Effects of Advanced Radiotherapy Techniques on Normal Tissue Toxicity in Breast Cancer

Thesis submitted to the University of Cambridge for Doctorate of Medicine

By

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Summary

Whole breast radiotherapy after breast conserving surgery is an effective adjuvant treatment, but is associated with some long-term side effects and breast tissue toxicities including breast shrinkage, breast fibrosis, skin changes and poor overall cosmesis. These breast-specific complications can have a detrimental psychological impact. New radiotherapy techniques including IMRT and IGRT have the potential to reduce late treatment related toxicities.

The aim of this thesis was to investigate if the use of IGRT and IMRT can reduce the breast tissue related late complications after whole breast radiotherapy. The project evaluated if the use of clip-based IGRT technique allows the use of smaller safety margins around the tumour bed in breast radiotherapy. It also involved the development of normal tissue complication probability (NTCP) model for breast fibrosis to quantify the clinical benefits of IGRT. The benefits of IMRT were assessed using clinician-based assessment, serial photographs for overall cosmesis and patient-reported outcome measures (PROMs). The project also evaluated if the type of surgical technique used to close the tumour bed has an impact on late breast tissue toxicities.
Using set-up errors data from IMPORT HIGH study, this work confirmed that the use of clip-based IGRT technique reduces tumour bed PTV margins as compared to standard portal imaging. The use of clip-based IGRT had a small but significant reduction on the heart dose, especially for left sided breast cancer patients. The NTCP model for breast fibrosis suggests that for moderate-severe fibrosis, the breast tissue behaves as a serial organ and the maximum radiotherapy dose is most predictive of the complication. These results were verified in the independent START trial dataset.

This research project confirmed that patients receiving IMRT have superior overall cosmesis and reduced risk of skin telangiectasia as compared to patients receiving standard radiotherapy. However, the benefits of simple IMRT could not be demonstrated using PROMs. The project showed that breast seroma is associated with increased rates of post-operative infection and haematoma. It is also an independent risk factor for tumour bed induration and inferior breast cosmesis at 5 years.

The future research in breast cancer radiotherapy would be directed at quantifying patient’s individual risks and benefits and offering risk adapted radiotherapy.
Declaration

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared and specified in the text.

It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution.

I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution.

It does not exceed the prescribed word limit of 40,000.
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This dissertation is the result of my own work. Some of the research work was done in collaboration and this has been specifically indicated at the end of each chapter.
List of publications

This is the list of papers, book chapters, presentations and invited lectures achieved during the course of my research.

Papers: published directly related to research thesis


EM Donovan, EJ Harris, M Mukesh, J Haviland, J Titley, C Griffin, CE Coles, PM Evans, the IMPORT trial Management group The IMPORT HIGH image-guided radiotherapy study: a model for assessing image-guided radiotherapy. *Clinical Oncology* 2015 (1): 3-5

EM Donovan, C Brooks, RA Mitchell, M Mukesh, CE Coles, PM Evans, EJ Harris, the IMPORT trial Management group. The effects of Image guidance on dose distribution in breast boost radiotherapy. *Clinical Oncology* 2014 (11): 671-676
MB Mukesh, W Qian, JS Wilkinson, L Dorling, GC Barnett, AM Moody, C Wilson, NTwyman, NG Burnet and Charlotte Coles. Patient reported outcome measures (PROMs) following simple IMRT: results from the Cambridge Breast IMRT trial. *Radiotherapy and Oncology* 2014 (111); 270-275

MB Mukesh, GC Barnett, JS Wilkinson, AM Moody, C Wilson, L Dorling, CCW Hak, WQian, NTwyman, NGBurnet, GC Wishart and CE Coles. A randomised controlled trial of Intensity Modulated Radiotherapy (IMRT) for early breast cancer: 5-year results confirm superior overall cosmesis. *Journal of Clinical Oncology* 2013 (31); 4488-4496

MB Mukesh, E Harris, S Collette, CE Coles, H Bartelink, PM Evans, P Graham, J Haviland, P Poortmans, J Yarnold, R Jena. Normal tissue complication probability (NTCP) parameters for breast fibrosis: pooled results from two randomised trials. *Radiotherapy and Oncology* 2013 (108); 293-298

CE Coles, AM Brunt, D Wheatley, MB Mukesh, JR Yarnold. Breast Radiotherapy: less is more? *Clinical Oncology* 2013 (25); 127-134

MB Mukesh, G Barnett, J Cumming, JS Wilkinson, AM Moody, C Wilson, GC Wishart, CE Coles. Association of breast tumour bed seroma with post-operative complications and late normal tissue toxicity: Results from the Cambridge Breast IMRT trial. *European Journal of Surgical Oncology* 2012 (38); 918-924

M Mukesh, E Harris, R Jena, P Evans, C Coles. Relationship between irradiated breast volume and late normal tissue complications: a systematic review. *Radiotherapy and Oncology* 2012 (104); 1-10
Papers: published during research period, but not directly related to research thesis


K Eyre, D Whitney, M Mukesh, C Wilson, C Coles. Optimization and comparison of MammoSite brachytherapy using a single source, a standard plan line source and both forward and inverse planned Multi-Lumen technique. *Brachytherapy* 2013 (12): 107-113

Book chapters


**Oral presentations directly related to research thesis**


**MB Mukesh,** E Harris, S Collette, CE Coles, H Bartelink, PM Evans, P Graham, J Haviland, P Poortmans, J Yarnold, R Jena. Normal tissue complication probability (NTCP) parameters for breast fibrosis: pooled results from two randomised trials. 2nd ESTRO International FORUM meeting, Geneva 2013.


Invited lectures

IMRT and IGRT in Breast cancer. Cambridge Course of Intensity Modulated and Image Guided Radiotherapy, Royal College of Radiologist (Years 2013, 2014, 2015 & 2016)

Improving Outcome with Whole Breast Irradiation after conserving surgery. Breast Cancer Conference, India 2014

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<td>$\Sigma$</td>
<td>Systematic error</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Random error</td>
</tr>
<tr>
<td>2-D</td>
<td>2-dimensional</td>
</tr>
<tr>
<td>3-D</td>
<td>3-dimensional</td>
</tr>
<tr>
<td>ABPI</td>
<td>Accelerated Partial Breast Irradiation</td>
</tr>
<tr>
<td>AP</td>
<td>Anterior-Posterior</td>
</tr>
<tr>
<td>BA</td>
<td>Bony anatomy</td>
</tr>
<tr>
<td>BASO</td>
<td>British Association of Surgical Oncology</td>
</tr>
<tr>
<td>BCS</td>
<td>Breast conserving surgery</td>
</tr>
<tr>
<td>BCTOS</td>
<td>Breast Cancer Treatment Outcome Scale</td>
</tr>
<tr>
<td>BED</td>
<td>Biologically equivalent dose</td>
</tr>
<tr>
<td>BEUD</td>
<td>Biologically equivalent uniform dose</td>
</tr>
<tr>
<td>BEV</td>
<td>Beam’s eye view</td>
</tr>
<tr>
<td>BIS</td>
<td>Body Image Score</td>
</tr>
<tr>
<td>CBCT</td>
<td>Cone beam computer tomography</td>
</tr>
<tr>
<td>CCD</td>
<td>Cranio-caudal distance</td>
</tr>
<tr>
<td>CLD</td>
<td>Central lung distance</td>
</tr>
<tr>
<td>COM</td>
<td>Centre of mass</td>
</tr>
<tr>
<td>CRT</td>
<td>Conformal radiotherapy</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CTV</td>
<td>Clinical Target Volume</td>
</tr>
<tr>
<td>DCIS</td>
<td>Ductal carcinoma in-situ</td>
</tr>
<tr>
<td>DRR</td>
<td>Digitally Reconstructed Radiograph</td>
</tr>
<tr>
<td>DVH</td>
<td>Dose Volume Histogram</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
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</tr>
<tr>
<td>e-NAL</td>
<td>extended no action level</td>
</tr>
<tr>
<td>EBCTCG</td>
<td>Early Breast Cancer Trialists’ Collaborative Group</td>
</tr>
<tr>
<td>EORTC</td>
<td>European organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>EQD2</td>
<td>Equivalent dose in 2Gy fractions</td>
</tr>
<tr>
<td>EUD</td>
<td>Equivalent uniform dose</td>
</tr>
<tr>
<td>GHS</td>
<td>Global health status</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
<tr>
<td>HDR</td>
<td>High dose rate</td>
</tr>
<tr>
<td>ICRU</td>
<td>International Commission on Radiation Units</td>
</tr>
<tr>
<td>IGRT</td>
<td>Image guided radiotherapy</td>
</tr>
<tr>
<td>IHC</td>
<td>Immunohistochemistry</td>
</tr>
<tr>
<td>IMRT</td>
<td>Intensity modulated radiotherapy</td>
</tr>
<tr>
<td>IORT</td>
<td>Intra-operative radiotherapy</td>
</tr>
<tr>
<td>IVPs</td>
<td>Image verification protocols</td>
</tr>
<tr>
<td>kV</td>
<td>Kilo-voltage</td>
</tr>
<tr>
<td>LKB</td>
<td>Lyman Kutcher Burman</td>
</tr>
<tr>
<td>LR</td>
<td>Left-Right</td>
</tr>
<tr>
<td>LRR</td>
<td>Loco-regional recurrence</td>
</tr>
<tr>
<td>M</td>
<td>Mean error</td>
</tr>
<tr>
<td>MBD</td>
<td>Mean breast dose</td>
</tr>
<tr>
<td>MHD</td>
<td>Mean heart dose</td>
</tr>
<tr>
<td>MLC</td>
<td>Multi-leaf collimator</td>
</tr>
<tr>
<td>MLE</td>
<td>Maximum Likelihood Estimation</td>
</tr>
<tr>
<td>MV</td>
<td>Mega-voltage</td>
</tr>
<tr>
<td>MVA</td>
<td>Multivariate analysis</td>
</tr>
<tr>
<td>NAL</td>
<td>No action level</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>--------------</td>
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</tr>
<tr>
<td>NTC</td>
<td>Normal tissue complication</td>
</tr>
<tr>
<td>NTCP</td>
<td>Normal Tissue Complication Probability</td>
</tr>
<tr>
<td>NTD</td>
<td>Normalised total dose</td>
</tr>
<tr>
<td>NTD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>Tolerance dose which results in a 50% chance of tissue injury</td>
</tr>
<tr>
<td>OL&lt;sub&gt;3D&lt;/sub&gt;</td>
<td>On-line bony anatomy verification</td>
</tr>
<tr>
<td>OL&lt;sub&gt;clip&lt;/sub&gt;</td>
<td>On-line clip verification</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>PBI</td>
<td>Partial Breast Irradiation</td>
</tr>
<tr>
<td>PI</td>
<td>Portal Image</td>
</tr>
<tr>
<td>PROMs</td>
<td>Patient reported outcome measures</td>
</tr>
<tr>
<td>PTV</td>
<td>Planning Target Volume</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>QUANTEC</td>
<td>Quantitative Analyses of Normal Tissue Effects in the Clinic</td>
</tr>
<tr>
<td>R&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Coefficient of Determination</td>
</tr>
<tr>
<td>RBE</td>
<td>Relative biological effectiveness</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>RMH/GOC</td>
<td>Royal Marsden Hospital and Gloucestershire Oncology Centre</td>
</tr>
<tr>
<td>ROI</td>
<td>Regions of interest</td>
</tr>
<tr>
<td>RTOG</td>
<td>Radiation Therapy Oncology Group</td>
</tr>
<tr>
<td>S&lt;sub&gt;Ba&lt;/sub&gt;</td>
<td>Bony anatomy set-up error</td>
</tr>
<tr>
<td>S&lt;sub&gt;Clips&lt;/sub&gt;</td>
<td>Clips set-up error</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SI</td>
<td>Superior-Inferior</td>
</tr>
<tr>
<td>TB</td>
<td>Tumour bed</td>
</tr>
<tr>
<td>TD5</td>
<td>Tolerance dose with 5% complication probability</td>
</tr>
<tr>
<td>TD50</td>
<td>Tolerance dose with 50% complication probability</td>
</tr>
<tr>
<td>UTC</td>
<td>Ultrasound tissue characterisation</td>
</tr>
<tr>
<td>-----</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>UVA</td>
<td>Univariate analysis</td>
</tr>
<tr>
<td>WBI</td>
<td>Whole Breast Irradiation</td>
</tr>
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</table>
1. Introduction

1.1 Role of radiotherapy in early stage breast cancer

Breast cancer is the most common cancer in women with approximately 1.4 million new cases diagnosed every year worldwide [1]. With the implementation of breast screening programmes, the majority of women in the western world are now diagnosed with breast cancer at an early stage and treated with breast conserving surgery (BCS). After BCS, microscopic tumour foci may remain in the conserved breast. If untreated, these tumour foci can lead to loco-regional recurrence or/and life-threatening distant metastasis. Breast irradiation after BCS can eradicate these undetected microscopic foci of disease and prevent cancer recurrence. Several randomised controlled trials have shown that the addition of radiotherapy after BCS reduces the risk of loco-regional recurrence [2, 3]. The Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) systematic meta-analysis also confirms that whole breast radiotherapy reduces the risk of loco-regional or distant cancer recurrence by around half at 10 years [4]. The addition of breast radiotherapy also reduces breast cancer death rates at 15 years and these results are not significantly different between lymph node positive and lymph node negative patients. Overall, for every four recurrences avoided by year ten with radiotherapy, about one breast cancer death can be avoided by year fifteen [4]. BCS followed by whole breast radiotherapy is the current standard of care for most women with early stage breast cancer as it offers preservation of the breast with similar overall survival to patients undergoing mastectomy [2, 5].
1.2 Current challenges with breast radiotherapy

Whole breast radiotherapy is an effective adjuvant treatment, but is associated with some long-term side effects and toxicities. Apart from the uncommon risk of radiation induced secondary cancer and cardiovascular mortality, breast radiotherapy is also associated with breast tissue related complications including breast shrinkage, breast fibrosis, skin changes and poor overall cosmesis. Several radiotherapy factors have been linked to these breast tissue related late complications.

Traditionally, breast radiotherapy has been planned using a single plane 2-dimensional (2-D) technique. Though straightforward, it does not take into account the 3 dimensional (3-D) shape of the breast and can lead to substantial unwanted dose inhomogeneities, particularly in women with large breasts [6]. Apart from overdosing part of the breast, hot spots created with the inhomogeneous dose can also lead to the so called “double trouble” effect, due to an increase in both total dose and dose per fraction [7]. This double trouble effect may increase the risk of late complications including breast fibrosis and inferior cosmesis.

Studies have shown that the majority of local relapses in the conserved breast appear in the region of the primary tumour, commonly referred to as the tumour bed [8]. A higher radiotherapy dose is often given to the tumour bed (TB) as compared to the whole breast as a risk-adapted radiotherapy approach. This additional irradiation is known as the tumour bed boost. The addition of a tumour bed boost to whole breast irradiation (WBI) reduces the relative risk of local recurrence by half [9-11]. In the multi-centre EORTC 22881/10882 trial, the addition of TB boost improved local control rates with the cumulative local recurrence of
10.2% versus 6.2% for the no boost and boost group respectively (p<0.0001) [9]. Conversely, this additional irradiation also increases the probability of treatment-related complications with higher rates of breast fibrosis and inferior cosmesis [9, 12].

Current radiotherapy protocols using a photon boost typically add a margin of 10 mm around the tumour bed to create the tumour bed boost volume. This generous margin is added to the tumour bed to account for the significant day-to-day shift in patient position and reduce the risk of geographical miss [13]. A relatively large volume of normal breast tissue around the tumour bed can be treated to a high radiation dose because of this additional margin, which potentially increases the risk of late breast tissue complication rates.

1.3 Impact of late breast tissue complication on patients

The diagnosis of breast cancer has a major impact on patients and their families. Women not only have to cope with the fear of cancer recurrence but also altered body image post-surgery. Thankfully, the breast cancer specific mortality rates are coming down in the western world with increasing use of breast cancer screening, systemic chemotherapy, biological agents like trastuzumab, endocrine therapy and radiotherapy [14]. As more women survive their cancer, many are left to deal with the treatment-related complications for life. These breast-specific complications and altered body image not only have a detrimental psychological impact but also have an influence on patient’s quality of life [15]. The current challenge to clinicians is to minimise the treatment-related morbidity without compromising treatment efficacy.
1.4 Advances in radiotherapy techniques

Several advances have been made in the radiotherapy techniques in the past two decades. Intensity modulated radiotherapy (IMRT) technique allows variable radiation fluence through the beam, so a homogeneous dose is delivered to the target volume. Its role is well established for head & neck and prostate cancer radiotherapy [16, 17] but clinical data for breast cancer is more limited [18-20]. The use of IMRT has been shown to improve dose inhomogeneity to the breast [20-22] and has the potential to reduce late breast tissue complications.

Image guided radiotherapy (IGRT) allows correction of positional discrepancies and can be used in real time, before each treatment, so that daily treatment can be accurately targeted [23]. The X-ray imaging facility helps in monitoring the exact position of the target, so the margin for the day-to-day shift can be reduced. In breast radiotherapy, the use of IGRT may allow the use of smaller margins around the tumour bed. This may reduce the volume of healthy tissue exposed to high irradiation dose and potentially reduce late breast and non-breast tissue related complications.

1.5 Aims of the thesis

The current challenge in the radiotherapy management of early stage breast cancer is to recognise and evaluate new treatment strategies which widen the therapeutic window i.e. reduce treatment related toxicities without compromising cancer cure. New radiotherapy techniques including IMRT and IGRT have the potential to reduce late treatment related toxicities and should be evaluated in patients with breast cancer. The multi-modality management of breast cancer warrants that as we
evaluate new techniques, a better understanding and optimisation of other treatment factors is also addressed. My research work investigates if the use of IGRT and IMRT can reduce the breast tissue related late complications after whole breast radiotherapy. The specific aims of the research project are outlined below.

1.5.1 Objective 1: Evaluate the use of image guided radiotherapy (IGRT) in breast cancer

A difference in the position of the tumour bed (target) between the planning CT scan and treatment session can lead to geographical miss of the target, potentially increasing the risk of cancer recurrence and/or increasing toxicity to the normal surrounding tissue. Due to the uncertainty in patient and target position with each treatment session, a safety margin is routinely added around the tumour bed. The use of IGRT allows for the correction of positional discrepancies and has the potential to reduce the safety margin.

Surgical clips inserted into the wall of the tumour bed are a good surrogate for the tumour bed [24-26]. It is also feasible to use these surgical clips for IGRT in breast radiotherapy [27]. My aim was to evaluate if the use of clip-based IGRT technique allows the use of smaller safety margins around the tumour bed in breast radiotherapy. This will be evaluated by using the daily set-up data collected from a large cohort of patients treated within a UK breast radiotherapy trial.

The use of smaller safety margins will also reduce the volume of normal breast tissue around the tumour bed which is treated to a high radiation dose. I will perform a systematic review of the literature for the relationship between irradiated breast volume and breast tissue related complications to ascertain the potential clinical benefits of using breast IGRT.
1.5.2 Objective 2: Develop a normal tissue complication probability (NTCP) model for breast fibrosis

NTCP models are used to quantify the effects of radiation dose and treatment volume on radiotherapy related complications. NTCP models can be used to quantify the potential clinical benefits of using breast IGRT. I will develop a NTCP model for breast fibrosis to quantify the clinical benefits of smaller planning margins around the tumour bed as breast fibrosis is a common sequela after whole breast radiotherapy and adversely affects overall cosmesis. This will be done by pooling individual patient data from randomised controlled trials.

1.5.3 Objective 3: Evaluate the benefits of intensity modulated radiotherapy (IMRT) in breast cancer

The use of IMRT has been shown to improve dose inhomogeneity to the breast. However, there is paucity of clinical data to show that improved dose homogeneity using IMRT will reduce the late breast tissue complications. I will evaluate the benefits of simple field-in-field breast IMRT within the context of a large randomised controlled trial. The benefits of IMRT will be assessed using clinician-based assessment and serial photographs. In addition, the benefits of IMRT will also be assessed using patient-reported outcome measures (PROMs), as they provide patient’s perception of their own health condition and treatment toxicity.

1.5.4 Objective 4: Surgical technique affecting normal tissue complications in breast cancer

Apart from radiotherapy dose (dose homogeneity) and treatment volume, other treatment factors such as surgical techniques also affect breast tissue related late toxicities. While implementing newer radiotherapy techniques, other treatment factors should also be optimised. I will also investigate if the type of surgical
technique used to close the tumour bed has an impact on late breast tissue toxicity using data from a randomised controlled trial.
2. Relationship between irradiated breast volume and late breast tissue complications: a systematic review

* This work was published as an original article in Radiotherapy & Oncology in 2012 (Appendix)

2.1 Introduction

The aim of radiation therapy is to deliver a tumoricidal dose for optimal loco-regional control with relative sparing of the surrounding normal tissues. The precise knowledge of tumoricidal and tolerance doses to various tissues including dose volume effect is necessary when using 3D-conformal, intensity modulated radiotherapy and image guided radiotherapy techniques. Emami and colleagues[28] were amongst the first to publish a comprehensive review of radiation tolerance for normal tissues, including quantifying late normal tissue complication (NTC) as a function of volume of organ irradiated. This review, although informative was limited by the availability of few comprehensive databases, with most of the data on dose volume effect interpolated or extrapolated from whole organ data, or based on the experience of the involved clinicians. Since that publication, an update on the dose volume effect of radiation on the normal tissues has been published in form of “Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC)” report [29].

For years, the radiation dose-volume effect for the breast has been exploited as boost treatment for breast cancer patients at high risk of recurrence i.e. treating a small volume of breast tissue to a higher dose (boost) to improve local control rates [9-11]. More recently, breast dose-volume effect has been exploited in trials of Partial Breast Irradiation (PBI) for patients at low risk of recurrence: the irradiated
volume is confined to the region around the tumour bed with the aim of reducing toxicity whilst maintaining local control rates. However, there is paucity of published data on the dose-volume effect of irradiation on breast tissue including the QUANTEC report.

This systematic review evaluates the evidence for a relationship between the volume of breast tissue irradiated and the late breast tissue complications including overall cosmesis, breast fibrosis, breast induration and telangiectasia. It also explores the hypothesis that a modest dose reduction to part of the breast facilitates dose escalation to the tumour bed, with lower than expected NTC.

2.2 Methods

I performed a systematic search via Medline and Embase with the following search strategy “Breast neoplasm” AND “radiotherapy OR Irradiation”. This was combined with “AND fibrosis”, “AND cosme*”, “AND side effect*”, “AND toxicity”, “AND shrinkage” and “AND normal tissue”. The search was then expanded to include related articles and a reference list of articles published up to December 2011. This review was published as an original article in a peer-reviewed journal in 2012. Subsequent to this, new trial data on PBI has been reported and a Cochrane meta-analysis comparing PBI with WBI has been published. This has been covered later in section 2.8.

2.3 Impact of boost volume on breast tissue complications

2.3.1 EORTC 22881-10882 “boost versus no boost” trial (level I evidence)

The EORTC “boost versus no boost” trial randomised 5318 patients with early breast cancer between tumour bed boost of 16Gy versus no boost treatment after whole
breast irradiation (WBI) [9]. The boost was delivered using electrons or tangential photon fields in daily fractionation of 2Gy, or with iridium-192 implant at a dose rate of 0.5Gy per hour. At 10 years, the use of tumour bed boost of 16Gy increased the rates of moderate to severe breast fibrosis by 15% (28.1% versus 13.2%; p <0.0001). In this trial, 251 patients with microscopically incomplete tumour excision were also randomised to either a low dose boost of 10Gy (126 patients) or a high dose boost of 26Gy (125 patients) [30]. The cumulative incidence of moderate/severe fibrosis for low dose and high dose boost at ten years was 24% and 54% respectively. Hence a dose escalation of 16Gy to the boost volume in the incomplete tumour excision group increased the rates of moderate/severe fibrosis by 30%, compared with a 15% increase in the complete excision group for the same 16 Gy increase in dose.

On review of the treatment protocol, the boost volume for complete excision group was tumour bed plus 1.5 cm margin as compared to tumour bed plus 3 cm margin in the incomplete tumour excision group. This suggests a dose volume relationship for breast tissue as an increase in irradiated breast volume in the incomplete excision group doubled the risk of moderate/severe fibrosis for the same dose escalation of 16Gy. However, it is also possible that the increase risk of breast fibrosis is secondary to a combination of larger boost volume and a steeper dose response curve as the total dose was increased up to 76 Gy in the incomplete excision group. The trial group also reported that on univariate analysis, patients with large boost volume are more likely to develop sub-optimal cosmesis at 3 years [31] and breast fibrosis at 10 years [32]. However, boost volume was not a significant variable affecting fibrosis and cosmesis in multivariate analysis.
2.3.2 Brachytherapy boost (level IV evidence)

Borger et. al. [33] reported on the dose-volume effect of brachytherapy boost for breast fibrosis. 404 patients were treated with external beam radiotherapy, 50Gy in 2Gy daily fractions to the whole breast, followed by an iridium implant boost (dose rate 0.57± 0.11Gy/hour) of 15Gy (101 patients), 25Gy (301 patients) and 20Gy (2 patients). At a median follow up of 70 months, a fourfold higher risk of fibrosis was observed for each 100cm³ increase in irradiated boost volume, and a tenfold higher risk of fibrosis was observed when the total dose exceeded 79Gy compared to doses below 70 Gy.

McRae and colleagues from Georgetown University Medical Centre also reported on the relationship between brachytherapy boost volume and soft tissue complication [34]. Retrospective brachytherapy plans for 5 patients with radiation induced soft tissue damage were compared to 51 patients who experienced no severe complication after WBI followed by Iridium-192 boost. The mean boost volume for patients who developed soft tissue damage was significantly higher for all dose levels between 10Gy and 50Gy when compared to patients with no reported complications (p<0.05), suggesting a volume-NTC relationship at any specific dose. Similarly, Olivotto et. al. [35] reported an association between the volume of brachytherapy boost and late cosmetic outcome. 497 patients received WBI (46 to 50Gy over 4.5 to 5 weeks) followed by low dose rate Iridium-192 implant boost to bring the tumour bed dose to 60Gy. At a median follow up of 76 months, the volume of boost, measured by the number of Iridium seeds used, was a significant factor for fair/poor cosmesis. Patients with <70 seeds had a 15% risk of fair/poor cosmesis compared to 38% for patients containing ≥100 seeds (p<0.01). The use of greater number of seeds
would imply a larger volume of irradiated breast tissue, indicating towards a radiation volume effect on cosmesis. Several other single and multi-centre studies have reported on the relationship between volume of brachytherapy boost and Normal Tissue Complications (NTC) risk and are summarised in Table 1.
<table>
<thead>
<tr>
<th>First author, Institute and radiation technique</th>
<th>Number of patients (median follow up)</th>
<th>TNM/stage</th>
<th>Comments on NTC assessment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borger et. al. [33] Netherlands Cancer Institute WBI 50Gy in 25 fractions over 5 weeks followed by low dose rate Iridium implant boost of 15 Gy (101 pts), 25Gy (301 pts) and 20Gy (2 pts)</td>
<td>404 patients median follow up 70 months (range 30-133 months)</td>
<td>Stage 1-2</td>
<td>4 trained physicians scored fibrosis by palpating induration in the tumour bed. Four-scale scoring system: no fibrosis = no difference in consistency between the two breasts, grade 1 = a small difference, grade 2 = a moderate difference, grade 3 = a large difference. The scores of the four investigators were averaged to obtain the final result per patient</td>
<td>Implant volume (100% dose) associated with risk of fibrosis Odds ratio 4.2 (95% CI 2.3-8.0) per 100cm³ increase in boost volume</td>
</tr>
<tr>
<td>McRae et. al [34] Georgetown University Medical centre, Washington WBI 50Gy in 25 fractions over 5 weeks using Cobalt followed by low dose rate Iridium 192 boost of</td>
<td>56 patients with a minimum follow up of 2.5 years</td>
<td>Stage 1-3</td>
<td>Radiation injury to connective tissue or fat necrosis requiring prolonged medical or surgical management</td>
<td>Mean boost volume significantly higher for all dose level between 10Gy and 50Gy for patients who developed soft tissue damage as compare to patients with no reported complications (p&lt;0.05)</td>
</tr>
<tr>
<td>20Gy</td>
<td>Dewar et. al. [36] Institut Gustave- Roussy, France WBI 45 Gy in 2.5Gy per fraction using two tangential fields followed by tumour bed boost of 15Gy in 6 fractions using one to two fields on the cobalt unit</td>
<td>592 patients mean follow up 78 months (standard deviation 35 months)</td>
<td>T1-2 N0-1 Fibrosis and/or telangiectasia of the whole breast/the tumour bed graded as absent, slight, moderate or severe by the radiation oncologist. Cosmetic outcome graded as excellent, good, fair and poor</td>
<td>Area of field to the tumour bed (&gt;30cm³) associated with increased risk of fibrosis (p&lt;0.02) and telangiectasia (p&lt;0.01) on multivariate analysis. No relationship between cosmesis and area of field to the tumour bed</td>
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<td></td>
<td>Olivotto et. al [35] Joint Center for Radiation Therapy, Boston WBI 46-50 Gy in 4.5-5 weeks, followed by low dose rate Iridium-192 boost (10-27 Gy)</td>
<td>497/593 with Iridium-192 boost Median follow up 76 months (range 37-186 months)</td>
<td>T1-2 N0-1 Overall cosmesis scored as excellent, good, fair or poor by the physician. Excellent if treated breast looked the same as the opposite breast, good if minimal but identifiable effects of radiation, fair when significant effects of radiation and a poor if severe normal tissue sequelae</td>
<td>Boost volume measured by number of Ir-192 seeds associated with increased risk of fair/poor cosmesis (p&lt;0.0001 for trend)</td>
</tr>
<tr>
<td></td>
<td>Clarke et. al. [37]</td>
<td>64/78 patients</td>
<td>Stage1-2 Cosmetic result scored as excellent</td>
<td>6% patients developed</td>
</tr>
<tr>
<td>Paul A. Bissinger</td>
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<tr>
<td>Memorial Center for Radiation Therapy, Stanford WBI 45-55Gy in 1.8-2.5 Gy per fraction followed by low dose rate Iridium-192 boost (18-25 Gy)</td>
<td>with Iridium 192 boost</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Median follow up</td>
<td></td>
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<tr>
<td></td>
<td>42 months (range 30-120 months)</td>
<td>(treated breast looked the same as the opposite breast), satisfactory (mild to moderate breast asymmetry with &lt; 1/3 volume loss secondary to surgery or retraction from fibrosis) or unsatisfactory (marked breast asymmetry or severe fibrosis with &gt;1/3 volume loss). Breast fibrosis scored as mild, moderate or severe.</td>
<td>moderate/severe fibrosis with no correlation between fibrosis and implanted boost volume. Surgical factors like poorly planned excision scar and large volume excision main factors for unsatisfactory cosmesis.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wazer et. al. [38]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tufts University School of Medicine, Boston WBI 50 to 50.4Gy at 1.8-2Gy per fraction followed by low dose rate Iridium-192 boost of 20Gy</td>
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<tr>
<td>Wronczewska et al. [39] Nicolaus Copernicus University, Poland WBI 50-50.4Gy in 1-8-2Gy fraction followed by high dose rate Iridium-192 boost of 5-20Gy</td>
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2.3.3 *Intra-operative RT (IORT) boost using low energy X-ray (level IV evidence)*

IORT using low energy X-ray of 50kV can be used to deliver a single fraction of high dose radiation boost to the tumour bed after breast conserving surgery. Advocates for IORT cite several potential advantages of using this approach: delivery of radiation immediately after surgery prevents tumour cell proliferation; change in cytokines pattern into a less stimulating microenvironment, which is postulated to decrease local recurrence rates; and reduced risk of geographical miss [40, 41].

The University of Heidelberg, Germany reported on the late toxicity data (at 3 years) for 79 cases treated with this approach [42]. All patients received 20Gy intra-operative boost using 50kv X-ray followed by 46-50 Gy in 2Gy daily fraction of WBI ± supra/infra-clavicular fossa irradiation. 35% patients developed grade 2-3 breast fibrosis. They observed the applicator size for IORT significantly correlated with late breast fibrosis (spearman rank correlation coefficient 0.496, p<0.001). A larger
applicator size would imply a larger volume of irradiated breast tissue, suggesting a radiation volume effect on late breast tissue toxicity.

2.3.4 Cobalt unit boost (level IV evidence)

Dewar et. al. [36] reported on the Institute Gustave-Roussy experience for cosmetic outcome after breast-conserving surgery and radiotherapy. 592 patients received WBI (45Gy in 2.5Gy per fraction, four times weekly) using two tangential fields, each field treated on alternate days followed by tumour bed boost of 15Gy in 6 fractions using one-two fields on the cobalt unit. In addition to applied dose per fraction, the area of field to the tumour bed (>30cm$^3$) was associated with an increased risk of fibrosis (p<0.02) and telangiectasia (p<0.01) in multivariate analysis.

2.3.5 Other boost studies (level IV evidence)

The Fox Chase Cancer Center, Philadelphia reported on tumour bed boost parameters associated with overall cosmesis and fibrosis for 3186 patients treated at their centre from 1970-2008 [43]. All patients received whole breast irradiation (46-50Gy) followed by a tumour bed boost of 10-18Gy using electrons or photons. With a median follow up of 78 months, smaller boost cut-out size was a borderline predictor of excellent cosmesis (p=0.05) and lower risk of breast fibrosis (p<0.0001) on univariate analysis. Neither fibrosis nor worse cosmesis remained significantly associated with higher field size on multivariate analysis. However, no information on the actual treated boost volume was available and no distinction was made between physician and patient cosmetic score.
2.4 Partial Breast Irradiation (PBI) studies

WBI is the current standard of care after breast-conserving surgery. In the last decade, PBI has been explored as an alternative to WBI in low risk patients. PBI involves irradiation of a limited volume of breast tissue around the tumour bed and is currently under investigation in several randomised Phase II and III trials (Table 2). This is based on the rationale that the majority of local recurrences are located close to the area of surgical resection/index quadrant and foci of breast disease outside the index quadrant are often new primary tumours [2, 5]. Irradiating a limited volume of breast tissue could potentially reduce treatment related morbidity.
<table>
<thead>
<tr>
<th>Trial/Institute</th>
<th>Control arm (WBI)</th>
<th>Test arms (PBI): treatment modality</th>
<th>Median follow up (months)</th>
<th>Target accrual</th>
<th>Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christie group trial [44]</td>
<td>WBI 40Gy in 15 fractions with matched field for regional nodes</td>
<td>PBI: 40-42.5Gy in 8 fractions using electrons</td>
<td>65 months</td>
<td>708</td>
<td>Yes</td>
</tr>
<tr>
<td>Yorkshire Breast Cancer Group trial [45]</td>
<td>WBI 40Gy in 15 fractions with 15Gy boost</td>
<td>PBI using direct cobalt, caesium or electrons beam or a small mega-voltage tangential pair to a dose of 55Gy in 20 fractions</td>
<td>96 months</td>
<td>174 (pre-mature closure)</td>
<td>Yes</td>
</tr>
<tr>
<td>Hungarian National Institute of Oncology [46]</td>
<td>WBI using Cobalt or photons beam to a dose of 50Gy in 25 fractions over 5 weeks</td>
<td>HDR Ir-192 (85 pts) to a dose of 36.4Gy in 7 fractions over 4 days or Electrons (40 pts) to a dose of 50Gy in 25 fractions prescribed to the 80% isodose</td>
<td>66 months</td>
<td>258</td>
<td>Yes</td>
</tr>
<tr>
<td>TARGIT [47]</td>
<td>WBI 40–56Gy with optional boost of 10–16Gy</td>
<td>PBI: 20Gy single fraction using Intra-operative 50 KV photons</td>
<td>24 months</td>
<td>2232</td>
<td>Yes</td>
</tr>
<tr>
<td>IMPORT LOW [49, 50]</td>
<td>WBI 40Gy in 15 fractions, no boost</td>
<td>Arm 1: 36Gy in 15 fractions to the low risk volume of the breast and 40Gy in 15 fractions to the index quadrant</td>
<td>NA</td>
<td>2000 (closed 2010)</td>
<td>No*</td>
</tr>
<tr>
<td>Study</td>
<td>Technique Details</td>
<td>Dose Details</td>
<td>Regimen Duration</td>
<td>Status</td>
<td>Note</td>
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<tr>
<td>GEC-ESTRO[51]</td>
<td>WBI 50-50.4Gy in 25-28 fractions with 10Gy optional boost</td>
<td>PBI: 32 Gy in 8 fractions or 30.3Gy in 7 fractions HDR or 50Gy PDR</td>
<td>NA</td>
<td>1170</td>
<td>No*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(activated 2004)</td>
<td></td>
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<tr>
<td>NSABP-39 [52]</td>
<td>WBI 50-50.4Gy in 25-28 fractions with 10-16Gy optional boost</td>
<td>PBI: 34Gy in 10 fractions over five days using single/multi-source brachytherapy or 38.5Gy in 10 fractions over 5 days using 3D-CRT</td>
<td>NA</td>
<td>4300</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(activated 2005)</td>
<td></td>
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<tr>
<td>RAPID [53]</td>
<td>WBI 42.5Gy in 16 fractions with optional 10Gy boost</td>
<td>PBI: 38.5Gy in 10 fractions BD over 5-8 days using 3D-CRT</td>
<td>NA</td>
<td>2128</td>
<td>No*</td>
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<tr>
<td></td>
<td></td>
<td>(activated 2006)</td>
<td></td>
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<tr>
<td>IRMA [54]</td>
<td>WBI 45Gy in 18 fractions or 50Gy in 25 fractions or 50.4Gy in 28 fractions with optional 10 − 16Gy boost</td>
<td>PBI: 38.5Gy in 10 fractions BD over 5 days using 3D-CRT</td>
<td>NA</td>
<td>3302</td>
<td>No</td>
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<td></td>
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<td>(activated 2007)</td>
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<tr>
<td>Danish Breast Cancer Co-operative Group [55]</td>
<td>WBI 40Gy in 15 fraction</td>
<td>PBI: 40Gy in 15 fraction using 3D-CRT</td>
<td>NA</td>
<td>628</td>
<td>No</td>
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<td></td>
<td></td>
<td>(activated 2009)</td>
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<tr>
<td>SHARE[56]</td>
<td>WBI 50Gy in 25 fractions + 16 Gy boost or WBI 40-42.5Gy in 15-16 fractions without boost</td>
<td>PBI: 40Gy in 10 fractions BD over 5 to 7 days using 3D-CRT</td>
<td>NA</td>
<td>2796</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(activated 2010)</td>
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</table>

*No: Not reported at the time of original systematic review
2.4.1 Randomised controlled trials of Partial Breast Irradiation (PBI) versus Whole Breast Irradiation (WBI) (level I evidence)

At the time of original systematic review, four randomised controlled trials (RCT) comparing WBI versus PBI had reported on their outcome.

The Christie group were the first to report in 1993 [44]. They randomised 708 patients with breast cancer ≤ 4cm in diameter to PBI or WBI plus regional lymph nodes irradiation. PBI involved tumour bed irradiation (average field size 8cm x 6 cm) to 40-42.5Gy in 8 fractions over 10 days using electrons and WBI involved treating the whole breast to 40Gy in 15 fractions over 21 days using a tangential pair with matched field for regional nodes. After a median follow up of 65 months, recurrence rates were higher in the PBI arm as compared to the WBI arm (19.6% versus 11%; p=0.0008). Possible reasons for higher recurrence rates in the PBI arm were difficulty in defining the target volume, leading to geographical miss and including patients with infiltrating lobular carcinoma and ductal carcinoma with an extensive intra-ductal component. Patients with PBI also had significantly higher rates of marked breast fibrosis (14% versus 5%) and telangiectasia (33% vs. 12%) when compared to WBI.

The Yorkshire Breast Cancer Group randomised 174 patients between WBI (40Gy in 15 fractions over 21 days) followed by tumour bed boost (15Gy in 5 fractions) and PBI using a variety of techniques, including a direct cobalt or caesium beams, electrons or a small megavoltage tangential pair to a dose of 55Gy in 20 fractions over 28 days [45]. The trial closed prematurely due to poor accrual with higher loco-regional recurrence rates in the PBI group as compared to the WBI group (24% versus 9%). It has been suggested that higher recurrence in the PBI arm was secondary to difficulty in accurate definition of the target volume (tumour bed). Treatment related morbidity with PBI and WBI has not been reported. Both these trials pioneered the concept of PBI at a time when patient selection and tumour bed localisation was at an early stage of development. Subsequent randomised trials have used more stringent protocols for both of these factors.

The Hungarian National Institute of Oncology PBI trial [46] and TARGIT trial [47] have more recently reported their outcomes. The Hungarian PBI trial randomised 258 patients with T1
N0-1 Grade ≤2 breast cancer to WBI or PBI after breast-conserving surgery [46]. WBI was delivered using Cobalt or photon beams to a dose of 50Gy in 2Gy daily fractions and PBI was delivered using high dose rate (HDR) Iridium-192 brachytherapy (85 pts) to a dose of 36.4Gy in 5.2Gy per fraction over 4 days or electrons (40 pts) to a dose of 50Gy in 2Gy daily fractions prescribed to the 80% isodose. At a median follow up of 122 months, the local recurrence rates were not significantly different in the two trial arms. The cosmetic results using Harvard criteria [57] were favourable in the PBI arm. The rate of excellent to good cosmesis was 81% for the PBI group and 63% for the WBI group (p=0.0015) [58].

The TARGIT-A trial randomised 2232 patients with early breast cancer to WBI (40–56Gy) ± a boost of 10–16Gy and intra-operative PBI using low energy x-rays (50 kV) to a dose of 20Gy to the tumour bed attenuating to 5–7Gy at 1 cm depth [47]. Patients with adverse histological features including invasive lobular carcinoma or an extensive intra-ductal component also received WBI without boost in the PBI arm. At two years, the local recurrence rate was similar with no significant difference in the rate of toxicity, but the type of toxicity was significantly different in both arms. WBI arm had higher RTOG grade 3-4 toxicity for dermatitis, telangiectasia or breast pain (2.1% versus 0.5%; p=0.002). In contrast, patients receiving intra-operative PBI experienced a different spectrum of side effects. Breast seroma needing more than three aspirations was more common in the intra-operative PBI group (2.1 % versus 0.8%; p=0.012) and more patients reported skin breakdown or delayed healing, required surgical evacuation of haematoma and intravenous antibiotics or surgical intervention for infection. The cosmetic results have not been reported.

2.4.2 Case-matched pair studies (level III evidence)

Four case match pair studies have also compared breast tissue complications between partial and whole breast irradiation after BCS. Polgar et. al [59] prospectively selected 45 patients with T1N0-1 breast cancer treated with PBI using HDR Iridium-192 implants to a dose of 30.3-36.4Gy in 7 fractions over 4 days and matched 80 patients (eligible for PBI) treated with WBI 50Gy in 2Gy daily fractions with or without a tumour bed boost of 10-16Gy. At a median follow up of 7 years, the ipsilateral breast recurrence rates were not
significantly different in the two groups. Excellent/good cosmesis using Harvard criteria [57] was seen in 84.4% patients in the PBI arm and 68.3% patients in the WBI arm (p=0.04). However, a trend of increased incidence of RTOG grade 2-3 fibrosis was seen in the PBI group as compared to WBI group without boost (20% versus 5.8%; p=0.06).

The William Beaumont group matched 174 patients treated with PBI (low dose rate iodine-125 implant, 50Gy over 96 hours, dose rate of 0.52 Gy/hour or HDR implant 32Gy in 8 fractions, each separated by 6 hours), with 174 patients treated with WBI with a median total dose of 60Gy to the tumour bed [60]. With 36 months follow up, cosmetic outcome was more favourable in the PBI group as compared to the WBI group (excellent/good cosmesis 90% versus 83%; p=0.17), although this was not statistically significant.

King et. al. [61] matched 51 patients treated with PBI (low dose rate Ir-192 implant 45Gy over 4 days or HDR implant 32Gy in 8 fractions over 4 days) with 94 patients treated with WBI to a mean dose of 59Gy after breast-conserving surgery. A blinded panel of healthcare professionals scored cosmesis on a four-part scale (excellent, good, fair, poor) after reviewing photographic slides. At 20 months follow up, 75% patients in the PBI group and 84% patients with WBI had excellent/good cosmesis (p=not significant). Grade I and II treatment complications including skin erythema, desquamation, discoloration, hyperpigmentation, dimpling; breast pain, tenderness, shrinkage or fibrosis were significantly more common with WBI than PBI (80% versus 22%, p=0.001). Grade III treatment complications requiring surgical intervention were not significantly different in the two groups (8% versus 5%, p=not significant).

Tata Memorial Hospital, India matched 27 patients treated with PBI using HDR brachytherapy 34Gy in 10 fractions over 6-8 days with 67 patients treated with WBI (45Gy in 25# over 5 weeks followed by a tumour bed boost using electrons 15Gy in 6 fractions or interstitial HDR brachytherapy with a single 10Gy fraction [62]. At a median follow up of 43 months, cosmetic outcome was superior in the PBI group as compared to the WBI group (excellent/good cosmesis 88.9% versus 56%; p=0.003). No significant difference was seen in the rates of moderate/severe breast fibrosis.
2.4.3 Effect of treatment volume on NTC in PBI series

There are several publications reporting on the efficacy and low toxicity using PBI with only a few evaluating the impact of treatment volume on NTC. The current literature on the volume effect of PBI for 3D-CRT/IMRT, electrons and single/multi-source brachytherapy is summarised below.

2.4.3.1 3D-CRT/IMRT based PBI (level IV evidence)

Jagsi et. al. [63] reported on the cosmetic outcome of 32 patients treated with PBI using IMRT at deep inspiration breath hold. All patients received 38.5Gy twice daily fractionation over five consecutive days. At a median follow up of 2.5 years, 22% patients were scored as unacceptable cosmesis. Retrospective comparison between patients with acceptable and unacceptable cosmesis showed the mean proportion of breast volume receiving a minimum of 100% of the prescribed dose i.e.38.5Gy (V100) was lower in patients with acceptable cosmesis as compare to patients with unacceptable cosmesis (15.5% versus 23.0%; p=0.02). The mean proportion of breast volume receiving a minimum of 50% of the prescribed dose i.e. 19.25Gy (V50) was also smaller in the acceptable cosmesis group as compared to unacceptable cosmesis group (p=0.02).

Hepel et. al. [64] also reported on a positive correlation between the volume of breast tissue treated with PBI and overall cosmesis. 60 patients received PBI to a dose of 38.5Gy twice daily fractionation over one week using 3D-CRT. At a median follow up of 15 months, 18% patients developed fair-poor cosmesis and 25% developed Grade 2-4 subcutaneous fibrosis. In univariate analysis, the size of 3D-CRT target volume in proportion to the overall breast volume (PTV_Eval/WBV) correlated with fair/poor cosmesis (p=0.02) and grade 2-4 subcutaneous fibrosis (p=0.10). These two publications suggested an association between breast volume irradiated in PBI and normal tissue complications.

In contrast, Chen and colleagues from the William Beaumont group reported no association between overall cosmesis and PTV_Eval/WBV[65, 66]. 94 patients received PBI to a dose of 38.5Gy twice daily fractionation over five consecutive days using 3D-CRT. Of the 56 patients with cosmesis assessment of ≥48 months, 11% patients had fair to poor cosmesis and 3%
patients had Grade 3 fibrosis with no association between cosmesis/subcutaneous toxicity and PTV_Eval volume.

2.4.3.2 Single source brachytherapy/multi-source brachytherapy (level IV evidence)

Multi-source brachytherapy has been used for PBI for many years with most publications focusing on local control rates and limited reporting of normal tissue toxicity. Some have reported on factors associated with normal tissue toxicity and have commented on a positive correlation between NTC and the implant volume. Yeo et. al [67] reported on the efficacy and safety of PBI using multi-source brachytherapy for 48 patients with a median follow up of 53 months. A dose of 34Gy in 10 fractions over five days was delivered to the tumour bed plus a 1-2 cm margin. 14% patients developed Grade 2 subcutaneous toxicity with V100 and V150 significantly higher in these patients (p=0.018 and 0.034 respectively). No patient had poor cosmesis.

Wazer et al [68] reported on the variables associated with late toxicity and long term cosmetic outcome after multi-source brachytherapy PBI using pooled data from Tufts University, Brown University and Virginia Commonwealth University. The data for 75 patients with a median follow-up of 6 years were analysed. The number of dwell positions (i.e. total volume of implanted breast tissue) correlated with late cosmetic outcome (p=0.04). Lawenda and colleagues reported no association between implant volume and overall cosmetic outcome for 48 patients treated with low dose rate brachytherapy at their centre from 1997-2001 [69]. The purpose of the study was to evaluate dose escalation in PBI and the total dose was escalated in three groups of 50 Gy, 55 Gy and 60 Gy and implant volume was divided into four groups. A non-significant trend between dose escalation and fibrosis was seen but they also observed a decline in the incidence of breast fibrosis with increase in implant volume, a finding contrary to current published literature.

2.5 Breast fractionation studies

The Royal Marsden Hospital and Gloucestershire Oncology Centre (RMH/GOC) trial [70] randomised 1410 patients with early breast cancer into three WBI regimens. The control
arm consisted of 50Gy in 25 fractions over 5 weeks. The two test arms were (1) 39Gy in 13 fractions over 5 weeks and (2) 42.9Gy in 13 fractions over 5 weeks, respectively. The equivalent dose in 2 Gy fractions (EQD2) using a α/β ratio of 3.1 Gy for palpable breast induration, are 46.7Gy and 53.8Gy for test arms 1 and 2 respectively. The risk of moderate to severe induration at 10 years between arm 1 and 2 was 27% and 51% respectively suggesting a 24% increased risk of induration with a dose escalation of 7 Gy to the whole breast (3.3 % increase per Gy). Compared to this fractionation effect, an escalated dose to tumour bed alone i.e. boost of 15.5 Gy in 7 fractions (EQD2 of 16 Gy) increased the risk of induration by 17% (1.05% increase per Gy). This data indicates a radiation volume-effect for breast tissue, as the effect of induration per Gy of radiation increases with breast volume irradiated.

2.6 Dose modulating effect on the breast

The normal tissue dose volume effect can be therapeutically exploited by radiating a small volume of tissue to a higher dose and reducing the overall dose to the rest of the organ i.e. modulating the dose across the normal tissue to reduce late side effects. This approach has been successfully implemented in prostate cancer radiotherapy by using IMRT [71]. The St. George and Wollongong trial from Sydney suggests that this modulation effect is also present in breast tissue [72]. The trial randomised 688 patients with T1-2N0-1 breast cancer between standard arm of WBI with 50Gy in 2Gy daily fractions (no boost) and test arm of WBI of 45Gy in 1.8Gy daily fractions plus a 16Gy tumour bed boost. The overall cosmesis was scored by a five-person panel using digital photographs as excellent, good, fair and poor. 79% patients in the test arm with boost and 68% patients in the standard arm had excellent/good cosmesis (p=0.016). The rate of moderate to severe breast fibrosis at five years was similar in both treatment arms. These results are contrary to the current literature of worse cosmetic outcome and higher rates of breast fibrosis with additional boost radiation. One possible explanation for these results is that a modest dose reduction to the whole breast allowed dose escalation to the tumour bed without the expected increase in normal tissue toxicity and indicates towards a volume effect.
2.7 Limitations of the review

Late breast tissue toxicity post radiotherapy is influenced by several patient and treatment related factors including type of surgical closure (discussed later in chapter 7). Many studies included in this review have not accounted for other confounding factors including extent of surgical excision, total delivered dose, dose fractionation, post-operative complications and brachytherapy dose inhomogeneity. For example, surgical excision volume and baseline surgical cosmesis are significant factors affecting cosmesis [31, 73-75]. A larger surgical excision would also imply a larger brachytherapy boost/target volume and a larger applicator size for IORT. Based on the current reports, it is difficult to draw strong support on the independent volume effect on late breast tissue complications.

A variety of treatment approaches have been used including photons, electrons, intra-operative techniques and brachytherapy. In addition, the reported studies have used different endpoints (fibrosis, cosmesis and telangiectasia) with several different scoring methods and a diverse period of follow up. These challenges make it difficult to draw firm conclusions on the qualitative and quantitative effect of dose-volume relationship for breast tissue.

2.8 New data on dose volume effect

The systematic review from 2012 seems to suggest that treatment volume is an important parameter affecting late breast tissue complications. However, more robust data from the randomised trials was unavailable at the time of that review. Subsequently, several randomised controlled trials comparing WBI with PBI have been reported and a Cochrane review has been published.

2.8.1 Randomised controlled trials of Partial Breast Irradiation (PBI) versus Whole Breast Irradiation (WBI)

IMPORT LOW trial is one of the few randomised trials to compare PBI versus WBI, with volume of breast irradiated as the solitary randomisation variable. The trial compares WBI with two dose level of PBI delivered using IMRT in women with low risk breast cancer [49,
The control arm (WBI) delivered 40Gy in 15 fractions over 3 weeks to the whole breast. Arm 1 delivered synchronous 40Gy in 15 fractions to the partial breast PTV and 36Gy in 15 fractions to the remainder of the whole breast. Arm 2 (PBI) delivered 40Gy in 15 fractions to the partial breast PTV alone (figure 1). The trial recruited 2018 patients and at five-years, breast tissue toxicities were favourable with PBI as compared to WBI [76]. On clinician-based toxicity assessment, patients receiving PBI developed less moderate-marked normal tissue effects as compared to patients receiving WBI (14% versus 20%; p=0.004). Similarly using PROMs, fewer patients reported “changes in breast appearance” and “breast harder/firmer to touch” with PBI as compared to WBI.

