EFFICACY AND MECHANISM EVALUATION

VOLUME 1 ISSUE 3 NOVEMBER 2014
ISSN 2050-4365

A multicentre observational study evaluating image-guided radiotherapy for more accurate partial-breast intensity-modulated radiotherapy: comparison with standard imaging technique

Emma J Harris, Mukesh Mukesh, Rajesh Jena, Angela Baker, Harry Bartelink, Corrinne Brooks, June Dean, Ellen M Donovan, Sandra Collette, Sally Eagle, John D Fenwick, Peter H Graham, Jo S Haviland, Anna M Kirby, Helen Mayles, Robert A Mitchell, Rosalind Perry, Philip Poortmans, Andrew Poynter, Glyn Shentall, Jenny Titley, Alistair Thompson, John R Yarnold, Charlotte E Coles and Philip M Evans on behalf of the IMPORT Trials Management Group

NHS National Institute for Health Research

DOI 10.3310/eme01030

A multicentre observational study evaluating image-guided radiotherapy for more accurate partial-breast intensity-modulated radiotherapy: comparison with standard imaging technique

Emma J Harris,[1†] Mukesh Mukesh,[2†] Rajesh Jena,[2] Angela Baker,[3] Harry Bartelink,[4] Corrinne Brooks,[1] June Dean,[2] Ellen M Donovan,[1] Sandra Collette,[5] Sally Eagle,[6] John D Fenwick,[7] Peter H Graham,[8] Jo S Haviland,[9] Anna M Kirby,[10] Helen Mayles,[3] Robert A Mitchell,[1] Rosalind Perry,[11] Philip Poortmans,[12] Andrew Poynter,[13] Glyn Shentall,[14] Jenny Titley,[9] Alistair Thompson,[15] John R Yarnold,[10] Charlotte E Coles[2‡] and Philip M Evans[1,16*‡] on behalf of the IMPORT Trials Management Group

[1]Joint Department of Physics at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, UK
[2]Oncology Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[3]Department of Radiotherapy and Physics, The Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, UK
[4]Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, the Netherlands
[5]Statistics Department, EORTC Headquarters, Brussels, Belgium
[6]Department of Radiotherapy, Royal Marsden Hospital NHS Foundation Trust, London, UK
[7]Department of Oncology, University of Oxford, Oxford, UK
[8]Cancer Care Centre, St George Hospital, Kogarah, Sydney, NSW, Australia
[9]ICR-CTSU, Institute of Cancer Research, London, UK
[10]Breast Unit, Royal Marsden NHS Foundation Trust, London, UK
[11]Radiotherapy Department, Ipswich Hospitals NHS Trust, Ipswich, UK
[12]Department of Radiation Oncology, Dr Bernard Verbeeten Instituut, Tilburg, the Netherlands
[13]Radiotherapy Department, Peterborough City Hospital, Peterborough, UK
[14]Rosemere Cancer Centre, Lancashire Teaching Hospitals NHS Trust, Preston, UK
[15]School of Medicine, University of Dundee, Dundee, UK
[16]Centre for Vision, Speech and Signal Processing, Faculty of Engineering and Physical Sciences, University of Surrey, Guildford, UK

*Corresponding author
†Joint first authors
‡Joint principal investigators

Declared competing interests of authors: Jenny Titley is employed by the Institute of Cancer Research Clinical Trials and Statistics Unit, which receives some funds from Cancer Research UK.

Published November 2014
DOI: 10.3310/eme01030

This report should be referenced as follows:

Harris EJ, Mukesh M, Jena R, Baker A, Bartelink H, Brooks C, *et al*. A multicentre observational study evaluating image-guided radiotherapy for more accurate partial-breast intensity-modulated radiotherapy: comparison with standard imaging technique. *Efficacy Mech Eval* 2014;**1**(3).

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

The full EME archive is freely available to view online at www.journalslibrary.nihr.ac.uk/eme. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Efficacy and Mechanism Evaluation* journal
Reports are published in *Efficacy and Mechanism Evaluation* (EME) if (1) they have resulted from work for the EME programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

EME programme

The Efficacy and Mechanism Evaluation (EME) programme was set up in 2008 as part of the National Institute for Health Research (NIHR) and the Medical Research Council (MRC) coordinated strategy for clinical trials. The EME programme is broadly aimed at supporting 'science driven' studies with an expectation of substantial health gain and aims to support excellent clinical science with an ultimate view to improving health or patient care.

Its remit includes evaluations of new treatments, including therapeutics (small molecule and biologic), psychological interventions, public health, diagnostics and medical devices. Treatments or interventions intended to prevent disease are also included.

The EME programme supports laboratory based or similar studies that are embedded within the main study if relevant to the remit of the EME programme. Studies that use validated surrogate markers as indicators of health outcome are also considered.

For more information about the EME programme please visit the website: http://www.nets.nihr.ac.uk/programmes/eme

This report

The research reported in this issue of the journal was funded by the EME programme as project number 09/150/16. The contractual start date was in March 2011. The final report began editorial review in September 2013 and was accepted for publication in March 2014. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research. The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, MRC, NETSCC, the EME programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the EME programme or the Department of Health.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

Abstract

A multicentre observational study evaluating image-guided radiotherapy for more accurate partial-breast intensity-modulated radiotherapy: comparison with standard imaging technique

Emma J Harris,[1†] Mukesh Mukesh,[2†] Rajesh Jena,[2] Angela Baker,[3] Harry Bartelink,[4] Corrinne Brooks,[1] June Dean,[2] Ellen M Donovan,[1] Sandra Collette,[5] Sally Eagle,[6] John D Fenwick,[7] Peter H Graham,[8] Jo S Haviland,[9] Anna M Kirby,[10] Helen Mayles,[3] Robert A Mitchell,[1] Rosalind Perry,[11] Philip Poortmans,[12] Andrew Poynter,[13] Glyn Shentall,[14] Jenny Titley,[9] Alistair Thompson,[15] John R Yarnold,[10] Charlotte E Coles[2‡] and Philip M Evans[1,16*‡] on behalf of the IMPORT Trials Management Group

[1]Joint Department of Physics at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, UK
[2]Oncology Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[3]Department of Radiotherapy and Physics, The Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, UK
[4]Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, the Netherlands
[5]Statistics Department, EORTC Headquarters, Brussels, Belgium
[6]Department of Radiotherapy, Royal Marsden Hospital NHS Foundation Trust, London, UK
[7]Department of Oncology, University of Oxford, Oxford, UK
[8]Cancer Care Centre, St George Hospital, Kogarah, Sydney, NSW, Australia
[9]ICR-CTSU, Institute of Cancer Research, London, UK
[10]Breast Unit, Royal Marsden NHS Foundation Trust, London, UK
[11]Radiotherapy Department, Ipswich Hospitals NHS Trust, Ipswich, UK
[12]Department of Radiation Oncology, Dr Bernard Verbeeten Instituut, Tilburg, the Netherlands
[13]Radiotherapy Department, Peterborough City Hospital, Peterborough, UK
[14]Rosemere Cancer Centre, Lancashire Teaching Hospitals NHS Trust, Preston, UK
[15]School of Medicine, University of Dundee, Dundee, UK
[16]Centre for Vision, Speech and Signal Processing, Faculty of Engineering and Physical Sciences, University of Surrey, Guildford, UK

*Corresponding author p.evans@surrey.ac.uk
[†]Joint first authors
[‡]Joint principal investigators

Background: Whole-breast radiotherapy (WBRT) is the standard treatment for breast cancer following breast-conserving surgery. Evidence shows that tumour recurrences occur near the original cancer: the tumour bed. New treatment developments include increasing dose to the tumour bed during WBRT (synchronous integrated boost) and irradiating only the region around the tumour bed, for patients at high and low risk of tumour recurrence, respectively. Currently, standard imaging uses bony anatomy to ensure accurate delivery of WBRT. It is debatable whether or not more targeted treatments such as synchronous integrated boost and partial-breast radiotherapy require image-guided radiotherapy (IGRT) focusing on implanted tumour bed clips (clip-based IGRT).

Objectives: Primary – to compare accuracy of patient set-up using standard imaging compared with clip-based IGRT. Secondary – comparison of imaging techniques using (1) tumour bed radiotherapy safety margins, (2) volume of breast tissue irradiated around tumour bed, (3) estimated breast toxicity following development of a normal tissue control probability model and (4) time taken.

Design: Multicentre observational study embedded within a national randomised trial: IMPORT-HIGH (Intensity Modulated and Partial Organ Radiotherapy – HIGHer-risk patient group) testing synchronous integrated boost and using clip-based IGRT.

Setting: Five radiotherapy departments, participating in IMPORT-HIGH.

Participants: Two-hundred and eighteen patients receiving breast radiotherapy within IMPORT-HIGH.

Interventions: There was no direct intervention in patients' treatment. Experimental and control intervention were clip-based IGRT and standard imaging, respectively. IMPORT-HIGH patients received clip-based IGRT as routine; standard imaging data were obtained from clip-based IGRT images.

Main outcome measures: Difference in (1) set-up errors, (2) safety margins, (3) volume of breast tissue irradiated, (4) breast toxicity and (5) time, between clip-based IGRT and standard imaging.

Results: The primary outcome of overall mean difference in clip-based IGRT and standard imaging using daily set-up errors was 2–2.6 mm ($p < 0.001$). Heterogeneity testing between centres found a statistically significant difference in set-up errors at one centre. For four centres (179 patients), clip-based IGRT gave a mean decrease in the systematic set-up error of between 1 mm and 2 mm compared with standard imaging. Secondary outcomes were as follows: clip-based IGRT and standard imaging safety margins were less than 5 mm and 8 mm, respectively. Using clip-based IGRT, the median volume of tissue receiving 95% of prescribed boost dose decreased by 29 cm^3 (range 11–193 cm^3) compared with standard imaging. Difference in median time required to perform clip-based IGRT compared with standard imaging was X-ray imaging technique dependent (range 8–76 seconds). It was not possible to estimate differences in breast toxicity, the normal tissue control probability model indicated that for breast fibrosis maximum radiotherapy dose is more important than volume of tissue irradiated.

Conclusions and implications for clinical practice: Margins of less than 8 mm cannot be used safely without clip-based IGRT for patients receiving concomitant tumour bed boost, as there is a risk of geographical miss of the tumour bed being treated. In principle, smaller but accurately placed margins may influence local control and toxicity rates, but this needs to be evaluated from mature clinical trial data in the future.

Funding: This project was funded by the Efficacy and Mechanism Evaluation (EME) programme, a MRC and NIHR partnership.

Contents

List of tables

List of figures

List of abbreviations

2D-kVPI	two-dimensional kilovoltage planar imaging
2D-MV	two-dimensional megavoltage
3D	three-dimensional
3D-CRT	three-dimensional conformal radiotherapy
$\gamma 50$ and m	the steepness parameter of the dose–response curve
AP	anterior–posterior
APBI	accelerated partial-breast irradiation
BASO	British Association of Surgical Oncology
BCS	breast-conserving surgery
BEUD	biologically equivalent uniform dose
$BEUD_3$	biologically equivalent uniform dose using an $\alpha:\beta$ ratio of 3 Gy
$BEUD_3 50$	biologically equivalent uniform dose to the whole breast which produces a 50% complication rate using an $\alpha:\beta$ ratio of 3 Gy
BEUD50	biologically equivalent uniform dose to the whole breast which produces a 50% complication rate
CBCT	cone beam computed tomography
CCD	craniocaudal distance
CI	confidence interval
CLD	central lung distance
COM	centre of mass
CT	computed tomography
CTV	clinical target volume
CTV-TB	tumour bed clinical target volume
CVS	Clarity Visualisation Score
DRR	digitally reconstructed radiograph
DVH	dose–volume histogram
e-NAL	extended no-action level
EORTC	European Organisation for Research and Treatment of Cancer
EQD2	equivalent dose in 2-Gy fractions
EUD	equivalent uniform dose
GOC	Gloucestershire Oncology Centre
HDR	high dose rate
IGRT	image-guided radiotherapy
IMPORT	Intensity Modulated and Partial Organ Radiotherapy Trial
IMPORT-HIGH	Intensity Modulated and Partial Organ Radiotherapy Trial – HIGHer-risk patient group
IMPORT-LOW	Intensity Modulated and Partial Organ Radiotherapy Trial – LOWer-risk patient group
IMRT	intensity-modulated radiotherapy
IORT	interoperative radiotherapy
IVP	image verification protocol
kV-CBCT	kilovoltage cone beam computed tomography
LDR	low dose rate
LKB	Lyman–Kutcher–Burman
LR	lateral
MC	Monte Carlo
MCE	major coronary event
MLE	maximum likelihood estimation
MV-CT	megavoltage computed tomography
n	volume parameter of the organ being assessed
NAL	no-action level
NTCP	normal-tissue complication probability
NTD_{50}	tolerance dose which results in 50% chance of tissue injury

PBI	partial-breast irradiation
PTV	planning target volume
PTV-TB	tumour bed planning target volume
QUANTEC	Quantitative Analyses of Normal Tissue Effects in the Clinic
RAPID	Randomised Trial of Accelerated Partial Breast Irradiation
RCT	randomised controlled trial
RMH	Royal Marsden Hospital
ROI	region of interest
RTOG	Radiation Therapy Oncology Group
SD	standard deviation
SI	superior–inferior
SIB	simultaneous integrated boost
START	UK Standardisation of Breast Radiotherapy
TARGIT	TARGeted Intraoperative radioTherapy
TD50	the homogeneous dose to the organ that leads to 50% patients experiencing the defined toxicity at 5 years
WBI	whole-breast irradiation
WBRT	whole-breast radiotherapy

Plain English summary

Whole-breast radiotherapy (WBRT) is the standard treatment for breast cancer following breast-conserving surgery (lumpectomy). Cancer recurrences are most likely to occur near the original cancer: the tumour bed. A new technique aims to reduce recurrence by delivering a higher dose to the tumour bed ('boost') during WBRT. Currently, X-rays of the rib cage (standard imaging) are used to ensure accurate delivery of breast radiotherapy. Newer imaging using surgical clips within the tumour bed (clip-based imaging) may be preferable for boost radiotherapy.

The main objective was to compare accuracy of radiotherapy boost with standard and clip-based imaging. The bigger 'safety margin' required around the tumour bed was calculated and a mathematical model was constructed to estimate whether or not the extra volume irradiated caused more side effects. Two hundred and eighteen patients receiving breast radiotherapy, within a national breast boost trial, were studied; all had clip-based imaging, but standard images of the rib cage were available for comparison.

Results show that clip-based imaging is more accurate than standard imaging for boost radiotherapy and safety margins are 5 mm and 8 mm, respectively. The volume of breast tissue irradiated decreased by 29 cm^3 (range 11–193 cm^3) using clip-based imaging, but estimation of side effects was not possible using the model.

In conclusion, margins less than 8 mm cannot be used safely without clip-based imaging for patients receiving boost radiotherapy as the higher-dose boost treatment may 'miss' the tumour bed. Smaller margins may reduce both cancer recurrence and side effects, but long-term results from ongoing trials are needed.

Scientific summary

Background

The role of breast radiotherapy after breast-conserving surgery (BCS) is well established, with the 2005 systematic overview of the Early Breast Cancer Trialists' Collaborative Group demonstrating a 70% proportional reduction in local tumour recurrence risk following radiotherapy for patients treated with BCS for early-stage breast cancer.

A wealth of evidence confirms that most recurrences occur close to the primary tumour, in the region referred to as the tumour bed. For this reason a higher radiotherapy dose may be given to the tumour bed than to the rest of the breast. This extra tumour bed 'boost' typically reduces local relapse risk by 50%, at the expense of a 30% increase in the risk of moderate/severe breast fibrosis, and is usually given after whole-breast radiotherapy (WBRT). New treatment developments include increasing dose to the tumour bed during WBRT (synchronous integrated boost) and simply irradiating the region around the tumour bed (partial-breast radiotherapy), for patients at high and low risk of tumour recurrence, respectively.

Currently, standard imaging uses bony anatomy to ensure accurate delivery of WBRT. In addition, a relatively wide safety margin of normal tissue is added to the breast to account for uncertainties in its position on each day of treatment. New imaging techniques use titanium clips implanted in the tumour bed during surgery, which are imaged with X-rays during treatment. This is called clip-based image-guided radiotherapy (clip-based IGRT) and has been used in conjunction with synchronous integrated boost and partial-breast radiotherapy as it is perceived to locate the tumour bed more accurately than standard imaging. This perception has led to the use of smaller safety margins around the tumour bed under the premise that the smaller volume irradiated will reduce late normal tissue toxicity (mainly fibrosis) and facilitate dose escalation, which may reduce tumour recurrence. Despite this shift in breast radiotherapy practice, two questions remain largely unanswered. First, what is the accuracy of clip-based IGRT compared with standard imaging? Second, if clip-based IGRT irradiates a smaller volume of normal breast tissue around the tumour bed, can we predict how this would reduce side effects?

The UK Intensity Modulated and Partial Organ Radiotherapy Trial – HIGHer-risk patient group (IMPORT-HIGH) trial provided a unique opportunity to answer the above questions and is led by members of the group involved in this study. It is a randomised trial of radiotherapy dose escalation using a synchronous integrated boost, in women at higher than average risk of local cancer recurrence after BCS. The programme of work presented in this report is a substudy of the IMPORT-HIGH trial. There was no intervention in patients' treatment, IMPORT-HIGH patients received clip-based IGRT as routine and standard imaging data were obtained from clip-based IGRT images. This novel substudy design allows direct comparison of clip-based IGRT with standard imaging, but does not pose the ethical dilemma of randomising patients to potentially less accurate imaging for synchronous integrated boost radiotherapy.

Objectives

The primary objective was:

- to compare the spatial accuracy of breast radiotherapy based on imaging (1) titanium surgical clips implanted in the tumour bed (clip-based IGRT) and (2) bony anatomy and lung position during curative radiotherapy for early breast cancer (standard imaging).

The secondary objectives compared standard imaging with clip-based IGRT for:

1. adequate radiotherapy safety margins around the tumour bed to avoid geographical miss
2. volume of breast tissue irradiated around tumour bed
3. estimated breast toxicity following development of a normal tissue control probability model
4. time taken for each imaging method.

Methods

This project was a staged programme of work with five main studies. These may be split into two sets. The first set involved study of the evidence for a dose–volume effect in breast radiotherapy. The second set involved an analysis of the effects of clip-based IGRT on treatment margins.

The set of studies to evaluate evidence for a dose–volume effect in breast radiotherapy had two component studies. The first was a review of the published literature and the second was a quantitative analysis of dose–volume effect for breast tissue.

The literature review evaluated evidence from a range of radiotherapy studies. These included randomised trials evaluating a boost to the tumour bed compared with no boost, with the boost delivered via a range of modalities and approaches, including brachytherapy, cobalt-60, interoperative irradiation, electrons and photons. A second area of analysis of the literature was the evidence from studies of partial-breast irradiation (PBI), which is a mode of treatment with current clinical and research activity. A third area of analysis was evidence from breast fractionation studies.

In the second study, data from two large randomised trials were analysed: the Cambridge intensity-modulated radiotherapy (IMRT) trial and the European Organisation for Research and Treatment of Cancer (EORTC) 22881–10882 'boost versus no boost' trial. The Cambridge trial was a single-centre study, which recruited 1145 patients with stage T1–3 N0–1 M0 invasive breast cancer or ductal carcinoma in situ. Patients received WBRT, followed by an electron boost to the tumour bed in selected cases ($n = 728$). Breast fibrosis was assessed at 2 years and 5 years after completion of radiotherapy. The EORTC study was a multicentre trial that recruited 5569 patients with stage T1–2 N0–1 M0 invasive breast cancer. Patients received WBRT and were randomised to four boost levels: (1) no boost ($n = 2657$); (2) 10-Gy boost ($n = 126$); (3) 16-Gy boost ($n = 2661$); or (4) 26-Gy boost ($n = 125$). Breast fibrosis was assessed clinically at follow-up. The relationship between partial-breast volume irradiated to high dose and probability of moderate or severe fibrosis was fitted using two standard normal tissue complication probability (NTCP) models: the Lyman–Kutcher–Burman (LKB) and Niemierko models. These models use three parameters to describe the dose response: the uniform dose to the whole breast to produce 50% complication probability, the steepness of the dose–response curve and the volume effect.

The second set of studies examined the effects of clip-based IGRT. They were carried out as part of a substudy of the IMPORT-HIGH national trial. The clip-based IGRT approach used in the IMPORT-HIGH trial was the use of titanium surgical clips implanted at the time of BCS and imaged using X-rays. The first study compared the clip-based IGRT method with two other approaches: the use of X-ray imaging of bony anatomy (standard imaging) and the use of a laser-based set-up using skin markers (no imaging). In the first analysis, the set-up accuracy of these methods was analysed and the resulting safety margins for set-up error needed were determined. The time required to perform image matching of clips and bony anatomy was also measured and recorded. A second study evaluated the patient and treatment characteristics that influenced the resulting set-up errors. The third study evaluated the effects of the margins required for the three set-up methods on the radiotherapy planning of the patient's treatment.

Two hundred and eighteen patients recruited by five centres to the IMPORT-HIGH trial contributed to this study. The centres used a range of imaging methods to visualise the titanium clips and bony anatomy.

Centre A used kilovoltage cone beam computed tomography (kV-CBCT) ($n = 79$), centre B used megavoltage-energy computed tomography ($n = 40$) and centres C, D and E used two-dimensional kilovoltage planar imaging (2D-kVPI) ($n = 39$, $n = 30$ and $n = 30$, respectively).

Patient random and systematic set-up errors were measured for bony anatomy and clip-based IGRT. The differences between the two measurement sets were used to generate delta errors which described the extra uncertainty produced by the use of bony anatomy matching in the absence of clip-based IGRT. Differences in set-up errors, delta errors and times between centres, imaging modalities and imaging protocols were investigated. Population random and systematic set-up errors were determined and used to generate the necessary margins for error to achieve target coverage, using standard margin formulae and for a variety of image verification protocols.

Patient and treatment characteristics that influence set-up accuracy were studied using patient characteristics of position of the tumour bed and breast volume. Surgery characteristics included seroma visibility, surgery closing technique, number of clips and clip position. Radiotherapy characteristics included IMPORT-HIGH trial arm, time between surgery and chemotherapy and time between chemotherapy and radiotherapy.

The effects of the different safety margins using clip-based IGRT and standard imaging were studied by replanning 60 patients from the IMPORT-HIGH trial. Treatment plans were generated for two planning target volume (PTV) margins: 5 mm (achievable with clip-based IGRT) and 8 mm (required for bony anatomy-based verification). Two types of plan were generated: 30 patients were planned using a sequential, conformal photon boost to the tumour bed and 30 using the simultaneous integrated boost technique. The plans were generated to fit the dose constraints required by the IMPORT-HIGH trial.

Results

In the literature review, one of the strongest pieces of evidence for a dose–volume effect was from a study by Borger *et al.* using low-dose iridium implants (Borger JH, Kemperman H, Smitt HS, Hart A, van Dongen J, Lebesque J, *et al.* Dose and volume effects on fibrosis after breast conservation therapy. *Int J Radiat Oncol Biol Phys* 1994;**30**:1073–81). This study found evidence that, for every 100-cm^3 increase in the volume of the boost region, the risk of fibrosis increased by a factor of 4 and that a twofold increase in boost volume results in an 11% reduction in the normal tissue tolerance dose. Other studies supporting volume effect for breast tissue included trials comparing brachytherapy-based PBI and intraoperative radiotherapy with whole-breast irradiation. The brachytherapy and intraoperative dose distribution can differ from the external beam radiotherapy and, therefore, it is unclear whether or not these results can be extrapolated to external beam techniques. There is some evidence to support volume effect using external beam techniques. The Royal Marsden Gloucester trial used an electron boost and showed that, for every gray increase in boost dose, the risk of moderate to severe breast induration increases by 1%. In comparison, a 1-Gy increase to the whole breast can increase the risk of moderate to severe breast induration by 3%, indicating a dose–volume effect. Two large studies, Intensity Modulated and Partial Organ Radiotherapy Trial – LOWer-risk patient group (IMPORT-LOW) and Danish Breast Cancer Cooperative Group trial, used external beam radiotherapy for PBI and will provide more robust data on dose–volume effect in the near future.

Individual patient data of 5856 patients from the Cambridge trial and EORTC trial were used to develop the NTCP model of breast fibrosis. The best fit for the Niemierko model gave a value for the biologically equivalent uniform dose (BEUD) to the whole breast, which produces a 50% complication rate (BEUD50) of 136.4 Gy. The parameter describing the steepness of the dose response was $\gamma 50 = 0.9$ and the parameter for the volume response was $n = 0.011$. The best fit for the LKB model was (BEUD50 = 132 Gy, $m = 0.35$ and $n = 0.012$). The n parameter describing the volume effect ranges between 0 (for no volume effect) and 1 (for a strong volume effect). Hence, these results, from both models, strongly imply that the

risk of moderate or severe breast fibrosis is mainly associated with radiotherapy dose and that the change in volume of tissue irradiated does not change the risk of breast fibrosis. These results were validated on an independent dataset from the START (UK Standardisation of Breast Radiotherapy) trial. One of the secondary objectives of the programme was to estimate the reduced risk of late adverse effects resulting from the smaller tissue volume irradiated. However, based on the results of 'no volume effect', it was not possible to predict a reduction in risk of breast fibrosis if a smaller tissue volume is irradiated. Clearly, any model has limitations and the mature results from the clinical trials addressing this question are awaited.

The primary research objective of this study was to compare the accuracy of clip-based IGRT and standard imaging using bony anatomy. The random and systematic set-up errors for bony anatomy and clip-based IGRT were found to be 3 mm averaged over the five centres, with no strong evidence for differences between the centres. The delta errors (difference between clips and bony anatomy) were found to be between 2 mm and 3 mm. The margin formulae showed that the use of no imaging (i.e. laser-based set-up) requires a PTV margin of 8–10 mm; the use of standard imaging allows this to be reduced to 7–9 mm and the use of clip-based IGRT with a suitable verification protocol allows the margin to be reduced to 4–5 mm. The time taken to perform clip match was quicker than bony anatomy match using 2D-kVPI technique, but not when using kV-CBCT imaging (secondary objective).

For the study of patient, surgery and radiotherapy characteristics that influence set-up errors, laser-based set-up (no imaging) was found to be significantly influenced by breast volume, seroma visibility and surgical closing technique. Bony anatomy (standard imaging)-based set-up was found to be influenced by both breast volume and tumour bed axial position.

The results of the replanning study showed that the reduced margins that were achievable with clip-based IGRT compared with standard imaging (5 mm vs. 8 mm, respectively) led to a reduction of 29 cm^3 (range 11–193 cm^3) in the volume of breast tissue receiving a high dose. Using the clip-based IGRT margin (5 mm), 56 of the 60 cases met all the IMPORT-HIGH treatment planning criteria. Using the standard imaging margin (8 mm), four sequential boost plans and 10 concomitant boost plans breached mandatory planning constraints. The use of smaller PTV margins with clip-based IGRT also allowed a small reduction in the radiotherapy dose to the contralateral breast, heart and lung.

Conclusions and implications for clinical practice

This research demonstrates the benefits of clip-based IGRT over standard imaging, with a reduction in PTV margins. Margins < 8 mm cannot be safely used without clip-based IGRT for patients receiving concomitant tumour bed boost as there is a risk of geographical miss of the tumour bed being treated within the high-dose region.

The existing literature suggests a volume effect for breast tissue, but our NTCP model could not demonstrate a volume effect for breast fibrosis. We anticipate mature results from the ongoing clinical trials to provide a definitive answer. In principle, these smaller, but accurately placed, margins may also influence local control rates, but again this needs to be evaluated from mature clinical trial data in the future.

Funding

This project was funded by the Efficacy and Mechanism Evaluation (EME) programme, a MRC and NIHR partnership.

Chapter 1 Introduction

Structure of this report

The work in this report is based on a substudy of a national randomised controlled trial (RCT) called IMPORT-HIGH (Intensity Modulated and Partial Organ Radiotherapy Trial – HIGHer-risk patient group; CRUK/06/003). This trial was funded by Cancer Research UK under grant number C1491/A16831. The substudy is known as IMPORT-IGRT (Intensity Modulated and Partial Organ Radiotherapy Trial – Image-Guided RadioTherapy study).

The work described is a staged Efficacy and Mechanism Evaluation programme study and, hence, the structure of the report reflects the stages of the programme.

The report starts with a review of the background to the problem of target localisation in breast radiotherapy and the expected advantages of image-guided radiotherapy (IGRT) to solve various aspects of the problem. The research objectives are listed at the end of this first chapter.

Subsequent chapters then address each component of the study. These generally fall into two groups: (1) radiobiological side effects of radiotherapy on normal breast tissue and (2) a study of the role of image guidance to improve treatment accuracy, reduce margins for error and, consequently, reduce effects on normal tissue. Two chapters discuss radiobiology: *Chapter 2* is a critical review of the literature on the relationship between irradiated volume of breast tissue and late breast tissue complications and *Chapter 3* is the analysis of pooled results from two randomised trials. Three chapters discuss aspects of the role of clip-based IGRT. The first of these, *Chapter 4*, presents a comparison of standard imaging and clip-based IGRT for five centres participating in the IMPORT-HIGH trial. *Chapter 5* presents an analysis of factors that influence the relationship between set-up errors and margins generated using visual set-up, standard imaging and clip-based IGRT. In this analysis, clip-based IGRT is taken as the gold standard. *Chapter 6* presents an analysis of the volume of tissue spared high-dose irradiation using clip-based IGRT compared with standard imaging approaches.

The final chapter summarises the findings of this project and presents the key conclusions from this research programme.

Background

Radical radiotherapy following breast-conserving surgery (BCS) is a proven alternative to mastectomy for a majority of women developing breast cancer. The success of the treatment was highlighted in the 2005 systematic overview of the Early Breast Cancer Trialists' Collaborative Group,[1] which showed a 70% proportional reduction in local tumour recurrence risk following radiotherapy for patients treated with BCS for early-stage breast cancer.

