Benefits and Risks of Radiotherapy for Early Breast Cancer



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For those affected by breast cancer.

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0.2 Abstract

0.2.1 Benefits

A recent EBCTCG meta-analysis demonstrated that regional lymph node radiotherapy for early breast cancer given within eight trials, starting 1989-2008, improved breast cancer survival. To place this evidence in the context of current radiotherapy protocols, radiotherapy regimens used in these trials were systematically described, reconstructed, and used to estimate doses received by modern definitions of internal mammary lymph nodes (IMNs). Estimated average ESTRO IMN CTV V80% was 77%. Current IMN radiotherapy regimens likely achieve better IMN coverage and provide greater relative breast cancer survival benefits than those previously reported.

0.2.2 Risks

0.2.2.1 Radiation-induced heart disease

Typical heart doses from modern UK IMN radiotherapy were estimated using meta-analysis of breast cancer regimens published in the UK during 2015-2023. Average mean heart doses from modern IMN regimens were ∼3Gy and ∼1Gy from left and right-sided regimens respectively, which may reflect the recent use of heart-sparing techniques. For a typical 50-year-old receiving modern UK IMN radiotherapy the corresponding estimated 30-year mortality risk for heart disease is ≤1%.

0.2.2.2 Radiation-induced lung cancer

The average mean whole lung dose from UK IMN radiotherapy published 2015-2023 was ∼7Gy, corresponding to 30-year absolute lung cancer mortality risks of ∼6% for long-term continuing smokers and ≤ 1% for non-smokers.

To develop an improved dose-response relationship for radiation-induced lung cancer lung lobe dose distributions were estimated from regimens used in the Netherlands during 1970-2010 as long term clinical outcomes are available for a cohort of women who received them.

To guide the selection of lung-sparing IMN radiotherapy, temporal trends in mean whole lung doses from IMN radiotherapy during 1970-2025 were synthesised. Exploratory analyses suggest there have been minimal reductions in mean whole lung doses from IMN radiotherapy over the past 55 years, and that proton beam therapy (PBT) may be lung-sparing.

To determine the clinical risks of PBT for early breast cancer, systematic review of worldwide clinical outcomes from studies of adjuvant PBT for early breast cancer published 2000-2022 was conducted. Outcomes from 1452 patients were summarised. After whole breast/chest wall ± lymph nodes scanning PBT, the most prevalent severe adverse outcome was dermatitis (∼6%). Other severe outcomes included infection, pain and pneumonitis (each ≤1%).

0.2.3 Conclusions

Overall, it is likely that the relative benefits of radiotherapy for early breast cancer have improved over recent decades. Current IMN radiotherapy regimens likely achieve better IMN coverage and provide greater relative breast cancer survival benefits than those previously reported. The relative and absolute risks of radiation-induced heart disease have likely fallen over recent decades. Reductions in the relative risks of radiation-induced lung cancer may have been more modest, but the absolute risks are low for the majority of women. For some long-term continuing smokers the absolute 30-year mortality risks of radiation-induced lung cancer may outweigh the benefits of IMN irradiation. For these women, primary risk-reducing strategies such as smoking cessation if applicable, omission of radiotherapy, and/or the use of advanced lung-sparing radiotherapy techniques, such as PBT, may be indicated.

The information in this thesis may be used to support patient consent, smoking-cessation initiatives, the development and selection of radiotherapy techniques that improve IMN coverage and lung-sparing, such as PBT, the development of an improved dose-response relationship for radiation-induced lung cancer, and clinical guidelines on dose objectives and constraints.

Abbreviations: EBCTCG=Early Breast Cancer Trialists' Collaborative Group, ESTRO= European Society of Therapeutic Radiology and Oncology, CTV=clinical target volume.

0.3 Abbreviations

Ax Axillary lymph nodes

Br Breast

CW Chest wall

cDVH Cumulative dose volume histogram

CI Confidence interval

CRT Conformal radiotherapy

CT Computed tomography

CTCAE Common Terminology Criteria for Adverse Events

CTV Clinical target volume

2D two-dimensional

3D three-dimensional

4D four-dimensional

DBCG Danish Breast Cancer Group

DIBH Deep Inspiration Breath Hold

DNA Deoxyribonucleic acid

EBCTCG Early Breast Cancer Trialists' Collaborative Group

EORTC European Organisation For Research And Treatment Of Cancer

ERR Excess rate ratio

ESTRO European Society of Therapeutic Radiology and Oncology

Gy Gray

HER Human epidermal growth factor receptor

IAEA International Atomic Energy Agency

ID Identity

ISOG Italian Senology Group

KROG Korean Radiation Oncology Group

LLL Left lower lobe

LUL Left upper lobe

IMN Internal mammary lymph nodes

IMPT Intensity modulated proton therapy

IMRT Intensity modulated radiotherapy

IQR Interquartile range

NICE National Institute for Health and Care Excellence

OAR Organs at risk

PBT Proton beam therapy

PTV Planning target volume

RADCOMP Radiotherapy Comparative Effectiveness

RBE Relative Biological Effectiveness

RLL Right lower lobe

RML Right middle lobe

RR Rate ratio

RTOG Radiation Therapy Oncology Group

RUL Right upper lobe

SE Standard error

SF Supraclavicular fossa lymph nodes

UK United Kingdom

VMAT Volumetric Modulated Arc Therapy

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Chapter 1

Introduction

Holt F, Ntentas G, Duane F, Dodwell D, Taylor C.

Co-authored publication relating to Chapter 1:
Kerr, A, Dodwell D, McGale P, **Holt F**, Duane F, Mannu G, Darby SC, Taylor C.
Adjuvant and neoadjuvant breast cancer treatments: A systematic review of their effects on mortality.
Cancer Treat Rev 2022;105,102375.

1.1 Choosing treatments for breast cancer that improve clinical outcomes

Every year more than 55,000 women in the UK and more than 2 million worldwide are diagnosed with breast cancer.[1, 2] For each of these individuals, decisions must be made on whether and how to treat their cancer. Oncologists must weigh information on the potential benefits and risks of available treatment options to determine which may provide the greatest overall benefits, and then have a meaningful dialogue with the individual about their preferences.[3]

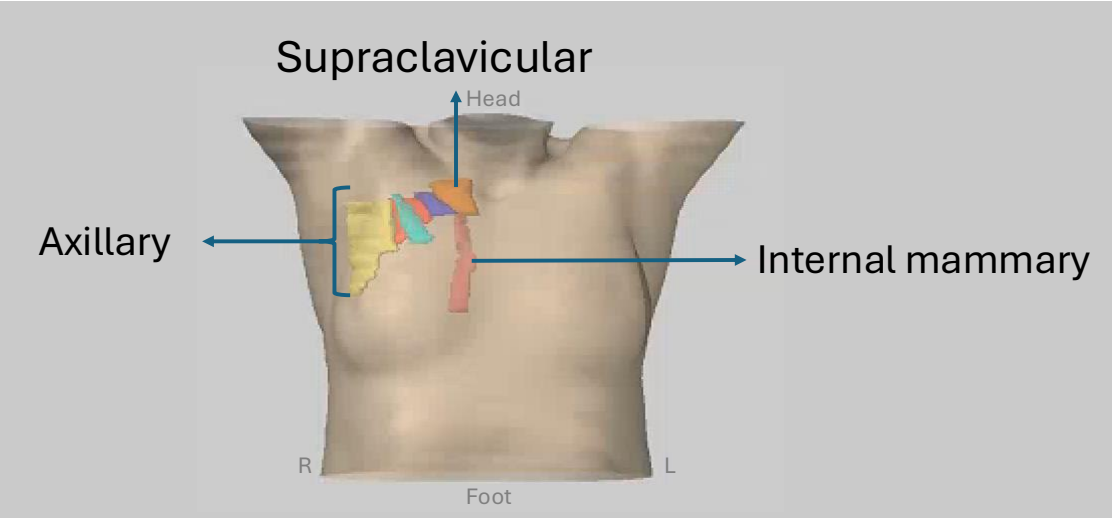


Figure 1.1: Breast cancer may metastasise via the regional lymph nodes.
The lymph node regions for the right breast, as defined by the European Society for Radiotherapy and Oncology (ESTRO) contouring guidelines, are illustrated on a 3D reconstruction of a thoracic CT scan shown in the coronal view. The axillary lymph nodes comprise of levels 1, 2 and 3, shown in yellow, red and purple respectively. The interpectoral nodes are shown in turquoise.
Abbreviations: CT=computed tomography, 3d=three-dimensional, L=left, R=right.

When an individual is diagnosed with breast cancer, their prognosis depends on their life expectancy prior to diagnosis, the biology of their particular breast cancer, the extent to which their cancer has already grown and spread, and their

risk of death from causes other than breast cancer. Whilst the mechanisms of metastasis in breast cancer are complex and an area of ongoing research, some breast cancers spread via the lymphatics to the regional lymph nodes: the axillary lymph nodes under the arm, the supraclavicular fossa nodes in the lower neck, and the internal mammary lymph nodes (IMNs) behind the sternum. (Figure 1.1) For those with advanced breast cancer—cancer that has metastasised beyond the breast and/or regional lymph nodes—systemic anti-cancer treatments may be offered with palliative intent. For those with early breast cancers—those in which all detected invasive cancer cells are within the breast or regional lymph nodes—a combination of local and systemic treatments is usually offered with curative intent.

Most women diagnosed with early breast cancer receive primary surgery. Other treatments, such as radiotherapy, chemotherapy, anti-HER2 therapy and endocrine therapy, may be given before (neoadjuvant) or after (adjuvant) surgery to further reduce the risk of breast cancer recurrence and mortality.[4] These neoadjuvant and adjuvant treatments for early breast cancer are selected for their predicted likelihood of improving outcomes. At a population level, the prognosis for women diagnosed with early breast cancer has improved over recent decades increasing the numbers of long-term survivors.[5] Therefore, rare long-term morbidity and mortality risks of treatment options are important to consider as well as the more common short-term adverse effects.

PREDICT Breast, is a widely used prediction model that supports some of these clinical decisions by providing quantitative estimates of the survival benefits of some treatment options for individuals according to certain characteristics.[6] However, the majority of published prediction models are not suitable for clinical

use.[7] Currently, there are no decision aids for radiotherapy for early breast cancer recommended for clinical use. More up-to-date information is needed to estimate individual benefits and risks of different types of radiotherapy for early breast cancer.

1.2 Radiotherapy for early breast cancer

Over the past decade, more than 60% of women diagnosed with early breast cancer in England received adjuvant radiotherapy.[8] Adjuvant radiotherapy is administered to treat any remaining microscopic breast cancer foci after surgery has removed all accessible and visible cancer.

The relative survival benefits and risks of radiotherapy for early breast cancer are related to the distribution of radiation doses received by the volumes of clinical targets and the organs at risk (OARs). (Figure 1.2)

In current clinical practice, standard radiotherapy refers to the use of photons (high energy x-rays), with or without electrons, to destroy cancer cells by damaging their DNA. In order to deliver radiotherapy accurately to the parts of the patient most likely harbouring undetected cancer cells, it is carefully planned on a CT planning scan which is taken with the patient in a reproducible position—most commonly with the patient lying supine on an elevated treatment couch with their arms abducted by more than 90 degrees. First, radiotherapy planning software is used to record the delineation—contour—of the clinical target volumes (partial breast/whole breast/chest wall, ± regional lymph nodes) and OARs (including the heart and lungs) on the CT planning scan according to standard definitions within contouring guidelines.[9–13] Second, radiotherapy treatment planning software is

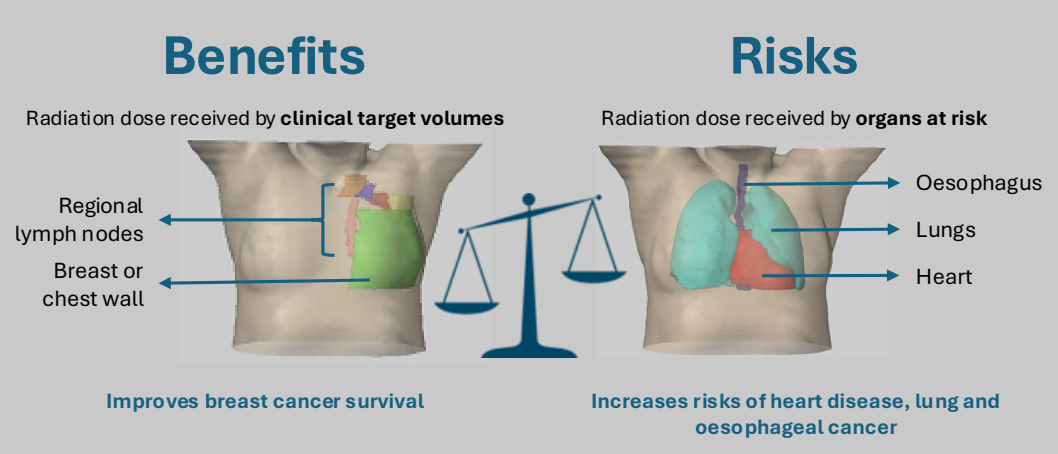


Figure 1.2: Relative survival benefits and risks from radiotherapy for early breast cancer relate to radiation dose distributions received by clinical target volumes and organs at risk.
Volumes are shown on a 3D reconstruction of a thoracic CT scan in the coronal view.
Abbreviations: CT=computed tomography, 3D=three dimensional.

used to select the optimum number and arrangement of radiation beams needed to shape the dose distribution to meet clinical target dose objectives, and dose constraints for OARs. Each individual radiotherapy regimen is later delivered following the personalised radiotherapy plan, which includes information on the clinical targets, the total radiation dose and fractionation to be delivered, as well as the beam types, energies and arrangements.

1.2.1 Advances in radiotherapy for early breast cancer

1.2.1.1 Clinical targets

For many decades, clinical guidelines for treating invasive breast cancer have recommended breast radiotherapy after breast-conserving surgery for most women.[4] In more recent years, clinical guidelines have included options for limiting radio-

therapy exposure to skin and soft tissue for women expected to have a very low risk of breast cancer recurrence. Omission of radiotherapy, or certain partial breast radiotherapy techniques, may be considered for eligible women.[14–16] Though the long-term effects on breast cancer outcomes remain uncertain, the aim of partial breast irradiation is to focus radiation dose around the site of surgery where recurrences are most likely to occur and in doing so limit exposure of more distant normal breast tissue to radiation.[4, 16]

For women considered at high risk of invasive breast cancer recurrence, clinical guidelines have long recommended chest wall radiotherapy after mastectomy. More recently, new post mastectomy radiotherapy clinical target volumes have been defined to account for different types of surgical breast reconstruction.[11] Regardless of the type of surgery to the breast, women at high risk of invasive breast cancer recurrence may also be recommended regional lymph node radiotherapy. Extending clinical targets to include these lymph nodes is recognised to come at the expense of increasing radiation exposure to normal tissues and organs including the heart, lungs and oesophagus.[17–19] The supraclavicular and IMNs lie in close proximity to the lungs and oesophagus, and there is a very close anatomical relationship between the IMNs and the heart. (Figure 1.3)

1.2.1.2 Radiotherapy doses and fractionation

In general, conventionally fractionated radiotherapy refers to the use of 1.8-2Gy fraction sizes. A typical conventionally fractionated regimen for early breast cancer uses a total dose of 50-50.4Gy given in 1.8-2Gy fractions over 5 weeks. However, for many years various hypofractionated radiotherapy regimens have also been used for breast cancer, meaning that biologically equivalent regimens with total doses

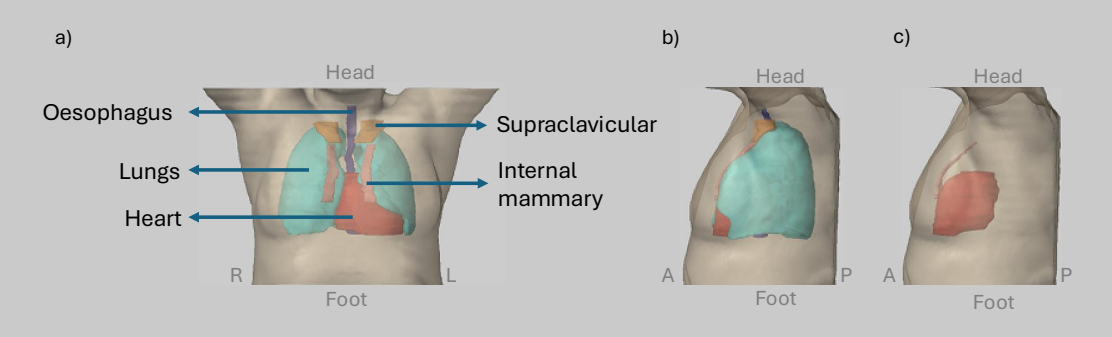


Figure 1.3: Anatomical relationships between the supraclavicular and internal mammary lymph nodes clinical target volumes and organs at risk.
Volumes are illustrated on a 3D reconstruction of a thoracic CT scan in the coronal view (a) and the sagittal view (b and c).
Abbreviations: A=anterior, L=left, P=posterior, R=right.

given in fewer but larger fractions over shorter periods of time have been used. As well as being more convenient and cheaper than conventionally fractionated radiotherapy, trials have reported hypofractionated regimens result in similar or reduced skin adverse effects, and similar oncological outcomes.[20]

In the UK, moderately hypofractionated radiotherapy—fraction sizes of 2.65-3.3Gy for 13-16 fractions over 3-5 weeks—was adopted as the standard of care after results from the START randomised controlled trials conducted during 1998 to 2002 demonstrated it was at least as effective for local breast cancer control as conventionally fractionated regimens, with similar late normal tissue effects.[21] This remained the case until 2020 when the 5-year results of the FAST-Forward trial reported that ultrafractionated radiotherapy—fraction sizes of 5.2Gy over one week—to the conserved breast or unreconstructed post mastectomy chest wall led to non-inferior local breast cancer control and similar acute normal tissue effects compared with moderately fractionated radiotherapy.[22, 23] Although the highly anticipated results of the FAST-Forward nodal sub-study may inform whether

ultrafractioned radiotherapy is also adopted when irradiating the regional lymph nodes, the primary endpoint of this randomised controlled trial is to assess non-inferiority in patient-reported arm/hand swelling compared with hypofractionated radiotherapy. The optimum effective dose of radiotherapy to the regional lymph nodes remains unknown.

1.2.1.3 Beam types

Photons ± electrons are the standard beam types used in radiotherapy for breast cancer. Proton beam therapy (PBT) uses high energy positively charged particles as an alternative to standard photons. In standard photon radiotherapy the beam penetrates the patient delivering dose to the target before continuing to exit the patient in a straight line, through normal healthy tissue. Thanks to their physical properties, proton beams enter the patient, deposit the majority of the dose at the site of the target and then stop, sparing distal normal healthy tissues and organs.

Dosimetry studies have demonstrated that PBT can lower radiation exposure of the heart, lungs and oesophagus doses compared with photon radiotherapy without compromising coverage of the clinical target, especially for those receiving regional lymph node radiotherapy.[24–30] However, it is not currently available within the NHS outside of a clinical trial setting as **there is a lack of evidence to confirm that the dosimetric advantages translate into superior clinical outcomes compared with those achievable with the latest photon planning methods and techniques**.[31, 32] There are several sources of uncertainties around how planned PBT dose distributions on CT scans relate to PBT dose distributions received by a patient, and also around predictions of the biological effects of PBT.[33, 34]

Planning PBT for an individual patient requires estimates of the range of proton beams (the depth at which proton beams deposit dose) as they traverse tissues of particular densities. These dose calculations are usually mapped onto patients' CT planning scan data as this provides estimates of tissue densities. Inaccuracies arising from both CT imaging data and dose calculations contribute to range uncertainty. This range uncertainty is also affected by any inaccuracies that arise from delivery of the proton beam plan and patient positioning.[35] Advances in planning techniques such as robust optimisation of intensity modulated proton therapy (IMPT) may help to minimise the clinical effect of range uncertainties.[36, 37]

PBT is currently planned and delivered assuming that protons are 10% more biologically effective than photons, but the relative biological effectiveness (RBE, ratio of dose from photon radiotherapy to PBT to produce the same clinical effect) has been shown to vary according to dose, PBT properties, target tissue type, and clinical endpoint.[34, 38, 39] There are concerns that the increased biological effectiveness at the end of the physical range of the proton beam in combination with physical range uncertainty may result in very high doses of radiation being deposited in critical organs compromising the safety of PBT. Indeed incorporation of variations in RBE into PBT dose calculations may significantly change how we interpret predictions of clinical outcomes made using photon-based dose-response relationships.[40–43]

Quantitative synthesis of all available knowledge of clinical outcomes after the most advanced PBT techniques is therefore needed to improve evaluation of its benefits and risks to support patient selection, informed consent, and selection of radiotherapy technology and techniques.

1.2.1.4 Radiotherapy planning methods and techniques

Radiotherapy planning methods for breast cancer have advanced considerably over recent decades following the replacement of 2D planning with 3D planning using CT scans. The now commonplace intensity modulated radiotherapy (IMRT) planning methods use beams of different intensities, as well as different shapes, to improve upon the target dose homogeneity of older 3D conformal radiotherapy (3DCRT) and reduce short-term skin adverse effects.[44–46] For forward-planned IMRT, so called field-in-field planning, beam intensities and shapes are manually selected to achieve a dose distribution. For inverse-planned IMRT, the dose distribution is achieved by manually selecting the dose objectives and constraints and then allowing a computer algorithm to optimise the beams.

Modern radiotherapy delivery techniques have also improved dose distributions received by clinical targets. Traditionally tangential fields covering the breast or chest wall were delivered at fixed gantry angles matched to direct anterior fields covering the regional lymph nodes. Now rotational IMRT techniques are available such as volumetric modulated arc therapy (VMAT), in which the gantry continuously rotates during radiation delivery. However, whilst VMAT techniques for breast cancer can improve target dose coverage, they can also increase the volumes of normal tissues and organs receiving low radiation doses.[47] The long-term clinical impact of these dose distributions is uncertain.[48–50] In UK clinical practice, VMAT techniques are usually only incorporated into breast radiotherapy plans to better spare the heart and lungs in particularly challenging cases. For most women, breath-hold techniques are recommended for heart and lung sparing during left breast cancer radiotherapy and/or radiotherapy inclusive of the IMNs.[51–53]

For PBT, passive scattering techniques, which spread a narrow proton beam so that it is wide enough to cover the clinical target, have been replaced with uniform scanning or pencil beam scanning techniques, which use magnetic fields to steer narrow proton beams across the clinic target. Pencil beam scanning has also facilitated development of IMRT planning methods for PBT, called IMPT.

1.2.2 Benefits

1.2.2.1 Relative survival and quality of life benefits

The benefits of radiotherapy for early breast cancer are improvements in breast cancer outcomes——reductions in breast cancer recurrence and death from breast cancer——and have been estimated from meta-analyses of randomised controlled trials. They vary according to the extent of the breast cancer, the type of breast cancer surgery, and the clinical targets irradiated.[4]

Meta-analysis of breast cancer outcomes from 10801 women showed that breast radiotherapy after breast-conserving surgery halves the rate of any breast cancer recurrence (RR=0.52, 95% CI 0.48-0.56) and reduces the breast cancer death rate by about a sixth (RR=0.82, 95% CI 0.75-0.90).[54] Radiotherapy to the chest wall after mastectomy in patients with 1-3 positive lymph nodes reduces the rate of breast cancer recurrence by about a third (RR=0.68, 95% CI 0.57–0.82), and breast cancer death by a fifth (RR=0.80, 95% CI 0.67-0.95), based on data from 1314 women.[55] For some women, modern radiotherapy to the regional lymph nodes further reduces rates of breast cancer recurrence (RR=0.88, 95% CI 0.81–0.95) and death (RR=0.87, 95% CI 0.80–0.94) by about an eighth, based on data from 12167 women.[56]

1.2.2.2 Absolute benefits

The studies estimating these relative benefits also expressed them as absolute benefits using the rates of breast cancer recurrences and deaths within the trials.[54–56] Up-to-date estimates of the absolute benefits of radiotherapy for early breast cancer can be made by applying the relative benefits to contemporary population rates of breast cancer recurrences and deaths. However, this assumes that radiation dose distributions to clinical targets, and therefore the relative benefits of radiotherapy for early breast cancer, have not changed with advances in radiotherapy. To incorporate advances in radiation dose distributions into estimates of absolute benefits, a radiation dose-response relationship for breast cancer survival is needed.

1.2.2.3 Radiation dose-response relationship for breast cancer survival

Theoretically the relative survival benefits of radiotherapy for early breast cancer relate to the quantity of the clinical target volume receiving sufficient radiation dose to kill cancer cells. Though this has not been demonstrated, relationships between radiation dose and local breast cancer control have been described.

Radiation dose and local control

Although *ablative* radiotherapy targeted at unresected breast cancer is not currently part of routine UK practice, early clinical studies of this are interesting because they illustrate how increasing radiation doses improved the probability of local breast cancer control; and that to achieve the same probability of control, higher radiation doses are needed when ablating unresected breast cancer

compared with giving adjuvant irradiation to undetectable breast cancer. They also demonstrated that there is a trade-off between achieving a high probability of breast cancer control and causing adverse clinical effects.[57]

Radiation dose and breast cancer survival

In UK clinical practice today, the total prescribed radiation doses and fractionations recommended in national clinical guidelines are determined from randomised controlled trials measuring locoregional breast cancer control and morbidity.[21, 22, 51] However, **there is a lack of information on the radiation doses received by the regional lymph nodes associated with breast cancer survival.** This is partly because few women receiving regional lymph node radiotherapy were included in these trials. Optimum radiation doses required to effectively and safely treat the breast's regional lymph nodes may differ systematically from those required when treating only the whole breast or chest wall. Compared with breast cancer limited to the breast, breast cancer extending to the regional lymph nodes is associated with a poorer prognosis and may differ in terms of biology and radiosensitivity. In contemporary clinical practice, adjuvant radiotherapy to the regional lymph nodes is usually administered to unresected lymph nodes that may contain varying sizes and types of cancer foci, and may or may not have received various systemic anti-cancer treatments. Furthermore, regional lymph node radiotherapy poses greater clinical risks than radiotherapy confined to the whole breast or chest wall because it increases radiation doses received by OARs such as the heart, lungs and oesophagus. More information on how radiation doses relate to breast cancer survival is needed to inform current dose objectives in clinical practice.

1.2.3 Risks

1.2.3.1 Relative mortality risks

A meta-analysis of 75 randomised trials of radiotherapy versus no radiotherapy involving 40781 women showed that the main mortality risks of radiotherapy for breast cancer are heart disease (RR=1.30, 95% CI 1.15–1.46) and lung cancer (RR=1.64, 95% CI 1.22–2.21).[58] These radiation risks vary according to the doses received by the heart and lungs respectively. Doses received by OARs vary between individuals depending upon the patient's unique anatomy, breast cancer laterality, radiotherapy clinical targets, and the radiotherapy techniques used. In general, the mortality risks of radiotherapy for early breast cancer increase with the extent of clinical target volumes irradiated, and are highest for comprehensive nodal irradiation inclusive of the axillary, supraclavicular and IMNs.[17, 18] The risks of death from heart disease are greater for left compared with right breast cancer because of the higher cardiac radiation doses received.

1.2.3.2 Radiation dose-response relationships for radiation-induced heart disease and lung cancer

Mean whole organ doses are currently considered the best predictors of radiation-induced heart disease and lung cancer. For radiation-induced heart disease the published dose–response relationship with the most events in patients with individual dosimetry included 963 cases and 1205 controls, and the rates of major coronary events increased linearly with mean whole heart dose by 7.4% per Gy (95% CI 2.9–14.5).[59]

For radiation-induced lung cancer there are five published dose–response rela-

tionships based on individual patient or trial-level dosimetry. These were combined in a published data meta-analysis and the rate ratio per Gy per mean whole lung dose was 11.0% (95% CI 6.0–19.0).[58]

Since 2016 the UK national standards for postoperative breast cancer radiotherapy have recommended dose constraints for these OARs. For women receiving radiotherapy for left breast cancer not including the IMNs, it is recommended that >90% of patients should receive a mean heart dose of <2Gy. For women receiving radiotherapy including the IMNs, the following dose constraints were recommended: the heart volume receiving at least 17Gy (V17Gy) should be <10%, the ipsilateral lung V17Gy should be <35%.[51]

The clinical effects of various radiation dose distributions received by structures of the heart have been studied, and considerable resources dedicated to reducing exposure of all heart structures to radiation.[60–62] However, **our understanding of the dosimetric determinants of radiation-induced lung cancers remains incomplete and mean whole lung dose may not be the optimal dose metric for predicting the risks.** Development of a dose-response relationship for radiation-induced lung cancer is planned using doses received by anatomical lung lobes rather than the whole lungs. By incorporating information about the spatial distribution of radiation dose across the lungs, this dose-response-relationship may better predict the risks of lung cancer. **More information is also needed to guide the selection of lung-sparing radiotherapy.**

1.2.3.3 Absolute mortality risks

Radiation doses received by the heart and lungs are associated with *relative* clinical risks. However, **up-to-date *absolute* risks are needed to inform patients**

and clinical decision making. It is possible to estimate the typical—population average—absolute mortality risks of radiotherapy for early breast cancer for women with different risk factors using information on mean doses received by the whole heart and lungs, the aforementioned published dose-response relationships, and population baseline rates of heart disease and lung cancer. Up-to-date information on doses received by OARs from modern radiotherapy for early breast cancer are needed.[58, 59]

1.2.3.4 Morbidity risks

Whilst estimates of the mortality risks of radiotherapy for early breast cancer are critical to allow clinicians to weigh them against estimated survival benefits, other adverse clinical effects occur more frequently and may be especially relevant to individuals in clinical scenarios where the mortality risks are estimated and perceived as very low. In the UK, expert consensus opinion on the frequency of early and late adverse effects reported within recent randomised controlled trials of radiotherapy for early breast cancer has been used to develop national breast radiotherapy consent forms.[63] In summary, expected early adverse effects, usually occurring within 90 days of radiotherapy, commonly include fatigue and effects on the skin and soft tissue of the breast or chest wall such as skin reactions, discomfort, oedema.[63] Pneumonitis is considered rare. Expected late effects may include skin changes, breast or chest wall discomfort, breast or chest wall oedema, shoulder stiffness, and arm lymphoedema.[63] Rarely morbidity may result from brachial plexopathy, lung fibrosis, or rib fractures.

1.2.4 How the benefits and risks of radiotherapy for early breast cancer may be changing

Radiotherapy technology and techniques continue to advance, facilitating better coverage of breast cancer clinical targets and better avoidance of OARs for the majority of women. Such improvements in dose distributions are likely to have resulted in greater *relative* benefits of radiotherapy for early breast cancer than previously estimated. However, there have also been substantial improvements in the prognosis of women diagnosed with early breast cancer over recent decades, which means the *absolute* survival benefits of radiotherapy for early breast cancer used in clinic today may be lower than in past trials.[5]

1.2.5 Balancing the benefits and risks

For the majority of women, the survival benefits of modern radiotherapy for early breast cancer likely outweigh the risks.[58] However, for some the risks are higher, such as those with pre-existing risk factors for heart disease and second cancers, particularly smoking.[58] Despite advances in radiation therapy technology and techniques, and national recommendations on dose constraints, doses received by OARs may remain higher than recommended for some patients, especially those with unusual anatomy or who require more extensive radiation including the regional lymph nodes.

This thesis focuses in particular on providing information on the benefits and risks of radiotherapy for early breast for those women eligible for regional lymph node irradiation, for whom the absolute benefits and risks may be finely balanced. Knowledge of the benefits and risks of regional lymph node radiotherapy is needed

to support patient selection for treatment, inform patient consent, and support selection of radiotherapy regimens.

1.3 Research questions

In summary, women with breast cancer and their oncologists require up-to-date quantitative estimates of the benefits and risks of radiotherapy for early breast cancer to inform treatment decisions. As breast cancer survival is improving, and radiotherapy advancing, new estimates are needed. This thesis addresses the following research questions:

Benefits

- To place the latest evidence on clinical outcomes from IMN radiotherapy into the context of current IMN radiotherapy protocols, what radiation doses received by modern IMN CTVs may have been associated with improved breast cancer survival? (Chapter 2)

Risks

- What radiation doses are typically received by OARs from modern UK breast radiotherapy to different clinical targets, and what are the associated absolute mortality risks? (Chapter 3)

- To support development of a novel dose-response relationship for radiation-induced lung cancer, what radiation doses were received by the anatomical lung lobes from radiotherapy regimens for early breast cancer used during 1970-2010? (Chapter 4)

- To guide selection of lung-sparing IMN regimens, how may radiation doses received by the lungs from IMN radiotherapy have varied over the years with

advances in radiotherapy? (Chapter 5)

- PBT achieves better planned dose distributions than standard photon radiotherapy. What are the *clinical* benefits and risks of PBT for early breast cancer? (Chapter 6)

1.4 Thesis Aim and Overview

1.4.1 Aim

The overarching aim of this thesis is to provide up-to-date information on the benefits and risks of radiotherapy for early breast cancer to inform clinical decisions.

1.4.2 Overview

An overview of the structure of this thesis is shown in Figure 1.4.2. Specifically, it advances knowledge of the benefits of radiotherapy for early breast cancer by first providing estimates of **radiation doses received by modern IMN volumes** that are associated with improved breast cancer survival. (Chapter 2)

It then provides up-to-date estimates of **radiation doses received by the heart, lungs, and oesophagus** from modern UK radiotherapy for early breast cancer and demonstrates how these may be combined with published dose-response relationships to estimate the **absolute mortality risks of heart disease and lung cancer**. (Chapter 3)

In support of development of an improved dose-response relationship for radiation-induced lung cancer, radiation doses received by the **anatomical lobes of the**

lungs from different types of radiotherapy for early breast cancer are described. (Chapter 4)

To guide the selection of lung-sparing radiotherapy, temporal trends in mean **whole lung doses** from IMN radiotherapy are explored in relation to advances in radiotherapy. (Chapter 5)

Finally, estimates of the **prevalence of all published clinical outcomes from PBT** for early breast cancer are provided. (Chapter 6)

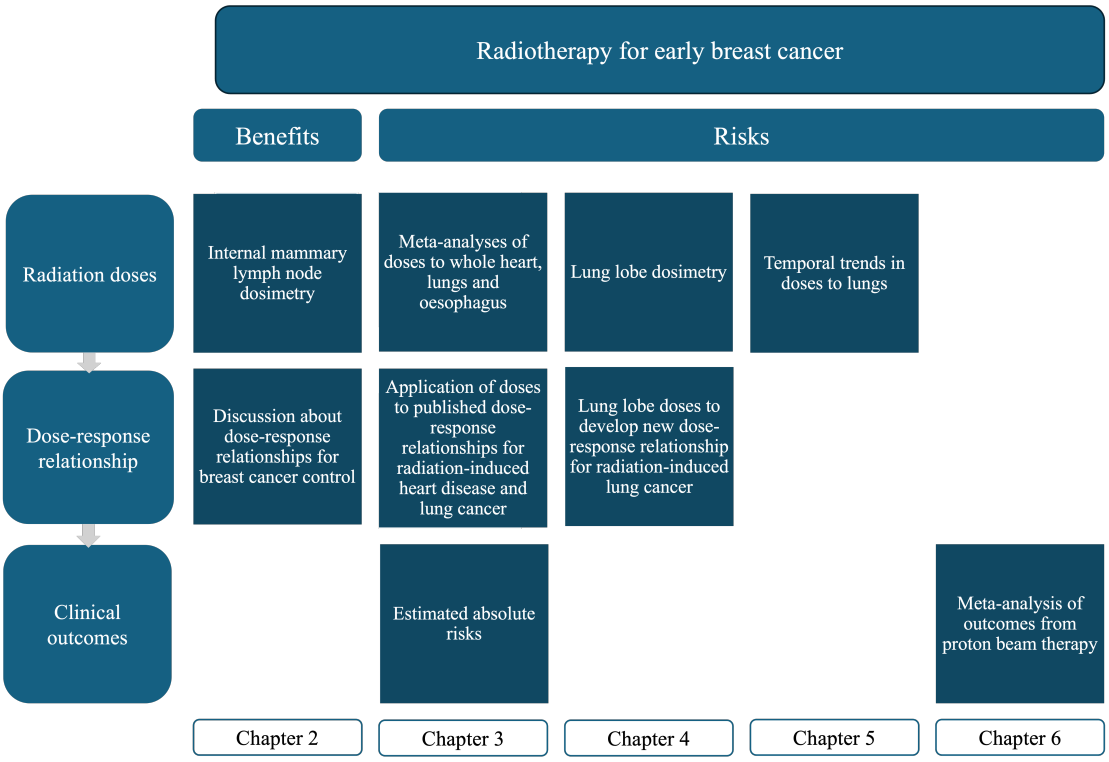


Figure 1.4: Thesis Overview

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Chapter 2

Internal mammary lymph node doses from radiotherapy regimens for early breast cancer in randomised trials starting 1989-2008.

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EBCTCG*
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Lancet 2023 25;402(10416):1991-2003.

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2.1 Abstract

2.1.1 Background

The association between internal mammary lymph node (IMN) dosimetry and survival from early breast cancer is unknown. A recent EBCTCG meta-analysis demonstrated that regional lymph node radiotherapy for early breast cancer given within seven randomised trials and one study allocating radiotherapy according to breast cancer laterality, starting 1989-2008, improved breast cancer survival. Various radiotherapy regimens were used in these trials, but few estimates of doses to lymph node clinical target volumes (CTVs) were made because these trials were conducted prior to the routine use of standardised lymph node contouring guidelines, CT-based radiotherapy planning, and trial quality assurance.

We systematically described all regional lymph node radiotherapy regimens within these trials, and then estimated radiation doses to modern definitions of IMN CTVs from the internal mammary lymph node regimens. The aim was to place the clinical evidence from the meta-analysis into the context of current internal mammary lymph node radiotherapy protocols.

2.1.2 Methods

First, published regional lymph node radiotherapy regimens were systematically described and categorised by the beam types and arrangements of radiotherapy fields targeting the regional lymph nodes.

Second, regimens targeting the IMNs were reconstructed on a CT planning scan selected to represent average thoracic anatomy.

Third, average doses to IMN CTVs as defined by ESTRO, RADCOMP and RTOG guidelines were estimated for each category of IMN radiotherapy regimen. Average mean whole heart and lung doses were also estimated. Doses from each radiotherapy regimen were weighted by the number of patients estimated to have received it.

2.1.3 Results

A total of 37 radiotherapy regional lymph node regimens were identified. Thirty-five of these targeted the IMNs and were received by an estimated 4979 patients within six trials. Eight different categories of beam type and arrangement targeting the IMNs were used. Overall average ESTRO IMN CTV V80% was 76.8%. This ranged from 41.4–93.2% for the different beam types and arrangements. RADCOMP IMN CTV V80% was 77.2% (range 43.6–93.5%) and RTOG IMN CTV was 74.5% (range 39.9–87.0%).

Average mean whole heart doses from IMN regimens for right and left breast cancer respectively were 5.9Gy (range 1.2-14.2Gy) and 10.2Gy (range 5.3-22.0Gy). Average mean whole lung dose was 7.8Gy (range 6.2-16.2Gy).

2.1.4 Conclusions

Our estimated doses to modern IMN CTVs from radiotherapy regimens used in these studies are likely lower than those achieved today. Current IMN radiotherapy regimens likely provide greater relative breast cancer survival benefits than those previously reported.

Estimated heart doses from internal mammary lymph node radiotherapy regi-

mens in these studies are substantially higher than those achieved today. However, estimated lung doses are only slightly higher, warranting further investigation.

2.2 Introduction

The benefit to women with early breast cancer from irradiating the regional lymph nodes in addition to the breast or chest wall was uncertain for many years, leading to wide variation in clinical guidelines and practice, particularly those concerning the internal mammary lymph nodes (IMNs).[1, 2] However, recently an Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of 16 randomised trials (14324 women) of regional lymph node radiotherapy versus not (including one study that irradiated lymph nodes only if the cancer was right-sided) has demonstrated that in eight trials starting 1989-2008 (12167 patients) the addition of regional lymph node radiotherapy to whole breast/chest wall irradiation reduced breast cancer recurrence and mortality by around an eighth (RR for recurrence=0.88, 95%CI 0.81-0.95, p=0.0008, RR for mortality=0.87, 95%CI 0.80-0.94, p=0.001) with no significant heterogeneity between the trials.[3] Most of this evidence was from six trials in which the IMNs were targeted. There was no significant variation in the proportional benefits of regional lymph node irradiation according to most patient and tumour factors. The only breast cancer characteristic associated with a slight increase in the proportional benefit of regional lymph node radiotherapy was central or medial location within the breast. This knowledge may reduce variation in indications for regional lymph node radiotherapy and increase the appropriate use of regional lymph node radiotherapy for early breast cancer, particularly IMN irradiation.

The largest trial starting 1989-2008 included in the meta-analysis was the EORTC 22922 trial which, during 1996 to 2004, randomised 4004 women with axillary lymph node positive early breast cancer (or cancer with central/medial

location within the breast) equally between whole breast/chest wall + IMN and medial supraclavicular lymph node radiotherapy and whole breast/chest wall radiotherapy alone.[4, 5] After a median 15.7 years of follow up, significant reductions in breast cancer recurrence and survival were found, but no significant effects on overall survival.[5] Broadly, IMN radiotherapy consisted of 50Gy in 2Gy fractions delivered over 5 weeks through mixed photon and electron beams arranged directly anterior. However, the trial protocol allowed deviation from the standard radiotherapy technique leading to variation in practice, and individual patient dosimetry is unavailable. Though individual patient dosimetry would be very informative, even if it were available it would not be possible to relate within-trial variations in lymph node dosimetry to clinical outcomes because patients were not randomly assigned between different regional lymph node radiotherapy techniques and, therefore, patient selection for particular radiotherapy techniques may bias outcomes.[6]

The second largest trial starting 1989-2008 was the Danish Breast Cancer Group (DBCG) IMN nationwide population-based cohort study that allocated 1492 patients with axillary lymph node positive right breast cancer to IMN irradiation, and 1597 women with axillary lymph node positive left breast cancer to no IMN irradiation during 2003 and 2007.[7, 8] This trial was included in the meta-analysis of randomised trials because allocated on the basis of laterality rather than from randomisation was considered equivalent to mendelian randomisation.[3] Danish national clinical protocols ceased support for left IMN irradiation in 2003 because of concerns that if given to patients receiving anthracycline chemotherapy, the risks of death from radiation-induced heart disease may outweigh the previously identified benefits to breast cancer survival. Irradiation of right IMNs with

48Gy in 2Gy fractions over 5 weeks delivered through an anterior electron field or inclusion in photon partially wide tangents was found to reduce distant metastases and breast cancer mortality and improve overall survival, compared with omitting radiotherapy to the left IMNs.[7, 8]

The third largest trial was the Canadian MA-20 trial which, during 2000 to 2007, randomly assigned 1832 women with lymph node positive, or high-risk lymph node negative breast cancer, equally between whole breast + regional lymph node irradiation and whole breast irradiation alone.[9] Internal mammary lymph node radiotherapy was given using a total dose of 50Gy divided in 25 fractions over five weeks; photon beams were arranged as partially wide tangents. After 10 years of follow up, regional lymph node irradiation was found to significantly reduce the rate of breast cancer recurrence but had no significant impact on overall survival.

Of the six trials investigating IMN radiotherapy, the three smaller trials did not detect any significant differences in breast cancer outcomes. One of these, a Finnish trial (Tampere) randomised 262 women between breast + IMN radiotherapy using photon wide tangents, or breast radiotherapy alone, during 1989 to 1991. After a median of 2.7 years no difference in rates of breast cancer recurrence was detected.[10] The other, a Korean Radiation Oncology Group (KROG) trial (08-06), randomised 735 women with lymph node positive breast cancer to receive internal mammary lymph node radiation or not between 2008 and 2013. Several different radiotherapy techniques were permitted by the trial protocol for selection at physicians' discretion.[11]

Improvements in breast cancer outcomes could also not be detected by a French trial named Lyon Sud, however, only data on *any death* from this trial contributed to the EBCTCG meta-analysis.[3, 12] Open from 1991 to 1997, it randomly as-

signed 1407 women with lymph node positive breast cancer, and/or medial/central breast cancer, receiving chest wall and supraclavicular lymph node radiotherapy after mastectomy and axillary lymph node dissection to receive IMN radiotherapy or not.[12] IMN radiotherapy consisted of 50Gy of mixed photons and electrons arranged directly anterior.

Two trials starting 1989-2008 included in the EBCTCG meta-analysis did not investigate internal mammary lymph node irradiation. The Italian Oncological Senology Group Milan (ISOG Milan) trial investigated axillary radiotherapy alone.[13] Four hundred and thirty five women with clinically node negative breast cancer were randomised to axillary radiotherapy versus not. The patients in this trial did not receive axillary dissection and a parallel direct anterior/posterior radiotherapy field nominally targeted the axillary lymph nodes. However, the inferior border of axillary field was matched to the superior border of breast tangents which specifically avoided the lower axillary lymph nodes. Therefore, we expect this regimen to have poorly covered modern axillary lymph node CTV levels 1 and 2. The International Atomic Energy Agency (IAEA) trial randomised 476 women receiving 40Gy in 15 fractions targeting the chest wall to the addition of supraclavicular lymph node irradiation or not, during 1989 to 1991. Details of the radiotherapy regimens have not been published.[14]

Although the EBCTCG meta-analysis provides oncologists with evidence to support the use of regional lymph node radiotherapy for early breast cancer, the association between regional lymph node CTV dosimetry and the reported survival benefits from early breast cancer remains unknown. This uncertainty exists because various regimens were used to irradiate the regional lymph nodes in the trials included in the EBCTCG meta-analysis, and doses received by the lymph

nodes and organs at risk (OAR) were rarely estimated for included patients. This was in keeping with both the resources available and trial conduct at the time. Most of the trials included in the meta-analysis started prior to the widespread use of Computer Tomography (CT)-based radiotherapy planning and prior to the publication of standardised contouring guidelines for delineation of the regional lymph nodes on CT scans. The Radiation Therapy Oncology Group (RTOG) and European Society of Therapeutic Radiology and Oncology (ESTRO) contouring guidelines used around the world in clinical practice today were published in 2009 and 2016 respectively.[15–17] The most recent version of the Radiotherapy Comparative Effectiveness (RADCOMP) guidelines, developed for use in trials of proton beam therapy for early breast cancer, was published in 2016.[18]

The trials included in the meta-analysis were also conducted at a time when radiotherapy quality assurance was in its infancy; it was challenging and expensive to do comprehensively. Although aspects of quality assurance were performed in seven of the eight trials starting 1989-2008, dosimetry audits were limited.[3]

Since the trials included in the EBCTCG meta-analysis were conducted, radiotherapy technology and techniques have improved making it likely that IMN radiotherapy delivered nowadays offers a greater than one eighth improvement in breast cancer recurrence and survival. Information from these trials cannot answer what the optimal doses to the internal mammary lymph nodes should be to achieve maximum survival benefit today, and clinicians will still need to rely on up-to-date dosimetry studies to demonstrate the dose-optimising capacities of the latest radiotherapy techniques. Information from the eight trials starting 1989-2008 in the EBCTCG meta-analysis provides a unique opportunity to retrospectively estimate doses to the IMNs and associate these estimates with the

most recent unconfounded estimates of relative clinical benefits identified by the EBCTCG meta-analysis.

Here we first summarise the radiotherapy regimens used in the eight trials starting 1989-2008 included in the EBCTCG meta-analysis and the limited published estimates of doses to lymph node CTVs and OARs achieved at planning. Second we retrospectively estimate the dose distributions to the IMN CTVs and OARs from all IMN radiotherapy regimens used in these eight trials. The aim is to provide oncologists and trialists with information needed to place the clinical evidence from the EBCTCG meta-analysis into the context of current and future regional lymph node radiotherapy practice. We do this by categorising radiotherapy regimens using beam types and arrangements rather than trial name, and by describing the estimated dose distributions using clinically-relevant dose metrics extracted from modern definitions of IMN CTVs and OARs.

2.3 Methods

2.3.1 Published radiotherapy regimens and doses

2.3.1.1 Data extraction

Descriptions of regional lymph node radiotherapy regimens used in the eight trials starting 1989-2008 included in the EBCTCG meta-analysis were extracted from trial publications and protocols.[3] (Appendix 1) Information included details on: breast cancer laterality; radiotherapy clinical targets (breast/chest wall, axilla [levels 1-3], supraclavicular fossa [level 4], internal mammary lymph nodes); beam types, energies, and arrangements; radiation dose prescriptions; radiotherapy field

borders; and techniques to reduce doses to OARs and increase homogeneity of doses to CTVs.

Doses resulting from each regimen were also extracted from trial publications. For doses to CTVs, information included clinical target volume contour definitions, dose objectives and average doses achieved at planning. (Table A.1) For doses to OARs, information included description of the OAR, dose constraints and average doses achieved at planning. The number of patients whose doses contributed to the averages were also extracted. (Table A.2)

2.3.1.2 Estimation of the number of patients who received each radiotherapy regimen

The number of patients who received each of the radiotherapy regimens was sought from trial publications. Where this information was missing, the patient eligibility criteria for each radiotherapy regimen was defined (e.g. breast cancer laterality and location, extent of lymph node involvement, and breast surgery type), and the number of patients eligible for each plan estimated. (Table A.3, Figures A.1, A.2, A.3, A.4, A.5, A.6, A.7)

2.3.1.3 Categorisation of radiotherapy regimens

Despite variation in radiotherapy regimens used in the trials, there was no significant heterogeneity in breast cancer outcomes between trials included in the meta-analysis, therefore the data cannot be used to create a dose-response relationship for treating breast cancer. Categorisation of radiotherapy regimens in this study helps to describe the heterogeneity in radiotherapy trial regimens and therefore relate radiotherapy in the trials to current clinical practice. Radiother-

apy regimens were categorised according to the beam type (photons, electrons, or mixed) and arrangement (parallel direct anterior/posterior, direct anterior, oblique anterior, partially wide tangents, or wide tangents) of radiotherapy fields for each clinical target (breast, chest wall, axilla, supraclavicular, IMN). Fields comprising mixed beam types were subcategorised by the percentage of the total field dose comprising each beam type e.g. mixed (20% photons, 80% electrons). For each category, the numbers of radiotherapy regimens and patients who received the regimens were estimated. (Tables 2.1, A.4, A.5, A.6, A.7, A.8, A.9, A.10)

2.3.2 Estimated radiation doses

To estimate radiation doses from all regional lymph node radiotherapy regimens used in the trials included in the EBCTCG meta-analysis, first inter-patient variability was assessed and a representative CT planning scan selected. Second, all radiotherapy regimens were reconstructed on this representative CT scan, and doses extracted and analysed.

2.3.2.1 Inter-patient variability assessment and representative CT scan selection

Individual patient anatomy varies and is known to effect estimated radiation dose distributions. In the absence of information on the body measurements of women included in the trials within the EBCTCG meta-analysis, a breast cancer radiotherapy CT planning scan was selected from a random sample for having average body measurements and regional lymph node doses.

CT planning scan sampling

Five anonymised radiotherapy planning CT scans were randomly selected from a database of 37 consecutive patients who received adjuvant radiotherapy to the whole breast ± regional lymph nodes for early breast cancer between May and June 2018 at the Oxford Cancer Centre, UK. Ethics approval was provided by University of Oxford Clinical Trials and Research Group. Scan slice thickness was 0.25cm. IV contrast was not used. The patients were scanned in the supine position with both arms above the head.

Body measurements

It is recognised that breast and chest shape may affect radiation dose distributions used to treat breast cancer. Anatomical measurements were taken from each of the CT scans including breast volume, breast separation, sternal soft tissue thickness and Haller index. (Figure 2.1) Breast separation—the distance between entry points of two opposing beams on the central plane—has been shown to influence dose 'hot spots' within the breast when regimens using photon tangents are used.[19] Sternal soft tissue thickness——the perpendicular distance in centimetres from the manubriosternal angle to the skin surface——was considered relevant when considering IMN doses from electron beams. General body habitus, which may relate to sternal soft tissue thickness for some women, has been shown to affect IMN radiation doses.[20] Haller index——the maximum transverse width of the chest divided by the minimum anteroposterior distance——was measured on a single axial CT image at thoracic vertebral level 8, where measurements have been shown to be least variable compared with other vertebral levels.[21] Haller

index is used in clinical practice to assess the severity of clinical pectus excavatum, which was not demonstrated on any of the randomly selected CT scans. Here it was taken to describe the shape of the thorax.

To allow comparison between doses received by the lymph nodes from radiotherapy regimens targeting the chest wall + regional lymph nodes, and the whole breast + regional lymph nodes with other anatomical differences between patients controlled for, mastectomy was simulated on each of the five CT scans. To simulate mastectomy, the breast was contoured and assigned a CT value for air. Between 0.5-1cm of breast tissue was retained within the body contour to account for residual subcutaneous tissue. Final mastectomy body contour was reviewed and agreed with a breast surgeon to ensure that the virtual mastectomy was consistent with surgical practice. (GM)

Reconstruction of radiotherapy regimens

To assess inter-patient variability in radiation doses received by the IMNs, the five most commonly received radiotherapy regimens for right breast cancer described in the trials starting 1989-2008 included in the EBCTCG meta-analysis were reconstructed on all five CT scans using detailed methods as described in the section below on reconstruction of radiotherapy regimens. To control for within patient differences in right- and left-sided anatomy, regimens targeting the same laterality were selected.

Contouring

In 2009, the RTOG contouring guidelines were published describing the cranial, caudal, anterior, posterior, lateral and medial anatomical boundaries of each of

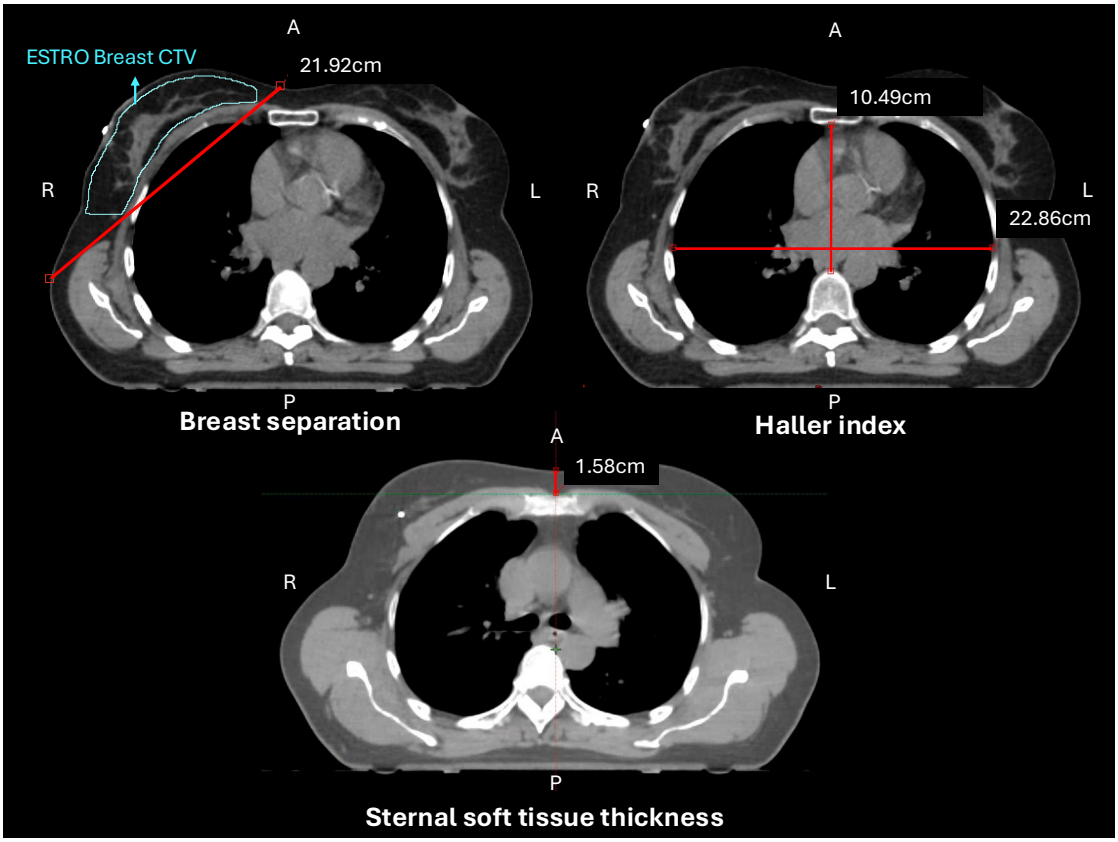


Figure 2.1: CT body measurements definitions used in this study.
These are demonstrated on an axial CT scan. Breast separation is the distance between entry points of two opposing beams on the central plane. Sternal soft tissue thickness is the perpendicular distance in centimetres from the manubriosternal angle to the skin surface. Haller index is the maximum transverse width of the chest divided by the minimum anteroposterior distance. Abbreviations: A=anterior, L=left, P=posterior, R=right.

the five lymph node regions (axillary levels 1-3, supraclavicular and internal mammary).[15] More conservative ESTRO consensus CTVs, published in 2015, restrict volumes to covering lymphovascular vessels and their surrounding fatty tissue, where most lymph nodes reside.[16, 17] More recently, RADCOMP guidelines were developed for use in an ongoing randomised trial of proton versus photon regional lymph node radiotherapy for early breast cancer, but these are not currently recommended for use outside of the RTOG 3509/3510 studies.[18]

For the internal mammary lymph nodes, there are few differences between the RTOG, ESTRO and RADCOMP contouring guidelines.[22] All of these guidelines recommend covering the internal mammary vessels down to the cranial aspect of the 4th rib, but there are differences in their recommendations for the margins around the internal mammary vessels, and also the superior border of the internal mammary lymph node volume. The RTOG recommends covering the internal mammary vessels without a margin, whereas ESTRO and RADCOMP guidelines cover the vessels with a margin. The superior border of the internal mammary lymph node CTV is defined by the RTOG guidelines as the superior aspect of the medial 1st rib, whereas the ESTRO and RADCOMP guidelines define it as the caudal border of the supraclavicular lymph node volume, which encompasses the subclavian vein (with a 5mm margin in the case of ESTRO). This means that ESTRO and RADCOMP volumes extend higher—more cranially—than the RTOG volume.

Having noted the similarities between ESTRO, RADCOMP and RTOG IMN CTVs, it was considered sufficient to assess inter-patient variation in IMN doses using ESTRO contouring guidelines only.

Data extraction and analysis

Data extraction and analysis for assessment of inter-patient variability were the same as those detailed in the section below on data extraction and analysis from all reconstructed radiotherapy regimens. For assessment of inter-patient variability in lymph node doses, summary dose metrics (structure volume [cc], mean dose [Gy], V80%, V85%, V90%, and V95%) grouped by radiotherapy regimen were tabulated. Doses were also examined for their relationship to patient CT body

measurements. (Table A.14, Figure A.9)

Representative CT scan selection

The scan with closest to median body measurements and V80% to the IMN CTV was selected as representative of average anatomy.

2.3.2.2 Estimated radiation doses from all regimens on a representative CT scan

Reconstruction of all radiotherapy regimens

All radiotherapy regimens described in the trial protocols and publications were applied to the representative patient CT scan. Where appropriate this was done using body surface reconstructions in the beam's eye view, and digitally constructed radiographs as they would have been done prior to 3D CT planning. Varian Eclipse Treatment Planning System 16.1 was used. The dose calculation algorithms used were Acuros 16.1 for photons, and Electron Monte Carlo 16.1. Dose was calculated using the 0.25cm calculation grid. Contours and plans were peer reviewed by a consultant breast cancer oncologist. (FD) Physics planning support was provided by a medical physicist. (GN)

Contouring

Breast and lymph node CTVs and OARs were delineated using published contouring guidelines.[15–18, 23, 24] For CTVs, ESTRO and RTOG guidelines were selected to ensure applicability of results to international audiences. The RADCOMP guidelines are not currently recommended for use outside of the setting

of the randomised trial comparing proton with photon regional lymph node radiotherapy for early breast cancer. They were selected to enable comparison of results from this study with those of future studies.

Data extraction and analysis

For each of the reconstructed radiotherapy regimens, cumulative dose volume histograms (cDVHs) for CTVs and the heart and lungs were exported as a text file from the treatment planning system for each target and at risk volume with dose bins of 0.1Gy. The text files were then imported into R (version 4.4.2) for analysis using the RadOnc package.[25, 26]

If the prescribed dose for a radiotherapy regimen did not approximate 2Gy per fraction, the linear quadratic equation was used to convert the cDVH data into equivalent doses in 2Gy per fraction. An α/β ratio of 3.7Gy was assumed as per the α/β ratio for ipsilateral breast cancer relapse reported in the FAST-Forward trial.[27] An α/β ratio of 2Gy was assumed for heart disease.[28] To the best of our knowledge α/β ratios are unavailable for second lung cancer and therefore the doses extracted from the lungs remain unadjusted for fraction size.

For each reconstructed radiotherapy regimen the following summary dose metrics were then calculated for all CTVs and OARs: structure volume (cc) and mean dose (Gy). For lymph node CTVs, further dose metrics were calculated: V80%, V85%, V90%, V95%. These dose metrics were selected as they were considered most relevant for oncologists and trialists writing radiotherapy protocols today.

Finally, average dose metrics for intended CTVs and OARs were created for each category of radiotherapy regimen, weighted by the number of patients estimated to have received each radiotherapy regimen.

2.4 Results

2.4.1 Published regional lymph node radiotherapy regimens

From the eight modern trials included in the EBCTCG meta-analysis, 37 published regional lymph node radiotherapy regimens were identified from seven trials. These regimens were received by an estimated 4979 of the 6033 (83%) patients who received regional lymph node radiotherapy within the eight trials. (Tables 2.1, A.4, A.5, A.6, A.7, A.8, A.9, A.10)

The IMNs were the most commonly targeted lymph nodes. Thirty five of 37 identified regimens targeted the IMNs. These regimens were received by an estimated 4758 of patients within six trials. (Table 2.1) This was also the clinical target for which there was the greatest variation in beam types and arrangements used. Eight different combinations of beam types and arrangements were identified. (Figures 2.2 and 2.3) Most often the IMNs were targeted by photon partially wide tangents (9 regimens, 1371 patients). The second most commonly used IMN fields comprised mixed (photon and electron) beams arranged directly anterior (18 regimens, 1972 patients). This beam type was subdivided into four types according to the percentage of the total field dose prescribed using photons: 52%, 30%, 28% or 20%. Mixed (photon and electron) direct anterior fields most often comprised 52% photons (8 regimens, 1217 patients). Least often the IMNs were targeted by electron beams. Direct anterior electron beams were used in three regimens received by 1019 patients; an oblique anterior electron beams was used in one regimen received by 265 patients.

Table 2.1: Beam types and arrangements for clinical targets of regional lymph node regimens published in eight trials starting 1989-2008

Beam type, arrangement	Regimens N=37 no.	Regimens N=37 %	Est. patients N=4979 no.
Regimens targeting internal mammary lymph nodes			
All beam types, arrangements	**35**	***95***	**4758**
Photons, Partially wide tangents	9	*24*	1371
Mixed (52% Photons, 48% Electrons), Direct anterior	8	*22*	1217
Electrons, Direct anterior	3	*8*	1019
Mixed (28% Photons, 72% Electrons), Direct anterior	2	*5*	641
Electrons, Oblique anterior	1	*3*	265
Photons, Wide tangents	4	*11*	131
Mixed (20% Photons, 80% Electrons), Oblique anterior	4	*11*	57
Mixed (30% Photons, 70% Electrons), Oblique anterior	4	*11*	57
Regimens targeting supraclavicular lymph nodes			
All beam types, arrangements	**31**	***84***	**4627**
Photons, Oblique anterior	19	*51*	2425
Photons, Direct anterior	8	*22*	1217
Unspecified	2	*5*	641
Photons, Parallel anterior/posterior	2	*5*	344
Regimens targeting axillary level 3 lymph nodes*			
All beam types, arrangements	**9**	***24***	**2629**
Photons, Oblique anterior	5	*14*	2064
Photons, Parallel direct anterior/posterior	4	*11*	565
Regimens targeting the breast			
All beam types, arrangements	**22**	***59***	**2867**
Photons, Partially wide tangents	7	*19*	1285
Photons, Tangents	10	*27*	1186
Photons, Matched tangents	1	*3*	265
Photons, Wide tangents	4	*11*	131
Regimens targeting the chest wall			
All beam types, arrangements	**15**	***41***	**2112**
Photons, Tangents	10	*27*	1007
Electrons, Direct anterior	1	*3*	962
Photons, Partially wide tangents	2	*5*	86
Electrons, Oblique anterior	2	*5*	57

Footnotes

*Regimens targeting levels 1 and 2 were covered by breast/chest wall fields.

See Table A.3 and Figures A.1, A.2, A.3, A.4, A.5, A.6, A.7 for method of estimation of number of patients.

See Tables A.4, A.5, A.6, A.7, A.8, A.9, A.10 for details of individual radiotherapy regimens.

See Tables A.11, A.12, A.13 for a summary of lymph node categories by trial.

Abbreviations: Est.=estimated, N=total number, no.=number.

The supraclavicular nodes were targeted in 31/37 regimens received by an estimated 4627 patients within five trials. (Table 2.1) There was little variation in the beam types and arrangements used. All fields targeting the supraclavicular nodes used photon beams. Most commonly an oblique (19 regimens, 2425 patients) or direct (8 regimens, 1217 patients) anterior beam arrangement was used. Two regimens received by 344 patients used parallel anterior/posterior beam arrangement. For two regimens received by 641 patients within one trial (Lyon Sud), there was insufficient information to categorise the supraclavicular beam arrangement.

Axillary lymph nodes were targeted least frequently. Nine of 37 regimens received by 2629 patients in three trials targeted axillary level 3 lymph nodes. (Table 2.1) Photon beams were used for all fields targeting these lymph nodes, and only two beam arrangements were used: oblique anterior beams in five regimens received by 2064 patients; and parallel direct anterior/posterior beams in four regimens received by 565 patients. (Table 2.1) Regimens targeting axillary level 1 and 2 lymph nodes were not categorised by their targeting beam types and arrangements because, with the exception of one regimen used in the DBCG-IMN trial, these modern lymph node volumes were covered by breast/chest wall fields.

The breast was targeted after breast conserving surgery in 22/37 regimens received by 2867 of patients in six trials. (Table 2.1) All fields targeting the breast used photon beams. The most commonly used beam arrangement was partially wide tangents, used in seven regimens received by 1285 patients. Tangents were used in 10 regimens received by 1186 patients, tangents matched to direct internal mammary fields used in one regimen received by 265 patients, and wide tangents used in four regimens received by 131 patients.

The chest wall after mastectomy was targeted in 15/37 regimens received by

2112 patients in four trials. (Table 2.1) Photons were used for chest wall fields in 12 regimens received by 1093 patients. Electrons were used in three regimens received by 1019 patients. The most commonly used beam arrangement was tangents (10 regimens, 1007 patients). Direct anterior beams were used in one regimen received by 962 patients, partially wide tangents in two regimens received by 86 patients and oblique anterior beams in two regimens received by 57 patients.

Right breast cancers were the target of 20/37 regimens received by 3206 patients. (Data not shown.) Left breast cancers were the target of 17/37 regimens received by 1773 patients. This imbalance was because in one trial (DBCG-IMN) using three regimens for 1492 patients, internal mammary lymph node radiotherapy was received only by women with right breast cancer.[7] In all other trials regional lymph node radiotherapy was received by women with both right and left breast cancers. (Table A.3)

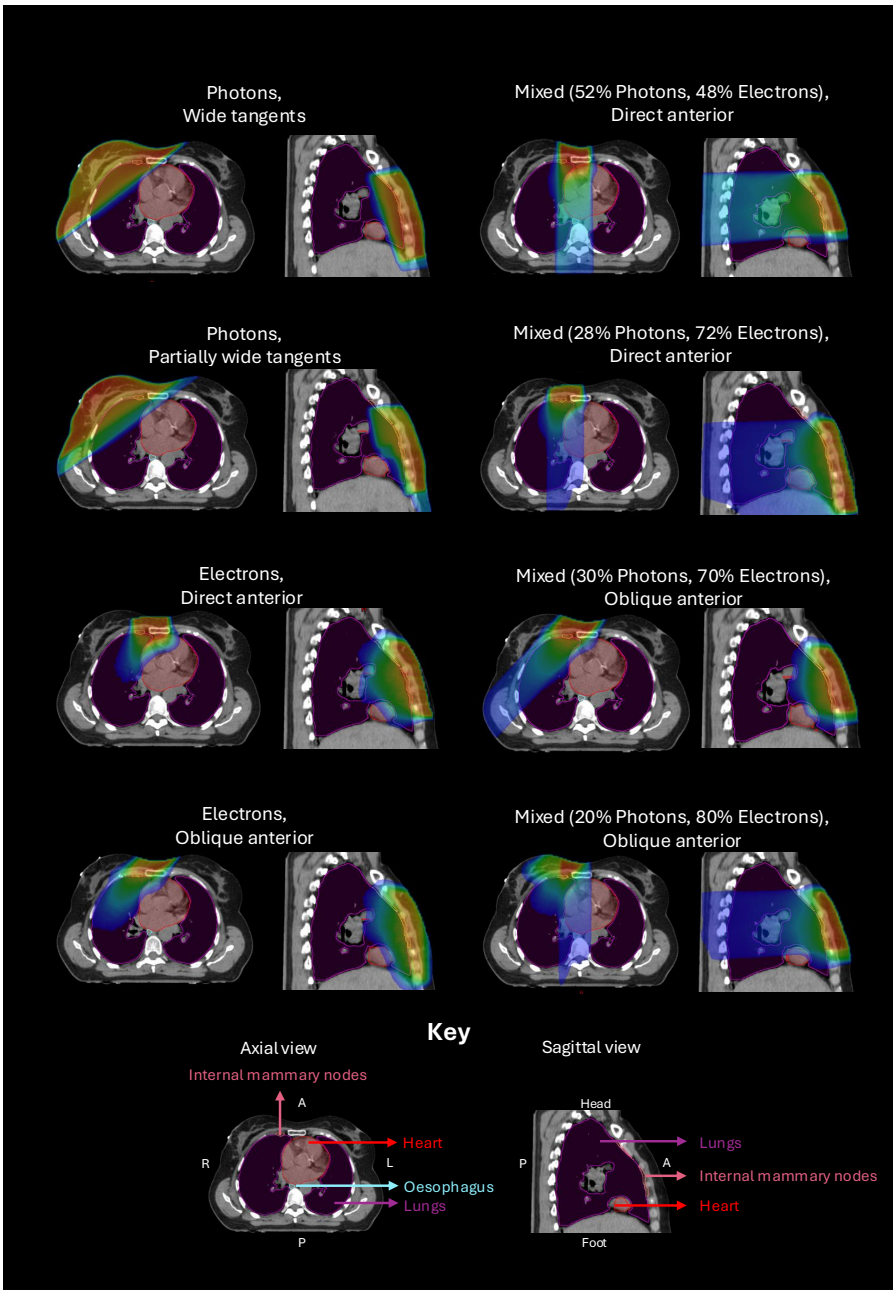


Figure 2.2: Right internal mammary lymph node field beam types and arrangements used in trials of regional lymph node radiotherapy regimens for early breast cancer starting 1989-2008.
For clarity, here dose distributions are illustrated only from fields targeting the internal mammary lymph nodes. Numerical estimated doses received by the internal mammary lymph nodes presented in this study were calculated from whole regimens, not individual fields. Abbreviations: A=anterior, L=left, P=posterior, R=right.

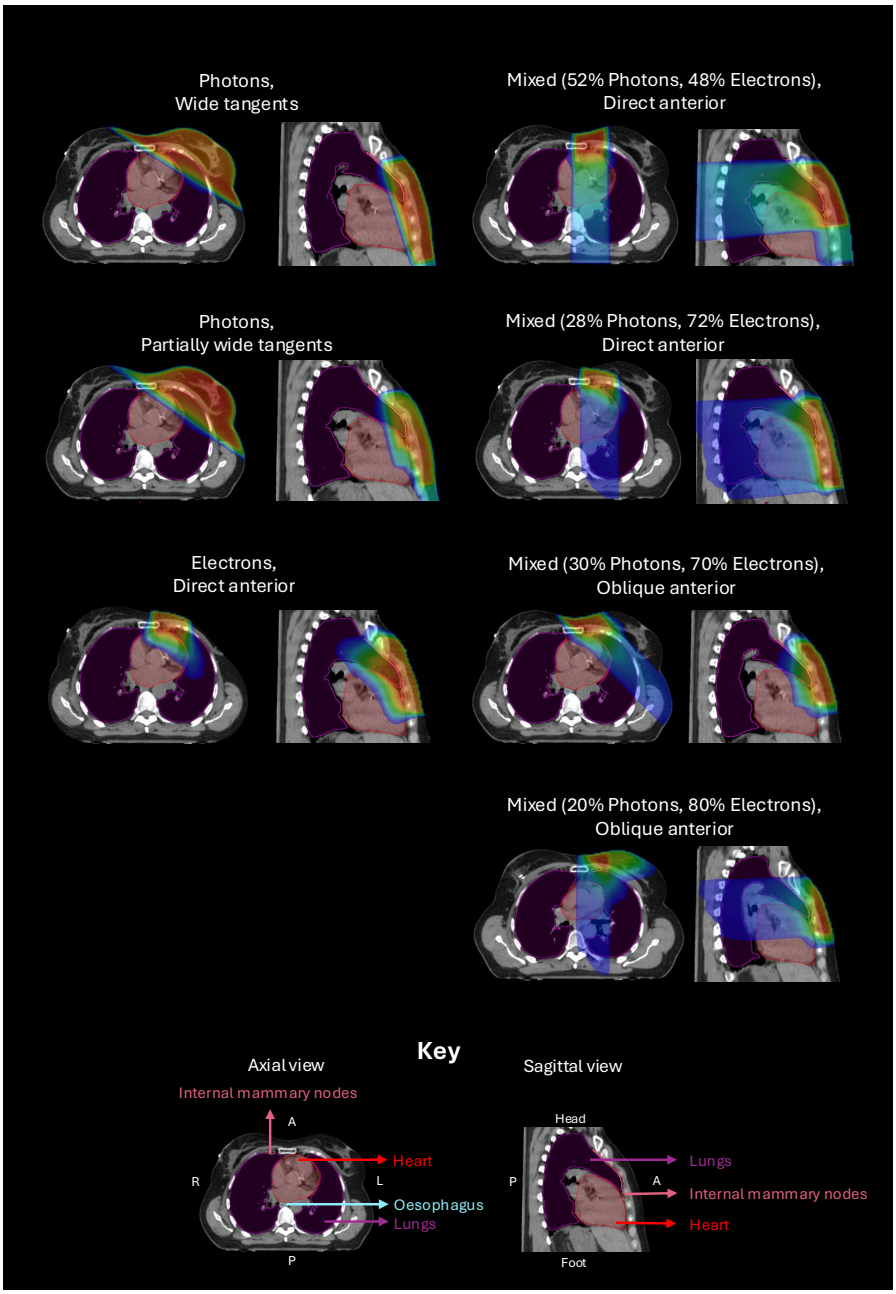


Figure 2.3: Left internal mammary lymph node field beam types and arrangements used in trials of regional lymph node radiotherapy regimens for early breast cancer starting 1989-2008.

For clarity, here dose distributions are illustrated only from fields targeting the internal mammary lymph nodes. Numerical estimated doses received by the internal mammary lymph nodes presented in this study were calculated from whole regimens, not individual fields. Abbreviations: A=anterior, L=left, P=posterior, R=right.

2.4.2 Published regional lymph node radiation doses

Published target volume radiation doses estimated from patient planning CT scans within the trials were published for 134 patients across three of the eight trials. The only target volume for which dose metrics were published was the IMN, and the reported contour definitions and dose metrics were different for each of the three trials preventing quantitative synthesis of the data. (Table A.1)

The contour definitions of IMN volumes were stated for two trials: the DBCG-IMN trial referred to the Danish Breast Cancer contouring guidelines, and the KROG 08-06 trial protocols described the IMN volume extending caudally from the jugulo-subclavian junction to the 4th rib, ventrally from the pleura to the dorsal aspect of the surface of the pectoralis major muscle and sternum, and medially and laterally 5mm margin from the internal mammary vessels. (Table A.1)

The dose metric reported from EORTC 22922 was mean dose to the IMN of 48.7Gy (total prescribed dose 50Gy in 25 fractions) estimated from 45 patients.[29] From the DBCG-IMN trial it was reported that, on average, from 38 patients, at least 73.2% of the IMN volume received 43.2Gy (i.e. 90% of the total prescribed dose of 48Gy).[30] From the KROG 08-06 trial, dose conformity of the IMN ranged from 101-105% of the total prescribed dose (50Gy in 28 fractions) for 51 patients.[31] (Table A.1)

Doses to OARs were published using data from a total of 451 patients across two of the eight trials. Average mean heart doses ranged from 1-5Gy, and the volume of the heart receiving at least 20Gy ranged from 0.1-6%. For the ipsilateral lung, the volume receiving at least 20Gy ranged from 31-36%. (Table A.2)

2.4.3 Estimated radiation doses

2.4.3.1 Inter-patient variability assessment and representative CT scan selection

Inter-patient variability in body measurements and radiation doses to IMN CTVs from the five most commonly received radiotherapy regimens used in the trials, starting 1989-2008, included in the EBCTCG meta-analysis were assessed from CT scans of five randomly selected patients.

Breast volume (range 44-1059cc), separation (11.33-22.58cm) and sternal soft tissue thickness (0.31-2.75 cm) varied considerably between patients. Haller index, which reflects the shape of the thorax, was similar across all patients ranging from 2.0-3.1. (Table A.14)

The five most commonly received regional lymph node radiotherapy regimens for right breast cancer were together received by an estimated 2103/4979 (42%) of patients for whom reconstruction of radiotherapy was possible from published data. (Tables A.4, A.5, A.6, A.7) They were categorised as follows: (1) direct anterior electron internal mammary field, oblique anterior photon axilla field, with matched direct anterior electron chest wall field used after mastectomy (962/4979, 19% of patients, DBCG-IMN), (2) direct anterior mixed photons (28%) and electrons (72%) internal mammary field, with matched photon tangents used after breast conserving surgery (311/4979, 6% of patients, Lyon Sud), (3) photon partially wide tangents with photon oblique anterior supraclavicular and apex of axilla field used after breast conserving surgery (286/4979, 6% of patients, MA-20), (4) direct anterior mixed photons (52%) and electrons (48%) internal mammary field, direct anterior photon supraclavicular field with matched photon tangents

used after breast conserving surgery (279/4979, 6% of patients, EORTC 22922) and (5) oblique anterior electron internal mammary field, oblique anterior photon axilla field, with matched photon tangents used after breast conserving surgery (265/4979, 5% of patients, DBCG-IMN).[4, 7, 9, 12] Regimens targeting right breast cancer were selected over left because the most commonly received regimen overall was from DBCG-IMN in which the intervention arm included only patients with right breast cancers.[7]

The most commonly targeted lymph nodes were the internal mammary lymph nodes and therefore dose metrics for right IMN CTVs were used to assess inter-patient variability. Contoured right ESTRO IMN CTVs varied from 5.8-11.4 cc. (Table A.14) Estimated radiation doses to these volumes varied systematically according to the generating radiotherapy regimen and the extracted dose metric. Inter-patient variation was also observed. The smallest inter-patient variation was observed for a regimen using a direct anterior electron beam to target the IMN. From five patients, the V80%——the volume of the right IMN CTV receiving at least 80% of the prescribed dose——ranged from 81.7-100.0%. The regimen with the greatest inter-patient variation in V80% used an electron oblique anterior internal mammary field: V80% ranged from 6.7–97.4%. (Figure A.9, Table A.14)

Although the sample size was too small to fully assess the relationship between body measurements and regional lymph node doses, exploratory analysis indicates that some of the inter-patient variability in radiation doses received by right ESTRO IMN CTVs from radiotherapy regimens including electron beams in internal mammary fields may be explained by variation in sternal soft tissue thickness. (Figure 2.1, Figure A.9, Table A.14) For radiotherapy regimens including electron beams in internal mammary fields, the doses received by the IMN CTVs decreased

with increasing sternal soft tissue thickness. For the radiotherapy regimen targeting the IMN with photon partially wide tangents, there was a less clear relationship between sternal soft tissue thickness and dose. This finding is expected given our understanding of photon beam attenuation and the angle of the beam in relation to anatomy.