**Figure 1 : IMPORT LOW trial schema**

**CONTROL**

40Gy/15Fr

**TEST ARM 1**

36Gy/15Fr

40Gy/15Fr

**TEST ARM 2**

40Gy/15Fr

**Control**: Whole breast irradiation, 40Gy in 15 fractions over 3 weeks

**Arm 1**: 36Gy in 15 fractions to the low risk volume of the breast and 40Gy in 15 fractions to the index quadrant over 3 weeks

**Arm 2**: Partial breast irradiation, 40Gy in 15 fractions over 3 weeks to the index quadrant only

The Danish Breast Cancer Cooperative Group trial (not reported) is a Phase 2 study comparing PBI to WBI in low risk breast cancer patients with both treatment arms receiving 40Gy in 15 fractions over 3 weeks with volume of breast irradiated as the solitary randomisation variable [55]. The primary endpoint for this study is grade 2-3 breast fibrosis after radiotherapy and the secondary endpoints are other late morbidity, local recurrence and genetic risk profiling for development of late radiation morbidity.
2.8.2 Accelerated PBI (ABPI) trial versus WBI

The RAPID trial is the 3D-CRT based APBI trial of 2135 patients which has reported on interim toxicity outcome at 3 years [77]. Patients in the WBI arm received 50Gy in 25 fractions or 42.5 Gy in 16 fractions with additional 10Gy tumour bed boost in 20% patients. Patients in the accelerated PBI (ABPI) received 38.5Gy in 10 fractions over 5-8 days using 3D-CRT. Radiation toxicity was assessed by a trained nurse observer, patient self-report of toxicity and panel of experienced radiation oncologists reviewing digital photographs for global cosmesis. The trained nurse assessment and patient self-assessment found worse cosmesis for patients in the APBI arm as compared to patients in the WBI arm at 3 years. Patients receiving ABPI also had higher grade ≥2 breast fibrosis (1% versus 9%) and skin telangiectasia (1% versus 5%) as compared to WBI patients. Using digital photographic assessment, patients receiving ABPI scored worse cosmesis as compared to WBI (35% versus 17%; p<0.001) at 3 years.

The Florence IMRT based APBI trial of 520 patients has conversely reported less acute and late toxicity with ABPI as compared to WBI [78]. The ABPI was delivered using IMRT to a dose of 30Gy in 5 non-consecutive fractions days over 2 weeks. The WBI arm received 50Gy in 25 fractions with additional 10Gy tumour bed boost. Acute and late toxicity was assessed using the RTOG/EORTC scoring scheme and the cosmesis was scored using the Harvard breast cosmesis scale. The acute grade ≥2 skin toxicity was much higher in the WBI arm as compared to ABPI arm (37.7% versus 2%; p=0.001). The late skin toxicity and cosmetic outcome was not dissimilar between the two study arms. Only 2 patients in the WBI arm had grade ≥2 late skin toxicity and physician rated cosmesis was scored as good-excellent for nearly all patients in the study except 2 patients who had received WBI.

The different toxicity results between the RAPID and Florence APBI studies can be partially explained by calculating the EQD2 for the APBI arms. Using the α/β ratio of 3 and repair half-time of 4.4 hours, ABPI patients in the RAPID trial received equivalent dose of ~66Gy as compared to ~54 Gy in the Florence trial. In addition, the Florence trial had a smaller number of patients and therefore the trial was underpowered for assessing normal tissue toxicity endpoints. The authors of the Florence study have also suggested that as compared
to 3D-CRT, the use of IMRT for APBI can reduce the volume of breast tissue receiving 50% of the prescribed dose and potentially induce less radiation toxicity.

The GEC-ESTRO APBI study compared WBI with APBI using interstitial brachytherapy and reported on five year breast tissue toxicity [79]. A total of 1328 patients were randomised between WBI of 50Gy in 25 fractions with 10Gy tumour bed boost or interstitial brachytherapy with 32Gy in 8 fractions or 30.1 Gy in seven fractions with twice daily fractionation using HDR brachytherapy or 50 Gy pulsed rate brachytherapy. The WBI was delivered using 2 tangential opposing megavoltage photon beams. The treating clinician (non-masked) scored late toxicity using RTOG/EORTC scoring schema and overall cosmesis using Harvard breast cosmesis scale. During clinical visits, patients also self-reported on their cosmetic results. There was no centrally blinded assessment of toxicity using digital photographs. At five years, the cumulative late toxicity of Grade ≥2 was worse among the WBI arm as compared to APBI arm (27% versus 23.3%; p=0.12). The grade 2-3 late skin toxicity was higher in the WBI arm as compared to APBI arm (10.7% versus 6.9%; p=0.20). The grade 2-3 late subcutaneous tissue side effects were lower in the WBI arm as compared to the ABPI arm (9.75 versus 12.0%; p=0.28). The cosmetic outcome was also similar between WBI and APBI arms using both patients’ view (excellent to good 91% and 92% respectively) and physician assessment (90% and 93% respectively). It has been acknowledged by the GEC-ESTRO study group that the use of current standard 3D conformal radiotherapy/IMRT could have mitigated some of the Grade 2-3 side effects in the WBI arm.

2.8.3 Intra-operative radiotherapy based PBI versus WBI

The ELIOT trial from the European Institute of Oncology, Milan compared intra-operative radiotherapy using electrons with WBI [80]. The intra-operative arm patients received single dose of 21Gy to the tumour bed at the time of surgery and WBI patients received 50Gy in 25 fractions followed by 10Gy tumour bed boost. A total of 1305 patients were randomised and at a median follow up of 5.8 years, higher Ipsilateral breast tumour recurrences were seen in the intra-operative trial arm as compared to WBI (4.4% versus 0.4%; p=0.0001). The toxicity data was available for 876 patients which showed no difference for breast fibrosis, mammary retraction, pain or burning between the 2 trial arms. Patients receiving intra-operative radiotherapy had higher rates of fat necrosis and those in WBI arm had higher
overall skin side effects including erythema, hyperpigmentation and pruritus. No further details about treatment toxicity with WBI and intra-operative radiotherapy has been reported.

2.8.4 Dose modulation effect on the breast

This dose modulating effect on the breast tissue is further investigated in the IMPORT High trial [49, 81]. The trial randomises high risk patients between three groups; standard arm: 40Gy in 15 fractions to the whole breast over 3 weeks with a 16Gy in 2Gy daily fraction sequential tumour bed boost, Test arm 1: 36Gy in 15 fraction to the low risk volume of the breast, 40Gy in 15 fractions to the index quadrant + concomitant tumour bed boost of 48Gy in 15 fractions and Test arm 3: 36Gy in 15 fractions to the low risk volume of the breast, 40Gy in 15 fractions to the index quadrant + concomitant tumour bed boost of 53Gy in 15 fractions (figure 2). The trial tests the hypothesis that decreasing the radiation dose to the whole breast tissue by a very small amount (40 Gy to 36Gy) and treating an iso-effective dose to the index quadrant and tumour bed (Arm 1), may result in less normal tissue side effects compared to the control group. It will also test if decreasing the radiation dose to the whole breast tissue by a very small amount allows dose escalation to the tumour bed (area of highest risk of local recurrence) without an increase in normal tissue side effects (Arm 2). The results from the IMPORT HIGH trial are expected soon.
2.9 What do we conclude about the volume effect on late breast complications?

The above studies indicate that there is both quantitative and qualitative evidence of dose-volume effect for breast tissue.

2.9.1 Quantitative effect of treatment volume

The study by Borger et. al [33] using low dose rate iridium implants provides the most robust quantitative data on the dose-volume relationship. For every 100cm³ increase in irradiated boost volume, the risk of fibrosis increases four-fold and a two-fold increase in boost volume will result in an 11% decrease in tolerance dose (NTD50). It is however difficult to be certain as to how the low dose rate brachytherapy data can be extrapolated to HDR brachytherapy, electron and photon boost techniques. The RMH/GOC trial [70] which used electron boost provides indirect quantitative information on the dose volume relationship for NTC. For every Gy increase in boost dose, the risk of moderate to severe breast
induration increases by 1% as compared to 3% when the whole breast dose is increased by one Gy.

2.9.2 Qualitative effect of treatment volume

The result from the IMPORT Low trial provides the strongest qualitative evidence of volume effect for breast tissue. The trial showed less moderate-marked normal tissue effects with PBI and fewer patients reporting “changes in breast appearance” and “breast harder/firmer to touch” with PBI as compared to WBI. It is the only reported randomised trial using similar dose fractionation schedule and radiotherapy technique between PBI and WBI, with the volume of breast irradiated as the solitary randomisation variable.

The result from the Hungarian PBI trial [46] also provides a qualitative indication on a volume – NTC relationship. They report superior cosmetic outcome and reduced NTC rate in the PBI arm when compared to the WBI at both five and ten years though the study population was small. The larger GEC-ESTRO APBI trial using interstitial brachytherapy [79] suggests favourable cumulative toxicity with PBI and reported no difference in subcutaneous side-effects and breast cosmesis between PBI and WBI.

The results from the RAPID trial using 3D-CRT based APBI conversely showed worse results with PBI as compared to WBI, supporting a weak volume effect for breast tissue [77]. Similarly, the randomised trial from Christie had reported a higher rate of breast fibrosis and telangiectasia in the PBI arm [44]. A dose-response relationship for late radiation effects including telangiectasia and breast fibrosis is well established [9, 82, 83] and these dissimilar results can possibly be explained by calculating the 2Gy equivalent dose (EQD2) for the PBI and WBI groups using an α/β ratio of 3.1 [70] for fibrosis. The PBI group in the RAPID study and Christie trial received around 66Gy and 63-70Gy respectively. In comparison, the WBI group received 50-60Gy in RAPID and 45Gy in the Christie study. This would indicate towards a strong effect of total radiation dose on late radiation effects which cannot be mitigated by radiating a smaller amount of breast tissue.
2.10 Chapter contributions

I am grateful to Dr Charlotte Coles and Professor John Yarnold for their guidance with this work.

I was responsible for doing an independent literature search for this chapter using PubMed and Medline. After reading and analysing all the relevant papers and abstract, I wrote the original manuscript which was subsequently published in the peer reviewed Radiotherapy & Oncology journal (appendix).
3. Image-guided radiotherapy in Breast Cancer

* A part of this work has been published as original articles in Clinical Oncology in 2014 and British Journal of Radiology in 2016 (Appendix)

3.1 Introduction

This chapter addresses the important issue of image guidance and accuracy for breast radiotherapy. A safety margin is routinely added around the radiotherapy target (tumour bed in breast boost radiotherapy), to avoid geographical miss of the target. In this chapter, I investigate if these safety margins can be safely reduced for photon-based tumour bed boost by the use of image guided radiotherapy and the likely benefits of using a smaller margin.

The breast radiotherapy process can be divided into three steps:

3.1.1 Simulation (step1)

A planning computed tomography (CT) scan is performed while the patient is in the position that will be used during radiotherapy treatment delivery. The patient is immobilised using breast board/vacuum bag and pre-defined tattoo marks are placed on the skin surface.

3.1.2 Radiotherapy planning (step 2)

The planning CT scan is used to identify and contour the clinical target volumes (tumour bed and whole breast) and organs at risk (lung, heart, contralateral breast). The treatment is planned using a treatment planning system which allows the user to design the dose delivery. Typically, a fixed number of radiation beams are added and the plan is optimised by adjusting the beam angle and beam aperture, to cover the target volumes and spare organs at risk.
3.1.3 Treatment verification and delivery

Radiotherapy treatment is delivered over a series of fractions, to allow preferential DNA repair to take place in normal cells but not the cancer cells. Before each radiotherapy fraction, the planned patient position is reproduced by aligning to patient skin tattoos using laser light beams. Verification images are taken while the patient is on the treatment couch to confirm correct positioning and treatment is delivered.

3.2 The role of Image guided radiotherapy (IGRT)

A difference in target position between the planning CT scan and treatment session can lead to geographical miss of the target, potentially increasing the risk of cancer recurrence and/or increasing toxicity to the normal tissue. Set-up error (difference between the actual and planned position of the target) is an undesirable but inherent part of the radiation treatment process. Due to the uncertainty in patient and target position with each fraction (set-up errors), a safety margin is routinely added around the clinical target volume to form a planning target volume (PTV). This PTV margin not only accounts for the daily interfraction and Intrafraction motion (figure 3), but also for other geometrical uncertainties associated with the radiotherapy equipment. Interfraction motion includes differences in patients positioning between radiotherapy fractions. Intrafraction motion includes movement that occurs during each radiotherapy fraction, for example respiratory motion and tissue deformation.
**Figure 3**: Set-up errors and PTV margin in radiotherapy

A. Target volume requiring radiotherapy dose
B. Day to day variation in position of the target volume
C. Safety margins (black arrows) around the target volume to account for daily positional and other errors and create a planning target volume

As discussed in section 3.1.3, pre-defined skin tattoo marks and laser beams are currently used to position patients for breast radiotherapy. Though simple to use, the set-up errors using this technique are large. Studies have reported that positional error using surface markers could range from 1-30 mm [84-86]. These large positional errors mean that by using skin marks and laser beams as verification method, a relatively large PTV margin has to be used (commonly 10 mm).

Due to the addition of a large PTV margin, a considerable volume of the healthy surrounding tissue is unnecessarily irradiated to the treatment dose, increasing the risk of radiation related adverse events. This also limits our ability to safely escalate the radiation dose to the target. IGRT can be used to reduce both interfraction and Intrafraction errors and potentially reduce the PTV margin.

### 3.3 Current Image guided radiotherapy techniques in breast cancer

#### 3.3.1 Portal imaging

Two-dimensional megavoltage (2D-MV) portal imaging is the current standard IGRT verification technique for breast radiotherapy. The breast radiation treatment is usually
carried out using lateral and medial tangential beams and these high energy (megavoltage) treatment beams are used to generate portal images (PI). The position of the ribs and lung on PI are compared to a digitally reconstructed radiograph (DRR) generated from planning CT images to identify the day to day variation in patient positioning (figure 4).

Parameters including central lung distance (CLD), defined as distance between the posterior field edge and the interior chest wall at the central axis and cranio-caudal distance (CCD), defined as distance between skin and the caudal beam edge are compared between the PI and DRR, to calculate positional errors in both the transverse and longitudinal direction (figure 5). These positional errors can be corrected daily using daily correction protocol (discussed in section 3.8.5). However, the time between on-line verification and radiation delivery has to be short. More commonly, the average displacement over 3 fractions is calculated and the patient is re-positioned for all subsequent fractions if the mean error exceeds pre-defined limits (typically 3mm).

**Figure 4 : Standard portal image verification technique**

<table>
<thead>
<tr>
<th>Digitally reconstructed radiograph (DRR) from planning CT scan</th>
<th>Mega-voltage Portal Image (PI)</th>
</tr>
</thead>
</table>

The standard verification technique compares the digitally reconstructed radiograph generated from planning CT scan (left) with the mega-voltage portal image (right)
3.3.2 Limitations of Portal Imaging

Though simple and effective, the portal images (PI) provide information about the patient’s position based on bony anatomy, and not the breast tissue. In addition, the tumour bed (area at highest risk of cancer recurrence) is not directly visualised on the PI. The chest wall is used as a surrogate for the breast and the tumour bed.

In recent years, studies have shown that bony anatomy (chest wall) is a poor surrogate for both the tumour bed and the whole breast. Hasan and colleagues study of 27 patients treated with accelerated partial breast irradiation indicated that (a) the whole breast can move independent of bony anatomy and (b) the tumour bed can also move independent of the whole breast [24].

3.4 Planning target volume (PTV) margin in breast radiotherapy

Due to our inability to directly visualise the tumour bed for positional verification and correct for Intrafraction motion, a PTV margin of 10 mm is commonly added to the tumour bed, to generate a planning target volume (PTV) for the photon tumour bed boost [13].
Due to the additional PTV margin around the tumour bed, a large volume of normal breast tissue is treated to a high radiation dose. This can potentially increase the risk of late breast tissue toxicity as summarised in section 2. An increase in PTV margin will also increase the radiation dose to contralateral breast, heart and ipsilateral lung [87]. If we could safely reduce set-up errors, PTV margin around the tumour bed could also be safely reduced. This is a desirable aim to reduce the risk of late breast and other normal tissue toxicity post radiotherapy.

3.5 Fiducial marker-based image guided radiotherapy (IGRT) technique in breast cancer

3.5.1 Use of fiducial markers (surgical clips) as a tumour bed surrogate

The British Association of Surgical Oncology (BASO) have recommended that all patients undergoing breast conserving surgery should have surgical clips inserted into the wall of the tumour bed [88]. Clips are currently used as fiducial markers, for the accurate localisation the tumour bed [89]. My study is centred on the concept that clips are a better surrogate for the tumour bed as compared to bony anatomy. Several studies have shown clips to be a better surrogate [24-26] and they are summarised below.

The use of surgical clips as a surrogate for the tumour bed was evaluated in twenty-eight patients by Weed et al. [25]. Each patient underwent two planning CT scans on separate days. The tumour bed and clips were identified as separate regions of interest (ROI). The scans were then fused based on bony anatomy and the displacement of the tumour bed was compared to the displacement of the clips over time. The study found that the displacement of clips tracked the displacement of the excision cavity during radiation therapy. An average displacement error of 3mm was seen between the two ROIs, attributed to the finite thickness of the CT slices and use of limited number of clips. Hasan et al [24] also demonstrated that surgical clips are a better surrogate for tumour bed compared to bony anatomy and breast surface. Twenty-seven patients underwent two CT scans in treatment position, one initial planning CT scan and a second scan at an average of 27 days after the first scan. The centre of mass (COM) of the lumpectomy cavity was determined on
both CT scans for each patient. Localisation of the tumour bed was performed using CT registration of the following: bony anatomy, COM of surgical clips embedded in the excision cavity and breast surface. The distance between COMs using the three-registration methods were compared ($\Delta$COM$_{\text{bony anatomy}}$, $\Delta$COM$_{\text{clips}}$ and $\Delta$COM$_{\text{breast surface}}$). It was observed that localisation of the tumour bed using surgical clips is most accurate compared to localisation using bony anatomy and breast surface. Topolnjak et al [26] compared the residual error (surrogate error) between excision cavity and surgical clips placed in the excision cavity to determine if surgical clips are a good surrogate for the tumour bed and quantify the stability of the clip position. Twenty-one breast cancer patients were treated with 28 fractions and cone beam CT (CBCT) scans were regularly acquired for set-up correction protocol. The CBCT scans were registered to the planning CT scan using grey value registration of the excision cavity and chamfer matching of the clips. The study showed that surgical clips are an excellent surrogate for excision cavity with small residual errors of 0.7-1.3 mm.

3.5.2 Feasibility of fiducial markers for image guided radiotherapy in breast cancer

We now know that surgical clips are a better surrogate of the lumpectomy cavity (tumour bed), as compared to bony anatomy. A number of small studies have evaluated the feasibility of using these surgical clips for image guided breast radiotherapy [27, 90, 91].

The IMPORT HIGH trial group used gold fiducial markers (small seeds that can be sutured on to the cavity wall) as a tumour bed surrogate for IGRT to estimate safe PTV margin around the breast tumour bed [27]. Treatment verification and daily on-line correction were performed on 42 patients with 2D-MV (high energy) portal image or kV (low energy) planar image or cone beam CT. The study concluded that using extended no action level (e-NAL) or daily on-line correction strategy (discussed in section 3.8.5), the tumour bed PTV margin can be safely reduced to 5mm. Leonard et al. [90] also demonstrated the feasibility of gold seed fiducial markers for IGRT using orthogonal and lateral MV portal films in 20 patients.
3.6 What are the current challenges in implementing clip-based IGRT?

2D-MV portal imaging verification method using bony anatomy is relatively simple and easy to use whereas additional verification time and resources are required for clip-based IGRT technique. The benefit of clip-based IGRT over portal imaging needs to be quantified by comparing the PTV margin and verification time for both techniques.

In addition, most of the feasibility studies of fiducial marker-based IGRT were based on small numbers of patients, often using gold seeds as fiducial markers. The use of gold seeds as fiducial markers is quite expensive (~£200/patient), considering that breast radiotherapy constitutes a large part of radiotherapy department work load. Titanium clips can be used as an alternative fiducial marker (~£1/patient), though due to their low density, they cannot be visualised on 2D-MV portal image. Several different imaging modalities can be used for titanium clip-based IGRT: kV planar images, kV cone beam CT and Megavoltage CT (TomoTherapy). It is currently unclear if the PTV margin depends on the type of IGRT imaging modality used.

My thesis work quantifies the benefits of clip-based IGRT over bony anatomy-based IGRT in breast radiotherapy, by comparing the PTV margin and verification time. This large study uses the inexpensive titanium clips and a variety of IGRT methods to compare the PTV margin. The additional imaging dose from IGRT can potentially increase the risk of secondary cancer, though the imaging dose is significantly lower (one-thousandth) as compared to the treatment dose. The estimation of secondary cancer risk with IGRT is outside the remit of my research work and will not be discussed further.
3.7 Hypothesis

3.7.1 Primary hypothesis

The primary hypothesis tested in this study is that clip-based IGRT technique can be used to safely reduce PTV margin around the tumour bed, compared to bony anatomy-based verification technique (now referred to as standard verification technique).

3.7.2 Secondary hypothesis

The following secondary hypotheses were also addressed:

   a. Clip-based IGRT reduces the volume of breast tissue and other surrounding organs receiving high radiation dose.

   b. PTV margins are not influenced by the type of imaging modality used for clip-based IGRT.

   c. Time required to perform clip-based IGRT is similar to bony anatomy-based verification.

3.8 Materials and Methods

3.8.1 Study population and patient characteristics

All patients participating in the national Phase 3 IMPORT HIGH trial had titanium clips inserted into the walls of the TB and received clip-based IGRT (using on-line and off-line verification protocol) for their tumour bed boost as routine. The verification image data from the trial were used to calculate the set-up error with the clip-based IGRT technique. These imaging data were also used to calculate the set-up error if bony anatomy was used for verification (ignoring the information from the clips). All patients had previously consented for their imaging data to be used for research purposes. As the imaging data were retrospectively analysed, it had no direct impact on the study population.
Imaging data were collected from five different centres participating in the IMPORT HIGH trial: Addenbrooke’s Hospital, Royal Marsden Hospital (RMH), Ipswich Hospital, Cheltenham Hospital and Clatterbridge Hospital. Ipswich, Cheltenham and Clatterbridge centres used a pair of orthogonal 2D-kV planar images (2D-kV) and daily on-line image verification protocol, RMH used cone beam CT (kV-CBCT) with an e-NAL verification protocol, and Addenbrooke’s used Mega Voltage CT (MV-CT) (Tomotherapy) with a daily on-line image verification protocol for treatment verification and positional correction (figure 6). The details of different image verification protocols (IVPs) are discussed later.
**Figure 6: Bony anatomy and clip-based verification using kV-CBCT, MV-CT and 2D-kV**

<table>
<thead>
<tr>
<th>BONY ANATOMY VERIFICATION</th>
<th>CLIP-BASED VERIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>kV-cone Beam CT</strong></td>
<td></td>
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<tr>
<td><img src="kvc.png" alt="Kv-cone Beam CT Image" /></td>
<td><img src="kvc.png" alt="Kv-cone Beam CT Image" /></td>
</tr>
</tbody>
</table>

The green image represents the cone beam CT and the purple image represents the planning CT. The titanium clips are seen as radio-opaque white markers in the breast parenchyma. On the left, images have been matched using bony anatomy and on the right, images have been matched using surgical clips. A big discrepancy between clip and bony anatomy match is seen.

<table>
<thead>
<tr>
<th><strong>MV-CT (tomoTherapy)</strong></th>
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<tbody>
<tr>
<td><img src="mvct.png" alt="MV-CT Image" /></td>
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</tbody>
</table>

In the checker box scheme, the yellow image represents the MV-CT and the grey image represents the planning CT. On the left, the images have been matched using the bony anatomy (ribs) and on the right, the images have been matched using surgical clips. A big discrepancy between clip and bony anatomy match is seen.

<table>
<thead>
<tr>
<th><strong>2D-kV Planar</strong></th>
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<tbody>
<tr>
<td><img src="2dkv.png" alt="2D-kV Planar Image" /></td>
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</table>

The surgical clips are seen on the 2D-kV planar images and the position of clips on planning CT are shown as yellow cross. On the left, the images have been matched using the bony anatomy and on the right, the images have been matched using surgical clips. A big discrepancy between clip and bony anatomy match is seen.
3.8.2 Measurement of set-up errors

All patients were positioned using laser alignment of skin tattoos. Two or three tattoos were used: one anterior-medial at the midline and one or two lateral. Bony anatomy (BA)-based set-up errors were measured using automatic bony anatomy registration software for kV-CBCT (Synergy, Elekta Ltd, Crawley, UK) and manually for MV-CT and 2D-kV. For automatic bony anatomy registration, a region of interest containing the sternum and the ipsilateral ribs to the treated breast were selected and 3-dimensional bone match (chamfer matching) was used. Then clip-based set-up errors were measured by manually adjusting alignment of images from their BA-matched position. If clip migration were observed, image matching was done excluding these clips. BA set-up errors ($S_{BA}$) and clip set-up errors ($S_{clip}$) in the lateral (LR), superior-inferior (SI) and anterior-posterior (AP) directions were recorded. The times required to perform clip and BA measurements were also recorded. Only images with sufficient information on bony anatomy were used. Intra- and inter-observer errors were assessed using three images from three patients and a minimum of two observers.

For RMH patients, e-NAL corrections applied for actual treatment were removed from the measured set-up errors so that the effects of various image verification protocols (IVPs) could be studied.

3.8.3 Estimation of PTV margin

Radiotherapy positional errors are classified into systematic errors and random errors. Systematic errors occur if the mean irradiation geometry in a fractionated treatment differs from the geometry of the treatment plan. Fraction to fraction variation around the mean deviation leads to random errors. Systematic errors can shift the cumulative dose distribution relative to the target and contribute more towards the PTV margin as compared to random errors which blur the dose distribution.

The PTV margin calculation is based on the population systematic error ($\Sigma$) and the population random error ($\sigma$).
PTV margin = $2.5 \sum + 0.7 \sigma$ ..............................[92]

For a given population, systematic error ($\Sigma$) is the mean of the standard deviation (SD) of all patients’ mean set-up errors and random error ($\sigma$) is root mean square of the SD of all patients’ daily errors.

For this project, verification images of the study population were used to measure the distance of bony anatomy (BA) and clips (IGRT) from a reference position to determine bony set-up error ($S_{BA}$) and clip set-up error ($S_{Clips}$). The additional PTV margin required if standard bony anatomy verification technique is used over clip-based IGRT was calculated using the difference in the distance between bony anatomy and clip position. For each patient $S_{Diff} = S_{BA} - S_{Clips}$ were generated. The mean and SD of the $S_{Diff}$ for the study population were used to generate the systematic error (delta $\Sigma$) and random error (delta $\sigma$) for the margin formula.

Individual patient and population mean error (M), systematic ($\Sigma$) and random ($\sigma$) errors were calculated for BA and clip error data. Bland-Altman analysis, least squares linear regression and calculation of the Coefficient of Determination ($R^2$) between $S_{BA}$ and $S_{Clips}$ were also performed.

As the tumour bed has previously received radiation during whole breast irradiation, the coefficient of 0.7 in front of $\sigma$ is not applicable. Using van-Herk probability of correct target coverage, the margin formula was modified by reducing the contribution of the $\sigma$ error to 0.3 [92].

PTV margin = $2.5 \sum + 0.3 \sigma$ ..............................[93]

3.8.4 Difference among centres and imaging modalities

Centre and imaging modality differences in systematic ($\Sigma$) and random ($\sigma$) errors were tested using Levene’s, Kruskal-Wallis (KW) and Shapiro-Wilk tests. Sensitivity analyses were
performed by removing one centre at a time and repeating tests using Holms-Bonferroni correction.

3.8.5 Effect of verification protocols on PTV margin

The PTV margin required for safe treatment may not only depend on the method of verification used (bony anatomy or clip-based IGRT), but also on the type of verification protocol used. Four different verification protocols were investigated to calculate the PTV margin.

a. **No correction protocol**: No imaging is undertaken and patient is positioned using laser-based set-up.

b. **No action level (NAL)**: The systematic error is calculated after 3 treatment fractions and systematic set-up error is corrected for all subsequent fractions, regardless of the magnitude of the error [94].

c. **Extended-no action level (e-NAL)**: The first stage of the protocol follows NAL strategy with additional once weekly verification and correction [95].

d. **Daily correction protocol**: Patient position is verified daily against the planning CT scan and corrected (if required).

$S_{BA}$ and $S_{Clips}$ data were not available for all 15 treatment fractions as e-NAL protocol was used for many patients. In order to evaluate the effect of the image verification protocols (IVPs) for a 15-fraction treatment, a simulation of set-up errors was performed. For each patient, if $N$ was the total number of images analysed, in cases with $N < 15$, a normal distribution with mean and standard deviation equal to the patient’s real set-up data was sampled 15-$N$ times. Combined real and simulated patient set-up data were used to simulate the IVPs using Matlab (Mathworks, Natick, MA, USA). The smallest number of images available per patient was $N=5$. To test if 5 images were adequate to describe a patients’ set-up data, the mean and standard deviations of set-up errors of 28 patients with $N = 15$ were determined, for all 15 set-up errors and 5 set-up errors (fractions 1, 2, 3, 7 and 11). When using 5 images compared to 15 images, the mean differences in the patients’ mean and standard deviation of set-up errors were 0.006cm and 0.013cm, respectively.
Having obtained 15 measures of set-up error for each patient, these data were used to simulate the effect of different IVPs on set-up errors, and hence PTV margin. Simulated IVPs included: on-line BA (OL\textsubscript{BA}), on-line clip (OL\textsubscript{clip}), e-NAL BA (e-NAL\textsubscript{BA}) and e-NAL clip (eNAL\textsubscript{clip}). Post IVP simulation, any remaining systematic and random errors were calculated for the patient population. Set-up error simulation and error calculation were repeated 1000 times for each IVP. Error values from repeat simulations were averaged to give more precise results giving less than 0.1% uncertainty (SD) from random sampling.

This study used clips as a surrogate for the tumour bed. Surrogate systematic and random errors of 1.1mm were added in quadrature to the set-up errors [12], to account for the uncertainty introduced by the localisation of clips rather than the tumour bed.

\[
PTV \textit{margin} = 2.5 \sqrt{\Sigma_{\text{set-up}}^2 + \Sigma_{\text{surrogate}}^2} + 0.3 \sqrt{\sigma_{\text{set-up}}^2 + \sigma_{\text{surrogate}}^2}
\]

3.8.6 Set-up errors for portal imaging based verification technique (2D-MV)

As discussed before, 2D–MV portal imaging is the current standard treatment verification method for breast radiotherapy. No portal imaging data were routinely collected as part of the study. The 2D-MV set-up error data (\(S_{2D-MV}\)) were derived from \(S_{BA}\) using the method previously proposed by Topolnjak et al. [96]. Topolanjak et al. conducted a phantom experiment to quantify the accuracy of 2D-MV and kV-CBCT and measured the likely relationship between bony anatomy set-up errors measured in the LR, SI and AP direction using kV-CBCT and the U and V directions in the plane of the portal images using 2D-MV

\[
S_{2D-MV} = \beta S_{BA} + \alpha + \text{rand} x \eta \]

[96]

Where parameters \(\beta\) (slope) and \(\alpha\) (intercept) were determined from regression analysis, \(\eta\) is the standard deviation of the differences between 2D-MV and kV-CBCT set-up errors measured by Topolnjak et al. [96] and \text{rand} is a random number sampled from a normal distribution.
Tangential portal imaging will not provide a measure of set-up error in all three ordinal directions. In this study, it was assumed that any error in the U direction (rotational error) can be decomposed into an LR and AP error.

In this study, for the LR and AP directions, $\beta = 0.82$, $\alpha = 0.66$ mm and $\eta = 0.18$ mm were used. For the SI direction $\beta = 0.43$, $\alpha = -0.28$ mm and $\eta = 0.32$ mm were used [96]. Bony anatomy based IVP simulations were repeated using $S_{2D-MV}$.

3.8.7 Sample size calculation

$S_{\text{diff}}$ for the first 100 patients was collected and analysed to calculate the required sample size. The calculations were based on the 95% confidence interval (CI) that will give the required precision of 0.05 cm on the margin estimate. The sample size calculations/results are presented in the results section.

3.8.8 Effect of different IGRT imaging modalities on PTV margin

The difference in random and systematic error between different centres and imaging modalities were calculated using single factor ANOVA analysis for difference between means and the non-parametric Levene’s test for difference between variance.

3.8.9 Verification time for bony anatomy verification technique and clip-based IGRT

The time required for positional verification between the two techniques were compared using Wilcoxon signed ranks test.
3.8.10 Effects of different PTV margin (bony anatomy versus clip-based IGRT) on normal tissues

The impact of different PTV margins on radiation dose to breast tissue and surrounding organs at risk (contralateral breast, lung and heart) was examined for 30 patients treated within the IMPORT-HIGH trial.

All 30 patients’ tumour beds CTV (CTV_{TB}) were expanded using two different PTV margins: PTV_{TB_Clip} and PTV_{TB_BA}. Two radiotherapy plans were generated, one each for PTV_{TB_Clip} and PTV_{TB_BA} using Philips Pinnacle planning system. The whole breast dose was 40Gy in 15 fractions (phase 1), followed by sequential conformal photon boost of 16Gy in 8 fractions (phase 2). Plan assessment criteria and organs at risk constraint for the IMPORT HIGH trial (table 3) were used for the composite plan of phase 1 and phase 2.

**Table 3 : IMPORT High plan assessment criteria and organ at risk constraints**

<table>
<thead>
<tr>
<th>Target</th>
<th>Minimum Dose</th>
<th>Median Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole breast</td>
<td>&gt; 90% volume &gt; 36 Gy</td>
<td>40 to 44 Gy</td>
<td>&lt; 5% volume &lt; 56 Gy</td>
</tr>
<tr>
<td>Tumour bed PTV</td>
<td>&gt; 95% volume &gt; 53.2Gy</td>
<td>55.5 to 56.5 Gy</td>
<td>&lt; 5% volume &lt; 60 Gy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organ at Risk</th>
<th>Dose (Gy)</th>
<th>Maximum Allowed Volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral Lung</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Contralateral Lung</td>
<td>2.5</td>
<td>15</td>
</tr>
<tr>
<td>Contralateral Heart</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Contralateral Breast</td>
<td>Mean Dose &lt; 0.5Gy</td>
<td>Permitted Maximum Mean Dose 1.5 Gy</td>
</tr>
</tbody>
</table>

The following metrics between the two radiotherapy plans were compared using the Wilcoxon signed ranks test.

a. Volume of breast receiving 95% dose (Breast V_{95})
b. Volume of ipsilateral lung receiving 18Gy (Ipsi_Lung V₁₈)
c. Ipsilateral mean lung dose (Ipsi_MLD)
d. Volume of contralateral lung receiving 2.5Gy (Contra_Lung V₂.₅)
e. Volume of heart receiving 13Gy (Heart V₁₃)
f. Mean heart dose (MHD)
g. Mean breast dose for contralateral breast (Contra_MBD)

3.9 Results

3.9.1 Sample size calculations

Bony set-up error (Sₐ) and clip set-up error (Sₐ) of 112 patients from three different centres were initially collected for the sample size calculation.

<table>
<thead>
<tr>
<th>Radiotherapy centre</th>
<th>Imaging modality</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addenbrooke’s (ADD)</td>
<td>MV-CT (TomoTherapy)</td>
<td>20</td>
</tr>
<tr>
<td>Royal Marsden Hospital (RMH)</td>
<td>Cone Beam CT (CBCT)</td>
<td>76</td>
</tr>
<tr>
<td>Clatterbridge Oncology Centre (COC)</td>
<td>2D-kV Planar images</td>
<td>16</td>
</tr>
</tbody>
</table>

The additional margins required if standard bony anatomy verification is used instead of clip-based IGRT were calculated from Sₐ in left-right (LR), superior-inferior (SI) and anterior-posterior (AP) directions. These results are summarised for the three centres in table 4.
Table 4: Mean and Variance of SDIFF for all 112 patients and individual centres

<table>
<thead>
<tr>
<th>Centre</th>
<th>Mean (cm)</th>
<th>Variance (cm)</th>
<th>Difference in PTV margin (cm) between bony anatomy and clip-based verification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR</td>
<td>SI</td>
<td>AP</td>
</tr>
<tr>
<td>All</td>
<td>-0.02</td>
<td>-0.03</td>
<td>-0.03</td>
</tr>
<tr>
<td>COC</td>
<td>0.03</td>
<td>0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>ADD</td>
<td>0.00</td>
<td>0.02</td>
<td>-0.01</td>
</tr>
<tr>
<td>RMH</td>
<td>-0.03</td>
<td>-0.06</td>
<td>-0.04</td>
</tr>
</tbody>
</table>

Bone and clips-based set-up data collected and analysed from 112 patients for sample size calculations. The highlighted data were used in the sample size calculations.

The variances of $S_{DIFF}$ in the 3 directions for all centres were:

$S_{DIFF}^{2}_{LR} = 0.039$, $S_{DIFF}^{2}_{SI} = 0.043$ and $S_{DIFF}^{2}_{AP} = 0.044$

Taking the largest variance $S_{DIFF}^{2}_{AP} = 0.044$, the 95% confidence interval (CI) was calculated from the chi-square distribution table using the following:

Lower limit = $\frac{(n-1) S_{DIFF}^{2}}{\chi^2_u}$ to Upper limit = $\frac{(n-1) S_{DIFF}^{2}}{\chi^2_l}$

Where $\chi^2_u$ = upper 2.5% point of $\chi^2$ distribution for 111 degrees of freedom = 83.735
And $\chi^2_l$ = lower 2.5% point of $\chi^2$ distribution for 111 degrees of freedom = 142.049

Hence 95% CI for variance is $0.344$ (111 x $0.044/142.049$) to $0.0583$
(111 x $0.044/83.735$) and the 95% CI for standard deviation = $0.1855$ ($\sqrt{0.344}$) to $0.2415$
($\sqrt{0.0583}$). Based on this calculation, we were confident that the margin lies in the region of $0.4637cm$ to $0.6037cm$ (SD x 2.5) in 95% of the cases. This is an overall width of $0.140cm$.

As I wanted an overall precision of 0.05cm (overall width of 0.1cm), the above formula was applied for different sample sizes on the chi-square distribution table. It was estimated that
a sample size of 200 patients would be required to accurately calculate PTV margin for bony anatomy and clips-based IGRT.

3.9.2 Overall study population

The bony anatomy set-up error ($S_{BA}$) and clip set-up error ($S_C$) for 218 patients from five different centres were collected. Each centre uses a different imaging technique as summarised below.

**Number of patients from five participating centres**

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Centre</th>
<th>Imaging modality</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royal Marsden Hospital (RMH)</td>
<td>A</td>
<td>cone Beam CT (CBCT)</td>
<td>79</td>
</tr>
<tr>
<td>Addenbrooke’s (ADD)</td>
<td>B</td>
<td>MV-CT (TomoTherapy)</td>
<td>40</td>
</tr>
<tr>
<td>Clatterbridge Oncology centre (COC)</td>
<td>C</td>
<td>2D-kV Planar images</td>
<td>39</td>
</tr>
<tr>
<td>Cheltenham (CHE)</td>
<td>D</td>
<td>2D-kV Planar images</td>
<td>30</td>
</tr>
<tr>
<td>Ipswich (IPS)</td>
<td>E</td>
<td>2D-kV Planar images</td>
<td>30</td>
</tr>
</tbody>
</table>

3.9.3 Set-up errors using bony anatomy and clip-based verification

The intraobserver and interobserver errors were less than 1.4mm for all three imaging modalities. No significant difference was seen in inter-observer set-up errors between the five centres ($p=0.34$). The whole population mean error is expected to be zero [97]. In this study, the overall mean error was found to be significantly different from zero for Addenbrooke’s (centre B) and Ipswich (centre E). At Addenbrooke’s, this is due to couch sag associated with TomoTherapy [98] where the carbon fibre couch top sags in the superior-inferior and longitudinal direction as it enters the treatment bore. The error does not apply to the actual treatment, since it is corrected by the image guidance [98]. Ipswich centre is investigating the cause for their non-zero mean error.
The systematic errors ($\Sigma$) and random errors ($\sigma$) using bony anatomy verification and titanium clips based verification were 2-4 mm across all centres. Individual centre and overall errors are summarised in table 5. Individual patient systematic error using bony anatomy and surgical clips are compared in figure 7. The coefficients of determination ($R^2$) were 0.57, 0.42 and 0.82 in the LR, SI and AP directions respectively, suggesting that bony anatomy-based verification underestimates the patient systematic error by up to 23% compared to clip-based verification.

3.9.4 Difference in set-up error using bony anatomy and clips (delta error)

The difference in set-up errors using bony anatomy and clips ($\Sigma_{\Delta}$ and $\sigma_{\Delta}$) for individual centres and all patients are summarised in table 6.

The time required to perform bony anatomy ($T_{BA}$) and clips ($T_{clips}$) based verification are also summarised in table 6. The time required for each technique varied with the type of imaging modality used. For centres using 2D-kV modality, $T_{BA}$ was greater than $T_{clips}$ ($p<0.001$). In contrast, centre “A” using kV-CBCT found mean time $T_{clips} > T_{BA}$ (96 seconds versus 29 seconds respectively). No significant time difference was found for MV-CT imaging ($p = 0.35$).

3.9.5 Effect of imaging modality and centres on set-up errors

There was a small but statistically significant difference in bony anatomy and clip set-up errors between centres ($p<0.05$). The smallest delta error was seen for centre B using MV-CT and the largest delta error was seen for centre C using 2D-kV (Table 6).

Using the single factor ANOVA test, a significant difference between means of delta error was seen between different centres in the LR and SI direction ($p<0.05$). No significant difference between means of delta error was seen among centres using 2D-kV imaging modality. The Bartlett-Box test also indicated non-homogeneity of variance among centres (table 7). After excluding data of patients with MV-CT imaging, the variance of delta errors was similar between centres.
Table 5: Systematic and random errors using bony anatomy and clip-based verification for each centre and for all centres combined

<table>
<thead>
<tr>
<th>Centre</th>
<th>No. Patients</th>
<th>Total Number of images</th>
<th>Bony Anatomy Systematic Error $\Sigma_{BA} (cm)$</th>
<th>Bony Anatomy Random Error $\sigma_{BA} (cm)$</th>
<th>Clips Systematic Error $\Sigma_{clip} (cm)$</th>
<th>Clips Random Error $\sigma_{clip} (cm)$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR</td>
<td>SI</td>
<td>AP</td>
<td>LR</td>
<td>SI</td>
<td>AP</td>
</tr>
<tr>
<td>ALL</td>
<td>218</td>
<td>1574</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>A (kVCBCT)</td>
<td>79</td>
<td>504</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>B (MV-CT)</td>
<td>40</td>
<td>200</td>
<td>0.3</td>
<td>0.2</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>C (2D-kv)</td>
<td>39</td>
<td>510</td>
<td>0.4</td>
<td>0.3</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>D (2D-kv)</td>
<td>30</td>
<td>180</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>E (2D-kv)</td>
<td>30</td>
<td>180</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

The whole study population systematic and random error using bony anatomy and clip-based verification methods were 3 mm in LR (left-right), SI (superior-inferior) and AP (anterior-posterior) direction.
Table 6: Delta errors (difference between bony anatomy and clips) in the LR, SI and AP directions and the magnitude of their 3D vector. Time required for image matching with both techniques has also been summarised.

<table>
<thead>
<tr>
<th>Centre</th>
<th>Delta Errors (range)</th>
<th>Time (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Absolute Delta (cm)</td>
<td>T\textsubscript{bony anatomy}</td>
</tr>
<tr>
<td></td>
<td>LR</td>
<td>SI</td>
</tr>
<tr>
<td>ALL</td>
<td>0.20 (0, 1.65)</td>
<td>0.26 (0)</td>
</tr>
<tr>
<td>A (kV-CBCT)</td>
<td>0.19 (0, 1.7)</td>
<td>0.24 (0, 3.2)</td>
</tr>
<tr>
<td>B (MV-CT)</td>
<td>0.14 (0, 0.7)</td>
<td>0.12 (0, 1.2)</td>
</tr>
<tr>
<td>C (2D-kV)</td>
<td>0.23 (0, 1.7)</td>
<td>0.29 (0, 2.4)</td>
</tr>
<tr>
<td>D (2D-kV)</td>
<td>0.21 (0, 1.3)</td>
<td>0.32 (0, 1.3)</td>
</tr>
<tr>
<td>E (2D-kV)</td>
<td>0.20 (0, 1.5)</td>
<td>0.31 (0, 1.4)</td>
</tr>
</tbody>
</table>

(a) Delta error was smallest on MV-CT imaging modality and largest using the 2D-kV imaging modality.
(b) Time required for set-up verification varies between the various IGRT techniques. On 2D-kV modality bony anatomy verification was quicker as compared to clip-based verification. Using kV-CBCT, clip based verification was faster.
Figure 7: Plots of mean clip set-up error versus mean bony anatomy set-up error in the LR, SI and AP directions. Dotted lines are the lines of best fit (least squares). $R^2$ = Coefficient of determination.

Bland-Altman plots comparing individual patient systematic error using bony anatomy and surgical clips based verification. The coefficient of determination ($R^2$) are 0.57, 0.42 and 0.82 in the left-right (LR), superior-inferior (SI) and anterior-posterior (AP) directions respectively.
Table 7: Test of homogeneity of variances of delta errors from all centres, those using techniques 2D-KV technique and after excluding centre using MV-CT

<table>
<thead>
<tr>
<th></th>
<th>LR</th>
<th>SI</th>
<th>AP</th>
</tr>
</thead>
<tbody>
<tr>
<td>All centres</td>
<td>0.00</td>
<td>0.00</td>
<td>0.22</td>
</tr>
<tr>
<td>2D-kV (CCO,CHE,IPS)</td>
<td>0.67</td>
<td>0.79</td>
<td>0.93</td>
</tr>
<tr>
<td>2D-kV &amp; kV-CBCT (RMH,CCO,CHE,IPS)</td>
<td>0.85</td>
<td>0.05</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Bartlett-Box test shows non-homogeneity of variance among centres. If patients with MV-CT imaging are excluded, the variance of delta error is not statistically different between the other centres.

3.9.6 Residual set-up errors using bony anatomy and clip-based verification and the effects of verification protocols

The PTV margin should be estimated on a sample group which is representative of the whole population. In view of significant heterogeneity in delta error using MV-CT, set-up data of centre B (n=40 patients) were not included in the simulations of PTV margin estimation. Based on the set-up data of 178 patients, the overall width of 95% confidence interval on the PTV margin is ~0.10 cm giving a precision of ± 0.05 cm.

The mean (M), systematic (Σ) and random (σ) residual error were calculated using the following image verification protocols (IVP):

a. No correction protocol - NO IMAGING
b. Extended- no action level using bony anatomy- e-NALBA

c. Extended- no action level using clips - e-NALclips

d. Daily correction protocol (On-line correction) using bony anatomy - OLBA
e. Daily correction protocol (On-line correction) using clips – OL_clips

The results are summarised in Table 8. In all cases, the variation (1 SD) in residual errors due to random sampling was less than 0.01 mm. Residual systematic and random errors were smaller for clip-based verification as compared to BA based verification, irrespective of the IVP method.

I found that for kV based imaging modalities, on-line IVP produces smaller errors than e-NAL for both clips and bones. Using, on-line BA based verification, systematic errors were larger than those for off-line clip-based verification (e-NAL_{clip}), by up to 0.11 cm (Fisher-test, p-values <0.001). Off-line BA verification (e-NAL_{BA}) increased systematic error further by ~ 0.05 cm (Fisher-test, p-values <0.001).

2D-MV based image verification increased systematic error for both on-line and off-line protocols by an average of ~0.3 cm (Fisher-test, p<0.001). For off-line imaging of BA (e-NAL_{BA}), the difference between kV and 2D-MV was significant in the SI direction only. For 2D-MV imaging of BA, there were no significant difference in systematic errors between on-line and off-line IVPs (p=0.12).

The overall mean error (M) for 2D-MV IVPs was non-zero (Table 8). This is likely due to the use of simulation technique to generate 2D-MV set-up errors and reflects the relationship between kV-CBCT and 2D-MV set-up errors.
Table 8: Mean, Systematic and Random errors using different image verification protocols

<table>
<thead>
<tr>
<th>IVP</th>
<th>M(cm)</th>
<th>Σ(cm)</th>
<th>σ(cm)</th>
<th>PTV Margin (cm)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR</td>
<td>SI</td>
<td>AP</td>
<td>LR</td>
</tr>
<tr>
<td>No Imaging</td>
<td>-0.06</td>
<td>0.00</td>
<td>0.00</td>
<td>0.27</td>
</tr>
<tr>
<td>OL_{clips} (2D-kV or kV-CBCT)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.05</td>
</tr>
<tr>
<td>eNAL_{clips} (2D-kV or kV-CBCT)</td>
<td>-0.01</td>
<td>0.00</td>
<td>0.02</td>
<td>0.08</td>
</tr>
<tr>
<td>OL_{BA} (2D-kV or kV-CBCT)</td>
<td>-0.01</td>
<td>-0.01</td>
<td>-0.03</td>
<td>0.16</td>
</tr>
<tr>
<td>eNAL_{BA} (2D-kV or kV-CBCT)</td>
<td>0.00</td>
<td>0.01</td>
<td>0.05</td>
<td>0.19</td>
</tr>
<tr>
<td>OL_{BA} (2D-MV)</td>
<td>-0.64</td>
<td>0.27</td>
<td>-0.60</td>
<td>0.19</td>
</tr>
<tr>
<td>eNAL_{BA} (2D-MV)</td>
<td>-0.45</td>
<td>0.21</td>
<td>-0.43</td>
<td>0.23</td>
</tr>
</tbody>
</table>

* Respiratory motion not explicitly included in the PTV margin formula (see section 3.11)

OL_{clips}: on-line clip-based verification  
eNAL_{clips}: extended no action level clip-based verification
OL_{BA}: on-line bony anatomy-based verification  
eNAL_{BA}: extended no action level bony-anatomy based verification

PTV margins using different image verification protocols. A 10mm tumour bed margin is required with no imaging protocol. A 5 mm margin is adequate if clip-based verification is used (on-line/extended –no action level). Use of bony anatomy-based verification will require larger PTV margin ~8mm.
3.9.7 PTV margin using different image verification protocols

The estimated PTV margin using different IVPs are given in Table 8. Based on this study, a tumour bed boost PTV margin of 1 cm is required if no imaging modality is used. If standard bony verification technique is used (2D-MV), a PTV margin of 0.8cm is required. This can be reduced to 0.6 to 0.7 cm if 2D-kV/ kV-CBCT based bony anatomy verification is used. The use of clip-based IGRT allows to half the boost PTV margin to 0.5cm (as in the IMPORT HIGH study), for both on-line and e-NAL verification protocols.