For every 100 women treated, radiotherapy prevents 20 local cancer relapses in the breast and five cancer-related deaths 10 years post treatment.[1] Approximately 30,000 women are given radiotherapy for early breast cancer in the UK every year, resulting in the prevention of 6000 local tumour relapses and 1500 deaths from cancer. An estimated 1500 local tumour relapses occur despite radiotherapy, with a disproportionate number affecting women < 50 years old, who have three times the risk of local relapse risk of women in older age groups.[2] A wealth of evidence confirms that most relapses occur close to the primary tumour, in the region referred to as the tumour bed.[3] This is the reason for giving a higher dose of radiotherapy to the tumour bed than to the rest of the breast. This extra dose to the tumour bed is called

the boost and typically reduces local relapse risk by 50% at the expense of a 30% increase in the risk of moderate or severe hardening of breast tissue due to fibrosis.[2,4] Currently used protocols require a wide margin of healthy tissue to be added around the tumour bed to compensate for substantial (5–10 mm) variations in the patient position from one day of treatment to the next, which consequently limits the radiation dose that can be safely delivered. The challenge is to safely reduce the volume of healthy tissue included in the boost treatment in order to reduce the risk of late complications, with the consequence of allowing dose escalation to be done safely and potentially increase cure rates. The hypothesis tested in this programme was that modern radiotherapy technology (including treatment machines equipped with online X-ray imaging facilities that can monitor the position of internal organs relative to the treatment beam accurately) allows a substantial reduction in the safety margin around the tumour bed, thus reducing both exposure of healthy tissue and chronic complication with the inherent possibility of safe dose escalation.

The UK IMPORT-HIGH trial provided a unique opportunity to test this novel approach. IMPORT-HIGH is led by members of the group involved in this study. It is a randomised trial of radiotherapy dose escalation in women at higher than average risk of local cancer recurrence after surgery. The two main challenges for this current project are (1) direct measurement of the magnitude of tumour bed margin reduction and, therefore, tumour bed boost volume reduction achieved by tumour bed imaging and (2) estimation of the reduction in rates of moderate and severe fibrosis (breast hardening). The success of this project was judged based on these two challenges.

Radiotherapy delivery for breast cancer is a two-stage process. First, the patient undergoes computed tomography (CT) of the breast and chest region. During this procedure the patient is lying in a comfortable position that is reproducible during subsequent visits for treatment. The CT data set obtained is a basis for planning the treatment. This involves finding the optimum method of targeting the therapeutic radiation beam to deliver the desired dose distribution. Once the treatment plan is available, the patient commences a treatment programme consisting of a sequence of daily treatment visits, called fractions, typically over a period of 3 weeks. The positioning of the patient during these fractions is the same as that for the planning CT. This is achieved using the positioning of tattoos on the patient's skin surface relative to the treatment beam (with the help of a set of laser lights that are fixed relative to the position of the treatment beam).

The treatment beam is a high-energy X-ray beam. This is chosen as it penetrates well through tissue and interacts fairly uniformly with various tissue types (e.g. fat and muscle). A consequence of this is that the radiation dose distribution is well behaved in the different tissue types, but the high-energy X-ray beam is not optimal for imaging, which ideally requires substantial differences in how the beam interacts with different tissues. During most standard approaches to treatment, images are acquired using the high-energy X-ray beam, but these show only tissues whose density is greatly different from soft tissues, for example the ribs and lungs, not the soft tissues of the breast in the region where the tumour bed is. The images are compared with the planning CT images, collected before treatment, to identify discrepancies in the positioning of ribs and lung within the beam, referred to as set-up errors. If set-up errors are found to exceed predefined limits, then the patient is repositioned before the next treatment fraction is delivered. This repositioning is of the order of several millimetres. It is small on the scale of the human body but significant for radiotherapy accuracy. A major problem with this approach is that the positions of the lungs and ribs do not necessarily predict with sufficient accuracy the location of the tumour bed. As a consequence, wide margins of healthy tissue need to be added to the tumour bed boost volume.

Standard practice uses the high-energy X-ray beam produced by the treatment machine to identify the position of the ribs and lungs within the beam. The high-energy X-rays are too penetrating to show the soft tissues of the breast, including the tumour bed, which can move more than a centimetre relative to the bony anatomy and lungs. The inability to directly visualise the tumour bed means that its position cannot be measured directly, requiring a safety margin to avoid geometric miss and, hence, the exposure of a volume of normal breast tissue to higher doses than needed. The volume of tissue including this

safety margin is known as the tumour bed boost volume. The need for this safety margin can substantially increase the volume of tissue irradiated.

The larger volume of healthy tissue irradiated around the tumour bed also places limits on the total dose that can be safely delivered. The hypothesis under test in this study is that, if the tumour bed is imaged directly during treatment, the volume of healthy tissue in the tumour bed boost volume can be reduced, leading to a smaller volume of healthy tissue irradiated and, hence, to fewer treatment complications. An alternative strategy, in women at highest risk of local recurrence, is to allow safe dose escalation to the tumour bed, with expected better local cancer cure rates. Before justifying these expectations, a simple surgical technique will be described that has enabled the tumour bed to be imaged directly on each day of a patient's radiotherapy.

As part of the enabling infrastructure for the UK IMPORT-HIGH study, UK breast surgeons were asked to attach standard titanium surgical clips to the walls of the tumour excision cavity. This accurately demarks the position of the tumour bed. Pilot work was undertaken in preparation for the UK IMPORT-HIGH trial and, as a consequence, clips are now recommended for all patients undergoing breast conservation surgery by the British Association of Surgical Oncology (BASO).[5] The key advantage of this approach is that surgical clips can be visualised directly using the low-energy X-ray facility on the treatment machine. Furthermore, it has been confirmed that boost treatments verified using the position of clips are more accurate than those relying on only imaging of the positioning of the ribs and lungs.[6]

Discrepancies between the expected, planned positions of the surgical clips (based on the planning X-ray CT performed before the treatment) and the actual positions of the clips (based on imaging on the treatment machine) are corrected using small movements of the patient, of typically a few millimetres. The use of X-ray imaging of surgical clips to verify radiotherapy accuracy in real time, i.e. immediately before each treatment fraction is given, is referred to as clip-based IGRT. The pilot study for the IMPORT-HIGH trial suggests that clip-based IGRT is likely to allow smaller safety margins of healthy breast tissue around the tumour bed.[7]

If the standard imaging method is used to verify the accuracy of the patient's treatment, no information about the tumour bed is available. In a comparison of clip-based IGRT and bony anatomy set-up (i.e. the standard imaging approach), an additional safety margin of 4.5–5.5 mm was needed for standard imaging.[8] Another study found the set-up error to be, on average, 4 mm [with 3-mm variation at 1 standard deviation (SD)] greater when using standard set-up than with clip-based IGRT.[9] In a recent review of the growing literature reporting significant changes in the size and position of the tumour bed, Kim *et al.*[10] highlighted the fact that clinical factors, such as the time between surgery and chemotherapy, and the planning CT scan influence the size of the change in the tumour bed that occurs during treatment. If large changes occur, then standard imaging is unable to detect this and, consequently, errors in patient positioning will increase in the presence of such changes. For any subset of patients in whom clinical factors result in large changes in the size and position of the tumour bed, we would expect that the inaccuracy of standard imaging compared with clip-based IGRT would be greater and subsequently greater margins would need to be applied to ensure good target coverage. An example of this is the subset of patients who receive chemotherapy and in whom, consequently, the time interval between surgery and the start of radiotherapy is longer. A 5-mm safety margin is added around the tumour bed in the IMPORT-HIGH trial, compared with a 10-mm margin when the standard set-up is used. In summary, reducing margins around the tumour bed translates into smaller volumes exposed to high doses and fewer expected late side effects, such as hardness and tenderness of the breast. Clinical evidence justifying this expectation is now discussed.

Risks and benefits in breast radiotherapy

The dose–response relationships for tumour control and normal tissue damage in radiotherapy are long established and well understood. In the UK Standardisation of Breast Radiotherapy (START) trials (conducted by members of the IMPORT-HIGH trial group and the group undertaking this study), physical morbidity was defined in terms of breast shrinkage, distortion and fibrosis. This was scored by (1) independent expert observers using serial clinical photographs, (2) examination by physicians in the clinic and (3) patient self-assessment at regular time points over 5 years of follow-up.[4,11] We reported that one-third of women experienced minor or marked change in photographic breast appearance (in terms of shrinkage and distortion). These chronic effects increase in incidence and severity even 5 years after radiotherapy. The photographic changes were in accordance with prospective patient self-assessments of adverse effects, including moderate or marked change in skin appearance (reported by around 30% of patients), breast hardness (> 40%) and breast shrinkage (> 20%). A study of 254 patients undergoing BCS and radiotherapy reported that physical changes in breast tissue had a marked bearing on subsequent psychological outcome.[12] Patients completed questionnaires assessing satisfaction with treatment outcome and scored psychosocial morbidity using the Hospital Anxiety and Depression (HAD) Scale, the Body Image questionnaire and the Rosenberg Self-esteem scale. There was a strong association between the breast appearance and levels of anxiety ($r = -0.81$, $p < 0.001$), depression ($r = -0.7$, $p < 0.001$), body image ($r = -0.4$, $p < 0.001$), sexuality ($\chi^2 = 22$, $p = 0.001$) and self-esteem ($r = -0.64$, $p < 0.001$). Similar findings were recorded in the START trials, which detected a significant association between body image and anxiety and depression.[13]

The START trials confirmed a steep dose–response curve for radiotherapy complications: a 10% increase in whole-breast radiotherapy (WBRT) dose doubled the rate of late adverse effects. A clear volume response was also observed, with the adverse effect of radiotherapy on normal tissue varying according to the volume of tissue irradiated. The magnitude of the volume response can be generated in different ways, most directly by comparing the outcome of the same dose schedule delivered to different partial volumes of breast tissue. In a retrospective study of a radiotherapy boost dose delivered using radioactive implants in 404 patients, a fourfold increase in risk of breast fibrosis (hardness) was reported for each 100-cm^3 increment in boost volume, suggesting a very steep volume response[14] and confirming the desirability to review the evidence for a volume effect.

These findings are consistent with a univariate analysis of 364 patients randomised to a radiotherapy tumour bed boost dose after WBRT, which reported a hazard ratio for poor cosmesis of 0.45 [95% confidence interval (CI) 0.29 to 0.76) for boost volumes dichotomised to < 200 cm^3 compared with boost volumes > 200 cm^3].[15] Another approach to quantify the increased risk of late side effects is to compare the increased risk of late side effects after a boost dose to the tumour bed with the same dose delivered to the whole breast. Such an analysis has been performed in 723 patients in the START pilot trial randomised to tumour bed boost dose, compared with no tumour bed boost.[14] Patients randomised to a tumour bed boost of 15.5 Gy in seven fractions had a 17% higher risk of moderate or marked breast hardness at 10 years. The same randomised trial compared two dose levels of WBRT. The dose of WBRT causing a 17% increased risk of breast hardening was estimated to be 4.5 Gy. This value is much lower than the 15.5 Gy that causes the same level of breast hardening when given to a boost volume of about 200 cm^3, representing 20–30% of whole-breast volume.

From previous work, including our own pilot study,[7] we estimated that the margins of a conventional tumour bed boost volume can be safely reduced by approximately 5 mm in all spatial dimensions using clip-based IGRT. From our pilot study the average tumour bed boost volume required is approximately 70 cm^3, reduced from 110 cm^3, a reduction in the total volume of the average breast boost dose by approximately 40 cm^3, and was expected (after Borger *et al.*[14]) to reduce the risk of moderate to severe fibrosis by up to a factor of 1.7.

We considered a randomised trial to be a cumbersome and expensive technology to apply to address the problems discussed above. On the other hand, the lack of empirical research data justifying the widespread use of clip-based IGRT means that the necessary resources to implement clip-based IGRT in routine clinical practice are not available, and the position was that expensive and potentially valuable equipment was often left idle.

Whatever research methodology is used, the preferred primary end point should measure treatment accuracy. Gains in accuracy can be derived directly (without assumptions) from data collected in an ongoing clinical trial that uses clip-based IGRT to verify treatment accuracy as part of its technical quality assurance protocol. The UK IMPORT-HIGH trial provided a very reliable context in which to test the hypothesis that more accurate treatment verification allows a substantial reduction in the volume of breast tissue exposed to high boost doses of radiotherapy. By generating direct estimates of the mean volume of breast spared by daily clip-based IGRT, it should be possible to estimate the expected reductions in late adverse effects. These estimates were largely based on published results of randomised trials conducted by members of our collaboration.[4,11,16,17] A consequence of this is the possibility to estimate the degree to which dose could be safely escalated in the group of patients at highest risk of local recurrence, and the predicted consequent benefits in terms of improved local tumour control.

The study aimed to quantify the benefits of clip-based IGRT using titanium clips in breast cancer patients using a study design that did not jeopardise patient care. Accurate tumour bed localisation has been shown to be important to ensure the accuracy of WBRT.[7,18] However, the results of this study should be applicable for all patients with breast cancer, including those prescribed partial-breast radiotherapy. Proven, quantified benefit from clip-based IGRT for breast cancer patients with higher risk of recurrence would justify the routine adoption of clip-based IGRT in all UK centres and, hence, ensure equity of access and optimal treatment for all breast cancer patients.

Research hypotheses

1. Clip-based IGRT provides a more accurate method of locating the tumour bed compared with standard imaging.
2. Clip-based IGRT allows smaller margins than standard imaging, which translate into less toxicity and improved quality of life for patients.

Research objectives

The primary objective was:

- to compare the spatial accuracy of breast radiotherapy based on imaging (1) titanium surgical clips implanted in the tumour bed (clip-based IGRT) and (2) bony anatomy and lung position during curative radiotherapy for early breast cancer (standard imaging).

Secondary objectives were to compare standard imaging with clip-based IGRT for:

1. adequate radiotherapy safety margins around the tumour bed to avoid geographical miss
2. volume of breast tissue irradiated around tumour bed
3. estimated breast toxicity following the development of a normal tissue control probability model
4. time taken for each imaging method.

Chapter 2 A critical review of the relationship between irradiated breast volume and late breast tissue complications

This chapter describes a critical review of the literature which aimed to understand the quality and scope of evidence for the relationship between irradiated breast volume and late breast tissue complications. This work supported a secondary objective of this study, the estimation of the reduction in risk of late breast toxicity which results from using clip-based IGRT, and helped to inform clinical recommendations based on all study outcomes.

This chapter is based on the peer-refereed scientific journal paper:

Mukesh M, Harris E, Jena R, Evans P, Coles C. Relationship between irradiated breast volume and late normal tissue complications: a systematic review. *Radiother Oncol* 2012;**104**:1–10.[19]

Introduction

In radiotherapy, the aim is to deliver a tumoricidal dose for optimal locoregional control while maintaining relative sparing of the surrounding normal tissues. Accurate knowledge of the tumoricidal and tolerance doses to the various tissues along with the effects of irradiating partial volumes of organs (i.e. the dose–volume effect) is essential for all types of modern radiotherapy, including conformal radiotherapy, intensity-modulated radiotherapy (IMRT) and IGRT.

Emami *et al.*[20] pioneered this field with a comprehensive review of the current knowledge of radiation tolerance doses for normal tissues. This included quantification of late normal tissue complication probability (NTCP) as a function of the volume of the organ irradiated. Although this review was informative, it was limited by the available data, with most of the dose–volume data based on interpolated or extrapolated from whole-organ data, or based on the expert experience of the involved clinicians. Since that work was published, an update on the dose–volume effect of radiation on the normal tissues has been published in the 'QUantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC)' report.[21] This can be utilised in treatment planning to estimate the effect of irradiated volume on tissue tolerance.[22,23]

For many years, the radiation dose–volume effect for the breast has been exploited in the boost treatment for breast cancer patients who are at high risk of recurrence. This involves treating a small volume of breast tissue to a higher dose with improved local control rates.[2,24,25] More recently, the dose–volume effect has been exploited in trials of partial-breast irradiation (PBI) for patients at low risk of recurrence. In PBI, the irradiated volume is confined to the region around the tumour bed and the aim is to reduce toxicity while maintaining the local control rate. However, there is a paucity of published data on the dose–volume effect of irradiation on breast tissue, including the QUANTEC report.

The critical review presented in this chapter of the report evaluates the evidence for a relationship between the volume of breast tissue irradiated and late complication rates. These complications include cosmesis, breast fibrosis, breast induration and telangiectasia. It also explores the evidence for a modest reduction in dose to part of the breast allowing dose escalation to the tumour bed, with lower NTCP expected.

Methods

MEDLINE and EMBASE were used to perform a literature search 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, and was conducted from 1 January 1975 up to 1 May 2012.

Impact of boost volume on breast tissue complications

European Organisation for Research and Treatment of Cancer 22881–10882 'boost versus no boost' trial (level I evidence)

In the European Organisation for Research and Treatment of Cancer (EORTC) 'boost versus no boost' trial, 5318 patients with early breast cancer were randomised between a tumour bed boost of 16 Gy and no boost after whole-breast irradiation (WBI).[2] The boost dose was delivered using electrons or tangential photon fields with a daily fractionation of 2 Gy, or using an ^{192}Ir implant at a dose rate of 0.5 Gy/hour. The results showed that, at 10 years, the use of tumour bed boost of 16 Gy increased the rates of moderate to severe breast fibrosis by 15% (28.1% vs. 13.2%; $p < 0.0001$). Two hundred and fifty-one patients with microscopically incomplete tumour excision were also randomised to either a low-dose boost of 10 Gy (126 patients) or a high-dose boost of 26 Gy (125 patients).[26] The cumulative incidence of moderate/severe fibrosis for low- and high-dose boost at 10 years was found to be 24% and 54%, respectively. Thus, dose escalation of 16 Gy to the boost volume in the incomplete tumour excision group increased the rates of moderate or severe fibrosis by 30%, compared with a 15% increase in the complete excision group for the same 16-Gy increase in dose.

The boost volume for the complete excision group was tumour bed plus 1.5-cm margin as compared with 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 16 Gy. However, it may be the case 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 suboptimal cosmesis at 3 years[15] and breast fibrosis at 10 years.[27] However, boost volume was not a significant variable affecting fibrosis and cosmesis in multivariate analysis.

Brachytherapy boost (level IV evidence)

Borger *et al.*[14] reported on the dose–volume effect of brachytherapy boost for breast fibrosis. The patient group was 404 patients who were treated with external beam radiotherapy (50 Gy in 2-Gy daily fractions to the whole breast). This was followed by an iridium implant boost (dose rate 0.57 Gy/hour, SD 0.11 Gy/hour). Brachytherapy doses fell into three groups: 15 Gy for 101 patients, 25 Gy for 301 patients and 20 Gy for two patients. With a median follow-up period of 70 months, a four times higher risk of fibrosis was observed for each 100-cm^3 increase in irradiated boost volume, and a 10-fold higher risk of fibrosis was observed when the total dose exceeded 79 Gy compared with doses below 70 Gy.

In another study, from Georgetown University Medical Centre, McRae *et al.*[28] also reported on the relationship between brachytherapy boost volume and soft-tissue complication. Retrospective brachytherapy plans for five patients with radiation-induced soft-tissue damage were compared with 51 patients who did not experience severe complication after WBI followed by ^{192}Ir boost. The mean boost volume for patients who developed soft-tissue damage was significantly higher for all dose levels between 10 Gy and 50 Gy than for patients with no reported complications ($p < 0.05$), suggesting a relationship between volume and NTCP at any dose studied. Similarly, Olivotto *et al.*[29] reported an association between the brachytherapy boost volume and late cosmetic outcome for 497 patients who received WBI (46–50 Gy over 4.5–5 weeks) followed by a low dose rate (LDR) boost with ^{192}Ir to bring the tumour bed dose to 60 Gy. At a median follow-up of 76 months, the boost volume, measured by the number of iridium seeds used, was found to

be a significant factor for fair/poor cosmesis. Patients with < 70 seeds had a 15% risk of fair/poor cosmesis, compared with 38% for patients with ≥ 100 seeds ($p < 0.01$). The use of a greater number of seeds implies a larger volume of irradiated breast tissue and hence a radiation volume effect for cosmesis. Several other single and multicentre studies have reported on the relationship between volume of brachytherapy boost and NTCP risk and are summarised in *Table 1*.

Intraoperative radiotherapy boost using low-energy X-ray (level IV evidence)

Intraoperative radiotherapy (IORT) uses low-energy X-rays of 50 kV and can be used to deliver a single-fraction, high-dose radiation boost to the tumour bed after lumpectomy. Advocates of IORT highlight several potential advantages of using this approach including delivery of radiation immediately after surgery to prevent tumour cell proliferation; change in cytokine pattern into a less stimulating microenvironment, which is expected to reduce the local recurrence rates; and reduced risk of geographical miss.[34,35]

The University of Heidelberg reported on late toxicity data (at 3 years) for 79 cases treated with the IORT method.[36] All patients received a 20-Gy intraoperative boost using a 50-kV X-ray set followed by 46–50 Gy in 2-Gy daily fractions of WBI with or without supraclavicular or infraclavicular fossa irradiation. Thirty-five per cent of patients developed grade 2–3 breast fibrosis. They observed that the size of the applicator used for IORT significantly correlated with late breast fibrosis (Spearman's rank correlation coefficient = 0.496, $p < 0.001$). A larger applicator size would imply a larger volume of irradiated breast tissue, which in turn would suggest a radiation volume effect on late breast tissue toxicity.

Cobalt unit based boost (level IV evidence)

Dewar *et al.*[30] from the Institute Gustave-Roussy reported on cosmetic outcome after BCS and radiotherapy. Five hundred and ninety-two patients received WBI (45 Gy in 2.5 Gy per fraction, four times weekly). They were treated using two tangential fields, with each field treated on alternate days. This was followed by tumour bed boost of 15 Gy in six fractions using a cobalt unit. Multivariate analysis showed that, in addition to applied dose per fraction, the area of field to the tumour bed (> 30 cm^3) was associated with an increased risk of fibrosis ($p < 0.02$) and telangiectasia ($p < 0.01$).

Other boost studies (level IV evidence)

The Fox Chase Cancer Centre, Philadelphia, PA, USA, recently presented a reported on tumour bed boost parameters associated with overall cosmesis and fibrosis for a group of 3186 patients who were treated at the centre from 1970 to 2008.[37] All patients received WBRT (46–50 Gy) followed by a tumour bed boost of 10–18 Gy using either electrons or photons. Median follow-up was 78 months. Smaller boost cut-out size was found to be a borderline predictor of excellent cosmesis ($p = 0.05$) and lower risk of breast fibrosis ($p < 0.0001$) based on univariate analysis. Neither fibrosis nor cosmesis was found to remain significantly associated with higher field size on multivariate analysis. However, no information was available on the size of the treated boost volume and no distinction was made between physician and patient cosmetic score in their report.

Partial-breast irradiation studies

Whole-breast irradiation is considered the current standard of care following BCS and, in the last decade, PBI has been explored as an alternative treatment to WBI in low-risk patients. PBI involves irradiation of the volume of breast tissue around the tumour bed and is currently under investigation in several randomised Phase II and III trials (*Table 2*). This treatment approach is based on the rationale that the majority of local recurrences are located close to the area of surgical resection/the index quadrant and the foci of breast disease outside the index quadrant are often new primary tumours[51,52] and that irradiating a limited volume of breast would reduce treatment-related morbidity.

TABLE 1 Effect of brachytherapy boost volume on NTCP

Study details	Study						
	Borger *et al.*[14]	McRae *et al.*[28]	Dewar *et al.*[30]	Olivotto *et al.*[29]	Clarke *et al.*[31]	Wazer *et al.*[32]	Wronczewska *et al.*[33]
Institute	Netherlands Cancer Institute, Amsterdam, the Netherlands	Georgetown University Medical Centre, Washington, DC, USA	Institut Gustave-Roussy, France	Joint Center for Radiation Therapy, Boston, MA, USA	Paul A Bissinger Memorial Centre for Radiation Therapy, Stanford, CA, USA	Tufts University School of Medicine, Boston, MA, USA	Nicolaus Copernicus University, Poland
Treatment method	WBI 50 Gy in 25 fractions over 5 weeks, then LDR iridium implant boost of: 15 Gy (101 patients), 25 Gy (301 patients) and 20 Gy (two patients)	WBI 50 Gy in 25 fractions over 5 weeks (^{60}Co) then LDR ^{192}Ir boost of 20 Gy	WBI 45 Gy with 2.5 Gy per fraction using two tangential fields, then tumour bed boost of 15 Gy in six fractions using ^{60}Co	WBI 46–50 Gy in 4.5–5 weeks, then LDR ^{192}Ir boost of 10–27 Gy	WBI 45–55 Gy in 1.8–2.5 Gy per fraction then LDR ^{192}Ir boost of 18–25 Gy	WBI 50–50.4 Gy at 1.8–2 Gy per fraction, then LDR ^{192}Ir boost of 20 Gy	WBI 50–50.4 Gy at 1.8–2 Gy per fraction, then HDR ^{192}Ir boost of 5–20 Gy
Patient number	404	56	592	497/593 with ^{192}Ir boost	64/78 with ^{192}Ir boost	127	54
Follow-up	Median 70 months (range 30–133 months)	Minimum 2.5 years	Mean follow-up 78 months (SD 35 months)	Median follow-up 76 months (range 37–186 months)	Median follow-up 42 months (range 30–120 months)	Median follow-up 80 months (SD 34 months)	Mean follow-up 65 months (range 41–89 months)
TNM/stage	Stage 1–2	Stage 1–3	T1–2 N0–1	T1–2 N0–1	Stage 1–2	Stage 1–2	Not disclosed

Study details	Study						
	Borger *et al.*[14]	McRae *et al.*[28]	Dewar *et al.*[30]	Olivotto *et al.*[29]	Clarke *et al.*[31]	Wazer *et al.*[32]	Wronczewska *et al.*[33]
NTCP assessment	Four trained physicians scored fibrosis by palpating induration in the tumour bed A four-scale scoring system was used to obtain the final result per patient	Radiation injury to connective tissue or fat necrosis which required medical or surgical management	Fibrosis or telangiectasia of the whole breast or the tumour bed graded by radiation oncologist on four-point scale. Cosmetic outcome graded on four-point scale	Overall cosmesis graded by physician on four-point scale Range from excellent if the treated breast looked as if it were untreated to poor if severe normal tissue sequelae	Cosmetic result scored on three-point scale as excellent, satisfactory or unsatisfactory Breast fibrosis scored as mild, moderate or severe	Cosmetic score scored by two examiners on a four-point scale as excellent, good, fair or poor. The lowest examiner score was used in analysis	Cosmesis and breast fibrosis independently assessed by two doctors by comparison with contralateral breast
Study results	Association between implant volume and risk of fibrosis. Odds ratio 4.2 (95% CI 2.3 to 8.0) per 100-cm^3 boost volume increase	Patients who developed soft-tissue damage had significantly higher boost volume in 10–50 Gy range than patients with no complications ($p < 0.05$)	Relationship between area of field to the tumour bed (> 30 cm^3) and risk of fibrosis ($p < 0.02$) and telangiectasia ($p < 0.01$). No relationship for cosmesis	Boost volume (measured by number of ^{192}Ir seeds) associated with increased risk of fair/poor cosmesis ($p < 0.0001$)	6% of patients had moderate/severe fibrosis. No correlation between fibrosis risk and boost volume. Main factors for poor cosmesis were surgical factors such as poorly planned excision scar and excision volume	No correlation detected between volume of implant and cosmetic score	Boost volume irradiated to 100% dose is significantly associated with risk of breast fibrosis ($p = 0.0236$)

HDR, high dose rate; TNM, tumour node metastasis.

TABLE 2 Phase II and III RCTs comparing WBI against PBI

	Trial											
	Christie group trial[38]	Yorkshire Breast Cancer Group trial[39]	Hungarian National Institute of Oncology[40]	TARGIT[41]	ELIOT[42]	IMPORT-LOW[43,44]	GEC-ESTRO[45]	NSABP-39[46]	RAPID[47]	IRMA[48]	Danish Breast Cancer Co-operative Group[49]	SHARE[50]
Control arm (WBI) boost	40 Gy, 15 fractions	40 Gy, 15 fractions. 15-Gy boost	50 Gy, 25 fractions. Cobalt or X-rays	40–56 Gy, 1 fraction. 10- to 16-Gy optional boost	40 Gy, 15 fractions. 15-Gy boost	40 Gy, 15 fractions	50–50.4 Gy, 25–28 fractions. 10-Gy optional boost	50–50.4 Gy, 25–28 fractions. 10- to 16-Gy optional boost	42.5 Gy, 16 fractions. 10-Gy optional boost	45–50.4 Gy 18–25 fractions 10- to 16-Gy optional boost	40 Gy, 15 fractions	40–50 Gy, 15–25 fractions. 16 Gy optional boost
Test arms (PBI) and treatment modality	40–42.5 Gy, eight fractions. Electrons	55 Gy, 20 fractions. Cobalt, caesium, electrons or megavoltage tangential pair	(a) 50 Gy, 25 fractions, ($n=40$). Electrons –80% isodose (b) 36.4 Gy, seven fractions over 4 days ($n=85$). HDR ^{192}Ir	20 Gy, 1 fraction. Intraoperative, 50-kV X-rays	21 Gy, one fraction. Intraoperative electrons	(a) 40 Gy, 15 fractions (IQ only). 3D-CRT (b) 36 Gy, 15 fractions (LRV) + 40 Gy, 15 fractions (IQ). 3D-CRT	(a) 30.3–32 Gy, 7–8 fractions. HDR (b) 50 Gy. PDR	(a) 38.5 Gy, 10 fractions. 3D-CRT (b) 34 Gy, 10 fractions; twice-a-day brachytherapy	38.5 Gy, 10 fractions in 5–8 days. 3D-CRT	38.5 Gy, 10 fractions; twice a day 3D-CRT	40 Gy, 15 fractions. 3D-CRT	40 Gy, 10 fractions in 3–7 days. 3D-CRT
Median follow-up (months)	65	96	66	24	NA	NA	NA	NA	NA	NA	NA	NA
Target accrual (patients)	708	174 (early stop)	258	2232	1300 (2007 close)	2000 (2010 close)	1170 (2004 start)	4300 (2005 start)	2128 (2006 start)	3302 (2007 start)	628 (2009 start)	2796 (2010 start)
Reported	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	No

3D-CRT, three-dimensional conformal radiotherapy; ELIOT, Electron Intra Operative Radiation Therapy; GEC-ESTRO, Groupe Européen de Curiethérapie and the European SocieTy for Radiotherapy & Oncology; HDR, high dose rate; IMPORT-LOW, Intensity Modulated and Partial Organ Radiotherapy Trial – LOWer-risk patient group; IQ, index quadrant; LRV, low-risk volume of breast; NA, not applicable; NSABP-39, National Surgical Adjuvant Breast and Bowel Project; RAPID, Randomised Trial of Accelerated Partial Breast Irradiation; TARGIT, TARGeted Intraoperative radioTherapy; SHARE, Standard or Hypofractionated Radiotherapy Versus Accelerated Partial Breast Irradiation (APBI) for Breast Cancer.

