result of this uncertainty is variation in clinical practice as demonstrated in chapter 1. Subsequently in chapter 3, an individual patient-level state transition model was developed to simulate the natural history of disease of Hodgkin lymphoma taking into account risk-modifying patient characteristics such as age, sex, smoking status, and the radiation dose to various organs. The model was run for a range of patient presentations, with the results suggesting that for the majority of illustrative patients who did not smoke, treatment with CMT provided more quality-adjusted life years (QALYs) than treatment with chemotherapy alone. For the analysis, organ at risk (OAR) doses were based on the RAPID trial and therefore based on radiotherapy technologies and techniques (involved-field radiotherapy) that were available in the early 2000s. However, due to the acknowledgement of the risks of radiotherapy, there has been continued incremental adoption of new RT technologies and techniques in order to minimise collateral irradiation without compromising disease control.[43]

Recently, there has been great interest in the use of proton beam therapy (PBT) as an alternative to traditional photon-based RT. Beams of protons and photons have markedly different percentage depth dose, which plots the absorbed dose deposited by a radiation beam as it travels through a medium. Whereas beams of photons deposit energy more consistently along their path, thus collaterally irradiating normal healthy tissue both proximal and distal to the intended target, protons deposit most of their energy at the end of their limited range (termed the 'Bragg peak') and can therefore reduce proximal irradiation and virtually eliminate distal irradiation of normal tissues.

To compare new radiotherapy technologies and techniques, comparative planning studies are often performed.[122] Here, for a cohort of patients, each patient undergoes imaging scans as normal on which their radiotherapy treatment is planned through the delineation and contouring of target volumes and surrounding organs, and subsequent optimisation of radiotherapy beam angles and modulation. Plans based on the technologies and techniques under comparison are also created. These plans allow for the comparison of dosimetry, i.e. the calculation and assessment of the planned ionizing radiation dose absorbed by patient. And various dose metrics can be calculated such as mean heart dose. Such comparative planning studies have consistently shown improved dosimetry with the use of PBT, but importantly, these studies also show large variation in dosimetry benefit across patients due to heterogeneity in anatomy and disease location.[134]

Dosimetry alone, however, provides limited actionable information for decision making purposes. What is required is the translation of differences in dosimetry into its predicted effect on patient health, preferably in the form of quality-adjusted life years (QALYs). Furthermore, another consideration in the decision to treat patients with PBT is its greater cost and limited capacity. Recently, the UK Department of Health invested a reported £250 million (reported in their initial announcement of funding, actual costs are thought to be far more) in

the construction of two high-energy centres at The Christies NHS Foundation Trust, Manchester, and The University College London Hospitals NHS Foundation Trust, London. This capital cost is orders of magnitude greater than a conventional photon centre. And despite this large investment, their combined capacity to treat 1300 patients per year corresponds to around 1% of national radiotherapy episodes.

In combination, heterogeneity in patient benefit, higher healthcare costs, and capacity constraints presents a need to identify which HL patients would benefit most, with the Particle Therapy Cooperative Group (PTCOG) Lymphoma Subcommittee recommending a model-based approach incorporating patient dosimetry.[45]

This chapter focuses on the decision to use conventional photon-RT or PBT in the case where CMT has been chosen as treatment for chemo-responsive intermediate-stage classical HL (ISHL) patients following PET-CT response-adapted treatment. The previously described microsimulation model is augmented and utilised to estimate not only the difference in expected QALYs between conventional photon-RT and PBT but also resulting future healthcare costs. The model is applied to a clinically relevant population of illustrative patients, differing by age at treatment, sex, smoking status, and RT modality. This chapter changes focus from early-stage to intermediate-stage lymphoma (ISHL) due to the availability of normal tissue radiation doses from a comparative planning study of 61 ISHL patients treated with pencil beam scanning PBT and re-planned with volumetric arc therapy (VMAT), both in deep inspiration breath hold (DIBH) (see section 1.2.3).[135] Furthermore threshold analysis is performed to derive the maximum cost difference between PBT and VMAT necessary for PBT to be considered cost-effective in a UK setting for each illustrative patient.

4.2 Methods

This chapter develops the microsimulation model into a full cost-effectiveness model. The cost-effectiveness model is designed to compare the joint cost and QALY outcomes for an individual with ISHL, under either a combined modality treatment strategy using photon beams to deliver radiotherapy or the scenario in which proton beams are used instead. As a cost-effectiveness analysis set in the UK, the model and applications follow NICE's guide to the methods of technology appraisal. Briefly, and repeated below, the model assesses health outcomes and cost-effectiveness over a life time horizon. The perspective is that of the National Health Service/Personal Social Services, with, where possible, only costs attributable to the intervention and resultant direct sequalae included. As in the previous chapter, future health outcomes are discounted at the recommended 3.5% rate, as are costs in this application. Below, changes to the model from the previous chapter are described in detail.

4.2.1 Intermediate stage Hodgkin lymphoma sub-model

Although it will be assumed initial disease control and hence the risk of first relapse is equivalent regardless of whether the patient was treated with conventional photon RT or PBT, the course of HL still requires explicit modelling as it is a competing risk of death. In the previous chapter, the RAPID trial in early-stage disease was used as the basis for the risk of first relapse with different risks under a chemotherapy alone or CMT treatment scenario. Instead this chapter focuses on intermediate-stage disease. For clarity, historically "early-stage" disease included both those with stage I or II disease and "favourable" features, i.e. without the presence of risk factors, and "unfavourable" features, i.e. with the presence of risk factors. More recently there has been a transition towards terming these characterisations as "early stage" disease and "intermediate stage" disease, to avoid the negative conitation of

"unfavourable", and this is followed here. The previous chapter focused on this newer definition of "early stage" disease, however, the same decision between CMT verses chemotherapy-alone is pertinant to those with what is now termed "intermediate stage" disease. Indeed, the previously described H10 trial looked at PET-response adapted treatment approaches in both early stage "favourable" and "favourable" patients (Table 4 .16 repeats the summary of the trials given in section 1.2.5).

Table 4.16: Summary of each PET-response adaptive trial

	RAPID	**HD16**	**H10 favourable**	**H10 unfavourable**
Population	cHL stage IA or IIA, n = 602	cHL stage I and II or NLPHL stage IB, IIA, or IIB, n = 1150	cHL stage I and II with no unfavourable* characteristics, n = 754	cHL stage I and II with at least one unfavourable* characteristic, n = 1196
Control arm	3x ABVD + 30Gy RT if PET negative	2x ABVD + 20Gy RT if PET negative	3x ABVD + 30Gy RT if PET negative	4x ABVD + 30Gy RT if PET negative
Experimental arm	3x ABVD if PET negative	2x ABVD if PET negative	4x ABVD if PET negative	6x ABVD if PET negative
PFS outcome	3-year: 94.6% (95% CI, 91.5 to 97.7) vs 90.8% (86.9 to 94.8)	5-year: 93.4% (90.4% to 96.5%) vs 86.1% (81.4% to 90.9%)	5-year: 99.0% (95.9 to 99.7) and 87.1% (82.1 to 90.8)	5-year: 92.1% (88.0 to 94.8) and 89.6% (85.5 to 92.6)
OS outcome	3-year: 97.1% (94.8 to 99.4 vs 99.0% (97.6 to 100)	5-year: 98.1% (96.5% to 99.8%) vs 98.4% (96.5% to 100.0%)	5 year: 100% vs 99.6% (96.9 to 99.9)	5 year: 96.7% (92.9 to 97.8) vs 98.3% (96.0 to 99.3)

* Unfavourable characteristics: age ≥ 50 years or more than three nodal areas or mediastinal-thoracic ratio ≥ 0.35 or no B symptoms and erythrocyte sedimentation rate [ESR] ≥ 50 or B symptoms and ESR ≥ 30

Therefore in this chapter, the risk of first relapse was based on the standard therapy PET-negative arm of the H10U trial, with patients assumed to begin the model after being treated with an initial four cycles of ABVD chemotherapy followed by 30Gy of RT.

The annual probability of first relapse in the initial 5 years following the start of the model simulation was derived from the standard therapy (4xABVD chemotherapy plus 30Gy RT) PET-negative arm of the trial. Again, this was derived through reconstruction of individual patient time-to-event data using the per-protocol Kaplan–Meier (KM) plots of progression-free survival (PFS) from the H10 trial publication. The commonly used Guyot et al (2012)[87] procdeure was performed for this reconstruction and parametric survival curves (Exponential,

Weibull, Gamma, log-Normal, log-Logistic, Generalised gamma, Generalised F and Gompertz distributions) were fitted subsequently fit to the reconstructed data, with yearly transition probabilities derived from the best fitting parametric model, informed by the Akaike and Bayesian information criteria.

gives the derived transition probabilities. Notably, the 5-year PFS in H10u was 92.1% (88.0 to 94.8), compared to a 3-year PFS of 94.6% (95% CI, 91.5 to 97.7) seen in the RAPID trial (which was used in the preceding chapter to inform the ESHL model). These corresponded, from their best fitting parametric curves, to a 2.9%, 2.2%, 1.3%, 0.9%, and 0.7% yearly probability of relapse over 5 years for the ISHL sub-model and a 1·3% yearly probability of relapse over 5 years in the ESHL model. Assuming no other competing risks of death, the probability of not relapsing at 5-years based on these probabilities is 92.2% for the ISHL model and 93.6% in the ESHL model. Only the risk of first relapse changes between the ISHL and ESHL model; thereafter, transition probabilites are the same. Health states are the same between models, as are the utility decrements.

Table 4.17: Health state transitions in the ISHL sub-model

Transition	Estimate and Description
Remission to First relapse	Yearly transition probabilities for the first 5 years after initial treatment obtained from a generalized F distribution: mu = 1.64229, sigma = -0.4577225, shape 1 = -48.84879, shape 2 = -6.897889. This corresponds to a 2.9%, 2.2%, 1.3%, 0.9%, and 0.7% yearly probability of relapse over the 5 years.[27]
Remission to Cured	As before
First relapse to Second relapse	As before
First relapse to Cured	As before

Second relapse to Dead from HL	As before
Second relapse to Cured	As before

4.2.2 Incorporating healthcare costs

In order to evaluate the possible cost-effectiveness of PBT, the previously developed model was augmented to also calculate UK National Health Service (NHS) costs attributable to the late effects. For each late effect, a systematic literature search was performed to identify appropriate studies on which to base these costs. The systematic literature search for the cost of breast and lung cancer, stroke, and CHD can be found in Appendix B: Additional material for Chapter 4.

The study chosen to provide breast and lung cancer costs gave yearly average per-patient costs by year since cancer incidence up to 10 years post-diagnosis for breast cancer, and five years for lung cancer.[136] This study was the only study identified which provided long-term costs (>2 years after diagnosis) for these two cancers, therefore no other study was considered suitable. Two published studies were identified relating to the costs of CHD. Both publications were part of the same project, one focusing on methodology whilst the other focusing on presentation of the lifetime costs of stable coronary artery disease. Lifetime costs were abstracted from this later study which is based on English individual patient-level data and model-based extrapolation.[137] This singular lifetime cost was applied if a patient transitioned from the no CHD to diseased state.

Finally, for ischaemic stroke, costs were taken from a study which estimated UK costs using a discrete event simulation model informed by routine registry and audit data.[138] Here again, only two studies provided life time estimates of cost. Both studies were by the same set of

authors, with one publication focusing on societal cost, and the other focusing on NHS costs, with this later study chosen given the perspective of this model. The study provided age-group specific (<65, <75, <85) costs for the first year following a stoke, which were accrued in our model when a patient transitioned from no ischaemic stroke to diseased, and costs for subsequent years, which accrued ever year thereafter.

In our model costs are reported for the year 2014/15, which was the reporting year of the stroke study. The cancer costs and CHD costs were inflated to 2014/15 year using the Hospital and Community Health Services (HCHS) Index. Due to the lack of alternative studies, no sensitivity analysis was performed using alternative cost inputs. Inflation of healthcare costs to a more contemporary year was not performed. Doing so would be unlike to significantly impact the cost outcomes estimated by the model as the late effect events typically occur far into the future, where discount has greatly reduced the net present value. Nonetheless this is a limitation of the analysis.

4.2.3 Comparative dosimetry and application of the model

Lifetime QALYs and healthcare costs generated by the model are a function of the simulated patient's age at treatment, sex, smoking status, and three or four OAR doses metrics, namely mean lung dose (MLD), mean heart dose (MHD), mean dose to the common carotid artery (MDCCA) and, for females, mean breast dose (MBD). In this analysis, mean organ doses of 61 ISHL patients from a planning study that compared radiation doses from patients treated with pencil beam scanning PBT in DIBH and re-planned with VMAT in DIBH were utilized based on a prior study undertaken at NDPH.[135] The planning method used for most patients was butterfly VMAT (BVMAT), but for more complex volumes additional plans were produced using BVMAT with additional partial or full arcs and a "best-plan" chosen based on planning target volume (PTV) coverage and OAR doses. Full details of patient contouring,

planning, and dosimetry analysis can be found in the study publications.[135,139] In the study, photon radiotherapy doses were calculated in terms of Grays (Gy) and proton beam radiotherapy doses were calculated in terms of Gy equivalents assuming a fixed relative biologic effectiveness of 1.1, i.e. that the cell killing potential of protons is 10% greater than photons. Variable relative biological effectiveness was not considered in the study or in this chapter. In the dose response models, a Gy of photon radiotherapy is assumed to have the same effect as a Gy equivalent of proton radiotherapy. Hereafter, Gy is used for both types of radiotherapy. In the results section, tabulations of patient dosimetry for these 61 patients are provided.

To provide a comprehensive range of clinically relevant patient presentations and a wide range of dosimetric differences, the 61 mean organ dose pairs were combined with two ages at treatment; 20y and 40y, each sex, and three smoking statuses; never, former, and current. For the female combinations, only OAR dose metrics for the 40 patients who were female, and therefore had MBDs, were used. Therefore in total, 606 (Female:2x3x40 + Male:2x3x61) distinct patient presentations resulting from the age, sex, smoking status, and OAR radiation doses were run through the model, generating for each their expected difference in life years, QALYs, and life time healthcare costs attributable to late effects between treatment with PBT and VMAT. The simulations were run both undiscounted and with a 3.5% annual discount rate applied to future health outcomes and costs as recommended by the UK's National Institute for Health and Care Excellence (NICE) for cost-effectiveness analysis. Simulations were run 10,000 times per individual to reduce Monte Carlo error as in the preceding chapter. Probabilistic sensitivity analysis was not performed due to the previous findings of narrow confidence intervals. Internal model validation checks were performed as described in section 3.3.5.

PBT is not currently commissioned for the treatment of lymphoma in adults in the UK, due to a lack of evidence regarding clinical- and cost-effectiveness.[140] In England, NICE makes treatment reimbursement recommendations based on consideration of cost-effectiveness judged according to the incremental cost-effectiveness ratio (ICER). This is the ratio of the difference in costs and QALYs between the treatment and its next best comparator. The ICER is then compared to NICE's willingness-to-pay threshold which is stated to be in the range of £20,000 to £30,000 per QALY. Due to the nascency of PBT in the UK, published peer-reviewed estimates of treatment cost do not currently exist, which precludes direct estimation of the ICER of PBT over VMAT. However, for a given willingness-to-pay threshold, it is possible to calculate the maximum cost of PBT over VMAT for PBT to be considered cost-effective, sometimes referred to as threshold analysis. The rearrangement of the ICER equation underlying this estimation is as follows.

$$ICER = \frac{Cost_{PBT} - Cost_{BVMAT}}{QALYs_{PBT} - QALYs_{BVMAT}}$$

Let,

$$k = Willingness¿ pay\ threshold$$

$$\Delta Cost_{RT} = The\ difference \in upront\ cost\ of\ delivering\ PBT \wedge BVMAT$$

$$\Delta Cost_{Late\ effects} = The\ difference \in healthcare\ costs¿ late\ effects$$

$$\Delta QALYs = The\ difference \in QALYs$$

Then to be considered cost effective,

$$k > \frac{\Delta Cost_{RT} + \Delta Cost_{Late\ effects}}{\Delta QALYs}$$

$$(k * \Delta QALYs) + \Delta Cost_{Late\ effects} > \Delta Cost_{RT}$$

Using the QALY and healthcare cost outcomes generated by this model, the maximum excess cost at which PBT might be considered cost-effective for each of the patient presentations was calculated, under the £30,000 per QALY willingness-to-pay threshold.

Finally, difference in results according to four pre-treatment indicators of difference in comparative dosimetry were investigated.[135] Three relate to improved cardiac sparing, of which two were explored in the prior comparative study; 1) The longitudinal overlap of the clinical target volume (CTV) and heart (dichotomized into above or below 40%); and 2) CTV extension above or below the seventh thoracic level (T7); Additionally the International Lymphoma Radiation Oncology Group (ILROG) guidelines identified 3) CTV extension above or below the origin of the left main stem coronary artery (LMSCA) as another indicative factor.[141] And fourthly, relating to improved lung and breast sparing, irradiation or not of the axilla. These indicators were assessed to see whether they translated into larger differences in QALYs and greater cost-effectiveness of PBT.

4.3 Results

4.3.1 Comparative dosimetry

Across all 61 comparatively planned ISHL patients, PBT modestly reduced the MHD, MLD and MBD by, on average, -0.47 Gy, -2.18 Gy and -0.97 Gy respectively, as shown in Table 4 .18. Conversely, PBT on average increased MDCCA by 1.51 Gy. Table 4 .18 also gives the average differences in mean doses for the dichotomies of the four indicators outlined above. For the three indicators relating to improved cardiac sparing, the longitudinal overlap of the clinical target volume (CTV) and heart produced the largest difference. Those with an overlap of <40% had on average a 0.66 Gy higher MHD with PBT, whereas for those with an overlap

of ≥40%, PBT reduced MHD by 2.96 Gy. There was also a greater reduction in lung and breast doses with PBT for patients receiving radiation to the axilla.

Table 4.18 Average differences in organ-at-risk mean doses between PBT and VMAT for all 61 comparatively planned ISHL patients and for indicative patient subgroups

OAR dose metric	All patients Average dose difference* (range) Gy	P value	Average dose difference* by patient subgroup (Gy)											
			Longitudinal overlap CTV/ Heart			CTV inferior extension vs T7			CTV inferior extension vs LMSCA			Axillary involvement		
			<40% overlap (n = 42)	≥40% overlap (n = 19)	P value†	At or above T7 (n = 20)	Below T7 (n = 41)	P value†	Above (n = 13)	Belo w (n = 48)	P value	Yes (n = 27)	No (n = 34)	P value†
MHD	-0.5 *(-12.5 to 5.8)*	0.64	0.7	-3.0	< .01	1.0	-1.2	< .01	1.2	-0.9	< .001	-0.3	-0.6	0.66
MDCCA	1.5 *(-1.6 to 7.9)*	0.02	1.4	1.8	0.16	1.5	1.5	0.96	1.2	1.6	0.14	1.2	1.8	0.04
MLD	-2.2 *(-6.7 to 0.4)*	< .001	-1.8	-3.0	< .01	-2.0	-2.3	0.38	-1.8	-2.3	0.11	-2.6	-1.8	0.03
MBD	-1.0 *(-6.0 to 1.1)*	0.01	-0.7	-1.6	0.08	-0.8	-1.1	0.53	-0.6	-1.0	0.25	-1.5	-0.4	< .01

PBT, proton beam therapy; VMAT, volumetric-arc therapy; ISHL Intermediate stage Hodgkin lymphoma; OAR, organs-at-risk; Gy, Gray; CTV, clinical target volume; T7, seventh thoracic level; LMSCA, left main stem coronary artery; MHD, mean heart dose to the whole heart; MDCCA, mean dose to the common carotid arteries; MBD, mean breast dose to bilateral breast tissue; MLD, mean lung dose to the whole lungs

** This is the average (mean) of the paired PBT–VMAT dose differences. Negative values indicate that proton beam therapy reduced the organ dose compared to photon radiotherapy.*

†*Based on two-sample t-test*

4.3.2 Quality-adjusted life years

Nearly all of the 606 illustrative patients were estimated to gain an increase in QALYs with the use of PBT over VMAT. For only a small minority of the illustrative patients (63 of 606),

whose mean radiation doses from VMAT were smaller for one or more organ, did VMAT provide greater QALYs. Across all simulated patients, PBT provided a mean gain of 0.307 undiscounted (0.073 discounted) QALYs, ranging from -0.342 (-0.067) to 2.171 (0.686). Patient characteristics influenced the number of QALYs gained or lost with PBT, with smoking status, OAR doses, and health discount rate having the largest impact. Table 4.4 provides the mean number of QALYs gained after treatment for PBT and VMAT by age at treatment, sex, smoking status, and discount (3.5% or 0%) for the 61 OAR doses, and figure 4.1 illustrates the differences in QALYs for these same groupings.