3.9.8 Effects of PTV margin on surrounding normal tissue

Thirty patients were planned using a 5 mm and 8 mm PTV margin for PTV_{TB_Clips} PTV_{TB_BA} respectively (figure 8). The median volume of breast tissue (normal tissue and the tumour bed) irradiated to 53.2Gy (Breast V_{55}) with 5mm PTV margin was 91cc (range 30-863cc) as compared to 125cc (range 42-1005cc) using an 8 mm margin (p<0.01). The radiation dose to organs at risk (summarised in section 3.8.10) was also higher for PTV_{TB_BA} plan as compared to the PTV_{TB_Clips} plan (table 9 and table 10).
Figure 8: PTVTB_Chips (yellow) and PTVTB_BA (red) for a patient with right breast cancer

Table 9: Dosimetric data given as median and range for each parameter for ipsilateral and contralateral lung

<table>
<thead>
<tr>
<th></th>
<th>PTV_TB = 5 mm</th>
<th>PTV_TB = 8 mm</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsi_Lung V18 (%)</td>
<td>9.3 (1.9-13.2)</td>
<td>9.8 (2.3-14.7)</td>
<td>0.6 (0.4-1.6)*</td>
</tr>
<tr>
<td>Ipsi_MLD (Gy)</td>
<td>5.5 (2.6-7.3)</td>
<td>5.8 (2.9-8.8)</td>
<td>0.4 (0.3-1.5)*</td>
</tr>
<tr>
<td>Contra_Lung V2.5 (%)</td>
<td>0.0 (0.0-12.2)</td>
<td>0.1 (0.0-13.9)</td>
<td>0.1 (0.0-1.7)*</td>
</tr>
</tbody>
</table>

*p <0.01

Dose to both ipsilateral and contralateral lung is reduced with a smaller 5 mm planning target volume (PTV) margin.
Table 10: Heart and contralateral breast dose parameters given for left and right side cases separately

<table>
<thead>
<tr>
<th></th>
<th>Left breast cases</th>
<th></th>
<th>Right breast cases</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PTV_TB = 5 mm</td>
<td>PTV_TB = 8 mm</td>
<td>Difference</td>
<td>PTV_TB = 5 mm</td>
</tr>
<tr>
<td>Heart V13 (%)</td>
<td>0.3 (0.0-3.9)</td>
<td>0.5 (0.0-6.3)</td>
<td>0.2 (0.0-2.4)*</td>
<td>0.0 (0.0-0.0)</td>
</tr>
<tr>
<td>MHD (Gy)</td>
<td>2.0 (1.1-5.1)</td>
<td>2.3 (1.1-6.0)</td>
<td>0.3 (0.0-0.9)*</td>
<td>1.3 (0.4-1.7)</td>
</tr>
<tr>
<td>Contra_MBD (Gy)</td>
<td>0.4 (0.1-1.3)</td>
<td>0.5 (0.2-1.4)</td>
<td>0.1 (0.0-0.1)*</td>
<td>0.4 (0.3-0.7)</td>
</tr>
</tbody>
</table>

*p < 0.01
MHD: mean heart dose
MBD: mean breast dose

Use of a smaller PTV margin of 5 mm reduces the dose to the heart and contralateral breast

3.10 Discussion

3.10.1 Bony anatomy (BA) based verification versus clip-based verification

This large multicentre multimodality study has compared the set-up errors of bony anatomy and clip-based verification. It demonstrates that a PTV boost margin of 5 mm is adequate if clip-based verification (2D-kV and kV-CBCT) is used both for online and off-line IVP. However, if standard portal imaging (2D-MV) is used, an increase in PTV margin of ~3mm is necessary. The major strengths of this study include its large patient cohort, use of different imaging modalities and direct
comparison of bony anatomy verification against clip-based verification. As this study used the inexpensive titanium clips, these results are applicable to the current breast radiotherapy practice and can be implemented in all centres using simultaneous integrated boost breast radiotherapy.

In this study, the measured population systematic and random errors (for the TB) using no imaging protocol had a range 2.5 mm and 3.4mm, suggesting that a PTV margin of 10mm is required if no IVP is used. Similar results have been reported by Topolnijak et al. [96] who reported kV-CBCT measured systematic errors of 0.31, 0.38 and 0.25 cm in the LR, SI and AP direction respectively based on 20 patients.

This current study found that the BA-based verification underestimate patients’ systematic error as compared to clip-based verification. Other authors have reported differences between set-up errors measured bony and clip using small patients’ cohorts [99, 100]. Gierga et al. [99] used 2D-kV in 12 patients and reported a median 3D delta error of 0.54 cm, upper and lower quartile values were 0.75 cm and 0.41 cm respectively. Fatunase et al. [100] reported a mean 3D delta error of 0.6 cm using kV-CBCT in 10 patients. In the current study, 1379 images (after excluding MV-CBCT images) were analysed and the mean, median, and upper and lower quartile 3D vector difference between bones and clips (delta) were 0.48, 0.42, 0.25 cm and 0.66 cm respectively. This would imply that the PTV margin of 5mm (as used in the IMPORT HIGH study) will be insufficient if BA is used as a surrogate for the tumour bed instead of fiducial markers and a larger PTV margin of ~8mm is required if 2D-MV based bony anatomy verification (online and offline protocols) is used. For patients treated with simultaneous integrated boost using IMRT and steep dose gradient (as in IMPORT HIGH study), it is preferable to use smaller PTV margin, to limit the high dose to non-target healthy surrounding tissue.
Similar results have been reported by Penninkhof and colleagues [101]. Two orthogonal planar kV images and one 2D-MV portal image were acquired for 80 patients throughout their radiotherapy treatment. Surgical clips-based registration was performed on all kV images and set up errors (systematic and random) were estimated for a no correction protocol, NAL protocol and e-NAL protocol. The 2D-MV portal images were independently registered with the DRR using lung contour and caudal side of the external breast contour for estimating 2D-MV set-up errors.

Using a no imaging protocol, the systematic set-up errors for tumour bed were 0.26cm, 0.25cm and 0.34 cm in LR, SI and AP direction respectively. Using 2D-MV portal images with e-NAL correction protocol, the systematic set-up errors for tumour bed were 0.23cm, 0.24cm and 0.28 cm in LR, SI and AP direction respectively. The use of NAL and e-NAL correction protocol with clip-based registration significantly reduced the systematic set-up errors. For e-NAL correction protocol, the systematic set-up errors for tumour bed were 0.08cm, 0.06cm and 0.09 cm in LR, SI and AP direction respectively. The study concluded that using clip-based registration with correction protocol, a PTV margin of ≤5 mm for the tumour bed is adequate.

3.10.2 Effects of different imaging modalities (2D-kV, kV-CBCT and MV-CT)

In my study, different imaging modalities including 2D-kV, kV-CBCT and MV-CT were used for clip-based and bony anatomy-based verification. The effect of different imaging modalities on PTV margin has previously been unclear. In this study, there was a subtle difference in set-up errors measured with 2D-kV planar and kV-CBCT imaging. However, the results using MV-CT imaging modality were different. The
differences between BA and clip set-up errors were larger with kV imaging compared to MV-CT imaging (3D delta error of 0.32 cm versus 0.17 cm). It is possible that the poorer image resolution of the MV-CT and higher imaging energy renders clip-based set-up error measurement less straight forward. Clip-based set-up verification was done by manually adjusting the alignment of the images from their bony anatomy matched position. As clips do not show up well on the MV-CT, realignment of images was restricted, which may account for the smaller differences between clips and BA set-up errors.

3.10.3 Time required for bony anatomy (BA) versus clip-based verification

The time required for clip-based verification compared to BA was imaging technique dependent. Clip-based verification was quicker using the 2D-kV method compared to bony anatomy-based verification. For kV-CBCT, the opposite was true, with bony anatomy-based verification requiring less time due to the automated bony registration algorithm facility. The MV-CT-based clip verification was most time consuming (average >2 minutes), again possibly due to the poor visualisation of clips on MV-CT.

3.11 Limitations of the study

This study assumes that there is no significant difference among patient populations from the five different participating centres. This is reasonable as all patients fulfilled the eligibility criteria of the IMPORT high trial. Using the ANOVA test, followed by sensitivity analysis to compare breast size and TB PTV size between centres, only centre D (Cheltenham) had a significantly smaller mean TB PTV volume which did not
lead to significant difference in set-up errors. Patients from five different centres may increase the applicability of the study results to the general population.

This study suggests that compared to clip-based IGRT, the use of 2D-MV (portal imaging) requires an increase in the PTV margin to 0.8cm. However, no 2D-MV set-up data was collected as part of the study and generated using the method proposed by Topolnjak et al [96]. This is a simplification as the 2D-MV data is simulated. The relationship between 2D-MV BA and clip-based set-up errors will affect the PTV margin. For example, lower correlation between 2D-MV BA and clips will lead to greater PTV margin. If the correlation is too low, there may be no benefit in using 2D-MV imaging compared to no imaging. In this work, the lowest correlation between 2D-MV BA and clip set-up errors was in the SI direction, with the Pearson product moment correlation coefficient, $r=0.48$.

A study of 38 patients by Sijtsema et al. [102] suggests that using one tangential portal image and an anterior-posterior portal image may moderately increase the correlation between 2D-MV error and clip set-up errors ($r > 0.5$) (table 11). Further work is required to confirm the relationship between 2D-MV BA and clip set-up errors.
Table 11: Linear regression parameters slope ($\beta$) and intercept ($\alpha$) and where available associated confidence intervals (CI) and Pearson Correlation coefficient ($r$) for real and simulated set-up errors

<table>
<thead>
<tr>
<th>Study (no of images)</th>
<th>Direction</th>
<th>$\beta$ (CI)</th>
<th>$\alpha$ (CI) (cm)</th>
<th>$r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>This study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>kV BA v. kV clip systematic (n = 178)</td>
<td>LR</td>
<td>0.74 (0.63, 0.85)</td>
<td>-0.02 (-0.05, 0.01)</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>SI</td>
<td>0.69 (0.54, 0.83)</td>
<td>-0.016 (-0.05, 0.02)</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>AP</td>
<td>0.84 (0.75, 0.93)</td>
<td>-0.042 (-0.07, 0.00)</td>
<td>0.81</td>
</tr>
<tr>
<td>This study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2DMV BA v. kV clip systematic (n = 178)</td>
<td>LR</td>
<td>0.60 (0.48, 0.68)</td>
<td>0.63 (0.6, 0.66)</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>SI</td>
<td>0.3 (0.21, 0.36)</td>
<td>-0.28 (-0.31, -0.27)</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>AP</td>
<td>0.7 (0.60, 0.74)</td>
<td>-0.63 (0.61, 0.66)</td>
<td>0.77</td>
</tr>
<tr>
<td>Topolnjak [96]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2DMV BA v. kVCBCT BA) (n = 39)</td>
<td>U (AP/LR)</td>
<td>0.82 (0.66,0.98)</td>
<td>0.66 (0.091.22)</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>V (SI)</td>
<td>0.43 (0.21,0.66)</td>
<td>-0.28 (-1.18,0.62)</td>
<td>0.55</td>
</tr>
<tr>
<td>Sijtsema [102]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Tangs 2DMV v. kVCBCT clip) (n = 38)</td>
<td>LR</td>
<td>-</td>
<td>-</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>SI</td>
<td>0.69</td>
<td>0.85</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>AP</td>
<td>0.71</td>
<td>1.98</td>
<td>0.72</td>
</tr>
<tr>
<td>Sijtsema [102]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Tangs + AP 2DMV BA v. kVCBCT clip) (n = 38)</td>
<td>LR</td>
<td>1.21</td>
<td>-0.33</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>SI</td>
<td>1.06</td>
<td>2.05</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>AP</td>
<td>1.51</td>
<td>1.80</td>
<td>0.69</td>
</tr>
</tbody>
</table>

n is the number of data points
For the IVP simulation, patient positions are corrected for by subtracting the measured set-up error and adding a residual error that reflects incomplete correction. The uncertainty in measured set-up errors, imperfect couch shift and respiration motion commonly accounts for the incomplete correction of set-up errors. In this study, the effect of respiratory motion was not explicitly included within the PTV margin calculations. It is currently debated if respiratory motion should be added in linearity or in quadrature within the PTV margin formula [97]. Several authors have estimated the respiratory motion in breast radiotherapy patients, with most reporting target motion of less than 4 mm [103]. This would suggest that for most patients, the breathing component of the PTV margin will be ~2 mm. If this is added as a random error in quadrature, the impact of respiratory motion is likely to be small.

For example, if the population systematic and random errors are 3mm, the required PTV margin will be 7.59mm (equation 1). If a 2 mm respiration motion is added as a random error in quadrature, the required PTV margin will be 7.6 mm (equation 2)

\[
\text{PTV margin} = 2.5 \times \text{systematic error} + 0.3 \times \text{random error}
\]

\[
\text{PTV margin (exclude respiratory)} = (2.5 \times 0.3) + (0.3 \times 0.3) \quad \quad \quad \text{(1)}
\]
\[
= 7.59 \text{ mm}
\]

\[
\text{PTV margin (include respiratory)} = (2.5 \times 0.3) + (0.3 \times \sqrt{0.3^2 + 0.2^2}) \quad \quad \text{(2)}
\]
\[
= 7.6 \text{ mm}
\]
3.12 Dosimetric and clinical implications of the study

After re-planning 30 patients, the use of clip-based IGRT led to a modest reduction in breast tissue receiving high radiation dose compared to bony anatomy-based verification. As summarised in chapter 2, there is evidence to support a dose-volume relationship for breast tissue. Based on these results, one should anticipate that the use of clip-based IGRT will reduce the risk of late breast tissue toxicity, though this cannot be quantified.

Apart from breast tissue, the use of clip-based IGRT had a small but significant impact on the heart dose, especially for left sided breast cancer patients. The MHD was reduced from 2.3Gy to 2.0Gy. Darby et al [104] have recently estimated that for every 1Gy increase in mean dose to the heart, the relative risk of a major coronary event also increase by 7.4%. In addition, there appears to be no threshold in mean dose at which coronary event might be prevented. A smaller PTV for tumour bed close to the coronary artery may have an even bigger impact in reducing the risk of a coronary event. Overall, one can anticipate that use of clip-based IGRT will reduce the risk of coronary events as compared to bony anatomy-based verification method. Although the magnitude of this reduction is quite small, it is a worthwhile outcome to improve patient outcome.

3.13 Conclusions

This study confirms that the use of bony anatomy as a surrogate for the tumour bed can lead to underestimation of set-up errors in breast radiotherapy. It confirms our hypothesis that the clip-based IGRT technique is more accurate and can safely
reduce the PTV margin around the tumour bed as compared to the bony anatomy-based verification technique. It is reassuring that a tighter PTV margin can be safely used for patients receiving simultaneous integrated boost and IMRT with steep dose gradient. Smaller PTV margins are likely to reduce the risk of late cardiac and breast tissue toxicity. There is no significant difference between kV-CBCT and 2D-kV measured set-up errors, and similar PTV margins can be used for both imaging modalities. Poor image resolution on MV-CT may account for the small difference between bony anatomy and clip-based verification. Treatment verification time for clips and bony anatomy depends on imaging modality. Implementation of IGRT into routine use will improve accuracy, reduce PTV margins and overall reduce normal tissue toxicity. This is an important development in external beam radiotherapy for breast cancer.

3.14 Chapter contributions

This work was done in collaboration with the Joint Department of Physics, The Royal Marsden/Institute of Cancer Research, Sutton. I am grateful to the IMPORT HIGH trial group for giving me the opportunity to be part of the IMPORT HIGH IGRT sub-study. I would particularly like to thank

Emma Harris and Ellen Donovan (Collaborating Physicist): for their invaluable help with data collection, data simulation, re-planning and statistical analysis

Jenny Titley and Yat Tsang (IMPORT trial group): for their help with data collection.

Helen Mayles (Clatterbridge), Ros Perry (Ipswich), June Dean (Addenbrooke’s), Angela Baker (Clatterbridge) and Sally Eagle (RMH): for their help with collection of set-up data
I was involved in the concept and design of the study. I collected the set-up data from Cambridge (MV-CT) and Ipswich (kV Planar). In addition, I also collected all the clinical data including visibility of seroma, number of clips, tumour bed location, etc.

Dr Emma Harris was involved in the data simulation and statistical analysis which was interpreted and analysed by both of us. The radiotherapy plans using separate PTV margins were clinically assessed by me. I contributed in writing up the original manuscripts which was subsequently published in the peer reviewed Clinical Oncology journal and British Journal of Radiology (appendix).
4. Normal tissue complication probability (NTCP) modeling for breast tissue

* This work has been published as an original article in Radiotherapy & Oncology in 2013 (Appendix)

4.1 Introduction

In chapter 3, I demonstrated that the PTV margin around the tumour bed can be safely reduced by using IGRT technique. As the volume of breast tissue irradiated to high dose is reduced, one would anticipate that late breast toxicity will be reduced. Clinicians would however like to estimate the possible benefits i.e. quantify the reduction in risk of late breast toxicity with IGRT.

In Chapter 2, I summarised the current published literature on radiation dose and treatment volume effect for breast tissue. However, the systematic review does not quantify the effect of radiation dose and treatment volume on breast toxicity. In this chapter, the dose-volume effect for late breast tissue toxicity has been quantified by using normal tissue complication probability (NTCP) model.

4.1.1 Dose-volume effect for normal tissue

The first comprehensive review on the radiation dose volume effect for normal tissue was published in 1991 by Emami and colleagues [28]. The radiation tolerance doses for normal tissues were reported as TD5 (tolerance dose with 5% complication probability) and TD50 (tolerance dose with 50% complication probability), when whole, 2/3 and 1/3 of the organ were uniformly irradiated. This report was informative and highly significant at the time of publication. However, due to limited availability of comprehensive datasets, most of the data on dose–volume effect was interpolated or extrapolated from whole organ data, or based on the experience of
the involved clinicians. As radiotherapy techniques have evolved with the use of conformal radiotherapy/IMRT, normal tissue is therapeutically irradiated in a non-uniform manner, making it difficult to estimate radiation complication probability.

With the availability of larger datasets, the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) articles have summarised the quantitative effects of radiotherapy dose and treatment volume on late normal tissue complications [105]. However, the radiation dose-volume effect for breast tissue was not included in the Emami and QUANTEC reports.

4.1.2 Dose effect for breast tissue

A radiation dose response relationship with late breast toxicity is well established, with worse cosmesis and increased risk of fibrosis as whole breast dose escalates over 50Gy [57, 106]. Similarly, higher tumour bed boost dose has been shown to increase the risk of breast fibrosis [30].

4.1.3 Volume effect for breast tissue

To date, the effect of volume parameter on late breast toxicity is not clear. The large EORTC 22881-10882 “boost versus no boost” trial reported higher breast fibrosis rates and worse cosmesis among patients treated with larger boost volumes [31, 32, 107]. Collette et al [32] demonstrated that at ten years, large boost volume was associated with increased risk of moderate-severe breast fibrosis (clinical) on univariate analysis. Photographic assessment of 348 patients from the trial using the BCCT.core software also found that at a minimum follow up of 6 years, larger boost volume was associated with asymmetry features related with breast fibrosis [107].

The two asymmetric features were the pBOD (the relative breast overlap difference); p<0.002 and pLBC (the relative lower breast contour); p<0.001. Vrieling et al. [31] from the same group had previously reported worse cosmetic outcome in patients with boost volume >200 cm3 as compared to ≤200 cm3 (odds ratio 0.47 95%CI 0.29–0.76; p = 0.002) in univariate analysis after three years of follow up. Apart from the
EORTC trial, other trials comparing partial breast irradiation (PBI) and whole breast irradiation (WBI) have also reported reduced late breast toxicity and superior cosmetic outcome with PBI [46, 47]. All these results are hypothesis generating, suggesting a volume effect for breast tissue.

4.1.4 Purpose of this work

The purpose of this work was to develop a NTCP model for breast tissue and quantify the dose-volume effect by predicting the probability of a complication for a non-uniform irradiated breast. Fibrosis is a common sequela of breast RT and adversely affects overall cosmesis, it can be assessed using a scoring system and is likely to impact on patient physical and psychological wellbeing [15]. Hence, this work relates to the development of NTCP model for moderate-severe breast fibrosis.

4.2 Hypothesis

This chapter address the hypothesis that the breast tissue displays a significant radiation dose-volume effect for moderate to severe fibrosis and a normal tissue complication probability model can effectively predict the probability of breast fibrosis based on the interplay of treatment volumes and overall radiation doses.

4.3 Materials and Methods

4.3.1 What is required for the NTCP modeling exercise?

For an NTCP modeling exercise, one requires a dataset with diverse dose and volume data and a meaningful quantitative toxicity endpoint. Individual patient data from randomised controlled trials (RCTs) provides the most robust data on radiation dose and toxicity. Additionally, pooling of data from different RCTs increases the diversity
of the dataset and the generalisation of results to the wider population [108]. The toxicity endpoint in this study was set as moderate-severe breast fibrosis.

For this study, I approached principal investigators (PI) of published breast radiotherapy trials, where dose-volume and toxicity data was available. Three PI replied and agreed to collaborate by sharing patients’ data. Dr. Charlotte Coles from the Cambridge Breast IMRT trial [21, 109], Professor Harry Bartelink from the EORTC 22881-10882 “boost versus no boost” trial [9, 30] and Dr. Peter Graham from the St. George and Wollongong trial [110]. After initial assessment of the data, it was found that the moderate-severe breast fibrosis rate of 3% with 50Gy WBI dose in the St George and Wollongong trial is much smaller than the published literature, including the Cambridge and EORTC trial. As those results may not be generalised to other centres, only individual patient data from EORTC 22881-10882 “boost versus no boost” trial and the Cambridge Breast IMRT trial were pooled together for the modeling exercise. To my knowledge, no other dataset of this magnitude had previously been collated for the purpose of the NTCP modeling for breast tissue.

4.3.2 Patient cohort and toxicity scoring

4.3.2.1 Cambridge Breast IMRT trial

This single centre trial recruited 1145 patients with invasive breast cancer (stage T1-T3N0-1M0) or ductal carcinoma in situ who received breast conserving therapy (BCT). All patients received 40Gy in 15 fractions over 3 weeks to the whole breast. In selected cases, this was followed by an electron tumour bed boost of 9Gy in 3 fractions over 3 days (n=728). Breast fibrosis was clinically assessed at 2 and 5 years after completion of RT and scored on a four-point scale (0=none, 1= a little, 2= quite a bit (~ moderate) and 3= very much (~ severe)).
4.3.2.2 EORTC 22881-10882 “boost versus no boost” trial

This multi-centre trial recruited 5569 patients with invasive breast cancer (stage T1-T2N0-1M0) who received BCT. All patients received 50Gy in 25 fractions over 5 weeks to the whole breast and were randomised between no boost (n=2657), 10Gy in 5 fractions boost (n=126), 16Gy in 8 fractions boost (n=2661) and 26Gy in 13 fractions boost (n=125). Electrons (63%), photons (29%) and low dose rate brachytherapy (9%) were used to deliver the boost dose. Breast fibrosis was clinically assessed and scored on a four-point scale (1 = none, 2 = minor, 3 = moderate, and 4 = severe) at every follow up visit.

4.3.2.3 Exclusion criteria

The brachytherapy technique can lead to significant dose heterogeneity and its boost volumes are usually much smaller than external beam techniques [111]. Hence, patients with brachytherapy boost were excluded from the analysis. In addition, patients with missing data/toxicity score were also excluded. Overall, 571 patients from the Cambridge trial and 275 patients from the EORTC trial were excluded from the analysis.

4.3.3 Dose-Volume data

The accuracy with which NTCP model parameters can be estimated depends on the quality of both the dosimetric information and the clinical follow up data. The late toxicity scores and boost volumes were recorded in both the trials but limited dose-distribution data was available. Therefore, a more simplistic two-compartment dose-volume histogram (DVH) model was used. The first step of the DVH was the tumour bed volume receiving whole breast dose plus boost dose and the second step of the DVH was the remaining breast volume (whole breast volume minus tumour bed volume) receiving whole breast dose only (figure 9).
Figure 9: Two step dose volume histogram model

DVH step 1: Tumour bed receiving whole breast dose plus tumour bed boost
DVH step 2: Whole breast minus tumour bed receiving whole breast dose alone

Whole breast volume was only recorded in the Cambridge trial. Hence, a Monte Carlo (MC) simulation method was used to generate breast volume data for the EORTC patients. The MC simulation used the breast volume distribution from the Cambridge trial and an acceptance-rejection test of boost/breast volume ratio between 5-40% (the range of boost volume to breast volume ratio observed in the Cambridge data). It was assumed that the distribution of breast volume and boost/breast volume ratio in the EORTC trial is the same as in the Cambridge trial.
4.3.4 NTCP modeling

4.3.4.1 Introduction to NTCP modeling

In this study two established radiobiological models were used: Lyman Kutcher Burman (LKB) model [112] and the Niemierko model [113]. Both models assume that for whole or partial organ irradiation, the dose-response curve follows a basic sigmoid shape. Both of these models are based on three parameters:

\( \text{TD50/5:} \) homogeneous dose to the organ which leads to 50% patients experiencing the defined toxicity at 5 years

\( \gamma_{50} \text{ or } m: \) steepness of the dose-response curve

\( n \text{ or } a: \) volume parameter of the organ being assessed, where \( a=1/n \)

For the purpose of estimating these parameters, each patient’s two-compartment DVH was converted into a generalised equivalent uniform dose (EUD) using the Kutcher-Burman histogram reduction method. The EUD is the dose that, when delivered uniformly to the organ, will lead to the same complication probability as the actual dose distribution.

\[
EUD = \left( \sum_i v_i(D_i)^2 \right)^n
\]

where \( v_i \) is the \( i \)-th relative sub-volume of the organ irradiated with dose \( D_i \) in the differential dose-volume histogram. The parameter “\( n \)” describes the volume effect of the irradiated organ or tissue.

If \( n=1 \), the assessed organ has a parallel architecture with a strong volume dependence on late complication rate and EUD is the mean dose.
If n=0, the assessed organ has a serial architecture with no volume dependence on late complication rate and EUD tends to be the maximum dose.

As radiotherapy associated complications are dependent on fraction size, a biologically equivalent uniform dose \( \text{BEUD}_3 \) was generated using the EUD and \( \alpha/\beta \) ratio of 3Gy in the linear quadratic model [70].

\[
\text{BEUD}_3 = \text{EUD} \left(1 + \frac{\text{EUD}}{N \times \alpha \beta} \right)
\]

4.3.4.2 Lyman Kutcher Burman (LKB) model

\[
\text{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{0}^{x} e^{-\left(\frac{y^2}{2}\right)} dy
\]

where

\[
x = \frac{\text{BEUD}_3 - \text{BEUD}_{50}}{m\text{BEUD}_{50}}
\]
4.3.4.3 Niemierko model

\[ NTCP = \frac{1}{1 + \left( \frac{BEUD_{50}}{BEUD_{3}} \right)^{4.750}} \]

4.3.4.4 NTCP model programming

Both NTCP models were written by Dr. Raj Jena in Object Pascal (Delphi, Embarcadero technologies, San Francisco, CA, USA). I independently tested each model version and advised Dr Jena on how to improve on the programmed models. Several iterations were used before the final version 11 was used. The previous iterations have been summarised in table 12.
Table 12: Summary of iterations used to develop the final NTCP model optimisation programme

<table>
<thead>
<tr>
<th>Version</th>
<th>Programme characteristics</th>
<th>Limitations</th>
<th>Action taken</th>
</tr>
</thead>
</table>
| 1       | a. Use sum of square method for parameter estimation  
          b. Based on Cambridge cohort alone  
          c. Use Niemierko model | a. Small number of patients in large boost volume bins  
                          b. Previous published data from Borger et al [33] suggest dominant volume effect at high radiation doses. Maximum dose in the Cambridge cohort was EDD2= 56.2Gy | Develop collaboration with EORTC “boost versus no boost” trial and St. George and Wollongong trial |
| 2       | a. Use sum of square method for parameter estimation  
          b. Based on Cambridge and EORTC cohort  
          c. Examined best volume parameter by testing fixing NTCP parameters as BED50=105Gy, $\alpha/\beta=3$ and $y50=1.4$. Different values of “n” published in the literature were tested: 0.06, 0.15 and 0.78.  
          d. Use Niemierko model | a. Published studies on NTCP modeling for breast fibrosis have several limitations (summarised in section 4.6). My study had the most comprehensive data and more extensive parameter search is possible | All values of n from 0.1 to 1.0 were tested using fixed parameters |
| 3       | a. Use sum of square method for parameter estimation  
          b. Parameter “n” best fit estimated from 0.1-1.0  
          c. Use Niemierko model | a. Accept published data for BED50 and y50. Correlation between parameters can lead to inaccurate value for n if estimated BED50 and/or y50 incorrect | Re-write the programme which allows optimisation for n, BED50 and y50 |
| 4 | a. Use sum of square method for parameter estimation  
b. Best fit parameter estimation for n, BED50 and γ50  
c. Use Niemierko model | a. Sum of square methods use summative dose-volume data. Information from individual patient data is not used.  
b. Sum of square method cannot generate 95% confidence interval for NTCP parameters | Change parameter estimation method to maximum likelihood estimation (MLE) method |
|---|---|---|---|
| 5 | a. Use MLE method for parameter estimation  
b. Best fit parameter estimation for n, BED50 and γ50  
c. Use Niemierko model  
d. EORTC breast volume generated by Monte-Carlo method using mean and standard deviation of Cambridge cohort breast volume. No acceptance-rejection test was used | a. Monte-Carlo method generated unacceptable boost-breast volume ratios | EORTC cohort breast volume generated using acceptance rejection test of  
i. boost/breast volume ratio between 5-40%  
ii. Follow Cambridge breast volume distribution. |
| 6 | a. Use MLE method for parameter estimation  
b. Best fit parameter estimation for n, BED50 and γ50  
c. Use Niemierko model  
d. EORTC breast volume generated using acceptance-rejection test | a. Lyman Kutcher Burman (LKB) is more often used in published NTCP studies. | Re-write the programme to include both LKB and Niemierko model |
| 7 | a. Use MLE method for parameter estimation  
b. Both LKB and Niemierko models used  
c. Cambridge dataset dose level included no boost and 9Gy/3# boost. EORTC dataset dose levels of no boost, 10Gy/5#, 16Gy/8# and 26Gy/13# used | a. Many patients in the EORTC trial treated with other different fractionations (table 13) | NTCP programme revised to include all different dose and fractionations used, so analysis done on actual dose delivered. |
<table>
<thead>
<tr>
<th></th>
<th>a. Use MLE method for parameter estimation</th>
<th>b. Both LKB and Niemerko models used</th>
<th>c. All delivered dose and fractionations included</th>
<th>d. Restricted BED50 (90-120Gy), γ50 (1-3Gy) and m(0.1-0.6)</th>
<th>a. Possibility of inaccurate results as parameters restricted with narrow range</th>
<th>Revised programme with BED50 (90-150Gy), γ50 (0.5-3Gy) and m (0.05-0.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>a. Use MLE method for parameter estimation</td>
<td>b. Both LKB and Niemerko models used</td>
<td>c. Random Grid search 10,000 steps</td>
<td>a. Possibility of different results with repeat iterations.</td>
<td>Random grid search changed to step wise grid search. Grid size increased from 10 to 50 steps.</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>a. Use MLE method for parameter estimation</td>
<td>b. Both LKB and Niemerko models used</td>
<td>c. Step wise grid search</td>
<td>a. Model did not generate 95% confidence interval (CI)</td>
<td>Revise the programme so parameter 95% CI generated using profile likelihood estimation method</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td><strong>FINAL VERSION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. Use MLE method for parameter estimation</td>
<td>b. EORTC breast volume generated using acceptance-rejection test</td>
<td>c. Both LKB and Niemerko models used</td>
<td>d. All delivered dose and fractionations included</td>
<td>e. Step wise grid search with 50 steps for each parameter</td>
<td>f. BED50 (90-150Gy), γ50 (0.5-3Gy) and m (0.05-0.8). α/β ratio fixed at 3Gy</td>
</tr>
</tbody>
</table>
4.3.5 Estimation of NTCP parameters with 95% confidence interval

A Maximum Likelihood Estimation (MLE) method [114] was used to find the best fit values of the model parameters BEUD50, γ50/m and n. This method uses maximum log likelihood (ln L) to estimates the probability that the observed pattern of complications can be best described by the parameters.

\[
\ln L = \sum_{y(i)=1} \ln[NTCP(TD50(1), m, n)] + \sum_{y(i)=0} \ln[1 - NTCP(TD50(1), m, n)]
\]

where \(y(i)=1\) if moderate-severe fibrosis is present and \(y(i)=0\) if moderate-severe fibrosis is absent.

A value of \(n\) value closer to one suggests that the organ has a parallel architecture with a strong volume dependence whilst a value of \(n\) closer to zero suggest that the organ has a serial architecture with no volume dependence on late complication rate. A full sequential parameter search was performed with the following parameter constrains:

BEUD3 (0-150), n (0.01-1.0), γ50 (0.5-3.0) and m (0.1-0.8). The 95% confidence intervals (CI) for the optimally fit parameters were obtained using the Profile Likelihood Estimation method [115]. The parameter of interest was varied around its optimal values, while the other parameters were fixed in the MLE to generate the upper and lower 95% CI. This method takes non-linearity and non-symmetrical CI into consideration but does not account for the correlation between parameters.
4.3.6 Goodness of fit estimation

Results from the START-pilot trial [70] were used to assess the goodness of fit of the predicted NTCP models. The START-pilot trial randomised 1410 patients into one of three whole breast RT dose fractionations: 50Gy in 25 fractions or 39Gy in 13 fractions or 42.9Gy in 13 fractions. Patients were also sub-randomised for tumour bed boost to a dose of 14Gy in 7 fractions using electrons. Summative data on moderate and severe breast induration at five years was used for all three whole breast dose fractionations with and without boost for the goodness of fit estimation. The goodness-of-fit statistic was obtained by calculating the Pearson chi-square statistic from the observed and predicted rates of breast fibrosis. The statistic is denoted as $\chi^2$ and as a rule large values of $\chi^2$ (and small $p$-values) indicate a lack of fit of the model.

$$\chi^2 = \sum \frac{(O - E)^2}{E}$$

‘O’ is observed rates of fibrosis
‘E’ is expected rates of fibrosis from the model

4.4 Results

4.4.1 Toxicity outcome data

Individual dose-volume and toxicity data of 574 patients from the Cambridge trial and 5282 patients from the EORTC trial were used for the NTCP modeling. 26.8% (154/574) patients in the Cambridge trial and 20.7% (1096/5282) patients in the
EORTC trial developed moderate-severe breast fibrosis. The patient’s radiotherapy dose volume characteristics are summarised in table 13.
Table 13: Dose-volume characteristics from the Cambridge and the EORTC dataset used for the NTCP model

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Mean boost volume (range) cm³</th>
<th>Moderate-severe fibrosis rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambridge dataset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(assessed at 5-year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Boost</td>
<td>235</td>
<td>-</td>
<td>40/235 (17%)</td>
</tr>
<tr>
<td>Boost</td>
<td>339</td>
<td>161.2 (33.6-540)</td>
<td>114/339 (33.6%)</td>
</tr>
<tr>
<td>EORTC dataset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cumulative incidence at 10 years)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No boost</td>
<td>2656</td>
<td>-</td>
<td>341/2656 (12.8%)</td>
</tr>
<tr>
<td>≥6Gy to &lt;10Gy</td>
<td>6</td>
<td>238 (108-372)</td>
<td>1/6 (16.7%)</td>
</tr>
<tr>
<td>10Gy</td>
<td>117</td>
<td>204.7 (42-1176)</td>
<td>28/117 (23.9%)</td>
</tr>
<tr>
<td>12Gy</td>
<td>31</td>
<td>185.9 (48-606)</td>
<td>11/31 (35.5%)</td>
</tr>
<tr>
<td>14Gy</td>
<td>93</td>
<td>273.4 (48-735)</td>
<td>23/93 (24.7%)</td>
</tr>
<tr>
<td>16Gy</td>
<td>2257</td>
<td>209 (22-1386)</td>
<td>635/2257 (28.1%)</td>
</tr>
<tr>
<td>&gt;16Gy to ≤20Gy</td>
<td>39</td>
<td>193.1 (52-630)</td>
<td>9/39 (23.1%)</td>
</tr>
<tr>
<td>26Gy</td>
<td>83</td>
<td>198.5 (43-630)</td>
<td>48/83 (57.8%)</td>
</tr>
</tbody>
</table>

* The NTCP parameter estimation was based on the actual tumour bed boost dose delivered and not on the intention to treat boost dose.
4.4.2 Best fit NTCP parameters

Using the MLE method, the best estimated NTCP parameters for the Niemierko model were \( \text{BEUD}_3(50) = 136.4 \text{Gy} \), \( \gamma_{50} = 0.9 \) and \( n=0.011 \). The 95\% CI for parameters were \( \text{BEUD}_3(50) = 132.8-140 \text{Gy} \), \( \gamma_{50} = 0.84-0.97 \) and \( n= 0.01-0.03 \). For the LKB model, the best estimated parameters were \( \text{BEUD}_3(50) = 132 \text{Gy} \), \( m= 0.35 \) and \( n= 0.012 \) with 95\% CI of \( \text{BEUD}_3(50) = 128.8-135.6 \text{Gy} \), \( m= 0.326-0.374 \) and \( n= 0.01-0.03 \). Both models imply that the risk of moderate-severe breast fibrosis is strongly associated with radiotherapy dose and the effect of volume parameter is small.

4.4.3 Goodness of fit estimation

The observed rates of moderate-severe fibrosis in the RMH/GOC trial were in good agreement to the predicted rates of fibrosis using the LKB model (figure 10) and the Niemierko model (figure 11). Using the Pearson chi-square test with 5 degrees of freedom, the \( \chi^2 \) was \( 0.053 \) (\( p=0.95 \)) for the LKB model and \( \chi^2 \) was \( 0.058 \) (\( p=0.95 \)) for the Niemierko model suggesting a good fit of both the models.
Figure 10: Lyman Kutcher Burman Model with independent validation dataset from the START pilot study

The probability of moderate-severe breast fibrosis versus biological equivalent dose using $\alpha/\beta$ of 3 Gy (BED$_3$). The solid line is based on the best fit parameters (BED$_3$ = 132 Gy and m= 0.35) and the dashed lines are upper and lower 95%CI. The summative toxicity data of the three dose fractionations ± boost at five years from the START pilot trial are plotted.
Figure 11: Niemierko Model with independent validation dataset from the START pilot study

The probability of moderate-severe breast fibrosis versus biological equivalent dose using $\alpha/\beta$ of 3 Gy (BED$_3$). The solid line is based on the best fit parameters (BED$_3$ = 136.4 Gy and y$_50$= 0.9) and the dashed lines are upper and lower 95% CI. The summative toxicity data of the three dose fractionations ± boost at five years from the START pilot trial are plotted.
4.5 Other NTCP studies for breast fibrosis

Three other studies have previously estimated the NTCP parameters for breast fibrosis and these results are summarised in table 14. Borger et al [33] model was based on 404 patients treated with WBI (50Gy in 25 fractions over 5 weeks) followed by low dose rate Iridium-192 based tumour bed boost (15-25Gy). BEUD was calculated using \( \alpha/\beta \) of 2Gy and repair half-time of 1.5 hours. The implant positions were re-constructed on the available radiographs and dose-volume calculations were performed. The best fit NTCP parameters in the study were TD50=72Gy and n= 0.16 ± 0.04. Though informative, the model parameters were estimated from patients with brachytherapy boost alone. It is not appropriate to compare parameters generated from brachytherapy to external beam techniques due to the difference in dose distribution and a possible different radiobiological effect. For this reason, patients with brachytherapy boost were excluded in the current study. Avanzo et al [116] estimated the best fit parameters for the model using average dosimetric parameters (prescription dose, fraction dose, median follow up and dose-volume data) from three WBI studies without boost and four external beam PBI studies. Three PBI studies used twice daily fractionation, and BEUD calculations included a repair half-time of 4.4 hours in the model. As the median follow up of the PBI studies was short (1.3-4.2 years), a latency function correction was included. The parameters were estimated using the weighted least square method, with the number of patients in each dataset as weights. The parameters for moderate-severe breast fibrosis model were BEUD50= 105.8, n=0.15 and m=0.22. The authors acknowledged that the gold standard approach to estimate NTCP parameters is the use of individual dosimetric data/clinical outcome. However, given the necessity to
estimate some parameters, MLE based parameter estimates are more precise when compared to weighted least square method [117].

In contrast to this work, Alexander et al [118] reported a strong effect of volume parameter on breast fibrosis. This study included summative data of 806 patients from the START- pilot trial [70], 590 patients from a German study [119] and 150 post-mastectomy patients treated during the 1960’s [120]. All patients received WBI and no partial volume data was available for the fitting analysis. The dose-volume data were generated using an anthropomorphic phantom and parameters were estimated for a relative seriality model and Lyman model. The study suggested a parallel architecture for breast tissue with a strong volume effect on breast fibrosis (n=0.78). However, these results cannot be generalised for several reasons:

a. The study did not make allowance for the tumour bed boost doses (additional RT dose) in the models.
b. The toxicity outcome used is different between the studies. The START-pilot and German study assessed breast fibrosis on clinical examination, whereas the post-mastectomy study scored fibrosis on photographs.
c. The planning techniques for post-mastectomy radiotherapy study (1960’s) would be considered outdated by present standards. One would also expect different NTCP parameters for breast fibrosis after BCS and tissue fibrosis after mastectomy.
d. The study corrected time latency for radiotherapy associated toxicity for breast conservative studies (START-pilot & German) based on the results of the historic post-mastectomy series.
Table 14: Summarised results of the best fit NTCP parameters for moderate-severe breast fibrosis
* these studies used summative dosimetric and toxicity data

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>BEUD&lt;sub&gt;3&lt;/sub&gt;(50)</th>
<th>[EUD2]&lt;sub&gt;3&lt;/sub&gt;(50)</th>
<th>γ50</th>
<th>m</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borger et al [33]</td>
<td>404</td>
<td>NTD&lt;sub&gt;50&lt;/sub&gt;=72 Gy (α/β = 2Gy) (t&lt;sub&gt;1/2&lt;/sub&gt; = 1.5hrs)</td>
<td></td>
<td></td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>Alexander et al* [118]</td>
<td></td>
<td>104 Gy</td>
<td>104 Gy</td>
<td>-</td>
<td>1.47</td>
<td>0.27</td>
</tr>
<tr>
<td>- LKB model</td>
<td>1546</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Relative seriality model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avanzo et al* [116]</td>
<td></td>
<td>105.8 Gy</td>
<td>107.2 Gy</td>
<td>-</td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>- with repair correction (t&lt;sub&gt;1/2&lt;/sub&gt; = 4.4hrs)</td>
<td>2562</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- without repair correction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current study</td>
<td></td>
<td>132 Gy</td>
<td>136.4 Gy</td>
<td>0.9</td>
<td></td>
<td>0.35</td>
</tr>
<tr>
<td>- LKB model</td>
<td>5856</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Niemierko model</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

NTD: Normalised total dose
BEUD<sub>3</sub>(50): Biologically equivalent uniform dose using α/β of 3Gy
[EUD2]<sub>3</sub>(50): Equivalent uniform dose in 2Gy per fraction using α/β of 3Gy
γ50/m: slope of the dose response curve
n: volume parameter
t<sub>1/2</sub>: repair half-time
s: describes the serial/parallel architecture of the organ. A large value indicates a serial structure and a small value indicates a parallel structure
4.6 Limitations of the present study

It is recognised that there are several limitations of this study. One of the intrinsic difficulties in modeling for breast tissue is the lack of detailed dosimetric data. A two-compartment DVH was used in the study, with the assumption that a homogeneous dose was delivered to the breast during WBI. The EORTC whole breast volume data was generated using MC simulation, using parameters from the Cambridge trial. It is clear that using simulated data for the EORTC patients can lead to large uncertainties. A plot of boost volume against moderate-severe fibrosis suggests that the volume effect is likely to be weak (figure 12) and the model parameters will not be affected by the distribution of the simulated breast volumes. To test this hypothesis, ten additional breast volume datasets were generated for the EORTC patients using the MC method. Furthermore, the variance of the first two simulated datasets was changed by 0.5 and 2 times the original value. Repeat simulations and changing the variance of breast volume distribution did not significantly change the estimated NTCP parameters (in keeping with weak volume effect).

Other limitations of the study include the use of both photons and electron boost modalities without any correction for their different relative biological effectiveness (RBE). Bentzen et al. [121] previously reported RBE for electrons was 0.88 relative to photons at 4.1mm depth. As the RBE difference at depths other than 4.1mm is unknown, no attempts were made to correct for this. The duration of follow up was different between the EORTC (10 years) and Cambridge datasets (5 years). However, no suitable adjustment could be made in the MLE method for latency. In addition, current literature indicates that the majority of the breast fibrosis events take place by five years’ time point [32]. For this analysis, the score for fibrosis was used for all
sites in the breast (boost area or elsewhere). It is not expected to influence on my results, as it is most often located at the boost area (where the highest dose is given). Moreover, the worst score ever was reported. Although improvement of fibrosis is not expected, erroneous scoring of oedema early after treatment might be possible.

It is also important to consider that the LKB and Niemierko mathematical models provide a simplified representation of a complex biological pathway [122]. The development of late radiotherapy complications is multi-factorial, and much of the variability cannot be explained by dosimetric factors alone. For example, large breast volume is an independent risk factor for late complications [123, 124], which is not incorporated in the NTCP models. Apart from dose volume parameter, other patient (smoking, diabetes), treatment (type of surgery, chemotherapy, endocrine therapy and post-operative complications) and genetic factors also influence on breast fibrosis [32]. These factors were not available for the analysis in the patient cohort and not accounted for in the current mathematical model. Inclusion of other biological factors (patient, genetics, chemotherapy, endocrine therapy) may further improve the predictive power of the NTCP models [105, 125].
Figure 12: Tumour bed boost volume plotted against incidence of moderate-severe fibrosis for EORTC 16Gy in 8 fractions boost (red) and Cambridge 9Gy in 3 fractions boost (blue)

4.7 Discussion

A better understanding of the dose-volume effect for breast tissue is timely as many patients now receive non-uniform breast irradiation in form of accelerated PBI, simultaneous integrated boost and risk adapted radiotherapy [50, 52, 126, 127]. The EORTC 22881-10882 trial breast fibrosis nomogram showed a strong association between radiotherapy dose and fibrosis, with large boost volumes as a prognostic factor on univariate analysis only [32]. The purpose of this study was to specifically look at the volume effect by developing a predictive NTCP model. This was approached by pooling individual data from two large prospective trials (5856
patients), that offered robust information on radiotherapy dose, boost volume and late toxicity.

Using the MLE method, the volume parameter ‘n’ was close to zero for both the LKB model and the Niemierko model. This suggests that for moderate-severe fibrosis, the breast tissue behaves as a serial organ and the maximum RT dose is most predictive of the complication. The summative data of 1410 patients from an independent dataset with six radiotherapy dose levels had a good fit when applied to both the LKB and Niemierko models (figure 10 and 11).

Two other published studies have suggested a weak volume effect. However, one was based on brachytherapy tumour bed boost and the other based on summative patient data. The Alexander et al [118] study indicating a large volume effect has major limitations as previously discussed in section 4.5. To my knowledge, my study is the largest dose-volume study for breast fibrosis using individual patient data.

Parameter correlation leads to uncertainty of parameter estimates, independent of the size and diversity of the dataset [128]. An effective method to decrease the uncertainty is fixing one or more model parameters. Hence the α/β was fixed as 3Gy in my study based on the previously published literature [70]. There is no evidence to suggest the superiority of one model (LKB versus Niemierko) over another [129]. However, similar values of the estimated parameters from the two models strengthen the results of my study.

I believe that there are several possible reasons to explain the difficulty in demonstrating the effects of volume parameter for breast fibrosis. Breast fibrosis may represent a focal effect, with the maximum radiotherapy dose as the most
predictive factor. It is also possible that our current scoring methods for breast fibrosis are not sensitive to the volume effect. Breast fibrosis is often graded as mild-severe based on the severity; however, the scoring system does not take into account the extent of fibrosis i.e. small discrete region of fibrosis and widespread region of fibrosis are potentially scored alike. It has been suggested that NTCP parameters are influenced by the severity of the measured toxicity [130]. For rectum, Rancati et al. estimated that the best fit ‘n’ parameter was 0.23 for ≥ grade 2 rectal bleeding, which decreased to 0.06 when only severe rectal bleeding (grade3) was considered [130]. It is plausible that a volume effect for breast tissue may have been seen for mild fibrosis, but this endpoint was considered to be of less clinical significance and not assessed.

Other toxicity endpoints like photographically assessed breast shrinkage may also be more sensitive to the volume effect as it represents global organ effect, is more objective and scored independent of surgical changes. The current study only focused on breast fibrosis as photographic assessment and patient reported scoring were not available for the majority of the patients included in the study.

4.8 Future work

These results will need validation from newer studies with detailed dosimetric and clinical outcome data. The IMPORT trials [49] are collecting comprehensive dosimetric and toxicity data and one could envisage substituting detailed DVH and toxicity data from these trials in the analysis as it becomes available in the future. There is also a need to investigate quantitative methods, which define both the severity and extent of breast fibrosis. The use of conventional ultrasound images
with ultrasound tissue characterisation (UTC) is being explored as an objective non-invasive method of assessing radiotherapy toxicity in breast tissue [131, 132]. It is based on the principle of ultrasound-backscatter spectroscopy and can assess dermal, hypodermal and glandular tissue toxicity. Small studies have shown good interobserver and intraobserver correlation, with toxicity scores also correlating well with clinical toxicity scores [131]. Another method of interest is the use of ultrasound elastography to assess radiation fibrosis [133] and work is ongoing to further develop this technique.

The use of patient-reported toxicity scoring for NTCP modeling may also be useful. A small area of fibrosis in the breast may not be perceived as toxicity by the patient, whereas a large area of fibrosis in a small breast is likely to be considered as significant toxicity by the patient. Hence, patient-reported breast fibrosis scoring may be more sensitive to the change in treatment volume.

4.9 Conclusions

This large multi-centre pooled study suggests that contrary to previous beliefs, the effect of volume parameter is small and the maximum radiotherapy dose is the most important parameter to influence late breast fibrosis.

However, this may reflect limitations in our current scoring system. Other radiotherapy-associated complications should also be analysed to determine the effects of dose-volume parameters, and patient-reported outcomes should complement clinician score-based models in the future. Inclusion of other clinical factors is desirable for future NTCP modelling work.
4.10 Chapter contributions

I would like to sincerely thank the following individuals for their help and support with this work.

Professor Harry Bartelink & Peter Graham: for supporting this project and sharing trial data
Raj Jena: for supervising the Monte Carlo simulation exercise and programme NTCP models in Object Pascal
Emma Harris: for assisting with figure 10 and 11
Jo Haviland: for providing summative toxicity outcome data of the START-pilot study

I was involved in the concept and design of this study. After analysing all the available dosimetric data from the Cambridge Breast IMRT study, I approached Professor Harry Bartelink (EORTC boost trial), Dr Peter Graham (St. George and wollongong trial) and Dr P Romestaing (French breast boost trial) to share their study data. I was responsible for data cleaning and analysis before using the data for NTCP modeling. Dr Raj Jena very kindly programmed the NTCP model in Object Pascal. The programme was developed over eleven iterations and I was responsible for testing each model version. Dr Jena developed the next version of the model based on my feedback and suggestions. I wrote the original manuscript which was subsequently published in the peer reviewed Radiotherapy & Oncology journal (appendix).
5. Intensity modulated radiotherapy (IMRT) in Breast cancer

*This work has been published as an original article in Journal of Clinical Oncology with an accompanying editorial in 2013 (Appendix)*

5.1 Introduction

This chapter address the important issue of the effects of intensity modulated radiotherapy in breast cancer on breast tissue related complications.

5.1.1 What is intensity modulated radiotherapy (IMRT)?

IMRT is a method of delivering radiation therapy using beams with non-uniform radiation fluence [134]. It can be used to reduce dose inhomogeneity within the target volume, deliberately creating inhomogeneous dose distribution and sculpture dose around the concave target volume to spare the surrounding normal tissue from high radiation dose.

5.1.2 What is the scope of IMRT in breast radiotherapy?

Radiation therapy to the whole breast is the current standard of care for early stage breast cancer and ductal carcinoma in situ. The treatment is typically delivered by two opposing tangential fields to cover the entire breast. Though a simple method, the distribution of radiation dose can be quite inhomogeneous due to the variation in the breast contour. The radiation beam has to traverse through more tissue along the centre of the breast as compared to inferior and superior aspect of the breast.
This often leads to higher radiation dose at the inferior aspect of the breast tissue and sometimes superiorly as well.

The simplest form of breast IMRT for nearly 30 years was the use of physical wedges, which can reduce the fluence of the radiation beam from the chest wall to the sub-areolar region, and create a more homogeneous dose distribution in the breast. However, one major drawback of the physical wedge is that it can only correct for dose inhomogeneity in a 2-dimensional plane, usually at the level of the nipple. As the breast contour changes superiorly to inferiorly and medial to lateral, significant dose inhomogeneity can be present in the superior and/or inferior portion of the breast. Buchholz et al [135] looked at the off-axis inhomogeneity for eleven patients treated with opposed tangential fields and lateral wedge to minimise the dose inhomogeneity in the central plane. On average, 10% of the breast volume (range 1-40%) received ≥110% of the prescribed dose and dose inhomogeneity was positively correlated with increasing breast sizes (Spearman correlation coefficient = 0.72, p = 0.01).

Improvements in technology allow different fluence of radiation beam in multiple planes, resulting in improved homogeneity throughout the breast tissue. Many studies using inverse and forward planning IMRT methods (discussed later in the chapter) have shown improved dose homogeneity across the whole breast [22, 136, 137]. Kestin et al [22] showed that by using multiple static multileaf collimator (MLC) segment based IMRT, only 0.1% of the treatment volume received > 110% of the prescribed dose as compared to 10% with standard wedges. Similarly, Chui et al [137] used a series of pencil beams to modulate the dose across the breast tissue as a simple IMRT method and showed a more homogeneous dose distribution in the breast as compared to standard tangential beams.
Apart from improving breast dose homogeneity, IMRT techniques may also be beneficial for simultaneous integrated tumour bed boosts, partial breast irradiation and treatment of internal mammary nodal region [138, 139]. These areas were outside the remit of my research work and are not discussed further.

5.1.3 Inverse versus forward planned IMRT

The term “IMRT” covers a spectrum of techniques, ranging from relatively simple to highly complex. For majority of patients treated with breast radiotherapy, it appears that a simple form of IMRT may be the most appropriate technique. This simple IMRT is often referred to as forward planned IMRT or field-in-field dose homogenisation IMRT, where small radiotherapy fields are added to the main treatment fields to improve dose inhomogeneity to the breast (the target). The technique is relatively straightforward with the treatment delivery similar to standard radiotherapy.