Note

Where two PBI treatment options were given, these are listed as (a) and (b).

Randomised controlled trials of partial-breast irradiation versus whole-breast irradiation (level I evidence)

Four RCTs comparing WBI with PBI have reported on their outcome.[38–41]

A group from The Christie Hospital reported in 1993.[38] Their study randomised 708 patients with breast tumours ≤ 4 cm in diameter to PBI or WBI plus regional lymph node irradiation. PBI involved irradiating the tumour bed (with average field size 8 cm × 6 cm) to 40–42.5 Gy in eight fractions over 10 days using electrons. WBI involved treating the whole breast to 40 Gy in 15 fractions over 21 days using tangential fields with a matched field for regional lymph nodes. After a median follow-up of 65 months, recurrence rates were higher in the PBI arm than in the WBI arm (19.6% vs. 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 the inclusion of patients with infiltrating lobular carcinoma and ductal carcinoma with an extensive intraductal component. Patients with PBI were also found to have significantly higher rates of marked breast fibrosis (14% vs. 5%) and telangiectasia (33% vs. 12%) than WBI.

In another study, the Yorkshire Breast Cancer Group[39] randomised 174 patients between WBI (with 40 Gy in 15 fractions over 21 days followed by a tumour bed boost of 15 Gy in five fractions) and PBI, which used a variety of techniques, including direct cobalt or caesium beams, electrons or a small megavoltage tangential pair to a dose of 55 Gy in 20 fractions over 28 days. The trial closed prematurely because of poor accrual and higher locoregional recurrence rates in the PBI group than in the WBI group (24% vs. 9%). It may be that the higher recurrence rate in the PBI arm was secondary to the difficulty of accurately defining the tumour bed. Treatment-related morbidity with PBI and WBI has not been reported. These two studies pioneered the concept of PBI at a time when patient selection and tumour bed localisation were still very much under development. Subsequent randomised trials have more developed technology and used more stringent protocols for both of these factors.

The Hungarian National Institute of Oncology PBI trial[40] and TARGeted Intraoperative radioTherapy (TARGIT) trial[41] have reported their outcomes more recently. The Hungarian PBI trial randomised 258 patients with stage T1 N0–1 grade ≤ 2 breast cancer to WBI or PBI following BCS.[40] WBI was carried out using cobalt or photon beams to deliver a dose of 50 Gy in a 2-Gy daily fraction. PBI was delivered using high-dose-rate (HDR) ^{192}Ir brachytherapy (for 85 patients) and a dose of 36.4 Gy in 5.2 Gy per fraction over 4 days or electrons (for 40 patients) to a dose of 50 Gy in 2-Gy daily fractions prescribed to the 80% isodose level. At a median follow-up of 122 months, the local recurrence rates were not significantly different in the two arms of the trial. The cosmetic results using Harvard criteria[53] were found to be favourable in the PBI arm. The rate for a cosmesis score of excellent to good was 81% for the PBI group and 63% for the WBI group ($p = 0.0015$).

The TARGIT-A trial randomised 2232 patients with early breast cancer to either WBI (40–56 Gy) with or without a boost of 10–16 Gy or intraoperative PBI using low-energy X-rays (50 kV and a dose of 20 Gy to the tumour bed attenuating to 5–7 Gy at 1 cm depth).[41] Patients with adverse histological features, which included invasive lobular carcinoma or an extensive intraductal component, also received WBI without a boost in the PBI arm. At 2 years, the local recurrence rate was similar with no significant difference in the rate of toxicity, but the type of toxicity was significantly different between the two trial arms. The WBI arm had higher Radiation Therapy Oncology Group (RTOG) grade 3–4 toxicity for dermatitis, telangiectasia or breast pain (2.1% vs. 0.5%; $p = 0.002$), whereas patients receiving intraoperative PBI experienced a different range of side effects. Breast seroma needing more than three aspirations was more common in the IORT PBI group (2.1% vs. 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. Cosmetic results have yet to be reported.

Case-matched pair studies (level III evidence)

There have been four case-matched pair studies that have compared breast tissue complications for partial and WBI.[54–57]

Polgar *et al.*[54] selected 45 patients prospectively with stage T1 N0–1 breast cancer who were treated with PBI using HDR ^{192}Ir implants to a dose of 30.3–36.4 Gy delivered in seven fractions over 4 days and matched them to 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. Analysis at a median follow-up of 7 years showed no significant difference in the ipsilateral breast recurrence rates in the two groups. Excellent or good cosmesis measured using Harvard criteria[53] 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 compared with the WBI group without a boost dose (20% vs. 5.8%; $p = 0.06$).

The William Beaumont group matched 174 patients treated with PBI (with LDR ^{192}Ir implants delivering 50 Gy over 96 hours at a dose rate of 0.52 Gy/hour or HDR implants delivering 32 Gy in eight fractions, each separated by 6 hours) with 174 patients treated with WBI with a median total tumour bed dose of 60 Gy.[55] At a follow-up of 36 months, cosmetic outcome was more favourable in the PBI group than in the WBI group (excellent or good cosmesis was seen in 90% vs. 83% of patients) This difference was not found to be statistically significant ($p = 0.17$).

King *et al.*[56] matched 51 patients treated with PBI delivered with LDR ^{192}Ir implants to achieve 45 Gy over 4 days (or HDR implants of 32 Gy in eight fractions over 4 days) with 94 patients treated with WBI to a mean dose of 59 Gy following BCS. A blinded panel of experts scored photographic assessment of cosmesis on a four-part scale (excellent, good, fair, poor). At 20 months' follow-up, 75% patients in the PBI group and 84% patients with WBI had excellent or good cosmesis (not statistically significant). Grade 1 and 2 treatment complications including skin erythema, desquamation, discoloration, hyperpigmentation, dimpling and breast pain, tenderness, shrinkage or fibrosis were significantly more common in the WBI arm than in the PBI study arm (80% vs. 22%; $p = 0.001$). Grade 3 treatment complications requiring surgical intervention were not found to be different in the two groups (8% vs. 5%, $p = 0.23$).

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 fractions over 5 weeks) followed by a tumour bed boost using electrons (15 Gy in six fractions or interstitial HDR brachytherapy with a single 10-Gy fraction).[57] The authors reported that, at a median follow-up of 43 months, cosmetic outcome was more superior in the PBI group than in the WBI group (excellent or good cosmesis was 88.9% vs. 56%; $p = 0.003$). No significant difference was seen in the rates of moderate or severe breast fibrosis.

Effect of treatment volume on normal tissue complication probability in partial-breast irradiation series

There are several publications reporting on the efficacy and low toxicity achievable with PBI, but only a few evaluate the impact of treatment volume on NTCP. The current literature on the volume effect of PBI for three-dimensional conformal radiotherapy (3D-CRT)/IMRT, electrons and brachytherapy is summarised below.

Three-dimensional conformal radiotherapy and intensity-modulated radiotherapy-based partial-breast irradiation (level IV evidence)

Jagsi *et al.*[58] presented the cosmetic outcome of 32 patients treated with PBI using IMRT at deep inspiration breath hold. The patients received 38.5 Gy twice a day over 5 consecutive days. At a median follow-up of 2.5 years, 22% of patients were scored as having unacceptable cosmesis. Retrospective comparison between patients with acceptable and unacceptable cosmesis showed that the mean percentage volume of the breast receiving a minimum of 100% of the prescribed dose, i.e. 38.5 Gy (V100) was lower in patients with acceptable cosmesis than in patients with unacceptable cosmesis (15.5% vs. 23.0%; $p = 0.02$). The mean percentage volume of breast receiving a minimum of 50% of the prescribed dose, i.e. 19.25 Gy, was also smaller in the group with acceptable cosmesis than in the unacceptable cosmesis group ($p = 0.02$).

Hepel *et al.*[59] also reported on a positive correlation between the volume of breast tissue treated with PBI and cosmesis outcome. Sixty patients were treated with PBI to a dose of 38.5 Gy in twice-a-day fractionations over 1 week using 3D-CRT. At a median follow-up of 15 months, 18% of patients developed fair or poor cosmesis and 25% developed grade 2–4 subcutaneous fibrosis. In univariate analysis, the ratio of the size of 3D-CRT target volume to the whole-breast volume was found to correlate with fair or poor cosmesis ($p = 0.02$) and with grade 2–4 subcutaneous fibrosis ($p = 0.10$). Jagsi *et al.*[58] and Hepel *et al.*[59] also suggested an association between breast volume irradiated in PBI and normal tissue complication rates.

In contrast, Chen *et al.* from the William Beaumont group reported no association between overall cosmesis and the ratio of the size of 3D-CRT target volume to the whole-breast volume.[60,61] In their study, 94 patients received PBI with a dose of 38.5 Gy in twice-daily fractions over 5 consecutive days using 3D-CRT. Of the 56 patients with cosmesis assessment of > 48 months, 11% had fair to poor cosmesis and 3% had grade 3 fibrosis with no association between cosmesis or subcutaneous toxicity and this ratio.

Single-source brachytherapy and multisource brachytherapy (level IV evidence)

Multisource brachytherapy has been used for PBI for many years. Most publications on the results of this technique focus on local control rates and there is limited reporting of normal tissue toxicity. Some have reported on factors associated with normal tissue toxicity and have commented on a positive correlation between NTCP and the implant volume. Yeo *et al.*[62] reported on the efficacy and safety of PBI using multisource brachytherapy for 48 patients, with a median follow-up of 53 months. A dose of 34 Gy in 10 fractions over 5 days was delivered to the tumour bed plus a margin of 1–2 cm. Fourteen per cent of patients developed grade 2 subcutaneous toxicity with V100 and V150 significantly higher in these patients ($p = 0.018$ and 0.034, respectively). No patients were found to have poor cosmesis.

Wazer *et al.*[63] studied late toxicity and long-term cosmetic outcome after multisource brachytherapy PBI using pooled data from Tufts University, Brown University and Virginia Commonwealth University. The number of dwell positions, a determinant of total volume of implanted breast tissue, was found to correlate with late cosmetic outcome ($p = 0.04$).

Lawenda *et al.*[64] found no association between implant volume and overall cosmetic outcome for 48 patients treated with LDR brachytherapy at their centre from 1997 to 2001.The purpose of the study was to evaluate the effects of dose escalation in PBI. The dose was escalated in three groups of 50 Gy, 55 Gy and 60 Gy, and implant volume was divided into four groups. A trend between dose escalation and fibrosis was seen (not found to be significant). They also observed a decline in the incidence of breast fibrosis with increase in implant volume, a finding contrary to other published literature.

Breast fractionation studies

The Royal Marsden Hospital (RMH) and Gloucestershire Oncology Centre (GOC) trial[16] randomised 1410 early breast cancer patients between three fractionation schedules for WBI. The control arm treatment was 50 Gy in 25 fractions delivered in 5 weeks. Two test arms were used: (1) 39 Gy in 13 fractions over 5 weeks and (2) 42.9 Gy in 13 fractions over 5 weeks. The equivalent doses in 2-Gy fractions (EQD2s) (using an $\alpha:\beta$ ratio of 3.1 Gy for palpable breast induration) were calculated to be 46.7 Gy and 53.8 Gy, respectively. The risk of moderate to severe induration at 10 years for the two test arms was 27% and 51%, respectively, suggesting a 24% increased risk of induration with a dose escalation of 7 Gy to the whole breast (or 3.3% increased risk per gray). Compared with this fractionation effect, an escalated dose to the tumour bed alone, i.e. a boost of 15.5 Gy delivered in seven fractions (EQD2 of 16 Gy), increased the risk of induration by 17% (equivalent to a 1.05% increase per Gy). The increased risk of induration, per Gy of dose seen with increased breast volume irradiated indicates a radiation-volume effect for breast tissue.

Dose-modulating effect on the breast

The dose–volume effect in normal tissue can be exploited therapeutically by radiating a small volume of tissue to a higher dose and reducing the overall dose to the rest of the organ. This has been successfully demonstrated in prostate cancer radiotherapy with IMRT.[65] A trial at Saint George and Wollongong in Sydney, NSW, Australia, suggests that this modulation effect is also present in breast tissue.[66] This trial randomised 688 patients with stages T1–2 N0–1 breast cancer between a standard arm of WBI (50 Gy in 2-Gy daily fractions and no boost) and a test arm of WBI (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, with a scale of excellent, good, fair and poor. Seventy-nine per cent of patients in the test arm with boost and 68% of patients in the standard arm had excellent or good cosmesis ($p = 0.016$). The rate of moderate to severe breast fibrosis at 5 years was similar in the treatment arms. These results are contrary to the current literature of worse cosmetic outcome and higher rates of breast fibrosis with additional boost radiation. A possible explanation for these results is that a modest reduction in dose to the whole breast allowed dose escalation to the tumour bed without the expected increase in normal tissue toxicity and provides evidence of a volume effect.

Limitations of this review

Late breast tissue toxicity post radiotherapy is influenced by several patient- and treatment-related factors. Many of the studies reviewed have not accounted for other confounding factors including extent of surgical excision, total delivered dose, dose fractionation, postoperative complications and brachytherapy dose inhomogeneity, for example surgical excision volume and baseline surgical cosmesis are significant factors affecting cosmesis.[15,67–69] Larger surgical excision would also imply larger brachytherapy boost and/or 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, intraoperative techniques and brachytherapy. In addition, the reported studies have used different end points (fibrosis, cosmesis and telangiectasia), with several different scoring methods and a range of periods at which follow-up was obtained. These factors all make it difficult to draw firm conclusions on the dose–volume relationship for breast tissue.

Conclusions

Quantitative effect of treatment volume

The study by Borger *et al.*,[14] which used LDR iridium implants, provided the most robust quantitative data on the dose–volume relationship. For every 100-cm^3 increase in the boost volume, the risk of fibrosis increased by a factor of 4, and a twofold increase in boost volume resulted in an 11% reduction in tolerance dose [NTD_{50} (tolerance dose which results in a 50% chance of tissue injury)]. It is, however, difficult to be certain as to how the LDR brachytherapy data can be extrapolated to other techniques such as HDR brachytherapy, electron and photon boost techniques. The RMH/GOC trial,[16] which used electron boost, provides indirect quantitative information on the dose–volume relationship for NTCP. For every 1-Gy increase in boost dose, the risk of moderate to severe breast induration was found to increase by 1%, compared with 3% when the whole-breast dose is increased by 1 Gy.

Qualitative effect of treatment volume

The results from the Hungarian PBI trial[40] and TARGIT trial[41] provide strong qualitative evidence of a dependence of NTCP on volume irradiated. These studies report both improved cosmetic outcome and reduced NTCP in the PBI arm compared with WBI. However, there are significant differences in the radiotherapy techniques and fractionation schedules used by these two groups, making it difficult to draw quantitative conclusions on the radiation volume effect on breast tissue. The other reported randomised trial from Christie reported higher rates of breast fibrosis and telangiectasia in the PBI arm.[38]
A dose–response relationship for late radiation effects including telangiectasia and breast fibrosis is well known,[2,70,71] and these dissimilar results may be explainable if one calculates the EQD2 for the PBI and WBI groups using an $\alpha:\beta$ ratio of 3.1[16] for fibrosis. The WBI group received a lower dose of 45 Gy (EQD2), compared with 63–70 Gy for the PBI group in the Christie study.

The four matched case series[54–57] which compared PBI and WBI also showed favourable cosmesis and lower NTCP risk with PBI, with the exception of higher grade 2–3 fibrosis observed in the Hungarian series.[54] It is possible that significant dose heterogeneity with the use of ^{192}Ir implants could explain the increased grade 2–3 fibrosis in the PBI arm in the Hungarian series. As in the randomised trials, this study evaluated PBI and WBI using different radiotherapy techniques and fractionation.

Future work

The current literature suggests that treatment volume is an important parameter affecting late breast tissue complications, but that more robust data are needed. This is expected to come from the below-mentioned randomised trials which will quantify the impact of volume of breast irradiated on NTCP.

Randomised controlled trials of partial-breast irradiation compared with whole-breast irradiation

The Intensity Modulated and Partial Organ Radiotherapy Trial – LOWer-risk patient group (IMPORT-LOW) and the Danish Breast Cancer Cooperative Group trial (which has not yet reported) are two randomised trials comparing PBI and WBI, with volume of breast irradiated as the solitary randomisation variable. IMPORT-LOW is a randomised Phase III trial comparing WBI with two dose levels delivered as PBI using IMRT in women with low risk of recurrence from their breast cancer. It has completed target accrual of 2000 patients in 2010.[43,44] The control arm is WBI delivering 40 Gy in 15 fractions over 3 weeks to the whole breast. Test arm 1 delivers synchronously 40 Gy in 15 fractions to the partial-breast planning target volume (PTV) and 36 Gy in 15 fractions to the remainder of the whole breast. Arm 2 uses PBI to deliver 40 Gy in 15 fractions to the partial-breast PTV alone (*Figure 1*). The primary end point is local tumour

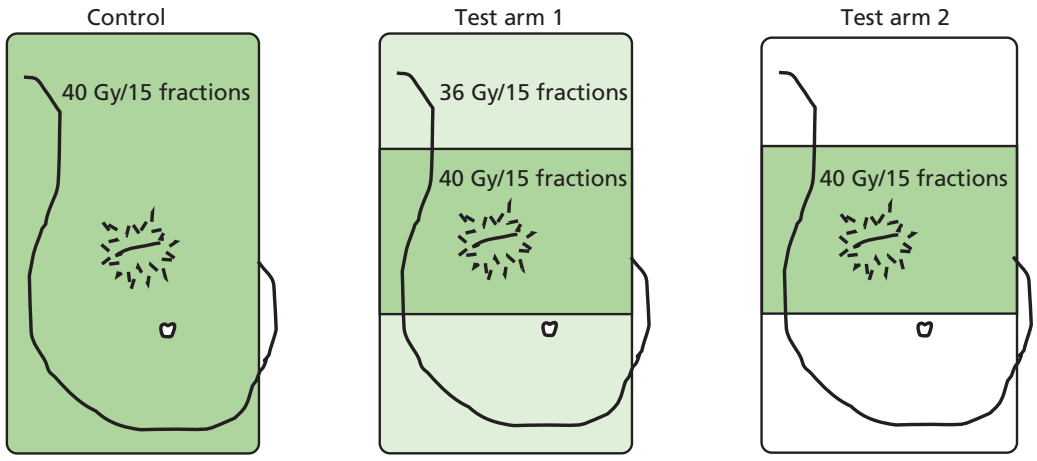

FIGURE 1 The IMPORT-LOW patient group trial schema. Control: WBI, 40 Gy in 15 fractions over 3 weeks. Arm 1: 36 Gy in 15 fractions to the low-risk volume of the breast and 40 Gy in 15 fractions to the index quadrant over 3 weeks. Arm 2: PBI, 40 Gy in 15 fractions over 3 weeks to the index quadrant only.

control in the treated breast. Secondary end points include location of tumour relapse, occurrence of contralateral primary tumours, regional and distant metastases, late adverse effects in normal tissues, quality of life and economic evaluation.

The trial implemented by the Danish Breast Cancer Cooperative Group is a Phase II study comparing PBI with WBI in low-risk breast cancer patients. Both treatment arms receive 40 Gy in 15 fractions over 3 weeks.[49] The primary end point for this study is grade 2–3 breast fibrosis after radiotherapy. Secondary end points are other late morbidity, local recurrence and genetic risk profiling for development of late radiation morbidity. The results on these two trials in terms of late normal tissue effects will not become available for several years, but are expected to provide definitive data regarding the effects of irradiated breast volume on normal tissue effects.

Three-dimensional conformal radiotherapy- or intensity-modulated radiotherapy-based partial-breast irradiation trial

The 3D-CRT/IMRT-based PBI series[58–60] discussed above have produced conflicting reports on the relationship between the treated volume and NTCP. The mature data from the ongoing Phase III NSABP B-39/RTOG 0413 trial[46] ($n = 4300$) is expected to provide more definitive data on whether or not an association between breast volume irradiated in accelerated PBI (APBI) and normal tissue complications exists.

Dose-modulation effect on the breast

This dose-modulating effect on the breast tissue is further investigated in the IMPORT-HIGH trial (of which this study is a substudy).[43,44] The trial randomises patients at higher risk of recurrence between three groups: (1) a standard arm of 40 Gy in 15 fractions to the whole breast over 3 weeks, with a sequential tumour bed boost of 16 Gy in 2-Gy daily fractions; (2) test arm 1 of 36 Gy in 15 fractions to the low-risk volume of the breast, 40 Gy in 15 fractions to the index quadrant plus a concomitant tumour bed boost of 48 Gy in 15 fractions; and (3) test arm 2 of 36 Gy in 15 fractions to the low-risk volume of the breast, 40 Gy in 15 fractions to the index quadrant plus a concomitant tumour bed boost of 53 Gy in 15 fractions. The trial planning schema is shown in *Figure 2*. This trial tests the hypothesis that decreasing the radiation dose to the whole-breast volume by a very small amount (40 Gy to 36 Gy) and treating an isoeffective dose to the index quadrant and tumour bed (test arm 1) may result in fewer normal tissue side effects than in 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 (the area of highest risk of local recurrence) without an increase in normal tissue side effects (test arm 2).

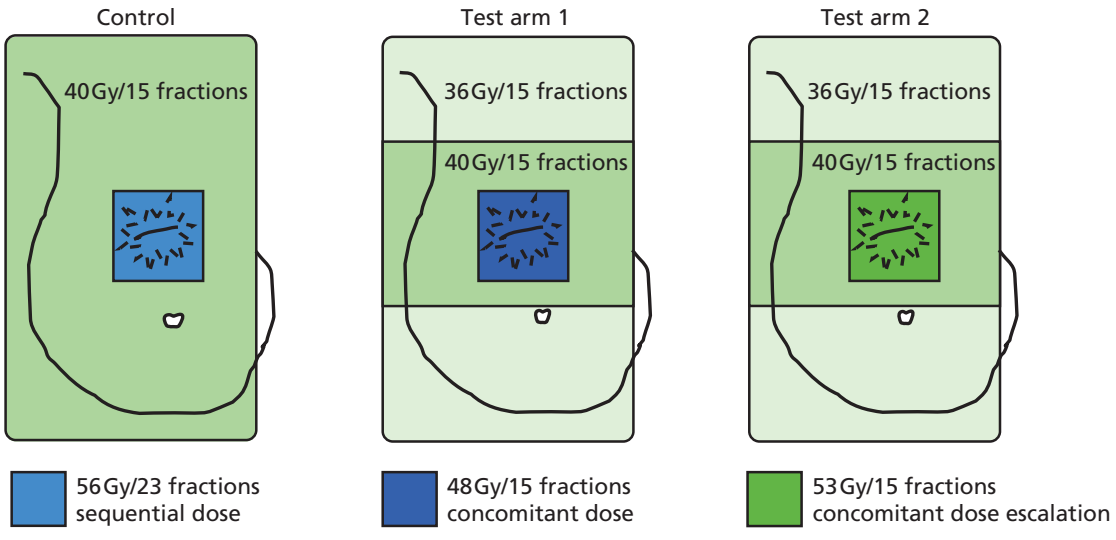

FIGURE 2 The IMPORT-HIGH trial schema. Control: 40 Gy in 15 fractions to the whole breast followed by a sequential photon boost of 16 Gy in 8 fractions to the tumour bed (total – 56 Gy in 23 fractions, sequential dose). Test arms 1 and 2: 36 Gy in 15 fractions to the low-risk volume of the breast, 40 Gy in 15 fractions to the index quadrant and dose escalation to the tumour bed with two dose levels of 48 Gy and 53 Gy in 15 fractions as concomitant boost.

Contextual discussion

This chapter presents the results of a critical review of the relationship between the irradiated volume of breast and late tissue complication rates resulting from radiotherapy for breast cancer. The review is also published as a peer-reviewed scientific journal paper.[19]

An understanding of the relationship between the dose delivered to tissue and its effect on that tissue is essential to understand the impact of radiotherapy on the patient in terms of side effects caused. This relationship is usually analysed in terms of two aspects:

1. First, the dose level used is important, and the dose–effect relationship follows a sigmoidal curve with a sharp change in effect from small to substantial at a dose value referred to as the tolerance dose.
2. Second, there is a dependence on the fraction of the volume of tissue irradiated to the dose level. This 'volume effect' relationship varies for different organs. Some organs (such as lung) have a strong volume effect with a rapid decrease in effect as the fractional or percentage volume irradiated to high dose decreases and others (such as the spinal cord) have little or no dependence on volume, with the maximum dose value being the strongest determinant of side effects.

The clinical studies analysed in this chapter were chosen as they explore the effects of dose level and/or the volume effect in breast cancer patients treated with radiotherapy.

The published studies explore a range of parameters, with many of them providing evidence for the effects of brachytherapy boost volume on side effects and many providing a comparison of whole- and partial-breast treatment.

One of the main challenges in the interpretation of these studies is that they represent a variety of treatment techniques and, hence, there is the risk that differences in the dose distributions that are intrinsic to them may confound analysis of the basic effects of dose and volume. Of the techniques, brachytherapy gives an intrinsically very non-uniform dose distribution. External beam treatment results in a much more uniform dose to the target. This is often accompanied with a boost to the tumour bed (delivered using brachytherapy, external beam electrons or X-rays). A third method is IORT using low-energy radiography. Again, this will result in a different type of dose distribution to the other two methods.

A second challenge is that of dose rate and fractionation. IORT involves a single fraction. External beam treatment has traditionally been delivered in 2-Gy fractions, with some studies investigating hypofractionation. In order to compare the equivalent dose from treatments with different dose rates and different fractionation models, it is necessary to estimate how to correct for these differences. This is achieved by scaling the dose values to a common fractionation schedule, using a model to describe the radiobiological effects of the different regimes.

The side effects of importance in radiotherapy are long term and typically develop many months after treatment. The data available in the literature have a range of follow-up times and contain analysis of a range of patient cohort sizes (e.g. see *Tables 1* and *2*). This, too, presents a challenge in interpreting the data from the range of studies published.

Quantitative analysis of outcome data is needed to provide predictive power. The primary example of this is probably the study of Borger *et al.*[14] This showed a dose–volume relationship from analysis of low-dose brachytherapy. An outstanding challenge is to determine how this may be extrapolated to other treatments, particularly external beam treatment, which, as discussed above, can be administered in different dose rates and distributions of dose. Furthermore, new approaches to breast radiotherapy involve delivery of dose distributions that are different from those in the earlier studies; examples include PBI using external beam and the TARGIT approach.

The analysis in this review chapter and its associated paper[19] has shown that much work needs to be done to further develop understanding of the dose and volume effects in breast radiotherapy. New studies such as IMPORT (Intensity Modulated and Partial Organ Radiotherapy Trial) and the Danish Breast Cancer Cooperative Group trial will provide very valuable data in this respect.

For the purposes of the work presented in this report, we have analysed outcome data from three independent clinical trials that provide a test of the volume effect for side effects in radiotherapy for breast cancer. This study is presented in *Chapter 3*.

Since our original review was published, early toxicity data have been reported for the Randomised Trial of Accelerated Partial Breast Irradiation (RAPID) trial.[72] The trial randomised 2135 women between 3D-CRT APBI and WBI. The 3D-CRT APBI dose was 38.5 Gy in 10 fractions twice daily and the WBI dose was 42.5 Gy in 16 fractions or 50 Gy in 25 fractions, with additional tumour bed boost in selected patients. It was anticipated that patients in the 3D-CRT PBI arm would have fewer late breast complications as a smaller breast volume was irradiated. At 3 years, women who received 3D-CRT PBI were found to have worse cosmetic outcome than women with WBI. On trained nurses' assessment, 29% of women had adverse cosmesis with 3D-CRT PBI, compared with 17% with WBI. Based on clinician-reviewed clinical photographs, 35% of women had adverse cosmetic outcome with 3D-PBI, compared with 17% with WBI. These results could suggest no real volume effect for breast tissue, but can be better explained if one looks at the isoeffective radiation dose (EQD2) for the 3D-CRT APBI. Assuming the breast $\alpha:\beta$ ratio of 3 Gy,[73] 38.5 Gy in 10 fractions twice daily will have an isoeffective dose of 53 Gy. However, if 6 hours is not adequate for complete normal tissue recovery, the isoeffective dose could be much higher at $\approx$65 Gy. These results highlight that the relationship between irradiated breast volume and late breast complications cannot be studied in isolation.

The Electron Intra Operative Radiation Therapy (ELIOT) trial from the European Institute of Oncology, Milan, Italy, randomised 1305 patients between WBI 50 Gy in 25 fractions with 10 Gy tumour bed boost and PBI using a single intraoperative electron-based radiotherapy dose of 21 Gy.[74] At a median follow-up of 5 years, toxicity data on 876 patients were available. Patients in the PBI arm developed less skin-related toxicity (erythema, dryness, hyperpigmentation and pruritus) but no difference was seen for breast pain, breast fibrosis and breast retraction. Conversely, patients in the PBI arm developed more fat necrosis than patients in the WBI arm.