As expected, mean doses were less variable between patients than other dose-volume metrics. (Figure A.9) However, the volumes of the right IMN CTV receiving at least 80-95% of the prescribed dose were used to summarise doses as they are useful metrics for dose objectives within clinical protocols because they encourage adequate coverage of the entire CTV.

The CT planning scan with ID number one had median breast volume, breast separation, sternal soft tissue thickness, and right ESTRO IMN doses for the majority of regimens and was therefore selected as the representative patient. (Table A.14)

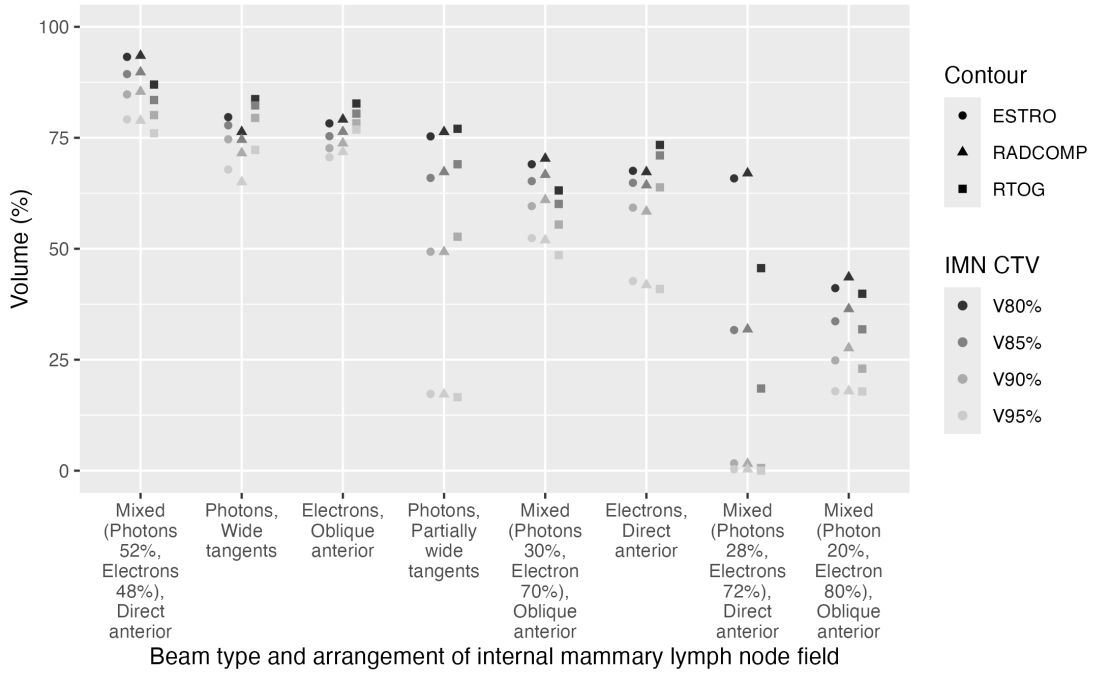


Figure 2.4: Average percentages of the ipsilateral internal mammary lymph node clinical target volume receiving at least 80, 85, 90 and 95% of the total prescribed radiation dose from reconstructions of internal mammary lymph node radiotherapy regimens for early breast cancer used in trials starting 1989-2008.
Averages are provided for each category of beam type and arrangement of the internal mammary lymph node field, and contour used to define the internal mammary lymph node clinical target volume. Average doses for a category of beam type and arrangement were weighted by the number of patients estimated to have received each radiotherapy regimen within the category, and are presented in Table 2.2.
Abbreviations: ESTRO=European Society of Therapeutic Radiology and Oncology, IMN=internal mammary lymph node, CTV=clinical target volume, RADCOMP=Radiotherapy Comparative Effectiveness, RTOG=Radiation Therapy Oncology Group, Vx%=Volume receiving at least x% of the total prescribed dose.

Table 2.2: Estimated average dose metrics for internal mammary lymph node clinical target volumes from radiotherapy regimens targeting these nodes in unconfounded trials starting 1989-2008

IMN beam type, arrangement	**Est. pts**	**Average dose metrics for IMN CTV (%)***														
		ESTRO					**RADCOMP**					**RTOG**				
		Mean	**V80%**	**V85%**	**V90%**	**V95%**	**Mean**	**V80%**	**V85%**	**V90%**	**V95%**	**Mean**	**V80%**	**V85%**	**V90%**	**V95%**
Photons, Partially wide tangents	1371	79.9	75.3	66.0	49.3	17.3	80.3	76.3	67.3	49.3	17.2	80.5	77.0	69.0	52.7	16.6
Mixed (52% Photons, 48% Electrons), Direct anterior	1217	118.5	93.2	89.3	84.8	79.1	117.6	93.5	89.8	85.4	78.9	111.2	87.0	83.5	80.1	76.0
Electrons, Direct anterior	1019	82.3	67.6	64.9	59.3	42.7	82.2	67.3	64.3	58.4	41.8	84.1	73.4	71.0	63.8	40.9
Mixed (28% Photons, 72% Electrons), Direct anterior	641	77.7	65.9	31.7	1.6	0.3	77.9	67.0	31.9	1.6	0.3	59.9	45.6	18.5	0.6	0.0
Electrons, Oblique anterior	265	117.2	78.2	75.4	72.7	70.6	117.6	79.1	76.4	73.8	71.8	122.3	82.7	80.4	78.3	76.9
Photons, Wide tangents	131	85.0	79.7	77.8	74.7	67.8	81.6	76.3	74.6	71.6	65.0	89.0	83.7	82.3	79.5	72.3
Mixed (20% Photons, 80% Electrons), Oblique anterior	57	73.8	41.1	33.7	24.8	17.9	75.3	43.6	36.4	27.6	17.9	70.8	39.9	31.8	23.0	17.8
Mixed (30% Photons, 70% Electrons), Oblique anterior	57	103.5	69.0	65.2	59.6	52.4	113.0	70.3	66.7	61.0	51.9	91.7	63.1	60.1	55.5	48.6
ALL	**4758**	**92.4**	**76.8**	**67.5**	**55.9**	**41.1**	**92.4**	**77.2**	**68.0**	**55.9**	**40.8**	**88.9**	**74.5**	**66.8**	**56.9**	**40.0**

Footnotes

*Doses and volumes were averaged across all radiotherapy regimens targeting the internal mammary lymph nodes, categorised by internal mammary lymph node beam type and arrangement.
They were weighted according to the estimated number of patients that received each regimen.
Abbreviations: CTV=clinical target volume, Est.=estimated, ESTRO=European Society of Therapeutic Radiology and Oncology, Gy=Gray, IMN=internal mammary lymph nodes, pts=patients, RADCOMP=Radiotherapy Comparative Effectiveness, RTOG=Radiation Therapy Oncology Group, Vx%=Volume receiving at least x% of the total prescribed dose.

2.4.3.2 Estimated radiation doses from all regimens on a representative CT scan

Internal mammary lymph nodes

Doses to IMN CTVs were estimated for 4758 patients across six trials. (Tables 2.2, A.11) Doses were similar across the different contours used. Overall, average V80% for ESTRO, RADCOMP, and RTOG IMN CTVs were 76.8%, 77.2% and 74.5% respectively. V85%, V90% and V95% estimates were also comparable between contours. (Table 2.2, Figure 2.4)

However, doses varied considerably according to the beam type and arrangement of the IMN field. From all IMN beam types and field arrangements, average percentages of ESTRO IMN CTVs receiving at least 80%, 85%, 90% and 95% of the prescribed dose were 76.8% (range 41.1–93.2%), 67.5% (range 31.7-89.3%), 55.9% (range 1.6–84.8%), and 41.1% (range 0.3%-79.1%) respectively. (Table 2.2, Figure 2.4)

The ESTRO IMN CTV receiving at least 80% of the total prescribed dose was highest from regimens using mixed photons (52%)/electrons (48%) beams arranged directly anterior (93.2%). Regimens using photon beams arranged as wide tangents (ESTRO IMN CTV V80% 79.7%), electrons arranged obliquely (ESTRO IMN CTV V80% 78.2%) and photons arranged as partially wide tangents (ESTRO IMN CTV V80% 75.3%) also achieved above average coverage of the ESTRO IMN CTV with at least 80% of the prescribed dose. Mixed photons (30%)/electrons (70%) beams arranged obliquely anterior (ESTRO IMN CTV V80% 69.0%), electron beams arranged directly anterior (ESTRO IMN CTV V80% 67.6%), mixed photons (28%)/electrons (72%) beams arranged directly anterior (ESTRO IMN

CTV V80% 65.9%) and mixed photons (20%)/electrons (80%) beams arranged obliquely anterior (ESTRO IMN CTV V80% 41.1%) provided below average coverage. (Table 2.2, Figure 2.4)

Table 2.3: Estimated average mean dose received by whole organs at risk from internal mammary radiotherapy regimens used in trials starting 1989-2008

IMN beam type, arrangement	**Est.pts**	**Average mean dose received by whole organ at risk (Gy)***		
		Heart		**Lungs**
		Right	**Left**	
Photons, Partially wide tangents	1371	1.2	5.3	7.1
Mixed (Photons 52%, Electrons 48%), Direct anterior	1217	14.2	22.0	8.2
Electrons, Direct anterior	1019	4.2	7.0	7.3
Mixed (Photons 28%, Electrons 72%), Direct anterior	641	4.5	9.1	7.9
Electrons, Oblique anterior	265	4.6	NA	10.9
Photons, Wide tangents	131	1.7	6.2	6.2
Mixed (Photons 20%, Electrons 80%), Oblique anterior	57	4.5	6.4	6.8
Mixed (Photons 30%, Electrons 70%), Oblique anterior	57	4.3	10.1	16.2
All	**4758**	**5.9**	**10.2**	**7.8**

Footnotes

*Doses were averaged across all radiotherapy regimens targeting the internal mammary lymph nodes, categorised by beam type and arrangement of the IMN fields.
They were weighted according to the estimated number of patients that received each regimen.
Abbreviations: Gy=Gray, IMN=internal mammary lymph node, NA=not applicable.

Organs at risk

From IMN regimens, average mean whole heart doses were 5.9Gy from regimens for right breast cancer (ranging from 1.2-14.2Gy according to the IMN beam type and arrangement) and 10.2Gy (range 5.3-22.0Gy) from regimens for left breast cancer. Average mean whole lung dose (including both right and left lungs) was 7.8Gy (range 6.2-16.2Gy) from regimens of any laterality.

2.4.4 Discussion

2.4.4.1 Estimated doses received by internal mammary lymph nodes

This study provides a comprehensive summary of all 37 published regional lymph node radiotherapy regimens shown to improve survival in unconfounded trials starting 1989-2008, and provides estimates of the numbers of patients who received them. From all IMN regimen beam types and arrangements, estimates of radiation doses received by three modern definitions of IMN CTVs using metrics commonly used in clinical protocols are provided, thereby explaining the heterogeneity in trial radiotherapy protocols and allowing oncologists to place the results of the meta-analysis in the context of their current radiotherapy practice. It provides overall estimates of the radiation doses received by modern IMN CTVs from IMN regimens that may be associated with reducing the breast cancer recurrence and death rates by around one eighth.

The vast majority of patients in the trials, starting 1989-2008, received one of eight categories of beam types and arrangements targeting the IMNs. From IMN regimens, the estimated average IMN CTVs receiving at least 80% of the prescribed dose were 76.8%, 77.2% and 74.5% for ESTRO, RADCOMP and RTOG volume

definitions respectively. Coverage of the targeted IMN CTVs with radiation dose varied considerably according to the IMN beam types and arrangements. These estimated doses may be associated with a reduction in the risk of breast cancer recurrence and mortality of an eighth, and they are likely lower than may be achieved with modern radiotherapy techniques confirming that the relative benefits to breast cancer survival of regional lymph node radiotherapy today are likely greater than estimated from the trials included in the EBCTCG meta-analysis.[32–36]

2.4.4.2 Estimated doses received by organs at risk

It is not possible to relate doses to OARs from these regimes to clinical outcomes seen in the trials as few trials reported relevant adverse clinical outcomes. As presented in the supplementary appendix of the EBCTCG meta-analsysis, heart toxicity in patients who received regional lymph node radiotherapy was reported in four of the seven trials included in this study. From EORTC 22922, heart toxicity was reported for 8.6% of patients who received regional lymph node radiotherapy compared with 7.2% in the control group. For Lyon Sud, 2% of patients had heart toxicity in both intervention and control groups. From MA-20, heart toxicity was reported in 0.9% of patients receiving regional lymph node radiotherapy, compared with 0.3% in the control group, and from KROG 08-06, it was <1% of patients compared with none.[3] For DBCG-IMN, <1% deaths from heart disease were recorded for each group. Lung toxicity was reported in four of the seven trials. It was reported in 5.1% of patients within EORTC 22922 (2.3% in the control group), and 0.4% in MA-20 (0.3% in the control group).[3]. Fourteen percent mild to moderate lung fibrosis was reported from the Tampere trial intervention group

compared with 7% in the control arm. No lung toxicity was reported from KROG 08-06.[3] These unconfounded trials were not designed to assess the adverse effects of regional lymph node radiotherapy for early breast cancer. The mortality risks of radiotherapy for early breast cancer have been summarised elsewhere.[37] Doses received by the heart in these trials starting 1989-2008 included in the EBCTCG meta-analysis are likely to be higher than those received by women receiving radiotherapy using modern techniques today.[38, 39] However, doses received by the lungs from regimens targeting the IMNs may be similar to modern doses.[39, 40] (Chapters 3 and 5)

2.4.4.3 Comparisons with other studies

To our knowledge two other studies have retrospectively estimated doses from regimens used in the EORTC 22922 trial.[20, 41] Borm et al. estimated mean doses received by ESTRO IMN CTV from one reconstructed regimen used in the EORTC 22922 on patients with three types of body habitus.[20] The estimated IMN CTV mean dose received by a patient with "standard" anatomy was 41.8Gy ±6.3 i.e. around 84% of the prescribed dose. This is lower than our estimate of 119% of the prescribed dose. It is likely that the differences in our estimates are due to variation in choice of placement of the overlap between the tangential field and the mixed photon/electron field. It has been acknowledged in the literature that for the standard radiotherapy technique used in EORTC 22922 the absolute maximal dose can exceed 180% at this overlap.[6, 42] Mean IMN CTV doses estimated by Borm et al. were higher when doses were estimated for a "slender patient with small breasts" (41.6Gy ±13.4) and lower when estimated for an "obese patient with large breasts" (36.5Gy ±11.3) in keeping with our findings of the relationship

between doses to the IMN and body measurements.[20]

More recently, Siman-Tov et al. retrospectively estimated radiation doses received from IMN radiotherapy delivered in the EORTC 22922 trial.[41] Trial regimens were retrospectively categorised as "standard", "standard-modified" and "individualised" and doses estimated from 10 patient CT scans for each category of regimen. Mean ESTRO IMN Planning Target Volume (PTV) doses were 50.8Gy, 50.5Gy and 43.4Gy for each radiotherapy regimen category respectively. It is not possible to directly compare the IMN dose estimates with ours given our choice to estimate doses to the CTV rather than PTV to make the results applicable to centres requiring different CTV to PTV margins.[41] However, the results presented by Siman-Tov et al. demonstrate that the "individualised" radiotherapy techniques permitted in this trial likely achieved lower heart doses at the expense of some coverage of the IMNs. We were unable to reconstruct these more "individualised" radiotherapy techniques as details of these techniques were unavailable. Mean heart doses from "standard", "standard-modified" and "individualised" EORTC 22922 regimens were 18.3Gy, 16.6Gy and 9.5Gy respectively. Mean whole lung doses (calculated as the average of published right and left lung doses) were 8.75Gy, 11.1Gy, and 9.3Gy. The mean whole heart and lung doses are comparable with our average estimates of 18.1Gy and 8.2Gy from all EORTC 22922 regimens.

Borm et al. also retrospectively estimated doses received by ESTRO IMN CTVs from a single radiotherapy regimen used in the MA-20 trial. The estimated mean dose was 37.8Gy $\pm$16.2 i.e. 76% of the prescribed dose, in keeping with our estimate of 84%.[20]

2.4.4.4 Strengths and weaknesses

This study has several strengths. First, the overall estimates of doses received by regional lymph nodes were made by combining estimated doses from all regimens within each trial, and weighting estimates from each regimen by the estimated numbers of patients receiving them. Second, reconstruction of regimens was performed within a research team impartial to the resulting dose estimates. It is possible for the researcher reconstructing and extracting doses from historical regimens on modern treatment planning systems to use information from the full CT dataset and estimated dose distributions to improve historical regimens. Impartiality is therefore important to the integrity of the results because it prevents bias towards better doses. Although estimates derived from retrospective dosimetry inherently carry uncertainties, these have been shown to be minimal for the representative CT method used in this study.[43] The representative CT used for the study was selected for average body measurements from a random sample. Third, estimated doses have been presented in terms of clinically-useful dose metrics (e.g. V80%) and internationally-recognised CTV contours to allow the results to be related to current clinical protocols around the world.

When interpreting the clinical implications of our estimated doses it is important to recognise the limitations of the data that were available. First, for 17% (1051/6033) of women included in the unconfounded trials starting 1989-2008 insufficient published information was available to reconstruct radiation dose distributions to at least one regional lymph node CTV. Second, the extent to which the representative patient CT scan used for reconstruction of radiotherapy regimens in this study represented women in the trials remains unknown because details of

trial participants' body measurements and individual anatomy were unavailable. Third, further local calculations are required for oncologists wishing to compare the results of this study with their current clinical protocols if their current protocols define dose objectives to a locally-defined PTV rather than a CTV.

2.4.4.5 Clinical Implications

Although publication of the EBCTCG meta-analysis may reduce variation in indications for regional lymph node radiotherapy, it is likely that there is still considerable variation in adjuvant IMN radiotherapy dose objectives and radiotherapy techniques. In the UK, the degree of variation in dose objectives for IMN radiotherapy is unknown. Regarding radiotherapy techniques, it is common to use photons arranged as partially wide tangents to cover the internal mammary nodes, and an oblique anterior beam to cover the supraclavicular nodes. Volumetric Modulated Arc Therapy (a type of rotational intensity modulated therapy) may be used for selected patients in centres with the required resources. Proton beam therapy is also available within the setting of clinical trial for selected patients.

The dose estimates in this study represent estimates of radiation doses associated with the benefits to breast cancer outcomes described in the EBCTCG meta-analysis. The estimated doses do not represent recommended dose objectives to achieve maximum potential clinical benefit, nor can they be used to choose between radiotherapy techniques available today. Given that radiotherapy techniques for targeting the regional lymph nodes have advanced since these unconfounded trials, our estimated doses received by the IMNs received by women in unconfounded trials are likely lower than received by women today, and our estimated doses to the heart likely exceed those that may be received by most women today.

These estimated doses suggest that overall, the relative benefits of lymph node radiotherapy today are likely to be higher than estimated in the meta-analysis. These dose estimates provide the link that may allow oncologists to justify the dose objectives within their regional lymph node radiotherapy protocols for early breast cancer with the highest quality available clinical evidence.

For example, it is likely reassuring to oncologists that on average women deriving a survival benefit from regional lymph node radiotherapy of around one eighth may have received radiotherapy that covered at least 80% of the internal mammary ESTRO CTVs with an estimated 77% of the total prescribed dose, because it is likely that clinical protocols today achieve more ambitious dose objectives for the majority of women. This should not encourage the lowering of current dose objectives because other population changes mean that higher doses may be required to achieve overall absolute benefits for some women today. Instead, this information may provide oncologists with an understanding that their current clinical protocols likely provide a greater proportional survival benefit than historically effective radiotherapy.

2.4.4.6 Research Implications

This study highlights the need for further research in specific areas. First, further research into how best to optimise lymph node dose for individuals is needed. Here we have provided an overall estimate of average doses to the internal mammary lymph nodes that gives rise to an increase in breast cancer survival of around an eighth at a population level. However, for individuals, the optimum radiation dose required by the internal mammary lymph nodes to achieve maximum probability of breast cancer control is likely to vary according to the extent of cancer in the

lymph nodes and how this is distributed. Further research is needed to ascertain the doses being received by the IMNs from radiotherapy used in clinical practice today, including an understanding of variation in the practice of giving lymph node boost doses to macroscopic disease. The aim of presenting doses to RADCOMP CTVs was to provide trialists investigating proton beam therapy for early breast cancer with an indication of how modern dose distributions from proton beam therapy may compare with those in previous unconfounded trials.

Second, further work is needed to more fully assess variation in coverage of the internal mammary lymph nodes with modern radiotherapy techniques according to different anatomical factors. Exploratory analyses suggest the relationship between BMI and outcomes from internal mammary radiotherapy merits further investigation.

2.4.5 Conclusions

Estimated doses to modern lymph node volumes are associated with an approximately one eighth improvement in breast cancer survival. Higher lymph node doses from regional lymph node radiotherapy regimens given in clinic today likely achieve greater relative improvements in breast cancer survival. Given that at a population level breast cancer mortality risks are falling, future breast cancer radiotherapy likely needs to deliver higher relative benefits to ensure regional lymph node radiotherapy continues to provide substantial absolute survival benefits.

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Georgios Ntentas supervised the project, provided physics expertise in reviewing radiotherapy reconstructions and draft manuscripts.
Sarah Darby supervised the statistical analyses and data presentation, and reviewed and edited draft manuscripts.
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Chapter 3

Estimated doses received by the heart, lungs, oesophagus and risks from typical UK radiotherapy for early breast cancer during 2015-2023.

Holt F, Ivanova A, Wang Z, Darby S, Duane F, Ntentas G, Oliveros S, Lavery B, Shah K, Eichoholz A, Dodwell D, Taylor C.

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Estimating absolute risks from typical UK radiotherapy for early breast cancer during 2015-2023

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Background

Breast cancer radiotherapy can increase the risks of heart disease, lung cancer and oesophageal cancer due to incidental irradiation of the heart, lungs and oesophagus respectively.[1] The absolute risks depend on radiation doses received by these organs and on patients' pre-existing risk factors.[1-3]

Part 1. Estimating typical doses to organs at risk from modern UK breast cancer radiotherapy to different clinical targets

Methods

A systematic review was conducted of mean doses to the whole heart, lungs or oesophagus from UK radiotherapy for early breast cancer during 2015-2023.

Average whole heart, lung and oesophagus doses from irradiation of different target regions were summarised using meta-analysis.

Results

For whole heart dose, thirteen studies reported 41 average doses from 2893 individual dose estimates. Average doses ranged from 1.0 to 2.9 Gy, depending on laterality and target regions irradiated.

For whole lung dose, six studies reported 17 average doses from 2230 individual estimates. Target region-specific average whole lung doses ranged from 2.6 to 7.1 Gy.

For oesophagus dose, two studies reported five average doses ranging from 1.4 to 5.8 Gy, based on 76 individual estimates.

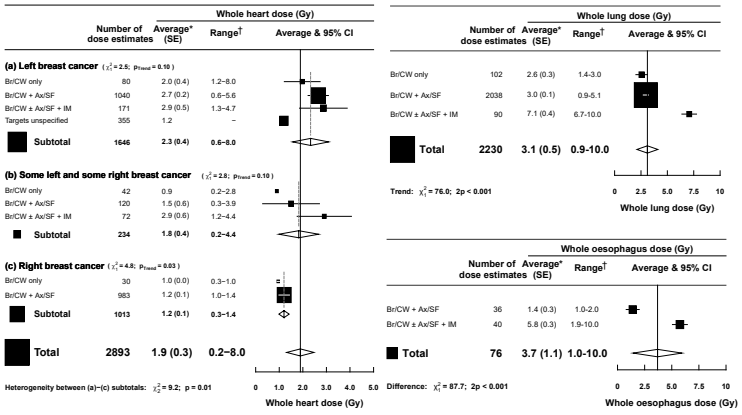


Figure 1. Estimated typical mean whole organ doses from UK breast cancer radiotherapy according to breast cancer laterality and radiotherapy clinical targets
*Average mean whole organ dose, weighted by the number of individual dose estimates, was calculated for each category of radiotherapy clinical targets.
† The range refers to the range of individual dose estimates. Where this was unavailable, the range of reported average doses was used.
Abbreviations: Ax=axilla lymph nodes, Br=breast, CW=chest wall, IM=internal mammary lymph node, SF=supraclavicular fossa lymph nodes

Part 2. Estimating absolute risks

Methods

Average heart and lung doses were combined with epidemiological studies to estimate the absolute 30-year radiation-induced risks of death from heart disease and lung cancer for a typical woman who receives radiotherapy when aged 50 years.[1,2]

Results

The absolute 30-year risks of radiation-induced death from ischaemic heart disease ranged from 0.2% to 0.7%, depending on pre-existing cardiac risk factors. Estimated absolute 30-year risks of radiation-induced death from lung cancer ranged from 0.2 to 0.4% for non-smokers and 2.3 to 6.2% for long-term continuing smokers.

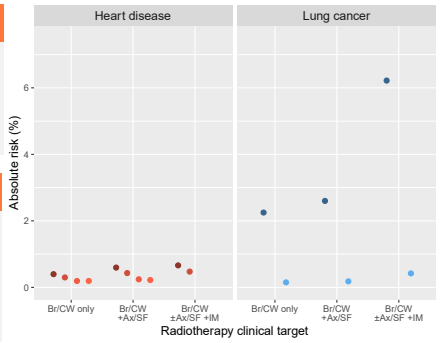


Figure 2. Estimated absolute risks (%) of death from radiation-induced disease by age 80 years for a woman receiving modern UK radiotherapy for early breast cancer when aged 50 years.
Absolute risks were estimated using typical doses to whole organs at risk (Gy) from modern UK radiotherapy for early breast cancer shown in Figure 1.
Cardiovascular risk factors: existing cardiovascular disease, diabetes, COPD, long-term continuous smoking and body mass index >30kg/m².
Abbreviations: Ax=axilla lymph nodes, Br=breast, CW=chest wall, IM= internal mammary lymph nodes, SF=supraclavicular fossa lymph nodes

- Left cancer, at least one cardiac risk factor
- Left cancer, no cardiac risk factors
- Right cancer, at least one cardiac risk factor
- Right cancer, no cardiac risk factors
- Long−term continuing smoker
- Non−smoker

Conclusion

For a typical 50-year-old non-smoker with no cardiac risk factors, the estimated 30-year absolute risks of radiation-induced disease from UK breast cancer radiotherapy would be ≤1%. For long-term continuing smokers, the absolute risks are likely to be a few percent.

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Figure 3.1: Poster presented at the UK Breast Cancer Group Meeting, 2023

Prior to publication of the full manuscript in Clinical Oncology, this study won a prize at the UK Breast Cancer Group meeting. Poster and oral presentations were given and the abstract was published:

Holt F, Ivanova A, Wang Z, Darby S, Duane F, Ntentas G, Oliveros S, Lavery B, Shah K, Eichoholz A, Dodwell D, Taylor C. Estimated Absolute Risks from Typical UK Radiotherapy for Early Breast Cancer During 2015–2023. **Clinical Oncology 2024;36(4):e107.**

3.1 Abstract

3.1.1 Background

Breast cancer radiotherapy can increase the risks of heart disease, lung cancer and oesophageal cancer. At present, the best dosimetric predictors of these risks are mean doses to the whole heart, lungs and oesophagus, respectively. We aimed to estimate typical doses to these organs and resulting risks from UK breast cancer radiotherapy.

3.1.2 Methods

A systematic review and meta-analysis was conducted of planned or delivered mean doses to the whole heart, lungs or oesophagus from UK breast cancer radiotherapy in studies published during 2015-2023. Average mean doses were summarised for combinations of laterality and clinical targets. Heart disease and lung cancer mortality risks were then estimated using established models.

3.1.3 Results

For whole heart, thirteen studies reported 2893 doses. Average mean doses were higher in left than in right-sided radiotherapy and increased with extent of clinical targets. For left-sided radiotherapy, average mean heart doses were: 2.0Gy (range 1.2-8.0Gy) breast or chest wall, 2.7Gy (range 0.6-5.6Gy) breast or chest wall +axilla/supraclavicular nodes (Ax/SF) and 2.9Gy (range 1.3-4.7Gy) breast or chest wall ±Ax/SF +internal mammary lymph nodes (IMN). For right-sided radiotherapy, average mean heart doses were: 1.0Gy (range 0.3-1.0Gy) breast or

chest wall and 1.2Gy (range 1.0-1.4Gy) breast or chest wall +Ax/SF. There were no whole heart dose estimates from right internal mammary radiotherapy.

For whole lung, six studies reported 2230 doses. Average mean lung doses increased with extent of targets irradiated: 2.6Gy (range 1.4-3.0Gy) breast or chest wall, 3.0Gy (range 0.9-5.1Gy) breast or chest wall +Ax/SF and 7.1Gy (range 6.7-10.0Gy) breast or chest wall ±Ax/SF +IMN.

For whole oesophagus, two studies reported 76 doses. Average mean oesophagus doses increased with extent of targets irradiated: 1.4Gy (range 1.0-2.0Gy) breast or chest wall +Ax/SF and 5.8Gy (range 1.9-10.0Gy) breast or chest wall ±Ax/SF +IMN.

3.1.4 Conclusion

The typical doses to these organs may be combined with dose-response relationships to estimate radiation risks. Estimated 30-year absolute lung cancer mortality risks from modern UK breast cancer radiotherapy for patients irradiated when aged 50 years were 2 to 6% for long-term continuing smokers, and <1% for non-smokers. Estimated 30-year mortality risks for heart disease were <1%.

3.2 Introduction

Adjuvant radiotherapy is received by around two thirds of patients as part of their treatment for early breast cancer in the UK.[1] Radiotherapy reduces the risk of breast cancer death when targeted at the whole breast after breast conserving surgery or, in lymph node positive breast cancer, when targeted at the chest wall after mastectomy, with additional survival benefits when targeted also at the regional lymph nodes.[2–4] Randomised trials have, however, shown that radiotherapy can increase the risks of death from heart disease, lung cancer and oesophageal cancer.[5]

To inform clinical decisions, oncologists need to weigh the absolute magnitudes of the benefits from radiotherapy against the absolute magnitudes of its risks. Radiation risks of heart disease, lung cancer and oesophageal cancer vary according to the doses received by the heart, lungs and oesophagus respectively. Organ doses in breast cancer radiotherapy vary according to individual anatomy, breast cancer laterality, radiotherapy targets irradiated and techniques used.[6–8] For a given combination of technique and target, organ doses may also vary according to geographical region. This is because techniques may be applied differently across different cancer centres. In previous systematic reviews, heart and lung doses from tangential breast or chest wall radiotherapy were typically lower in the UK than in some other countries.[7, 8] This may be due to availability of specialised techniques.[9–16]

In this study, we estimate typical mean doses to the whole heart, lungs and oesophagus from modern UK breast cancer radiotherapy and the extent to which they vary. We focus on mean organ doses because the dose-response relationships

with the largest numbers of events in patients with individual dosimetry, are based on mean doses to the heart, lungs and oesophagus.[17] We then illustrate how these typical mean doses might be used to estimate the absolute risks of death from heart disease and lung cancer from UK radiotherapy by combining them with published dose-response relationships and cause-specific mortality rates.

3.3 Methods

A systematic review of mean radiation doses to the whole heart, lungs or oesophagus from UK radiotherapy for early breast cancer published during 2015-2023 was performed with reference to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[18] This date range was used because our aim was to assess modern radiotherapy. The review was registered on the International Prospective Register of Systematic Reviews.[19]

3.3.1 Study eligibility

Eligible studies were those reporting planned or delivered mean whole organ doses (Gy) to the heart, lungs or oesophagus from UK radiotherapy for early breast cancer published between 1st January 2015 and 12th June 2023. Eligible studies included at least one radiotherapy plan generated since 1st January 2015. Studies where only some dose estimates were produced during 1st January 2015 to 12th June 2023 were included. A similar approach was taken for radiotherapy that had been re-planned as part of a study, regardless of whether dates were specified, if the publication date fell within 1st January 2015 to 12th June 2023. We excluded studies that specified all radiotherapy was planned prior to 2015.

Studies were categorised as dosimetry (i.e. studies that reported doses from radiotherapy plans done for research purposes only), observational/audit (i.e. studies that reported doses delivered to patients in routine practice only), dosimetry & observational (i.e. studies that included doses in both research and routine practice) and interventional (i.e. studies that reported doses received by patients in clinical trials). Early breast cancer was defined as disease confined to the breast or axillary lymph nodes that could be removed surgically. Patients of any age or sex were included. For the heart and oesophagus, whole organ doses were eligible. For the lungs, whole organ dose referred to the dose distributed among both lungs. Studies that reported separate mean ipsilateral lung dose and mean contralateral lung dose were eligible since these doses could be averaged to estimate mean whole lung dose.

3.3.2 Study identification

Eligible studies were identified by searching MEDLINE and Embase. The search strategy used terms for breast cancer, radiotherapy and dose (Appendix B.1). Studies from the UK were identified using a National Institute for Health and Care Excellence (NICE) validated search filter which has been shown to retrieve UK-focused evidence with high recall.[20] Two reviewers (AI and FH) independently assessed titles and abstracts returned by the search for eligibility. To minimise the risk of including duplicate study cohorts, study datasets were compared using available information on geographical location, dates of radiotherapy plans, radiotherapy descriptions and numbers of patients irradiated. Studies were excluded if they included radiation doses already reported first in another publication (e.g.

some reviews).

3.3.3 Data extraction

A data extraction form was designed, with definitions of treatment planning methods and radiotherapy techniques informed by previous similar reviews (Appendix B.2).[6–8] Two reviewers (AI and FH) independently extracted the data using Covidence systematic review software.[21] Differences were resolved through consensus.

From each included study the following information was sought: first author, year of publication, geographical location of the cancer centre where the radiotherapy was planned, study design and years during which radiotherapy was planned or delivered. The radiotherapy description included treatment planning methods, radiotherapy technique, beam type and energy, use of breathing control, laterality of the cancer(s), clinical targets, target dose and fractionation, and whether a boost to the tumour bed was given. Patient treatment position and contouring guidelines were also noted.

Dose terms were as follows: "whole organ dose" refers to the dose averaged over the whole organ. "Mean whole organ dose" is the mean of whole organ doses for a particular group of patients in a study (ie each row of tables B.2, B.4, B.6). "Average mean whole organ dose" is the average dose for several groups of patients combined (ie several rows in tables B.2, B.4, B.6). Dose statistics extracted were the mean (or median, where mean was not reported), standard deviation and range for the whole heart, lung or oesophagus. For each mean whole organ dose statistic, the total number of contributing individual dose estimates was recorded. The total

number of patients and CT planning scans from which individual dose estimates were created were counted, as were the number and percentage of dose estimates delivered to patients. Some dosimetry studies may have included CT scans and/or radiotherapy plans that had been previously used in other studies, however, to the best of our knowledge the reported individual organ dose estimates were unique to each study.

The number of patients described as having unusual anatomy was sought. For one study, mean whole organ doses were reported in six categories of target dose and laterality, but the number of individual patients, and hence dose estimates, in each category was not reported.[22] The likely number of patients in each of the six categories was therefore estimated by considering the published percentages of patients who received left and right-sided radiotherapy within each of the dose levels in the trial (56Gy, 53Gy, 48Gy).

3.3.4 Data analysis

Included studies were grouped according to the organ(s) at risk for which they reported doses. Clinical targets were grouped as: breast or chest wall only (Br/CW only); breast or chest wall with either axilla or supraclavicular nodes (Br/CW +Ax/SF); breast or chest wall with either axilla or supraclavicular nodes, also including internal mammary nodes (Br/CW ±Ax/SF +IMN). Laterality for each mean whole organ dose estimate was defined as all patients had left-sided cancer (L); all patients had right-sided cancer (R); some patients had left- and some had right-sided cancer (L/R). No patients were reported with bilateral cancer.

For heart, dose estimates were categorised first by breast cancer laterality, then

by radiotherapy clinical targets. For lung, ipsilateral and contralateral lung doses were averaged to estimate whole lung dose, since the dose-response relationship for radiation-induced lung cancer is based on whole lung dose.[5] Mean whole lung doses were then categorised by radiotherapy clinical targets. For oesophagus, mean whole oesophagus doses were categorised by clinical targets.

For each combination of radiotherapy clinical targets and laterality, the overall average mean whole heart dose was calculated by weighting the mean whole heart dose in each study by the number of individual dose estimates it was based on. The standard error (SE) of each overall average was then calculated in similar fashion.[23] Tests of heterogeneity between the overall average mean whole heart dose in the three laterality groups and tests of trend in average mean whole heart dose across the extent of the clinical targets irradiated were carried out using variance-weighted least squares. Average mean whole lung and oesophagus doses and trends across the extent of clinical targets irradiated were carried out similarly. Calculations were carried out using the data analysis tool available in the statistical software R version 4.2.2.[24]

3.3.5 Analyses using individual patient doses in a single UK centre

Organ doses received in routine practice may be higher than those in papers where authors have chosen to publish their doses. Therefore, the extent to which published laterality- and target-specific doses are reflected in routine clinical practice was assessed. Organ doses were estimated for patients irradiated in one cancer centre (Oxford). Fifty consecutive patients in the centre's CT planning database

who received radiotherapy for early breast cancer during May and June 2018 were selected. The heart, lungs and oesophagus were contoured and individual patient whole organ doses were estimated. For each organ, mean whole organ doses were then estimated for different clinical situations.

3.4 Results

Fourteen studies published during 2015-2023 reported mean whole organ doses (Gy) to the heart, lungs and/or oesophagus from UK radiotherapy for early breast cancer (Figure B.1, Appendix B.4). Heart dose was reported in 13 studies, lung dose in 6 studies and oesophagus dose in 2 studies.

3.4.1 Heart

Mean whole heart doses were reported from a total of 2893 individual dose estimates (Figure 3.2, Tables B.1, B.2). Of these, 2505 (87%) were delivered to patients. The other 388 (13%) were from dosimetry studies (Table B.1). Two large studies included 2313 (80%) of the doses. The largest study reported doses in a clinical trial (IMPORT HIGH), involving 39 radiotherapy centres throughout the UK and 1958 patients.[22] Patients in IMPORT HIGH underwent breast cancer radiotherapy between 2009 and 2015. As the regimens from 2015 could not be separated from those of 2009 to 2014, this study was considered to fall within the scope of the review as per the predetermined inclusion criteria.

The second largest study was a national audit of breast cancer radiotherapy practice in the UK, reporting doses on 355 patients.[25] The audit presented summary heart doses in routine clinical practice, but doses were not provided sepa-

rately according to clinical targets. The remaining 11 studies each included between 10 and 98 whole heart dose estimates.

There were 2314 whole heart dose estimates (80%) from intensity modulated radiotherapy (IMRT) techniques using photons (Table B.2), 28 (1%) from newer IMRT techniques using protons and 196 (7%) from older photon techniques using tangential fields with fixed gantry angles. Breathing control could not be ascertained for 2545 (88%) of whole heart dose estimates. The use of deep inspiratory breath hold was specified for 212 (7%) and free breathing for 136 (5%) of estimates (Table B.2).

There were 1646 whole heart doses from left-sided radiotherapy, 1013 from right-sided radiotherapy and 234 from mixed laterality (some left and some right) (Figure 3.2). For left-sided radiotherapy, average mean whole heart dose (Gy) from UK radiotherapy was 2.3Gy (SE 0.4Gy), with a wide range (0.6-8.0Gy) for individual patients. For right-sided radiotherapy, average mean whole heart dose was 1.2Gy (SE 0.1Gy, range 0.3-1.4Gy). For mixed laterality, it was 1.8Gy (SE 0.4Gy, range 0.2-4.4Gy). Average mean whole heart dose increased with the extent of clinical targets irradiated. For left-sided radiotherapy, it was 2.0Gy (SE 0.4Gy) from breast or chest wall only, 2.7Gy (SE 0.2Gy) from breast or chest wall +Ax/SF and 2.9Gy (SE 0.5Gy) from breast or chest wall ±Ax/SF +IMN. For right-sided radiotherapy, average mean whole heart dose was 1.0Gy (SE 0.0Gy) from breast or chest wall only and 1.2Gy (SE 0.1Gy) from breast or chest wall +Ax/SF. There were no whole heart dose estimates from right internal mammary radiotherapy.

In IMPORT HIGH, 22 mean whole heart doses from left radiotherapy were 2.4, 2.7 and 2.9Gy, based on 316, 319 and 340 dose estimates respectively (Table B.2). In other studies, mean whole heart doses in left radiotherapy varied from 0.4 to

6.4Gy based on between 3 and 355 dose estimates. For right radiotherapy, mean whole heart doses in IMPORT HIGH were 1.0, 1.3 and 1.4Gy, based on 316, 340 and 327 dose estimates respectively. In other studies, mean whole heart doses in right radiotherapy were 0.9 and 1.0Gy, each based on 15 doses.

3.4.2 Lungs

Six of the fourteen studies included both ipsilateral and contralateral lung doses (Tables B.3, B.4). This gave rise to a total of 2230 whole lung dose estimates (Figure 3.3). Of these, 2049 (92%) were delivered to patients. The largest study was the IMPORT HIGH clinical trial, which included 1958 (88%) of the whole lung doses.[22]

All whole lung dose estimates were from intensity modulated radiotherapy (IMRT) using photons (Table B.4). Breathing control could not be ascertained for 2180 (98%) of whole lung dose estimates. The use of deep inspiratory breath hold was specified for 50 (2%) of estimates (Table B.4).

There were 102 whole lung dose estimates from radiotherapy to the breast or chest wall only, 2038 from radiotherapy to the breast or chest wall +Ax/SF nodes and 90 from radiotherapy to the breast or chest wall ±Ax/SF +IMN. Average mean whole lung dose increased with the extent of clinical targets irradiated, taking values 2.6Gy (SE 0.3Gy, range 1.4-3.0Gy) from the breast or chest wall only, 3.0Gy (SE 0.1Gy, range 0.9-5.1Gy) from the breast or chest wall +Ax/SF nodes and 7.1Gy (SE 0.4Gy, range 6.7-10.0Gy) from the breast or chest wall ±Ax/SF +IMN (Figure 3.3).

In IMPORT HIGH, 22 mean whole lung doses were 0.4, 0.5 and 0.6Gy, based

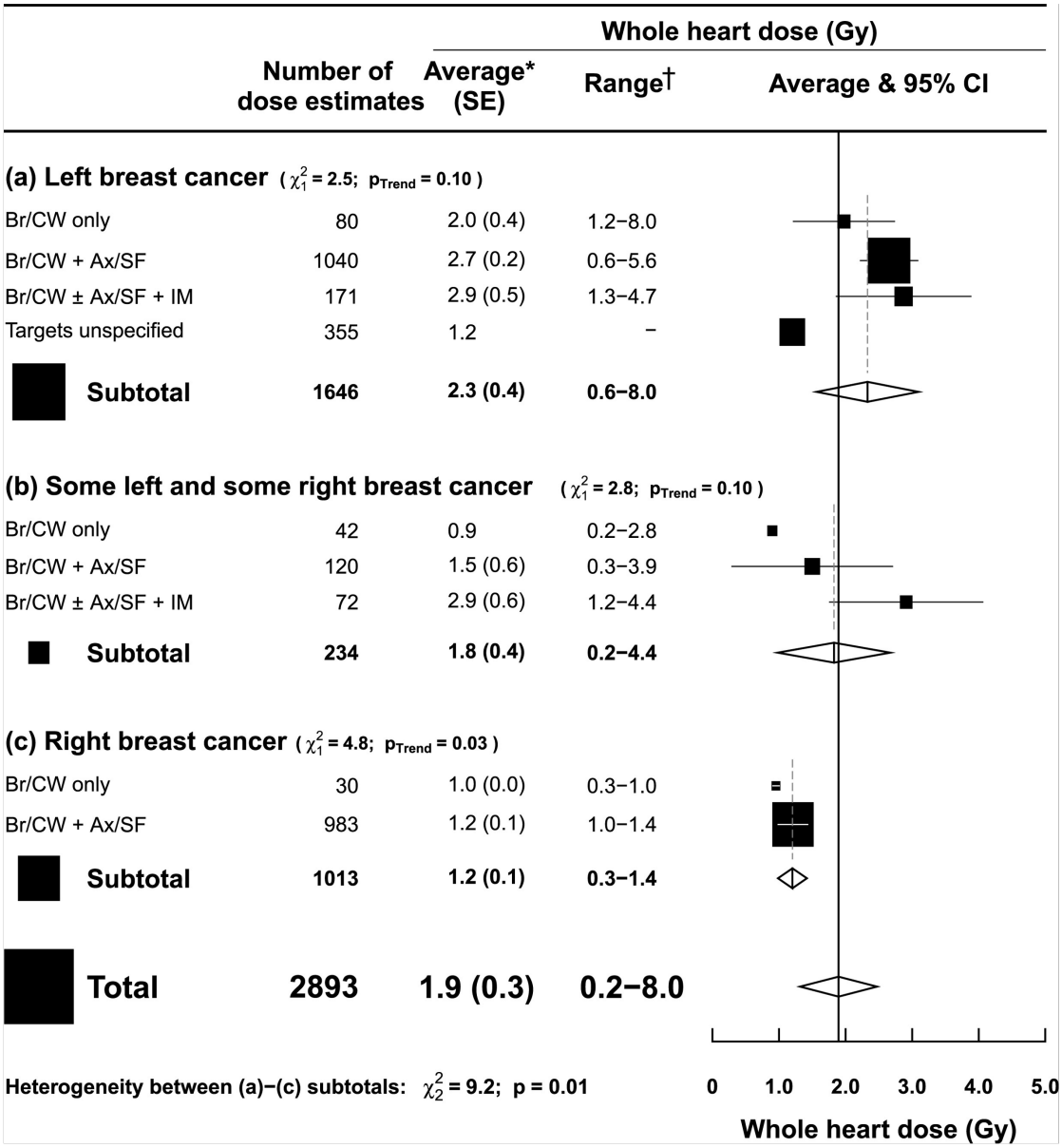


Figure 3.2: Estimated typical mean whole heart doses from UK breast cancer radiotherapy according to breast cancer laterality and clinical targets

*Average mean whole heart dose, weighted by the number of individual dose estimates, was calculated for each category of breast cancer laterality and clinical targets.

†The range refers to the range of individual dose estimates. Where this was unavailable, the range of reported mean doses was used.

P_{trend} values are for association of average dose with increasing targets irradiated

Abbreviations: Ax=axilla lymph nodes, Br=breast, CI=confidence interval, CW=chest wall, Gy=gray, IM=internal mammary lymph nodes, SE=standard error, SF=supraclavicular fossa lymph nodes

on 632, 659 and 667 dose estimates respectively (Table B.4). In other studies, mean whole lung doses varied from 0.2 to 3.3Gy based on between 5 and 40 dose estimates.

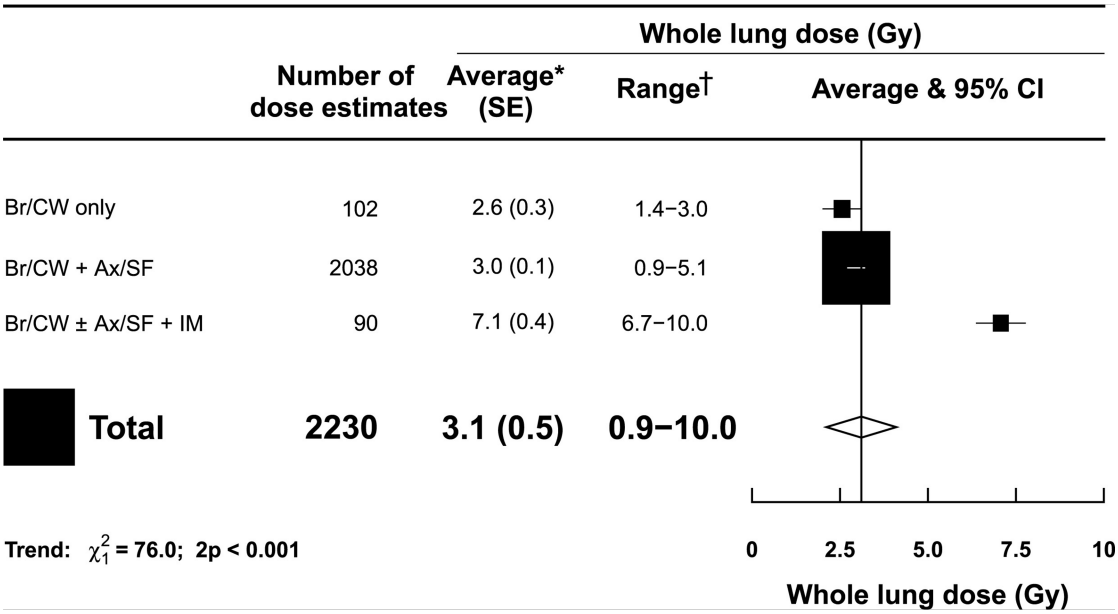


Figure 3.3: Estimated typical mean whole lung doses from UK breast cancer radiotherapy according to clinical targets
*Average mean whole lung dose, weighted by the number of individual dose estimates, was calculated for each category of clinical targets.
†The range refers to the range of individual dose estimates. Where this was unavailable, the range of reported mean doses was used.
P_{trend} values are for association of average dose with increasing targets irradiated.
Abbreviations: Ax=axilla lymph nodes, Br=breast, CI=confidence interval, CW=chest wall, Gy=gray, IM=internal mammary lymph nodes, SE=standard error, SF=supraclavicular fossa lymph nodes.

3.4.3 Oesophagus

Two of the fourteen studies reported whole oesophagus doses from a total of 76 individual estimates. Of these 76 doses, 20 (26%) were delivered to patients and the rest were estimated for research purposes (Figure 3.4, Tables B.5, B.6).

Just over half of the whole oesophagus doses were from intensity modulated radiotherapy (IMRT) techniques using photons (40/76, 53%), with the other 36 (47%) doses from older photon radiotherapy techniques using tangential fields with fixed gantry angles (Table B.6). Breathing control was not specified for any patient group. Average mean whole oesophagus dose increased with the extent of clinical targets irradiated (Figure 3.4). It was 1.4Gy (SE 0.3Gy, range 1.0-2.0Gy) from radiotherapy to the breast or chest wall +Ax/SF, based on 36 individual dose estimates, and 5.8Gy (SE 0.3Gy, range 1.9-10.0Gy) from radiotherapy to the breast or chest wall ±Ax/SF +IMN, based on 40 individual dose estimates.

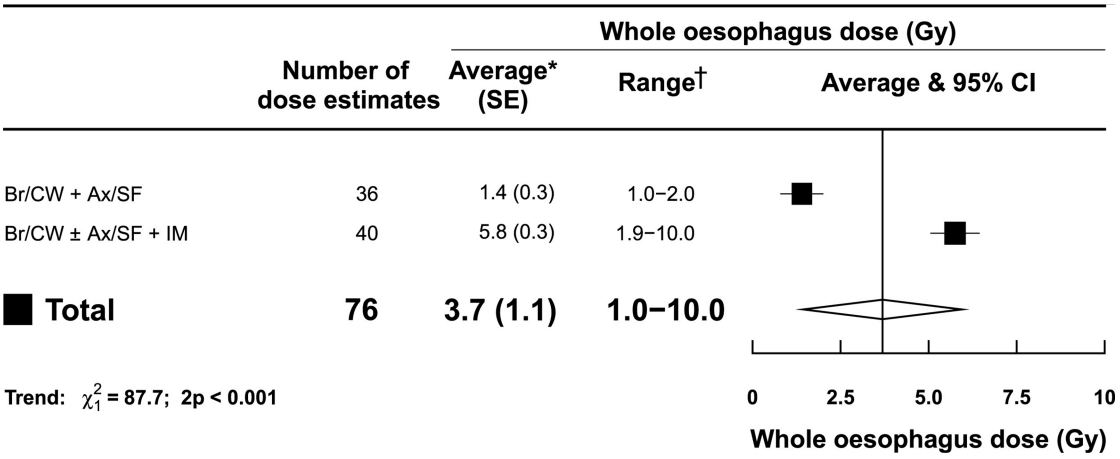


Figure 3.4: Estimated typical mean whole oesophagus doses from UK breast cancer radiotherapy according to clinical targets

*Average mean whole oesophagus dose, weighted by the number of individual dose estimates, was calculated for each category of clinical targets.

†The range refers to the range of individual dose estimates. Where this was unavailable, the range of reported mean doses was used.

P_{trend} values are for association of average dose with increasing targets irradiated.

Abbreviations: Ax=axilla lymph nodes, Br=breast, CI=confidence interval, CW=chest wall, Gy=gray, IM=internal mammary lymph nodes, SE=standard error, SF=supraclavicular fossa lymph nodes.

3.4.4 Analyses using individual patient doses in a single UK centre

(See Appendix B.11, Table B.7) Of 50 patients, 30 received left-sided radiotherapy and 20 right-sided radiotherapy. Patients were irradiated using forward-planned IMRT, with DIBH in left radiotherapy. Breast or chest wall radiation was received by 35 patients, breast or chest wall +Ax/SF by 14 patients and breast or chest wall ±Ax/SF +IMN radiotherapy by one patient. Mean whole heart dose was higher in left than in right-sided radiotherapy; left 1.3Gy (range 0.6-2.9Gy) and right 0.4Gy (range 0.2-0.8Gy). For lung, mean whole organ dose was 3.8Gy (range 2.0-6.8Gy) and for oesophagus it was 0.5Gy (range 0.1-2.4Gy).

Comparing mean doses in the single centre audit with average mean doses in the review of UK published doses, audit doses were lower for whole heart and oesophagus: heart, audit 1.0Gy (range 0.2-2.9Gy) versus review 1.9Gy (range 0.6-8.0Gy); oesophagus, audit 0.5Gy (range 0.1-2.4Gy) versus review 3.7Gy (range 1.0-10.0Gy). For heart and oesophagus, all target and laterality-specific organ doses were also lower in the audit than in the review.

In contrast, for whole lung, mean audit doses were slightly higher than average mean doses in the review: audit 3.8Gy (range 2.0-6.8Gy) versus review 3.1Gy (0.9-10.0Gy). Target-specific doses were also slightly higher in the audit than in the review: breast or chest wall: audit 3.5Gy versus review 2.6Gy and breast or chest wall +Ax/SF: audit 4.6Gy versus review 3.0Gy.

3.5 Discussion

This systematic review and meta-analysis provides up-to-date estimates of typical doses to the whole heart, lungs and oesophagus from UK radiotherapy for early breast cancer. Published average mean whole organ doses were around 2Gy for heart, 3Gy for lung and 4Gy for oesophagus. For all organs, doses increased with the extent of radiotherapy clinical targets included. Heart doses also varied according to breast cancer laterality.

3.5.1 Strengths and limitations

This study has several strengths. It summarises doses received by all three organs (heart, lung and oesophagus) implicated in the main mortality risks of breast cancer radiotherapy.[5] To the best of our knowledge it is the largest quantitative synthesis of organ doses from modern UK breast cancer radiotherapy. Studies were identified and data extracted independently by both an oncologist and a radiation health sciences officer. The literature search used a validated method of identifying UK studies and the analyses used an established method of dose meta-analysis.[6–8, 20] The search strategy was wide, so it is likely that all relevant studies were identified. Summary doses were based on more than 5000 individual dose estimates in fourteen studies. Average mean whole organ doses were weighted according to the number of patients contributing to each, so that the doses for different clinical scenarios are likely to be representative of typical doses received by patients in these scenarios. An audit of 50 patients in a single cancer centre enabled the published doses to be compared with doses in routine clinical practice in patients irradiated according to national UK guidance. The extent to which

the doses received by these patients reflect practice in other UK centres is not known. Routine UK practice can be assessed by national audits where all cancer centres are invited to contribute data. For heart, mean whole organ doses from a national audit were included in our study, with 355 patients from 47 of the 58 UK radiotherapy centres.[25] National audit doses were unavailable for lung and oesophagus. In future, national collection of organ doses may enable more comprehensive assessment of routine practice.

There were several limitations in our study. First, individual patient doses were not usually reported in publications, so standard error and range could not be presented for some mean whole organ doses. Second, methods of contouring the organs were rarely reported for included studies. This may have contributed to the wide range of reported doses. Third, only 76 estimates of oesophagus dose were available. Fourth, dose-volume measures were not extracted. Previous reviews found that comparable heart and lung dose-volume parameters in contemporary breast cancer radiotherapy were infrequently reported.[7, 8] Nevertheless, mean whole organ doses are currently the best available predictors of radiation-induced heart disease and cancer.[17] Future epidemiological studies including detailed individual patient three-dimensional doses to the heart, lungs or oesophagus may provide further information on whether dose-volume measures, or doses to parts of organs, improve prediction of radiation-induced heart disease or cancer.[26, 27]

A fifth limitation of our study is that most heart and lung doses were from a single clinical trial (IMPORT HIGH). Practice in radiotherapy centres that recruited to this trial may differ from routine practice in other centres. For example, centres recruiting to the trial had contouring protocols and dosimetry quality assurance, which may not be available in other centres. However, 39 of the 58 (67%)

UK centres entered patients into IMPORT HIGH, so the organ doses from this trial represent practice in the majority of UK centres. In addition, the 39 centres that recruited to IMPORT HIGH are likely to treat more patients per year than the other 19 centres that did not recruit to IMPORT HIGH. Therefore the radiotherapy practices in these 39 centres are likely to reflect those available to most UK breast cancer patients. In addition, large multicentre trials such as IMPORT HIGH have improved consistency and increased quality assurance nationwide in routine radiotherapy.

3.5.2 Typical absolute radiation-induced mortality risks

The average mean whole organ doses from different combinations of breast cancer laterality and clinical targets irradiated may be used to estimate typical radiation mortality risks using published dose-response relationships (Appendix B.12). For an individual, the absolute risk of death from heart disease or lung cancer attributable to radiotherapy may be estimated using their background death rate in the absence of radiotherapy together with the percentage increase in death rate arising from radiotherapy for the organs exposed.

For ischaemic heart disease, the mortality rate was estimated by Darby et al (2013) to increase by 7.4% per Gy (95% CI 2.9-14.5) mean whole heart dose.[28] The study included 963 irradiated women with major coronary events and 1205 irradiated controls. In that study the mean radiation dose to the heart was a better predictor of the rate of major coronary events than the mean dose to the left anterior descending coronary artery. In addition, the mean dose to the left anterior descending coronary artery was not significantly associated with the rate

of major coronary events after the mean dose to the heart was taken into account. In a sub-study of the 456 cases with available information on the site of cardiac injury, mean segment dose was associated with injury for all individual segments of the left ventricle and coronary arteries.[29] For estimation of cardiac radiation-risks in the clinic today, the mean whole heart dose is the best predictor currently available. However, some uncertainties remain, including the possible effects of fractionation or beam modality on the slope of the dose-response.

An indication of absolute risks from typical doses in different clinical situations was given in the online Appendix of Darby 2013 by combining the 7.4% per Gy dose-response with population-based mortality rates for ischaemic heart disease.[28] Some of these absolute risks are reproduced in Text S5 and can be used to give approximate indications of the cardiac risks for patients today. The average mean heart doses found in our study with known laterality and targets varied from 1.0 to 2.9Gy (Figure 3.2). This suggests that, for a patient aged 50 years when irradiated, typical UK radiotherapy would increase their absolute 30-year risk of death from ischaemic heart disease by between 0.2% and 0.7% (Table 3.1, Figure 3.5, Appendix B.12). These estimates do not take into account the competing risk of death from breast cancer. In addition, death rates from ischaemic heart disease have reduced during the past 20 years, so the radiation-induced heart disease mortality risks for patients today may be somewhat lower than this.

For lung cancer, in an EBCTCG meta-analysis, the rate of incident radiation-induced lung cancer increased by 11% per Gy mean whole lung dose.[5] The EBCTCG publication applied this dose-response relationship to population mortality data, suggesting an absolute increase in risk of lung cancer death from 5Gy whole lung dose of 0.3% for a non-smoker and 4.4% for a long-term continuing

smoker. Whole lung doses in typical UK breast cancer radiotherapy in our study were usually lower than 5Gy. The average mean whole lung dose for radiotherapy to the breast or chest wall was 2.6Gy, for radiotherapy to the breast or chest wall +Ax/SF it was 3.0Gy and for breast or chest wall ±Ax/SF +IMN it was 7.1Gy (Figure 3.3). If absolute lung cancer mortality risk increased linearly with increasing dose, the corresponding 30-year absolute risks from these doses for a lifelong non-smoker would be 0.2%, 0.2% and 0.4% respectively, while the corresponding risks for a long-term continuing smoker would be 2.3%, 2.6% and 6.2% (Table 3.1, Figure 3.5, Appendix B.12). The risks of radiation-induced lung cancer mortality in ex-smokers are likely to be much closer to those in never-smokers than in current smokers because stopping smoking substantially reduces lung cancer risk, and if a patient stops smoking at the time of radiotherapy, much of the increased risk associated with smoking could be avoided.[5]

For oesophageal cancer, estimates of absolute risk from different oesophagus doses are currently unavailable. However, oesophageal cancer in the general population is uncommon, so absolute oesophageal cancer death risks are likely to be lower than the risks of death from heart disease or lung cancer.[1]

Table 3.1: Estimated typical absolute 30-year risks (%) of radiotherapy-induced mortality for a patient who receives modern UK breast cancer radiotherapy with typical heart and lung doses when aged 50 years

Targets irradiated	**Absolute risks (%) of radiotherapy-induced mortality**					
	Ischaemic heart disease				**Lung cancer**	
	Left cancer, no cardiac risk factors	**Left cancer, ≥1 cardiac risk factor**	**Right cancer, no cardiac risk factors**	**Right cancer, ≥1 cardiac risk factor**	**Non-smoker**	**Long-term continuing smoker**
Br/CW only	0.3	0.4	0.2	0.2	0.2	2.3
Br/CW +Ax/SF	0.4	0.6	0.2	0.2	0.2	2.6
Br/CW ±Ax/SF +IMN	0.5	0.7	–	–	0.4	6.2

Footnotes

Absolute risks were estimated using average mean doses to whole organs at risk (Gy) from modern UK radiotherapy for early breast cancer (Figures 3.2 and 3.3) and the dose-response relationships described in Appendix B.12.

Cardiac risk factors include smoking, see Appendix B.12 for details.

These data are illustrated in Figure 3.5.

Risks of radiation-induced lung cancer mortality in ex-smokers are likely to be much closer to those in never-smokers than in current smokers because stopping smoking substantially reduces lung cancer risk.

Figure 3.2 shows average mean whole heart doses for nine categories of laterality and target.

Absolute risks in this table and Figure 3.5 are shown for the following five categories i.e., all categories excluding "targets unspecified" and "some left and some right."

Breast cancer laterality and target: Average mean whole heart dose (Gy).

Left Br/CW only: 2.0.

Left Br/CW +Ax/SF: 2.7.

Left Br/CW ±Ax/SF +IMN: 2.9.

Right Br/CW only: 1.0.

Right Br/CW +Ax/SF: 1.2.

Abbreviations: Ax=axilla lymph nodes, Br=breast, CW=chest wall, IMN=internal mammary lymph nodes, SF=supraclavicular fossa lymph nodes, "-"=doses were unavailable for these categories.

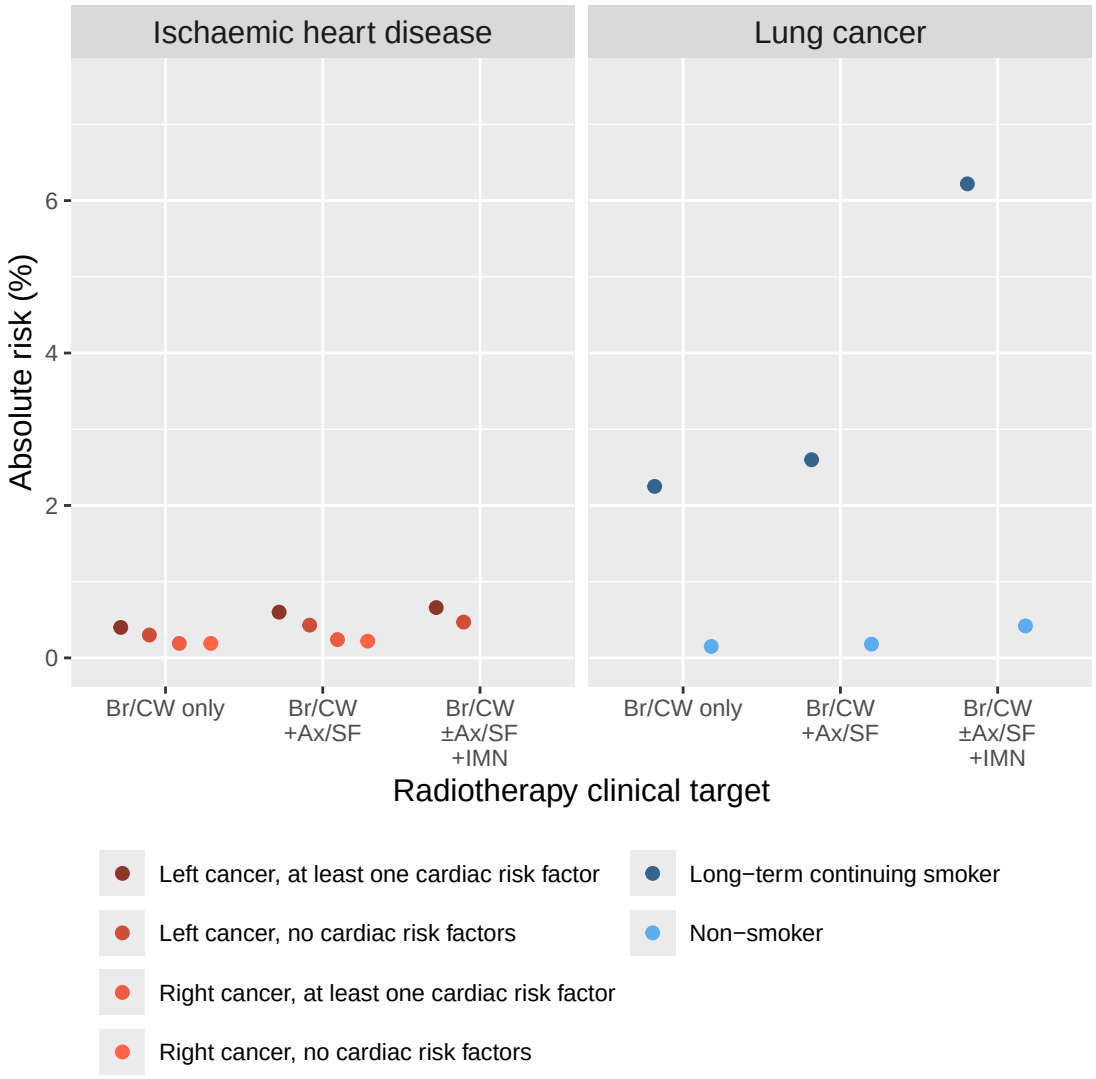


Figure 3.5: Estimated typical absolute 30-year risks (%) of radiotherapy-induced mortality for a patient who receives modern UK breast cancer radiotherapy with typical heart and lung doses when aged 50 years.

Absolute risks were estimated using average mean doses to whole organs at risk (Gy) from modern UK radiotherapy for early breast cancer (Figures 3.2 and 3.3) and the dose-response relationships described in Appendix B.12.

Cardiac risk factors include smoking, see Appendix B.12 for details.

The risks are shown in Table 3.1. Risks of radiation-induced lung cancer mortality in ex-smokers are likely to be much closer to those in never-smokers than in current smokers because stopping smoking substantially reduces lung cancer risk.

Figure 3.2 shows average mean whole heart doses for nine categories of laterality and target. Absolute risks in Table 3.1 and in this figure are shown for the following five categories, i.e., all categories excluding "targets unspecified" and "some left and some right": Breast cancer laterality and target: Average mean whole heart dose (Gy).

Left Br/CW only: 2.0.

Left Br/CW +Ax/SF: 2.7.

Left Br/CW ±Ax/SF +IMN: 2.9.

Right Br/CW only: 1.0.

Right Br/CW +Ax/SF: 1.2.

Abbreviations: Ax=axilla lymph nodes, Br=breast, CW=chest wall, IMN=internal mammary lymph nodes, SF=supraclavicular fossa lymph nodes.

3.5.3 Implications for current clinical practice

The typical doses and absolute risks presented in this study are reassuring for the majority of patients. The current version of the Royal College of Radiologists' breast cancer radiotherapy consent form categorises the "increased risk of heart disease in later life" and "a different cancer in the treatment area" as rare (occurring with a frequency of less than 1%).[30] This statement aligns with the evidence we present for most patients irradiated for breast cancer, who are non-smokers or ex-smokers. For patients who are long-term continuing smokers, i.e., those who are likely to keep smoking, the risks are higher than 1% and the consent form can be annotated to reflect this. These risks are particularly relevant in clinical situations where radiotherapy has not been shown to reduce breast cancer mortality, for example after surgery for carcinoma in situ. These doses and risks may be used in the UK to help guide clinical decisions about radiotherapy benefits and risks for patients today. They can also inform UK national guidelines on optimal dose constraints for breast cancer radiotherapy.

3.5.4 Implications for future research

Although the methods of estimating absolute risks of death from radiation-induced heart disease and lung cancer illustrated in this study are based on the highest-quality published evidence, further work is needed to facilitate their routine estimation.[17] For example, more information is needed on how the risks vary according to age at irradiation, or the type of systemic therapy given in addition to radiation. Information is also needed on the absolute risks of oesophageal cancer from different oesophagus radiation doses. Work is underway to produce estimates that

take into account the competing risks of breast cancer death and other causes of death using up-to-date population data.

3.6 Conclusions

This study provides estimates of typical doses to organs at risk from modern UK breast cancer radiotherapy and illustrates how these may be used in combination with epidemiological data to estimate absolute radiotherapy risks. For a typical 50-year old long-term continuing smoker, the estimated 30-year absolute mortality risks of lung cancer from modern UK breast cancer radiotherapy range from 2 to 6%. However, most breast cancer patients considered for radiotherapy in the UK today are non-smokers or ex-smokers with no cardiac risk factors, and their risks of lung cancer or heart disease death are likely to be less than 1%.

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Addie Ivanova performed the systematic review of radiation doses for her MSc in Radiation Biology. She registered the review protocol, identified eligible studies, extracted the data, and conducted provisional analyses of the data that she presented in her dissertation. She produced the original drafts for Figure S1, Text S3, and Tables S2, S4 and S6. Her provisional analyses also informed the meta-analyses presented in Figures 1-3. She reviewed and edited draft manuscripts.
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Georgios Ntentas supervised the project, provided physics expertise, and reviewed and edited draft manuscripts.
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Carolyn Taylor conceptualised and supervised the project including acquiring funding, provided clinical oncology expertise, conceptualised the data analysis, reviewed and edited draft manuscripts.

Chapter 4

Estimated doses to the lung lobes from radiotherapy regimens for early breast cancer regimens delivered in the Netherlands during 1970-2010.

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Submission for publication is planned.

4.1 Abstract

4.1.1 Background

Exposure of the lungs to radiation has been shown to increase the risk of developing lung cancer more than a decade later. Currently, mean whole lung dose is considered the best dosimetric predictor of radiation-induced lung cancer after breast cancer radiotherapy, but the optimal dose-response relationship is unknown. There is also a lack of information on the relative effectiveness of lung-sparing techniques according to clinical targets of breast cancer radiotherapy.

In a previous study, the relationship between heart doses and radiation-induced heart disease was estimated using data from 754 women irradiated for breast cancer in the Netherlands during 1970-2010. The heart doses were estimated from reconstructions of forty-four breast cancer radiotherapy regimens identified from the radiotherapy charts of the 754 women.

Here we estimate doses received by the lung lobes from these regimens, delivered in the Netherlands during 1970-2010, and compare the variation in these doses with the variation in mean whole lung doses from the same regimens. Long-term clinical outcomes are available for these women, and therefore these dose estimates may be used to develop a new dose-response relationship for radiation-induced lung cancer that incorporates more information on the spatial distribution of radiation dose throughout the lungs compared with mean whole lung dose.

We also categorise these lung doses according to determining features of the radiotherapy regimens: clinical targets; beam types and arrangements; dose fractionation and treatment planning method, so that variation in lung doses according to these factors may be later explored.

The aim is to describe the spatial variation in lung lobe doses from historical breast cancer radiotherapy, so that we can better predict risks of radiation-induced lung cancer from modern breast cancer radiotherapy and guide future selection of lung-sparing radiotherapy.

4.1.2 Methods

First, all five anatomical lung lobes were contoured on a patient CT scan: right upper lobe (RUL), right middle lobe (RML), right lower lobe (RLL), left upper lobe (LUL) and left lower lobe (LLL). Forty four breast cancer regimens delivered in the Netherlands during 1970-2010 had already been reconstructed on this CT scan for a previous study.

Second, mean lung lobe doses from the 44 breast cancer regimens were estimated and described.

Third, the variation in lung lobe doses was described according to radiotherapy clinical targets.

4.1.3 Results

From 22 right radiotherapy regimens, medians (interquartile ranges, IQRs) of estimated mean radiation doses (Gy) received by the RUL, RML, RLL and whole lungs were: 18.2Gy (IQR 7.1), 21.3Gy (IQR 10.4), 9.1Gy (IQR 7.4Gy) and 8.8Gy (3.7Gy). From equivalent left regimens, estimated doses received by the LUL, LLL and whole lungs were 11.7Gy (IQR 7.4), 15.1Gy (IQR 10.3) and 7.8Gy (IQR 5.8).

From IMN fields of 16 right IMN regimens, medians (IQRs) of estimated mean radiation doses (as percentages of total prescribed IMN field doses) received by

the RUL, RML, RLL and whole lungs were: 38.8% (IQR 15.9), 26.7% (IQR 7.4), 24.7% (IQR 20.8), and 19.4% (IQR 8.8). From equivalent left fields, estimated doses received by the LUL, LLL and whole lungs were 26.6% (IQR 6.2), 19.6% (IQR 20.0) and 12.7% (IQR 6.0).

From supraclavicular lymph node fields of three right supraclavicular lymph node regimens, medians (IQRs) of estimated mean radiation doses received by the RUL, RML, RLL and whole lungs were: 23.4% (IQR 5.1), 13.3% (IQR 6.4), 10.2% (4.0) and 9.8% (IQR 0.4). From equivalent left fields, estimated doses received by the LUL, LLL and whole lungs were 29.3% (IQR 1.35), 13.7% (IQR 4.95) and 12.1% (IQR 1.4).

From breast or chest wall fields of 14 right breast or chest wall regimens, medians (IQRs) of estimated mean radiation doses received by the RUL, RML, RLL and whole lungs were: 6.0% (IQR 12.0), 22.6% (IQR 30.1), 3.2% (IQR 2.1) and 4.4% (IQR 6.8). From equivalent left fields, medians (IQRs) of estimated mean radiation doses received by the LUL, LLL and whole lungs were: 14.1% (IQR 17.7), 2.6% (IQR 1.3) and 4.3% (IQR 5.4).

4.1.4 Conclusions

There was considerable variation in mean lung lobe doses compared with mean whole lung doses from radiotherapy regimens delivered in the Netherlands during 1970-2010, with the greatest variation in doses from IMN fields. The planned dose-response relationship for radiation-induced lung cancer using these lung lobe doses may better predict risks of radiation-induced lung cancer from modern breast cancer radiotherapy and the descriptions of variation in doses according to reg-

imen clinical targets may support efforts to guide the selection of lung-sparing techniques.

4.2 Introduction

During radiotherapy for early breast cancer, some radiation dose is received by the lungs. The early adverse clinical effects of this—usually occurring within six months—include radiation pneumonitis. Later effects—usually emerging after six months—include lung fibrosis. More than a decade after receiving radiotherapy for breast cancer there is an increased relative risk of death from radiation-induced lung cancer.[1, 2]

Several patient- and treatment-related factors have been considered to increase the risks of developing radiation-induced lung cancer such as genetic factors, age at the time of receiving radiotherapy, smoking status, the volume of lung irradiated and the radiation dose received.[1]

Currently, mean whole lung dose is considered the best dosimetric predictor of radiation-induced lung cancer. A recent systematic review identified the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2017 meta-analysis of excess rate ratio per gray (ERR/Gy) for radiation-induced lung cancer as the prediction model based on the highest number of lung cancer events.[3] This found that the rate of incident radiation-induced lung cancer increases by 11% per Gy mean whole lung dose (95% CI, 6-19%), and assumes that the dose-response relationship does not depart from linearity.[1, 4–7]

As illustrated in Chapter 3, the relative risks of radiation-induced lung cancer estimated using the EBCTCG 2017 model can be combined with population data to estimate the absolute mortality risks.[8] For example, the estimated average mean whole lung dose from modern UK IMN regimens of 7.1Gy (SE 0.4, range 6.7-10.0) corresponds to a 30-year absolute risk of death from radiation-induced

lung cancer of approximately 0.4% for a 50-year-old lifelong non-smoker and 6.2% for a 50-year-old long-term continuing smoker, assuming the absolute risks increase linearly with increasing dose.[8] As shown in Chapter 5, few advances in breast cancer radiotherapy over recent decades have been shown to reduce mean whole lung dose, which may indicate a lack of innovation or adoption of lung-sparing techniques, but may also indicate that mean whole lung dose is insufficiently sensitive to some advances in radiotherapy beam arrangements and treatment planning methods.

The estimated 30-year absolute risks of radiation-induced lung cancer from modern UK IMN radiotherapy for a typical 50-year-old long-term continuing smoker may outweigh the estimated absolute benefits of IMN radiotherapy for some women. Together with the lack of reduction in mean whole lung doses with advances in IMN radiotherapy over the past 55 years, this information highlights a clinical need for lung-sparing IMN radiotherapy.

Whilst dosimetry studies have shown proton beam therapy to lower mean whole lung doses from IMN radiotherapy (Chapter 5), there is a lack of information on the relative clinical merits of lung-sparing techniques used in photon IMN radiotherapy. The optimal dose-response relationship for radiation-induced lung cancer after radiotherapy for early breast cancer is unknown. Further information is needed to explore whether a dose metric that incorporates more information on the spatial distribution of radiation dose throughout the lungs may better predict the risks of radiation-induced lung cancer from modern breast cancer radiotherapy and may better distinguish the lung-sparing properties of modern breast cancer radiotherapy.[9] This requires information on lung doses, their associated determining factors, and thier associated long-term clinical outcomes from women irradiated

in past decades.

The Cancer Epidemiology Group of Netherlands Cancer Institute are developing a new dose-response relationship for radiation-induced lung cancer using data from women irradiated for breast cancer at the Netherlands Cancer Institute or Erasmus MC Cancer Institute during 1970-2010. Inputs into this model will include various patient- and treatment-related factors. Previously, data from the same cohort of women were used to develop dose-response relationships for heart disease from breast cancer radiotherapy.[10–12] For this previous study 44 breast cancer radiotherapy regimens were identified from 754 radiotherapy charts of women irradiated in the Netherlands during 1970-2010.[10] The radiotherapy regimens using megavoltage and electron fields were then reconstructed on a patient CT scan to estimate doses received by the heart. The method for selecting this CT scan, and the methods of reconstruction using the 3D treatment planning system, have been previously described.[10–12]

To develop a dose-response relationship for radiation-induced lung cancer, estimates of radiation doses to individual anatomical lobes of the lungs from the same radiotherapy regimens that have have already been reconstructed are required. These doses may then be related to the development of radiation-induced lung cancers in the same cohort of women.

Here we present mean radiation doses to the five anatomical lung lobes from the typical breast cancer regimens delivered in the Netherlands during 1970-2010, as for these women long-term clinical outcomes, including development of lung cancer, are available. By incorporating information on spatial variation in dose throughout the lungs, this dose-response relationship for radiation-induced lung cancer may better predict the risks of radiation-induced lung cancer.

We also categorise these lung doses according to determining features of the radiotherapy regimens: clinical targets; beam types and arrangements; dose fractionation and treatment planning method, so that variation in lung doses according to these factors may be later explored.

This may support efforts to guide future selection of lung-sparing radiotherapy.

4.2.1 Methods

First, doses received by the five lung lobes were estimated for 44 breast cancer radiotherapy regimens used at the Netherlands Cancer Institute or the Erasmus MC Cancer Institute during 1970-2010.

4.2.1.1 Reconstruction of radiotherapy regimens

These were reconstructed and published by FD in 2022.[10]

4.2.1.2 Contouring

For this study, the following lung volumes were contoured on the same patient CT scan: whole lungs, right whole lung, left whole lung, right upper lobe, right middle lobe, right lower lobe, left upper lobe and left lower lobe. (Figure 4.1) The whole lungs and separate right and left lungs were delineated using the guidance of a published contouring atlas.[13] Individual lung lobe contours were independently reviewed and agreed with specialists in both Clinical Oncology (FD) and Radiology (LW).