Inverse planned IMRT techniques are more complex where clinicians have to delineate volumes of interest (target and critical organs) and volume-based optimisation is performed using a computer algorithm. The algorithm creates a fluence map of the required dose distribution by balancing the conflicting requirements of the target and the critical organs. These techniques can produce a large volume of low dose to surrounding tissues. As a result, complex IMRT tends to be restricted to cases where a very steep dose gradient is required, e.g. simultaneous integrated boost, treatment of internal mammary nodal region and patients with pectus excavatum who would otherwise receive an unacceptably high dose to surrounding organs at risk (lungs and heart).
Mihai et al [140] compared the breast dose homogeneity of forward and inverse planned IMRT techniques on a cohort of 30 patients. The study found that inverse planning significantly improves V105 (mean dose 9.7% versus 14.5%; p=0.002) and the V110 (mean value 1.4% versus 3.2%; p=0.006). However, it was concluded that the difference in V110 is too small (1.8%) to be of clinical significance and from a practical point, forward or inverse planned IMRT should be considered as equivalent. Similar results were reported by Descovich et al [141], where breast V105 was significantly smaller with hybrid direct aperture optimisation (inverse planned IMRT) technique as compared to forward planned IMRT but no clinically significant difference was seen for V110 (0.4% versus 1.6%). Based on these dosimetric results, one should expect a similar outcome for late breast toxicity with both forward and inverse planned IMRT techniques.

5.1.4 Current challenges in the universal implementation of IMRT in breast radiotherapy

It is expected that improved dose homogeneity with IMRT using forward or inverse planned methods will reduce acute and late breast tissue toxicity. At the time of my research period, there was little randomised controlled trial data to confirm the superiority of IMRT over standard radiotherapy in breast cancer [18, 20, 109]. Donovan et al [20] showed reduction in late breast tissue toxicity with IMRT among women who were judged to be at higher than average risk of radiation-induced toxicity based on breast size and/or breast shape. Worldwide, the whole breast radiotherapy practice is gradually shifting from standard 2-dimensional radiotherapy (2D-RT) to IMRT [142, 143]. However, sceptics have pointed out that breast IMRT is more complex and time consuming than standard 2D-RT, and long term benefits
should be established before its universal adoption [144, 145]. It has also been postulated that removing hot-spots with IMRT can lead to dose de-escalation especially to the skin, and a theoretical increased risk of local relapse [146].

5.1.5 Aims of this work

In this chapter, I examine if the correction of dose-inhomogeneity using a simple method of forward-planned IMRT translates into clinical benefits of reduced late breast tissue toxicity. The benefits of IMRT are evaluated within the context of the large Cambridge Breast IMRT trial [21].

5.2 Hypothesis

This chapter addresses the hypothesis that improvement in dose inhomogeneity with the use of IMRT will reduce clinical-assessed breast normal tissue complications at 5 years.

5.3 Materials and methods

5.3.1 Cambridge Breast IMRT trial

The single-centre Cambridge Breast IMRT trial opened in April 2003 and was closed to recruitment in June 2007 [21]. The Cambridge Research Ethics Committee provided ethical approval for the study. The National Cancer Research Institute Studies group accepted this trial as a portfolio trial in April 2002 and it was adopted by the National Cancer Research Network in March 2003.
5.3.2 Trial eligibility criteria

Women with operable unilateral histologically-confirmed invasive breast cancer (T1-T3, N0-1, M0) or ductal carcinoma in situ (DCIS) requiring radiotherapy after breast conservation surgery were eligible for the trial. All patients with invasive breast cancer underwent sentinel node biopsy and/or axillary clearance (if lymph node positive). Other eligibility criteria included age >18 years, no history of contralateral breast cancer, no previous malignancy in the previous 5 years (except skin basal cell or squamous carcinoma or in situ carcinoma of the cervix) and availability for follow up. All patients provided written informed consent. A total of 1145 patients were recruited.

5.3.3 Sample size calculation

The sample size was based on a standard event rate of 40% in the control arm at 2 years. The difference to be detected was estimated to be 10% with the hazard ratio of 0.7. Assuming a minimum average follow up of 2 years and 80% power, and a type I error of 0.05, 358 patients and 125 events were required in each of the randomised arms. This sample size was increased by 10% to adjust for possible loss of patient follow-up by 2 years.

5.3.4 Randomisation

A standard radiotherapy plan consisting of paired wedged tangents was produced for all trial patients. Patients with satisfactory dose homogeneity were not randomised (29%), but treated with standard RT and followed up as for the
randomised patients. Patients whose plan had significant dose inhomogeneities, defined as ≥2 cm³ volume receiving >107% of the prescribed dose (V107), were randomised between standard radiotherapy (control arm) and forward planned IMRT (interventional arm). Randomisation was performed using permuted blocks of mixed block size and stratified for T stage and adjuvant therapy. Patients were informed of their randomisation arm if they enquired at the time of radiotherapy treatment.

5.3.5 Radiotherapy technique

Patients in the control arm were treated with wedged tangential fields to the breast and patients in the interventional arm were re-planned with a simple, forward planned IMRT technique to reduce the volume receiving >107% and <95% of the prescribed dose.

5.3.5.1 Standard radiotherapy plan

A whole breast planning target volume (PTV) was first contoured for the patient using a field-based approach. The PTV consisted of the volume of breast enclosed by the field: 5 mm from the skin surface, the lung–chest wall interface/ posterior field edge, and superior and inferior field margins. A standard plan consisting of paired wedged tangents using 6MV photons was produced for the patient. Mixed energies of 6 and 15 MV photons were sometimes used in patients with larger breast separations and dose calculations were done using a correction for lung inhomogeneity.
5.3.5.2 Forward planned simple IMRT plan

The simple, manual forward planned IMRT plan was built on the original standard treatment plan by adding further “top-up” fields to shield areas of high dose and boost areas of lower dose. These additional fields were based on the original treatment field sizes and were typically weighted to 10% of the original treatment beams. The dose arrays were locked, and then by viewing the isodose distribution along the beam’s eye view (BEV) the multi-leaf collimators (MLCs) were manipulated to shield the areas of the breast receiving doses greater than 107% of the prescription (figure 13). Occasionally a wedge was added to the additional fields to provide a wedge in the superior/inferior direction. The isodose distributions were recalculated and dose–volume histograms (DVHs) were exported and compared with the original plan. Further adjustments to the MLC shapes and beam weightings could be made iteratively to increase the volume of the PTV receiving doses between 95% and 107% of that prescribed.

All patients were treated to a dose of 40 Gy in 15 fractions, 5 days a week over 3 weeks, with 6 MV photons prescribed to the ICRU 50 reference point. Mixed energies of 6 and 15 MV photons were used in patients with large breast separation. Nodal irradiation and a sequential tumour bed boost were administered according to local protocol. After completion of radiotherapy, all patients were treated similarly irrespective of their allocated treatment arm.
Figure 13: Comparison of dose homogeneity between standard radiotherapy (control arm) and forward planned IMRT (intervention arm)

**Blue colour wash displays 95% of the prescribed dose (PD), green represents 105% PD, turquoise represents 107% PD and dark brown represents 110% PD.**

**Top panel** shows dose distribution using standard two wedged tangential fields in beam field view (left) and axial view (right). Regions of unplanned high dose can be seen medially, laterally and the inframammary region.

**Bottom panel** shows dose distribution with forward planned IMRT with addition of two top-up fields. There is better dose homogeneity across the breast tissue and previous regions of unplanned high dose of 107% or more of the prescribed dose have been avoided.
5.3.5 Breast toxicity endpoints

Patients were assessed at two and five years after completion of radiotherapy using serial photographs and clinical examination. The primary outcome of the study was photographic assessment of late cosmetic effects and the secondary outcome was clinical assessment of breast late normal tissue changes (induration, telangiectasia and breast oedema). Toxicity assessors were unaware of the patient’s treatment arm. My thesis work is related to the five-year toxicity outcome with IMRT, which has been summarised below.

5.3.5.1 Photographic assessment

Frontal photographs of both breasts were taken after primary surgery and before radiotherapy (baseline) and repeated at two- and five-years post radiotherapy. Two photographs were taken, one with the hands resting on the hips, the other with the arms raised above the head. The five years photographs were compared with post-operative baseline photographs for radiotherapy-associated breast shrinkage and scored on a validated 3-point scale (none/minimal = 1, mild = 2, marked = 3). A multidisciplinary team of seven clinicians (four oncologists, one radiographer, one surgeon and one breast care nurse) were involved in photographic assessment, a panel of three being present at any one time. This method has been validated and shown to be quicker than using 3 independent scorers with re-scoring of discrepancies and final resolution through discussion [147]. The inter-observer variability of this assessment has been validated before [109]. The panel also scored overall cosmesis on photographs taken at 5 years by assessing the global breast appearance (looking at breast shrinkage, breast distortion and skin changes), independent of baseline cosmetic appearance. The overall breast appearance
(cosmesis) was scored using a 3 point score of good, moderate and poor cosmesis (figure 14) as per the UK FAST trial [148] and Royal Marsden Hospital IMRT trial [20], with moderate-poor score regarded as sub-optimal cosmesis. In addition, post-operative baseline photographs were scored for surgical cosmesis using a 3-point score (good, moderate and poor).

5.3.5.2 Clinical assessment

The treated breast was assessed at five years for breast oedema, skin telangiectasia, breast shrinkage, pigmentation changes and palpable induration. Each of these endpoints was graded 0 to 3 (none, a little, quite a bit, very much) on the scale used in the START trials [149, 150]. All five-year clinical assessments were performed by a single trained research radiographer.

The planned photographic and clinical assessments were not performed in the case of local tumour relapse, metastatic disease, new cancer diagnosis, further breast surgery, poor health or patient refusal. Patients who were unable to attend the five years follow up appointment were contacted via telephone to assess their well-being and requested to complete their patients reported outcome measures (PROMs) questionnaires. The results for PROMs will be presented in Chapter 6.
Figure 14: Overall cosmesis scoring based on serial photographs

The overall cosmesis was scored by comparing baseline photographs (top panel) with photographs taken 5 years post-radiotherapy (bottom panel). The patient with good cosmesis had no/little breast shrinkage, skin changes or breast distortion. In comparison, patient with poor cosmesis had marked breast shrinkage with skin changes and distortion of shape.
5.3.6 Statistical analysis

The baseline demographics for patients with 5-years follow up data was compared using the student t-test, Pearson’s chi-square test and Fisher’s exact test for heterogeneity and trend. Toxicity end-points were compared across the randomised patients on univariate analysis using polychotomous logistic regression analysis. Stepwise multivariate polychotomous logistic regression was used to analyse the patient- and treatment-related factors that were significantly associated with late toxicity following radiotherapy on univariate analysis (p<0.1). Univariate (UVA) and multivariate (MVA) odds ratios (OR) were generated.

Baseline surgical cosmesis was an important determinant factor for breast toxicity endpoints at two years in this trial [109]. Hence, data from all trial patients (randomised and non-randomised) were used to assess the effect of baseline (pre-radiotherapy) surgical cosmesis on late toxicity end-points at five years using polychotomous logistic regression. In addition, baseline surgical cosmesis was included in the multivariate analysis of final overall cosmesis between the randomised patients.

The five-year loco-regional recurrence and overall survival rates were compared between randomised patients using the Mantel-Haenszel (logrank) test. The length of follow up or time to an event was measured from the date of randomisation and analysis was performed according to intention-to-treat. All randomised patients were included in this analysis, not just those who were available for the five-year toxicity assessment. Details of local recurrences and deaths were obtained from local hospital and cancer registry records. All statistical analysis was done using STATA.
5.4 Results

5.4.1 Patients demographics

The late breast tissue toxicity outcome of 654/1145 (57%) patients (control arm: 237, IMRT arm: 228, non-randomised arm: 189) were available at five years. The baseline patient, tumour and treatment characteristics of the 654 patients are summarised in table 15. The characteristics are well balanced between the two randomised arms, with the exception of volume of breast tissue receiving >107% of the prescribed dose (as expected). Patients in the non-randomised arm were younger with smaller tumour size and less frequently received systemic chemotherapy. The mean breast volume was also significantly larger in the two randomised arms as compared to the non-randomised arm. Reasons for patients with no 5-year assessments from the study are summarised in the CONSORT diagram (figure 15).

5.4.2 5-year Toxicity in Control arm (Standard radiotherapy) versus Intervention arm (IMRT)

On univariate analysis, fewer patients in the IMRT arm developed sub-optimal overall cosmesis (OR 0·68, 95% CI 0·48-0·96; p=0·027) and skin telangiectasia (OR 0·58, 95% CI 0·36-0·92; p=0·021) as compared to the control arm (table 16). However, no significant difference was seen for photographically assessed breast shrinkage (OR 0·79, 95% CI 0·55-1·14; p=0·21), breast oedema (OR 0·74, 95% CI 0·48-1·15; p=0·18), tumour bed induration (OR 0·76, 95% CI 0·54-1·06; p=0·11) and pigmentation (OR 0·80, 95% CI 0·46-1·38; p=0·42) between the randomised patients.
Table 15: Patient, tumour and treatment characteristics of 654 patients with five-year toxicity data

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* breast volume (cm$^3$) receiving >107% of the prescribed dose

$^\lambda$ Fisher exact test
Table 16: Comparison of skin telangiectasia and overall final cosmesis between the control and IMRT arms at five years

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<th>IMRT Number of patients (%)</th>
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<th>Odds ratio* (multivariate analysis)</th>
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<tbody>
<tr>
<td>None</td>
<td>179 (76)</td>
<td>193 (85)</td>
<td>OR 0.58 (p=0.021)</td>
<td>OR 0.57 (p=0.031)</td>
</tr>
<tr>
<td>A little</td>
<td>24 (10)</td>
<td>16 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quite a bit</td>
<td>18 (8)</td>
<td>12 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very much</td>
<td>14 (6)</td>
<td>7 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall final</td>
<td></td>
<td></td>
<td>OR 0.68 (p=0.027)</td>
<td>OR 0.65 (p=0.038)</td>
</tr>
<tr>
<td>cosmesis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>84 (37)</td>
<td>95 (43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>95 (41)</td>
<td>102 (45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>50 (22)</td>
<td>26 (12)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* based on polychotomous logistic regression analysis
Figure 15: CONSORT diagram

T1-3, N0-1, M0 invasive breast cancer/DCIS requiring RT
Breast conservation surgery with complete tumour excision.
1283 patients approached to participate in trial

1145 patients recruited to trial
Dosimetry with standard breast plan:
ICRU recommendations

< 2 cm³ of breast tissue > 107%

≥ 2 cm³ of breast tissue > 107%

815 randomised

330 patients were ineligible for
randomisation and received standard 2D-RT

141 withdrawn

Tumour-related (52)
Breast cancer-related death (21)
Non-breast cancer-related death (13)
Local recurrence (11)
Contralateral new primary (5)
Alive with metastatic disease (1)
New cancer (1)

Patient-related (115)
Moved out of area (15)
Withdrawal consent (11)
Transport issues (14)
Not known (5)
Social issues including work commitment/carer (14)
Unable to contact (11)
Elective reconstruction/implants (3)
Unwell to attend (9)
Patient choice: reason not stated (33)

CONTROL
404 allocated standard RT

167 withdrawn

Tumour-related (54)
Breast cancer-related death (17)
Non-breast cancer-related death (20)
Local recurrence (6)
Contralateral new primary (5)
Alive with metastatic disease (2)
New cancer (4)

INTERVENTION
411 allocated IMRT

183 withdrawn

Patient-related (129)
Moved out of area (13)
Withdrawal consent (16)
Transport issues (19)
Not known (6)
Social issues including work commitment/carer (19)
Unable to contact (10)
Elective reconstruction/implants (6)
Unwell to attend (9)
Patient choice: reason not stated (31)
On MVA, the benefits of IMRT over standard RT (control arm) were maintained for both overall cosmesis (OR 0.65, 95% CI 0.44-0.98, p=0.038) and skin telangiectasia (OR 0.57, 95% CI 0.34-0.95; p=0.031). Large breast volume (p=0.02), poorer baseline surgical cosmesis (p<0.001) and tumour bed boost (p=0.003) were also associated with sub-optimal overall cosmesis on the MVA. Skin telangiectasia was also associated with older age (p=0.005), post-operative breast infection (p<0.001), increasing breast volume (p<0.001) and tumour bed boost (p=0.023). The full details of the covariates included in the MVA are summarised in table 17 and 18.

Table 17: Final covariates included in the multivariate analysis (MVA) for skin telangiectasia

<table>
<thead>
<tr>
<th>Telangiectasia</th>
<th>Odds ratio</th>
<th>Standard error</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT group</td>
<td>0.57</td>
<td>0.15</td>
<td>0.031</td>
<td>0.34 – 0.95</td>
</tr>
<tr>
<td>Age</td>
<td>1.05</td>
<td>0.17</td>
<td>0.005</td>
<td>1.01 – 1.08</td>
</tr>
<tr>
<td>Post-op infection</td>
<td>3.53</td>
<td>0.91</td>
<td>0.000</td>
<td>1.97 – 5.71</td>
</tr>
<tr>
<td>Breast volume</td>
<td>1.001</td>
<td>0.00022</td>
<td>0.000</td>
<td>1.0009-1.0018</td>
</tr>
<tr>
<td>Tumour bed boost</td>
<td>1.86</td>
<td>0.51</td>
<td>0.023</td>
<td>1.08 – 3.19</td>
</tr>
</tbody>
</table>

Table 18: Final covariates included in the multivariate analysis (MVA) for final cosmesis

<table>
<thead>
<tr>
<th>Final cosmesis</th>
<th>Odds ratio</th>
<th>Standard error</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT group</td>
<td>0.65</td>
<td>0.13</td>
<td>0.038</td>
<td>0.44 – 0.98</td>
</tr>
<tr>
<td>Breast volume</td>
<td>1.0004</td>
<td>0.00018</td>
<td>0.020</td>
<td>1.000067-1.00078</td>
</tr>
<tr>
<td>Surgical cosmesis</td>
<td>8.64</td>
<td>1.57</td>
<td>0.000</td>
<td>6.04 – 12.34</td>
</tr>
<tr>
<td>Tumour bed boost</td>
<td>1.89</td>
<td>0.40</td>
<td>0.003</td>
<td>1.25 – 2.86</td>
</tr>
</tbody>
</table>
5.4.3 Impact of pre-radiotherapy surgical cosmesis on late toxicity endpoints

Patients with moderate to poor baseline surgical cosmesis more frequently developed sub-optimal final cosmesis (OR 8.15, 95% CI 6.09-10.92; p<0.001), tumour bed induration (OR 1.80, 95% CI 1.44-2.26; p<0.001) and photographically assessed breast shrinkage (OR 1.54, 95% CI 1.21-1.96; p<0.001) at five years in the study.

5.4.4 Loco-regional recurrence (LRR) and Overall survival (OS)

There was no statistically significant difference in five years LRR rates and OS rates between the randomised patients (control: 404 patients and IMRT: 410 patients). The five-year LRR rates for the control and IMRT arms were 2.56% and 1.35% respectively; p=0.36 (figure 16). The five years OS rates for the control and IMRT arms were 92.5% and 91.7% respectively; p=0.88.
5.5 Discussion

5.5.1 Late breast toxicity endpoints

This large single-centre randomised trial confirms that improved dose homogeneity with IMRT decreases clinician-assessed late breast tissue toxicity. At five years, patients receiving IMRT had superior overall cosmesis and reduced risk of skin telangiectasia as compared to patients receiving standard radiotherapy. However, no significant difference was observed for photographically-assessed breast shrinkage or clinically-assessed breast oedema, breast pigmentation and breast induration.
To date, only two other randomised trials have compared standard radiotherapy with IMRT following BCS for early breast cancer. The multi-centre Canadian study compared acute toxicity for 331 patients randomised after BCS between IMRT (forward or inverse planned) and standard radiotherapy using wedges [18]. Patients in the IMRT arm experienced significantly less moist desquamation during or up to 6 weeks post RT as compared to standard treatment (31.2% versus 47.8% p=0.002). Women of all breast sizes were included in the study, and on MVA the use of IMRT and small breast size were significantly associated with decreased risk of moist desquamation. No significant difference was seen in the quality of life and pain scores between the two arms. Late toxicity has not yet been reported. A single centre study by Donovan et al [20] randomised 306 patients between forward planned IMRT and standard radiotherapy. Of the 240 patients evaluated at 5 years, patients who received standard radiotherapy were 1.7 times more likely to develop any change in breast appearance on photographic assessment (95% CI 1.2-2.5; p=0.008) as compared to patients treated with IMRT. In addition, fewer patients developed palpable induration in the centre of the breast, pectoral fold, infra-mammary fold and boost site with IMRT. Some retrospective case-matched studies have also compared standard radiotherapy with IMRT for breast cancer (table 19). Most have reported on acute toxicities alone apart from the William Beaumont series, which showed reduced breast oedema and skin telangiectasia with IMRT at five years [151].

Fewer patients developed breast induration with IMRT in the Donovan study [20], yet a similar reduction in induration was not seen in the interventional arm of the larger Cambridge Breast IMRT trial. The different entry criteria for the two trials may explain these dissimilar results. In the Donovan et al. study, women were eligible if they were judged to be at higher than average risk of radiation-induced toxicity
based on breast size and/or breast shape. The mean percentage breast volumes receiving >105% prescribed dose between standard and IMRT arm were 11.7% versus 1% respectively [152]. In contrast, women of all breast sizes were eligible for the Cambridge Breast IMRT trial, if their V107 was ≥ 2cm³ on a standard radiotherapy plan. The mean percentage breast volumes receiving >107% prescribed dose was only 2.9% in the control arm of the trial which decreased to 0.6% with IMRT [21]. It is also plausible that these dissimilar results are due to the subjective nature of clinical assessment, with different interpretation of induration between clinicians of the two studies.
<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients (Median Follow up)</th>
<th>Acute toxicity</th>
<th>Late toxicity</th>
</tr>
</thead>
</table>
| Freedman et al [19] | 804 (Not reported)                | a. Reduced risk of Grade 2-3 acute dermatitis with IMRT (52% versus 75%; p<0.0001)  
  b. Total time spend with Grade 2-3 dermatitis reduced with IMRT | Not reported                                                                  |
| Morganti et al [153]| 332 IMRT (24 months) Standard (42 months) | a. Lower Grade 2-3 skin toxicity in MARA-1 arm as compared to C-RT (14.1% versus 36.7%)  
  b. Higher Grade 2-3 skin toxicity in the MARA-2 arm as compared to C-RT (47.1% versus 36.7%) ** | Not reported                                                                  |
| McDonald et al [154]| 240 IMRT (6-3 years) Standard (7-5 years) | Reduced risk of Grade 2-3 skin toxicity with IMRT (39% versus 52%; p=0.047)          | Insufficient data to report on late cosmesis.                                      |
| Horsolia et al [151]| 172 IMRT (4-6 years) Standard (5 years) | Reduced risk of Grade 2-3 dermatitis, breast oedema and hyper-pigmentation (p<0.001) with IMRT | a. Reduced breast oedema (1% versus 25% p<0.001) and trend towards reduced hyper-pigmentation with IMRT  
  b. No difference on overall cosmetic score |
| Freedman et al [155]| 133 (Not reported)                | Reduced risk of moist desquamation with IMRT (21% versus 38%; p=0.001)              | Not reported                                                                  |
| Freedman et al [155]| 133 (Not reported)                | Reduced risk of moist desquamation with IMRT (21% versus 38%; p=0.001)              | Not reported                                                                  |

* 60.4Gy in 32 fractions over 6-4 weeks (C-RT) compared with 44Gy in 16 fractions over 3.2 weeks (MARA-1)  
** 60.4Gy in 32 fractions over 6-4 weeks (C-RT) compared with 60Gy in 25 fractions over 5 weeks (MARA-2)
The current study found tumour bed boost as an independent risk factor for sub-optimal cosmesis and skin telangiectasia, as previously shown in the EORTC 22881-10882 “boost versus no boost” trial [12]. Large breasted women more frequently develop late breast tissue toxicity and this has been linked to their sub-optimal dosimetry [156]. The current study found large breast volume as a risk factor for sub-optimal cosmesis and skin telangiectasia, independent of dose inhomogeneity. Similar results were also seen in the UK FAST hypofractionated trial at two-year follow up [123]. The FAST Trialists group postulated that in large breasted women, the major component of the breast is adipose tissue, which is perhaps more sensitive to the effects of radiotherapy and hence more likely to develop late toxicity.

5.5.2 Baseline surgical cosmesis and late breast toxicity

This study also highlights the importance of optimal surgical cosmesis as patients with moderate-poor surgical cosmesis are more likely to develop breast shrinkage, breast induration and sub-optimal final cosmesis. The effects of surgical methods and technique on late breast toxicity will be discussed further in chapter 7.

5.5.3 Effect of IMRT on local control rates

The local control and survival rates with both standard radiotherapy and IMRT are excellent. It is generally accepted that simple IMRT, which removes regions of unwanted high dose should not impact on local control and/or survival rates. Therefore, this study was not intended to detect a difference in local control and/or survival rates between standard radiotherapy and IMRT. However, it has been
postulated that removing hot-spots with IMRT can lead to dose de-escalation especially to the skin, and a theoretical increased risk of local relapse [146]. At 5 years, there was no statistical difference in LRR and OS rates between the randomised patients of the study. In addition, no difference in the contralateral breast cancer incidence was seen between the control and IMRT arm at five years in the study (5 cases each).

5.6 Limitations

The potential benefits of IMRT may have been underestimated as a significant number of patients were withdrawn from the five-year analysis. The routine clinical follow up of patients’ post radiotherapy was based at their regional referring hospitals and many patients turned down their five-year trial appointment at Cambridge due to travel difficulties, social issues and personal choice (see CONSORT diagram). Patients were also withdrawn from the analysis due to cancer-related factors including local or systemic relapse, new cancer or death. The referral hospitals were contacted for information on loco-regional relapse, metastasis and survival but data on late breast tissue toxicity was not available routinely.

5.7 Conclusions

This study confirms that improved dose homogeneity with IMRT translates into superior overall cosmesis and reduces the risk of skin telangiectasia five years following breast radiotherapy. The postulated increase risk of local cancer recurrence with IMRT was also unfounded. Although breast IMRT has been implemented by many centres, there has not been universal adoption of this
technique to date. These results should act as an evidence-based lever for change for radiotherapy centres that are yet to implement breast IMRT. In addition, surgical cosmesis should be optimised prior to radiotherapy delivery, as this also has a significant effect on late breast toxicity and overall cosmesis.

5.8 Chapter contributions

Dr Charlotte Coles is the Principal investigator for the Cambridge Breast IMRT trial and was responsible for the study concept and design. I am grateful for the Cambridge breast IMRT trial group for giving me the opportunity to be part of the trial group and allowing unlimited access to the trial database. Some other individuals who supported this work include

Gillian Barnett & Wendi Qian: for their assistance with the statistical analysis
Tony Geater: for assisting with the figure 13
Richard Hardy: for assisting with the trial database
Jenny Wilkinson (Cambridge IMRT trial radiographer): for her constant support and data collection

I was responsible for collecting some of the trial data and cleaning up the database for statistical analysis. I was involved in the photographic scoring of cosmetic outcome for the trial which is the primary endpoint of the study. The statistical analysis was supported by Gillian Barnett and Wendi Qian and I was responsible for data analysis and interpretation of statistical results. I wrote the original manuscript with guidance from Dr Charlotte Coles which was subsequently published in the peer reviewed Journal of Clinical Oncology (appendix).
6. Patient reported outcome measures (PROMs) with Intensity modulated radiotherapy (IMRT) in Breast cancer

* This work has been published as an original article in Radiotherapy & Oncology in 2014 (Appendix)

6.1 Introduction

This chapter address the important issue of the effects of intensity modulated radiotherapy in breast cancer on treatment complications as reported by patients.

6.1.1 What is patient reported outcome measures (PROMs)?

Clinician-based assessment tools including physical examination and/or photographic assessment are the most commonly used methods to score and report on breast radiotherapy toxicity [147, 149, 150]. Though useful, these assessments do not take into consideration the views and concerns of the patients. Patient-reported outcome measures (PROMs) provides patients’ perception of their own health condition and treatment toxicity. It involves the use of a self-administered questionnaire by the patient themselves or via interviews.

6.1.2 The use of PROMs in breast radiotherapy

Most patients now survive their breast cancer and some encounter long term treatment associated toxicity. Late complications post-radiotherapy negatively impacts on patients psycho-social well-being [15] and is an important cancer survivorship issue. As the patient is most entitled to judge the extent of her
treatment toxicity, the benefits of any intervention to reduce treatment associated toxicity (including IMRT) should also be assessed using PROMs.

6.1.3 Aims of this work

In this chapter, I examine the following questions within the context of the large Cambridge Breast IMRT trial [21]:

a. Does the correction of radiation dose-inhomogeneity using a simple method of forward-planned IMRT translate into improvement in PROMs at five years post-radiotherapy?

b. What other clinical factors influence PROMs at five years post-radiotherapy?

c. What is the trend of different PROMs domains over a five-year period post-surgery and radiotherapy?

6.2 Hypothesis

This chapter addresses the hypothesis that the improvement in dose inhomogeneity with the use of IMRT will improve PROMs at 5 years.

6.3 Materials and methods

6.3.1 Cambridge Breast IMRT trial

The details of the trial including the eligibility criteria, randomisation method and radiotherapy techniques have been described in chapter 5. All patients enrolled in
the trial were approached to participate in the PROMs study. The participation into the PROMs study was voluntary.

6.3.2 Patient reported outcome measures (PROMs) tools

6.3.2.1 European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30)

The EORTC QLQ-C30 is an integrated system for assessing the quality of life of cancer patients [157, 158]. It includes five functional scales, three symptom scales, a global health status and six single items (appendix). This work only includes the use of global health status (GHS) generated from the EORTC QLQ-C30 to provide a summary of patients’ quality of life when considering breast related toxicity. The questionnaire was completed by patients at baseline (post-surgery & pre-radiotherapy), 6 months, 2 years and 5 years after completion of radiotherapy.

6.3.2.2 European Organization for Research and Treatment of Cancer breast cancer module (EORTC QLQ-BR23)

The breast cancer module incorporates five multi-item scales to assess systemic therapy side effects, arm symptoms, breast symptoms, body image and sexual functioning [157, 158]. In addition, single items assess sexual enjoyment, hair loss and future perspective (appendix). This work includes the use of four breast symptoms: (1) skin problems on or in the area of affected breast, (2) pain in the area of affected breast, (3) oversensitivity in the area of affected breast and (4) swelling in the area of affected breast. The questionnaire was completed by patients at baseline (pre-radiotherapy), 6 months, 2 years and 5 years after completion of radiotherapy.
6.3.2.3 Breast radiotherapy specific questions

Four post-radiotherapy breast specific questions were added to the patients’ questionnaire to judge the direct effects of radiotherapy on the breast tissue: (1) change in skin appearance in the area of the affected breast since radiotherapy (2) overall change in breast appearance since radiotherapy (3) firmness to touch of the affected breast since radiotherapy and (4) reduction in size of the affected breast since radiotherapy. The changes were scored in a four-point likert scale (none, a little, quite a bit and very much). I classified “quite a bit” as moderate and “very much” as severe toxicity for the analysis. The breast radiotherapy specific questionnaire was completed by patients at 6 months, 2 years and 5 years after completion of radiotherapy.

The PROMs questionnaire was directly mailed to all participating patients except in cases of cancer recurrence, new cancer diagnosis, further breast surgery or patient refusal.

6.3.3 Statistical analysis

6.3.3.1 Benefits of IMRT versus standard radiotherapy at 5 year

The benefits of simple IMRT over standard radiotherapy were assessed by using (a) standard t-test for global health score and (b) logistic regression analysis for each breast related symptom, to compare the proportion of patients reporting moderate-severe (quite a bit/very much) changes for the four breast symptom questions (BR23) and four additional radiotherapy-specific questions at five years.
6.3.3.2 Factors affecting PROMs at 5 years

In chapter 5, I demonstrated that the use of IMRT, age, post-operative infection, baseline surgical cosmesis and tumour bed boost independently affected clinicians assessed toxicity at five years. The effect of these variables on each PROMs domain were analysed using the multivariate logistic regression analysis.

6.3.3.3 Trend of PROMs domains over time

Due to the longitudinal nature of the data, collected at baseline, 6 months, 2 years and 5 years, repeated mixed models were applied to explore the time trend for global health score and the proportion of patients reporting moderate-severe breast related symptoms.

6.4 Results

727/815 (89%) patients completed the baseline PROMs study questionnaire. 684/815 (84%) patients completed the questionnaire at 6 months, 658/815 (81%) at 2 years and 498/815 (61%) at five years.

6.4.1 Patients demographics

The baseline patient, tumour and treatment characteristics of the 498 patients who completed the PROMs questionnaire at five years are summarised in table 20. All characteristics are well balanced between the two groups including baseline surgical cosmesis, baseline HADS score and baseline body image score (table 20), with the exception that more patients in the standard radiotherapy group received SCF
radiotherapy (4.7% versus 1.6%; p=0.05). The baseline global health score and breast symptom score (BR23) were also similar between the two groups.

The reasons for patients’ non-participation in the PROMs study at five years were also similar between the two groups and summarised in table 21.

Table 20: Demographics for patients who completed the PROMs questionnaire at five years

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control arm (n=254)</th>
<th>IMRT arm (n=244)</th>
<th>P value for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>60 (33-80)</td>
<td>59 (34-78)</td>
<td>0.18</td>
</tr>
<tr>
<td>Tumour size (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>15.9 (0-40)</td>
<td>16.4 (2-45)</td>
<td>0.50</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCIS</td>
<td>25 (9.8)</td>
<td>25 (10.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Ductal carcinoma</td>
<td>167 (65.8)</td>
<td>163 (66.8)</td>
<td></td>
</tr>
<tr>
<td>Lobular carcinoma</td>
<td>23 (9.1)</td>
<td>24 (9.8)</td>
<td></td>
</tr>
<tr>
<td>Other invasive histology</td>
<td>28 (11.0)</td>
<td>26 (10.7)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>11 (4.3)</td>
<td>6 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Histological grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>56 (25.2)</td>
<td>45 (20.7)</td>
<td>0.23</td>
</tr>
<tr>
<td>Grade 2</td>
<td>120 (54.0)</td>
<td>114 (52.5)</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>46 (20.7)</td>
<td>56 (25.8)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0)</td>
<td>2 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Axillary surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>22 (8.7)</td>
<td>24 (9.8)</td>
<td>0.35</td>
</tr>
<tr>
<td>Yes</td>
<td>230 (90.6)</td>
<td>220 (90.2)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (0.8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------</td>
<td>-------</td>
<td>-----</td>
</tr>
<tr>
<td><strong>Nodal status</strong></td>
<td></td>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>Positive</td>
<td>38 (15.0)</td>
<td>35 (14.4)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>192 (75.6)</td>
<td>184 (75.4)</td>
<td></td>
</tr>
<tr>
<td>Not assessed (DCIS)</td>
<td>21 (8.2)</td>
<td>23 (9.4)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (1.2)</td>
<td>2 (0.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Breast volume (cm³)</strong></td>
<td></td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>Mean (range)</td>
<td>1320.5 (329-3151)</td>
<td>1254.4 (285-3436)</td>
<td></td>
</tr>
<tr>
<td><strong>Tumour bed boost</strong></td>
<td></td>
<td></td>
<td>0.27</td>
</tr>
<tr>
<td>Yes</td>
<td>146 (57.5)</td>
<td>152 (62.3)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>108 (42.5)</td>
<td>92 (37.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Radiotherapy (axilla)</strong></td>
<td></td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>Yes</td>
<td>2 (0.8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>252 (99.2)</td>
<td>244 (100)</td>
<td></td>
</tr>
<tr>
<td><strong>Radiotherapy (SCF)</strong></td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Yes</td>
<td>12 (4.7)</td>
<td>4 (1.6)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>242 (95.3)</td>
<td>240 (98.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Endocrine therapy</strong></td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>Yes</td>
<td>214 (84.3)</td>
<td>195 (79.9)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>37 (14.6)</td>
<td>48 (19.7)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (1.2)</td>
<td>1 (0.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>Yes</td>
<td>52 (20.5)</td>
<td>47 (19.3)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>197 (77.5)</td>
<td>196 (80.3)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (2.0)</td>
<td>1 (0.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Anxiety score</strong></td>
<td></td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>0-7</td>
<td>179 (70.5)</td>
<td>164 (67.2)</td>
<td></td>
</tr>
<tr>
<td>8-10</td>
<td>37 (14.6)</td>
<td>42 (17.2)</td>
<td></td>
</tr>
<tr>
<td>≥11</td>
<td>18 (7.1)</td>
<td>16 (6.6)</td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>20 (7.9)</td>
<td>22 (9.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Depression score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>Standard RT arm</td>
<td>IMRT arm</td>
<td>p-value</td>
</tr>
<tr>
<td>-------</td>
<td>----------------</td>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td>0-7</td>
<td>219 (86.2)</td>
<td>206 (84.4)</td>
<td>0.86</td>
</tr>
<tr>
<td>8-10</td>
<td>11 (4.3)</td>
<td>10 (4.1)</td>
<td></td>
</tr>
<tr>
<td>≥11</td>
<td>4 (1.6)</td>
<td>6 (2.5)</td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>20 (7.9)</td>
<td>22 (9.0)</td>
<td></td>
</tr>
</tbody>
</table>

**Baseline Body Image Score (BIS)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Standard RT arm</th>
<th>IMRT arm</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (range)</td>
<td>3.4 (0-24)</td>
<td>3.7 (0-30)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

**Baseline surgical cosmesis**

<table>
<thead>
<tr>
<th>Group</th>
<th>Standard RT arm</th>
<th>IMRT arm</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>113 (44.5)</td>
<td>98 (40.2)</td>
<td>0.45</td>
</tr>
<tr>
<td>2</td>
<td>77 (30.3)</td>
<td>80 (32.8)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>29 (11.4)</td>
<td>23 (9.4)</td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>35 (13.8)</td>
<td>43 (17.6)</td>
<td></td>
</tr>
</tbody>
</table>

Data in parentheses are percentages

**Table 21 : Reasons for patients’ non-participation in patient reported outcome measures (PROMs) study at five years**

<table>
<thead>
<tr>
<th>Reason for non-participation</th>
<th>Standard RT arm</th>
<th>IMRT arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not enter PROMs study</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Death</td>
<td>31</td>
<td>34</td>
</tr>
<tr>
<td>Metastatic disease (alive)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other cancer</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Moved out of area</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Too unwell with other co-morbidities</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Mastectomy/reconstruction</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Patient choice: reason not stated</td>
<td>70</td>
<td>77</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>150</strong></td>
<td><strong>166</strong></td>
</tr>
</tbody>
</table>
6.4.2 5-year PROMs in Control arm (Standard radiotherapy) versus Intervention arm (IMRT)

There was no significant difference in five-year “global health scores” between the two groups with the mean GHS scores of 78.7 and 78.2 for standard radiotherapy and simple IMRT groups respectively (p=0.80). No patient in the control group (0%) and 2/240 (1.9%) patients in the IMRT group reported moderate-severe “swelling in area of affected breast” at five years. The proportion of patients reporting moderate-severe changes for other breast specific PROMs domain at five years was small (4.2%-17.7%). There was no significant difference in any PROMs domain with simple IMRT, as compared to standard radiotherapy at five years in the study (figure 17).

Figure 17: Forrest Plot of moderate-severe toxicity assessed using PROMs at five years between standard radiotherapy (control) and simple IMRT

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IMRT Events Total</th>
<th>Control Events Total</th>
<th>Odds Ratio, 95% CI</th>
<th>Odds Ratio, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain in area of affected breast</td>
<td>14 240</td>
<td>13 248</td>
<td>1.12 [0.62, 2.43]</td>
<td></td>
</tr>
<tr>
<td>Oversensitive in area of affected breast</td>
<td>12 240</td>
<td>12 248</td>
<td>1.94 [0.46, 2.35]</td>
<td></td>
</tr>
<tr>
<td>Skin problem in area of affected breast</td>
<td>10 240</td>
<td>11 249</td>
<td>0.94 [0.39, 2.28]</td>
<td></td>
</tr>
<tr>
<td>Swelling in area of affected breast</td>
<td>2 241</td>
<td>0 248</td>
<td>5.10 [0.25, 107.75]</td>
<td></td>
</tr>
<tr>
<td>Change in skin appearance since RT</td>
<td>13 208</td>
<td>11 246</td>
<td>1.23 [0.54, 2.81]</td>
<td></td>
</tr>
<tr>
<td>Change in breast appearance since RT</td>
<td>41 232</td>
<td>30 231</td>
<td>1.44 [0.86, 2.40]</td>
<td></td>
</tr>
<tr>
<td>Breast shrinkage since RT</td>
<td>31 251</td>
<td>31 230</td>
<td>0.98 [0.58, 1.70]</td>
<td></td>
</tr>
<tr>
<td>Breast hardness since RT</td>
<td>15 233</td>
<td>21 233</td>
<td>0.89 [0.35, 2.38]</td>
<td></td>
</tr>
</tbody>
</table>

6.4.3 Clinical factors affecting PROMs at five years post radiotherapy

I found post-operative infection (yes versus no) as an independent risk factor for “change in breast appearance” (odds ratio (OR)=1.84, 95% CI=1.03 to 3.3, p=0.04),
“breast hardness” (OR=2.38, 95%CI=1.1 to 5.0, p=0.02), “pain in affected breast” (OR=2.5, 95%CI=1.1 to 5.9, p=0.03) and “oversensitivity in affected breast” (OR=5.4, 95%CI=2.3 to 12.6, p<0.0001) at five years. Large breast volume as a continuous variable was an independent risk factor for “change in skin appearance” (p=0.003), “breast hardness” (p=0.008), “pain in affected breast” (p=0.005) and “skin problem in the affected breast” (p=0.013) at five years. Young age and poor baseline cosmesis also affected some PROMs domains. These results of multivariate logistic regression analyses are summarised in Tables 22 and 23.
### Table 22: Multivariate analysis for the BR23 questions

<table>
<thead>
<tr>
<th>PROMs Question</th>
<th>IMRT</th>
<th>Age</th>
<th>Post-operative infection</th>
<th>Breast volume</th>
<th>Baseline surgical cosmetics</th>
<th>Breast RT Boost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain in affected breast</td>
<td>0.57</td>
<td>0.33</td>
<td><strong>0.03 (2.5; 1.1-5.9)</strong></td>
<td><strong>0.005 (0.99; 0.99-1.0)</strong></td>
<td>0.13</td>
<td>0.17</td>
</tr>
<tr>
<td>Swelling in area of affected breast</td>
<td>0.95</td>
<td>0.88</td>
<td>0.96</td>
<td>0.45</td>
<td>0.97</td>
<td>0.96</td>
</tr>
<tr>
<td>Oversensitivity in area of the affected breast</td>
<td>0.84</td>
<td>0.82</td>
<td>&lt;<strong>0.0001 (5.4; 2.3-12.6)</strong></td>
<td>0.66</td>
<td>0.57</td>
<td>0.11</td>
</tr>
<tr>
<td>Skin problem on affected breast</td>
<td>0.99</td>
<td>0.88</td>
<td>0.07</td>
<td><strong>0.013 (0.99; 0.99-1.0)</strong></td>
<td>0.89</td>
<td>0.82</td>
</tr>
</tbody>
</table>

*Odds ratios are given only for p-value <0.05*
Table 23: Multivariate analysis for Breast radiotherapy specific questions

<table>
<thead>
<tr>
<th>PROMs Question</th>
<th>IMRT</th>
<th>Age</th>
<th>Post-operative infection</th>
<th>Breast volume</th>
<th>Baseline surgical cosmesis</th>
<th>Breast RT Boost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in skin appearance since RT</td>
<td>0.54</td>
<td>0.03 (1.05; 1.0-1.1)</td>
<td>0.35</td>
<td>0.003 (0.99; 0.99-1.0)</td>
<td>0.19</td>
<td>0.18</td>
</tr>
<tr>
<td>Change in Breast appearance since RT</td>
<td>0.29</td>
<td>0.44</td>
<td>0.04 (1.84; 1.03-3.3)</td>
<td>0.06</td>
<td>0.18</td>
<td>0.06</td>
</tr>
<tr>
<td>Breast Hardness since RT</td>
<td>0.36</td>
<td>0.03 (1.05; 1.0-1.1)</td>
<td>0.02 (2.38; 1.1-5.0)</td>
<td>0.008 (0.99; 0.99-1.0)</td>
<td>0.04 (0.45; 0.2-0.98)</td>
<td>0.27</td>
</tr>
<tr>
<td>Breast shrinkage since RT</td>
<td>0.6</td>
<td>0.07</td>
<td>0.29</td>
<td>0.12</td>
<td>0.19</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Odds ratios are given only for p-value <0.05
6.4.4 Trend of different PROMs domains over a five-year period post-surgery

There was no difference in PROMs time trends between standard radiotherapy group and simple IMRT group (results not shown), and hence time trend data for the whole patient cohort has been reported together.

6.4.4.1 Time trend for Global health score

A significant improvement was seen in “global health score” over five years (p=0.009). The mean pre-RT baseline global health score was 76.3, which improved to 76.7, 78.6 and 78.5 at 6 months, 2 years and 5 years respectively.

6.4.4.2 Time trend for four breast symptom questions (BR23)

A trend for improvement was also seen over time for the breast symptoms questions (BR23). Patients reported on the breast symptoms questions (BR23) at baseline (pre-RT), 6 months, 2 years and 5 years after completion of radiotherapy. As compared to baseline pre-radiotherapy, more patients reported moderate-severe toxicity for all four breast symptoms at 6 months, which subsequently improved over time (p<0.0001) (figure 18). A large proportion of patients who reported moderate-severe toxicity at baseline reported no-mild change at successive time points (figure 19). On the contrary, only a small proportion of patients who reported no-mild changes at baseline subsequently reported moderate-severe toxicity (figure 19).
Figure 18: Time Trend for BR23 PROMs for patients with all four assessments

<table>
<thead>
<tr>
<th>Pain in affected Breast</th>
<th>Oversensitivity affected Breast</th>
<th>Skin Problem affected Breast</th>
<th>Swelling affected Breast</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Bar chart showing percentage of patients over time]</td>
<td>[Bar chart showing percentage of patients over time]</td>
<td>[Bar chart showing percentage of patients over time]</td>
<td>[Bar chart showing percentage of patients over time]</td>
</tr>
<tr>
<td>Follow up time point (in months)</td>
<td>Follow up time point (in months)</td>
<td>Follow up time point (in months)</td>
<td>Follow up time point (in months)</td>
</tr>
</tbody>
</table>
Figure 19: Time Trend for BR23 PROMs

<table>
<thead>
<tr>
<th></th>
<th>Pain in affected Breast</th>
<th>Oversensitivity affected Breast</th>
<th>Skin Problem affected Breast</th>
<th>Swelling affected Breast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time trend for patients with not at all / a little score at baseline</td>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
<td><img src="image3.png" alt="Graph" /></td>
<td><img src="image4.png" alt="Graph" /></td>
</tr>
<tr>
<td>Time trend for patients with quite a lot / very much score at baseline</td>
<td><img src="image5.png" alt="Graph" /></td>
<td><img src="image6.png" alt="Graph" /></td>
<td><img src="image7.png" alt="Graph" /></td>
<td><img src="image8.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

Follow up time point (in months)
6.4.4.3 Time trend for four breast radiotherapy specific questions

Patients reported on the breast RT-specific questions at 6 months, 2 years and 5 years after completion of radiotherapy. The proportion of patients reporting moderate-severe “change in skin appearance since RT” and “breast hardness since RT” reduced over time (p<0.0001) (figure 20). No significant change was seen in the proportion of patients reporting “change in breast appearance since RT” (p= 0.14) and “breast shrinkage since RT” (p=0.47). For patients reporting moderate-severe toxicity at 6 months, there was a gradual decrease in the proportion of patients reporting moderate-severe toxicity at successive time points (figure 21). Only a small proportion of patients who reported no-mild changes at 6 months subsequently reported moderate-severe toxicity (figure 21).
Figure 20: Time trend for Breast RT PROMs for patients with all four assessments

<table>
<thead>
<tr>
<th>Change in Breast appearance</th>
<th>Breast Hardness</th>
<th>Breast Shrinkage</th>
<th>Change In Skin appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of patients</td>
<td>Percentage of patients</td>
<td>Percentage of patients</td>
<td>Percentage of patients</td>
</tr>
<tr>
<td>Follow up time point (in months)</td>
<td>Follow up time point (in months)</td>
<td>Follow up time point (in months)</td>
<td>Follow up time point (in months)</td>
</tr>
</tbody>
</table>
Figure 21: Time Trend for Breast RT PROMs

<table>
<thead>
<tr>
<th>Change in Breast appearance</th>
<th>Breast Hardness</th>
<th>Breast Shrinkage</th>
<th>Change in Skin appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of patients</td>
<td>Percentage of patients</td>
<td>Percentage of patients</td>
<td>Percentage of patients</td>
</tr>
</tbody>
</table>

**Time trend for patients with not at all/a little score at 6 months**

**Time trend for patients with quite a lot/very much score at 6 months**

<table>
<thead>
<tr>
<th>Follow up time point (in months)</th>
<th>Follow up time point (in months)</th>
<th>Follow up time point (in months)</th>
<th>Follow up time point (in months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of patients</td>
<td>Percentage of patients</td>
<td>Percentage of patients</td>
<td>Percentage of patients</td>
</tr>
</tbody>
</table>
6.5 Discussion

6.5.1 5-year PROMs between standard radiotherapy and simple IMRT

In Chapter 5, I had demonstrated that the use of simple IMRT improves overall breast cosmesis and reduces the risk of skin telangiectasia as compared to standard radiotherapy using clinicians’ assessment. I anticipated that an improvement in dose homogeneity with simple IMRT would also translate into an improvement in PROMs. However, this study could not demonstrate the benefits of simple IMRT over standard radiotherapy using four breast symptom questions and four breast radiotherapy-specific questions at five years.

There are several possible explanations for these results. Both clinician and patient assessment can be subjective in nature. In this study, many clinicians-based assessments were done using clinical photographs, where a panel of three multidisciplinary members were present at any one time during toxicity scoring on clinical photographs. The interobserver variability of multidisciplinary assessment has previously been validated [109], suggesting that clinicians’ assessment can be made objective in nature. On the other hand, PROMs are often more subjective in nature, i.e. how objective cosmesis/toxicity is perceived and felt by the patient and may not be concordant with clinician assessment [159]. Using clinician-based assessments, moderate-severe breast toxicities was reported quite frequently (range 3-49% for different endpoints) at 5 years (chapter 5). In comparison, the proportion of patients reporting moderate-severe breast toxicity at five years was smaller, ranging from 0%-17.7% for different endpoints. It is possible that the lower PROMs toxicity rates reduced the power of the study to demonstrate the advantages of
simple IMRT over standard RT. It is also possible that the PROMs questions (BR23 breast symptom and RT-specific questions) used in the current study are not as sensitive as clinicians’ assessment to differentiate small differences in breast RT toxicity outcomes. In the Cambridge Breast IMRT trial, the mean percentage breast volumes receiving >107% prescribed dose was only 2.9% in the control arm which decreased to 0.6% with simple IMRT [21]. Similar PROMs questions were used in the START trials [160] and were found to be sensitive to radiotherapy fractionation changes. A significantly different dose was delivered to the whole breast between the different fractionated regimens in the START trial. One can only speculate that different whole breast dose lead to a larger dose difference then seen in the Cambridge Breast IMRT trial. This caused a bigger difference in toxicity, which was easier to detect using PROMs. A partial volume effect on the sensitivity of BR23 and breast RT-specific questions could also explain why no differences were seen between the two study arms using PROMs in the current study.

To date, no randomised trials have been able to demonstrate an improvement in PROMs with IMRT for breast cancer [18, 20]. The multi-centre Canadian study compared acute toxicity and quality of life (QOL) for 331 patients randomised after BCS between IMRT (forward or inverse planned) and standard RT using wedges [18]. The QOL data was assessed using EORTC QLQ-C30 and BR23 modules at baseline pre-radiotherapy, last week of radiotherapy and one month later. No significant difference in QOL was seen between the two treatment arms. The Donovan et al [20] single centre study randomised 306 breast patients between forward planned IMRT and standard radiotherapy and collected QOL data at baseline pre-radiotherapy, 1, 2 and 5 years post treatment using the EORTC QLQ-C30 and BR23 modules. In addition, patients were asked to evaluate breast hardness, pain and tenderness before radiotherapy and then at 2 and 5 years. Using photographic assessment at 5
years, patients receiving 2D standard radiotherapy were 1.7 times more likely to have change in breast appearance as compared to forward planned IMRT. Similar to the Cambridge Breast IMRT trial, after adjusting for baseline scores, no significant difference in PROMs was seen between the randomised patients by five years.

6.5.2 Clinical factors affecting PROMs at five years post radiotherapy

Clinical factors affecting PROMs after breast radiotherapy have not been widely investigated in the past. In this study, I found non-radiotherapy factors had the biggest impact on patient’s outcome. Post-operative infection and large breast volume were identified as the main risk factors to influence on patient reported breast toxicity in this study. In addition, young age and poor baseline surgical cosmesis were also found to influence on the symptoms of skin appearance and breast hardness.