Newer breast radiotherapy techniques including PBI and simultaneous integrated boost (SIB) are being evolved, with an expectation that reducing the irradiated breast volume will reduce late breast tissue complications. Our published systemic review and subsequent trial data point towards a volume effect for breast tissue. However, data from some of the PBI versus WBI trials have been either inconclusive or, sometimes, conflicting. It is important to recognise that the relationship between irradiated breast volume and late breast tissue complications cannot be studied in isolation. Many other covariables including surgical factors, systemic therapies and radiation factors influence late breast tissue complications. Some of the PBI trials have used brachytherapy or intraoperative electrons/low-energy photons which have different dosimetric and radiobiological features from WBI. In addition, some of the trials have used APBI. This can have a significant impact on normal tissue recovery and, hence, late toxicity, which is highlighted from the RAPID trial results.

In addition, the current review does not allow clinicians and patients to predict the proportional reduction in late breast tissue toxicity if irradiated breast volume is reduced. The quantitative data supporting the dose–volume effect of breast tissue are quite limited in the published literature. More work is needed to further quantify and qualify the volume effect for breast tissue. Mature toxicity data from PBI trials are eagerly awaited and should be available in the next few years. In addition, most of these trials are collecting detailed radiation dose–volume data, which will allow a better qualitative understanding of the dose–volume effect for breast tissue.

Chapter 3 Normal-tissue complication modelling for breast tissue

This chapter describes the development of a NTCP model which may be used to relate the volume of normal tissue irradiated to the risk of toxicity. This model is required to address a secondary objective of this study, i.e. to estimate the reduced risk of late adverse effects resulting from the smaller tissue volume irradiated.

This chapter is based on the peer-reviewed scientific-refereed journal paper:

Mukesh MB, Harris E, Collette S, Coles CE, Bartelink H, Evans PM, *et al.* Normal tissue complication probability (NTCP) parameters for breast fibrosis: pooled results from two randomised trials. *Radiother Oncol* 2013;**108**:293–8.[75]

The goal of this stage of the work was to develop a NTCP model for breast tissue and predict the probability of complication to quantify the dose–volume effect for a non-uniform irradiation of the patient's breast. Fibrosis is a common sequela of breast radiotherapy and adversely affects overall cosmesis. It can be assessed using a scoring system and has been shown to impact on patient physical and psychological well-being.[12] Hence, this work relates to the development of a NTCP model for moderate to severe breast fibrosis.

The hypothesis in this work was that breast tissue displays a significant dose–volume effect to radiation which manifests itself as moderate to severe fibrosis and that an NTCP model can effectively predict the probability of breast fibrosis based on the interaction of radiation dose and the treatment volume.

Materials and methods

This analysis required diverse data sets with a range of dose and volume data plus quantitative toxicity end point data. RCTs were felt to provide the most robust data to this end. In addition, pooling data from a set of RCTs was felt to increase the diversity of the data set and enable generalisation of the findings to a broader population.[76] Moderate to severe breast fibrosis was chosen as the toxicity end point for this study.

The principal investigators of three trials kindly agreed to collaborate by sharing their patient data:

i. Dr Charlotte Coles from the Cambridge Breast IMRT trial[67,77]
ii. Professor Harry Bartelink from the EORTC 22881–10882 'boost versus no boost' trial[2,26]
iii. Dr Peter Graham from the St George and Wollongong trial.[66]

Preliminary assessment of the available data showed that the moderate to severe breast fibrosis rate of 3% with 50 Gy WBI in the St George and Wollongong trial was smaller than that in the published literature (including the Cambridge and EORTC trials). Hence, for this study only individual patient data from the EORTC 22881–10882 'boost versus no boost' trial and the Cambridge Breast IMRT trials were pooled.

Patient cohort details and toxicity scoring: Cambridge

This was a single-centre trial which recruited 1145 patients with invasive breast cancer (stage T1–T3 N0–1 M0) or ductal carcinoma in situ who received BSC and radiotherapy. All patients received 40 Gy in 15 fractions over 3 weeks to the whole breast, which was followed by an electron tumour bed boost of 9 Gy in three fractions over 3 days in selected cases ($n = 728$). The level of breast fibrosis was assessed clinically at 2 and 5 years after completion of radiotherapy and scored on a four-point scale (0 = none, 1 = a little, 2 = moderate and 3 = severe).

Patient cohort details and toxicity scoring: European Organisation for Research and Treatment of Cancer

This was a multicentre trial that recruited 5569 patients with invasive breast cancer (stage T1–T2 N0–1 M0) who received surgery and radiotherapy. All patients received 50 Gy in 25 fractions over 5 weeks to the whole breast and were randomised by three boost levels: (1) no boost ($n = 2657$), (2) 10 Gy in five fractions boost ($n = 126$), (3) 16 Gy in eight fractions boost ($n = 2661$) or (4) 26 Gy in 13 fractions boost ($n = 125$). The boost was delivered using electrons (63%), photons (29%) or LDR brachytherapy (9%). Breast fibrosis was assessed clinically at each follow-up visit and scored on a four-point scale (1 = none, 2 = minor, 3 = moderate and 4 = severe).

Exclusion criteria

As brachytherapy may lead to significant dose heterogeneity and the boost volumes used are usually much smaller than external beam techniques,[78] patients with brachytherapy boost were excluded from the analysis, as were patients for whom data or toxicity scores were missing (Cambridge trial, 571; EORTC trial, 275).

Dose–volume data

The accuracy with which NTCP model parameters can be estimated depends on the quality of dosimetry and follow-up data. The late toxicity scores and boost volumes were recorded in both trials, but limited data on the dose distributions were available. Consequently, a more simplistic two-compartment dose–volume histogram (DVH) model was used. The first step of the DVH was the tumour bed volume receiving the whole-breast dose plus the 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 3*).

The whole-breast volume was recorded only in the Cambridge trial. Based on the Cambridge data, estimates of the whole-breast volume for the EORTC trial patients could be estimated. Hence, a Monte Carlo (MC) simulation method was written which generated breast volume data for these patients. The MC simulation used the breast volume distribution from the Cambridge trial and an acceptance–rejection test for the randomly generated volumes to ensure the ratio of boost to breast volume was between 5% and 40% (the range of boost volume to breast volume ratio observed in the Cambridge data). In doing this, the assumption was made that the distribution of breast volume and the ratio of boost to breast volume in the EORTC trial was the same as that in the Cambridge trial.

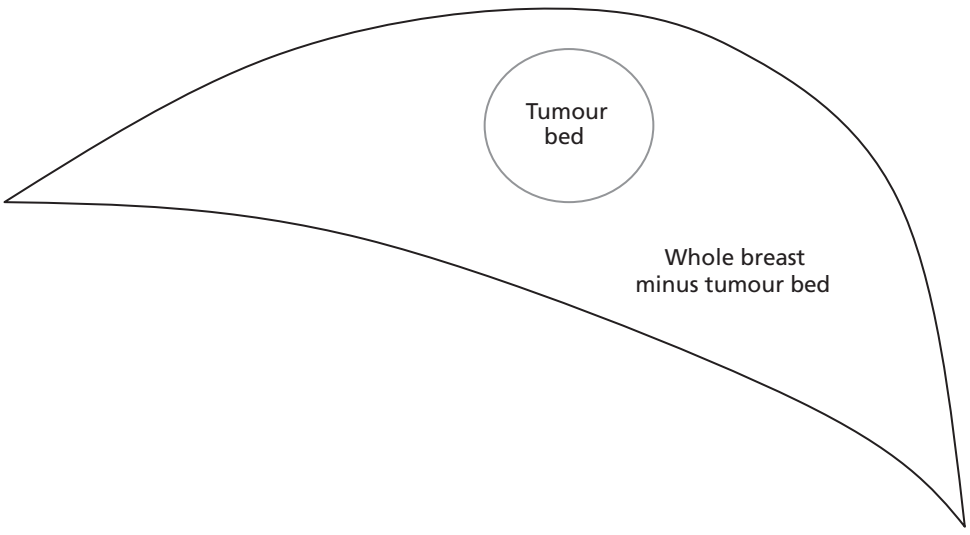

FIGURE 3 The two-step DVH model. DVH step 1: tumour bed receiving the whole-breast dose plus the tumour bed boost. DVH step 2: whole-breast volume minus the tumour bed receiving whole-breast dose alone.

Normal-tissue complication probability modelling

In this study two established radiobiological models were used: the Lyman–Kutcher–Burman (LKB) model[79] and the Niemierko model.[80] Both assume that the dose–response relationship follows a sigmoid curve. Both describe the response with three parameters:

- **TD50:** the homogeneous dose to the organ that leads to 50% patients experiencing the defined toxicity at 5 years
- **γ50 and *m*:** the steepness parameter of the dose–response curve
- ***n*:** volume parameter of the organ being assessed.

To estimate 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, when delivered uniformly to the organ, that will lead to the same complication probability as the actual dose distribution.

$$\mathrm{EUD} = \left(\sum_i v_i (D_i)^{\frac{1}{n}}\right)^n, \tag{1}$$

where v_i is the ith subvolume of the organ irradiated with dose D_i in the differential DVH.

For the volume parameter, n, if $n = 1$, the organ has a parallel structure with a strong volume dependence on late complication rate and EUD is the mean dose. If $n = 0$, the organ has a serial structure with no volume dependence on late complication rate and EUD tends to be the maximum dose.

As complications due to radiotherapy depend on fraction size, a biologically equivalent uniform dose (BEUD) using an $\alpha:\beta$ ratio of 3 Gy (BEUD_3) was generated using the EUD and the $\alpha:\beta$ ratio of 3 Gy in the linear quadratic model.

$$\mathrm{BEUD}_3 = \mathrm{EUD}\left(1 + \frac{\mathrm{EUD}}{N \times \alpha/\beta}\right) \tag{2}$$

In the LKB model:

$$\mathrm{NTCP} = \frac{1}{\sqrt{2\pi}} \int_0^x e^{-\left(\frac{x^2}{2}\right)} dx, \tag{3}$$

where

$$x = \frac{\mathrm{BEUD}_3 - \mathrm{BEUD}_3 50}{\mathrm{mBEUD}_3 50}. \tag{4}$$

In the Niemierko model:

$$\mathrm{NTCP} = \frac{1}{1 + \left(\frac{\mathrm{BEUD}_3 50}{\mathrm{BEUD}_3}\right)^{4\gamma 50}}. \tag{5}$$

The two NTCP models were written in Object Pascal (Delphi, Embarcadero Technologies, San Francisco, CA, USA).

A maximum likelihood estimation (MLE) method[81] was used to find the best-fit values of the model parameters BEUD50, γ50, *m* and *n*. This method estimates the probability that the observed pattern of complications can be best described by the parameters of the model.

$$\ln L = \sum_{y(i)=1} \ln[\mathrm{NTCP}(\mathrm{TD50}(1), m, n)] + \sum_{y(i)=0} \ln[1-\mathrm{NTCP}(\mathrm{TD50}(1), m, n)], \quad (6)$$

where $y(i) = 1$ if moderate or severe fibrosis is observed and $y(i) = 0$ if moderate or severe fibrosis is absent.

As discussed above, a value of *n* close to 1 suggests that the organ has a parallel structure with a strong volume dependence, while a value of *n* close to 0 suggests that the organ has a serial structure with little or no volume dependence on late complication rate. A full sequential parameter search was carried out using the following parameter constraints: BEUD_3 (0–150), *n* (0.01–1.0), γ50 (0.5–3.0) and *m* (0.1–0.8). The 95% CIs for the optimally fit parameters were obtained using the profile likelihood estimation method.[82] 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 an asymmetrical CI into consideration, but does not account for correlations between parameters.

Results from the START pilot trial[16] were used to assess the goodness of fit of the predicted NTCP models. The START pilot trial randomised 1410 patients into three WBRT dose fractionations: (1) 50 Gy in 25 fractions, (2) 39 Gy in 13 fractions or (3) 42.9 Gy in 13 fractions. Patients were also subrandomised for tumour bed boost to a dose of 14 Gy in seven fractions using electrons. Cumulative data on moderate or severe breast induration at 5 years were used for all three whole-breast dose fractionation regimes with and without the boost to test the goodness of fit. The goodness-of-fit statistic was obtained by calculating the Pearson's chi-squared statistic for the observed and predicted rates of breast fibrosis. The statistic is denoted as χ^2 and a large value of χ^2 (and small *p*-values) indicate a lack of fit of the model.

$$\chi^2 = \sum \frac{(O-E)^2}{E}. \quad (7)$$

O is the observed rate of fibrosis and *E* is the rate of fibrosis predicted by the model.

Results

Dose–volume and toxicity data for 574 patients from the Cambridge trial and 5282 patients from the EORTC trial were used for the NTCP modelling. In the Cambridge and EORTC trials, 26.8% (154/574) and 20.7% (1096/5282) of patients developed moderate to severe breast fibrosis, respectively. The patients' radiotherapy dose–volume characteristics are summarised in *Table 3*.

The best estimated NTCP parameters for the Niemierko model from the MLE method were BEUD to the whole breast, which produces a 50% complication rate using an $\alpha:\beta$ ratio of 3 Gy ($\mathrm{BEUD}_3 50 = 136.4$ Gy), $\gamma 50 = 0.9$ and $n = 0.011$. The 95% CIs for parameters were $\mathrm{BEUD}_3 50 = 132.8$ to 140 Gy, $\gamma 50 = 0.84$ to 0.97 and $n = 0.01$ to 0.03. The best estimated parameters for the LKB model were $\mathrm{BEUD}_3 50 = 132$ Gy, $m = 0.35$ and $n = 0.012$, with 95% CIs of $\mathrm{BEUD}_3 50 = 128.8$ to 135.6 Gy, $m = 0.326$ to 0.374 and $n = 0.01$ to 0.03. The results of both models strongly imply that the risk of moderate to severe breast fibrosis is strongly associated with radiotherapy dose and the effect of volume (i.e. the volume parameter) is small. The $\mathrm{BEUD}_3 50$ values of 136.4 Gy and 132 Gy correspond to EQD2 values of 79.2 Gy and 81.8 Gy, respectively.

TABLE 3 Dose–volume characteristics from the Cambridge and the EORTC data sets used for the NTCP model

Dosimetry characteristic	Number of patients	Mean boost volume, cm^3 (range)	Number of patients with moderate to severe fibrosis
Cambridge data set (assessed at 5 years)			
No boost	235	–	40/235 (17%)
Boost	339	161.2 (33.6–540)	114/339 (33.6%)
EORTC data set (cumulative incidence at 10 years)[a]			
No boost	2656	–	341/2656 (12.8%)
≥ 6 Gy to < 10 Gy	6	238 (108–372)	1/6 (16.7%)
10 Gy	117	204.7 (42–1176)	28/117 (23.9%)
12 Gy	31	185.9 (48–606)	11/31 (35.5%)
14 Gy	93	273.4 (48–735)	23/93 (24.7%)
16 Gy	2257	209 (22–1386)	635/2257 (28.1%)
> 16 Gy to ≤ 20 Gy	39	193.1 (52–630)	9/39 (23.1%)
26 Gy	83	198.5 (43–630)	48/83 (57.8%)

a The NTCP parameter estimation was based on the actual tumour bed boost dose delivered and not on the intention-to-treat boost dose.

The observed rates of moderate to severe fibrosis in the RMH/GOC trial were in good agreement with the predicted rates of fibrosis using the LKB model (*Figure 4*) and the Niemierko model (*Figure 5*). Using the Pearson's chi-squared test with five degrees of freedom, χ^2 was 0.053 ($p = 0.95$) for the LKB model and χ^2 was 0.058 ($p = 0.95$) for the Niemierko model, suggesting a good fit for both models.

Three previous studies have estimated the NTCP parameters for breast fibrosis and these results are summarised in *Table 4*. The Borger *et al.*[14] model was based on 404 patients treated with WBI (50 Gy in 25 fractions over 5 weeks) followed by LDR ^{192}Ir tumour bed boost (15–25 Gy). The BEUD was calculated

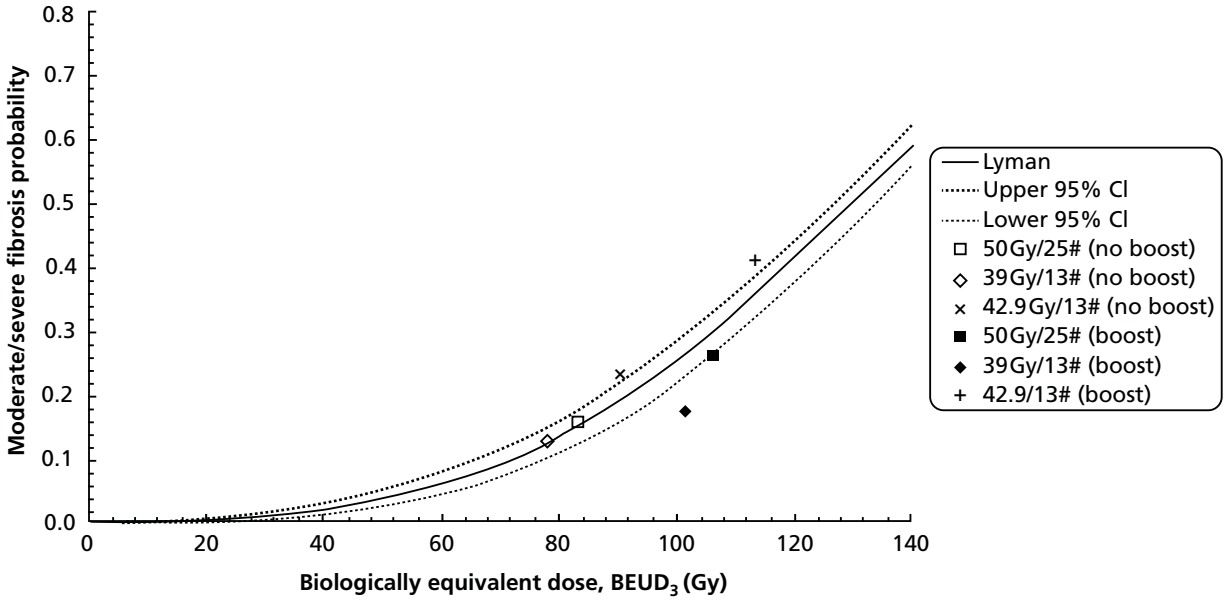

FIGURE 4 Lyman–Kutcher–Burman model: the probability of moderate to severe breast fibrosis vs. $BEUD_3$. The solid line is based on the best fit parameters ($BEUD_3 = 132$ Gy and $m = 0.35$) and the dashed lines are upper and lower 95% CI. The summative toxicity data of the three dose fractionations ± boost at 5 years from the START pilot trial are plotted.

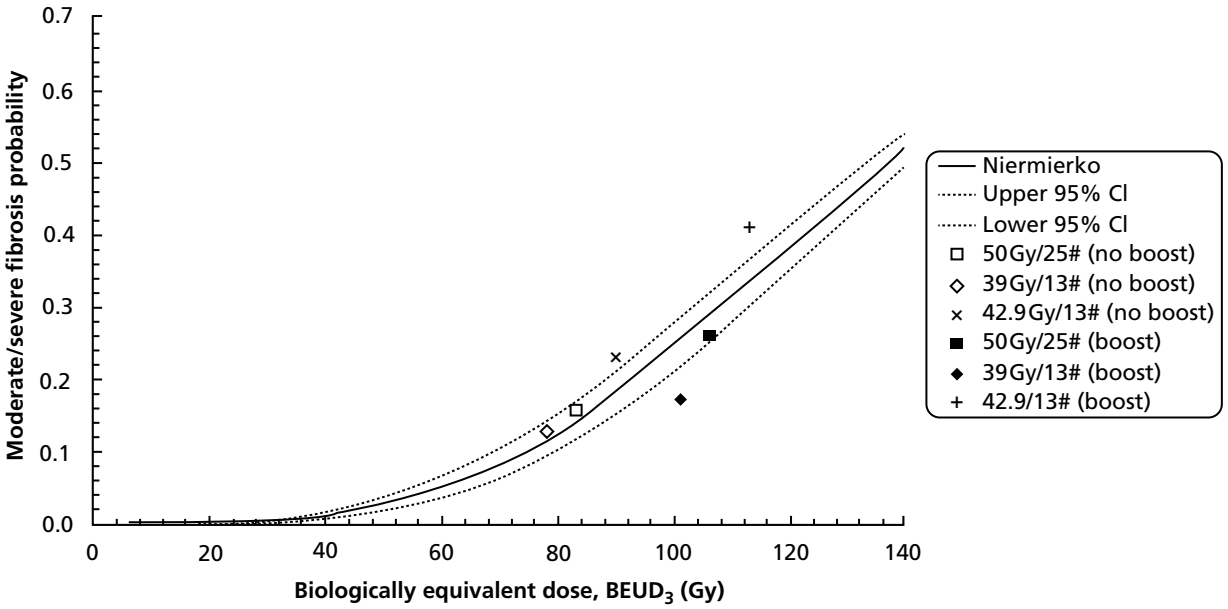

FIGURE 5 Niemierko model: the probability of moderate to severe breast fibrosis vs. $BEUD_3$. The solid line is based on the best fit parameters ($BEUD_3 = 136.4$ Gy and $\gamma 50 = 0.9$) and the dashed lines are upper and lower 95% CI. The summative toxicity data of the three dose fractionations ± boost at 5 years from the START pilot trial are plotted.

TABLE 4 Summarised results of the best-fit NTCP parameters for moderate to severe breast fibrosis

Study	Number of patients	$BEUD_3 50$	$\gamma 50$	*m*	*n*
Borger *et al.*[14]	404	$NTD_{50} = 72$ Gy ($\alpha:\beta = 2$Gy) ($t_{1/2} = 1.5$ hours)			0.16
[a]Alexander *et al.*[83]	1546	–	–	–	–
LKB model		104 Gy	–	0.27	0.78
Relative seriality model		104 Gy	1.47	–	($s = 0.12$)
[a]Avanzo *et al.*[84]	2562	–	–	–	–
With repair correction ($t_{1/2} = 4.4$ hours)		105.8 Gy	–	0.22	0.15
Without repair correction		107.2 Gy		0.22	0.06
Current study	5856	–	–	–	–
LKB model		132 Gy	–	–	0.012
Niemierko model		136.4 Gy	0.9	0.35	0.011

γ50/m, slope of the dose–response curve; *n*, volume parameter; the serial/parallel architecture of the organ. A large value indicates a serial structure and a small value indicates a parallel structure; $t_{1/2}$, repair half-time.
a These studies used summative dosimetric and toxicity data.

using an $\alpha:\beta$ ratio of 2 Gy and a repair half-time of 1.5 hours. The positions of the implants were reconstructed on radiographs and dose distributions were calculated. The best-fit model parameters in the study were found to be TD50 = 72 Gy and $n = 0.16 \pm 0.04$. The model parameters were estimated from patients with brachytherapy boost alone, and it is not clear how to compare parameters generated from brachytherapy with external beam techniques owing to inherent differences in the dose distributions and possibly different radiobiological effects. Hence, patients with brachytherapy boost were excluded from the current study. Avanzo *et al.*[84] estimated the best-fit parameters for the model using average values of 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 of the PBI studies used twice-a-day 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 also included. The parameters were estimated using the weighted least squares fitting method, with the number of patients in each data set used as weighting. The parameters found for moderate and severe breast fibrosis from the model were BEUD50 = 105.8, $n = 0.15$ and $m = 0.22$.

Alexander *et al.*[83] reported that the volume parameter exhibited a strong effect on breast fibrosis. This study included summative data of 806 patients from the START pilot trial,[16] 590 patients from a German study[85] and 150 post-mastectomy patients treated in the 1960s.[86] 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 structure for breast tissue with a strong volume effect for breast fibrosis ($n = 0.78$). However, these results cannot be generalised for several reasons:

1. The study did not account for the tumour bed boost doses (additional radiotherapy dose) in the models.
2. Different toxicity outcome measures are used in the studies. The START pilot and German study assessed breast fibrosis based on clinical examination, whereas the post-mastectomy study used photographic assessment.
3. The planning techniques for the post-mastectomy study based on 1960s' data are outmoded by present standards. Different NTCP parameters may be expected for breast fibrosis after BCS and tissue fibrosis after mastectomy.
4. The study corrected for latency time (START pilot and German) based on the results of the historic post-mastectomy series.

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 a variety of modern techniques: accelerated PBI, simultaneous integrated boost and risk-adapted radiotherapy.[43,46,87,88] The EORTC 22881-10882 trial breast fibrosis nomogram showed a strong association between radiotherapy dose and risk of fibrosis, with large boost volumes as a prognostic factor based on univariate analysis only.[27] The purpose of this study was specifically to investigate the volume effect by developing a NTCP model based on the data. 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 analyses. This finding suggests that, for moderate and severe fibrosis, the breast tissue behaves as a serial organ and the maximum radiotherapy dose is the best predictor of complication. The summative data of 1410 patients from an independent data set with six radiotherapy dose levels were found to have a good fit to both the LKB and Niemierko models (see *Figures 4* and *5*).

Two other published studies have suggested a weak volume effect. However, one was based on a tumour bed boost using brachytherapy and the other was based on summative patient data. The Alexander *et al.* study,[83] indicating a large volume effect, has major limitations. To our knowledge, this is the largest dose–volume study for breast fibrosis using individual patient data. Parameter correlation leads to uncertainty in the estimation of those parameters, independent of the size and diversity of the data set.[89] An effective method to decrease the uncertainty is fixing one or more of the model parameters. Hence, the $\alpha:\beta$ ratio was fixed as 3 Gy in this study based on the previously published literature.[16] There is no evidence to suggest the superiority of one model (LKB or Niemierko) over another.[90] However, similar values of the estimated parameters from the two models strengthen the results of this study.

There are several possible reasons to explain the difficulty in demonstrating a volume effect for breast fibrosis, and can be considered limitations to the current study. Breast fibrosis may represent a focal effect, with the maximum radiotherapy dose as the most predictive factor of that focal effect. It is also possible that current scoring methods for breast fibrosis are not sensitive to the volume effect. Breast fibrosis is often graded as mild to severe based on the severity; however, the scoring system does not take into account the extent of fibrosis. For example, a small discrete region of fibrosis and a widespread region of fibrosis are potentially scored alike. It has been suggested that NTCP parameters are influenced by the severity of the measured toxicity.[91] For rectum, Rancati *et al.* estimated that 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.[91] It is plausible that a volume effect for breast tissue may have been seen for mild fibrosis, but this end point was considered to be of less clinical significance and, therefore, not assessed.

Other toxicity end points may also be more sensitive to the volume effect; an example is photographic assessment of breast shrinkage as it represents an effect across the whole-organ is more objective and is scored independent of surgical changes. The current study focused only on breast fibrosis measured using photographic assessment, as patient-reported scoring was not available for the majority of the patients included in the study.

Conclusions

Modelled NTCP parameters suggest that, for moderate and severe fibrosis, the breast tissue behaves as a serial organ and the maximum radiotherapy dose is the best predictor of complication. The derived model predicts close to zero effect of volume of irradiated tissue on the risk of toxicity. Evidence of a volume effect reported in the literature warrants further investigation (see *Chapter 2*). Further work will use IMPORT-HIGH toxicity and dosimetry data to test model parameters using similar methodology to that reported here.

Chapter 4 A multi-institutional investigation of image-guided radiotherapy for breast cancer

This chapter addresses the main research objective of the study, i.e. the difference in spatial accuracy between clip-based IGRT and standard imaging. Differences in daily set-up errors measured using clip-based IGRT and standard imaging were assessed and overall accuracy was defined as the difference in population systematic set-up error obtained using clip-based IGRT compared with standard imaging. This chapter also addresses two secondary objectives: the decrease in safety margin provided by clip-based IGRT and the time required to perform clip-based IGRT and standard imaging verification. Differences between centres and imaging modalities are also investigated.

Introduction

The breast radiotherapy process can be divided into three steps:

1. Simulation: planning CT is performed while the patient is in the position that will be used during radiotherapy treatment delivery. The patient is immobilised using a breast board/vacuum bag and predefined tattoo marks are placed on the surface of the skin.
2. Radiotherapy planning: planning CT is used to identify and contour the target volumes (tumour bed and whole breast) and organs at risk (lung, heart, contralateral breast). Radiotherapy beams are designed to optimally cover the target volumes and spare the organs at risk.
3. Treatment verification and delivery: radiotherapy treatment is delivered over a series of sessions (called fractions), to allow preferential deoxyribonucleic acid (DNA) repair to take place in normal cells but not the cancerous cells. Before each radiotherapy fraction, the patient position is reproduced using laser light beams; predefined tattoo marks on the patient's skin are aligned with the lasers. Verification images are taken while the patient is on the treatment couch to confirm correct positioning and treatment is delivered.

A difference in patient position between the planning CT scan and treatment session can lead to geographical miss of the target, potentially increasing the risk of cancer recurrence. Owing to the uncertainty in patient and target position with each fraction (subsequently called set-up errors), a PTV margin is routinely added around the target volume. This PTV margin accounts not only for the daily interfraction and intrafraction motion (*Figure 6*), but also for beam penumbra and other geometrical uncertainties associated with the radiotherapy equipment. Interfraction motion includes differences in patient positioning between radiotherapy fractions. Intrafraction motion includes movement that occurs during each radiotherapy fraction, for example respiratory motion and tissue deformation.