Table 4.19 QALY results by age, sex, smoking status and discount (3.5% or 0%) for all 61 comparatively planning ISHL patients

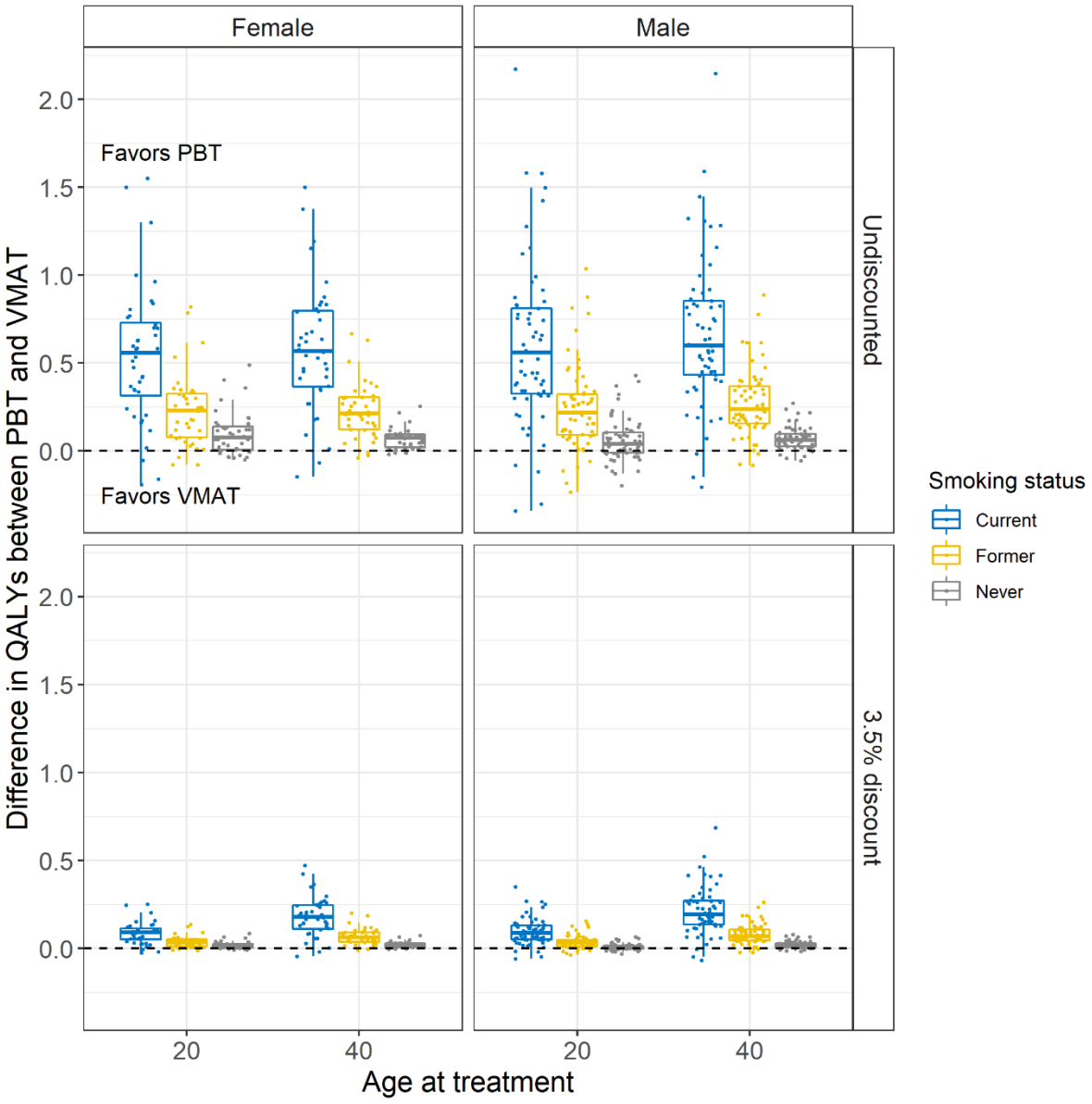
Discount	**Sex**	**Age**	**QALYs PBT**	**QALYs VMAT**	**Difference**
Undiscounted	Female			Never smokers, Mean (range)	
		20	48.8 (48.4 to 49.0)	48.7 (48.2 to 49.1)	0.10 (-0.05 to 0.49)
		40	32.2 (32.1 to 32.4)	32.2 (31.9 to 32.4)	0.07 (-0.02 to 0.25)
				Former smoker, Mean (range)	
		20	48.2 (47.6 to 48.7)	48.0 (47.1 to 48.6)	0.23 (-0.08 to 0.82)
		40	31.7 (31.2 to 32.1)	31.5 (30.7 to 32.0)	0.23 (-0.04 to 0.67)
				Current smoker, Mean (range)	
		20	46.9 (45.6 to 47.9)	46.4 (44.5 to 47.7)	0.54 (-0.19 to 1.54)
		40	30.5 (29.3 to 31.3)	29.9 (28.1 to 31.0)	0.58 (-0.15 to 1.50)
	Male			Never smokers, Mean (range)	
		20	46.2 (45.9 to 46.6)	46.2 (45.7 to 46.5)	0.06 (-0.20 to 0.43)
		40	29.9 (29.7 to 30.0)	29.8 (29.5 to 30.0)	0.07 (-0.05 to 0.27)
				Former smoker, Mean (range)	
		20	45.6 (44.9 to 46.2)	45.3 (44.3 to 46.1)	0.24 (-0.23 to 1.03)

		40	29.2 (28.7 to 29.7)	29.0 (28.1 to 29.5)	0.27 (-0.08 to 0.89)
			Current smoker, Mean (range)		
		20	44.0 (42.6 to 45.3)	43.4 (41.5 to 45.0)	0.60 (-0.34 to 2.17)
		40	27.8 (26.5 to 28.8)	27.1 (25.3 to 28.5)	0.67 (-0.21 to 2.15)
3.5% discount	Female		Never smokers, Mean (range)		
		20	21.3 (21.3 to 21.4)	21.3 (21.2 to 21.4)	0.02 (-0.01 to 0.09)
		40	17.2 (17.2 to 17.3)	17.2 (17.1 to 17.3)	0.02 (-0.00 to 0.07)
			Former smoker, Mean (range)		
		20	21.3 (21.2 to 21.3)	21.2 (21.1 to 21.3)	0.04 (-0.01 to 0.14)
		40	17.1 (17.0 to 17.2)	17.0 (16.8 to 17.2)	0.07 (-0.01 to 0.20)
			Current smoker, Mean (range)		
		20	21.1 (20.9 to 21.2)	21.0 (20.7 to 21.2)	0.09 (-0.03 to 0.25)
		40	16.7 (16.4 to 17.0)	16.5 (16.0 to 16.9)	0.18 (-0.05 to 0.47)
	Male		Never smokers, Mean (range)		
		20	20.9 (20.9 to 21.0)	20.9 (20.8 to 21.0)	0.01 (-0.03 to 0.06)
		40	16.6 (16.5 to 16.6)	16.55 (16.5 to 16.6)	0.02 (-0.02 to 0.08)
			Former smoker, Mean (range)		
		20	20.8 (20.7 to 20.9)	20.8 (20.6 to 20.9)	0.04 (-0.04 to 0.16)
		40	16.4 (16.2 to 16.5)	16.3 (16.0 to 16.5)	0.08 (-0.02 to 0.26)
			Current smoker, Mean (range)		
		20	20.6 (20.3 to 20.8)	20.5 (20.2 to 20.7)	0.10 (-0.06 to 0.35)
		40	15.9 (15.5 to 16.3)	15.7 (15.1 to 16.2)	0.21 (-0.07 to 0.69)

Current smokers gained the most QALYs, averaging 0.605 undiscounted QALYs, ranging from -0.342 to 2.171 across the age, sex and OAR doses combinations. This average fell to 0.146 QALYs (range -0.067 to 0.686) when future health was discounted at a rate of 3.5%. In

contrast, the benefit to the never smoker patients was far lower. Undiscounted, the benefit averaged 0.074 QALYs (range -0.196 to 0.491), whilst with discounting the benefit averaged 0.017 (range -0.030 to 0.086). As shown in figure 1, patient sex had minimal impact on the average QALYs gained with PBT. Similarly, age at treatment had little effect in the undiscounted analysis. However, with the application of the 3.5% to future health and cost outcomes, QALYs gained increased with older at treatment, especially for current smokers. For instance, a 40y-old male current smoker on average gained 0.213 QALYs, compared with 0.096 QALYs for a 20y-old male current smoker.

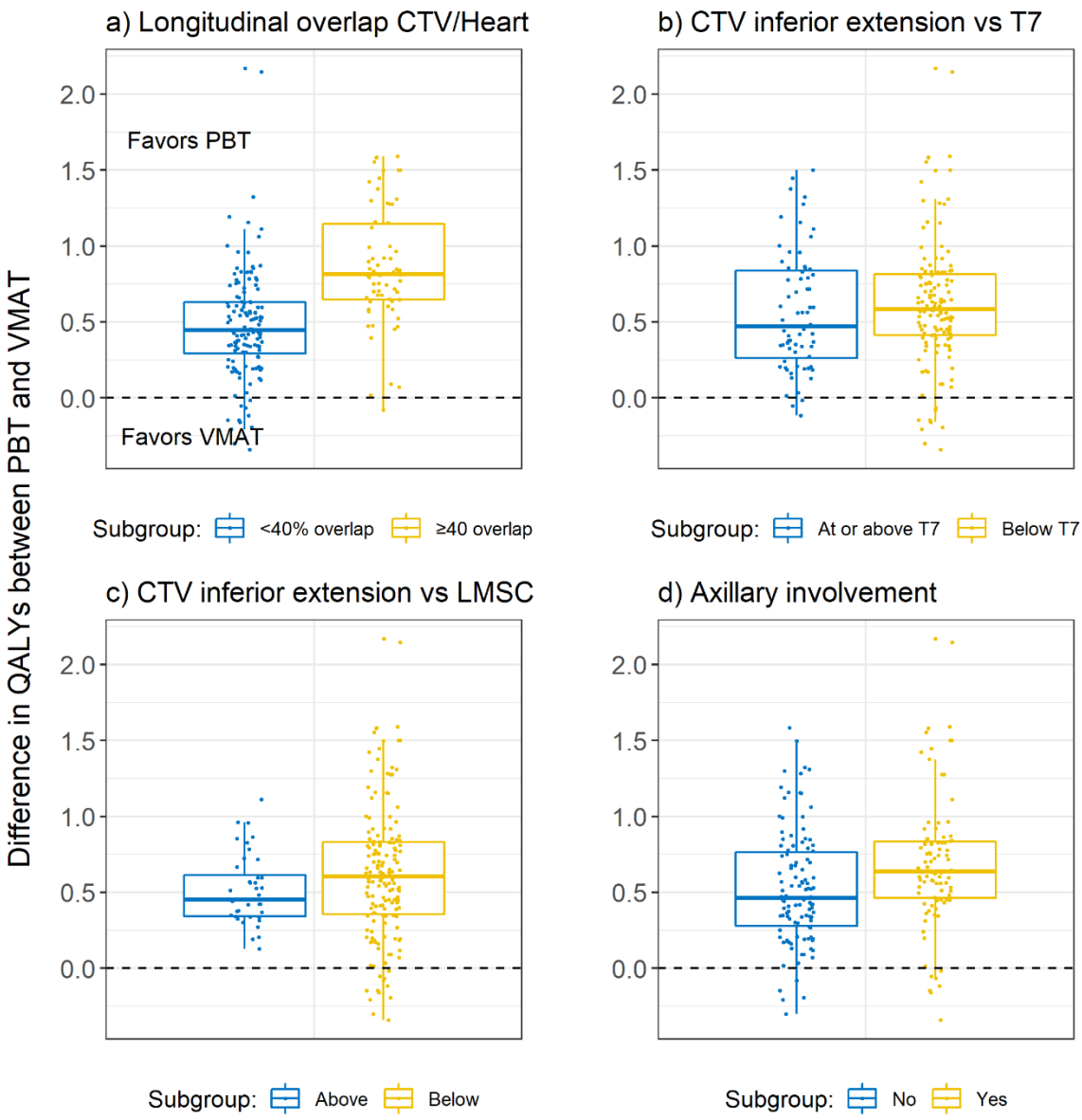
Figure 4.14 Box plots of the estimated difference in quality-adjusted life years between PBT and VMAT by age, sex, smoking status, and discount rate.



Visual exploration (Figure 4 .15) of differences according to pre-treatment planning characteristics suggests the longitudinal overlap of the CTV to the heart, with a threshold of 40%, may be indicative of a higher QALY benefit. The mean undiscounted benefit in all current smokers with an overlap greater than or equal to 40% was 0.866 QALYs, compared to 0.478 QALYs in those with smaller or no overlap. In never smokers the benefit was 0.141 QALYs and 0.041 QALYs respectively. CTV below T7, CTV in relation to the origin of the LMSCA, and axilla involvement appeared less predictive. The same pattern of results occurred when using the former smoker illustrative patients.

Figure 4.15 Box plots of the estimated difference in undiscounted quality-adjusted life years between PBT and VMAT according to pre-treatment planning characteristics for all

current smoker illustrative patients.

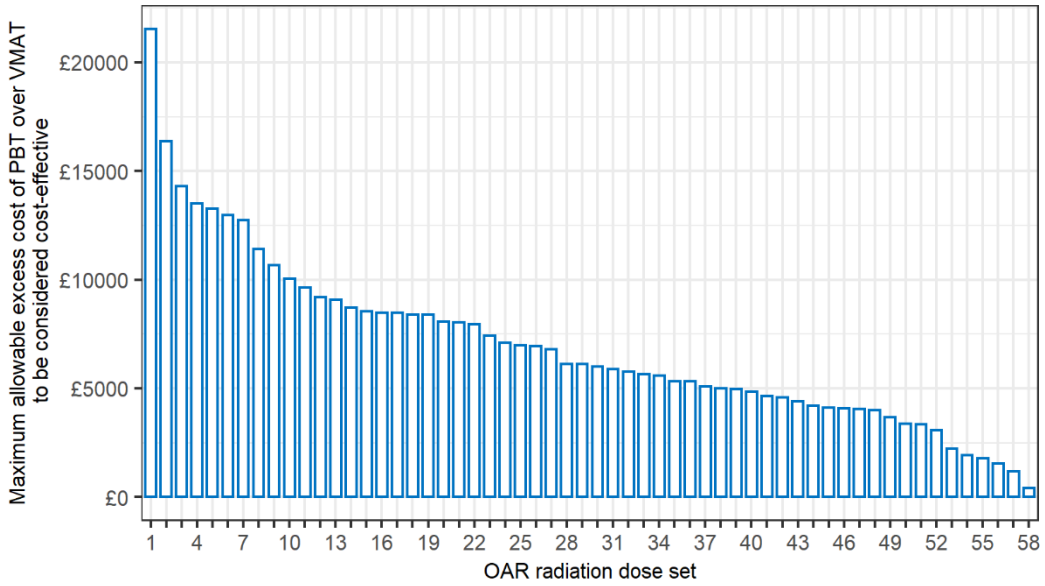


4.3.3 Maximum additional cost of PBT to be considered cost-effective

In line with the results for QALYs, smoking status had a significant effect on the maximum additional cost of PBT over VMAT to be considered cost-effective. Using the £30,000 cost-effectiveness threshold, the maximum allowable excess cost of PBT (compared to photon-RT) averaged £4812 for the current smoker illustrative patients compared to £645 for never smokers, but varied considerably, with a maximum of £21,538 and £3127 respectively. Figure 4 .16 highlights this variation using the 40y-old male current smoker as an example, with

each column being one of the 58 different OAR dose sets from the planning study, excluding three (of the 61) OAR dose sets which led to a reduction in QALYs with the use of PBT.

Figure 4.16 Distribution of the maximum allowable excess cost of PBT over VMAT to be considered cost-effective for male current smoker illustrative patients. Each column of the x axis, ordered from highest addition cost to lowest, constitutes one of the 58 (of the 61) OAR radiation sets from the comparative planning study.



Grouping by CTV and heart overlap, the maximum allowable excess cost of PBT under a £30,000 threshold for current smokers averaged £6593 for patients with an overlap greater or equal to 40% and £3886 for those with an overlap below 40%. The equivalent accepted costs for never smokers were £993 and £426. Full tabular results of the estimated difference in QALYs, difference in late effects related healthcare costs, and maximum excess upfront cost of PBT to be considered cost-effective are provided in Table 4 .20.

Table 4.20 Difference in QALYs, health care costs and maximum additional upfront cost of PBT to be considered cost-effective at £30,000 threshold

Discount	**Sex**	**Age**	**QALYs**	**Cost (£)**	**Maximum cost PBT (£)**
Undiscounted	Female		Never smokers, Mean (range)		
		20	0.099 -0.05 to 0.491	357.234 -1630 to 1692	-
		40	0.067 -0.019 to 0.254	93.913 -668 to 635	-
			Former smoker, Mean (range)		
		20	0.228 -0.079 to 0.819	329.063 -1733 to 1956	-
		40	0.227 -0.038 to 0.669	-152.278 -1401 to 536	-
			Current smoker, Mean (range)		
		20	0.54 -0.192 to 1.553	839.099 -1098 to 2602	-
		40	0.584 -0.147 to 1.501	-329.27 -1784 to 746	-
	Male		Never smokers, Mean (range)		
		20	0.062 -0.196 to 0.43	629.151 -1693 to 4037	-
		40	0.072 -0.054 to 0.273	209.879 -609 to 1525	-
			Former smoker, Mean (range)		
		20	0.243 -0.235 to 1.038	632.69 -1757 to 3878	-
		40	0.271 -0.082 to 0.888	30.651 -1032 to 1356	-
			Current smoker, Mean (range)		

		20	0.596 -0.342 to 2.171	1250.805 -1583 to 4598	-
		40	0.669 -0.205 to 2.146	-39.878 -1586 to 1839	-
3.5%	Female	Never smokers, Mean (range)			
discount		20	0.018 -0.008 to 0.086	-5.297 -554 to 221	544 -392 to 3128
		40	0.02 -0.005 to 0.074	-8.145 -333 to 184	620 -158 to 2509
		Former smoker, Mean (range)			
		20	0.037 -0.01 to 0.135	-28.032 -605 to 294	1128 -403 to 4655
		40	0.068 -0.01 to 0.202	-106.242 -621 to 149	2135 -357 to 6622
		Current smoker, Mean (range)			
		20	0.087 -0.026 to 0.252	-6.984 -613 to 385	2608 -960 to 8125
		40	0.181 -0.045 to 0.471	-260.119 -965 to 183	5677 -1519 to 15101
	Male	Never smokers, Mean (range)			
		20	0.009 -0.03 to 0.065	91.056 -365 to 619	189 -1314 to 2338
		40	0.021 -0.017 to 0.08	54.39 -237 to 459	575 -727 to 2546
		Former smoker, Mean (range)			
		20	0.036 -0.036 to 0.157	69 -571 to 636	1024 -1533 to 5102
		40	0.081 -0.023 to 0.265	-29.652 -465 to 412	2452 -927 to 8387
		Current smoker, Mean (range)			
		20	0.096 -0.06 to 0.351	113.575 -774 to 825	2766 -2447 to 11039
		40	0.213 -0.067 to 0.686	-133.615 -949 to 584	6538 -2313 to 21539

4.4 Discussion

4.4.1 Study findings

In terms of QALYs, the results show variation in the benefit estimated from using PBT. The benefit varied greatly according to OAR doses, which are a consequence of different disease

distributions and patient anatomy. Smoking status also had a significant impact on the magnitude of the predicted benefit of PBT, through its influence on incidence rates of lung cancer, CHD and stroke, and current smokers received the greatest gains in QALYs. Age at treatment had an impact on QALYs gained when future health and costs were discounted, suggesting a greater absolute benefit of PBT at older ages at treatment, i.e. the difference in QALYs increases, as opposed to the absolute QALYs themselves. This is due to the interaction between the monotonically increasing incidence rates of cancers and cardiovascular disease with age, and the increasing impact of discounting the further away from year of treatment. Therefore, although younger patients have a longer time at risk, late effects in the model are far more likely to occur in older age, by which time their net present impact has been substantially reduced by the discount factor. Sex had minimal impact on results, despite the added risk of radiation-induced breast cancer in females. This is due to the distribution of the age-specific annual rates for the three other late effects, with baseline incidence and case-fatality rates for lung cancer, CHD and ischemic stroke being higher at younger ages for males than for females of the same age.

Few studies have looked at the cost and cost-effectiveness of PBT, and no peer-reviewed studies have been performed in a UK setting for any cancer site.[142] Estimating the cost of PBT is a non-trivial exercise,[143] and as yet there remains no NHS reference cost for the preparation and delivery of a fraction of PBT, nor any other published costing study. As such, estimates of the maximum additional upfront cost difference at which PBT might be considered cost-effective under a £30,000 willingness-to-pay threshold were presented.

The UK's Department for Health does present a crude per patient incremental cost estimate compared to conventional photon RT in its strategic outline case for the development of a national PBT service in England.[144] At £34,359, this is far above the average of the individual patient maximum cost estimates. This is corroborated by private treatment costs at the now

closed Rutherford group of radiotherapy centres, where costs were between £27,000-48,000. With an estimated mean cost of a course of photon radiotherapy of approximate £3,600[145], this suggests PBT is currently unlikely to be considered cost-effective for the average ISHL patient in the UK setting.

Only one other cost-effectiveness study of PBT in HL, in a US setting, has been performed. This study focused on the risk of CHD only. The results of the study, which also used comparative dosimetry, suggested PBT is also unlikely to be cost-effective in a US setting.[146]

Model-based selection of patients to novel RT technologies based on estimated comparative outcomes necessitates the generation of OAR dose estimates from dual treatment plans. However, generating dual treatment plans for all patients is time consuming and costly. To partially address that, pre-treatment predictive factors have been proposed for initial planning selection as a more pragmatic approach, and to this end, four predictive indicators previously identified were assessed.[135,141] The longitudinal overlap of the CTV in relation to the heart with a threshold of 40% appears to be predictive of benefit, aligning with findings of improved 30-year absolute mortality risk from CVD in the comparative planning study.[135] However, the sample of comparatively planned patients is small from a statistical perspective, and our synthetic generation of illustrative patients precluded the use of formal statistical testing of difference.

The range of doses from the comparative planning study encompass cases presented explicitly in the ILROG and PTCOG studies, as well as summary doses from other comparative planning studies.[45,141,147,148] Suggesting this sample of patients is representative of the majority of possible disease presentations. Nonetheless, due to the rapid advancement of PBT techniques and natural lag in the publication of comparative planning studies, more advanced

PBT techniques may now, and in the future, generate larger dosimetric differences between PBT and VMAT.

The model accounts for the increased risk of the most clinically important late effects,[22,23,93] however RT has been shown to increase the risk of a number of other rarer second malignancies, such as esophageal and thyroid cancer, as well as other cardiovascular events such as valvular heart disease and heart failure.[104,105,149,150] Inclusion of all possible late effects is challenged by the availability of incidence and case-fatality data, but it should be noted their omission may underestimate the total comparative benefit of PBT. This underestimation is likely to be small however, given our inclusion of the most important late effects in terms of mortality.[94]

4.4.2 Study limitations

This study builds on the model developed in chapter 3, and therefore inherits the same set of limitations outlined previously. Joint estimation of parameter uncertainty through probabilistic sensitivity analysis was not performed in this analysis due to the previous finding of narrow confidence intervals around health outcomes. This is the result of much of the natural history of Hodgkin lymphoma (as few people relapse) being derived from population-based mortality and incidence rates which inherently have little to no uncertainty attached. Beyond parameter uncertainty, structural and methodological uncertainty is harder to quantify and incorporate into the outcome estimates. Here for instance, the choice to use population-based incidence rates is a structural choice. Similarly in the model's application to the context of proton beam therapy, unknown methodological uncertainty exists. It is assumed, and is widely assumed in the literature, that the dose-response model developed on historically treated cohorts irradiated with photon accurately generalise to protons. However, this cannot be validated until follow-up time is sufficient to observe late effects outcomes

from this new modality. Therefore, the results, including the estimated maximum additional costs of PBT to be considered cost effectiveness, should be taken in the context of this unknown uncertainty, which is of unknown magnitude, and as such the results can only be interpreted as exploratory.

4.4.3 Policy inference

Despite the limitations inherent in the use of models to predict future outcomes, it is only through studies such as this that the predicted impact of novel RT technologies aimed at reducing the burden of late effects can be explored. Results from this study suggest that taken as a whole, ISHL patients may only gain modestly from PBT in terms of QALYs, however certain patients who are predisposed to poorer outcomes, such as smokers, or those with large difference in radiation dose to OARs are predicted a larger gain in quality-adjusted life expectancy. Due to the additional cost of PBT and the inherent devaluation of future events resulting from the use of discounting in economic evaluations, our results suggest PBT for ISHL is unlikely to be cost-effective for most ISHL patients in the UK. Nonetheless, this model is readily generalizable to future comparisons of alternative radiotherapy technologies which may offer a means of reducing the does to key organs-at-risk, requiring only the addition of applicable comparative planning data.

5 Inequalities in geographic access and patient representation in lymphoma clinical trials across England

5.1 Background

Evidence generated by clinical trials have featured heavily so far in this thesis: Chapter 2 and 3 focused on informing the decision to omit radiotherapy in light of immature clinical trial follow-up, whilst in chapter 4 a cost-effectiveness analysis of PBT was performed to inform the decision to conduct a future clinical trial. At their most fundamental level, clinical trials cannot be performed without the participation of patients, and in this final analytical chapter I focus on barriers to participation in lymphoma clinical trials in England.