6.5.3 Time trend for PROMs

A better understanding of how various PROMs domains progress over time can help patients to make informed decisions about their treatments. For clinicians, this information can also facilitate counselling of patients for radiotherapy, restructuring the support network and targeting intervention to patients, when they are most susceptible to treatment-related toxicity.

Patients reported worse toxicity than baseline for all four BR23 breast symptoms at 6 months in this study, which then improved over time (figure 18). These results most likely represent unresolved acute post-radiotherapy changes (skin erythema and
breast oedema), which are expected to improve over a period of time [161, 162]. On the other hand, long term radiotherapy changes like skin telangiectasia, breast shrinkage and breast induration addressed via the radiotherapy-specific questions are expected to progress over time [163]. However in this study, patients reported an improvement in skin appearance and breast hardness over time (figure 20). Only a non-significant increase was seen in the proportion of patients reporting moderate-severe breast shrinkage and change in breast appearance over time. There are several potential explanations for these results. The current study found that patients’ global health improved over time. It is likely that for some patients, as the global quality of life improves, “changes in the breast post radiotherapy” are no longer of significant concern. It is also plausible that at early follow up (6 months and 2 years), symptoms like breast hardness and change in breast appearance were over-reported, as patients found it difficult to differentiate between post-surgical and post-radiotherapy changes. Over time, some patients’ may under-report toxicity as they have previously discussed the risks and benefits of treatment and therefore anticipate some changes in the treated breast.

Other studies have also reported a similar trend with an improvement in radiotherapy associated PROMs over time [164, 165]. Whelan et al. [164] randomised 837 patients between adjuvant radiotherapy and no further treatment after breast conserving therapy and compared the proportion of patients troubled by “irritation of the skin”, “breast pain” and “upset by the breast appearance”. The proportion of patients reporting skin irritation and breast pain decreased over time (p=0.0001) with no significant difference between radiotherapy and no radiotherapy patients by two years. In addition, the proportion of patients reporting “upset by the breast appearance” was also similar between the randomised groups over two years. In the Australian Pulling Through Study, the prevalence of skin/tissue reaction to
radiotherapy decreased from 54% at 6 months to 8% at 6 years [165]. Heil et al [166] used the Breast Cancer Treatment Outcome Scale (BCTOS) to assess the functional, aesthetic and breast sensitivity status of 138 patients treated with BCS and adjuvant radiotherapy. At one year, no significant change was seen for aesthetic and functional status, whereas an improvement was seen in the breast sensitivity status (p<0.0001).

6.6 Limitations

All patients from the IMRT trial were offered participation in the PROMs study and no separate statistical power assessment was performed. Nevertheless, this study of more than 800 patients is one of the largest PROMs studies for early stage breast cancer patients. A significant number of patients did not complete their PROMs questionnaire at five years, which possibly affected the power of the study. This was predominantly due to patient choice or refusal, though patients were also excluded if they had cancer recurrence, new cancer diagnosis and/or further breast surgery. This is reasonable as there is significant deterioration in quality of life among patients with recurrent cancer and/or mastectomy [167, 168]. Overall, the baseline demographics for patients who completed their five-year questionnaire were similar and there was no trend to suggest that patients reporting problem at baseline or at 6 months more frequently participated at five years. The reasons for patients’ non-participation at five years were also not dissimilar between the two randomised groups (table 21).
6.7 Conclusions

Contrary to clinician-assessed outcome, the benefits of simple breast IMRT on PROMs could not be demonstrated. Non-radiotherapy factors including large breast volume, young age and surgical factors influence PROMs and hence, surgical factors should be optimised. It is reassuring to note that only a small proportion of patients reported moderate-severe breast changes post radiotherapy, and most PROMs improved over time.

6.8 Chapter contributions

Dr Charlotte Coles is the Principal investigator for the Cambridge Breast IMRT trial and was responsible for the study concept and design. I am grateful for the Cambridge breast IMRT trial group for giving me the opportunity to be part of the trial group and allowing unlimited access to the trial database. Some other individuals who supported this work include

Gillian Barnett, Leila Dorling & Wendi Qian: for their assistance with the statistical analysis

Richard Hardy: for assisting with the trial database

Jenny Wilkinson (Cambridge IMRT trial radiographer): for her constant encouragement and data collection

I was involved in collecting some of the trial data and cleaning up the database. All the quality of life questionnaire raw data was analysed and compiled by me for statistical analysis. The statistical analysis was supported by Gillian Barnett, Leila Dorling and Wendi Qian. I was responsible for interpretation of statistical results. I wrote the original manuscript with guidance from Dr Charlotte Coles which was
subsequently published in the peer reviewed Radiotherapy & Oncology journal (appendix).
7. Effects of surgical techniques on late breast tissue toxicity

* This work has been published as an original article in the European Journal of Surgical Oncology in 2012 (Appendix)

The 5 year results from the Cambridge Breast IMRT trial (chapter 5) confirmed that patients with sub-optimal baseline surgical cosmesis more frequently developed late breast tissue complications including sub-optimal final cosmesis, breast fibrosis and breast shrinkage. In this chapter, I describe how the surgical management of the tumour bed affects late breast tissue toxicity.

7.1 Introduction

7.1.1 What is a tumour bed?

Breast conserving surgery (BCS) involves resection of the tumour within a cylinder of tissue from subcutaneous fat down to pectoral muscle and including a clear radial margin of normal breast tissue that is tumour-free. The breast tissue adjacent to the site of the wide local excision is called the tumour bed.

7.1.2 Types of tumour bed closure techniques

There are two main approaches of managing the dead space left after tumour excision. One surgical approach involves simple skin closure anterior to the cavity, allowing for seroma fluid to accumulate in the tumour bed. The second approach involves obliteration of the tumour bed cavity by mobilisation of breast tissue from subcutaneous fat and underlying muscle to allow approximation and suturing of the breast tissue in layers from deep to superficial. Seroma fluid is less likely to
accumulate in the tumour bed with the full thickness closure [169]. There is currently no consensus among breast surgeons about the optimal surgical management of the tumour bed.

Advocates of both the standard closure and full thickness closure cite superior cosmesis in supporting their practice. It has been proposed that seroma collection with the standard closure technique is advantageous to the patient, as it preserves the normal tissue contour even after a large volume resection [170, 171]. The seroma is eventually replaced by scar tissue as the cavity consolidates. This approach has been widely advocated in surgical textbooks and is also supported by the National Surgical Adjuvant Breast Project workshops [2, 172-174]. Some authors argue, however that full thickness closure offers better cosmesis [175-179]. Apart from overall cosmesis, the type of surgical closure can also influence the rate of post-operative infection and haematoma formation. There is however limited literature associating the standard closure technique with an increased rate of post-operative infection or haematoma [180-182].

7.2 Methods

7.2.1 Study population

The study population consisted of 648 patients from the Cambridge Breast IMRT trial [21]. The full details of the trial have previously been reported in chapter 5. All patients had previously provided written consent for their data to be used for research purposes.
7.2.2 Assessment of surgical technique

During the trial recruitment phase, both standard and full thickness closure surgical techniques were used, with the majority of surgeons using the former method. The operation record was not collected as part of the trial protocol; a retrospective review of the operative notes was not useful as the type of closure was not stated in most cases. Therefore, the presence of a seroma at the time of radiotherapy planning was used as a surrogate for standard wound closure over the tumour bed.

7.2.3 Assessment of breast seroma

The clinical assessment of breast seroma is subjective and can be difficult to appreciate in patients with high body mass index (BMI) [183]. I used the radiotherapy planning CT scans in this study to define the breast seroma, as this method is more objective and independent of BMI. The seroma was identified on the axial CT images and graded as not visible/subtle or easily visible (Figure 22). All visible seroma were contoured on axial CT slices and the total seroma volume was recorded.

7.2.4 Outcome measures

7.2.4.1 Post-operative infection and haematoma

The data on post-operative infection and/or haematoma had been collected at the time of the patient’s radiotherapy planning CT scan. Post-operative infection was defined as skin redness which required antibiotic treatment. Post-operative haematoma was identified from surgical notes and/or medical correspondence.
Figure 22: Radiotherapy planning CT scan of two patients, one with breast seroma (right) and one with no seroma (left)

- **Breast Seroma**
  - Easily visible tumour bed seroma in the right breast
  - No tumour bed seroma in the left breast
7.2.4.2 Breast tissue toxicity assessment

The breast tissue toxicity (breast shrinkage, overall cosmesis, breast oedema, whole breast induration and tumour bed induration) were assessed using clinical assessments and serial photographs. The full details of these methods have been reported in chapter 5. In addition, the EORTC BR23 questionnaire was used to assess breast pain following radiotherapy [158].

7.2.5 Statistical analysis

7.2.5.1 Univariate and multivariate analysis

The statistical analysis was done using STATA version 10.1 (STATA statistical software, release10; Stata Corporation, College station, TX). Logistic regression was used to test for an association between presence or absence of tumour bed seroma and the development of post-operative infection or haematoma. The effect of seroma on the incidence of breast tissue toxicity was tested using polychotomous logistic regression, which enables analysis of the toxicity end-points as the dependent variables, and takes into account multiple ordered values. No numerical relationship is assumed between these grades; it is only assumed that lower grades correspond to milder reactions. Factors that were significantly associated with late toxicity following radiotherapy on univariate analysis (p < 0.1) from the previous reports (chapter 5) were included in the multivariate analysis.

While polychotomous logistic regression provides good power to detect an association between risk factors and late normal tissue toxicity, the parameters estimated do not have an easily interpretable meaning. In order to aid the interpretation, the endpoints were dichotomized. Hence, univariate and multivariate
analysis was performed using these dichotomized endpoints, i.e. dividing endpoints into two groups of no/mild toxicity and moderate/severe toxicity to obtain meaningful odds ratios.

7.2.5.2 Re-evaluation after exclusion of chemotherapy patients

Some patients received adjuvant chemotherapy after BCS and hence their radiotherapy planning CT scan was done 4-6 months post-surgery. Some of these patients may have had a seroma which resolved before their radiotherapy planning CT scan. Hence, the analysis was repeated after excluding these patients, to see if there was more of an effect on the measured endpoints.

7.3 Results

7.3.1 Baseline patient characteristics

The seroma was easily visible in 237/648 (36.6 %) patients. The median seroma volume was 2.8 cc (range 0-202 cc). The median time from surgery to RT for chemotherapy and non-chemotherapy patients was 222 days and 60 days respectively.

The baseline patient demographics and clinical characteristics are presented below in Table 26. The patients in the no/subtle seroma arm were relatively younger and more likely to be node positive, reflecting a higher risk group than the easily visible seroma group. This higher risk patient group was also more likely to have received adjuvant chemotherapy and a radiotherapy tumour bed boost.
Table 24: Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>No/subtle seroma (411)</th>
<th>visible seroma (237)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>57</td>
<td>60</td>
</tr>
<tr>
<td>DCIS</td>
<td>34/398 (8%)</td>
<td>28/231 (12%)</td>
</tr>
<tr>
<td><strong>AJCC staging</strong></td>
<td>368 patients</td>
<td>206 patients</td>
</tr>
<tr>
<td>T1N0</td>
<td>228 (62%)</td>
<td>152 (74%)</td>
</tr>
<tr>
<td>T2N0</td>
<td>62 (17%)</td>
<td>32 (16%)</td>
</tr>
<tr>
<td>T1N1</td>
<td>53 (14%)</td>
<td>15 (7%)</td>
</tr>
<tr>
<td>T2N1</td>
<td>25 (7%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td><strong>Location of tumour</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>27/392 (7%)</td>
<td>10/231 (4%)</td>
</tr>
<tr>
<td>Lower</td>
<td>12/392 (3%)</td>
<td>4/231 (2%)</td>
</tr>
<tr>
<td>Lower medial</td>
<td>25/392 (6%)</td>
<td>18/231 (8%)</td>
</tr>
<tr>
<td>Lower outer</td>
<td>50/392 (13%)</td>
<td>24/231 (10%)</td>
</tr>
<tr>
<td>Upper</td>
<td>26/392 (7%)</td>
<td>9/231 (4%)</td>
</tr>
<tr>
<td>Upper medial</td>
<td>70/392 (18%)</td>
<td>43/231 (19%)</td>
</tr>
<tr>
<td>Upper outer</td>
<td>182/392 (46%)</td>
<td>123/231 (53%)</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td>110/407 (27%)</td>
<td>12/234 (5%)</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>273/399 (68%)</td>
<td>147/232 (63%)</td>
</tr>
<tr>
<td>Aromatase inhibitor</td>
<td>28/399 (7%)</td>
<td>23/232 (10%)</td>
</tr>
<tr>
<td>Tumour boost</td>
<td>284/409 (69%)</td>
<td>123/237 (52%)</td>
</tr>
</tbody>
</table>
7.3.2 Post-operative infection and Haematoma

The overall rate of post-operative infection was 19.7%. It was more common in patients with visible seroma as compared to no/subtle seroma (26% vs.16%, p=0.004) (table 27). The overall rate of post-operative haematoma identified was 7.9%. It was also more common in patients with visible seroma as compared to no/subtle seroma (12% vs. 6%, p = 0.02). These results were similar after excluding patients with adjuvant chemotherapy (table 28).

Table 25 : Association between breast seroma and post-operative infection and haematoma

<table>
<thead>
<tr>
<th></th>
<th>No/Subtle seroma (%)</th>
<th>Visible seroma (%)</th>
<th>p value</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-operative infection</td>
<td>63/401 (15.7)</td>
<td>60/232 (25.8)</td>
<td>0.004</td>
<td>1.8 (1.2-2.7)</td>
</tr>
<tr>
<td>Post-operative haematoma</td>
<td>22/372(5.9)</td>
<td>23/196 (11.7)</td>
<td>0.02</td>
<td>2.1 (1.1-3.9)</td>
</tr>
</tbody>
</table>

Table 26 : Association between breast seroma and post-operative infection and haematoma after excluding adjuvant chemotherapy patients

<table>
<thead>
<tr>
<th></th>
<th>No/Subtle seroma (%)</th>
<th>Visible seroma (%)</th>
<th>p value</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-operative infection</td>
<td>47/293(16.0)</td>
<td>56/221(25.3)</td>
<td>0.01</td>
<td>1.8 (1.1-2.7)</td>
</tr>
<tr>
<td>Post-operative haematoma</td>
<td>14/268(5.2)</td>
<td>23/187(12.3)</td>
<td>0.008</td>
<td>2.5 (1.3-5.1)</td>
</tr>
</tbody>
</table>
7.3.3 2-year breast tissue toxicity

The results of univariate and multivariate analysis for the association between breast seroma and normal tissue toxicity at 2 years using dichotomized endpoints are summarised below in table 29. The results using polychotomous logistic regression led to identical conclusions. On univariate analysis, presence of easily visible breast seroma was associated with worse breast cosmesis, whole breast induration, tumour bed induration and breast oedema at 2 years. On multivariate analysis, the presence of easily visible seroma was associated with whole breast induration, tumour bed induration and breast oedema but was no longer associated with worse overall cosmesis. There was no significant association between the presence of seroma and the development of either breast shrinkage or breast pain at 2 years on univariate and multivariate analysis. These results were similar after excluding patients with adjuvant chemotherapy (table 30).
Table 27: Association between breast seroma and breast tissue toxicity at 2 years using dichotomized endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>No. of patients</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cosmesis</td>
<td>492</td>
<td>1.5</td>
<td>1.0-2.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Breast shrinkage assessed using serial photographs</td>
<td>491</td>
<td>1.1</td>
<td>0.7-1.6</td>
<td>0.58</td>
</tr>
<tr>
<td>Whole breast induration</td>
<td>536</td>
<td>1.6</td>
<td>1.1-2.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Tumour bed induration</td>
<td>536</td>
<td>1.5</td>
<td>1.1-2.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Breast oedema</td>
<td>537</td>
<td>1.6</td>
<td>0.98-2.4</td>
<td>0.06</td>
</tr>
<tr>
<td>Breast pain</td>
<td>487</td>
<td>0.85</td>
<td>0.4-1.7</td>
<td>0.65</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>No. of patients</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cosmesis</td>
<td>484</td>
<td>1.2</td>
<td>0.7-2.2</td>
<td>0.46</td>
</tr>
<tr>
<td>Breast shrinkage assessed using serial photographs</td>
<td>486</td>
<td>1.3</td>
<td>0.8-2.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Whole breast induration</td>
<td>488</td>
<td>1.6</td>
<td>1.1-2.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Tumour bed induration</td>
<td>478</td>
<td>1.6</td>
<td>1.1-2.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Breast oedema</td>
<td>513</td>
<td>1.7</td>
<td>1.01-3.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Breast pain</td>
<td>475</td>
<td>0.9</td>
<td>0.4-1.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Table 28: Association between breast seroma and breast tissue toxicity at 2 years using dichotomized endpoints after excluding chemotherapy patients

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>No. of patients</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cosmesis</td>
<td>400</td>
<td>1.8</td>
<td>1.2-2.7</td>
<td>0.006</td>
</tr>
<tr>
<td>Breast shrinkage assessed using serial photos</td>
<td>399</td>
<td>1.2</td>
<td>0.8-1.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Whole breast induration</td>
<td>439</td>
<td>1.7</td>
<td>1.2-2.6</td>
<td>0.005</td>
</tr>
<tr>
<td>Tumour bed induration</td>
<td>439</td>
<td>1.7</td>
<td>1.2-2.5</td>
<td>0.007</td>
</tr>
<tr>
<td>Breast oedema</td>
<td>440</td>
<td>1.4</td>
<td>0.8-2.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Breast pain</td>
<td>402</td>
<td>0.93</td>
<td>0.4-1.9</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Multivariate analysis

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>No. of patients</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cosmesis</td>
<td>392</td>
<td>1.4</td>
<td>0.7-2.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Breast shrinkage assessed using serial photos</td>
<td>394</td>
<td>1.3</td>
<td>0.8-2.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Whole breast induration</td>
<td>398</td>
<td>2.0</td>
<td>0.9-4.5</td>
<td>0.09</td>
</tr>
<tr>
<td>Tumour bed induration</td>
<td>389</td>
<td>1.8</td>
<td>1.1-2.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Breast oedema</td>
<td>420</td>
<td>1.4</td>
<td>0.8-2.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Breast pain</td>
<td>392</td>
<td>0.8</td>
<td>0.4-1.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>

7.3.4 5-year breast tissue toxicity

The results of univariate and multivariate analysis for the association between breast seroma and normal tissue toxicity at 5 years using dichotomized endpoints are summarised below in table 31. Again, the results using polychotomous logistic regression led to identical conclusions. On univariate and multivariate analysis, presence of easily visible breast seroma was associated with worse breast cosmesis,
whole breast induration and tumour bed induration. However, the presence of seroma was no longer associated with breast oedema at 5 years. These results were similar after excluding patients with adjuvant chemotherapy (table 32).

Table 29: Association between breast seroma and breast tissue toxicity at 5 years using dichotomized endpoints

<table>
<thead>
<tr>
<th>Univariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endpoint</td>
</tr>
<tr>
<td>Overall cosmesis</td>
</tr>
<tr>
<td>Breast shrinkage assessed using serial photographs</td>
</tr>
<tr>
<td>Whole breast induration</td>
</tr>
<tr>
<td>Tumour bed induration</td>
</tr>
<tr>
<td>Breast oedema</td>
</tr>
<tr>
<td>Breast pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endpoint</td>
</tr>
<tr>
<td>Overall cosmesis</td>
</tr>
<tr>
<td>Breast shrinkage assessed using serial photographs</td>
</tr>
<tr>
<td>Whole breast induration</td>
</tr>
<tr>
<td>Tumour bed induration</td>
</tr>
<tr>
<td>Breast oedema</td>
</tr>
<tr>
<td>Breast pain</td>
</tr>
</tbody>
</table>
Table 30: Association between breast seroma and breast tissue toxicity at 5 years using dichotomized endpoints after excluding chemotherapy patients

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>No. of patients</th>
<th>Odds ratio</th>
<th>95%CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cosmesis</td>
<td>253</td>
<td>2.2</td>
<td>1.3-3.6</td>
<td>0.003</td>
</tr>
<tr>
<td>Breast shrinkage assessed using serial photographs</td>
<td>251</td>
<td>1.2</td>
<td>0.7-2.0</td>
<td>0.45</td>
</tr>
<tr>
<td>Whole breast induration</td>
<td>264</td>
<td>2.0</td>
<td>1.1-3.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Tumour bed induration</td>
<td>264</td>
<td>2.0</td>
<td>1.1-3.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Breast oedema</td>
<td>264</td>
<td>1.7</td>
<td>0.7-4.5</td>
<td>0.26</td>
</tr>
<tr>
<td>Breast pain</td>
<td>285</td>
<td>1.4</td>
<td>0.6-3.4</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Multivariate analysis

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>No. of patients</th>
<th>Odds ratio</th>
<th>95%CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cosmesis</td>
<td>233</td>
<td>1.8</td>
<td>0.97-3.3</td>
<td>0.06</td>
</tr>
<tr>
<td>Breast shrinkage assessed using serial photographs</td>
<td>248</td>
<td>1.1</td>
<td>0.7-1.9</td>
<td>0.68</td>
</tr>
<tr>
<td>Whole breast induration</td>
<td>243</td>
<td>4.6</td>
<td>1.4-15.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Tumour bed induration</td>
<td>236</td>
<td>2.4</td>
<td>1.2-4.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Breast oedema</td>
<td>254</td>
<td>2.2</td>
<td>0.7-6.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Breast pain</td>
<td>278</td>
<td>1.3</td>
<td>0.5-3.3</td>
<td>0.7</td>
</tr>
</tbody>
</table>

7.4 Discussion

The ultimate goal of BCS and post-operative radiotherapy is to achieve optimal local control with a good cosmetic outcome and minimal side effects. Currently, there is debate as to which surgical management of the breast tumour bed (standard versus full thickness closure technique) best achieves this ultimate goal. This study used the presence of seroma on the radiotherapy planning CT scan as a surrogate for the
standard closure surgical technique. The results show a strong association between tumour bed seroma and post-operative infection and haematoma. The presence of breast seroma also appears to be associated with increased breast tissue toxicity at 2 and 5 years.

### 7.4.1 Association between tumour bed seroma and post-operative infection and haematoma

This study found that patients with tumour bed seroma are 1.8 times more likely to develop post-operative infection than patients with no/subtle seroma. Of note, the infection rate of 19.7% in this study is higher than previously reported in the literature. It is suspected that some patients may have received antibiotics as a precaution for skin redness and not true infection, thus the association with “true” post-operative infection may in fact be stronger.

It is postulated that a fluid-filled seroma cavity can act as a culture medium for bacterial growth, hence increasing the risk of infection, in keeping with previously published reports [182, 184]. Hall and Hall reported an association between the presence of seroma and wound infection for 218 women with non-reconstructive breast surgery (p<0.001) [184]. Indelicato et al reported an increased rate of acute infection in patients with standard tumour bed closure as compared to full thickness closure (11.7% vs. 5.25; p=0.009) [182].

This study also found that patients with tumour bed seroma are 2.1 times more likely to develop post-operative haematoma than patients with no/subtle seroma. It could be hypothesised that despite meticulous haemostasis, small blood vessels can still bleed into the tumour bed following standard wound closure alone. In comparison, the opposed breast parenchyma with full thickness closure may promote better
haemostasis. Paterson et al reported an increased rate of haematoma in patients with standard wound closure as compared to deep wound approximation (54.4% vs. 31.4%; p=0.004) [180] and Law et al. reported an increased risk of haematoma in patients with standard wound closure in comparison to full thickness closure[69].

7.4.2 Association between tumour bed seroma and late normal tissue toxicity

This study shows that the presence of a tumour bed seroma appears to be an independent risk factor for developing breast tissue toxicity. The patients with an easily visible seroma on the radiotherapy planning CT scan had a higher rate of whole breast induration and tumour bed induration compared to patients with no/subtle seroma at 2 and 5 years. Breast oedema is a transitional phenomenon which peaks in the first few years after radiotherapy and resolves in most patients by 5 years [161, 185]. This study showed an independent association between breast seroma and breast oedema at 2 years, but not at 5 years. Conversely, the presence of breast seroma was associated with worse overall cosmesis at 5 years, but not at 2 years. It is likely that follow up of 2 years may have been insufficient to express the final level of late toxicity for overall cosmesis.

Schultze et al.[186] reported on the cosmetic outcome of 97 patients with breast seroma after BCS and concluded that post-operative seroma and haematoma have an adverse effect on the resulting cosmesis. Based on the EORTC trial 22881–10882 ‘boost versus no boost’, Collette et al. [32] reported complications after BCS (haematoma, oedema, seroma and local infection) as predictors for moderate or severe breast fibrosis in the patients receiving breast boost.
The increased risk of breast tissue toxicity with breast seroma may be due to various reasons. The breast seroma is rich in fibrin which can organize, possibly leading to tumour bed induration. An organised seroma can also pull the surgical edges together by retraction [176] possibly leading to inferior cosmesis. It is well known that the volume of seroma changes during breast radiotherapy [21, 187], and these changes in volume can lead to significant dose heterogeneity, potentially leading to inferior overall cosmesis. Huh et al. looked at the inter-fractional dose variation due to seroma for three breast cancer patients with conventional technique and IMRT [187]. They found the change in breast seroma volume had a significant effect on the dose inhomogeneity in the treatment volume (3.7-13.9% for conventional treatment and 6.7-20.7% for IMRT treatment).

7.5 Limitations of the study

There are some limitations of this study. Firstly, the exact surgical technique for each study patient is unknown: it has been assumed that the presence of a seroma at the time of radiotherapy planning infers the use of the standard technique for surgical wound closure. The standard closure technique was more commonly used during the trial but only 36% patients had visible seroma at the time of planning CT scan. It is possible that some patients with standard closure did not develop seroma. Conversely, there may be some patients who had a full thickness closure and still developed seroma. Patients receiving adjuvant chemotherapy had a delay of 4-6 months between their surgery and planning CT scan. This would have also allowed for the resolution of seroma among some patients.
Secondly, there is an imbalance in baseline characteristics between the clearly visible seroma and subtle/no seroma groups, with the latter consisting of more high risk young and/or node positive patients. This relative imbalance is expected as more patients in this higher risk group received post-operative chemotherapy, thus any seroma had more opportunity to resolve before the radiotherapy planning CT scan [188]. In addition, this group were more likely to receive a radiotherapy tumour bed boost. Both chemotherapy and radiotherapy boost treatments have previously been reported as risk factors for normal tissue toxicity [32]. Thus, this imbalance between the two groups is more likely to underestimate the effect of tumour bed seroma on breast tissue toxicity. The presence of haematoma may not be recorded in medical notes/correspondence for all patients and therefore may be underestimated in this study.

7.6 Conclusions

This study shows that breast seroma is associated with increased rates of post-operative infection and haematoma. It is also an independent risk factor for tumour bed induration and inferior breast cosmesis at 5 years. It is apparent that late treatment toxicity can cause considerable physical and psychological morbidity. As mechanical closure of the tumour bed is an effective way to reduce seroma formation, full thickness surgical closure may be desirable for patients undergoing breast conservation and radiotherapy.
7.7 Chapter contributions

I would like to sincerely thank the following individuals for their help and support with this work.

**Jade Cumming**: for her contribution in collecting data on breast seroma

**Gillian Barnett**: for her assistance with the statistical analysis

I along with Dr Charlotte Coles was involved in the concept and design of the study. Along with Ms. Cumming, I reviewed the planning CT scan for all patients and collected data on breast seroma. I was responsible for data cleaning before statistical analysis and interpretation of statistical results. I wrote the original manuscript which was subsequently published in the peer reviewed European Journal of Surgical Oncology (appendix).
8. Conclusions

The conclusions from the five experimental chapters are summarised below:

8.1 Conclusions for chapter 3

The use of bony anatomy as a surrogate for the tumour bed can lead to underestimation of set-up errors in breast radiotherapy. The clip-based IGRT technique is more accurate and can safely reduce the PTV margin around the tumour bed as compared to the bony anatomy-based verification technique. Smaller PTV margins are likely to reduce the risk of late cardiac and breast tissue toxicity. There is no significant difference between kV-CBCT and 2D-kV measured set-up errors, and similar PTV margin can be used for both imaging modalities.

8.2 Conclusions for chapter 4

The multi-centre pooled study suggests that the effect of volume parameter is small and the maximum radiotherapy dose is the most important parameter to influence late breast fibrosis. There are potential limitations in our current radiotherapy toxicity scoring system.

8.3 Conclusions for chapter 5

Improved dose homogeneity with simple IMRT translates into superior overall cosmesis and reduces the risk of skin telangiectasia five years following breast RT. In addition, surgical cosmesis should be optimised prior to radiotherapy delivery, as this also has a significant effect on late breast toxicity and overall cosmesis.
8.4 Conclusions for chapter 6

The benefits of simple breast IMRT on PROMs could not be demonstrated. Non-radiotherapy factors including large breast volume, young age and surgical factors influence PROMs and hence, surgical factors should be optimised. Only a small proportion of patients report moderate-severe breast changes post-radiotherapy and most PROMs improve over time.

8.5 Conclusions for chapter 7

Breast seroma is associated with increased rates of post-operative infection and haematoma. It is an independent risk factor for tumour bed induration and inferior breast cosmesis at five years. As mechanical closure of the tumour bed is an effective way to reduce seroma formation, full thickness surgical closure may be desirable for patients undergoing breast conservation and radiotherapy.

8.6 Evaluation of hypotheses

_Hypothesis 1: Image guided radiotherapy (IGRT) using tumour bed clips will reduce the safety margin around the tumour bed and the volume of normal breast tissue irradiated to high doses as compared to standard treatment verification technique._

This hypothesis was proven. The use of clip-based IGRT technique reduces the PTV margin around the tumour bed as compared to the bony anatomy-based verification technique. The volume of normal breast tissue irradiated to high doses was also reduced using clip-based IGRT technique.
Hypothesis 2: Breast tissue displays a significant radiation dose-volume effect for breast fibrosis and a normal tissue complication probability model can effectively predict the probability of breast fibrosis based on the interplay of treatment volumes and overall radiation doses.

This hypothesis was not proven. In this research project, the effect of volume parameter on breast fibrosis was small and the maximum radiotherapy dose was the most important parameter to influence late breast fibrosis.

Hypothesis 3: Improvement in dose inhomogeneity with the use of Intensity modulated radiotherapy (IMRT) will reduce clinician-assessed breast normal tissue complications at 5 years.

This hypothesis was proven. Improved dose homogeneity with simple IMRT leads to superior overall cosmesis and reduces the risk of skin telangiectasia five years following breast radiotherapy.

Hypothesis 4: Improvement in dose inhomogeneity with the use of Intensity modulated radiotherapy (IMRT) will improve patient reported outcome measures at 5 years.

This hypothesis was not proven. Improved dose homogeneity with simple IMRT did not lead to improvement in PROMs in this research project.

Hypothesis 5: The type of surgical technique used to close the tumour bed has an impact on late breast tissue related complications at 2 and 5 years.
This hypothesis was proven. Breast seroma was associated with increased rates of post-operative infection and haematoma. It also had an effect on tumour bed induration and inferior breast cosmesis at five years.
9. Direction of future research

9.1 Background

The aim of any cancer therapy is to cure patients without causing treatment related side effects. Whole breast radiotherapy is an effective adjuvant treatment after breast conserving surgery but is associated with some acute and long term side effects. There is considerable variation among patients with regards to the benefits and side effects of adjuvant radiotherapy. With this in mind, the concept of risk-adapted radiotherapy is emerging. Individualising radiotherapy decisions based on patient’s risk of cancer recurrence and potential risk of treatment related side effects is desirable. The future research in breast cancer radiotherapy would be directed at quantifying patient’s individual risks and benefits.

9.2 Risk-adapted breast radiotherapy

Apart from histological features, the use of adjuvant chemotherapy in breast cancer is now based on the molecular profile of the tumour [189]. The likelihood of local cancer recurrence after breast conserving surgery may also be influenced by the tumour histological features and molecular profile. One could potentially identify low risk patients where radiotherapy can be safely omitted and high-risk patients who would benefit from radiotherapy dose escalation or concomitant chemoradiotherapy (Figure 23).
Figure 23: Risk adaptive radiotherapy based on loco-regional cancer risk

Loco-regional risk and patient selection

<table>
<thead>
<tr>
<th>Very low</th>
<th>Very high</th>
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<tbody>
<tr>
<td>Omit RT</td>
<td>Whole breast RT</td>
</tr>
<tr>
<td>PRIME</td>
<td>FAST-Forward</td>
</tr>
<tr>
<td>TIME</td>
<td>with TB boost</td>
</tr>
<tr>
<td>LUMINA</td>
<td>(SIB)</td>
</tr>
<tr>
<td>IDEA</td>
<td>EORTC boost trial</td>
</tr>
<tr>
<td>PRECISION</td>
<td>IMPORT High</td>
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<td>EXPERT</td>
<td>Hypofractional SIB</td>
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<tr>
<td></td>
<td>EORTC ENI study</td>
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<td></td>
<td>MA 20</td>
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<td></td>
<td>Danish IMC trial</td>
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<td></td>
<td>Concurrent</td>
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<td></td>
<td>Chemo-RT</td>
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<td>breast/nodes</td>
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<td>OTT 1159</td>
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<td></td>
<td>OTC 1202</td>
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<td></td>
<td>Radio-PARP</td>
</tr>
</tbody>
</table>

9.2.1 Breast radiotherapy for very low risk patients

Whole breast radiotherapy not only affects healthy breast tissue but is also associated with a small increased risk of cardio-vascular mortality and radiation induced secondary cancers [104, 190]. We need to identify patients who are at a very low risk of local recurrence after breast conserving surgery, and for whom, breast radiotherapy can be safely omitted. The Canadian Lumina study is currently enrolling patients with luminal A tumour (based on immunohistochemistry) who are deemed to be at low risk of recurrence. These patients will only receive adjuvant endocrine treatment and no radiotherapy and would be followed-up for ten years to
test the hypothesis [191]. Similarly, a UK based PRIME-Time study has been designed, where inexpensive immunohistochemistry (IHC) markers and clinical (C) features will be used to create a IHC4+C recurrence probability score [192]. For patients with likely very low risk of local recurrence on the IHC4+C score, whole breast radiotherapy treatment would be omitted. I have been a member of the PRIMETIME protocol development group which has now become the trial management group. I will be actively involved in this national research study which is now open to recruitment.

9.2.2 Breast radiotherapy for high risk patients

It is now established that factors including young age of breast cancer diagnosis, Estrogen receptor negative status, Grade 3 histology and node positive tumours are at much higher risk of loco-regional recurrence after whole breast radiotherapy. For this group of patients, radiotherapy dose escalation may be desirable and higher risk of treatment related complications would be more acceptable. There is on-going research to see if more complex intensity modulated radiotherapy (IMRT) could be used to create desirable dose inhomogeneity in the breast tissue with dose escalation to the tumour bed [193]. With new data supporting the role of elective nodal irradiation, more research is also required to see how complex IMRT solutions could be used to safely deliver elective nodal irradiation in breast radiotherapy.

Concomitant chemo-radiotherapy has been successfully used in different tumours including lung cancer and rectal cancer. For patients with locally advanced breast cancer, concomitant chemo-radiotherapy may be desirable and requires more scientific research. Two phase I-II Canadian studies (OTC 1159 and OTC 1202) are currently looking at concurrent neo-adjuvant radiation with weekly docetaxel in
patients with locally advanced breast cancer. The studies will be looking at the response rate as well as acute toxicities as endpoint.
9.3 Individualised tumour bed margins in breast radiotherapy

My research work has demonstrated that clip-based IGRT technique is more accurate and can safely reduce the PTV margin around the tumour bed as compared to the bony anatomy-based verification technique. As we work towards individualising radiotherapy treatment, research is also required to see if individualisation of PTV margins is feasible. The IMPORT-HIGH IGRT data would allow us to investigate if any patient and treatment related factors influence TB set-up errors and if patient specific and non-isotropic margins could be used in breast radiotherapy.

9.4 Normal tissue complication probability models for breast radiotherapy

During my research work on the NTCP modeling for breast tissue, it became apparent that detailed dosimetric data for breast radiotherapy is not routinely collected. This was not only due to the lack of CT-based planning for breast radiotherapy in the past but also due to the challenges in electronically storing large datasets. Nearly all of the breast radiotherapy planning is now CT-based and improvements in computer hardware now allow for detailed dosimetric data to be electronically stored. In the coming years, mature toxicity data would be available from breast trials including IMPORT High and Dutch Young Boost trial. More accurate NTCP modelling for breast tissue toxicity would be feasible in the near future. This will allow clinicians to quantify individual patient risk of treatment related side effects after reviewing their radiotherapy treatment plan and examining the dose distribution.
9.5 Concordance between Clinician and Patient reported toxicity outcome after breast radiotherapy

Many breast cancer patients are now discharged early from clinical follow-up and may not wish to attend hospital appointments for trial follow-up alone. If patient reported outcome measures (PROMs) could replace clinician assessments, clinical trials could be run more cost effectively and the burden of trial follow-up on patients could be reduced. During my research project, the benefits of simple IMRT were assessed using both clinician and patient reported outcome measures (chapter 5 and 6). The benefits of simple IMRT were demonstrated using clinician assessment with better overall cosmesis and reduced skin telangiectasia. However, similar results were seen using patient reported outcome measures. More research is required to understand the difference in outcome between clinicians and patients. We have reported on concordance analysis between clinicians and patients based assessment using the data from the Cambridge Breast IMRT trial and START trialist group [194, 195].

Further work is required to address how PROMs can replace clinician assessment in breast radiotherapy trials in the future.
References


We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:  

Your birthdate:  

Today's date:  

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
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<tbody>
<tr>
<td>1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?</td>
<td>1</td>
<td>2</td>
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<td>2. Do you have any trouble taking a long walk?</td>
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<tr>
<td>3. Do you have any trouble taking a short walk outside of the house?</td>
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<tr>
<td>4. Do you need to stay in bed or a chair during the day?</td>
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<td>2</td>
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<tr>
<td>5. Do you need help with eating, dressing, washing yourself or using the toilet?</td>
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<td>Question</td>
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<td>6. Were you limited in doing either your work or other daily activities?</td>
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<td>7. Were you limited in pursuing your hobbies or other leisure time activities?</td>
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<tr>
<td>8. Were you short of breath?</td>
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<tr>
<td>9. Have you had pain?</td>
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<td>10. Did you need to rest?</td>
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<td>11. Have you had trouble sleeping?</td>
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<td>12. Have you felt weak?</td>
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<td>13. Have you lacked appetite?</td>
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<td>14. Have you felt nauseated?</td>
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<td>15. Have you vomited?</td>
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<tr>
<td>16. Have you been constipated?</td>
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<tr>
<td>17. Have you had diarrhea?</td>
<td>1</td>
<td>2</td>
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<td>18. Were you tired?</td>
<td>1</td>
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<tr>
<td>19. Did pain interfere with your daily activities?</td>
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<tr>
<td>20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?</td>
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</table>
EORTC QLQ-C30

During the past week

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
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<th>Quite a bit</th>
<th>Very much</th>
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<tbody>
<tr>
<td>21. Did you feel tense?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22. Did you worry?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23. Did you feel irritable?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24. Did you feel depressed?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>25. Have you had difficulty remembering things?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>26. Has your physical condition or medical treatment interfered with your family life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>27. Has your physical condition or medical treatment interfered with your social activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>28. Has your physical condition or medical treatment caused you financial difficulties?</td>
<td>1</td>
<td>2</td>
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</tbody>
</table>

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

   | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
---|---|---|---|---|---|---|---|
   | Very poor | Excellent |

30. How would you rate your overall quality of life during the past week?

   | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
---|---|---|---|---|---|---|---|
   | Very poor | Excellent |
Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
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</thead>
<tbody>
<tr>
<td>31. Did you have a dry mouth?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>32. Did food and drink taste different than usual?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>33. Wore your eyes painful, irritated or watery?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>34. Have you lost any hair?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>36. Did you feel ill or unwell?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>37. Did you have hot flushes?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>38. Did you have headaches?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>39. Have you felt physically less attractive as a result of your disease or treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>40. Have you been feeling less feminine as a result of your disease or treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>41. Did you find it difficult to look at yourself naked?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>42. Have you been dissatisfied with your body?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>43. Were you worried about your health in the future?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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</tbody>
</table>
### During the past four weeks

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>44. To what extent were you interested in sex?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>45. To what extent were you sexually active? (with or without intercourse)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### During the past week

<table>
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<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>47. Did you have any pain in your arm or shoulder?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>48. Did you have a swollen arm or hand?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>49. Was it difficult to raise your arm or to move it sideways?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>50. Have you had any pain in the area of your affected breast?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>51. Was the area of your affected breast swollen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>52. Was the area of your affected breast oversensitive?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>53. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Systematic review

Relationship between irradiated breast volume and late normal tissue complications: A systematic review

Mukesh Mukesh, Emma Harris, Raj Jena, Philip Evans, Charlotte Coles

Cambridge University Hospitals NHS Foundation Trust; Institute of Cancer Research and Royal Marsden NHS Foundation Trust, Sutton, UK

Abstract

The concept of radiation dose–volume effect has been exploited in breast cancer as boost treatment for high-risk patients and more recently in trials of Partial Breast Irradiation for low-risk patients. However, there appears to be paucity of published data on the dose–volume effect of irradiation on breast tissue including the recently published report on Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC). This systematic review looks at the current literature for relationship between irradiated breast volume and normal tissue complications and introduces the concept of dose modulation.

The aim of radiation therapy is to deliver a tumouricidal dose for optimal loco-regional control with relative sparing of the surrounding normal tissues. The precise knowledge of tumouricidal and tolerance doses to various tissues including dose–volume effect is necessary when using 3D-conformal and intensity modulated radiotherapy techniques. Emami and colleagues [1] were amongst the first to publish a comprehensive review of radiation tolerance for normal tissues, including quantification of late normal tissue complication (NTC) as a function of volume of organ irradiated. This review, although informative was limited by the availability of few comprehensive databases, with most of the data on dose–volume effect interpolated or extrapolated from whole organ data, or based on the experience of the involved clinicians. However it did provide a firm framework for quantifying the volumetric and dosimetric measures which may influence normal tissue complications. Since that publication, an update on the dose–volume effect of radiation on the normal tissues has been published in form of “Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC)” report [2]. This report helps in our understanding of the normal tissue radiation tolerance and can be utilised in clinical treatment planning as it provides an estimate of the effect of change in irradiated volume on normal organ tolerance [3,4]. This information can be exploited by dose escalation to the target volume with only a small amount of surrounding normal tissue receiving a higher dose. For example, the rectum is a critical normal structure during dose escalation in prostate cancer radiotherapy. Use of intensity modulated radiotherapy (IMRT) allows safe dose escalation by reducing the volume of rectum receiving high dose with favourable normal tissue complication rates compared to 3D-conformal radiotherapy [5].

For years, the radiation dose–volume effect for the breast has been exploited as boost treatment for breast cancer patients at high risk of recurrence i.e. treating a small volume of breast tissue to a higher dose (boost) to improve local control rates [6–8]. More recently, breast dose–volume effect has been exploited in trials of Partial Breast Irradiation (PBI) for patients at low risk of recurrence: the irradiated volume is confined to the region around the tumour bed with the aim of reducing toxicity whilst maintaining local control rates. Despite there being very good evidence for a radiation dose–volume effect in many organs including lung and rectum, there appears to be a paucity of published data on dose–volume effect of radiation on breast tissue. This systematic review evaluates the evidence for a relationship between the volume of breast tissue irradiated and the late NTCs including overall cosmesis, breast fibrosis, breast induration and telangiectasia. It also explores the hypothesis that a modest dose reduction to part of the breast facilitates dose escalation to the tumour bed, with lower than expected NTC.

Materials and methods

A systematic search was performed via Medline and Embase with the search strategy “breast neoplasm” AND “radiotherapy
OR irradiation. This was combined with “AND fibrosis,” “AND
cosmes,” “AND side effects,” “AND toxicity,” “AND shrinkage”
and “AND normal tissue”. The search was expanded to include re-
lated articles and a reference list of articles. The effects on NTC for
the following parameters are reported in this manuscript:
(a) Boost volume
(b) Partial Breast Irradiation (PBI)
(c) Fractionation regimens

Results

Impact of boost volume on normal tissue complications

EORTC 22881-10882 “boost versus no boost” trial (level I evidence)

The EORTC “boost versus no boost” trial randomised 5318 pa-
tients with early breast cancer between extra irradiation to the tu-
mour bed (boost of 16 Gy) versus no boost treatment after whole
breast irradiation (WBI) [6]. The boost was delivered using elec-
trons or tangential photon fields in daily fractionation of 2 Gy, or
with Iridium-192 implant at a dose rate of 0.5 Gy/h. At 10 years,
reduced incidence of local recurrence was seen in the boost arm as
compared to the no boost arm (6.2% versus 10.2%; \( p < 0.0001 \)).
However, an extra irradiation of 16 Gy to the tumour bed also in-
creased the rates of moderate to severe breast fibrosis by 15% at
ten years (28.1% versus 33.2%; \( p < 0.0001 \)). In this trial, 251 pa-
tients with microscopically incomplete tumour excision were also ran-
domised to either a low dose boost of 10 Gy (126 patients) or a
high dose boost of 26 Gy (125 patients) [9]. The cumulative inci-
dence of moderate/severe fibrosis for low dose and high dose boost
at ten years was 24% and 54%, respectively. Hence a dose escalation
of 16 Gy to the boost volume in the incomplete tumour excision
group increased the rates of moderate/severe fibrosis by 30%, com-
pared with a 15% increase in the complete excision group for the
same 16 Gy increase in dose.

On review of the treatment protocol, the boost volume for com-
plete excision group was tumour bed plus 1.5 cm margin as com-
pared to tumour bed plus 3 cm margin in the incomplete tumour
excision group. It demonstrates that an increase in irradiated
breast volume in the incomplete excision group doubled the risk
of moderate/severe fibrosis for the same dose escalation of 16 Gy,
supporting a dose–volume relationship for breast tissue. Furth-
more, Collette et al. [10] reported on factors predicting the risk of
breast fibrosis at ten years. The boost volume was associated with
an increased risk of moderate or severe fibrosis in univariate anal-
ysis. Vrielig et al. [11] from the same group had previously re-
ported worse cosmetic outcome in patients with boost volume
>200 cm\(^3\) as compared to \(<200 \text{ cm}^3\) (odds ratio 0.47 95%CI 0.29–
0.76; \( p = 0.002 \)) in univariate analysis after three years of follow
up. However, boost volume was not a significant variable affecting
fibrosis and cosmesis in multivariate analysis.

Brachytherapy boost (level IV evidence)

Borger et al. [12] reported on the dose and volume effect on
breast fibrosis after using brachytherapy boost. Four hundred and
four patients were treated with external beam radiotherapy, 50 Gy in
2 Gy daily fractions to the whole breast, followed by an iridium
implant boost (dose rate 0.57 ± 0.11 Gy/h) of 15 Gy (101
patients), 25 Gy (301 patients) and 20 Gy (2 patients). At a median
follow up of 70 months, a fourfold higher risk of fibrosis was ob-
served for each 100 cm\(^3\) increase in irradiated boost volume,
and a tenfold higher risk of fibrosis was observed when the total dose
exceeded 79 Gy compared to doses below 70 Gy.

McRae and colleagues from Georgetown University Medical
Centre reported on the relationship between brachytherapy boost
volume and soft tissue complication in 1987 [13]. Retrospective
brachytherapy plans for 5 patients with radiation induced soft tis-
sue damage were compared to 51 patients who experienced no se-
vere complication after breast conserving surgery (BCS) and WBI
followed by Iridium-192 boost. The mean boost volume for pa-
tients who developed soft tissue damage was significantly higher
for all dose levels between 10 Gy and 50 Gy when compared to pa-
tients with no reported complications \(( p < 0.05 \)) suggesting a vol-
ume–NTC relationship at any specific dose.

Olivotto et al. [14] also reported an association between the vol-
ume of brachytherapy boost and late cosmetic outcome. Five hun-
dred and ninety-three patients received breast-conserving surgery
followed by WBI (46–50 Gy over 4.5–5 weeks). Four hundred and
ninety-seven patients received low dose rate Iridium-192 implant
boost to bring the tumour bed dose to 60 Gy. At a median follow up
of 76 months, the volume of boost, measured by the number of
Iridium seeds used, was a significant factor for fair/poor cosmesis.
Patients with <70 seeds had a 13% risk of fair/poor cosmesis com-
pared to 38% for patients containing \( > 100 \text{ seeds} \) \(( p < 0.01 \)). The use
of a greater number of seeds would imply a larger volume of irradia-
ted breast tissue, indicating towards a radiation volume effect on
cosmesis. Several other single and multi-centre studies have re-
ported on the relationship between volume of brachytherapy boost
and NTC risk and are summarised in Table 1.

Intra-operative RT (IORT) boost using low energy X-ray (level IV
evidence)

IORT using low energy X-ray of 50 kV can be used to deliver a
single fraction of high dose radiation boost to the tumour bed after
lumpectomy. Advocates for IORT cite several potential advantages
of using this approach: delivery of radiation immediately after
surgery prevents tumour cell proliferation; change in cytokines
pattern into a less stimulating microenvironment, which is postu-
lated to decrease local recurrence rates; and reduced risk of geo-
graphical miss [15,16].

The University of Heidelberg, Germany reported on the late tox-
icity data (at 3 years) for 79 cases treated with this approach [17].
All patients received 20 Gy intra-operative boost using 50 kV X-ray
followed by 46–50 Gy in 2 Gy daily fraction of WBI ± supra/infra-
clavicular fossa irradiation. Thirty-five percent patients developed
grade 2–3 breast fibrosis. They observed the applicator size for
IORT significantly correlated with late breast fibrosis (spearman
rank correlation coefficient 0.496, \( p < 0.001 \)). A larger applicator
size would imply a larger volume of irradiated breast tissue sug-
gest a radiation volume effect on late normal tissue toxicity.

Cobalt unit based boost (level IV evidence)

Dewar et al. [18] reported on the Institute Gustave-Roussy
experience for cosmetic outcome after breast-conserving surgery
and radiotherapy. Five hundred and ninety-two patients received
WBI (45 Gy in 2.5 Gy per fraction, four times weekly) using two
tangential fields, each field treated on alternate days followed by
tumour bed boost of 15 Gy in 6 fractions using one-two fields on
the cobalt unit. In addition to applied dose per fraction, the area
of field to the tumour bed (>30 cm\(^2\)) was associated with an
increased risk of fibrosis \(( p < 0.02 \)) and telangiectasia \(( p < 0.01 \)) in
multivariate analysis.

Other studies (level IV evidence)

The Fox Chase Cancer Center, Philadelphia recently reported on
tumour bed boost parameters associated with overall cosmesis and
fibrosis for 3186 patients treated at their centre from 1970–2008
[19]. All patients received whole breast irradiation (46–50 Gy)
followed by a tumour bed boost of 10–18 Gy using electrons or pho-
tons. With a median follow up of 78 months, smaller boost cut–out
size was a borderline predictor of excellent cosmesis \(( p = 0.05 \)) and
lower risk of breast fibrosis \(( p < 0.0001 \)) on univariate analysis.
Partial Breast Irradiation (PBI)

Randomised controlled trials of Partial Breast Irradiation (PBI) versus whole breast irradiation (WBI) (level I evidence)

WBI is the current standard of care after breast-conserving surgery and the latest Early Breast Cancer Trialist Collaborative Group (EBCTG) systematic review confirmed an absolute 5% reduction in 15 year breast cancer mortality using WBI [20]. In the last decade, PBI has been explored as an alternative to WBI in low risk patients. PBI involves irradiation of a limited volume of breast tissue around the tumour bed and is currently under investigation in several randomised phase II and III trials (Table 2). It is based on the rationale that the majority of local recurrences are located close to the area of surgical resection/index quadrant, foci of breast disease outside that the majority of local recurrences are located close to the area of surgical resection/index quadrant, foci of breast disease outside the index quadrant are often new primary tumours [21,22] and irradiating a limited volume of breast would reduce treatment related morbidity. To date, four randomised controlled trials (RCT) comparing WBI versus PBI have reported on their outcome.

The Christie group were the first to report in 1999 [23]. They randomised 708 patients with breast cancer ≤ 4 cm in diameter to PBI or WBI plus regional lymph nodes irradiation. PBI involved tumour bed irradiation (average field size 8 cm x 6 cm) to 40–42.5 Gy in 8 fractions over 10 days using electrons and WBI
involved treating the whole breast to 40 Gy in 15 fractions over 21 days using a tangential pair with matched field for regional nodes. After a median follow up of 65 months, recurrence rates were higher in the PBI arm as compared to WBI arm (19.6% versus 11%; p = 0.0008). The possible reasons for higher recurrence rates in the PBI arm were difficulty in defining the target volume, leading to geographical miss and including patients with infiltrating lobular carcinoma and ductal carcinoma with an extensive intra-ductal component. Patients with PBI also had significantly higher rates of adverse histological features including invasive lobular carcinoma (14% versus 5%) and telangiectasia (33% versus 12%) when compared to WBI.