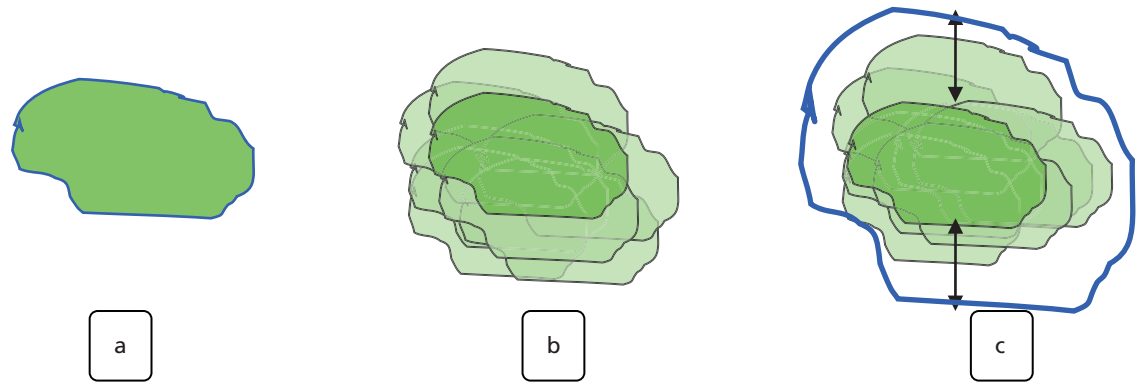

FIGURE 6 Set-up errors and PTV margin in radiotherapy. (a) Target volume requiring radiotherapy dose; (b) day-to-day variation in position of the target volume; and (c) safety margins (black arrows) around the target volume to account for positional errors and create a PTV.

Predefined skin tattoo marks and laser beams are currently used to position patients for breast radiotherapy. Although it is 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 to 30 mm.[92–94] These large positional errors mean that a relatively large PTV margin has to be used (commonly 10 mm).

Owing to the addition of a large PTV margin, a considerable volume of the healthy surrounding tissue is unnecessarily irradiated to treatment dose, increasing the risk of radiation-related adverse events. It also limits our ability to safely escalate the radiation dose to the target. IGRT techniques can be used to reduce both interfractional and intrafractional errors and potentially reduce the PTV margins.

Two-dimensional megavoltage (2D-MV) portal imaging method is the current standard imaging verification technique for breast radiotherapy. The breast radiation treatment is usually carried out using lateral (LR) and medial tangential beams and these high-energy (megavoltage) treatment beams are used to generate portal images. The position of the ribs and lung on the portal images are compared with a digitally reconstructed radiograph (DRR) generated from planning CT images to identify the day-to-day variation in patient positioning (*Figure 7*).

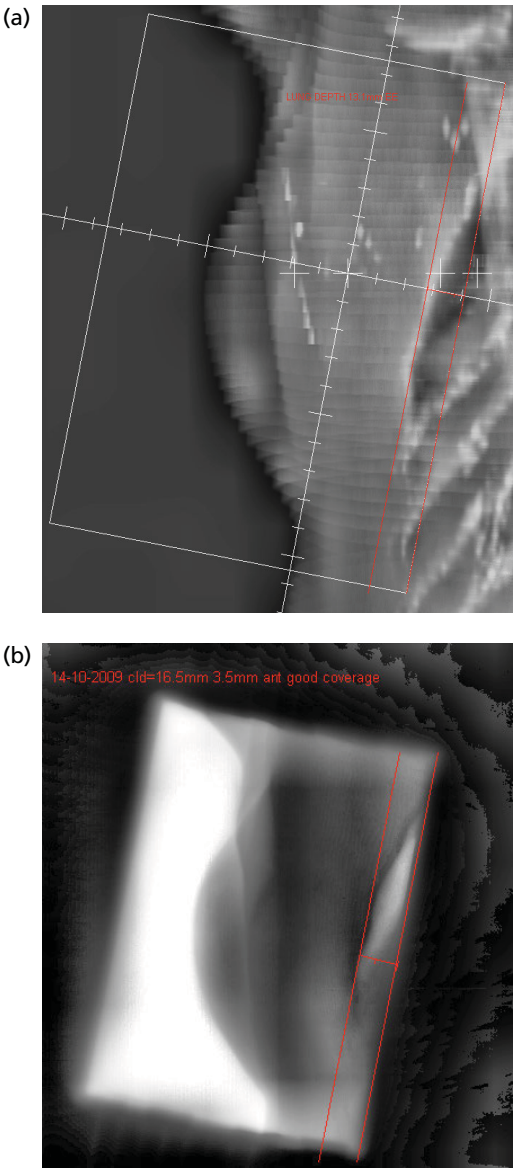

FIGURE 7 Standard verification technique compares DRR and megavoltage portal image. (a) DRR from planning CT scan; and (b) megavoltage portal image.

Parameters including central lung distance (CLD), defined as the distance between the posterior field edge and the interior chest wall at the central axis, and craniocaudal distance (CCD), defined as the distance between the skin and the caudal beam edge, are compared between the portal images and DRR to calculate positional errors in both the transverse and longitudinal direction (*Figure 8*). If the positional errors exceed predefined limits (commonly set as 5 mm), the patient is repositioned before the next treatment is delivered.

Although they are simple and effective, the portal images 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) cannot be directly visualised on the portal images. 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 *et al.*'s[9] study of 27 patients treated with APBI indicated that (a) the whole breast can move independently of bony anatomy and (b) the tumour bed can also move independently of the whole breast.

Owing 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 PTV for photon tumour bed boost.[95]

Because of 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. Apart from ipsilateral breast, an increase in PTV margin will also increase the radiation dose to contralateral breast, heart and ipsilateral lung. If we could safely reduce set-up errors, PTV margins around the tumour bed can also be safely reduced. This is desirable to reduce the risk of late breast and other normal tissue toxicity.

The BASO has recommended that all patients undergoing BCS should have surgical clips on the wall of the tumour bed.[96] Clips are currently used as fiducial markers, for the accurate localisation the tumour bed.[97] In addition, clips have been shown to be a better surrogate for the tumour bed than bony anatomy and are used for IGRT.[6,9,98] In this report we call this approach clip-based IGRT.

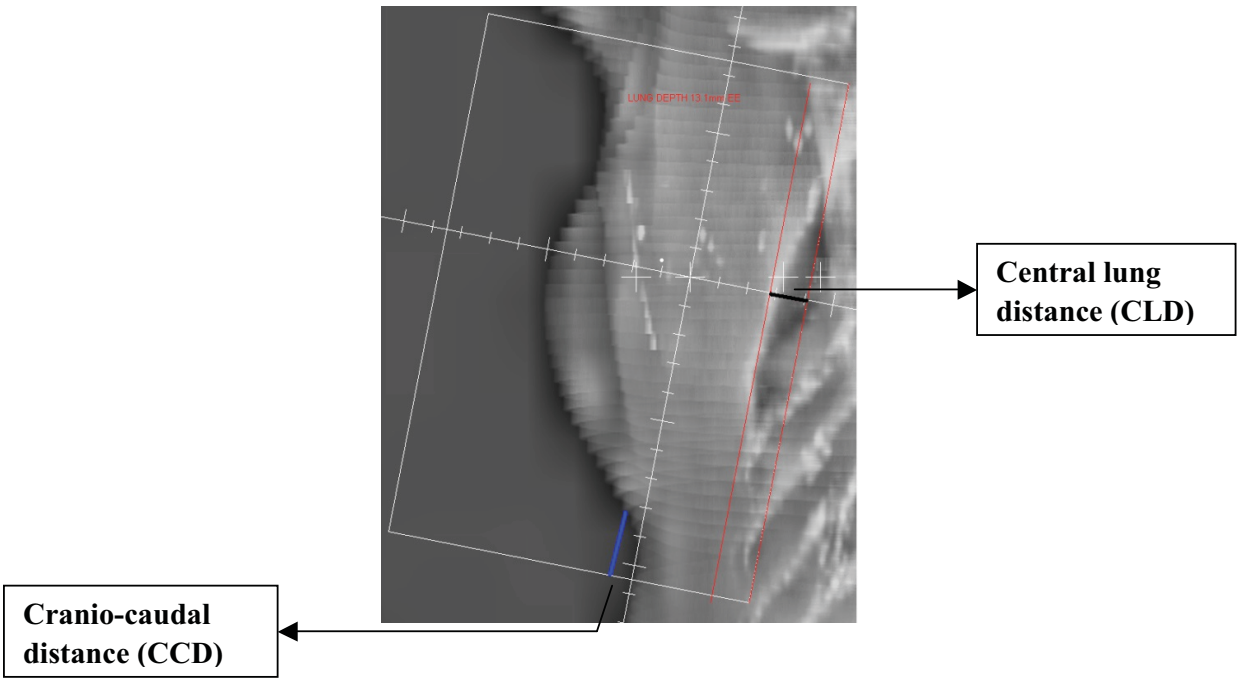

FIGURE 8 Measurement of CLD in black and CCD in blue on a DRR.

The use of surgical clips as a surrogate for the tumour bed was evaluated in 28 patients by Weed *et al.*[6] Each patient underwent planning CT on two separate days. The tumour bed and clips were identified as regions of interest (ROIs). The scans were then fused based on bony anatomy and the displacement of the tumour bed was compared with 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 3 mm was seen between the two ROIs, which were attributed to the finite thickness of the CT slices and use of a limited number of clips. Hasan *et al.*[9] also demonstrated that surgical clips are a better surrogate for tumour bed than bony anatomy and breast surface. Twenty-seven patients twice underwent CT in the treatment position, initial planning CT and then further CT at an average of 27 days after the first procedure. 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 processes were compared ($\Delta COM_{bony\ anatomy}$, ΔCOM_{clips} and $\Delta COM_{breast\ surface}$). It was observed that localisation of the tumour bed using surgical clips is more accurate than localisation using bony anatomy and breast surface. Topolnjak *et al.*[98] 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 clips' 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 a good surrogate for excision cavity with small residual errors of 0.7–1.3 mm.

It is now known that surgical clips are a better surrogate of the surgical cavity (tumour bed) than bony anatomy. A number of studies have evaluated the feasibility of using these surgical clips for image-guided breast radiotherapy.[99–101]

The IMPORT-HIGH trial group used gold seed fiducial markers (small metallic seeds that can be sutured onto the cavity wall) as a tumour bed surrogate for IGRT to estimate safe PTV margins around the breast tumour bed.[99] Treatment verification and daily online correction were performed on 42 patients with 2D-MV (high-energy) portal image or kV (low-energy) planar image or CBCT. The study concluded that by using extended no-action level (e-NAL) or daily online correction strategy (discussed later), the tumour bed PTV margins can be safely reduced to 5 mm. Leonard *et al.*[100] also demonstrated the feasibility of gold seed fiducial markers for marker-based IGRT using orthogonal and LR megavoltage portal films in 20 patients.

Two-dimensional megavoltage portal imaging verification method using bony anatomy is relatively simple and easy to use, whereas additional verification time and resources are required for marker-based IGRT technique. The benefit of clip-based IGRT over portal imaging needs to be quantified by comparing the PTV margins and verification time for both techniques. In addition, most of the feasibility studies of fiducial marker-based IGRT were based on a small number of patients, 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 workload. Titanium clips can be used as an alternative fiducial marker (≈£1/patient), although, owing to their low density, they cannot be visualised on 2D-MV portal image. Several different imaging modalities can be used for titanium surgical clip-based IGRT: kV planar images, kV cone beam CT and megavoltage CT (MV-CT) (TomoTherapy®; Accuracy Inc. Sunnyvale, CA, USA). It is currently unclear if the PTV margin depends on the type of IGRT imaging modality used.

Materials and methods

The sample size calculation was carried out by the Institute of Cancer Research – Clinical Trials and Statistics Unit (ICR-CTSU). The study statistician (JH) was responsible for overseeing all statistical analyses. In this study, the primary research objective was to compare the accuracy of clip-based IGRT with that of

standard imaging. This study proposed to use accuracy to determine two secondary research objectives of this study: volume of normal tissue irradiated and the probability of adverse effects (fibrosis) using the following steps:

- Accuracy is calculated using the mean set-up error for each patient (patient systematic error). The mean set-up error for each patient is the mean of the 15 set-up errors measured at each fraction. The accuracy of standard imaging compared with clip-based IGRT will determine the additional safety margin.
- The technique-specific safety margin is calculated from the distribution of the patients' overall set-up errors. The size of the margin is approximately 2.5 times the SD of the mean set-up errors for all patients (population systematic error).[102]
- The volume of normal tissue irradiated when standard imaging is used is then calculated by simply adding this margin to the treatment volume used for IMPORT-HIGH (which uses clip-based IGRT).
- The probability of adverse effects (fibrosis) for clip-based IGRT and standard imaging will be determined from the volumes of tissue irradiated with each of these methods and using the relationship between incidence of fibrosis and volume determined using radiobiological modelling.

This study was designed to generate two sets of data: the mean set-up error from the number of patients receiving curative breast radiotherapy using clip-based IGRT and using standard imaging.

A difference in the SD (or variance) of these data sets will result in a difference in safety margin and the volumes of normal tissue irradiated. Thus, the sample size calculation was based on finding a significant difference in the variance of these two data sets. To perform the sample size calculation the SD of set-up errors for clip-based IGRT and standard imaging the correlation between the data sets was estimated using evidence from the literature:

- *Standard deviation:* from a small study of 20 patients, Topolnjak *et al.*[103] found that, if standard imaging were used daily, the SD of the set-up errors was between 2.7 mm and 3.8 mm. In a similar study of 10 patients by Kim *et al.*[101] the SD of set-up errors was measured to be between 0.9 mm and 1.4 mm when daily clip-based IGRT is used. Kim *et al.* estimate that this range of values rises from 2.2 mm to 2.6 mm when other factors such as deformation of the breast are taken into account. To calculate the sample size, based on these studies, the aim was to detect differences in SDs corresponding to a decrease from 3 mm for standard imaging to 2 mm for clip-based IGRT.
- *Correlation:* because no similar studies have previously been performed directly comparing clip-based IGRT and standard imaging the correlation between the two data sets is unknown. Work by Penninkhof *et al.*[104] shows that set-up errors measured in the same patient using two imaging techniques to image bony anatomy are highly correlated (≈0.85). It was expected that the correlation between set-up errors for clip-based IGRT and standard imaging is high (> 0.5), as they will be measured in the same patient, but not as high as for two techniques measuring bony anatomy (i.e. < 0.85).

The sample size required was determined for high correlation (0.7) and very low correlation (0.1). Using computer simulations based on Fisher's test,[105] the number of patients required to detect a 1-mm difference in the SDs from 2 mm to 3 mm (assuming correlation = 0.7, power = 80%, $\alpha = 0.05$) was determined. Using the same analysis but assuming very low correlation (0.1), with 250 patients it was found that it was possible to detect the same difference (2 mm vs. 3 mm) in SDs (power = 80% and $\alpha = 0.05$).

This sample size calculation was based on estimates from studies using small numbers of patients and a definitive value for the correlation between set-up errors measured using the two techniques was not available. We based the study on the requirement for a larger cohort of patients, 250, which allows for smaller correlations. It was proposed that an independent data monitoring committee confidentially review the data after the first 100 patients, and advise on the final sample size.

All patients participating in the national Phase III IMPORT-HIGH trial have surgical clips inserted into the walls of the tumour bed and are receiving clip-based IGRT as routine. The daily verification image data for clip-based IGRT were used to calculate the set-up error with this clip-based 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, they had no direct impact on the study population.

Imaging data were collected from five different centres participating in the IMPORT-HIGH trial: Addenbrookes Hospital, RMH, Ipswich Hospital, Cheltenham Hospital and Clatterbridge Hospital. The five centres were chosen because they were early implementers and high recruiters of the IMPORT-HIGH trial. Combined, these five centres used all three imaging techniques used in the IMPORT study, which represented current national practice. Ipswich, Cheltenham and Clatterbridge centres used two-dimensional kilovoltage planar imaging (2D-kVPI) and a daily online image verification protocol (IVP), RMH used kilovoltage CBCT (kV-CBCT) with an e-NAL verification protocol, and Addenbrookes used MV-CT (TomoTherapy®) with daily online IVP for treatment verification and positional correction (*Figure 9*). The details of different IVPs are discussed later.

Bony anatomy-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-kVPI. Then clip-based IGRT set-up errors were measured by manually adjusting alignment of images from their bony anatomy-matched position. Bony anatomy set-up (S_{BA}) and clip set-up errors (S_{clip}) in the LR, superior–inferior (SI) and anterior–posterior (AP) directions were recorded. The time taken to perform bony anatomy- (T_{BA}) and clip-based (T_{clips}) image assessment (a secondary objective of this study) was also recorded. Only images with sufficient information on bony anatomy were used. Intra- and inter-observer errors were assessed using nine 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 IVPs could be studied.

Radiotherapy positional errors are classified into systematic 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 is called a random error. Systematic error can shift the cumulative dose distribution relative to the target and contributes more towards the PTV margin than random error, which blurs the dose distribution.

The PTV margin calculation is based on the population systematic error (Σ) and the population random error (σ).[102]

$$\text{PTV margin} = 2.5\Sigma + 0.7\sigma \tag{8}$$

For a given population, systematic error (Σ) is the mean of the SD of all patients' mean set-up errors and random error (σ) 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 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 the 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 delta error, $S_{DIFF} = S_{BA} - S_{clips}$ was generated. The mean and SD of the S_{DIFF}, S_{BA} and S_{clips} for the study population was used to generate the systematic error ($\Delta\Sigma$) and random error ($\Delta\sigma$) for the margin formula.

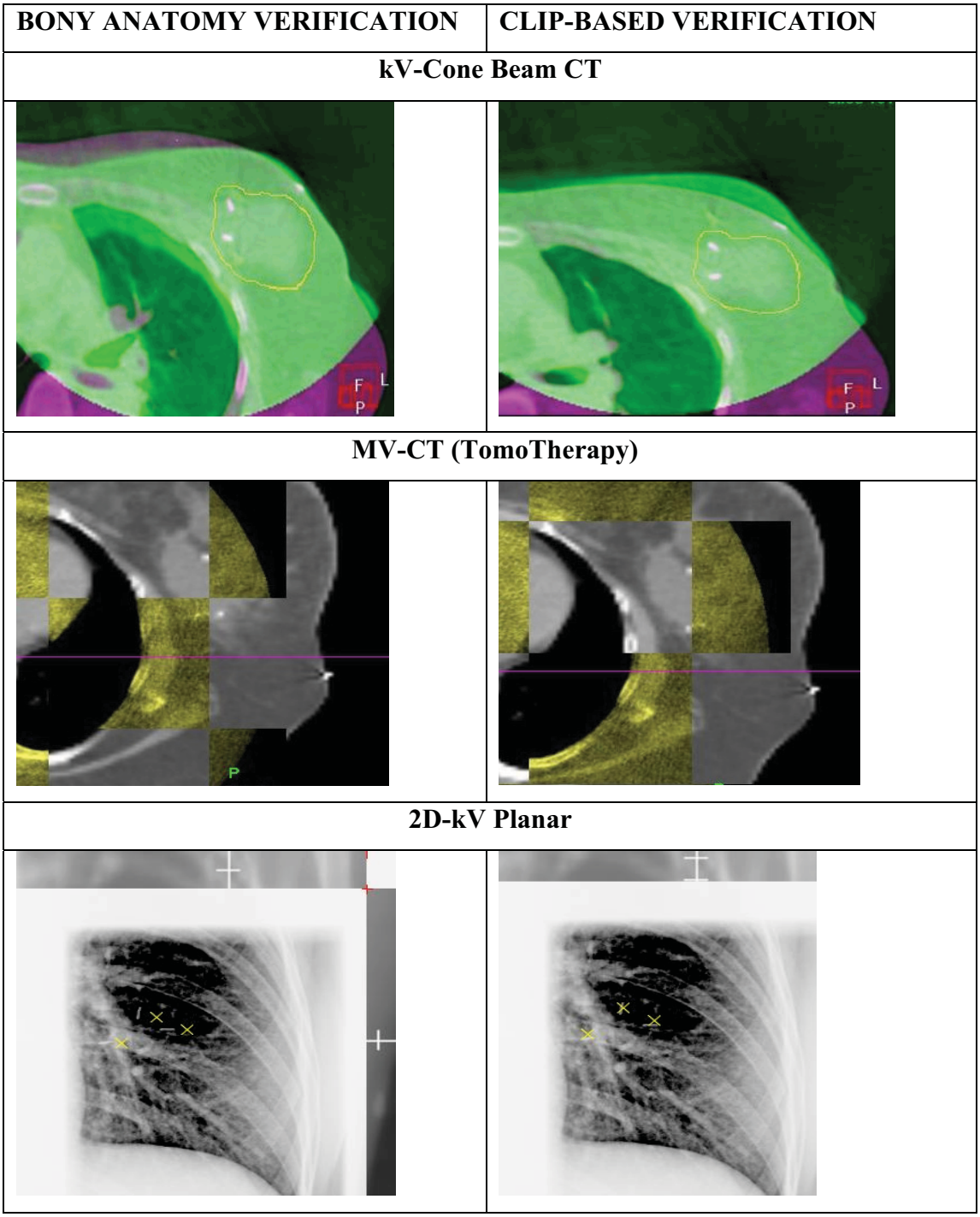

FIGURE 9 Bony anatomy and clip-based verification using kV-CBCT, MV-CT and 2D-kVPI.

S_{DIFF} for the first 112 patients was collected and analysed to calculate the required sample size. The calculations were based on the 95% CI that will give the required precision of 0.05 cm on the PTV margin estimate.

Individual patient and population mean (M), systematic (Σ) and random (σ) errors were calculated for bony anatomy (standard imaging) and clips (clip-based IGRT) 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 background radiation during WBI, the margin formula was modified by reducing the contribution of the σ error.

$$\text{PTV margin} = 2.5\Sigma + 0.3\sigma \tag{9}$$

The PTV margins required for safe treatment may depend not only on the method of verification used (standard imaging using 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 margins:

1. No-correction protocol: no imaging is undertaken and the patient is positioned using laser-based set-up.
2. No-action level (NAL): the systematic error is calculated after three treatment fractions and systematic set-up error is corrected for all subsequent fractions, regardless of the magnitude of the error.[102]
3. e-NAL: the first stage of the protocol follows NAL strategy with additional once-weekly verification and correction.[106]
4. Daily correction protocol: patient position is verified daily against the planning CT scan and corrected (if required).

Data for S_{BA} and S_{clips} were not available for all 15 treatment fractions. In order to evaluate the effect of 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 SD equal to the patient's real set-up data was sampled n minus 15 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 five images were adequate to describe a patient's set-up data, the mean and SDs of set-up errors of 28 patients with $n = 15$ were determined, for all 15 set-up errors and for five set-up errors (fractions 1, 2, 3, 7 and 11). When using five images compared with 15 images, the mean difference in patient's mean and SD of set-up errors was 0.006 cm and 0.013 cm, 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 margins. Simulated IVPs included online bony anatomy (OL_{BA}), online clip (OL_{clips}), e-NAL bony anatomy ($e\text{-}NAL_{BA}$) and e-NAL clip ($eNAL_{clips}$). 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 (1 SD) from random sampling.

This study used clips as a surrogate for the tumour bed. Surrogate systematic and random errors of 1.1 mm were added in quadrature to the set-up errors,[101] to account for the uncertainty introduced by the localisation of clips rather than the tumour bed.

$$\text{PTV margin} = 2.5\sqrt{\Sigma^2_{\text{set-up}} + \Sigma^2_{\text{surrogate}}} + 0.3\sqrt{\sigma^2_{\text{set-up}} + \sigma^2_{\text{surrogate}}} \tag{10}$$

As discussed above, 2D-MV portal imaging is the current standard treatment verification method for breast radiotherapy. No portal imaging data were collected as part of the study. The 2D-MV portal imaging set-up error data ($S_{2D\text{-}MV}$) were derived from S_{BA} using the method previously proposed by Topolnjak *et al.*[103]

$$S_{2D-MV} = \beta s_{BA} + \alpha + \text{rand} \times \eta \quad (11)$$

where parameters β (slope) and α (intercept) were determined from regression analysis, η is the SD of the differences between 2D-MV imaging and kV-CBCT imaging set-up errors measured by Topolnjak *et al.*[103] and 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. It was assumed that three-dimensional (3D) set-up errors are available from 2D-MV imaging, which is possible if anterior and LR portal images are used.[107]

In this study, for the LR and AP directions, values of $\beta = 0.82$, $\alpha = 0.66$ mm and $\eta = 0.18$ mm were used. For the SI direction value of $\beta = 0.43$, $\alpha = -0.28$ mm and $\eta = 0.32$ mm were used.[103] Bony anatomy-based IVP simulation was repeated using $S_{2D\text{-}MV}$.

Statistical analyses

Data were tested for heterogeneity between imaging techniques and radiotherapy centres. All data were tested for normality using the Shapiro–Wilk test. Shapiro–Wilk tests indicated some data were not normally distributed. The overall patient mean S_{DIFF} was tested for significant difference from zero using a one-sample Student's *t*-test. For S_{DIFF}, the difference in absolute S_{DIFF} between centres and imaging techniques was tested using Kruskal–Wallis followed by sensitivity analysis. Differences in overall mean patient systematic error M, population systematic error Σ and population random error σ between modalities, centres and imaging protocols were tested. For M, the difference from zero was calculated using a one-sample Student's *t*-test (all data) or Wilcoxon signed-rank test (per centre). For Σ, non-parametric Levene's test was used to test for difference in the variance of mean patient errors. For σ, the Kruskal–Wallis test was used to test for differences in patients' random errors. For all tests, data were considered to be significantly different if $p < 0.05$. Sensitivity analysis was performed by removing data from one centre at a time and repeating tests using Holm–Bonferroni correction. The time required for positional verification between clip-based IGRT and standard imaging was compared using the Wilcoxon signed-rank test.

Results

Study sample size calculation

Using computer simulations based on Fisher's test,[105] with 128 patients, it was possible to detect a 1-mm difference in the SDs from 2 mm to 3 mm, assuming correlation = 0.7, power = 80%, $\alpha = 0.05$; using the same analysis but assuming very low correlation (0.1), with 250 patients it was possible to detect the same difference (2 mm vs. 3 mm) in SDs (power = 80% and $\alpha = 0.05$).

Bony set-up error (S_{BA}) and clip set-up error (S_{clips}) of 112 patients from three different centres were initially collected for the review of the sample size.

The additional margin required if standard imaging verification is used instead of clip-based IGRT was calculated from S_{DIFF} in LR, SI and AP directions. These results are summarised for the three centres in *Table 5*.

TABLE 5 Mean and variance of S_{DIFF} for all 112 patients and individual centres

	Mean (cm)			Variance (cm)			Margin (cm)		
Centre	LR	SI	AP	LR	SI	AP	LR	SI	AP
All	–0.02	–0.03	–0.03	0.039[a]	0.043[a]	0.044[a]	0.54	0.59	0.59
CCC	0.03	0.03	0.01	0.043	0.030	0.022	0.56	0.50	0.42
ADD	0.00	0.02	–0.01	0.018	0.035	0.032	0.38	0.56	0.51
RMH	–0.03	–0.06	–0.04	0.044	0.046	0.052	0.57	0.60	0.63

ADD, Addenbrookes; CCC, Clatterbridge Cancer Centre.
a Data used in the sample size calculation.

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

$$S_{DIFF^2LR} = 0.039,\ S_{DIFF^2SI} = 0.043 \text{ and } S_{DIFF^2AP} = 0.044 \quad (12)$$

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

$$\text{Lower limit} = (n-1)\ S_{DIFF^2/\chi^2L} \text{ to upper limit} = (n-1)\ S_{DIFF^2/\chi^2U} \quad (13)$$

where χ^2_U = upper 2.5% point of chi-squared distribution for 111 degrees of freedom = 83.735, and χ^2_L = lower 2.5% point of chi-squared distribution for 111 degrees of freedom = 142.049. Hence, 95% CI for variance is 0.344(111 × 0.044/142.049) to 0.0583(111 × 0.044/83.735) and the 95% CI for SD = 0.1855 ($\sqrt{0.344}$) to 0.2415($\sqrt{0.0583}$). Based on this calculation, there was 95% confidence that the margin lay in the region of 0.4637 cm to 0.6037 cm (SD × 2.5). This is an overall width of 0.140 cm.

As the overall precision required was 0.05 (overall width of 0.1 cm), the above formula was applied for different sample sizes and produced an estimate that a sample size of 200 patients would be required for this study.

The bony anatomy set-up error (S_{BA}) and clip set-up error (S_{clips}) for 218 patients from five different centres were collected. Each centre uses a different imaging technique, as summarised in *Table 6*.

TABLE 6 Summary of imaging technique and patient accrual for each centre

Hospital	Centre	Imaging modality	Number of patients
RMH	A	CBCT	79
ADD	B	MV-CT (TomoTherapy)	40
CCC	C	2D-kVPI	39
CHE	D	2D-kVPI	30
IPS	E	2D-kVPI	30

ADD, Addenbrookes; CCC, Clatterbridge Cancer Centre; CHE, Cheltenham; IPS, Ipswich.

The intraobserver and interobserver errors were < 1.4 mm for all three imaging modalities. No significant difference was seen in interobserver errors between the five centres [analysis of variance (ANOVA), $p = 0.34$]. The overall mean error was found to be significantly different from zero for Addenbrookes (centre B) and Ipswich (centre E). At Addenbrookes, this is due to couch sag associated with TomoTherapy.[108] The Ipswich centre is investigating the cause of its non-zero mean error.

The systematic errors (Σ) and random errors (σ) using bony anatomy verification and titanium clip-based verification were mostly 2–4 mm across all centres. Individual centre and overall errors are summarised in *Table 7*. Individual patient systematic error using bony anatomy and surgical clips are compared in *Figure 10* using Bland–Altman analysis. The bias and limits of agreement ($\pm$ 1.96 SD) between bony anatomy and clip systematic errors were 0.0 ± 0.21 cm, 0.0 ± 0.26 cm and 0.1 ± 0.22 cm in the LR, SI and AP directions, respectively. Using linear regression analysis to compare bony anatomy and surgical clips systematic errors, 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 with clip-based verification. The difference in set-up errors using bony anatomy and clips (Σ_{DIFF} and σ_{DIFF}) for individual centres and all patients are summarised in *Table 8*.