In general, patients across the spectrum of diseases exhibit a high degree of willingness to participate in clinical trials, yet only a small proportion typically enrol, frequently stated as 5%.[151–153] And those that do enrol are often different to the incident diseased population as a whole, with implications for the generalisability of findings and equity in the use of research funds.[55,154,155] From a patient's perspective, geographic accessibility such as the distance and travel time to a study centre are key factors in their ability and willingness to participate.[156–158] Furthermore, geography, through catchment, influences a patient's knowledge of nationally available clinical trials, with patient participation often elicited by their local treating team where a specific trial may, or may not, be open for recruitment.[153] As a consequence, half of cancer patients report not participating due to a lack of available trials at their healthcare organisation, representing a larger barrier than the sometimes restrictive eligibility criteria for the trials themselves.[159]

Furthermore, equality in access to research opportunities is a key tenet in the philosophies of research bodies which fund clinical trials.[55,56] However, fundamentally, geographic accessibility is a reflection of the geographic position of research sites. The location of such sites reflects the needs and consideration of the trial organisers: Investigators feel the pressure to deliver research to time and budget which leads to the selection of sites based on

professional networks, historical precedent, and typical throughput of local patients at individual sites.[160] This limits capacity to consider the geographical distribution of disease prevalence and equity concerns when planning research sites.[160]

The objective of this chapter is to elucidate the connected themes of patient representation and geographic access. The scope of this chapter increases to cover all lymphomas due to the relative scarcity of clinical trials in any one particular lymphoma subtype, and to take advantage of access to the unique lymphoma cancer registry dataset. Firstly, it begins with a systematic identification and summary of the characteristics of and recruitment to previous lymphoma clinical trials conducted in England. Secondly, using this information, the representativeness of recruited patients in terms of age and sex is compared to the incident lymphoma population. Thirdly, research active clinical trial centres are defined and the distances, travel times, and catchment of these centres to small geographic units of England are mapped. Here, these measures are used as a proxy for the geographic accessibility of trials across England, with increasing distance and travel times and being out of catchment acting as a barrier to enrolment and implicitly capturing factors such as the cost of travel and time off work through multicollinearity (i.e. cost of travel will be highly correlated with distance). Finally, the association of these geographic accessibility measure with the national geographic distribution of demographic characteristics is assessed, and whether they align with underrepresentation. Ultimately, the elucidation of some of the barriers to participation in lymphoma clinical trials in England may enable more clinical evidence to be generated, removing some evidential uncertainty, as seen in chapter 2, which leads to variation in care, and improving data available for the purpose of modelling long term outcomes as in chapters 3 and 4.

5.2 Methods

5.2.1 Clinical trial identification and enrolled patient characteristics

Lymphoma-specific interventional clinical trials in England were identified through the National Institute for Health and Care Research (NIHR) Open Data Platform (ODP).[161] The search was performed in December 2022 with no lower restriction of the date of trial opening, however trials were excluded if they were flagged as being withdrawn during setup, in setup, or pending approval. The NIHR ODP provides uniquely rich data on clinical trials in comparison to clinical trial registers such as *clinicaltrials.gov*. It reports specifically on clinical trials within the NIHR clinical research network (CRN) portfolio of trials in England, and from 2009, information is available for each clinical trial on the participating NHS Trusts (In England, NHS Trusts are responsible for the provision of secondary care and are typically the recruiting sites of interventional oncology trials) and the total number of patients recruited to the trial. Furthermore, from the financial year 2014/15, the annual number of patients recruited at each participating NHS Trust for each clinical trial was also available. Permission to use and publish NIHR ODP data was granted by the NIHR and the Department of Health and Social Care.

For each clinical trial identified, an extensive search for related publications utilising the various trial identifiers from the NIHR ODP was performed to extract the characteristics of the enrolled patients and age eligibility restrictions. Age and sex were the only consistently reported patient characteristics in the studies, and hence the only extracted.

5.2.2 English lymphoma population data

Again for this study, the same National Cancer Registration Dataset as described in Chapter 2 is used. The dataset in total comprised of data on every individual diagnosed with lymphoma in England between 1st Jan 1997 and 31st Dec 2017 (the amended data release up to 31st December 2020 came after the completion of this study). Only diagnoses between 1st Jan 2014 and 31st Dec 2017 were used in this study to align with data time points of the other data used in this study. The National Cancer Registration Dataset contains age at diagnosis and sex, enabling comparison with the characteristics of enrolled patients found in the trial publications. Patient ethnicity and IMD income domain quintile is also included. Additionally, the allocation of each patient to their most probable NHS Trust of care, as describe in chapter 2, is again used for this study. From this allocation, NHS Trusts were defined as providing lymphoma care in England if they had at least one assigned patient.

A nuance of examining NHS Trusts over time is that the organisation of NHS Trusts has changed slightly due to mergers and dissolutions. The current naming configuration of NHS Trusts as of 2022 was used as the basis for this study, with NHS Trusts identified from the NIHR ODP or English cancer registry data that no longer exist mapped to the most applicable 2022 NHS Trust. Points of longitude and latitude were obtained for each NHS Trust as defined in 2022 to be used in the analysis of distance and travel times.[162]

5.2.3 English geography data

To measure distance and travel times across England, small geographically defined area units of England called Lower Layer Super Output Areas (LSOAs) were utilised, which contain on average 1500 people. Boundaries and population weighted centroids for each LSOA from the 2021 UK Census were obtained from the Office for National Statistics (ONS).[163] There were 33750 LSOAs.

Sociodemographic characteristics of each LSOA, based on the 2021 UK census, were also obtained from the ONS.[164] This included population size, age, sex, and ethnicity. Additionally the most recently (2019) published deciles of Index of Multiple Deprivation (IMD) based on all seven domains of deprivation and a rurality indicator were obtained (areas falling outside of settlements with more than 10,000 resident population), both of which were applicable to LSOAs defined for the 2011 census.[165,166] Therefore a mapping published by the ONS was used to convert the 2011 LSOAs their approximate 2021 LSOA.[167] Finally, an indicator of whether the LSOA was either coastal or on the English border was created. At present there is no standard definition of LSOA coastal status, therefore, the indicator was based on the European Union definition of coastal areas: Local authority units that border the coastline or have at least 50 % of their surface area within a distance of 10km from the coastline. To do this, a 5km buffer was applied to the centroid of each LSOA. LSOA's whose 5km buffer intersected the full extent boundaries of England were categorised as a coastal/border LSOA.[168,169] Border LSOAs were included in this coastal categorisation category as the full extent boundary includes the inland border between England and Wales and Scotland. In total 4152 of the 33750 LSOA were classed as coastal/border.

5.2.4 Study outcomes

5.2.4.1 Representativeness of enrolled patients

Using the trial-level data obtained from the NIHR ODP, the characteristics of the identified studies was assessed including phase, randomisation status, line of treatment, and total number of patients recruited. To assess representativeness, the extracted age and sex distributions of enrolled patients from each trial were pooled for each lymphoma subtype and by trial characteristics such as 1st line focus and age restriction. To do this for age, firstly, where participant age was reported in terms of median and (inter quartile) range, the mean and standard deviation was approximated using a common procedure.[170] Next the mean ages of participants within each subtype was pooled in a cumulative manner on the basis of each trial's reported (or derived in the case of the aforementioned approximation) mean age and number of patients recruited. The pooled standard deviation was calculated cumulatively trial by trial using the following equations where $x1$ refers the previous pooled results and $n1$ the previous pooled number of patients, and $x2$ and $n2$ refer the next trial to be pooled:

$$1¿\, Cumulative\, age = \frac{mean(x1)*n1 + mean(x2)*n2}{n1+n2}$$

$$2¿\, Cumulative\, variance = \frac{(n1-1)*var(x1) + (n2-1)*var(x2)}{n1+n2-1} + \frac{(n1*n2)*(mean(x1)-mean(x2))^2}{(n1+n2)*(n1+n2-1)}$$

The combined mean age and sex distribution of the enrolled population was compared to that in the Cancer Registry data. Two tailed Welch's t-test and chi-square test were used respectively. A P value of <0.05 was considered statistically significant.

5.2.4.2 Calculating distances and travel time

A number of distance measures for each LSOA were calculated for the analyses, using the haversine formula which approximates the shortest distance between two points on a sphere.

Firstly, using each LSOA's population-weighted centroid, the distance to their nearest NHS Trust that provided lymphoma care was calculated. Next, the distance from each LSOA centroid to the nearest 'research active' NHS Trust was calculated

This required first the decision as to what 'research active' and 'research inactive' constitutes. The NIHR ODP data enables the use of the participation of NHS Trusts in trials and recruitment volume to construct such measures of NHS Trust trial activity, with subjective judgment needed to determine how these are used to construct the measures. For ease of interpretation, trial activity was chosen to be measured as a dichotomy, with an NHS trust being classified as either 'research active' or 'research inactive' in five different ways according to the meeting of criteria as defined below.

For definition 1), the primary definition, NHS Trusts were dichotomised into being 'research active' or 'research inactive' according to the number of patients recruited into clinical trials. Here, to take into account the differing size of the catchment population treated by each NHS Trust, the total number of patients recruited by each NHS Trust was divided by the mean annual number of incident patients with lymphoma coming under their care, calculated from the assignment of patients to their treatment decision making NHS trust (constructed in section 5.2.2). NHS Trusts were ordered by weighted recruitment, with the NHS Trusts who recruited above the median defined as 'research active'.

Furthermore, as secondary definitions, noting the heterogeneity of lymphomas, 'research active' (and those not meeting the condition: 'research inactive') NHS trusts ser defined as; 2) an NHS Trust that participated in at least one lymphoma clinical trial, irrespective of lymphoma subtype; 3) 4) & 5) an NHS Trust that participated in at least one trial specifically in diffuse large B-cell lymphoma (DLBCL), Hodgkin lymphoma (HL) and follicular lymphoma (FL) trial respectively. These three subtypes were chosen to provide coverage of

lymphoma subtypes; DLBCL and FL being the most common non-Hodgkin subtypes, with aggressive and indolent behaviours respectively, and Hodgkin lymphoma which has a distinct age at incidence distribution.

To calculate travel times by car the HERE REST application programming interface (API) was used, accessed through the R package *hereR*.[171] Use of such APIs can be costly and requires a large amount of processing time. Due to the prohibitive cost, travel time by car was directly calculated only for definition 2). Here, for each LSOA, the travel time between the population-weighted centroid and all the research active defined NHS trusts (under def 2) was calculated, with the shortest taken forward. To then estimate travel times for the other definitions, a regression model was fitted on the distance (left hand side variable) and travel time (right hand side variable) pairs under definition 2). A random intercept and slope multilevel linear regression model was used to account for differing geography in which LSOA sit, with LSOAs nested within larger upper tier local authorities. This hierarchic regression structure gave an R^2 value, a measure of explained variation, of 0.97. The coefficients from this regression were then applied to the distances in definitions 1), 3), 4) and 5) to give an estimated travel time by car.

Using these distances and travel times by car, maps of England were created graphing their distribution across the country. This was done using the *R* package *tmap*.[172] Furthermore, multivariate linear regression was used to assess associations between the distance of each LSOA to their nearest research active NHS Trust with LSOA sociodemographic characteristics, namely, mean age, sex, ethnicity, IMD decile, rurality, and coastal status.

5.2.4.3 Assessing catchment

To measure geographic-associated knowledge barriers to access, the proportion of the total English mean annual incident population treated in ‘research active’ and ‘inactive’ NHS

Trusts, according to the five definitions were calculated. Here, the mean annual incidence was calculated using patients diagnosed between 2014 and 2017 in the English Cancer Registry data. This time range was specified to align with the time point at which the NIHR ODP data provides recruitment number by NHS Trust

Furthermore, the mean age, sex proportion, white British ethnicity proportion and IMD income domain quintile characteristics of Cancer Registry patients treated in 'research active' NHS trusts were compared against those treated in 'research inactive' NHS trusts. Two tailed Welch's t-test and chi-square test, including test for trend for IMD quintile, were again utilised where appropriate.

5.3 Results

5.3.1 Lymphoma-specific clinical studies

76 interventional clinical trials in lymphoma were identified in the NIHR ODP, and a complete table of studies is provided in Table 5 .21. The earliest study recorded in the NIHR ODP opened in 1993, and the latest, after exclusion for study status, opened in 2021. Most of the identified clinical trials were phase II and phase III, with an almost equal proportion randomised and non-randomised. A full tabular break down of the characteristics of the clinical trials is given in Table 5 .21.

Table 5.21: Characteristics of the 76 identified interventional clinical trials in lymphoma

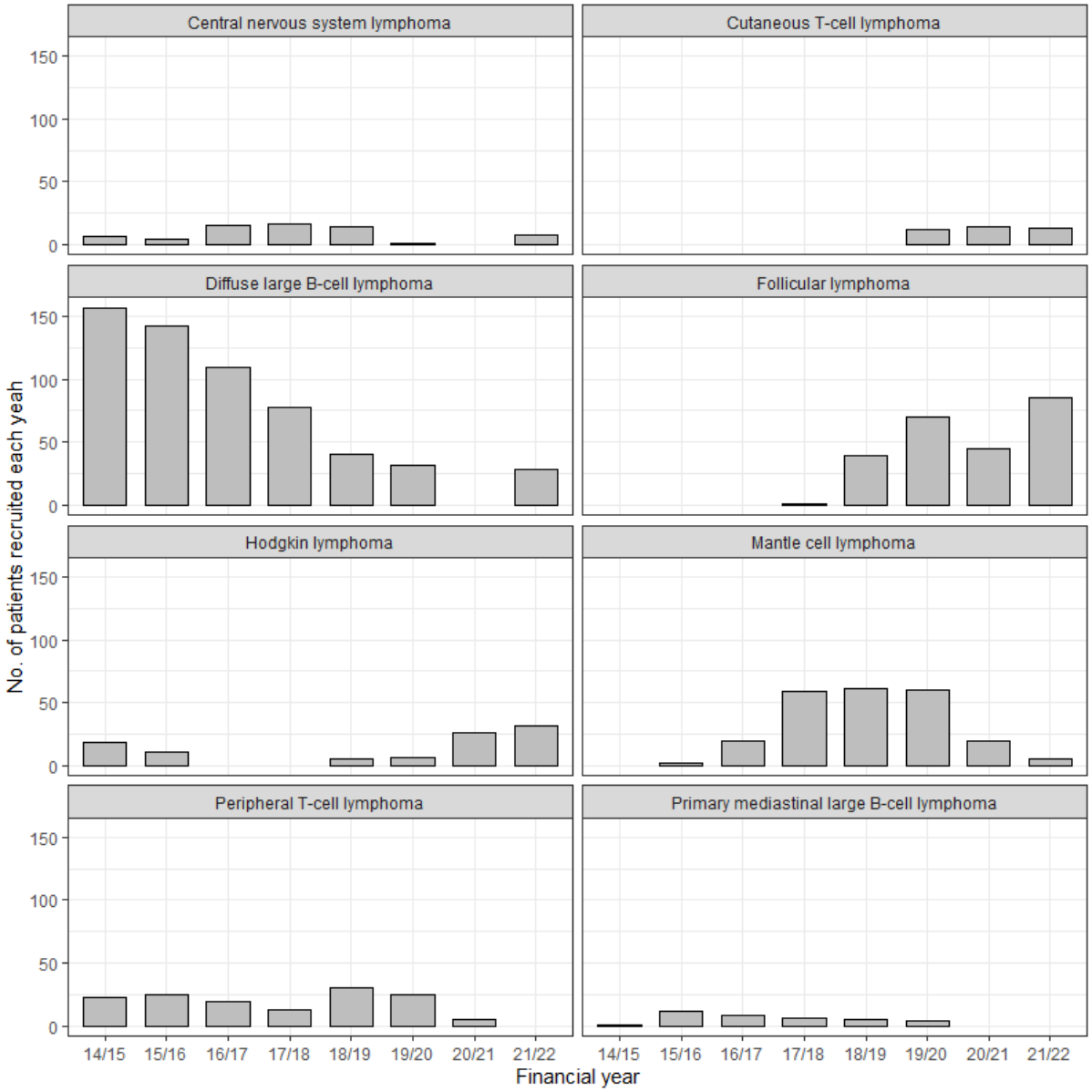
	Categories	No. (%) or ratio
Phase	I	5 (7%)
	I/II	4 (5%)
	II	34 (45%)
	II/III	2 (3%)

	III	29 (38%)
	NA	2 (3%)
Randomised	Randomised	41 (54%)
	Non-randomised	34 (45%)
	Both	1 (1%)
Lymphoma subtype	Diffuse large B-cell	14 (18%)
	Hodgkin	12 (16%)
	Follicular	10 (13%)
	Mantle cell	7 (9%)
	Peripheral T-cell	6 (8%)
	Primary CNS	5 (7%)
	Waldenström's macroglobulinaemia	4 (5%)
	Cutaneous T-cell	3 (4%)
	Burkitt	2 (3%)
	Primary mediastinal large B-cell	2 (3%)
	Marginal zone	1 (1%)
	Other/mixtures	10 (13%)
Treatment line	First line	42 (55%)
	Relapse/refractory	30 (39%)
	Other	4 (5%)
Opening year	1993 - 2000	8 (11%)
	2001 - 2005	13 (17%)
	2006 - 2010	22 (29%)
	2011 - 2015	16 (21%)
	2015 - 2022	17 (22%)
Total no. of English patients enrolled	0 - 50	42 (55%)
	51 - 100	9 (12%)
	101 - 200	7 (9%)
	200+	11 (14%)
	Open to recruitment	7 (9%)
Age eligibility restrictions	No information	5/76
	Lower age restriction of 16 years	18/72
	Lower age restriction of 18 years	49/72
	Lower age restriction above 18 years	4/72
	Any upper age restriction	4/72

5.3.2 Temporal variation in study access

Using the NIHR ODP annual recruitment data from 2014/15 to 2021/22 (annual recruitment data was not available before 2014/2015, whilst was the last year of enrolment in included studies 2021/22), we found temporal variation in the recruitment of patients to clinical trials for each lymphoma subtype (Figure 5.1). Overall, DLBCL had the highest number of patients enrolled, in keeping with it being the subtype of highest incidence. Yet yearly recruitment ranged from >150 patients in 2014/15 to no patients in 2020/21 reflecting variation in trial recruitment due to whether clinical trials were open.

Figure 5.17: Number of patients recruited each year by lymphoma diagnostic subtype.



There were five lymphoma subtypes (DLBCL, HL, mantle cell lymphoma (MCL), peripheral T-cell lymphoma (PTCL) and primary mediastinal B-Cell lymphoma (PMBCL)) with a 1st line clinical trial open to enrolment in the years 2014/15 through to 2021/22, and therefore having more granular recruitment data within the NIHR ODP. To provide an estimate of the proportion of all newly diagnosed patients enrolling, we took the average annual number of patients recruited to the 1st line clinical trials and weighted this by the mean annual number of patients diagnosed over the years 2014 to 2017 from the English cancer registry. This ratio of the mean annual number patients enrolled over the mean annual number diagnosed suggests

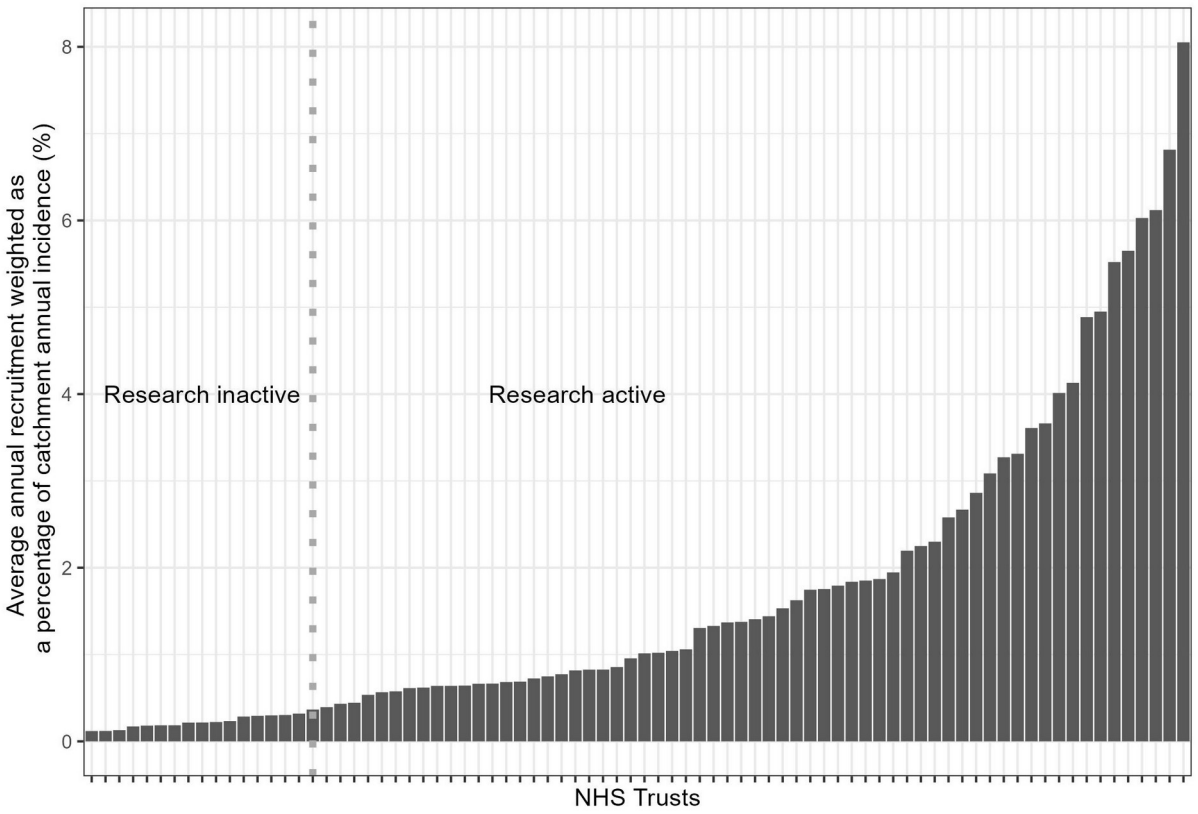
approximately 1/100 newly diagnosed patients with DLBCL, 1/200 newly diagnosed patients with HL, 1/20 newly diagnosed patients with MCL, 1/100 newly diagnosed patients with PTCL and patients with 1/10 newly diagnosed PMBCL participate in a 1st line clinical trial.

5.3.3 NHS trust clinical trial activity

There were 127 NHS Trusts identified as providing care for patients with lymphoma from the NCRAS data. Out of these 110 (87%) NHS Trusts were identified in the NIHR ODP as having participated in a lymphoma trial since 2009 (the year from which the NIHR ODP provides NHS Trust recruitment totals), including those that did not recruit any patients. The average number of patients recruited at these NHS Trusts was 36 patients, with a range from 0 to 252. Using the annual recruitment data available from the financial year 2014/15 onwards, there were 80 (63%) NHS Trusts that recruited one or more patients to a clinical trial between then and 2021/22.

In Figure 2 the average annual recruitment for the 80 NHS Trusts, weighted by the size of their annual incident population, is presented. Definition 1) of research activity is based on the 50th percentile of the 127 NHS Trusts ordered by this weighted recruitment, i.e. the 80 NHS Trusts with positive recruitment and the 47 with zero recruitment. Under this definition, 63 NHS Trusts were considered ‘research active’, whilst 64 (containing the 47 NHS-trust without recruitment and the 17 lowest positive recruiting trusts) were considered ‘inactive’.