4.2.1.3 Dose calculations

Radiation doses received by the lung lobes were calculated for each of the 44 radiotherapy regimens used in the Netherlands during 1970-2010. First the mean percentage radiation dose received by each of the lung volumes was extracted for each of the fields comprising the 44 radiotherapy regimens using the most frequently prescribed total field dose (100%). Then for each lung volume, the mean radiation dose (Gy) from the regimen was estimated by taking the sum of the mean doses (Gy) from each field.

The analytical anisotropic algorithm was used to calculate doses for photon plans, Monte Carlo was used for electron plans, and pencil beam was used for cobalt plans.

Doses to lung volumes for regimens using orthovoltage IMN fields were estimated from 2D manual planning calculations. First the orthovoltage field borders were defined on the patient CT scan using the CT-based treatment planning system. Sixteen axial CT images spaced 1.5cm apart, spanning the whole lungs from top to bottom, were printed and scaled to life size. Sample CT images spaced 4.5cm apart were then selected for dose calculation. These slices were selected to ensure all lung structures were appropriately represented. Isodose distributions for 250kV x-rays were superimposed on these printed CT scans, and the dose distributions were mapped onto the lung structures. An applied dose was used in keeping with the descriptions of the regimen abstracted from the original radiotherapy charts. The isodose shift method was used to correct for tissue inhomogeneity within the lungs. For each lung structure, the mean percentage dose was estimated by measuring the proportion of structure included within each isodose level. An average

dose to the structure was then calculated using the individual estimates from each of the sampled CT images.

4.2.1.4 Variation in lung lobe doses from 44 typical breast cancer regimens first used in the Netherlands during 1970-2010

Lung doses from each regimen are expressed in gray as it is not possible to express the results of plansums as a percentage of the total prescribed dose. Mean doses in gray were summarised using descriptive statistics calculated using R (version 4.4.2).

4.2.1.5 Variation in lung lobe doses from breast cancer regimens according to clinical targets

Lung doses are known to vary according to breast cancer radiotherapy clinical targets, therefore to explore variation in lung volume doses, regimens were categorised according to breast cancer radiotherapy clinical targets (breast or chest wall, supraclavicular fossa lymph nodes and internal mammary lymph nodes). Lung doses from each field could be expressed as percentages of the prescribed field doses as no plansums were necessary. This had the advantage of facilitating comparison of doses from fields with varying prescribed doses. Mean doses as percentages of the prescribed field doses were summarised using descriptive statistics calculated using R (version 4.4.2). [14]

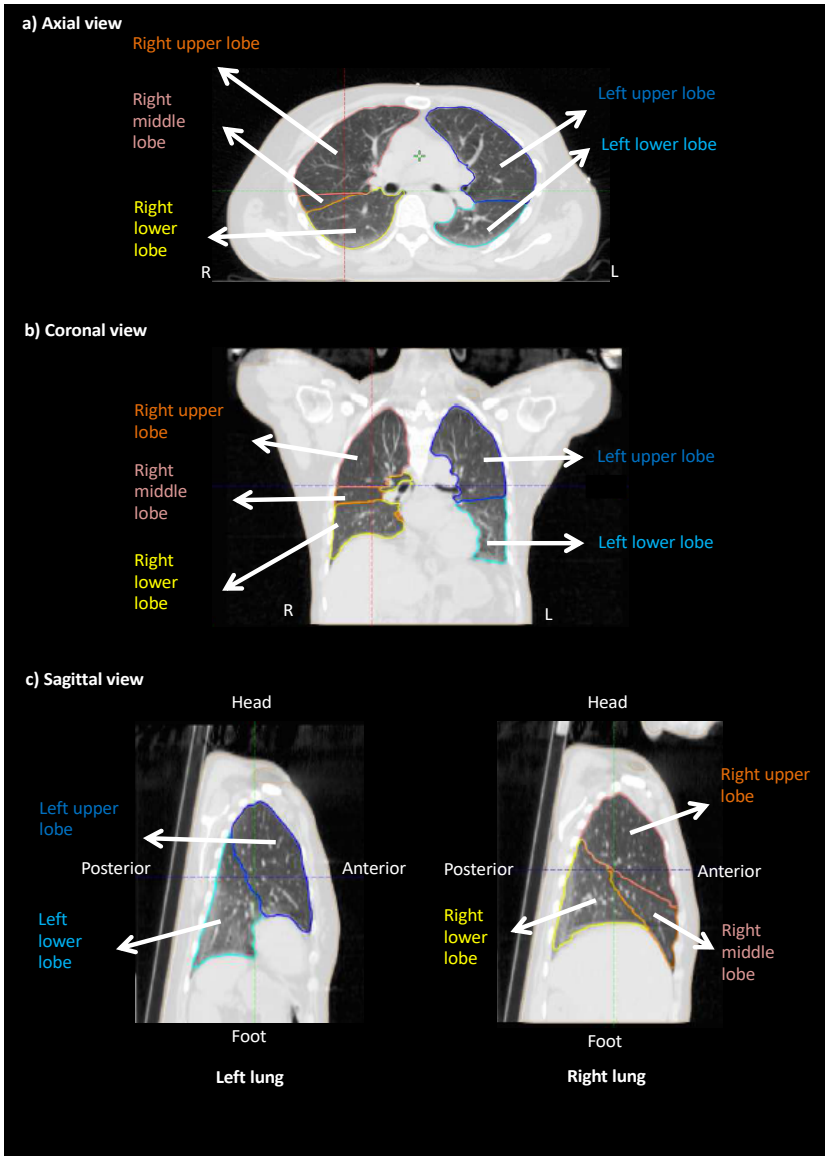


Figure 4.1: Contours of the five main anatomical lobes of the lung in the (a) axial, (b) coronal, and (c) sagittal views.

4.3 Results

4.3.0.1 Variation in lung lobe doses from 44 typical breast cancer regimens first used in the Netherlands during 1970-2010

The five main anatomical lung lobes are shown in Figure 4.1. There was considerable variation in doses received by these lung lobes from the 44 typical radiotherapy regimens used in the Netherlands during 1970 to 2010. (Figure 4.2, Tables 4.1, 4.2) In summary, from 22 right radiotherapy regimens, the medians (interquartile ranges, IQRs) of estimated mean radiation doses received by the right upper lobe, right middle lobe, right lower lobe and whole lungs were: 18.2Gy (IQR 7.1), 21.3Gy (IQR 10.4), 9.1Gy (IQR 7.4Gy) and 8.8Gy (3.7Gy). From equivalent left regimens, estimated doses received by the left upper lobe, left lower lobe and whole lungs were 11.7Gy (IQR 7.4), 15.1Gy (IQR 10.3) and 7.8Gy (IQR 5.8).

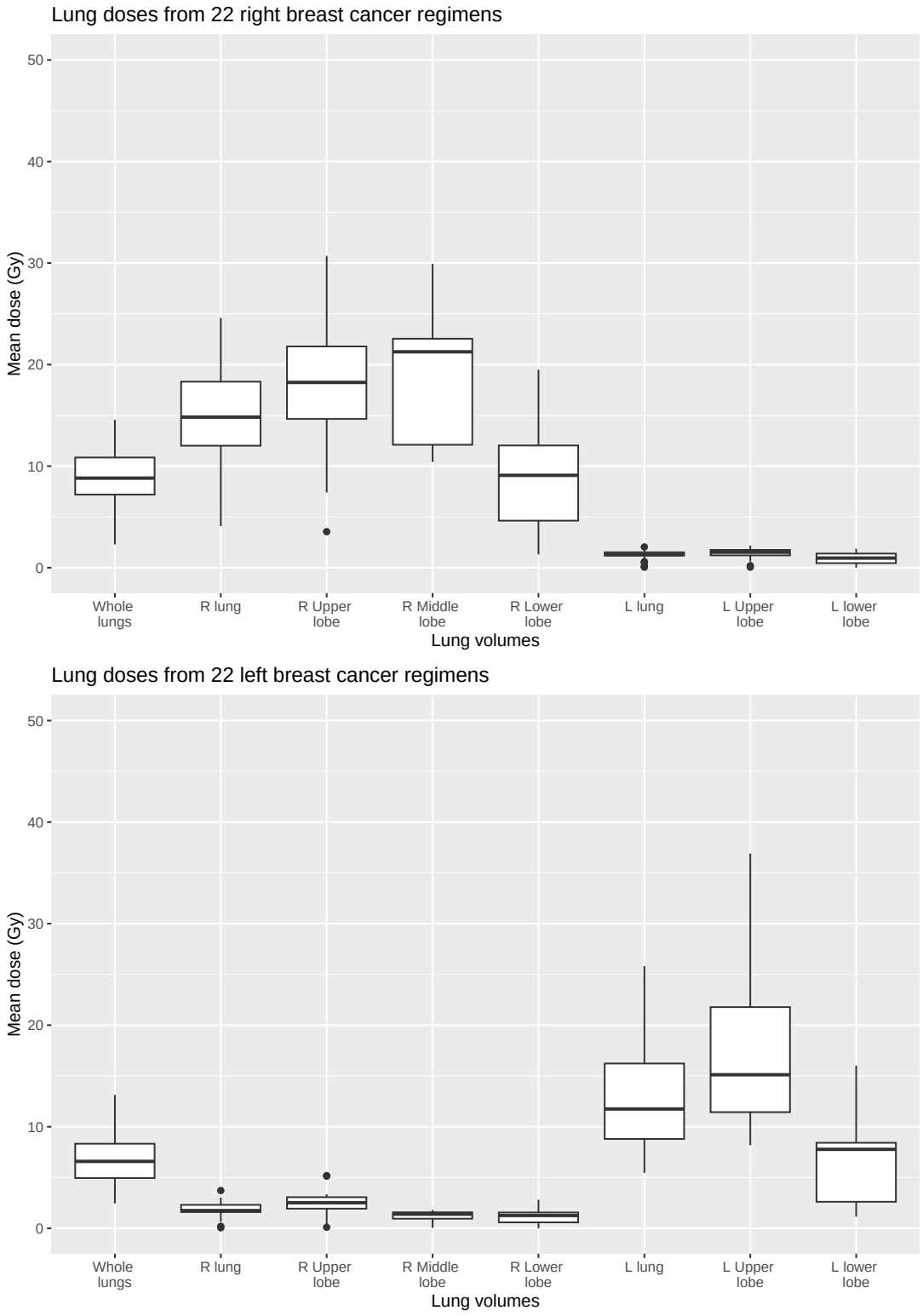


Figure 4.2: Variation in mean lung doses from 44 typical breast cancer regimens first used in regimens in the Netherlands during 1970-2010.
See Table C.1 for summary data. See Tables 4.1 and 4.2 for field doses comprising the 44 regimens.
Abbreviations: L=left, R=right.

Table 4.1: Lung lobe doses from 22 typical right breast cancer regimens used in the Netherlands during 1970-2010

Years of RT	Field arrange-ment	Beam energy	Target(s)‡§	Dose (100%) (Gy)¶	Dose/ fraction (Gy)	Field borders	Mean lung doses (%)#							
							Whole lung	R lung	L lung	RUL	RML	RLL	LUL	LLL
Tangential fields (n=290)														
1970-1973	Tangents	250 keV	Chest wall	15.0	3.0	Superior - clavicular head Inferior - 1cm below infra-mammary fold Medial - midline Lateral - mid-axillary line	nc	nc	nc	nc	nc	nc	nc	nc
1975-1989	Tangents	Co^{60}	Breast	50.0	2.0	Superior - clavicular head Inferior - 1cm below infra-mammary fold Medial - midline Lateral - mid-axillary line	9.6	16.4	1.2	15.2	45.1	4.6	1.4	0.8
1981-2001	Tangents	4-8 MV	Breast	44.0-52.0	2.0	Superior - clavicular head Inferior - 1cm below infra-mammary fold Medial - midline Lateral - mid-axillary line	9.1	16.1	0.3	14.8	44.4	4.5	0.4	0.1
2000-2009	Tangents	6-18 MV	Breast/ chest wall	46.2-51.5	1.7-2.5	Superior - clavicular head Inferior - 1cm below infra-mammary fold Medial - 1cm from midline ipsi Lateral - mid-axillary line	4.6	8.2	0.1	7.1	23.2	2.6	0.1	0.0

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Lung lobe doses from 22 typical right breast cancer regimens used in the Netherlands during 1970-2010 *Continued.*

Years of RT	Field arrange-ment	Beam energy	Target(s)‡§	Dose (100%) (Gy)¶	Dose/ fraction (Gy)	Field borders	Mean lung doses (%)#							
							Whole lung	R lung	L lung	RUL	RML	RLL	LUL	LLL
Megavoltage IMC fields (n=200)														
Megavoltage														
1971-1984	Direct IMC	Co^{60}	IMC	40.0-53.0	2.1-3.3	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	19.4	32.5	3.0	38.8	26.6	27.3	2.9	3.1
1973-1985	Direct IMC, matching chest wall	Co^{60}	IMC§	39.6-40.0	2.5-3.3	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	19.4	32.5	3.0	38.8	26.6	27.3	2.9	3.1
		9 MeV	Chest wall	36.8-37.6	2.3-2.4	Superior - middle of 2nd costal cartilage Inferior - 1cm below infra-mammary fold Medial - matched to lateral border of IMC field Lateral - mid-axillary line	7.0	12.6	0.0	14.0	29.2	3.5	0.1	0.0
1977-1989	Direct IMC, matching tangents	Co^{60}	IMC§	43.0-53.8	1.9-2.9	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	19.4	32.5	3.0	38.8	26.6	27.3	2.9	3.1
		6 MV	Breast	40.0-50.0	1.8-2.0	Superior - clavicular head Inferior - 1cm below infra-mammary fold Medial - matched to lateral border of IMC field Lateral - mid-axillary line	2.7	4.8	0.0	3.1	13.9	2.5	0.1	0.0
1975-1993	Direct IMC, direct SF/axilla/ lateral thorax	4-6 MV	IMC	40.1-56.3	2.2-3.0	Superior - suprasternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	25.2	42.7	3.4	50.1	35.1	36.8	3.4	3.5
		8 MV	SF/axilla/ lateral thorax	44.5-56.3	2.2-2.5	Superior - inferior border of C6 vertebra Infero-lateral - where rib 7 touches the lung contour Infero-medial - rib 2 Medial - 1cm from midline contra Lateral - 3cm lateral to humeral head	9.8	16.4	1.5	22.7	13.3	10.2	1.8	1.0
1979-2006	Direct IMC, matching tangents	4-8 MV	IMC§	16.0-52.0	2.0-2.5	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	25.2	42.6	3.4	50.2	35.1	36.5	3.4	3.5
		4-25 MV	Breast	50.0-52.0	2.0	Superior - middle of 2nd costal cartilage Inferior - 1cm below inframmary fold Medial - matched to IMC field Lateral - mid-axillary line	2.7	4.8	0.0	3.1	13.9	2.5	0.1	0.0

Continued on next page.

Lung lobe doses from 22 typical right breast cancer regimens used in the Netherlands during 1970-2010 *Continued.*

Years of RT	Field arrange-ment	Beam energy	Target(s)‡§	Dose (100%) (Gy)¶	Dose/ fraction (Gy)	Field borders	Mean lung doses (%)#							
							Whole lung	R lung	L lung	RUL	RML	RLL	LUL	LLL
Mixed megavoltage/electron														
1979-1987	Direct IMC, matching tangents	Co^{60}	IMC§	15.4-36.0	1.5-2.0	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	19.4	32.5	3.0	38.9	26.8	27.2	2.9	3.1
		12 MeV	IMC§	9.7-30.0	1.9-2.7	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	13.3	21.9	2.7	31.5	26.1	7.8	3.8	1.0
		6 MV	Breast	45.0-50.0	1.8-2.0	Superior - middle of 2nd costal cartilage Inferior - 1cm below infra-mammary fold Medial - matched to lateral border of IMC field Lateral - mid-axillary line	2.7	4.8	0.0	3.1	13.9	2.5	0.1	0.0
1981-1999	Direct IMC, matching tangents	6-8 MV	IMC§	22.5-40.0	2.0-2.5	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	25.2	42.6	3.4	50.2	35.1	36.5	3.4	3.5
		10-12 MeV	IMC§	10.0-26.0	2.0-2.5	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	13.3	21.9	2.7	31.5	26.1	7.8	3.8	1.0
		6-8 MV	Breast	47.5-50.0	2.0-2.5	Superior - middle of 2nd costal cartilage Inferior - 1cm below infra-mammary fold Medial - matched to IMC field Lateral - mid-axillary line	2.7	4.8	0.0	3.1	13.9	2.5	0.1	0.0
1991-2000	Direct IMC, matching chest wall	4-8 MV	IMC§	22.5-26.7	2.0-2.5	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	24.1	41.1	2.7	52.2	28.6	33.0	2.8	2.6
		10-12 MeV	IMC§	22.5-26.0	2.0-2.5	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	12.6	20.6	2.7	31.1	20.8	7.5	3.8	1.0
		6-10 MeV	Chest wall	40.0-50.0	2.0-2.5	Superior - middle of 2nd costal cartilage Inferior - 1cm below infra-mammary fold Medial-superior - matched to lateral border of IMC field Medial-inferior - midline sternum Lateral - mid-axillary line	9.7	17.4	0.1	17.4	42.8	5.9	0.1	0.1

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Lung lobe doses from 22 typical right breast cancer regimens used in the Netherlands during 1970-2010 *Continued.*

Years of RT	Field arrange-ment	Beam energy	Target(s)‡§	Dose (100%) (Gy)¶	Dose/ fraction (Gy)	Field borders	Mean lung doses (%)#							
							Whole lung	R lung	L lung	RUL	RML	RLL	LUL	LLL
1993-2006	Direct IMC	6-8 MV	IMC	18.0-19.3	2.0-2.8	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	25.2	42.7	3.4	50.1	35.1	36.8	3.4	3.5
		10-12 MeV	IMC	21.4-32.0	2.0-2.7	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	13.3	21.9	2.7	31.5	25.9	8.0	3.8	1.0
2000-2005	Direct IMC, matching tangents	6-10 MV	IMC§	15.8-18.0	2.0-2.3	Superior - cricoid cartilage Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	21.4	35.6	3.5	46.5	26.3	26.4	3.5	3.5
		8-17 MeV	IMC§	32.0-33.8	2.1-2.3	Superior - cricoid cartilage Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	13.3	21.9	2.7	31.5	26.1	7.8	3.8	1.0
		6-10 MV	Breast/chest wall	49.6-50.0	2.0-2.2	Superior - middle of 2nd costal cartilage Inferior - 1cm below infra-mammary fold Medial - 4.5cm from midline ipsi matched to IMC field Lateral - mid-axillary line	4.1	7.4	0.1	4.9	21.9	3.7	0.1	0.0
2003-2010	Oblique IMC, matching tangents	6-10 MV	IMC§	16.6-18.1	1.7-2.0	Superior - clavicular head Inferior - xiphoid tip Medial - 2cm from midline contra Lateral - 4cm from midline ipsi	20.4	36.6	0.3	43.2	60.8	17.1	0.4	0.2
		10-20 MeV	IMC§	32.0-34.9	1.7-2.1	Superior - clavicular head Inferior - xiphoid tip Medial - 2cm from midline contra Lateral - 4cm from midline ipsi	11.8	20.2	1.2	27.1	33.0	5.7	1.5	0.8
		6-10 MV	Breast/chest wall	50.0-51.5	1.7-2.0	Superior - middle of 2nd costal cartilage Inferior - 1cm below infra-mammary fold Medial - 3.5cm from midline ipsi matched to IMC field Lateral - mid-axillary line	3.1	5.5	0.1	3.6	16.0	2.9	0.1	0.0

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Lung lobe doses from 22 typical right breast cancer regimens used in the Netherlands during 1970-2010 *Continued.*

Years of RT	Field arrangement	Beam energy	Target(s)‡§	Dose (100%) (Gy)¶	Dose/ fraction (Gy)	Field borders	Mean lung doses (%)#							
							Whole lung	R lung	L lung	RUL	RML	RLL	LUL	LLL
Orthovoltage or mixed orthovoltage/megavoltage IMC fields (n=172)——														
1971-1985	Direct IMC	250 keV	IMC	36.2-48.8	2.2-2.7	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	17	27	4	34	28	23	4	4
1981-1989	Direct IMC	250 keV	IMC	17.2-21.5	1.8-2.5	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	17	27	4	34	28	23	4	4
		Co^{60}	IMC	19.1-31.9	2.1-2.9	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	19.4	32.5	3.0	38.8	26.6	27.3	2.9	3.1
1989-1992	Direct IMC	250 keV	IMC	16.8-23.5	1.8-2.5	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	17	27	4	34	28	23	4	4
		4-8 MV	IMC	21.9-24.0	2.0-2.7	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	25.2	42.7	3.4	50.1	35.1	36.8	3.4	3.5

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Lung lobe doses from 22 typical right breast cancer regimens used in the Netherlands during 1970-2010 *Continued.*

Years of RT	Field arrangement	Beam energy	Target(s)‡§	Dose (100%) (Gy)¶	Dose/ fraction (Gy)	Field borders	Mean lung doses (%)#							
							Whole lung	R lung	L lung	RUL	RML	RLL	LUL	LLL
Electron chest wall or IMC fields (n=92)														
1975-1985	Direct IMC	10-16 MeV	IMC	45.0	3.0	Superior - sternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	13.3	21.9	2.7	31.5	25.9	8.0	3.8	1.0
1978-1985	Direct IMC, matching tangents	10-13 MeV	IMC	30.0-45.0	2.0-3.0	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	13.3	21.9	2.7	31.5	26.1	7.8	3.8	1.0
		6 MV	Breast	33.4-50.0	1.8-2.2	Superior - middle of 2nd costal cartilage Inferior - 1cm below infra-mammary fold Medial - matched to lateral border of IMC field Lateral - mid-axillary line	2.7	4.8	0.0	3.1	13.9	2.5	0.1	0.0
1970-1998	Direct chest wall	10-13 MeV	Chest wall	40.1-60.0	2.0-3.0	Superior - matched SF/axillary field Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 1cm medial to lateral lung contour	17.5	30.1	1.7	41.3	49.8	6.5	2.7	0.3
1972-2003	Direct chest wall, direct SF/axilla/ lateral thorax	8-13 MeV	Chest wall**	40.0-50.0	2.0-3.0	Superior - matched to SF/axillary field Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 1cm medial to lateral lung contour	17.5	30.1	1.7	41.3	49.8	6.5	2.7	0.3
		8 MV	SF/axilla/ lateral thorax	43.0-53.0	2.0-2.7	Superior - inferior border of C6 vertebra Infero-lateral - where rib 7 touches the lung contour Infero-medial - rib 2 Medial - 1cm from midline contra Lateral - 3cm lateral to humeral head	10.0	17.0	1.2	23.4	14.0	10.3	1.4	0.8

Footnotes

‡Where SF was targeted as a separate field, estimated doses from a reconstructed 6MV direct right SF field with lateral margin to the humeral head: Dmean Combined lung 9.3 %,Dmean Right lung 16.1 %, Dmean Right Upper Lobe 32.8%, Dmean Right Middle Lobe 1.3%, Dmean Right Lower Lobe 2.4%. Other structures received ¡ 1.5 %.
Separate boost fields were not reconstructed as information was lacking on the location of the surgical bed.
§For IMC fields matched to breast or chest wall fields the inferior border reached the 5th intercostal space including the xiphoid process in many cases. This was to allow coverage of the breast or chest wall tissue medially. The typical field size was 18-25 cm.
¶Usual total dose (100%) to the target tissues. For tangents the total dose was delivered to the centre of the breast or chest wall apart from orthovoltage tangents where the total dose was the skin dose at the surface of the breast. For direct regimens this was the Dmax.
——Some orthovoltage IMC fields were matched to an electron chest wall field or a tangential pair to the breast. Lung doses for these field combinations were not calculated as it was not possible to create a radiotherapy plan using both manual planning and CT-planning.
*For many women who were treated with direct electron chest wall fields the internal mammary chain also received a therapeutic dose.
#Mean lung doses estimated using manual planning are given to nearest Gy.
Abbreviations: AP=antero-postero, Co60=cobalt 60, contra=contralateral, Gy=gray, IMC=internal mammary chain, ipsi=ipsilateral, keV=kilovoltage, L=left, LLL=left lower lobe, LUL=left upper lobe, MV=megavoltage; MeV=mega electron volts, nc=not calculated, R=right, RLL=right lower lobe, RML=right middle lobe, RT=radiotherapy, RUL=right upper lobe, SF= supraclavicular fossa, SSD=source-surface distance.

Table 4.2: Lung lobe doses from 22 typical left breast cancer regimens used in the Netherlands during 1970-2010

Years of RT	Field arrange-ment	Beam energy	Target(s)‡§	Dose (100%) (Gy)¶	Dose/ fraction (Gy)	Field borders	Mean lung doses (%)#							
							Whole lung	R lung	L lung	RUL	RML	RLL	LUL	LLL
Tangential fields (n=290)														
1970-1973	Tangents	250 keV	Chest wall	15.0	3.0	Superior - clavicular head Inferior - 1cm below inframammary fold Medial - midline Lateral - mid-axillary line	nc	nc	nc	nc	nc	nc	nc	nc
1975-1989	Tangents	Co^{60}	Breast	50.0	2.0	Superior - clavicular head Inferior - 1cm below inframammary fold Medial - midline Lateral - mid-axillary line	7.2	1.3	14.5	1.4	1.6	0.9	22.3	2.9
1981-2001	Tangents	4-8 MV	Breast	44.0-52.0	2.0	Superior - clavicular head Inferior - 1cm below inframammary fold Medial - midline Lateral - mid-axillary line	6.8	0.4	14.8	0.6	0.5	0.1	22.8	3.0
2000-2009	Tangents	6-18 MV	Breast/chest wall	46.2-51.5	1.7-2.5	Superior - clavicular head Inferior - 1cm below inframammary fold Medial - 1cm from midline ipsi Lateral - mid-axillary line	4.9	0.1	10.9	0.2	0.1	0.0	16.6	2.3

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Lung lobe doses from 22 typical left breast cancer regimens used in the Netherlands during 1970-2010 *Continued.*

Years of RT	Field arrangement	Beam energy	Target(s)‡§	Dose (100%) (Gy)¶	Dose/ fraction (Gy)	Field borders	Mean lung doses (%)#							
							Whole lung	R lung	L lung	RUL	RML	RLL	LUL	LLL
Megavoltage IMC fields (n=200)														
Megavoltage														
1971-1984	Direct IMC	Co^{60}	IMC	40.0-53.0	2.1-3.3	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	12.7	3.9	23.6	4.5	2.2	3.8	26.6	19.1
1973-1985	Direct IMC, matching chest wall	Co^{60}	IMC§	39.6-40.0	2.5-3.3	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	12.7	3.9	23.6	4.5	2.2	3.8	26.6	19.1
		9 MeV	Chest wall	36.8-37.6	2.3-2.4	Superior - middle of 2nd costal cartilage Inferior - 1cm below inframammary fold Medial - matched to lateral border of IMC field Lateral - mid-axillary line	4.7	0.1	10.5	0.1	0.0	0.1	16.4	1.7
1977-1989	Direct IMC, matching tangents	Co^{60}	IMC§	43.0-53.8	1.9-2.9	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	13.9	4.3	26.0	5.0	2.5	4.2	29.3	21.1
		6 MV	Breast	40.0-50.0	1.8-2.0	Superior - clavicular head Inferior - 1cm below inframammary fold Medial - matched to lateral border of IMC field Lateral - mid-axillary line	1.7	0.1	3.7	0.1	0.1	0.0	5.0	1.7
1975-1993	Direct IMC, direct SCF/axilla/ lateral thorax	4-6 MV	IMC	40.1-56.3	2.2-3.0	Superior - suprasternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	15.7	4.9	29.3	6.0	3.2	4.3	32.5	24.5
		8 MV	SCF/axilla/ lateral thorax	44.5-56.3	2.2-2.5	Superior - inferior border of C6 vertebra Infero-lateral - where rib 7 touches the lung contour Infero-medial - rib 2 Medial - 1cm from midline contra Lateral - 3cm lateral to humeral head	12.1	3.9	22.3	6.2	1.1	2.4	27.9	13.7
1979-2006	Direct IMC, matching tangents	4-8 MV	IMC§	16.0-52.0	2.0-2.5	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	17.4	5.4	32.3	6.6	3.5	4.8	35.8	27.1
		4-25 MV	Breast	50.0-52.0	2.0	Superior - middle of 2nd costal cartilage Inferior - 1cm below inframmary fold Medial - matched to IMC field Lateral - mid-axillary line	1.7	0.1	3.7	0.1	0.1	0.0	5.0	1.7

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Lung lobe doses from 22 typical left breast cancer regimens used in the Netherlands during 1970-2010 *Continued.*

Years of RT	Field arrange-ment	Beam energy	Target(s)‡§	Dose (100%) (Gy)¶	Dose/ fraction (Gy)	Field borders	Mean lung doses (%)#							
							Whole lung	R lung	L lung	RUL	RML	RLL	LUL	LLL
Mixed megavoltage/electron														
1979-1987	Direct IMC, matching tangents	Co^{60}	IMC§	15.4-36.0	1.5-2.0	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	13.9	4.3	26.0	5.0	2.5	4.2	29.3	21.1
		12 MeV	IMC§	9.7-30.0	1.9-2.7	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	9.7	3.7	17.3	5.6	3.5	1.3	26.3	4.1
		6 MV	Breast	45.0-50.0	1.8-2.0	Superior - middle of 2nd costal cartilage Inferior - 1cm below inframammary fold Medial - matched to lateral border of IMC field Lateral - mid-axillary line	1.7	0.1	3.7	0.1	0.1	0.0	5.0	1.7
1981-1999	Direct IMC, matching tangents	6-8 MV	IMC§	22.5-40.0	2.0-2.5	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	17.4	5.4	32.3	6.6	3.5	4.8	35.8	27.1
		10-12 MeV	IMC§	10.0-26.0	2.0-2.5	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	9.7	3.7	17.3	5.6	3.5	1.3	26.3	4.1
		6-8 MV	Breast	47.5-50.0	2.0-2.5	Superior - middle of 2nd costal cartilage Inferior - 1cm below inframammary fold Medial - matched to IMC field Lateral - mid-axillary line	1.7	0.1	3.7	0.1	0.1	0.0	5.0	1.7
1991-2000	Direct IMC, matching chest wall	4-8 MV	IMC§	22.5-26.7	2.0-2.5	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	17.0	4.8	32.3	6.3	2.7	3.8	37.7	24.0
		10-12 MeV	IMC§	22.5-26.0	2.0-2.5	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	9.8	3.7	17.4	5.7	3.5	1.3	26.3	4.0
		6-10 MeV	Chest wall	40.0-50.0	2.0-2.5	Superior - middle of 2nd costal cartilage Inferior - 1cm below inframammary fold Medial-superior - matched to lateral border of IMC field Medial-inferior - midline sternum Lateral - mid-axillary line	7.5	0.1	16.7	0.1	0.1	0.1	25.1	4.3

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Lung lobe doses from 22 typical left breast cancer regimens used in the Netherlands during 1970-2010 *Continued.*

Years of RT	Field arrange-ment	Beam energy	Target(s)‡§	Dose (100%) (Gy)¶	Dose/ fraction (Gy)	Field borders	Mean lung doses (%)#							
							Whole lung	R lung	L lung	RUL	RML	RLL	LUL	LLL
1993-2006	Direct IMC	6-8 MV	IMC	18.0-19.3	2.0-2.8	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	15.7	4.9	29.3	6.0	3.2	4.3	32.5	24.5
		10-12 MeV	IMC	21.4-32.0	2.0-2.7	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	9.7	3.7	17.2	5.6	3.5	1.3	26.1	4.0
2000-2005	Direct IMC, matching tangents	6-10 MV	IMC§	15.8-18.0	2.0-2.3	Superior - cricoid cartilage Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	21.6	5.3	41.9	6.5	3.2	4.7	50.3	29.7
		8-17 MeV	IMC§	32.0-33.8	2.1-2.3	Superior - cricoid cartilage Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	9.7	3.7	17.3	5.6	3.5	1.3	26.3	4.1
		6-10 MV	Breast/chest wall	49.6-50.0	2.0-2.2	Superior - middle of 2nd costal cartilage Inferior - 1cm below inframammary fold Medial - 4.5cm from midline ipsi matched to IMC field Lateral - mid-axillary line	3.8	0.1	8.3	0.2	0.1	0.0	11.8	3.0
2003-2010	Oblique IMC, matching tangents	6-10 MV	IMC§	16.6-18.1	1.7-2.0	Superior - clavicular head Inferior - xiphoid tip Medial - 2cm from midline contra Lateral - 4cm from midline ipsi	16.6	0.5	36.7	0.8	0.4	0.3	50.4	16.6
		10-20 MeV	IMC§	32.0-34.9	1.7-2.1	Superior - clavicular head Inferior - xiphoid tip Medial - 2cm from midline contra Lateral - 4cm from midline ipsi	8.5	1.7	17.1	2.2	1.8	1.0	26.6	3.3
		6-10 MV	Breast/chest wall	50.0-51.5	1.7-2.0	Superior - middle of 2nd costal cartilage Inferior - 1cm below inframammary fold Medial - 3.5cm from midline ipsi matched to IMC field Lateral - mid-axillary line	3.8	0.1	8.3	0.2	0.1	0.0	11.8	3.0

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Lung lobe doses from 22 typical left breast cancer regimens used in the Netherlands during 1970-2010 *Continued.*

Years of RT	Field arrange-ment	Beam energy	Target(s)‡§	Dose (100%) (Gy)¶	Dose/ fraction (Gy)	Field borders	Mean lung doses (%)#							
							Whole lung	R lung	L lung	RUL	RML	RLL	LUL	LLL
Orthovoltage or mixed orthovoltage/megavoltage IMC fields (n=172)——														
1971-1985	Direct IMC	250 keV	IMC	36.2-48.8	2.2-2.7	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	12	5	20	8	3	4	22	20
1981-1989	Direct IMC	250 keV	IMC	17.2-21.5	1.8-2.5	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	12	5	20	8	3	4	22	20
		Co^{60}	IMC	19.1-31.9	2.1-2.9	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	12.7	3.9	23.6	4.5	2.2	3.8	26.6	19.1
1989-1992	Direct IMC	250 keV	IMC	16.8-23.5	1.8-2.5	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	12	5	20	8	3	4	22	20
		4-8 MV	IMC	21.9-24.0	2.0-2.7	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	15.7	4.9	29.3	6.0	3.2	4.3	32.5	24.5

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Lung lobe doses from 22 typical left breast cancer regimens used in the Netherlands during 1970-2010 *Continued.*

Years of RT	Field arrangement	Beam energy	Target(s)‡§	Dose (100%) (Gy)¶	Dose/ fraction (Gy)	Field borders	Mean lung doses (%)#							
							Whole lung	R lung	L lung	RUL	RML	RLL	LUL	LLL
Electron chest wall or IMC fields (n=92)														
1975-1985	Direct IMC	10-16 MeV	IMC	45.0	3.0	Superior - sternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	9.7	3.7	17.2	5.6	3.5	1.3	26.1	4.0
1978-1985	Direct IMC, matching tangents	10-13 MeV	IMC	30.0-45.0	2.0-3.0	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	9.7	3.7	17.3	5.6	3.5	1.3	26.3	4.1
		6 MV	Breast	33.4-50.0	1.8-2.2	Superior - middle of 2nd costal cartilage Inferior - 1cm below inframammary fold Medial - matched to lateral border of IMC field Lateral - mid-axillary line	1.7	0.1	3.7	0.1	0.1	0.0	5.0	1.7
1970-1998	Direct chest wall	10-13 MeV	Chest wall††	40.1-60.0	2.0-3.0	Superior - matched SCF/axillary field Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 1cm medial to lateral lung contour	15.4	3.1	30.8	5.4	2.4	0.4	48.4	4.7
1972-2003	Direct chest wall, direct SCF/axilla/ lateral thorax	8-13 MeV	Chest wall**	40.0-50.0	2.0-3.0	Superior - matched to SCF/axillary field Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 1cm medial to lateral lung contour	15.4	3.1	30.8	5.4	2.4	0.4	48.4	4.7
		8 MV	SCF/axilla/ lateral thorax	43.0-53.0	2.0-2.7	Superior - inferior border of C6 vertebra Infero-lateral - where rib 7 touches the lung contour Infero-medial - rib 2 Medial - 1cm from midline contra Lateral - 3cm lateral to humeral head	12.1	3.2	23.3	5.3	0.7	1.5	29.3	14.1

Footnotes

‡Where SF was targeted as a separate field, estimated doses from a reconstructed 6MV direct left SF field with lateral margin to the humeral head: Dmean Combined lung 9.3%, Dmean Left lung 20.0%, Dmean Left Upper Lobe 30.6%, Dmean Left Lower Lobe 4.2%. Other structures received ¡ 1.5 %.

Separate boost fields were not reconstructed as information was lacking on the location of the surgical bed.

§For IMC fields matched to breast or chest wall fields the inferior border reached the 5th intercostal space including the xiphoid process in many cases. This was to allow coverage of the breast or chest wall tissue medially. The typical field size was 18-25 cm.

¶Usual total dose (100%) to the target tissues. For tangents the total dose was delivered to the centre of the breast or chest wall apart from orthovoltage tangents where the total dose was the skin dose at the surface of the breast. For direct regimens this was the Dmax.

——Some orthovoltage IMC fields were matched to an electron chest wall field or a tangential pair to the breast. Lung doses for these field combinations were not calculated as it was not possible to create a radiotherapy plan using both manual planning and CT-planning.

*For many women who were treated with direct electron chest wall fields the internal mammary chain also received a therapeutic dose.

#Mean lung doses estimated using manual planning are given to nearest Gy.

Abbreviations: AP=antero-postero, Co60=cobalt 60, contra=contralateral, Gy=gray, IMC=internal mammary chain, ipsi=ipsilateral, keV=kilovoltage, MV=megavoltage, MeV=mega electron volts, nc=not calculated, RT=radiotherapy, SF= supraclavicular fossa, SSD=source-surface distance.

4.3.0.2 Variation in lung lobe doses from breast cancer regimens according to clinical targets

Thirty two (16 right-sided and 16 left-sided) of the 44 typical radiotherapy regimens used in the Netherlands during 1970 to 2010 targeted IMNs, six (three right-sided and three left-sided) targeted the supraclavicular lymph nodes, and 28 (14 right-sided and 14 left-sided) targeted the breast or chest wall. (Tables 4.1, 4.2)

4.3.0.3 Fields targeting the internal mammary lymph nodes

Of the 32 typical regimens targeting IMNs, all used a direct anterior field arrangement to target the IMNs except one, which used an oblique anterior field. Across all 16 unilateral regimens there was considerable variation in IMN field beam type and energy. Overall two regimens used electron beams, one orthovoltage photons, three Co60 photons, one mixed photons (Co60) and electrons, one mixed photons (orthovoltage and megavoltage), two megavoltage photons, and five mixed photons (megavoltage) with electrons. In keeping with advances in radiotherapy technology, the 12 regimens first used prior to 1990 were more likely to have used lower photon beam energies (orthovoltage or Co60) than the four regimens introduced after 1990 that used higher energies (megavoltage).

Overall, there was considerable variation in lung lobe doses from radiotherapy fields targeting the internal mammary lymph nodes. (Figure 4.3, Table C.2) On average, higher mean doses (expressed as a percentage of the IMN field dose) were received by the ipsilateral whole right lung (median dose 32.5%, IQR 15.8%, range 20.2-42.7%) compared with the left (median dose 23.6%, IQR 12%, range 17.1-

41.9%), and by the upper lung lobes (Right upper lobe: median dose 38.8%, IQR 15.9%, range 27.1-52.2%; Left upper lobe: median dose 26.6%, IQR 6.2%, range 22.0-50.4%) compared with the lower lobes (Right lower lobe: median dose 24.7%, IQR 20.8%, range 5.7-36.8%; Left lower lobe: median dose 19.6%, IQR 20.0%, range 3.3-29.7%). Variation in lung lobe dose estimates was greatest for the lower lobes.

In combination across all lung lobes, the variation in mean lung lobe doses was greater than the variation in mean whole lung doses from IMN regimens.

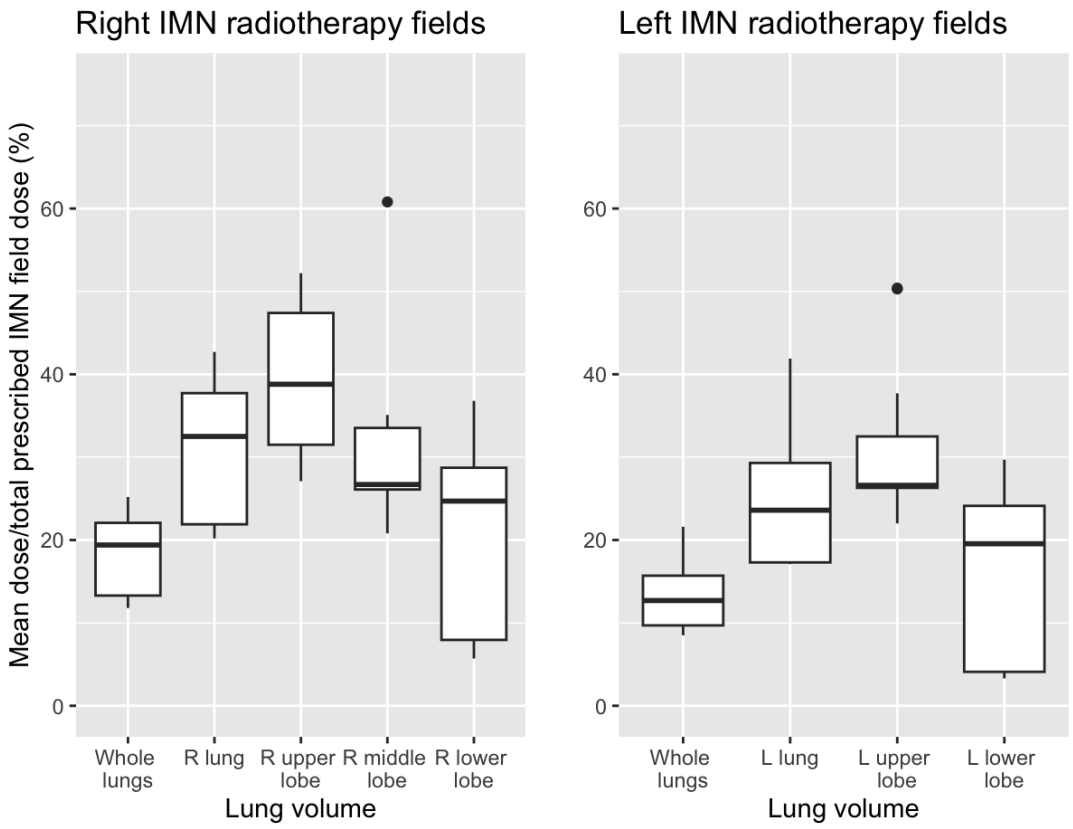


Figure 4.3: Variation in mean ipsilateral lung lobe doses from breast cancer radiotherapy fields targeting internal mammary lymph nodes first used in regimens in the Netherlands during 1970-2010.
See Table C.2 for summary data.
Abbreviations: IMN=internal mammary lymph nodes, L=left, R=right.

4.3.0.4 Fields targeting the supraclavicular lymph nodes

All six (three right-sided and three left-sided) of the typical regimens targeting the supraclavicular lymph nodes used used megavoltage photon beams arranged directly anterior. (Tables 4.1, 4.2). From the three right supraclavicular lymph node fields, medians (IQRs) of estimated mean radiation doses received by the right lung volumes were: 16.4% (IQR 0.5) (right lung), 23.4% (IQR 5.1) (right upper lobe), 13.3% (IQR 6.4) (right middle lobe) and 10.2% (4.0) (right lower lobe). (Figure 4.4, Table C.3) Mean whole lung dose from right supraclavicular lymph node fields was 9.8% (IQR 0.4).

From three left supraclavicular fields, medians (IQRs) in mean radiation doses received by the left lung, left upper and lower lung lobes were 22.3% (IQR 1.65), 29.3% (IQR 1.35), and 13.7% (IQR 4.95). Mean whole lung dose from left supraclavicular lymph node fields was 12.1% (IQR 1.4).

In keeping with the anatomical location of the supraclavicular lymph nodes, upper lobe doses were higher than lower (and right middle) lobe doses. In combination across all lung lobes, the variation in mean lung lobe doses was greater than the variation in mean whole lung doses from supraclavicular lymph node regimens.

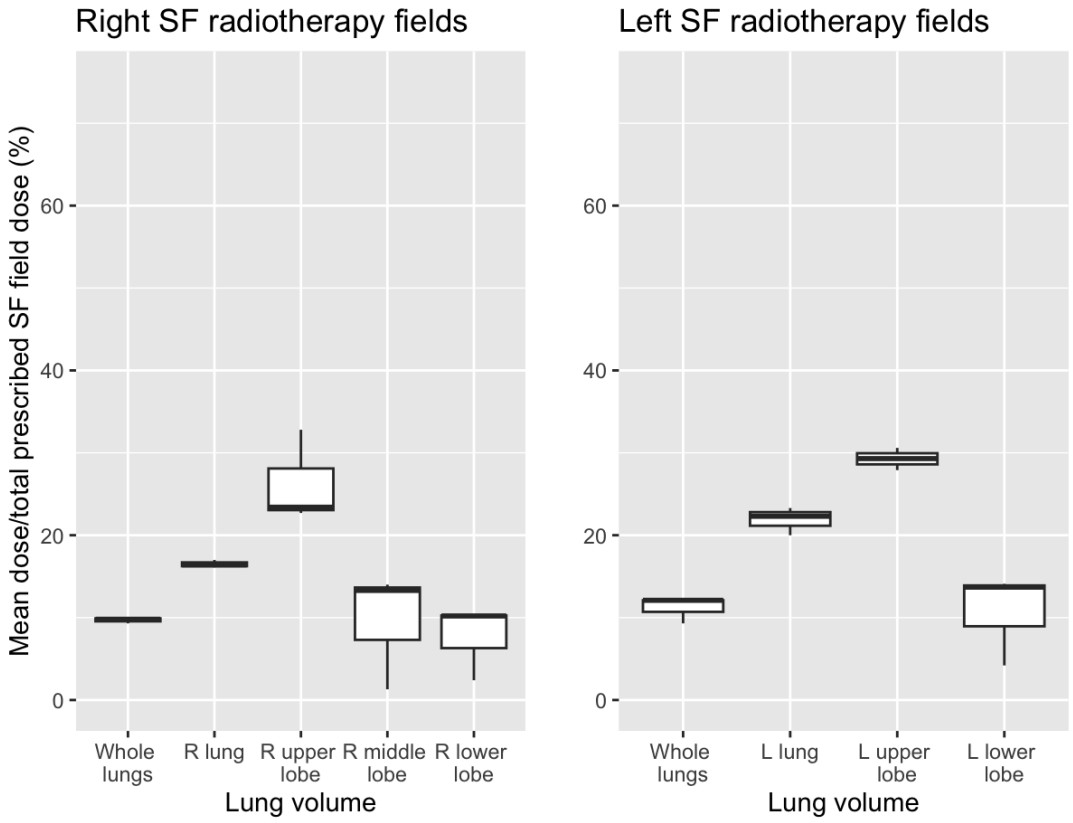


Figure 4.4: Variation in mean ipsilateral lung lobe doses from breast cancer radiotherapy fields targeting the supraclavicular lymph nodes first used in regimens in the Netherlands during 1970-2010.
See Table C.3 for summary data.
Abbreviations: SF=supraclavicular fossa lymph nodes, L=left, R=right.

4.3.0.5 Fields targeting the breast or chest wall

There were 28 (14 right-sided and 14 left-sided) typical regimens targeting the breast or chest wall. Within each of the 14 unilateral regimens, beam arrangements and types varied. Three unilateral regimens used beams arranged as tangents (one using Co60, and two using megavoltage photons), seven used megavoltage photon tangents matched medially to fields targeting the internal mammary lymph nodes, and four comprised direct anterior electron fields. (Tables 4.1, 4.2)

From 14 right breast or chest wall fields, medians (IQRs) of estimated mean radiation doses received by the right lung volumes were: 7.8% (IQR 11.5) (right lung), 6.0% (IQR 12.0) (right upper lobe), 22.6% (IQR 30.1) (right middle lobe), and 3.2% (IQR 2.1) (right lower lobe). (Figure 4.5, Table C.4) Mean whole lung dose from right breast or chest wall fields was 4.4% (IQR 6.8).

From 14 left breast or chest wall fields, medians (IQRs) of estimated mean radiation doses received by the left lung volumes were: 9.4% (IQR 11.0) (left lung), 14.1% (IQR 17.7) (left upper lobe), and 2.6% (IQR 1.3) (left lower lobe). Mean whole lung dose from left breast or chest wall fields was 4.3% (IQR 5.4).

In combination across all lung lobes, the variation in mean lung lobe doses was greater than the variation in mean whole lung doses from breast or chest wall regimens.

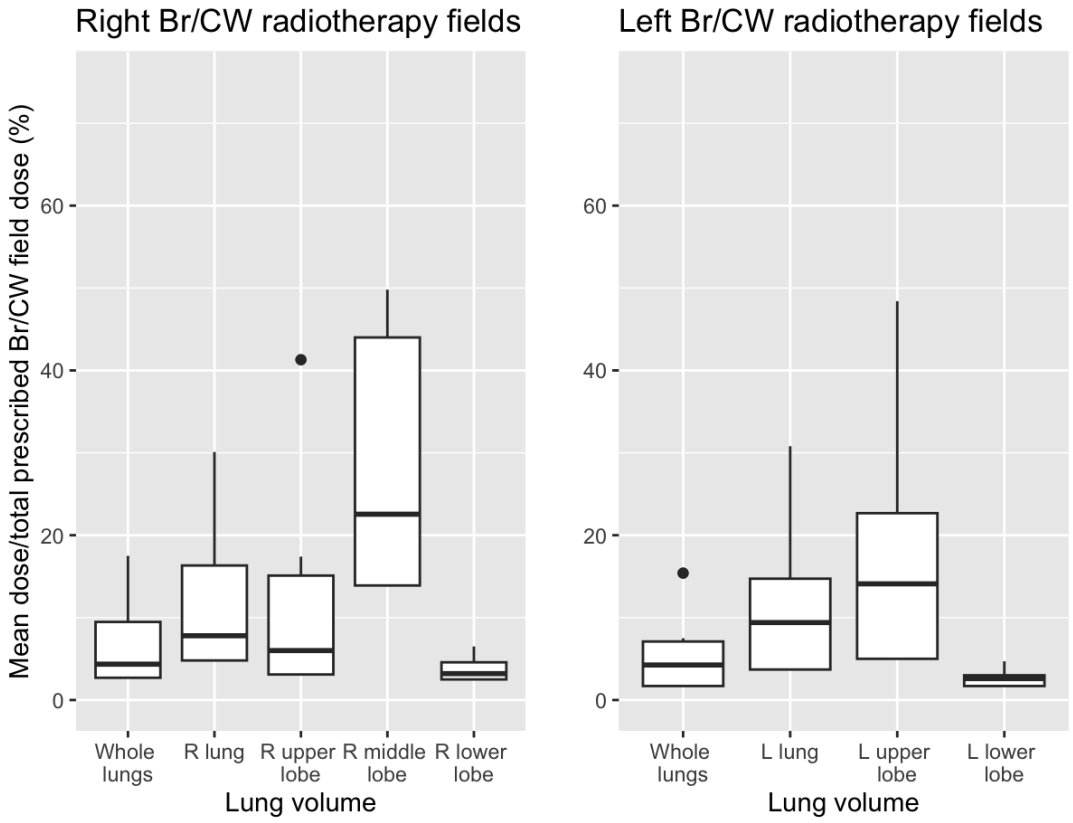


Figure 4.5: Variation in mean ipsilateral lung lobe doses from breast cancer radiotherapy fields targeting the breast or chest wall first used in regimens in the Netherlands during 1970-2010.
See Table C.4 for summary data.
Abbreviations: Br=breast, CW=chest wall, L=left, R=right.

4.4 Discussion

Mean whole lung dose is currently the best available predictor of radiation-induced lung cancer, but it may not be the optimum metric. This study provides estimated mean doses to the five anatomical lung lobes from 44 typical breast cancer regimens delivered in the Netherlands during 1970-2010 and illustrates the greater magnitude of variation in these estimates compared with those provided by mean whole lung dose estimates alone. These lung lobe doses may be used to develop a dose-response relationship for radiation-induced lung cancer that, by incorporating more information on the spatial distribution of radiation dose throughout the lungs than those currently available, better predicts risks of radiation-induced lung cancer.

We also categorise these doses according to clinical target and other determining features as this may further knowledge of effective lung-sparing techniques for different types of radiotherapy for early breast cancer.

4.4.1 Strengths and weaknesses

CT-guided planning was not routinely available in the Netherlands during the time period investigated in this study, and therefore lung lobe doses for individual patients are unattainable. However, such a historical cohort is needed to create a dose-response relationship for radiation-induced lung cancer because it can take decades for radiation-induced lung cancer to manifest clinically. Therefore the main strengths of this study are that it retrospectively estimates lung lobe doses using an established methodology on a cohort of patients for whom there is long-term follow up data including information on development of radiation-induced

lung cancer. To the best of our knowledge this is the first study to report lung lobe doses from breast cancer radiotherapy for the purposes of creating a dose-response relationship for radiation-induced lung cancer.

Another strength of this study is that it provides detailed descriptions of the determining regimens for the estimated lung doses, including radiotherapy clinical targets. These may support our understanding of the effectiveness of components of different breast cancer radiotherapy regimens in lung-sparing (See Chapter 5). There are five other published studies reporting lung doses for the purpose of creating a dose-response relationship for radiation-induced lung cancer.[1, 4–7] To the best of our knowledge this is the first to report doses according to radiotherapy clinical targets.

Estimates from retrospective dosimetry studies have inherent uncertainties but the representative CT method used in this study has not been shown to carry systematic uncertainty into retrospectively estimated cardiac doses.[15]

Lung doses estimated from the CT scan used in this study may vary from those received by the patients in the cohort because of differences in individual patients' anatomy and patient set-up positions for each fraction. Furthermore, the dose-volume estimates do not account for respiratory motion. Mean percentage ipsilateral lung doses from internal mammary lymph node radiotherapy have been estimated to vary with respiratory motion by approximately 1.2%.[16] In this study the CT scan was taken during free breathing because the patients in this study were treated prior to the introduction of lung-sparing techniques, such as deep inspiration breath hold, that are considered standard nowadays.

The sources of variation inherent in the representative CT method are unlikely to change the conclusions of this study as we are describing and considering the

relative differences in lung dose distributions, however, this may need to be considered by future users of the planned dose-response relationship as it is not known whether contemporary lung lobe doses derived from 4D radiotherapy plans systematically differ from those derived from 3D planning using free breathing CT scans.

4.4.2 Clinical implications

In UK breast cancer radiotherapy practice today, the lung is most at risk when targeting the IMNs in patients who are long-term continuing smokers, and various IMN regimens are available.[1, 8] For example, photon radiotherapy may be delivered using partially wide tangents or rotational IMRT, or proton beam therapy may be delivered within the setting of a clinical trial. There is a lack of clinical evidence to determine which of these modern regimens carries the lowest risk of radiation-induced lung cancer, and there have been concerns from modelling studies that multi-field photon beam arrangements used in intensity modulated radiotherapy may increase the risks due to the volume of lung receiving low dose radiation.[17] It is planned that the lung lobe doses presented in this study will be used to create a new dose-response relationship which may better support the estimation of risks of radiation-induced lung cancer from modern breast cancer radiotherapy, and also support the selection of lung-sparing techniques.

Although lung-sparing IMN radiotherapy is mainly needed to reduce the risks for long-term continuing smokers, lung-sparing is also likely to reduce the risks of morbidity from other types of radiation-induced lung injury in non-smokers.

4.5 Conclusions

There is considerable variation in mean lung lobe doses compared with mean whole lung doses from radiotherapy regimens for early breast cancer used in the Netherlands during 1970-2010. The planned dose-response relationship for radiation-induced lung cancer using mean lung lobe doses may better predict risks of radiation-induced lung cancer from modern breast cancer radiotherapy, and guide selection of lung-sparing techniques.

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I, **Francesca Holt**, wrote the original draft manuscript. I contoured the lung lobes, performed 2D manual planning calculations, and extracted radiation doses to the lungs from the treatment planning system as appropriate. I devised and conducted the analyses to compare these lung doses with those from more modern radiotherapy regimens.
Frances Duane previously identified and tabulated radiotherapy regimens from charts of women irradiated in the Netherlands during 1970-2010 and reconstructed them on a typical CT scan to estimate doses to the heart. She supervised this project, in particular advising on the manual dose calculations.
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Floora Leeuwen, **Berthe Aleman** and **Michael Schaapveld** conceptualised the project.
Georgios Ntentas supervised the project, provided physics expertise, and reviewed and edited draft manuscripts.
David Dodwell supervised the project, provided clinical oncology expertise, and reviewed and edited draft manuscripts.
Carolyn Taylor supervised the project, provided clinical oncology expertise, and reviewed and edited draft manuscripts.

Chapter 5

Mean whole lung doses from internal mammary lymph node radiotherapy for early breast cancer during 1970-2025.

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Submission for publication is planned.

5.1 Abstract

5.1.1 Background

There is a current clinical need in the UK to reduce the risks of radiation-induced lung cancer after internal mammary lymph node (IMN) radiotherapy for early breast cancer for long-term continuing smokers. Whilst smoking cessation and omission of radiotherapy will reduce the risks, adopting effective lung-sparing techniques during IMN radiotherapy may preserve the benefits of IMN irradiation whilst also also reducing the risks of radiation-induced lung cancer, and other forms of radiation-induced lung injuries in all women. There is a lack of information on lung doses specifically from IMN regimens. To support the development, selection, and application of lung-sparing IMN radiotherapy, more information is needed on the doses received by the lungs specifically from IMN radiotherapy and how these are changing with advances in radiotherapy.

Here we present temporal trends in mean whole lung doses from IMN radiotherapy over the past 55 years and exploratory analyses on how these may have been influenced by advances in breast cancer radiotherapy.

5.1.2 Methods

First, mean whole lung doses from IMN radiotherapy for early breast cancer over the past 55 years were collated from Chapters 2, 3 and 4 of this thesis.

Second, preliminary literature searches identified studies reporting mean whole lung doses, or both mean ipsilateral and contralateral lung doses, from IMN radiotherapy for early breast cancer.

Third, these doses were categorised according to their determining IMN radiotherapy regimen fractionation, beam types, arrangements and treatment planning methods. Temporal trends in doses, including within each of these categories, were explored.

5.1.3 Results

Average mean whole lung dose representing 5912 individual estimates collated from IMN regimens spanning 55 years (1970 to 2025) was 8.0Gy, with no clear trends over time. From conventionally and moderately fractionated IMN radiotherapies average doses were 7.9Gy and 7.4Gy respectively.

From different IMN beam types, average mean whole lung doses varied considerably: 9.4Gy from Co60 photons, 8.7Gy from mixed megavoltage photons and electrons, 8.3Gy from mixed orthovoltage and megavoltage photons, 8.0Gy from electrons, 7.5Gy from megavoltage photons, 6.1Gy from mixed orthovoltage and Co60 photons, 6.0Gy from scattered protons, 5.4Gy from orthovoltage photons, 5.3Gy from scanned protons, and 3.0Gy from mixed electrons and scattered protons.

From different beam arrangements, average mean whole lung doses were 11.9Gy from oblique anterior beams, 8.7Gy from IMRT static beams, 8.1Gy from anterior beams (angle not specified), 7.8Gy from direct anterior beams, 7.8Gy from IMRT rotational beams, 7.1Gy from partially wide tangents, and 6.8Gy from wide tangents.

From different treatment planning methods, average mean whole lung doses were 9.8Gy from hybrid, 8.4Gy from forward-planned IMRT, 8.1Gy from inverse-

planned IMRT, 8.0Gy from 3D conformal and 7.6Gy from 2D conformal.

5.1.4 Conclusions

From these data and exploratory analyses, there have been minimal reductions in mean whole lung doses from IMN radiotherapy for early breast cancer over the past 55 years despite considerable advances in radiotherapy beam arrangements and treatment planning methods. Exploratory analyses indicate that mean whole lung dose varies most according to IMN beam type. Proton beam therapy (PBT) appears to have led to the greatest systematic reduction in mean whole lung dose from IMN radiotherapy in recent decades, more so than other advances in radiotherapy. More data and/or other dose metrics may be needed to distinguish the lung-sparing properties of advanced photon techniques.

5.2 Introduction

It has been estimated that on average the mean whole lung dose from modern UK IMN radiotherapy for early breast cancer is around 7Gy with corresponding 30-year absolute risks of death from lung cancer estimated to be ∼0.4% for a lifelong non-smoker and ∼6.2% for a long-term continuing smoker.[1] This indicates a current clinical need to reduce the risks of radiation-induced lung cancer after IMN radiotherapy for early breast cancer for long-term continuing smokers, and there may be future clinical need to reduce the relative risks for those with less well-studied or emerging risk factors.

To support the development, selection, and application of lung-sparing IMN radiotherapy, more information is needed on the doses received by the lungs specifically from IMN radiotherapy and how these have changed with advances in IMN radiotherapy. Inclusion of the IMNs in the clinical targets of radiotherapy for early breast cancer is relatively uncommon, therefore data on doses and clinical outcomes from IMN radiotherapy are few.

Radiotherapy for early breast cancer has changed considerably over recent decades. (Chapter 1) In order to improve clinical target dose coverage and reduce short-term morbidity, whilst improving convenience for patients and reducing costs, prescribed radiation doses have been hypofractionated, and intensity modulated radiotherapy planning methods have been adopted.[2, 3] To minimise radiation dose to the heart, and thereby reduce the risks of ischaemic heart disease, national guidelines for breast cancer radiotherapy now include dose constraints for mean heart dose, beam arrangements for IMN radiotherapy have moved away from direct anterior beams to more "tailored" radiotherapy, and deep inspira-

tion breath hold (DIBH) has become standard for patients receiving radiotherapy for left breast cancer, or inclusive of the IMNs.[4, 5] In contrast, few changes in breast cancer radiotherapy have been specifically adopted to reduce the risks of lung cancer. It is acknowledged in the literature that there is no threshold below which radiation dose to the lung is considered safe, though recommended lung dose constraints within current clinical guidelines are likely derived from studies relating various lung dose-volume parameters to incidence of radiation pneumonitis rather than radiation-induced lung cancer.[5–9] It has been shown that DIBH reduces lung as well as heart doses, and this has been embedded into UK clinical practice.[10] PBT has also been shown to reduce lung doses in dosimetry studies, though is not currently widely available due to a lack of clinical evidence.[10]

Here we present temporal trends in mean whole lung doses from IMN radiotherapy over the past 55 years and exploratory analyses on how these may have been influenced by advances in breast cancer radiotherapy. Ultimately better understanding of how lung radiation dose distributions are influenced by advances in radiotherapy may support the selection of future lung-sparing radiotherapy practices.

5.3 Methods

5.3.1 Study eligibility

For this exploratory analysis of the temporal trends in mean whole lung doses from IMN radiotherapy for early breast cancer over the past 55 years, mean whole lung doses presented in this thesis were collated and compared with others published

within systematic reviews of lung doses from radiotherapy for early breast cancer. Systematic reviews were eligible for inclusion if they included publications reporting mean whole lung dose from any type of IMN radiotherapy for early breast cancer, or if they reported both mean ipsilateral and contralateral lung doses, since these could be averaged to estimate mean whole lung dose.

5.3.2 Study identification

5.3.2.1 Doses presented within this thesis

Estimated mean whole lung doses from IMN regimens for early breast cancer were collated from studies presented in Chapters 2, 3 and 4 of this thesis. All estimated doses presented in Chapter 2 contributed to this study as they were all from IMN radiotherapy regimens used in five randomised trials of IMN radiotherapy, and one study allocating IMN radiotherapy according to breast cancer laterality, starting 1989-2008. From mean whole lung doses presented in Chapter 3, only doses from UK studies of IMN radiotherapy published during 2015-2023 were selected. Similarly, from all lung doses presented in Chapter 4 only the mean whole lung doses retrospectively estimated from 32 IMN regimens used in the Netherlands Cancer Institute or the Erasmus MC Cancer Institute during 1970-2010 were selected.

From the two retrospective dosimetry studies presented in Chapters 2 and 4, mean whole lung doses for each reconstructed regimen were abstracted. The number of patients the doses were estimated to represent was also recorded. From the systematic review study presented in Chapter 3, published average mean whole lung doses were abstracted. For each published average mean whole lung dose, the total number of contributing individual dose estimates was recorded.

5.3.2.2 Other published doses

For this exploratory analysis, a preliminary literature search was conducted to identify systematic reviews of lung doses from radiotherapy for early breast cancer. MEDLINE was searched via PubMed using the following search terms: (lung dose) AND (breast cancer radiotherapy). A filter for systematic reviews was applied. Searches were conducted March 2025. Titles and abstracts were screened for inclusion against eligibility criteria.

From eligible systematic reviews, included publications were selected for data extraction if they reported either mean whole lung doses or both mean ipsilateral and contralateral lung doses.

5.3.3 Data extraction

From each included study the following information was abstracted: first author, year radiotherapy was delivered, and year of publication. The average mean whole lung dose or average mean ipsilateral and contralateral lung doses were abstracted, and for each average mean whole lung dose, the total number of contributing individual dose estimates was recorded.

Each of the average mean whole lung doses was then categorised according to the following details of IMN radiotherapy regimens from which the doses were estimated: total prescribed dose and fractionation, IMN beam type, beam arrangement, and treatment planning method. (See Appendix D.1 for category definitions.)

5.3.4 Data analysis

First, where published average mean whole lung doses were unavailable, these were estimated by taking the average of mean ipsilateral and mean contralateral lung doses.

Second, where mean whole lung doses in Gy for each regimen were unavailable, these were calculated. With the exception of lung doses presented in Chapter 4, all included studies provided mean whole lung doses from regimens not individual fields. However, in Chapter 4 mean whole lung dose estimates are reported as percentage of the prescribed dose to each radiotherapy field within a given regimen. To convert this percentage into Gy, the mean whole lung dose in Gy for each regimen was estimated by taking the sum of the mean whole lung doses from each field.

Third, to allow comparison between lung doses from regimens with different total doses, mean whole lung doses as a percentage of the regimen total prescribed dose were also calculated. Where the regimen total prescribed dose in Gy was available or could be assumed, mean whole lung doses in Gy were also calculated as a percentage of the regimen total prescribed dose. The regimen total prescribed dose in Gy was assumed in two scenarios. First, where the total dose for all fields comprising a regimen were the same, this total dose was assumed to be the total regimen dose. Second, where the sum of doses prescribed to each field targeting the IMNs was equal to the total dose prescribed to fields targeting the breast or chest wall, the latter was assumed to be the total regimen dose. Where the regimen total dose could not be assumed, mean whole lung dose as a percentage of the total prescribed dose was not calculated. It was not possible to adjust the mean whole

lung doses for fraction size using the equivalent dose in 2Gy fractions because to the best of our knowledge α/β ratios are unavailable for second lung cancer.

Fourth, to assess the temporal trends in mean whole lung doses, doses were plotted against the year the radiotherapy was delivered. For published data, this was often unavailable and therefore year of publication was used.

Finally, for each category of fractionation, IMN beam type, IMN beam arrangement, and treatment planning method, the overall average mean whole lung dose was calculated by weighting the abstracted average dose by the number of individual dose estimates it represented. Calculations were carried out using R (version 4.4.2).[11]

Table 5.1: Average mean whole lung doses (Gy) from IMN regimens, by regimen fractionation, beam type, arrangement, and planning method.

IMN regimen categories*	No.†	Mean whole lung dose (Gy)			
		Average‡	IQR	Min.	Max.
Data source					
Retro. dosimetry, international trials, 1989-2008	4796	7.8	3.6	3.6	43.5
Retro. dosimetry, Netherlands cohort, 1970-2010	430	7.6	3.8	4.4	14.6
Systematic review, UK, 2015-2023	91	7.1	1.0	4.1	8.5
Systematic review, international, 2010-2015	545	9.9	2.8	3.0	48.5
Systematic review, international, 2015-2023	30	3.7	0.3	3.4	4.4
Systematic review, international, 2018-2023	20	9.6	0.2	9.5	9.8
Decade					
1971-1980	282	7.3	4.2	4.4	14.6
1981-1990	202	6.6	3.7	3.6	10.9
1991-2000	2830	7.8	2.8	5.0	12.1
2001-2010	2066	8.4	3.1	4.5	48.5
2011-2020	452	8.2	2.7	3.0	12.1
2021-2023	80	6.9	0.7	5.3	7.6
Fractionation					
Conventional	4734	7.9	3.0	3.0	43.5
Moderately hypofractionated	944	7.4	2.3	4.1	9.8
Not possible to calculate (retrospective dosimetry)	174	9.1	4.5	4.9	14.6
Not specified (published doses)	60	20.8	10.5	7.5	48.5
IMN beam type					
Photons (Co60)	68	9.4	2.7	5.5	11.8
Mixed (Photons (MV), Electrons)	2182	8.7	3.4	4.5	48.5
Mixed (Photons (OrthoV), Photons (MV))	23	8.3	1.7	6.6	10.0
Electrons	1477	8.0	2.8	4.4	12.1
Photons (MV)	1941	7.5	2.4	3.6	20.5
Mixed (Photons (OrthoV), Photons (Co60))	33	6.1	1.2	4.9	7.3
Scattered Protons	12	6.0	0.0	6.0	6.0
Photons (OrthoV)	116	5.4	0.9	4.5	6.3
Scanned Protons	50	5.3	3.0	3.4	8.0
Mixed (Electrons, Scattered Protons)	10	3.0	0.0	3.0	3.0
IMN beam arrangement					
Oblique anterior	478	11.9	3.1	4.5	48.5
IMRT static	184	8.7	4.1	3.4	20.5
NS anterior	54	8.1	1.0	7.1	9.1
Direct anterior	3409	7.8	4.0	3.0	14.6
IMRT rotational	190	7.8	1.5	5.8	9.8
Partially wide tangents	1432	7.1	3.3	5.1	9.5
Wide tangents	165	6.8	4.1	3.6	10.3
IMN treatment planning method					
Hybrid	10	9.8	0.0	9.8	9.8
IMRT, Forward planned	70	8.4	2.0	4.1	10.2
IMRT, Inverse planned	320	8.1	1.9	3.4	20.5
3D conformal	5082	8.0	3.7	3.0	48.5
2D conformal	430	7.6	3.8	4.4	14.6
All individual dose estimates	**5912**	**8.0**	**3.0**	**3.0**	**48.5**

Footnotes

*See Appendix D.1 for IMN regimen category definitions.

†Number of individual dose estimates.

‡The weighted average mean whole lung doses, weighted by the number of contributing individual dose estimates.

Abbreviations: Co60=cobalt 60, Gy=Gray, IMN=internal mammary lymph nodes, IQR=interquartile range, IMRT=intensity modulated radiotherapy, Max.=maximum, Min.=minimum, MV=megavoltage, NS=not specified, OrthoV=orthovoltage, Retro.=retrospective.

5.4 Results

The overall average mean whole lung dose representing 5912 individual estimates collated from IMN regimens spanning 55 years (1970 to 2025) was 8.0Gy (IQR 3.0). (Table 5.1, Figure 5.1)

5.4.1 Data sources

5.4.1.1 Doses presented within this thesis

The average mean whole lung doses representing 4796 individual estimates presented within Chapter 2 (Retrospective dosimetry, international randomised trials, 1989-2008), 430 dose estimates within Chapter 4 (Retrospective dosimetry, Netherlands cohort, 1970-2010) and 91 estimates within Chapter 3 (Systematic review, UK, 2015-2023) were 7.8Gy (IQR 3.6), 7.6Gy (IQR 3.8) and 7.1Gy (IQR 1.0) respectively. (Table 5.1, Figure 5.1)

5.4.1.2 Other published doses

Twenty published studies, identified from three other published systematic reviews of lung doses from breast cancer radiotherapy, provided average mean whole lung doses from a total of 595 individual dose estimates. (Figure D.2, Appendix D.3, Table 5.1) Average mean whole lung doses were 9.9Gy (IQR 2.8) from studies published during 2010-2015 and 9.6Gy (IQR 0.2) from studies published 2018-2023. One systematic review, including studies published 2015-2023, reported doses only from PBT. The average mean whole lung dose from this data source was 3.7Gy (IQR 0.3). (Table 5.1)

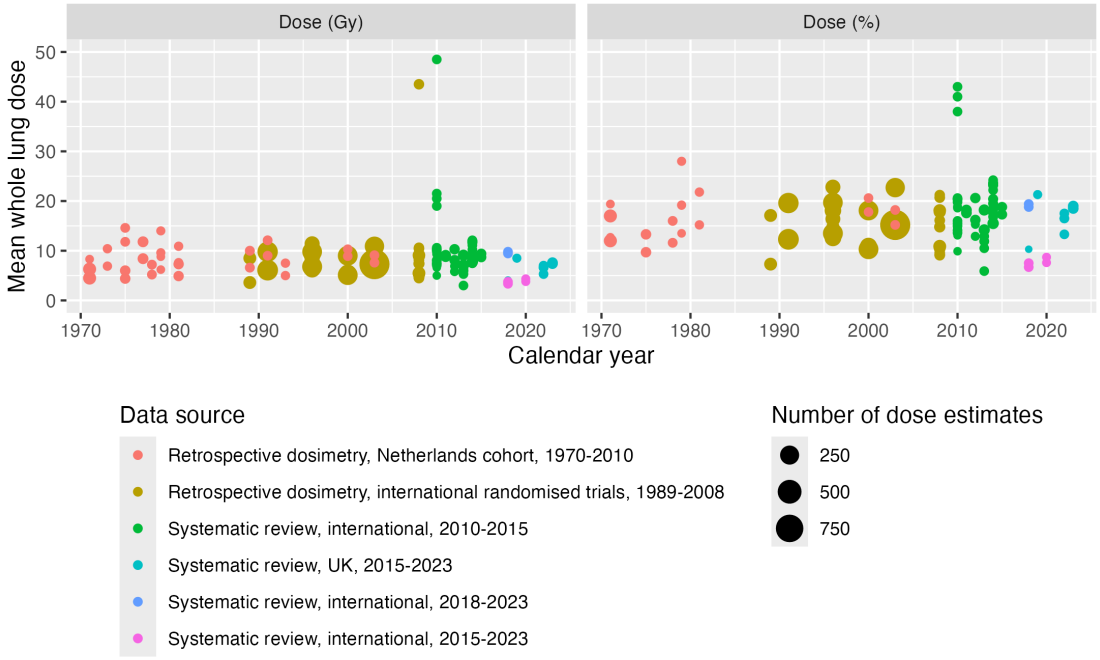


Figure 5.1: Mean whole lung doses in Gray (left) and percentage of regimen total prescribed dose (right) according to data source.
See Table 5.1 for summary statistics for each category.

5.4.2 Decade

Average mean whole lung doses from IMN regimens by calendar decade varied from 6.6Gy (IQR 3.7) to 8.4Gy (IQR 3.1) over the past five decades, with no clear trend over time. (Table 5.1, Figure 5.1)

5.4.3 Regimen total prescribed dose and fractionation

It was possible to estimate lung doses as a percentage of the regimen total prescribed dose for 115/129 (89%) of lung doses measured in Gray. (Table D.1) For the remaining 14/129 (11%) of the lung doses it was not possible. No clear temporal trend in mean whole lung doses described as a percentage of the regimen total prescribed doses was observed. (Figure 5.1)

Although it is not possible to adjust for fraction size, the majority (4734/5912, 80%) of individual dose estimates were ascertained from conventionally fractionated IMN regimens. Furthermore, the estimates from moderately hypofractionated radiotherapy (944/5912, 16%) were distributed during the years 1971-1991 and 2014-2023. (Table 5.1, Figure 5.2) Average mean whole lung doses from conventionally and moderately fractionated IMN radiotherapy were 7.9Gy (IQR 3.0) and 7.4Gy (IQR 7.4). For 174/5912 (3%) of retrospectively estimated doses, it was not possible to calculate fraction sizes. Average mean whole lung dose was 9.1Gy (IQR 4.5) for this category. For 60/5912 (1%) of individual published doses, fractionation was not specified. Average mean whole lung dose from these was 20.8Gy (IQR 10.5). No regimens using ultrahypofractionated radiotherapy were identified.

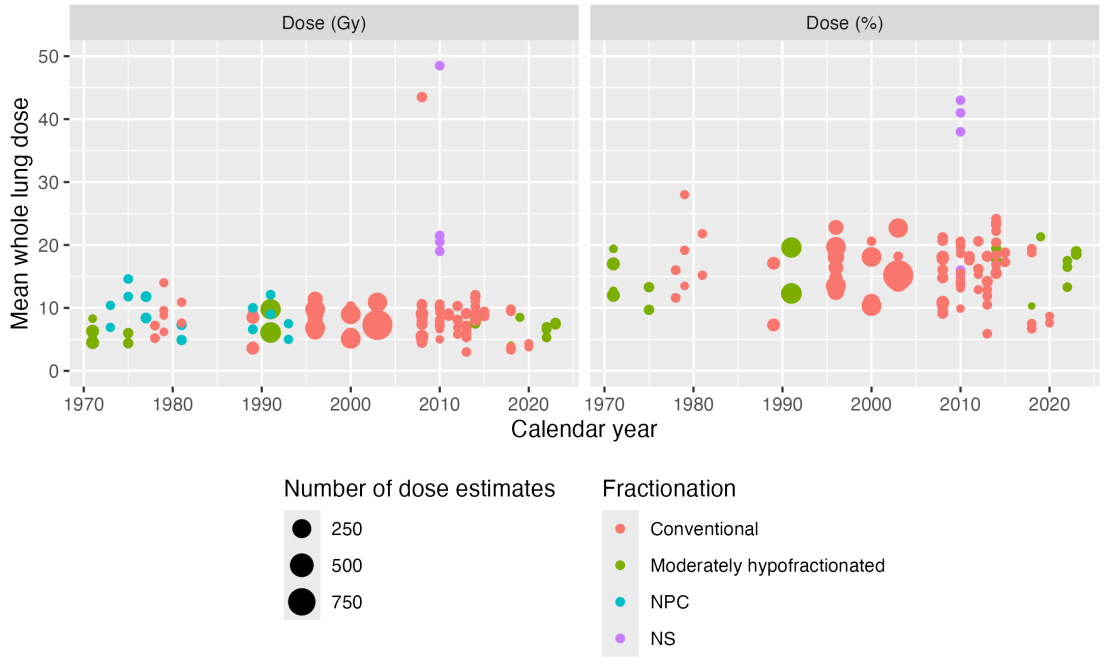


Figure 5.2: Mean whole lung doses in Gray (left) and percentage of regimen total prescribed dose (right) according to IMN regimen fractionation.
See Appendix D.1 for fraction size definitions.
See Table 5.1 for summary statistics for each category.
Abbreviations: NPC=not possible to calculate, NS=not specified.

5.4.4 IMN beam type

There was considerable variation in average mean whole lung doses from IMN regimens according to IMN beam type, ranging from 3.0-9.4Gy. (Table 5.1, Figure 5.3) Average mean whole lung doses were 9.4Gy (IQR 2.7) from Co60 photons, 8.7Gy (IQR 3.4) from mixed megavoltage photons and electrons, 8.3Gy (IQR 1.7) from mixed orthovoltage and megavoltage photons, 8.0Gy (IQR 2.8) from electrons, 7.5Gy (IQR 2.4) from megavoltage photons, 6.1Gy (IQR 1.2) from mixed orthovoltage and Co60 photons, 6.0Gy (IQR 0.0) from scattered protons, 5.4Gy (IQR 0.9) from orthovoltage photons, 5.3Gy (IQR 3.0) from scanned protons, and 3.0Gy (IQR 0.0) from mixed electrons and scattered protons.