The time required to perform bony anatomy- (T_{BA}) and clip-based (T_{clips}) image assessment are also summarised in *Table 8*. If all centres and all imaging techniques were considered there was no significant difference between bony anatomy- (T_{BA}) and clip-based (T_{clips}) imaging (Wilcoxon signed-rank, $p = 0.36$). The ranges in times were 8–240 seconds for clip-based IGRT image assessment and 8–178 seconds for bony anatomy-based image assessment.

The time required for image assessment varied with the type of imaging modality used. For all centres using 2D-kVPI modality, T_{BA} was greater than T_{clips} (Wilcoxon signed-rank test, $p < 0.001$). In contrast, centre A, using kV-CBCT, found median time $T_{clips} > T_{BA}$, 92 seconds compared with 26 seconds (Wilcoxon's signed-rank test, $p < 0.001$). No significant time difference was found for MV-CT (Wilcoxon signed-rank test, $p = 0.92$). The time to perform both clip- and bony anatomy-based image assessment varied significantly between the three centres using 2D-kVPI (Kruskal–Wallis, $p < 0.001$). Using sensitivity analysis, it was found that centre C required significantly less time to match both clips and bones than centres D and E.

TABLE 7 Systematic and random errors using bony anatomy and clip verification for each centre individually and for all centres combined

Centre	Number of patients	Total number of images	Bony anatomy random error, σ_{BA} (cm)			Bony anatomy systematic error, Σ_{BA} (cm)			Clips random error, σ_{clip} (cm)			Clips systematic error, Σ_{clip} (cm)		
			LR	SI	AP	LR	SI	AP	LR	SI	AP	LR	SI	AP
All	218	1574	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
A (kV-CBCT)	79	504	0.3	0.3	0.3	0.2	0.3	0.3	0.3	0.3	0.3	0.3	0.2	0.3
B (MV-CT)	40	200	0.4	0.3	0.4	0.3	0.2	0.4	0.4	0.3	0.5	0.3	0.2	0.4
C (2D-kVPI)	39	510	0.3	0.4	0.2	0.4	0.3	0.1	0.3	0.3	0.3	0.3	0.3	0.2
D (2D-kVPI)	30	180	0.3	0.4	0.3	0.2	0.3	0.3	0.3	0.3	0.3	0.2	0.2	0.2
E (2D-kVPI)	30	180	0.3	0.4	0.4	0.2	0.3	0.3	0.4	0.3	0.4	0.3	0.3	0.3

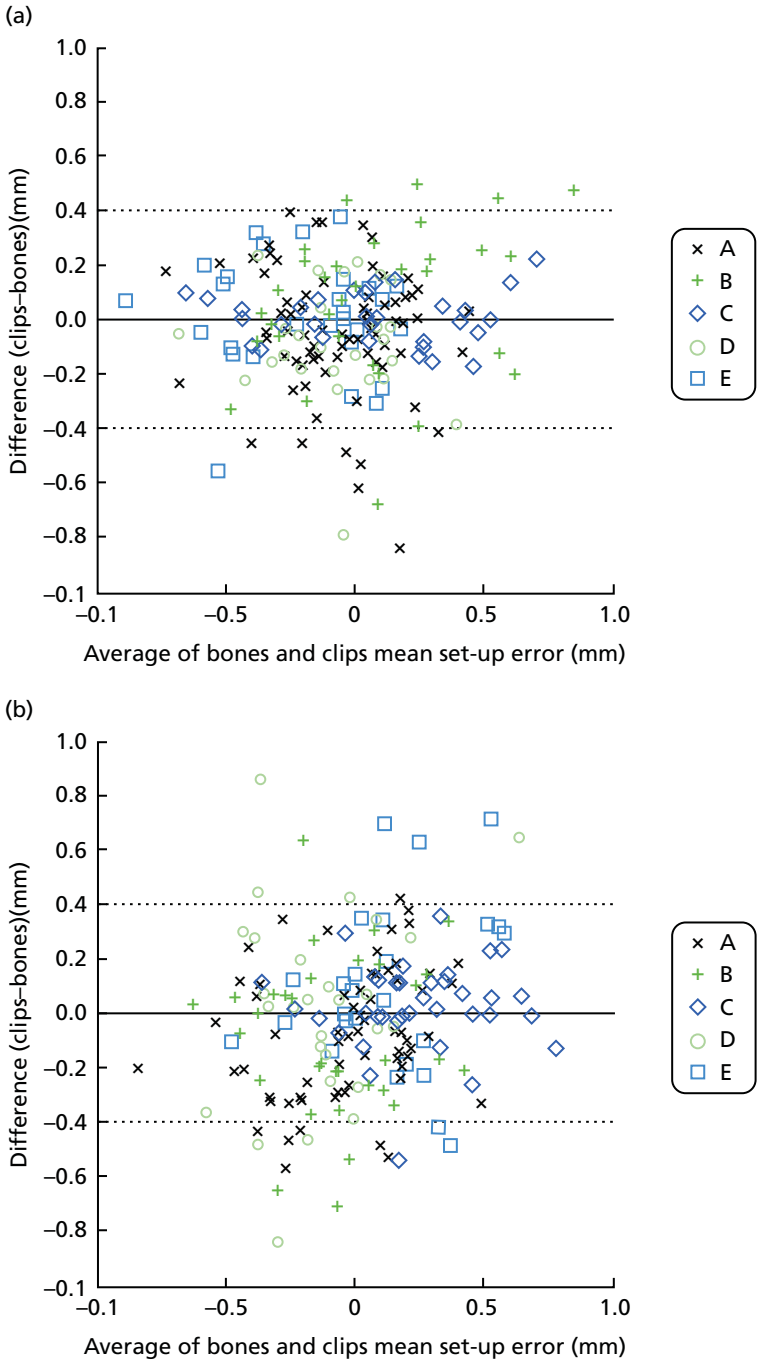

FIGURE 10 Bland–Altman plots of average of bony anatomy and clips mean set-up error vs. difference between mean clip set-up error and mean bony anatomy set-up error in the (a) LR, (b) SI and (c) AP directions. Solid line indicates mean difference between mean clip and mean bony anatomy set-up errors (the bias) and the dotted lines represent the limits of agreement (± 1.96 SD). (*continued*)

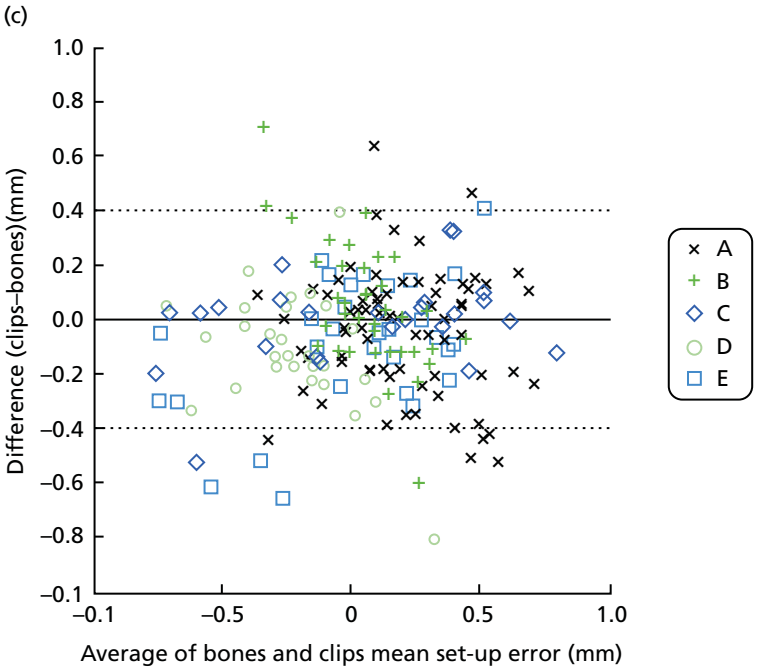

FIGURE 10 Bland–Altman plots of average of bony anatomy and clips mean set-up error vs. difference between mean clip set-up error and mean bony anatomy set-up error in the (a) LR, (b) SI and (c) AP directions. Solid line indicates mean difference between mean clip and mean bony anatomy set-up errors (the bias) and the dotted lines represent the limits of agreement (± 1.96 SD).

TABLE 8 Delta errors (difference between bony anatomy and clips, S_{DIFF}) 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

	Delta error (S_{DIFF}), mean absolute delta [cm (range)]				Time, median [seconds (range)]	
Centre	LR	SI	AP	3D vector	T_{BA}	T_{clips}
All	0.20 (0–1.7)	0.26 (0–3.2)	0.21 (0–2.0)	0.32 (0–10.2)	73 (8–240)	66 (8–178)
A (kV-CBCT)	0.19 (0–0.7)	0.24 (0–3.2)	0.22 (0–1.7)	0.28 (0–10.2)	26 (8–51)	92 (11–177)
B (MV-CT)	0.14 (0–0.7)	0.12 (0–1.2)	0.18 (0–1.3)	0.17 (0–2.0)	102 (70–230)	110 (25–178)
C (2D-kVPI)	0.23 (0–1.7)	0.29 (0–2.4)	0.20 (0–2.0)	0.38 (0–6.29)	22 (20–76)	16 (8–52)
D (2D-kVPI)	0.21 (0–1.3)	0.32 (0–1.3)	0.21 (0–1.0)	0.35 (0–2.2)	79 (60–154)	28 (20–85)
E (2D-kVPI)	0.20 (0–1.5)	0.31 (0–1.4)	0.23 (0–1.0)	0.36 (0–3.3)	110 (28–240)	34 (16–120)

There was a small but statistically significant difference in the difference between standard imaging and clip-based IGRT set-up errors (delta errors) between centres (Kruskal–Wallis, $p < 0.05$). The smallest delta error, $S_{DIFF,}$ was seen for centre B using MV-CT and the largest delta error was seen for centre C using 2D-kVPI (see *Table 8*). Using the Kruskal–Wallis test, a significant difference between delta errors was seen between different centres in the LR and SI directions ($p < 0.05$). No significant difference between delta error was seen among centres using 2D-kVPI modality. Non-parametric Levene's test and Bartlett's box test also indicated non-homogeneity of variance among centres (*Table 9*). After excluding data of patients with MV-CT imaging, the variances in delta error were similar between centres.

TABLE 9 Test of homogeneity of variances of delta errors from all centres, those using 2D-kVPI technique only and after excluding the centre using MV-CT

	p-value		
Centres	LR	SI	AP
All centres	0.00	0.00	0.22
2D-kVPI (CCC, CHE, IPS)	0.67	0.79	0.93
2D-kVPI and kV-CBCT (RMH, CCC, CHE, IPS)	0.85	0.05	0.92

CCC, Clatterbridge Cancer Centre; CHE, Cheltenham; IPS, Ipswich.

The PTV margins should be estimated using a sample group which is representative of the whole population. In view of significant heterogeneity 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% CI on the PTV margins is ~0.107 cm, giving a precision of ± 0.05 cm.

The mean (M), systematic (Σ) and random (σ) residual errors were calculated using the following IVPs:

(a) no-correction protocol – no imaging
(b) e-NAL using bony anatomy – e-NAL_{BA}
(c) e-NAL using clips – e-NAL_{clips}
(d) daily correction protocol (online correction) using bony anatomy – OL_{BA}
(e) daily correction protocol (online correction) using clips – OL_{clips}.

The results are summarised in *Table 10*. When using five images compared with 15 images, the mean difference in patient mean and SD of set-up errors was 0.006 cm and 0.013 cm, respectively. 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 than for bony anatomy verification, irrespective of the IVP method.

The study showed that, for kV-based imaging modalities, online IVP produces smaller errors than e-NAL for both clips and bones. Using online bony anatomy-based verification, systematic errors were larger than those for offline clip-based verification (e-NAL_{clips}), by up to 0.11 cm (non-parametric Levene's test, $p < 0.001$). Offline bony anatomy verification (e-NAL_{BA}) increased systematic error further by ~ 0.05 cm (non-parametric Levene's test, $p < 0.001$).

TABLE 10 Mean, random and systematic errors using different IVPs

	M (cm)			σ (cm)			Σ (cm)		
IVP	LR	SI	AP	LR	SI	AP	LR	SI	AP
No imaging	–0.06	0.00	0.00	0.34	0.30	0.34	0.27	0.25	0.32
OL_{clips} (2D-kVPI or kV-CBCT)	0.00	0.00	0.00	0.20	0.20	0.20	0.05	0.05	0.05
$eNAL_{clip}$ (2D-kVPI or kV-CBCT)	–0.01	0.00	0.02	0.30	0.30	0.32	0.08	0.07	0.10
OL_{BA} (2D-kVPI or kV-CBCT)	–0.01	–0.01	–0.03	0.30	0.38	0.33	0.16	0.18	0.12
$eNAL_{BA}$ (2D-kVPI or kV-CBCT)	0.00	0.01	0.05	0.32	0.35	0.32	0.19	0.23	0.19
OL_{BA} (2D-MV)	–0.64	0.27	–0.60	0.43	0.45	0.43	0.19	0.21	0.19
$eNAL_{BA}$ (2D-MV)	–0.45	0.21	–0.43	0.38	0.32	0.40	0.23	0.26	0.23

Two-dimensional megavoltage-based image verification increased systematic error for both online and offline protocols by an average of ≈0.3 cm (non-parametric Levene's test, $p < 0.001$). For offline imaging of bony anatomy (e-NAL_{BA}), the difference between kV and 2D-MV imaging was significant in the SI direction only. For 2D-MV imaging of bony anatomy, there was no significant difference in systematic errors between online and offline IVPs ($p = 0.12$).

The overall mean error (*M)* for 2D-MV IVPs was non-zero (see *Table 10*). This is probably because of the use of a simulation technique to generate 2D-MV imaging set-up errors and reflects the relationship between kV-CBCT and 2D-MV imaging set-up errors.

The estimated PTV margin using different IVPs is given in *Figure 11*. Based on this study, a tumour bed boost PTV margin of 1 cm is required if no imaging modality is used. If the standard bony verification technique is used (2D-MV imaging), a PTV margin of 0.8 cm is required. This can be reduced to 0.6–0.7 cm if 2D-kVPI- or kV-CBCT-based bony anatomy verification is used. The use of clip-based verification (clip-based IGRT) allows a 0.5-cm boost PTV margin for both online and e-NAL protocols.

Discussion

This large multicentre multimodality study has compared the set-up errors of bony anatomy and clip-based verification. It demonstrates that PTV boost margins of 5 mm are adequate if clip-based IGRT (2D-kVPI and kV-CBCT) is used for both online and offline IVP. However, if standard portal imaging (2D-MV) is used, an increase in PTV margin of ≈3 mm is necessary. The major strengths of the study include its large patient cohort, use of different imaging modalities and direct comparison of bony anatomy verification against clip-based verification.

In this study, the measured population random and systematic errors (for the tumour bed) were within 2–4 mm, suggesting that a PTV margin of 10 mm is required if no IVP is used. Similar results have been reported by Topolnjak *et al.*,[103] who reported kV-CBCT-measured systematic errors of 0.31 cm, 0.38 cm and 0.25 cm in the LR, SI and AP direction, respectively, based on 20 patients. This current study found that the anatomy-based verification underestimates patients' systematic error compared with

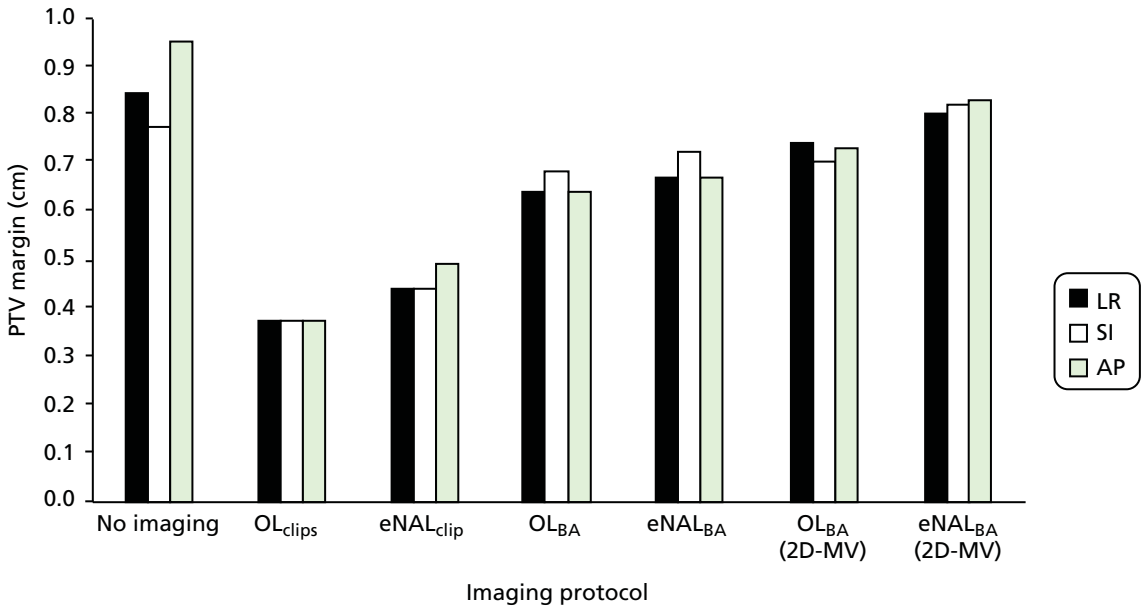

FIGURE 11 Tumour bed PTV margins required for the different imaging verification protocols considered in this study. Margins are given for the LR, SI and AP directions.

clip-based IGRT. Other authors have reported differences between set-up errors measured using bony anatomy and clip-based IGRT methods in patient cohorts.[109,110] Gierga *et al.*[109] used 2D-kVPI 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.*[110] reported a mean 3D delta error of 0.6 cm, using kV-CBCT in 10 patients. In the current study, 1379 images were analysed and the mean, median, and upper and lower quartile 3D vector difference between bony anatomy- and clip-based IGRT (delta) were 0.35 cm, 0.18 cm, 0.06 cm and 0.41 cm, respectively (see *Table 8*). This implies that the PTV margins of 5 mm (as used in the IMPORT-HIGH study) may be insufficient if bony anatomy is used as a surrogate for the tumour bed and that a larger PTV margin of ~8 mm is required if 2D-MV-based bony anatomy verification (online and offline protocols) is used.

Similar results have been reported by Penninkhof *et al.*[104] Two orthogonal planar kV images and one 2D-MV portal image were acquired for 80 patients throughout their radiotherapy. Surgical clips-based registration was performed on all kV images and set-up errors (systematic and random) were estimated for 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.

Time required for clip-based IGRT image assessment compared with standard imaging image assessment was imaging technique dependent. Clip-based IGRT verification was quicker than bony anatomy verification when using the 2D-kV imaging. For kV-CBCT, bony anatomy verification was quickest, most likely because automatic bone registration was used. Clip-based IGRT verification using MV-CT took the greatest amount of time (mean > 2 minutes). This may be due to poor visualisation of clips on MV-CT images.

The differences may be explained by differences in observers; at centre C images were matched by a senior radiographer (AB), at centre D by a physicist (EH) and a senior radiographer (RP) and at centre E by a physicist (EH) only.

Overall, differences in median times between bony anatomy and clip-based verification for each modality were small, the greatest difference being 76 seconds, for kV-CBCT. IMPORT image data were obtained retrospectively and, therefore, no times for image data acquisition were available. This was a limitation of our study; however, bony anatomy- (T_{BA}) and clip-based (T_{clips}) verification data are useful for any future cost–benefit analysis, which is beyond the scope of our study.

Conclusion

The work described in this chapter addressed the main objective of this programme of work, to compare the spatial accuracy of breast radiotherapy using clip-based IGRT and standard imaging during curative radiotherapy for early breast cancer. The study concluded that accuracy of clip-based IGRT was greater than standard imaging for breast boost to the tumour bed. The use of three common imaging protocols (online, NAL and e-NAL correction protocols) with clip-based IGRT improved accuracy by between 2 mm and 4 mm, compared with standard imaging. Using no-imaging protocol, the systematic set-up errors for tumour bed were 0.26 cm, 0.25 cm and 0.34 cm in LR, SI and AP directions, respectively. Using standard imaging (2D-MV portal images) with the e-NAL correction protocol, the systematic set-up errors for tumour bed were 0.23 cm, 0.24 cm and 0.28 cm in LR, SI and AP directions, respectively.

Two secondary objectives were also addressed: the decrease in safety margin given by clip-based IGRT and the time required to perform clip-based IGRT and standard image assessment. Using clip-based IGRT safety (PTV) margins were decreased compared with standard imaging. The study concluded that, using clip-based registration and the correction protocol, a PTV margin of $\leq$ 5 mm for the tumour bed is adequate. The time required for clip-based IGRT verification compared with bony anatomy (standard imaging) verification was technique dependent.

Chapter 5 The effect of patient and treatment characteristics on set-up accuracy

The work presented in this chapter uses data presented in *Chapter 4* and is directly related to the primary research objective. The study investigated differences in set-up accuracy using standard imaging between different patient groups, to determine if some patients may benefit more from clip-based IGRT than others.

Introduction

Treatment set-up errors and, hence, PTV margins may be influenced by characteristics of the patient and the treatment. Examples of such characteristics include breast size, tumour bed position and surgical closing technique. In addition, it is possible that different patient groups may require different PTV margins which depend on the type of set-up used, for example laser on skin marks or bony anatomy imaging. Currently, uniform tumour bed PTV (PTV-TB) margins are used across the whole patient population. If the type of imaging and/or patient and treatment characteristics do influence the size of treatment set-up errors, then uniform margins may be suboptimal. If margins are too large, this results in the unnecessary irradiation of normal tissues and, conversely, smaller PTV margins may lead to the risk of geographical miss of the tumour bed.

The aims of the study described in this chapter are to test whether or not a set of patient and treatment variables influence set-up errors and to explore the feasibility of individualised PTV-TB margins in breast boost radiotherapy.

Materials and methods

Data from 218 patients, from the cohort described in *Chapter 4*, were used in this work. These data consisted of images plus a set of characteristics hypothesised by five clinical oncologists (MM, AK, RJ, CEC and JY) and one breast surgeon (AT) to have an effect on set-up errors. These characteristics formed three groups: patient related, surgery related and treatment related.

The image data from the whole cohort ($n = 218$) were used to calculate treatment set-up errors based on (1) a laser-based set-up (no imaging) and (2) a bony anatomy-based set-up (standard imaging). The population systematic errors (Σ_{laser}, Σ_{BA}) were calculated from the variance of the individual patients' systematic set-up errors.

The patient, surgical and treatment characteristics are summarised in *Table 11*. Tumour bed locations were categorised into regions in the axial and sagittal plane as shown in *Figure 12*. Breast volume was obtained from the radiotherapy planning CT. Data on surgery, i.e. apposed (closed) or unapposed (open) cavity, and seroma were obtained from the surgical notes. A single radiation oncologist rated seroma visibility as not visible/subtle or easily visible and determined the presence of one or more clips placed at the posterior fascia and number of clips placed in the excision cavity.

Table 11 shows how the data were divided within each patient-, surgical- or treatment-related characteristic. For continuous characteristics, the data were dichotomised above and below the median value. For each of the characteristics, differences between population systematic errors between the groups were tested.

TABLE 11 Patient and treatment characteristics

Characteristics	Number of patients with data in each group	Total number of patients with data	Median value
Patient related			
Tumour bed axial location (1/2/3/4) (see *Figure 12*)	30/96/33/59	218	
Tumour bed SI location (1/2/3) (see *Figure 12*)	107/90/21	218	
Breast volume (above median/below median)	109/109	218	855 cm^3
Surgery related			
Seroma visibility (not visible/easily visible)	158/60	218	
Surgical closing technique (closed/open)	113/88	201	
Number of clips (above median/below median)	109/109	218	6
Clip in posterior fascia (no/yes)	40/178	218	
Radiotherapy			
Time: surgery to chemotherapy (days)	101/102	203	133
Time: chemotherapy to radiotherapy (days)	102/102	204	20
Trial arm (control or test)	72/146	218	

Characteristics have been categorised according to the information they provide. Median values are given for continuous characteristics.

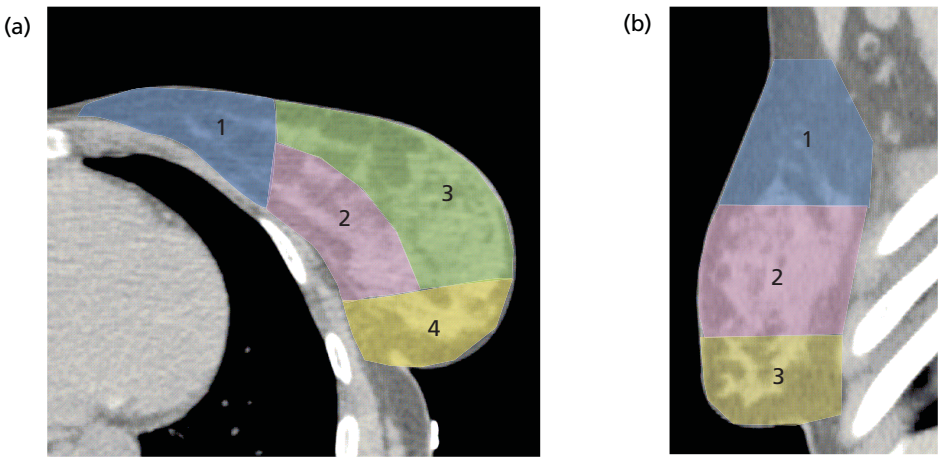

FIGURE 12 Schematic diagram to show (a) tumour bed location viewed on axial CT slice [1 (blue) = medial, 2 (pink) = chest wall, 3 (green) = anterior and 4 (yellow) = LR]; and (b) tumour bed location in the SI direction viewed on sagittal CT slice (1 = superior, 2 = middle and 3 = inferior).

Statistical analyses

Data were tested for normality using the Shapiro–Wilk test. Fisher's *F*-test or Levene's test was used to test for the significance of any difference in the variance of population systematic errors for both laser and bony anatomy set-up (Σ_{laser}, Σ_{bone}). Where the data were non-normal, the non-parametric Levene's test was used. Significance testing was performed with and without adjustment for multitesting (Holm–Bonferroni method). Associations between characteristics which gave significantly different systematic errors were investigated using the Wilcoxon and Kruskal–Wallis tests.

Results

A total of 1574 images were analysed to provide the set-up data. There was a minimum of five images per patient.

Table 12 presents results for the laser-based set-up; this includes only those results where differences were statistically significant. Of the 10 characteristics investigated, three showed a statistically significant difference between the laser-based systematic set-up errors Σ_{laser}. One of these was a patient characteristic (breast volume) and the other two were surgical characteristics (closing technique and seroma visibility). On application of Holm–Bonferroni correction, only seroma visibility gave a statistically significant difference between patient groups (in the AP and SI directions). The largest difference in Σ_{laser}, of 1 mm, was for the breast volume; all other differences were < 1 mm. Differences in Σ_{laser} for breast volume were significant only in the SI direction. No association between breast size, tumour bed position, seroma visibility and surgical closing technique was found.

Table 13 gives the results for the bony anatomy-based set-up, again only for characteristics where differences were statistically significant. There were only two characteristics where this was the case, both

TABLE 12 Systematic (Σ_{laser}) laser set-up (no imaging) errors for patients grouped using patient- and treatment-related characteristics

Characteristic	Group 1	Σ_{laser} (cm)	Group 2	Σ_{laser} (cm)	*p*-value	Direction and magnitude of difference in $\sum$ (cm)
Breast volume	< 855 cm^3	0.25	≥ 855 cm^3	0.32	0.03	SI 0.07
Seroma visibility	Not visible/subtle	0.28	Easily visible	0.35	0.02	LR 0.07
	Not visible/subtle	0.26	Easily visible	0.32	0.002	SI 0.06
	Not visible/subtle	0.31	Easily visible	0.41	0.005	AP 0.10
Surgical closing technique	Closed	0.27	Open	0.33	0.02	LR 0.06
	Closed	0.25	Open	0.32	0.04	SI 0.07

For Σ_{laser}, *p*-values from the non-parametric Levene's test are given. Values are shown only for characteristics that gave a significant difference between patient groups ($p < 0.05$, without Holm–Bonferroni adjustment). The directions in which differences occur are indicated.

TABLE 13 Systematic standard imaging set-up errors (Σ_{BA}) for patient groups determined using patient- and treatment-related characteristics

Characteristic	Group 1	Σ_{BA} (cm)	Group 2	Σ_{BA} (cm)	*p*-value	Direction and magnitude of difference in $\sum_{BA}$ (cm)
Tumour bed axial location	1, 2 and 3	0.21	4	0.27	0.04	LR 0.06
Tumour bed axial location	1	0.16	2, 3 and 4	0.23	0.002	AP 0.07
Breast volume	< 855 cm^3	0.19	≥ 855 cm^3	0.27	0.015	SI 0.08

p-values for non-parametric Levene's test are given. Values are shown only for characteristics that gave a significant difference in systematic bony anatomy verification error between patient groups ($p < 0.05$, without Holm–Bonferroni adjustment). The direction in which errors were different is indicated.

of which were patient related: breast volume and tumour bed axial position. Both characteristics gave significant differences when Holm–Bonferroni correction was applied, although tumour bed axial location no longer affected set-up error in the LR direction. All differences in population systematic error Σ_{bone} were < 1 mm. Again, breast volume differences were significant in the SI direction and neither of the other directions. No radiotherapy characteristic, clip placement or number, or tumour bed SI position was related to population systematic set-up errors in this study.

Discussion

The purpose of this work was to identify whether or not a set of patient and treatment variables influences set-up errors, and to explore the feasibility of individualised tumour bed PTV margins in breast boost radiotherapy using no imaging or standard imaging. The study has shown that two patient characteristics (breast volume and TB axial location) and two surgical characteristics (closing technique and seroma visibility) affect laser and bony anatomy-based set-up accuracy. No radiotherapy characteristics were found to have a significant effect on set-up errors.