Figure 5.18: Mean annual percentage of lymphoma patients recruited by each positively recruiting NHS Trust weighted by the size of their catchment annual incident population.



Under the less restrictive definition 2) of research activity, whether an NHS Trust recruited one or more patients to any trial, 96 NHS Trusts were considered ‘research active’. Specifically looking at recruitment to diffuse large B-cell lymphoma (DLBCL), Hodgkin lymphoma (HL) and follicular lymphoma (FL) trials, 70, 17, and 29 NHS Trusts respectively were considered ‘research active’.

5.3.4 Representativeness of participating patients

Published full articles and conference abstracts were searched for all 76 clinical trials. Publications were identified for 57 of the trials. Of the 19 without publications, 6 were completed trials, 11 were still open to recruitment or in follow-up, one trial did not recruit any patients in England, and one trial was terminated without publication. Summary age and sex statistics of enrolled patients were routinely reported in almost all publications, but no other patient-specific information was commonly reported such as patient ethnicity or indices of deprivation. Links to the publications, information extracted, and summary calculations are provided in Appendix C: Additional material for Chapter 5.

Across the specified lymphoma subtypes, the majority of enrolled patients were male and the male proportion was consistently higher than that of the total English lymphoma population. This difference in sex proportion was statistically significant for DLBCL, FL, MCL, and PTCL, where the percentage of males recruited was 2.3%, 2.7%, 5.6% and 6.1% higher than the percentage of male patients in the total subtype population. Full results are provided in Table 5 .22.

Table 5.22: Comparison of mean age and sex ratio between enrolled patients and incident population

	Clinical trials (1993 - 2021)			English population (1997 - 2017)			P value	
	Total No. of patients enrolled; sex (age)	**Prop. male**	**Age at enrolment; Mean, SD**	**Total No. of patients**	**Prop. male**	**Age at diagnosis; Mean, SD**	**Sex prop.**	**age**
Diffuse large B-cell	1757 (2957)	0.567	56.2 (12.3)	-	-	-	-	-
CNS (DLBCL)	334 (334)	0.593	57.0 (9.5)	-	-	-		
Combined	2091 (3291)	0.571	56.3 (12.0)	65440	0.548	67.2 (14.7)	0.039	< .0001
Hodgkin	3385 (3416)	0.585	41.7 (13.4)	27319	0.571	46.6 (19.8)	0.129	< .0001
Follicular	3005 (3005)	0.506	57.5 (11.2)	33911	0.479	63.6 (13.6)	< .001	< .0001
Mantle	612 (612)	0.766	63.1 (9.6)	5219	0.710	70.0 (11.8)	< .01	< .0001
Peripheral T-cell	213 (231)	0.718	60.1 (12.8)	7061	0.600	63.7 (16.1)	< .0001	< .0001
Cutaneous T-cell	57 (57)	0.667	63.0 (11.5)	6230	0.606	62.2 (16.3)	0.425	0.609
Burkitt	58 (58)	0.793	41.8 (12.8)	2101	0.707	53.7 (19.0)	0.200	< .0001
Primary mediastinal large B-cell	125 (125)	0.384	33.7 (10.5)	360	0.397	41.5 (16.8)	0.877	< .0001
Marginal zone	401 (401)	0.491	57.3 (9.0)	12782	0.476	67.8 (13.6)	0.576	< .0001

Similarly for age, the mean age of participants was consistently lower than that of the mean age at diagnosis of the population, and this difference was statistically significant for all subtypes except cutaneous T-cell lymphoma. For some subtypes the absolute difference was substantial with patients recruited to DLBCL, Burkitt lymphoma (BL), and marginal zone lymphoma (MZL) being on average 10.9, 11.9, and 10.5 years younger than the average age of the total respective subtype populations. In terms of percentage difference (the absolute difference divided by the mean age at diagnosis of the population) there was a 17.6% difference across all subtypes in age between the enrolled population and the total incident population, ranging from 24.9% in BL to 1.2% in cutaneous T-cell lymphoma (CTCL).

Restricting the age comparison to include first line trials only, such that age of enrolment more closely reflected age of diagnosis, had little impact on combined mean age and standard deviation (Appendix C: Additional material for Chapter 5). Neither did the results change when restricting the age comparison to trials with no age limiting eligibility criteria (Appendix C: Additional material for Chapter 5).

5.3.5 Distance, travel time, and trial knowledge

The median distance (travel time) from the centroid of each LSOA to the nearest 'research active' NHS Trust, under definition 1) of research activity (dichotomizing at the median), was 15.6km (22.1mins) with an interquartile range of 5.5km to 21.6km (12.7mins to 28.1mins) and maximum of 115.7km (97.1mins). Figure 5 .19 maps this distribution of distances across England. Analogous maps for the four other definitions are provided in Figure 5 .20 through Figure 5 .23. Average distances (travel times) for all definitions of research activity are given in Table 5 .23. Distances and travel times increased greatly when focusing on the HL and FL 'research active' centres.

Figure 5.19: Distance from each LSOA to nearest 'research active' NHS Trust under definition 1): an NHS Trust that recruited more than the median of average annual Trust

recruitment weighted by annual Trust incidence.

Distance to nearest NHS Trust that is research active under definition 1)

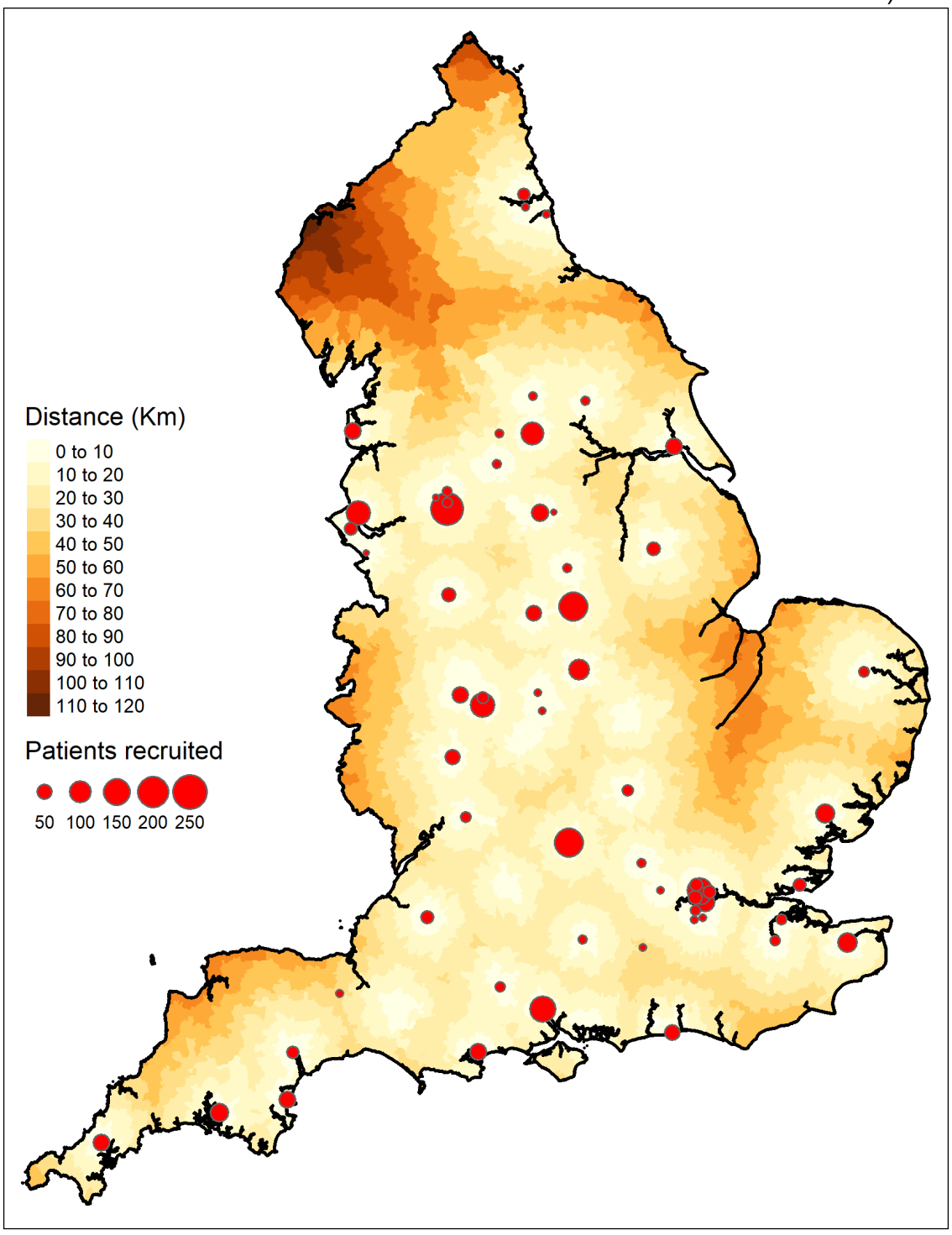


Figure 5.20: Distance from each LSOA to nearest research active NHS Trust under definition 2): an NHS Trust that recruited to any clinical trial.

Figure 5.21: Distance from each LSOA to nearest research active NHS Trust under definition 3): an NHS Trust that recruited to any DLBCL clinical trial.

Figure 5.22: Distance from each LSOA to nearest research active NHS Trust under definition 4): an NHS Trust that recruited to any HL clinical trial.

Figure 5.23: Distance from each LSOA to nearest research active NHS Trust under definition 5): an NHS Trust that recruited to any FL clinical trial.

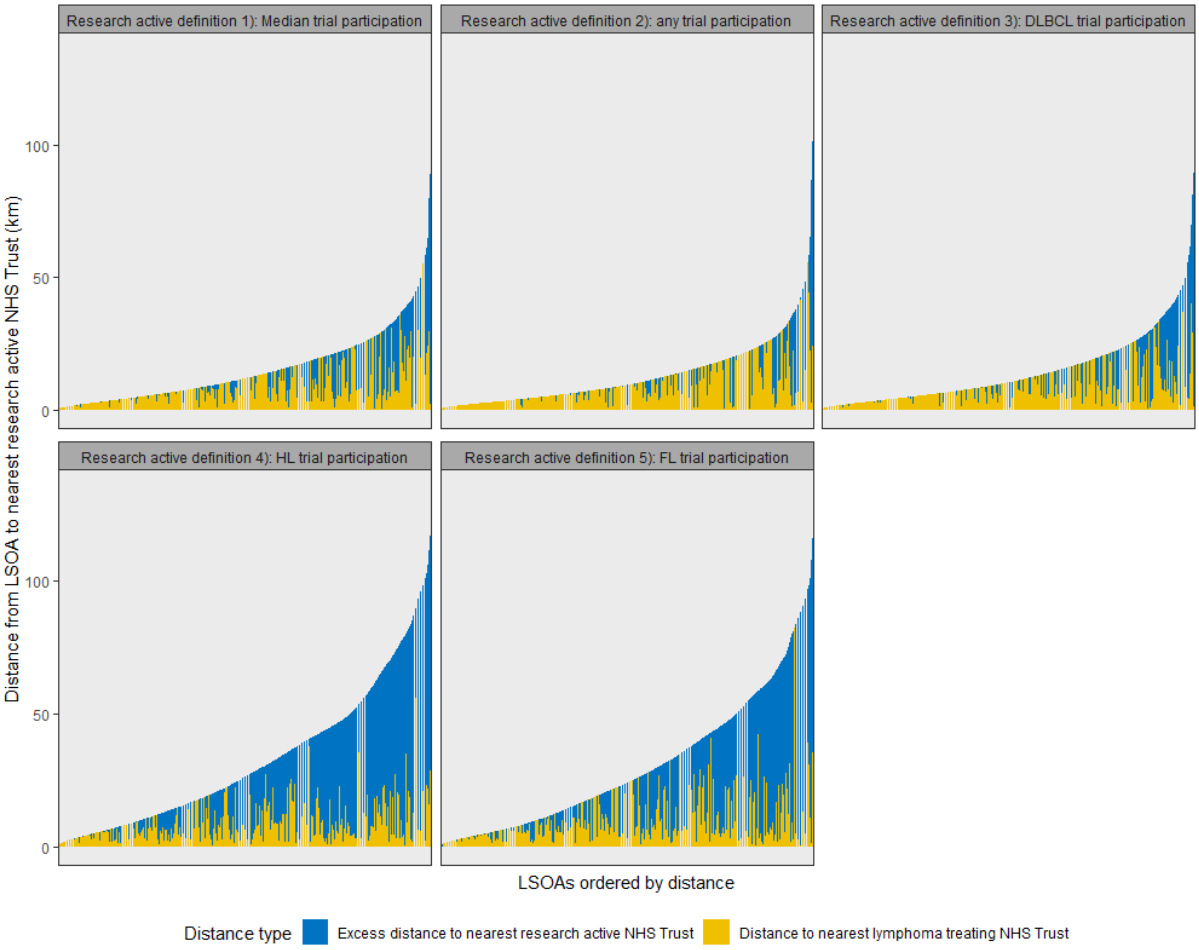
Research active definitions	Mean distance (car travel time)	Interquartile range
1) An NHS Trust that recruited more than the median of average annual Trust recruitment weighted by annual Trust incidence.	15.6km (22.1mins)	5.5 – 21.6km (12.7 – 28.1mins)
2) An NHS Trust that participated in at least one lymphoma clinical trial	13.2km (19.3mins)	4.5 – 18.2km (11.4 – 24.6mins)
3) An NHS Trust that participated in at least one DLBCL trial	14.7km (21.0mins)	5.1 – 20.2km (12.2 – 26.6mins)
4) An NHS Trust that participated in at least one HL trial	32.6km (40.1mins)	11.2 – 46.6km (21.9 – 51.5mins)
5) An NHS Trust that participated in at least one FL trial	30.2km (39.1mins)	9.4 – 45.1km (18.9 – 52.6mins)

For nearly half (46.5%) of all LSOAs, their nearest lymphoma treating NHS Trust was not 'research active', under definition 1). This increased to 75%, and 84% when using the FL, and HL trials definitions respectively.

graphs the distribution of total distance from each LSOA to the nearest 'research active' NHS Trust for all 5 'research active' definitions. This includes the excess distance where their nearest 'research active' NHS is not their nearest lymphoma treating NHS trust.

Figure 5.24: Distribution of total travel times to nearest 'research active' NHS Trust under definition 1), including excess distance where the 'research active' NHS trust is not the

closes lymphoma treating NHS Trust.



Results from the linear regression analyses of LSOA characteristics on distance to nearest 'research active' NHS Trust, according to definition 1), are given in Table 5 .24. Results for the other definitions are given in Appendix A: Additional material for Chapter 5. Greater distances were positively associated with LSOA mean age, percentage male, and percentage white British ethnicity. Each of these covariates were continuous, therefore the coefficients can be interpreted as a one unit change (one year for age, one percent for male sex and white British ethnicity) in the covariate, all else held constant, increases the distance by 1km. Therefore, a one year increase in mean age of the LSOA increases its distance to its nearest 'research active' NHS trust by 0.4km. A positive association was also observed for rural status, and coastal/border status. As binary variables, the coefficients suggest a coastal/border (rural) LSOA is on average 2.75km (8.003km) further from its nearest 'research active' NHS

trust than a non-coastal/border (urban) LSOA. There was a negative association with IMD decile. which was considered a continuous variable, with more deprived areas having less distance/time to travel.

Table 5.24: Multivariable linear regression regarding the association between LSOA characteristics and distance (km) to nearest 'research active' NHS Trust

LSOA characteristics (n =33750)	**Coefficient**	**Standard error**	**95% CI**	**P value**
Mean age	0.400	0.022	0.356 to 0.443	<0.001
Percentage male	0.386	0.035	0.317 to 0.455	<0.001
Percentage white British	0.123	0.004	0.115 to 0.131	<0.001
IMD decile	-0.216	0.028	-0.271 to -0.161	<0.001
Rural status	8.003	0.207	7.600 to 8.409	<0.001
Coastal/border status	2.750	0.225	2.309 to 3.191	<0.001
Constant	-22.189	2.036	-26.180 to -18.200	<0.001

5.3.6 NHS trust research activity and patient characteristics

Utilising again our assignment of patients in the English Cancer Registry to their NHS Trust of care, and the resulting mean annual number of patients diagnosed over the years 2014 to 2017 from the English cancer registry, we calculated the relative proportion of lymphoma patients, by subtype, cared for by each NHS Trust. For DLCBL, FL, and HL respectively, 66.7%, 25.1% and 32.1% of patients were treated in 'research active' NHS trusts using the subtype specific definition.

Table 5 .25 compares the characteristics of patients with DLBCL, HL, and FL between DLBCL/HL/FL 'research active' and 'inactive' NHS Trusts. For all three diseases, there was a statistically significant difference in mean age given by their respective two tailed Welch's t-tests. The magnitude of the difference was most marked for HL, with the mean age of patients under the care of 'research active' NHS Trusts 5.6 years less than that in 'research

inactive' NHS Trusts. Elsewhere, there was also a statistically significant difference in the distribution of patient IMD income domain quintile.

Table 5.25: Comparison of Cancer Registry patient characteristics between 'research active' and 'inactive' NHS Trusts

Disease		'Research active' NHS trusts	'Research inactive' NHS trusts	P value
DLBCL	No. patients	19769	9809	-
	Age: Mean (SD)	67.8 (14.6)	69.1 (13.9)	<0.001
	Males (%)	55%	55.4%	0.504
	White British ethnicity (%)	87.4%	87.3%	0.867
	IMD income domain: % in two most deprived quintiles	34.1%	34.5%	0.304
HL	No. patients	2419	7166	-
	Age: Mean (SD)	43.6 (19.9)	49.2 (20.7)	<0.001
	Males (%)	54.9%	56.2%	0.272
	White British ethnicity (%)	77.9%	80.9%	0.001
	IMD income domain: % in two most deprived quintiles	44.2%	39.2%	<0.001
FL	No. patients	4682	9324	-
	Age: Mean (SD)	64.5 (13.6)	65.0 (13.1)	0.041
	Males (%)	47.4%	48.8%	0.130
	White British ethnicity (%)	87.9%	88.4%	0.346
	IMD income domain: % in two most deprived quintiles	33.3%	31.9%	0.115

5.4 Discussion

The analyses of this study identified underrepresentation of older and female participants in lymphoma clinical trials. These results align with a recent study of representation in pivotal US clinical trials in lymphomas.[173] However, further parallel comparisons by ethnicity and deprivation were constrained by the lack of such reporting in UK trial publications. Furthermore, the findings demonstrate that the current (and historically precedent) location of

trial sites causes significant disparities in geographic barriers across England. Coastal and rural LSOAs face the largest distances, and greater distance was associated with higher area mean age. For most LSOAs in England, their nearest NHS Trust is not 'research active'. Most patients in these LSOAs would therefore be required to change the NHS Trust they are treated at to access the trial. LSOAs whose nearest NHS Trust is 'research active' were found to have a lower mean age than LSOAs whose nearest NHS Trust was not.

It was consistently found that, even in trials with no explicit upper age restriction, older patients are underrepresented. Coupled with the other results, this finding may relate to the geographical availability of 'research active' hospitals. Increased distance/travel time has a well-studied deleterious effect on participation.[174–176] And a lack of trial availability at a patient's treating centre is one of the most significant barriers to access.[159] This relates both to a lack of knowledge of available trials and, if a suitable trial is identified for the patient, the need to change hospital and treating doctor in order to participate, which has a compounding effect on willingness to travel.[158] Nonetheless, age increases the likelihood of other common ineligibility criteria such as comorbid conditions and performance status which could not be adjusted for. The underrepresentation of females did not correlate with the geographic access measures. Such underrepresentation has been widely shown across trials for many diseases, although England specific analyses relating to oncology trials is lacking.[177,178] Women generally appear to exhibit a lower willingness to participate than men, which may relate in part to intrinsic risk preferences.[179,180] Here, a systematic review of cardiovascular trials found women were less likely to participate in studies led by men, perhaps amplifying trial participation disparities in cancer trials when viewed alongside current gender inequity in cancer research leadership.[181–183]

Whilst many geographic access studies make use of *clininicaltrials.gov* to identify trials, our study makes novel use of the NIHR ODP for identification, providing unique data on site-

specific annual recruitment.[155,184–187] Furthermore, this study make unique complimentary use of individual patient-level data on English patients with lymphoma from NCRAS, enabling a more complete appraisal of the landscape of clinical trials for lymphoma. However, a limitation in using the NIHR ODP is that it contains only those trials receiving support from the NIHR clinical research network (CRN). Some industry-sponsored phase I studies will have been missed consequently, but these studies tend to recruit a relatively small number of patients with relapsed disease and limited conventional treatment options so their inclusion would not substantially affect the conclusion of this study. There may be potential limitations with the English cancer registry data with respect to the accuracy of lymphoma subtype classification. Notably, the high estimate of 1/10 PMBCL patients participating in 1st line clinical trials may be partially driven by misclassification of PMBCL as DLBCL or NHL not otherwise specified.

Further limitations of this study include the need to subjectively define and categorise research activity, which may not reflect temporal changes over our 20-year timeframe. The measures of geographic access capture proximity and travel time by car, however, many patients will not have access to a car or be fit to drive, greatly increasing the time and travel burden to their nearest centre. Those more deprived for instance, have far lower car ownership, approximately a third of households in the lowest income quintile lack access to a car compared to approximately 10% in the highest quintile.[188] Therefore, although this study found more deprived patients tended to be closer to 'research active' NHS Trusts, more deprived patients may experience additional socio-economic mediated geographic barriers to trial inclusion that are not possible to measure in this study. Moreover, although distance and travel times are likely to be highly correlated with factors such as travel costs and time off work, and therefore act as a proxy for geography accessibility, they will not capture other

factors such as health literacy and cultural preferences. Such factors were beyond the scope of this work, but are also a significant factor in trial participation.[159]

Due to a lack of definition and subsequent official coding, coastal and border LSOA's were defined using a radius categorisation (section 5.2.3). Combining coastal and border LSOAs was necessary as no LSOA flag exists for proximity to the border is available. However, individuals in border LSOA's may be closer and have the option of seeking care in the respective Welsh/Scottish local region, and this should be noted as a limitation in regards to the geographic access analyses. It should also be noted that LSOA characteristics were taken from the 2021 census. With populations transient over time, association observed in the study are relevant to this snap shot afforded by the census, however, LSOA characteristics may have since changed.

Finally, the study brings together disparate datasets on trial recruitment and individual patient cancer registry data, which intersect at the NHS trust level, therefore the analysis is constrained by a lack of individual-patient linkage. Future work, given the availability of patient linkages between trial and cancer registries, may look to assess the revealed effects of distance, travel times and catchment, which may be heterogeneous across sociodemographic characteristics. Additionally, as yet, relapse/refractory disease is not identifiable in the English cancer registry data, which would further allow for the observation of patient preferences towards clinical trials, with geographic accessibility's effect also likely to depend on the progression of a patient's illness. Furthermore, such data would enable both variation in treatment, as explored in chapter 2, and variation in clinical trial activity to be simultaneously explored, potentially offering insights in how the two may overlap and influence the other at the NHS trust level.