The Yorkshire Breast Cancer Group randomised 174 patients between WBI (40 Gy in 15 fractions over 21 days) followed by tumour bed boost (15 Gy in 5 fractions) and PBI using a variety of techniques, including a direct cobalt or caesium beams, electrons or a small mega-voltage tangential pair to a dose of 55 Gy in 20 fractions over 28 days [24]. The trial closed prematurely due to poor accrual with higher loco-regional recurrence rates in the PBI group as compared to the WBI group (24% versus 9%). It has been suggested that higher recurrence in the PBI arm was secondary to difficulty in accurate definition of the target volume (tumour bed). Treatment related morbidity with PBI and WBI has not been reported. Both these trials pioneered the concept of PBI at a time when patient selection and tumour bed localisation was at an early stage of development. Subsequent randomised trials have used more stringent protocols for both of these factors.

The Hungarian National Institute of Oncology PBI trial [25] and TARGIT trial [26] have more recently reported their outcomes. The Hungarian PBI trial randomised 258 patients with T1 NO-1 grade ≤2 breast cancer to WBI or PBI after breast-conserving surgery [25]. WBI was delivered using Cobalt or photon beams to a dose of 50 Gy in 2 Gy daily fractions and PBI was delivered using high dose rate (H.D.R.) Iridium-192 brachytherapy (85 pts) to a dose of 36.4 Gy in 5.2 Gy per fraction over 4 days or electrons (40 pts) to a dose of 50 Gy in 2 Gy daily fractions prescribed to the 80% isodose. At a median follow up of 66 months (range 18–101 months), the local recurrence rates were not significantly different in the two trial arms. The cosmetic results using Harvard criteria [27] were favourable in the PBI arm. The rate of excellent to good cosmesis was 77.6% for the PBI group and 62.9% for the WBI group (p = 0.009).

The TARGIT-A trial randomised 2232 patients with early breast cancer to WBI (40–56 Gy) ± a boost of 10–16 Gy and intra-operative PBI using low energy X-rays (50 kV) to a dose of 20 Gy to the tumour bed attenuating to 5–7 Gy at 1 cm depth [26]. Patients with adverse histological features including invasive lobular carcinoma or an extensive intra-ductal component also received WBI without boost in the PBI arm. At two years, the local recurrence rate was similar with no significant difference in the rate of toxicity, but the type of toxicity was significantly different in both arms. WBI arm had higher RTOG grade 3–4 toxicity for dermatitis, telangiectasia or breast pain (2.1% versus 0.5%; p = 0.002). In contrast,
patients receiving intra-operative PBI experienced a different spectrum of side effects. Breast seroma needing more than three aspirations was more common in the intra-operative PBI group (2.1% versus 0.8%; p = 0.012) and more patients reported skin breakdown or delayed healing, required surgical evacuation of haematoma and intravenous antibiotics or surgical intervention for infection. The cosmetic results have not been reported.

Case-matched pair studies (level III evidence)

Four case match pair studies have also compared normal tissue complications between partial and whole breast irradiation after BCS. Polgar et al. [28] prospectively selected 45 patients with T1NO-1 breast cancer treated with PBI using HDR Iridium-192 implants to a dose of 30.3–36.4 Gy in 7 fractions over 4 days and matched 80 patients (eligible for PBI) treated with WBI 50 Gy in 2 Gy daily fractions with or without a tumour bed boost of 10–16 Gy. At a median follow up of 7 years, the ipsilateral breast recurrence rates were not significantly different in the two groups. Excellent/good cosmesis using Harvard criteria [27] was seen in 84.4% patients in the PBI arm and 68.3% patients in the WBI arm (p = 0.04). However, a trend of increased incidence of RTOG grade 2–3 fibrosis was seen in the PBI group as compare to WBI group without boost (20% versus 5.8%; p = 0.06).

The William Beaumont group matched 174 patients treated with PBI (low dose rate Iodine-125 implant, 50 Gy over 96 h, dose rate of 0.52 Gy/h or HDR implant 32 Gy in 8 fractions, each separated by 6 h), with 174 patients treated with WBI with a median total dose of 60 Gy to the tumour bed [29]. With 36 months follow up, cosmetic outcome was more favourable in the PBI group as compared to the WBI group (excellent/good cosmesis 90% versus 83%; p = 0.17), although this was not statistically significant.

King et al. [30] matched 51 patients treated with PBI (low dose rate Iridium-192 implant 45 Gy over 4 days or HDR implant 32 Gy in 8 fractions over 4 days) with 94 patients treated with WBI to a mean dose of 59 Gy after breast-conserving surgery. A blinded panel of healthcare professionals scored cosmesis on a four-part scale (excellent, good, fair, poor) after reviewing photographic slides. At 20 months follow up, 75% patients in the PBI group and 84% patients with WBI had excellent/good cosmesis (p = not significant). Grade I and II treatment complications including skin erythema, desquamation, discoloration, hyperpigmentation, dimpling; breast pain, tenderness, shrinkage or fibrosis were significantly more common with WBI than PBI (80% versus 22%, p = 0.001). Grade III treatment complications requiring surgical intervention were not significantly different in the two groups (8% versus 5%, p = not significant).

Tata Memorial Hospital, India matched 27 patients treated with PBI using HDR brachytherapy 34 Gy in 10 fractions over 6–8 days with 67 patients treated with WBI (45 Gy in 25+ over 5 weeks followed by a tumour bed boost using electrons 15 Gy in 6 fractions or interstitial HDR brachytherapy with a single 10 Gy fraction [31]. At a median follow up of 43 months, cosmetic outcome was superior in the PBI group as compare to the WBI group (excellent/good cosmesis 88.9% versus 56%; p = 0.003). No significant difference was seen in the rates of moderate/severe breast fibrosis.

Effect of treatment volume on NTC in PBI series

There are several publications reporting on the efficiency and low toxicity using PBI with only a few evaluating the impact of treatment volume on NTC. The current literature on the volume effect of PBI for 3D-CRT/IMRT, electrons and single/multi source brachytherapy is summarised below.

3D-CRT/IMRT based PBI (level IV evidence)

Jagsi et al. [32] reported on the cosmetic outcome of 32 patients treated with PBI using IMRT at deep inspiration breath hold. All patients received 38.5 Gy twice daily fractionation over five consecutive days. At a median follow up of 2.5 years, 22% patients were scored as unacceptable cosmesis. Retrospective comparison between patients with acceptable and unacceptable cosmesis showed the mean proportion of breast volume receiving a minimum of 100% of the prescribed dose i.e. 38.5 Gy (V100) was lower in patients with acceptable cosmesis as compare to patients with unacceptable cosmesis (15.5% versus 23.0%; p = 0.02). The mean proportion of breast volume receiving a minimum of 50% of the prescribed dose i.e. 19.25 Gy (V50) was also smaller in the acceptable cosmesis group as compare to unacceptable cosmesis (p = 0.02).

Hepel et al. [33] also reported on a positive correlation between the volume of breast tissue treated with PBI and overall cosmesis. Sixty patients received PBI to a dose of 38.5 Gy twice daily fractionation over one week using 3D-CRT. At a median follow up of 15 months, 18% patients developed fair-poor cosmesis and 25% developed grade 2–4 subcutaneous fibrosis. In univariate analysis, the size of 3D-CRT target volume in proportion to the overall breast volume (PTV_Eval/WBV) correlated with fair/poor cosmesis (p = 0.02) and grade 2–4 subcutaneous fibrosis (p = 0.10). These two publications suggested an association between breast volume irradiated in PBI and normal tissue complications.

In contrast, Chen and colleagues from the William Beaumont group reported no association between overall cosmesis and PTV_Eval/WBV [34,35]. Ninety-four patients received PBI to a dose of 38.5 Gy twice daily fractionation over five consecutive days using 3D-CRT. Of the 56 patients with cosmesis assessment of ≥48 months, 11% patients had fair to poor cosmesis and 3% patients had grade 3 fibrosis with no association between cosmesis/subcutaneous toxicity and PTV_Eval volume.

Single source brachytherapy/multi-source brachytherapy (level IV evidence)

Multi-source brachytherapy has been used for PBI for many years with most publications focusing on local control rates and limited reporting of normal tissue toxicity. Some have reported on factors associated with normal tissue toxicity and have commented on a positive correlation between NTC and the implant volume. Yeo et al. [36] reported on the efficacy and safety of PBI using multi-source brachytherapy for 48 patients with a median follow up of 53 months. A dose of 34 Gy in 10 fractions over five days was delivered to the tumour bed plus a 1–2 cm margin. Fourteen percent patients developed grade 2 subcutaneous toxicity with V100 and V150 significantly higher in these patients (p = 0.018 and 0.034, respectively). No patient had poor cosmesis.

Wazer et al. [37] reported on the variables associated with late toxicity and long term cosmetic outcome after multi-source brachytherapy PBI using pooled data from Tufts University, Brown University and Virginia Commonwealth University. The data for 75 patients with a median follow up of 6 years were analysed. The number of dwell positions (i.e. total volume of implanted breast tissue) correlated with late cosmetic outcome (p = 0.04). Lawenda and colleagues reported no association between implant volume and overall cosmetic outcome for 48 patients treated with low dose rate brachytherapy at their centre from 1997–2001 [38]. The purpose of the study was to evaluate dose escalation in PBI and the total dose was escalated in three groups of 50 Gy, 55 Gy and 60 Gy and implant volume was divided into four groups. A non significant trend between dose escalation and fibrosis was seen but they also observed a decline in the incidence of breast fibrosis with increase in implant volume, a finding contrary to current published literature.

The Mammosite single source brachytherapy device (Hologic Inc., Medford MA, USA) has been used for PBI since approval by the FDA in 2002. Many groups have reported on its efficacy with
conflicting reports on the correlation between balloon volume and overall cosmesis/fibrosis [39–43]. The American Society of Breast Surgeons Mammosite Breast Brachytherapy registry trial is the biggest series published to date [44]. The series reported on factors associated with optimal cosmetic outcome and includes 1440 patients with a median follow up of 43 months. On multiple regression analysis, the balloon filling volume was not a significant variable affecting cosmesis ($p = 0.085$). Breast related wound infection and balloon to skin distance were found to be the most important variables affecting cosmesis.

**Breast fractionation studies**

The Royal Marsden Hospital and Gloucestershire Oncology Centre (RMH/GOC) trial [45] randomised 1410 patients with early breast cancer into three WBI regimens. The control arm consisted of 50 Gy in 25 fractions over 5 weeks. The two test arms were (1) 39 Gy in 13 fractions over 5 weeks and (2) 42.9 Gy in 13 fractions of 50 Gy in 25 fractions over 5 weeks. The two test arms were (1) breast cancer into three WBI regimens. The control arm consisted (3.3% increase per Gy). Compared to this fractionation effect, an induration with a dose escalation of 7 Gy to the whole breast was 27% and 51%, respectively suggesting a 24% increased risk of are 46.7 Gy and 53.8 Gy for test arms 1 and 2, respectively. The risk of moderate to severe induration at 10 years between Arm 1 and 2 was 27% and 51%, respectively suggesting a 24% increased risk of induration with a dose escalation of 7 Gy to the whole breast (3.3% increase per Gy). Compared to this fractionation effect, an escalated dose to tumour bed alone i.e. boost of 15.5 Gy in 7 fractions (EQD2 of 16 Gy) increased the risk of induration by 17% (1.05% increase per Gy). These data indicate a radiation volume-effect for breast tissue, as the effect of induration per Gy of radiation increases with breast volume irradiated.

**Discussion**

With the increasing use of CT planning, Partial Breast Irradiation techniques, simultaneous boost techniques and dose escalation studies, a better understanding of the dose-volume relationship for breast tissue is required. The current literature suggests that volumetric parameters affect NTC, although it is poorly quantified with some conflicting clinical results.

This overview faces several challenges. The late normal tissue toxicity post radiotherapy is influenced by several patient and treatment related factors (Table 3). These parameters were variable in the identified studies. A variety of treatment approaches have been used including photons, electrons, intra-operative techniques and brachytherapy. In addition, the reported studies have used different endpoints (fibrosis, cosmesis and telangiectasia) with several different scoring methods and a diverse period of follow up. These challenges make it difficult to draw firm conclusions on the qualitative and quantitative effect of dose–volume relationship for breast tissue. Some studies have also used bra size and chest wall separation as a surrogate for breast size. These methods though useful can have inherent inconsistency; pre-operative bra size may not reflect the true post-operative breast volume and chest wall separation only provide 2-dimensional information of the breast and may not necessarily represent volume of breast above or below the central axis. Breast volume in cm³ or ml should be a preferred method for reporting breast size.

The study by Borger et al. [12] using low dose rate iridium implants provides the most robust quantitative data on the dose-volume relationship. Seven independent factors were associated with breast fibrosis: old age, long follow up, clinical tumour size, cobalt-60 beam irradiation, total dose, implant volume and chemother-apy. For every 100 cm³ increase in irradiated boost volume, the risk of fibrosis increase four-fold and a two fold increase in boost volume will result in an 11% decrease in tolerance dose (NTD50). It is however difficult to be certain as to how the low dose rate brachytherapy data can be extrapolated to HDR brachytherapy, electron and photon boost techniques. The RMH/GOC trial [45] which used electron boost provides indirect quantitative information on the dose–volume relationship for NTC. For every Gy increase in boost dose, the risk of moderate to severe breast induration increases by 1% as compared to 3% when the whole breast dose is increased by one Gy. The EORTC boost trials [6,9] also provided quantitative information on the volumetric effect where increasing the tumour bed margin from 1.5 cm to 3 cm doubles the rates of moderate/severe fibrosis from 15% to 30%. However, it is possible that the increase in NTC is secondary to a combination of larger boost volume and a steeper dose–response curve as total dose increased up to 76 Gy in the incomplete excision group. The EORTC boost trial also reported boost volume as a predictor of moderate/severe fibrosis and worsecosmesisinunivariateanalysisbutnotinmultivariableanalysis. There are several possible explanations for this: (1) There is no true independent volumetric effect. (2) Other factors such as total surgical excision volume, post-operative complications, concomitant chemotherapy, quality of radiation and boost treatment were more dominant variables affecting NTC when compared to the boost volume. (3) Total boost volume was dependent on the boost technique, with the smallest boost volume for interstitial technique (60 cm³), more than twice the volume with electron boost (144 cm³) and nearly five times as large with photon boost (288 cm³) [46]. The rate of fibrosis was similar despite a considerable smaller treatment volume using interstitial brachytherapy. It

<table>
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<th>Table 3</th>
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<td><strong>Patient and treatment factors associated with late normal tissue complications.</strong></td>
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<td><strong>Factors</strong></td>
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<td>Increasing age [56,75]</td>
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<td>Smoking [53,75]</td>
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<td>Genetic variation [47,85]</td>
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Dose inhomogeneity (double trouble) [87,88] Hypofractionation and dose inhomogeneity (triple trouble) [88]
is possible that the effect of heterogeneity of dose distribution (which may lead to increased fibrosis) is neutralised by a smaller treatment volume. A direct comparison of boost volume using different boost techniques is not practical.

Randomised controlled trials including the Hungarian PBI trial [25] and TARGIT trial [26] provides a strong qualitative indication on a volume–NTC relationship. They report superior cosmetic outcomes and reduced NTC rate in the PBI arm when compared to the WBI. However, these are significant differences in the radiotherapy techniques and fractionation schedules between the two groups, making it difficult to draw conclusions on the radiation volume effect on breast tissue. The other reported randomised trial from Christie had reported a higher rate of breast fibrosis and telangiectasia in the WBI arm [23]. A dose–response relationship for late radiation effects including telangiectasia and breast fibrosis is well established [6,47,48] and these dissimilar results can possibly be explained by calculating the 2 Gy equivalent dose (EQD2) for the PBI and WBI groups using an α/β ratio of 3.1 [45] for fibrosis. The WBI group had received a lower dose of 45 Gy EQD2, compared to 63–70 Gy for the PBI group in the Christie trial.

The four matched case series [28–31] comparing PBI and WBI also showed favourable cosmesis and lower NTC risk with PBI except for higher grade 2–3 fibrosis in the Hungarian series [28]. It is possible that significant dose heterogeneity with the mean dose non-uniformity ratio of 0.45 using Iridium-192 implants could explain the increased grade 2–3 fibrosis in the PBI arm in the Hungarian series. These case series are a retrospective analysis with a small number of patients and other factors known to influence NTC including breast volume, post-surgical cosmesis, boost radiation, chemotherapy and smoking are not considered. Also, similar to the randomised trials, they evaluated PBI and WBI using different radiotherapy techniques and fractionation.

IMPORT LOW trial and The Danish Breast Cancer Cooperative Group trial (not reported) are two of the few randomised trials comparing Partial Breast Irradiation (PBI) versus whole breast irradiation (WBI) with volume of breast irradiated as the solitary randomisation variable. IMPORT LOW is a randomised Phase 3 trial comparing WBI with two dose level of PBI delivered using IMRT in women with low risk breast cancer and has completed target accrual of 2000 patients in 2010 [49,50]. The control arm (WBI) delivers 40 Gy in 15 fractions over 3 weeks to the whole breast. Arm 1 delivers synchronous 40 Gy in 15 fractions to the partial breast PTV and 36 Gy in 15 fractions to the remainder of the whole breast. Arm 2 (PBI) delivers 40 Gy in 15 fractions to the partial breast PTV alone (Supplementary material- Fig. 1). The primary endpoint is local tumour control in the ipsilateral breast and the secondary endpoints include location of tumour relapse, contralateral primary tumours, regional and distant metastases, late adverse effects in normal tissues, quality of life (QOL) and economic evaluation.

The Danish Breast Cancer Cooperative Group trial is a Phase 2 study comparing PBI to WBI in low risk breast cancer patients with both treatment arms receiving 40 Gy in 15 fractions over 3 weeks [51]. The primary endpoint for this study is grade 2–3 breast fibrosis after radiotherapy and the secondary endpoints are other late morbidity, local recurrence and genetic risk profiling for development of late radiation morbidity. The results on these two trials regarding late normal tissue effects will not become available for several years, but will be able to give definitive data regarding the effects of irradiated breast volume on normal tissue effects.

The 3D-CRT/IMRT based PBI series [32–34] have conflicting reports on the relationship between the treated volume and NTC. These reports have been compared by Bentzen and colleague [52] which may explain these contradictory results. Post surgical defect and cosmesis are important variable influencing overall cosmesis [53] and the mean excision cavity volume was possibly smaller for William Beaumont group as compared to the other two series. Chen et. al. [34] optimised the IMRT plans with hot spots of <110% as compared to the other two series which accepted the hot spots of <120%. In addition, Jagsi et al. [32] used breath hold which may have reduced the spread of planned APBI beams seen with free breathing. Ultimately, mature data from the ongoing Phase 3 NSABP B-39/RTOG 0413 trial will answer if an association between breast volume irradiated in APBI and normal tissue complications is real.

Other studies evaluating the relationship between volume of breast irradiated and NTC are mainly single centre case series. A variety of treatment modalities have been used including brachytherapy, IORT using low energy X-ray, 3D-CRT/IMRT. Overall, most studies support a positive association between the boost/treatment volume and NTC risks. However, this association is confounded by other factors including extent of surgical excision, total delivered dose, dose fractionation, post-operative complications and brachytherapy dose inhomogeneity. Surgical excision volume and baseline surgical cosmesis are significant factors affecting cosmesis [11,54–56]. A larger surgical excision would also imply a larger brachytherapy boost volume and a larger applicator size for IORT. It is difficult to draw strong support on the independent volume effect on NTC based on the results of these case series. A small number of studies in the literature have suggested no independent dose–volume relationship for breast tissue. The Fox Chase Cancer Center series [19] with more than 3000 patients showed no independent association between boost cut-out size and cosmesis/breast fibrosis. Only the bra cup size and electron energy were found as independent variables associated with fibrosis. This is however a retrospective series of patients treated over 38 years, with a variable boost dose of 10–18 Gy. There was no information on the actual treated boost volume and no distinction was made between physician and patient cosmetic score. Surgical and radiotherapy techniques have also improved over the last four decades, which may also affect overall cosmesis and breast fibrosis. The brachytherapy boost series with no volume–NTC correlation [57,58] had small number of patients with fewer NTC events. It is possible that surgical and other radio-therapeutic parameters variables were dominant in affecting NTC than a small difference in boost volume. Studies using mammosite have also consistently showed a lack of correlation between NTC and mammosite balloon volume. This could be secondary to a small absolute difference in irradiated breast volume with change in balloon fill and a relatively smaller target volume for mammosite brachytherapy as compare to 3D-CRT [59,60].

Future directions

More robust data are required to quantify the impact of volumetric parameter on breast NTC probability. The current PBI versus WBI trials database with mature follow up and prospectively collected dosimetric data will provide more qualitative and quantitative data which may help in creating NTC analytical function in the future. Meanwhile, efforts should be made to avoid unnecessary treatment of normal breast tissue by optimal localisation of tumour bed using implanted surgical markers and/or ultrasound [61,62] and using conformal radiotherapy techniques with simultaneously integrated boost [63]. The use of image guided radiotherapy (IGRT) with correction strategy can reduce irradiated breast tissue during PBI and boost treatment [64], and will need further investigation within clinical trials.

A better understanding of tissue dose–volume relationship can be clinically exploited in high risk patients. For example, dose escalation in prostate radiotherapy exploits the radiation dose–volume principle: a small volume of rectum can receive a higher dose with no increase in toxicity, by reducing the dose to rest of the rectal volume using IMRT [5]. The St. George and Wollongong trial from
Sydney suggests that this modulation effect is also present in breast tissue [65]. The trial randomised 688 patients with T1-2N0-1 breast cancer between standard arm of WBI with 50 Gy in 2 Gy daily fractions (no boost) and test arm of WBI of 45 Gy in 1.8 Gy daily fractions plus a 16 Gy tumour bed boost. The overall cosmesis was scored by a five person panel using digital photographs as excellent, good, fair and poor. 79% patients in the test arm with boost and 68% patients in the standard arm had excellent/good cosmesis (p = 0.016). The rate of moderate to severe breast fibrosis at five years was similar in both treatment arms. These results are contrary to the current literature of worse cosmetic outcome and higher rates of breast fibrosis with additional boost radiation. One possible explanation for these results is that a modest dose reduction to the whole breast allowed dose escalation to the tumour bed without the expected increase in normal tissue toxicity.

This dose modulating effect on the breast is further investigated in the IMPORT High trial [50,66] which is currently open to recruitment. The trial randomises high risk patients between three groups; standard arm: 40 Gy in 15 fractions to the whole breast over 3 weeks with a 16 Gy in 2 Gy daily fraction sequential tumour bed boost, Test arm 1: 36 Gy in 15 fraction to the low risk volume of the breast, 40 Gy in 15 fractions to the index quadrant + concomitant tumour bed boost of 48 Gy in 15 fractions and Test arm 3: 36 Gy in 15 fractions to the low risk volume of the breast, 40 Gy in 15 fractions to the index quadrant + concomitant tumour bed boost of 53 Gy in 15 fractions (Supplementary-Fig. 2). The trial tests the hypothesis that decreasing the radiation dose to the whole breast tissue by a very small amount (40 Gy to 36 Gy) and treating an iso-effective dose to the index quadrant and tumour bed (Arm 1), may result in less normal tissue side effects compared to the control group. It will also test if decreasing the radiation dose to the whole breast tissue by a very small amount allows dose escalation to the tumour bed (area of highest risk of local recurrence) without an increase in normal tissue side effects (Arm 2).

Conclusions

Adjuvant breast radiotherapy reduces local recurrence and improves overall survival but at a cost of increased normal tissue side effects. This can have a significant physical and psychological impact on patients [67]. Many factors influence NTC after breast RT including breast volume, post-surgical cosmesis, boost radiation, chemotherapy and smoking. In addition, the current literature seems to suggest that volumetric parameter is also important. More direct evidence will emerge from the IMPORT LOW, Danish Breast Cancer Co-operative Group trial and the dosimetric data collected prospectively from the various Accelerated PBI trials. There is emerging evidence to support the hypothesis that a modest dose reduction to part of the breast facilitate dose escalation to the tumour bed, and this concept will be tested further within a second larger randomised controlled trial.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.radonc.2012.04.025.

References


Original Article

The Effect of Image Guidance on Dose Distributions in Breast Boost Radiotherapy

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Abstract

Aims: To determine the effect of image-guided radiotherapy on the dose distributions in breast boost treatments.

Materials and methods: Computed tomography images from a cohort of 60 patients treated within the IMPORT HIGH trial (CRUK/06/003) were used to create sequential and concomitant boost treatment plans (30 cases each). Two treatment plans were created for each case using tumour bed planning target volume (PTV) margins of 5 mm (achieved with image-guided radiotherapy) and 8 mm (required for bony anatomy verification). Dose data were collected for breast, lung and heart; differences with margin size were tested for statistical significance.

Results: A median decrease of 29 cm³ (range 11–193 cm³) of breast tissue receiving 95% of the prescribed dose was observed where image-guided radiotherapy margins were used. Decreases in doses to lungs, contralateral breast and heart were modest, but statistically significant (P < 0.01). Plan quality was compromised with the 8 mm PTV margin in one in eight sequential boost plans and one third of concomitant boost plans. Tumour bed PTV coverage was <95% (>91%) of the prescribed dose in 12 cases; in addition, the required partial breast median dose was exceeded in nine concomitant boost cases by 0.5–3.7 Gy.

Conclusions: The use of image guidance and, hence, a reduced tumour bed PTV margin, in breast boost radiotherapy resulted in a modest reduction in radiation dose to breast, lung and heart tissues. Reduced margins enabled by image guidance were necessary to discriminate between dose levels to multiple PTVs in the concomitant breast boost plans investigated.

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Key words: Breast boost; image-guided radiotherapy; margin reduction; organs at risk; treatment planning

Introduction

Whole breast radiotherapy (WBRT) after breast-conserving surgery is standard treatment for patients with breast cancer. Patients with a high risk of recurrence receive a radiotherapy boost dose to the tumour bed [1]. Although clinical localisation and treatment with electron beams is common, accurate localisation of the tumour bed is achieved only if internal markers are used to indicate its position on computed tomography images [2,3]. This improved localisation enables conformal photon dose distributions to be created that deliver the boost dose to the tumour bed, while ensuring the dose to normal tissues is minimised.

This is relevant particularly for studies in which escalated doses are being tested with sequential or integrated boost techniques [4,5].

Standard imaging verification for breast radiotherapy uses bony anatomy landmarks, and often the breast contour, to match megavoltage electronic portal images to pretreatment digitally reconstructed radiographs. This imaging is appropriate for WBRT with standard dose prescriptions and results in planning target volume (PTV) margins of 10 mm. Conformal dose distributions and higher boost doses require knowledge of the tumour bed position. Although megavoltage imaging is straightforward and widely available, it requires a tumour bed surrogate, such as the ribs, as neither the tumour bed nor internal markers, such as surgical clips, can be visualised on megavoltage images. The tumour bed may be identified with gold markers, which are visible on megavoltage images, but these are not widely...
used surrogates [6]. Imaging at kilovoltage energies is required to visualise surgical clips and, hence, determine tumour bed positions more accurately. This information and an appropriate verification correction protocol enable a decrease in tumour bed PTV and doses to non-target tissues, potentially reducing adverse effects from radiotherapy and enabling the use of higher boost doses with the aim of improved local control.

Coles et al. [7] raised the possible positive effect of image guidance on tumour bed boost volumes in their discussion of hypofractionation. This work quantified the magnitude of the changes in breast tissue and organ at risk doses in breast boost radiotherapy that resulted from an image-guided margin compared with a larger margin derived from standard imaging.

Materials and Methods

This study forms part of a National Institute for Health Research (NIHR) Efficacy and Mechanisms Evaluation (EME) programme investigating image guidance in breast radiotherapy and is embedded within the UK IMPORT HIGH trial [4]. Ethical approval was granted for the EME study by the Cambridgeshire 4 Research Ethics Committee on 22 October 2010.

The IMPORT HIGH trial is testing the hypothesis that adjusting the fraction size is a more effective strategy of dose escalation than adjusting the fraction number, for women at greater than average risk of local recurrence. For the test arms, this results in a planned dose distribution with three dose levels across the breast: an escalated dose to the tumour bed; a standard dose to the partial breast containing the tumour bed and a reduced dose to the rest of the breast. This pattern reflects the potential local recurrence variation in the breast for women at greater than average risk of local recurrence; the tumour bed boost dose is delivered concomitantly with the whole and partial breast doses. The control arm of the trial is WBRT and a sequential photon boost to the tumour bed.

Target Structures and Organ at Risk Delineation

Computed tomography planning data sets from 60 patients treated between July 2009 and December 2011, within the IMPORT HIGH trial at one centre, were selected consecutively from an alphabetically ordered list. Surgical clips marking the position of the tumour bed had been inserted at the time of breast-conserving surgery. The clinical target volume of the tumour bed (CTV_TB) encompassed the surgical clips, any seroma and any architectural distortion. Whole breast target volumes (WB_TV) were defined from the whole breast treatment fields and excluded the lung and ribcage and tissue within 5 mm of the skin surface. This volume is not an ICRU 50/62 defined PTV; it is used in the IMPORT HIGH Trial as a reporting structure and to provide consistency across a large number of participating centres and clinicians. The trial protocol recommends the CTV_TB is less than 5% of the WB_TV to restrict the extent of the high dose volume, to facilitate planning and to limit any possible adverse effects. The ipsilateral lung, contralateral lung, heart and contralateral breast were delineated as organ at risk structures.

Tumour Bed Planning Target Volume

The CTV_TB was expanded to create two PTVs (PTV_TB) for each data set. These are illustrated in Figure 1. The first used a 5 mm margin as required by the IMPORT HIGH trial and all patients were treated with plans based on this margin, with verification carried out using image guidance and tumour bed clip-based matching. Population set-up errors are not the topic of this paper. However, analyses of imaging data from the trials by Coles et al. [6] and Harris et al. [8] have described how image guidance using tumour

![Figure 1](image_url)

**Fig 1.** Axial (A) and sagittal (B) views showing the clinical target volume of the tumour bed (CTV_TB; red), the planning target volume of the tumour bed (PTV_TB) = 5 mm (yellow) and its corresponding 95% isodose line (purple), PTV_TB = 8 mm (sky blue) and its 95% isodose line (green). Small circles indicate tumour bed surgical clips.
bed markers and set-up error correction strategies reduced population set-up errors. Applying a standard margin formula [9] to these population errors gave a PTV_{TB} margin estimate of <5 mm as required.

The second PTV_{TB} margin was 8 mm. This margin was derived from an analysis of 1574 images from 218 verification data sets from patients treated within IMPORT HIGH (with image-guided verification based on tumour bed markers as given in the trial protocol). The images were re-matched using bony anatomy as a surrogate for the tumour bed. A no action level protocol [10] was simulated based on data from fractions 1–3, assuming all systematic errors were corrected on fraction 4; this is typical of a standard breast imaging verification protocol. The calculated population systematic (2.7 mm) and random errors (4.0 mm) were used to derive the 8 mm margin via a standard margin formula [9]. This represents a standard bony anatomy verification margin for breast radiotherapy for comparison with the image guidance-based margin of 5 mm.

Planning

Thirty cases were planned with a sequential conformal photon boost to the tumour bed and 30 with a concomitant boost. The sequential boost consisted of phase 1 WBRT of 40 Gy in 15 fractions followed by a phase 2 of 16 Gy in eight fractions to the tumour bed boost volume only. The concomitant boost was delivered in 15 fractions with a total dose of 36 Gy to the whole breast via tangential fields; 40 Gy to the partial breast and an escalated dose to the tumour bed via co-planar conformal fields. The escalated dose was 48 Gy or 53 Gy (15 patients each) depending on randomisation [4]. Plan assessment criteria and organ at risk constraints for the IMPORT HIGH trial were used to guide the planning (Table 1). Plans were generated using Philips Pinnacle3 v8.0 and v9.0 treatment planning system using the forward planned method described by Donovan et al. [11]. The dose calculation used a collapsed cone convolution algorithm with a 0.25 × 0.25 × 0.25 cm grid. Beam energy was 6 MV predominately; 10 MV was used to improve coverage in cases with large chest wall separation and/or large seroma.

Analysis

The main assessment metric used was the volume of tissue receiving 95% of the tumour bed dose, i.e. the effect on breast tissue of the plans resulting from the two different PTV_{TB} margins. Data were collected on doses to the lungs, heart and contralateral breast from the plan assessment criteria shown in Table 1 and mean heart and lung doses. The data were tested for normality and the Wilcoxon signed ranks test used to test for the statistical significance of the differences in the metrics between plans with 5 and 8 mm PTV_{TB} margins. Data were dichotomised by tumour bed laterality and the Mann–Whitney test statistic used to determine the statistical significance of any differences. In addition, data were collected on the number of plans that passed or failed the trial PTV coverage criteria.

Results

Patient Characteristics

Thirty-five patients had left-side and 25 right-side disease. The median (range) of CTV_{TB} volume was 10.2 cm³ (2.4–205.0 cm³); PTV_{TB,5} mm was 37.6 cm³ (14.7–296.6 cm³); PTV_{TB,8} mm was 59.1 cm³ (23.7–358.5 cm³). There was no statistically significant difference in CTV_{TB} or PTV_{TB} volumes (grouped into 5 or 8 mm) between the sequential and concomitant boost plans, or the concomitant boost plans at 48 or 53 Gy.

Effect on Breast Tissue

Table 2 summarises the volumes of breast tissue receiving 95% of the tumour bed dose. The absolute

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of IMPORT HIGH planning requirements. Bold indicates mandatory criteria; where two dose levels are given these are for the 48 or 53 Gy test arm doses of the IMPORT HIGH trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum dose</td>
<td>Median dose</td>
</tr>
<tr>
<td>Sequential boost</td>
<td>Whole breast</td>
</tr>
<tr>
<td>Tumour bed PTV</td>
<td>&gt;95% volume &gt;53.2 Gy</td>
</tr>
<tr>
<td>Concomitant boost</td>
<td>Whole breast</td>
</tr>
<tr>
<td>Partial breast PTV</td>
<td>&gt;90% volume &gt;36 Gy</td>
</tr>
<tr>
<td>Tumour bed PTV</td>
<td>&gt;95% volume</td>
</tr>
<tr>
<td>&gt;45.6 or 50.4 Gy</td>
<td></td>
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Max (Gy) | Maximum allowed volume (%) |
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<tbody>
<tr>
<td>Organs at risk</td>
<td>Ipsilateral lung</td>
</tr>
<tr>
<td></td>
<td>Contralateral lung</td>
</tr>
<tr>
<td></td>
<td>Heart</td>
</tr>
<tr>
<td></td>
<td>Contralateral breast</td>
</tr>
</tbody>
</table>

PTV, planning target volume.
Dosimetric data given as median (range) for each parameter. Differences were statistically significant (P < 0.01).}

<table>
<thead>
<tr>
<th>Volume of breast tissue receiving 95% of the tumour bed prescription dose for 5 and 8 mm planning target volume of the tumour bed (PTV_TB) margins for sequential and concomitant boost plans (30 cases each). Data are given as median (range) and presented in absolute volume (cm³) and as a percentage of the whole breast volume. Differences were statistically significant (P &lt; 0.01)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High dose volume (cm³)</strong></td>
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<tr>
<td><strong>PTV_TB = 5 mm</strong></td>
</tr>
<tr>
<td>Sequential boost</td>
</tr>
<tr>
<td>Concomitant boost</td>
</tr>
<tr>
<td>Percentage of whole breast volume (%)</td>
</tr>
<tr>
<td>Sequential boost</td>
</tr>
<tr>
<td>Concomitant boost</td>
</tr>
</tbody>
</table>

Volumes of breast tissue receiving a high dose were statistically significantly different between the two plan types (P < 0.01); the 95% volumes were larger in the sequential boost plans. Although it is strongly recommended that the CTV_TB is less than 5% of the whole breast volume, it is not mandatory and cases are not excluded if this value is exceeded. The cases were chosen from an alphabetically ordered list in sequence. By chance there were four cases with CTV_TB volumes >5% in the sequential boost cohort, whereas there was only one in the concomitant boost cohort.

The magnitude of the change in volume between a PTV_TB of 5 mm to that of 8 mm was not different between sequential and concomitant boost plans; between left and right breasts or between the 48 and 53 Gy boost dose. The difference data were combined. The median decrease in the high-dose volume was 29 cm³ (range 11–193 cm³) when the margin was reduced from 8 mm to 5 mm. This equates to an additional 3.3% (median) up to 11.8% (maximum) of the whole breast being spared high-dose irradiation for these boost treatments from the use of image guidance.

**Organs at Risk**

As anticipated, all dose measures for the organs at risk increased with the use of the 8 mm standard verification margin, albeit modestly (Table 3). Only mean heart dose and V_{13Gy} for the heart had a statistically significant association with tumour bed laterality (P < 0.01); values were higher in the left breast group.

**Impact on Treatment Plans**

Where the image-guided margin of 5 mm was used, 56 cases met all plan assessment criteria (given in Table 1). Minimum dose coverage of the tumour bed was below 95% (above 91%) in the remaining four cases (two sequential and two concomitant boost). These were all left breast treatments where the tumour bed and chest wall were in close proximity, the PTV_TB extended into lung and overlay the heart (see Figure 2); a compromise was accepted between coverage and heart dose for the clinical treatment. Additionally, in one of the two failing concomitant boost cases the whole breast maximum dose-volume limit was exceeded; 9.7% rather than 5% or less. This patient had a CTV_TB of 49 cm³ (because of a large seroma), whereas the median CTV_TB volume of patients in the study was 9 cm³. Hence, the difficulty in obtaining a dose distribution meeting all the requirements.

As the IMPORT HIGH plan objectives were set for a 5 mm PTV_TB it was expected that increasing the margin to 8 mm would cause more plans to fail. This was observed as four sequential boost plans and 10 concomitant boost plans breached a mandatory planning constraint. In all the sequential boost cases and eight of the concomitant cases, the PTV_TB coverage was below 95% (between 91 and 94%).

<table>
<thead>
<tr>
<th><strong>Table 3</strong></th>
<th>Dosimetric data given as median (range) for each parameter. Differences in bold were statistically significant (P &lt; 0.01). There were 60 cases in each group except where indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PTV_TB = 5 mm</strong></td>
<td><strong>PTV_TB = 8 mm</strong></td>
</tr>
<tr>
<td>Ipsilateral lung V_{18Gy} (%)</td>
<td>9.6 (19, 27.6)</td>
</tr>
<tr>
<td>Ipsilateral lung mean dose (Gy)</td>
<td>5.6 (2.6, 11.3)</td>
</tr>
<tr>
<td>Contralateral lung V_{2.5Gy} (%)</td>
<td>0.0 (0.0, 12.2)</td>
</tr>
<tr>
<td>Sequential boost (30 cases)</td>
<td>1.6 (0.0, 13.4)</td>
</tr>
<tr>
<td>Concomitant boost (30 cases)</td>
<td>0.4 (0.1, 1.2)</td>
</tr>
<tr>
<td>Contralateral lung mean dose (Gy)</td>
<td>5.0 (0.0, 1.8)</td>
</tr>
<tr>
<td>Heart mean dose (Gy)</td>
<td>1.2 (0.4, 2.2)</td>
</tr>
<tr>
<td>Right breast (25 cases)</td>
<td>1.9 (0.6, 5.1)</td>
</tr>
<tr>
<td>Heart V_{13Gy} (%)</td>
<td>0.0 (0.0, 0.0)</td>
</tr>
<tr>
<td>Right breast cases (25)</td>
<td>0.2 (0.0, 5.5)</td>
</tr>
</tbody>
</table>

PTV_TB, planning target volume of the tumour bed.
In three concomitant boost cases, the maximum dose in the whole breast volume was exceeded by 2% in two cases and by 5% in the third. In nine concomitant boost cases the advised median dose to the partial breast of 40–44 Gy was exceeded by 0.5–3.7 Gy.

**Discussion**

The purpose of this work was to evaluate the effect of image guidance on normal tissue doses in breast boost radiotherapy. It forms part of a substudy of the IMPORT HIGH trial, which aims to evaluate the effect of image guidance [7]. Image guidance enables smaller PTV margins as population set-up errors are reduced. We show in other work [6,7] that image guidance does not need to be intensive (e.g., online and daily) to be effective, but it does require an appropriate verification strategy, i.e., one in which important structures (e.g., the tumour bed) can be visualised and corrections to couch position in the three cardinal directions are determined. These corrections have to be enacted so that systematic and random errors are reduced and the smaller margin is achieved in practice. Although it is predictable that smaller margins decrease the doses to organs at risk, we have quantified the benefit of image guidance for the sequential and concomitant photon breast boost techniques investigated.

We have shown that a reduction of 29 cm³ (11–193 cm³) in breast tissue receiving a high dose is obtained using internal markers, image guidance and a PTV_TB margin of 5 mm compared with an 8 mm margin based on bony anatomy with a standard verification protocol. Evidence suggests that there is a dose/volume relationship for normal tissue toxicity in breast tissue. However, these dose/volume constraints have yet to be quantified [12] and it is unclear what effect is expected at the dose levels and volumes we report. Bartelink et al. [13] reported that by administering a boost of 16 Gy after WBRT of 50 Gy, rates of fibrosis increased by about 15% from 13.2% (no boost group) to 28.1% at 10 years. Patients in the Bartelink study had a PTV margin of 1.5 cm compared with our much smaller values of 5 and 8 mm. If there is a dose–volume effect, we predict a lower rate of fibrosis than that in the European Organization for Research and Treatment of Cancer (EORTC) study, given the smaller volumes irradiated to a high dose within our treatment cohort.

The effect of the larger PTV_TB margin was modest on the reported organ at risk doses for both sequential and concomitant boost plans. The delivery of most of the therapeutic dose was via standard tangential fields, thus maintaining organ at risk sparing, even in these complex situations with an increased PTV_TB margin. The implications of the recent work by Darby et al. [14] are that even the small changes in mean heart dose presented here may be important given the linear relationship between mean heart dose and major coronary events. A modest change in mean heart dose is not a trivial change in the predicted absolute numbers of major coronary events within the survivor population, as this population is large and growing.

An interesting finding was the difficulty in meeting the set planning criteria in the boost plans when the PTV_TB margin was changed by only 3 mm. This was apparent particularly for the concomitant boost plans where one in three failed at least one of the criteria. In all cases where the low dose coverage of PTV_TB was less than 95%, the tumour bed was adjacent to the chest wall. The increase to an 8 mm margin caused the PTV_TB to protrude into the lung, hence 95% dose coverage was difficult because of the reduced lateral scatter component in lung tissue compared with chest wall or breast tissue; 5 mm PTV_TB margins in a conformal photon boost plan are beneficial particularly for these cases.

The compromised median dose in the partial breast (nine cases) is of particular importance to the IMPORT HIGH trial as this requires discrimination between the dose levels of the whole, partial and tumour bed regions of the breast. The larger PTV_TB with the 8 mm margin encroached into the partial breast volume, the consequence of this was to blur the distinction between the dose levels of these volumes.
and hence the median dose to the partial breast increased. This work shows the importance of image guidance to achieve small margins, thus enabling the dose distributions required for concomitant boost plans of this complexity; this is in addition to its benefits in reducing tissue doses.

Conclusion

Image-guided margins resulted in modest reductions in radiation doses to non-target breast, lung and heart tissues for both sequential and concomitant boost treatments compared with margins derived from standard imaging based on bony anatomy as a surrogate for the tumour bed. Concomitant boost treatments benefit from the reduced margins achieved with image guidance as discrimination between dose levels of the multiple PTVs is not compromised.

Acknowledgements

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References

A multicentre study of the evidence for customized margins in photon breast boost radiotherapy

**Objective:** To determine if subsets of patients may benefit from smaller or larger margins when using laser setup and bony anatomy verification of breast tumour bed (TB) boost radiotherapy (RT).

**Methods:** Verification imaging data acquired using cone-beam CT, megavoltage CT or two-dimensional kilovoltage imaging on 218 patients were used. TB setup errors for laser-only setup (Δlaser) and for bony anatomy verification (Δbone) were determined using clips implanted into the TB as a gold standard for the TB position. Cases were grouped by centre, patient and treatment-related factors, including breast volume, TB position, seroma visibility and surgical technique. Systematic (Σ) and random (σ) TB setup errors were compared between groups, and TB planning target volume margins (MPTV) were calculated.

**Results:** For the study population, Δlaser was between 2.8 and 3.4 mm, and Δbone was between 2.2 and 2.6 mm, respectively. Females with larger breasts (p = 0.03), easily visible seroma (p = 0.02) and open surgical technique (p = 0.04) had larger Δbone. Females with medial tumours (p = 0.01) had smaller Δbone.

**Conclusion:** If clips are not used, margins should be 8 and 10 mm for bony anatomy verification and laser setup, respectively. Individualization of TB margins may be considered based on breast volume, TB and seroma visibility.

**Advances in knowledge:** Setup accuracy using lasers and bony anatomy is influenced by patient and treatment factors. Some patients may benefit from clip-based image guidance more than others.

**INTRODUCTION**

Cancer recurrence within the breast is most likely to occur in the region of the tumour bed (TB). A radiotherapy (RT) boost to the TB reduces the risk of local relapse and is recommended for patients at higher risk of recurrence. It has also been shown that an RT boost to the TB can increase the risk of normal tissue toxicity such as fibrosis. The risk of fibrosis may increase as the volume of the TB planning target volume (PTV) increases. A larger PTV may also affect the dose delivered to other normal tissues. For example, recent work by Darby et al suggests there is no safe dose threshold for cardiac tissues. A suitable boost PTV margin will encompass the TB throughout the course of RT and treat minimal non-target tissue to reduce the risk of both local relapse and normal tissue toxicity.

Titanium surgical clips and gold fiducial markers have been shown to be effective imaging surrogates for the TB. Here, we refer to both surgical clips and gold markers as clips. TB clips can in...
boost RT. Increasingly, photon boosts are used as it is easier to visualize and optimize planned dose distribution compared with electron boosts. Combining photon boost and TB clips enables the use of image-guided RT to verify the position of the TB. It has been shown that using clips, PTV margins of 5 mm can be used safely to deliver both sequential and synchronous photon boost RT with steep dose gradients. Clip-based image-guided RT and 5-mm PTV margins are strongly recommended by the Intensity Modulated Partial Organ Radiotherapy (IMPORT) trials group. However, this is not routine practice worldwide. A common alternative imaging verification method is X-ray (megavoltage or kilovoltage) imaging of bony anatomy, and if imaging is not available, a laser-based setup using skin marks is used. Neither X-ray imaging using bony anatomy nor laser setup can directly verify the position of the TB in the absence of implanted markers. This is because the breast can move independently from the chest wall and the TB may change in shape and size within the breast, e.g. reabsorption of the TB seroma fluid.

This study aimed to investigate the consequences of using laser-only verification or bony anatomy verification on setup accuracy in TB boost RT. The study used imaging data from five UK IMPORT High trial centres. These data were from kilovoltage cone-beam CT (kVCBCT), megavoltage CT (MVCT) and two-dimensional kilovoltage (2DkV) planar imaging. Analysis involved matching of clips and bony anatomy to reference images. The study investigated:

1. TB setup errors for (i) bony anatomy verification and (ii) laser-based setup, using TB clip position as the gold standard TB position.
2. Influence of patient-, surgery- and RT-related factors on TB setup errors, including breast volume, position of the TB, the presence of scroma, surgical technique, the presence of posterior fascia clip(s), number of clips, time from surgery to CT, time from CT to RT and trial arm.
3. Time required to match verification images with reference images to bony anatomy and clips.

**METHODS AND MATERIALS**

National Health Service Research Ethics Committee (REC) approval for this study was granted as a substantial amendment to IMPORT High trial centres. All IMPORT High patients consented for their imaging and planning data to be used for research.

**Patients**

218 patients, from 5 cancer centres were included (Centres A–E). All patients received whole breast RT and TB boost as part of the UK IMPORT High trial (testing sequential vs synchronous integrated boost). Patients consented for their data to be used for research purposes. All patients had surgical clips implanted into the TB and were treated using clip-based verification (using online or offline verification protocols) for their TB boost. This was a retrospective study, which had no impact on the patients’ treatment. Patients were selected sequentially, by the date of their treatment.

**Patient setup and imaging**

All patients were positioned using laser alignment of tattoos. Two or three tattoos were marked: one anterior, medial at the midline and one or two lateral. All centres used an immobilization wedge beneath the knees, centre B used ankle immobilization also, and all patients were treated in supine position using a breast board with either one or two arms abducted.

All patients had CT imaging for treatment planning. At treatment, patients were initially positioned using lasers (laser setup) and then imaged using either kVCBCT (Synergy, Elekta Ltd, UK) (Centre A, n = 79), MVCT (TomoTherapy, Accuray Inc., Sunnyvale, CA) (Centre B, n = 39) or orthogonal (0° and 90°) 2DkV fields (OBI Varian Oncology Systems Inc., Paolo Alto, CA) (Centres C, D and E, n = 40, 30 and 30, respectively). For Centre A, using an offline protocol, the mean number of images acquired was 5.2 for control arm patients (sequential boost) and 7 for test arm patients (synchronous boost). For centres an online protocol (B–E), the number of images acquired was 8 and 15 for control and test arm patients, respectively.

**Imaging data analysis**

All image data analysis for this study was performed offline. For each image, matching of the reference and verification images was performed using clip match and bony anatomy match (Figure 1). Clip match gave the translational shift between clip position after laser set-up and the reference clip position (on planning CT). Bony anatomy match gave the translational shift between bony anatomy position after laser set-up and the reference bony anatomy position (on planning CT). Shifts in the left–right (LR), superior–inferior (SI) and anteroposterior (AP) directions were recorded. The time to perform the clip and bone matches was recorded. One or two observers performed the matching of all images at each centre (Centre A, EH; Centre B, MM; Centre C, AB; Centre D, EH; and Centre E, EH and RP) and were blinded to image matches recorded during treatment.

Interobserver error analysis was carried out by three observers who matched three images from three patients selected at random, at Centres A (CBCT), B (MVCT) and C (2DkV). Mean setup error across observers was calculated per image, and the difference between each observer’s measurement and mean was determined. Interobserver error was the standard deviation in differences, calculated for each imaging technique. For intraobserver analysis, three observers, EH (CBCT and 2DkV), MM (MVCT) and AB (2DkV), were asked to match three images on three different days. Mean setup errors across repeat measurements were calculated per image, and the difference between each observer’s measurement and mean was determined. The intraobserver error was the standard deviation in differences calculated for each observer.

**Tumour bed setup errors and margins**

TB setup error after laser-based setup was the distance between the position of the TB clips after laser setup and the reference TB clip position, i.e. TB clip position was used as the gold standard for TB position. This was referred to as $d_{\text{laser}}$ and was the TB setup error if no imaging verification was used. TB
setup errors after bony anatomy verification were the distance
to the reference TB position. This was referred to as $d_{\text{bone}}$ and was the
TB setup error if imaging verification of bony anatomy was
performed and the patient was shifted to ensure bony anatomy
position was correct. An individual patient’s systematic and
random setup errors, for laser and bony anatomy verification,
were calculated using the mean and root mean square of
$d_{\text{laser}}$ and $d_{\text{bone}}$ using all images available for the patient. The group
systematic TB setup error for laser setup ($S_{\text{laser}}$) and bony anat-
omy verification ($S_{\text{bone}}$) and the group random TB setup error
for laser setup ($s_{\text{laser}}$) and bony anatomy verification ($s_{\text{bone}}$) were
calculated following refs.9 and.12 For bony anatomy verification,
TB setup errors are for an online imaging protocol with no action
level. A TB PTV margin (MTB) formulation for breast boost was
used to estimate the tumour bed margin required for laser setup
and bony anatomy verification:13

$$MTB = 2.5\sum + 0.3s,$$

To estimate $M_{\text{TB}}$, setup errors were added in quadrature with the
errors associated with using clips as a surrogate for the TB. TB
surrogate systematic and random errors were 1.2 and 0.9 mm,
respectively, based on the findings of.14

Patient- and treatment-related factors
Patient and treatment factors were collected (Table 1). Patient-
related factors included breast volume (whole-breast PTV con-
strained by skin surface and chest wall) and TB position
(Figure 2). Factors relating to patients’ surgery included apposed
(closed) or unapposed (open) cavity, the latter allowing seroma
fluid to accumulate. Seroma visibility was scored by a single
radiation oncologist (MM), who rated seroma as not visible/
subtle or easily visible15 and determined the number of clips
placed at the posterior fascia and in the excision cavity. RT-related
factors were days between CT and RT ($t_{CT-RT}$), days between surgery and RT ($t_{Surgery-RT}$) and trial arm.

Statistical methods
Cases were grouped according to patient- and treatment-related factors. Cases were dichotomized above and below the median value for breast volume, number of clips, time from surgery to planning CT ($t_{S-CT}$) and time from planning CT to RT ($t_{CT-RT}$). Additionally, cases were grouped according to TB position, seroma visibility, surgical closing technique, the presence of clip in the posterior fascia and trial arm (synchronous or sequential boost).

All data were tested for normality using Shapiro–Wilks test, and results indicated that the majority of the data (90%) were non-normal. Differences between median $d_{laser}$ and $d_{bone}$ and differences between centres were tested using Wilcoxon and Kruskal–Wallis tests.