On average, doses of >6Gy arose from IMN regimens using photon and/or electron beams. Mean whole lung doses of ≤6Gy arose from proton±electron beams, or orthovoltage photon beams. Furthermore, in this dataset, there was a pattern in the use of beam types over time. Older IMN regimens used lower energy photon beams±electrons, newer regimens used higher energy photon beams±electrons. PBT IMN regimens featured only during the most recent two decades. (Figure 5.3)

5.4.5 IMN beam arrangement

On average, mean whole lung doses from IMN regimens using anterior beams and IMRT arrangements were higher than from those using tangents. Oblique, unspecified, and direct anterior arrangements resulted in mean whole lung doses of 11.9Gy (IQR 3.1), 8.1Gy (IQR 1.0) and 7.8Gy (IQR 4.0) respectively. Static and rotational IMRT arrangements result in mean whole lung doses of 8.7Gy (IQR 4.1)

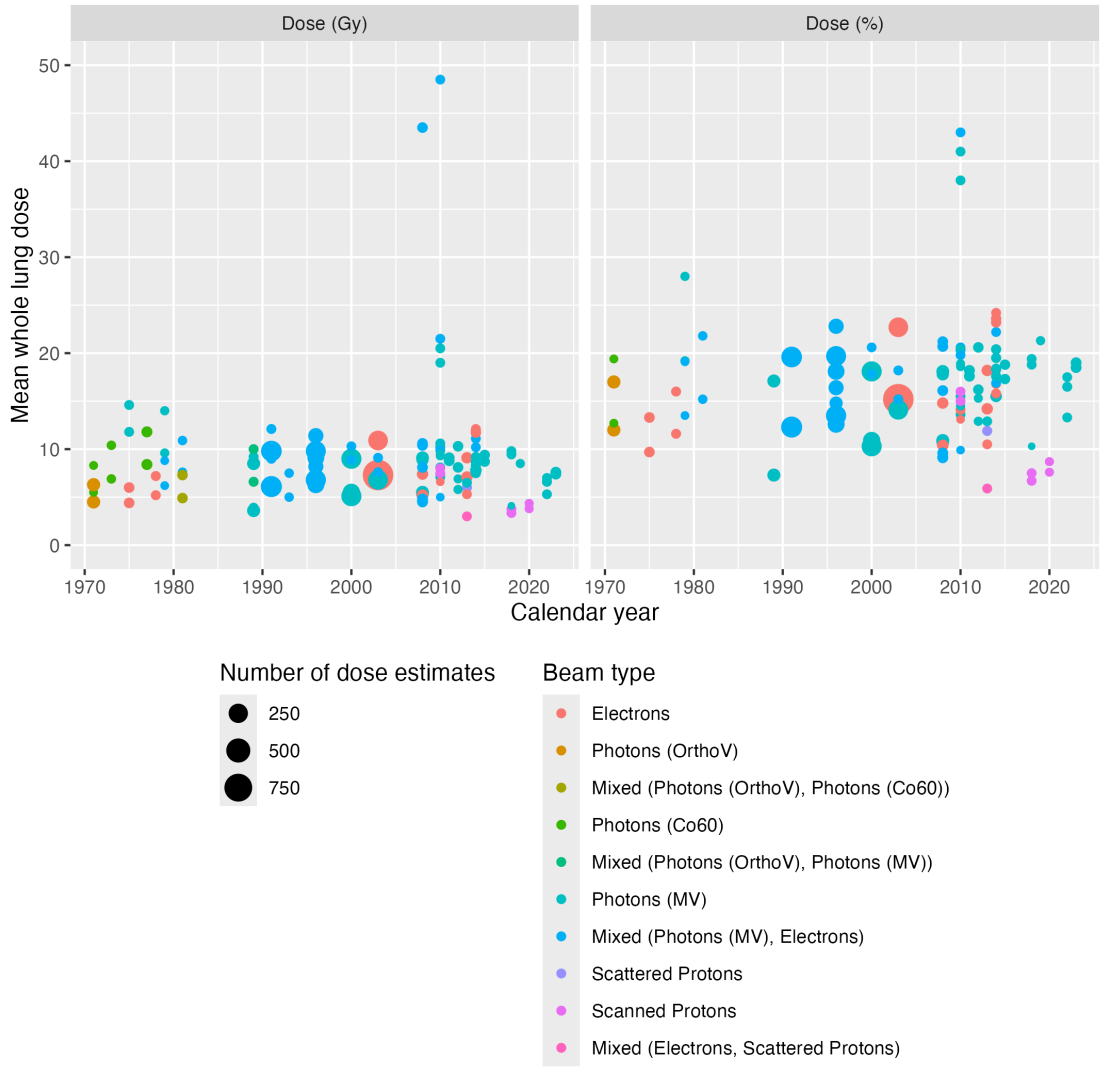


Figure 5.3: Mean whole lung doses in Gray (left) and percentage of regimen total prescribed dose (right) according to IMN field beam type.
See Table 5.1 for summary statistics for each category.
Abbreviations: Co60=cobolt60, MV=megavoltage, OrthoV=orthovoltage.

and 7.8Gy (IQR 1.5). Average mean whole lung doses were lower from regimens using partially wide (7.1Gy, IQR 3.3) or wide (6.8Gy, IQR 4.1) tangents.

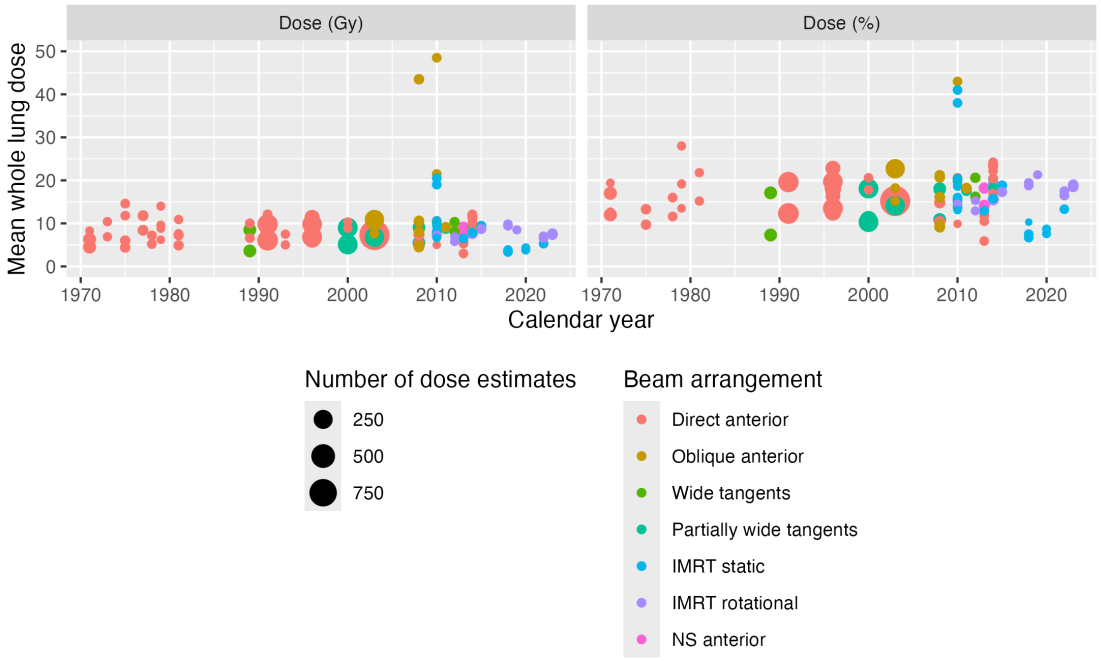


Figure 5.4: Mean whole lung doses in Gray (left) and percentage of regimen total prescribed dose (right) according to IMN beam arrangement
See Appendix D.1 for beam arrangement definitions.
See Table 5.1 for summary statistics for each category.
Abbreviations: IMRT=intensity modulated radiotherapy, NS=not specified.

5.4.6 Treatment planning method

Average mean whole lung doses were 8.8Gy (IQR 0.0), 8.4Gy (IQR 2.0) and 8.1Gy (IQR 1.9) from hybrid, forward-planned IMRT and inverse-planned IMRT treatment planning methods respectively. Doses arising from 3D and 2D conformal planning methods were 8.0Gy (IQR 3.7) and 7.6Gy (IQR 3.8).

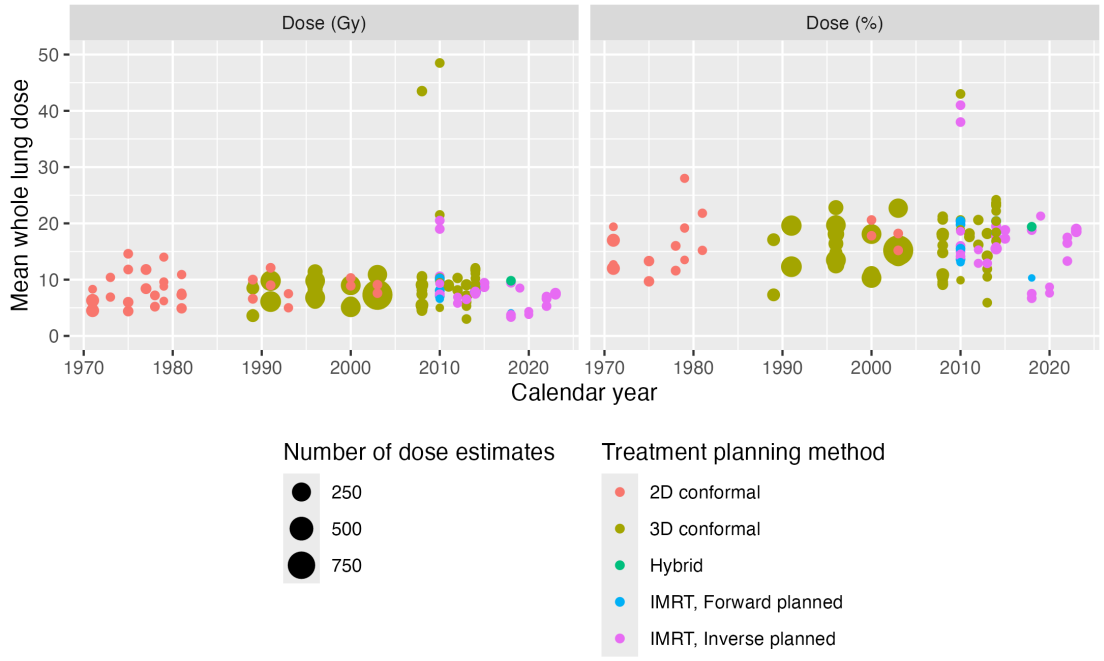


Figure 5.5: Mean whole lung doses in Gray (left) and percentage of regimen total prescribed dose (right) according to IMN treatment planning method.
See Appendix D.1 for beam arrangement definitions.
See Table 5.1 for summary statistics for each category.
Abbreviations: 2D=2 dimensional, 3D=3 dimensional, IMRT=intensity modulated radiotherapy.

5.5 Discussion

From exploratory analyses of temporal trends in mean whole lung doses from IMN radiotherapy for early breast cancer, there have been minimal reductions in exposure of the lungs to radiation over the past 55 years despite considerable advances in IMN regimen fractionation, beam arrangements and treatment planning methods. These data suggest that lung-sparing for IMN radiotherapy for early breast cancer is an unmet clinical need, which PBT may address, but larger datasets and/or alternative dose metrics may be needed to distinguish the lung-sparing properties of modern photon beam arrangements and treatment planning methods.

5.5.1 Strengths and limitations

Though exploratory, to the best of our knowledge the analysis of mean whole lung doses from IMN regimens over the past 55 years is the largest and most up-to-date series specifically from IMN radiotherapy. A strength of this study is the wide range of IMN regimens represented in the dose data. It is a strength that was made possible by combining data from retrospective dosimetry studies with data from published studies.

However, this approach does requires an understanding of the uncertainties surrounding doses estimated from retrospective dosimetry when interpreting the data. (See Chapter 4)

A limitation of this study is the lack of information on DIBH. More detailed analyses of these provisional data are planned.

5.5.2 Clinical implications

Although the risks of radiation-induced lung cancer from IMN radiotherapy may be reduced with smoking cessation support or omission of IMN radiotherapy for some long-term continuing smokers, lung-sparing radiotherapy is an option which preserves the benefits of IMN irradiation and may simultaneously reduce the risks of morbidity associated with other radiation-induced lung injuries. These exploratory analyses of mean whole lung doses over the past 55 years from a wide range of IMN regimens suggest that lung-sparing for IMN radiotherapy for early breast cancer remains a long-standing unmet clinical need, which PBT may help to address. Further development, selection and application of lung-sparing strategies are needed.

In the meantime, the lack of data on doses and clinical outcomes from IMN radiotherapy for early breast cancer highlighted by this study may be in part addressed by including doses received by the lungs from IMN radiotherapy in national audits of radiotherapy for early breast cancer. This was also highlighted by work estimating the absolute risks of UK radiotherapy presented in Chapter 3.[1]

5.6 Conclusions

Overall, there have been minimal reductions in mean whole lung doses from IMN radiotherapy for early breast cancer over the past 55 years despite considerable advances in radiotherapy beam types, arrangements and treatment planning methods. However, exploratory analyses indicate that recent rises in the use of PBT may systematically reduce lung exposure from IMN radiotherapy. More data and

alternative dose metrics are needed to distinguish the relative lung-sparing properties of modern photon radiotherapy.

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I, **Francesca Holt** conceptualised and conducted the study, and wrote the original draft manuscript.
Georgios Ntentas, **David Dodwell**, **Frances Duane** and **Carolyn Taylor** supervised and reviewed draft manuscripts.

Chapter 6

Proton beam therapy for early breast cancer: a systematic review and meta-analysis of clinical outcomes.

Holt F, Probert J, Darby SC, Haviland JS, Coles CE, Kirby AM, Liu Z, Dodwell D, Ntentas G, Duane F, Taylor C.
Int J Radiation Oncol Biol Phys 2023;117(4):869-882.

Co-authored publication relating to Chapter 6:
Kirby AM, **Holt F**, Taylor C, Haviland JS, MacKenzie M, Coles CE.
Should patients requiring radiotherapy for breast cancer be treated with proton beam therapy?
BMJ 2023;381:e072896.

OXFORD POPULATION HEALTH

Proton beam therapy for early breast cancer: adverse outcomes

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Background

Proton beam therapy is increasingly available to some patients with early breast cancer because it achieves better planned dose distributions than standard photon radiotherapy and may therefore reduce the risks. However, there is a lack of clinical evidence.

Methods

A systematic review and quantitative synthesis of adverse clinical outcomes from studies of adjuvant proton beam therapy for early breast cancer published during 2000-2022 was undertaken. Eligible studies were identified by searching Ovid MEDLINE® and EMBASE.

Results

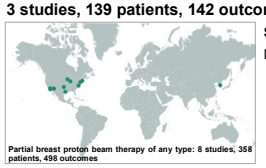
Studies

Thirty-two studies (1452 patients) published during 2000-2022 reported clinical outcomes after adjuvant proton beam therapy for early breast cancer. 28/32 studies (1359 patients) were conducted in the USA. There were no randomised comparisons with photon radiotherapy. Most studies had median follow up of <24 months (range 2-59).

Proton beam therapy was delivered using a scattered beam in seven studies (258 patients) starting 2003-2015. Scanning proton beam therapy was used in 22 studies (1041 patients) starting 2000-2019.

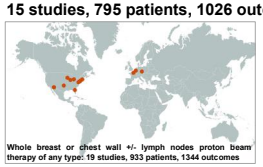
Figure 1. Severe adverse outcomes after scanning proton beam therapy

Partial breast
3 studies, 139 patients, 142 outcomes reported



Severe outcomes
None

Whole breast or chest wall +/- lymph nodes
15 studies, 795 patients, 1026 outcomes reported



Severe outcomes

Dermatitis	6%
Infection	1%
Pain	<1%
Pneumonitis	<1%

*Global distribution of centres reporting clinical outcomes after **all** types of proton beam therapy (scattering and scanning) for early breast cancer during 2000-2022 by clinical target.*

Adverse outcomes after newer scanning proton beam therapy

Adverse outcomes were graded using each study's specified grading system. Adverse outcomes after newer scanning proton beam therapy are the most relevant to today's clinical practice and were all graded using Common Terminology Criteria for Adverse Events versions 4.0 or 5.0 where a grading system was specified.

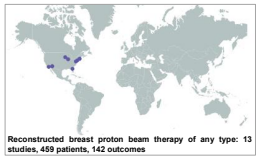
Severe
Adverse outcomes are shown in Figure 1.

Mild and moderate
Partial breast
Adverse outcomes were most commonly graded as mild and related to effects on breast skin and soft tissue.
Whole breast or chest wall +/- regional lymph nodes
Adverse outcomes were most commonly graded as mild or moderate and related to effects on breast or chest wall skin and soft tissue, the oesophagus, lungs, ribs, lymphatics, and brachial plexus.

Grade unspecified
Breast reconstruction outcomes are shown in Figure 2.

Figure 2. Reconstruction outcomes after scanning proton beam therapy

Reconstructed breast +/- lymph nodes
10 studies, 348 patients, 77 outcomes reported



Reconstruction outcomes

Infection	13%
Capsular contraction	14%
Implant revision	8%
Implant removal	19%
Autologous revision	3%

*Global distribution of centres reporting reconstruction outcomes after **all** types of proton beam therapy (scattering and scanning) for early breast cancer during 2000-2022.*

The most common adverse outcome

Dermatitis was the most commonly reported adverse outcome.

There were fewer reports of severe dermatitis after the latest scanning proton beam therapy than after the older scattering proton beam therapy. There were fewer severe adverse outcomes reported after partial breast proton beam therapy than after whole breast or chest wall +/- regional lymph nodes proton beam therapy (Figure 3).

Meta-analysis of the percentage of patients with severe dermatitis after whole breast or chest wall +/- regional lymph nodes scanning proton beam therapy estimates that dermatitis is severe in 6% (95%CI 4-8) of assessed patients with no significant heterogeneity (Figure 4).

Figure 3. Dermatitis after proton beam therapy for early breast cancer

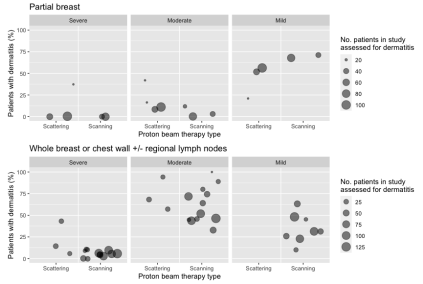
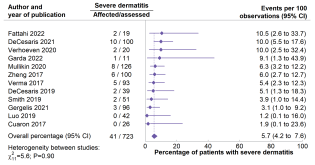


Figure 4. Severe dermatitis after whole breast or chest wall +/- regional lymph nodes scanning proton beam therapy



Discussion

This is the first quantitative summary of all published adverse clinical outcomes after proton beam therapy for early breast cancer.

There were few adverse outcomes from partial breast or whole breast or chest wall +/- regional lymph nodes proton beam therapy reported as severe. The most common severe adverse outcome after whole breast or chest wall +/- regional lymph nodes scanning proton beam therapy was dermatitis which occurred in 6% (95%CI 4-8) of patients. Other severe adverse outcomes after scanning PBT were rare, ≤1%.

Ongoing randomised trials are needed to provide information on the longer-term safety of proton beam therapy compared with standard photon radiotherapy.

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Figure 6.1: Poster presented at the European Breast Cancer Conference, 2022

In 2022, prior to publication of the full manuscript in the International Journal of Radiology Biology and Physics, I presented this project orally at the British Breast Group meeting and in poster format at the 13th European Breast Cancer Conference. The proceedings of the latter conference were published:

Holt F, Probert J, Darby SC, Haviland JS, Coles CE, Kirby AM, Liu Z, Dodwell D, Ntentas G, Duane F, Taylor C. Proton beam therapy for early breast cancer: a systematic review and quantitative synthesis of adverse clinical outcomes. **Eur J Cancer, 2022; 175:S46-S47**

6.1 Abstract

6.1.1 Background

Adjuvant proton beam therapy (PBT) is increasingly available to patients with breast cancer. It achieves better planned dose distributions than standard photon radiotherapy and therefore may reduce the risks. However, clinical evidence is lacking.

6.1.2 Methods

A systematic review of clinical outcomes from studies of adjuvant PBT for early breast cancer published 2000-2022 was undertaken. Early breast cancer was defined as when all detected invasive cancer cells are in the breast or nearby lymph nodes and can be removed surgically. Adverse outcomes were summarised quantitatively, and the prevalence of the most common ones estimated using meta-analysis.

6.1.3 Results

Thirty two studies (1452 patients) reported clinical outcomes after adjuvant PBT for early breast cancer. Median follow up ranged from 2-59 months. There were no published randomised trials comparing PBT with photon radiotherapy. Scattering PBT was delivered in seven studies (258 patients) starting 2003-2015 and scanning PBT in 22 studies (1041 patients) starting 2000-2019. Two studies (123 patients) starting 2011 used both PBT types. For one study (30 patients) PBT type was unspecified.

Adverse events were less severe after scanning than after scattering PBT. They also varied by clinical target. For partial breast PBT, 498 adverse events were reported (8 studies, 358 patients). None were categorised as severe after scanning PBT. For whole breast or chest wall ± regional lymph nodes PBT, 1344 adverse events were reported (19 studies, 933 patients). After scanning PBT, 4% (44/1026) of events were severe. The most prevalent severe outcome after scanning PBT was dermatitis which occurred in 5.7% (95% CI 4.2-7.6) of patients. Other severe adverse outcomes included infection, pain and pneumonitis (each $\leq$1%). Of the 141 reconstruction events reported (13 studies, 459 patients), the most prevalent after scanning PBT was prosthetic implant removal (34/181, 19%).

6.1.4 Conclusions

This is a quantitative summary of all published clinical outcomes after adjuvant PBT for early breast cancer. Ongoing randomised trials will provide information on its longer-term safety compared with standard photon radiotherapy.

6.2 Introduction

Adjuvant photon radiotherapy is given to around two thirds of women with breast cancer.[1] It reduces the risk of breast cancer death when targeted at the whole breast after breast conserving surgery, or the chest wall after mastectomy in lymph node positive cancer.[2, 3] Inclusion of the regional lymph nodes further improves survival.[4] However, when irradiating these clinical targets, incidental irradiation of the nearby heart, lungs and oesophagus can increase the risks of death from heart disease, lung and oesophageal cancer respectively.[5–7]

During the past few decades, advances in breast cancer photon radiotherapy have reduced incidental irradiation of the surrounding organs and homogenised dose to clinical targets, likely contributing to improved clinical outcomes.[8] For the majority of women receiving modern photon radiotherapy who do not smoke, the absolute mortality risks are now estimated to be less than 1%.[6] However, for some women, the risks of heart disease and second cancers may be higher. For example, it may be more difficult to spare nearby organs from radiation when treating patients with left-sided breast cancers, those requiring internal mammary lymph node irradiation, and those with unfavorable cardiothoracic anatomy.[9–11] Absolute radiation-risks of heart disease and lung cancer may also be higher for women who are long-term continuing smokers or have pre-existing heart disease.[5, 6] In women with one or more of these risk factors, there may be a role for proton beam therapy (PBT).[9–11]

Adjuvant PBT is being considered as an alternative to standard photon radiotherapy because it may further reduce radiation-related risks for patients with early breast cancer.[5–7, 12–14] Dosimetry studies have demonstrated that when irradi-

ating the breast or chest wall ± regional lymph nodes PBT can achieve lower doses to the heart, lungs and oesophagus compared with photon radiotherapy without compromising coverage of the clinical target.[9–11]

The availability of PBT for breast cancer has increased over recent decades, and the technology has advanced. Since 1990 around 95 PBT centres have opened for clinical use worldwide including 41 in the USA and 30 in Europe.[15] Early PBT was delivered using passive scattering which spreads a narrow proton beam so that it is wide enough to cover the clinical target. By 2014 most centres were delivering PBT via uniform scanning or pencil beam scanning both of which use magnetic fields to steer narrow proton beams across the clinic target, enabling better sparing of normal tissues.[16] In particular better skin-sparing is possible with pencil beam scanning technology because of its enhanced dose modification capabilities.

Although PBT for breast cancer is increasingly available and the technology and techniques to deliver it are improving, its place as a cost-effective, clinically-beneficial alternative to photon radiotherapy has not yet been proven. Lack of clinical evidence is the main reason that the majority of European PBT centres are not using protons to treat patients with breast cancer routinely.[17]

Synthesis of all available knowledge of clinical outcomes after the most advanced PBT techniques is needed to improve our knowledge of its clinical benefits and risks. This systematic review aims to summarise and quantify all clinical outcomes after adjuvant PBT for early breast cancer published before September 2022 to inform clinicians and patients, and to guide the design of future clinical trials. We also summarise ongoing studies of PBT in early breast cancer.

6.3 Methods

A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines.[18] Search methods, inclusion criteria, and data abstraction were specified in the study protocol registered on PROSPERO and are described below.

6.3.1 Study eligibility

Two groups of studies were included in the review. In the first group, eligible studies were those that reported clinical outcomes in patients who received adjuvant PBT for early breast cancer after curative intent surgery and were published in full text or abstract form between 1st January 2000 and 1st September 2022 (Appendix E.1, Figure E.1). Breast cancer was defined as early when all detected invasive cancer cells were in the breast or regional lymph nodes and could be removed surgically. Patients of any age or sex were included. Studies providing only the outcomes of clinical investigations (e.g. echocardiogram findings) rather than outcomes from clinical history or examination were excluded because such surrogates for clinical outcomes have yet to be validated for clinical use in this context. Studies were excluded if they were case reports or if clinical outcome data could not be extracted.

The second group of eligible studies included all ongoing clinical studies of adjuvant PBT in women with early breast cancer after curative intent surgery (Appendix E.1, Figure E.2). These studies were recruiting patients, or had completed recruitment and were in follow-up, but had not yet published their results.

6.3.2 Study Identification

Publications reporting clinical outcomes after adjuvant PBT for early breast cancer were identified by searching Ovid MEDLINE® and Embase using the following terms: breast cancer NOT advanced/metastatic/inoperable, AND proton radiotherapy (Appendix E.1). Full text publications and abstracts were included to capture the clinical outcomes from as many patients as possible.

Ongoing clinical studies of PBT in breast cancer were identified from the ClinicalTrials.gov website, the World Health Organisation International Clinical Trials Registry Platform, and the Cochrane Central Register of Controlled Trials using the search terms 'breast cancer' AND 'proton' (Appendix E.1).[19–21]

6.3.3 Data abstraction

From eligible published studies reporting clinical outcomes, the following information was abstracted: study author, years of study and location, study design, number of patients, number of breast cancers, details of primary and reconstructive breast cancer surgery, details of PBT beam delivery type and technique, PBT dose (Gy) and fractionation, median follow-up, breast cancer outcomes, number, type and severity of adverse clinical outcomes, and the clinical definitions and severity grading systems used. Where the PBT delivery type or clinical target were unspecified, the corresponding authors of the studies were contacted for further information.

To prevent counting of individual patient clinical outcomes more than once, studies analysing multi-institutional registry data on clinical outcomes after PBT for early breast cancer were excluded from further analysis (Figure E.1, Table

E.1). The remaining publications were grouped into the individual studies they were reporting on using trial IDs. Publications without trial ID were grouped as an individual study if the abstracted information suggested that the publications were reporting upon the same patients. Each of the resulting studies was assigned one main study publication from which reported clinical outcomes contributed to data analysis. The main study publication was selected as the most recent full text publication presenting clinical outcomes, or the most recent abstract where a full text publication was not available.

From eligible ongoing clinical studies, the following information was abstracted: study design, study location and years, estimated number of patients, details of planned PBT intervention, and planned study outcomes.

6.3.4 Data analysis

Individual published studies were categorised by PBT clinical target: partial breast, whole breast or chest wall ± regional lymph nodes, and reconstructed breast ± regional lymph nodes. It was not possible to separate clinical targets further as this level of detail was not published in the majority of studies. Within these three groups, studies were categorised by PBT delivery type: scattering, scattering or scanning, scanning, and unspecified. Scattering PBT included both passive and double scattering. Scanning PBT included both uniform scanning and pencil beam scanning.

Adverse clinical outcomes reported in individual published studies were categorised as mild (or grade 1), moderate (or grade 2), severe (or grade 3), or unspecified, using the study's specified grading system (for definitions of dermatitis see

Table E.2). For each study, the number of patients reported to be affected by, and the number assessed for each grade of each type of reported adverse outcome was counted. Where a study reported the number of events for an outcome at more than one point in time, then only the time point with the highest number of severe events was counted for that outcome in that study, although different time points may have been selected for different outcomes.

Within each category of PBT clinical target and PBT delivery type, adverse outcomes were ranked in descending order of severity using the percentage of patients affected. Where the percentages of patients affected were the same, adverse outcomes were arranged in descending order of the number of patients affected.

The highest number of severe adverse events was reported for dermatitis in women who received PBT to the whole breast or chest wall ± regional lymph nodes. Fisher's exact test was used to evaluate the proportions of severe dermatitis reported between studies using scattering and scanning PBT. Then, because the outcomes after scanning PBT are most relevant to current clinical practice, we quantified the prevalence of dermatitis after scanning PBT for early breast cancer to the whole breast or chest wall ± regional lymph nodes using meta-analysis of proportions.[22] Confidence intervals for the observed prevalence in individual studies were calculated using the exact binomial method. Between-study heterogeneity was assessed by p-value from Wald-type tests and, as heterogeneity was present in some cases, pooled estimates were obtained using generalized linear mixed models with a logit link function (using R package metafor). Random effects models were used since such analyses are often highly heterogeneous. Individual study weights were derived from the likelihood contribution of each individual study. The overall prevalence estimates presented may be interpreted as the me-

dian prevalence from multiple studies.

For breast cancer outcomes, the number of patients affected by, and assessed for, locoregional recurrence, distant recurrence, breast cancer death and death from any cause were counted. Analyses of these data were not possible as information regarding the time point of individual breast cancer outcomes was missing from most publications. Ongoing clinical studies were categorised by study design into randomised and non-randomised studies, then by PBT clinical target. Summarised data were tabulated.

6.4 Results

6.4.1 Published studies

Thirty two individual published studies (1452 patients) reporting clinical outcomes after adjuvant PBT for early breast cancer were identified. Study start dates ranged from 2003 to 2019 (Figure E.1, Table 6.1). There were no randomised studies comparing PBT with photon radiotherapy. Clinical outcomes were published in full text for 21 studies (775 patients) and in abstracts for 11 studies (677 patients).

The majority of studies (28/32 studies, 1359 patients) were conducted in the USA (Table 6.1, Figure 6.2). One centre in the Republic of Korea (30 patients) reported clinical outcomes after partial breast PBT and one centre located in each of the Czech Republic (42 patients), the Netherlands (20 patients), and France (one patient) reported clinical outcomes after PBT to the whole breast or chest wall ± regional lymph nodes. No centre outside the USA reported clinical outcomes after

PBT to the reconstructed breast.

PBT clinical targets under investigation have changed with time. The partial breast was targeted in eight studies (358 patients) published since 2006. Reported study start dates ranged from 2003 to 2015 (Table 6.1). The whole breast or chest wall ± regional lymph nodes has been targeted in 19 studies (933 patients) published since 2016. Reported study start dates ranged from 2011 to 2019 (Table 6.1). Reconstruction outcomes after PBT to the reconstructed breast ± regional lymph nodes were reported in 13 studies (459 patients) published since 2016. Reported study start dates ranged from 2000 to 2016 (Table 6.1).

PBT delivery types have also changed with time. PBT was delivered using a scattered beam in seven studies (258 patients) published since 2006. Reported start dates ranged from 2003 to 2015. Scanning PBT was used in 22 studies (1041 patients) published since 2017. Reported start dates ranged from 2000 to 2019. Two studies (123 patients) both starting in 2011 used both PBT types. One study (30 patients) did not specify the type of PBT used. (Table 6.1) Adverse outcomes varied by clinical target and PBT delivery type (Tables 6.2, 6.3, 6.4).

Table 6.1: Individual studies reporting clinical outcomes after proton beam therapy for early breast cancer published 2000-2022 according to clinical target and proton beam therapy type

Author and year of publication*	Country	Year study started	Pts received PBT (N=1452)	Total dose (Gy)/ No. fractions	Median follow up (months)
Partial breast (358 patients)					
Scattering (189 patients)					
Galland-Girodet 2014[10-13]†	USA	2003	19	32/8	–
Kozak 2006[9] †	USA	2004	20	32/8	12
Pasalic 2021[1-3]	USA	2010	100	34/10	24
Bush 2011[4-8]	USA	–	50	40/10	48
Scanning (139 patients)					
Choi 2022[16-18]	USA	2013	38	40/10	35
Giap 2017[19, 20] ‡§	USA	2014	25	40/10	19
Mutter 2019[14, 15]	USA	2015	76	22/3	12
Type unspecified (30 patients)					
Chang 2013[21-22]	Republic of Korea	2007	30	30/5	59
Whole breast or Chest wall ± regional lymph nodes (933 patients)					
Scattering (69 patients)					
Bradley 2016[26-33] §	USA	2012	18	50/28	20
Liang 2018[25]	USA	2012	23	50/25-28	–
Sayan 2022[23, 24]	USA	2015	28	40-50/–	27
Scattering or scanning (69 patients)					
Jimenez 2019[34-38] §	USA	2011	69	45-50/25-28	55
Scanning (795 patients)					
Verma 2017[43-46] §	USA	2011	91	50/25-28	16
Luo 2019[49-52] §	USA	2013	42	50/–	35
Pasztorova 2018[53] ‡	Czech Republic	2015	42	40/15 or 50/25	7
DeCesaris 2019[54]	USA	2015	39	45-50/25-28	–
Smith 2019[47, 48] §	USA	2015	51	50/25	19
Gergelis 2021[42] ‡§	USA	2015	96	50/25	–
Garda 2022[60]	USA	2015	11	50/25	32
DeCesaris 2021[41] ‡	USA	2016	100	50/25-28	15
Fattahi 2022[58, 59]	USA	2016	19	50/25	24
Loap 2021[61]	France	2019	1	50/25	6
Zheng 2017[40] ‡¦	USA	–	100	45-50/25-28	–
Cuaron 2017[56] ‡	USA	–	26	49/–	15
Mullikin 2020[39] ‡§	USA	–	126	50/25	18
Verhoeven 2020[57] ‡	Netherlands	–	20	40/15	–
Salari 2021[55] ‡	USA	–	31	43/16 or 50/25	2
Reconstructed breast only ± regional lymph nodes (161 patients)					
Scattering or scanning (54 patients)					
Jimenez 2020[62] ‡	USA	2011	54	–	–
Scanning (107 patients)					
Naoum 2022[65-66]	USA	2000	17	–	–
Anderson 2021[67-68]	USA	2010	4	50/–	–
Nichols 2020[63] ‡	USA	–	57	50/–	14
DeCesaris 2021[64]	USA	–	29	50/28	5

Footnotes

The main study publication is referenced first, followed by other study publications (see Appendix E.5 for references).

†Two fractions delivered daily. In all other studies where duration of treatment was reported, one fraction was delivered daily.

‡Main study publication an abstract rather than a full text.

§Studies included some patients who had breast reconstructions.

¦Adverse outcomes data obtained from the Proton Collaborative Group trial REG001-09.

Abbreviations: Gy=Gray, N=total number, No.=number, PBT=proton beam therapy, Pts=patients, USA=United States of America, "–"=unspecified.

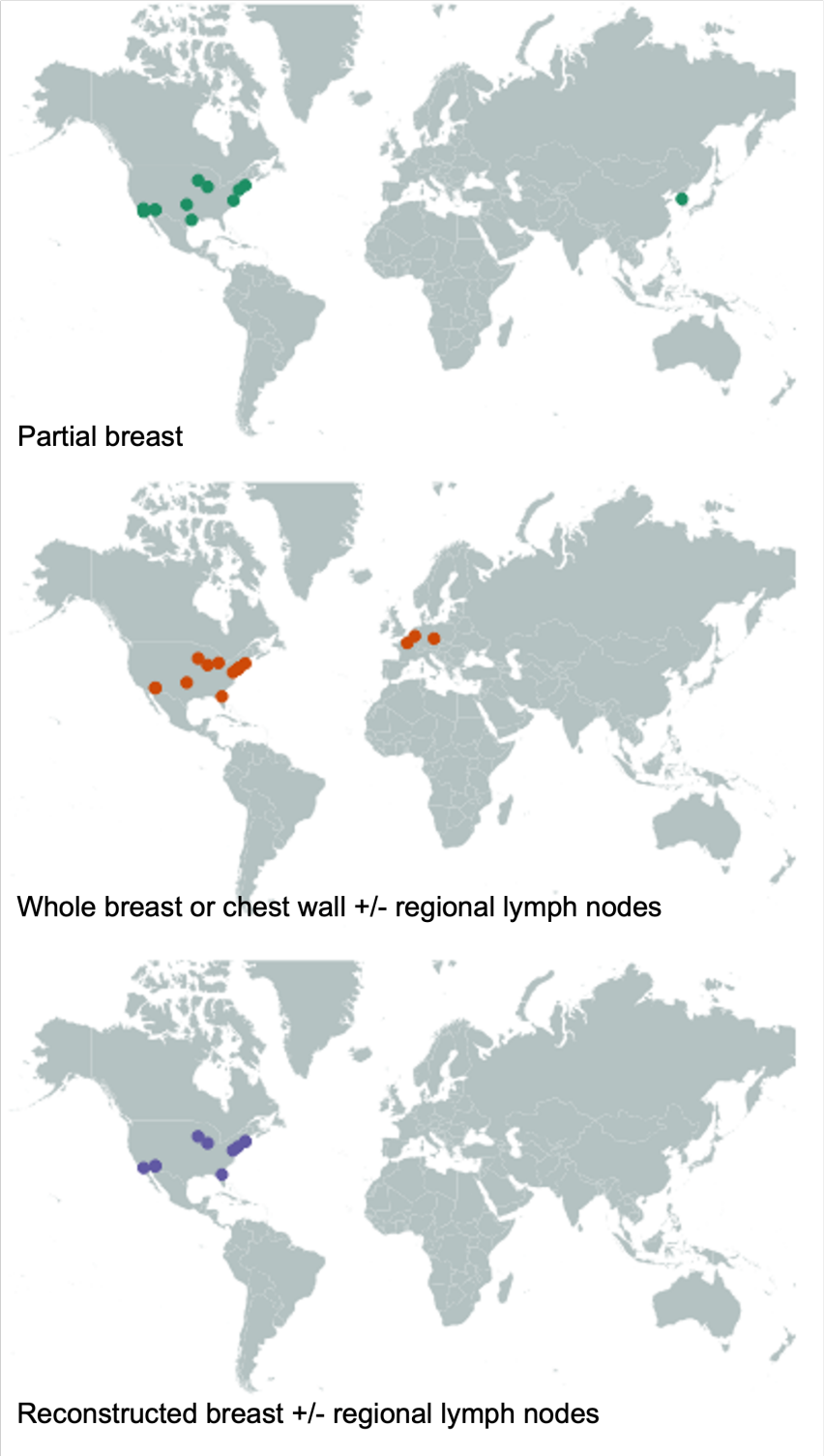


Figure 6.2: Global distribution of centres reporting clinical outcomes after proton beam therapy for early breast cancer in studies published 2000-2022 according to clinical target.

6.4.2 Partial breast PBT: adverse outcomes

PBT dose and fractionation varied according to clinical target. All eight studies of partial breast PBT investigated accelerated partial breast irradiation (Table 6.1). Six of these used total doses ranging from 32 to 40Gy in 3.4 to 4Gy fractions given across 4 and 14 days. The other two studies used higher doses per fraction: 21.9Gy in 3 daily fractions (7.3Gy per fraction), and 30Gy in 5 daily fractions (6Gy per fraction).

Scattering PBT was received by 53% (189/358) of patients and scanning PBT by 39% (139/358). For 8% (30/358) of patients PBT type was unspecified (Table 6.1). Median follow-up of patients across studies ranged from 12 to 59 months.

For partial breast PBT, 498 adverse events were reported. These spanned 14 types of adverse outcomes, all of which related to effects on breast skin and soft tissue (Table 6.2). These adverse outcomes were reported using Common Terminology Criteria for Adverse Events (CTCAE) versions 2.0 or 4.0 in four studies, categories of 'mild', 'moderate' and 'severe' in two studies, and the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) grading system in one study (Tables E.4, E.5). For the remaining study, the system used to grade adverse outcomes was unspecified. The timing of adverse outcomes was between 0 and 84 months where specified. Information on timing was missing in 23% (12/52) of instances (Tables E.4, E.5). Of the 498 adverse events reported, 2% (8/498) were graded as severe, 13% (67/498) as moderate, and 79% (393/498) as mild. Grade was unspecified in 6% (30/498) of events. The only outcome with severe events was dermatitis. Severe dermatitis events were all graded using a system that enabled classification as 'mild', 'mod-

erate' or 'severe', and were reported at two months post PBT. There were more reports (p=0.02) of severe dermatitis in patients assessed after scattering PBT (4%, 7/169) than after scanning PBT (0%, 0/114). There was one event (3%, 1/30) after PBT of unspecified type (Table 6.2, Figure 6.3, Table E.4).

Table 6.2: Partial breast proton beam therapy: Adverse outcomes published 2000-2022 according to proton beam therapy type

Adverse outcome	**Severe**		**Moderate**		**Mild**		**Unspecified**	
	Affected/ assessed	*%*	**Affected/ assessed**	*%*	**Affected/ assessed**	*%*	**Affected/ assessed**	*%*
	Scattering (296 adverse events)							
Dermatitis *	7/169	***4***	26/188	***14***	86/169	***51***	–	–
Atrophy	–	–	10/19	***53***	–	–	–	–
Fibrosis †	0/19	***0***	1/19	***5***	3/19	***16***	10/19	***53***
Fatigue	0/100	***0***	4/100	***4***	10/100	***10***	–	–
Pain ‡	0/119	***0***	3/119	***3***	34/119	***29***	4/19	***21***
Hyperpigmentation	0/100	***0***	2/100	***2***	44/100	***44***	–	–
Infection	0/100	***0***	1/100	***1***	0/100	***0***	0/50	***0***
Breast oedema	0/119	***0***	1/119	***1***	15/119	***13***	–	–
Fat necrosis	0/163	***0***	1/163	***1***	0/163	***0***	2/69	***3***
Telangiectasia	–	–	–	–	20/150	***13***	10/39	***26***
Rib fractures	–	–	–	–	–	–	2/89	***2***
Pneumonitis §	0/20	***0***	0/20	***0***	0/20	***0***	0/50	***0***
Cardiac	–	–	–	–	–	–	0/50	***0***
Subtotal	**7/909**	***1***	**49/947**	***5***	**212/1059**	***20***	**28/385**	***7***
	Scanning (142 adverse events)							
Dermatitis *	0/114	***0***	4/139	***3***	79/114	***69***	–	–
Fatigue	0/38	***0***	1/38	***3***	13/43	***30***	–	–
Lymphoedema	0/38	***0***	1/38	***3***	2/38	***5***	–	–
Breast oedema	0/76	***0***	0/76	***0***	17/76	***22***	–	–
Hyperpigmentation	0/72	***0***	0/72	***0***	13/72	***18***	–	–
Pain ‡	0/114	***0***	0/114	***0***	9/114	***8***	–	–
Telangiectasia	0/110	***0***	0/110	***0***	2/110	***2***	–	–
Fibrosis †	0/76	***0***	0/76	***0***	1/76	***1***	–	–
Infection	0/76	***0***	0/76	***0***	0/76	***0***	–	–
Pneumonitis §	0/76	***0***	0/76	***0***	0/76	***0***	–	–
Rib fractures	–	–	–	–	–	–	0/76	***0***
Subtotal	**0/790**	***0***	**6/815**	***1***	**136/795**	***17***	**0/76**	***0***
	Type unspecified (60 adverse events)							
Dermatitis *	1/30	***3***	1/30	***3***	6/30	***20***	–	–
Hyperpigmentation	0/30	***0***	9/30	***30***	21/30	***70***	–	–
Fibrosis †	0/30	***0***	2/30	***7***	7/30	***23***	–	–
Pain ‡	0/30	***0***	0/30	***0***	11/30	***37***	–	–
Rib fractures	–	–	–	–	–	–	2/30	***7***
Subtotal	**1/120**	***1***	**12/120**	***10***	**45/120**	***38***	**2/30**	***7***
Total *(all PBT types)*	**8/1819**	***0***	**67/1882**	**4**	**393/1974**	**20**	**30/491**	***6***

Footnotes

Denominators vary as not all studies assessed all grades of all adverse outcomes. See Tables E.4, E.5 & E.6 for outcomes by study.

Includes acute skin colour change

†Includes reports of induration.

‡Includes reports of pain from skin, breast and unspecified pain.

§Includes reports of cough and dyspnoea.

¦Includes reports of dysphagia.

See Table E.3 for outcomes excluded from this analysis.

Abbreviations: PBT=proton beam therapy type, "–"=unspecified.

6.4.3 Whole breast or chest wall ± regional lymph nodes PBT: adverse outcomes

Studies of whole breast or chest wall ± regional lymph nodes PBT reported outcomes after 45 to 50Gy total dose in 1.8 or 2Gy fractions in 15/19 studies (Table 6.1). The other 4/19 studies included patients receiving hypofractionated regimens of 40 to 43Gy in 15 or 16 fractions.

Scattering PBT was received by 7% (69/933) of patients and scanning PBT by 85% (795/933). One study (69/933, 7%) used either scattering or scanning (Table 6.1). Median follow-up ranged from 2 to 55 months.

For whole breast or chest wall ± regional lymph nodes PBT, 1344 adverse events were reported. These spanned 15 types of adverse outcomes relating to effects on breast or chest wall skin and soft tissue, oesophagus, lungs, ribs, lymphatics, and brachial plexus (Table 6.3). These adverse outcomes were reported using Common Terminology Criteria for Adverse events (versions 3.0, 4.0 or 5.0) in 14 studies, and RTOG/EORTC in one study (Tables E.4, E.6). For the remaining four studies, the system used to grade adverse outcomes was unspecified. Where specified, the adverse outcomes were assessed between 0 and 39 months after PBT, but information on the timing was missing in 58% (59/104) instances (Tables E.4, E.6). Of the 1344 adverse events, 5% (65/1344) were graded as severe, 45% (604/1344) as moderate, and 47% (629/1344) as mild. For 3% (46/1344) of adverse events the grade was unspecified. The most prevalent severe outcome was dermatitis. Outcomes of severe dermatitis were all graded using CTCAE versions 3.0-5.0 and were reported within 6 months post PBT where specified. The grading system was unspecified in 13% (2/16) of studies reporting on severe dermatitis, and

the timing unspecified in 69% (11/16) of studies. Severe dermatitis was reported in 22% (15/69) of assessed patients after scattering PBT compared with only 6% (41/723) after scanning PBT ($p<0.001$). Two reports of severe dermatitis (3%, 2/69) occurred in a study of scattering or scanning PBT (Table 6.3, Figure 6.3, Table E.4). Other severe adverse outcomes were infection, pain and pneumonitis. Outcomes of severe infection were all graded using CTCAE versions 4.0-5.0, and were reported between 4 to 32 months where specified. The timing was unspecified in 50% (2/4) of studies reporting upon severe infection. Severe infection was reported in 17% of patients (3/18) after scattering PBT, 1% (1/69) after scattering or scanning, and in 1% (1/137) after scanning PBT. Severe pain was reported in one patient (1/246, <1%), as was pneumonitis (1/257, <1%). Both of these outcomes were graded using CTCAE v4.0 and occurred after scanning PBT (Tables 6.3, E.6). The timing of the outcome of severe pain was unspecified. The outcome of pneumonitis was reported at 12 months.

Meta-analysis of the percentage of patients affected by severe dermatitis after scanning PBT to the whole breast or chest wall ± regional lymph nodes included 41 events from 723 patients in 12 studies (Figure 6.4). Although the estimated number of patients with severe dermatitis per 100 patients assessed in different studies varied from 0-10.5 in different studies, there was no significant heterogeneity between studies ($p=0.90$). Overall, severe dermatitis occurred in 5.7 (95% CI 4.2-7.6) per 100 patients.

Meta-analysis of the percentage of patients affected by moderate dermatitis included 343 events from 624 patients in 12 studies (Figure E.3). The estimated number of patients with moderate dermatitis per 100 patients assessed in different studies varied from 33.3 to 100.0. There was significant heterogeneity between

the studies ($p<0.001$) and the overall estimate, allowing for heterogeneity was 59.3 (48.5-69.3) per 100 patients. Meta-analysis of the percentage of patients affected by mild dermatitis (Figure E.3) included 174 events from 482 patients in eight studies. The estimated number of patients with mild dermatitis per 100 patients assessed in different studies varied from 10.0 to 62.7. There was significant heterogeneity between the studies (<0.001) and the overall estimate, allowing for heterogeneity was 33.7 (23.8-45.3) per 100 patients.

Table 6.3: Whole breast or chest wall ± regional lymph nodes proton beam therapy: Adverse outcomes published 2000-2022 according to proton beam therapy type

Adverse outcome	**Severe**		**Moderate**		**Mild**		**Unspecified**	
	Affected/ assessed	**%**	**Affected/ assessed**	**%**	**Affected/ assessed**	**%**	**Affected/ assessed**	**%**
	Scattering (104 adverse events)							
Dermatitis	15/69	***22***	49/69	***71***	–	–	–	–
Infection	3/18	***17***	3/18	***17***	–	–	–	–
Fatigue	0/18	***0***	6/18	***33***	–	–	–	–
Pain ‡	0/18	***0***	9/28	***32***	–	–	1/18	***6***
Oesophagitis ¦	0/18	***0***	6/46	***13***	–	–	–	–
Pneumonitis §	0/18	***0***	2/18	***11***	–	–	–	–
Lymphoedema	0/18	***0***	1/18	***6***	–	–	5/28	***18***
Atrophy	0/18	***0***	1/18	***6***	–	–	–	–
Cardiac	0/18	***0***	–	–	–	–	2/18	***11***
Rib fractures	–	–	–	–	–	–	1/18	***6***
Subtotal	**18/213**	***8***	**77/233**	***33***	–	–	**9/82**	***11***
	Scattering or scanning (214 adverse events)							
Dermatitis	2/69	***3***	57/69	***83***	10/69	***14***	–	–
Infection	1/69	***1***	0/69	***0***	0/69	***0***	–	–
Fatigue	0/69	***0***	24/69	***35***	38/69	***55***	–	–
Oesophagitis ¦	0/69	***0***	5/69	***7***	19/69	***28***	–	–
Pneumonitis §	0/69	***0***	1/69	***1***	3/69	***4***	–	–
Hyperpigmentation	–	–	–	–	36/69	***52***	–	–
Telangiectasia	–	–	–	–	11/69	***16***	–	–
Rib fractures	0/69	***0***	0/69	***0***	5/69	***7***	–	–
Lymphoedema	0/69	***0***	0/69	***0***	1/69	***1***	–	–
Atrophy	–	–	–	–	1/69	***1***	–	–
Subtotal	**3/483**	***1***	**87/483**	***18***	**124/690**	***18***	–	–
	Scanning (1026 adverse events)							
Dermatitis	41/723	***6***	343/624	***55***	174/482	***36***	5/31	***16***
Infection	1/137	***1***	2/156	***1***	0/137	***0***	7/91	***8***
Pain ‡	1/246	***<1***	37/372	***10***	57/266	***21***	6/31	***19***
Pneumonitis §	1/257	***<1***	0/257	***0***	2/276	***1***	–	–
Oesophagitis ¦	0/336	***0***	43/355	***12***	62/355	***17***	2/100	***2***
Fatigue	0/144	***0***	7/144	***5***	61/144	***42***	–	–
Decreased shoulder movement	0/11	***0***	1/30	***3***	6/30	***20***	–	–
Fibrosis †	0/11	***0***	1/37	***3***	9/56	***16***	–	–
Lymphoedema	0/153	***0***	3/172	***2***	21/172	***12***	3/91	***3***
Hyperpigmentation	0/176	***0***	3/218	***1***	106/244	***43***	8/19	***42***
Brachial plexopathy	0/204	***0***	0/204	***0***	3/204	***1***	–	–
Telangiectasia	0/139	***0***	0/181	***0***	3/207	***1***	0/13	***0***
Rib fractures	0/205	***0***	0/205	***0***	1/205	***0***	6/203	***3***
Cardiac	0/220	***0***	0/220	***0***	0/220	***0***	–	–
Subtotal	**44/2962**	***1***	**440/3175**	***14***	**505/2998**	***17***	**37/579**	***6***
Total*(all PBT types)*	**65/3658**	***2***	**604/3891**	***16***	**629/3688**	***17***	**46/661**	***7***

Footnotes
As for Table 2a.

6.4.4 Reconstructed breast ± regional lymph nodes PBT: adverse reconstruction outcomes

There were 13 studies that reported reconstruction outcomes after reconstructed breast ± regional lymph node PBT (Table 6.4). Five of these were studies that only included patients with breast reconstructions. The remaining eight were studies that included some patients with breast reconstructions and some without (Table 6.1). Of the 11/13 studies that specified the PBT total dose and fractionation, 10 reported outcomes after 45 to 50Gy total dose given in 1.8 or 2Gy fractions. One study reported outcomes after 40Gy in 10 fractions.

Scattering PBT was delivered to 1% of irradiated breast reconstructions (4/459), scanning or scattering to 23% (107/459), and scanning PBT to 76% (348/459) (Table 6.4). Median follow-up of patients across studies ranged from 5 to 55 months.

For reconstructed breast PBT, 141 adverse reconstruction events were reported. These included infection in 11% (22/200) of assessed patients, and capsular contraction in 18% (47/258). For infection, the severity was unspecified in 60% (3/5) of studies reporting this outcome, and the timing unspecified in all studies. For capsular contraction, the grade and timing were unspecified in 85% (6/7) of studies reporting this outcome. Some adverse events required surgical intervention. For implant reconstructions, 12% (15/130) required surgical revision and 19% (55/286) required removal. For autologous reconstructions, 3% (1/32) required surgical revision and 50% (1/2) required surgical replacement (Table 6.4). The timings of these outcomes were unspecified.

Table 6.4: Reconstructed breast proton beam therapy: Adverse reconstruction outcomes published 2000-2022 according to proton beam therapy type.

Author and year of publication	**FU (mo)**	**No. recon.**	**Adverse reconstruction outcomes**											
			Infection		**Capsular contraction**		**Prosthetic reconstruction**				**Autologous reconstruction**			
							Revised		**Removed**		**Revised**		**Replaced**	
			Affected/ assessed	**%**	**Affected/ assessed**	**%**	**Affected/ assessed**	**%**	**Affected/ assessed**	**%**	**Affected/ assessed**	**%**	**Affected/ assessed**	**%**
Scattering (1 reconstruction outcome)														
Bradley 2016 *	20	4	1/4	***25***	–	–	–	–	–	–	–	–	–	–
Scattering or scanning (63 reconstruction outcomes)														
Jimenez 2020 †	–	54	2/54	***4***	14/54	***26***	1/54	***2***	16/54	***30***	–	–	–	–
Jimenez 2019	55	53	–	–	12/51	***24***	12/51	***24***	5/51	***10***	–	–	1/2	***50***
Subtotal	–	**107**	**2/54**	***4***	**26/105**	***25***	**13/105**	***12***	**21/105**	***20***	–	–	**1/2**	***50***
Scanning (77 reconstruction outcomes)														
Mullikin 2020 *	18	66	2/66	***3***	–	–	–	–	–	–	–	–	–	–
Gergelis 2021	–	62	–	–	–	–	–	–	–	–	–	–	–	–
Nichols 2020 †	14	57	–	–	4/54	***7***	–	–	11/54	***20***	0/3	***0***	–	–
Smith 2019	19	51	16/51	***31***	1/51	***2***	–	–	8/51	***16***	–	–	–	–
Verma 2017	16	31	–	–	–	–	–	–	–	–	–	–	–	–
DeCesaris 2021 †	5	29	–	–	–	–	–	–	2/29	***7***	1/29	***3***	–	–
Luo 2019	35	26	1/25	***4***	6/25	***24***	2/25	***8***	3/26	***12***	–	–	–	–
Naoum 2022 †‡	–	17	–	–	8/17	***47***	–	–	9/17	***53***	–	–	–	–
Giap 2017	19	5	–	–	–	–	–	–	–	–	–	–	–	–
Anderson 2021 †§	–	4	–	–	2/6	***33***	–	–	1/4	***25***	–	–	–	-
Subtotal	–	**348**	**19/142**	***13***	**21/153**	***14***	**2/25**	***8***	**34/181**	***19***	**1/32**	***3***	–	–
Total *(all PBT types)*	–	**459**	**22/200**	***11***	**47/258**	***18***	**15/130**	***12***	**55/286**	***19***	**1/32**	***3***	**1/2**	***50***

Footnotes

*Reported severe infections. For all other studies, infections were grade unspecified.

†Studies investigating proton beam therapy to the reconstructed breast only. Other studies reported outcomes in some patients with breast reconstructions and some without.

‡Capsular contraction was defined as requiring capsulotomy. Capsular contraction was not defined in the other studies.

§No. affected/assessed for capsular contraction were extracted from abstract where 6 patients with this outcome were reported upon.

Abbreviations: FU=follow up, mo=months, No.=number, recon=reconstructed breast, "–"=unspecified.

6.4.5 Breast cancer outcomes

In total 19 locoregional recurrences were reported from 867 patients in 19 studies, 53 distant recurrences were reported from 811 patients in 16 studies. There were nine breast cancer deaths reported from 383 patients assessed in nine studies, and 22 deaths from any cause reported from 499 patients assessed in 11 studies. Further analysis was not performed because most studies did not provide information on the timings of these events.

6.4.6 Ongoing studies

Twenty two ongoing studies (9791 patients) collecting clinical outcomes after PBT for early breast cancer were identified including six randomised (3298 patients) and 14 non-randomised studies (6493 patients) (Figure E.2, Tables E.7, E.8). One randomised study (NCT02603341) has two associated ancillary observational studies (NCT04361240 and NCT03270072).

All randomised studies are investigating PBT to the whole breast or chest wall ± regional lymph nodes. Five are comparing PBT with photon radiotherapy, and one is comparing standard fractionation PBT with hypofractionated PBT. Three of the six randomised studies are located in the USA, one in Denmark, one in the UK, and one in Thailand.

Of the 14 non-randomised studies, six studies are investigating PBT to the partial breast (765 patients) and three are investigating PBT to the whole breast or chest wall ± regional lymph nodes (285 patients). All nine of these studies are located in the USA. The PBT clinical target could not be ascertained in the other five non-randomised studies (5443 patients). Two of these are located in Japan,

one in the USA, one in China, and one in India.

For all ongoing studies of PBT to the whole breast chest wall ± regional lymph nodes, planned primary outcomes are assessing adverse outcomes, with measures of efficacy as secondary outcomes. For ongoing studies of partial breast PBT, planned primary outcomes measures include efficacy (two studies), cosmesis (two studies), and adverse outcomes (two studies).

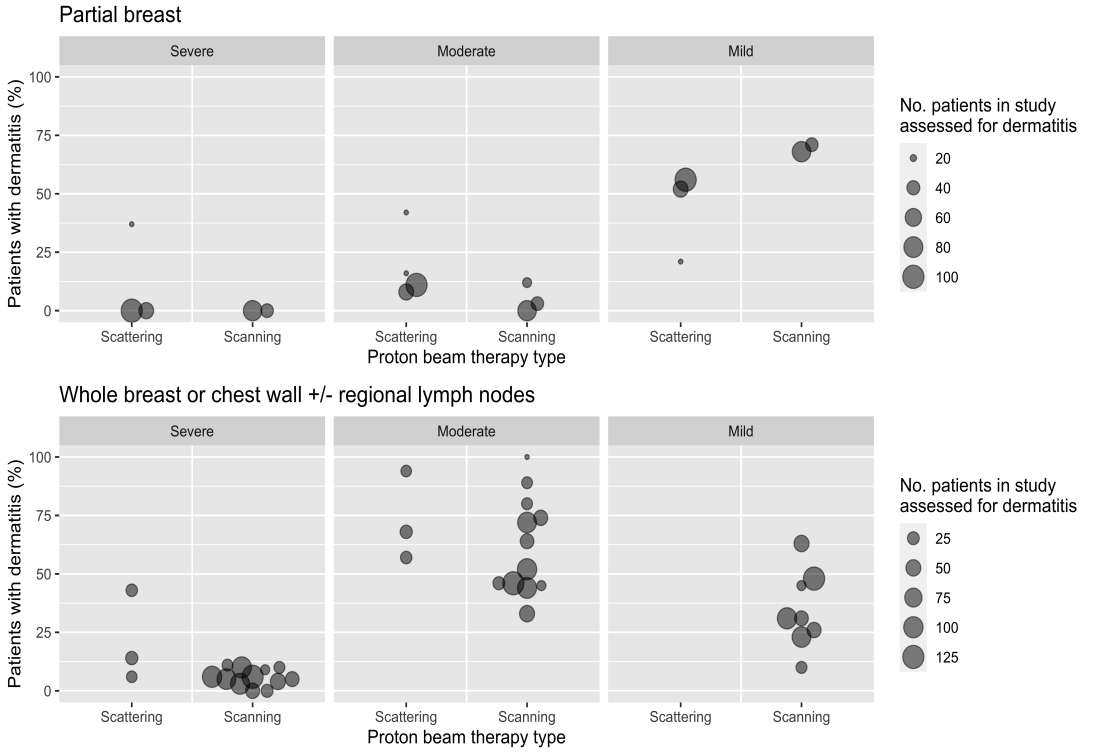


Figure 6.3: Percentage of patients with dermatitis after proton beam therapy for breast cancer in studies published 2000-2022, according to clinical target and proton beam therapy type.
For each individual study reporting dermatitis, the percentage of patients with each grade of dermatitis was plotted.
See Table E.4 for patients with unspecified grade of dermatitis, patients who received scanning or scattering proton beam therapy, and unspecified proton beam type.
Abbreviations: No.=number, PBT=proton beam therapy.

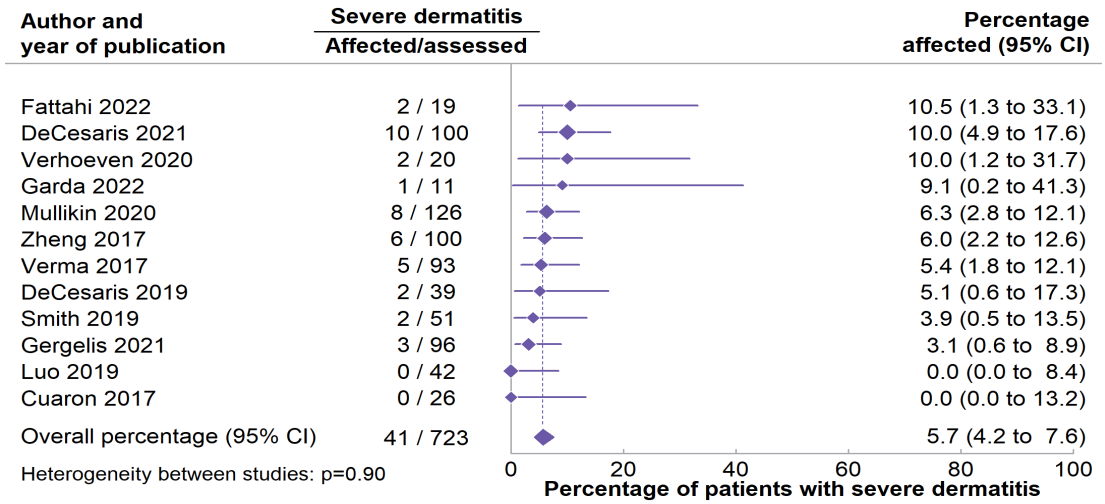


Figure 6.4: Meta-analysis of the percentage of patients with severe dermatitis after whole breast or chest wall ± regional lymph nodes scanning proton beam therapy in studies published 2000-2022.
See Figure E.3 for meta-analyses of the percentage of patients with moderate and mild dermatitis.

6.5 Discussion

This systematic review provides a quantitative summary of reported adverse clinical outcomes after different types of PBT for early breast cancer using data published during 2000-2022. Most studies had median follow-up of less than two years, with little data on outcomes beyond three years. The commonest reported adverse outcome overall was dermatitis. Adverse outcomes were less severe after PBT using the latest scanning technology than after PBT using the older scattering technology, suggesting that advances in PBT technology have improved the clinical safety of PBT for early breast cancer within the first three years. Adverse outcomes were also less severe after PBT to the partial breast, than after PBT to the whole breast or chest wall ± regional lymph nodes, as expected given that the

partial breast is a smaller and more superficial target volume.

The main strength of this review is that it provides quantitative estimates of the prevalence of adverse outcomes after PBT for early breast cancer using published data. To the best of our knowledge it is also the first systematic review to summarise reconstruction outcomes after PBT for early breast cancer. Our searches were systematic with inclusive search terms, so we are likely to have identified and assessed all relevant studies. We included data from all eligible studies published as either abstracts or full texts since the year 2000, making it the largest review of its kind. Quantitative synthesis of available data was made possible by categorizing adverse events by severity, and extracting numbers of patients with each type of adverse outcome and the numbers assessed from each study at the time point at which the highest number of patients were reported with severe adverse outcomes.

There are three other published systematic reviews summarizing clinical outcomes after adjuvant PBT for early breast cancer.[12, 23, 24] These were published during 2016-2022. Alterio et al. 2022 summarised clinical outcomes from five studies (326 patients) investigating adjuvant PBT to the partial breast.[23] Kammerer et al. 2018 summarised clinical outcomes from 3 studies (135 patients) of adjuvant PBT to the whole breast or chest wall ± regional lymph nodes.[12] Verma et al. 2016 summarised clinical outcomes from 4 studies (102 patients) of adjuvant PBT to the whole breast or chest wall ± regional lymph nodes and 5 studies (197 patients) of adjuvant PBT to the partial breast.[24] These reviews included fewer studies and reported fewer clinical outcomes than our review and all presented qualitative summaries of the data.

A limitation of our study is that the estimates of the prevalence of adverse out-

comes provided are informed by published summary data rather than individual patient data. This means that some instances of duplication of patient outcomes may remain undetected despite careful grouping of publications into individual studies. In addition, the extent to which patients in these studies represent patients being considered for PBT today is uncertain because detailed information on characteristics of patients selected for these studies was lacking. Information on the timing of reported outcomes was often missing. Therefore it was neither possible to classify adverse outcomes into acute and late effects, nor to summarise the duration of these outcomes. These factors need to be considered when applying our overall summary estimates of prevalence of adverse effects to patients in the clinic today. For breast cancer outcomes, missing information on the timing of individual outcomes prevented further analysis of these outcomes.

For partial breast PBT most adverse outcomes were graded as mild and there were no severe adverse outcomes from scanning PBT to the partial breast. However, the main justification of the extra cost of PBT compared with standard photon radiotherapy is the predicted reduction in the risks of cardiovascular disease and second cancers. For partial breast photon radiotherapy, these risks are likely to be very small for most patients because radiation doses to the heart, lungs and oesophagus are usually <1Gy.[10, 11, 25] Therefore it is more difficult to justify the excess costs of partial breast PBT compared with partial breast photon radiotherapy.

For PBT to the whole breast or chest wall ± regional lymph nodes, the most frequently reported severe adverse outcome was dermatitis. This was most commonly defined as moist desquamation in areas other than skin folds and creases, or bleeding induced by minor trauma or abrasion. Although the timing of severe

dermatitis was mostly unreported, where it was specified it peaked at less than six months post PBT. It occurred in around 6% of patients after scanning PBT, which is of a similar magnitude to expected rates of dermatitis using the latest hypofractionated (40Gy/15 fractions and 26Gy/5 fractions) photon radiotherapy techniques to the whole breast or chest wall.[26] Other severe adverse outcomes after scanning PBT included infection, pain and pneumonitis. These occurred in $\leq$1% of patients. This reassuring safety information supports the rationale for ongoing clinical trials of PBT to the whole breast or chest wall $\pm$ regional lymph nodes for early breast cancer and it may inform patient consent whilst we await the results of randomised controlled trials.

For scanning PBT to the reconstructed breast, the most commonly reported adverse outcome was removal of prosthetic implant, which occurred in 19% of patients assessed. This may be higher than expected in current clinical practice using photon radiotherapy where estimates are around 9%.[27, 28] However, estimates of the prevalence of reconstruction outcomes after radiotherapy vary considerably and without information on the timing of reconstruction outcomes comparison between studies is difficult. Published data only include reconstruction outcomes of 348 breast reconstructions irradiated with scanning PBT for early breast cancer after a median follow up less than three years, so further data are needed.

Our review demonstrates the need for more data on clinical outcomes after PBT for early breast cancer. There were no published randomised controlled trials comparing PBT with photon radiotherapy. In most studies there were less than 2 years of follow up, with insufficient data to assess long-term clinical outcomes of PBT. Furthermore, most studies presented outcomes from patients irradiated in single privately-funded centres in the USA. Ongoing studies include five ran-

domised trials that compare PBT with photon radiotherapy, and plan to recruit 3210 patients. One of these trials (98 patients) includes patients with breast reconstruction and aims to assess unplanned surgical interventions. More clinical trials of PBT in early breast cancer are being planned, and our data may guide their design.

6.6 Conclusion

PBT technology has advanced over the past two decades so that most patients with early breast cancer receiving PBT would now have it delivered using scanning technology. Published studies with few outcomes reported beyond three years suggest that the most common severe adverse outcome after scanning PBT to the whole breast or chest wall ± regional lymph nodes is dermatitis which occurs in 6% of patients (95% CI 4-8). Other severe adverse outcomes from scanning PBT to the whole breast or chest wall ± regional lymph nodes are much rarer, ≤1%. No severe adverse outcomes after partial breast scanning PBT have been reported. Our estimates of the prevalence of adverse outcomes after irradiation of different clinical targets may inform clinicians and patients considering PBT. However, few published data are available. Over the next 15 years, ongoing randomised clinical trials are likely to provide information on the longer-term safety of PBT compared with photons in patients with early breast cancer.

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Jake Probert independently extracted the data, wrote the statistical methods in paragraph 4 of the "Data analysis" section and conducted these analyses. He produced figure 3. He also contributed to reviewing and editing the final draft manuscript.
Sarah Darby supervised the statistical analyses and data presentation, and reviewed and edited draft manuscripts.
Jo Haviland conceptualised the project, provided advice on the methods, and reviewed and edited draft manuscripts.
Charlotte Coles and **Anna Kirby** conceptualised the project, provided clinical oncology expertise, and reviewed and edited draft manuscripts.
Zulian Liu drafted the initial review protocol and literature search strategy.
David Dodwell and **Frances Duane** supervised the project, provided clinical oncology expertise, and reviewed and edited draft manuscripts.
Georgios Ntentas supervised the project, provided physics expertise, and reviewed and edited draft manuscripts.
Carolyn Taylor conceptualised and supervised the project including acquiring funding, provided clinical oncology expertise, and reviewed and edited draft manuscripts.

Chapter 7

Discussion

Holt F, Ntentas G, Duane F, Dodwell D, Taylor C.

7.1 Summary of findings and clinical implications

This thesis provides up-to-date information on the benefits and risks of radiotherapy for early breast cancer.

Radiation doses received by the internal mammary lymph nodes (IMNs), heart and lungs in all unconfounded trials of regional lymph node radiotherapy for early breast cancer worldwide, starting 1989-2008, were retrospectively estimated. These estimated doses may be associated with reductions in breast cancer mortality of around an eighth (RR 0.87, 95% CI 0.80-0.94) corresponding to around 3.0% (1.1-4.9) absolute survival gains depending on the extend of lymph node involvement with breast cancer.[1] Since these trials, it is likely that advances in radiotherapy have improved coverage of the IMNs, improving the relative breast cancer survival benefits. Mean whole heart doses estimated from these same reconstructed IMN regimens were higher than those estimated from systematic review of all UK IMN regimens for early breast cancer published during 2015-2023, suggesting advances in radiotherapy have reduced the relative risks of radiation-induced heart disease. However, mean whole lung doses estimated from the historical trial regimens were similar to those estimated from published modern UK IMN regimens, suggesting reductions in the relative risks of radiation-induced lung cancer have been more modest. Estimation of the typical absolute mortality risks of modern UK breast cancer radiotherapy demonstrated that the greatest risk is lung cancer in long-term continuing smokers. For a typical 50-year-old long-term continuing smoker, the 30-year absolute risk of radiation-induced lung cancer is around 6%. This may outweigh the absolute breast cancer survival benefits of IMN irradiation for

some women. In support of development of a new dose-response relationship for radiation-induced lung cancer that may better predict risks from modern breast cancer radiotherapy, doses to the anatomical lobes of the lungs from radiotherapy for early breast cancer regimens delivered in the Netherlands during 1970-2010 were estimated. Exploratory analyses of temporal trends in mean whole lung doses from IMN radiotherapy for early breast cancer over the past 55 years suggest that lung-sparing in this context is a long-standing unmet clinical need that proton beam therapy (PBT) may address, but that more data and alternative dose metrics may be needed to distinguish the relative lung-sparing properties of modern photon radiotherapies. Systematic review of all clinical outcomes from worldwide studies of adjuvant PBT for early breast cancer published 2000-2022 demonstrated the prevalence of short-term adverse outcomes, including breast reconstruction outcomes. The evidence supports the use of more advanced scanning PBT for early breast cancer as this results in a lower prevalence of severe radiation-induced dermatitis than older scattering PBT.

7.1.1 Radiotherapy to the breast or chest wall

7.1.1.1 Risks

The estimated doses received by the heart and lungs from modern UK radiotherapy for early breast cancer targeting the breast or chest wall translate into 30-year absolute risks of death from radiation-induced ischaemic heart disease and lung cancer of less than 1%. (**Chapter 3**, Figure 7.1) These absolute risks are reassuringly low and in keeping with current consensus opinion on the risks of radiotherapy for early breast cancer used to inform patient consent.[2]

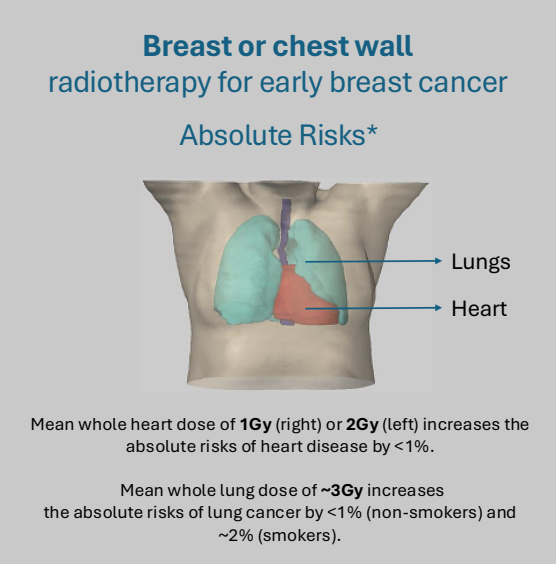


Figure 7.1: Key novel findings from this thesis on the absolute risks of breast or chest wall radiotherapy for early breast cancer.
*30-year absolute risks for a typical 50-year-old woman receiving modern UK breast cancer radiotherapy. See Chapter 3 for details.

7.1.2 Internal mammary lymph node radiotherapy for early breast cancer

7.1.2.1 Benefits

A recent meta-analysis demonstrated that regional lymph node radiotherapy for early breast cancer given within seven randomised trials and one study allocating radiotherapy according to breast cancer laterality, starting 1989-2008, improved 15-year breast cancer survival by around an eighth (RR 0.87, 95% CI 0.80-0.94) corresponding to 3.0% (1.1-4.9) absolute gains.[1] Radiation doses associated with these survival benefits were unknown. **Chapter 2** provides a systematic description and categorisation of the regional lymph node radiotherapy regimens used in these trials. These regimens were reconstructed using modern radiotherapy treat-

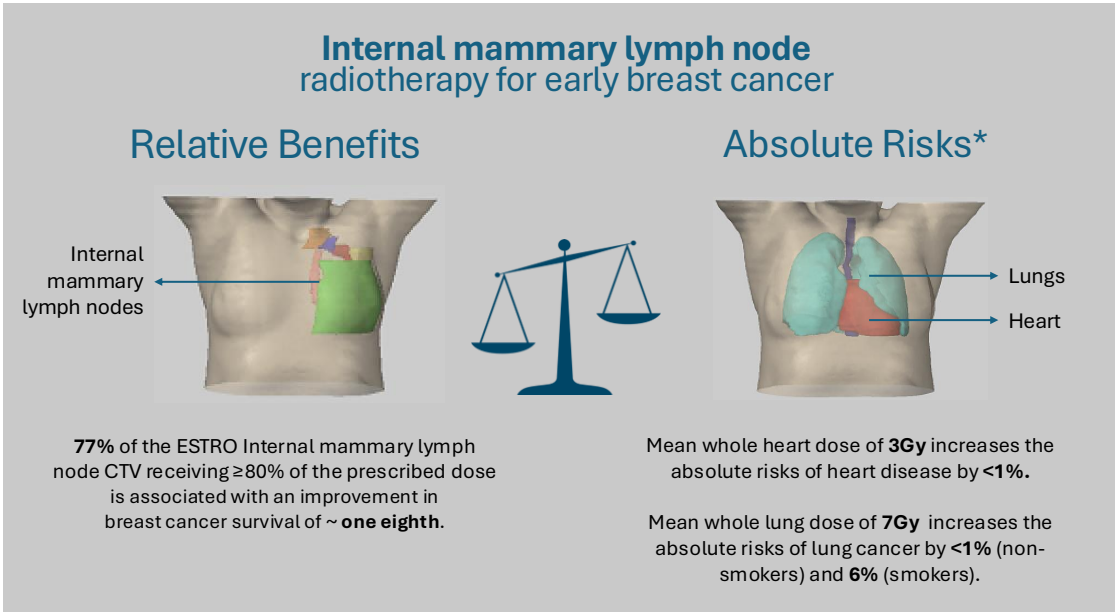


Figure 7.2: Key novel findings from this thesis on the relative benefits and absolute risks of internal mammary radiotherapy for early breast cancer.
Estimated relative benefits of photon±electron-based internal mammary radiotherapy are from Early Breast Cancer Trialists' Collaborative Group meta-analysis of international randomised trials. See Chapter 2 for details.
30-year absolute risks for a typical 50-year-old woman receiving modern UK breast cancer radiotherapy. See Chapter 3 for details.

ment planning software, and the doses received by modern IMN CTVs and organs at risk (OARs) estimated.

Of the 37 regimens identified from trial publications and protocols, 35 targeted the IMNs. The radiotherapy fields targeting these lymph nodes fell into eight categories of beam types and arrangements. Beam types included photons, electrons and mixed types (photons and electrons). Beam arrangements included wide tangents, partially wide tangents, and direct or oblique anterior beams. Most commonly, photon beams arranged as partially wide tangents were used. Estimated doses received by the IMN CTVs from the 35 regimens varied according to these beam types and arrangements. The overall average volume of the IMN CTVs that received at least 80% of the prescribed dose, weighted according to the number of women estimated to have received each regimen, was 77% when the volume was defined by the ESTRO contouring guidelines. Similarly, on average, at least 75% and 77% of the RTOG and RADCOMP IMN CTVs received at least 80% of the prescribed dose respectively.

If at a population level today we achieve more ambitious average dose objectives for IMN CTVs than these, it is likely that our IMN radiotherapy will increase 15-year breast cancer survival rates by more than ∼an eighth (RR 0.87, 95% CI 0.80-0.94).[1] (Figure 7.2) Information on radiotherapy regimens received by individual patients in the trials was lacking and there was insufficient variation in the relative benefits of breast cancer outcomes between trials to create a dose-response relationship for IMN doses and breast cancer outcomes. Therefore, it is not possible to estimate what the minimum dose objectives should be to ensure acceptable oncological benefits today. However, it is important to recognise that because breast cancer survival rates are generally improving at a population level,

a more than one eighth survival benefit may be needed to achieve net absolute benefits for some individual patients in clinic today.[3] Therefore, these results should not encourage the lowering of current dose objectives for the IMN CTVs. Clinicians will still need to adopt advances in radiation technology that overall improve photon dose distributions.

7.1.2.2 Risks of radiation-induced heart disease

From IMN radiotherapy regimens given in trials starting 1989-2008, the heart received an estimated average mean dose of 10Gy from regimens for left breast cancer and 6Gy from regimens for right breast cancer, with considerable variation observed according to the beam type and arrangement of the radiation fields targeting the IMNs. (**Chapter 2**)

In **Chapter 3**, meta-analysis provides up-to-date estimates of typical doses received by the whole heart from UK radiotherapy for early breast cancer published 2015-2023. There is also an illustration of how these doses may be used to estimate the absolute risks of death from radiation-induced heart disease.

Overall, the average mean whole heart dose from modern UK radiotherapy for early breast cancer was around 2Gy. As expected, heart doses varied according to breast cancer laterality, and the extent of radiotherapy clinical targets.