This study of lymphoma trials, despite the above limitations, may be replicated in other cancer sites and diseases to gain a fuller understanding of geographic inequalities in clinical trial access across England. Reducing inequalities in access aligns with the principles of many research funders and features significantly in the UK's recent policy paper on the future of clinical research delivery and the independent Lord O'Shaughnessy review on commercial clinical trials in the UK.[55–57] Redressing geographic access inequalities, however, will likely require explicit consideration during trial development. Any redistribution or expansion of the number of trial centres involved to improve access may have consequences on recruitment rates and research costs.[55] Here, future work modelling such trade-offs may be warranted to better inform such decisions, with modelling frameworks potentially adapted from the wider literature, such as work assessing the impact of centralising specialist cancer services on travel times, equity, and 30-day emergency readmission rates.[189,190]

6 Discussion

In this thesis, four thematically linked analytical studies were performed with the aim of informing the current and future treatment of Hodgkin lymphoma. This theme was introduced through a brief overview of the historical evolution of treatment practices for Hodgkin lymphoma, leading to a summary of current treatment approaches and uncertainties. In particular, there remains uncertainty in the use or omission of radiotherapy in early-stage patients who achieve complete metabolic response at their interim PET scan. Three phase III randomised controlled trials have demonstrated a statistically significant reduction in progression free survival when radiotherapy is omitted. [27–29] However, due to the usual latency of radiation-related sequelae (late effects), the current length of follow-up is insufficient to determine whether superior disease control with CMT outweighs the risks. Moreover, the size of the trials, and relative scarcity of event, may mean the trials are not of sufficient size to demonstrate long-term differences in overall survival. In Chapter 2, this introduction was taken forward with the preposition that such evidential uncertainty may result in excess variation in the utilisation of radiotherapy due to latent predilections of a patient's treating clinical team (who are a part of an NHS trust) towards or against radiotherapy.

6.1 Variation in radiotherapy delivery in England: study summary and limitations

To assess excess variation, English cancer registration data was obtained for all classical Hodgkin lymphoma patients diagnosed between 1st Jan 2014 and 31st December 2020. Additionally, cancer registration data was obtained for all diffuse large B-cell lymphoma patients diagnosed in this time period, for which the same treatment paradigm and evidential

uncertainty holds. Regression modelling of frontline radiotherapy utilisation in these patients, nested within their treating NHS trust, was performed through a hierarchical mixed-effects logistic model. Calculation of the resulting median odds ratio suggested that the NHS trust in which a patient is treated was associated with whether a patient received radiotherapy treatment. The size of this association was greater than that of gender, for which there is an established awareness of the added risk of second primary breast cancer which is commonly used as a rationale for radiotherapy avoidance. This implies that the NHS trust at which a patient is treated may be a significant determinant of whether or not they receive radiotherapy, although causality cannot be proven. A key limitation of this study is that such associations may be the result of unobserved patient characteristics which could not be controlled for in the regression analysis, such as proximity of the patient's tumour to the heart. However, such characteristics, once conditioned for factors included such as age and sex, would not be expected to systematically differ between NHS trusts. Furthermore, there was a high degree of correlation between the delivery rate of radiotherapy for cHL and DLBCL, providing support for the interpretation that treating teams exhibit differing preferences towards or against the use of frontline curative radiotherapy.

6.2 Informing radiotherapy omission and the use of Proton Beam Therapy in classical Hodgkin lymphoma: study summaries and limitations

To directly address the evidential uncertainty in optimal treatment approach in early-stage Hodgkin lymphoma patients, Chapter 3 focused on the development of a natural history of disease model capable of simulating the life course of a patient under different treatment scenarios. The model produced as outcomes the simulated patient's resulting life expectancy and quality-adjusted life expectancy, two readily understandable outcome measures which

combine and summarize the many trade-offs between the risks and benefits of omitting RT into a single metric. To account for factors that may influence the risks and benefits of omitting RT, the outcomes produced by the model are dependent on the specified age of the patient at diagnosis, their sex, and their expected dose to the breast (if female), lung, and heart tissue, and the carotid arteries. Furthermore, a key consideration for a patient's life course is their underlying health, which affects their underlying risk of late effects. The model therefore also incorporated smoking status due to its large and well characterised impact on cardiovascular disease and lung cancer risk.

In an application of the model, 90 patient presentations were considered consisting of the exhaustive combination of five different disease presentations (and resulting mean dose to the breast, lung, heart and carotid arteries), three ages at treatment (20y, 35y, and 50y), three smoking risk categories (never, former, and current smoker) and both sexes. For each patient presentation, the difference in (quality-adjusted) life expectancy was compared between the patient receiving combined modality treatment vs chemotherapy alone, with initial disease control informed by the UK-based RAPID trial.

The results for the never-smoking patient examples suggests, in the context of the model and its assumptions, that CMT provided more benefit over chemotherapy-alone, irrespective of age, sex, and OAR doses, with otherwise good underlying health. Only in smokers, due to their significant baseline risks of late effects, could the radiation-related excess risks be large enough to warrant radiotherapy omission based on the model. The results highlight the interplay between harms that occur close to the present (relapse), far in the future (late effects), and undiscounted versus discounted analysis of overall health outcomes.

In Chapter 4, the model was further developed to compare the QALY benefit of using PBT over conventional photon-based RT (within CMT), as well as it's likely cost-effectiveness in

the English healthcare setting. With the recent opening of two PBT centre in England, and the resulting interest in the initiation of clinical trials, the objective of this research was to provide an early economic evaluation to inform potential trial decision making. In the study, predicted mean doses to the aforementioned organs using proton beam therapy and conventional photon beam therapy were provided by a comparative planning study of 61 intermediate-stage Hodgkin lymphoma patients. These comparative doses were used, alongside different ages at diagnosis, patient sex, and smoking statuses to create a range of patient presentation and assess the range of possible patient benefits in terms of QALYs through PBT. Additionally, healthcare costs relating to the late effects were incorporated into the model. This enabled threshold analysis, whereby, for a given willingness-to-pay threshold, the cost difference between PBT conventional photon beam therapy required for PBT to be considered cost-effective could be calculated. The results of the study found that although PBT did increase QALYs for most modelled example patients, it was unlikely to be cost-effective given preliminary published costs of PBT.

Again, caution must be placed on these results, which are the outcome of the model structure, assumptions, and data used. Both studies are underpinned by the same natural history of disease model, and as such, both share many of the same limitations. The model was designed to simulate concurrently both the risks from disease relapse and the risk of four radiotherapy induced late effects. On the former, the risk of first relapse can be informed by the relevant trial that it is chosen to simulate. Subsequently, the model assumes all relapsed patients would be eligible and undergo ASCT, however, in practice patients may be ineligible for ASCT due to age and comorbidities, and some patients do not respond adequately to induction chemotherapy. Data on outcomes after subsequent relapses are limited, and treatments are ever evolving, making modelling uncertain past this point. On the latter, four late effects were incorporated into the model. Whilst these four contribute much to the overall risks of

radiotherapy, omission of other later effects underestimates the risks of radiotherapy. Linear no threshold dose-response models were chosen to individualise and propagate risk in the natural history of disease model. An advantage of such models is their simplicity - the relationship between dose and risk is based on mean organ dose. However, such dose-response models were estimated from cohorts treated with historic photon radiotherapy techniques, and whether these can be translated to make predictions for contemporary photon radiotherapy and PBT cannot be tested directly due to the inherent latency of late effects. These same dose-response models were utilised when evaluating late effects incidence related to proton beams, necessitating the assumption of equivalence between modalities after the conversion of proton beam therapy plans into Gy equivalents. Here, the radiobiological effectiveness of PBT relative to photons was held constant at 10%, with variation in effectiveness not considered. Finally, the ability to capture and propagate uncertain was limited. Parameter uncertainty was captured through probabilistic sensitivity analysis; however, the resulting confidence intervals were small, reflecting the limited parameter set with known uncertainty. Moreover, structural and methodological uncertainties were not explored, with many permutations possible due to the extensive scope of the model.

6.3 Inequalities in geographic access and patient representation in lymphoma clinical trials: study summary and limitations

Finally, continuing the clinical trial theme, in Chapter 6 a ‘meta-research’ study was performed involving novel analysis of the landscape of past lymphoma clinical trials across England. Two sources of data were used in compliment for this study. Firstly, aggregate data on lymphoma-specific clinical trials performed in England was obtained. For this, the NIHR Open Data Platform was used to identify studies within the NIHR Clinical Research Network.

The platform provided information on patient recruitment counts to the trials in the NIHR CRN portfolio, as well as recruitment counts by NHS trust. A limitation however is that some smaller (phase I) industry funded trials may not be within the portfolio. This trial data was supplemented by identifying related publications in the literature and extracting information on the age and sex characteristics of the trial participants. Secondly, individual-level patient data on all patients diagnosed with lymphoma in England between the years 2014 and 2017 was obtained from the National Cancer Registration and Analysis Service (NCRAS), providing the characteristics of the whole English lymphoma population. Finally, English geographic and sociodemographic data was obtained, including geographic boundaries and population weighted centroids for English Lower Layer Super Output Areas (LSOAs), and population size, age, sex, and ethnicity, and deprivation.

Using the aggregate trial data, recruitment patterns by lymphoma subtype over time were described, highlighting variability in the number of individuals recruited from year to year. Combining this data with the number of individuals diagnosed with each lymphoma subtype in England each year, as given by the NCRAS data, enabled approximation of the proportion of newly diagnosed patients entering 1st line clinical trials. For DLBCL, the most common lymphoma, only 1/100 newly diagnosed patients with DLBCL were estimated to participate in a 1st line clinical trial. Next, using the two data sources, the representativeness of trial participants in terms of age and gender was assessed. Compared to the incident population, older and female participants were found to be underrepresented in trials for most lymphoma subtypes.

The study then assessed geographic access to lymphoma clinical trials across England. For this, NHS trusts were dichotomised as being either `research active` or `research inactive`. The primary definition of research activity was created by dichotomising NHS trusts according to the number of patients recruited into clinical trials. Each English LSOA was

mapped to their nearest NHS trust and nearest ‘research active’ NHS trust, and the distances calculated. For most LSOAs in England, their nearest NHS Trust was not ‘research active’, and as such patients in these LSOAs would likely be required to change the NHS Trust they are treated at to access trials. A regression analysis was performed that related distance to nearest ‘research active’ NHS trust to the LSOA characteristics. Greater distances were positively associated with LSOA mean age, percentage male, and percentage white British ethnicity, rural status, and coastal/border status. There was a negative association with IMD decile, with more deprived areas having less distance/time to travel.

These findings offer insights into under representation and geographic inequalities in access to lymphoma trials, which is a current topical subject for policy makers. However, the study is limited by the lack of linkage between the trial participation dataset and the individual patient dataset, and as such the associations found, for instance, between poorer geographic access + age, should not be considered causal in nature.

6.4 Conclusion

This thesis aimed to inform current and future treatment of Hodgkin lymphoma. In chapter 2 strong evidence is presenting demonstrating variability in the use of front-line curative intent radiotherapy between NHS trusts. This study provided the rationale for the development of a model capable of estimating the long-term effects of chemotherapy-alone and CMT strategies, including for the evaluation of novel radiotherapy techniques. Using the model to understand the lifetime expected outcomes of different treatment approaches, evidence was provided that combined modality treatment may be preferential for the treatment of early-stage Hodgkin lymphoma patients without a history of smoking. This study was developed into an original research manuscript and was published in the journal Blood Advances.[191] It has subsequently

been cited to reinforce the role of RT, and to call for more individualised tools to inform treatment choice.[192,193] The model, given its ability to incorporate alternative clinical trial outcomes, may serve to inform future treatment comparisons. However, any inference from the model must be taken with understanding of its underlying structure, assumptions, and data, and appropriate caution used. Equitability in future trials is a pertinent policy making concern, and this thesis provides clear evidence that older and female lymphoma patients have historically been underrepresented. The study was published in the British Journal of Haematology, with an associated commentary highlighting the need for greater knowledge about factors influencing clinical trial participation and practical frameworks to enhance diversity in clinical trials.[194,195] It is hoped the framework of the study is used to provided evidence on representation in other disease areas and spurs further research into equitable clinical trial recruitment.

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Appendices

Appendix A: Additional material for Chapter 3

Appendix A table 1. Late effects incidence and case fatality rates

Sex	Age	CHD IR	Breast cancer IR	Lung cancer IR	Stroke IR	CHD CFR	Breast cancer CFR	Lung cancer CFR	Stroke CFR
male	0	0	0	0	1.54E-06	0	0	0	0.000217
male	1	0	0	0	1.54E-06	0	0	0	0.000217
male	2	0	0	0	1.54E-06	0	0	0	0.000217
male	3	0	0	0	1.54E-06	0	0	0	0.000217
male	4	0	0	0	1.54E-06	0	0	0	0.000217
male	5	0	0	0	1.54E-06	0	0	0	0.000217
male	6	0	0	0	1.54E-06	0	0	0	0.000217
male	7	0	0	0	1.54E-06	0	0	0	0.000217
male	8	0	0	0	1.54E-06	0	0	0	0.000217
male	9	0	0	0	1.54E-06	0	0	0	0.000217
male	10	0	0	0	1.54E-06	0	0	0	0.000217
male	11	0	0	0	1.54E-06	0	0	0	0.000217
male	12	0	0	0	1.54E-06	0	0	0	0.000217
male	13	0	0	0	1.54E-06	0	0	0	0.000217
male	14	0	0	0	1.54E-06	0	0	0	0.000217
male	15	0	0	0	1.54E-06	0	0	0	0.000217
male	16	0	0	0	1.54E-06	0	0	0	0.000217
male	17	0	0	0	1.54E-06	0	0	0	0.000217
male	18	0	0	0	1.54E-06	0	0	0	0.000217
male	19	0	0	0	1.54E-06	0	0	0	0.000217
male	20	0	0	0	1.54E-06	0	0	0	0.000217
male	21	0	0	0	1.54E-06	0	0	0	0.000217

male	22	0	0	0	1.54E-06	0	0	0	0.000217
male	23	0	0	0	1.54E-06	0	0	0	0.000217
male	24	0	0	0	4.93E-06	0	0	0	0.000555
male	25	0	0	0	1.13E-05	0	0	0	0.001021
male	26	0	0	0	2.18E-05	0	0	0	0.001626
male	27	0	0	0	3.75E-05	0	0	0	0.002379
male	28	9.9E-06	0	0	5.93E-05	8.91E-05	0	0	0.003282
male	29	2.49E-05	0	0	8.62E-05	0.000343	0	0	0.004315
male	30	4.49E-05	0	0	0.000117	0.000893	0	0.002816	0.005452
male	31	6.99E-05	0	0	0.000151	0.001868	0	0.013119	0.006665
male	32	0.0001	0	0	0.000187	0.0034	0	0.0322	0.007929
male	33	0.000135	0	0	0.000223	0.005564	0	0.061535	0.009212
male	34	0.000173	0	0	0.00026	0.008221	0	0.098784	0.010465
male	35	0.000215	0	5.43E-05	0.000297	0.011175	0	0.140657	0.011636
male	36	0.000257	0	7.75E-05	0.000334	0.014233	0	0.183859	0.01267
male	37	0.0003	0	0.0001	0.000371	0.0172	0	0.2251	0.013515
male	38	0.000343	0	0.00012	0.000407	0.019906	0	0.261435	0.014131
male	39	0.000389	0	0.000139	0.000443	0.022277	0	0.291315	0.014534
male	40	0.000444	0	0.000158	0.000479	0.024266	0	0.313537	0.014754
male	41	0.000513	0	0.000178	0.000514	0.025823	0	0.326899	0.01482
male	42	0.0006	0	0.0002	0.000548	0.0269	0	0.3302	0.014764
male	43	0.000709	0	0.000226	0.000583	0.027469	0	0.323093	0.014615
male	44	0.000837	0	0.000257	0.000617	0.027586	0	0.308651	0.014409
male	45	0.000981	0	0.000296	0.000653	0.027329	0	0.290802	0.014182
male	46	0.001136	0	0.000343	0.000691	0.026775	0	0.273476	0.013971
male	47	0.0013	0	0.0004	0.000732	0.026	0	0.2606	0.013813
male	48	0.001468	0	0.000468	0.000776	0.02508	0	0.255182	0.013736
male	49	0.001635	0	0.000545	0.000826	0.024078	0	0.256549	0.013734
male	50	0.001799	0	0.000628	0.000883	0.023057	0	0.263104	0.013795

male	51	0.001956	0	0.000714	0.000949	0.022077	0	0.273252	0.013906
male	52	0.0021	0	0.0008	0.001026	0.0212	0	0.2854	0.014053
male	53	0.00223	0	0.000884	0.001116	0.020475	0	0.298156	0.014226
male	54	0.00235	0	0.000971	0.00122	0.019898	0	0.31095	0.014427
male	55	0.002464	0	0.001065	0.001339	0.019453	0	0.323416	0.014661
male	56	0.002579	0	0.001173	0.001475	0.019126	0	0.335188	0.014933
male	57	0.0027	0	0.0013	0.001628	0.0189	0	0.3459	0.015247
male	58	0.00283	0	0.00145	0.001799	0.018763	0	0.35524	0.015606
male	59	0.002968	0	0.00162	0.001991	0.018717	0	0.363112	0.016013
male	60	0.003111	0	0.001804	0.002203	0.018771	0	0.369474	0.016467
male	61	0.003256	0	0.001999	0.002438	0.018929	0	0.374284	0.016968
male	62	0.0034	0	0.0022	0.002696	0.0192	0	0.3775	0.017517
male	63	0.003541	0	0.002402	0.002979	0.019585	0	0.379137	0.018116
male	64	0.003685	0	0.002604	0.003284	0.020068	0	0.379442	0.018772
male	65	0.003838	0	0.002805	0.003608	0.020628	0	0.378718	0.019492
male	66	0.004007	0	0.003004	0.003948	0.021246	0	0.377269	0.020287
male	67	0.0042	0	0.0032	0.004302	0.0219	0	0.3754	0.021165
male	68	0.004421	0	0.003392	0.004666	0.022576	0	0.373389	0.022137
male	69	0.004666	0	0.00358	0.00504	0.02328	0	0.371418	0.023226
male	70	0.004931	0	0.003761	0.005425	0.024027	0	0.369642	0.024459
male	71	0.005211	0	0.003935	0.005821	0.024829	0	0.368217	0.025863
male	72	0.0055	0	0.0041	0.006227	0.0257	0	0.3673	0.027464
male	73	0.005795	0	0.004255	0.006643	0.026654	0	0.367004	0.029287
male	74	0.006104	0	0.004402	0.007072	0.02771	0	0.367268	0.031353
male	75	0.006435	0	0.004541	0.007516	0.028889	0	0.367991	0.033682
male	76	0.006797	0	0.004673	0.007977	0.030213	0	0.369069	0.036296
male	77	0.0072	0	0.0048	0.008457	0.0317	0	0.3704	0.039213
male	78	0.007651	0	0.004922	0.008958	0.033366	0	0.371873	0.042443
male	79	0.008149	0	0.005036	0.009478	0.035198	0	0.373342	0.045947

male	80	0.008691	0	0.005139	0.010019	0.037177	0	0.374655	0.049673
male	81	0.009276	0	0.005228	0.010577	0.039284	0	0.375659	0.053573
male	82	0.0099	0	0.0053	0.011152	0.0415	0	0.3762	0.057594
male	83	0.010559	0	0.005353	0.011743	0.043806	0	0.376129	0.061666
male	84	0.011241	0	0.005392	0.012342	0.04618	0	0.375313	0.065638
male	85	0.011935	0	0.005425	0.012942	0.048601	0	0.373623	0.069336
male	86	0.012625	0	0.005458	0.013534	0.051048	0	0.370928	0.072589
male	87	0.0133	0	0.0055	0.014112	0.0535	0	0.3671	0.075223
male	88	0.013945	0	0.005554	0.014666	0.055916	0	0.36211	0.07711
male	89	0.014545	0	0.005618	0.015193	0.058179	0	0.356336	0.078296
male	90	0.015082	0	0.005684	0.015687	0.060155	0	0.350257	0.078871
male	91	0.015539	0	0.005747	0.016143	0.061707	0	0.344352	0.078923
male	92	0.0159	0	0.0058	0.016557	0.0627	0	0.3391	0.078543
male	93	0.016152	0	0.005839	0.016925	0.063044	0	0.334862	0.07782
male	94	0.016304	0	0.005865	0.017243	0.062824	0	0.331529	0.076844
male	95	0.01637	0	0.005882	0.017512	0.062173	0	0.328876	0.075705
male	96	0.016364	0	0.005893	0.01773	0.061221	0	0.326675	0.074495
male	97	0.0163	0	0.0059	0.017894	0.0601	0	0.3247	0.073303
male	98	0.016191	0	0.0059	0.018007	0.058921	0	0.3247	0.072198
male	99	0.016053	0	0.0059	0.018084	0.057717	0	0.3247	0.071167
male	100	0.0159	0	0.0059	0.018143	0.0565	0	0.3247	0.070171
female	0	0	0	0	7.88E-05	0	0	0	0.003157
female	1	0	0	0	7.88E-05	0	0	0	0.003088
female	2	0	0	0	7.87E-05	0	0	0	0.003008
female	3	0	0	0	7.86E-05	0	0	0	0.002911
female	4	0	0	0	7.85E-05	0	0	0	0.002799
female	5	0	0	0	7.84E-05	0	0	0	0.002679
female	6	0	0	0	7.83E-05	0	0	0	0.002555
female	7	0	0	0	7.82E-05	0	0	0	0.002432

female	8	0	0	0	7.82E-05	0	0	0	0.002316
female	9	0	0	0	7.82E-05	0	0	0	0.00221
female	10	0	0	0	7.83E-05	0	0	0	0.002117
female	11	0	0	0	7.84E-05	0	0	0	0.00204
female	12	0	0	0	7.85E-05	0	0	0	0.001983
female	13	0	0	0	7.87E-05	0	0	0	0.001946
female	14	0	0	0	7.88E-05	0	0	0	0.001931
female	15	0	0	0	7.90E-05	0	0	0	0.001934
female	16	0	0	0	7.92E-05	0	0	0	0.001954
female	17	0	0	0	7.93E-05	0	0	0	0.00199
female	18	0	0	0	7.94E-05	0	0	0	0.00204
female	19	0	0	0	7.95E-05	0	0	0	0.002106
female	20	0	4.54E-05	0	7.96E-05	0	0	0	0.002188
female	21	0	7.04E-05	0	7.98E-05	0	0	0	0.00229
female	22	0	0.0001	0	8.01E-05	0	0	0	0.002411
female	23	0	0.000134	0	8.05E-05	0	0	0	0.002555
female	24	0	0.000172	0	8.11E-05	0	0	0	0.002722
female	25	0	0.000213	0	8.19E-05	0	0.0008	0	0.002916
female	26	0	0.000256	0	8.32E-05	0	0.001898	0	0.003137
female	27	0	0.0003	0	8.49E-05	0	0.0037	0	0.003389
female	28	0	0.000345	0	8.72E-05	0	0.006294	0	0.003672
female	29	0	0.000395	0	9.04E-05	0	0.009438	0	0.003988
female	30	0	0.000451	0	9.47E-05	0	0.012804	0.000971	0.004334
female	31	0	0.000519	0	0.000101	0	0.016067	0.001864	0.004712
female	32	0	0.0006	0	0.000108	0	0.0189	0.0032	0.005121
female	33	1.41E-05	0.000698	0	0.000118	3.97E-05	0.02104	0.005091	0.005561
female	34	3.33E-05	0.000809	0	0.00013	8.06E-05	0.022477	0.007709	0.006028
female	35	5.56E-05	0.000933	5.51E-05	0.000143	0.000102	0.023263	0.011242	0.00652
female	36	7.85E-05	0.001064	7.81E-05	0.000158	8.18E-05	0.023453	0.015876	0.007035