Differences in systematic and random TB setup errors between (i) techniques (laser setup and bony anatomy verification), (ii) centres and (iii) between groups by patient- or treatment-related factors were tested. Non-parametric Levene’s test was used to test for differences in the variance of patient systematic $d_{laser}$ and $d_{bone}$. Kruskal–Wallis test was used to test for differences in the patients’ random $d_{laser}$ and $d_{bone}$. Relationships between variables shown to give significantly different systematic errors were investigated using Kruskal–Wallis tests. For factors with two or more groups, sensitivity analysis was performed by removing one group at a time and repeating tests using Holms–Bonferroni correction.

RESULTS
Tumour bed setup errors and margins
Unless otherwise stated, all differences were statistically significant, and $p$-values were <0.001. The number of patients and images (fractions) analysed for each centre is given in Table 2. At Centres A and C, all available images were analysed. At Centres B, D and E, five, six and six images per patient were analysed, respectively. Using only five images was validated by a comparison of setup data calculated using 15 images vs 5 images for 28 cases. The mean differences in patients’ mean and standard deviation of setup errors were 0.006 and 0.013 cm, respectively.

Table 1. Patient and treatment factors

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of patients with data in each group</th>
<th>Total number of patients with data</th>
<th>Median value (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient related:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB axial position (1/2/3/4) (Figure 1.)</td>
<td>30/96/33/59</td>
<td>218</td>
<td></td>
</tr>
<tr>
<td>TB SI position (1/2/3) (Figure 1.)</td>
<td>107/90/21</td>
<td>218</td>
<td></td>
</tr>
<tr>
<td>Breast volume (above median/below median) (cm$^3$)</td>
<td>109/109</td>
<td>218</td>
<td>855 (118–2847)</td>
</tr>
<tr>
<td>Surgery related:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seroma visibility (not visible/easily visible)</td>
<td>158/60</td>
<td>218</td>
<td></td>
</tr>
<tr>
<td>Surgical closing technique (closed/open)</td>
<td>113/88</td>
<td>201</td>
<td></td>
</tr>
<tr>
<td>Number of clips (above median/below median)</td>
<td>109/109</td>
<td>218</td>
<td>6 (4–14)</td>
</tr>
<tr>
<td>Clip in posterior fascia (no/yes)</td>
<td>40/178</td>
<td>218</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy related:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from surgery to CT (days)</td>
<td>101/102</td>
<td>203</td>
<td>133 (32–481)</td>
</tr>
<tr>
<td>Time from CT to RT (days)</td>
<td>102/102</td>
<td>204</td>
<td>20 (3–112)</td>
</tr>
<tr>
<td>Trial arm [synchronous (test) or sequential (control)]</td>
<td>72/146</td>
<td>218</td>
<td></td>
</tr>
</tbody>
</table>

RT, radiotherapy; SI, superior–inferior; TB, tumour bed.
Factors have been categorized according to the information they provide.
Median values and ranges are given for continuous variables.

Figure 2. Schematic diagram showing (a) tumour bed (TB) position viewed on axial CT slice (1 =medial, 2 =chest wall, 3 =anterior and 4 =lateral) and (b) TB superior–inferior position viewed on sagittal CT slice (1 = superior, 2 = middle and 3 = inferior).
Mean (and 95th percentile) absolute values of $d_{\text{laser}}$ and $d_{\text{bone}}$ in the LR, SI and AP directions are given in Table 2. Over all data, the mean absolute TB setup error for laser-only setup ($d_{\text{laser}}$) and for bony anatomy verification ($d_{\text{bone}}$) was $<4$ and $3$ mm in all directions, respectively. Compared with other centres, mean $d_{\text{laser}}$ and $d_{\text{bone}}$ was significantly greater and smaller in all directions for Centre B (MVCT), respectively. Variation between centres was greatest in the AP direction. $d_{\text{laser}}$ was statistically significantly greater than $d_{\text{bone}}$ in all directions across all centres.

Group systematic ($\Sigma$) and random ($\sigma$) errors for laser setup and bone verification are given in Table 3. Combining the data from all centres, $\Sigma_{\text{laser}}$ was statistically significantly greater than $\Sigma_{\text{bone}}$ in the LR and AP directions but not in the SI direction. Centre B had smaller $\Sigma_{\text{bone}}$ compared with other centres in all directions and had larger $\Sigma_{\text{laser}}$ compared with other centres ($p = 0.002$). TB margins for laser setup and bony anatomy verification are given in Table 4.

Association of tumour bed setup errors with patient- and treatment-related factors
Breast volume, seroma visibility and surgical technique were found to influence $\Sigma_{\text{laser}}$ (Table 3). Females with larger breasts ($p = 0.03$), easily visible seroma ($p = 0.04$) and who have received an open surgical closing technique ($p = 0.04$) had larger $\Sigma_{\text{laser}}$. Breast volume and TB axial position were found to influence $\Sigma_{\text{bone}}$. Breast volume and TB axial position were found to influence $\Sigma_{\text{bone}}$ (Table 3). $\Sigma_{\text{bone}}$ was larger in one direction for females with larger breasts ($p = 0.04$) and lateral tumours ($p = 0.04$). Females with medial tumours ($p = 0.002$) had smaller $\Sigma_{\text{bone}}$. No statistically significant associations between breast volume, TB position, seroma visibility and surgical closing technique were found.

Random TB setup errors (Table 6) for laser setup ($\sigma_{\text{laser}}$) were influenced by breast volume and seroma visibility. Random TB setup errors for bony anatomy verification ($\sigma_{\text{bone}}$) were influenced by TB axial position, breast volume, surgical closing technique and trial arm ($p-values < 0.05$).

The difference in combined timing data for matching using bony anatomy and clips was not statistically significant ($p = 0.29$). Within individual centres, the time to match images using bony anatomy ($t_{\text{bone}}$) and clips ($t_{\text{clip}}$) was different except for in Centre B. There was a statistically significant difference between matching times between all centres except between Centres D and E. The time required to analyse MVCT images was greatest.

**DISCUSSION**

Tumour bed setup errors and margins
TB setup errors using laser setup were slightly larger than those of bony anatomy verification. This study found the mean three-dimensional $d_{\text{bone}}$ (magnitude of the 3D vector for $d_{\text{bone}}$) to be 4.1 mm, smaller than that reported in previous studies on small cohorts ($n < 12$) with median of 5.4 mm and mean of 6 mm.
Although our results differ from those smaller studies, they are in keeping with a larger study by Penninkhof et al (n = 80) who found $\Sigma_{\text{laser}}$ to be 2.6 mm (LR), 2.5 mm (SI) and 3.4 mm (AP). Penninkhof et al also evaluated the systematic error after an offline 2D portal imaging protocol and found systematic error $\Sigma_{\text{bone}}$ of 2.3 mm (LR), 2.4 mm (SI) and 2.8 mm (AP), which were similar to values of $\Sigma_{\text{bone}}$ in the present study.

Variation in tumour bed setup errors between centres

There were small but statistically significant differences in absolute TB setup errors between centres. These were greatest in the AP direction. At Centre E, the cause was unknown and was investigated. At Centre B, a non-zero mean systematic mean error was due to couch sag, discussed in a previous report, which introduced the large mean absolute errors (Table 2) and overall systematic error (Table 3). Both Centres B and E used an online imaging protocol, which will remove these errors. Best practice is to eliminate such errors.

Centre B had smaller $d_{\text{bone}}$ in all directions. The poorer imaging resolution of MVCT and higher X-ray energy made MVCT matching less straightforward and is evident from longer matching times (Table 2). Poorer visibility of landmarks, making it harder to match images, may have accounted for the smaller difference between clips and bony anatomy at Centre B. Poorer image quality was proposed as a contributing factor to smaller estimated setup errors using megavoltage compared with kilovoltage imaging. Exclusion of centre B in the overall calculation of 3D TB setup error for bony anatomy verification gave 3D $d_{\text{bone}} = 4.8$ mm, which is closer to values reported in and.

Influence of patient- and treatment-related factors on setup errors

Breast volume, seroma visibility and surgical closing technique affected TB systematic errors for laser setup. Changes in clip positions (relative to each other) over a course of RT may affect the accuracy of laser setup to skin marks. Penninkhof found patients with open surgical technique had greater clip motion compared with those with closed surgical technique, although the difference in motion was not significant (p = 0.22). Previously, we observed greater changes in clip positions in patients with large seroma.

Axial TB position and breast volume affected TB systematic errors for bone verification. These factors and trial arm (synchronous or sequential boost) affected TB random errors. Hasan et al reported correlation between mean 3D TB setup errors for bony anatomy verification (3D $d_{\text{bone}}$) and breast volume. Our study showed that TBs in Regions 1 (medial) and 4 (lateral) had smaller and larger TB systematic errors in the AP and LR directions, respectively. It is likely that there was less movement of medial breast tissue compared with bony anatomy and significant movement of lateral breast tissue, which may help explain these results. Hasan et al reported correlation of 3D $d_{\text{bone}}$ with TB distance from the chest wall determined using planning CT (n = 27). Similarly, Topolnjak et al showed that the distance of the TB from the chest wall was correlated with the difference between TB setup errors for the chest wall and breast surface (r = 0.5, p = 0.034).

Time to perform clip and bony anatomy match

The time for matching using clips ($t_{\text{clip}}$) or bony anatomy ($t_{\text{bone}}$) was significantly different at individual centres. For Centre A (kVCBCT), $t_{\text{bone}}$ was less than $t_{\text{clip}}$ because bone matching was automated using chamfer matching (XVI synergy, Elekta Ltd, Crawley, UK). For centres C, D and E, $t_{\text{bone}}$ was greater than $t_{\text{clip}}$ indicating that 2DkV imaging bony anatomy matching was less time efficient than using clips. The differences

### Table 3. Systematic and random tumour bed (TB) setup errors for laser-only setup and bone verification for each centre and all centres combined

<table>
<thead>
<tr>
<th>Centre</th>
<th>Laser setup random error $\sigma_{\text{laser}}$ (mm)</th>
<th>Laser setup systematic error $\Sigma_{\text{laser}}$ (mm)</th>
<th>Bone verification random error $\sigma_{\text{bone}}$ (mm)</th>
<th>Bone verification systematic error $\Sigma_{\text{bone}}$ (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR</td>
<td>SI</td>
<td>AP</td>
<td>LR</td>
</tr>
<tr>
<td>ALL</td>
<td>3.3</td>
<td>2.9</td>
<td>3.3</td>
<td>3.1</td>
</tr>
<tr>
<td>A (kVCBCT)</td>
<td>4.4</td>
<td>3.2</td>
<td>4.7</td>
<td>3.3</td>
</tr>
<tr>
<td>C (2DkV)</td>
<td>4.1</td>
<td>2.6</td>
<td>3.5</td>
<td>3.7</td>
</tr>
<tr>
<td>D (2DkV)</td>
<td>4.2</td>
<td>3.0</td>
<td>3.1</td>
<td>2.5</td>
</tr>
<tr>
<td>E (2DkV)</td>
<td>4.1</td>
<td>2.6</td>
<td>3.5</td>
<td>3.7</td>
</tr>
</tbody>
</table>

### Table 4. Tumour bed planning target volume margins ($M_{\text{TB}}$) across all centres combined

<table>
<thead>
<tr>
<th>Laser setup $M_{\text{TB}}$ (mm)</th>
<th>Bone verification $M_{\text{TB}}$ (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR</td>
<td>SI</td>
</tr>
<tr>
<td>9.0</td>
<td>9.0</td>
</tr>
</tbody>
</table>

AP, anteroposterior; LR, left-right; SI, superior-inferior.
in time to match bony anatomy between centres using 2DkV imaging are unknown but may be a result of different observers.

Clinical relevance
The IMPORT High trial protocol recommends clip verification and a 5-mm PTV isotropic margin for boost RT. We calculated that a 9–10 mm and 7–8 mm margin is required for laser setup and bony anatomy verification, respectively (Table 4). Larger margins are likely to increase PTV volume and the dose to normal breast tissue and the heart. Where possible, clip verification should be used; if this is not available, bony anatomy verification (CBCT or 2DkV) offers modest reduction in PTV volume compared with laser-only setup. For bony anatomy verification, we assumed an online protocol with no action level; if an action level or offline protocol is used, these margins may be greater. In addition, clips may reduce setup error for the whole breast RT (SI WB); using bony anatomy as a surrogate for the whole breast, we found that SI WB was significantly smaller in all directions after clip setup compared with after laser setup (data not given). This implied that in a synchronous boost setting, clip setup would allow a whole-breast PTV margin reduction. Further work is required to quantify this reduction.

Table 6. Systematic tumour bed (TB) setup errors for laser setup ($\Sigma_{\text{laser}}$) and for bone verification ($\Sigma_{\text{bone}}$) for groups determined using patient- and treatment-related factors

<table>
<thead>
<tr>
<th>Laser</th>
<th>Factor</th>
<th>Group 1</th>
<th>$\Sigma_{\text{laser}}$ (mm)</th>
<th>Group 2</th>
<th>$\Sigma_{\text{laser}}$ (mm)</th>
<th>p-value</th>
<th>Direction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Breast volume</td>
<td>$&lt;855,\text{cm}^3$</td>
<td>2.5</td>
<td>$\geq855,\text{cm}^3$</td>
<td>4.2</td>
<td>0.03</td>
<td>SI</td>
</tr>
<tr>
<td></td>
<td>Seroma visibility</td>
<td>Not visible/subtle</td>
<td>2.8</td>
<td>Easily visible</td>
<td>3.5</td>
<td>0.02</td>
<td>LR</td>
</tr>
<tr>
<td></td>
<td>Not visible/subtle</td>
<td>2.6</td>
<td>Easily visible</td>
<td>3.2</td>
<td>0.002</td>
<td>SI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not visible/subtle</td>
<td>3.1</td>
<td>Easily visible</td>
<td>4.1</td>
<td>0.005</td>
<td>AP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgical closing technique</td>
<td>Closed</td>
<td>2.7</td>
<td>Open</td>
<td>3.3</td>
<td>0.02</td>
<td>LR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Closed</td>
<td>2.5</td>
<td>Open</td>
<td>3.2</td>
<td>0.04</td>
<td>SI</td>
</tr>
</tbody>
</table>

Table 6. Random tumour bed (TB) setup errors for laser setup ($\sigma_{\text{laser}}$) and for bone verification ($\sigma_{\text{bone}}$) for groups determined using patient- and treatment-related factors

<table>
<thead>
<tr>
<th>Laser</th>
<th>Factor</th>
<th>Group 1</th>
<th>$\sigma_{\text{laser}}$ (mm)</th>
<th>Group 2</th>
<th>$\sigma_{\text{laser}}$ (mm)</th>
<th>p-value</th>
<th>Direction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TB PTV volume</td>
<td>$&lt;39.5,\text{cm}^3$</td>
<td>2.6</td>
<td>$\geq39.5,\text{cm}^3$</td>
<td>2.8</td>
<td>0.041</td>
<td>LR</td>
</tr>
<tr>
<td></td>
<td>TB PTV volume</td>
<td>$&lt;39.5,\text{cm}^3$</td>
<td>2.6</td>
<td>$\geq39.5,\text{cm}^3$</td>
<td>3.1</td>
<td>0.023</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td>Breast volume</td>
<td>$&lt;855,\text{cm}$</td>
<td>2.4</td>
<td>$\geq855,\text{cm}$</td>
<td>3.1</td>
<td>0.006</td>
<td>LR</td>
</tr>
<tr>
<td></td>
<td>Breast volume</td>
<td>$&lt;855,\text{cm}$</td>
<td>2.4</td>
<td>$\geq855,\text{cm}$</td>
<td>2.8</td>
<td>0.02</td>
<td>SI</td>
</tr>
<tr>
<td></td>
<td>Seroma visibility</td>
<td>Not visible/subtle</td>
<td>2.6</td>
<td>Easily visible</td>
<td>3.1</td>
<td>0.034</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td>TB PTV volume</td>
<td>$&lt;39.5,\text{cm}^3$</td>
<td>1.9</td>
<td>$\geq855,\text{cm}^3$</td>
<td>2.7</td>
<td>0.015</td>
<td>SI</td>
</tr>
</tbody>
</table>

Table 6. Random tumour bed (TB) setup errors for laser setup ($\sigma_{\text{laser}}$) and for bone verification ($\sigma_{\text{bone}}$) for groups determined using patient- and treatment-related factors

<table>
<thead>
<tr>
<th>Laser</th>
<th>Factor</th>
<th>Group 1</th>
<th>$\sigma_{\text{bone}}$ (mm)</th>
<th>Group 2</th>
<th>$\sigma_{\text{bone}}$ (mm)</th>
<th>p-value</th>
<th>Direction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TB axial position</td>
<td>1, 2 and 3</td>
<td>2.1</td>
<td>4</td>
<td>2.7</td>
<td>0.04</td>
<td>LR</td>
</tr>
<tr>
<td></td>
<td>TB axial position</td>
<td>1</td>
<td>1.6</td>
<td>2, 3 and 4</td>
<td>2.3</td>
<td>0.002</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td>Breast volume</td>
<td>$&lt;855,\text{cm}$</td>
<td>1.9</td>
<td>$\geq855,\text{cm}^3$</td>
<td>2.7</td>
<td>0.015</td>
<td>SI</td>
</tr>
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<td>Easily visible</td>
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<td>2, 3 and 4</td>
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AP, anteroposterior; LR, left–right; SI, superior–inferior; TB, tumour bed.

P-values for univariate non-parametric Levene’s test are given. Data given only for factors that gave a significant difference in systematic bony anatomy verification error between patient groups ($p < 0.05$).
Association of patient- and treatment-related factors with TB setup errors suggests that individualization of treatment margins could be considered. Non-isotropic margins are not currently employed in breast RT. This work suggests that patient-specific margins and non-isotropic margins should be considered. It also suggests that some patients benefit more from clip-based verification compared with bony anatomy verification than others. If appropriate margins are applied, patients with large breasts or laterally located TBs will benefit from a greater reduction in the breast tissue irradiated if clips are used. Conversely, patients with smaller breasts or medially located tumours may benefit less from clip-based verification.

Study limitations
This study assumed no significant difference among patient populations from the five different centres. Comparison of patient- and treatment-related factors between the five centres found small differences between centres in the number of clips and seroma visibility only. Centres B and E had significantly greater seroma visibility [patients with easily visible seroma: A, 22%; B, 38%; C, 17%; D, 13%; and E: 53% (p = 0.024)] and median number of clips [A, C and D, 6; B, 7; and E, 5 (p = 0.012)]. A large source of systematic error in breast boost RT, delineation error, has not been included in this analysis. Observer variation has been calculated in terms of the variation in TB volume (for example15); however, it is unclear how this will affect TB margins and there remains an opportunity for this to be explored. This work identifies the requirement for larger TB PTV margins if laser setup or bony anatomy verification is used, which results in a modest increase in the volume of normal breast tissue receiving the boost dose.14 The clinical effect of an increase in volume of normal tissue irradiated is not yet fully understood.15

CONCLUSION
Patients with larger breasts, easily visible seroma and open surgical closing technique have greater setup errors when laser-only setup is used. Patients with larger breasts and laterally located tumours have greater setup errors when bony anatomy verification is used. If margins derived from patient setup errors are applied, these groups of patients will benefit from a greater reduction in breast tissue irradiated if clips are used. Clip verification enables smaller margins than bony anatomy verification and should be used where possible. If clips are not available, bony anatomy verification may give modest improvements in TB setup errors compared with laser setup, and individualization of TB margins may be considered based on breast volume, the position of the TB and seroma visibility.

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The authors acknowledge the IMPORT Trials’ Management Group and all participating patients, Jenny Titley and Lone Gothard for invaluable help with data collection and Sairanne Wickers of University College London Hospitals NHS Foundation Trust for useful discussion.

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REFERENCES


NTCP for breast fibrosis

Normal tissue complication probability (NTCP) parameters for breast fibrosis: Pooled results from two randomised trials

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Abstract

Introduction: The dose–volume effect of radiation therapy on breast tissue is poorly understood. We estimate NTCP parameters for breast fibrosis after external beam radiotherapy.

Materials and methods: We pooled individual patient data of 5856 patients from 2 trials including whole breast irradiation followed with or without a boost. A two-compartment dose volume histogram model was used with boost volume as the first compartment and the remaining breast volume as second compartment. Results from START-pilot trial (n = 1410) were used to test the predicted models.

Results: 26.8% patients in the Cambridge trial (5 years) and 20.7% patients in the EORTC trial (10 years) developed moderate-severe breast fibrosis. The best fit NTCP parameters were BEUD(50) = 136.4 Gy, n = 0.9 and m = 0.011 for the Niemierko model and BEUD(50) = 132 Gy, m = 0.35 and n = 0.012 for the Lyman Kutcher Burman model. The observed rates of fibrosis in the START-pilot trial agreed well with the predicted rates.

Conclusions: This large multi-centre pooled study suggests that the effect of volume parameter is small and the maximum RT dose is the most important parameter to influence breast fibrosis. A small value of volume parameter ‘n’ does not fit with the hypothesis that breast tissue is a parallel organ. However, this may reflect limitations in our current scoring system of fibrosis.

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Radiation therapy (RT) has an established role in the management of early stage breast cancer to improve loco-regional control and overall survival [1]. However, a proportion of patients develop RT related complications including breast fibrosis, breast shrinkage and telangiectasia, which contribute to physical and psychological morbidity. Clinicians estimate the likelihood of a complication based on published literature and personal experience. The Emami et al. [2] seminal paper was among the first to provide a comprehensive review of radiation tolerance for normal tissues, estimating the tolerance doses (TD5 and TD50) for whole, 2/3 and 1/3 organ irradiation. More recently, Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) articles summarised the quantitative effects of RT dose and treatment volume on late normal tissue complications [3]. However, very few investigators have studied the radiation dose–volume effect for breast tissue [4–6].

The influence of RT dose on late normal tissue complications is well established [7–9], however the effect of treated breast volume is unclear with conflicting reports in the literature [10]. The large EORTC 22881-10882 “boost versus no boost” trial reported higher breast fibrosis rates among patients treated with larger boost volumes on univariate analysis [11]. These results were hypothesis generating, consistent with a volume effect for breast fibrosis. Newer techniques aim to exploit a volume effect for breast tissue, including partial breast irradiation (PBI) [12], simultaneous integrated tumour bed boost (SIB) [13] and image guided RT (IGRT) [14], with the aim of reducing late normal tissue complications. As these techniques become part of routine practice, a better understanding of the dose–volume effect of radiation on breast tissue is required.

The normal tissue complication probability (NTCP) models can be used to estimate dose–volume effect by predicting the probability of a complication for a non-uniform irradiated organ. For the modelling exercise, one requires a dataset with diverse dose and volume data and a meaningful quantitative toxicity endpoint.
The purpose of this study is to test the volume effect hypothesis and quantify the effect of volume parameter by estimating the NTCP model parameters for breast fibrosis as measured by induration score. Fibrosis is a common sequela of breast RT and adversely affects overall cosmesis, it can be assessed using a scoring system and is likely to impact on patient physical and psychological well-being [15]. Individual patient data from randomised controlled trials (RCTs) provide the most robust data on RT dose and toxicity. Additionally, pooling of data from different RCTs increases the diversity of the dataset and the generalisation of results to the wider population [16]. Hence, the individual patient data from two large RCTs were pooled together: EORTC 22881-10882 “boost versus no boost” trial [8,9] and the Cambridge Breast IMRT trial [17,18]. To our knowledge, no other dataset of this magnitude has previously been pooled for the purpose of NTCP modelling for breast tissue.

Materials and methods

Patient cohort and toxicity scoring

Cambridge Breast IMRT trial [17,18]: This single centre trial recruited 1145 patients with invasive breast cancer (stage T1-T3N0-1M0) or ductal carcinoma in situ who received breast conserving therapy (BCT). All patients received 40 Gy in 15 fractions over 3 weeks to the whole breast followed by an electron tumour bed boost of 9 Gy in 3 fractions over 3 days in selected cases (n = 728). Breast fibrosis was clinically assessed at 2 and 5 years after completion of RT and scored on a four point scale (0 = none, 1 = a little, 2 = quite a bit (~moderate) and 3 = very much (~severe)).

EORTC 22881-10882 “boost versus no boost” trial [8,9]: This multi-centre trial recruited 5569 patients with invasive breast cancer (stage T1-T2N0-1M0) who received BCT. All patients received 50 Gy in 25 fractions over 5 weeks to the whole breast and were randomised between no boost (n = 2657), 10 Gy in 5 fractions boost (n = 126), 16 Gy in 8 fractions boost (n = 2661) and 26 Gy in 13 fractions boost (n = 125). Electrons (63%), photons (29%) and low dose rate brachytherapy (9%) were used to deliver the boost dose. Breast fibrosis was clinically assessed and scored on a four point scale (1 = none, 2 = mild, 3 = moderate, and 4 = severe) at every follow up visit.

The brachytherapy technique can lead to significant dose heterogeneity and its boost volumes are usually much smaller than external beam techniques [19]. Hence, patients with brachytherapy boost were excluded from the analysis as were patients with missing data/toxicity score (Cambridge trial: 571 and EORTC trial: 275).

Dose–volume data

The accuracy with which NTCP model parameters can be estimated depends on the quality of both the dosimetric information and clinical follow up data. The late toxicity scores and boost volumes were recorded in the trials but limited dose–distribution data were available. Therefore, a more simplistic two-compartment dose–volume histogram (DVH) model was used. The first step of the DVH was the tumour bed volume receiving whole breast dose plus boost dose and the second step of the DVH was the remaining breast volume (whole breast volume minus tumour bed volume) receiving whole breast dose only.

Whole breast volume was only recorded in the Cambridge trial. Hence, a Monte Carlo (MC) simulation method was used to generate breast volume data for the EORTC patients. The MC simulation used the breast volume distribution from the Cambridge trial and an acceptance–rejection test of boost/breast volume ratio between 5–40% (the range of boost volume to breast volume ratio observed in the Cambridge data). It was assumed that the distribution of breast volume and boost/breast volume ratio in the EORTC trial is the same as in the Cambridge trial.

NTCP modelling

Two radiobiological models were used: Lyman Kutcher Burman (LKB) model [20] and the Niemierko model [21]. Both models assume that for whole or partial organ irradiation, the dose–response curve follows a basic sigmoid shape. Full details of the mathematical modelling are given in appendix 1.

Estimation of NTCP parameters with 95% confidence interval

A Maximum Likelihood Estimation (MLE) method [22] was used to find the best fit values of the model parameters (BEUD50 [biologically equivalent uniform dose leading to 50% toxicity], γ/50/m [steepness of the dose–response curve] and n [volume parameter]). A n value closer to one suggests that the organ has a parallel architecture with a strong volume dependence whilst a value of n closer to zero suggests that the organ has a serial architecture with no volume dependence on late complication rate. A full sequential parameter search was performed with the following parameter constraints: BEUD50(0–150), n (0.01–1.0), γ/50 (0.5–3.0) and m (0.1–0.8). The 95% confidence intervals (CI) for the optimally fit parameters were obtained using the Profile Likelihood Estimation method [23].

Goodness of fit estimation

Results from the START-pilot trial [24] were used to independently assess the goodness of fit of the predicted NTCP models. The START-pilot trial randomised 1410 patients into one of three whole breast RT dose fractionations: 50 Gy in 25 fractions or 39 Gy in 13 fractions or 42.9 Gy in 13 fractions. Patients were also sub-randomised for tumour bed boost to a dose of 14 Gy in 7 fractions using electrons. Breast induration was clinically assessed at annual follow-up and scored on a four point scale (0 = none, 1 = mild, 2 = moderate and 3 = marked (~severe)). Summative data on moderate and severe breast induration at five years were used for all three whole breast dose fractionations with and without boost for the goodness of fit estimation. The goodness-of-fit statistic was obtained by calculating the Pearson chi-square statistic ($\chi^2$) from the observed and predicted rates of breast fibrosis.

Results

Individual dose–volume and toxicity data of 574 patients (50%) from the Cambridge trial and 5282 patients (95%) from the EORTC trial were available for the NTCP modelling. 26.8% (154/574) patients developed moderate-severe breast fibrosis by 5 years in the Cambridge trial and 20.7% (1096/5282) patients developed moderate-severe breast fibrosis by 10 years in the EORTC trial. The patient’s RT dose volume characteristics are summarised in Table 1.

Using the MLE method, the best fit NTCP parameters for the Niemierko model were BEUD50(50) = 136.4 Gy, γ/50 = 0.9 and n = 0.011. The 95% CI for parameters were BEUD50(50) = 132.8–140 Gy, γ/50 = 0.84–0.97 and n = 0.01–0.03. For the LKB model, the best fit parameters were BEUD50(50) = 132 Gy, m = 0.35 and n = 0.012 with 95% CI of BEUD50(50) = 128.8–135.6 Gy, m = 0.326–0.374 and n = 0.01–0.03. Both models imply that the risk of moderate–severe breast fibrosis is strongly associated with RT dose and the effect of the volume parameter is small. Using an α/β of 3 Gy and n = 0.01, EQD2 (the equivalent dose in 2 Gy per fraction) leading to 50%
Using the Pearson chi-square test with 5 degrees of freedom, the results of the pilot trial were in good agreement with the predicted rates of fibrosis.

Fig. 1. Lyman Kutcher Burman model – the probability of moderate–severe breast fibrosis versus biological equivalent dose using α/β of 3 Gy (BED3). The solid line is based on the best fit parameters (BED3 = 136.4 Gy and m = 0.35) and the dashed lines are upper and lower 95% CI. The summative toxicity data of the three dose fractions ± boost at five years from the START pilot trial are plotted.

Fig. 2. Niemierko model – the probability of moderate–severe breast fibrosis versus biological equivalent dose using α/β of 3 Gy (BED3). The solid line is based on the best fit parameters (BED3 = 132 Gy and m = 0.35) and the dashed lines are upper and lower 95% CI. The summative toxicity data of the three dose fractions ± boost at five years from the START pilot trial are plotted.

The observed rates of moderate–severe induration in the START pilot trial were in good agreement with the predicted rates of fibrosis using the LKB model (Fig. 1) and the Niemierko model (Fig. 2). Using the Pearson chi-square test with 5 degrees of freedom, the χ² test was 0.053 (p = 0.95) for the LKB model and χ² was 0.058 (p = 0.95) for the Niemierko model suggesting a good fit of the models.

**Discussion**

A better understanding of the dose–volume effect for breast tissue is timely as many patients now receive non-uniform breast irradiation in the form of accelerated PBI, SIB and risk adapted RT [12, 13, 25, 26]. The EORTC 22881-10882 trial breast fibrosis nomogram showed a strong association between RT dose and fibrosis, with large boost volumes as a prognostic factor on univariate analysis only [11]. The purpose of this study was to specifically look at the volume effect by developing a predictive NTCP model. This was approached by pooling individual data from two large prospective trials (5856 patients), that offered robust information on RT dose, boost volume and late toxicity.

Using the MLE method, the volume parameter ‘n’ was close to zero for both the LKB model and the Niemierko model. This suggests that for moderate–severe fibrosis, the breast tissue behaves as a serial organ and the maximum RT dose is most predictive of the complication. The summative data of 1410 patients from an independent dataset with six RT dose levels had a good fit on both the LKB and Niemierko models (Figs. 1 and 2).

Parameter correlation leads to uncertainty of parameter estimates, independent of the size and diversity of the dataset [27]. An effective method to decrease the uncertainty is fixing one or more model parameters. Hence the α/β was fixed as 3 Gy in the study based on the previously published literature [24]. There is no evidence to suggest the superiority of one model over another [28]. However, similar values of the estimated parameters from the two models strengthen the results of this study.

Three other studies have previously estimated the NTCP parameters for breast fibrosis and these results are summarised in Table 2. Borger et al. [4] model was based on 404 patients treated with WBI (50 Gy in 25 fractions over 5 weeks) followed by low dose rate iridium-192 based tumour bed boost (15–25 Gy). BEUD was calculated using α/β of 2 Gy and repair half-time of 1.5 h. The implant positions were re-constructed on the available radiographs and dose–volume calculations were performed. The best fit NTCP parameters in the study were TD50 = 72 Gy and n = 0.16 ± 0.04. Though informative, the model parameters were estimated from patients with brachytherapy boost alone. It is not evident to compare parameters generated from brachytherapy to external beam techniques due to the difference in dose distribution and a possible different radiobiological effect. For this reason, patients with brachytherapy boost were excluded in the current study. Avanzo et al. [5] estimated the best fit parameters for the model using average dosimetric parameters (prescription dose, fraction dose, median follow up time) and the best fit parameters for the model were estimated from patients with brachytherapy boost alone.
and dose–volume data) from three WBI studies without boost and four external beam PBI studies. Three PBI studies used twice daily fractionation, and BEUD calculations included a repair half-time of 4.4 h in the model. As the median follow up of the PBI studies was short (1.3–4.2 years), a latency function correction was included. The parameters were estimated using weighted least square method, with the number of patients in each dataset as weights. The parameters for moderate-severe breast fibrosis model were BEUD3(50) = 105.8 Gy, n = 0.22 and m = 0.22. The authors acknowledged that the gold standard approach to estimate NTCP parameters is the use of individual dosimetric data/clinical outcome. MLE method based parameter estimates are also more precise as compared to weighted least square method [29].

On the contrary, Alexander et al. [6] reported a strong effect of volume parameter on breast fibrosis. This study included summative data of 806 patients from the START-pilot trial [24], 590 patients from a Germany study [30] and 150 post-mastectomy patients treated during the 1960s [31]. All patients received WBI and no partial volume data were available for the fitting analysis. The dose–volume data were generated using an anthropomorphic phantom and parameters were estimated for a relative seriality model and Lyman model. The study suggested a parallel architecture for breast tissue with a strong volume effect on breast fibrosis. This study included summative dosimetric and toxicity data. [5]

<table>
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<th>Number of patients</th>
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<td>Avanzo et al. [5]</td>
<td>Relative seriality model</td>
</tr>
<tr>
<td>Current study</td>
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<tr>
<td>Current study</td>
<td>Without repair correction</td>
</tr>
<tr>
<td>Niemierko model</td>
<td>NTFC model</td>
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<td>(\gamma = 0.78)</td>
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<td>(m)</td>
<td>(n)</td>
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<td>(0.012)</td>
</tr>
<tr>
<td>Current study</td>
<td>(0.011)</td>
</tr>
</tbody>
</table>

NTD: Normalised total dose.
BEUD3(50): Biologically equivalent uniform dose using \(a/\beta = 3\) Gy.
\(\gamma/\gamma_0\): Slope of the dose response curve.
\(n\): Volume parameter.
\(t_{1/2}\): Repair half-time.
\(s\): Describes the serial/parallel architecture of the organ. A value closer to 1 indicates a serial structure and a value closer to 0 indicates a parallel structure.

* These studies used summative dosimetric and toxicity data.

Overall, most studies have indicated a small volume effect for breast fibrosis. There are several possible reasons to explain the difficulty in demonstrating the effects of volume parameter for breast fibrosis. Breast fibrosis may represent a focal RT effect, with the maximum RT dose as the most predictive factor. It is also possible that our current scoring methods for breast fibrosis are not sensitive to the volume effect. Breast fibrosis is often graded as mild-severe based on the severity; however the scoring system does not take into account the extent of fibrosis i.e. small discrete region of fibrosis and widespread region of fibrosis are potentially scored alike. It has been suggested that NTCP parameters are influenced by the severity of measured toxicity [32]. For rectum, Rancati et al. estimated the best fit \(n\) parameter was 0.23 for \(\geq\) grade 2 rectal bleeding, which decreased to 0.06 when only severe rectal bleeding (grade 3) was considered [32]. It is plausible that a volume effect for breast tissue may have been seen for mild fibrosis, but this endpoint was considered to be of less clinical significance. Apart from RT parameters, breast fibrosis can also be influenced by surgical techniques [33] and systemic therapy [34], which are not accounted for in the mathematical model.

There is a need to investigate quantitative methods, which define both the severity and extent of breast fibrosis. The use of patient-reported toxicity scoring for NTCP modelling may also be useful. A small area of fibrosis in the breast may not be perceived as toxicity by the patient, whereas a large area of fibrosis in a small breast is likely to be considered as significant toxicity by the patient. Hence, patient-reported breast fibrosis scoring may be more sensitive to the change in treatment volume. Other toxicity endpoints like photographic assessed breast shrinkage may also be more sensitive to the volume effect as it represents global organ effect, is more objective and scored independent of surgical changes. The current study focused on breast fibrosis as photographic assessment and patient reported scoring were not available for the majority of the patients included in the study [35,36].

**Limitations**

It is recognised that there are several limitations of this study. One of the intrinsic difficulties in modelling for breast tissue is the lack of detailed dosimetric data. A two-compartment DVH was used with the assumption that a homogeneous dose was delivered to the breast during WBI. The EORTC whole breast volume data were generated using MC simulation, using parameters from the Cambridge trial. It is clear that using simulated data for the EORTC patients can lead to large uncertainties. A plot of boost volume against moderate–severe fibrosis suggests that the volume effect is likely to be weak (Appendix Fig. 3) and the model parameters will not be affected by the distribution of the simulated...
breast volumes. To test this hypothesis, ten additional breast volume datasets were generated for the EORTC patients using the MC method. Furthermore, the variance of the first two simulated datasets was changed by 0.5 and 2 times the original value. Repeat simulations and changing the variance of breast volume distribution did not significantly change the estimated NTCP parameters (in keeping with weak volume effect). Simulation techniques are a powerful tool for modelling exercise. However, when applying simulated parameter from one population to the outcome data of another population, it is assumed that the two populations are identical. This may not be true in all cases.

Other limitations of the study include the use of both photons and electron boost modalities without any correction for their different radiobiological effectiveness (RBE). Bentzen et al. [37] previously reported RBE for electrons was 0.88 relative to photons at 4.1 mm depth. As the RBE difference at depths other than 4.1 mm is unknown, no attempts were made to correct for this.

The duration of follow up was different between the EORTC (10 years) and Cambridge datasets (5 years). However, no suitable adjustment could be made in the MLE method for latency. In addition, current literature indicates that the majority of the breast fibrosis events take place by five years time point [11]. For this analysis, the score for fibrosis was used independent from the site in the breast (boost area or elsewhere). It is not expected to influence on our results, as it is most often located at the boost area (where the highest dose is given). Moreover, the worst score ever was reported. Although improvement of fibrosis is not expected, erroneous scoring of oedema early after treatment might be possible. Large breast volume has been reported as an independent risk factor for breast shrinkage and change in breast appearance [38,39]. However, one of the inherent limitations with NTCP modelling exercise is that it is driven by partial dose volume data, independent of whole organ volume. Apart from dose volume parameter, other patient (smoking, diabetes), treatment (type of surgery, chemotherapy, endocrine therapy and post-operative complications) and genetic factors also influence on breast fibrosis [11]. These factors were not available for the analysis in the current study.

Conclusions

This large multi-centre pooled study suggests that the effect of volume parameter is small and the maximum RT dose is the most important parameter to influence late breast fibrosis. However, this may reflect limitations in our current scoring system. Other RT associated complications should also be analysed to determine the effects of dose–volume parameters and patient-reported outcomes should complement clinician score-based models in the future. Inclusion of other clinical factors is desirable for future NTCP modelling work.

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Disclaimer

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Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2013.07.006.

References


Randomized Controlled Trial of Intensity-Modulated Radiotherapy for Early Breast Cancer: 5-Year Results Confirm Superior Overall Cosmesis


Processed as a Rapid Communication manuscript. See accompanying editorial on page 4483

ABSTRACT

Purpose
There are few randomized controlled trial data to confirm that improved homogeneity with simple intensity-modulated radiotherapy (IMRT) decreases late breast tissue toxicity. The Cambridge Breast IMRT trial investigated this hypothesis, and the 5-year results are reported.

Patients and Methods
Standard tangential plans of 1,145 trial patients were analyzed; 815 patients had inhomogeneous plans (≥ 2 cm³ receiving 107% of prescribed dose: 40 Gy in 15 fractions over 3 weeks) and were randomly assigned to standard radiotherapy (RT) or replanned with simple IMRT; 330 patients with satisfactory dose homogeneity were treated with standard RT and underwent the same follow-up as the randomly assigned patients. Breast tissue toxicities were assessed at 5 years using validated methods: photographic assessment (overall cosmesis and breast shrinkage compared with baseline pre-RT photographs) and clinical assessment (telangiectasia, induration, edema, and pigmentation). Comparisons between different groups were analyzed using polychotomous logistic regression.

Results
On univariate analysis, compared with standard RT, fewer patients in the simple IMRT group developed suboptimal overall cosmesis (odds ratio [OR], 0.68; 95% CI, 0.48 to 0.96; P = .027) and skin telangiectasia (OR, 0.58; 95% CI, 0.36 to 0.92; P = .021). No evidence of difference was seen for breast shrinkage, breast edema, tumor bed induration, or pigmentation. The benefit of IMRT was maintained on multivariate analysis for both overall cosmesis (P = .038) and skin telangiectasia (P = .031).

Conclusion
Improved dose homogeneity with simple IMRT translates into superior overall cosmesis and reduces the risk of skin telangiectasia. These results are practice changing and should encourage centers still using two-dimensional RT to implement simple breast IMRT.

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INTRODUCTION

Radiation therapy (RT) has an established role in the management of early-stage breast cancer. However, some patients develop RT-related complications, including breast fibrosis, breast shrinkage, poor breast cosmesis, and telangiectasia, which contribute to their psychological morbidity. With improving breast cancer survival, there is increasing focus on reducing treatment-related complications. The use of advanced RT techniques like intensity-modulated RT (IMRT) offers an opportunity to reduce RT-related complications. The overall aim of IMRT is to improve coverage of the RT target and/or to minimize dose to surrounding normal tissues. The term IMRT covers a spectrum of techniques, ranging from relatively simple to highly complex. For the majority of patients treated with breast RT, it seems that a simple form of IMRT may be the most appropriate technique. This simple IMRT uses additional irradiation fields to smooth out the dose to the breast (ie, target). More complex IMRT techniques can produce a large volume of low-dose radiation to surrounding tissues. As a result, complex IMRT tends to be restricted to cases in which a steep dose gradient is required (eg, in patients with pectus...
excavatum, who would otherwise receive unacceptably high dose to surrounding organs at risk [ie, lungs and heart]).

Studies have shown improved dose homogeneity across the breast with the use of simple and complex IMRT,3,4 and it would be expected that improved dose homogeneity would reduce late breast tissue toxicity. However, there are few randomized controlled trial data to confirm the advantage of IMRT over standard RT in breast cancer.5-7 Donovan et al5 showed reduction in late breast tissue toxicity with IMRT among women who were judged to be at higher than average risk of radiation-induced toxicity based on breast size and/or breast shape. Worldwide, the practice of whole-breast RT is gradually shifting from standard two-dimensional RT to IMRT.8,9 However, skeptics have pointed out that breast IMRT is being clinically implemented with a paucity of data on its long-term benefits.10,11

The large randomized Cambridge Breast IMRT trial was designed to investigate whether the correction of dose inhomogeneity using simple IMRT would decrease late breast tissue toxicity.12 It included women with all breast sizes, and the interim results at 2 years showed statistically significant reduction in the risk of telangiectasia with IMRT as compared with standard RT.6 However, the 2-year time point was considered insufficient for patients to experience their final level of toxicity and demonstrate the full benefits of IMRT. The pre-planned long-term results of the trial at 5 years are reported here to determine if improved dose homogeneity with simple IMRT translates into clinical benefits of reduced late breast tissue toxicity.

**PATIENTS AND METHODS**

The single-center Cambridge Breast IMRT trial opened in April 2003 and was closed to recruitment in June 2007. The Cambridge Research Ethics Committee provided ethical approval of the study. The National Cancer Research Institute group accepted this trial as a portfolio trial in April 2002, and it was adopted by the National Cancer Research Network in March 2003.

**Study Population**

Women with operable unilateral, histologically confirmed invasive breast cancer (T1-3, N0-1, M0) or ductal carcinoma in situ requiring RT after breast-conservation surgery were eligible for the trial (Fig 1). All patients with

![CONSORT diagram of Cambridge Breast Intensity-Modulated Radiotherapy (IMRT) trial](https://www.jco.org)

---

< 2 cm³ of breast tissue > 107%

Ineligible for random assignment and received standard 2D-RT (n = 330)

Withdrawn (n = 141)

Tumor-related (n = 52)

Breast cancer-related (n = 21)

death

Non-breast cancer-related (n = 13)

death

Local recurrence (n = 11)

Contralateral new primary (n = 5)

Alive with metastatic disease (n = 1)

New cancer (n = 1)

Patient-related (n = 115)

Moved out of area (n = 15)

Withdraw consent (n = 11)

Transport issues (n = 14)

Social issues including work commitment/carer (n = 14)

Unable to contact (n = 11)

Erective reconstruction/implants (n = 3)

Unwell to attend (n = 9)

Patient choice: reason not stated (n = 33)

Tumor-related (n = 54)

Breast cancer-related (n = 17)

death

Non-breast cancer-related (n = 6)

death

Local recurrence (n = 20)

Contralateral new primary (n = 5)

Alive with metastatic disease (n = 2)

New cancer (n = 4)

Patient-related (n = 129)

Moved out of area (n = 13)

Withdraw consent (n = 16)

Transport issues (n = 19)

Social issues including work commitment/carer (n = 19)

Unable to contact (n = 10)

Erective reconstruction/implants (n = 6)

Unwell to attend (n = 9)

Patient choice: reason not stated (n = 31)

≥ 2 cm³ of breast tissue > 107%

Random assignment (n = 815)

Control

Allocated standard RT (n = 404)

Withdrawn (n = 167)

Tumor-related (n = 15)

Breast cancer-related (n = 11)

death

Non-breast cancer-related (n = 5)

death

Local recurrence (n = 3)

Contralateral new primary (n = 3)

Alive with metastatic disease (n = 2)

New cancer (n = 4)

Patient-related (n = 31)

Moved out of area (n = 9)

Withdraw consent (n = 10)

Transport issues (n = 6)

Social issues including work commitment/carer (n = 6)

Unable to contact (n = 2)

Erective reconstruction/implants (n = 3)

Unwell to attend (n = 9)

Patient choice: reason not stated (n = 31)

Intervention

Allocated IMRT (n = 411)

Withdrawn (n = 183)

Tumor-related (n = 54)

Breast cancer-related (n = 17)

death

Non-breast cancer-related (n = 6)

death

Local recurrence (n = 20)

Contralateral new primary (n = 5)

Alive with metastatic disease (n = 2)

New cancer (n = 4)

Patient-related (n = 129)

Moved out of area (n = 13)

Withdraw consent (n = 16)

Transport issues (n = 19)

Social issues including work commitment/carer (n = 19)

Unable to contact (n = 10)

Erective reconstruction/implants (n = 6)

Unwell to attend (n = 9)

Patient choice: reason not stated (n = 31)

CONSORT diagram of Cambridge Breast Intensity-Modulated Radiotherapy (IMRT) trial. 2D, two dimensional; DCIS, ductal carcinoma in situ; ICRU, International Commission on Radiation Units; RT, radiotherapy.

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invasive breast cancer underwent sentinel node biopsy and/or axillary clearance (if lymph node positive). Other eligibility criteria included age > 18 years, no history of contralateral breast cancer, no malignancy in the previous 5 years (except skin basal cell or squamous carcinoma or in situ carcinoma of cervix), and availability for follow-up. All patients provided written informed consent. A total of 1,145 patients were recruited.

Sample Size Calculation

The sample size was based on a standard event rate of 40% in the control arm at 2 years. The difference to be detected was estimated to be 10%, with a hazard ratio of 0.7. Assuming a minimal average follow-up of 2 years, 80% power, and type I error of 0.05, 358 patients and 125 events were required in each of the randomly assigned arms. This sample size was increased by 10% to adjust for possible loss to follow-up by 2 years.

Random Assignment

A standard RT plan consisting of paired wedged tangents was produced for all trial patients. Patients with satisfactory dose homogeneity (29%) were not randomly assigned but instead treated with standard RT and observed for the same follow-up as the randomly assigned patients. Patients whose plan had significant dose inhomogeneity, defined as ≥ 2 cm³ volume receiving > 107% of the prescribed dose, were randomly assigned between standard RT (control arm) and forward-planned field-in-field dose homogenization IMRT (simple IMRT; intervention arm; Fig 2). Random assignment was performed using permuted blocks of mixed block size and was stratified for T stage and adjuvant therapy. Patients were informed of their randomly assigned arm if they enquired at the time of RT treatment.

RT Technique

Patients in the control arm were treated with wedged tangential fields to the breast, and patients in the interventional arm were replanned with a simple IMRT technique to reduce the volume receiving > 107% and < 95% of the prescribed dose. The full details of the RT planning technique are described in the Appendix (online only).

All patients were treated to a dose of 40 Gy in 15 fractions, 5 days per week over 3 weeks, with 6-MV photons prescribed to the ICRU (International Commission on Radiation Units) 50 reference point. Mixed energies of 6- and 15-MV photons were used in patients with large breast separation. Nodal irradiation and sequential tumor bed boost were administered according to local protocol. After completion of RT, all patients were treated similarly irrespective of their allocated treatment arm.

Outcome Measures: Breast Toxicity End Points

Patients were assessed at 2 and 5 years after completion of RT using serial photographs and clinical examination. The primary outcome of the study was photographic assessment of late cosmetic effects, and the secondary outcome was clinical assessment of breast late normal tissue changes (induration, telangiectasia, and breast edema). Toxicity assessors were unaware of a patient’s treatment arm. This article reports these end points at 5 years from completion of RT. Photographic assessment. Frontal photographs of both breasts were taken after primary surgery and before RT (baseline) and repeated at 2 and 5 years post-RT. Two photographs were taken: one with the hands resting on the
hips, and the other with the arms raised above the head. The 5-year photographs were compared with postoperative baseline photographs for RT-associated breast shrinkage and scored on a validated three-point scale (1, none/minimal; 2, mild; 3, marked). A multidisciplinary team of seven clinicians (four oncologists, one radiographer, one surgeon, and one breast care nurse) were involved in photographic assessment, with a panel of three being present at any one time. This method has been validated and shown to be quicker than using three independent scorers with rescoring of discrepancies and final resolution through discussion and was used to score the UK START (Standardisation of Breast Radiotherapy) trial photographs.15 The interobserver variability of this assessment has been validated before by our group.6 The panel also scored overall cosmesis on photographs taken at 5 years by assessing the global breast appearance (looking at breast shrinkage, breast distortion, and skin changes), independent of baseline cosmetic appearance. The overall breast appearance (cosmesis) was scored using a three-point score (good, moderate, and poor) as per the United Kingdom FAST (Faster Radiotherapy for Breast Cancer Patients) study14 and Royal Marsden Hospital IMRT trial,3 with moderate to poor scores regarded as suboptimal cosmesis. In addition, postoperative baseline photographs were scored for surgical cosmesis using a three-point score (good, moderate, and poor). Other computerized methods for photo scoring, like BCCT (breast cancer conservative treatment) core software (Breast Research Group, Porto, Portugal),15 were not available at the time of study design and hence not used in this study. Clinical assessment. The treated breast was assessed at 5 years for breast edema, skin telangiectasia, breast shrinkage, pigmentation changes, and palpable induration. Each of these end points was graded from 0 to 3 (none, a little, quite a bit, very much) on the scale used in the START trials.16-17 All 5-year clinical assessments were performed by a single trained research radiographer (I.S.W.).

The planned photographic and clinical assessments were not performed in cases of local tumor relapse, metastatic disease, new cancer diagnosis, additional breast surgery, poor health, and patient refusal. Patients who were unable to attend the 5-year follow-up appointment were contacted via telephone to assess their well being.

Statistical Analysis

The baseline demographics for patients with 5-year follow-up data were compared using the student t test, Pearson’s χ² test, and Fisher’s exact test for heterogeneity and trend. Toxicity end points were compared between the randomly assigned patients on univariate analysis using polytomous logistic regression analysis. Stepwise multivariate polytomous logistic regression was used to analyze the patient- and treatment-related factors that were significantly associated with late toxicity after RT on univariate analysis (P < .1). Univariate and multivariate odds ratios (ORs) were generated. Baseline surgical cosmesis was an important determinant factor for breast toxicity end points at 2 years in this trial.6 Hence, data from all trial patients (those randomly assigned and not randomly assigned) were used to assess the effect of baseline (pre-RT) surgical cosmesis on late toxicity end points at 5 years using polytomous logistic regression. In addition, baseline surgical cosmesis was included in the multivariate analysis of final overall cosmesis between the randomly assigned patients.

The 5-year locoregional recurrence (LRR) and overall survival (OS) rates were compared between randomly assigned patients using the Mantel-Haenszel (log-rank) test. The length of follow-up or time to an event was measured from the date of random assignment, and analysis was performed according to intention to treat. All randomly assigned patients were included in this analysis, not just those who were available for the 5-year toxicity assessment. Details of local recurrences and deaths were obtained from local hospital and cancer registry records. All statistical analyses were performed using STATA statistical software (version 10.1; STATA, College Station, TX).