From modern UK radiotherapy regimens targeting the left IMNs, the average mean whole heart dose was around 3Gy. From right IMN regimens, it was around 1Gy. These estimates are substantially lower than those estimated from comparable regimens used in randomised trials starting 1989-2008 (10Gy from left regimens, and 6Gy from right). The published modern UK left IMN regimens mainly used photon beams to target the IMNs with around a sixth of estimates

from PBT regimens. The most common planning method was IMRT and just over half of estimates were from rotational IMRT. Around two thirds of regimens used deep inspiration breath hold. For a typical 50-year-old receiving modern UK radiotherapy for early breast cancer inclusive of IMNs (around 3Gy mean whole heart dose), the estimated 30-year absolute risk of death from radiation-induced ischaemic heart disease is $\leq$1% regardless of the presence of established cardiovascular risk factors. (Figure 7.2)

The observed reductions in mean heart doses are likely due to enormous national and international efforts over recent decades to appropriately select patients for and deliver heart-sparing techniques such as changing beam angles, use of multileaf collimator shielding, IMRT including VMAT, and deep inspiration breath hold techniques, as well as PBT.[4–6] Information on typical doses received by the heart from modern UK IMN radiotherapy and the associated 30-year absolute risks of death from heart disease from IMN radiotherapy is reassuring. The absolute risks of heart disease are now <1%, and in keeping with current consensus opinion on the risks of radiotherapy for early breast cancer used to support patient consent.[2]

7.1.2.3 Risks of radiation-induced lung cancer

From IMN radiotherapy regimens given in trials starting 1989-2008, the lungs received an average estimated mean dose of 8Gy from regimens of any laterality. This varied according to the beam type and arrangements used to target the IMNs but on average was only slightly higher than the estimated average of 7Gy received by the lungs from modern UK left IMN regimens. (**Chapters 2 and 3**)

For a typical 50-year-old non-smoker or ex-smoker receiving 7Gy mean whole

lung dose, the estimated 30-year absolute risk of death from lung cancer is ≤1%. However, for a typical 50-year-old long-term continuing smoker, the estimated 30-year absolute mortality risk of lung cancer is around 6%. (**Chapter 3**) (Figure 7.2)

These results build on existing knowledge that heart disease and second cancers are the main mortality risks of breast cancer radiotherapy.[7] Together with estimated typical heart doses and 30-year absolute risks of death from ischaemic heart disease, these findings suggest that the main radiation-induced mortality risk of IMN irradiation is currently lung cancer in long-term continuing smokers——smoking has been shown to multiply the risks of radiation-induced cancers after radiotherapy for Hodgkin's lymphoma.[8] For these women, consent for this type of radiotherapy requires an amendment to current national consent forms reflecting the higher than 1% risk of developing a radiation-induced cancer.[2] These estimates also suggest that for a few women with low estimated absolute benefits from regional lymph node radiotherapy and/or high estimated absolute mortality risks, the mortality risks of breast cancer radiotherapy may outweigh the survival benefits. For these women, primary risk-reducing strategies such as smoking cessation if applicable, omission of radiotherapy, and/or the use of advanced lung-sparing radiotherapy techniques, such as PBT, may be indicated.

Although mean whole lung dose is currently considered the best predictor of radiation-induced lung cancer, the optimal dosimetric determinants are unknown. In support of the development of an improved epidemiological dose-response relationship for lung cancer that incorporates more information on the spatial distribution of dose within the lung volumes, radiation doses received by the anatomical lobes of the lungs were retrospectively estimated from radiotherapy regimens for

early breast cancer used at the Netherlands Cancer Institute or Erasmus MC Cancer Institute during 1970-2010 and are compared with mean whole lung doses from the same regimens in **Chapter 4**.

Overall, weighted average mean whole lung dose from IMN irradiation described in this thesis and in published studies was around 8Gy or 16% of the prescribed dose.[9–11] (**Chapter 5**) Exploratory analyses suggest that there have been minimal reductions in mean whole lung doses from IMN radiotherapy over the past 55 years, despite the application of many advances in IMN fractionation, beam arrangements and treatment planning methods. (**Chapter 5**) PBT may systematically reduce mean whole lung doses. Comparison with lung-sparing from modern deep inspiration breath hold techniques are needed.

7.1.3 Proton beam therapy to the breast or chest wall ± regional lymph nodes

7.1.3.1 Risks

PBT may reduce the risks of breast cancer radiotherapy, however, clinical evidence is lacking while we wait for the results of ongoing randomised trials. To support patient consent, clinical decision making and future trial design, **Chapter 6** summarises all adverse clinical outcomes after PBT for early breast cancer published from 2000 to 2022.[12] Graded adverse outcomes were extracted from publications, counted, and their variation according to PBT delivery type (scattering or scanning), and extent of clinical targets demonstrated.

As expected there were no published randomised trials comparing PBT with standard photon radiation therapy, but 32 studies reporting clinical outcomes from

1452 patients were analysed. Given most studies had median follow-up of <2 years, with little data on outcomes beyond 3 years, it was not possible to evaluate the long-term morbidity and mortality risks of PBT for early breast cancer. However, analysis of available outcomes provided evidence that reported short-term clinical risks, the most prevalent of which was dermatitis, were less severe after the more advanced scanning delivery type of PBT compared with the older scattering PBT.[12] (Chapter 6)

Another key finding was that for whole breast or chest wall ± regional lymph nodes scanning PBT, 4% of reported adverse events were graded as severe. The most prevalent severe adverse outcome after scanning PBT was dermatitis, which occurred in 5.7% (95%CI, 4.2-7.6) of patients. Other severe adverse outcomes included infection, pain and pneumonitis (each ≤1%). (Figure 7.3) There was insufficient information to determine which outcomes were specifically from radiotherapy inclusive of the IMNs. The estimated risks from PBT to the whole breast/chest wall ± regional lymph nodes may underestimate those from IMN PBT. There were no severe adverse outcomes reported from partial breast PBT.

Short-term adverse outcomes from standard photon radiotherapy for early breast cancer are more common than long-term adverse outcomes, and can negatively impact quality of life. In the context of limited resources to fund and conduct trials with several decades of long-term follow-up, reducing dose-limiting short-term adverse effects has driven many changes to breast cancer radiotherapy practice, such as the recent widespread recommendation for ultrahypofractionated breast radiotherapy. In contrast to clinical outcomes related to breast cancer, radiation-induced heart disease, and radiation-induced lung cancer, which can occur in both untreated and irradiated patients, radiation dermatitis is a distinct

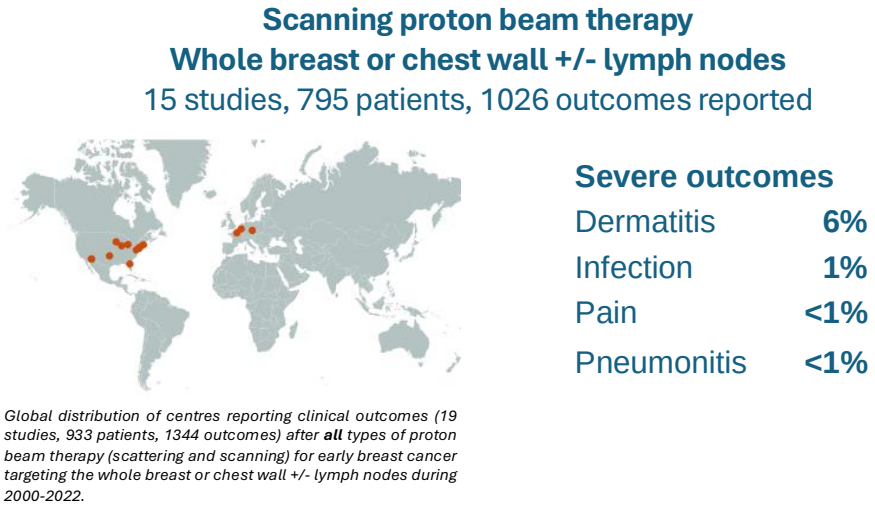


Figure 7.3: Key novel findings from this thesis on the risks of proton beam therapy to the breast or chest wall ± lymph nodes for early breast cancer.

clinical entity whose time- and site-specific clinical manifestations are very unlikely to occur in the absence of radiation; therefore, it was both possible and meaningful to summarise these clinical outcomes in a meta-analysis of non-randomised data, and doing so has advanced existing knowledge of the risks of PBT for early breast cancer. These estimated prevalences of adverse effects may be used to inform patients of the risks of PBT for early breast cancer whilst we await data from randomised trials, and be used in support of the use of scanning rather than scattering PBT as a means of reducing severe dermatitis from radiotherapy for early breast cancer.

7.1.4 Proton beam therapy to the reconstructed breast

7.1.4.1 Risks

Breast reconstructions are increasingly used following mastectomy for early breast cancer. From scanning PBT to the reconstructed breast, the most commonly reported adverse outcome was removal of prosthetic implant, which occurred in 19% of assessed patients. This may be higher than expected in current clinical practice using photon radiation therapy where estimates are around 9%.[13, 14] However, estimates of the prevalence of reconstruction outcomes after radiation therapy vary considerably, and without information on their timing, comparison between studies is difficult. (Figure 7.4)

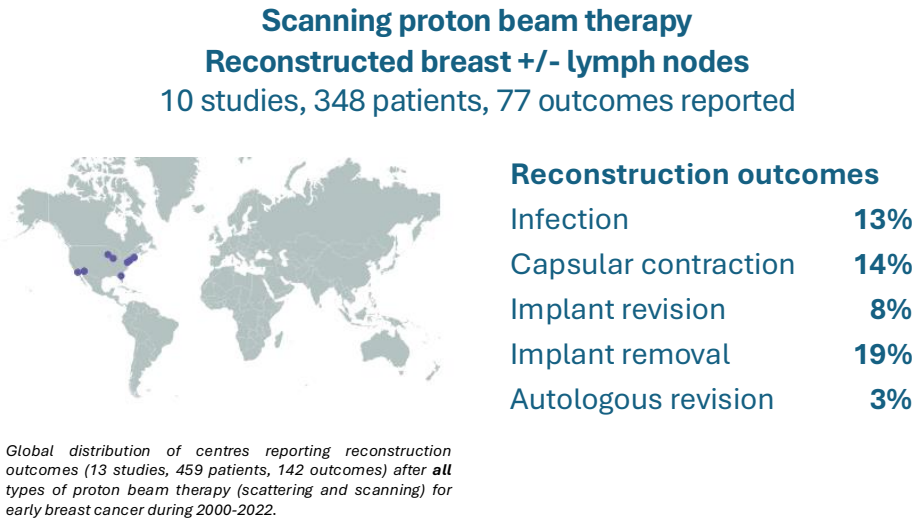


Figure 7.4: Key novel findings from this thesis on the risks of proton beam therapy to the reconstructed breast for early breast cancer.

7.2 Future work

Overall, findings from this thesis suggest that further work is needed in the following areas.

First, further work is needed to more fully assess variation in coverage of the IMNs with modern radiotherapy techniques according to different anatomical factors. Exploratory analyses suggest that measures of body habitus (such as sternal soft tissue thickness) may modify the relationship between IMN beam types and arrangements and coverage of the IMNs, which merits further investigation.

Second, a systematic review of recent doses received by the regional lymph nodes and OARs during regional lymph node radiotherapy for early breast cancer outside of clinical trials may identify optimal modern techniques for IMN coverage and heart- and lung-sparing. It may also be valuable for this to include any published data on lymph node boosts and primary radiotherapy.

Third, further research is needed on clinical outcomes from all types of radiotherapy following different types of breast reconstructions.

Fourth, future studies should investigate estimates of the benefits and risks of radiotherapy for early breast cancer according to patient smoking status and measures of body habitus, as well as types of radiotherapy.

7.3 Conclusions

Overall, it is likely that the relative benefits of radiotherapy for early breast cancer have improved over recent decades. Current IMN radiotherapy regimens likely achieve better IMN coverage and provide greater relative breast cancer sur-

vival benefits than those previously reported. The relative and absolute risks of radiation-induced heart disease have likely fallen over recent decades. Reductions in the relative risks of radiation-induced lung cancer may have been more modest, but the absolute risks are low for the majority of women. For some long-term continuing smokers the absolute 30-year mortality risks of radiation-induced lung cancer may outweigh the benefits of IMN irradiation. For these women, primary risk-reducing strategies such as smoking cessation if applicable, omission of radiotherapy, and/or the use of advanced lung-sparing radiotherapy techniques, such as PBT, may be indicated.

The information in this thesis may be used to support patient consent, smoking-cessation initiatives, the development and selection of radiotherapy techniques that improve IMN coverage and lung-sparing, such as PBT, the development of an improved dose-response relationship for radiation-induced lung cancer, and clinical guidelines on dose objectives and constraints.

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Appendix A

Supplementary material for Chapter 2: Internal mammary lymph node doses from radiotherapy regimens for early breast cancer in randomised trials starting 1989-2008.

A.1 List of trial publications searched for descriptions of radiotherapy regimens received by patients in the eight trials of regional lymph node radiotherapy, starting 1989-2008, included in the EBCTCG 2023 meta-analysis

A.1.1 EORTC 22922

- Kaidar-Person O, Giasafaki P, Boersma L et al. Mapping the location of local and regional recurrences according to breast cancer surgery and radiation therapy: Results from EORTC 22922/10925. Radiotherapy Oncol 2023;185:109698.
- Kaidar-Person O, Boersma LJ, De Brouwer P et al. The EORTC 22922/10925 trial investigating regional nodal irradiation in stage I-III breast cancer: Outcomes according to locoregional and systemic therapies. Radiotherapy Oncol 2024;201:110563.
- Kaidar-Person O, Fortpied C, Hol S, et al. OC-0934 Outcomes of the EORTC 22922/10925 randomised trial according to the technique for nodal irradiation. Radiotherapy Oncol 2022;170:S824-S5.
- Kaidar-Person O, Fortpied C, Hol S, et al. The association of internal mammary and medial supraclavicular lymph node radiation technique with clinical outcomes: Results from the EORTC 22922/10925 randomised trial. Radiotherapy Oncol 2022;172:99-110.

- Poortmans PM, Collette S, Struikmans H, et al. Fifteen-year results of the randomised EORTC trial 22922/10925 investigating internal mammary and medial supraclavicular (IM-MS) lymph node irradiation in stage I-III breast cancer. J Clin Oncol 2018;36(15_suppl): 504.

- Poortmans PM, Fourquet A, Collette L, et al. 6N Irradiation of the internal mammary and medial supraclavicular lymph node chain in stage I to III breast cancer: state of the day of EORTC phase III trial 22922/10925 with 4004 patients. Eur J Cancer Supplements 2010;8(3).

- Poortmans PM, Kouloulias V, van Tienhoven G, et al. Quality assurance in the EORTC randomized trial 22922/10925 investigating the role of irradiation of the internal mammary and medial supraclavicular lymph node chain works. Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft 2006;182(10):576-82.

- Poortmans PM, Kouloulias VE, Venselaar JL, et al. Quality assurance of EORTC trial 22922/10925 investigating the role of internal mammary—medial supraclavicular irradiation in stage I-III breast cancer: the individual case review. Eur J Cancer 2003;39(14):2035-42.

- Poortmans PM, van den Bogaert W, Venselaar JL, et al. EORTC randomised phase III trial 22922/10925 investigating the role of internal mammary chain (IMC) irradiation in stage I-III breast cancer: A quality assurance report on the dummy run. Eur J Cancer 1998;34.

- Poortmans PM, Collette S, Kirkove C, et al. Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. N Engl J Med 2015;373(4):317-

27.

- Poortmans PM, Struikmans H, De Brouwer P, et al. Side Effects 15 Years After Lymph Node Irradiation in Breast Cancer: Randomized EORTC Trial 22922/10925. JNCI 2021;113(10):1360-8.

- Poortmans PM, Weltens C, Fortpied C, et al. Internal mammary and medial supraclavicular lymph node chain irradiation in stage I–III breast cancer (EORTC 22922/10925): 15-year results of a randomised, phase 3 trial. Lancet Oncol 2020;21(12):1602-10.

- Poortmans PM, Venselaar JL, Struikmans H, et al. The potential impact of treatment variations on the results of radiotherapy of the internal mammary lymph node chain: a quality-assurance report on the dummy run of EORTC Phase III randomized trial 22922/10925 in Stage I–III breast cancer. Int J Radiat Oncol Biol Phys 2001;49(5):1399-408.

- Kouloulias VE. Quality assurance in radiotherapy. Eur J Cancer 2003;39(4):415-22.

- Matzinger O, Heimsoth I, Poortmans PM, et al. Toxicity at three years with and without irradiation of the internal mammary and medial supraclavicular lymph node chain in stage I to III breast cancer (EORTC trial 22922/10925). Acta Oncologica 2010;49(1):24-34.

- Musat E, Poortmans PM, Van den Bogaert W, et al. Quality assurance in breast cancer: EORTC experiences in the phase III trial on irradiation of the internal mammary nodes. Eur J Cancer 2007;43(4):718-24.

A.1.2 DBCG-IMN

- Thorsen LBJ, Overgaard J, Matthiessen LW et al. Internal Mammary Node Irradiation in Patients With Node-Positive Early Breast Cancer: Fifteen-Year Results From the Danish Breast Cancer Group Internal Mammary Node Study. J Clin Oncol 2022;40(36):4198-4206.

- Thomsen MS, Berg M, Nielsen HM, et al. Post-mastectomy radiotherapy in Denmark: from 2D to 3D treatment planning guidelines of The Danish Breast Cancer Cooperative Group. Acta Oncologica 2008;47(4):654-61.

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A.1.3 MA-20

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- Whelan TJ, Olivotto IA, Parulekar WR, et al. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med 2015;373(4):307-16.

A.1.4 Lyon Sud

- Hennequin C, Bossard N, Servagi-Vernat S, et al. Ten-year survival results of a randomized trial of irradiation of internal mammary nodes after mastectomy. Int J Radiat Oncol Biol Phys 2013;86(5):860-6.

- Romestaing P, Belot A, Hennequin C, et al. Ten-year Results of a Random-

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A.1.5 KROG 08-06

- Choi J, Kim YB, Shin KH, et al. Radiation Pneumonitis in Association with Internal Mammary Node Irradiation in Breast Cancer Patients: An Ancillary Result from the KROG 08-06 Study. Journal of Breast Cancer 2016; 19(3): 275-82.

- Chung Y, Kim JW, Shin KH, et al. Dummy run of quality assurance program in a phase 3 randomized trial investigating the role of internal mammary lymph node irradiation in breast cancer patients: Korean Radiation Oncology Group 08-06 study. Int J Radiat Oncol Biol Phys 2015;91(2):419-26.

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A.1.6 IAEA

- Rosenblatt E, Jones GW, El-Mongy M, et al. OC-0189: Irradiation of the supraclavicular nodal region in postmastectomy radiotherapy; an IAEA randomized trial. Radiother Oncol 2015;115:S94-S5.

A.1.7 ISOG Milan

- Zurrida S, Orecchia R, Galimberti V, et al. Axillary radiotherapy instead of axillary dissection: a randomized trial. Italian Oncological Senology Group. Annals of Surgical Oncology 2002;9(2):156-60.

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A.1.8 Tampere

- Kaija H, Maunu P. Tangential breast irradiation with or without internal mammary chain irradiation: results of a randomized trial. Radiother Oncol 1995;36(3):172-6.

A.2 Published doses received by clinical target volumes from three trials of regional lymph node radiotherapy starting 1989-2008

Table A.1: Published doses received by clinical target volumes from eight trials of regional lymph node radiotherapy starting 1989-2008

Trial name[ref]	**IMN contour definition**	**Published doses to ipsilateral IMN CTVs**		
		Dose objectives	**Average dose metrics***	**No. pts (N=134)**
EORTC 22922[1†]	–	–	Mean dose 48.7Gy	45
DBCG-IMN[2]	As per DBCG guidelines	V90% = 100%	V90% = 73.2%	38
KROG 08-06[3‡]	Extends caudally from the jugulo-subclavian junction to the 4th rib, ventrally from the pleura to the dorsal aspect of the surface of the pectoralis major muscle and sternum, and medially and laterally 5mm margin from the internal mammary vessels.	Dose conformity 90-107% of prescribed dose	Dose conformity 101-105% of prescribed dose	51

Footnotes

There were no published doses to any other clinical targets.

No dose information was available from study publications relating to Tampere, ISOG Milan, Lyon Sud, MA-20, and IAEA trials.

*Average refers to the mean of doses achieved at planning from the number of patients stated, except for the KROG 08-06 trial where average refers to the median dose.

†Mean dose to a point representing the estimated anatomic location of the internal mammary lymph nodes on a CT slice.

‡Median doses varied according to breast cancer laterality and type of breast surgery.

Abbreviations: BCS=breast conserving surgery, CTV=clinical target volume, Gy=Gray, IMN=internal mammary lymph node, pts=patients, ref=reference, Vx%=volume receiving at least x% of the prescribed dose, "-"=unspecified.

A.2.1 References for Table A.1

1. Poortmans PM, Kouloulias VE, Venselaar JL, et al. Quality assurance of EORTC trial 22922/10925 investigating the role of internal mammary—medial supraclavicular irradiation in stage I-III breast cancer: the individual case review. Eur J Cancer 2003;39(14):2035-42.

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A.3 Published doses received by organs at risk from two trials of regional lymph node radiotherapy starting 1989-2008

Table A.2: Published doses received by organs at risk from two trials of regional lymph node radiotherapy starting 1989-2008

Trial[ref]	**Organ at risk**	**Published doses to organs at risk**		
		Dose constraints	**Average dose metrics achieved at planning***	**No. pts N=451**
DBCG-IMN[1]	Heart	-	Mean dose 1.1 Gy	38
		V20Gy <10%	V20Gy 0.1%	
		V40Gy <5%	V40Gy <0.1%	
	Ipsilateral lung	V20Gy <35%	V20Gy 31.4%	
KROG 08-06[2,3†]	Heart	-	Mean 3.4-5.1Gy	51
		V20Gy <10%	V20Gy 1-6%	
	Ipsilateral lung	Mean dose <18Gy	Mean dose 17.8Gy	362
		-	V10Gy 43.8%	
		-	V20Gy 36%	
		-	V30Gy 27.4%	
		-	V40Gy 18.7%	

Footnotes

Left anterior descending artery doses were also available from DBCG-IMN and KROG 08-06 trials but are not presented here as LAD doses were not measured in the current study.

No dose information was available from study publications relating to Tampere, ISOG Milan, Lyon Sud, MA-20, and IAEA trials.

*Average refers to the mean of doses achieved at planning from the number of patients stated, except for the KROG 08-06 trial where average refers to the median dose.

†Median doses varied according to breast cancer laterality and type of breast surgery.

Abbreviations: Gy=Gray, pts=patients, ref=reference, VxGy=volume receiving at least x dose in Gy (for example "V20Gy 0.1%" means that 0.1% of the volume received at least 20Gy.), "-"=unspecified.

A.3.1 References for Table A.2

1. Thorsen LBJ, Thomsen MS, Berg M, et al. CT-planned internal mammary node radiotherapy in the DBCG-IMN study: benefit versus potentially harmful effects. Acta Oncologica (Stockholm, Sweden) 2014;53(8):1027-34.

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A.4 Method for estimation of the number of patients who received each radiotherapy regimen within the eight trials of regional lymph node radiotherapy starting 1989-2008

The total number of patients receiving regional lymph node radiotherapy in each trial is available. (Table A.3) Where possible the number of patients receiving each radiotherapy regimen within the eight trials of regional lymph node radiotherapy, starting 1989-2008, was extracted from trial publications. Where this information was unavailable, an estimate was made.

To estimate the number of patients receiving each radiotherapy regimen, first patient eligibility criteria for each regional lymph node radiotherapy regimen were extracted from trial publications. These consisted of breast cancer laterality, quadrant and type of surgery.

Second, the number of patients meeting each eligibility criterion for each regimen was extracted from trial publications. (Table A.3) Where the number of patients in the trial intervention group meeting the eligibility criterion was unspecified in trial publications, it was estimated using published percentages of patients meeting the criterion across the whole trial or in other trial subgroups.

Where the number of patients meeting eligibility criteria was unavailable, the remaining patients in the intervention group were divided equally between the radiotherapy regimens. (See Figures A.1, A.2, A.3, A.4, A.5, A.6 and A.7)

Table A.3: Published numbers of patients receiving regional lymph node radiotherapy in trials of regional lymph node radiotherapy starting 1989-2008, by breast cancer laterality, quadrant and surgery

Trial name	**Number of patients in trial regional lymph node radiotherapy group**						
	Breast cancer location					**Surgery**	
	All	**Left breast**	**Right breast**	**Lateral quadrant**	**Medial or central quadrant**	**BCS**	**Mastectomy**
EORTC 22922	2002	1028	974	–	–	–	–
DBCG-IMN	1492	0	1492	907	582	–	–
MA-20	916	–	–	564	352	916	0
Lyon Sud*	672	330	311	232	440	0	672
KROG 08-06†	362	171	181	208	153	180	182
IAEA	237	–	–	–	–	0	237
ISOG Milan	221	–	–	–	–	221	0
Tampere	131	–	–	98	33	131	0
Total patients	**6033**	**1529**	**2958**	**2009**	**1560**	**1448**	**1091**

Footnotes

*Information on laterality was missing for 31 patients.

†The number of left and right breast cancers are published as 171 (50%) and 181 (50%) respectively.

Therefore these numbers were not used in estimates.

Abbreviations: BCS=breast conserving surgery, "-"=unspecified.

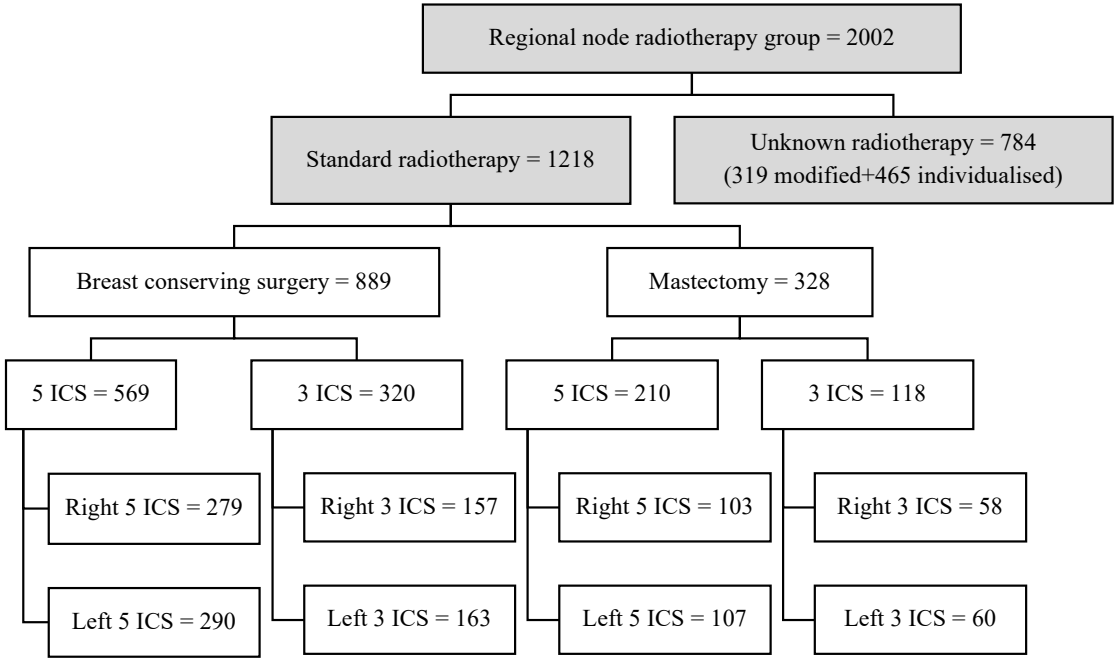


Figure A.1: EORTC 22922 trial: estimation of the number of patients receiving each radiotherapy regimen

Published numbers are shaded in grey. Estimated numbers are unshaded. Regimen descriptions refer to internal mammary lymph node field beam types and arrangements. Standard modified radiotherapy refers to minor adaptations for beam size and gantry angle, match line setting, proportion and energy of electrons. Individualised radiotherapy refers to radiotherapy that used individual localisation of IM lymph node chain for each patient and/or individualisation of all beam settings including number and shapes, energy prescription points and relative beam weights. Published information used for estimates:

- Whole trial standard radiotherapy group: 663/2440 mastectomy, 1777/2440 breast conserving surgery.
- Whole trial group: 2544/4004 medial cancers and half of unknown location cancers, 1461/4004 lateral cancers and half of unknown location cancers.
- Regional node radiotherapy group: 974/2002 right, 1028/2002 left.

Abbreviations: ICS=intercostal space.

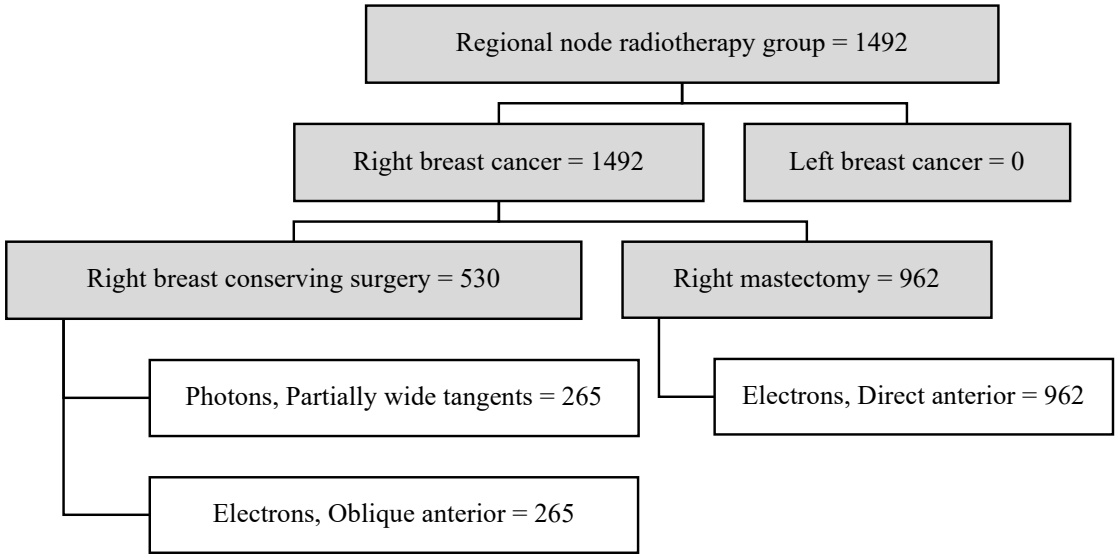


Figure A.2: DBCG-IMN trial: estimation of the number of patients receiving each radiotherapy regimen
Published numbers are shaded in grey. Estimated numbers are unshaded. Regimen descriptions refer to internal mammary lymph node field beam types and arrangements. Assumptions used for estimates:

- 50% of patients who received right breast conserving surgery received radiotherapy using "Photons, Partially wide tangents" and 50% received "Electrons, Oblique anterior".

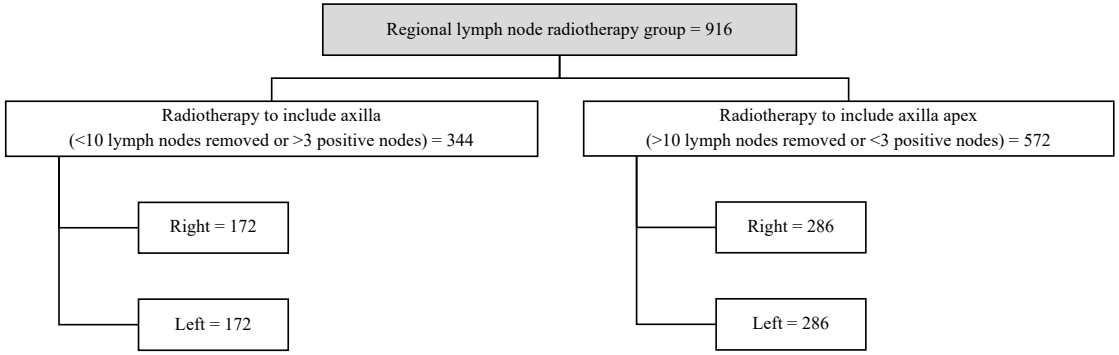


Figure A.3: MA-20 trial: estimation of the number of patients receiving each radiotherapy regimen
Published numbers are shaded in grey. Estimated numbers are unshaded. Published information used for estimates:

- Regional node radiotherapy group, <10 nodes removed = 294.
- Regional node radiotherapy group, >3 positive nodes = 50.
- (294+50 = 344 radiotherapy to axilla. 916-344 = 572 radiotherapy to axilla apex.)

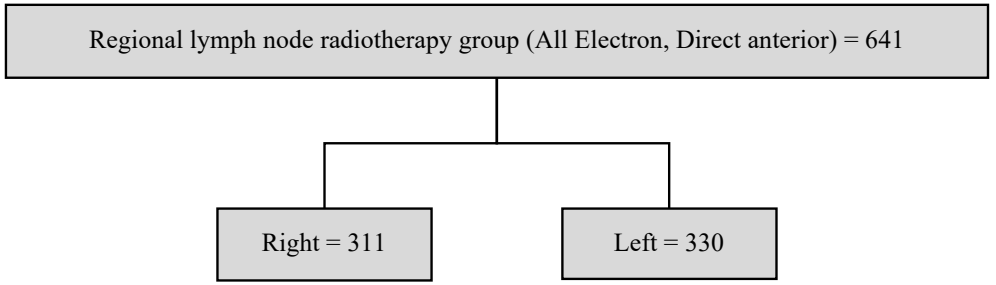


Figure A.4: Lyon Sud trial: estimation of the number of patients receiving each radiotherapy regimen

Published numbers are shaded in grey. Estimated numbers are unshaded. Regimen description refers to internal mammary lymph node field beam type and arrangement. Assumptions used for estimates:

- 50% right, 50% left breast cancers.

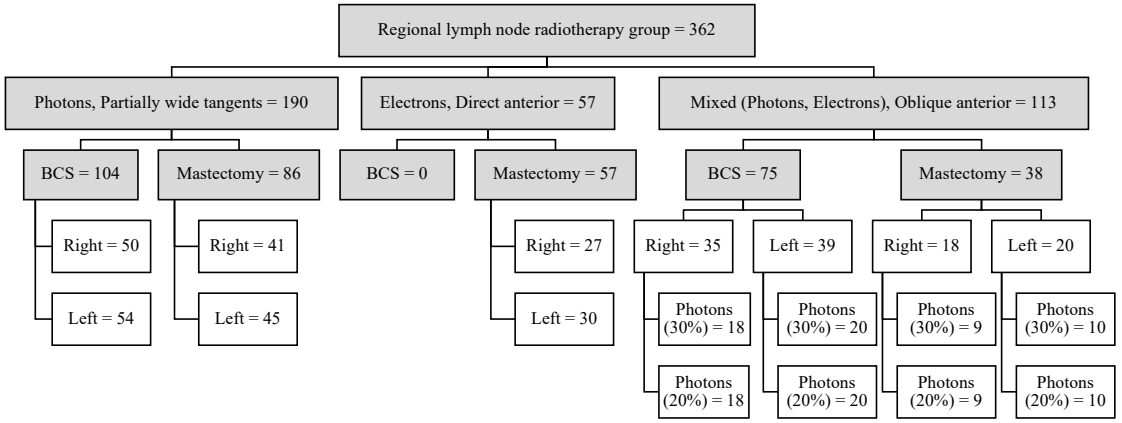


Figure A.5: KROG 08-06 trial: estimation of the number of patients receiving each radiotherapy regimen
Published numbers are shaded in grey. Estimated numbers are unshaded. Regimen descriptions refer to internal mammary lymph node field beam types and arrangements. Published information used for estimates:

- Regional node radiotherapy group, patients with medio-centrally located tumours: 73/153 right, 80/153 left.

Assumptions used for estimates:

- 50% of patients who received "Mixed (Photons, electrons), Oblique anterior" regimens were estimated to have received 20% of prescribed dose using photons, and 50% were estimated to have received 30% of prescribed dose using photons.

Abbreviations: BCS=breast conserving surgery.

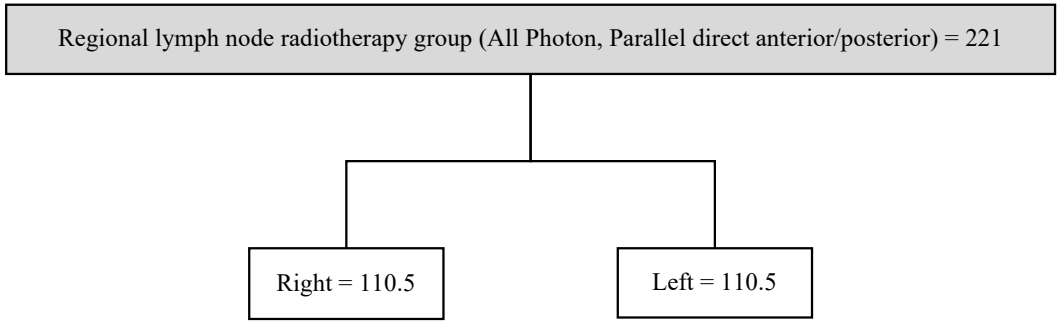


Figure A.6: ISOG Milan trial: estimation of the number of patients receiving each radiotherapy regimen

Published numbers are shaded in grey. Estimated numbers are unshaded. Regimen description refers to axilla field beam type and arrangement. Assumptions used for estimates:

- 50% right, 50% left breast cancers.

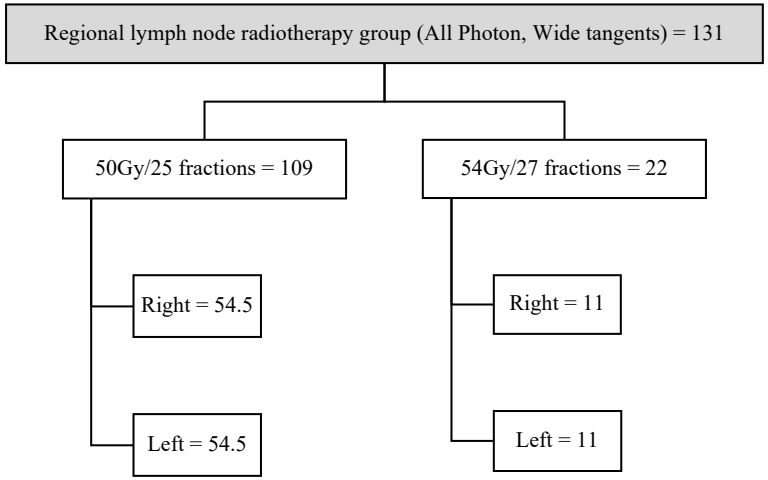


Figure A.7: Tampere trial: estimation of the number of patients receiving each radiotherapy regimen
Published numbers are shaded in grey. Estimated numbers are unshaded. Regimen description refers to internal mammary lymph node field beam type and arrangement. Assumptions used for estimates:

- 50% right, 50% left breast cancer

A.5 Descriptions of all published radiotherapy regimens from eight trials of regional lymph node radiotherapy starting 1989-2008

All published descriptions of radiotherapy regimens used in eight trials of regional lymph node radiotherapy starting 1989-2008 are presented in the following tables with the exception of those for which there was insufficient information to reconstruct any radiotherapy regimens targeting the regional lymph nodes. For IAEA, no information was available.

Please note that where patient position was specified, all patients were treated supine, and no trials described whether or not deep inspiration breath-hold techniques were used.

A.5.1 EORTC 22922

Table A.4: EORTC 22922: Descriptions of eight radiotherapy regimens received by an estimated 1217 patients

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
290	L	**Breast:** Photons, Tangents	10 MV	50 / 25	According to ICRU 50	**Sup:** Superior edge of 1st rib **Med:** Matched to lateral edge of internal mammary field
		Supraclavicular: Photons, Direct anterior	10 MV	50 / 25	According to ICRU 50	**Sup:** 3cm above head of clavicle **Inf:** Superior edge of 1st rib **Med:** 1cm across midline **Lat:** Middle of clavicle
		Internal mammary: Photons, Direct anterior	10 MV	26 / 13	3cm depth	**Sup:** Superior edge of 1st rib **Inf:** Inferior edge of 4th rib, extended to 5th ICS in medial lower quadrant tumours **Med:** 1cm across midline **Lat:** 5cm lateral to midline
		Internal mammary: Electrons, Direct anterior	12-14 MeV	24 / 12	Dmax 85% isodose to cover PTV	**Sup:** Superior edge of 1st rib **Inf:** Inferior edge of 4th rib, extended to 5th ICS in medial lower quadrant tumours **Med:** 1cm across midline **Lat:** 5cm lateral to midline
279	R	**Breast:** Photons, Tangents	10 MV	50 / 25	According to ICRU 50	**Sup:** Superior edge of 1st rib **Med:** Matched to lateral edge of internal mammary field
		Supraclavicular: Photons, Direct anterior	10 MV	50 / 25	According to ICRU 50	**Sup:** 3cm above head of clavicle **Inf:** Superior edge of 1st rib **Med:** 1cm across midline **Lat:** Middle of clavicle

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
		Internal mammary: Photons, Direct anterior	10 MV	26 / 13	3cm depth	**Sup:** Superior edge of 1st rib **Inf:** Inferior edge of 4th rib, extended to 5th ICS in medial lower quadrant tumours **Med:** 1cm across midline **Lat:** 5cm lateral to midline
		Internal mammary: Electrons, Direct anterior	12-14 MeV	24 / 12	Dmax 85% isodose to cover PTV	**Sup:** Superior edge of 1st rib **Inf:** Inferior edge of 4th rib, extended to 5th ICS in medial lower quadrant tumours **Med:** 1cm across midline **Lat:** 5cm lateral to midline
163	L	**Breast**: Photons, Tangents	10 MV	50 / 25	According to ICRU 50	**Sup:** Superior edge of 1st rib **Med:** Matched to lateral edge of internal mammary field
		Supraclavicular: Photons, Direct anterior	10 MV	50 / 25	According to ICRU 50	**Sup:** 3cm above head of clavicle **Inf:** Superior edge of 1st rib textbfMed: 1cm across midline **Lat:** Middle of clavicle
		Internal mammary: Photons, Direct anterior	10 MV	26 / 13	3cm depth	**Sup:** Superior edge of 1st rib **Inf:** Inferior edge of 4th rib, extended to 5th ICS in medial lower quadrant tumours **Med:** 1cm across midline **Lat:** 5cm lateral to midline

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
		Internal mammary: Electrons, Direct anterior	12-14 MeV	24 / 12	Dmax 85% isodose to cover PTV	**Sup:** Superior edge of 1st rib **Inf:** Inferior edge of 4th rib, extended to 5th ICS in medial lower quadrant tumours **Med:** 1cm across midline **Lat:** 5cm lateral to midline
157	R	**Breast:** Photons, Tangents	10 MV	50 / 25	According to ICRU 50	**Sup:** Superior edge of 1st rib **Med:** Matched to lateral edge of internal mammary field
		Supraclavicular: Photons, Direct anterior	10 MV	50 / 25	According to ICRU 50	**Sup:** 3cm above head of clavicle **Inf:** Superior edge of 1st rib **Med:** 1cm across midline **Lat:** Middle of clavicle
		Internal mammary: Photons, Direct anterior	10 MV	26 / 13	3cm depth	**Sup:** Superior edge of 1st rib **Inf:** Inferior edge of 4th rib, extended to 5th ICS in medial lower quadrant tumours **Med:** 1cm across midline **Lat:** 5cm lateral to midline
		Internal mammary: Electrons, Direct anterior	12-14 MeV	24 / 12	Dmax 85% isodose to cover PTV	**Sup:** Superior edge of 1st rib **Inf:** Inferior edge of 4th rib, extended to 5th ICS in medial lower quadrant tumours **Med:** 1cm across midline **Lat:** 5cm lateral to midline
107	L	**Chest wall:** Photons, Tangents	10 MV	50 / 25	According to ICRU 50	**Sup:** Superior edge of 1st rib **Med:** Matched to lateral edge of internal mammary field

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
		Supraclavicular: Photons, Direct anterior	10 MV	50 / 25	According to ICRU 50	**Sup:** 3cm above head of clavicle **Inf:** Superior edge of 1st rib **Med:** 1cm across midline **Lat:** Middle of clavicle
		Internal mammary: Photons, Direct anterior	10 MV	26 / 13	3cm depth	**Sup:** Superior edge of 1st rib **Inf:** Inferior edge of 4th rib, extended to 5th ICS in medial lower quadrant tumours **Med:** 1cm across midline **Lat:** 5cm lateral to midline
		Internal mammary: Electrons, Direct anterior	12-14 MeV	24 / 12	Dmax 85% isodose to cover PTV	**Sup:** Superior edge of 1st rib **Inf:** Inferior edge of 4th rib, extended to 5th ICS in medial lower quadrant tumours **Med:** 1cm across midline **Lat:** 5cm lateral to midline
103	R	**Chest wall:** Photons, Tangents	10 MV	50 / 25	According to ICRU 50	**Sup:** Superior edge of 1st rib **Med:** Matched to lateral edge of internal mammary field
		Supraclavicular: Photons, Direct anterior	10 MV	50 / 25	According to ICRU 50	**Sup:** 3cm above head of clavicle **Inf:** Superior edge of 1st rib **Med:** 1cm across midline **Lat:** Middle of clavicle
		Internal mammary: Photons, Direct anterior	10 MV	26 / 13	3cm depth	**Sup:** Superior edge of 1st rib **Inf:** Inferior edge of 4th rib, extended to 5th ICS in medial lower quadrant tumours **Med:** 1cm across midline **Lat:** 5cm lateral to midline

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
		Internal mammary: Electrons, Direct anterior	12-14 MeV	24 / 12	Dmax 85% isodose to cover PTV	**Sup:** Superior edge of 1st rib **Inf:** Inferior edge of 4th rib, extended to 5th ICS in medial lower quadrant tumours **Med:** 1cm across midline **Lat:** 5cm lateral to midline
60	L	**Chest wall:** Photons, Tangents	10 MV	50 / 25	According to ICRU 50	**Sup:** Superior edge of 1st rib **Med:** Matched to lateral edge of internal mammary field
		Supraclavicular: Photons, Direct anterior	10 MV	50 / 25	According to ICRU 50	**Sup:** 3cm above head of clavicle **Inf:** Superior edge of 1st rib **Med:** 1cm across midline **Lat:** Middle of clavicle
		Internal mammary: Photons, Direct anterior	10 MV	26 / 13	3cm depth on beam axis	**Sup:** Superior edge of 1st rib **Inf:** Inferior edge of 4th rib, extended to 5th ICS in medial lower quadrant tumours **Med:** 1cm across midline **Lat:** 5cm lateral to midline
		Internal mammary: Electrons, Direct anterior	12-14 MeV	24 / 12	Dmax 85% isodose to cover PTV	**Sup:** Superior edge of 1st rib **Inf:** Inferior edge of 4th rib, extended to 5th ICS in medial lower quadrant tumours **Med:** 1cm across midline **Lat:** 5cm lateral to midline
58	R	**Chest wall:** Photons, Tangents	10 MV	50 / 25	According to ICRU 50	**Sup:** Superior edge of 1st rib **Med:** Matched to lateral edge of internal mammary field

Pts R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
	Supraclavicular: Photons, Direct anterior	10 MV	50 / 25	According to ICRU 50	**Sup:** 3cm above head of clavicle **Inf:** Superior edge of 1st rib **Med:** 1cm across midline **Lat:** Middle of clavicle
	Internal mammary: Photons, Direct anterior	10 MV	26 / 13	3cm depth on beam axis	**Sup:** Superior edge of 1st rib **Inf:** Inferior edge of 4th rib, extended to 5th ICS in medial lower quadrant tumours **Med:** 1cm across midline **Lat:** 5cm lateral to midline
	Internal mammary: Electrons, Direct anterior	12-14 MeV	24 / 12	Dmax 85% isodose to cover PTV	**Sup:** Superior edge of 1st rib **Inf:** Inferior edge of 4th rib, extended to 5th ICS in medial lower quadrant tumours **Med:** 1cm across midline **Lat:** 5cm lateral to midline

Footnotes

Techniques for sparing organs at risk:

Block larynx if needed.

Abbreviations: cm=centimetres, Dmax=maximum dose, ICRU=International Commission on Radiation Units and Measurements, ICS=intercostal space, Inf=inferior, fr=fractions, Gy=Gray, L=lateral, L=left, Med=medial, MeV=megaelectron volts, MV=megavolts, pts=patients, PTV=planning target volume, R=right, Sup=superior, "-"=unspecified.

A.5.2 DBCG-IMN

Table A.5: DBCG-IMN: Descriptions of three radiotherapy regimens received by an estimated 1492 patients

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
962	R	**Chest wall:** Electrons, Direct anterior	6 MeV	48 / 24	85% isodose to cover 0.5cm below skin surface to largest distance to pleura minus 1cm at 6cm lateral to midline in 2nd-4th ICS	**Sup:** Lower edge of clavicular head **Inf:** 1cm below infra-mammary groove 3cm inferior to inferior border of internal mammary field **Med:** Matched to internal mammary field **Lat:** 1cm inside of bony chest wall as seen on DRR in beam's eye view
		Axilla levels 2-3, Supraclavicular: Photons, Oblique anterior (10-15^{o})	6-15 MV	48 / 24	–	**Sup:** Lower edge of C6 **Inf:** 1cm below infra-mammary groove **Med:** 1cm contralateral to midline **Lat:** 1cm lateral of surgical neck of humerus
		Internal mammary: Electrons, Direct anterior	9-12 MeV	48 / 24	85% isodose to cover 0.5cm below skin surface to largest distance to pleura minus 1cm at 6cm lateral to midline in 2nd-4th ICS	**Sup:** Lower edge of clavicular head **Inf:** Middle of 5th rib at costosternal junction **Med:** 1cm contralateral to midline **Lat:** Field width 6cm at the top, 5cm at the bottom.

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
265	R	**Breast:** Photons, Matched tangents	6 MV	48 / 24	–	**Sup:** Matched to lower edge of axillary/periclavicular field **Inf:** 1cm below infra-mammary groove **Med:** 4cm on ipsilateral side of midline and matched to lateral border of internal mammary field **Lat:** Mid-axillary line
		Axilla level 3, Supraclavicular: Photons, Oblique anterior (10-15^{o})	6-15 MV	48 / 24	–	**Sup:** Lower edge of C6 **Inf:** Lower limit of clavicular head **Med:** 1cm contralateral to midline **Lat:** 1cm lateral of surgical neck of humerus
		Internal mammary: Electrons, Oblique anterior (10^{o} less than medial tangent)	9-15 MeV	48 / 24	85% isodose to cover 0.5cm below skin surface to largest distance to pleura minus 1cm at 6cm lateral to midline in 2nd-4th ICS	**Sup:** Lower limit of clavicular head **Inf:** Middle of 5th rib at costosternal junction **Med:** 1cm contralateral to midline **Lat:** Matched to medial tangential field border
265	R	**Breast, Internal mammary:** Photons, Partially wide tangents	6 MV	48 / 24	–	**Sup:** Matched to lower edge of axillary/periclavicular field **Inf:** 1cm below infra-mammary groove **Med:** 3cm contralateral to midline **Lat:** Mid-axillary line

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
		Axilla level 3, Supraclavicular: Photons, Oblique anterior (10-15^{o})	6-15 MV	48 / 24	–	**Sup:** Lower edge of C6 **Inf:** Lower limit of clavicular head **Med:** 1cm contralateral to midline **Lat:** 1cm lateral of surgical neck of humerus

Footnotes

Techniques for sparing organs at risk:

Collimators to lung guided by breast markings. In case of CLD >3cm, lateral field border moved anteriorly until CLD <3cm.

Collimators to larynx and humeral head.

Techniques for target homogeneity:

15MV

Abbreviations: cm=centimetres, C6=6th cervical vertebra, DRR=digitally reconstructed radiograph, ICRU=International Commission on Radiation Units and Measurements, ICS=intercostal space, Inf=inferior, fr=fractions, Gy=Gray, L=lateral, L=left, Med=medial, MeV=megaelectron volts, MV=megavolts, pts=patients, PTV=planning target volume, R=right, Sup=superior, "-"=unspecified.

A.5.3 MA-20

Table A.6: MA-20: Descriptions of four radiotherapy regimens received by an estimated 916 patients

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
286	L	**Breast, Internal mammary:** Photons, Partially wide tangents	4-18 MV(or Co60)	50 / 25	Mid-separation 80% isodose to cover CTV	**Sup:** Lower edge of clavicle, matched to inferior border of the supraclavicular/axillary field **Inf:** Horizontal line 1-1.5cm below the infra-mammary crease or the lower breast, whichever is more inferior **Med:** 3cm contralateral to mid sternum superiorly with cardiac and lung shielding inferior to 3rd ICS **Lat:** Mid-axillary line to include breast and lower axilla with 1-1.5cm margin
		Axilla level 3, Supraclavicular: Photons, Oblique anterior (5-10^{o})	4-18 MV(or Co60)	50 / 25	3cm depth	**Sup:** Includes supraclavicular fossa **Inf:** Lower edge of clavicle. Co-planar match to superior border of tangents using asymmetric collimation or half beam block **Med:** Includes head of clavicle. Excludes spinal cord lying on pedicles of the thoracic vertebrae. **Lat:** Includes coracoid process medial to humeral head

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
286	R	**Breast, Internal mammary:** Photons, Partially wide tangents	4-18 MV(or Co60)	50 / 25	Mid-separation 80% isodose to cover CTV	**Sup:** Lower edge of clavicle, matched to inferior border of the supraclavicular/axillary field **Inf:** Horizontal line 1-1.5cm below the infra-mammary crease or the lower breast, whichever is more inferior **Med:** 3cm contralateral to mid sternum superiorly with cardiac and lung shielding inferior to 3rd ICS **Lat:** Mid-axillary line to include breast and lower axilla with 1-1.5cm margin
		Axilla level 3, Supraclavicular: Photons, Oblique anterior (5-10^{o})	4-18 MV(or Co60)	50 / 25	3cm depth	**Sup:** Includes supraclavicular fossa **Inf:** Lower edge of clavicle. Co-planar match to superior border of tangents using asymmetric collimation or half beam block **Med:** Includes head of clavicle. Excludes spinal cord lying on pedicles of the thoracic vertebrae. **Lat:** Includes coracoid process medial to humeral head

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
172	L	**Breast, Internal mammary:** Photons, Partially wide tangents	4-18 MV(or Co60)	50 / 25	Mid-separation 80% isodose to cover CTV	**Sup:** Lower edge of clavicle, matched to inferior border of the supraclavicular/axillary field **Inf:** Horizontal line 1-1.5cm below the infra-mammary crease or the lower breast, whichever is more inferior. **Med:** 3cm contralateral to mid sternum superiorly with cardiac and lung shielding inferior to 3rd ICS **Lat:** Mid-axillary line to include breast and lower axilla with 1-1.5cm margin
		Axilla levels 1-3, Supraclavicular: Photons, Parallel direct anterior/posterior*	4-18 MV(or Co60)	45 / 25	For parallel anterior/posterior, mid-separation	**Sup:** Includes supraclavicular fossa **Inf:** Lower end of clavicle. Co-planar match to superior border of tangents using asymmetric collimation or half beam block. **Med:** Includes head of clavicle. Excludes spinal cord lying on pedicles of the thoracic vertebrae. **Lat:** If <10 axillary nodes removed or >3 positive axillary nodes, lateral field extended to include levels 1 and 2 axillary lymph nodes. Include surgical neck of humerus.

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
172	R	**Breast, Internal mammary:** Photons, Partially wide tangents	4-18 MV(or Co60)	50 / 25	Mid-separation 80% isodose to cover CTV	**Sup:** Lower edge of clavicle, matched to inferior border of the supraclavicular/axillary field **Inf:** Horizontal line 1-1.5cm below the infra-mammary crease or the lower breast, whichever is more inferior. **Med:** 3cm contralateral to mid sternum superiorly with cardiac and lung shielding inferior to 3rd ICS **Lat:** Mid-axillary line to include breast and lower axilla with 1-1.5cm margin
		Axilla levels 1-3, Supraclavicular: Photons, Parallel direct anterior/posterior*	4-18 MV(or Co60)	45 / 25	For parallel anterior/posterior, mid-separation	**Sup:** Includes supraclavicular fossa **Inf:** Lower end of clavicle. Co-planar match to superior border of tangents using asymmetric collimation or half beam block. **Med:** Includes head of clavicle. Excludes spinal cord lying on pedicles of the thoracic vertebrae. **Lat:** If <10 axillary nodes removed or >3 positive axillary nodes, lateral field extended to include levels 1 and 2 axillary lymph nodes. Include surgical neck of humerus.

Footnotes

The number of patients treated with mixed photon electron fields to the internal mammary lymph nodes was

unspecified, and no further details of these four possible radiotherapy regimens were provided.

Techniques for sparing organs at risk:

Small shield anterior larynx lead acceptable.

Small anterior square or curved lead shield acromioclavicular joint and superior lateral aspect of the humeral head.

Cardiac and lung shielding below 3rd ICS. Lung tissue above 3rd ICS >2cm and <3.5cm. Below 3rd ICS <2cm.

Techniques for target homogeneity:

±7% central axis, wedges, compensators or IMRT

MA-20 internal mammary target description:

1cm around internal mammary vessels in the first 3 ICSs.

Alternatively posterior patch technique used where collimator of posterior field is rotated so that the superior border is parallel to the clavicle. The other borders are: inferiorly, blocked to match superior border of the breast tangents; medially, to include 2cm of lung; and laterally, to include the medial aspect of the humeral head. Anterior field prescribed at Dmax. Dose determined from anterior field to the midplane of the axilla (usually 70-80% of prescribed dose). Posterior field prescribed daily to supplement the mid-plane axillary dose to achieve 1.8Gy/day.

Abbreviations: cm=centimetres, Co60=Cobalt60, CTV=clinical target volume, fr=fractions, Gy=Gray, ICS=intercostal space, IMRT=intensity modulated radiotherapy, Inf= inferior, Lat=lateral, L=left, Med=medial, MeV=megaelectron volts, MV=megavolts, pts=patients, R=right, Sup=superior, "-"=unspecified.

A.5.4 Lyon Sud

Table A.7: Lyon Sud: Descriptions of two radiotherapy regimens received by an estimated 4979 patients

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
330	L	**Chest wall:** –, Tangents	–	50 / –	–	**Med:** 6cm lateral to midline
		Supraclavicular: –	–	50 / –	3cm depth	–
		Internal mammary: Photons, Direct anterior	4-6 MV (or Co60)	12.5 / 5	3cm depth	**Sup:** Superior to 1st ICS **Inf:** 14cm from superior border to cover 5 ICSs **Med:** Midline **Lat:** 6cm lateral to midline
		Internal mammary: Electrons, Direct anterior	9-12 MeV	32.5 / 13	–	**Sup:** Superior to 1st ICS **Inf:** 14cm from superior border to cover 5 ICSs **Med:** Midline **Lat:** 6cm lateral to midline
311	R	**Chest wall:** –, Tangents	–	50 / –	–	**Med:** 6cm lateral to midline
		Supraclavicular: –	–	50 / –	3cm depth	–
		Internal mammary: Photons, Direct anterior	4-6 MV (or Co60)	12.5 / 5	3cm depth	**Sup:** Superior to 1st ICS **Inf:** 14cm from superior border to cover 5 ICSs **Med:** Midline **Lat:** 6cm lateral to midline

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
		Internal mammary: Electrons, Direct anterior	9-12 MeV	32.5 / 13	–	**Sup:** Superior to 1st ICS **Inf:** 14cm from superior border to cover 5 ICSs **Med:** Midline **Lat:** 6cm lateral to midline

Footnotes

Techniques for target homogeneity:

Wedges

Abbreviations: cm=centimetres, Co60=Cobalt60, ICS=intercostal space, Inf=inferior, Lat=lateral, L=left, Med=medial, MeV=megaelectron volts, MV=megavolts, Gy=Gray, fr=fractions, R=right, Sup=superior, "-"=unspecified.

A.5.5 KROG 08-06

Table A.8: KROG 08-06: Descriptions of 14 radiotherapy regimens received by an estimated 361 patients

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
54	L	**Breast, Internal mammary:** Photons, Partially wide tangents	6 MV	50 / 28	–	**Sup:** Head of clavicle **Inf:** First 3 ICSs
		Supraclavicular: Photons, Oblique anterior (5-15^{o})	4-6 MV	50 / 28	3cm depth or 95% isodose to cover target volume	**Inf:** Head of clavicle **Med:** Midline
50	R	**Breast, Internal mammary:** Photons, Partially wide tangents	6 MV	50 / 28	–	**Sup:** Head of clavicle **Inf:** First 3 ICSs
		Supraclavicular: Photons, Oblique anterior (5-15^{o})	4-6 MV	50 / 28	3cm depth or 95% isodose to cover target volume	**Inf:** Head of clavicle **Med:** Midline **Lat:** Midline
45	L	**Chest wall, Internal mammary:** Photons, Partially wide tangents	6 MV	50 / 28	–	**Inf:** First 3 ICSs
		Supraclavicular: Photons, Oblique anterior (5-15^{o})	4-6 MV	50 / 28	3cm depth or 95% isodose to cover target volume	**Inf:** Head of clavicle **Med:** Midline

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
41	R	**Chest wall, Internal mammary:** Photons, Partially wide tangents	6 MV	50 / 28	–	**Inf:** First 3 ICSs
		Supraclavicular: Photons, Oblique anterior (5-15^{o})	4-6 MV	50 / 28	3cm depth or 95% isodose to cover target volume	**Inf:** Head of clavicle **Med:** Midline
30	L	**Chest wall:** Electrons, Oblique or Parallel anterior/posterior	6-9 MeV	50 / 28	–	–
		Supraclavicular: Photons, Oblique anterior (10^{o}) or Parallel anterior/posterior	–	50 / 28	–	–
		Internal mammary: Electrons, Anterior	9-12 MeV	50 / 28	80-90% isodose to cover anterior pleural surface	–
27	R	**Chest wall:** Electrons, Oblique or Parallel anterior/posterior	6-9 MeV	50 / 28	–	–

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
		Supraclavicular: Photons, Oblique anterior (10º) or Parallel anterior/posterior	–	50 / 28	–	–
		Internal mammary: Electrons, Anterior	9-12 MeV	50 / 28	80-90% isodose to cover anterior pleural surface	–
20	L	**Breast**: Photons, Tangents	6 MV	50 / 28	95% isodose	–
		Supraclavicular: Photons, Oblique anterior (5-15º)	4-6 MV	50 / 28	3cm depth or 95% isodose to cover target volume	**Inf:** Head of clavicle **Med:** Midline
		Internal mammary: Photons, Direct anterior	6 MV	10 / 28	–	**Lat:** 1cm overlap with medial tangent at skin
		Internal mammary: Electrons, Oblique anterior (5º less than medial tangent)	–	40 / 28	–	–
20	L	**Breast:** Photons, Tangents	6 MV	50 / 28	95% isodose	–
		Supraclavicular: Photons, Oblique anterior (5-15º)	4-6 MV	50 / 28	3cm depth or 95% isodose to cover target volume	**Inf:** Head of clavicle **Med:** Midline

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
		Internal mammary: Photons, Oblique anterior	6 MV	15 / 28	3cm depth	**Sup:** Head of clavicle **Med:** 1-2cm across midline4cm lateral to midline
		Internal mammary: Electrons, Oblique anterior (10^{o} less than photon field)	–	35 / 28	–	**Sup:** Head of clavicle **Med:** 1-2cm across midline **Lat:** 4cm lateral to midline
18	R	**Breast:** Photons, Tangents	6 MV	50 / 28	95% isodose	–
		Supraclavicular: Photons, Oblique anterior (5-15^{o})	4-6 MV	50 / 28	3cm depth or 95% isodose to cover target volume	**Inf:** Head of clavicle **Med:** Midline
		Internal mammary: Photons, Direct anterior	6 MV	10 / 28	–	**Lat:** 1cm overlap with medial tangent at skin
		Internal mammary: Electrons, Oblique anterior (5^{o} less than medial tangent)	–	40 / 28	–	–
18	R	**Breast**: Photons, Tangents	6 MV	50 / 28	95% isodose	–
		Supraclavicular: Photons, Oblique anterior (5-15^{o})	4-6 MV	50 / 28	3cm depth or 95% isodose to cover target volume	**Inf:** Head of clavicle **Med:** Midline

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
		Internal mammary: Photons, Oblique anterior	6 MV	15 / 28	3cm depth	**Sup:** Head of clavicle **Med:** 1-2cm across midline **Lat:** 4cm lateral to midline
		Internal mammary: Electrons, Oblique anterior (10^{o} less than photon field)	–	35 / 28	–	**Sup:** Head of clavicle **Med:** 1-2cm across midline **Lat:** 4cm lateral to midline
10	L	**Chest wall:** Photons, Tangents	6 MV	50 / 28	95% isodose	–
		Supraclavicular: Photons, Oblique anterior (5-15^{o})	4-6 MV	50 / 28	3cm depth or 95% isodose to cover target volume	**Inf:** Head of clavicle **Med:** Midline
		Internal mammary: Photons, Direct anterior	6 MV	10 / 28	–	**Lat:** 1cm overlap with medial tangent at skin
		Internal mammary: Electrons, Oblique anterior (5^{o} less than medial tangent)	–	40 / 28	–	–
10	L	**Chest wall:** Photons, Tangents	6 MV	50 / 28	95% isodose	–
		Supraclavicular: Photons, Oblique anterior (5-15^{o})	4-6 MV	50 / 28	3cm depth or 95% isodose to cover target volume	**Inf:** Head of clavicle **Med:** Midline

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
		Internal mammary: Photons, Oblique anterior	6 MV	15 / 28	3cm depth	**Sup:** Head of clavicle **Med:** 1-2cm across midline **Lat:** 4cm lateral to midline
		Internal mammary: Electrons, Oblique anterior (10^{o} less than photon field)	–	35 / 28	–	**Sup:** Head of clavicle **Med:** 1-2cm across midline **Lat:** 4cm lateral to midline
9	R	**Chest wall:** Photons, Tangents	6 MV	50 / 28	95% isodose	–
		Supraclavicular: Photons, Oblique anterior (5-15^{o})	4-6 MV	50 / 28	3cm depth or 95% isodose to cover target volume	**Inf:** Head of clavicle **Med:** Midline
		Internal mammary: Photons, Direct anterior	6 MV	10 / 28	–	**Lat:** 1cm overlap with medial tangent at skin
		Internal mammary: Electrons, Oblique anterior (5^{o} less than medial tangent)	–	40 / 28	–	–
9	R	**Chest wall:** Photons, Tangents	6 MV	50 / 28	95% isodose	–
		Supraclavicular: Photons, Oblique anterior (5-15^{o})	4-6 MV	50 / 28	3cm depth or 95% isodose to cover target volume	**Inf:** Head of clavicle **Med:** Midline

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
		Internal mammary: Photons, Oblique anterior	6 MV	15 / 28	3cm depth	**Sup:** Head of clavicle **Med:** 1-2cm across midline **Lat:** 4cm lateral to midline
		Internal mammary: Electrons, Oblique anterior (10^{o} less than photon field)	–	35 / 28	–	**Sup:** Head of clavicle **Med:** 1-2cm across midline **Lat:** 4cm lateral to midline

Footnotes

All published descriptions within this trial are presented except that used for one patient who received direct electrons to the chest wall and internal mammary lymph nodes and for whom breast cancer laterality was unspecified.

Techniques for sparing organs at risk:

CLD <3cm. Predicted risk of pneumonitis <45%.

When internal mammary and heart volumes overlap, heart should be shielded and inferior medial chest wall treated with supplemental electrons.

Small larynx lead block should not shield medial supraclavicular nodes.

Bolus can be used to reduce heart and lung dose.

Techniques for target homogeneity:

Inhomogeneity constraint $\leq$12% on central CT slice.

KROG 08-06 internal mammary target description:

Cranial: Jugulo-subclavian junction.

Caudal: 4th rib.

Ventral: Dorsal surface pectorals major muscle, dorsal surface of sternum.

Dorsal: Pleura or 5mm fat tissue dorsal of internal mammary vessels.

Lateral: 5mm lateral of internal mammary vessels, lateral border of brachiocephalic vein.

Medial: 5mm medial of internal mammary vessels, medial border of brachiocephalic vein.

KROG 08-06 medial supraclavicular target description:

Cranial: Caudal cricoid cartilage.

Caudal: Cranial jugulo-subclavian junction, caudal external jugular vein.

Ventral: Dorsal surface sternocleidomastoid muscle.

Dorsal: Dorsal border internal carotid artery, ventral border scalene's anterior muscle.

Lateral: Lateral border sternocleidomastoid muscle and scalene's anterior muscle.

Medial: Medial edge internal carotid artery and internal jugular vein.

KROG 08-06 lateral supraclavicular target description:

Cranial: Cranial omohyoid muscle.

Caudal: Caudal external jugular vein, transverse cervical vessels.

Ventral: Clavicle, skin.

Dorsal: Ventral surface omohyoid muscle, elevator scapulae muscle, scalene's medius muscle.

Lateral: Clavicle, trapezius muscle.

Medial: Lateral border sternocleidomastoid muscle and scalene's anterior muscle.

Abbreviations: cm=centimetres, CLD=central lung distance, CTV=clinical target volume, fr=fractions, Gy=Gray, Inf=inferior, Lat=lateral, L=left, Med=medial, MeV=megaelectron volts, MV=megavolts, pts=patients, R=right, Sup=superior, "-"=unspecified.

A.5.6 ISOG Milan

Table A.9: ISOG Milan: Descriptions of two radiotherapy regimens received by an estimated 221 patients

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
110.5	L	**Breast:** Photons, Tangents	6 MV	50 / 25	According to ICRU	–
		Axilla levels 1-3: Photons, Parallel direct anterior/posterior	6 MV	50 / 25	Midplane or slightly anterior	**Sup:** Upper margin of clavicle **Inf:** 0.5cm from upper limit of tangents **Med:** Margin of vertebral bodies **Lat:** Anterior axillary fold
110.5	R	**Breast:** Photons, Tangents	6 MV	50 / 25	According to ICRU	–
		Axilla levels 1-3: Photons, Parallel direct anterior/posterior	6 MV	50 / 25	Midplane or slightly anterior	**Sup:** Upper margin of clavicle **Inf:** 0.5cm from upper limit of tangents **Med:** Margin of vertebral bodies **Lat:** Anterior axillary fold

Footnotes

Techniques for sparing organs at risk:

CLD <2cm

Shoulder shielded

Techniques for target homogeneity:

Inhomogeneity constraint $\leq$5%

Wedges

Abbreviations: cm=centimetres, Gy=Gray, fr=fractions, ICRU=International Commission on Radiation Units and Measurements, Inf=inferior, Lat=lateral, L=left, Med=medial, MV=megavolts, pts=patients, R=right, Sup=superior, "-"=unspecified.

A.5.7 Tampere

Table A.10: Tampere: Descriptions of four radiotherapy regimens received by an estimated 131 patients

Pts	R/L	Field clinical target(s): beam type, arrangement	Beam energy	Total dose (Gy)/fr	Prescription point	Field borders
54.5	L	**Breast, Internal mammary**: Photons, Wide tangents	5 MV	50 / 25	According to ICRU	**Sup:** Superior to breast **Inf:** Inferior to breast
54.5	R	**Breast, Internal mammary**: Photons, Wide tangents	5 MV	50 / 25	According to ICRU	**Sup:** Superior to breast **Inf:** Inferior to breast
11	L	**Breast, Internal mammary**: Photons, Wide tangents	5 MV	54 / 27	According to ICRU	**Sup:** Superior to breast **Inf:** Inferior to breast
11	R	**Breast, Internal mammary**: Photons, Wide tangents	5 MV	54 / 27	According to ICRU	**Sup:** Superior to breast **Inf:** Inferior to breast

Footnotes

Techniques for sparing organs at risk:

Inhomogeneity constraint $\leq$10%

Wedges

Techniques for target homogeneity:

In some cases irradiated lung volume was reduced by increasing the 180º difference between the beam axes by 6-8º, and collimator rotation.

Abbreviations: Gy=Gray, fr=fractions, ICRU=International Commission on Radiation Units and Measurements, Inf=inferior, L=left, pts=patients, R=right, Sup=superior, "-"=unspecified.

A.6 Internal mammary lymph node beam types and arrangements used in six trials starting 1989-2008

Table A.11: Internal mammary lymph node beam types and arrangements used in six trials starting 1989-2008

IMN beam type, arrangement	**Trial**	**Regimens N=35**		**Est. patients N=4758**
		no.	*%*	**no.**
Photons, Partially wide tangents	**All trials**	**9**	***26***	**1371**
	KROG 08-06	4	*11*	190
	MA-20	4	*11*	916
	DBCG-IMN	1	*3*	265
Mixed (52% Photons, 48% Electrons), Direct anterior	**EORTC 22922**	**8**	***23***	**1217**
Electrons, Direct anterior	**All trials**	**3**	***9***	**1019**
	KROG 08-06	2	*6*	57
	DBCG-IMN	1	*3*	962
Mixed (28% Photons, 72% Electrons), Direct anterior	**Lyon Sud**	**2**	***6***	**641**
Electrons, Oblique anterior	**DBCG-IMN**	**1**	***3***	**265**
Photons, Wide tangents	**Tampere**	**4**	***11***	**131**
Mixed (30% Photons, 70% Electrons), Oblique anterior	**KROG 08-06**	**4**	***11***	**57**
Mixed (20% Photons, 80% Electrons), Oblique anterior	**KROG 08-06**	**4**	***11***	**57**

Footnotes
Abbreviations: IMN=internal mammary lymph node, N=total number, no.=number.

A.7 Supraclavicular lymph node beam types and arrangements used in five trials starting 1989-2008

Table A.12: Supraclavicular lymph node beam types and arrangements used in five trials starting 1989-2008

Supraclavicular beam type, arrangement	**Trial**	**Regimens N=31**		**Est. patients N=4627**
		no.	*%*	**no.**
Photons, Oblique anterior	**All trials**	**19**	***61***	**2425**
	KROG 08-06	14	*45*	361
	DBCG-IMN	3	*10*	1492
	MA-20	2	*6*	572
Photons, Direct anterior	**EORTC 22922**	**8**	***26***	**1217**
Unspecified	**Lyon Sud**	**2**	***6***	**641**
Photons, parallel anterior/posterior	**MA-20**	**2**	***6***	**344**

Footnotes
N=total number, no.=number.

A.8 Axillary level 3 lymph node beam types and arrangements used in four trials starting 1989-2008

Table A.13: Axillary level 3 lymph node beam types and arrangements used in four trials starting 1989-2008

Axillary level 3 beam type, arrangement	**Trial**	**Regimens N=9**		**Est. patients N=2629**
		no.	**%**	**no.**
	All trials	**5**	***56***	**2064**
Photons, Oblique anterior	DBCG-IMN	3	*33*	1492
	MA-20	2	*22*	572
	All trials	**4**	***44***	**565**
Photons, Parallel direct anterior/posterior	MA-20	2	*22*	344
	ISOG Milan	2	*22*	221

Footnotes
N=total number, no.=number.

A.9 Inter-patient and inter-regimen variability in CT body measurements and doses received by ESTRO internal mammary lymph node clinical target volumes from radiotherapy for right breast cancer

Table A.14: Inter-patient and inter-regimen variability in CT body measurements and doses received by ESTRO internal mammary lymph node clinical target volumes from radiotherapy for right breast cancer

Trial	IMN beam type, arrangement	Total dose (Gy)	CT ID	Body measurement				Dose metrics for ESTRO IMN CTV (%)					
				R breast volume (cc)	Breast separation (cm)	Sternal soft tissue thickness (cm)	Haller Index	Volume (cc)	Mean	V80%	V85%	V90%	V95%
DBCG-IMN	Electrons, Direct anterior	48	4	0	11.33	0.31	2.6	7.4	98.0	100.0	100.0	91.5	33.9
			2	0	12.75	0.93	3.1	5.8	83.5	76.2	72.4	66.0	34.6
			3	0	22.58	2.75	2.0	10.2	87.2	74.9	68.1	59.8	43.5
			1	0	21.92	1.58	2.2	7.2	82.1	67.2	64.5	58.8	41.8
			5	0	22.23	1.69	2.5	11.4	81.7	65.2	57.0	32.5	10.1
Lyon Sud	Mixed (28% Photons, 72% Electrons), Direct anterior	50	4	0	11.33	0.31	2.6	7.4	90.7	95.7	88.2	60.5	15.6
			2	0	12.75	0.93	3.1	5.8	84.6	81.1	69.6	19.8	2.0
			1	0	21.92	1.58	2.2	7.2	76.2	63.1	28.8	3.2	0.7
			5	0	22.23	1.69	2.5	11.4	71.0	49.9	41.7	22.8	7.4
			3	0	22.58	2.75	2.0	10.2	66.6	29.0	16.3	7.8	4.1
MA-20	Photons, Partially wide tangents	50	1	456	21.92	1.58	2.2	7.2	86.7	85.2	74.4	56.0	15.7
			4	44	11.33	0.31	2.6	7.4	84.9	80.5	76.3	67.0	43.2
			5	1059	22.23	1.69	2.5	11.4	82.0	75.7	54.9	32.0	10.2
			2	105	12.75	0.93	3.1	5.8	78.0	66.1	61.6	53.6	35.8
			3	537	22.58	2.75	2.0	10.2	69.2	47.1	26.2	0.2	0.0
EORTC 22922	Mixed (52% Photons, 48% Electrons), Direct anterior	50	2	105	12.75	0.93	3.1	5.8	115.6	100.0	99.8	98.9	97.0
			4	44	11.33	0.31	2.6	7.4	109.4	98.8	96.7	94.8	92.9
			1	456	21.92	1.58	2.2	7.2	112.6	89.6	85.1	80.2	73.2
			3	537	22.58	2.75	2.0	10.2	103.3	79.7	74.9	68.7	62.7
			5	1059	22.23	1.69	2.5	11.4	103.7	65.2	61.1	57.9	54.4
DBCG-IMN	Electrons, Oblique anterior	48	4	44	11.33	0.31	2.6	7.4	98.6	97.4	91.9	79.4	55.0
			2	105	12.75	0.93	3.1	5.8	99.2	92.6	88.7	84.6	80.6
			1	456	21.92	1.58	2.2	7.2	117.2	78.2	75.4	72.7	70.6
			5	1059	22.23	1.69	2.5	11.4	71.4	47.3	42.2	25.2	7.1
			3	537	22.58	2.75	2.0	10.2	54.2	6.7	2.2	1.2	1.2

Footnotes
CT with ID=1 was selected as the representative patient.
Doses are for equivalent dose in 2Gy per fraction.
Data are presented in Figures A.9 and A.9.
Abbreviations: cc=cubic centimetres, cm=centimetres, CT=computer tomography scan, CTV=clinical target volume, ESTRO=European Society of Therapeutic Radiology and Oncology, Gy=Gray, ID=identification number, IMN=internal mammary lymph nodes, R=right, Vx%=Volume receiving at least x% of the total prescribed dose.