female	37	0.0001	0.0012	0.0001	0.000174	0	0.0231	0.0218	0.007569
female	38	0.000118	0.001339	0.000119	0.000192	-0.00014	0.022274	0.029137	0.008119
female	39	0.000135	0.001479	0.000137	0.00021	-0.00026	0.02112	0.037758	0.00868
female	40	0.000153	0.001619	0.000155	0.00023	-0.00025	0.019799	0.04747	0.009245
female	41	0.000174	0.00176	0.000176	0.000252	2.09E-06	0.018471	0.058082	0.009809
female	42	0.0002	0.0019	0.0002	0.000277	0.0006	0.0173	0.0694	0.010365
female	43	0.000233	0.002038	0.00023	0.000304	0.001622	0.016409	0.081201	0.010907
female	44	0.000271	0.002171	0.000266	0.000334	0.003025	0.015774	0.093139	0.011428
female	45	0.000313	0.002295	0.000306	0.000368	0.004737	0.015335	0.104836	0.011921
female	46	0.000357	0.002406	0.000351	0.000407	0.006686	0.015031	0.115916	0.012381
female	47	0.0004	0.0025	0.0004	0.000451	0.0088	0.0148	0.126	0.012799
female	48	0.000441	0.002575	0.000453	0.000502	0.01099	0.014592	0.134838	0.013172
female	49	0.000481	0.002635	0.000509	0.00056	0.013099	0.014392	0.142686	0.013497
female	50	0.000521	0.002688	0.000569	0.000626	0.014952	0.014196	0.149924	0.013778
female	51	0.00056	0.002741	0.000632	0.0007	0.016378	0.014	0.156935	0.014014
female	52	0.0006	0.0028	0.0007	0.000783	0.0172	0.0138	0.1641	0.014207
female	53	0.000642	0.002871	0.000771	0.000877	0.017313	0.013592	0.171674	0.01436
female	54	0.000689	0.002951	0.000847	0.000981	0.01688	0.013376	0.179407	0.014487
female	55	0.000746	0.003035	0.000927	0.001097	0.01613	0.013154	0.186923	0.014602
female	56	0.000815	0.00312	0.001011	0.001223	0.015294	0.012928	0.193846	0.01472
female	57	0.0009	0.0032	0.0011	0.001362	0.0146	0.0127	0.1998	0.014856
female	58	0.001004	0.003272	0.001194	0.001514	0.01423	0.012473	0.204506	0.015024
female	59	0.001122	0.003337	0.001291	0.001681	0.014169	0.012257	0.208077	0.01523
female	60	0.001248	0.003396	0.001392	0.001866	0.014353	0.012064	0.210726	0.01548
female	61	0.001376	0.00345	0.001495	0.002074	0.014718	0.011908	0.212663	0.015778
female	62	0.0015	0.0035	0.0016	0.002306	0.0152	0.0118	0.2141	0.016131
female	63	0.001616	0.003547	0.001706	0.002564	0.015746	0.01175	0.215232	0.016543
female	64	0.001728	0.003592	0.00181	0.002848	0.016353	0.011758	0.216187	0.017024
female	65	0.001842	0.003633	0.001912	0.003154	0.017026	0.011821	0.217076	0.017581

female	66	0.001964	0.003669	0.002009	0.003479	0.017772	0.011936	0.21801	0.018224
female	67	0.0021	0.0037	0.0021	0.003821	0.0186	0.0121	0.2191	0.018962
female	68	0.002255	0.003726	0.002183	0.004177	0.019515	0.012312	0.22041	0.019807
female	69	0.002432	0.003747	0.002262	0.004551	0.020519	0.012575	0.221812	0.020788
female	70	0.002631	0.003766	0.002339	0.004947	0.021617	0.012891	0.223128	0.021935
female	71	0.002853	0.003783	0.002417	0.005369	0.02281	0.013265	0.224183	0.023281
female	72	0.0031	0.0038	0.0025	0.005822	0.0241	0.0137	0.2248	0.024858
female	73	0.003372	0.003818	0.002589	0.006309	0.025489	0.014199	0.224816	0.026699
female	74	0.003669	0.003838	0.00268	0.006831	0.026971	0.01476	0.22412	0.028853
female	75	0.00399	0.003858	0.002766	0.007388	0.028538	0.015382	0.222617	0.031369
female	76	0.004334	0.003879	0.002842	0.00798	0.030184	0.016063	0.220209	0.034297
female	77	0.0047	0.0039	0.0029	0.008608	0.0319	0.0168	0.2168	0.037688
female	78	0.005087	0.003921	0.002937	0.009271	0.033686	0.017586	0.212345	0.041576
female	79	0.005493	0.003941	0.002958	0.009958	0.035562	0.018388	0.207009	0.045944
female	80	0.005915	0.003961	0.00297	0.010661	0.037555	0.019167	0.201012	0.050759
female	81	0.006351	0.003981	0.002982	0.011368	0.039692	0.019884	0.194569	0.055986
female	82	0.0068	0.004	0.003	0.012069	0.042	0.0205	0.1879	0.061594
female	83	0.007259	0.004019	0.00303	0.012754	0.044527	0.020984	0.181184	0.067514
female	84	0.007728	0.004038	0.00307	0.013413	0.047411	0.021337	0.174447	0.073535
female	85	0.008207	0.004058	0.003114	0.014041	0.050812	0.021569	0.167679	0.079413
female	86	0.008698	0.004078	0.003159	0.014629	0.054888	0.021686	0.160867	0.0849
female	87	0.0092	0.0041	0.0032	0.015168	0.0598	0.0217	0.154	0.089752
female	88	0.009711	0.004123	0.003233	0.015654	0.065596	0.021621	0.147114	0.093775
female	89	0.010215	0.004146	0.003259	0.016088	0.07188	0.021474	0.140437	0.096987
female	90	0.010693	0.004168	0.003278	0.016473	0.078146	0.021287	0.134242	0.099456
female	91	0.011128	0.004186	0.003291	0.016812	0.083889	0.021086	0.128805	0.101252
female	92	0.0115	0.0042	0.0033	0.01711	0.0886	0.0209	0.1244	0.102445
female	93	0.011795	0.004208	0.003305	0.017368	0.091896	0.02075	0.121212	0.103109
female	94	0.012016	0.00421	0.003306	0.017588	0.09388	0.020633	0.119069	0.103337

female	95	0.012169	0.004209	0.003305	0.017772	0.094775	0.020541	0.117711	0.103228
female	96	0.012262	0.004205	0.003303	0.017921	0.094807	0.020466	0.116875	0.102879
female	97	0.0123	0.0042	0.0033	0.018036	0.0942	0.0204	0.1163	0.102389
female	98	0.012293	0.0042	0.0033	0.01812	0.093164	0.0204	0.1163	0.101841
female	99	0.012254	0.0042	0.0033	0.018183	0.091851	0.0204	0.1163	0.101265
female	100	0.0122	0.0042	0.0033	0.018234	0.0904	0.0204	0.1163	0.100675

Appendix A table 3. Incidence and case fatality rate trends

		Incidence trend				Case fatality trend			
Age band	Sex	CHD	Breast cancer	Lung cancer	Stroke	CHD	Breast cancer	Lung cancer	Stroke
[0,35)	male	-0.0146	0	0	-0.0169	-0.0146	0	0	-0.0169
[35,65)	male	-0.01858	0	-0.0143	-0.02011	-0.01858	0	0	-0.02011
[65,Inf)	male	-0.01872	0	-0.01078	-0.01768	-0.01872	0	0	-0.01768
[0,35)	female	0	-0.00973	0	-0.02028	0	0	0	-0.02028
[35,65)	female	-0.02305	-0.00805	-0.01693	-0.0201	-0.02305	0	0	-0.0201
[65,Inf)	female	-0.02578	-0.01192	-0.01936	-0.02018	-0.02578	0	0	-0.02018

Results tables for never smokers

Appendix A table 3. Mean difference - Female patients, undiscounted

Example organ-at-risk dose set	**Age**	**Outcome**	**Mean and 95% CI**
1: Unilateral neck only (IFRT)	20	Life years	0.82 (0.782 to 0.858)
		QALYs	1.091 (1.046 to 1.135)
	35	Life years	0.75 (0.721 to 0.779)
		QALYs	0.924 (0.891 to 0.956)
	50	Life years	0.515 (0.496 to 0.535)

		QALYs	0.635 (0.612 to 0.658)
2: Average doses for all PET-negative RAPID patients	20	Life years	0.505 (0.464 to 0.546)
		QALYs	0.819 (0.772 to 0.866)
	35	Life years	0.546 (0.517 to 0.574)
		QALYs	0.746 (0.713 to 0.779)
	50	Life years	0.402 (0.382 to 0.423)
		QALYs	0.54 (0.517 to 0.564)
3: Average doses for PET-negative RAPID patients with mediastinal involvement	20	Life years	0.235 (0.194 to 0.277)
		QALYs	0.588 (0.542 to 0.635)
	35	Life years	0.388 (0.358 to 0.417)
		QALYs	0.616 (0.583 to 0.649)
	50	Life years	0.312 (0.292 to 0.332)
		QALYs	0.464 (0.441 to 0.486)
4: Bilateral neck and whole mediastinum (IFRT)	20	Life years	-0.343 (-0.389 to -0.296)
		QALYs	0.139 (0.088 to 0.19)
	35	Life years	0.071 (0.039 to 0.102)
		QALYs	0.376 (0.342 to 0.41)
	50	Life years	0.041 (0.014 to 0.069)
		QALYs	0.25 (0.221 to 0.278)
5: Mantle field (including bilateral axillae)	20	Life years	-0.957 (-1.003 to -0.911)
		QALYs	-0.359 (-0.408 to -0.309)
	35	Life years	-0.195 (-0.228 to -0.162)
		QALYs	0.172 (0.138 to 0.207)
	50	Life years	-0.094 (-0.12 to -0.067)
		QALYs	0.15 (0.124 to 0.177)

Appendix A table 4. Mean difference - Female patients, with future health discount rate of 3.5%

Example organ-at-risk dose set	Age	Outcome	Mean and 95% CI

1: Unilateral neck only (IFRT)	20	Life years	0.377 (0.365 to 0.389)
		QALYs	0.502 (0.486 to 0.518)
	35	Life years	0.334 (0.323 to 0.344)
		QALYs	0.431 (0.418 to 0.445)
	50	Life years	0.261 (0.251 to 0.27)
		QALYs	0.342 (0.33 to 0.353)
2: Average doses for all PET-negative RAPID patients	20	Life years	0.335 (0.322 to 0.347)
		QALYs	0.46 (0.444 to 0.476)
	35	Life years	0.307 (0.296 to 0.318)
		QALYs	0.402 (0.388 to 0.415)
	50	Life years	0.225 (0.216 to 0.234)
		QALYs	0.308 (0.296 to 0.319)
3: Average doses for PET-negative RAPID patients with mediastinal involvement	20	Life years	0.297 (0.285 to 0.309)
		QALYs	0.411 (0.395 to 0.426)
	35	Life years	0.259 (0.249 to 0.27)
		QALYs	0.359 (0.345 to 0.372)
	50	Life years	0.192 (0.183 to 0.202)
		QALYs	0.279 (0.268 to 0.291)
4: Bilateral neck and whole mediastinum (IFRT)	20	Life years	0.22 (0.207 to 0.233)
		QALYs	0.357 (0.34 to 0.373)
	35	Life years	0.194 (0.182 to 0.206)
		QALYs	0.316 (0.301 to 0.331)
	50	Life years	0.113 (0.103 to 0.123)
		QALYs	0.218 (0.207 to 0.23)
5: Mantle field (including bilateral axillae)	20	Life years	0.112 (0.1 to 0.125)
		QALYs	0.272 (0.256 to 0.288)
	35	Life years	0.13 (0.118 to 0.141)
		QALYs	0.258 (0.244 to 0.272)
	50	Life years	0.056 (0.045 to 0.067)

		QALYs	0.173 (0.16 to 0.185)

Appendix A table 5. Mean difference - Male patients, undiscounted

Example organ-at-risk dose set	Age	Outcome	Mean and 95% CI
1: Unilateral neck only (IFRT)	20	Life years	0.851 (0.816 to 0.886)
		QALYs	1.095 (1.054 to 1.137)
	35	Life years	0.695 (0.669 to 0.721)
		QALYs	0.868 (0.838 to 0.898)
	50	Life years	0.402 (0.384 to 0.42)
		QALYs	0.517 (0.497 to 0.538)
2: Average doses for all PET-negative RAPID patients	20	Life years	0.564 (0.526 to 0.602)
		QALYs	0.844 (0.801 to 0.888)
	35	Life years	0.436 (0.41 to 0.461)
		QALYs	0.629 (0.6 to 0.658)
	50	Life years	0.286 (0.265 to 0.306)
		QALYs	0.436 (0.414 to 0.459)
3: Average doses for PET-negative RAPID patients with mediastinal involvement	20	Life years	0.227 (0.187 to 0.267)
		QALYs	0.556 (0.512 to 0.599)
	35	Life years	0.273 (0.246 to 0.301)
		QALYs	0.526 (0.495 to 0.557)
	50	Life years	0.162 (0.141 to 0.182)
		QALYs	0.334 (0.312 to 0.356)
4: Bilateral neck and whole mediastinum (IFRT)	20	Life years	-0.386 (-0.436 to -0.335)
		QALYs	0.084 (0.031 to 0.137)
	35	Life years	-0.179 (-0.213 to -0.145)
		QALYs	0.161 (0.126 to 0.196)
	50	Life years	-0.147 (-0.173 to -0.121)

		QALYs	0.107 (0.083 to 0.131)
5: Mantle field (including bilateral axillae)	20	Life years	-0.458 (-0.51 to -0.405)
		QALYs	0.016 (-0.037 to 0.069)
	35	Life years	-0.291 (-0.327 to -0.255)
		QALYs	0.079 (0.042 to 0.115)
	50	Life years	-0.239 (-0.267 to -0.211)
		QALYs	0.042 (0.016 to 0.068)

Appendix A table 6. Mean difference - Male patients, with future health discount rate of 3.5%

Example organ-at-risk dose set	Age	Outcome	Mean and 95% CI
1: Unilateral neck only (IFRT)	20	Life years	0.376 (0.365 to 0.388)
		QALYs	0.488 (0.473 to 0.503)
	35	Life years	0.324 (0.314 to 0.334)
		QALYs	0.419 (0.406 to 0.432)
	50	Life years	0.233 (0.225 to 0.241)
		QALYs	0.314 (0.304 to 0.325)
2: Average doses for all PET-negative RAPID patients	20	Life years	0.339 (0.327 to 0.352)
		QALYs	0.452 (0.436 to 0.468)
	35	Life years	0.271 (0.261 to 0.281)
		QALYs	0.372 (0.359 to 0.385)
	50	Life years	0.183 (0.175 to 0.192)
		QALYs	0.265 (0.255 to 0.275)
3: Average doses for PET-negative RAPID patients with mediastinal involvement	20	Life years	0.301 (0.288 to 0.314)
		QALYs	0.424 (0.408 to 0.44)
	35	Life years	0.223 (0.213 to 0.234)
		QALYs	0.325 (0.312 to 0.338)
	50	Life years	0.141 (0.132 to 0.15)

		QALYs	0.233 (0.222 to 0.243)
4: Bilateral neck and whole mediastinum (IFRT)	20	Life years	0.208 (0.195 to 0.221)
		QALYs	0.343 (0.326 to 0.359)
	35	Life years	0.121 (0.109 to 0.133)
		QALYs	0.247 (0.234 to 0.261)
	50	Life years	0.031 (0.02 to 0.042)
		QALYs	0.152 (0.14 to 0.164)
5: Mantle field RT (including bilateral axillae)	20	Life years	0.199 (0.186 to 0.212)
		QALYs	0.342 (0.325 to 0.359)
	35	Life years	0.11 (0.098 to 0.122)
		QALYs	0.243 (0.229 to 0.257)
	50	Life years	-0.009 (-0.021 to 0.004)
		QALYs	0.117 (0.104 to 0.13)

Results tables for former smokers

Appendix A table 7. Mean difference - Female patients, undiscounted

Example organ-at-risk dose set	Age	Outcome	Mean and 95% CI
1: Unilateral neck only (IFRT)	20	Life years	0.541 (0.501 to 0.581)
		QALYs	0.886 (0.841 to 0.932)
	35	Life years	0.464 (0.434 to 0.494)
		QALYs	0.709 (0.676 to 0.742)
	50	Life years	0.278 (0.257 to 0.3)
		QALYs	0.454 (0.431 to 0.478)
2: Average doses for all PET-negative RAPID patients	20	Life years	-0.03 (-0.077 to 0.016)
		QALYs	0.407 (0.358 to 0.455)
	35	Life years	0.053 (0.018 to 0.089)
		QALYs	0.379 (0.344 to 0.415)
	50	Life years	-0.017 (-0.045 to 0.011)

		QALYs	0.223 (0.196 to 0.25)
3: Average doses for PET-negative RAPID patients with mediastinal involvement	20	Life years	-0.542 (-0.592 to -0.492)
		QALYs	-0.001 (-0.053 to 0.05)
	35	Life years	-0.335 (-0.378 to -0.291)
		QALYs	0.088 (0.046 to 0.129)
	50	Life years	-0.288 (-0.323 to -0.254)
		QALYs	0.019 (-0.013 to 0.051)
4: Bilateral neck and whole mediastinum (IFRT)	20	Life years	-1.689 (-1.758 to -1.619)
		QALYs	-0.902 (-0.966 to -0.839)
	35	Life years	-1.245 (-1.306 to -1.183)
		QALYs	-0.611 (-0.664 to -0.559)
	50	Life years	-1.029 (-1.084 to -0.973)
		QALYs	-0.526 (-0.57 to -0.481)
5: Mantle field (including bilateral axillae)	20	Life years	-2.443 (-2.516 to -2.37)
		QALYs	-1.463 (-1.528 to -1.399)
	35	Life years	-1.692 (-1.764 to -1.619)
		QALYs	-0.954 (-1.013 to -0.896)
	50	Life years	-1.351 (-1.411 to -1.291)
		QALYs	-0.774 (-0.821 to -0.726)

Appendix A table 8. Mean difference - Female patients, with future health discount rate of 3.5%

Example organ-at-risk dose set	Age	Outcome	Mean and 95% CI
1: Unilateral neck only (IFRT)	20	Life years	0.337 (0.325 to 0.349)
		QALYs	0.463 (0.447 to 0.478)
	35	Life years	0.277 (0.266 to 0.288)
		QALYs	0.385 (0.371 to 0.399)
	50	Life years	0.183 (0.173 to 0.193)

		QALYs	0.279 (0.267 to 0.291)
2: Average doses for all PET-negative RAPID patients	20	Life years	0.269 (0.256 to 0.282)
		QALYs	0.406 (0.389 to 0.423)
	35	Life years	0.185 (0.173 to 0.197)
		QALYs	0.315 (0.3 to 0.33)
	50	Life years	0.079 (0.068 to 0.091)
		QALYs	0.198 (0.185 to 0.211)
3: Average doses for PET-negative RAPID patients with mediastinal involvement	20	Life years	0.191 (0.178 to 0.205)
		QALYs	0.339 (0.322 to 0.355)
	35	Life years	0.095 (0.082 to 0.109)
		QALYs	0.236 (0.22 to 0.251)
	50	Life years	-0.021 (-0.035 to -0.006)
		QALYs	0.116 (0.102 to 0.131)
4: Bilateral neck and whole mediastinum (IFRT)	20	Life years	0.052 (0.037 to 0.067)
		QALYs	0.234 (0.216 to 0.252)
	35	Life years	-0.113 (-0.13 to -0.096)
		QALYs	0.075 (0.058 to 0.092)
	50	Life years	-0.28 (-0.3 to -0.259)
		QALYs	-0.084 (-0.102 to -0.065)
5: Mantle field (including bilateral axillae)	20	Life years	-0.085 (-0.1 to -0.07)
		QALYs	0.111 (0.094 to 0.129)
	35	Life years	-0.21 (-0.228 to -0.191)
		QALYs	-0.004 (-0.022 to 0.014)
	50	Life years	-0.398 (-0.42 to -0.375)
		QALYs	-0.171 (-0.19 to -0.151)

Appendix A table 9. Mean difference - Male patients, undiscounted

Example organ-at-risk dose set	Age	Outcome	Mean and 95% CI
1: Unilateral neck only (IFRT)	20	Life years	0.543 (0.505 to 0.581)

		QALYs	0.873 (0.83 to 0.917)
	35	Life years	0.351 (0.322 to 0.38)
		QALYs	0.611 (0.58 to 0.643)
	50	Life years	0.113 (0.092 to 0.134)
		QALYs	0.311 (0.29 to 0.332)
2: Average doses for all PET-negative RAPID patients	20	Life years	-0.113 (-0.158 to -0.068)
		QALYs	0.324 (0.278 to 0.371)
	35	Life years	-0.171 (-0.208 to -0.134)
		QALYs	0.2 (0.165 to 0.236)
	50	Life years	-0.258 (-0.289 to -0.226)
		QALYs	0.036 (0.009 to 0.064)
3: Average doses for PET-negative RAPID patients with mediastinal involvement	20	Life years	-0.704 (-0.759 to -0.648)
		QALYs	-0.133 (-0.187 to -0.079)
	35	Life years	-0.665 (-0.713 to -0.617)
		QALYs	-0.184 (-0.226 to -0.142)
	50	Life years	-0.622 (-0.662 to -0.581)
		QALYs	-0.227 (-0.26 to -0.193)
4: Bilateral neck and whole mediastinum (IFRT)	20	Life years	-1.971 (-2.047 to -1.895)
		QALYs	-1.111 (-1.176 to -1.046)
	35	Life years	-1.779 (-1.85 to -1.708)
		QALYs	-1.035 (-1.093 to -0.978)
	50	Life years	-1.541 (-1.604 to -1.479)
		QALYs	-0.902 (-0.951 to -0.854)
5: Mantle field (including bilateral axillae)	20	Life years	-2.199 (-2.278 to -2.119)
		QALYs	-1.279 (-1.347 to -1.212)
	35	Life years	-2.094 (-2.174 to -2.014)
		QALYs	-1.243 (-1.307 to -1.18)
	50	Life years	-1.784 (-1.854 to -1.714)
		QALYs	-1.082 (-1.135 to -1.028)

Appendix A table 10. Mean difference - Male patients, with future health discount rate of 3.5%