RESULTS

The late breast tissue toxicity outcomes of 654 (57%) of 1,145 patients (control arm, 237; IMRT arm, 228; non–randomly assigned arm, 189) were available at 5 years. Baseline patient, tumor, and treatment characteristics of the 654 patients are summarized in Table 1. The characteristics are well balanced between the two randomly assigned arms, with the exception of volume of breast tissue receiving > 107% of the prescribed dose (as expected). Patients in the non–randomly assigned arm were younger, with smaller tumor size, and less frequently received systemic chemotherapy. The mean breast volume was also significantly larger in the two randomly assigned arms as compared with the non–randomly assigned arm. Reasons for patients with no 5-year assessments from the study are summarized in the CONSORT diagram (Fig 1).

Five-Year Toxicity in Control (standard RT) Versus Intervention Arm (IMRT)

On univariate analysis, fewer patients in the simple IMRT arm developed suboptimal overall cosmesis (OR, 0.68; 95% CI, 0.48 to 0.96; P = .027) or skin telangiectasia (OR, 0.58; 95% CI, 0.36 to 0.92; P = .021) as compared with the control arm (Table 2). However, no significant difference was seen for photographically assessed breast shrinkage (OR, 0.79; 95% CI, 0.55 to 1.14; P = .21), breast edema (OR, 0.74; 95% CI, 0.48 to 1.15; P = .18), tumor bed induration (OR, 0.76; 95% CI, 0.54 to 1.06; P = .11), or pigmentation (OR, 0.80; 95% CI, 0.46 to 1.38; P = .42) between the randomly assigned patients.

On multivariate analysis, the benefits of simple IMRT over standard RT (control arm) were maintained for both overall cosmesis (OR, 0.65; 95% CI, 0.44 to 0.98; P = .038) and skin telangiectasia (OR, 0.57; 95% CI, 0.34 to 0.95; P = .031). Large breast volume (P = .02), poorer baseline surgical cosmesis (P < .001), and tumor bed boost (P = .003) were also associated with suboptimal overall cosmesis on multivariate analysis. Skin telangiectasia was also associated with older age (P = .005), postoperative breast infection (P < .001), increasing breast volume (P < .001), and tumor bed boost (P = .023). The full details of the covariates included in the multivariate analysis are summarized in Appendix Tables A1 and A2 (online only).

Impact of Pre-RT Surgical Cosmesis on Late Toxicity End Points

Patients with moderate to poor baseline surgical cosmesis more frequently developed suboptimal final cosmesis (OR, 8.15; 95% CI, 6.09 to 10.92; P < .001), tumor bed induration (OR, 1.80; 95% CI, 1.44 to 2.26; P < .001), and photographically assessed breast shrinkage (OR, 1.54; 95% CI, 1.21 to 1.96; P < .001) at 5 years in the study.

LRR and OS

There was no statistically significant difference in 5-year LRR and OS rates between the randomly assigned patients (control arm, 404 patients; IMRT arm, 410 patients). The 5-year LRR rates for the control and IMRT arms were 2.56% and 1.35% respectively (P = .36). The 5-year OS rates for the control and IMRT arms were 92.5% and 91.7%, respectively (P = .88).

DISCUSSION

This large single-center trial confirms that improved dose homogeneity with simple IMRT decreases late breast tissue toxicity. At 5 years, patients receiving simple IMRT had superior overall cosmesis and reduced risk of skin telangiectasia as compared with patients receiving...
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standard RT. However, no significant difference was observed for photographically assessed breast shrinkage or clinically assessed breast edema, breast pigmentation, or breast induration.

To date, only two other randomized trials have compared standard RT with IMRT for early breast cancer. The multicenter Canadian study compared acute toxicity for 331 patients randomly assigned after breast-conservation surgery between IMRT (forward or inverse planned) and standard RT using wedges.7 Patients in the IMRT arm experienced significantly less moist desquamation during or up to 6 weeks post-RT as compared with standard treatment (31.2% vs 47.8%; P = .002). Women of all breast sizes were included in the study, and on multivariate analysis, use of IMRT and small breast size were significantly associated with decreased risk of moist desquamation. Late toxicity has not yet been reported. Donovan et al5 reported a single-center study in which 306 patients were randomly assigned between forward-planned IMRT and standard RT. Of the 240 patients evaluated at 5 years, patients who received standard RT were 1.7 times more likely to develop any change in breast appearance on photographic assessment (95% CI, 1.2 to 2.5; P = .008) as compared with patients treated with IMRT. In addition, fewer patients developed palpable induration in the center of the breast, pectoral fold, inframammary fold, and boost site with IMRT. Retrospective case-matched studies have also compared standard RT with IMRT for breast cancer (Appendix Table A3, online only).

Fewer patients developed breast induration with IMRT in the Donovan et al study; however, a similar reduction in induration was not seen in the interventional arm of the larger Cambridge Breast IMRT trial. The different entry criteria for the two trials may explain these dissimilar results. In the Donovan et al study, women were eligible if they were judged to be at higher than average risk of radiation-induced toxicity based on breast size and/or breast shape. The mean percentages of breast volumes receiving >107% of prescribed dose between standard and IMRT arm were 11.7% versus 1%, respectively.18 In contrast, women of all breast sizes were eligible

### Table 1. Patient, Tumor, and Treatment Characteristics of Patients With 5-Year Toxicity Data (n = 654) (continued)

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<td>126 67</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>4 1</td>
<td>0 0</td>
</tr>
<tr>
<td>Aromatase inhibitor</td>
<td>No</td>
<td>90 24</td>
<td>214 94</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>15 6</td>
<td>11 6</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>3 1</td>
<td>0 0</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>No</td>
<td>181 79</td>
<td>182 77</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>19 7</td>
<td>24 10</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>2 1</td>
<td>0 0</td>
</tr>
</tbody>
</table>

Abbreviations: DCIS, ductal carcinoma in situ; IMRT, intensity-modulated radiotherapy; SCF, supraclavicular fossa; V107, breast volume receiving >107% of prescribed dose.

*Fisher’s exact test.
†P = .18 for trend.
‡Breast volume receiving >107% of the prescribed dose.

### Table 2. Comparison of Skin Telangiectasia and Overall Final Cosmesis Between Control and IMRT Arms at 5 Years

<table>
<thead>
<tr>
<th>Effect</th>
<th>Control Arm</th>
<th>IMRT Arm</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. %</td>
<td>No. %</td>
<td>OR*</td>
<td>P</td>
</tr>
<tr>
<td>Skin telangiectasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>179 76</td>
<td>193 85</td>
<td>0.58</td>
<td>.021</td>
</tr>
<tr>
<td>A little</td>
<td>24 10</td>
<td>16 7</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Quite a bit</td>
<td>18 8</td>
<td>12 5</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Very much</td>
<td>14 6</td>
<td>7 3</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Overall final cosmesis</td>
<td></td>
<td></td>
<td>0.68</td>
<td>.027</td>
</tr>
<tr>
<td>Good</td>
<td>84 37</td>
<td>95 43</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>95 41</td>
<td>102 45</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>50 22</td>
<td>26 12</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IMRT, intensity-modulated radiotherapy; OR, odds ratio.
*Based on polychotomous logistic regression analysis.
for the Cambridge Breast IMRT trial, if their breast volume receiving > 107% of the prescribed dose was ≥ 2 cm³ on a standard RT plan. The mean percentage of breast volume receiving > 107% of the prescribed dose was only 2.9% in the control arm of the trial, which decreased to 0% with IMRT. It is also possible that these dissimilar results resulted from the subjective nature of clinical assessment, with different interpretation of induration between clinicians of the two studies.

Our study found tumor bed boost to be an independent risk factor for suboptimal cosmesis and skin telangiectasia, as previously shown in the EORTC (European Organisation for Research and Treatment of Cancer) 22881-10882 boost-versus—no boost trial. Large-breasted women more frequently develop late breast tissue toxicity, and this has been linked to their suboptimal dosimetry. Our study found large breast volume to be a risk factor for suboptimal cosmesis and skin telangiectasia, independent of dose inhomogeneity. Similar results were also seen in the UK FAST hypofractionated trial at 2 years. The FAST Trialists group postulated that in large-breasted women, the major component of the breast is adipose tissue, which is perhaps more sensitive to the effects of RT and hence more likely to develop late toxicity. However, one should also note that in postmenopausal patients, the major component of the breast is usually adipose tissue regardless of breast size.

Our study also highlights the importance of optimal surgical cosmesis, because patients with moderate to poor surgical cosmesis are more likely to develop breast shrinkage, breast induration, and suboptimal final cosmesis.

The local control and survival rates with both standard RT and IMRT are excellent. It is generally accepted that simple IMRT, which removes regions of high radiation dose should not affect local control and/or survival rates. Therefore, this trial was not intended to detect a difference in local control and/or survival rates between standard RT and IMRT. However, it has been postulated that removing hotspots with IMRT can lead to dose de-escalation, especially to the skin, and a theoretic increased risk of local relapse. At 5 years, there was no statistical difference in LRR and OS rates between the randomly assigned patients of the study.

Our study has some limitations. A significant number of patients were withdrawn from the 5-year analysis. The routine clinical follow-up of patients post-RT was based at their regional referring hospitals, and many patients turned down their 5-year trial appointment at Cambridge because of travel difficulties, social issues, or personal choice (Fig 1). Patients were also withdrawn from the analysis because of cancer-related factors, including local or systemic relapse, new cancer, or death. The referral hospitals were contacted for information on LRR, metastasis, and survival, but data on late breast tissue toxicity were not available routinely.

In conclusion, the 5-year results from this study are practice changing. Improved dose homogeneity with simple IMRT translates into superior overall cosmesis and reduces the risk of skin telangiectasia 5 years after breast RT. Although breast IMRT has been implemented by many centers, there has not been universal adoption of this technique to date. This study should act as an evidence-based lever for change for RT centers that have yet to implement breast IMRT. In addition, surgical cosmesis should be optimized before RT delivery, because this also has a significant effect on late breast toxicity and overall cosmesis.

The author(s) indicated no potential conflicts of interest.

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Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

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Appendix

Details of Standard Radiotherapy and Simple Intensity-Modulated Radiotherapy Technique Used in Study

Standard radiotherapy plan. A whole-breast planning target volume (PTV) was first contoured for the patient using a field-based approach. The PTV consisted of the volume of breast enclosed by the field: 5 mm from the skin surface, the lung–chest wall interface/posterior field edge, and superior and inferior field margins. A standard plan consisting of paired wedged tangents using 6-MV photons was produced for the patient. Mixed energies of 6- and 15-MV photons were sometimes used in patients with larger breast separations, and dose calculations were performed using a correction for lung inhomogeneity.

Simple intensity-modulated radiotherapy plan. The simple, manual forward-planned intensity-modulated radiotherapy (IMRT) plan built on the original standard treatment plan by adding additional top-up fields to shield high-dose areas and boost areas of lower dose. These additional fields were based on the original treatment field sizes and were typically weighted to 10% of the original treatment beams. The dose arrays were locked, and by viewing the isodose distribution along the beam’s eye view, the multileaf collimators (MLCs) were manipulated to shield the areas of the breast receiving doses > 107% of the prescription (Fig 1). Occasionally, a wedge was added to the additional fields to provide a wedge in the superior/inferior direction. The isodose distributions were recalculated, and dose-volume histograms were exported and compared with the original plan. Additional adjustments to the MLC shapes and beam weightings could be made iteratively to increase the volume of the PTV receiving doses between 95% and 107% of that prescribed.

| Table A1. Final Covariates Included in Multivariate Analysis for Skin Telangiectasia |
|-----------------------------------|-------|--------|---|------------------|
| Telangiectasia                     | OR    | SE     | P  | 95% CI           |
| IMRT group                         | 0.57  | 0.15   | .031 | 0.34 to 0.95     |
| Age                               | 1.05  | 0.17   | .005 | 1.01 to 1.08     |
| Postoperative infection            | 3.53  | 0.91   | .000 | 1.97 to 5.71     |
| Breast volume                     | 1.001 | 0.0022 | .000 | 1.0009 to 1.0018 |
| Tumor bed boost                   | 1.86  | 0.51   | .023 | 1.08 to 3.19     |

Abbreviations: IMRT, intensity-modulated radiotherapy; OR, odds ratio.

| Table A2. Final Covariates Included in Multivariate Analysis for Final Cosmesis |
|-----------------------------------|-------|--------|---|------------------|
| Final Cosmesis                    | OR    | SE     | P  | 95% CI           |
| IMRT group                         | 0.65  | 0.13   | .038 | 0.44 to 0.96     |
| Breast volume                     | 1.0004| 0.0018 | .020 | 1.000067 to 1.00078|
| Surgical cosmesis                 | 8.64  | 1.57   | .000 | 6.04 to 12.34    |
| Tumor bed boost                   | 1.89  | 0.40   | .003 | 1.25 to 2.86     |

Abbreviations: IMRT, intensity-modulated radiotherapy; OR, odds ratio.
### Table A3. Retrospective Matched Cohort Studies Comparing IMRT Versus Standard RT for Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Median Follow-Up</th>
<th>Acute Toxicity</th>
<th>Late Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedman GM et al: Int J Radiat Oncol Biol Phys 74: 689-694, 2009</td>
<td>804</td>
<td>NR</td>
<td>Reduced risk of grade 2 to 3 acute dermatitis with IMRT (52% v 75%; P &lt; .001)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total time spent with grade 2 to 3 dermatitis reduced with IMRT</td>
<td></td>
</tr>
<tr>
<td>Morganti AG et al: Radiother Oncol 90:86-92, 2009</td>
<td>332</td>
<td>IMRT, 24 months; standard RT, 42 months</td>
<td>Lower grade 2 to 3 skin toxicity in MARA-1 arm compared with C-RT (14.1% v 36.7%)*</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Higher grade 2 to 3 skin toxicity in MARA-2 arm compared with C-RT (47.1% v 36.7%†)</td>
<td></td>
</tr>
<tr>
<td>McDonald MW et al: Int J Radiat Oncol Biol Phys 72: 1031-1040, 2008</td>
<td>240</td>
<td>IMRT, 6.3 years; standard RT, 7.5 years</td>
<td>Reduced risk of grade 2 to 3 skin toxicity with IMRT (39% v 52%; P = .047)</td>
<td>Insufficient data to report on late cosmesis</td>
</tr>
<tr>
<td>Horsolia A et al: Int J Radiat Oncol Biol Phys 68: 1375-1380, 2007</td>
<td>172</td>
<td>IMRT, 4.6 years; standard RT, 5 years</td>
<td>Reduced risk of grade 2 to 3 dermatitis, breast edema, and hyperpigmentation (P &lt; .001) with IMRT</td>
<td>Reduced breast edema (1% v 25%; P &lt; .001) and trend toward reduced hyperpigmentation with IMRT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No difference on overall cosmetic score</td>
</tr>
<tr>
<td>Freedman GM et al: Am J Clin Oncol 29:66-70, 2006</td>
<td>133</td>
<td>NR</td>
<td>Reduced risk of moist desquamation with IMRT (21% v 38%; P = .001)</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: C-RT, conformal radiotherapy; IMRT, intensity-modulated radiotherapy; MARA, Modulated Accelerated Radiotherapy in Adjuvant Treatment of Breast Cancer; MARA-1, MARA protocol 1; MARA-2, MARA protocol 2; NR, not reported; RT, radiotherapy.

*60.4 Gy in 32 fractions over 6.4 weeks (C-RT) compared with 44 Gy in 16 fractions over 3.2 weeks (MARA-1).

†60.4 Gy in 32 fractions over 6.4 weeks (C-RT) compared with 60 Gy in 25 fractions over 5 weeks (MARA-2).
PROMs in breast cancer RT

Patient reported outcome measures (PROMs) following forward planned field-in-field IMRT: Results from the Cambridge Breast IMRT trial


Oncology Centre, Cambridge University Hospitals NHS Foundation Trust; Department of Oncology, Colchester Hospital University NHS Foundation Trust, Essex; Cambridge Cancer Trials Centre, Cambridge Clinical Trials Unit – Cancer Theme, Cambridge University Hospitals NHS Foundation Trust, Medical Research Council, Biostatistics Unit Hub for Trials Methodology; Cancer Research-UK Centre for Genetic Epidemiology & Dept of Oncology, University of Cambridge, Strangeways Research Laboratory; University of Cambridge, Department of Oncology, Oncology Centre, Addenbrooke’s Hospital; and Faculty of Health, Social Care & Education, Anglia Ruskin University, Cambridge, UK

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Abstract

Background: The use of intensity-modulated radiotherapy (IMRT) in breast cancer reduces clinician-assessed breast tissue toxicity including fibrosis, telangiectasia and sub-optimal cosmesis. Patient reported outcome measures (PROMs) are also important as they provide the patient’s perspective. This longitudinal study reports on (a) the effect of forward planned field-in-field IMRT (simple IMRT) compared to standard RT at 5 years after RT, (b) factors affecting PROMs at 5 years after RT and (c) the trend of PROMs over 5 years of follow up.

Methods: PROMs were assessed at baseline (pre-RT), 6, 24 and 60 months after completion of RT using global health (EORTC QLQ C30) and 4 breast symptom questions (BR23). Also, 4 breast RT-specific questions were included at 6, 24 and 60 months: change in skin appearance, firmness to touch, reduction in breast size and overall change in breast appearance since RT. The benefits of simple IMRT over standard RT at 5 years after RT were assessed using standard t-test for global health and logistic regression analysis for breast symptom questions and breast RT-specific questions. Clinical factors affecting PROMs at 5 years were investigated using a multivariate analysis. A repeated mixed model was applied to explore the trend over time for each of PROMs.

Results: (89%) 727/815, 84%, 81% and 61% patients completed questionnaires at baseline, 6, 24 and 60 months respectively. Patients reported worse toxicity for all four BR23 breast symptoms at 6 months, which then improved over time (p < 0.0001). They also reported improvement in skin appearance and breast hardness over time (p < 0.0001), with no significant change for breast shrinkage (p = 0.47) and overall breast appearance (p = 0.13). At 5 years, PROMs assessments did not demonstrate a benefit for simple IMRT over standard radiotherapy. Large breast volume, young age, baseline surgical cosmesis and post-operative infection were the most important variables to affect PROMs.

Conclusions: This study was unable to demonstrate the benefits of IMRT on PROMs at 5 years. PROMs are influenced by non-radiotherapy factors and surgical factors should be optimised to improve patients' outcome. Only a small proportion of patients report moderate–severe breast changes post radiotherapy, with most PROMs improving over time. The difference in clinician assessment and PROMs outcome requires further investigation.

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Radiation therapy (RT) has an established role in the management of early stage breast cancer to improve loco-regional control and overall survival [1]. However, post-RT some patients experience a spectrum of late breast adverse effect including skin changes, breast shrinkage, breast hardness and sub-optimal cosmesis, which negatively impact on their psycho-social well being [2]. With improving breast cancer survival, these radiotherapy associated toxicities could be an important cancer survivorship issue.

Traditionally, clinician-based assessment tools including physical examination and/or photographic assessment have been
used to score and report on breast RT toxicity [3–5]. More recently, patient-reported outcome measures (PROMs) have been introduced, as they provide patients’ perceptions of their own health condition and treatment toxicity. As the patient is most entitled to judge the extent of her treatment toxicity, the benefits of any intervention to reduce treatment-associated toxicity should also be assessed using PROMs.

The Cambridge Breast IMRT randomised trial was designed to test whether the correction of dose-inhomogeneity using a simple method of forward-planned field-in-field IMRT (simply IMRT) would decrease the late breast tissue toxicity at two and 5 years post treatment, as assessed by both clinicians and patients. However, the two-year time point was considered insufficient for patients to experience their final level of toxicity and demonstrate the full benefits of IMRT. The results on clinicians’ assessments have shown superior overall cosmesis and reduced risk of skin telangiectasia with simple IMRT at five years [6].

This study addresses the following questions: (a) Does the use of simple IMRT improve PROMs on breast-related symptoms or toxicities as compared to standard RT at five years? (b) What clinical factors independently influence PROMs at five years? and (c) What is the trend of different PROMs domains over a five-year period from date of randomisation?

Materials and methods

The Cambridge Breast IMRT trial opened in April 2003 and was closed to recruitment in June 2007. The Cambridge Research Ethics Committee provided ethical approval for the study. The National Cancer Research Institute Studies group accepted this trial as a portfolio trial in April 2002 and it was adopted by the National Cancer Research Network in March 2003. The full details of the trial have previously been published [7] and are only summarised here.

Study population

Women with operable unilateral histologically-confirmed invasive breast cancer (T1–T3, N0–1, M0) or ductal carcinoma in situ (DCIS) requiring RT after breast conservation surgery were eligible for the trial. All patients with invasive breast cancer underwent sentinel node biopsy and/or axillary clearance (if lymph node positive). Other eligibility criteria included age >18 years, no history of contralateral breast cancer, no malignancy in the previous 5 years (except skin basal cell or squamous carcinoma or in situ carcinoma of the cervix) and availability for follow up. A total of 815 patients were randomised and all patients provided written informed consent.

Randomisation and treatment

A standard RT plan consisting of paired wedged tangents was produced for all trial patients. Patients with satisfactory dose homogeneity were not randomised (non-randomised group), but were treated with standard RT and followed up as per the randomised patients. Patients whose plans had significant dose inhomogeneities, defined as >2 cm³ breast volume receiving >107% of the prescribed dose, were randomised with a ratio of 1:1 between standard RT (control group; n = 404 patients) and simple IMRT (IMRT group; n = 414 patients). Patients in the control group were treated with wedged tangential fields to the breast and patients in the IMRT group were treated with a simple, manual forward-planned IMRT technique to reduce the volumes receiving >107% and <95% of the prescribed dose. The full details of the simple IMRT technique have previously been reported [7]. Patients were informed of their randomisation arm if they enquired. All patients were treated to a dose of 40 Gy in 15 fractions, 5 days/week over 3 weeks. Nodal irradiation and tumour bed boost were administered according to the local protocol.

Patient reported outcome measures (PROMs)

All patients enrolled in the trial were approached to participate in the PROMs study. The participation into the PROMs study was voluntary and no information was collected on reasons for non-participation at baseline. The PROMs were assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire with the breast cancer module BR23 [8,9]. In addition, four post-RT breast specific questions were added to the questionnaire as per the START trial [10], to judge the direct effects of RT on the breast tissue: (1) change in skin appearance in the area of the affected breast since RT (2) overall change in breast appearance since RT (3) firmness to touch of the affected breast since RT and (4) reduction in size of the affected breast since RT. The changes were scored in a four-point Likert scale as none, a little, quite a bit and very much. We classified “quite a bit” as moderate and “very much” as severe toxicity for the analysis. The PROMs questionnaire was directly mailed to all participating patients at baseline (pre-RT), 6 months, 2 and 5 years after completion of RT, except in cases of cancer recurrence, new cancer diagnosis, further breast surgery or patient refusal. The completed questionnaires were sent back to the coordinating centre.

Statistical analysis

The eight breast related symptoms (four breast symptom questions [BR23] and four additional RT-specific questions) were analysed. In addition, the global health scores (GHS) generated from the EORTC QLQ-C30 questionnaire was also included in the study. This was to provide a summary of patients’ quality of life when considering breast related toxicity.

IMRT versus standard radiotherapy at 5 years

The benefits of simple IMRT over standard RT were assessed by using (a) standard t-test for global health score and (b) logistic regression analysis for each breast related symptom, to compare the proportion of patients reporting moderate–severe (quite a bit/very much) changes for the four breast symptom questions (BR23) and four additional RT-specific questions at five years (Table 1).

Factors affecting PROMs at 5 years

The use of IMRT, age, post-operative infection, baseline surgical cosmesis and tumour bed boost independently affected clinicians’ assessed toxicity at five years [6]. The effect of these variables on PROMs were also analysed using the multivariate logistic regression analysis.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of the four breast symptom questions (BR23) and four additional RT-specific questions.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast symptom scale questions (BR23)</td>
<td>RT-specific questions</td>
</tr>
<tr>
<td>Skin problems on or in area of affected breast</td>
<td>Change in breast appearance since radiotherapy</td>
</tr>
<tr>
<td>Pain in area of affected breast</td>
<td>Breast hardness since radiotherapy</td>
</tr>
<tr>
<td>Oversensitivity in area of affected breast</td>
<td>Breast shrinkage since radiotherapy</td>
</tr>
<tr>
<td>Swelling in area of affected breast</td>
<td>Change in skin appearance since radiotherapy</td>
</tr>
</tbody>
</table>
Trend of PROMs domains over time

Due to the longitudinal nature of the data, collected at baseline, 6 months, 2 years and five years, repeated mixed models were applied to explore the time trend for global health score and the proportion of patients reporting moderate–severe breast related symptoms.

Results

Between April 2003 and June 2007, a total of 815 patients were randomised. 727/815 (95%) patients completed the baseline PROMs study questionnaire. 684/815 (84%) patients completed the questionnaire at 6 months, 658/815 (81%) at 2 years and 498/815 (61%) at five years. The reasons for patients’ non-participation in the PROMs study at five years were summarised in Table 2. The demographics for patients who completed the PROMs questionnaire at five years are summarised in Table 3 (Supplementary material). Baseline characteristics including baseline GHS and breast symptom score (BR23) were similar between the two groups.

Five year PROMs between standard RT group versus IMRT group

No significant difference was seen in five-year “global health scores” between the two groups with the mean scores of 78.7 and 78.2 for standard RT and simple IMRT groups respectively (p = 0.80). No patient in the control group (0%) and 2/240 (1.9%) patients in the IMRT group reported moderate–severe “swelling in area of affected breast” at five years. The proportion of patients reporting moderate–severe changes for other breast specific PROMs domain at five years was small (4.2–17.7%). There was no evidence of improvement in any PROMs domain with simple IMRT, as compared to standard RT at five years in the study (Fig. 1).

Factors affecting patient reported outcome measures (PROMs)

The results of multivariate logistic regression analyses are summarised in Tables 4 and 5 (Supplementary material). Post-operative infection (yes versus no) was an independent risk factor for “change in breast appearance” (odds ratio (OR)=1.84, 95%CI = 1.03–3.3, p = 0.04), “breast hardness” (OR = 2.38, 95%CI = 1.1–5.0, p = 0.02), “pain in affected breast” (OR = 2.5, 95%CI = 1.1–5.9, p = 0.03) and “oversensitivity in affected breast” (OR = 5.4, 95%CI = 2.3–12.6, p < 0.0001) at five years. Large breast volume as a continuous variable was an independent risk factor for “change in skin appearance” (p = 0.003), “breast hardness” (p = 0.008), “pain in affected breast” (p = 0.005) and “skin problem in the affected breast” (p = 0.013) at five years. Young age and poor baseline cosmesis also affected some PROMs domains (Tables 4 and 5 (Supplementary material)).

Trend of PROMs domains over time

There was no difference in PROMs time trends between standard RT group and simple IMRT group (results not shown), and hence time trend data for the whole patient cohort have been reported together. A statistically significant improvement was seen in “global health score” over time (p = 0.009). The mean pre-RT baseline global health score was 76.3, which improved to 76.7, 78.6 and 78.5 at 6 months, two and five years respectively.

A trend for improvement was also seen over time for both breast symptoms questions (BR23) and breast RT-specific questions. Patients reported on the breast symptoms questions (BR23) at baseline (pre-RT), 6 months, two and five years after completion of RT. As compared to baseline pre-RT, more patients reported moderate–severe toxicity for all four breast symptoms at 6 months, which subsequently improved over time (p < 0.0001) (Fig. 2). A large proportion of patients who reported moderate–severe toxicity at baseline reported no-mild change at successive time points (Fig. 4 (Supplementary material)). On the contrary, only a small proportion of patients who reported no-mild changes at baseline subsequently reported moderate–severe toxicity (Fig. 4 (Supplementary material)).

Patients reported on the breast RT-specific questions at 6 months, two years and five years after completion of RT. The proportion of patients reporting moderate–severe “change in skin appearance since RT” and “breast hardness since RT” reduced over time.

---

Table 2
Reasons for patients’ non-participation in patient reported outcome measures (PROMs) study at five years.

<table>
<thead>
<tr>
<th>Reason for non participation</th>
<th>IMRT group</th>
<th>Standard RT group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not enter PROMs study</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Death</td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td>Metastatic disease (alive)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Other cancer</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Moved out of area</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Too unwell with other co-morbidities</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Mastectomy/reconstruction</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Patient choice: reason not stated</td>
<td>77</td>
<td>70</td>
</tr>
<tr>
<td>Total</td>
<td>166</td>
<td>150</td>
</tr>
</tbody>
</table>

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Fig. 1. Forrest Plot of moderate–severe toxicity assessed by patients at five years comparing standard radiotherapy (control) with simple IMRT.
time \((p < 0.0001)\) (Fig. 3). No significant change was seen in the proportion of patients reporting "change in breast appearance since RT" \((p = 0.14)\) and "breast shrinkage since RT" \((p = 0.47)\). For patients reporting moderate–severe toxicity at 6 months, there was a gradual decrease in the proportion of patients reporting moderate–severe toxicity at successive time points (Fig. 5 (Supplementary material)). Only a small proportion of patients who reported no-mild changes at 6 months subsequently reported moderate–severe toxicity (Fig. 5 (Supplementary material)).

### Discussion

The Cambridge Breast IMRT trial group recently reported superior overall cosmesis and reduced risk of skin telangiectasia with simple IMRT by using clinician-assessed toxicity tools [6]. It was anticipated that an improvement in dose homogeneity with simple IMRT would also translate into an improvement in PROMs. However, using four breast symptom questions and four RT-specific questions, this study could not demonstrate the benefits of simple IMRT over standard RT at five years.

There are several possible explanations for these results. Both clinician and patient assessment can be subjective in nature. In this study, many clinician based assessments were done using clinical photographs, where a panel of three multidisciplinary members were present at any one time during toxicity scoring on clinical photographs. The interobserver variability of multidisciplinary assessment has previously been validated [11], suggesting that clinicians’ assessment can be made objective in nature. On the other hand, PROMs are often more subjective in nature, i.e. how objective cosmesis/toxicity is perceived and felt by the patient and may not be concordant with clinician assessment [12]. The proportion of patients reporting moderate–severe breast toxicity at five years was small in this study, ranging from 0% to 17.7% for different end-points. In comparison, using clinician based assessments; moderate–severe breast toxicities were reported more frequently (range 3–49% for different endpoints) in this trial at 5 years [6]. It is possible that the low PROMs toxicity rates reduced the power of the study to demonstrate the advantages of simple IMRT over standard RT. It is also possible that the PROMs questions (BR23 breast symptom and RT-specific questions) used in the current study are not as sensitive as clinicians’ assessment to differentiate small differences in breast RT toxicity outcomes. In the current trial, the mean percentage breast volumes receiving >107% prescribed dose was only 29% in the control arm which decreased to 06% with simple IMRT [7]. Similar PROMs questions were used in the START trials [10] and were found to be sensitive to radiotherapy fractionation changes. A significantly different dose was delivered to the whole breast between the different fractionated regimes. One can only speculate that different whole breast dose caused a bigger difference in toxicity, which was easier to detect using PROMs. The partial volume effect on the sensitivity of BR23 and breast RT-specific questions could also explain why no differences were seen between the two study arms using PROMs in the current study. The lack of effect of tumour bed boost on PROMs in this study further supports the influence of partial volume effect on patients’ outcome.

To date, randomised trials have not been able to demonstrate an improvement in PROMs with IMRT for breast cancer [13,14]. The multi-centre Canadian study compared acute toxicity and quality of life (QOL) for 331 patients randomised after BCS between IMRT (forward or inverse planned) and standard RT using wedges [14]. The QOL data were assessed using EORTC QLQ-C30 and BR23 modules at baseline pre-RT, last week of RT and one month later. No significant difference in QOL was seen between the two treatment arms. The Donovan et al. [13] single centre study randomised 306 patients to IMRT or standard RT with longer follow-up.
breast patients between forward planned IMRT and standard RT and collected QOL data at baseline pre-RT, 1, 2 and 5 years post treatment using the EORTC QLQ-C30 and BR23 modules. In addition, patients were asked to evaluate breast hardness, pain and tenderness before RT and then at 2 and 5 years. After adjusting for baseline scores, no significant difference in PROMs was seen between the randomised patients by five years.

Factors affecting PROMs after breast radiotherapy have not been widely investigated in the past. In this study, non-radiotherapy factors had the biggest impact on patient’s outcome. Post-operative infection and large breast volume were identified as the main risk factors to influence on patient reported breast toxicity in this study. In addition, young age and poor baseline surgical cosmesis were also found to influence on the symptoms of skin appearance and breast hardness.

In this study, the time trend for different PROMs was also investigated. For clinicians, this information can facilitate counselling of patients for radiotherapy, restructuring the support network and targeting intervention to patients, when they are most susceptible to treatment-related toxicity. A better understanding of how various PROMs domains progress over time can also help patients to make informed decisions about their treatments.

Patients reported worse toxicity for all four BR23 breast symptoms at 6 months in this study, which then improved over time (Fig. 2). These results most likely represent unresolved acute post-RT changes (skin erythema and breast oedema), which are expected to improve over a period of time [15,16]. On the other hand, long term radiotherapy changes like skin telangiectasia, breast shrinkage and breast induration addressed via the RT-specific questions are expected to progress over time [17]. However, using these PROMs tools, this study found that patients reported an improvement in skin appearance and breast hardness over time (Fig. 3). Only a non-significant increase was seen in the proportion of patients reporting moderate–severe breast shrinkage and change in breast appearance over time. There are several potential explanations for these results. The current study found that patients’ global health improved over time. It is likely that for some patients, as the global quality of life improves, “changes in the breast post radiotherapy” are no longer of significant concern. It is also plausible that at early follow up (6 months and 2 years), symptoms like breast hardness and change in breast appearance were over-reported, as patients found it difficult to differentiate between post-surgical and post-radiotherapy changes.

Over time, some patients’ may under-report toxicity as they have previously discussed the risks and benefits of treatment and therefore anticipate some changes in the treated breast. Other studies have also reported a similar trend with an improvement in radiotherapy associated PROMs over time [18,19]. Whelan et al. [18] randomised 837 patients between adjuvant radiotherapy and no further treatment after breast conserving therapy and compared the proportion of patients troubled by “irritation of the skin”, “breast pain” and “upset by the breast appearance”. The proportion of patients reporting skin irritation and breast pain decreased over time ($p = 0.0001$) with no significant difference between radiotherapy and no radiotherapy patients by two years. In addition, the proportion of patients reporting “upset by the breast appearance” was also similar between the randomised groups over two years. In the Australian Pulling Through Study, the prevalence of skin/tissue reaction to radiotherapy decreased from 54% at 6 months to 8% at 6 years [19]. Heil et al. [20] used the Breast Cancer Treatment Outcome Scale (BCTOS) to assess the functional, aesthetic and breast sensitivity status of 138 patients treated with BCS and adjuvant radiotherapy. At one year, no significant change was seen for aesthetic and functional status, whereas an improvement was seen in the breast sensitivity status ($p < 0.0001$).

![Fig. 3. Time Trend for Breast RT PROMs for patients with all four assessments.](image-url)
Limitations

All patients from the Cambridge Breast IMRT trial were offered participation in the PROMs study and no separate statistical power assessment was performed. Nevertheless, this study of more than 800 patients is one of the largest PROMs studies for early stage breast cancer patients. A significant number of patients did not complete their PROMs questionnaire at five years, which possibly affected the power of the study. This was predominantly due to patient choice or refusal, though patients were also excluded if they had cancer recurrence, new cancer diagnosis and/or further breast surgery. This is reasonable as there is significant deterioration in quality of life among patients with recurrent cancer and/or mastectomy [21,22]. Overall, the baseline demographics for patients who completed their five year questionnaire were similar and there was no trend to suggest that patients reporting problem at baseline or at 6 months more frequently participated at five years. The reasons for patients’ non-participation at five years were also not dissimilar between the two randomised groups (Table 2).

Conclusions

Contrary to clinician-assessed outcome, this study could not demonstrate the benefits of simple breast IMRT on PROMs. Non-radiotherapy factors including large breast volume, young age and surgical factors influence PROMs and hence, surgical factors should be optimised. It is reassuring to note that only a small proportion of patients reported moderate–severe breast changes post radiotherapy, and most PROMs improved over time. The difference between clinician assessments and PROMs merits further investigation through ongoing breast radiotherapy trials.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2014.02.016.

References

Association of breast tumour bed seroma with post-operative complications and late normal tissue toxicity: Results from the Cambridge Breast IMRT trial

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Abstract

Aims: There are two main surgical techniques for managing the tumour bed after breast cancer excision. Firstly, closing the defect by suturing the cavity walls together and secondly leaving the tumour bed open thus allowing seroma fluid to collect. There is debate regarding which technique is preferable, as it has been reported that a post-operative seroma increase post-operative infection rates and late normal tissue side effects.

Methods: Data from 648 patients who participated in the Cambridge Breast IMRT trial were used. Seromas were identified on axial CT images at the time of radiotherapy planning and graded as not visible/subtle or easily visible. An association was sought between the presence of seroma and the development of post-operative infection, post-operative haematoma and 2 and 5 years normal tissue toxicity (assessed using serial photographs, clinical assessment and self assessment questionnaire).

Results: The presence of easily visible seroma was associated with increased risk of post-operative infection (OR = 1.80; p = 0.004) and post-operative haematoma (OR = 2.1; p = 0.02). Breast seroma was an independent risk factor for whole breast induration and tumour bed induration at 2 and 5 years. The presence of breast seroma was also associated with inferior overall cosmesis at 5 years. There was no significant association between the presence of seroma and the development of either breast shrinkage or breast pain.

Conclusion: The presence of seroma at the time of radiotherapy planning is associated with increased rates of post-operative infection and haematoma. It is also an independent risk factor for late normal tissue toxicity. This study suggests that full thickness surgical closure may be desirable for patients undergoing breast conservation and radiotherapy.

Keywords: Breast seroma; Post-operative complications; Normal tissue toxicity

Introduction

Breast conserving surgery (BCS) followed by post-operative radiotherapy is the standard of care for most early breast cancer patients. It has equivalent survival to mastectomy and offers good cosmesis in the majority of patients. Breast conserving surgery (BCS) involves resection of the tumour within a cylinder of tissue from subcutaneous fat down to pectoral muscle and including a clear radial margin of normal breast tissue that is tumour-free. The breast tissue adjacent to the site of the wide local excision is called the tumour bed. There is currently no consensus among breast surgeons about the optimal surgical management of the tumour bed. There are two main approaches of managing the dead space left after tumour excision. One surgical approach involves simple skin closure anterior to the cavity, allowing for seroma fluid to accumulate in the tumour bed. The second approach involves obliteration of the tumour bed cavity by mobilisation of breast tissue from subcutaneous fat and underlying muscle to allow approximation and suturing of the breast tissue in layers from deep to superficial. Seroma fluid is less likely to
accumulate in the tumour bed with the full thickness closure.³

Cosmetic outcome has been shown to be an important factor influencing patient psychosocial morbidity after treatment.⁴ Advocates of both the standard closure and full thickness closure cite superior cosmesis in supporting their practice. It has been proposed that seroma collection with the standard closure technique is advantageous to the patient, as it preserves the normal tissue contour even after a large volume resection.⁵,⁶ The seroma is eventually replaced by scar tissue as the cavity consolidates. This approach has been widely advocated in surgical textbooks and is also supported by the National Surgical Adjuvant Breast Project workshops.⁷ Some authors argue, however that full thickness closure offers better cosmesis.¹⁰ Apart from overall cosmesis, the type of surgical closure can also influence the rate of post-operative infection and haematoma formation. There is however limited literature associating the standard closure technique with an increased rate of post-operative infection or haematoma.¹⁵,¹⁶

In view of the controversy regarding surgical breast excision technique and its possible effects on infection and haematoma rates and the development of late normal tissue toxicity, an investigation using data from the large Cambridge Breast IMRT Trial was undertaken.¹⁸

Methods

Study population

The study population consisted of 648 patients from the Cambridge Breast IMRT trial.¹⁸ The full details of the trial have previously been reported¹⁸ and summarised in this report (Appendix 1: CONSORT diagram). Women were eligible for the trial if they had operable unilateral histologically confirmed invasive breast cancer (T1-3, N0-1, M0) or ductal carcinoma in situ requiring radiotherapy after complete macroscopic excision of the tumour by BCS. Ethical approval was obtained from the Cambridge Research Ethics Committee and written consent was obtained from all patients to use their data for research purposes. The study opened in April 2003 and closed to recruitment in June 2007.

Surgical technique

During the trial recruitment phase, both standard and full thickness closure surgical techniques were used, with the majority of surgeons using the former method. The operation record was not collected as part of the trial protocol; a retrospective review of the operative notes was not useful as the type of closure was not stated in most cases. Therefore, the presence of a seroma at the time of radiotherapy planning was used as a surrogate for standard wound closure over the tumour bed.

Assessment of seroma

Clinical assessment of breast seroma is subjective and can be difficult to appreciate in patients with high body mass index (BMI).¹⁹ Radiotherapy planning CT scans were used in this study to define the tumour bed seroma, as this method is more objective and independent of BMI. The seroma was identified on the axial CT images and graded as not visible/subtle or easily visible (Fig. 1). All visible seroma were contoured on axial CT slices using a pre-defined protocol and the total seroma volume was recorded. One clinical oncology specialist registrar and one advanced radiotherapy practitioner received specific training from the Chief Investigator of the Cambridge Breast IMRT trial before contouring the study images.

Collection of data

The data on post-operative infection and/or haematoma was collected at the time of the patient’s radiotherapy planning CT scan. Post-operative infection was defined as skin redness which required antibiotic treatment. Post-operative haematoma was identified from surgical notes and/or medical correspondence.

Patients had serial photographs of both breasts (frontal view) after primary surgery and before the start of radiotherapy (baseline), 2 years and 5 years post radiotherapy. Two photographs were taken, one with the hands resting on the hips and the other with the arms raised above the head. Breast shrinkage was scored using a validated 3 point score (none/minimal = 1, mild = 2, marked = 3) by a panel.
of assessors. A multidisciplinary team of seven clinicians (4 oncologists, 1 radiographer, 1 surgeon and 1 breast care nurse) were involved in photographic assessment, a panel of three being present at any one time. This method has been validated and shown to be as sensitive but quicker than using 3 independent scorers with re-scoring of discrepancies and final resolution through discussion. In addition, overall cosmesis was also assessed by the panel using the photographs taken at 2 and 5 years and scored using a 3 point score (good, moderate and poor cosmesis).

Clinical assessment was made 2 and 5 years after completion of radiotherapy for the presence of breast oedema, whole breast induration and tumour bed induration. The endpoints were graded 0–3 (none, a little, quite a bit and very much) on the scale used in the START trials. The EORTC BR23 questionnaire was used to assess pain and hypersensitivity in the treated breast following radiotherapy.

Statistical analysis

Logistic regression was used to test for an association between presence or absence of tumour bed seroma and the development of post-operative infection or haematoma. The effect of seroma on the incidence of normal tissue side effects was tested using polychotomous logistic regression, which enables analysis of the toxicity endpoints as the dependent variables, and takes into account multiple ordered values. No numerical relationship is assumed between these grades; it is only assumed that lower grades correspond to milder reactions.

The Cambridge Breast IMRT trial group has previously reported on the patient and treatment related factors that significantly impact on 2 years normal tissue toxicity following BCS and post-operative radiotherapy. Patient-related factors included: breast volume, age at randomisation, co-morbidity such as diabetes mellitus or cardiovascular disease and smoking history. Treatment-related factors included: specimen weight, surgical cosmesis, post-operative haematoma or infection, dosimetry, breast boost, use of chemotherapy and/or tamoxifen. Factors that were significantly associated with overall cosmesis or late toxicity following radiotherapy on univariate analysis (P < 0.1) from the previous reports were included in the multivariate analysis in this study.

While polychotomous logistic regression provides good power to detect an association between risk factors and late normal tissue toxicity, the parameters estimated do not have an easily interpretable meaning. In order to aid the interpretation, the endpoints were dichotomized. Hence, univariate and multivariate analysis was performed using these dichotomized endpoints, i.e. dividing endpoints into two groups of no/mild toxicity and moderate/severe toxicity to obtain meaningful odds ratios. STATA version 10.1 (STATA statistical software, release10; Stata Corporation, College station, TX) was used for statistical analysis.

Some patients received adjuvant chemotherapy after BCS and hence their radiotherapy planning CT scan was done 4–6 months post surgery. Some of these patients may have had a seroma which resolved before their radiotherapy planning CT scan. Hence, the analysis was repeated after excluding these patients, to see if there was more of an effect on the measured endpoints.

Results

Baseline patient characteristics (Table 1)

The seroma was easily visible in 237/648 (36.6%) patients. The median seroma volume was 2.8 cc (range 0–202 cc). The median time from surgery to RT for chemotherapy and non-chemotherapy patients was 222 days and 60 days respectively.

The baseline patient demographics and clinical characteristics are presented in Table 1. The patients in the no/subtle seroma arm were relatively younger and more likely to be node positive, reflecting a higher risk group than the easily visible seroma group. This higher risk patient group was also more likely to receive adjuvant chemotherapy and a radiotherapy tumour bed boost.

Post-operative infection and haematoma (Table 2)

The overall rate of post-operative infection was 19.7%. It was more common in patients with visible seroma as compared to no/subtle seroma (26% vs.16%, p = 0.004). The overall rate of post-operative haematoma identified was 7.9%. It was also more common in patients with visible

<table>
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<td>Age</td>
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<td>Mean (range)</td>
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<td>AJCC staging</td>
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<td>Aromatase inhibitor</td>
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<tr>
<td>Tumour boost</td>
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</table>

DCIS: ductal carcinoma in situ.  
AJCC: American Joint Committee on Cancer.
seroma as compared to no/subtle seroma (12% vs. 6%, \( p = 0.02 \)). These results were similar after excluding patients with adjuvant chemotherapy (Appendix 2).

2-year normal tissue toxicity (Table 3)

Table 3 shows the results of univariate and multivariate analysis for the association between breast seroma and normal tissue toxicity at 2 years using dichotomized endpoints. The results using polychotomous logistic regression led to identical conclusions (results not shown). On univariate analysis, presence of easily visible breast seroma was associated with worse breast cosmesis, whole breast induration, tumour bed induration and breast oedema at 2 years. On multivariate analysis, the presence of easily visible seroma was associated with whole breast induration, tumour bed induration and breast oedema but was no longer associated with worse overall cosmesis. There was no significant association between the presence of seroma and the development of either breast shrinkage or breast pain at 2 years on univariate and multivariate analysis. These results were similar after excluding patients with adjuvant chemotherapy (Appendix 3).

5-year normal tissue toxicity (Table 4)

Table 4 shows the results of univariate and multivariate analysis for the association between breast seroma and normal tissue toxicity at 5 years using dichotomized endpoints. Again, the results using polychotomous logistic regression led to identical conclusions (results not shown). On univariate and multivariate analysis, presence of easily visible breast seroma was associated with worse breast cosmesis, whole breast induration and tumour bed induration. However, the presence of seroma was no longer associated with breast oedema at 5 years. These results were similar after excluding patients with adjuvant chemotherapy (Appendix 4).

Discussion

The ultimate goal of BCS and post-operative radiotherapy is to achieve optimal local control with a good cosmetic outcome and minimal side effects. Currently, there is debate as to which surgical management of the breast tumour bed (standard versus full thickness closure technique) best achieves this ultimate goal. This study used the presence of seroma on the radiotherapy planning CT scan as a surrogate for the standard closure surgical technique. The results show a strong association between tumour bed seroma and post-operative infection and haematoma. The presence of breast seroma also appears to be associated with increased normal tissue toxicity at 2 and 5 years.

There are several limitations of this study. Firstly, the exact surgical technique for each study patient is unknown: it has been assumed that the presence of a seroma at the time of radiotherapy planning infers the use of the standard technique for surgical wound closure. The standard closure technique was more commonly used during the trial but only 36% patients had visible seroma at the time of planning CT scan. It is possible that some patients with standard closure did not develop seroma. Conversely, there may be some patients who had a full thickness closure and still...
developed seroma. Patients receiving adjuvant chemothera-
py had a delay of 4–6 months between their surgery and planning CT scan. This would have also allowed for
the resolution of seroma among some patients.

Secondly, there is an imbalance in baseline characteris-
tics between the clearly visible seroma and subtle/no se-
roma groups, with the latter consisting of more high risk
young and/or node positive patients. This relative im-
balance is expected as more patients in this higher risk group
received post-operative chemotherapy, thus any seroma
had more opportunity to resolve before the radiotherapy
planning CT scan. In addition, this group were more
likely to receive a radiotherapy tumour bed boost. Both
chemotherapy and radiotherapy boost treatments have pre-
viously been reported as risk factors for normal tissue tox-
icity. Thus this imbalance between the two groups is
more likely to underestimate the effect of tumour bed se-
roma on normal tissue toxicity. The presence of haema-
toma may not be recorded in medical notes/ correspondence for all patients and therefore may be
underestimated in this study.

Association between tumour bed seroma and post-
operative infection and haematoma

The current study found that patients with tumour bed
seroma are 1.8 times more likely to develop post-
operative infection then patients with no/ subtle seroma.
Of note, the infection rate of 19.7% in this study is higher
than previously reported in the literature. It is suspected
that some patients may have received antibiotics as a pre-
caution for skin redness and not true infection, thus the as-
association with “true” post-operative infection may in fact
be stronger.

It is postulated that a fluid filled seroma cavity can act as
a culture medium for bacterial growth, hence increasing the
risk of infection, in keeping with previously published re-
ports. Hall and Hall reported an association between
the presence of seroma and wound infection for 218 women
with non-reconstructive breast surgery \( p < 0.001 \). In-
delico et al. reported an increased rate of acute infection
in patients with standard tumour bed closure as compared
to full thickness closure \( (11.7\% \text{ vs. } 5.25\%; p = 0.009) \).

This study also found that patients with tumour bed se-
roma are 2.1 times more likely to develop post-operative
haematoma than patients with no/subtle seroma. It could
be hypothesised that despite meticulous haemostasis, small
blood vessels can still bleed into the tumour bed following
standard wound closure alone. In comparison, the opposed
breast parenchyma with full thickness closure may promote
better haemostasis. Paterson et al. reported an increased
rate of haematoma in patients with standard wound closure as
compared to deep wound approximation \( (54.4\% \text{ vs. } 31.4\%; p = 0.004) \) and Law et al. reported an increased
risk of haematoma in patients with standard wound closure in comparison to full thickness closure.

In addition, this group has previously reported that post-
operative infection is associated with increased risk of tel-
angiectasia and breast oversensitivity at 2 years and as
a result these post-operative complications could also im-
 pact on late normal tissue toxicity.

Association between tumour bed seroma and late
normal tissue toxicity

This study shows that the presence of a tumour bed se-
roma appears to be an independent risk factor for develop-
ing normal tissue toxicity. The patients with an easily
visible seroma on the radiotherapy planning CT scan had
a higher rate of whole breast induration and tumour bed in-
duration compared to patients with no/subtle seroma at 2
and 5 years. Breast oedema is a transitional phenomenon
which peaks in the first few years after radiotherapy and
resolves in most patients by 5 years. This study showed an independent association between breast seroma
and breast oedema at 2 years, but not at 5 years. Con-
versely, the presence of breast seroma was associated
with worse overall cosmesis at 5 years, but not at 2 years.
It is likely that follow up of 2 years may have been insuf-
ficient to express the final level of late toxicity for overall
cosmesis.

Schultze et al. reported on the cosmetic outcome of 97
patients with breast seroma after BCS and concluded that
post-operative seroma and haematoma have an adverse ef-
fect on the resulting cosmesis. Based on the EORTC trial
22881–10882 ‘boost versus no boost’, Collette et al. re-
ported complications after BCS (haematoma, oedema, se-
roma and local infection) as predictors for moderate or
severe breast fibrosis in the patients receiving breast boost.
The increased risk of normal tissue toxicity with breast
seroma may be due to various reasons. The breast serosa
is rich in fibrin which can organise, possibly leading to tu-
mour bed induration. An organised seroma can also pull the
surgical edges together by retraction possibly leading to
inferior cosmesis. It is well known that the volume of se-
roma changes during breast radiotherapy and these
changes in volume can lead to significant dose heterogene-
ity, potentially leading to inferior overall cosmesis. Huh
et al. looked at the inter-fractional dose variation due to se-
roma for three breast cancer patients with conventional
and IMRT. They found the change in breast se-
roma volume had a significant effect on the dose inhomo-
genity in the treatment volume \( (3.7–13.9\% \text{ for conventional
treatment and } 6.7–20.7\% \text{ for IMRT treatment}) \).

It is clear that the causes of late normal tissue toxicity
and poor cosmesis following BCS and radiotherapy are
multi-factorial. It is also apparent that these side effects
of treatment can cause considerable physical and psycho-
logical morbidity. Therefore, all aspects of treatment in-
cluding the surgical technique for wound and/or cavity
closure should be optimised to reduce this toxicity to
a minimum.
Conclusion

The presence of seroma in the breast tumour bed is associated with increased rates of post-operative infection and haematoma. It is also an independent risk factor for tumour bed induration and inferior breast cosmesis at 5 years. As mechanical closure of the tumour bed is an effective way to reduce seroma formation, full thickness surgical closure may be desirable for patients undergoing breast conservation and radiotherapy.

Conflict of interest statement

None.

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Appendix A. Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejso.2012.05.008

References