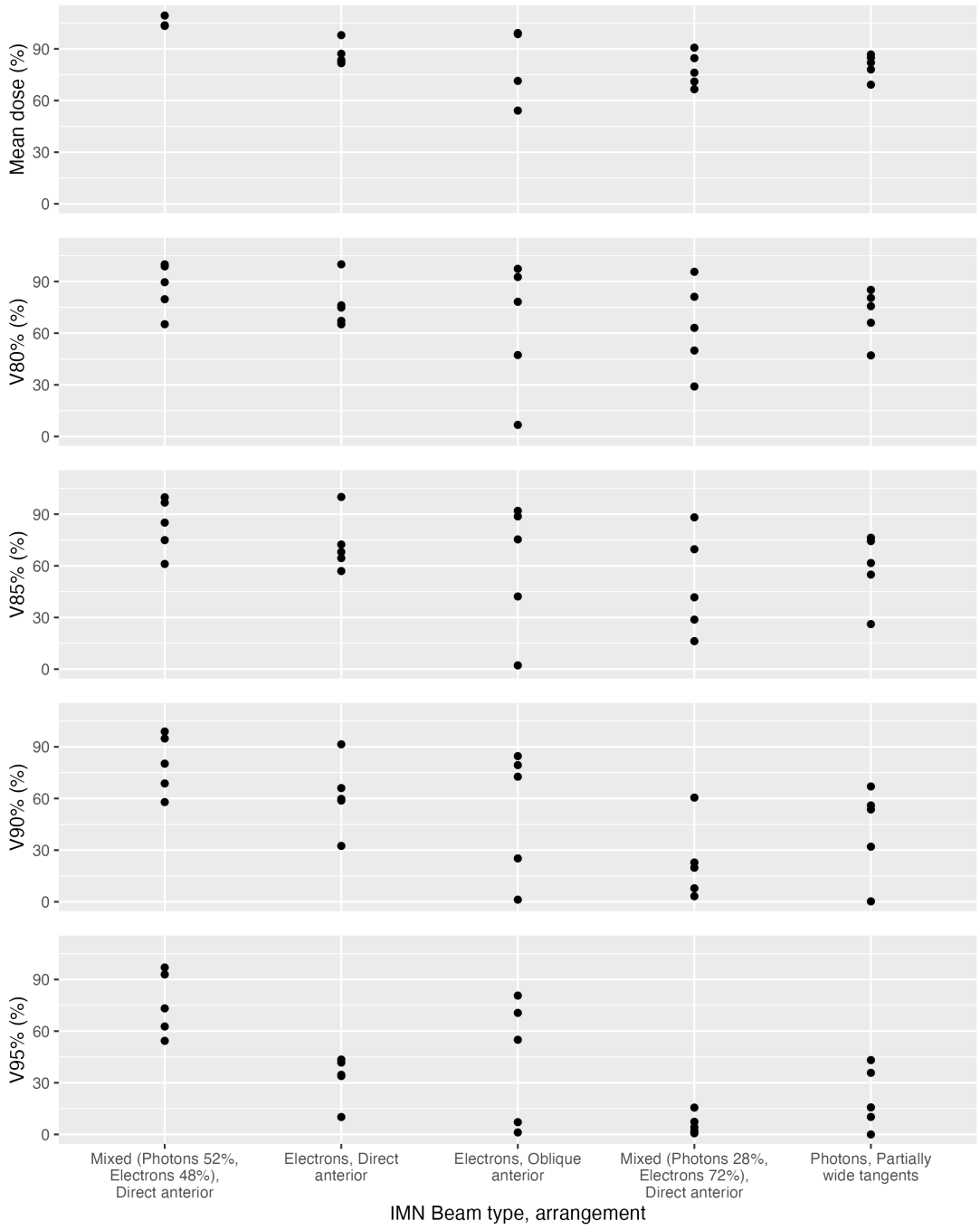


Figure A.8: Inter-patient variability in doses received by ESTRO internal mammary lymph node clinical target volumes from right breast cancer radiotherapy, from five randomly selected patients

Regimens represent the five most commonly used regimen categories for right breast cancer in eight trials of regional lymph node radiotherapy, starting 1989-2008, included in the EBCTCG 2023 meta-analysis.

Each data point represents a measure taken from one of five randomly selected patient CT scans.

Data are presented in Table A.14.

Abbreviations: Vx%=Volume receiving at least x% of the total prescribed dose, ESTRO=European Society of Therapeutic Radiology and Oncology.

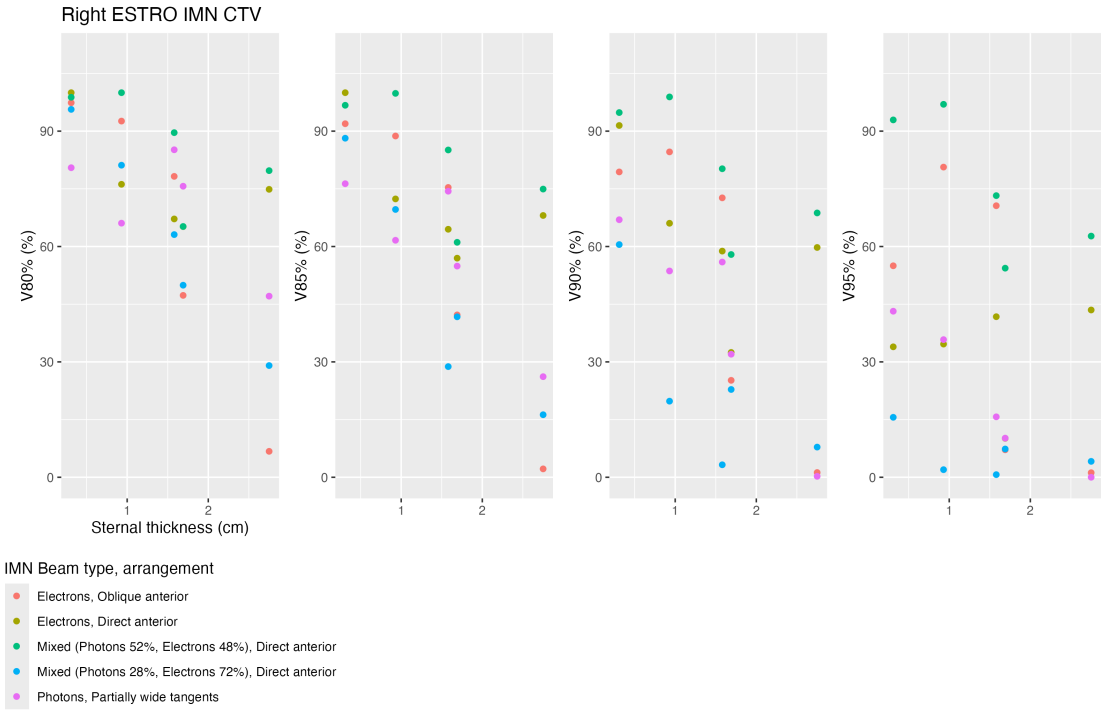


Figure A.9: Inter-regimen variability in doses received by ESTRO internal mammary lymph node clinical target volumes from five most commonly used internal mammary regimens for right breast cancer used in six trials starting 1989-2008
Dose data from each of five patient CT scans are arranged by sternal thickness. (See Table A.14)
Each of the five patient CT scans had five radiotherapy regimens reconstructions applied. Therefore inter-patient variation in dose distribution is represented by the spread of data points within a column.
Inter-regimen variation in dose distribution is represented by colour.
Variation in dose distribution also varies according to the dose-volume metric selected and this can be visualised by comparing the different panels.
Abbreviations: CTV=clinical target volume, ESTRO=European Society of Therapeutic Radiology and Oncology, IMN=internal mammary lymph node, Vx%=volume receiving at least x% of the total prescribed dose.

A.10 Average dose metrics for ESTRO lymph node clinical target volumes from each category of internal mammary lymph node radiotherapy regimen described in eight trials of regional lymph node radiotherapy starting 1989-2008

A.10.1 ESTRO L1 lymph node clinical target volume

Table A.15: Average dose metrics for ESTRO L1 lymph node clinical target volume from each category of internal mammary lymph node radiotherapy regimen described in eight trials of regional lymph node radiotherapy starting 1989-2008

IMN beam type, arrangement	**Pts**	**Average metrics (%) for ipsi. ESTRO L1 CTV**				
		Mean	**V80%**	**V85%**	**V90%**	**V95%**
Photons, Partially wide tangents	1371	76.5	66.0	52.8	29.2	10.3
Mixed (52% Photons, 48% Electrons), Direct anterior	1217	10.4	2.0	1.1	0.4	0.0
Electrons, Direct anterior	1019	88.6	92.0	79.5	54.8	19.3
Mixed (28% Photons, 72% Electrons), Direct anterior	641	49.0	20.7	12.2	9.7	3.7
Electrons, Oblique anterior	265	40.3	25.9	25.4	24.7	23.8
Photons, Wide tangents	131	54.8	43.7	38.4	22.7	10.8
Mixed (20% Photons, 80% Electrons), Oblique anterior	57	13.2	3.1	1.9	0.6	0.0
Mixed (30% Photons, 70% Electrons), Oblique anterior	57	33.9	3.7	1.5	0.5	0.0
ALL	**4758**	**54.6**	**44.7**	**36.7**	**23.6**	**9.2**

Footnotes

Doses and volumes were averaged across all radiotherapy regimens targeting the internal mammary lymph nodes, categorised by internal mammary lymph node beam type and arrangement. They were weighted according to the estimated number of patients that received each regimen.

Abbreviations: CTV=clinical target volume, ESTRO=European Society of Therapeutic Radiology and Oncology, IMN=internal mammary lymph nodes, ipsi.=ipsilateral, L=lymph node level, Pts=patients, Vx%=volume receiving at least x% of the total prescribed dose.

A.10.2 ESTRO L2 lymph node clinical target volume

Table A.16: Average dose metrics for ESTRO L2 lymph node clinical target volume from each category of internal mammary lymph node radiotherapy regimen described in eight trials of regional lymph node radiotherapy starting 1989-2008

IMN beam type, arrangement	**Pts**	**Average metrics (%) for ipsi. ESTRO L2 CTV**				
		Mean	**V80%**	**V85%**	**V90%**	**V95%**
Photons, Partially wide tangents	1371	82.0	70.9	39.6	15.4	4.4
Mixed (52% Photons, 48% Electrons), Direct anterior	1217	6.6	0.0	0.0	0.0	0.0
Electrons, Direct anterior	1019	68.5	57.5	43.9	11.5	0.4
Mixed (28% Photons, 72% Electrons), Direct anterior	641	74.1	38.8	3.3	0.0	0.0
Electrons, Oblique anterior	265	87.9	71.4	70.4	69.4	68.0
Photons, Wide tangents	131	18.5	11.1	8.7	1.9	0.0
Mixed (20% Photons, 80% Electrons), Oblique anterior	57	6.8	0.0	0.0	0.0	0.0
Mixed (30% Photons, 70% Electrons), Oblique anterior	57	26.4	0.6	0.4	0.3	0.2
ALL	**4758**	**55.8**	**42.3**	**25.4**	**10.8**	**5.1**

Footnotes

Doses and volumes were averaged across all radiotherapy regimens targeting the internal mammary lymph nodes, categorised by internal mammary lymph node beam type and arrangement. They were weighted according to the estimated number of patients that received each regimen.

Abbreviations: CTV=clinical target volume, ESTRO=European Society of Therapeutic Radiology and Oncology, IMN=internal mammary lymph nodes, ipsi.=ipsilateral, L=lymph node level, Pts=patients, Vx%=volume receiving at least x% of the total prescribed dose.

A.10.3 ESTRO L3 lymph node clinical target volume

Table A.17: Average dose metrics for ESTRO L3 lymph node clinical target volume from each category of internal mammary lymph node radiotherapy regimen described in eight trials of regional lymph node radiotherapy starting 1989-2008

IMN beam type, arrangement	**Pts**	**Average metrics (%) for ipsi. ESTRO L3 CTV**				
		Mean	**V80%**	**V85%**	**V90%**	**V95%**
Photons, Partially wide tangents	1371	93.0	99.4	89.3	66.4	35.9
Mixed (52% Photons, 48% Electrons), Direct anterior	1217	68.8	57.3	52.5	45.8	33.0
Electrons, Direct anterior	1019	98.0	96.1	95.6	86.9	66.3
Mixed (28% Photons, 72% Electrons), Direct anterior	641	85.0	89.8	51.6	7.1	0.2
Electrons, Oblique anterior	265	133.0	100.0	100.0	100.0	100.0
Photons, Wide tangents	131	3.3	0.0	0.0	0.0	0.0
Mixed (20% Photons, 80% Electrons), Oblique anterior	57	68.3	46.3	40.4	31.6	22.4
Mixed (30% Photons, 70% Electrons), Oblique anterior	57	214.1	59.1	54.1	46.7	39.2
ALL	**4758**	**87.7**	**82.8**	**73.3**	**56.9**	**39.3**

Footnotes

Doses and volumes were averaged across all radiotherapy regimens targeting the internal mammary lymph nodes, categorised by internal mammary lymph node beam type and arrangement. They were weighted according to the estimated number of patients that received each regimen.

Abbreviations: CTV=clinical target volume, ESTRO=European Society of Therapeutic Radiology and Oncology, IMN=internal mammary lymph nodes, ipsi.=ipsilateral, L=lymph node level, Pts=patients, Vx%=volume receiving at least x% of the total prescribed dose.

A.10.4 ESTRO L4 lymph node clinical target volume

Table A.18: Average dose metrics for ESTRO L4 lymph node clinical target volume from each category of internal mammary lymph node radiotherapy regimen described in eight trials of regional lymph node radiotherapy starting 1989-2008

IMN beam type, arrangement	**Pts**	**Average metrics (%) for ipsi. ESTRO L4 CTV**				
		Mean	**V80%**	**V85%**	**V90%**	**V95%**
Photons, Partially wide tangents	1371	85.1	86.7	78.5	55.6	28.4
Mixed (52% Photons, 48% Electrons), Direct anterior	1217	96.3	99.1	97.4	90.2	63.7
Electrons, Direct anterior	1019	98.5	96.7	95.9	93.0	79.7
Mixed (28% Photons, 72% Electrons), Direct anterior	641	84.8	89.2	43.6	12.6	0.0
Electrons, Oblique anterior	265	128.0	100.0	100.0	100.0	100.0
Photons, Wide tangents	131	1.9	0.0	0.0	0.0	0.0
Mixed (20% Photons, 80% Electrons), Oblique anterior	57	123.1	99.8	97.2	85.7	56.1
Mixed (30% Photons, 70% Electrons), Oblique anterior	57	477.3	99.8	97.8	89.3	66.5
ALL	**4758**	**96.0**	**91.0**	**81.8**	**68.4**	**48.6**

Footnotes

Doses and volumes were averaged across all radiotherapy regimens targeting the internal mammary lymph nodes, categorised by internal mammary lymph node beam type and arrangement. They were weighted according to the estimated number of patients that received each regimen.

Abbreviations: CTV=clinical target volume, ESTRO=European Society of Therapeutic Radiology and Oncology, IMN=internal mammary lymph nodes, ipsi.=ipsilateral, L=lymph node level, Pts=patients, Vx%=volume receiving at least x% of the total prescribed dose.

Appendix B

Supplementary material for Chapter 3: Estimated doses received by the heart, lungs, oesophagus and risks from typical UK radiotherapy for early breast cancer during 2015-2023.

B.1 Literature searches

Terms used in searching Ovid MEDLINE (1 January 2015 to 12 June 2023)

1. exp Breast Neoplasms/rt [Radiotherapy]
2. exp Breast Neoplasms/
3. (breast adj2 (cancer? or neoplas* or tumo?r? or carcinoma? or malignan*)).ti,ab,kf.
4. 2 or 3
5. exp Radiotherapy/
6. (radiotherap* or radiation therap*).ti,ab,kf.
7. external beam radiation.ti,ab,kf.
8. irradiat*.ti,ab,kf.
9. brachytherap*.ti,ab,kf.
10. (proton adj2 therap*).ti,ab,kf.
11. 5 or 6 or 7 or 9 or 9 or 10
12. 4 and 11
13. 1 or 12
14. radiation dosage/ or dose-response relationship, radiation/
15. (dose? or dosage? or dosimetr*).ti,ab,kf.
16. 14 or 15
17. exp United Kingdom/
18. (national health service* or nhs*).ti,ab,in.
19. (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.

20. (gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.

21. (bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's " or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.

22. (aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.

23. (armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.

24. (bath or "bath's" or ((Birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachuse tts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.

25. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24

26. (exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp oceania/) not (exp great britain/ or europe/)

27. 25 not 26

28. 13 and 16 and 27

29. limit 28 to yr="2015 -Current"

30. exp animals/ not humans/

31. 29 not 30

Terms used in searching Embase (1 January 2015 to 12 June 2023)

1. *breast cancer/rt or *breast radiotherapy/
2. exp *breast cancer/
3. (breast adj2 (cancer? or neoplas* or tumo?r? or carcinoma? or malignan*)).ti,ab,kf.
4. 2 or 3
5. *cancer radiotherapy/ or *adjuvant radiotherapy/ or *irradiation/
6. (radiotherap* or radiation therap*).ti,ab,kf.
7. external beam radiation.ti,ab,kf.
8. irradiat*.ti,ab,kf.
9. brachytherap*.ti,ab,kf.
10. (proton adj2 therap*).ti,ab,kf.
11. 5 or 6 or 7 or 8 or 9 or 10
12. 4 and 11
13. 1 or 12
14. radiation depth dose/ or radiation dose escalation/ or exp radiation dose fractionation/ or radiation dose reduction/ or exp radiotherapy dosage/
15. (dose or dosage? or dosing or dosimetr*).ti,ab,kf.
16. 14 or 15
17. 13 and 16
18. exp United Kingdom/
19. (national health service* or nhs*).ti,ab,in.
20. (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.

21. (gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.

22. (bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's " or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.

23. (aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.

24. (armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.

25. (bath or "bath's" or ((Birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachuse tts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.

26. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25

27. (exp africa/ or exp asia/ or exp Pacific Islands/ or "Australia and New Zealand"/ or "arctic and antarctic"/ or exp north america/ or exp "south and central america"/) not (exp United Kingdom/ or Europe/)

28. 26 not 27

29. 17 and 28

30. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/

31. Animal experiment/ not (human experiment/ or human/)

32. 30 or 31

33. 29 not 32

34. limit 33 to yr="2015 -Current"

35. conference*.pt. or conference abstract/

36. 34 not 35

B.2 Category definitions

Study design	
Dosimetry	A study in which radiotherapy plans were simulated for research purposes and planned doses were not delivered to patients.
Dosimetry & Observational	A study including some radiotherapy plans delivered to patients in routine practice and some plans simulated for research.
Observational/ audit	A study retrospectively reporting doses delivered to patients in routine clinical practice.
Interventional	A prospective clinical trial reporting doses delivered to trial patients randomised between different radiotherapy practices.

Treatment planning methods	
3D CRT	3D conformal radiotherapy using multi-CT patient contour slices with shaped fields.
3D CRT FIF	Multiple segments used (field-in-field)
IMRT	Intensity modulated radiotherapy using multi-CT patient contour slices with inverse-planned IMRT (assumes shaped fields and multiple segments as standard).
Hybrid	A combination of 3D CRT ± FIF tangents and inverse planned rotational IMRT.
PBT	Proton beam therapy
Auto.	Plans automatically created by running a computer programme.
MF	Manual flash used within plan to incorporate 'skin flash' in the radiotherapy field apertures. This is usually done by including around 2cm of air surrounding the breast within the field to ensure irradiation of all breast tissue should the target increase in size from the time of the planning CT.
RO-OM	Robust optimisation for organ motion used in creating the radiotherapy plan. This is done by optimising over a range of simulated CTs representing worst-case scenario plan changes. For example, changes in target breast tissue size from the time of planning CT may be simulated by Deformable image Registration based on user-defined organ motion.

Radiotherapy technique	
Tangents	Fixed gantry angles, tangential breast/chest wall fields ± matched direct SF/axilla direct field. This may include tangents, wide tangents, partially wide tangents.
Tangents FIF	Fixed gantry angles, tangential breast/chest wall fields ± matched direct SF/axilla direct field. Multiple segments used (FIF).
IMRT static	Multiple static direct or oblique fields of IMRT (step and shoot).
IMRT rotational	Dynamic fields using a series of arcs, gantry rotates during treatment, using Tomotherapy (helical delivery) or a linear accelerator (e.g. volumetric modulated arc therapy).
IMRT PBS	IMRT Pencil beam scanning proton beam therapy.

Abbreviations: Auto.=automated, 3D-CRT=3 dimensional conformal radiotherapy, FIF=field-in-field, IMRT=intensity modulated radiation therapy, PBT=proton beam therapy, PBS=pencil beam scanning, MF=manual flash, SF=supraclavicular lymph nodes, RO-OM=robust optimisation-organ motion.

B.3 Process of study identification

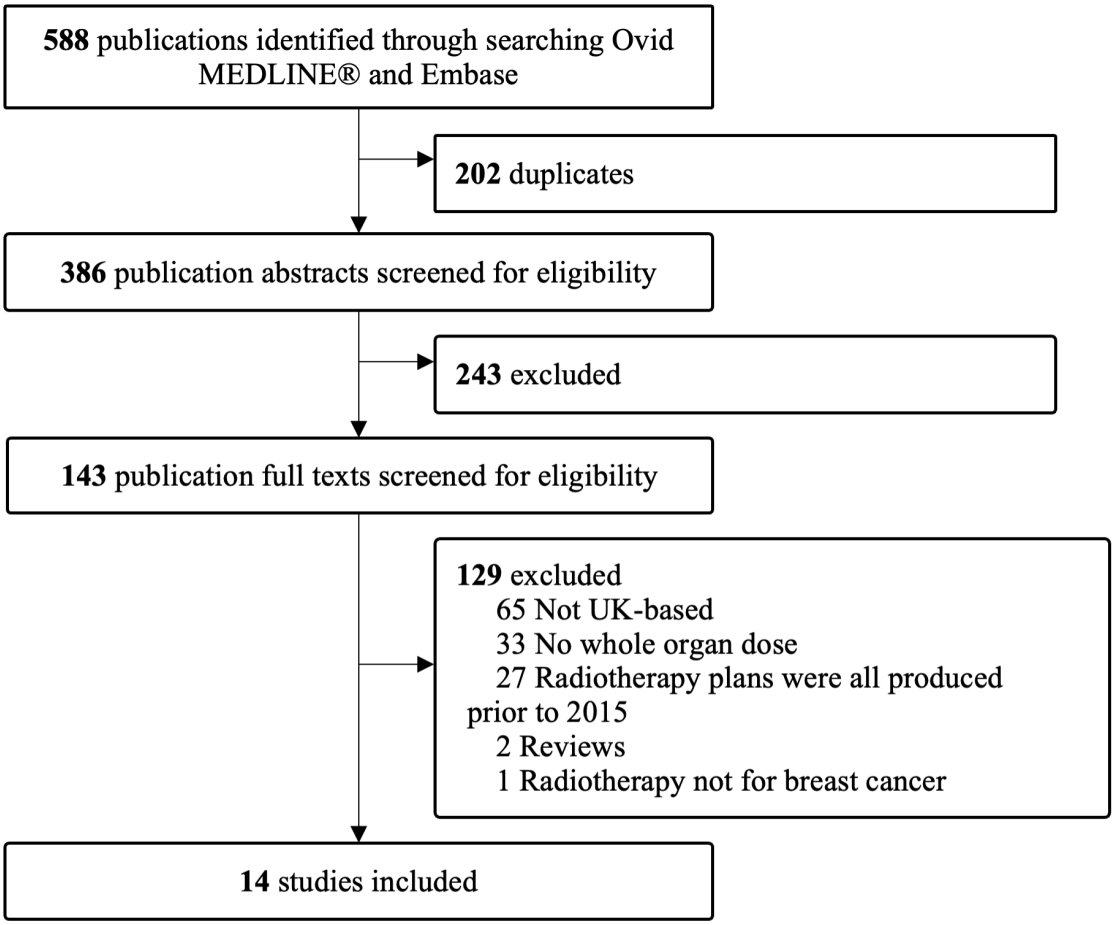


Figure B.1: Process of study identification

B.4 References for included studies

- Coles CE, Haviland JS, Kirby AM, et al. Dose-escalated simultaneous integrated boost radiotherapy in early breast cancer (IMPORT HIGH): a multicentre, phase 3, non-inferiority, open-label, randomised controlled trial. Lancet 2023;401(10394):2124-37.

- Dunlop A, Colgan R, Kirby A, Ranger A, Blasiak-Wal I. Evaluation of organ motion-based robust optimisation for VMAT planning for breast and internal mammary chain radiotherapy. Clin Transl Radiat Oncol 2019;16:60-6.

- Gleeson I. Comparing the robustness of different skin flash approaches using wide tangents, manual flash VMAT, and simulated organ motion robust optimization VMAT in breast and nodal radiotherapy. Med dosim 2022;47(3):264-72.

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- Ledsom D, Reilly AJ, Probst H. Assessment of deep inspiration breath hold (DIBH) amplitude and reduction in cardiac dose in left breast cancer patients. Radiography 2018;24(2):98-103.

- Locke I, Drinkwater K. Implementation of Royal College of Radiologists Consensus Statements and National Institute for Health and Care Excellence Guidance: Breast Radiotherapy Practice in the UK. Clin Oncol

2021;33(7):419-26.

- Mitchell RA, Wai P, Colgan R, Kirby AM, Donovan EM. Improving the efficiency of breast radiotherapy treatment planning using a semi-automated approach. J Appl Clin Med Phys 2017;18(1):18-24.

- Murphy SBD, Drury-Smith H. Which simultaneous-integrated boost (SIB) intensity-modulated radiotherapy (IMRT) technique is dosimetrically superior in the treatment of breast cancer; volumetric-modulated arc therapy (VMAT) or fixed field (ff) IMRT? J Radiother Pract 2017;16(3):272-9.

- Ranger A, Dunlop A, Grimwood A, et al. Voluntary versus ABC breath-hold in the context of VMAT for breast and locoregional lymph node radiotherapy including the internal mammary chain. Clin Transl Radiat Oncol 2021;27:164-8.

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- Ranger A, Dunlop A, Shah P, et al. Evaluation of a Novel Field-placement Algorithm for Locoregional Breast Cancer Radiotherapy Including the Internal Mammary Chain. Clin Oncol 2019; 31(1): 25-33.

- Welgemoed C, Coughlan S, McNaught P, Gujral D, Riddle P. A dosimetric study to improve the quality of nodal radiotherapy in breast cancer. BJR Open 2021;2(1):20210013.

- Wickers S, Thould C, Keeble J, et al. Identifying Surrogates for Heart and Ipsilateral Lung Dose to Guide Field Placement and Treatment Modality Selection during Virtual Simulation of Breast Radiotherapy. Clinical Oncology 2021;33(4):224-9.

B.5 Studies reporting whole heart doses from radiotherapy for early breast cancer published 2015-2023

Table B.1: Studies reporting whole heart doses from radiotherapy for early breast cancer published 2015-2023

Author, yr of publication & study location*	**Study design†**	**Pts**	**CT scans**	**Individual dose estimates‡**	**Individual dose estimates delivered to pts (%)**
Gleeson 2023 Cambridge	Dosimetry & Observational	41	41	82	41 (50)
Coles 2023 Multicentre	Interventional	1958	1958	1958	1958 (100)
Ranger 2022 London	Interventional	19	19	19	19 (100)
Gleeson 2022 Cambridge	Dosimetry & Observational	10	10	40	10 (25)
Wickers 2021 London	Dosimetry & Observational	59	59	59	50 (85)
Locke 2021 Multicentre	Observational/ Audit	355	355	355	355 (100)
Ranger 2021 London	Interventional	16	32	32	32 (100)
Dunlop 2019 London	Dosimetry	5	5	10	0 (0)
Ranger 2019 Unspecified	Dosimetry	20	20	40	0 (0)
Ranger 2018 Multicentre	Dosimetry	14	14	98	0 (0)
Ledsom 2018 Liverpool	Dosimetry	30	60	60	0 (0)
Murphy 2017 Unspecified	Dosimetry	30	30	60	0 (0)
Mitchell 2017 London	Dosimetry & Observational	40	40	80	40 (50)
ALL STUDIES		**2597**	**2643**	**2893**	**2505 (87)**

Footnotes

Years during which each study was conducted were available for four of the thirteen studies: Coles 2023 was conducted 2009-2015, Ranger 2022 was conducted 2017-2018, Wickers 2021 was completed in 2020 and Locke 2021 was completed in 2019.

†See Appendix B.2 for definitions.

‡This refers to the number of individual dose estimates contributing to each reported average dose. In some studies patients had more than one CT planning scan, and more than one radiotherapy plan may have been applied to each CT planning scan. Doses to all organs at risk were not always estimated from all plans.

There was no published information within included studies on the number of patients with unusual anatomy.

Abbreviations: CT=computed tomography, Pts=patients, yr=year.

B.6 Mean whole heart doses (Gy) and radiotherapy descriptions from thirteen UK breast cancer radiotherapy studies published during 2015-2023

Table B.2: Mean whole heart doses (Gy) and radiotherapy descriptions from thirteen UK breast cancer radiotherapy studies published during 2015-2023

Publication author & yr*	Location	Description of radiotherapy									No. dose estimates¶	Whole heart dose (Gy)#		
		Treatment planning†	Radiotherapy technique†	Beam energy (MV)‡	Breath control	R or L	Clinical targets irradiated§	Target dose (Gy)	Fr.	Boost		Mean or median	SD	Range
Coles 2023	Multicentre	IMRT/3D CRT	IMRT static	4-15	DIBH/FB	L	Br + Ax/SF	56	23	Seq.	316	2.4	NS	NS
		IMRT/3D CRT	IMRT static	4-15	DIBH/FB	R	Br + Ax/SF	56	23	Seq.	316	1.0	NS	NS
		IMRT	IMRT static	4-15	DIBH/FB	L	Br + Ax/SF	48	15	Sim.	319	2.7	NS	NS
		IMRT	IMRT static	4-15	DIBH/FB	R	Br + Ax/SF	48	15	Sim.	340	1.3	NS	NS
		IMRT	IMRT static	4-15	DIBH/FB	L	Br + Ax/SF	53	15	Sim.	340	2.9	NS	NS
		IMRT	IMRT static	4-15	DIBH/FB	R	Br + Ax/SF	53	15	Sim.	327	1.4	NS	NS
Dunlop 2019	London	IMRT	IMRT rotational	6	DIBH, V	L	Br ± Ax/SF + IMN	40	15	NS	5	3.9	NS	NS
		IMRT, RO	IMRT rotational	6	DIBH, V	L	Br ± Ax/SF + IMN	40	15	NS	5	3.8	NS	NS
Gleeson 2022	Cambridge	IMRT	IMRT static	6-10	DIBH	L/R	Br/CW ± Ax/SF + IMN	40	15	NS	10	1.2	0.3	NS
		IMRT	IMRT rotational	6	DIBH	L/R	Br/CW ± Ax/SF + IMN	40	15	NS	10	2.0	0.7	NS
		IMRT, MF	IMRT rotational	6	DIBH	L/R	Br/CW ± Ax/SF + IMN	40	15	NS	10	2.0	0.7	NS
		IMRT, RO	IMRT rotational	6	DIBH	L/R	Br/CW ± Ax/SF + IMN	40	15	NS	10	2.0	0.7	NS
Gleeson 2023	Cambridge	Hybrid	IMRT rotational	6	DIBH/FB	L/R	Br only	48	15	Sim.	21	0.9	0.6	0.2-2.8
		Hybrid, automated	IMRT rotational	6	DIBH/FB	L/R	Br only	48	15	Sim.	21	0.9	0.6	0.2-2.5
		IMRT	IMRT rotational	6	DIBH/FB	L/R	Br ± Ax/SF + IMN	40	15	No boost	20	2.8	0.6	1.6-3.9
		IMRT, automated	IMRT rotational	6	DIBH/FB	L/R	Br ± Ax/SF + IMN	40	15	No boost	20	3.0	0.4	2.2-3.7

Continued on next page.

Table B.2 Mean whole heart doses (Gy) and radiotherapy descriptions from thirteen UK breast cancer radiotherapy studies published during 2015-2023 *continued.*

Publication author & yr*	Location	Description of radiotherapy									No. dose estimates¶	Whole heart dose (Gy)#		
		Treatment planning†	Radiotherapy technique†	Beam energy (MV)‡	Breath control	R or L	Clinical targets irradiated§	Target dose (Gy)	Fr.	Boost		Mean or median	SD	Range
Ledsom 2018	Liverpool	3D CRT FIF	Tangents FIF	6-10	FB	L	Br + SF	40	15	NS	30	3.4	NS	1.8-5.6
		3D CRT FIF	Tangents FIF	6-10	DIBH, V	L	Br + SF	40	15	NS	30	1.3	NS	0.6-2.2
Locke 2021	Multicentre	NS	NS	NS	DIBH/FB	L	NS	NS	NS	NS	355	1.2	NS	-8.72
Mitchell 2017	London	IMRT	IMRT static	6-10	NS	L/R	Br + SF	40	15	NS	40	0.8	NS	0.3-2.4
		IMRT, automated	IMRT static	6-10	NS	L/R	Br + SF	40	15	NS	40	0.8	NS	0.3-2.5
Murphy 2017	NS	Hybrid	IMRT rotational	NS	DIBH, V/FB	L	Br only	48	15	Sim.	15	1.4	0.4	NS
		Hybrid	IMRT rotational	NS	DIBH, V/FB	R	Br only	48	15	Sim.	15	0.9	0.2	NS
		IMRT	IMRT static	NS	DIBH, V/FB	L	Br only	48	15	Sim.	15	1.5	0.5	NS
		IMRT	IMRT static	NS	DIBH, V/FB	R	Br only	48	15	Sim.	15	1.0	0.3	NS
Ranger 2018	Multicentre	3D CRT FIF	Tangents FIF	6-10	DIBH, V	L	Br/CW ± Ax/SF + IMN	40	15	NS	14	2.5	1.2	NS
		3D CRT FIF	Tangents FIF	6-10	FB	L	Br/CW ± Ax/SF + IMN	40	15	NS	14	5.3	1.0	NS
		IMRT	IMRT rotational	NS	DIBH, V	L	Br/CW ± Ax/SF + IMN	40	15	NS	14	2.6	1.0	NS
		IMRT	IMRT rotational	NS	FB	L	Br/CW ± Ax/SF + IMN	40	15	NS	14	4.5	1.3	NS
		IMRT	IMRT rotational	NS	FB	L	Br/CW ± Ax/SF + IMN	40	15	NS	14	6.4	1.4	NS
		PBT	IMRT PBS	Proton NS	DIBH, V	L	Br/CW ± Ax/SF + IMN	40	15	NS	14	0.5	0.1	NS
		PBT	IMRT PBS	Proton NS	FB	L	Br/CW ± Ax/SF + IMN	40	15	NS	14	1.0	0.1	NS

Continued on next page.

Table B.2 Mean whole heart doses (Gy) and radiotherapy descriptions from thirteen UK breast cancer radiotherapy studies published during 2015-2023 *continued.*

Publication author & yr*	Location	Description of radiotherapy								No. dose estimates¶	Whole heart dose (Gy)#		
		Treatment planning†	Radiotherapy technique†	Beam energy (MV)‡	Breath control	R or L	Clinical targets irradiated§	Target dose (Gy)	Fr.	Boost		Mean or median	SD	Range
Ranger 2019	NS	3D CRT	Tangents	6-10	DIBH, V	L	Br/CW ± Ax/SF + IMN	40	NS	NS	20	1.5	NS	1.3-4.6
		3D CRT	Tangents	6-10	DIBH, V	L	Br/CW ± Ax/SF + IMN	40	NS	NS	20	1.8	NS	1.4-4.2
Ranger 2021	London	IMRT	IMRT rotational	NS	DIBH, V	L/R	Br/CW ± Ax/SF + IMN	NS	15	NS	16	4.2	1.3	NS
		IMRT	IMRT rotational	NS	DIBH, ABC	L/R	Br/CW ± Ax/SF + IMN	NS	15	NS	16	4.4	1.3	NS
Ranger 2022	London	3D CRT FIF	Tangents FIF	6-10	DIBH,V	L	Br/CW ± Ax/SF + IMN	40	15	NS	9	2.6	1.2	NS
		IMRT	IMRT rotational	NS	DIBH, V/FB	L	Br/CW ± Ax/SF + IMN	40	15	NS	10	3.6	0.7	NS
Wickers 2021	London	3D CRT FIF	Tangents FIF	6-10	FB	L	Br/CW only	40	15	NS	50	2.3	NS	1.2-8.0
		3D CRT FIF	Tangents FIF	6-10	DIBH	L	Br/CW + SF	40	15	NS	5	2.6	NS	1.4-4.0
		3D CRT FIF	Tangents FIF	6-10	DIBH	L	Br/CW ± Ax/SF + IMN	40	15	NS	4	2.0	NS	1.5-4.7

Footnotes

Thirteen of the fourteen studies included in the review reported whole heart doses.

Average mean whole heart doses across all studies and subgroups of studies were weighted by the number of individual dose estimates contributing to the study mean doses.

See Appendix B.4 for references.

†See Appendix B.2 for definitions.

Where specified, all patients were planned in the supine position. Six studies did not specify patient position (Murphy 2017, Mitchell 2017, Ledsom 2018, Ranger 2019, Dunlop 2019, Locke 2021).

‡PBT uses proton beams, all other planning types specified the use of photons. Only one study did not specify radiotherapy beam type (Locke 2021).

§ When analysing dose by clinical targets irradiated, it was assumed that if a target was not specified, it was not irradiated. None of the included studies reported radiotherapy to the following targets: partial breast, breast reconstructions with prosthesis. One study (Ranger 2018) specified inclusion of three patients with autologous breast reconstruction.

¶This refers to the number of individual dose estimates contributing to each published mean dose. It was reported in all studies, with the exception of Coles 2023. For this study, the numbers of individual patients for whom dosimetry information was reported within each trial group were 632, 659 and 667. Of these patients, the numbers who received radiotherapy for left and right breast cancer were unavailable and therefore estimated by applying the percentage of patients with right and left breast cancers in each of the three trial groups to the numbers of patients with available dosimetry information.

#Details of heart contouring guidelines used to delineate organs at risk were published by Coles 2023, Gleeson 2023 and Ledsom 2018. All three studies stated the heart contour inferiorly extends to above the diaphragm, and superiorly extends to below the pulmonary arch.

Abbreviations: ABC=active breathing control, Ax=axilla lymph nodes, Br=breast, CW=chest wall, DIBH=deep inspiratory breath hold, FB=free breathing, Fr.=fraction, Gy=gray, IMN=internal mammary lymph nodes, L=left radiotherapy, MF=manual flash, MV=megavoltage, No.=number, PBS=pencil beam scanning, R=right radiotherapy, RO=robust optimisation, SD=standard deviation, Seq.=sequential, SF=supraclavicular fossa lymph nodes, Sim.=simultaneous, V=voluntary, NS=not specified, yr=year.

B.7 Studies reporting ipsilateral and contralateral lung doses from radiotherapy for early breast cancer published during 2015-2023

Table B.3: Studies reporting ipsilateral and contralateral lung doses doses from radiotherapy for early breast cancer published 2015-2023

Author, yr of publication & study location*	**Study design†**	**Pts**	**CT scans**	**Individual dose estimates‡**	**Individual dose estimates delivered to pts (%)**
Gleeson 2023 Cambridge	Dosimetry & Observational	41	41	82	41 (50)
Coles 2023 Multicentre	Interventional	1958	1958	1958	1958 (100)
Gleeson 2022 Cambridge	Dosimetry & Observational	10	10	40	10 (25)
Dunlop 2019 London	Dosimetry	5	5	10	0 (0)
Murphy 2017 Unspecified	Dosimetry	30	30	60	0 (0)
Mitchell 2017 London	Dosimetry & Observational	40	40	80	40 (50)
ALL STUDIES		**2084**	**2084**	**2230**	**2049 (92)**

Footnotes

Years during which the study was conducted was available for one of the six studies: Coles 2023 was conducted 2009-2015.

†See Appendix B.2 for definitions.

‡This refers to the number of individual dose estimates contributing to each reported average dose. In some studies patients had more than one CT planning scan, and more than one radiotherapy plan may have been applied to each CT planning scan. Doses to all organs at risk were not always estimated from all plans.

There was no published information within included studies on the number of patients with unusual anatomy.

Abbreviations: CT=computed tomography, pts=patients, yr=year.

B.8 Estimated mean whole lung doses (Gy) and radiotherapy descriptions from six UK breast cancer radiotherapy studies published during 2015-2023

Table B.4: Mean whole lung doses (Gy) and radiotherapy descriptions from six UK breast cancer radiotherapy studies published during 2015-2023

		Description of radiotherapy										Lung dose (Gy)#							
												Ipsilateral			Contralateral			Whole¶	
Publication author & yr*	Location	Treatment planning†	Radiotherapy technique†	Beam energy (MV)‡	Breath control	R or L	Clinical targets irradiated§	Target dose (Gy)	Fr.	Boost	No. dose est.¶	Mean /med.	SD	Range	Mean /med.	SD	Range	Mean /med.	Range
Coles 2023	Multi centre	IMRT/3D CRT	IMRT static	4-15	DIBH/FB	L/R	Br + Ax/SF	56	23	Seq.	632	5.2	NS	NS	0.4	NS	NS	2.8	NS
		IMRT	IMRT static	4-15	DIBH/FB	L/R	Br + Ax/SF	48	15	Sim.	659	5.4	NS	NS	0.5	NS	NS	3.0	NS
		IMRT	IMRT static	4-15	DIBH/FB	L/R	Br + Ax/SF	53	15	Sim.	667	5.7	NS	NS	0.6	NS	NS	3.2	NS
Dunlop 2019	London	IMRT	IMRT rotational	6	DIBH, V	L	Br ± Ax/SF + IMN	40	15	NS	5	13.6	NS	NS	3.3	NS	NS	8.5	NS
		IMRT, RO	IMRT rotational	6	DIBH, V	L	Br ± Ax/SF + IMN	40	15	NS	5	13.6	NS	NS	3.3	NS	NS	8.5	NS
Gleeson 2022	Cambridge	IMRT	IMRT static	6-10	DIBH	L/R	Br/CW ± Ax/SF + IMN	40	15	NS	10	10.0	1.7	NS	0.6	0.0	NS	5.3	NS
		IMRT	IMRT rotational	6	DIBH	L/R	Br/CW ± Ax/SF + IMN	40	15	NS	10	12.1	0.6	NS	1.0	0.2	NS	6.6	NS
		IMRT, MF	IMRT rotational	6	DIBH	L/R	Br/CW ± Ax/SF + IMN	40	15	NS	10	12.2	0.6	NS	1.0	0.2	NS	6.6	NS
		IMRT, RO	IMRT rotational	6	DIBH	L/R	Br/CW ± Ax/SF + IMN	40	15	NS	10	12.6	0.3	NS	1.3	1.0	NS	7.0	NS
Gleeson 2023	Cambridge	Hybrid	IMRT rotational	6	DIBH/FB	L/R	Br only	48	15	Sim.	21	3.7	0.6	2.8-5.4	0.3	0.1	0.1-0.6	2.0	1.5-3.0
		Hybrid, auto.	IMRT rotational	6	DIBH/FB	L/R	Br only	48	15	Sim.	21	3.7	0.6	2.7-5.2	0.3	0.1	0.1-0.6	2.0	1.4-2.9
		IMRT	IMRT rotational	6	DIBH/FB	L/R	Br ± Ax/SF + IMN	40	15	No boost	20	13.5	1.1	12.4-16.4	1.2	0.3	0.9-2.2	7.4	6.7-9.3
		IMRT, auto.	IMRT rotational	6	DIBH/FB	L/R	Br ± Ax/SF + IMN	40	15	No boost	20	13.9	1.6	12.3-18.3	1.2	0.1	1.1-1.6	7.6	6.7-10.0
Mitchell 2017	London	IMRT	IMRT static	6-10	NS	L/R	Br ±SF	40	15	NS	40	4.5	NS	1.7-9.7	0.2	NS	0.1-0.4	2.4	0.9-5.1
		IMRT, auto.	IMRT static	6-10	NS	L/R	Br ±SF	40	15	NS	40	4.6	NS	1.7-9.7	0.2	NS	0.1-0.4	2.4	0.9-5.1
Murphy 2017	NS	Hybrid	IMRT rotational	NS	DIBH, V/FB	L/R	Br only	48	15	Sim.	30	5.5	0.9	NS	0.5	0.1	NS	3.0	NS
		IMRT	IMRT static	NS	DIBH, V/FB	L/R	Br only	48	15	Sim.	30	5.4	0.8	NS	0.5	0.1	NS	3.0	NS

Footnotes

Six of the fourteen studies included in the review reported ipsilateral and contralateral lung doses.

Average mean whole lung doses across all studies and subgroups of studies were weighted by the number of individual dose estimates contributing to study mean doses.

See Appendix B.4 for references.

†See Appeddix B.2 for definitions.

Where specified, all patients were planned in the supine position. Three studies did not specify patient position (Murphy 2017, Mitchell 2017, Dunlop 2019).

‡When analysing dose by clinical targets irradiated, it was assumed that if a target was not specified, it was not irradiated. None of the included studies reported radiotherapy to the following targets: partial breast, breast reconstructions.

§ This refers to the number of individual dose estimates contributing to each published mean dose.

¶Whole lung dose was estimated by taking the average of the reported mean ipsilateral and contralateral lung doses. There were no published details of contouring guidelines used to delineate the lungs. One study described using auto-contouring to delineate the lungs (Mitchell 2017).

Abbreviations: auto.=automated, Ax=axilla lymph nodes, Br=breast, CW=chest wall, DIBH=deep inspiratory breath hold, est.=estimates, FB=free breathing, Gy=gray, IM=internal mammary lymph nodes, L=left radiotherapy, med.=median, MF=manual flash, MV=megavoltage, R=right radiotherapy, RO=robust optimisation, SD=standard deviation, Seq.=sequential, SF=supraclavicular fossa lymph nodes, Sim.=simultaneous, V=voluntary, NS=not specified.

B.9 Studies reporting whole oesophagus doses from radiotherapy for early breast cancer published during 2015-2023

Table B.5: Studies reporting whole oesophagus doses from radiotherapy for early breast cancer published 2015-2023

Author, yr of publication & study location*	**Study design†**	**Pts**	**CT scans**	**Individual dose estimates‡**	**Individual dose estimates delivered to pts (%)**
Gleeson 2023 Cambridge	Dosimetry & Observational	20	20	40	20 (50)
Welgemoed 2021 London	Dosimetry	12	12	36	0 (0)
ALL STUDIES		**32**	**32**	**76**	**20 (26)**

Footnotes

Years during which studies were conducted were unspecified for both studies.

†See Appendix B.2 for definitions.

‡This refers to the number of individual dose estimates contributing to each reported average dose. In some studies patients had more than one CT planning scan, and more than one radiotherapy plan may have been applied to each CT planning scan. Doses to all organs at risk were not always estimated from all plans.

There was no published information within included studies on the number of patients with unusual anatomy.

Abbreviations: CT=computed tomography, pts=patients, yr=year.

B.10 Mean whole oesophagus doses (Gy) and radiotherapy descriptions from two UK breast cancer radiotherapy studies published during 2015-2023

Table B.6: Mean whole oesophagus doses (Gy) and radiotherapy descriptions from two UK breast cancer radiotherapy studies published during 2015-2023

Publication author & yr*	Location	Description of radiotherapy									No. dose estimates¶	Whole oesophagus dose (Gy)#		
		Treatment planning†	Radiotherapy technique†	Beam energy (MV)‡	Breath control	R or L	Clinical targets irradiated§	Target dose (Gy)	Fr.	Boost		Mean or median	SD	Range
Gleeson 2023	Cambridge	IMRT	IMRT rotational	6	DIBH/FB	L/R	Br ± Ax/SF + IMN	40	15	No	20	5.4	2.0	1.9-10.0
		IMRT, auto.	IMRT rotational	6	DIBH/FB	L/R	Br ± Ax/SF + IMN	40	15	No	20	6.1	1.8	2.4-9.7
Welgemoed 2021	London	3D CRT FIF	Tangents FIF	6-10	NS	NS	Br/CW + Ax/SF	40	15	NS	12	1.2	0.3	NS
		3D CRT FIF	Tangents FIF	6-10	NS	NS	Br/CW + Ax/SF	40	15	NS	12	2.0	2.0	NS
		3D CRT FIF	Tangents FIF	6-10	NS	NS	Br/CW + Ax/SF	40	15	NS	12	1.0	0.4	NS

Footnotes

Two of fourteen studies included in the review reported doses to the whole oesophagus.

Average mean whole oesophagus doses across all studies and subgroups of studies were weighted by the number of individual dose estimates contributing to study mean doses.

Mean whole oesophagus doses included some radiotherapy plans for left and some for right cancers in one study (Gleeson 2023). The other study did not specify laterality of radiotherapy (Welgemoed 2021).

See Appendix B.4 for references.

†See Appendix B.2 for definitions.

All patients were planned in the supine position.

‡ When analysing dose by clinical targets irradiated, it was assumed that if a target was not specified, it was not irradiated. None of the included studies reported radiotherapy to the following targets: partial breast, breast reconstructions.

§This refers to the number of individual dose estimates contributing to each published mean dose.

¶There were no published details of contouring guidelines used to delineate the oesophagus.

Abbreviations: auto.=automated, Ax=axilla lymph nodes, Br=breast, CW=chest wall, DIBH=deep inspiratory breath hold, FB=free breathing, Gy=gray, IMN=internal mammary lymph nodes, L=left radiotherapy, MV=megavoltage, R=right radiotherapy, SD=standard deviation, SF=supraclavicular fossa lymph nodes, V=voluntary, NS=not specified.

B.11 Estimated radiation doses to heart, lungs and oesophagus from breast cancer radiotherapy in the Oxford Cancer Centre, 2018

B.11.1 Introduction

Estimated typical organ doses from modern UK breast cancer radiotherapy using published data may not represent routine clinical practice. Published dosimetry and interventional studies may report lower doses to organs than those delivered in routine clinical practice because the radiotherapy in such studies may use more advanced radiotherapy techniques than those available routinely. Even centres publishing routinely-collected observational/audit data may report lower doses than typical because these centres may be more engaged with practices to minimise organ doses. The extent to which our average published organ doses represent routine clinical practice is uncertain.

Here we present whole organ doses to the heart, lungs and oesophagus from 50 patients irradiated for early breast cancer at the Oxford Cancer Centre during 2018, outside of the setting of any clinical study. We then compare these with summary doses from published studies during 2015-2023.

B.11.2 Methods

Data analysis methods used to estimate typical doses from modern UK breast cancer radiotherapy using published doses were repeated using individual patient

data obtained from an audit conducted at the Oxford Cancer Centre during 2018. The purpose of the audit was to assess compliance with national standards for reducing risks of breast cancer radiotherapy.[1-2] The local research ethics committee at Oxford University Hospitals NHS Foundation Trust approved the audit and it was registered with the local Clinical Audit Lead.

B.11.3 Patient selection

Radiotherapy CT scans and plans were selected from 50 consecutive women on the CT planning database with radiotherapy for early breast cancer at the Oxford Cancer Centre during May and June 2018. They all consented for their data to be used for research.

B.11.4 Contouring organs on CT planning scans

For each patient's radiotherapy CT scan, the heart, lungs and oesophagus were retrospectively reviewed and contoured using published contouring guidelines.[3-4]

B.11.5 Data extraction

From each patient CT radiotherapy plan the following information was extracted: breast cancer laterality, radiotherapy clinical targets irradiated and whole (i.e. mean) doses (Gy) to heart, both lungs combined and oesophagus.

B.11.6 Data analysis

The dose data were anonymised and summarised. Whole organ doses (Gy) were categorised first by breast cancer laterality ("left" or "right"), and then by

clinical targets irradiated ("breast or chest wall only", "breast or chest wall + axilla/supraclavicular fossa lymph nodes", "breast or chest wall ±axilla/supraclavicular fossa + internal mammary lymph nodes"). Typical doses to organs were estimated by calculating the mean whole organ dose for each category of laterality and clinical targets irradiated.

These estimates of mean whole organ doses from 50 patients irradiated for early breast cancer at Oxford Cancer Centre during 2018 were then compared with the average mean whole organ doses from published studies of UK radiotherapy, 2015-2023.

B.11.7 Results

Of the 50 women irradiated for early breast cancer at Oxford Cancer Centre during 2018, 30 (60%) had left and 20 (40%) had right breast cancer. Radiotherapy to the breast or chest wall was received by 35 of the 50 (70%) women. Breast or chest wall + axilla/supraclavicular fossa lymph nodes radiotherapy was received by 14 (28%) of the women (Table B.7). Radiotherapy targeting the internal mammary nodes was received by one (2%) patient with right breast cancer. No patient with left breast cancer received radiotherapy to the internal mammary lymph nodes.

The mean whole heart dose for all 50 women was 1.0Gy (range 0.2-2.9) (Table B.7a). Mean whole heart dose was higher for women with left compared with right breast cancer (left 1.3Gy vs right 0.4Gy). It was slightly higher for women who received radiotherapy that included the supraclavicular fossa or axillary nodes compared with women receiving radiotherapy to the breast or chest wall

only (left: nodes 1.5Gy vs no nodes 1.2Gy, right: nodes 0.5 Gy vs no nodes 0.4Gy). For all combinations of laterality and targets, mean whole heart doses were lower in the audit compared with average mean whole heart doses in the review of published doses.

The mean whole lung dose for all 50 women in the audit was 3.8Gy (range 2.0-6.8) (Table B.7b). For women receiving radiotherapy that included the supraclavicular fossa or axillary nodes, the mean whole lung dose was higher than for women receiving breast or chest wall radiotherapy only (nodes 4.6Gy vs no nodes 3.5Gy). Target-specific average mean whole lung doses in the review of published data were compared with mean whole lung doses in the audit: for breast/chest wall only and for breast or chest wall + axilla/supraclavicular fossa lymph nodes, lung dose was higher in the audit than in the review of published doses (breast/chest wall: audit 3.5Gy, review 2.6Gy; breast or chest wall + axilla/supraclavicular fossa lymph nodes: audit 4.6Gy, review 3.0Gy). Only one patient in the audit received radiotherapy to the internal mammary chain.

For whole oesophagus, the mean dose for all 50 women treated in routine clinical practice was 0.5Gy (range 0.1-2.4) (Table B.7c). For the two target combinations available for comparison, oesophagus dose was lower in the audit than in the review of published doses.

Table B.7: Mean whole organ doses from 50 women irradiated for early breast cancer at the Oxford Cancer Centre during 2018 compared with doses from UK breast cancer radiotherapy studies published during 2015-2023

a. Heart

Clinical targets irradiated	**Whole heart dose (Gy)**					
	Audit			**Review***		
	Individual dose estimates (%)	**Mean**	**Range**	**Individual dose estimates (%)**	**Average mean**	**Range**
Left						
Br/CW only	19 (38)	1.2	0.6-2.6	80 (4)	2.0	1.2-8.0
Br/CW +Ax/SF	11 (22)	1.5	0.8-2.9	1040 (49)	2.7	0.6-5.6
Subtotal (left)	**30 (60)**	**1.3**	**0.6-2.9**	**1120 (53)**	**2.6**	**0.6-8.0**
Right						
Br/CW only	16 (32)	0.4	0.2-0.8	30 (1)	1.0	0.3-1.0
Br/CW +Ax/SF	3 (6)	0.5	0.3-0.7	983 (46)	1.2	1.0-1.4
Br/CW ±Ax/SF +IMN	1 (2)	0.5	–	–	–	–
Subtotal (right)	**20 (40)**	**0.4**	**0.2-0.8**	**1013 (47)**	**1.2**	**0.3-1.4**
TOTAL	**50**	**1.0**	**0.2-2.9**	**2133**	**1.9**	**0.3-8.0**

b. Lungs

Clinical targets irradiated	**Whole lung dose (Gy)**					
	Audit			**Review***		
	Individual dose estimates (%)	**Mean**	**Range**	**Individual dose estimates (%)**	**Average mean**	**Range**
Br/CW only	35 (70)	3.5	2.0-5.8	102 (5)	2.6	1.4-3.0
Br/CW +Ax/SF	14 (28)	4.6	2.8-6.8	2038 (91)	3.0	0.9-5.1
Br/CW ±Ax/SF +IMN	1 (2)	4.1	–	90 (4)	7.1	6.7-10.0
TOTAL	**50**	**3.8**	**2.0-6.8**	**2230**	**3.1**	**0.9-10.0**

c. Oesophagus

Clinical targets irradiated	Whole oesophagus dose (Gy)					
	Audit			Review*		
	Individual dose estimates (%)	Mean	Range	Individual dose estimates (%)	Average mean	Range
Br/CW only	35 (70)	0.3	0.1-0.4	–	–	–
Br/CW +Ax/SF	14 (28)	1.0	0.5-2.4	36 (47)	1.4	1.0-2.0
Br/CW ±Ax/SF +IMN	1 (2)	0.6	–	40 (53)	5.8	1.9-10.0
TOTAL	**50**	**0.5**	**0.1-2.4**	**76**	**3.7**	**1.0-10.0**

Footnotes
Data from review of UK breast cancer radiotherapy studies published during 2015-2023, the results of which are summarized in Figures 3.2, 3.3, 3.4.
Categories of laterality and targets were included in the table above if there was an equivalent category in the audit. Other categories, e.g. left breast/chest wall±axilla/supraclavicular + internal mammary radiotherapy, were omitted.
Abbreviations: Ax=axilla lymph nodes, Br=breast, CW=chest wall, Gy=gray, IMN=internal mammary lymph nodes, RT=radiotherapy, SF=supraclavicular lymph nodes, "–"=unspecified.

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B.12 Estimation of absolute mortality radiation risks from typical heart and lung doses in UK breast cancer radiotherapy

B.12.1 Ischaemic heart disease

In the Results section of this systematic review, estimated average mean heart doses from different combinations of laterality and targets irradiated were as follows (Figure 3.5):

Breast cancer laterality and target: Average mean whole heart dose (Gy)

Left breast/chest wall only: 2.0

Left breast/chest wall + axilla/supraclavicular nodes: 2.7

Left breast/chest wall ± axilla/supraclavicular + internal mammary nodes: 2.9

Right breast/chest wall only: 1.0

Right breast/chest wall + axilla/supraclavicular nodes: 1.2

In the Discussion section of this systematic review, approximate estimates of the 30-year absolute radiation-related risks of death from ischaemic heart disease are presented for typical patients who received breast cancer radiotherapy with the above doses when aged 50 years. These have been reproduced from previously published estimates indicating typical absolute risks of radiation-induced death from ischaemic heart disease by age 80 years for women irradiated at different ages, with and without cardiac risk factors, for different mean heart doses. The relevant section of the table is reproduced in Figure B.2. The estimates assume that the risk of death from radiation-related ischaemic heart disease increases by 7.4% per Gy increase in the mean whole heart dose. They also assume that

age-specific mortality rates from ischaemic heart disease and from other causes are equal to those of women in the 15 Western European countries during 2010.

For a woman with no known cardiac risk factors before her radiotherapy, the left-hand panel of the table in Figure B.2 was used. For left breast/chest wall radiotherapy, the UK average mean whole heart dose was 2.0Gy. The corresponding radiation risk from this dose would be 0.3% (red box, left-panel). For a patient *with* known cardiac risk factors before radiotherapy, the right-panel was used and the corresponding radiation-related increase in risk was 0.4% (red box right-panel). For left breast/chest wall + axilla/supraclavicular nodes, 2.7Gy whole heart dose was the UK average mean dose. This was rounded up to 3Gy since the table provides estimates from dose in Gy to the nearest whole number. The corresponding radiation risk is represented by the green boxes. It was 0.5% for a woman with no cardiac risk factors prior to radiotherapy and 0.7% for a women with prior cardiac risk factors.

This method was used to provide illustrative 30-year risks of radiation-induced heart disease mortality for other average mean heart doses (above) from UK breast cancer radiotherapy to different clinical targets.

These illustrative risks are from typical modern UK radiotherapy, and 2010 mortality rates from women in Western Europe. In reality heart doses vary from patient to patient, and mortality rates vary from population to population and from year to year, so an individual woman's absolute risk will vary around these typical values. In addition, there is unavoidable uncertainty in measuring doses in modern radiotherapy planning due to inter- and intra-fraction motion and contouring uncertainties. These estimates do not take into account competing causes of death, so they may overestimate cardiac risk for women at high risk of

Age at irradiation (years)	Mean heart dose (Gy)	No cardiac risk factor					At least one cardiac risk factor				
		Cumulative risk (%) by attained age				Absolute risk (%) of radiation-related IHD death by age 80 years	Cumulative risk (%) by attained age				Absolute risk (%) of radiation-related IHD death by age 80 years
		50	60	70	80		50	60	70	80	
50	0		0.09	0.5	1.9	0.0		0.3	0.9	3.4	0.0
	0.5		0.09	0.5	2.0	0.1		0.3	1.0	3.5	0.1
	1		0.09	0.5	2.1	0.2		0.3	1.0	3.6	0.2
	2		0.10	0.5	2.2	0.3		0.3	1.1	3.8	0.4
	3		0.11	0.6	2.4	0.5		0.3	1.1	4.1	0.7
	4		0.11	0.6	2.5	0.6		0.4	1.2	4.3	0.9
	5		0.12	0.6	2.7	0.8		0.4	1.3	4.6	1.2
	6		0.12	0.7	2.8	0.9		0.4	1.3	4.8	1.4
	7		0.13	0.7	2.9	1.0		0.4	1.4	5.0	1.6
	8		0.14	0.7	3.1	1.2		0.4	1.5	5.3	1.9
	9		0.14	0.8	3.2	1.3		0.5	1.5	5.5	2.1
	10		0.15	0.8	3.4	1.5		0.5	1.6	5.8	2.4

Figure B.2: From Table S12 in Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013; 368(11): 987-98.Copyright (2013) Massachusetts Medical Society. Reprinted with permission.

breast cancer death.

In Darby 2013 cardiac risk factors included:

- Myocardial infarction or coronary revascularisation procedure
- Pericarditis, endocarditis, myocarditis
- Cardiac valve disorders
- Cardiomyopathy
- Cardiac arrhythmia or conduction disorders
- Heart failure
- Other circulatory diseases:
  - Hypertension
  - Cerebrovascular disease
  - Peripheral vascular disease
  - Pulmonary embolism or deep vein thrombosis
- Other:
  - Diabetes
  - Chronic obstructive pulmonary disease
  - Long-term continuous smoking in the year prior to study registration
  - Body Mass Index >30kg/m2

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B.12.2 Lung cancer

Illustrative absolute radiation risks from average mean whole lung doses for different combinations of targets irradiated were estimated using the 2017 EBCTCG meta-analysis of radiotherapy side-effects. In this publication, the rate ratio for incident lung cancer increased by 11% per Gy increase in mean whole lung dose, based on based on data from 40,000 women in 75 randomised trials. In the EBCTCG meta-analysis, this dose-response relationship was combined with baseline annual rates of death from lung cancer for non-smokers in the American Cancer Prevention Study II and for smokers in the UK Million Women study. The estimated absolute 30-year risk of radiation-induced lung cancer death from 5Gy whole lung dose for a typical non-smoker aged 50 years at irradiation was 0.3%. For a long-term continuing smoker it was 4.4% (see Figure 3A in EBCTCG 2017). The risks of radiation-induced lung cancer mortality in ex-smokers are likely to be much closer to those in never-smokers than in current smokers because stopping smoking substantially reduces lung cancer risk.

These illustrative risks are from typical modern UK radiotherapy and from populations of patients in epidemiological studies. In reality lung doses vary from patient to patient, and mortality rates vary from population to population and year to year, so an individual woman's absolute risk will vary around these

Study	Clinical scenario	Whole lung dose (Gy)	Absolute 30-year radiation risk (%)	
			Non-smoker	Long term continuing smoker
EBCTCG 2017	Modern breast cancer radiotherapy worldwide 2010-2015	5	0.3	4.4
Current UK review	Breast/chest wall only	2.6	0.2	2.3
	Breast/chest wall + axilla/supraclavicular nodes	3.0	0.2	2.6
	Breast/chest wall±axilla/supraclavicular + internal mammary nodes	7.1	0.4	6.2

typical values. These estimates do not take into account the competing risk of death from breast cancer so the radiation-induced lung cancer risks for patients today may be somewhat lower than this.

In this systematic review, for breast/chest wall only radiotherapy, the average mean whole lung dose was about half of 5Gy (2.6Gy). Assuming that the relationship between whole lung dose and radiation-induced lung cancer is linear, the absolute risks from 2.6Gy would be approximately half the risks from 5Gy. We estimated absolute risks for different clinical scenarios by multiplying the risks from 5Gy in the EBCTCG meta-analysis by the fraction of whole lung dose received in each scenario. For example, breast/chest wall irradiation delivered 2.6Gy lung dose. Therefore the estimated absolute risk in a smoker would be $(2.6/5)x4.4 = 2.3\%$.

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Original Article

Estimated Doses to the Heart, Lungs and Oesophagus and Risks From Typical UK Radiotherapy for Early Breast Cancer During 2015–2023

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Abstract

Purpose: Breast cancer radiotherapy can increase the risks of heart disease, lung cancer and oesophageal cancer. At present, the best dosimetric predictors of these risks are mean doses to the whole heart, lungs and oesophagus, respectively. We aimed to estimate typical doses to these organs and resulting risks from UK breast cancer radiotherapy.

Methods: A systematic review and meta-analysis was conducted of planned or delivered mean doses to the whole heart, lungs or oesophagus from UK breast cancer radiotherapy in studies published during 2015–2023. Average mean doses were summarised for combinations of laterality and clinical targets. Heart disease and lung cancer mortality risks were then estimated using established models.

Results: For whole heart, thirteen studies reported 2893 doses. Average mean doses were higher in left than in right-sided radiotherapy and increased with extent of clinical targets. For left-sided radiotherapy, average mean heart doses were: 2.0 Gy (range 1.2–8.0 Gy) breast/chest wall, 2.7 Gy (range 0.6–5.6 Gy) breast/chest wall with either axilla or supraclavicular nodes and 2.9 Gy (range 1.3–4.7 Gy) breast/chest wall with nodes including internal mammary. For right-sided radiotherapy, average mean heart doses were: 1.0 Gy (range 0.3–1.0 Gy) breast/chest wall and 1.2 Gy (range 1.0–1.4 Gy) breast/chest wall with either axilla or supraclavicular nodes. There were no whole heart dose estimates from right internal mammary radiotherapy. For whole lung, six studies reported 2230 doses. Average mean lung doses increased with extent of targets irradiated: 2.6 Gy (range 1.4–3.0 Gy) breast/chest wall, 3.0 Gy (range 0.9–5.1 Gy) breast/chest wall with either axilla or supraclavicular nodes and 7.1 Gy (range 6.7–10.0 Gy) breast/chest wall with nodes including internal mammary. For whole oesophagus, two studies reported 76 doses. Average mean oesophagus doses increased with extent of targets irradiated: 1.4 Gy (range 1.0–2.0 Gy) breast/chest wall with either axilla or supraclavicular nodes and 5.8 Gy (range 1.9–10.0 Gy) breast/chest wall with nodes including internal mammary.

Conclusions: The typical doses to these organs may be combined with dose-response relationships to estimate radiation risks. Estimated 30-year absolute lung cancer mortality risks from modern UK breast cancer radiotherapy for patients irradiated when aged 50 years were 2–6% for long-term continuing smokers, and <1% for non-smokers. Estimated 30-year mortality risks for heart disease were <1%.

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Key words: Breast cancer radiotherapy; Heart dose; Lung dose; Oesophagus dose; Radiotherapy risks; UK radiotherapy

Introduction

Adjuvant radiotherapy is received by around two-thirds of patients as part of their treatment for early breast cancer in the UK [1]. Radiotherapy reduces the risk of breast cancer death when targeted at the whole breast after breast conserving surgery or, in lymph node positive breast cancer, when targeted at the chest wall after mastectomy, with additional survival benefits when targeted also at the regional lymph nodes [2–4]. Randomised trials have, however, shown that radiotherapy can increase the risks of death from heart disease, lung cancer and oesophageal cancer [5].

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To inform clinical decisions, oncologists need to weigh the absolute magnitudes of the benefits from radiotherapy against the absolute magnitudes of its risks. Radiation risks of heart disease, lung cancer and oesophageal cancer vary according to the doses received by the heart, lungs and oesophagus respectively. Organ doses in breast cancer radiotherapy vary according to individual anatomy, breast cancer laterality, radiotherapy targets irradiated and techniques used [6–8]. For a given combination of technique and target, organ doses may also vary according to geographical region. This is because techniques may be applied differently across different cancer centres. In previous systematic reviews, heart and lung doses from tangential breast or chest wall radiotherapy were typically lower in the UK than in some other countries [7,8]. This may be due to availability of specialised techniques [9–16].

In this study, we estimate typical mean doses to the whole heart, lungs and oesophagus from modern UK breast cancer radiotherapy and the extent to which they vary. We focus on mean organ doses because the dose-response relationships with the largest numbers of events in patients with individual dosimetry, are based on mean doses to the heart, lungs and oesophagus [17]. We then illustrate how these typical mean doses might be used to estimate the absolute risks of death from heart disease and lung cancer from UK radiotherapy by combining them with published dose-response relationships and cause-specific mortality rates.

Methods

A systematic review of mean radiation doses to the whole heart, lungs or oesophagus from UK radiotherapy for early breast cancer published during 2015–2023 was performed with reference to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [18]. This date range was used because our aim was to assess modern radiotherapy. The review was registered on the International Prospective Register of Systematic Reviews [19].

Study Eligibility

Eligible studies were those reporting planned or delivered mean whole organ doses (Gy) to the heart, lungs or oesophagus from UK radiotherapy for early breast cancer published between 1st January 2015 and 12th June 2023. Eligible studies included at least one radiotherapy plan generated since 1st January 2015. Studies where only some dose estimates were produced during 1st January 2015 to 12th June 2023 were included. A similar approach was taken for radiotherapy that had been re-planned as part of a study, regardless of whether dates were specified, if the publication date fell within 1st January 2015 to 12th June 2023. We excluded studies that specified all radiotherapy was planned prior to 2015.

Studies were categorised as dosimetry (i.e., studies that reported doses from radiotherapy plans done for research purposes only), observational/audit (i.e., studies that reported doses delivered to patients in routine practice only), dosimetry & observational (i.e., studies that included doses in both research and routine practice) and interventional (i.e., studies that reported doses received by patients in clinical trials). Early breast cancer was defined as disease confined to the breast or axillary lymph nodes that could be removed surgically. Patients of any age or sex were included. For the heart and oesophagus, whole organ doses were eligible. For the lungs, whole organ dose referred to the dose distributed among both lungs. Studies that reported separate mean ipsilateral lung dose and mean contralateral lung dose were eligible since these doses could be averaged to estimate mean whole lung dose.

Study Identification

Eligible studies were identified by searching MEDLINE and Embase. The search strategy used terms for breast cancer, radiotherapy and dose (Text S1). Studies from the UK were identified using a National Institute for Health and Care Excellence (NICE) validated search filter which has been shown to retrieve UK-focused evidence with high recall [20]. Two reviewers (AI and FH) independently assessed titles and abstracts returned by the search for eligibility. To minimise the risk of including duplicate study cohorts, study datasets were compared using available information on geographical location, dates of radiotherapy plans, radiotherapy descriptions and numbers of patients irradiated. Studies were excluded if the doses in them were already reported first in another publication (e.g. some reviews).

Data Extraction

A data extraction form was designed, with definitions of treatment planning methods and radiotherapy techniques informed by previous similar reviews (Text S2) [6–8]. Two reviewers (AI and FH) independently extracted the data using Covidence systematic review software [21]. Differences were resolved through consensus.

From each included study the following information was sought: first author, year of publication, geographical location of the cancer centre where the radiotherapy was planned, study design and years during which radiotherapy was planned or delivered. The radiotherapy description included treatment planning methods, radiotherapy technique, beam type and energy, use of breathing control, laterality of the cancer(s), clinical targets, target dose and fractionation, and whether a boost to the tumour bed was given. Patient treatment position and contouring guidelines were also noted.

Dose terms were as follows: “whole organ dose” refers to the dose averaged over the whole organ. ‘Mean whole organ dose’ is the mean of whole organ doses for a particular

group of patients in a study (i.e., each row of tables S2, S4 or S6). 'Average mean whole organ dose' is the average dose for several groups of patients combined (i.e., several rows in tables S2, S4 or S6). Dose statistics extracted were the mean (or median, where mean was not reported), standard deviation and range for the whole heart, lung or oesophagus. For each mean whole organ dose statistic, the total number of contributing individual dose estimates was recorded. The total number of patients and CT planning scans from which individual dose estimates were created were counted, as were the number and percentage of dose estimates delivered to patients. Some dosimetry studies may have included CT scans and/or radiotherapy plans that had been previously used in other studies, however, to the best of our knowledge the reported individual organ dose estimates were unique to each study.

The number of patients described as having unusual anatomy was sought. For one study (IMPORT HIGH trial), mean whole organ doses were reported in six categories of target dose and laterality, but the number of individual patients, and hence dose estimates, in each category was not reported [22]. The likely number of patients in each of the six categories was therefore estimated by considering the published percentages of patients who received left and right-sided radiotherapy within each of the dose levels in the trial (56Gy/53Gy/48Gy).

Data Analysis

Included studies were grouped according to the organ(s) at risk for which they reported doses. Clinical targets were grouped as: breast or chest wall only (Br/CW only); breast or chest wall with either axilla or supraclavicular nodes (Br/CW + Ax/SF); breast or chest wall with either axilla or supraclavicular nodes, also including internal mammary nodes (Br/CW ± Ax/SF + IM). Laterality for each mean whole organ dose estimate was defined as all patients had left-sided cancer (L); all patients had right-sided cancer (R); some patients had left- and some had right-sided cancer (L/R). No patients were reported with bilateral cancer.

For heart, dose estimates were categorised first by breast cancer laterality, then by radiotherapy clinical targets. For lung, ipsilateral and contralateral lung doses were averaged to estimate whole lung dose, since the dose-response relationship for radiation-induced lung cancer is based on whole lung dose [5]. Mean whole lung doses were then categorised by radiotherapy clinical targets. For oesophagus, mean whole oesophagus doses were categorised by clinical targets.

For each combination of radiotherapy clinical targets and laterality, the overall average mean whole heart dose was calculated by weighting the mean whole heart dose in each study by the number of individual dose estimates it was based on. The standard error (SE) of each overall average was then calculated in similar fashion [23]. Tests of heterogeneity between the overall average mean whole heart dose in the three laterality groups and tests of trend in average mean whole heart dose across the extent of the clinical targets irradiated were carried out using variance-weighted least squares. Average mean whole lung and oesophagus doses and trends across the extent of clinical targets irradiated were carried out similarly. Calculations were carried out using the data analysis tool available in the statistical software R version 4.2.2 [24].

Analyses Using Individual Patient Doses in a Single UK Centre

Organ doses received in routine practice may be higher than those in articles where authors have chosen to publish their doses. Therefore, the extent to which published laterality- and target-specific doses are reflected in routine clinical practice was assessed. Organ doses were estimated for patients irradiated in one cancer centre (Oxford). Fifty consecutive patients in the centre's CT planning database who received radiotherapy for early breast cancer during May and June 2018 were selected. The heart, lungs and oesophagus were contoured and individual patient whole organ doses were estimated. For each organ, mean whole organ doses were then estimated for different clinical situations.

Results

Fourteen studies published during 2015–2023 reported mean whole organ doses (Gy) to the heart, lungs and/or oesophagus from UK radiotherapy for early breast cancer (Figure S1, Text S3). Heart dose was reported in 13 studies, lung dose in 6 studies and oesophagus dose in 2 studies.

Heart Dose

Mean whole heart doses were reported from a total of 2893 individual dose estimates (Figure 1, Tables S1, S2). Of these, 2505 (87%) were delivered to patients. The other 388 (13%) were from dosimetry studies (Table S1). Two large studies included 2313 (80%) of the doses. The largest study reported doses in a clinical trial (IMPORT HIGH), involving 39 radiotherapy centres throughout the UK and 1958 patients [22]. Patients in IMPORT HIGH underwent breast cancer radiotherapy between 2009 and 2015. As the regimens from 2015 could not be separated from those of 2009–2014, this study was considered to fall within the scope of the review as per the predetermined inclusion criteria.

The second largest study was a national audit of breast cancer radiotherapy practice in the UK, reporting doses on 355 patients [25]. The audit presented summary heart doses in routine clinical practice, but doses were not provided separately according to clinical targets. The remaining 11 studies each included between 10 and 98 whole heart dose estimates.

There were 2314 whole heart dose estimates (80%) from intensity modulated radiotherapy (IMRT) techniques using photons (Table S2), 28 (1%) from newer IMRT techniques

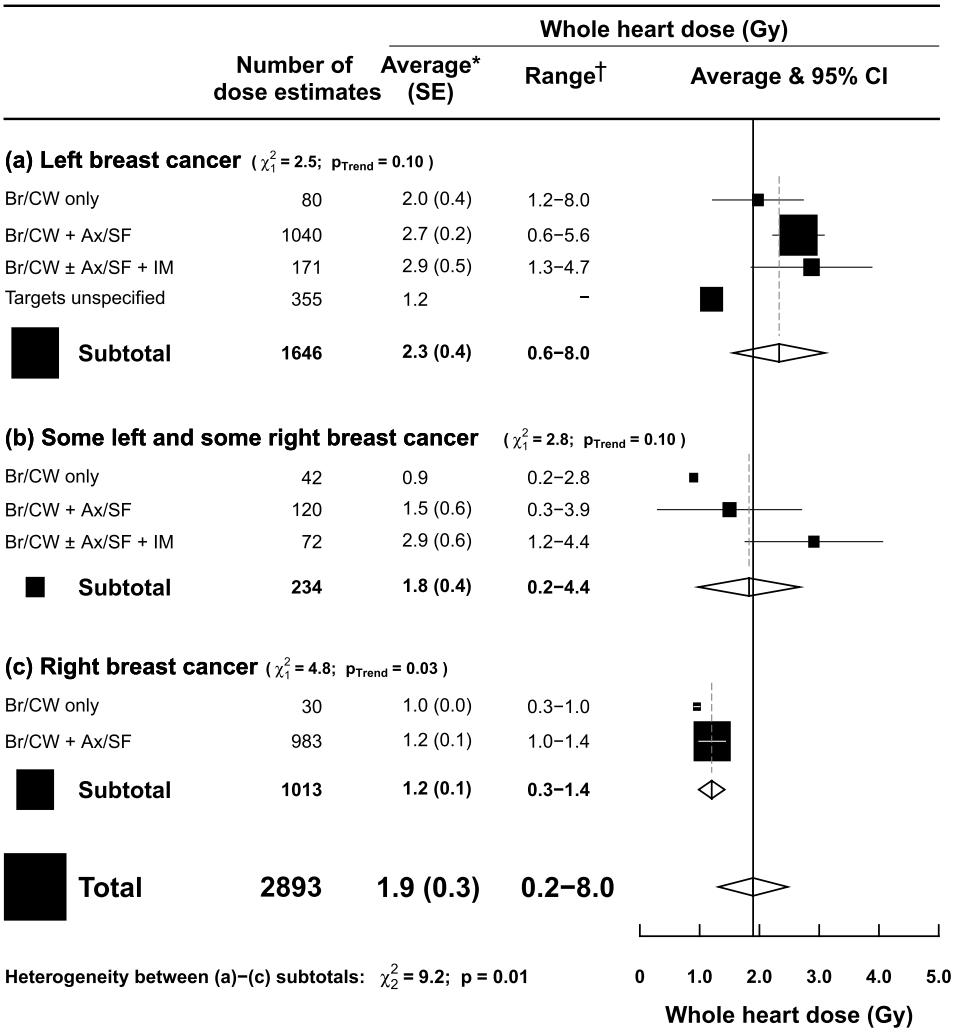


Fig 1. Estimated typical mean whole heart doses from UK breast cancer radiotherapy according to breast cancer laterality and clinical targets. *Average mean whole heart dose, weighted by the number of individual dose estimates, was calculated for each category of breast cancer laterality and clinical targets. †The range refers to the range of individual dose estimates. Where this was unavailable, the range of reported mean doses was used. P_{trend} values are for association of average dose with increasing targets irradiated.
Abbreviations: Ax=axilla lymph nodes, Br=breast, CI=confidence interval, CW=chest wall, Gy=gray, IM=internal mammary lymph nodes, SE=standard error, SF=supraclavicular fossa lymph nodes.

using protons and 196 (7%) from older photon techniques using tangential fields with fixed gantry angles. Breathing control could not be ascertained for 2545 (88%) of whole heart dose estimates. The use of deep inspiratory breath hold was specified for 212 (7%) and free breathing for 136 (5%) of estimates (Table S2).

There were 1646 whole heart doses from left-sided radiotherapy, 1013 from right-sided radiotherapy and 234 from mixed laterality (some left and some right) (Figure 1). For left-sided radiotherapy, average mean whole heart dose (Gy) from UK radiotherapy was 2.3 Gy (SE 0.4 Gy), with a wide range (0.6–8.0 Gy) for individual patients. For right-sided radiotherapy, average mean whole heart dose was 1.2 Gy (SE 0.1 Gy, range 0.3–1.4 Gy). For mixed laterality, it was 1.8 Gy (SE 0.4 Gy, range 0.2–4.4 Gy). Average mean whole heart dose increased with the extent of clinical targets irradiated. For left-sided radiotherapy, it was 2.0 Gy (SE 0.4 Gy) from breast/chest wall only, 2.7 Gy (SE 0.2 Gy) from breast/chest wall+axilla/supraclavicular nodes and 2.9 Gy (SE 0.5 Gy) from breast/chest wall±axilla/supraclavicular+internal mammary nodes. For right-sided radiotherapy, average mean whole heart dose was 1.0 Gy (SE 0.0 Gy) from breast/chest wall only and 1.2 Gy (SE 0.1 Gy) from breast/chest wall+axilla/supraclavicular nodes. There were no whole heart dose estimates from right internal mammary radiotherapy.