Population systematic errors for both laser and bony anatomy set-up (Σ_{laser} and Σ_{BA}) were greater (by 2 mm and 1 mm) for patients with a breast volume greater than 850 cm^3, but this was statistically significant only for the SI direction of movement. This may be because breast tissue moves more independently of bony anatomy and skin-based tattoos in larger-breasted women. Hasan *et al.*[9] had previously reported a weak correlation between the mean patient set-up error, measured using bony anatomy, and breast volume ($n = 27$ and $p = 0.02$). They did not investigate, however, the association of the population systematic set-up error with breast volume as we have done in this work.

If patients are set up at the time of treatment with lasers matched to skin marks, then those patients with easily visible seroma and open surgical cavities have a statistically significantly increased population systematic error, although this is small in magnitude (0.6–1.0 mm depending of the direction of movement). It is possible that this increase is due to changes in the location of the clips between the planning CT and treatment because of shrinking seroma or clip migration.[111] If this were the case, then Σ_{BA} would also be affected by seroma visibility and surgical closing technique. A greater value for Σ_{BA} was not observed, which indicates that the observed differences in Σ_{laser} are probably not due to changes in clip location.

If patients are set up using standard imaging, we found that population systematic errors were influenced by the tumour bed location. Patients with medially located tumour beds had smaller Σ_{BA} in the AP direction, while patients with laterally located tumour beds had larger Σ_{BA} in the LR direction, by 0.6 mm and 0.7 mm, respectively. It is likely that there is little movement of medial breast tissue compared with bony anatomy and greater movement of LR breast tissue, which may explain these results. This is also supported by Hasan *et al.*,[9] who found correlation of 3D bony anatomy verification errors with distance from the chest wall ($p = 0.003$). Similarly, Topolnjak *et al.*[98] showed that the distance of the tumour bed from the chest wall was correlated with the difference between tumour bed set-up error for chest wall and the breast surface ($r = 0.476$, $p = 0.034$).

All differences in population systematic error were small (< 1 mm); however, these systematic errors make the greatest contribution to PTV-TB margins (PTV margin $= 2.5\Sigma + 0.3\sigma$).[98] The largest difference in systematic errors (1 mm) was observed with a laser-based set-up in the AP direction between patients with easily visible or not visible seroma ($\Sigma_{laser} = 0.31$ cm for smaller-breasted patients compared with $\Sigma_{laser} = 0.41$ for larger-breasted patients). This gives a difference in PTV margin of 2.5 mm and indicates that larger margins for patients with large seroma may be appropriate for laser-based set-up. All other changes in margins were estimated to be ≤ 2 mm.

This study used univariate analysis to identify several variables which may be used to group patients with smaller or larger systematic errors. A limitation of this study is that no multivariate analysis has been employed. However, no standard multivariate statistical model was identified which was suitable to test the interaction of multiple variances. Care should be taken when interpreting *p*-values, presented in *Tables 12* and *13*, as these have not been adjusted for multiple testing. Using one method to control false-positive results, Holm–Bonferroni correction, differences between patients grouped using seroma visibility and tumour bed axial position remain significant. A further limitation of our study may be the use of only one observer to grade seroma visibility. In Lee *et al.*,[112] seroma visibility in 20 patients was scored by radiation oncologists and radiographers using the Clarity Visualisation Score (CVS), which grades seroma visibility on a scale of 1 to 5. There was a 0.2 difference in the median grade between the two groups (3.8 vs. 3.6). Among radiation oncologists, all grades agreed with median CVS within 1 grade except in 1 of 20 cases. These variations among observers are small and it is expected would be smaller still if only two ranks are used, as is the case in our study. Consequently, we expect any observer error to be small. Furthermore, to minimise intra-observer error, the radiation oncologist (MM) scoring seroma used a predefined protocol and has previously outlined/scored seroma visibility on nearly 800 patients.[113]

The consequences of small changes in PTV margins have been investigated and are described in *Chapter 6*. Reductions in margins may reduce the dose to normal tissues such as heart and lungs. Darby *et al.*[114] have recently reported evidence of a zero threshold for cardiac toxicity; therefore, even small changes in mean heart dose are of importance given the large numbers of patients receiving radiotherapy for breast cancer.

Conclusions

Patient- and surgical-related characteristics have limited effect on population systematic errors derived from laser-based (no imaging) and bony anatomy (standard imaging) set-up methods. Four groups have been identified that may benefit modestly from reduced PTV margins: women with breast volume of $< 850\ cm^3$ and those with invisible/subtle seroma, closed cavities or medial tumour bed locations.

Chapter 6 The impact of image guidance on dose distributions in breast boost radiotherapy

This work described in this chapter investigates the decrease in normal tissue irradiated to 95% of the breast boost dose if standard imaging is used, compared with clip-based IGRT, a secondary research objective of this study. It also investigates the effect of clip-based IGRT on dose to the heart and lungs, and the effect of the IMPORT-HIGH trial arm on the volume of tissue spared.

Introduction

Whole-breast irradiation following BSC is a standard treatment for patients with breast cancer. As part of their radiotherapy, patients at high risk of recurrence receive a boost dose to the region around the tumour bed.[115] Evidence shows that accurate localisation of the tumour bed can be achieved only if internal markers are used to indicate its position on imaging, particularly CT images.[116,117] This approach to improve localisation allows conformal photon dose distributions to be used to deliver the tumour bed boost dose while minimising dose to normal tissues. This further enables studies of dose escalation using sequential or integrated boost techniques.[118,119]

Accurate patient set-up and in-treatment verification are essential for the delivery of conformal radiotherapy and higher boost doses. As discussed in *Chapters 4* and *5*, standard verification imaging for breast radiotherapy uses bony anatomy and often the outline contour of the breast to match electronic portal images acquired at megavoltage energies to pretreatment images – often DRRs. This is widely available and requires a surrogate for the tumour bed, such as the patient's ribs, as neither the tumour bed nor implanted surrogate markers are visible on megavoltage images. Gold markers are visible on megavoltage images and have been demonstrated in this setting, but are not widely used surrogates.[99] Kilovoltage energy imaging is necessary to visualise surgical clips, hence determining tumour bed positions most accurately and bringing the potential to decrease PTV-TBs.

Previous studies have shown that PTV-TB margins of 5 mm can be achieved[99,120] using clip-based IGRT. The purpose of the work in this chapter was to evaluate the dosimetric impact in terms of doses to breast tissue and organs at risk as a result of the use of clip-based IGRT and the reduced margins it allows in breast boost radiotherapy.

Materials and methods

The CT data sets, used for treatment planning, for patients treated in the IMPORT-HIGH trial were selected sequentially from an alphabetically ordered list. The patients were treated between July 2009 and December 2011. As discussed above, the patients had surgical clips implanted close to the tumour bed during BCS. Two target volumes were defined. First, a clinical target volume (CTV) was defined for the tumour bed (CTV-TB). This encompassed the surgical clips, plus any seroma and architectural distortion. Second, a target volume for the whole breast was defined from the extent of the treatment fields for the whole breast. This excluded the lung and rib cage and tissue within 5 mm of the surface of the skin. On the treatment plans, organs at risk were delineated. These were the ipsilateral and contralateral lung and heart and contralateral breast.

The CTV-TB structure was expanded to create two PTVs for each data set as shown in *Figure 13*, the first using a 5-mm margin as required by IMPORT-HIGH. We have previously described[99,120] how the use of image guidance based on imaging the positions of markers implanted in the tumour bed, coupled to set up correction strategies, reduces population set-up errors to the extent that a 5-mm PTV-TB margin may

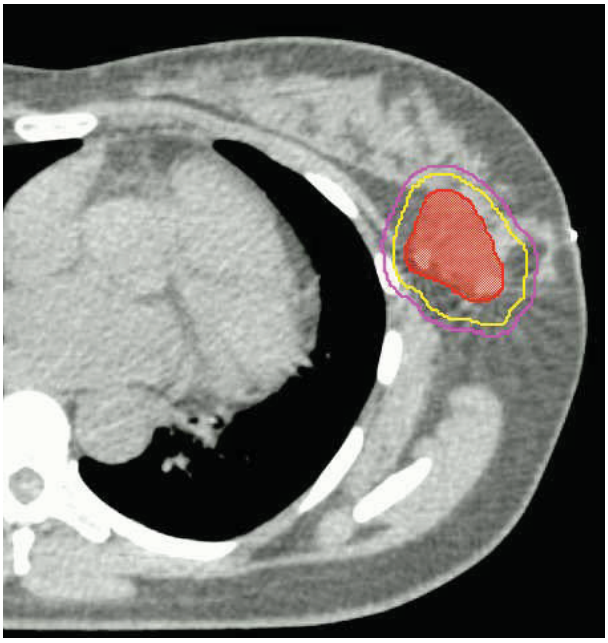

FIGURE 13 Section through a patient's treatment plan showing CTV-TB (red), PTV-TB = 5 mm (yellow) and PTV-TB = 8 mm (pink).

be achieved. The second PTV-TB margin was 8 mm and was derived from the analysis presented in *Chapter 4* for bony anatomy-based set-up measurement. Systematic errors in patient set-up were determined based on measurements from images of the first three fractions and a correction applied on fraction 4. This approach enabled a comparison between standard bony anatomy-based verification and the clip-based IGRT approach.

Thirty patients were planned using a sequential, conformal photon boost to the tumour bed and 30 using the SIB technique. The sequential boost technique delivered a phase 1 WBRT dose of 40 Gy in 15 fractions followed by 16 Gy in eight fractions to the tumour bed boost volume only for phase 2. The concomitant boost technique involved delivering 15 fractions with a total dose of 36 Gy to the whole breast using tangential fields, plus 40 Gy to the partial-breast volume and an escalated dose to the tumour bed via coplanar conformal fields. The escalated dose was 48 Gy or 53 Gy (15 patients each) depending on randomisation[44] (see *Figure 2*). The criteria for plan assessment and constraints on the organ at doses used for the IMPORT-HIGH trial were used to guide the planning (see *Table 14*). Plans were generated using the Philips Pinnacle[3] treatment planning system (v8.0 and v9.0, Philips Medical System, Eindhoven, the Netherlands). The forward treatment planned method reported by Donovan *et al.*[121] was used, with the collapsed cone convolution dose calculation algorithm on a 0.25 cm × 0.25 cm × 0.25 cm calculation grid. The beam quality used was 6 MV in most cases.

Statistical analysis

For the analysis of the treatment plans produced to determine the impact of clip-based IGRT on the breast boost plans, the main metric used was the volume of tissue receiving 95% of the tumour bed dose. Data were also collected on the doses to the lungs, heart and contralateral breast from the plan assessment criteria listed in *Table 14*. Mean heart and lung doses were also collected. The data were tested for normality and the Wilcoxon signed-rank test was used to test for statistical significance of the differences in the various metrics between the plans with 5-mm and 8-mm PTV-TB margins. Data were dichotomised by tumour bed laterality, and the Mann–Whitney *U*-test statistic was used to determine the significance of any differences observed. This work is novel and there were no similar studies in the literature on which to base estimates for sample size calculations. The heart is one of the most important organs at risk in breast radiotherapy. The results from planning the first 10 cases were used to estimate a sample size of 58 cases, which gave 90% power to determine a difference of 0.2 Gy at a significance level of 0.05. The additional cases were included to allow for any unforeseen problems with the data.

TABLE 14 Radiotherapy treatment planning constraints for IMPORT-HIGH

Volume	Minimum dose	Median dose	Maximum dose
Sequential boost			
Whole breast	**> 90% volume, > 36 Gy**	4–44 Gy	**< 5% volume, > 56 Gy**
PTV-TB	**> 95% volume, > 53.2 Gy**	**55.5–56.5 Gy**	**< 5% volume, > 60 Gy**
Concomitant boost			
Whole breast	**> 90% volume, > 32.4 Gy**	34–37 Gy	**< 5% volume, > 40 Gy**
Partial-breast PTV	**> 90% volume, > 36 Gy**	40–44 Gy	
PTV-TB	**> 95% volume, > 45.6 Gy or 50.4 Gy**	**47.5–48.5 Gy or 52.5–53.5 Gy**	**< 3% volume, > 51.4 Gy or 56.7 Gy**
Organs at risk	**Dose (Gy)**	**Maximum allowed volume (%)**	
Ipsilateral lung	18	**15**	
Contralateral lung	2.5	**15**	
Heart	13	**10**	
Contralateral breast	Mean dose < 0.5 Gy	Permitted maximum mean dose 1.5 Gy	

Note
Bold text indicates mandatory constraints. Where two dose levels are given they are for the 48-Gy or 53-Gy test arm doses.

Results

Of the patients recruited to this study, 35 had left breast disease and 25 had right breast disease. The median CTV-TB volume was 10.2 cm^3 (range 2.4–205.0 cm^3). There was no statistically significant difference in the CTV-TB or PTV-TB volumes (grouped into 5- and 8-mm margins) between the sequential and concomitant boost plans, or the concomitant boost plans at boost doses of 48 Gy or 53 Gy.

Table 15 summarises the volumes of breast tissue and the percentage of whole-breast volume receiving 95% of the dose prescribed to the tumour bed. There was a statistically significant difference ($p < 0.01$) between the volumes of breast tissue receiving a high dose for the two types of plan, with the volumes larger in the sequential boost plans. The magnitude of the volume changes between a PTV-TB of 5 mm and a PTV-TB of 8 mm was not different between (1) sequential and concomitant boost plans; (2) left and right breast plans; and (3) the 48-Gy and 53-Gy boost doses. The different data for sequential and concomitant boost treatments were combined and the median decrease in the high-dose volume for clip-based IGRT was found to be 29 cm^3 (range 11–193 cm^3). This equates to an additional 3.3% (median value), up to a maximum of 11.8%, of the whole-breast volume spared high-dose irradiation from these boost techniques, if clip-based IGRT is used.

All dose metrics for the organs at risk increased with the use of the 8-mm margin for standard verification, compared with the clip-based IGRT margins. This was as anticipated and a modest effect (*Table 16*). Of the various metrics, only mean heart dose and $V_{13\,Gy}$ for the heart had a statistically significant relationship with tumour bed laterality ($p < 0.01$), with higher values in the left breast group.

TABLE 15 Volumes of the breast receiving 95% of prescribed dose from plans based on 5-mm and 8-mm PTV-TB margins

	Breast volume receiving 95% of prescribed dose, median (range)		
Prescription	**PTV-TB = 5 mm**	**PTV-TB = 8 mm**	**Difference**
High-dose volume (cm^3)			
Sequential boost	91 (30–863)	125 (42–1005)	**33 (11–193)**
Concomitant boost	60 (19–228)	87 (30–260)	**23 (11–66)**
Both combined	69 (19–863)	100 (30–1005)	**29 (11–193)**
Percentage of whole-breast volume (%)			
Sequential boost	10 (4–35)	14 (5–41)	**4 (2–12)**
Concomitant boost	8 (2–19)	11 (4–24)	**3 (1–6)**
Both combined	3.0 (1–6)	4 (2–12)	**3 (1–12)**

Data are given as median (range) and presented in absolute volume (cm^3) and as a percentage of the whole-breast volume. Differences between 95% volumes for the two PTV-TBs were statistically significant ($p < 0.01$) and are given in column 4.

TABLE 16 Dosimetric data given as median (range) for each of the assessment criteria

	Dosimetric data, median (range)		
Dose metric	**PTV-TB = 5 mm**	**PTV-TB = 8 mm**	**Difference**
Ipsilateral lung V_{18Gy} (%)	9.6 (1.9 to 27.6)	10.0 (2.3 to 27.8)	0.3 (–0.9 to 5.0)
Ipsilateral lung mean dose (Gy)	5.6 (2.6 to 11.3)	6.1 (2.8 to 11.5)	0.3 (–0.7 to 2.7)
Contralateral lung $V_{2.5Gy}$ (%)			
Sequential boost	0.0 (0.0 to 12.2)	0.1 (0.0 to 13.9)	0.0 (–3.3 to 7.5)
Concomitant boost	1.6 (0.0 to 13.4)	3.2 (0.0 to 17.4)	1.0 (–2.5 to 16.1)
Contralateral lung mean dose (Gy)	0.4 (0.1 to 1.2)	0.5 (0.1 to 3.3)	0.1 (–0.2 to 3.1)
Contralateral breast mean dose (Gy)	5.0 (0.0 to 1.8)	5.0 (0.0 to 1.4)	0.1 (–1.3 to 0.4)
Heart mean dose (Gy)			
Right breast cases	1.2 (0.4 to 2.2)	1.4 (0.5 to 2.6)	0.2 (–0.3 to 1.6)
Left breast cases	1.9 (0.6 to 5.1)	2.1 (0.6 to 6.0)	0.2 (–0.2 to 1.0)
Heart V_{13Gy} (%)			
Right breast cases	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.2)	0.0 (0.0 to 0.2)
Left breast cases	0.2 (0.0 to 5.5)	0.4 (0.0 to 6.3)	0.1 (–0.1 to 2.4)

V_{18Gy}, percentage of lung volume receiving 18 Gy; V_{13Gy}, percentage of heart volume receiving 13 Gy. All differences were found to be statistically significant ($p < 0.01$).

In the case of the clip-based IGRT margins of 5 mm, 56 of the 60 cases met all the treatment planning criteria (see *Table 14*). The minimum dose coverage of the tumour bed was between 91% and 95% in the other four cases (two sequential and two concomitant boost). These were all left breast cases and had the tumour bed in close proximity to the chest wall, hence the PTV-TB extended into the lung and the heart (*Figure 14*). Thus, a compromise was accepted between target coverage and heart dose for the

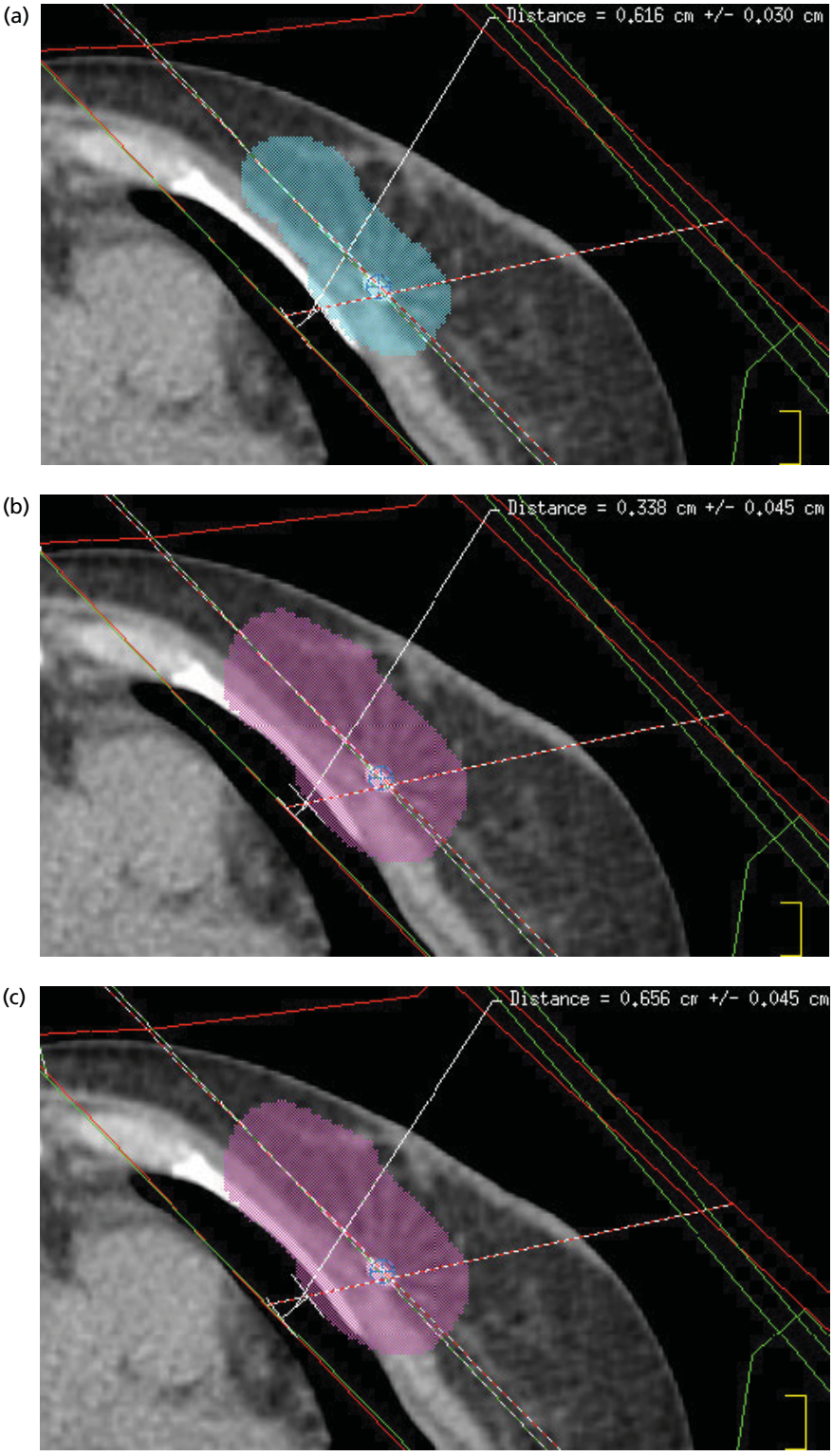

FIGURE 14 (a) An original PTV-TB with 5-mm margin and in close proximity to the lung. When PTV-TB is increased by a further 3 mm it expands into the lung; (b) achieving coverage requires an increase in the width of the tangential fields by 4 mm; and (c) which in turn increases the dose to the heart.

clinical treatment. In addition, in one of the two concomitant boost cases that failed the planning criteria, the maximum volume limit for the highest dose to whole breast was exceeded (9.7% compared with 5%). This patient had a large CTV-TB of 49 cm^3, whereas the median CTV-TB volume for the patients in the study was 9 cm^3, hence the difficulty in obtaining a dose distribution that met all of the treatment planning requirements.

As the planning objectives used in the IMPORT-HIGH trial were based on a PTV-TB margin of 5 mm, it was likely that increasing this margin to 8 mm would cause more plans to fail the criteria. This was found to be the case with four sequential boost plans and 10 concomitant boost plans breaching mandatory planning constraints. In all of the sequential boost cases and eight of the concomitant cases, the PTV-TB coverage was $< 95\%$ but $> 91\%$. In three of the concomitant boost cases, the maximum dose criterion in the whole-breast volume was exceeded by 2% in two cases and 5% in the third. In nine of the concomitant boost cases, the median dose constraint to the partial-breast volume of 40–44 Gy was exceeded by between 0.5 Gy and 3.7 Gy.

Discussion

The work presented in this chapter evaluated the impact of clip-based IGRT on normal tissue doses in breast radiotherapy. We have seen in *Chapters 4* and *5* that clip-based IGRT enables smaller PTV margins owing to the reduction of set-up errors across the patient population. The reduced margins achievable with the use of internal markers (and associated image guidance) led to a reduction of 29 cm^3 (range 11–193 cm^3) in the volume of breast tissue receiving a high dose. This is a consequence of the ability to reduce the PTV-TB margin from 8 mm to 5 mm.

In *Chapter 2*, we discussed the evidence for a dose–volume relationship for normal tissue toxicity in breast tissue. This is still an open question and the dose–volume constraints needed are still a subject of research.[19] Hence, it is unclear what outcome effect is expected at the dose levels and volumes reported in this chapter. In the EORTC study of Bartelink *et al.*[2] it was reported that a WBRT dose of 50 Gy followed by a boost dose of 16 Gy resulted in the 10-year risk of fibrosis increasing by approximately 15% from 13.2% (for the no-boost group) to 28.1% (for the boost group). Patients in this study were treated with a PTV margin of 15 mm compared with the much smaller values of 5 mm and 8 mm discussed here. The sequential boost prescription used in this study was 16 Gy in 2-Gy fractions and, hence, is expected to lead to a lower rate of fibrosis than that in the EORTC study, as a result of the smaller high-dose volumes.

The larger PTV-TB margin had a modest impact on the calculated doses to organs at risk for both types of boost plans: sequential and concomitant. The majority of the therapeutic dose was delivered using standard tangential fields, which maintained organ at risk sparing in these complex situations for all PTV-TB margins. The recent cardiac risk study of Darby *et al.*[114] suggests that small changes in heart dose are important as a consequence of the linear relationship between mean heart dose and major coronary events (MCEs). Hence, given the tens of thousands of women treated each year with radiotherapy for breast cancer, a modest reduction in heart dose may impact significantly on the rate of MCE in the survivor population.

One finding of this study was the increased difficulty in meeting the planning requirements for the boost with an increase in the PTV-TB margin of only 3 mm. This had most impact for the concomitant boost plans, in which one in three patients failed at least one of the dosimetry criteria.

The compromised median dose to the partial breast in nine cases is particularly relevant for the IMPORT-HIGH trial, which requires discrimination between the three dose levels of the whole breast, partial breast and tumour bed. This work shows that image guidance is necessary to achieve this level of dose discrimination – an additional benefit to reduced normal tissue doses.

Conclusions

The reduction in normal tissue irradiated when using clip-based IGRT was modest (29 cm^3). For breast radiotherapy methods involving a complex boost technique, image guidance is important as it allows the dose levels to be sufficiently discriminated. Its use allows some reduction in the dose to the breast, heart and lung for both sequential boost and concomitant boost approaches.

Chapter 7 Discussion and conclusions

The previous five chapters have summarised the key outcomes of this Efficacy and Mechanism Evaluation programme. The chapters have been grouped by the key stages of the programme. *Chapters 2* and *3* discussed the evidence for a dose–volume effect in breast radiotherapy following BCS. *Chapters 4–6* discussed the evaluation of clip-based IGRT in this setting.

The critical review in *Chapter 2* explored the evidence in the literature for a dose–volume effect in normal breast tissue. The review found differing results from studies addressing the relationship between irradiated breast volume and late breast tissue complications. For example, Borger *et al.*[14] reported strong evidence for a volume effect. They found that, for every 100-cm^3 increase in the boost volume, the risk of fibrosis increased by a factor of 4 and a twofold increase in boost volume results in an 11% reduction in tolerance dose (NTD_{50}). Borger's study used LDR iridium brachytherapy implants, which produce a very high-dose region within the implant and rapid fall-off of dose outside the implant. The other studies discussed in *Chapter 2* include PBI and IORT trials and matched case series that compared PBI with WBI. While these other studies generally suggested some evidence of a relationship between volume irradiated to high dose and NTCP, they did not quantify the volume effect. The brachytherapy and intraoperative dose distribution can differ from the external beam radiotherapy (teletherapy) and, therefore, it is unclear whether or not these results can be extrapolated to external beam techniques. Several ongoing external beam radiotherapy breast trials are designed to provide further data in this direction, for example IMPORT-LOW[43,44] and the Danish Breast Cancer Cooperative Group trial[49] are trials which compare PBI with WBI, and IMPORT-HIGH[43,44] is investigating the effects of three dose regions throughout the breast using IMRT for dose delivery, imaged with clip-based IGRT.

In *Chapter 3*, we addressed a secondary research objective of this study, i.e. to estimate the reduced risk of late adverse effects resulting from the smaller tissue volume irradiated, using data generated and published from earlier randomised trials conducted by members of our collaboration.

Individual patient data of 5856 patients from the Cambridge trial[67,77] and EORTC trial[67,77] were used for the analysis with moderate to severe breast fibrosis as the radiotherapy toxicity end point. Fits to the data using two standard models of NTCP (the LKB[79] and Niemierko[80] models) produced a volume parameter, '*n*', close to zero, suggesting that, for moderate and severe fibrosis, the breast acts as an organ with serial structure (as discussed in *Chapter 3*). These results were successfully validated on an independent data set and indicated that, for moderate to severe breast fibrosis, the maximum radiotherapy dose is the most important parameter, rather than volume of tissue irradiated. Based on this model, a change in volume of normal tissue irradiated will not change the risk of breast fibrosis. Clearly, any model has limitations and the mature results from the clinical trials addressing this question are awaited.

In *Chapter 4*, we addressed the primary research objective of this study, namely the difference in accuracy of clip-based IGRT and standard imaging using bony anatomy. We also addressed two secondary objectives: (1) the reduction in safety PTV margin and (2) the time required for clip-based IGRT and standard imaging. We presented results of the analysis of the impact of clip-based IGRT on set-up errors and treatment margins in patients recruited to the IMPORT-HIGH study. To our knowledge, this is the largest study to evaluate clip-based IGRT in the breast radiotherapy setting. This study found that clip-based IGRT was more accurate than standard imaging. The population systematic error was between 2 mm and 4 mm greater with standard imaging. A key finding of the study was that a PTV boost safety margin of 5 mm is sufficient if clip-based IGRT is employed. The clip-based IGRT approach was based on imaging the positions of titanium clips implanted in the tumour bed at the time of BCS. In contrast, standard imaging using bony anatomy required an 8-mm PTV boost safety margin, and no imaging (i.e. set-up based on laser-based alignment of the patient surface) required a 10-mm margin. These results indicate that, for patients receiving concomitant tumour bed boost, a margin less than 8 mm cannot be safely used without clip-based IGRT as there is a risk of geographical miss of the tumour bed being treated

within the high-dose region. The difference in time required to perform clip-based IGRT and standard image assessment was technique dependent. Clip-based IGRT was quicker than standard imaging when using 2D-kVPI technique, but not when using cone beam CT imaging.

Chapter 5 explored the factors influencing the primary objective. It tested the hypothesis that some characteristics of the patient and treatment may influence (1) the relationship between the set-up error measured with clip-based IGRT and with bony anatomy imaging (standard imaging) and (2) the relationship between the set-up error measured with clip-based IGRT and with laser-based alignment (no imaging). Patients with larger breasts required a larger PTV margin for both standard imaging and no imaging. Seroma visibility and surgery technique both affected no-imaging set-up errors, whereas tumour bed position affected standard imaging-based set-up errors. The work implies that clip-based IGRT may be of greater benefit than standard imaging or no imaging for some patient groups, and that treatment margins can be modified accordingly if clip-based IGRT is not available.