Example organ-at-risk dose set	Age	Outcome	Mean and 95% CI
1: Unilateral neck only (IFRT)	20	Life years	0.325 (0.313 to 0.338)
		QALYs	0.445 (0.429 to 0.46)
	35	Life years	0.245 (0.235 to 0.256)
		QALYs	0.356 (0.343 to 0.369)
	50	Life years	0.114 (0.104 to 0.124)
		QALYs	0.221 (0.21 to 0.232)
2: Average doses for all PET-negative RAPID patients	20	Life years	0.24 (0.227 to 0.253)
		QALYs	0.384 (0.367 to 0.4)
	35	Life years	0.113 (0.102 to 0.124)
		QALYs	0.251 (0.237 to 0.264)
	50	Life years	-0.015 (-0.027 to -0.003)
		QALYs	0.12 (0.108 to 0.132)
3: Average doses for PET-negative RAPID patients with mediastinal involvement	20	Life years	0.167 (0.153 to 0.181)
		QALYs	0.315 (0.299 to 0.332)
	35	Life years	0.01 (-0.004 to 0.024)
		QALYs	0.171 (0.157 to 0.186)
	50	Life years	-0.145 (-0.16 to -0.129)
		QALYs	0.027 (0.012 to 0.042)
4: Bilateral neck and whole mediastinum (IFRT)	20	Life years	-0.037 (-0.053 to -0.021)
		QALYs	0.156 (0.139 to 0.174)
	35	Life years	-0.274 (-0.294 to -0.253)
		QALYs	-0.052 (-0.071 to -0.032)
	50	Life years	-0.502 (-0.527 to -0.477)

		QALYs	-0.251 (-0.271 to -0.23)
5: Mantle field RT (including bilateral axillae)	20	Life years	-0.081 (-0.097 to -0.065)
		QALYs	0.116 (0.099 to 0.134)
	35	Life years	-0.36 (-0.382 to -0.338)
		QALYs	-0.122 (-0.142 to -0.103)
	50	Life years	-0.595 (-0.623 to -0.567)
		QALYs	-0.313 (-0.337 to -0.29)

Results tables for current smokers

Appendix A table 11. Mean difference - Female patients, undiscounted

Example organ-at-risk dose set	Age	Outcome	Mean and 95% CI
1: Unilateral neck only (IFRT)	20	Life years	-0.169 (-0.22 to -0.117)
		QALYs	0.32 (0.268 to 0.372)
	35	Life years	-0.171 (-0.211 to -0.13)
		QALYs	0.232 (0.194 to 0.271)
	50	Life years	-0.271 (-0.307 to -0.234)
		QALYs	0.032 (-0.001 to 0.064)
2: Average doses for all PET-negative RAPID patients	20	Life years	-1.31 (-1.375 to -1.244)
		QALYs	-0.587 (-0.648 to -0.526)
	35	Life years	-1.12 (-1.18 to -1.06)
		QALYs	-0.514 (-0.566 to -0.462)
	50	Life years	-0.982 (-1.034 to -0.93)
		QALYs	-0.492 (-0.534 to -0.45)
3: Average doses for PET-negative RAPID patients with mediastinal involvement	20	Life years	-2.254 (-2.337 to -2.172)
		QALYs	-1.323 (-1.394 to -1.251)
	35	Life years	-1.933 (-2.011 to -1.856)
		QALYs	-1.119 (-1.183 to -1.055)
	50	Life years	-1.574 (-1.641 to -1.506)

		QALYs	-0.936 (-0.989 to -0.883)
4: Bilateral neck and whole mediastinum (IFRT)	20	Life years	-4.42 (-4.537 to -4.304)
		QALYs	-3.007 (-3.099 to -2.914)
	35	Life years	-4.028 (-4.149 to -3.907)
		QALYs	-2.702 (-2.795 to -2.608)
	50	Life years	-3.321 (-3.426 to -3.216)
		QALYs	-2.236 (-2.316 to -2.156)
5: Mantle field (including bilateral axillae)	20	Life years	-5.374 (-5.502 to -5.246)
		QALYs	-3.696 (-3.798 to -3.595)
	35	Life years	-4.63 (-4.759 to -4.5)
		QALYs	-3.16 (-3.261 to -3.06)
	50	Life years	-3.753 (-3.863 to -3.643)
		QALYs	-2.554 (-2.637 to -2.471)

Appendix A table 12. Mean difference - Female patients, with future health discount rate of 3.5%

Example organ-at-risk dose set	Age	Outcome	Mean and 95% CI
1: Unilateral neck only (IFRT)	20	Life years	0.237 (0.224 to 0.25)
		QALYs	0.383 (0.367 to 0.4)
	35	Life years	0.113 (0.1 to 0.127)
		QALYs	0.252 (0.238 to 0.267)
	50	Life years	-0.004 (-0.018 to 0.01)
		QALYs	0.133 (0.119 to 0.147)
2: Average doses for all PET-negative RAPID patients	20	Life years	0.093 (0.078 to 0.108)
		QALYs	0.263 (0.246 to 0.28)
	35	Life years	-0.099 (-0.116 to -0.081)
		QALYs	0.088 (0.071 to 0.105)
	50	Life years	-0.258 (-0.278 to -0.239)

		QALYs	-0.062 (-0.079 to -0.044)
3: Average doses for PET-negative RAPID patients with mediastinal involvement	20	Life years	-0.069 (-0.085 to -0.053)
		QALYs	0.125 (0.107 to 0.143)
	35	Life years	-0.299 (-0.321 to -0.277)
		QALYs	-0.073 (-0.094 to -0.053)
	50	Life years	-0.517 (-0.543 to -0.492)
		QALYs	-0.262 (-0.283 to -0.24)
4: Bilateral neck and whole mediastinum (IFRT)	20	Life years	-0.382 (-0.403 to -0.36)
		QALYs	-0.119 (-0.14 to -0.098)
	35	Life years	-0.79 (-0.822 to -0.757)
		QALYs	-0.458 (-0.486 to -0.431)
	50	Life years	-1.121 (-1.164 to -1.079)
		QALYs	-0.723 (-0.756 to -0.689)
5: Mantle field (including bilateral axillae)	20	Life years	-0.542 (-0.565 to -0.519)
		QALYs	-0.254 (-0.276 to -0.232)
	35	Life years	-0.932 (-0.966 to -0.898)
		QALYs	-0.563 (-0.591 to -0.535)
	50	Life years	-1.331 (-1.375 to -1.287)
		QALYs	-0.888 (-0.923 to -0.853)

Appendix A table 13. Mean difference - Male patients, undiscounted

Example organ-at-risk dose set	Age	Outcome	Mean and 95% CI
1: Unilateral neck only (IFRT)	20	Life years	-0.267 (-0.318 to -0.216)
		QALYs	0.252 (0.202 to 0.302)
	35	Life years	-0.429 (-0.475 to -0.383)
		QALYs	0.03 (-0.011 to 0.072)
	50	Life years	-0.569 (-0.608 to -0.53)
		QALYs	-0.184 (-0.216 to -0.152)
2: Average doses for all PET-negative RAPID patients	20	Life years	-1.678 (-1.752 to -1.605)

		QALYs	-0.848 (-0.911 to -0.785)
	35	Life years	-1.607 (-1.677 to -1.538)
		QALYs	-0.858 (-0.914 to -0.802)
	50	Life years	-1.478 (-1.538 to -1.417)
		QALYs	-0.852 (-0.899 to -0.806)
3: Average doses for PET-negative RAPID patients with mediastinal involvement	20	Life years	-2.789 (-2.879 to -2.699)
		QALYs	-1.718 (-1.793 to -1.643)
	35	Life years	-2.628 (-2.716 to -2.54)
		QALYs	-1.65 (-1.719 to -1.582)
	50	Life years	-2.311 (-2.39 to -2.231)
		QALYs	-1.448 (-1.508 to -1.388)
4: Bilateral neck and whole mediastinum (IFRT)	20	Life years	-5.149 (-5.274 to -5.023)
		QALYs	-3.5 (-3.6 to -3.4)
	35	Life years	-4.819 (-4.944 to -4.694)
		QALYs	-3.289 (-3.384 to -3.193)
	50	Life years	-4.144 (-4.257 to -4.031)
		QALYs	-2.815 (-2.899 to -2.731)
5: Mantle field (including bilateral axillae)	20	Life years	-5.744 (-5.874 to -5.613)
		QALYs	-3.955 (-4.055 to -3.855)
	35	Life years	-5.455 (-5.592 to -5.317)
		QALYs	-3.743 (-3.847 to -3.639)
	50	Life years	-4.705 (-4.825 to -4.585)
		QALYs	-3.221 (-3.31 to -3.132)

Appendix A table 14. Mean difference - Male patients, with future health discount rate of 3.5%

Example organ-at-risk dose set	Age	Outcome	Mean and 95% CI

1: Unilateral neck only (IFRT)	20	Life years	0.21 (0.196 to 0.224)
		QALYs	0.362 (0.345 to 0.379)
	35	Life years	0.056 (0.042 to 0.069)
		QALYs	0.212 (0.197 to 0.227)
	50	Life years	-0.126 (-0.141 to -0.111)
		QALYs	0.035 (0.021 to 0.049)
2: Average doses for all PET-negative RAPID patients	20	Life years	0.02 (0.005 to 0.036)
		QALYs	0.208 (0.191 to 0.225)
	35	Life years	-0.237 (-0.256 to -0.219)
		QALYs	-0.021 (-0.038 to -0.003)
	50	Life years	-0.484 (-0.509 to -0.46)
		QALYs	-0.234 (-0.254 to -0.213)
3: Average doses for PET-negative RAPID patients with mediastinal involvement	20	Life years	-0.145 (-0.163 to -0.127)
		QALYs	0.07 (0.051 to 0.089)
	35	Life years	-0.475 (-0.499 to -0.451)
		QALYs	-0.208 (-0.229 to -0.188)
	50	Life years	-0.764 (-0.795 to -0.734)
		QALYs	-0.441 (-0.465 to -0.417)
4: Bilateral neck and whole mediastinum (IFRT)	20	Life years	-0.52 (-0.543 to -0.497)
		QALYs	-0.231 (-0.253 to -0.209)
	35	Life years	-1.085 (-1.119 to -1.052)
		QALYs	-0.688 (-0.716 to -0.659)
	50	Life years	-1.541 (-1.587 to -1.495)
		QALYs	-1.028 (-1.064 to -0.993)
5: Mantle field RT (including bilateral axillae)	20	Life years	-0.626 (-0.651 to -0.602)
		QALYs	-0.31 (-0.333 to -0.287)
	35	Life years	-1.237 (-1.276 to -1.197)
		QALYs	-0.8 (-0.831 to -0.768)
	50	Life years	-1.725 (-1.775 to -1.674)
		QALYs	-1.165 (-1.204 to -1.127)

Results tables without adjustment for smoking

Appendix A table 15. Mean difference - Female patients, undiscounted

Example organ-at-risk dose set	Age	Outcome	Mean and 95% CI
1: Unilateral neck only (IFRT)	20	Life years	0.615 (0.574 to 0.656)
		QALYs	0.945 (0.897 to 0.993)
	35	Life years	0.485 (0.456 to 0.514)
		QALYs	0.703 (0.67 to 0.735)
	50	Life years	0.312 (0.288 to 0.336)
		QALYs	0.471 (0.446 to 0.496)
2: Average doses for all PET-negative RAPID patients	20	Life years	0.059 (0.014 to 0.104)
		QALYs	0.489 (0.439 to 0.538)
	35	Life years	0.123 (0.09 to 0.155)
		QALYs	0.413 (0.38 to 0.447)
	50	Life years	0.097 (0.072 to 0.122)
		QALYs	0.307 (0.283 to 0.331)
3: Average doses for PET-negative RAPID patients with mediastinal involvement	20	Life years	-0.421 (-0.471 to -0.37)
		QALYs	0.097 (0.044 to 0.15)
	35	Life years	-0.19 (-0.229 to -0.151)
		QALYs	0.187 (0.149 to 0.225)
	50	Life years	-0.148 (-0.177 to -0.118)
		QALYs	0.123 (0.095 to 0.151)
4: Bilateral neck and whole mediastinum (IFRT)	20	Life years	-1.417 (-1.483 to -1.352)
		QALYs	-0.69 (-0.751 to -0.628)
	35	Life years	-0.997 (-1.052 to -0.942)
		QALYs	-0.427 (-0.475 to -0.379)
	50	Life years	-0.87 (-0.919 to -0.821)

		QALYs	-0.42 (-0.461 to -0.379)
5: Mantle field (including bilateral axillae)	20	Life years	-2.174 (-2.243 to -2.106)
		QALYs	-1.242 (-1.305 to -1.18)
	35	Life years	-1.441 (-1.504 to -1.379)
		QALYs	-0.778 (-0.83 to -0.725)
	50	Life years	-1.136 (-1.19 to -1.082)
		QALYs	-0.611 (-0.655 to -0.566)

Appendix A table 16. Mean difference - Female patients, with future health discount rate of 3.5%

Example organ-at-risk dose set	Age	Outcome	Mean and 95% CI
1: Unilateral neck only (IFRT)	20	Life years	0.344 (0.332 to 0.357)
		QALYs	0.472 (0.456 to 0.488)
	35	Life years	0.293 (0.282 to 0.304)
		QALYs	0.403 (0.389 to 0.417)
	50	Life years	0.198 (0.189 to 0.208)
		QALYs	0.287 (0.275 to 0.298)
2: Average doses for all PET-negative RAPID patients	20	Life years	0.279 (0.266 to 0.292)
		QALYs	0.418 (0.401 to 0.434)
	35	Life years	0.208 (0.196 to 0.22)
		QALYs	0.322 (0.308 to 0.337)
	50	Life years	0.111 (0.101 to 0.122)
		QALYs	0.223 (0.21 to 0.235)
3: Average doses for PET-negative RAPID patients with mediastinal involvement	20	Life years	0.203 (0.189 to 0.216)
		QALYs	0.345 (0.328 to 0.362)
	35	Life years	0.121 (0.109 to 0.134)
		QALYs	0.259 (0.244 to 0.273)

	50	Life years	0.009 (-0.004 to 0.023)
		QALYs	0.137 (0.122 to 0.153)
4: Bilateral neck and whole mediastinum (IFRT)	20	Life years	0.07 (0.056 to 0.084)
		QALYs	0.243 (0.226 to 0.26)
	35	Life years	-0.096 (-0.112 to -0.08)
		QALYs	0.079 (0.062 to 0.096)
	50	Life years	-0.219 (-0.236 to -0.202)
		QALYs	-0.035 (-0.051 to -0.019)
5: Mantle field (including bilateral axillae)	20	Life years	-0.073 (-0.088 to -0.058)
		QALYs	0.116 (0.099 to 0.134)
	35	Life years	-0.168 (-0.186 to -0.15)
		QALYs	0.023 (0.005 to 0.041)
	50	Life years	-0.313 (-0.333 to -0.294)
		QALYs	-0.104 (-0.121 to -0.086)

Appendix A table 17. Mean difference - Male patients, undiscounted

Example organ-at-risk dose set	Age	Outcome	Mean and 95% CI
1: Unilateral neck only (IFRT)	20	Life years	0.55 (0.512 to 0.589)
		QALYs	0.865 (0.821 to 0.908)
	35	Life years	0.359 (0.331 to 0.387)
		QALYs	0.607 (0.576 to 0.637)
	50	Life years	0.168 (0.149 to 0.187)
		QALYs	0.354 (0.334 to 0.374)
2: Average doses for all PET-negative RAPID patients	20	Life years	-0.108 (-0.152 to -0.063)
		QALYs	0.331 (0.284 to 0.377)
	35	Life years	-0.127 (-0.164 to -0.089)
		QALYs	0.241 (0.205 to 0.277)
	50	Life years	-0.182 (-0.211 to -0.153)
		QALYs	0.098 (0.072 to 0.125)

3: Average doses for PET-negative RAPID patients with mediastinal involvement	20	Life years	-0.668 (-0.72 to -0.616)
		QALYs	-0.115 (-0.166 to -0.064)
	35	Life years	-0.554 (-0.598 to -0.509)
		QALYs	-0.107 (-0.147 to -0.068)
	50	Life years	-0.522 (-0.558 to -0.486)
		QALYs	-0.163 (-0.194 to -0.132)
4: Bilateral neck and whole mediastinum (IFRT)	20	Life years	-1.977 (-2.054 to -1.901)
		QALYs	-1.158 (-1.225 to -1.091)
	35	Life years	-1.664 (-1.732 to -1.596)
		QALYs	-0.944 (-1 to -0.887)
	50	Life years	-1.448 (-1.504 to -1.392)
		QALYs	-0.847 (-0.891 to -0.803)
5: Mantle field (including bilateral axillae)	20	Life years	-2.187 (-2.266 to -2.108)
		QALYs	-1.259 (-1.327 to -1.191)
	35	Life years	-2.007 (-2.079 to -1.936)
		QALYs	-1.198 (-1.255 to -1.14)
	50	Life years	-1.71 (-1.777 to -1.642)
		QALYs	-1.03 (-1.082 to -0.978)

Appendix A table 18. Mean difference - Male patients, with future health discount rate of 3.5%

Example organ-at-risk dose set	Age	Outcome	Mean and 95% CI
1: Unilateral neck only (IFRT)	20	Life years	0.335 (0.323 to 0.347)
		QALYs	0.462 (0.447 to 0.478)
	35	Life years	0.242 (0.231 to 0.253)
		QALYs	0.352 (0.339 to 0.366)
	50	Life years	0.136 (0.127 to 0.145)

		QALYs	0.235 (0.224 to 0.245)
2: Average doses for all PET-negative RAPID patients	20	Life years	0.238 (0.226 to 0.25)
		QALYs	0.379 (0.363 to 0.394)
	35	Life years	0.131 (0.119 to 0.142)
		QALYs	0.258 (0.244 to 0.272)
	50	Life years	-0.004 (-0.017 to 0.009)
		QALYs	0.128 (0.115 to 0.142)
3: Average doses for PET-negative RAPID patients with mediastinal involvement	20	Life years	0.14 (0.126 to 0.153)
		QALYs	0.286 (0.27 to 0.303)
	35	Life years	0.023 (0.009 to 0.037)
		QALYs	0.178 (0.163 to 0.193)
	50	Life years	-0.126 (-0.141 to -0.112)
		QALYs	0.037 (0.023 to 0.05)
4: Bilateral neck and whole mediastinum (IFRT)	20	Life years	-0.041 (-0.057 to -0.025)
		QALYs	0.154 (0.136 to 0.172)
	35	Life years	-0.256 (-0.275 to -0.238)
		QALYs	-0.049 (-0.067 to -0.031)
	50	Life years	-0.44 (-0.462 to -0.418)
		QALYs	-0.201 (-0.22 to -0.182)
5: Mantle field RT (including bilateral axillae)	20	Life years	-0.096 (-0.113 to -0.079)
		QALYs	0.1 (0.081 to 0.118)
	35	Life years	-0.335 (-0.356 to -0.314)
		QALYs	-0.1 (-0.12 to -0.081)
	50	Life years	-0.56 (-0.587 to -0.534)
		QALYs	-0.293 (-0.315 to -0.27)

Appendix B: Additional material for Chapter 4

Systematic search of costing studies for breast and lung cancer, CHD, and stroke

In order to evaluate the possible cost-effectiveness of PBT, the previously developed model was augmented to also calculate costs attributable to late effects from the UK National Health Service (NHS) perspective. A systematic literature search was performed to identify appropriate studies on which to base these costs. MEDLINE, EMBASE and Web of Science were searched from 1 January 2010 to 29 June 2021. The search strategies for each disease, are presented in below.

Medline and Embase	Searches
1 (breast and lung cancer)	(cancer or carcinoma or neoplasm).ti,ab.
1 (coronary heart disease)	(coronary heart disease or coronary artery disease or ischaemic heart disease or ischemic heart disease).ti,ab.
1 (ischemic stroke)	stroke.ti,ab.
2	cost.ti,ab.
3	(UK or NHS or United Kingdom or England or Scotland or Wales or Northern Ireland).mp.
4	1 and 2 and 3
5	limit 4 to yr="2010 -Current"
6	limit 5 to english language

WoS	Searches
1	TS=(cost)
2 (breast and lung cancer)	(TS=(cancer)) OR TS=(carcinoma)
2 (coronary heart disease)	TS=("coronary heart disease") OR TS=("coronary artery disease") OR TS=("ischaemic heart disease") OR TS=("ischemic heart disease")
2 (ischemic stroke)	TS=(stroke)
3	((((((((((TS=(UK)) OR TS=(NHS)) OR TS=(United Kingdom)) OR TS=(England)) OR TS=(English)) OR TS=(Scotland)) OR TS=(Scottish)) OR TS=(Wales)) OR TS=(Welsh)) OR TS=(Northern Ireland)) OR TS=(Northern Irish)
4	1 and 2 and 3
5	Index Date: 01-01-2010 – 29-07-2021

General inclusion/exclusion criteria were as follows:

Inclusion criteria: Cancer/CHD/stroke patients of any age receiving healthcare in the UK; Studies that calculate per-patient costs

Exclusion criteria: Commentaries or studies that do not report patient-level costs; Studies which only calculate prevalence-based costs from aggregated expenditure data

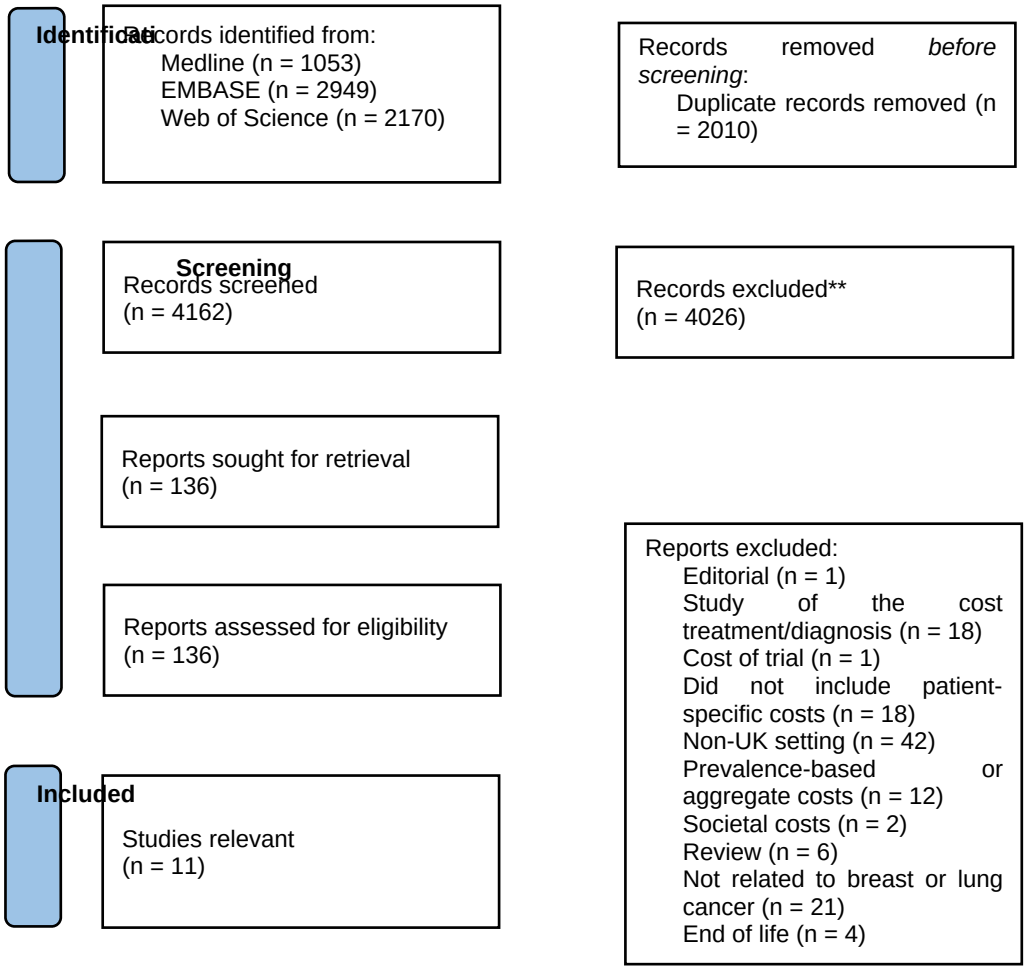
Ideally, the model would incorporate published estimates of the per-patient cost for a large number of years following diagnosis, or a single estimate of the lifetime cost. Recurrence and disease-related sequelae can occur many years after initial diagnosis and treatment, therefore, studies with a short time frame may not capture the full healthcare costs of a late effect. Preference was given to full articles over abstracts, and for the cancer focused literature, studies which estimated costs for both breast and lung cancer, and therefore used the same methods to measure both costs.