In IMPORT HIGH [22], mean whole heart doses from left radiotherapy were 2.4, 2.7 and 2.9 Gy, based on 316, 319 and 340 dose estimates respectively (Table S2). In other studies, mean whole heart doses in left radiotherapy varied from 0.5 to 6.4 Gy based on between 4 and 355 dose estimates. For right radiotherapy, mean whole heart doses in IMPORT

HIGH were 1.0, 1.3 and 1.4 Gy, based on 316, 340 and 327 dose estimates respectively. In other studies, mean whole heart doses in right radiotherapy were 0.9 and 1.0 Gy, each based on 15 doses.

Lung Dose

Six of the fourteen studies included both ipsilateral and contralateral lung doses (Tables S3, S4). This gave rise to a total of 2230 whole lung dose estimates (Figure 2). Of these, 2049 (92%) were delivered to patients. The largest study was the IMPORT HIGH clinical trial, which included 1958 (88%) of the whole lung doses [22].

All whole lung dose estimates were from intensity modulated radiotherapy (IMRT) using photons (Table S4). Breathing control could not be ascertained for 2180 (98%) of whole lung dose estimates. The use of deep inspiratory breath hold was specified for 50 (2%) of estimates (Table S4).

There were 102 whole lung dose estimates from radiotherapy to breast/chest wall only, 2038 from radiotherapy to breast/chest wall+axilla/supraclavicular nodes and 90 from radiotherapy to breast/chest wall±axilla/supraclavicular+internal mammary nodes. Average mean whole lung dose increased with the extent of clinical targets irradiated, taking values 2.6 Gy (SE 0.3 Gy, range 1.4–3.0 Gy) from breast/chest wall only, 3.0 Gy (SE 0.1 Gy, range 0.9–5.1 Gy) from breast/chest wall+axilla/supraclavicular nodes and 7.1 Gy (SE 0.4 Gy, range 6.7–10.0 Gy) from breast/chest wall±axilla/supraclavicular+internal mammary nodes (Figure 2).

In IMPORT HIGH [22], mean whole lung doses were 2.8, 3.0 and 3.2 Gy, based on 632, 659 and 667 dose estimates respectively (Table S4). In other studies, mean whole lung doses varied from 2.0 to 8.5 Gy based on between 5 and 40 dose estimates.

Oesophagus Dose

Two of the fourteen studies reported whole oesophagus doses from a total of 76 individual estimates. Of these 76 doses, 20 (26%) were delivered to patients and the rest were estimated for research purposes (Figure 3, Tables S5, S6).

Just over half of the whole oesophagus doses were from intensity modulated radiotherapy (IMRT) techniques using photons (40/76, 53%), with the other 36 (47%) doses from older photon radiotherapy techniques using tangential fields with fixed gantry angles (Table S6). Breathing control was not specified for any patient group. Average mean whole oesophagus dose increased with the extent of clinical targets irradiated (Figure 3). It was 1.4 Gy (SE 0.3 Gy, range 1.0–2.0 Gy) from radiotherapy to breast/chest wall+axilla/supraclavicular nodes, based on 36 individual dose estimates, and 5.8 Gy (SE 0.3 Gy, range 1.9–10.0 Gy) from radiotherapy to breast/chest wall±axilla/supraclavicular+internal mammary nodes, based on 40 individual dose estimates.

Analyses Using Individual Patient Doses in a Single UK Centre (Text S4, Table S7)

Of 50 patients, 30 received left-sided radiotherapy and 20 right-sided radiotherapy. Patients were irradiated using forward-planned IMRT, with DIBH in left radiotherapy. Breast/chest wall radiation was received by 35 patients, breast/chest wall+axilla/supraclavicular nodes by 14 patients and breast/chest wall±axilla/supraclavicular+internal mammary radiotherapy by one patient. Mean whole heart dose was higher in left than in right-sided radiotherapy; left 1.3 Gy (range 0.6–2.9 Gy) and right 0.4 Gy (range 0.2–0.8 Gy). For lung, mean whole organ dose

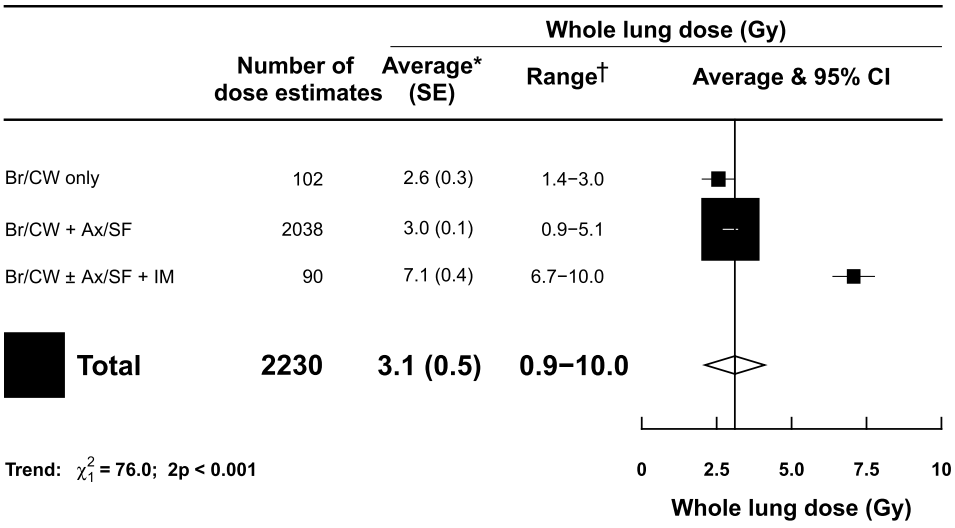


Fig 2. Estimated typical mean whole lung doses from UK breast cancer radiotherapy according to clinical targets.
*Average mean whole lung dose, weighted by the number of individual dose estimates, was calculated for each category of clinical targets. †The range refers to the range of individual dose estimates. Where this was unavailable, the range of reported mean doses was used. P_{trend} values are for association of average dose with increasing targets irradiated.
Abbreviations: Ax=axilla lymph nodes, Br=breast, CI=confidence interval, CW=chest wall, Gy=gray, IM=internal mammary lymph nodes, SE=standard error, SF=supraclavicular fossa lymph nodes.

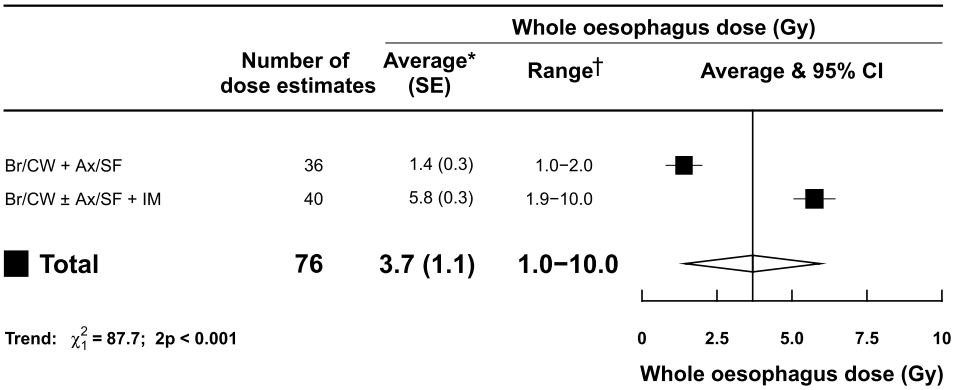


Fig 3. Estimated typical mean whole oesophagus doses from UK breast cancer radiotherapy according to clinical targets.
*Average mean whole oesophagus dose, weighted by the number of individual dose estimates, was calculated for each category of clinical targets. †The range refers to the range of individual dose estimates. Where this was unavailable, the range of reported mean doses was used. P_{trend} values are for association of average dose with increasing targets irradiated.
Abbreviations: Ax=axilla lymph nodes, Br=breast, CI=confidence interval, CW=chest wall, Gy=gray, IM=internal mammary lymph nodes, SE=standard error, SF=supraclavicular fossa lymph nodes.

was 3.8 Gy (range 2.0–6.8 Gy) and for oesophagus it was 0.5 Gy (range 0.1–2.4 Gy).

Comparing mean doses in the single centre audit with average mean doses in the review of UK published doses, audit doses were lower for whole heart and oesophagus: heart, audit 1.0 Gy (range 0.2–2.9 Gy) versus review 1.9 Gy (range 0.3–8.0 Gy); oesophagus, audit 0.5 Gy (range 0.1–2.4 Gy) versus review 3.7 Gy (range 1.0–10.0 Gy). For heart and oesophagus, all target and laterality-specific organ doses were also lower in the audit than in the review.

In contrast, for whole lung, mean audit doses were slightly higher than average mean doses in the review: audit 3.8 Gy (range 2.0–6.8 Gy) versus review 3.1 Gy (range 0.9–10.0 Gy). Target-specific doses were also slightly higher in the audit than in the review: breast/chest wall: audit 3.5 Gy versus review 2.6 Gy and breast or chest wall+axilla/supraclavicular fossa lymph nodes: audit 4.6 Gy versus review 3.0 Gy.

Discussion

This systematic review and meta-analysis provides up-to-date estimates of typical doses to the whole heart, lungs and oesophagus from UK radiotherapy for early breast cancer. Published average mean whole organ doses were around 2 Gy for heart, 3 Gy for lung and 4 Gy for oesophagus. For all organs, doses increased with the extent of radiotherapy clinical targets included. Heart doses also varied according to breast cancer laterality.

Strengths and Limitations

This study has several strengths. It summarises doses received by all three organs (heart, lung and oesophagus) implicated in the main mortality risks of breast cancer radiotherapy [5]. To the best of our knowledge it is the largest quantitative synthesis of organ doses from modern UK breast cancer radiotherapy. Studies were identified and data extracted independently by both an oncologist and a radiation health sciences officer. The literature search used a validated method of identifying UK studies and the analyses used an established method of dose meta-analysis [6–8,20]. The search strategy was wide, so it is likely that all relevant studies were identified. Summary doses were based on more than 5000 individual dose estimates in fourteen studies. Average mean whole organ doses were weighted according to the number of patients contributing to each, so that the doses for different clinical scenarios are likely to be representative of typical doses received by patients in these scenarios. An audit of 50 patients in a single cancer centre enabled the published doses to be compared with doses in routine clinical practice in patients irradiated according to national UK guidance. The extent to which the doses received by these patients reflect practice in other UK centres is not known. Routine UK practice can be assessed by national audits where all cancer centres are invited to contribute data. For heart, mean whole organ doses from a national audit were included in our study, with 355 patients from 47 of the 58 UK radiotherapy centres [25]. National audit doses were unavailable for lung and oesophagus. In future, national collection of organ doses may enable more comprehensive assessment of routine practice.

There were several limitations in our study. First, individual patient doses were not usually reported in publications, so standard error and range could not be presented for some mean whole organ doses. Second, methods of contouring the organs were rarely reported for included studies. This may have contributed to the wide range of reported doses. Third, only 76 estimates of oesophagus dose were available. Fourth, dose-volume measures were not extracted. Previous reviews found that comparable heart and lung dose-volume parameters in contemporary breast cancer radiotherapy were infrequently reported [7,8].

Nevertheless, mean whole organ doses are currently the best available predictors of radiation-induced heart disease and cancer [17]. Future epidemiological studies including detailed individual patient three-dimensional doses to the heart, lungs or oesophagus may provide further information on whether dose-volume measures, or doses to parts of organs, improve prediction of radiation-induced heart disease or cancer [26,27].

A fifth limitation of our study is that most heart and lung doses were from a single clinical trial (IMPORT HIGH). Practice in radiotherapy centres that recruited to this trial may differ from routine practice in other centres. For example, centres recruiting to the trial had contouring protocols and dosimetry quality assurance, which may not be available in other centres. However, 39 of the 58 (67%) UK centres entered patients into IMPORT HIGH, so the organ doses from this trial represent practice in the majority of UK centres. In addition, the 39 centres that recruited to IMPORT HIGH are likely to treat more patients per year than the other 19 centres that did not recruit to IMPORT HIGH. Therefore the radiotherapy practices in these 39 centres are likely to reflect those available to most UK breast cancer patients. In addition, large multicentre trials such as IMPORT HIGH have improved consistency and increased quality assurance nationwide in routine radiotherapy.

Typical Absolute Radiation-Induced Mortality Risks

The average mean whole organ doses from different combinations of breast cancer laterality and clinical targets irradiated may be used to estimate typical radiation mortality risks using published dose-response relationships (Text S5). For an individual, the absolute risk of death from heart disease or lung cancer attributable to radiotherapy may be estimated using their background death rate in the absence of radiotherapy together with the percentage increase in death rate arising from radiotherapy for the organs exposed.

For ischaemic heart disease, the mortality rate was estimated by Darby *et al.* (2013) to increase by 7.4% per Gy (95% CI 2.9–14.5) mean whole heart dose [28]. The study included 963 irradiated women with major coronary events and 1205 irradiated controls. In that study the mean radiation dose to the heart was a better predictor of the rate of major coronary events than the mean dose to the left anterior descending coronary artery. In addition, the mean dose to the left anterior descending coronary artery was not significantly associated with the rate of major coronary events after the mean dose to the heart was taken into account. In a sub-study of the 456 cases with available information on the site of cardiac injury, mean segment dose was associated with injury for all individual segments of the left ventricle and coronary arteries [29]. For estimation of cardiac radiation-risks in the clinic today, the mean whole heart dose is the best predictor currently available. However, some uncertainties remain, including the possible effects of fractionation or beam modality on the slope of the dose-response.

An indication of absolute risks from typical doses in different clinical situations was given in the online Appendix of Darby 2013 [28] by combining the 7.4% per Gy dose-response with population-based mortality rates for ischaemic heart disease. Some of these absolute risks are reproduced in Text S5 and can be used to give approximate

Table 1
Estimated typical absolute 30-year risks (%) of radiotherapy-induced mortality for a patient who receives modern UK breast cancer radiotherapy with typical heart and lung doses when aged 50 years

Targets irradiated	**Absolute risks (%) of radiotherapy-induced mortality**					
	Ischaemic heart disease				Lung cancer	
	Left cancer, no cardiac risk factors	Left cancer, ≥1 cardiac risk factor	Right cancer, no cardiac risk factors	Right cancer, ≥1 cardiac risk factor	Non-smoker	Long-term continuing smoker
Br/CW only	0.3	0.4	0.2	0.2	0.2	2.3
Br/CW +Ax/SF	0.4	0.6	0.2	0.2	0.2	2.6
Br/CW ±Ax/SF +IM	0.5	0.7	–	–	0.4	6.2

Footnotes.
Absolute risks were estimated using average mean doses to whole organs at risk (Gy) from modern UK radiotherapy for early breast cancer (Figures 1 and 2) and the dose-response relationships described in Text S5. Cardiac risk factors include smoking, see Text S5 for details. These data are illustrated in Figure 4. Risks of radiation-induced lung cancer mortality in ex-smokers are likely to be much closer to those in never-smokers than in current smokers because stopping smoking substantially reduces lung cancer risk.
Figure 1 shows average mean whole heart doses for nine categories of laterality and target. Absolute risks in this table and Figure 4 are shown for the following five categories, i.e., all categories excluding "targets unspecified" and "some left and some right."
Breast cancer laterality and target: Average mean whole heart dose (Gy).
Left Br/CW only: 2.0.
Left Br/CW+Ax/SF: 2.7.
Left Br/CW±Ax/SF+IM: 2.9.
Right Br/CW only: 1.0.
Right Br/CW+Ax/SF: 1.2.
Abbreviations: Ax=axilla lymph nodes, Br=breast, CW=chest wall, IM=internal mammary lymph nodes, SF=supraclavicular fossa lymph nodes, "–"=doses were unavailable for these categories.

indications of the cardiac risks for patients today. The average mean heart doses found in our study with known laterality and targets varied from 1.0 to 2.9 Gy (Figure 1). This suggests that, for a patient aged 50 years when irradiated, typical UK radiotherapy would increase their absolute 30-year risk of death from ischaemic heart disease by between 0.2% and 0.7% (Table 1, Figure 4, Text S5). These estimates do not take into account the competing risk of death from breast cancer. In addition, death rates from ischaemic heart disease have reduced during the past 20 years, so the radiation-induced heart disease mortality risks for patients today may be somewhat lower than this.

For lung cancer, in an EBCTCG meta-analysis, the rate of incident radiation-induced lung cancer increased by 11% per Gy mean whole lung dose [5]. The EBCTCG publication applied this dose-response relationship to population mortality data, suggesting an absolute increase in risk of lung cancer death from 5 Gy whole lung dose of 0.3% for a non-smoker and 4.4% for a long-term continuing smoker. Whole lung doses in typical UK breast cancer radiotherapy in our study were usually lower than 5 Gy. The average mean whole lung dose for radiotherapy to the breast/chest wall was 2.6 Gy, for radiotherapy to the breast/chest wall-+axilla/supraclavicular nodes it was 3.0, and for breast/

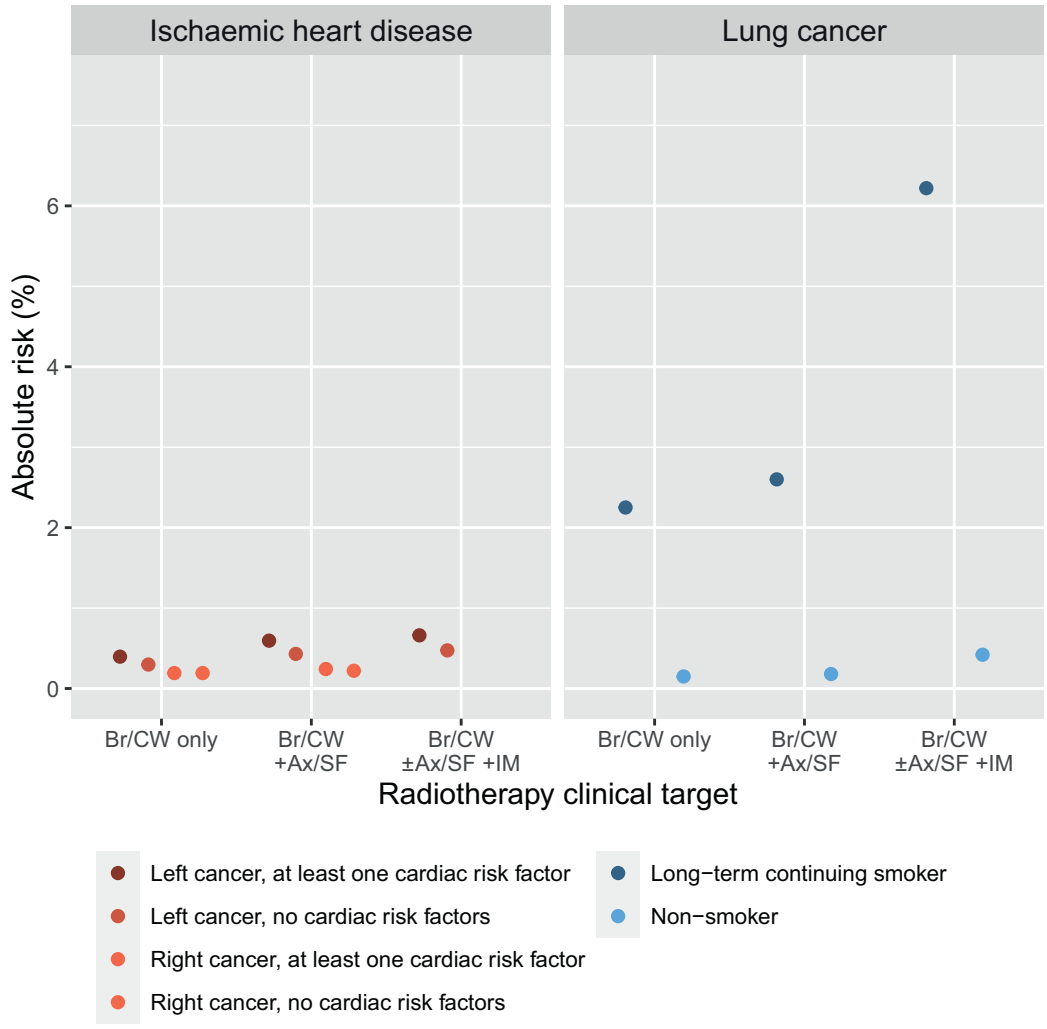


Fig 4. Estimated typical absolute 30-year risks (%) of radiotherapy-induced mortality for a patient who receives modern UK breast cancer radiotherapy with typical heart and lung doses when aged 50 years.
Absolute risks were estimated using average mean doses to whole organs at risk (Gy) from modern UK radiotherapy for early breast cancer (Figures 1 and 2) and the dose-response relationships described in Text S5. Cardiac risk factors include smoking, see Text S5 for details. The risks are shown in Table 1. Risks of radiation-induced lung cancer mortality in ex-smokers are likely to be much closer to those in never-smokers than in current smokers because stopping smoking substantially reduces lung cancer risk.
Figure 1 shows average mean whole heart doses for nine categories of laterality and target. Absolute risks in Table 1 and in this figure are shown for the following five categories, i.e., all categories excluding "targets unspecified" and "some left and some right":
Breast cancer laterality and target: Average mean whole heart dose (Gy), Left Br/CW only: 2.0, Left Br/CW+Ax/SF: 2.7, Left Br/CW±Ax/SF+IM: 2.9, Right Br/CW only: 1.0, Right Br/CW+Ax/SF: 1.2, Abbreviations: Ax=axilla lymph nodes, Br=breast, CW=chest wall, IM=internal mammary lymph nodes, SF=supraclavicular fossa lymph nodes.

chest wall±axilla/supraclavicular+internal mammary nodes it was 7.1 Gy (Figure 2). If absolute lung cancer mortality risk increased linearly with increasing dose, the corresponding 30-year absolute risks from these doses for a lifelong non-smoker would be 0.2%, 0.2% and 0.4% respectively, while the corresponding risks for a long-term continuing smoker would be 2.3%, 2.6% and 6.2% (Table 1, Figure 4, Text S5). The risks of radiation-induced lung cancer mortality in ex-smokers are likely to be much closer to those in never-smokers than in current smokers because stopping smoking substantially reduces lung cancer risk, and if a patient stops smoking at the time of radiotherapy, much of the increased risk associated with smoking could be avoided [5].

For oesophageal cancer, estimates of absolute risk from different oesophagus doses are currently unavailable. However, oesophageal cancer in the general population is uncommon, so absolute oesophageal cancer death risks are likely to be lower than the risks of death from heart disease or lung cancer [30].

Implications for Current Clinical Practice

The typical doses and absolute risks presented in this study are reassuring for the majority of patients. The current version of the Royal College of Radiologists' breast cancer radiotherapy consent form categorises the "increased risk of heart disease in later life" and "a different cancer in the treatment area" as rare (occurring with a frequency of less than 1%) [31]. This statement aligns with the evidence we present for most patients irradiated for breast cancer, who are non-smokers or ex-smokers. For patients who are long-term continuing smokers, i.e., those who are likely to keep smoking, the risks are higher than 1% and the consent form can be annotated to reflect this. These risks are particularly relevant in clinical situations where radiotherapy has not been shown to reduce breast cancer mortality, for example after surgery for carcinoma *in situ*. These doses and risks may be used in the UK to help guide clinical decisions about radiotherapy benefits and risks for patients today. They can also inform UK national guidelines on optimal dose constraints for breast cancer radiotherapy.

Implications for Future Research

Although the methods of estimating absolute risks of death from radiation-induced heart disease and lung cancer illustrated in this study are based on the highest-quality published evidence [17], further work is needed to facilitate their routine estimation. For example, more information is needed on how the risks vary according to age at irradiation, or the type of systemic therapy given in addition to radiation. Information is also needed on the absolute risks of oesophageal cancer from different oesophagus radiation doses. Work is underway to produce estimates that take into account the competing risks of breast cancer death and other causes of death using up-to-date population data.

Conclusions

This study provides estimates of typical doses to organs at risk from modern UK breast cancer radiotherapy and illustrates how these may be used in combination with epidemiological data to estimate absolute radiotherapy risks. For a typical 50-year old long-term continuing smoker, the estimated 30-year absolute mortality risks of lung cancer from modern UK breast cancer radiotherapy range from 2 to 6%. However, most breast cancer patients considered for radiotherapy in the UK today are non-smokers or ex-smokers with no cardiac risk factors, and their risks of lung cancer or heart disease death are likely to be less than 1%.

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Procedures for accessing the data for this study are available on: https://www.ndph.ox.ac.uk/about/data-access-policy.

Author Contributions

1. Guarantor of integrity of the entire study: FH/AI.
2. Study concept and design: CT/DD/SD/FH/AI.
3. Literature research: FH/AI.
4. Clinical studies: NA.
5. Data analysis: FH/ZW.
6. Statistical analysis: ZW/SD.
7. Manuscript preparation: All authors.
8. Manuscript editing: All authors.

Conflict of Interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests: Zhe Wang, Georgios Ntentas, Sileida

Oliveros, David Dodwell reports financial support was provided by Cancer Research UK. Francesca Holt reports financial support was provided by National Institute of Health and Social Care Research (NIHR). Georgios Ntentas reports financial support was provided by NIHR (NIHR301261), Health Education England. Carolyn Taylor reports financial support was provided by Cancer Research UK. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Statement of Searches

The search strategy is provided in the supplementary material. It was run in EMBASE and Medline and the returned records were screened against study inclusion and exclusion criteria.

Consent

A table in Text S5 (Supplementary material p23) is based on data produced by our team and published in the supplementary material (Table S12) of Darby SC, Ewertz M, McGale P *et al.* Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013; 368(11): 987-98. According to the New England Journal of Medicine author permissions, authors are allowed to include portions of their articles in other educational articles that they write.

https://www.nejm.org/author-center/permissions (accessed 3rd Jan 2024).

Tweet: UK breast cancer radiotherapy mortality risks from lung cancer or heart disease are <1% for non-smokers but may be a few percent for smokers.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2024.05.002.

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Appendix C

Supplementary material for Chapter 4: Estimated doses to the lung lobes from radiotherapy regimens for early breast cancer regimens delivered in the Netherlands during 1970-2010.

C.1 Variation in mean lung doses from 44 breast cancer radiotherapy regimens first used in regimens in the Netherlands during 1970-2010

Table C.1: Variation in mean lung doses from 44 breast cancer radiotherapy regimens first used in regimens in the Netherlands during 1970-2010.

Lung Volume	**Mean dose (Gy)**			
	Median	**IQR**	**Min.**	**Max.**
From 22 right radiotherapy regimens				
Whole lung	8.8	3.7	2.3	14.6
Right lung	14.8	6.3	4.1	24.6
Right upper lung lobe	18.2	7.1	3.6	30.7
Right middle lung lobe	21.3	10.4	10.4	30.0
Right lower lung lobe	9.1	7.4	1.3	19.5
Left lung	1.3	0.3	0.1	2.0
Left upper lung lobe	1.5	0.5	0.1	2.2
Left lower lung lobe	1.0	0.9	0	1.9
From 22 left radiotherapy regimens				
Whole lung	6.6	3.4	2.5	13.1
Right lung	1.7	0.7	0.1	3.7
Right upper lung lobe	2.5	1.1	0.1	5.2
Right middle lung lobe	1.4	0.6	0.1	1.8
Right lower lung lobe	1.3	1.0	0.0	2.8
Left lung	11.7	7.4	5.5	25.8
Left upper lung lobe	15.1	10.3	8.2	36.9
Left lower lung lobe	7.8	5.8	1.2	16.0

Footnotes
See Figure 4.2 for box plot.
Abbreviations: IQR=interquartile range, Max.=maximum, Min.=minimum.

C.2 Variation in mean ipsilateral lung doses from 32 breast cancer radiotherapy fields targeting internal mammary lymph nodes first used in regimens in the Netherlands during 1970-2010

Table C.2: Variation in mean ipsilateral lung doses from 32 breast cancer radiotherapy fields targeting internal mammary lymph nodes first used in regimens in the Netherlands during 1970-2010.

Lung Volume	**Mean dose/total prescribed IMN field dose (%)**			
	Median	**IQR**	**Min.**	**Max.**
From 16 right IMN radiotherapy fields				
Whole lung	19.4	8.8	11.8	25.2
Right lung	32.5	15.8	20.2	42.7
Right upper lung lobe	38.8	15.9	27.1	52.2
Right middle lung lobe	26.7	7.4	20.8	60.8
Right lower lung lobe	24.7	20.8	5.7	36.8
From 16 left IMN radiotherapy fields				
Whole lung	12.7	6.0	8.5	21.6
Left lung	23.6	12.0	17.1	41.9
Left upper lung lobe	26.6	6.2	22.0	50.4
Left lower lung lobe	19.6	20.0	3.3	29.7

Footnotes
See Figure 4.3 for box plot.
Abbreviations: IMN=internal mammary lymph nodes, IQR=interquartile range, Max.=maximum, Min.=minimum.

C.3 Variation in mean ipsilateral lung doses from 6 breast cancer radiotherapy fields targeting supraclavicular lymph nodes first used in regimens in the Netherlands during 1970-2010

Table C.3: Variation in mean ipsilateral lung doses from six breast cancer radiotherapy fields targeting the supraclavicular lymph nodes first used in regimens in the Netherlands during 1970-2010.

Lung Volume	**Mean dose/total prescribed SF field dose (%)**			
	Median	**IQR**	**Min.**	**Max.**
From 3 right SF radiotherapy fields				
Whole lung	9.8	0.4	9.3	10.0
Right lung	16.4	0.5	16.1	17.0
Right upper lung lobe	23.4	5.1	22.7	32.8
Right middle lung lobe	13.3	6.4	1.3	14.0
Right lower lung lobe	10.2	4.0	2.4	10.3
From 3 left SF radiotherapy fields				
Whole lung	12.1	1.4	9.3	12.1
Left lung	22.3	1.65	20.0	23.3
Left upper lung lobe	29.3	1.35	27.9	30.6
Left lower lung lobe	13.7	4.95	4.2	14.1

Footnotes
See Figure 4.4 for box plot.
Abbreviations: SF=supraclavicular lymph nodes, IQR=interquartile range, Max.=maximum, Min.=minimum.

C.4 Variation in mean ipsilateral lung doses from 28 breast cancer radiotherapy fields targeting breast or chest wall first used in regimens in the Netherlands during 1970-2010

Table C.4: Variation in mean ipsilateral lung doses from 28 breast cancer radiotherapy fields targeting the breast or chest wall first used in regimens in the Netherlands during 1970-2010.

Lung Volume	**Mean dose/total prescribed Br/CW field dose (%)**			
	Median	**IQR**	**Min.**	**Max.**
From 14 right Br/CW radiotherapy fields				
Whole lung	4.4	6.8	2.7	17.5
Right lung	7.8	11.5	4.8	30.1
Right upper lung lobe	6.0	12.0	3.1	41.3
Right middle lung lobe	22.6	30.1	13.9	49.8
Right lower lung lobe	3.2	2.1	2.5	6.5
From 14 left Br/CW radiotherapy fields				
Whole lung	4.3	5.4	1.7	15.4
Left lung	9.4	11.0	3.7	30.8
Left upper lung lobe	14.1	17.7	5.0	48.4
Left lower lung lobe	2.6	1.3	1.7	4.7

Footnotes
See Figure 4.5 for box plot.
Abbreviations: Br=breast, CW=chest wall, IQR=interquartile range, Max.=maximum, Min.=minimum.

Appendix D

Supplementary material for Chapter 5: Mean whole lung doses from internal mammary lymph node radiotherapy for early breast cancer 1970-2025.

D.1 Category Definitions

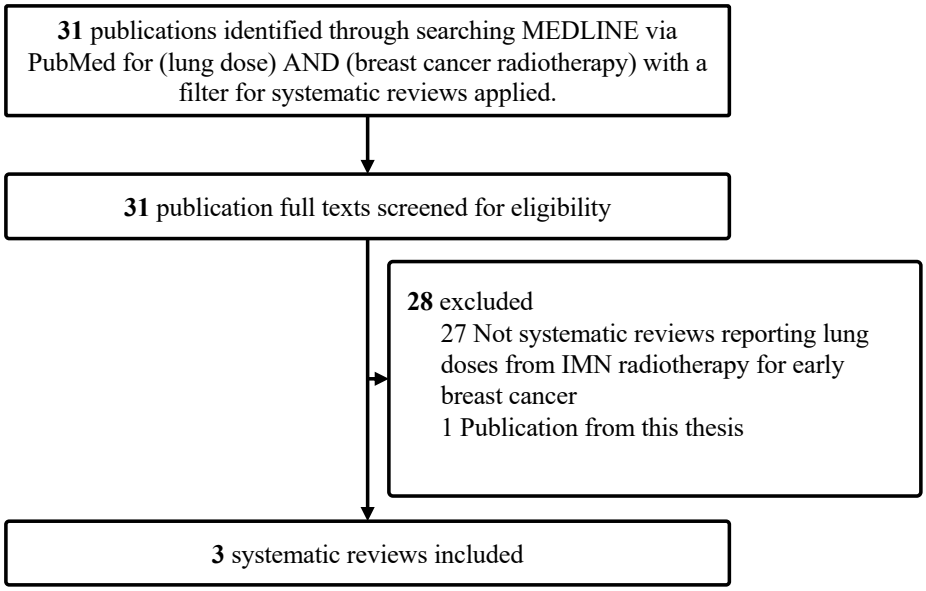
Fractionation	
Conventional	Fraction size of 1.8 to 2Gy.
Moderately hypofractionated	Fraction size of 2.65 to 3.3Gy.
Ultrafractionated	Fraction size of >5.2Gy.

IMN Beam arrangements	
Wide tangents	Fixed gantry angles of tangential breast/chest wall fields are rotated to extend the field across the midline to cover the internal mammary lymph nodes.
Partially wide tangents	Similar to wide tangents in that the gantry angles of tangential breast/chest wall fields are rotated to extend the field across the midline to cover the internal mammary lymph nodes, however, below the lymph nodes (e.g. the first three intercostal spaces), the remaining heart and lung are blocked by multileaf collimators.
Direct anterior	Gantry angle fixed at 0 degrees.
Oblique anterior	Gantry fixed at an acute angle.
IMRT static	Multiple static direct or oblique fields of IMRT (step and shoot).
IMRT rotational	Dynamic fields using a series of arcs, gantry rotates during treatment, using Tomotherapy (helical delivery) or a linear accelerator (e.g. volumetric modulated arc therapy).
IMPT	IMRT using pencil beam scanning proton beam therapy.

Treatment planning methods	
2D	Uses skin marking, and 2D x-ray images for planning.
3D conformal	Uses shaped fields planned on multiple CT images.
IMRT, forward-planned	Also called field-in-field planning, multiple CT images are used for planning and beam intensities and shapes are manually selected to achieve a dose distribution.
IMRT, inverse-planned	Multiple CT images are used for planning and the dose distribution is achieved by manually selecting the dose objectives and constraints and then allowing a computer algorithm to optimise the beams.
Hybrid	A combination of 3D Conformal and inverse-planned IMRT.
PBT	Proton beam therapy.

Abbreviations: CT=computed tomography, 2D=2 dimensional, 3D=3 dimensional, IMN=internal mammary lymph nodes, IMRT=intensity modulated radiotherapy, IMPT=intensity modulated proton beam therapy, PBT=proton beam therapy.

D.2 Process of study identification



D.2.1 References for three identified systematic reviews

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D.4 Average mean whole lung doses from internal mammary lymph node radiotherapy for early breast cancer, collated from this thesis and other published studies

Table D.1: Average mean whole lung doses from internal mammary lymph node radiotherapy for early breast cancer, collated from this thesis and other published studies

Study*	Yr RT†	No. doses‡	MLD (Gy)	(%)	Total dose (Gy)	Fr.§	IMN beam type§	IMN beam arrangement§	Treatment planning method§
Retrospective dosimetry, international trials, 1989-2008									
Kaija 1995	1989	54.5	3.6	7.3	50.0	C	MV	Wide tangents	3D conformal
Kaija 1995	1989	11.0	3.9	7.3	54.0	C	MV	Wide tangents	3D conformal
Kaija 1995	1989	54.5	8.5	17.1	50.0	C	MV	Wide tangents	3D conformal
Kaija 1995	1989	11.0	9.2	17.1	54.0	C	MV	Wide tangents	3D conformal
Hennequin 2013	1991	330.0	6.1	12.3	50.0	M	(MV, e^-)	Direct anterior	3D conformal
Hennequin 2013	1991	311.0	9.8	19.6	50.0	M	(MV, e^-)	Direct anterior	3D conformal
Poortmans 2015	1996	163.0	6.3	12.6	50.0	C	(MV, e^-)	Direct anterior	3D conformal
Poortmans 2015	1996	60.0	6.5	13.0	50.0	C	(MV, e^-)	Direct anterior	3D conformal
Poortmans 2015	1996	290.0	6.8	13.5	50.0	C	(MV, e^-)	Direct anterior	3D conformal
Poortmans 2015	1996	58.0	7.4	14.8	50.0	C	(MV, e^-)	Direct anterior	3D conformal
Poortmans 2015	1996	103.0	8.2	16.4	50.0	C	(MV, e^-)	Direct anterior	3D conformal
Poortmans 2015	1996	157.0	9.1	18.1	50.0	C	(MV, e^-)	Direct anterior	3D conformal
Poortmans 2015	1996	279.0	9.8	19.7	50.0	C	(MV, e^-)	Direct anterior	3D conformal
Poortmans 2015	1996	107.0	11.4	22.8	50.0	C	(MV, e^-)	Direct anterior	3D conformal
Whelan 2015	2000	286.0	5.1	10.3	50.0	C	MV	Partially wide tangents	3D conformal
Whelan 2015	2000	172.0	5.5	10.9	50.0	C	MV	Partially wide tangents	3D conformal

Study*	Yr RT†	No. doses‡	MLD (Gy)	(%)	Total dose (Gy)	Fr.§	IMN beam type§	IMN beam arrange-ment§	Treatment planning method§
Whelan 2015	2000	286.0	9.0	18.1	50.0	C	MV	Partially wide tangents	3D conformal
Whelan 2015	2000	172.0	9.1	18.1	50.0	C	MV	Partially wide tangents	3D conformal
Thorsen 2016	2003	265.0	6.8	14.1	48.0	C	MV	Partially wide tangents	3D conformal
Thorsen 2016	2003	962.0	7.3	15.2	48.0	C	e^-	Direct anterior	3D conformal
Thorsen 2016	2003	265.0	10.9	22.7	48.0	C	e^-	Oblique anterior	3D conformal
Kim 2022	2008	20.0	4.5	9.1	50.0	C	(MV, e^-)	Oblique anterior	3D conformal
Kim 2022	2008	20.0	4.6	9.2	50.0	C	(MV, e^-)	Oblique anterior	3D conformal
Kim 2022	2008	20.0	4.8	9.6	50.0	C	(MV, e^-)	Oblique anterior	3D conformal
Kim 2022	2008	30.0	5.2	10.4	50.0	C	e^-	Direct anterior	3D conformal
Kim 2022	2008	45.0	5.3	10.7	50.0	C	MV	Partially wide tangents	3D conformal
Kim 2022	2008	54.0	5.5	10.9	50.0	C	MV	Partially wide tangents	3D conformal
Kim 2022	2008	27.0	7.4	14.8	50.0	C	e^-	Direct anterior	3D conformal
Kim 2022	2008	18.0	8.1	16.1	50.0	C	(MV, e^-)	Oblique anterior	3D conformal

Study*	Yr RT†	No. doses‡	MLD (Gy)	(%)	Total dose (Gy)	Fr.§	IMN beam type§	IMN beam arrange-ment§	Treatment planning method§
Kim 2022	2008	18.0	8.1	16.1	50.0	C	(MV, e^-)	Oblique anterior	3D conformal
Kim 2022	2008	41.0	8.9	17.8	50.0	C	MV	Partially wide tangents	3D conformal
Kim 2022	2008	50.0	9.1	18.1	50.0	C	MV	Partially wide tangents	3D conformal
Kim 2022	2008	20.0	10.4	20.7	50.0	C	(MV, e^-)	Oblique anterior	3D conformal
Kim 2022	2008	18.0	10.6	21.2	50.0	C	(MV, e^-)	Oblique anterior	3D conformal
Kim 2022	2008	18.0	43.5	87.1	50.0	C	(MV, e^-)	Oblique anterior	3D conformal
Retrospective dosimetry, Netherlands cohort, 1970-2010									
NA	1971	58.0	4.5	12.0	37.2	M	OrthoV	Direct anterior	2D conformal
NA	1971	4.0	5.5	12.7	43.0	M	Co60	Direct anterior	2D conformal
NA	1971	58.0	6.3	17.0	37.2	M	OrthoV	Direct anterior	2D conformal
NA	1971	4.0	8.3	19.4	43.0	M	Co60	Direct anterior	2D conformal
NA	1973	7.5	6.9	NA	NPC	NPC	Co60	Direct anterior	2D conformal
NA	1973	7.5	10.4	NA	NPC	NPC	Co60	Direct anterior	2D conformal
NA	1975	18.0	4.4	9.7	45.0	M	e^-	Direct anterior	2D conformal
NA	1975	18.0	6.0	13.3	45.0	M	e^-	Direct anterior	2D conformal
NA	1975	10.5	11.8	NA	NPC	NPC	MV	Direct anterior	2D conformal
NA	1975	10.5	14.6	NA	NPC	NPC	MV	Direct anterior	2D conformal

Study*	Yr RT†	No. doses‡	MLD (Gy)	(%)	Total dose (Gy)	Fr.§	IMN beam type§	IMN beam arrange-ment§	Treatment planning method§
NA	1977	22.5	8.4	NA	NPC	NPC	Co60	Direct anterior	2D conformal
NA	1977	22.5	11.8	NA	NPC	NPC	Co60	Direct anterior	2D conformal
NA	1978	11.0	5.2	11.6	45.0	C	e^-	Direct anterior	2D conformal
NA	1978	11.0	7.2	16.0	45.0	C	e^-	Direct anterior	2D conformal
NA	1979	3.5	6.2	13.5	46.0	C	(MV, e^-)	Direct anterior	2D conformal
NA	1979	3.5	8.8	19.1	46.0	C	(MV, e^-)	Direct anterior	2D conformal
NA	1979	6.0	9.6	19.2	50.0	C	MV	Direct anterior	2D conformal
NA	1979	6.0	14.0	28.0	50.0	C	MV	Direct anterior	2D conformal
NA	1981	16.5	4.9	NA	NPC	NPC	(OrthoV, Co60)	Direct anterior	2D conformal
NA	1981	16.5	7.3	NA	NPC	NPC	(OrthoV, Co60)	Direct anterior	2D conformal
NA	1981	7.5	7.6	15.2	50.0	C	(MV, e^-)	Direct anterior	2D conformal
NA	1981	7.5	10.9	21.8	50.0	C	(MV, e^-)	Direct anterior	2D conformal
NA	1989	11.5	6.6	NA	NPC	NPC	(OrthoV, MV)	Direct anterior	2D conformal
NA	1989	11.5	10.0	NA	NPC	NPC	(OrthoV, MV)	Direct anterior	2D conformal
NA	1991	11.0	9.0	NA	NPC	NPC	(MV, e^-)	Direct anterior	2D conformal
NA	1991	11.0	12.1	NA	NPC	NPC	(MV, e^-)	Direct anterior	2D conformal
NA	1993	7.5	5.0	NA	NPC	NPC	(MV, e^-)	Direct anterior	2D conformal
NA	1993	7.5	7.5	NA	NPC	NPC	(MV, e^-)	Direct anterior	2D conformal
NA	2000	9.5	8.9	17.8	50.0	C	(MV, e^-)	Direct anterior	2D conformal

Study*	Yr RT†	No. doses‡	MLD (Gy)	(%)	Total dose (Gy)	Fr.§	IMN beam type§	IMN beam arrange-ment§	Treatment planning method§
NA	2000	9.5	10.3	20.6	50.0	C	(MV, e^-)	Direct anterior	2D conformal
NA	2003	10.5	7.6	15.2	50.0	C	(MV, e^-)	Oblique anterior	2D conformal
NA	2003	10.5	9.1	18.2	50.0	C	(MV, e^-)	Oblique anterior	2D conformal
Systematic review, UK, 2015-2023									
Holt 2024	2018	1.0	4.1	10.3	40.0	M	MV	IMRT static	IMRT, Forward
Dunlop 2019	2019	5.0	8.5	21.3	40.0	M	MV	IMRT rotational	IMRT, Inverse
Dunlop 2019	2019	5.0	8.5	21.3	40.0	M	MV	IMRT rotational	IMRT, Inverse
Gleeson 2022	2022	10.0	5.3	13.3	40.0	M	MV	IMRT static	IMRT, Inverse
Gleeson 2022	2022	10.0	6.6	16.5	40.0	M	MV	IMRT rotational	IMRT, Inverse
Gleeson 2022	2022	10.0	6.6	16.5	40.0	M	MV	IMRT rotational	IMRT, Inverse
Gleeson 2022	2022	10.0	7.0	17.5	40.0	M	MV	IMRT rotational	IMRT, Inverse
Gleeson 2023	2023	20.0	7.4	18.5	40.0	M	MV	IMRT rotational	IMRT, Inverse
Gleeson 2023	2023	20.0	7.6	19.0	40.0	M	MV	IMRT rotational	IMRT, Inverse
Systematic review, international, 2010-2015									

Study*	Yr RT†	No. doses‡	MLD (Gy)	(%)	Total dose (Gy)	Fr.§	IMN beam type§	IMN beam arrange-ment§	Treatment planning method§
Gauer 2010	2010	3.0	5.0	9.9	50.4	C	(MV, e^-)	Direct anterior	3D conformal
Gauer 2010	2010	3.0	6.6	13.1	50.4	C	e^-	IMRT static	IMRT, Forward
Jagsi 2010	2010	10.0	7.1	13.6	52.2	C	MV	IMRT static	IMRT, Forward
Popescu 2010	2010	5.0	7.3	14.5	50.0	C	MV	IMRT rotational	IMRT, Inverse
Jagsi 2010	2010	10.0	7.4	14.1	52.2	C	e^-	IMRT static	IMRT, Inverse
Gauer 2010	2010	3.0	7.4	14.6	50.4	C	MV	IMRT rotational	IMRT, Inverse
Ares 2010	2010	10.0	7.5	15.0	50.0	NS	Scanned $p+$	IMRT static	IMRT, Inverse
Ares 2010	2010	10.0	8.0	16.0	50.0	NS	Scanned $p+$	IMRT static	IMRT, Inverse
Jagsi 2010	2010	10.0	8.1	15.5	52.2	C	MV	IMRT static	IMRT, Forward
Popescu 2010	2010	5.0	9.3	18.6	50.0	C	MV	IMRT static	IMRT, Inverse
Popescu 2010	2010	5.0	9.5	18.9	50.0	C	MV	Partially wide tangents	3D conformal
Van der Laan 2010	2010	10.0	9.9	19.8	50.0	C	(MV, e^-)	IMRT static	IMRT, Forward
Van der Laan 2010	2010	10.0	10.2	20.4	50.0	C	MV	IMRT static	IMRT, Forward
Van der Laan 2010	2010	10.0	10.3	20.6	50.0	C	(MV, e^-)	Direct anterior	3D conformal
Jagsi 2010	2010	10.0	10.6	20.3	52.2	C	MV	IMRT static	IMRT, Inverse

Study*	Yr RT†	No. doses‡	MLD (Gy)	(%)	Total dose (Gy)	Fr.§	IMN beam type§	IMN beam arrange-ment§	Treatment planning method§
Ares 2010	2010	10.0	19.0	38.0	50.0	NS	MV	IMRT static	IMRT, Inverse
Ares 2010	2010	10.0	20.5	41.0	50.0	NS	MV	IMRT static	IMRT, Inverse
Ares 2010	2010	10.0	21.5	43.0	50.0	NS	(MV, e^-)	Oblique anterior	3D conformal
Ares 2010	2010	10.0	48.5	97.0	50.0	NS	(MV, e^-)	Oblique anterior	3D conformal
Erven 2011	2011	20.0	8.8	17.6	50.0	C	MV	Partially wide tangents	3D conformal
Erven 2011	2011	20.0	9.1	18.2	50.0	C	MV	Oblique anterior	3D conformal
Kainz 2012	2012	6.0	5.8	12.9	45.0	C	MV	IMRT rotational	IMRT, Inverse
Kainz 2012	2012	5.0	6.9	15.3	45.0	C	MV	IMRT rotational	IMRT, Inverse
Hejelstuen 2011	2012	17.0	8.1	16.2	50.0	C	MV	Wide tangents	3D conformal
Hejelstuen 2011	2012	17.0	10.3	20.6	50.0	C	MV	Wide tangents	3D conformal
Xu 2013	2013	10.0	3.0	5.9	50.4	C	(e^-, Scattered Protons)	Direct anterior	3D conformal
Xu 2013	2013	10.0	5.3	10.5	50.4	C	e^-	Direct anterior	3D conformal
Macdonald 2013	2013	12.0	6.0	11.9	50.4	C	Scattered Protons	Direct anterior	3D conformal
Xu 2013	2013	10.0	6.5	12.9	50.4	C	MV	IMRT static	IMRT, Inverse
Dincoglan 2013	2013	27.0	7.1	14.2	50.0	C	e^-	NS anterior	3D conformal

Study*	Yr RT†	No. doses‡	MLD (Gy)	(%)	Total dose (Gy)	Fr.§	IMN beam type§	IMN beam arrange-ment§	Treatment planning method§
Dincoglan 2013	2013	27.0	9.1	18.2	50.0	C	e^-	NS anterior	3D conformal
Osman 2014	2014	13.0	7.5	17.6	42.6	M	MV	IMRT rotational	IMRT, Inverse
Caudrelia 2014	2014	30.0	7.8	15.5	50.0	C	MV	IMRT rotational	IMRT, Inverse
Osman 2014	2014	13.0	7.8	18.3	42.6	M	MV	Partially wide tangents	IMRT, Forward
Wright 2014	2014	10.0	7.9	15.8	50.0	C	e^-	IMRT static	IMRT, Inverse
Osman 2014	2014	13.0	8.3	19.5	42.6	M	MV	IMRT rotational	IMRT, Inverse
Wright 2014	2014	10.0	8.4	16.8	50.0	C	e^-	Direct anterior	3D conformal
Wright 2014	2014	10.0	8.5	16.9	50.0	C	(MV, e^-)	Direct anterior	3D conformal
Osman 2014	2014	13.0	8.7	20.4	42.6	M	MV	Partially wide tangents	IMRT, Forward
Gultekin 2014	2014	10.0	9.2	18.4	50.0	C	MV	Partially wide tangents	3D conformal
Gultekin 2014	2014	10.0	10.2	20.4	50.0	C	(MV, e^-)	Direct anterior	3D conformal
Gultekin 2014	2014	10.0	11.1	22.2	50.0	C	(MV, e^-)	Direct anterior	3D conformal
Rudra 2014	2014	14.0	11.7	23.2	50.4	C	e^-	Direct anterior	3D conformal
Rudra 2014	2014	14.0	11.9	23.6	50.4	C	e^-	Direct anterior	3D conformal
Gultekin 2014	2014	10.0	12.1	24.2	50.0	C	e^-	Direct anterior	3D conformal
Zhang 2015	2015	15.0	8.7	17.3	50.0	C	MV	IMRT rotational	IMRT, Inverse

Study*	Yr RT†	No. doses‡	MLD (Gy)	(%)	Total dose (Gy)	Fr.§	IMN beam type§	IMN beam arrange-ment§	Treatment planning method§
Zhang 2015	2015	15.0	9.4	18.8	50.0	C	MV	IMRT static	IMRT, Inverse
Systematic review, international, 2015-2023									
Dasu 2018	2018	10.0	3.35	6.7	50.0	C	Scanned $p+$	IMRT static	IMRT, Inverse
Dasu 2019	2018	10.0	3.75	7.5	50.0	C	Scanned $p+$	IMRT static	IMRT, Inverse
Cartechini 2020	2020	5.0	3.8	7.6	50.0	C	Scanned $p+$	IMRT static	IMRT, Inverse
Cartechini 2020	2020	5.0	4.35	8.7	50.0	C	Scanned $p+$	IMRT static	IMRT, Inverse
Dumane 2018	2018	10.0	9.45	18.8	50.4	C	MV	IMRT rotational	IMRT, Inverse
Dumane 2018	2018	10.0	9.8	19.4	50.4	C	MV	IMRT rotational	Hybrid
Systematic review, international, 2018-2023									
Dumane 2018	2018	10.0	9.45	18.8	50.4	C	MV	IMRT rotational	IMRT, Inverse
Dumane 2018	2018	10.0	9.8	19.4	50.4	C	MV	IMRT rotational	Hybrid

Footnotes

See Appendix D.3 for study references.

†For data sourced from systematic reviews, where year RT first delivered was unavailable, it was substituted with year of publication.

‡Number of individual dose estimates contributing to the average.

§See Table D.1 for definitions

Abbreviations: C=conventional, Co60=cobalt 60 photons, 2D=2 dimensional, 3D=3 dimensional, e^-=electrons, Fr.=fractionation, Gy=Gray, IMN=internal mammary lymph node, IMRT=intensity modulated radiotherapy, M=moderately fractionated, MLD=mean lung dose, MV=megavoltage photons, NA=not applicable, No.=number, NS=not specified, NPC=not possible to calculate, OrthoV=orthovoltage photons, $p+$=protons, RT=radiotherapy, Yr=year.

Appendix E

Supplementary material for Chapter 6: Proton beam therapy for early breast cancer: a systematic review and meta-analysis of clinical outcomes.

E.1 Literature searches

Published studies

Terms used in searching Embase 1974 to 31st August 2022 and Ovid MEDLINE® 1946 to 1st September 2022.

1. exp breast cancer/
2. (breast$ adj5 (neoplas$ or carcinom$ or cancer$ or tumor$ or tumour$)).af.
3. 1 or 2
4. (advanced or metastatic or inoperable).ti.
5. locally advanced.af. or (neoadjuvant or adjuvant or early or operable).ti.
6. 4 not 5
7. 3 not 6
8. (proton$ and (therap$ or radiotherap$ or radiat$ or teletherap$)).af.
9. PBT.af.
10. 8 or 9
11. 7 and 10
12. human$/
13. nonhuman$/
14. 13 not (12 and 13)
15. 11 not 14
16. 15
17. limit 16 to yr="2000 -Current"

Abbreviations: exp=exploded term, $=unlimited truncation, adj5=terms next to each other, in any order, with up to 4 words in between, af=all fields, ti=title, yr=year.

Ongoing studies

Terms used in searching ClinicalTrials.gov to 30th September 2022, World Health Organisation International Clinical Trials Registry Platform to 30th October 2022, Cochrane Central Register of Controlled Trials to 30th September 2022.

1. breast cancer AND proton

E.2 Process of study identification

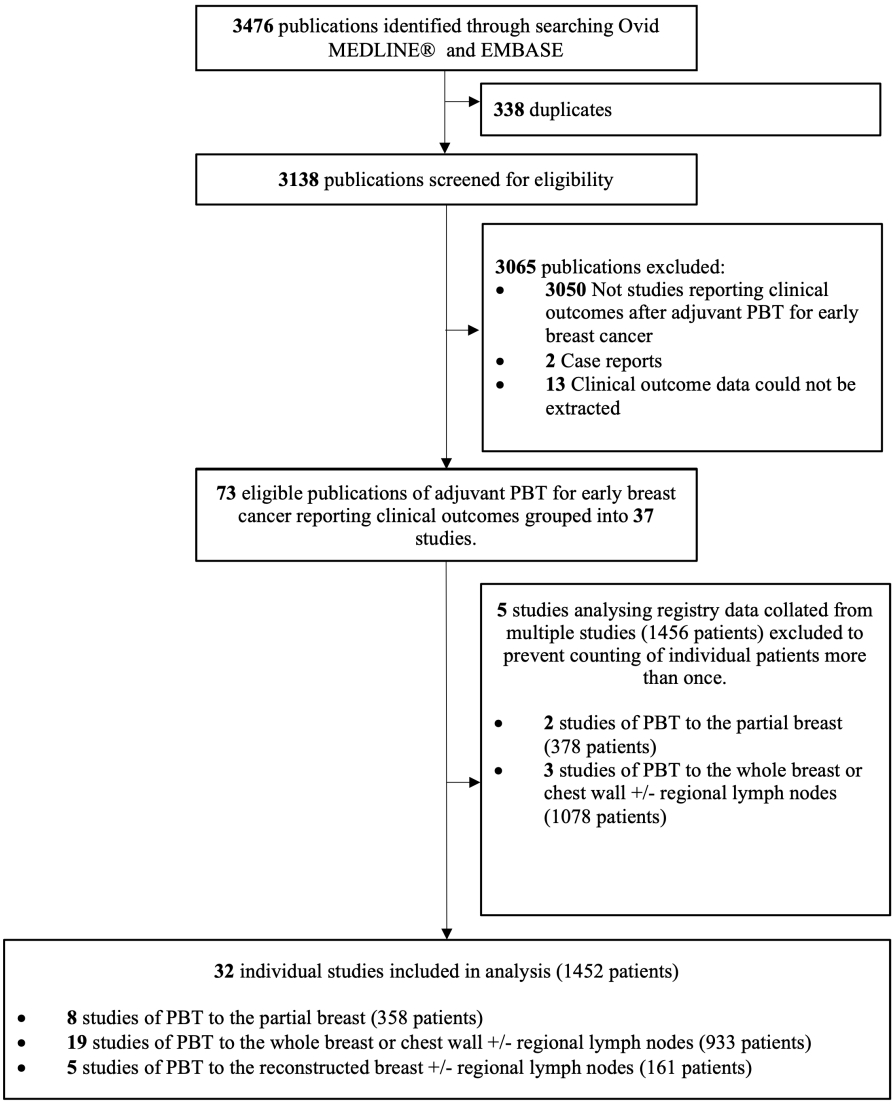


Figure E.1: Process of study identification: published studies
See Table E.1 for five studies analysing registry data collated from multiple studies.
Abbreviation: PBT=proton beam therapy.

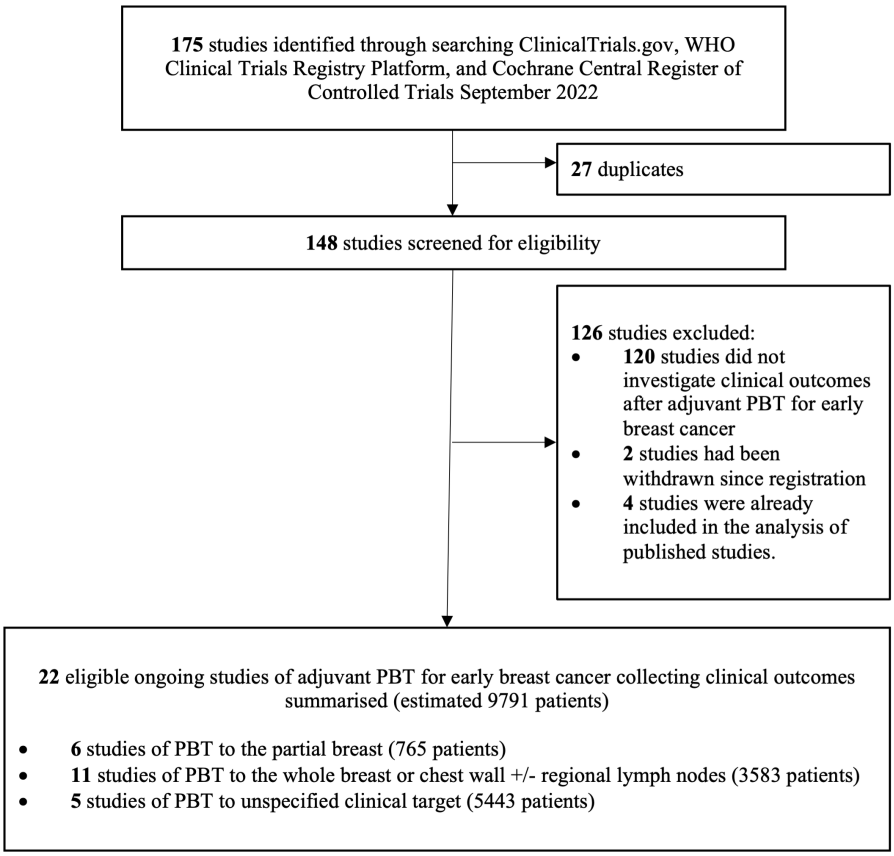


Figure E.2: Process of study identification: ongoing studies
Abbreviation: PBT=proton beam therapy.

E.3 Studies analysing multi-institutional registry data on clinical outcomes after proton beam therapy for early breast cancer

Table E.1: Studies analysing multi-institutional registry data on clinical outcomes after proton beam therapy for early breast cancer

Author and year of publication	Registry	Country	Year study started	Patients received PBT (N=1456)
Partial breast (378 patients)				
Scattering or scanning (335 patients)				
Fega 2017[1] *	PCG	USA	2011	335
Scanning (43 patients)				
Anderson 2019[2] *	PCG	International	–	43
Whole breast or chest wall ± regional lymph nodes (1078 patients)				
Scanning (82 patients)				
Thorpe 2020[3]	PCG	USA	2012	82
Type unspecified (996 patients)				
Chowdhary 2018[4]	NCD	USA	2004	871
Niska 2019[5] *	PCG	USA	2011	125

Footnotes
These studies analysing registry data collated from multiple institutions were excluded from the review to prevent counting of individual patients more than once. See Figure E.1.
Main study publication an abstract rather than a full text.
Abbreviations: N=total number, PBT=proton beam therapy, PCG=Proton Collaborative Group, NCD=National Cancer Database, USA=United States of America, "-"=unspecified.

E.3.1 References for Table E.1

1. Fega R, Vargas CE, Hartsell WF, et al. Clinical outcomes of breast proton radiation therapy: A multi-institutional analysis of the proton collaborative group registry. Int J Radiat Oncol Biol Phys. 2017;99 (Suppl):E182.

2. Anderson J, Niska JR, Thorpe CS, et al. Proton Beam Accelerated Partial-Breast Irradiation: Prospective Multi-Institutional PCG Registry Analysis. Int J Radiat Oncol Biol Phys. 2019;105 (Suppl):E49.

3. Thorpe CS, Niska JR, Anderson JD, et al. Acute toxicities after proton beam therapy following breast-conserving surgery for breast cancer: Multi-institutional prospective PCG registry analysis. Breast J. 2020;26:1760-64.

4. Chowdhary M, Barry P, Lee A, et al. Is proton therapy a "pro" for breast cancer? A comparison of proton vs. non-proton RT using the NCDB. Radiother and Oncol. 2019;133 (Suppl):S15.

5. Niska JR, Thorpe CS, Anderson J, et al. Post-Mastectomy Radiotherapy using Proton Beam Therapy: Prospective Multi-Institutional PCG Registry Analysis. Int J Radiat Oncol Biol Phys. 2019;105 (Suppl):E6.

E.4 Definitions of grades of radiation dermatitis by grading system.

Table E.2: Definitions of grades of radiation dermatitis by grading system.

Grading system *(Definition)*	**Grade 1**	**Grade 2**	**Grade 3**
CTCAE v4.0[1]&5.0[2] *(A finding of cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation.)*	Faint erythema or dry desquamation.	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema.	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion.
CTCAE v3.0[3] *(Dermatitis associated with radiation.)*	Faint erythema or dry desquamation.	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema.	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion.
CTC v2.0[4] *(Radiation dermatitis)*	Faint erythema or dry desquamation.	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema.	Radiation dermatitis grade 3 = confluent moist desquamation $\geq$1.5cm and not confined to skin folds; pitting oedema.
RTOG/EORTC[5] *(Skin (acute))*	Follicular, faint or dull erythema/epilation/dry desquamation/decreased sweating.	Tender or bright erythema, patchy moist desquamation/moderate edema.	Confluent, moist desquamation other than skin folds, pitting edema.

Footnotes

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events, CTC= Common Toxicity Criteria, EORTC= European Organisation for Research and Treatment of Cancer, RTOG=Radiation Therapy Oncology Group, v=version.

References for Table E.2

1. CTCAE version 5.0. NCI. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf Accessed September 20, 2022.

2. CTCAE version 4.03. NCI. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf Accessed Sept 2022 Accessed September 20, 2022.

3. CTCAE version 3.0. NCI. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf Accessed September 20, 2022.

4. CTC version 2.0. NCI. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf Accessed September 20, 2022.

5. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European organization for research and treatment of cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341-46.

E.5 References for Table 6.1

1. Pasalic D, Strom EA, Allen PK, et al. Proton Accelerated Partial Breast Irradiation: Clinical Outcomes at a Planned Interim Analysis of a Prospective Phase 2 Trial. Int J Radiat Oncol Biol Phys. 2021;109:441-8.

2. Ovalle V, Strom EA, Shaitelman S, et al. Proton Partial Breast Irradiation: Detailed Description of Acute Clinico-Radiologic Effects. Cancers. 2018;10:111.

3. Pasalic D, Strom EA, Allen PK, et al. Prospectively Assessed Outcomes for Proton Accelerated Partial Breast Irradiation. Int J Radiat Oncol Biol Phys. 2019;105(Suppl):S193.

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Table E.3: Adverse outcomes excluded from main analysis

Author and year of publication	Adverse outcome	Grading system	Reason for exclusion	Time assessed post-PBT (months)	Severe		Moderate		Mild		Unspecified	
					Affected/ Assessed	%	Affected/ Assessed	%	Affected/ Assessed	%	Affected/ Assessed	%
Partial breast												
Scattering												
Pasalic 2021	Pruritis	CTCAE v4.0	a	2	0/100	***0***	1/100	***1***	29/100	***29***	–	–
Kozak 2006	Moist desquamation	mild/moderate/severe	a	2	2/19	***11***	2/19	***11***	0/19	***0***	–	–
Scanning												
Choi 2022	Pruritus	CTCAE v4.0	a	35	0/38	***0***	0/38	***0***	1/38	***3***	–	–
	Vascular ischaemia	CTCAE v4.0	e	1	1/38	***3***	0/38	***0***	0/38	***0***	–	–
	Hot flashes	CTCAE v4.0	e	–	0/38	***0***	3/38	***8***	10/38	***26***	–	–
	Dyspnoea	CTCAE v4.0	e	–	0/38	***0***	1/38	***3***	0/38	***0***	–	–
	Cough	CTCAE v4.0	e	–	0/38	***0***	0/38	***0***	3/38	***8***	–	–
	Back pain	CTCAE v4.0	e	–	0/38	***0***	0/38	***0***	2/38	***5***	–	–
	Diarrhoea	CTCAE v4.0	e	–	0/38	***0***	0/38	***0***	1/38	***3***	–	–
	Arthralgia	CTCAE v4.0	e	–	0/38	***0***	0/38	***0***	2/38	***5***	–	–
Giap 2017	Dry skin	–	a	–	–	–	–	–	3/25	***12***	–	–
Mutter 2019	Seroma	CTCAE v4.0	e	0	0/76	***0***	0/76	***0***	25/76	***33***	–	–
Whole breast or Chest wall ± regional lymph nodes												
Scattering												
Bradley 2016	Nausea	CTCAE v4.0	e	–	0/18	***0***	1/18	***6***	–	–	–	–
Scattering or scanning												
Jimenez 2019	Seroma	CTCAE v4.0	e	–	1/69	***1***	0/69	***0***	0/69	***0***	–	–
Scanning												
Fattahi 2022	Wound dehiscence	CTCAE v5.0	e	–	–	–	–	–	–	–	1/19	***5***
Garda 2022	Limb oedema	CTCAE v4.0	c	32	0/11	***0***	0/11	***0***	2/11	***18***	–	–
Pasztorova 2018	Acute toxicity	RTOG	d	–	1/42	***2***	18/42	***43***	23/42	***55***	–	–
	Late toxicity	RTOG	d	–	3/42	***7***	7/42	***17***	12/42	***29***	–	–
Smith 2019	Haematoma	–	e	–	–	–	–	–	–	–	1/51	***2***
	Seroma		e	–	–	–	–	–	–	–	4/51	***8***
	Flap necrosis		e	–	–	–	–	–	–	–	2/51	***4***
Zheng 2017	Hot flashes	–	e	¿6	0/100	***0***	2/100	***2***	1/100	***1***	–	–
	Arthralgia		e	¿6	0/100	***0***	0/100	***0***	2/100	***2***	–	–
	Nipple deformation		b	¿6	0/100	***0***	0/100	***0***	2/100	***2***	–	–

Footnotes

a = May not be distinct from other included counts of dermatitis.

b = May or may not be distinct from other skin- or soft tissue- related adverse outcomes.

c = May or may not be distinct from included lymphoedema

d = Toxicity could not be categorised further.

e = Study authors categorised as unlikely related to radiotherapy.

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events, PBT=proton beam therapy, RTOG=Radiation Therapy Oncology Group, v=version, "-"=unspecified.

E.6 Dermatitis after proton beam therapy for early breast cancer in studies published 2000-2022 according to clinical target and proton beam therapy type

Table E.4: Dermatitis after proton beam therapy for early breast cancer in studies published 2000-2022 according to clinical target and proton beam therapy type

Author and year of publication	**PBT total dose (Gy) /fr.**	**Grading system**	**Time assessed post-PBT (months)**	**Total no. assessed**	**Severe**		**Moderate**		**Mild**	
					No. affected	*%*	**No. affected**	*%*	**No. affected**	*%*
Partial breast										
Scattering										
Kozak 2006	32/8*	mild/moderate/severe	2	19	7	***37***	3	***16***	4	***21***
Galland-Girodet 2014	32/8*	RTOG/EORTC	60	19	–	–	8	***42***	–	–
Pasalic 2021	34/10	CTCAE v4.0	1.5	100	0	***0***	11	***11***	56	***56***
Bush 2011	40/10	CTC v2.0	<3	50	0	***0***	4	***8***	26	***52***
Subtotal (partial breast, scattering)				**188**	7	***4***	26	***14***	86	***51***
Scanning										
Giap 2017	40/10	–	–	25	–	–	3	***12***	–	–
Choi 2022	40/10	CTCAE v4.0	35	38	0	***0***	1	***3***	27	***71***
Mutter 2019	22/3	CTCAE v4.0	0	76	0	***0***	0	***0***	52	***68***
Subtotal (partial breast, scanning)				**139**	0	***0***	4	***3***	79	***69***
Type unspecified										
Chang 2013	30/5	mild/moderate/severe	2	**30**	1	***3***	1	***3***	6	***20***
Total (partial breast)				**357**	8	***3***	31	***9***	171	***55***

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Dermatitis after proton beam therapy for early breast cancer in studies published 2000-2022 according to clinical target and proton beam therapy type *(Continued)*

Author and year of publication	PBT total dose (Gy) /fr.	Grading system	Time assessed post-PBT (months)	Total no. assessed	Severe		Moderate		Mild	
					No. affected	%	No. affected	%	No. affected	%
Whole breast or Chest wall ± regional lymph nodes										
Scattering										
Bradley 2016	50/28	CTCAE v4.0	<1	18	1	***6***	17	***94***	–	–
Sayan 2022	40-50/–	CTCAE v3.0	–	28	4	***14***	19	***68***	–	–
Liang 2018	50/25-28	CTCAE v4.0	–	23	10	***43***	13	***57***	–	–
Subtotal (whole breast or chest wall ± regional lymph nodes, scattering)				**69**	15	***22***	49	***71***	–	–
Scattering or scanning										
Jimenez 2019	45-50/25-28	CTCAE v4.0	–	**69**	2	***3***	57	***83***	10	***14***
Scanning										
Gergelis 2021	50/25	CTCAE v4.0	–	96	3	***3***	42	***44***	–	–
Mullikin 2020	50/25	CTCAE v5.0	–	126	8	***6***	58	***46***	60	***48***
Smith 2019	50/25	CTCAE v4.0	–	51	2	***4***	17	***33***	32	***63***
Luo 2019	50/–	CTCAE v4.0	<3	42	0	***0***	31	***74***	11	***26***
Verma 2017	50/25-28	CTCAE v4.0	–	93	5	***5***	67	***72***	21	***23***
Garda 2022	50/25	CTCAE v4.0	0	11	1	***9***	5	***45***	5	***45***
Loap 2021	50/25	–	–	1	–	–	1	***100***	–	–
DeCesaris 2021	50/25-28	–	–	100	10[†]	***10***	–	–	–	–
Verhoeven 2020	40/15	CTCAE v4.0	1	20	2	***10***	16	***80***	2	***10***
Fattahi 2022	50/25	CTCAE v5.0	–	19	2	***11***	17	***89***	–	–
DeCesaris 2019	45-50/25-28	CTCAE v4.0	–	39	2	***5***	25	***64***	12	***31***
Zheng 2017	45-50/25-28	–	<6	100	6	***6***	52	***52***	31	***31***
Cuaron 2017	49/–	CTCAE v4.0	–	26	0	***0***	12	***46***	–	–
Subtotal (whole breast or chest wall ± regional lymph nodes, scanning)				**724**	41	***6***	343	***55***	174	***36***
Total (whole breast or chest wall ± regional lymph nodes)				**862**	58	***7***	449	***52***	184	***21***
Total (all studies)				**1219**	66	***6***	480	***43***	355	***41***

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Dermatitis after proton beam therapy for early breast cancer in studies published 2000-2022 according to clinical target and proton beam therapy type *(Continued)*

Footnotes

Individual studies reporting dermatitis of a specified grade after PBT for early breast cancer. Summary percentages for each type of PBT are calculated using the total number of patients assessed for each grade of dermatitis. The total number of patients vary as not all studies assessed all grades of dermatitis.

Salari 2021 reported 5/16 patients with unspecified grade of dermatitis. These patients were excluded from this analysis.

Two fractions delivered daily. In all other studies where duration of treatment was reported, one fraction was delivered daily.

†One of the 10 severe adverse events was graded 4 for the reason of skin necrosis. All other severe adverse events were grade 3.

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events, EORTC=European Organisation for Research and Treatment of Cancer, fr=fractions, Gy=gray, No.=number, PBT=proton beam therapy, RTOG=Radiation Therapy Oncology Group, v=version, "-"=unspecified.

E.7 Adverse outcomes after proton beam therapy to the partial breast in studies published 2000-2022 according to proton beam therapy

Table E.5: Adverse outcomes after proton beam therapy to the partial breast in studies published 2000-2022 according to proton beam therapy.

Author and year of publication	**PBT dose (Gy)/fr.**	**Grading system**	**Time assessed post-PBT (months)**	**Total no. assessed**	**Severe**		**Moderate**		**Mild**		**Unspecified**	
					No. affected	**%**	**No. affected**	**%**	**No. affected**	**%**	**No. affected**	**%**
				Atrophy								
				Scattering								
Galland-Girodet 2014	32/8*	RTOG/EORTC	84	19	–	–	10	***53***	–	–	–	–
Total				**19**	–	–	10	***53***	–	–	–	–
				Breast oedema								
				Scattering								
Pasalic 2021	34/10*	CTCAE v4.0	2	100	0	***0***	0	***0***	10	***10***	–	–
Kozak 2006	32/8*	mild/moderate/severe	1	19	0	***0***	1	***5***	5	***26***	–	–
				Scanning								
Mutter 2019	22/3	CTCAE v4.0	0	76	0	***0***	0	***0***	17	***22***	–	–
Total				**195**	0	***0***	1	***1***	32	***16***	–	–
				Cardiac								
				Scattering								
Bush 2011	40/10	–	–	50	–	–	–	–	–	–	0	***0***
Total				**50**	–	–	–	–	–	–	0	***0***
				Fat necrosis								
				Scattering								
Pasalic 2021	34/10*	CTCAE v.40	36	100	0	***0***	0	***0***	0	***0***		–
Galland-Girodet 2014	32/8*	–	–	19	–	–	–	–	–	–	2	***11***
Bush 2011	40/10	–	–	50	0	***0***	0	***0***	0	***0***	0	***0***
Kozak 2006	32/8*	–	12	13	0	***0***	1	***8***	0	***0***	–	–
Total				**163**	0	***0***	1	***1***	**0**	***0***	2	***3***

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Adverse outcomes after proton beam therapy to the partial breast in studies published 2000-2022 according to proton beam therapy. *(Continued)*

Author and year of publication	**PBT dose (Gy)/fr.**	**Grading system**	**Time assessed post-PBT (months)**	**Total no. assessed**	**Severe**		**Moderate**		**Mild**		**Unspecified**	
					No. affected	**%**	**No. affected**	**%**	**No. affected**	**%**	**No. affected**	**%**
				Fatigue								
				Scattering								
Pasalic 2021	34/10*	CTCAE v4.0	12	100	0	***0***	4	***4***	10	***10***	–	–
				Scanning								
Choi 2022	40/10	CTCAE v4.0	35	38	0	***0***	1	***3***	8	***21***	–	–
Giap 2017	40/10	–	–	5	–	–	–	–	5	***100***	–	–
Total				**143**	0	***0***	5	***4***	23	***16***	–	–
				Fibrosis‡								
				Scattering								
Galland-Girodet 2014	32/8*	RTOG/EORTC	–	19	–	–	–	–	–	–	10	***53***
Kozak 2006	32/8*	mild/moderate/severe	1	19	0	***0***	1	***5***	3	***16***	–	–
				Scanning								
Mutter 2019	22/3	CTCAE v4.0	0	76	0	***0***	0	***0***	1	***1***	–	–
				Type unspecified								
Chang 2013	30/5	mild/moderate/severe	12	30	0	***0***	2	***7***	7	***23***	–	–
Total				**144**	0	***0***	3	***2***	11	***9***	10	***53***
				Hyperpigmentation								
				Scattering								
Pasalic 2021	34/10*	CTCAE v4.0	1.5	100	0	***0***	2	***2***	44	***44***	–	–
				Scanning								
Mutter 2019	22/3	CTCAE v4.0	3	72	0	***0***	0	***0***	13	***18***	–	–
				Type unspecified								
Chang 2013	30/5	mild/moderate/severe	2	30	0	***0***	9	***30***	21	***70***	–	–
Total				**202**	0	***0***	11	***5***	78	***39***		

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Adverse outcomes after proton beam therapy to the partial breast in studies published 2000-2022 according to proton beam therapy. *(Continued)*

Author and year of publication	PBT dose (Gy)/fr.	Grading system	Time assessed post-PBT (months)	Total no. assessed	Severe		Moderate		Mild		Unspecified	
					No. affected	%	No. affected	%	No. affected	%	No. affected	%
Infection												
Scattering												
Pasalic 2021	34/10*	CTCAE v4.0	1	100	0	***0***	1	***1***	0	***0***	–	–
Bush 2011	40/10	–	–	50	–	–	–	–	–	–	0	***0***
Scanning												
Mutter 2019	22/3	CTCAE v4.0	0	76	0	***0***	0	***0***	0	***0***	–	–
Total				**226**	0	***0***	1	***1***	0	***0***	0	***0***
Lymphoedema												
Scanning												
Choi 2022	40/10	CTCAE v4.0	35	38	0	***0***	1	***3***	2	***5***	–	–
Total				**38**	0	***0***	1	***3***	2	***5***	–	–
Pain§												
Scattering												
Pasalic 2021	34/10*	CTCAE v4.0	1.5	100	0	***0***	1	***1***	27	***27***	–	–
Galland-Girodet 2014	32/8*	RTOG/EORTC	36	19	–	–	–	–	–	–	4	***21***
Kozak 2006	32/8*	mild/moderate/severe	1	19	0	***0***	2	***11***	7	***37***	–	–
Scanning												
Mutter 2019	22/3	CTCAE v4.0	0	76	0	***0***	0	***0***	4	***5***	–	–
Choi 2022	40/10	CTCAE v4.0	35	38	0	***0***	0	***0***	5	***13***	–	–
Type unspecified												
Chang 2013	30/5	mild/moderate/severe	2	30	0	***0***	0	***0***	11	***37***	–	–
Total				**282**	0	***0***	3	***1***	54	***21***	4	***21***
Pneumonitis ¦												
Scattering												
Galland-Girodet 2014	32/8*	CTCAE v3.0	–	20	0	***0***	0	***0***	0	***0***	–	–
Bush 2011	40/10	–	–	50	–	–	–	–	–	–	0	***0***
Scanning												
Mutter 2019	22/3	CTCAE v4.0	0	76	0	***0***	0	***0***	0	***0***	–	–
Total				**146**	0	***0***	0	***0***	0	***0***	0	***0***

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Adverse outcomes after proton beam therapy to the partial breast in studies published 2000-2022 according to proton beam therapy. *(Continued)*

Author and year of publication	**PBT dose (Gy)/fr.**	**Grading system**	**Time assessed post-PBT (months)**	**Total no. assessed**	**Severe**		**Moderate**		**Mild**		**Unspecified**	
					No. affected	*%*	**No. affected**	*%*	**No. affected**	*%*	**No. affected**	*%*
				Rib fractures								
				Scattering								
Galland-Girodet 2014	32/8*	–	60	19	–	–	–	–	–	–	1	***5***
Bush 2011	40/10*	–	–	50	–	–	–	–	–	–	0	***0***
Kozak 2006	32/8*	–	6	20	–	–	–	–	–	–	1	***5***
				Scanning								
Mutter 2019	22/3	–	12	76	–	–	–	–	–	–	0	***0***
				Type unspecified								
Chang 2013	30/5	Symptoms†	24	30	–	–	–	–	–	–	2	***7***
Total				**195**	–	–	–	–	–	–	**4**	***2***

Continued on next page.

Adverse outcomes after proton beam therapy to the partial breast in studies published 2000-2022 according to proton beam therapy. *(Continued)*

Author and year of publication	**PBT dose (Gy)/fr.**	**Grading system**	**Time assessed post-PBT (months)**	**Total no. assessed**	**Severe**		**Moderate**		**Mild**		**Unspecified**	
					No. affected	*%*	**No. affected**	*%*	**No. affected**	*%*	**No. affected**	*%*
				Telangiectasia								
				Scattering								
Pasalic 2021	34/10*	CTCAE v4.0	18	100	–	–	–	–	17	***17***	–	–
Galland-Girodet 2014	32/8*	RTOG/EORTC	84	19	–	–	–	–	–	–	7	***37***
Bush 2011	40/10	CTC v2.0	–	50	–	–	–	–	3	***6***	–	–
Kozak 2006	32/8*	–	24	20	–	–	–	–	–	–	3	***15***
				Scanning								
Mutter 2019	22/3	CTCAE v4.0	3	72	0	***0***	0	***0***	1	***1***	–	–
Choi 2022	40/10	CTCAE v4.0	35	38	0	***0***	0	***0***	1	***3***	–	–
				Type unspecified								
Chang 2013	30/5	–	–	–	–	–	–	–	–	–	–	–
Total				**299**	0	***0***	0	***0***	22	***8***	10	***26***

Footnotes

Denominators for each study vary by adverse outcome as not all studies assessed all patients at all timepoints for all adverse outcomes.

Two fractions delivered daily. In all other studies where duration of treatment was reported, one PBT fraction was delivered daily.

†Symptomatic with traumatic change on bone scanning without dislocation.

‡Fibrosis includes reports of induration.

§Includes reports of pain from skin, breast and unspecified pain.

¦Includes reports of cough and dyspnoea.

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events, CTC=Common Toxicity Criteria, Gy=Gray, No.=number, PBT=proton beam therapy, RTOG/EORTC=Radiation Therapy Oncology Group and the European organization for research and treatment of cancer, v=version. Blank or "-"=unspecified.

E.8 Adverse outcomes after proton beam therapy to the whole breast or chest wall ± regional lymph nodes in studies published 2000-2022 according to proton beam therapy

Table E.6: Adverse outcomes after proton beam therapy to the whole breast or chest wall ± regional lymph nodes in studies published 2000-2022 according to proton beam therapy type.

Author and year of publication	PBT dose (Gy)/fr.	Grading system	Time assessed post-PBT (months)	Total no. assessed	Severe		Moderate		Mild		Unspecified	
					No. affected	%	No. affected	%	No. affected	%	No. affected	%
Atrophy												
Scattering												
Bradley 2016	50/28	CTCAE v4.0	–	18	0	***0***	1	***6***	–	–	–	–
Scattering or scanning proton beam therapy												
Jimenez 2019	45-50/25-28	CTCAE v4.0	–	69	–	–	–	–	1	***1***	–	–
Total				**87**	0	***0***	1	***6***	1	***1***	–	–
Brachial plexopathy												
Scanning												
Garda 2022	50/25	CTCAE v4.0	32	11	0	***0***	0	***0***	1	***9***	–	–
Smith 2019	50/25	CTCAE v4.0	0	51	0	***0***	0	***0***	1	***2***	–	–
Luo 2019	50/–	CTCAE v4.0	>3	42	0	***0***	0	***0***	0	***0***	–	–
Zheng 2017	45-50/25-28	–	>6	100	0	***0***	0	***0***	1	***1***	–	–
Total				**204**	0	***0***	0	***0***	3	***1***	–	–
Cardiac												
Scattering												
Bradley 2016	50/28	CTCAE v4.0	–	18	0	***0***	–	–	–	–	2	***11***
Scanning												
Loap 2021	50/25	–	–	1	0	***0***	0	***0***	0	***0***	–	–
DeCesaris 2021	50/25-28	–	–	100	0	***0***	0	***0***	0	***0***	–	–
Smith 2019	50/25	CTCAE v4.0	–	51	0	***0***	0	***0***	0	***0***	–	–
Luo 2019	50/–	CTCAE v4.0	–	42	0	***0***	0	***0***	0	***0***	–	–
Cuaron 2017	49/–	CTCAE v4.0	–	26	0	***0***	0	***0***	0	***0***	–	–
Total				**238**	0	***0***	0	***0***	0	***0***	2	***11***

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Adverse outcomes after proton beam therapy to the whole breast or chest wall ± regional lymph nodes in studies published 2000-2022 according to proton beam therapy type.*(Continued)*

Author and year of publication	PBT dose (Gy)/fr.	Grading system	Time assessed post-PBT (months)	Total no. assessed	Severe		Moderate		Mild		Unspecified	
					No. affected	%	No. affected	%	No. affected	%	No. affected	%
Decreased shoulder movement												
Scanning												
Garda 2022	50/25	CTCAE v4.0	3	11	0	***0***	0	***0***	4	***36***	–	–
Fattahi 2022	50/25	CTCAE v5.0	–	19	–	–	1	***5***	2	***11***	–	–
Total				**30**	0	***0***	1	***3***	6	***20***	–	–
Fatigue												
Scattering												
Bradley 2016	50/28	CTCAE v4.0	<3	18	0	***0***	6	***33***	–	–	–	–
Scattering or scanning												
Jimenez 2019	45-50/25-28	CTCAE v4.0	–	69	0	***0***	24	***35***	38	***55***	–	–
Scanning												
Garda 2022	50/25	CTCAE v4.0	0	11	0	***0***	1	***9***	7	***64***	–	–
Luo 2019	50/–	CTCAE v4.0	<3	42	0	***0***	1	***2***	12	***29***	–	–
Verma 2017	50/25-28	CTCAE v4.0	–	91	0	***0***	5	***5***	42	***46***	–	–
Total				**231**	0	***0***	37	***16***	99	***46***	–	–
Fibrosis§												
Scanning												
Garda 2022	50/25	CTCAE v4.0	32	11	0	***0***	0	***0***	4	***36***	–	–
Fattahi 2022	50/25	CTCAE v5.0	–	19	–	–	–	–	2	***11***	–	–
Cuaron 2017	49/–	CTCAE v4.0	–	26	–	–	1	***4***	3	***12***	–	–
Total				**56**	0	***0***	1	***3***	9	***16***	–	–

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Adverse outcomes after proton beam therapy to the whole breast or chest wall ± regional lymph nodes in studies published 2000-2022 according to proton beam therapy type.*(Continued)*

Author and year of publication	PBT dose (Gy)/fr.	Grading system	Time assessed post-PBT (months)	Total no. assessed	Severe		Moderate		Mild		Unspecified	
					No. affected	%	No. affected	%	No. affected	%	No. affected	%
Hyperpigmentation												
Scattering or scanning												
Jimenez 2019	45-50/25-28	CTCAE v4.0	–	69	–	–	–	–	36	***52***	–	–
Scanning												
Garda 2022	50/25	CTCAE v4.0	3	11	0	***0***	0	***0***	8	***73***	–	–
Fattahi 2022	50/25	CTCAE v5.1	–	19	–	–	–	–	–	–	8	***42***
Mullikin 2020	50/25	CTCAE v5.0	–	126	0	***0***	0	***0***	55	***44***	–	–
Luo 2019	50/–	CTCAE v4.0	>3	42	–	–	0	***0***	17	***40***	–	–
DeCesaris 2019	45-50/25-28	CTCAE v4.0	–	39	0	***0***	3	***8***	14	***36***	–	–
Cuaron 2017	49/–	CTCAE v4.0	–	26	–	–	–	–	12	***46***	–	–
Total				**332**	0	***0***	3	***1***	142	***45***	8	***42***
Infection												
Scattering												
Bradley 2016	50/28	CTCAE v4.0	–	18	3	***17***	3	***17***	–	–	–	–
Scattering or scanning												
Jimenez 2019	45-50/25-28	CTCAE v4.0	4	69	1	***1***	0	***0***	0	***0***	–	–
Scanning												
Garda 2022	50/25	CTCAE v4.0	32	11	0	***0***	0	***0***	0	***0***	–	–
Mullikin 2020	50/25	CTCAE v5.0	–	126	1	***1***	0	***0***	0	***0***	–	–
Fattahi 2022	50/25	CTCAE v5.0	–	19	–	–	2	***11***	–	–	–	–
Verma 2017	50/25-28	CTCAE v4.0	–	91	–	–	–	–	–	–	7	***8***
Total				**334**	5	***2***	5	***2***	0	***0***	7	***8***

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Adverse outcomes after proton beam therapy to the whole breast or chest wall ± regional lymph nodes in studies published 2000-2022 according to proton beam therapy type.*(Continued)*

Author and year of publication	**PBT dose (Gy)/fr.**	**Grading system**	**Time assessed post-PBT (months)**	**Total no. assessed**	**Severe**		**Moderate**		**Mild**		**Unspecified**	
					No. affected	*%*	**No. affected**	*%*	**No. affected**	*%*	**No. affected**	*%*
				Lymphoedema								
				Scattering								
Sayan 2022	40-50/–	CTCAE v3.0	–	28	–	–	–	–	–	–	5	***18***
Bradley 2016	50/28	CTCAE v4.0	–	18	0	***0***	1	***6***	–	–	–	–
				Scattering or scanning								
Jimenez 2019	45-50/25-28	CTCAE v4.0	–	69	0	***0***	0	***0***	1	***1***	–	–
				Scanning								
Garda 2022	50/25	CTCAE v4.0	0	11	0	***0***	0	***0***	2	***18***	–	–
Fattahi 2022	50/25	CTCAE v5.0	–	19	–	–	3	***16***	5	***26***	–	–
Luo 2019	50/–	CTCAE v4.0	>3	42	0	***0***	0	***0***	12	***29***	–	–
Zheng 2017	45-50/25-28	–	>6	100	0	***0***	0	***0***	2	***2***	–	–
Verma 2017	50/25-28	CTCAE v4.0	–	91	–	–	–	–	–	–	3	***3***
Total				**378**	0	***0***	4	***2***	22	***9***	8	***7***

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Adverse outcomes after proton beam therapy to the whole breast or chest wall ± regional lymph nodes in studies published 2000-2022 according to proton beam therapy type.*(Continued)*

Author and year of publication	**PBT dose (Gy)/fr.**	**Grading system**	**Time assessed post-PBT (months)**	**Total no. assessed**	**Severe**		**Moderate**		**Mild**		**Unspecified**	
					No. affected	**%**	**No. affected**	**%**	**No. affected**	**%**	**No. affected**	**%**
				Oesophagitis†								
				Scattering								
Sayan 2022	40-50/–	CTCAE v3.0	–	28	–	–	1	***4***	–	–	–	–
Bradley 2016	50/28	CTCAE v4.0	–	18	0	***0***	5	***28***	–	–	–	–
				Scattering or scanning								
Jimenez 2019	45-50/25-28	CTCAE v4.0	–	69	0	***0***	5	***7***	19	***28***	–	–
				Scanning								
Garda 2022	50/25	CTCAE v4.0	0	11	0	***0***	0	***0***	1	***9***	–	–
Verhoeven 2020	40/15	CTCAE v4.0	1	15	0	***0***	4	***27***	4	***27***	–	–
Mullikin 2020	50/25	CTCAE v5.0	–	126	0	***0***	0	***0***	9	***7***	–	–
Fattahi 2022	50/25	CTCAE v5.0	–	19			1	***5***	2	***11***	–	–
Smith 2019	50/25	CTCAE v4.0	–	51	0	***0***	1	***2***	3	***6***	–	–
Luo 2019	50/–	CTCAE v4.0	<3	42	0	***0***	7	***17***	15	***36***	–	–
Zheng 2017	45-50/25-28	–	<6	100	–	–	–	–	–	–	2	***2***
Verma 2017	50/25-28	CTCAE v4.0	–	91	0	***0***	30	***33***	28	***31***	–	–
Total				**570**	0	***0***	54	***11***	81	***19***	2	***2***

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Adverse outcomes after proton beam therapy to the whole breast or chest wall ± regional lymph nodes in studies published 2000-2022 according to proton beam therapy type.*(Continued)*

Author and year of publication	PBT dose (Gy)/fr.	Grading system	Time assessed post-PBT (months)	Total no. assessed	Severe		Moderate		Mild		Unspecified	
					No. affected	%	No. affected	%	No. affected	%	No. affected	%
Pain*												
Scattering												
Sayan 2022	40-50/–	CTCAE v3.0	–	28	–	–	9	***32***	–	–	–	–
Bradley 2016	50/28	CTCAE v4.0	<1	18	0	***0***	–	–	–	–	1	***6***
Scanning												
Garda 2022	50/25	CTCAE v4.0	0	11	0	***0***	0	***0***	1	***9***	–	–
Salari 2021	43 or 50/16 or 25	–	2	31	–	–	–	–	–	–	6	***19***
Loap 2021	50/25	–	–	1	–	–	–	–	1	***100***	–	–
Mullikin 2020	50/25	–	–	126	–	–	0	***0***	–	–	–	–
Fattahi 2022	50/25	CTCAE v5.0	–	19	–	–	–	–	2	***11***	–	–
Luo 2019	50/–	CTCAE v4.0	<3	42	0	***0***	10	***24***	5	***12***	–	–
Zheng 2017	45-50/25-28	–	<6	100	0	***0***	0	***0***	1	***1***	–	–
Verma 2017	50/25-28	CTCAE v4.0	–	93	1	***1***	27	***29***	47	***51***	–	–
Total				**469**	1	***0***	46	***12***	57	***21***	7	***14***

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Adverse outcomes after proton beam therapy to the whole breast or chest wall ± regional lymph nodes in studies published 2000-2022 according to proton beam therapy type.*(Continued)*

Author and year of publication	**PBT dose (Gy)/fr.**	**Grading system**	**Time assessed post-PBT (months)**	**Total no. assessed**	**Severe**		**Moderate**		**Mild**		**Unspecified**	
					No. affected	**%**	**No. affected**	**%**	**No. affected**	**%**	**No. affected**	**%**
				Pneumonitis‡								
				Scattering								
Bradley 2016	50/28	CTCAE v4.0	3	18	0	***0***	2	***11***	–	–	–	–
				Scattering or scanning								
Jimenez 2019	45-50/25-28	CTCAE v4.0	4	69	0	***0***	1	***1***	3	***4***	–	–
				Scanning								
Garda 2022	50/25	CTCAE v4.0	32	11	0	***0***	0	***0***	0	***0***	–	–
Loap 2021	50/25	–		1	0	***0***	0	***0***	0	***0***	–	–
Mullikin 2020	50/25	CTCAE v5.0	–	126	0	***0***	0	***0***	0	***0***	–	–
Fattahi 2022	50/25	CTCAE v5.0	–	19	–	–	–	–	2	***11***	–	–
Smith 2019	50/25	CTCAE v4.0	–	51	0	***0***	0	***0***	0	***0***	–	–
Luo 2019	50/–	CTCAE v4.0	12	42	1	***2***	0	***0***	0	***0***	–	–
Cuaron 2017	49/–	CTCAE v4.0	–	26	0	***0***	0	***0***	0	***0***	–	–
Total				**363**	1	***0***	3	***1***	5	***1***	–	–

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Adverse outcomes after proton beam therapy to the whole breast or chest wall ± regional lymph nodes in studies published 2000-2022 according to proton beam therapy type.*(Continued)*

Author and year of publication	PBT dose (Gy)/fr.	Grading system	Time assessed post-PBT (months)	Total no. assessed	Severe		Moderate		Mild		Unspecified	
					No. affected	%	No. affected	%	No. affected	%	No. affected	%
Rib fractures												
Scattering												
Bradley 2016	50/28	CTCAE v4.0	7	18	–	–	–	–	–	–	1	***6***
Scattering or scanning												
Jimenez 2019	45-50/25-28	CTCAE v4.0	16	69	0	***0***	0	***0***	5	***7***	–	–
Scanning												
Garda 2022	50/25	CTCAE v4.0	32	11	0	***0***	0	***0***	0	***0***	–	–
Mullikin 2020	50/25	CTCAE v5.0	14	126	0	***0***	0	***0***	1	***1***	–	–
Fattahi 2022	50/25	–	44	19	–	–	–	–	–	–	4	***21***
Smith 2019	50/25	–	–	51	–	–	–	–	–	–	0	***0***
Luo 2019	50/–	CTCAE v4.0	>3	42	0	***0***	0	***0***	0	***0***	0	***0***
Verma 2017	50/25-28	CTCAE v4.0	39	91	–	–	–	–	–	–	2	***2***
Cuaron 2017	49/–	CTCAE v4.0	–	26	0	***0***	0	***0***	0	***0***	–	–
Total				**453**	0	***0***	0	***0***	6	***2***	7	***3***

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Adverse outcomes after proton beam therapy to the whole breast or chest wall ± regional lymph nodes in studies published 2000-2022 according to proton beam therapy type.*(Continued)*

Author and year of publication	PBT dose (Gy)/fr.	Grading system	Time assessed post-PBT (months)	Total no. assessed	Severe		Moderate		Mild		Unspecified	
					No. affected	%	No. affected	%	No. affected	%	No. affected	%
Telangiectasia												
Scattering or scanning												
Jimenez 2019	45-50/25-28	CTCAE v4.0	12	69	–	–	–	–	11	***16***	–	–
Scanning												
Mullikin 2020	50/25	CTCAE v5.0	–	126	0	***0***	0	***0***	1	***1***	–	–
Fattahi 2022	50/25	CTCAE v5.0	0	13	0	***0***	0	***0***	0	***0***	0	***0***
Luo 2019	50/–	CTCAE v4.0	>3	42	–	–	0	***0***	1	***2***	–	–
Cuaron 2017	49/–	CTCAE v4.0	–	26	–	–	–	–	1	***4***	–	–
Total				**276**	**0**	***0***	**0**	***0***	**14**	***5***	**0**	***0***

Footnotes

Denominators for each study vary by adverse outcome as not all studies assessed all patients at all timepoints for all adverse outcomes.

Includes reports of pain from skin, breast and unspecified pain.

†Oesophagitis includes reports of dysphagia.

‡Pneumonitis includes reports of cough and dyspnoea.

§Fibrosis includes reports of induration.

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events, fr=fractions, Gy=Gray, No.=number, PBT=proton beam therapy, v=version. Blank or "-"=unspecified.

E.9 Meta-analyses of the percentage of patients with moderate and mild dermatitis after scanning proton beam therapy to the whole breast or chest wall ± regional lymph nodes.

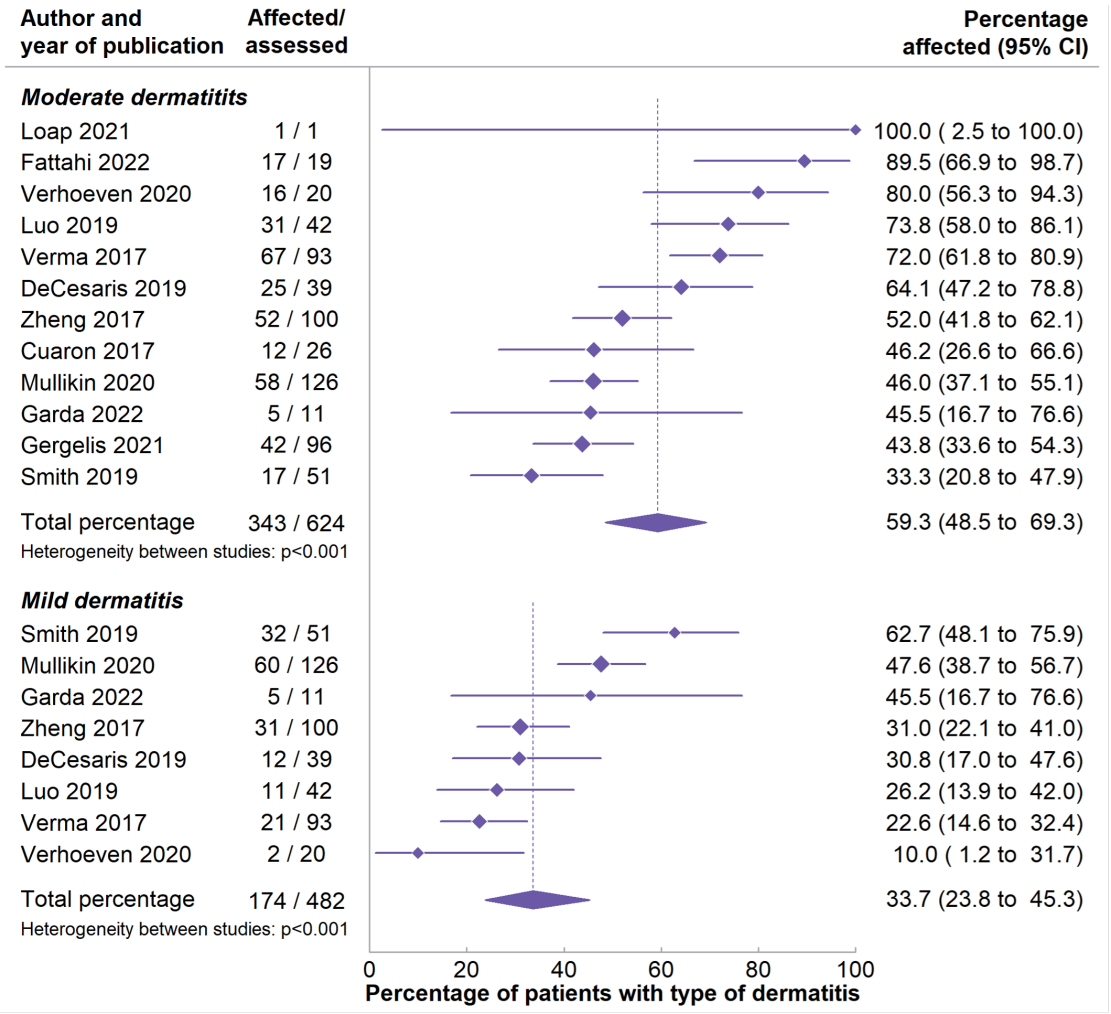


Figure E.3: Meta-analyses of the percentage of patients with moderate and mild dermatitis after scanning proton beam therapy to the whole breast or chest wall ± regional lymph nodes.
The estimates for the total percentages and confidence intervals allow for heterogeneity between studies.

E.10 Ongoing studies of proton beam therapy for early breast cancer

Table E.7: Ongoing randomised studies of proton beam therapy for early breast cancer

Study ID Country	Study yrs	Pts	Study arms: Intervention		Planned study outcomes	
			Beam type	Total dose (Gy) /fr.	Primary	Secondary
Whole breast/chest wall ± regional lymph nodes (3298 patients)						
NCT04291378 Denmark	2020-37	1502	PBT	50/25	Ischaemic and valvular heart disease at 10 years	Second cancers, distant failure, acute and late morbidity, patient reported outcome measures, incidence of cardiac disease on blood markers and imaging.
			Photon	50/25		
NCT02603341* USA	2016-32	1278	PBT	50/25 (±SIB)	Major cardiovascular events at 10 years.	Disease control, quality of life, association between radiation dose distribution to heart and other normal tissues with quality of life and cardiac toxicity, breast cancer specific survival, overall survival.
			Photon	50/25(±SIB)		
ISRCTN14220944 UK	2022-30	192	PBT: scanning	40/15	Mean heart dose, and patient-reported normal tissue toxicity in the breast at 2 years.	Lung and contralateral breast doses, clinician-reported toxicity at 1 year, health-related quality of life, health economic, changes to planned RT pathway, second cancers at 5 years, recurrence and survival at 5 years, incidence of major cardiac events at 5 years, other dosimetric.
			Photon: IMRT	40/15		
TCTR20210219004 Thailand	2021-21	140	PBT	Ultrahypofractionation	Acute skin toxicity at 3 months.	Cosmesis at 3 months, late toxicity at 1 year, locoregional recurrence and distant metastases at 2 years.
			Photon	Ultrahypofractionation		
NCT04443413 USA	2020-23	98	PBT	–/5 (±5 boost)	≥ grade 3 adverse events, unplanned surgical intervention after reconstruction at 2 years.	Acute and late toxicity, 5 year locoregional control, disease free survival, cause-specific survival, overall survival.
			Photon	–/25 (±4 boost)		
NCT02783690 USA	2016-25	88	PBT: scanning	40/15	≥ grade 3 adverse events, unplanned surgical intervention after reconstruction at 2 years	Acute and late toxicity, quality of life, cosmesis, ipsilateral breast tumour recurrence, distant recurrence, disease free survival, overall survival.
			PBT: scanning	50/25		

Footnotes as for Table E.8.

Table E.8: Ongoing non-randomised studies of proton beam therapy for early breast cancer.

Study ID Country	Study yrs	Pts	Study arms: Intervention		Planned study outcomes	
			Beam type	Total dose (Gy) /fr.	Primary	Secondary
Whole breast/chest wall ± regional lymph nodes (285 patients)						
NCT01758445 USA	2013-30	220	PBT	– /≥28 (± 6-9)	Acute and late toxicites at 5 years	Local control, regional control, disease free survival, second cancers, cardiac disease, quality of life, dosimetry
NCT02725840 USA	2016-22	41	PBT	–	Lung vascular damage on CT at 2 years;blood cytokines post radiation at 2 years;correlations between vascular damage on CT scans with pulmonary function test outcomes	≥Grade 2 lung toxicity, pattern of lung metastases, overall survival
			Photon: IMRT	–		
NCT02199366 USA	2014-21	24	PBT	–	Changes in cardiac function on cardiac MRI at baseline and 1 year	Major cardiac side effects (myocardial infarction, valve disorder, congestive heart failure, and angina), quality of life
			Photon	–		

Continued on next page.

Ongoing non-randomised studies of proton beam therapy for early breast cancer. *(Continued)*

Study ID Country	Study yrs	Pts	Study arms: Intervention		Planned study outcomes	
			Beam type	Total dose (Gy) /fr.	Primary	Secondary
Partial breast (765 patients)						
NCT01245712 USA	2010-22	200	PBT	– /10	Patient reported cosmesis at 1 year	Local control, acute ≥grade 3 dermatitis
NCT02453737 USA	2015-22	198	PBT	21.9/3	Change in rate of fair/poor cosmesis at 3 years compared with baseline	–
			Photon: 3DCRT	21.9/3		
			Brachytherapy	21.0/3		
NCT01310530 USA	2011-25	150	PBT	40/10	Breast cancer recurrence at 5 years	Breast cancer recurrence in low versus intermediate risk women, disease free survival, treatment side-effects.
NCT01766297* USA	2013-33	132	PBT	40/10	Freedom from ipsilateral breast tumour recurrence at 3 years	Acute and late toxicity, dosimetry, quality of life, recurrence pattern, overall survival.
NCT01839838 USA	2013-24	57	PBT	–	Adverse events at 5 years	–
NCT00599989 USA	2005-09	28	Photon: 3DCRT	–	Acute toxicity at 1 week, 4 weeks and 3 months	Site of disease recurrence, time to recurrence, late toxicity, cosmesis
			Interstitial brachytherapy	–		
			Intracavity balloon brachytherapy	–		
			PBT	– /10		

Continued on next page.

Ongoing non-randomised studies of proton beam therapy for early breast cancer. *(Continued)*

Study ID Country	Study yrs	Pts	Study arms: Intervention		Planned study outcomes	
			Beam type	Total dose (Gy) /fr.	Primary	Secondary
Clinical target not specified (5443 patients)						
NCT00991094 USA	2005-22	5000†	PBT	–	Acute and late toxicities	Symptom burden during 3 months post treatment
ChiCTR2000031985 China	2020-35	299	PBT	–	Heart injury	–
CTRI202011029415 India	2020-25	100	PBT	–	Rate of acute coronary events over 5 years	Locoregional control, disease free survival, overall survival, changes in cardiac function, cosmesis, quality of life over 5 years
JPRN-UMIN000017579 Japan	2015-25	24	PBT	62/26	Adverse events of normal tissue	Location of local recurrence, duration of distant recurrence, overall survival, cosmesis
JPRN-UMIN000016206 Japan	2015-	20	PBT	60-72/10	Local control Acute toxicity	–

Footnotes

Some patients enrolled in this randomised trial are also enrolled in ancillary observational studies: NCT04361240 study including 155 participants planned for 2020-23; NCT03270072 study including 100 participants planned for 2017-27.

†Includes patients with other cancers treated with proton beam therapy at University of Texas M.D. Anderson Cancer Center.

Abbreviations: CT=computed tomography; fr.=fractions, IMRT=Intensity Modulated Radiotherapy, MRI=magnetic resonance imaging, No.=number, PBT=proton beam therapy, Pts=pateints, 3DCRT=Three-dimensional conformal external-beam photon radiotherapy, SIB=simultaneous integrated boost, yrs=year, "-"=unspecified.

E.11 Publication arising from Chapter 6

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CLINICAL INVESTIGATION

Proton Beam Therapy for Early Breast Cancer: A Systematic Review and Meta-analysis of Clinical Outcomes

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Purpose: Adjuvant proton beam therapy (PBT) is increasingly available to patients with breast cancer. It achieves better planned dose distributions than standard photon radiation therapy and therefore may reduce the risks. However, clinical evidence is lacking.

Methods and Materials: A systematic review of clinical outcomes from studies of adjuvant PBT for early breast cancer published in 2000 to 2022 was undertaken. Early breast cancer was defined as when all detected invasive cancer cells are in the breast or nearby lymph nodes and can be removed surgically. Adverse outcomes were summarized quantitatively, and the prevalence of the most common ones were estimated using meta-analysis.

Results: Thirty-two studies (1452 patients) reported clinical outcomes after adjuvant PBT for early breast cancer. Median follow-up ranged from 2 to 59 months. There were no published randomized trials comparing PBT with photon radiation therapy. Scattering PBT was delivered in 7 studies (258 patients) starting 2003 to 2015 and scanning PBT in 22 studies (1041 patients) starting 2000 to 2019. Two studies (123 patients) starting 2011 used both PBT types. For 1 study (30 patients), PBT type was unspecified. Adverse events were less severe after scanning than after scattering PBT. They also varied by clinical

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All data generated and analyzed during this study are included in this published article (and its supplementary information files).

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target. For partial breast PBT, 498 adverse events were reported (8 studies, 358 patients). None were categorized as severe after scanning PBT. For whole breast or chest wall ± regional lymph nodes PBT, 1344 adverse events were reported (19 studies, 933 patients). After scanning PBT, 4% (44/1026) of events were severe. The most prevalent severe outcome after scanning PBT was dermatitis, which occurred in 5.7% (95% confidence interval, 4.2-7.6) of patients. Other severe adverse outcomes included infection, pain, and pneumonitis (each ≤1%). Of the 141 reconstruction events reported (13 studies, 459 patients), the most prevalent after scanning PBT was prosthetic implant removal (34/181, 19%).

Conclusions: This is a quantitative summary of all published clinical outcomes after adjuvant PBT for early breast cancer. Ongoing randomized trials will provide information on its longer-term safety compared with standard photon radiation therapy. © 2023 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

Introduction

Adjuvant photon radiation therapy is given to about two-thirds of women with breast cancer.[1] It reduces the risk of breast cancer death when targeted at the whole breast after breast conserving surgery, or the chest wall after mastectomy in lymph node positive cancer.[2,3] Inclusion of the regional lymph nodes further improves survival.[4] However, when irradiating these clinical targets, incidental irradiation of the nearby heart, lungs, and esophagus can increase the risks of death from heart disease, lung cancer, and esophageal cancer, respectively.[5-7]

During the past few decades, advances in breast cancer photon radiation therapy have reduced incidental irradiation of the surrounding organs and homogenized dose to clinical targets, likely contributing to improved clinical outcomes.[8] For the majority of women receiving modern photon radiation therapy who do not smoke, the absolute mortality risks are now estimated to be <1%.[6] However, for some women, the risks of heart disease and second cancers may be higher. For example, it may be more difficult to spare nearby organs from radiation when treating patients with left-sided breast cancers, those requiring internal mammary lymph node irradiation, and those with unfavorable cardiothoracic anatomy.[9-11] Absolute radiation risks of heart disease and lung cancer may also be higher for women who are long-term continuing smokers or who have pre-existing heart disease.[5,6] In women with 1 or more of these risk factors, there may be a role for proton beam therapy (PBT).[9-11]

Adjuvant PBT is being considered as an alternative to standard photon radiation therapy because it may further reduce radiation-related risks for patients with early breast cancer.[5-7,12-14] Dosimetry studies have demonstrated that when irradiating the breast or chest wall ± regional lymph nodes PBT can achieve lower doses to the heart, lungs and esophagus compared with photon radiation therapy without compromising coverage of the clinical target.[9-11]

The availability of PBT for breast cancer has increased over recent decades, and the technology has advanced. Since 1990 around 95 PBT centers have opened for clinical use worldwide including 41 in the United States and 30 in Europe.[15] Early PBT was delivered using passive scattering, which spreads a narrow proton beam so that it is wide enough to cover the clinical target. By 2014 most centers were delivering PBT via uniform scanning or pencil beam scanning both of which use magnetic fields to steer narrow proton beams across the clinic target, enabling better sparing of normal tissues.[16] In particular, better skin-sparing is possible with pencil beam scanning technology because of its enhanced dose modification capabilities.

Although PBT for breast cancer is increasingly available and the technology and techniques to deliver it are improving, its place as a cost-effective, clinically beneficial alternative to photon radiation therapy has not yet been proven. Lack of clinical evidence is the main reason that the majority of European PBT centers are not using protons to treat patients with breast cancer routinely.[17]

Synthesis of all available knowledge of clinical outcomes after the most advanced PBT techniques is needed to improve our knowledge of its clinical benefits and risks. This systematic review aims to summarize and quantify all clinical outcomes after adjuvant PBT for early breast cancer published before September 2022 to inform clinicians and patients, and to guide the design of future clinical trials. We also summarize ongoing studies of PBT in early breast cancer.

Methods and Materials

A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines.[18] Search methods, inclusion criteria, and data abstraction were specified in the study protocol registered in the International Prospective Register of Systematic Reviews (PROSPERO) and are described in the following.[19]

Study eligibility

Two groups of studies were included in the review. In the first group, eligible studies were those that reported clinical outcomes in patients who received adjuvant PBT for early breast cancer after curative intent surgery and were published in full text or abstract form between January 1, 2000, and September 1, 2022 (Appendix E1a, Fig. E1a). Breast cancer was defined as early when all detected invasive cancer cells were in the breast or regional lymph nodes and could

be removed surgically. Patients of any age or sex were included. Studies providing only the outcomes of clinical investigations (eg, echocardiogram findings) rather than outcomes from clinical history or examination were excluded because such surrogates for clinical outcomes have yet to be validated for clinical use in this context. Studies were excluded if they were case reports or if clinical outcome data could not be extracted.

The second group of eligible studies included all ongoing clinical studies of adjuvant PBT in women with early breast cancer after curative intent surgery (Appendix E1b, Fig. E1b). These studies were recruiting patients, or had completed recruitment and were in follow-up, but had not yet published their results.

Study identification

Publications reporting clinical outcomes after adjuvant PBT for early breast cancer were identified by searching Ovid MEDLINE and Embase using the following terms: breast cancer NOT advanced/metastatic/inoperable, AND proton radiotherapy (Appendix E1a). Full text publications and abstracts were included to capture the clinical outcomes from as many patients as possible.

Ongoing clinical studies of PBT in breast cancer were identified from the ClinicalTrials.gov website, the World Health Organization International Clinical Trials Registry Platform, and the Cochrane Central Register of Controlled Trials using the search terms "breast cancer" AND "proton" (Appendix E1b).[20-22]

Data abstraction

From eligible published studies reporting clinical outcomes, the following information was abstracted: study author, years of study and location, study design, number of patients, number of breast cancers, details of primary and reconstructive breast cancer surgery, details of PBT beam delivery type and technique, PBT dose (Gy) and fractionation, median follow-up, breast cancer outcomes, number, type and severity of adverse clinical outcomes, and the clinical definitions and severity grading systems used. Where the PBT delivery type or clinical target were unspecified, the corresponding authors of the studies were contacted for further information.

To prevent counting of individual patient clinical outcomes more than once, studies analyzing multi-institutional registry data on clinical outcomes after PBT for early breast cancer were excluded from further analysis (Fig. E1a, Table E1). The remaining publications were grouped into the individual studies they were reporting on using trial IDs. Publications without trial ID were grouped as an individual study if the abstracted information suggested that the publications were reporting upon the same patients. Each of the resulting studies was assigned 1 main study publication from which reported clinical outcomes contributed to data analysis. The main study publication was selected as the most recent full text publication presenting clinical outcomes, or the most recent abstract where a full text publication was not available.

From eligible ongoing clinical studies, the following information was abstracted: study design, study location and years, estimated number of patients, details of planned PBT intervention, and planned study outcomes.

Data analysis

Individual published studies were categorized by PBT clinical target: partial breast, whole breast or chest wall ± regional lymph nodes, and reconstructed breast ± regional lymph nodes. It was not possible to separate clinical targets further as this level of detail was not published in the majority of studies. Within these 3 groups, studies were categorized by PBT delivery type: scattering, scattering or scanning, scanning, and unspecified. Scattering PBT included both passive and double scattering. Scanning PBT included both uniform scanning and pencil beam scanning.

Adverse clinical outcomes reported in individual published studies were categorized as mild (or grade 1), moderate (or grade 2), severe (or grade 3), or unspecified, using the study's specified grading system (for definitions of dermatitis, see Table E2). For each study, the number of patients reported to be affected by, and the number assessed for each grade of each type of reported adverse outcome was counted. Where a study reported the number of events for an outcome at more than 1 point in time, then only the time point with the highest number of severe events was counted for that outcome in that study, although different time points may have been selected for different outcomes.

Within each category of PBT clinical target and PBT delivery type, adverse outcomes were ranked in descending order of severity using the percentage of patients affected. Where the percentages of patients affected were the same, adverse outcomes were arranged in descending order of the number of patients affected.

The highest number of severe adverse events was reported for dermatitis in women who received PBT to the whole breast or chest wall ± regional lymph nodes. The Fisher exact test was used to evaluate the proportions of severe dermatitis reported between studies using scattering and scanning PBT. Then, because the outcomes after scanning PBT are most relevant to current clinical practice, we quantified the prevalence of dermatitis after scanning PBT for early breast cancer to the whole breast or chest wall ± regional lymph nodes using meta-analysis of proportions.[23] Confidence intervals for the observed prevalence in individual studies were calculated using the exact binomial method. Between-study heterogeneity was assessed by P value from Wald-type tests and, as heterogeneity was present in some cases, pooled estimates were obtained using generalized linear mixed models with a logit link function (using R package *metafor*). Random effects models were used because such analyses are often highly heterogeneous. Individual study weights were derived from the likelihood contribution of each individual study. The overall

prevalence estimates presented may be interpreted as the median prevalence from multiple studies.

For breast cancer outcomes, the number of patients affected by, and assessed for, locoregional recurrence, distant recurrence, breast cancer death, and death from any cause were counted. Analyses of these data were not possible as information regarding the time point of individual breast cancer outcomes was missing from most publications. Ongoing clinical studies were categorized by study design into randomized and nonrandomized studies, then by PBT clinical target. Summarized data were tabulated.

Results

Published studies

Thirty-two individual published studies (1452 patients) reporting clinical outcomes after adjuvant PBT for early breast cancer were identified. Study start dates ranged from 2003 to 2019 (Fig. E1a, Table 1). There were no randomized studies comparing PBT with photon radiation therapy. Clinical outcomes were published in full text for 21 studies (775 patients) and in abstracts for 11 studies (677 patients).

The majority of studies (28/32 studies, 1359 patients) were conducted in the United States (Table 1, Fig. 1). One center in the Republic of Korea (30 patients) reported clinical outcomes after partial breast PBT and 1 center in the Czech Republic (42 patients), the Netherlands (20 patients), and France (1 patient) reported clinical outcomes after PBT to the whole breast or chest wall ± regional lymph nodes. No center outside the United States reported clinical outcomes after PBT to the reconstructed breast.

PBT clinical targets under investigation have changed with time. The partial breast was targeted in 8 studies (358 patients) published since 2006. Reported study start dates ranged from 2003 to 2015 (Table 1). The whole breast or chest wall ± regional lymph nodes has been targeted in 19 studies (933 patients) published since 2016. Reported study start dates ranged from 2011 to 2019 (Table 1). Reconstruction outcomes after PBT to the reconstructed breast ± regional lymph nodes were reported in 13 studies (459 patients) published since 2016. Reported study start dates ranged from 2000 to 2016 (Table 1).

PBT delivery types have also changed with time. PBT was delivered using a scattered beam in 7 studies (258 patients) published since 2006. Reported start dates ranged from 2003 to 2015. Scanning PBT was used in 22 studies (1041 patients) published since 2017. Reported start dates ranged from 2000 to 2019. Two studies (123 patients) both starting in 2011 used both PBT types. One study (30 patients) did not specify the type of PBT used (Table 1). Adverse outcomes varied by clinical target and PBT delivery type (Tables 2 and 3).

Partial breast PBT: Adverse outcomes

PBT dose and fractionation varied according to clinical target. All 8 studies of partial breast PBT investigated accelerated partial breast irradiation (Table 1). Six of these used total doses ranging from 32 to 40 Gy in 3.4 to 4 Gy fractions given across 4 and 14 days. The other 2 studies used higher doses per fraction: 21.9 Gy in 3 daily fractions (7.3 Gy per fraction), and 30 Gy in 5 daily fractions (6 Gy per fraction).

Scattering PBT was received by 53% (189/358) of patients and scanning PBT by 39% (139/358). For 8% (30/358) of patients PBT type was unspecified (Table 1). Median follow-up of patients across studies ranged from 12 to 59 months.

For partial breast PBT, 498 adverse events were reported. These spanned 14 types of adverse outcomes, all of which related to effects on breast skin and soft tissue (Table 2). These adverse outcomes were reported using Common Terminology Criteria for Adverse Events (CTCAE), versions 2.0 or 4.0, in 4 studies, categories of "mild," "moderate," and "severe" in 2 studies, and the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer grading system in 1 study (Tables E4 and E5). For the remaining study, the system used to grade adverse outcomes was unspecified. The timing of adverse outcomes was between 0 and 84 months where specified. Information on timing was missing in 23% (12/52) of instances (Tables E4 and E5). Of the 498 adverse events reported, 2% (8/498) were graded as severe, 13% (67/498) as moderate, and 79% (393/498) as mild. Grade was unspecified in 6% (30/498) of events. The only outcome with severe events was dermatitis. Severe dermatitis events were all graded using a system that enabled classification as "mild," "moderate," or "severe," and were reported at 2 months post-PBT. There were more reports (P = .02) of severe dermatitis in patients assessed after scattering PBT (4%, 7/169) than after scanning PBT (0%, 0/114). There was 1 event (3%, 1/30) after PBT of unspecified type (Table 2, Fig. 2, Table E4).

Whole breast or chest wall ± regional lymph nodes PBT: Adverse outcomes

Studies of whole breast or chest wall ± regional lymph nodes PBT reported outcomes after 45 to 50 Gy total dose in 1.8 or 2 Gy fractions in 15 of 19 studies (Table 1). The other 4 studies included patients receiving hypofractionated regimens of 40 to 43 Gy in 15 or 16 fractions.

Scattering PBT was received by 7% (69/933) of patients and scanning PBT by 85% (795/933). One study (69/933, 7%) used either scattering or scanning (Table 1). Median follow-up ranged from 2 to 55 months.

For whole breast or chest wall ± regional lymph nodes PBT, 1344 adverse events were reported. These spanned 15 types of adverse outcomes relating to effects on breast or chest wall skin and soft tissue, esophagus, lungs, ribs, lymphatics, and brachial plexus (Table 3). These adverse

Table 1 Individual studies reporting clinical outcomes after PBT for early breast cancer published 2000 to 2022 according to clinical target and PBT type

First author and year of publication*	Country	Year study started	No. patients received PBT (N = 1452)	Total dose (Gy)/ no. fractions	Median follow-up (mo)
Partial breast (358 patients)					
Scattering (189 patients)					
Galland-Girodet 2014[10-13†]	USA	2003	19	32/8	-
Kozak 2006[9†]	USA	2004	20	32/8	12
Pasalic 2021[1-3]	USA	2010	100	34/10	24
Bush 2011[4-8]	USA	-	50	40/10	48
Scanning (139 patients)					
Choi 2022[16-18]	USA	2013	38	40/10	35
Giap 2017[19,20‡,§]	USA	2014	25	40/10	19
Mutter 2019[14,15]	USA	2015	76	22/3	12
Type unspecified (30 patients)					
Chang 2013[21-22]	Republic of Korea	2007	30	30/5	59
Whole breast or chest wall ± regional lymph nodes (933 patients)					
Scattering (69 patients)					
Bradley 2016[26-33§]	USA	2012	18	50/28	20
Liang 2018[25]	USA	2012	23	50/25-28	-
Sayan 2022[23,24]	USA	2015	28	40-50/-	27
Scattering or scanning (69 patients)					
Jimenez 2019[34-38§]	USA	2011	69	45-50/25-28	55
Scanning (795 patients)					
Verma 2017[43-46§]	USA	2011	91	50/25-28	16
Luo 2019[49-52§]	USA	2013	42	50/-	35
Pasztorova 2018[53‡]	Czech Republic	2015	42	40/15 or 50/25	7
DeCesaris 2019[54]	USA	2015	39	45-50/25-28	-
Smith 2019[47,48§]	USA	2015	51	50/25	19
Gergelis 2021[42‡,§]	USA	2015	96	50/25	-
Garda 2022[60]	USA	2015	11	50/25	32
DeCesaris 2021[41‡]	USA	2016	100	50/25-28	15
Fattahi 2022[58,59]	USA	2016	19	50/25	24
Loap 2021[61]	France	2019	1	50/25	6
Zheng 2017[40‡,‖]	USA	-	100	45-50/25-28	-
Cuaron 2017[56‡]	USA	-	26	49/-	15
Mullikin 2020[39‡,§]	USA	-	126	50/25	18
Verhoeven 2020[57‡]	Netherlands	-	20	40/15	-
Salari 2021[55‡]	USA	-	31	43/16 or 50/25	2
Reconstructed breast only ± regional lymph nodes (161 patients)					
Scattering or scanning (54 patients)					
Jimenez 2020[62‡]	USA	2011	54	-	-

(*Continued*)

Table 1 (*Continued*)

First author and year of publication*	Country	Year study started	No. patients received PBT (N = 1452)	Total dose (Gy)/ no. fractions	Median follow-up (mo)
Scanning (107 patients)					
Naoum 2022[65,66]	USA	2000	17	-	-
Anderson 2021[67,68]	USA	2010	4	50/-	-
Nichols 2020[63‡]	USA	-	57	50/-	14
DeCesaris 2021[64]	USA	-	29	50/28	5

Abbreviations: "-" = not specified; PBT = proton beam therapy; USA = United States of America.
* The main study publication is referenced first, followed by other study publications (see Appendix E2 for references).
† Two fractions delivered daily. In all other studies where duration of treatment was reported, 1 fraction was delivered daily.
‡ Main study publication is an abstract rather than a full text.
§ Studies included some patients who had breast reconstructions.
‖ Adverse outcomes data obtained from the Proton Collaborative Group trial REG001-09.

outcomes were reported using CTCAE (versions 3.0-5.0) in 14 studies and Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer in 1 study (Tables E4 and E6). For the remaining 4 studies, the system used to grade adverse outcomes was unspecified. Where specified, the adverse outcomes were assessed between 0 and 39 months after PBT, but information on the timing was missing in 58% (59/104) of instances (Tables E4 and E6). Of the 1344 adverse events, 5% (65/1344) were graded as severe, 45% (604/1344) as moderate, and 47% (629/1344) as mild. For 3% (46/1344) of adverse events the grade was unspecified. The most prevalent severe outcome was dermatitis. Outcomes of severe dermatitis were all graded using CTCAE versions 3.0-5.0 and were reported within 6 months post-PBT where specified. The grading system was unspecified in 13% (2/16) of studies reporting on severe dermatitis, and the timing unspecified in 69% (11/16) of studies. Severe dermatitis was reported in 22% (15/69) of assessed patients after scattering PBT compared with only 6% (41/723) after scanning PBT ($P < .001$). Two reports of severe dermatitis (3%, 2/69) occurred in a study of scattering or scanning PBT (Table 3, Fig. 2, Table E4). Other severe adverse outcomes were infection, pain, and pneumonitis. Outcomes of severe infection were all graded using CTCAE versions 4.0-5.0 and were reported between 4 and 32 months where specified. The timing was unspecified in 50% (2/4) of studies reporting on severe infection. Severe infection was reported in 17% of patients (3/18) after scattering PBT, 1% (1/69) after scattering or scanning, and in 1% (1/137) after scanning PBT. Severe pain was reported in 1 patient (1/246, <1%), as was pneumonitis (1/257, <1%). Both of these outcomes were graded using CTCAE version 4.0 and occurred after scanning PBT (Tables 3 and E6). The timing of the outcome of severe pain was unspecified. The outcome of pneumonitis was reported at 12 months.

Meta-analysis of the percentage of patients affected by severe dermatitis after scanning PBT to the whole breast or chest wall ± regional lymph nodes included 41 events from 723 patients in 12 studies (Fig. 3). Although the estimated number of patients with severe dermatitis per 100 patients assessed in different studies varied from 0 to 10.5, there was no significant heterogeneity between studies ($P = .90$). Overall, severe dermatitis occurred in 5.7 (95% confidence interval, 4.2-7.6) per 100 patients.

Meta-analysis of the percentage of patients affected by moderate dermatitis included 343 events from 624 patients in 12 studies (Fig. E2). The estimated number of patients with moderate dermatitis per 100 patients assessed in different studies varied from 33.3 to 100.0. There was significant heterogeneity between the studies ($P < .001$) and the overall estimate, allowing for heterogeneity was 59.3 (48.5-69.3) per 100 patients. Meta-analysis of the percentage of patients affected by mild dermatitis (Fig. E2) included 174 events from 482 patients in 8 studies. The estimated number of patients with mild dermatitis per 100 patients assessed in different studies varied from 10.0 to 62.7. There was significant heterogeneity between the studies (<0.001) and the overall estimate, allowing for heterogeneity was 33.7 (23.8-45.3) per 100 patients.

Reconstructed breast ± regional lymph nodes PBT: Adverse reconstruction outcomes

There were 13 studies that reported reconstruction outcomes after reconstructed breast ± regional lymph node PBT (Table 4). Five of these were studies that only included patients with breast reconstructions. The remaining 8 were studies that included some patients with breast reconstructions and some without (Table 1). Of the 11 of 13 studies that specified the PBT total dose and fractionation, 10 reported outcomes after 45 to 50 Gy total dose given in 1.8 or 2 Gy fractions. One study reported outcomes after 40 Gy in 10 fractions.

Scattering PBT was delivered to 1% of irradiated breast reconstructions (4/459), scanning or scattering to 23% (107/459), and scanning PBT to 76% (348/459; Table 4). Median follow-up of patients across studies ranged from 5 to 55 months.

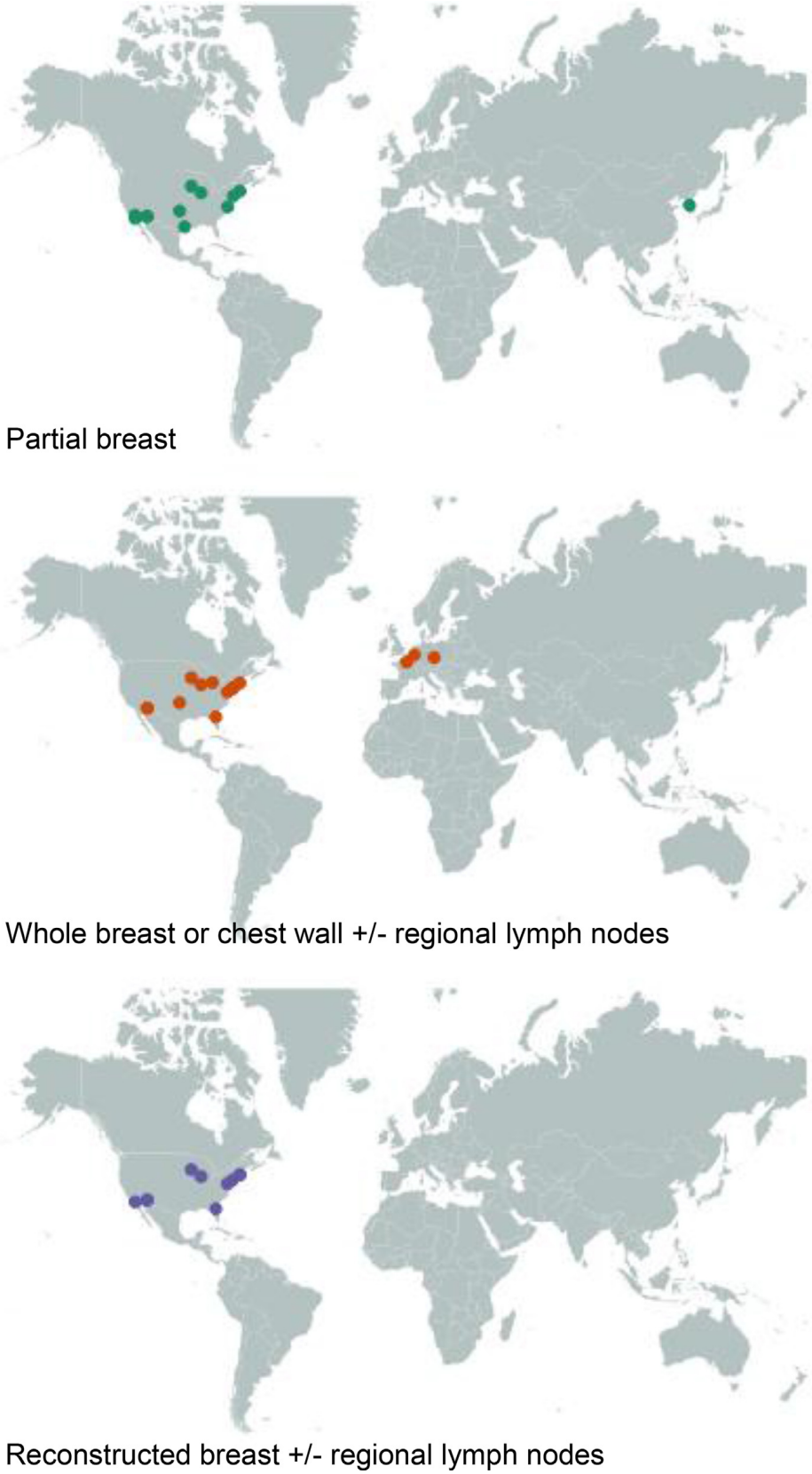


Fig. 1. Global distribution of centers reporting clinical outcomes after proton beam therapy for early breast cancer in studies published 2000 to 2022 according to clinical target.

For reconstructed breast PBT, 141 adverse reconstruction events were reported. These included infection in 11% (22/200) of assessed patients, and capsular contraction in 18% (47/258). For infection, the severity was unspecified in 60% (3/5) of studies reporting this outcome, and the timing unspecified in all studies. For capsular contraction, the grade

Table 2 Partial breast PBT: Adverse outcomes published 2000 to 2022 according to PBT type

	Severe		Moderate		Mild		Unspecified	
Adverse outcome	**Affected/assessed**	**%**	**Affected/assessed**	**%**	**Affected/assessed**	**%**	**Affected/assessed**	**%**
Scattering (296 adverse events)								
Dermatitis*	7/169	***4***	26/188	***14***	86/169	***51***	-	-
Atrophy	-	-	10/19	***53***	-	-	-	-
Fibrosis†	0/19	***0***	1/19	***5***	3/19	***16***	10/19	***53***
Fatigue	0/100	***0***	4/100	***4***	10/100	***10***	-	-
Pain‡	0/119	***0***	3/119	***3***	34/119	***29***	4/19	***21***
Hyperpigmentation	0/100	***0***	2/100	***2***	44/100	***44***	-	-
Infection	0/100	***0***	1/100	***1***	0/100	***0***	0/50	***0***
Breast edema	0/119	***0***	1/119	***1***	15/119	***13***	-	-
Fat necrosis	0/163	***0***	1/163	***1***	0/163	***0***	2/69	***3***
Telangiectasia	-	-	-	-	20/150	***13***	10/39	***26***
Rib fractures	-	-	-	-	-	-	2/89	***2***
Pneumonitis§	0/20	***0***	0/20	***0***	0/20	***0***	0/50	***0***
Cardiac	-	-	-	-	-	-	0/50	***0***
Subtotal	**7/909**	***1***	**49/947**	***5***	**212/1059**	***20***	**28/385**	***7***
Scanning (142 adverse events)								
Dermatitis*	0/114	***0***	4/139	***3***	79/114	***69***	-	-
Fatigue	0/38	***0***	1/38	***3***	13/43	***30***	-	-
Lymphoedema	0/38	***0***	1/38	***3***	2/38	***5***	-	-
Breast edema	0/76	***0***	0/76	***0***	17/76	***22***	-	-
Hyperpigmentation	0/72	***0***	0/72	***0***	13/72	***18***	-	-
Pain‡	0/114	***0***	0/114	***0***	9/114	***8***	-	-
Telangiectasia	0/110	***0***	0/110	***0***	2/110	***2***	-	-
Fibrosis†	0/76	***0***	0/76	***0***	1/76	***1***	-	-
Infection	0/76	***0***	0/76	***0***	0/76	***0***	-	-
Pneumonitis§	0/76	***0***	0/76	***0***	0/76	***0***	-	-
Rib fractures	-	-	-	-	-	-	0/76	***0***
Subtotal	**0/790**	***0***	**6/815**	***1***	**136/795**	***17***	**0/76**	***0***
Type unspecified (60 adverse events)								
Dermatitis*	1/30	***3***	1/30	***3***	6/30	***20***	-	-
Hyperpigmentation	0/30	***0***	9/30	***30***	21/30	***70***	-	-
Fibrosis†	0/30	***0***	2/30	***7***	7/30	***23***	-	-
Pain‡	0/30	***0***	0/30	***0***	11/30	***37***	-	-
Rib fractures	-	-	-	-	-	-	2/30	***7***
Subtotal	**1/120**	***1***	**12/120**	***10***	**45/120**	***38***	**2/30**	***7***
Total *(all PBT types)*	**8/1819**	***0***	**67/1882**	***4***	**393/1974**	***20***	**30/491**	***6***

Denominators vary because not all studies assessed all grades of all adverse outcomes. See Tables E4, E5, and E6 for outcomes by study. See Table E3 for outcomes excluded from this analysis.

Abbreviations: "-" = not specified; PBT = proton beam therapy.

* Includes acute skin color change.

† Includes reports of induration.

‡ Includes reports of pain from skin, breast, and unspecified pain.

§ Includes reports of cough and dyspnea.

‖ Includes reports of dysphagia.

Table 3 Whole breast or chest wall ± regional lymph nodes PBT: Adverse outcomes published 2000 to 2022 according to PBT type

	Severe		Moderate		Mild		Unspecified	
Adverse outcome	**Affected/assessed**	**%**	**Affected/assessed**	**%**	**Affected/assessed**	**%**	**Affected/assessed**	**%**
Scattering (104 adverse events)								
Dermatitis	15/69	***22***	49/69	***71***	-	-	-	-
Infection	3/18	***17***	3/18	***17***	-	-	-	-
Fatigue	0/18	***0***	6/18	***33***	-	-	-	-
Pain‡	0/18	***0***	9/28	***32***	-	-	1/18	***6***
Esophagitis‖	0/18	***0***	6/46	***13***	-	-	-	-
Pneumonitis§	0/18	***0***	2/18	***11***	-	-	-	-
Lymphoedema	0/18	***0***	1/18	***6***	-	-	5/28	***18***
Atrophy	0/18	***0***	1/18	***6***	-	-	-	-
Cardiac	0/18	***0***	-	-	-	-	2/18	***11***
Rib fractures	-	-	-	-	-	-	1/18	***6***
Subtotal	**18/213**	***8***	**77/233**	***33***	-	-	**9/82**	***11***
Scattering or scanning (214 adverse events)								
Dermatitis	2/69	***3***	57/69	***83***	10/69	***14***	-	-
Infection	1/69	***1***	0/69	***0***	0/69	***0***	-	-
Fatigue	0/69	***0***	24/69	***35***	38/69	***55***	-	-
Esophagitis‖	0/69	***0***	5/69	***7***	19/69	***28***	-	-
Pneumonitis§	0/69	***0***	1/69	***1***	3/69	***4***	-	-
Hyperpigmentation	-	-	-	-	36/69	***52***	-	-
Telangiectasia	-	-	-	-	11/69	***16***	-	-
Rib fractures	0/69	***0***	0/69	***0***	5/69	***7***	-	-
Lymphoedema	0/69	***0***	0/69	***0***	1/69	***1***	-	-
Atrophy	-	-	-	-	1/69	***1***	-	-
Subtotal	**3/483**	***1***	**87/483**	***18***	**124/690**	***18***	-	-
Scanning (1026 adverse events)								
Dermatitis	41/723	***6***	343/624	***55***	174/482	***36***	5/31	***16***
Infection	1/137	***1***	2/156	***1***	0/137	***0***	7/91	***8***
Pain‡	1/246	***<1***	37/372	***10***	57/266	***21***	6/31	***19***
Pneumonitis§	1/257	***<1***	0/257	***0***	2/276	***1***	-	-
Esophagitis‖	0/336	***0***	43/355	***12***	62/355	***17***	2/100	***2***
Fatigue	0/144	***0***	7/144	***5***	61/144	***42***	-	-
Decreased shoulder movement	0/11	***0***	1/30	***3***	6/30	***20***	-	-
Fibrosis†	0/11	***0***	1/37	***3***	9/56	***16***	-	-
Lymphoedema	0/153	***0***	3/172	***2***	21/172	***12***	3/91	***3***
Hyperpigmentation	0/176	***0***	3/218	***1***	106/244	***43***	8/19	***42***
Brachial plexopathy	0/204	***0***	0/204	***0***	3/204	***1***	-	-
Telangiectasia	0/139	***0***	0/181	***0***	3/207	***1***	0/13	***0***
Rib fractures	0/205	***0***	0/205	***0***	1/205	***0***	6/203	***3***
Cardiac	0/220	***0***	0/220	***0***	0/220	***0***	-	-
Subtotal	**44/2962**	***1***	**440/3175**	***14***	**505/2998**	***17***	**37/579**	***6***
Total *(all PBT types)*	**65/3658**	***2***	**604/3891**	***16***	**629/3688**	***17***	**46/661**	***7***

Denominators vary because not all studies assessed all grades of all adverse outcomes. See Tables E4, E5, and E6 for outcomes by study. See Table E3 for outcomes excluded from this analysis.

Abbreviations: "-" = not specified; PBT = proton beam therapy.

*Includes acute skin color change.

† Includes reports of induration.

‡ Includes reports of pain from skin, breast, and unspecified pain.

§ Includes reports of cough and dyspnea.

‖ Includes reports of dysphagia.

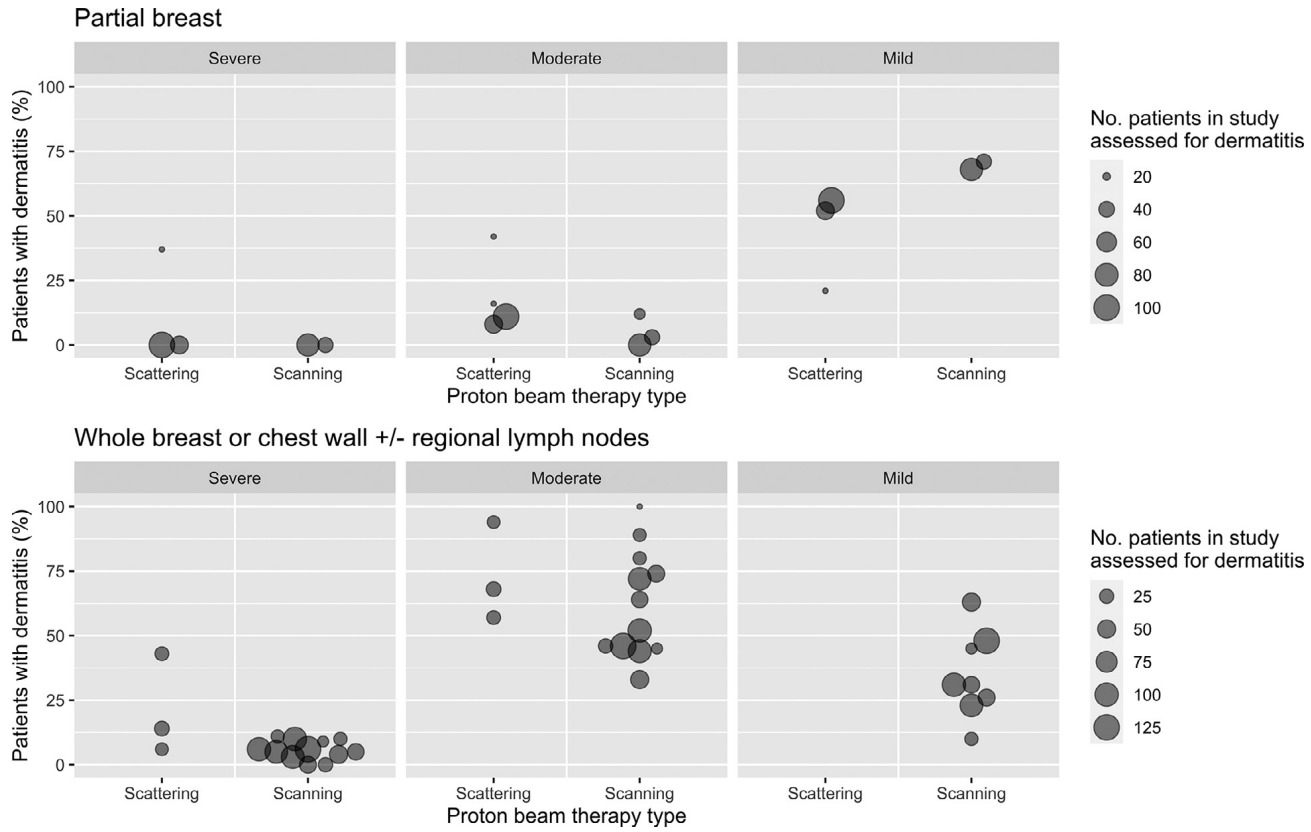


Fig. 2. Percentage of patients with dermatitis after PBT for breast cancer in studies published 2000 to 2022, according to clinical target and PBT type. For each individual study reporting dermatitis, the percentage of patients with each grade of dermatitis was plotted. See Table E4 for patients with unspecified grade of dermatitis, patients who received scanning or scattering proton beam therapy, and unspecified proton beam type. *Abbreviation*: PBT = proton beam therapy.

and timing were unspecified in 85% (6/7) of studies reporting this outcome. Some adverse events required surgical intervention. For implant reconstructions, 12% (15/130) required surgical revision and 19% (55/286) required removal. For autologous reconstructions, 3% (1/32) required surgical revision and 50% (1/2) required surgical replacement (Table 4). The timings of these outcomes were unspecified.

Breast cancer outcomes

In total 19 locoregional recurrences were reported from 867 patients in 19 studies, 53 distant recurrences were reported from 811 patients in 16 studies. There were 9 breast cancer deaths reported from 383 patients assessed in 9 studies, and 22 deaths from any cause reported from 499 patients assessed in 11 studies. Further analysis was not performed because most studies did not provide information on the timings of these events.

Ongoing studies

Twenty-two ongoing studies (9791 patients) collecting clinical outcomes after PBT for early breast cancer were identified including 6 randomized (3298 patients) and 14 nonrandomized studies (6493 patients) (Fig. E1b, Tables E7 and E8). One randomized study (NCT02603341) has 2 associated ancillary observational studies (NCT04361240 and NCT03270072).

All randomized studies are investigating PBT to the whole breast or chest wall ± regional lymph nodes. Five are comparing PBT with photon radiation therapy, and 1 is comparing standard fractionation PBT with hypofractionated PBT. Three of the 6 randomized studies are located in the United States, 1 in Denmark, 1 in the United Kingdom, and 1 in Thailand.

Of the 14 nonrandomized studies, 6 studies are investigating PBT to the partial breast (765 patients) and 3 are investigating PBT to the whole breast or chest wall ± regional lymph nodes (285 patients). All 9 of these studies are located in the United States. The PBT clinical target could not be ascertained in the other 5 nonrandomized studies (5443 patients). Two of these are located in Japan, 1 in the United States, 1 in China, and 1 in India.

For all ongoing studies of PBT to the whole breast or chest wall ± regional lymph nodes, planned primary outcomes are assessing adverse outcomes, with measures of efficacy as secondary outcomes. For ongoing studies of partial breast PBT, planned primary outcomes measures include efficacy (2 studies), cosmesis (2 studies), and adverse outcomes (2 studies).

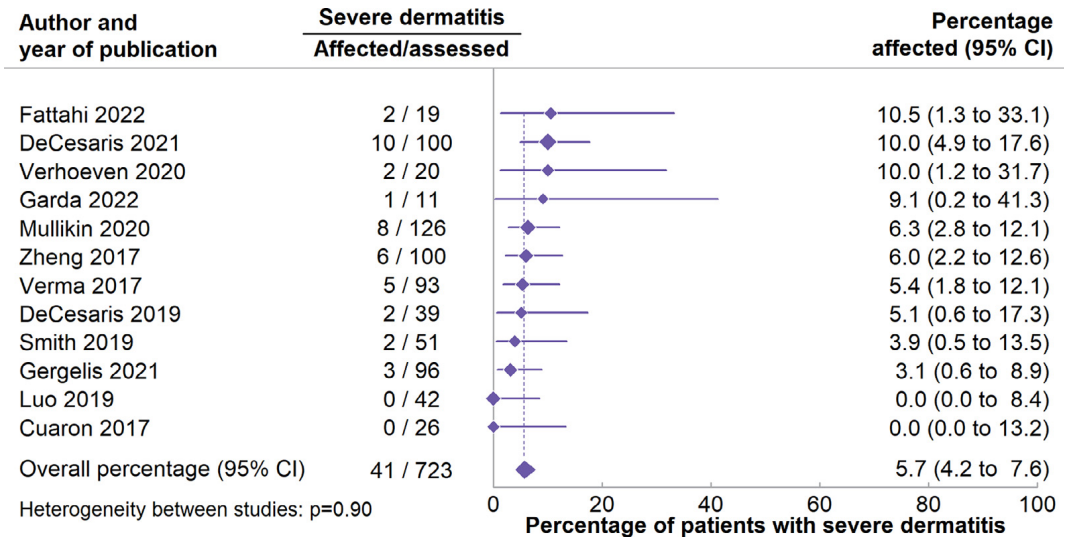


Fig. 3. Meta-analysis of the percentage of patients with severe dermatitis after whole breast or chest wall ± regional lymph nodes scanning proton beam therapy in studies published 2000 to 2022. See Fig. E2 for meta-analyses of the percentage of patients with moderate and mild dermatitis.

Discussion

This systematic review provides a quantitative summary of reported adverse clinical outcomes after different types of PBT for early breast cancer using data published during 2000 to 2022. Most studies had median follow-up of <2 years, with little data on outcomes beyond 3 years. The most common reported adverse outcome overall was dermatitis. Adverse outcomes were less severe after PBT using the latest scanning technology than after PBT using the older scattering technology, suggesting that advances in PBT technology have improved the clinical safety of PBT for early breast cancer within the first 3 years. Adverse outcomes were also less severe after PBT to the partial breast, than after PBT to the whole breast or chest wall ± regional lymph nodes, as expected given that the partial breast is a smaller and more superficial target volume.

The main strength of this review is that it provides quantitative estimates of the prevalence of adverse outcomes after PBT for early breast cancer using published data. To the best of our knowledge, it is also the first systematic review to summarize reconstruction outcomes after PBT for early breast cancer. Our searches were systematic with inclusive search terms, so we are likely to have identified and assessed all relevant studies. We included data from all eligible studies published as either abstracts or full texts since the year 2000, making it the largest review of its kind. Quantitative synthesis of available data was made possible by categorizing adverse events by severity and extracting numbers of patients with each type of adverse outcome and the numbers assessed from each study at the time point at which the highest number of patients were reported with severe adverse outcomes.

There are 3 other published systematic reviews summarizing clinical outcomes after adjuvant PBT for early breast cancer.[12,24,25] These were published during 2016 to 2022. Alterio et al summarized clinical outcomes from 5 studies (326 patients) investigating adjuvant PBT to the partial breast.[24] Kammerer et al summarized clinical outcomes from 3 studies (135 patients) of adjuvant PBT to the whole breast or chest wall ± regional lymph nodes.[12] Verma et al summarized clinical outcomes from 4 studies (102 patients) of adjuvant PBT to the whole breast or chest wall ± regional lymph nodes and 5 studies (197 patients) of adjuvant PBT to the partial breast.[25] These reviews included fewer studies and reported fewer clinical outcomes than our review and all presented qualitative summaries of the data.

A limitation of our study is that the estimates of the prevalence of adverse outcomes provided are informed by published summary data rather than individual patient data. This means that some instances of duplication of patient outcomes may remain undetected despite careful grouping of publications into individual studies. In addition, the extent to which patients in these studies represent patients being considered for PBT today is uncertain because detailed information on characteristics of patients selected for these studies was lacking. Information on the timing of reported outcomes was often missing. Therefore, it was neither possible to classify adverse outcomes into acute and late effects, nor to summarize the duration of these outcomes. These factors need to be considered when applying our overall summary estimates of prevalence of adverse effects to patients in the clinic today. For breast cancer outcomes, missing information on the timing of individual outcomes prevented further analysis of these outcomes.

For partial breast PBT most adverse outcomes were graded as mild and there were no severe adverse outcomes from scanning PBT to the partial breast. However, the main justification of the extra cost of PBT compared with standard photon radiation therapy is the predicted reduction in the risks of cardiovascular disease and second cancers. For

Table 4 Reconstructed breast PBT: Adverse reconstruction outcomes published 2000 to 2022 according to PBT type

			Adverse reconstruction outcomes											
							Prosthetic reconstruction				Autologous reconstruction			
			Infection		Capsular contraction		Revised		Removed		Revised		Replaced	
First author and year of publication	Median follow-up (mo)	No. recon.	Affected/ assessed	%	Affected/ assessed	%	Affected/ assessed	%	Affected/ assessed	%	Affected/ assessed	%	Affected/ assessed	%
Scattering (1 reconstruction outcome)														
Bradley 2016*	20	4	1/4	***25***	-	-	-	-	-	-	-	-	-	-
Scattering or scanning (63 reconstruction outcomes)														
Jimenez 2020†	-	54	2/54	***4***	14/54	***26***	1/54	***2***	16/54	***30***	-	-	-	-
Jimenez 2019	55	53	-	-	12/51	***24***	12/51	***24***	5/51	***10***	-	-	1/2	***50***
Subtotal	-	**107**	**2/54**	***4***	**26/105**	***25***	**13/105**	***12***	**21/105**	***20***	-	-	**1/2**	***50***
Scanning (77 reconstruction outcomes)														
Mullikin 2020*	18	66	2/66	***3***	-	-	-	-	-	-	-	-	-	-
Gergelis 2021	-	62	-	-	-	-	-	-	-	-	-	-	-	-
Nichols 2020†	14	57	-	-	4/54	***7***	-	-	11/54	***20***	0/3	***0***	-	-
Smith 2019	19	51	16/51	***31***	1/51	***2***	-	-	8/51	***16***	-	-	-	-
Verma 2017	16	31	-	-	-	-	-	-	-	-	-	-	-	-
DeCesaris 2021†	5	29	-	-	-	-	-	-	2/29	***7***	1/29	***3***	-	-
Luo 2019	35	26	1/25	***4***	6/25	***24***	2/25	***8***	3/26	***12***	-	-	-	-
Naoum 2022†,‡	-	17	-	-	8/17	***47***	-	-	9/17	***53***	-	-	-	-
Giap 2017	19	5	-	-	-	-	-	-	-	-	-	-	-	-
Anderson 2021†,§	-	4	-	-	2/6	***33***	-	-	1/4	***25***	-	-	-	-
Subtotal	-	**348**	**19/142**	***13***	**21/153**	***14***	**2/25**	***8***	**34/181**	***19***	**1/32**	***3***	-	-
Total *(all PBT types)*	-	**459**	**22/200**	***11***	**47/258**	***18***	**15/130**	***12***	**55/286**	***19***	**1/32**	***3***	**1/2**	***50***

Abbreviations: "-" = not specified; PBT = proton beam therapy; recon. = reconstructed breast.

* Reported severe infections. For all other studies, infections were grade unspecified.

† Studies investigating PBT to the reconstructed breast only. Other studies reported outcomes in some patients with breast reconstructions and some without.

‡ Capsular contraction was defined as requiring capsulotomy. Capsular contraction was not defined in the other studies.

§ No. affected/assessed for capsular contraction were extracted from abstract where 6 patients with this outcome were reported.

partial breast photon radiation therapy, these risks are likely to be very small for most patients because radiation doses to the heart, lungs and esophagus are usually <1 Gy.[9-11] Therefore it is more difficult to justify the excess costs of partial breast PBT compared with partial breast photon radiation therapy.

For PBT to the whole breast or chest wall ± regional lymph nodes, the most frequently reported severe adverse outcome was dermatitis. This was most commonly defined as moist desquamation in areas other than skin folds and creases, or bleeding induced by minor trauma or abrasion. Although the timing of severe dermatitis was mostly unreported, when it was specified it peaked at <6 months post-PBT. It occurred in around 6% of patients after scanning PBT, which is of a similar magnitude to expected rates of dermatitis using the latest hypofractionated (40 Gy/15 fractions and 26 Gy/5 fractions) photon radiation therapy techniques to the whole breast or chest wall.[26] Other severe adverse outcomes after scanning PBT included infection, pain, and pneumonitis. These occurred in ≤1% of patients. This reassuring safety information supports the rationale for ongoing clinical trials of PBT to the whole breast or chest wall ± regional lymph nodes for early breast cancer and it may inform patient consent while we await the results of randomized controlled trials.

For scanning PBT to the reconstructed breast, the most commonly reported adverse outcome was removal of prosthetic implant, which occurred in 19% of patients assessed. This may be higher than expected in current clinical practice using photon radiation therapy where estimates are around 9%.[27,28] However, estimates of the prevalence of reconstruction outcomes after radiation therapy vary considerably, and without information on their timing, comparison between studies is difficult.. Published data only include reconstruction outcomes of 348 breast reconstructions irradiated with scanning PBT for early breast cancer after a median follow-up <3 years, so further data are needed.

Our review demonstrates the need for more data on clinical outcomes after PBT for early breast cancer. There were no published randomized controlled trials comparing PBT with photon radiation therapy. In most studies there were <2 years of follow-up, with insufficient data to assess long-term clinical outcomes of PBT. Furthermore, most studies presented outcomes from patients irradiated in single privately funded centers in the United States. Ongoing studies include 5 randomized trials that compare PBT with photon radiation therapy, and plan to recruit 3210 patients. One of these trials (98 patients) includes patients with breast reconstruction and aims to assess unplanned surgical interventions. More clinical trials of PBT in early breast cancer are being planned, and our data may guide their design.

Conclusion

PBT technology has advanced during the past 2 decades so that most patients with early breast cancer receiving PBT would now have it delivered using scanning technology. Published studies with few outcomes reported beyond 3 years suggest that the most common severe adverse outcome after scanning PBT to the whole breast or chest wall ± regional lymph nodes is dermatitis which occurs in 6% of patients (95% confidence interval, 4-8). Other severe adverse outcomes from scanning PBT to the whole breast or chest wall ± regional lymph nodes are much rarer, ≤1%. No severe adverse outcomes after partial breast scanning PBT have been reported. Our estimates of the prevalence of adverse outcomes after irradiation of different clinical targets may inform clinicians and patients considering PBT. However, few published data are available. During the next 15 years, ongoing randomized clinical trials are likely to provide information on the longer-term safety of PBT compared with photons in patients with early breast cancer.

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