Results for Cancer

The search strategy for breast and lung cancer costs identified 6172 records. De-duplication using the reference manager's duplicate identifier tool reduced this to 4162 records. Titles were screened for relevance to cancer, greatly reducing the number of records to 136, which were retrieved. Articles for these 136 records were sought and assessed for eligibility. In total 11 studies were found to match the inclusion/exclusion criteria above, of which two studies looked at costs for both lung and breast cancer. Hall et al (2015)[196] included costs for only the first 15 months after diagnosis, whilst Laudicella et al (2016)[136] provided costs up to 10 and 5 years after diagnosis for breast and lung cancer respectively. For this reason, these costs from Laudicella et al (2016) were used for the model. A PRISMA 2020 flow diagram of the identification process and the characteristics of the 11 studies is given in below as well as references for the studies.

Publication Year	Author	Site	Article type	Time frame

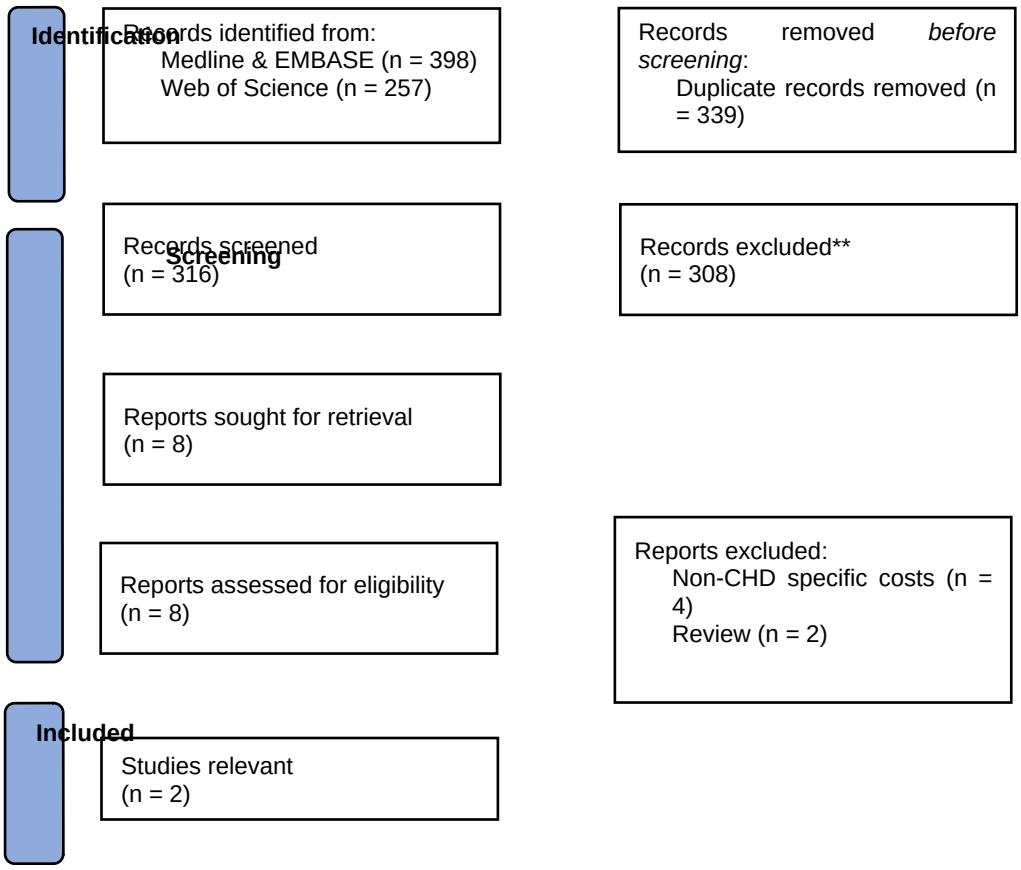
2020	Sun et al[197]	Breast	Full article	Diagnosis to 1 year
2020	Verleger et al[198]	Lung	Full article	Diagnosis through most recent visit/death
2018	Andreas et al[199]	Lung	Full article	Diagnosis to 2 year
2017	Solem et al[200]	Lung	Abstract	Diagnosis through most recent visit/death
2017	Solem et al[201]	Lung	Abstract	Diagnosis through most recent visit/death
2016	Laudicella et al[202]	Breast and Lung	Full article	Diagnosis to 10/5 years for breast/lung cancer
2016	Marti et al[203]	Breast	Full article	3-month period 12–15 months post-diagnosis
2016	Kennedy et al[204]	Lung	Full article	Diagnosis to 1 year
2015	McGuire et al[205]	Lung	Full article	Diagnosis to 2 year
2015	Hall et al[196]	Breast and Lung	Full article	Diagnosis to 15 months
2014	Hall et al[206]	Breast	Abstract	Diagnosis to 10 years or until death if earlier



Results for CHD

655 records were identified for CHD of which 316 remained after de-duplication. Screening titles and abstracts for relevance to the inclusion criteria excluded 308 records, leaving 8 sought for retrieval and full article review, which subsequently identified only two studies as meeting the requirements. Both publications were part of the same project, one focusing on methodology whilst the other focusing on presentation of the lifetime costs of stable coronary artery disease. Lifetime costs were abstracted from this later study. A PRISMA 2020 flow diagram of the identification process and the characteristics of the 8 studies is given below.

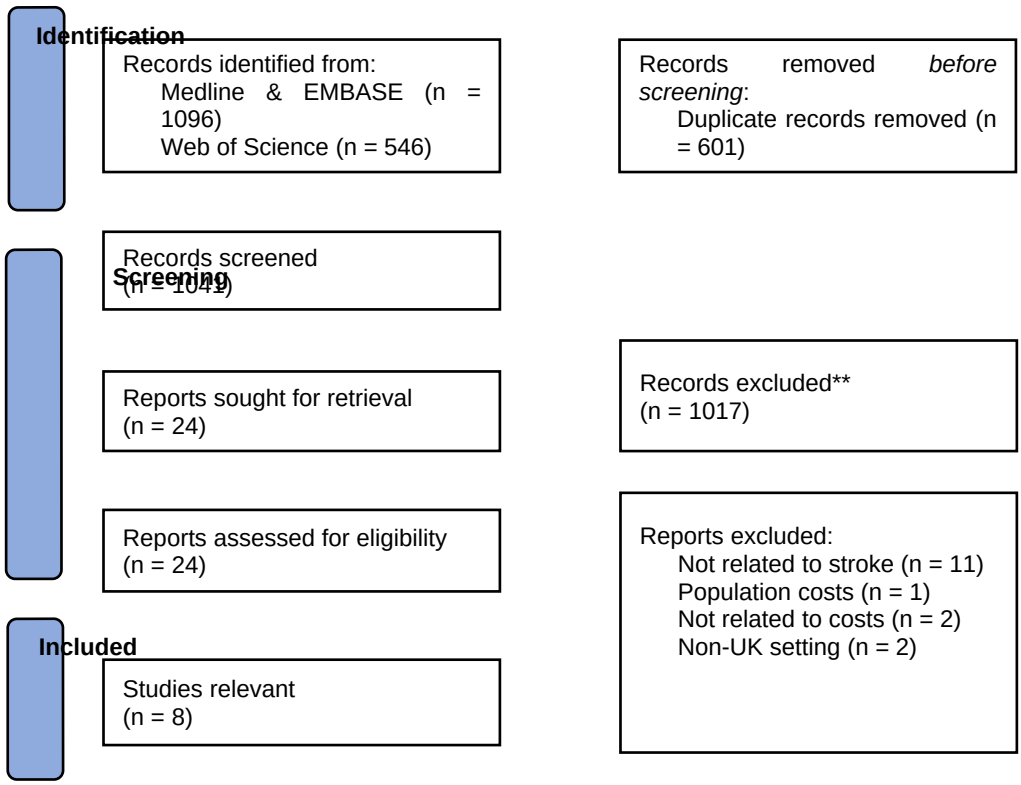
Publication Year	Author	Article type	Time frame
2016	Walker et al[207]	Full article	Lifetime
2016	Asaria et al[137]	Full article	Lifetime



Results for stroke

The search strategy for stroke costs identified 1642 records, reducing to 1041 records after de-duplication. Titles were screened for relevance to costs and CHD leaving 24 records for retrieval. Articles for these 24 records were sought and assessed for eligibility, of which 8 were found to be eligible. Only 2 of the studies looked at the lifetime costs. A PRISMA 2020 flow diagram of the identification process and the characteristics of the 8 studies is given in below as well as references for the studies. The more recent study by Patel et al (2020) builds on the discrete-simulation model informed by routine registry and audit data developed in Xu et al (2018), therefore, cost estimates from the former are used in our model.

Publication Year	Author	Article type	Time frame
2021	Bakhai et al[208]	Full article	1 year post-index
2020	Patel et al[138]	Full article	Lifetime
2018	Xu et al[209]	Full article	Lifetime
2015	Ali et al[210]	Full article	Period of acute care
2014	Yiin et al[211]	Full article	1 year
2012	Burton et al[212]	Full article	1 year
2012	Luengo-Fernandez et al[213]	Full article	5 years
2011	Gillespie et al[214]	Full article	Length of hospital care



Appendix C: Additional material for Chapter 5

Appendix C table 1. Studies identified in the NIHR ODP

A list of interventional clinical trials in lymphoma recorded in the NIHR ODP, with summary information extracted from related literature. A more comprehensive table can be found as an excel spreadsheet in the supporting information of the publication (open access).[194] In the spreadsheet, links are provided to the study publications, and the calculations to derived mean age and sex proportions are shown.

Clinical trial identifier	Short name	Start year	Phase	Line	Results status	Age	Total No.	Sub No.	Total Female	Mean age	SD
Diffuse large B-cell lymphoma											
NCT04546620	REMoDL-A	2021	II	1L	Open, With Recruitment	16 Years +					
NCT03422523	ARGO	2018	II	2L	Terminated	16 Years +					
NCT03571308	ACCEPT	2017	I/II	1L	To early	16 Years +					
NCT02752204	Torch	2015	II	2L	Full study	18 Years +	36		21	62.75	11.59
NCT01679119	INCA	2013	II	1L	Conference abstract	18 Years +	123			76.25	5.64
NCT02060656	LEGEND	2013	II	2L	Full study	18 Years +	40	21	13	53	14.29
								19		54	15.17
NCT01324596	REMoDL B	2011	III	1L	Full study	18 Years +	1077			59	10.16
NCT00788606	R-CHOP-B	2008	II	1L	Terminated	18 Years +					
NCT00974792	R-CODOX-M/IVAC	2008	II	1L	Full study	18 Years +	111		45	45.75	9.27
NCT00971763	RGCVP	2007	II	1L	Full study	18 Years +	62		21	73.75	8.17
NCT00137995	CORAL	2006	III	2L	Full study	18-65 Years	396	202	153	48	8.4
								194		48	8.44
ISCRTN 16017947	R-CHOP 14 vs 21	2005	III	1L	Full study	18 Years +	1080	540	498	53.75	11.34
								540		53	10.83
	LY T	2002	II	2L	Unable to locate						
NCT00039351	EORTC 20992	2002	II	1L	Full study	70 Years +	32		10	79.75	5.32
CNS lymphoma (DLBCL Histology)											
NCT04443829	CAROUSEL	2021	I	2L	Open, With Recruitment	16 Years +					
NCT02329080	IELSG 42 - Marietta	2016	II	2L	Full paper	18–70 Years	75		37	55.13	10.95
ISRCTN 12857473	TIER	2015	N/A	2L	Full paper	16 Years +	36		14	57.75	10.64
NCT01011920	IELSG32	2012	II	1L	Full paper	18–65 Years	219	75	83	57.33	10.58
								69		57.66	7.57
								75		57.66	7.56
CRUK/08/010	PCNSL	2008	I	1L	Full paper	18 Years +	4		2		
Hodgkin lymphoma											
NCT03617666	AVENuE	2019	II	1L	In follow-up	18–60 Years					
NCT03337919	ANIMATE	2018	II	2L	In follow-up	16 Years +					
NCT02567851	BREVITY:	2014	II	1L	Full study	16 Years +	35		13	77	7.73
	ReACH	2010	II	2L	Unable to locate						
NCT00908180	PAIRed Escalated	2010	II	2L	Full study	16-65 Years	31			34.75	11.44
Unable to locate	ABVD	2009	I	1L	Full study	18–60 Years	24		12	36.75	10.02
NCT00678327	RATHL	2008	III	1L	Full study	18 Years +	1203		547	40.75	9.3

NCT00666484	18-30	2008	II	1L	Full study	18–30 Years	47		22	23	4.59
Unable to locate	SHIELD Study	2004	II	1L	Full study	60 Years +	175	103	85	72.75	4.98
								35		66.25	3.09
								19		74.25	6.77
								18		75.75	7.41
NCT00943423	RAPID	2003	III	1L	Full study	16-75 Years	565	209	259	39.5	10.55
								211		39.75	10.72
								145		41.25	10.85
NCT00049595	Escalated BEACOPP (EORTC 20012)	2002	III	1L	Full study	16 to 60 years	547		136	38.48	8.41
ISRCTN 97144519	LY09	1998	III	1L	Full study	16 Years +	789	394	330	38.5	13.23
								395		39.13	14.75
Follicular lymphoma											
EudraCT 2016-004010-10	PETReA	2018	III	2L	In follow-up	18 Years +					
EudraCT 2011-000097-56	ReBeL Phase II	2016	II	2L	Phase 1 results	18 Years +	15		9	57.33	11.45
NCT00637832	PACIFICO	2009	III	2L	In follow-up	18 Years +					
NCT00637832	SCHRIFT	2008	II	2L	Full study	18 Years +	52		23	60.5	12.4
NCT00140582	PRIMA	2006	III	Other	Full study	18 Years +	1193		571	55.25	9.92
NCT00310167	FoRT	2006	III	Other	Full study	18 Years +	614		304	66.33	11.15
NCT00112931	Watch and Wait	2004	III	1L	Full study	18 Years +	463	187	251	57.5	9.95
								84		59.75	10.88
								192		58.5	11.02
ISRCTN65655917	EORTC 20981	2002	III	2L	Full study	18 Years +	465	231	238	53.75	9.17
								234		53.5	9.69
Unable to locate	BNLI MCD vs FMD	2000	III	1L	Unable to locate						
NCT00005589	EBMT-LYM1	1999	III	2L	Full study	18 Years +	203	103	87	51.25	6.97
								100		50	8.8
Mantle cell lymphoma											
ISRCTN11038174	ENRICH	2015	II/III	1L	In follow-up	60 years and over					
ISRCTN34386131	PICLLe	2011	I/II	2L	Full study	18 Years +	15		2	67.47	7.8
Unable to locate	Ofatumumab Study	2011	II	2L	Unable to locate						
CRUK/08/020	MiniAllo	2009	II	1L	Conference abstract	18 Years +	25		3	52.75	9.07
NCT00513955	Bortezomib Study	2007	II	2L	Full study	18 Years +	46	23	10	68.75	8.55
								23		64.75	6.48
NCT00641095	Mantle Cell P3	2006	III	1L	Full study	18 Years +	370	184	87	63.5	8.87
								186		64	9.59
NCT00053092	NCRI Mantle Cell Lymphoma Trial	2002	II	1L	Full study	18 Years +	156	78	41	60.5	8.51
								78		62.75	10.79
Peripheral T-cell lymphoma											
NCT03593018	ORACLE	2020	III	2L	In follow-up	18 Years +					
NCT03046953	AVAIL-T	2017	II	2L	Conference abstract	16 Years +	34		6	62.03	11.45
NCT03141203	RomiCar	2015	I/II	2L	Conference abstract	16 Years +	77		24	57	12.48
NCT01719835	CHEMO-T	2012	II	1L	Full study	18 Years +	87	43	25	62.33	11.5
								44		60.33	15.33
NCT00958854	AITL	2009	II	1L	Full study	18 Years +	15		5	69.75	11.21
CRUKE/04/016	CHOP-Campath	2007	I	1L	Full study	18 Years +	18			56	9.33
Waldenström's macroglobulinaemia											
NCT04061512	RAINBO	2020	II/	1L	Open, With	18 Years +					

NCT03630042	W PembroW M	2019	III II	2L	Recruitment Conference Abstract	18 Years +	17		3	66.75	11.41
NCT01592981	R2W:	2013	N/ A	1L	Full paper	18 Years +	60		16	66	9.51
NCT00608374	Waldenstr om's study	2001	III	1L	Full paper	18 Years +	414	207 207	137	67.68 67.35	2.79 2.26
Cutaneous T-cell lymphoma											
NCT03385226	PORT	2019	II	2L	Open, With Recruitment	18 Years +					
NCT01098656	EORTC 21081	2011	III	2L	Full paper	18 Years +	21		8	63.3	13.07
NCT00660231	GemBex	2008	II	2L	Full paper	18 Years +	36		11	62.75	10.64
Burkitt lymphoma											
EudraCT Number: 2013-004394-27	HOVON 127 BL	2020	III	1L	Did not recruit in UK	18–75 Years					
NCT00040690	LY10	2002	II	1L	Full paper	16 Years +	58		12	41.75	12.83
Primary mediastinal large B-cell lymphoma											
NCT01599559	IELSG 37	2013	III	1L	Conference abstract	18 Years +	545		336		
NCT00944567	IELSG 26	2009	III	1L	Full paper	18 Years +	125		77	33.66	10.5
Marginal zone lymphoma											
NCT00210353	IELSG19 /MALT Trial	2003	III	1L	Full paper	18 Years +	401		204	57.25	9.03
Other											
NCT03307746	RiVa	2017	II	2L	Conference Abstract	16 Years +	27			69.5	9.52
NCT02933320		2016	I/II	2L	Trial terminated early	18 Years +	14		6		
NCT01805375		2013	I	2L	Unable to locate	18 Years +					
Unable to locate	Intestinal t-cell trial (ITCL)	2008	II	1L	Unable to locate						
NCT00003215	MISTRA L	2002	III	1L	Full study	16 to 60 years	128	59 70	75	42.75 44.25	9.32 9.07
NCT00005590	SIGNIFIC ANT	1999	III	Ot her	Full study	16 Years +	1565	781 784	873	53.33 54.33	15.6 16.34
NCT00005867	NHL Good Risk	1998	III	1L	Unable to locate	18 to 59 Years					
	BNLI Radiation Dose	1997	III	Ot her	Full study	18 Years +	1001		473	59.5	11.46
ISRCTN98741793	BNLI 60+	1996	III	1L	Full study	60 Years +	784		373	72.25	4.49
	LY02	1993	III	1L	Full study	16 and 65 Years	457	234 223	180	44.25 44	8.79 8.66

Appendix C table 2. Combined mean age and standard deviation for alternative trial exclusions

Disease	All trials	First line only	No age restriction only	Phase II only
		Mean age (SD)		
Diffuse large B-cell lymphoma	56.2 (12.3)	57.5 (12.3)	57.2 (12.1)	64.3 (16.1)
DLBCL + CNS lymphoma	56.3 (12.0)	57.5 (12.0)	57.2 (12.1)	61.2 (16.1)
Hodgkin lymphoma	41.7 (13.4)	41.5 (13.4)	40.4 (11.5)	60.6 (21.5)
Follicular lymphoma	57.5 (11.2)	58.3 (10.6)	57.5 (11.2)	59.8 (12.2)
Mantle cell lymphoma	63.1 (9.6)	62.7 (9.6)	63.1 (9.6)	62.0 (10.0)

Peripheral T-cell lymphoma	60.1 (12.8)	61.6 (13.1)	60.0 (12.8)	60.5 (12.2)
Waldenström's macroglobulinaemia	67.3 (4.6)	67.3 (4.1)	67.3 (4.6)	66.8 (11.4)
Cutaneous T-cell lymphoma	63.0 (11.5)	NA	63.0 (11.5)	62.8 (10.6)
Burkitt lymphoma	41.8 (12.8)	41.8 (12.8)	NA	41.8 (12.8)
Primary mediastinal large B-cell lymphoma	33.7 (10.5)	33.7 (10.5)	NA	33.7 (10.5)
Marginal zone lymphoma	57.2 (9.0)	57.3 (9.0)	NA	
Other	57.6 (15.1)	57.6 (15.1)	56.2 (14.7)	69.5 (9.5)
All	54.0 (14.8)	-	-	-

Appendix C table 3. Coefficients, standard error, and P-values from the OLS regression of LSOA characteristics on the distance to their nearest research active NHS Trust under definition 2): an NHS Trust which participated in any trial.

LSOA characteristics	Coefficient	Standard error	P value
Mean age	0.47207	0.01997	<0.001
Percentage male	0.33268	0.03140	<0.001
Percentage white British	0.11317	0.00404	<0.001
IMD decile	-0.29459	0.02469	<0.001
Rural status	7.73630	0.18428	<0.001
Coastal/border status	2.79718	0.20105	<0.001
Constant	-23.95907	1.81294	<0.001

Appendix C table 4. Coefficients, standard error, and P-values from the OLS regression of LSOA characteristics on the distance to their nearest research active NHS Trust under definition 3): an NHS Trust which participated in any DLBCL trial.

LSOA characteristics	Coefficient	Standard error	P value
Mean age	0.442271	0.022177	<0.001
Percentage male	0.326540	0.034876	<0.001
Percentage white British	0.133320	0.004487	<0.001
IMD decile	-0.277210	0.027421	<0.001
Rural status	8.311566	0.204701	<0.001
Coastal/border status	2.009902	0.223326	<0.001
Constant	-22.090921	2.013801	<0.001

Appendix C table 5. Coefficients, standard error, and P-values from the OLS regression of LSOA characteristics on the distance to their nearest research active NHS Trust under definition 4): an NHS Trust which participated in any HL trial.

LSOA characteristics	Coefficient	Standard error	P value
Mean age	0.182938	0.041025	<0.001
Percentage male	0.903412	0.064516	<0.001
Percentage white British	0.352950	0.008301	<0.001
IMD decile	0.073756	0.073756	0.146
Rural status	10.860964	0.378672	<0.001
Coastal/border status	17.677702	0.413127	<0.001
Constant	-41.716139	3.725295	<0.001

Appendix C table 6. Coefficients, standard error, and P-values from the OLS regression of LSOA characteristics on the distance to their nearest research active NHS Trust under definition 5): an NHS Trust which participated in any FL trial.

LSOA characteristics	Coefficient	Standard error	P value
Mean age	0.59612	0.04171	<0.001
Percentage male	0.92193	0.06560	<0.001
Percentage white British	0.20641	0.00844	<0.001
IMD decile	-0.52459	0.05158	<0.001
Rural status	9.12268	0.38503	<0.001
Coastal/border status	0.78673	0.42006	<0.001
Constant	-45.84592	3.78783	0.006