Chapter 6 evaluated the reduction in volume of normal tissue receiving 95% of the high-boost dose of radiation when clip-based IGRT is used compared with standard imaging, which is a secondary objective of this study. The consequences of the results of the clip-based IGRT study on treatment planning were evaluated. The main quantitative finding was that the use of clip-based IGRT allowed the volume of breast tissue irradiated to a high dose to be reduced by 29 cm^3 (with a range of 11 cm^3 to 193 cm^3) for the 60 cases studied. The use of smaller PTV margins with clip-based IGRT also allowed a small reduction in the radiotherapy dose to the contralateral breast, heart and lung. The larger margins needed with standard imaging meant that the treatment planning constraints for the dose boost could not be met in some cases.

In conclusion, this research demonstrates the benefits of clip-based IGRT over standard imaging, with a reduction in PTV margins. Margins less than 8 mm cannot be safely used without clip-based IGRT for patients receiving concomitant tumour bed boost as there is a risk of geographical miss of the tumour bed being treated within the high-dose region. In principle, these smaller, but accurately placed, margins may influence local control rates, but this needs to be evaluated from mature clinical trial data in the future. We have not been able to develop a model that can predict the effect of irradiated volume on breast tissue toxicity, but mature results from the ongoing clinical trials may provide a definitive answer.

Acknowledgements

Contributions of authors

Emma J Harris (Research Physicist and Principal Clinical Scientist): study design, physics input and analysis for all aspects, and drafts of physics aspects of report.

Mukesh Mukesh (Clinical Research Fellow): clinical input and analysis for all aspects, and drafts of clinical oncology aspects of report.

Rajesh Jena (Clinician Scientist and Consultant in Radiation Oncology): study design and clinical oncology input to all aspects.

Angela Baker (Therapy Research Radiographer): data acquisition and analysis.

Harry Bartelink (Professor, Consultant Clinical Oncologist): input to analysis of NTCP parameters for breast fibrosis.

Corrinne Brooks (Planning Radiographer): treatment planning aspects.

June Dean (Therapy Radiographer): data acquisition and analysis.

Ellen M Donovan (Principal Clinical Scientist): treatment planning and margin modelling.

Sandra Collette (Statistician): input to analysis of NTCP parameters for breast fibrosis.

Sally Eagle (Therapy Superintendent Radiotherapy): data acquisition and analysis.

John D Fenwick (Physics Research Team Leader): study design and radiobiology.

Peter H Graham (Associate Professor Clinical Oncology): input to analysis of NTCP parameters for breast fibrosis.

Jo S Haviland (Medical Statistician): study design and study statistician.

Anna M Kirby (Consultant Clinical Oncologist): study design and clinical oncology input.

Helen Mayles (Head of Clinical Radiotherapy Physics): study design, management, and data acquisition and analysis.

Robert A Mitchell (Trainee Medical Physicist): treatment planning aspects.

Rosalind Perry (Treatment Area Superintendent Radiographer): study design, and data acquisition and analysis.

Philip Poortmans (Consultant Radiation Oncologist): input to analysis of NTCP parameters for breast fibrosis.

Andrew Poynter (Head of Radiotherapy Physics): study design, management, and data acquisition and analysis.

Glyn Shentall (Head of Radiotherapy Physics): study design, management, data analysis and manuscript preparation.

Jenny Titley (Trial Manager): study design, manager of study and interface to IMPORT-HIGH.

Alistair Thompson (Professor of Surgical Oncology): input on surgical aspects.

John R Yarnold (Professor and Consultant Clinical Oncologist): study design, clinical oncology input to all aspects and interface to IMPORT-HIGH.

Charlotte E Coles (Consultant In Clinical Oncology, joint chief investigator): study design, management, clinical oncology input to all aspects and interface to IMPORT-HIGH.

Philip M Evans (Professor of Medical Physics and Medical Imaging, joint chief investigator): study design, management and physics input to all aspects.

Other acknowledgements

- The IMPORT-HIGH trial patients who agreed to their imaging and radiotherapy planning data being used for this study.
- Sue Cross and Christine Rawlings from Torbay for their contribution to the development of the project and grant.
- Sandra Collette for input to the analysis of NTCP parameters for breast fibrosis.
- Alison Round for help with the work at Ipswich.
- The members of the IMPORT-HIGH and IMPORT-LOW trials trial management group for supporting this study as a substudy of IMPORT-HIGH.
- The members of the IMPORT-HIGH and IMPORT-LOW trials independent data monitoring committee for supporting this study as a substudy of IMPORT-HIGH.
- The members of the IMPORT-HIGH and IMPORT-LOW trials trial steering committee for supporting this study as a substudy of IMPORT-HIGH.
- The radiographers, physicists, engineers, clinical oncologists and surgeons at each centre who provided data for this study.

Dr Ellen Donovan is funded by a National Institute for Health Research/CSO Healthcare Scientist Post-Doctoral Fellowship.

Publications

Coles CE, Brunt Am, Wheatley D, Mukesh MB, Yarnold JR. Breast radiotherapy: less is more? *Clin Oncol* 2013;**25**:127–34.

Donovan EM, Castellano I, Eagle S, Harris E. Clinical implication of kilovoltage cone beam CT for the verification of sequential and integrated photon boost treatments for breast cancer patients. *Br J Radiol* 2012;**85**:e1051–7.

Eyre K, Whitney D, Mukesh M, Wilson C, Coles C. Optimization and comparison of balloon-based partial breast brachytherapy using a single source, a standard plan line source, and both forward and inverse planned multilumen techniques. *Brachytherapy* 2013;**12**:107–13.

Harris EJ, Donovan EM, Coles CE, de Boer HC, Poynter A, Rawlings C, *et al.* How does imaging frequency and soft tissue motion affect the PTV margin size in partial breast and boost radiotherapy? *Radiother Oncol* 2012;**103**:166–71.

Mukesh MB, Barnett G, Cumming J, Wilkinson JS, Moody AM, Wilson C, *et al.* Association of breast tumour bed seroma with post-operative complications and late normal tissue toxicity: results from the Cambridge Breast IMRT trial. *Eur J Surg Oncol* 2012;**38**:918–24.

Mukesh MB, Harris E, Collette S, Coles CE, Bartelink H, Wilkinson J, *et al.* Normal tissue complication probability (NTCP) parameters for breast fibrosis: pooled results from two randomised trials. *Radiother Oncol* 2013;**108**:293–8.

Mukesh M, Harris E, Jena R, Evans P, Coles C. Relationship between irradiated breast volume and late normal tissue complications: a systematic review. *Radiother Oncol* 2012;**104**:1–10.

Treece SJ, Mukesh M, Rimmer YL, Tudor SJ, Dean JC, Benson RJ, *et al.* The value of image-guided intensity-modulated radiotherapy in challenging clinical settings. *Br J Radiol* 2013;**86**:20120278.

References

1. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, *et al.* Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;**366**:2087–106. http://dx.doi.org/10.1016/S0140-6736(05)67887-7
2. Bartelink H, Horiot JC, Poortmans PM, Struikmans H, Van den Bogaert W, Fourquet A, *et al.* Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *J Clin Oncol* 2007;**25**:3259–65. http://dx.doi.org/10.1200/JCO.2007.11.4991
3. Jones H, Antonini N Collette L, Fourquet A, Hoogenraad WJ, Jager JJ, *et al.* The impact of a boost dose on the local recurrence rate in high risk patients after breast conserving therapy – results from the EORTC boost–no boost trial. *EJC Supplements* 2008;**6**:132–3. http://dx.doi.org/10.1016/S1359-6349(08)70601-3
4. Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bliss JM, *et al.* The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol* 2008;**9**:331–41. http://dx.doi.org/10.1016/S1470-2045(08)70077-9
5. Coles CE, Wilson CB, Cumming J, Benson JR, Forouhi P, Wilkinson JS, *et al.* Titanium clip placement to allow accurate tumour bed localisation following breast conserving surgery: audit on behalf of the IMPORT Trial Management Group. *Eur J Surg Oncol* 2009;**35**:578–82. http://dx.doi.org/10.1016/j.ejso.2008.09.005
6. Weed DW, Yan D, Martinez AA, Vicini FA, Wilkinson TJ, Wong J, *et al.* The validity of surgical clips as a radiographic surrogate for the lumpectomy cavity in image-guided accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys* 2004;**60**:484–92. http://dx.doi.org/10.1016/j.ijrobp.2004.03.012
7. Coles CE, Wishart GC, Wilkinson JS, Harris E, Poynter A, Twyman N, *et al.* The Import Gold Seed Study: evaluation of tumour bed localisation and image-guided radiotherapy for breast cancer. *Radiother Oncol* 2008;**88**:S103.
8. Topolnjak R, van Vliet-Vroegindeweij C, Sonke JJ, Minkema D, Remeijer P, Nijkamp J, *et al.* Breast-conserving therapy: radiotherapy margins for breast tumour bed boost. *Int J Radiat Oncol Biol Phys* 2008;**72**:1941–8. http://dx.doi.org/10.1016/j.ijrobp.2008.06.1924
9. Hasan Y, Kim L, Martinez A. Image guidance in external beam accelerated partial breast irradiation: comparison of surrogates for the lumpectomy cavity. *Int J Radiat Oncol Biol Phys* 2008;**70**:619–25. http://dx.doi.org/10.1016/j.ijrobp.2007.08.079
10. Kim LH, Vicini F, Yan D. What do lumpectomy cavity volume change imply for breast clinical target volumes? *Int J Radiat Oncol Biol Phys* 2008;**72**:1–3. http://dx.doi.org/10.1016/j.ijrobp.2008.04.080
11. Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bliss JM, *et al.* The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* 2008;**371**:1098–107. http://dx.doi.org/10.1016/S0140-6736(08)60348-7
12. Al-Ghazal SK, Fallowfield L, Blamey RW. Does cosmetic outcome from treatment of primary breast cancer influence psychosocial morbidity? *Eur J Surg Oncol* 1999;**25**:571–3. http://dx.doi.org/10.1053/ejso.1999.0708

13. Hopwood P, Mills J, Sumo G, Bliss JM. On behalf of the START Trial Management Group. Factors affecting short and long term body image concerns in early breast cancer: experience in the START (Standardisation of Breast Radiotherapy) Trial NCRI Conference 2006, 8th World Congress of Psycho-Oncology, 2006.

14. Borger JH, Kemperman H, Smitt HS, Hart A, van Dongen J, Lebesque J, *et al.* Dose and volume effects on fibrosis after breast conservation therapy. *Int J Radiat Oncol Biol Phys* 1994;**30**:1073–81. http://dx.doi.org/10.1016/0360-3016(94)90312-3

15. Vrieling C, Collette L, Fourquet A, Hoogenraad WJ, Horiot JH, Jager JJ, *et al.* The influence of patient, tumor and treatment factors on the cosmetic results after breast-conserving therapy in the EORTC 'boost vs. no boost' trial. EORTC Radiotherapy and Breast Cancer Cooperative Groups. *Radiother Oncol* 2000;**55**:219–32. http://dx.doi.org/10.1016/S0167-8140(00)00210-3

16. Yarnold J, Ashton A, Bliss JM, Homewood J, Harper C, Hanson J, *et al.* Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial. *Radiother Oncol* 2005;**75**:9–17. http://dx.doi.org/10.1016/j.radonc.2005.01.005

17. Owen JR, Ashton A, Bliss JM, Homewood J, Harper C, Hanson J, *et al.* Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. *Lancet Oncol* 2006;**7**:467–71. http://dx.doi.org/10.1016/S1470-2045(06)70699-4

18. Krawczyk JJ, Engel B. The importance of surgical clips for adequate tangential beam planning in breast conserving surgery and irradiation. *Int J Radiat Oncol Biol Phys* 1999;**43**:347–50. http://dx.doi.org/10.1016/S0360-3016(98)00402-7

19. Mukesh M, Harris E, Jena R, Evans P, Coles C. Relationship between irradiated breast volume and late normal tissue complications: a systematic review. *Radiother Oncol* 2012;**104**:1–10. http://dx.doi.org/10.1016/j.radonc.2012.04.025

20. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, *et al.* Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991;**21**:109–22. http://dx.doi.org/10.1016/0360-3016(91)90171-Y

21. Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, *et al.* QUantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. *Int J Radiat Oncol Biol Phys* 2010;**76**:S3–9. http://dx.doi.org/10.1016/j.ijrobp.2009.09.040

22. Deasy JO, Moiseenko V, Marks L, Chao KS, Nam J, Eisbruch A. Radiotherapy dose–volume effects on salivary gland function. *Int J Radiat Oncol Biol Phys* 2010;**76**:S58–63. http://dx.doi.org/10.1016/j.ijrobp.2009.06.090

23. Marks LB, Bentzen SM, Deasy JO, Kong FM, Bradley JD, Vogelius IS, *et al.* Radiation dose–volume effects in the lung. *Int J Radiat Oncol Biol Phys* 2010;**76**:S70–6. http://dx.doi.org/10.1016/j.ijrobp.2009.06.091

24. Romestaing P, Lehingue Y, Carrie C, Coquard R, Montbarbon X, Ardiet JM, *et al.* Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *J Clin Oncol* 1997;**15**:963–8.

25. Polgar C, Fodor J, Orosz Z, Major T, Takácsi-Nagy Z, Mangel LC, *et al.* Electron and high-dose-rate brachytherapy boost in the conservative treatment of stage I–II breast cancer first results of the randomized Budapest boost trial. *Strahlenther Onkol* 2002;**178**:615–23. http://dx.doi.org/10.1007/s00066-002-1053-1

26. Poortmans PM, Collette L, Horiot JC, Van den Bogaert WF, Fourquet A, Kuten A, *et al.* Impact of the boost dose of 10 Gy versus 26 Gy in patients with early stage breast cancer after a microscopically incomplete lumpectomy: 10-year results of the randomised EORTC boost trial. *Radiother Oncol* 2009;**90**:80–5. http://dx.doi.org/10.1016/j.radonc.2008.07.011

27. Collette S, Collette L, Budiharto T, Horiot JC, Poortmans PM, Struikmans H, *et al.* Predictors of the risk of fibrosis at 10 years after breast conserving therapy for early breast cancer: a study based on the EORTC Trial 22881–10882 'boost versus no boost'. *Eur J Cancer* 2008;**44**:2587–99. http://dx.doi.org/10.1016/j.ejca.2008.07.032

28. McRae D, Rodgers J, Dritschilo A. Dose–volume and complication in interstitial implants for breast carcinoma. *Int J Radiat Oncol Biol Phys* 1987;**13**:525–9. http://dx.doi.org/10.1016/0360-3016(87)90067-8

29. Olivotto IA, Rose MA, Osteen RT, Love S, Cady B, Silver B, *et al.* Late cosmetic outcome after conservative surgery and radiotherapy: analysis of causes of cosmetic failure. *Int J Radiat Oncol Biol Phys* 1989;**17**:747–53. http://dx.doi.org/10.1016/0360-3016(89)90061-8

30. Dewar JA, Benhamou S, Benhamou E, Arriagada R, Petit JY, Fontaine F, *et al.* Cosmetic results following lumpectomy, axillary dissection and radiotherapy for small breast cancers. *Radiother Oncol* 1988;**12**:273–80. http://dx.doi.org/10.1016/0167-8140(88)90016-3

31. Clarke D, Martinez A, Cox RS. Analysis of cosmetic results and complications in patients with stage I and II breast cancer treated by biopsy and irradiation. *Int J Radiat Oncol Biol Phys* 1983;**9**:1807–13. http://dx.doi.org/10.1016/0360-3016(83)90348-6

32. Wazer DE, Kramer B, Schmid C, Ruthazer R, Ulin K, Schmidt-Ullrich R. Factors determining outcome in patients treated with interstitial implantation as a radiation boost for breast conservation therapy. *Int J Radiat Oncol Biol Phys* 1997;**39**:381–93. http://dx.doi.org/10.1016/S0360-3016(97)00325-8

33. Wronczewska A, Makarewicz R, Kabacinska R, Zuchora A. Does interstitial HDR brachytherapy for breast cancer increase soft tissue fibrosis? *Rep Pract Oncol Radiother* 2005;**10**:119–23. http://dx.doi.org/10.1016/S1507-1367(05)71083-X

34. Herskind C, Griebel J, Kraus-Tiefenbacher U, Wenz F. Sphere of equivalence – a novel target volume concept for intraoperative radiotherapy using low-energy X rays. *Int J Radiat Oncol Biol Phys* 2008;**72**:1575–81. http://dx.doi.org/10.1016/j.ijrobp.2008.08.009

35. Belletti B, Vaidya JS, D'Andrea S, Entschladen F, Roncadin M, Lovat F, *et al.* Targeted intraoperative radiotherapy impairs the stimulation of breast cancer cell proliferation and invasion caused by surgical wounding. *Clin Cancer Res* 2008;**14**:1325–32. http://dx.doi.org/10.1158/1078-0432.CCR-07-4453

36. Wenz F, Welzel G, Blank E, Hermann B, Steil V, Sütterlin M, *et al.* Intraoperative radiotherapy as a boost during breast-conserving surgery using low-kilovoltage X-rays: the first 5 years of experience with a novel approach. *Int J Radiat Oncol Biol Phys* 2010;**77**:1309–14. http://dx.doi.org/10.1016/j.ijrobp.2009.06.085

37. Murphy C, Anderson PR, Li T, Bleicher RJ, Sigurdson ER, Goldstein LJ, *et al.* Impact of the radiation boost on outcomes after breast-conserving surgery and radiation. *Int J Radiat Oncol Biol Phys* 2011;**81**:69–76. http://dx.doi.org/10.1016/j.ijrobp.2010.04.067

38. Ribeiro GG, Magee B, Swindell R, Harris M, Banerjee SS. The Christie Hospital breast conservation trial: an update at 8 years from inception. *Clin Oncol* 1993;**5**:278–83. http://dx.doi.org/10.1016/S0936-6555(05)80900-8

39. Dodwell DJ, Dyker K, Brown J, Hawkins K, Cohen D, Stead M, *et al.* A randomised study of whole-breast vs. tumour bed irradiation after local excision and axillary dissection for early breast cancer. *Clin Oncol* 2005;**17**:618–22. http://dx.doi.org/10.1016/j.clon.2005.07.018

40. Polgar C, Fodor J, Major T, Sulyok Z, Kásler M. Breast-conserving treatment with partial or whole-breast irradiation for low-risk invasive breast carcinoma – 5-year results of a randomized trial. *Int J Radiat Oncol Biol Phys* 2007;**69**:694–702. http://dx.doi.org/10.1016/j.ijrobp.2007.04.022

41. Vaidya JS, Joseph DJ, Tobias JS, Tobias JS, Joseph DJ, Keshtgar M, *et al.* Targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet* 2010;**376**:91–102. http://dx.doi.org/10.1016/S0140-6736(10)60837-9

42. Orecchia R, Ciocca M, Lazzari R, Garibaldi C, Leonardi MC, Luini A, *et al.* Intraoperative radiation therapy with electrons (ELIOT) in early-stage breast cancer. *Breast* 2003;**12**:483–90. http://dx.doi.org/10.1016/S0960-9776(03)00156-5

43. Yarnold J, Coles C. On behalf of the IMPORT-LOW Trial Management Group. *Intensity-Modulated and Partial Organ Radiotherapy*. Randomised trial testing intensity-modulated and partial organ radiotherapy following breast conservative surgery for early breast cancer. Trial protocol, version 6; 2009, Institute of Cancer Research, Sutton, UK. pp. 1–74 URL: www.clinicaltrials.gov/ct2/show/NCT00814567 (accessed 19 September 2014).

44. Coles C, Yarnold J. The IMPORT trials are launched (September 2006). *Clin Oncol* 2006;**18**:587–90. http://dx.doi.org/10.1016/j.clon.2006.07.010

45. Strnad V, Polgar C. On behalf of the European Brachytherapy Breast Cancer GEC-ESTRO Working Group. *GEC-ESTRO APBI Trial: Interstitial Brachytherapy Alone Versus External Beam Radiation Therapy After Breast Conserving Surgery for Low Risk Invasive Carcinoma and Low Risk Duct Carcinoma In-situ (DCIS) of the Female Breast*. 2006. URL: www.apbi.uni-erlangen.de/outline/outline.html (accessed 19 September 2014).

46. Wolmark N, Curran W. On behalf of NSABP and RTOG of the American College of Radiology (ACR). *NSABP Protocol B-39. RTOG Protocol 0413A Randomized Phase III Study of Conventional Whole-breast Irradiation Versus Partial Breast Irradiation for Women with Stage 0, I, or II Breast Cancer. National Surgical Adjuvant Breast and Bowel Project (NSABP). Trial Protocol*. 2007. pp. 1–132. URL: www.clinicaltrials.gov/ct2/show/NCT00103181 (accessed 19 September 2014).

47. Ontario Clinical Oncology Group (OCOG), Canadian Institutes of Health Research (CIHR), Canadian Breast Cancer Research Alliance. *RAPID: Randomized Trial of Accelerated Partial Breast Irradiation*. 2008. URL: www.clinicaltrials.gov/ct2/show/NCT00282035 (accessed 19 September 2014).

48. Armaroli L, Barbieri E, Bertoni F, Busutti L, Cardinali M, Cartei F, *et al. Breast Cancer with Low Risk of Local Reccurance: Partial and Accelerated Radiation with Three-Dimensional Conformational Radiotherapy (3DCRT) vs. Standard Radiotherapy After Conserving Surgery (Phase III Study)*. URL: http://groups.eortc.be/radio/res/irma/synopsis_trial_irma1.pdf (accessed 19 September 2014).

49. Danish Breast Cancer Co-operative Group. *Partial Breast Versus Whole-breast Irradiation in Elderly Women Operated on for Early Breast Cancer*. URL: www.clinicaltrials.gov/ct2/show/NCT00892814 (accessed 19 September 2014).

50. Belkacemi Y, Lartigau E. On behalf of Federation Nationale des Centres de Lutte Contre le Cancer. *Standard or Hypofractionated Radiotherapy Versus Accelerated Partial Breast Irradiation (APBI) for Breast Cancer (SHARE)*. 2010. URL: www.clinicaltrials.gov/ct2/show/NCT01247233 (accessed 19 September 2014).

51. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, *et al.* Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002;**347**:1233–41. http://dx.doi.org/10.1056/NEJMoa022152

52. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, Aguilar M, *et al.* Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002;**347**:1227–32. http://dx.doi.org/10.1056/NEJMoa020989

53. Harris JR, Levene MB, Svensson G, Hellman S. Analysis of cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast. *Int J Radiat Oncol Biol Phys* 1979;**5**:257–61. http://dx.doi.org/10.1016/0360-3016(79)90729-6

54. Polgar C, Major T, Fodor J, Németh G, Orosz Z, Sulyok Z, *et al.* High-dose-rate brachytherapy alone versus whole-breast radiotherapy with or without tumor bed boost after breast conserving surgery: seven-year results of a comparative study. *Int J Radiat Oncol Biol Phys* 2004;**60**:1173–81. http://dx.doi.org/10.1016/j.ijrobp.2004.05.012

55. Vicini FA, Baglan KL, Kestin LL, Mitchell C, Chen PY, Frazier RC, *et al.* Accelerated treatment of breast cancer. *J Clin Oncol* 2001;**19**:1993–2001.

56. King TA, Bolton JS, Kuske RR, Fuhrman GM, Scroggins TG, Jiang XZ. Long-term results of wide-field brachytherapy as the sole method of radiation therapy after segmental mastectomy for T(is,1,2) breast cancer. *Am J Surg* 2000;**180**:299–304. http://dx.doi.org/10.1016/S0002-9610(00)00454-2

57. Wadasadawala T, Sarin R, Budrukkar A, Jalali R, Munshi A, Badwe R. Accelerated partial-breast irradiation vs conventional whole-breast radiotherapy in early breast cancer: a case–control study of disease control, cosmesis, and complications. *J Cancer Res Ther* 2009;**5**:93–101. http://dx.doi.org/10.4103/0973-1482.52794

58. Jagsi R, Ben-David MA, Moran JM, Marsh RB, Griffith KA, Hayman JA, *et al.* Unacceptable cosmesis in a protocol investigating intensity-modulated radiotherapy with active breathing control for accelerated partial-breast irradiation. *Int J Radiat Oncol Biol Phys* 2010;**76**:71–8. http://dx.doi.org/10.1016/j.ijrobp.2009.01.041

59. Hepel JT, Tokita M, MacAusland SG, Evans SB, Hiatt JR, Price LL, *et al.* Toxicity of three-dimensional conformal radiotherapy for accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys* 2009;**75**:1290–6. http://dx.doi.org/10.1016/j.ijrobp.2009.01.009

60. Chen PY, Wallace M, Mitchell C, Grills I, Kestin L, Fowler A, *et al.* Four-year efficacy, cosmesis, and toxicity using three-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys* 2010;**76**:991–7. http://dx.doi.org/10.1016/j.ijrobp.2009.03.012

61. Shaitelman SF, Kim LH, Grills IS, Chen PY, Ye H, Kestin LL, Yan D, *et al.* Predictors of long-term toxicity using three-dimensional conformal external beam radiotherapy to deliver accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys* 2011;**81**:788–94. http://dx.doi.org/10.1016/j.ijrobp.2010.06.062

62. Yeo SG, Kim J, Kwak GH, Kim JY, Park K, Kim ES, *et al.* Accelerated partial breast irradiation using multicatheter brachytherapy for select early-stage breast cancer: local control and toxicity. *Radiat Oncol* 2010;**5**:56. http://dx.doi.org/10.1186/1748-717X-5-56

63. Wazer DE, Kaufman S, Cuttino L, DiPetrillo T, Arthur DW. Accelerated partial breast irradiation: an analysis of variables associated with late toxicity and long-term cosmetic outcome after high-dose-rate interstitial brachytherapy. *Int J Radiat Oncol Biol Phys* 2006;**64**:489–95. http://dx.doi.org/10.1016/j.ijrobp.2005.06.028

64. Lawenda BD, Taghian AG, Kachnic LA, Hamdi H, Smith BL, Gadd MA, *et al.* Dose–volume analysis of radiotherapy for T1N0 invasive breast cancer treated by local excision and partial breast irradiation by low-dose-rate interstitial implant. *Int J Radiat Oncol Biol Phys* 2003;**56**:671–80. http://dx.doi.org/10.1016/S0360-3016(03)00071-3

65. Zelefsky MJ, Levin EJ, Hunt M, Yamada Y, Shippy AM, Jackson A, *et al.* Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;**70**:1124–9. http://dx.doi.org/10.1016/j.ijrobp.2007.11.044

66. Hau E, Browne LH, Khanna S, Cail S, Cert G, Chin Y, Clark C, *et al.* Radiotherapy breast boost with reduced whole-breast dose is associated with improved cosmesis: the results of a comprehensive assessment from the St. George and Wollongong randomized breast boost trial. *Int J Radiat Oncol Biol Phys* 2012;**82**:682–9. http://dx.doi.org/10.1016/j.ijrobp.2010.11.025

67. Barnett GC, Wilkinson JS, Moody AM, Wilson CB, Twyman N, Wishart GC, *et al.* Randomized controlled trial of forward-planned intensity-modulated radiotherapy for early breast cancer: interim results at 2 years. *Int J Radiat Oncol Biol Phys* 2012;**82**:715–23. http://dx.doi.org/10.1016/j.ijrobp.2010.10.068

68. Munshi A, Kakkar S, Bhutani R, Jalali R, Budrukkar A, Dinshaw KA. Factors influencing cosmetic outcome in breast conservation. *Clin Oncol* 2009;**21**:285–93. http://dx.doi.org/10.1016/j.clon.2009.02.001

69. Taylor ME, Perez CA, Halverson KJ, Kuske RR, Philpott GW, Garcia DM, *et al.* Factors influencing cosmetic results after conservation therapy for breast cancer. *Int J Radiat Oncol Biol Phys* 1995;**31**:753–64. http://dx.doi.org/10.1016/0360-3016(94)00480-3

70. Turesson I, Nyman J, Holmberg E, Oden A. Prognostic factors for acute and late skin reactions in radiotherapy patients. *Int J Radiat Oncol Biol Phys* 1996;**36**:1065–75. http://dx.doi.org/10.1016/S0360-3016(96)00426-9

71. Van Limbergen E, Rijnders A, van der Schueren E, Lerut T, Christiaens R. Cosmetic evaluation of breast conserving treatment for mammary cancer. 2. A quantitative analysis of the influence of radiation dose, fractionation schedules and surgical treatment techniques on cosmetic results. *Radiother Oncol* 1989;**16**:253–67. http://dx.doi.org/10.1016/0167-8140(89)90037-6

72. Olivotto IA, Whelan TJ, Parpia S, Kim DH, Berrang T, Truong PT, *et al.* Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. *J Clin Oncol* 2013:**31**;4038–45. http://dx.doi.org/10.1200/JCO.2013.50.5511

73. Yarnold J, Bentzen SM, Coles C, Haviland J. Hypofractionated whole-breast radiotherapy for women with early breast cancer: myths and realities. *Int J Rad Oncol Biol Phys* 2011:**79**;1–9. http://dx.doi.org/10.1016/j.ijrobp.2010.08.035

74. Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, *et al.* Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol* 2013:**14**;1269–77. http://dx.doi.org/10.1016/S1470-2045(13)70497-2

75. Mukesh MB, Harris E, Collette S, Coles CE, Bartelink H, Evans PM, *et al.* Normal tissue complication probability (NTCP) parameters for breast fibrosis: pooled results from two randomised trials. *Radiother Oncol* 2013;**108**:293–8. http://dx.doi.org/10.1016/j.radonc.2013.07.006

76. Deasy JO, Bentzen SM, Jackson A, Ten Haken RK, Yorke ED, Constine LS, *et al.* Improving normal tissue complication probability models: the need to adopt a "data-pooling" culture. *Int J Radiat Oncol Biol Phys* 2010;**76**:S151–4. http://dx.doi.org/10.1016/j.ijrobp.2009.06.094

77. Barnett GC, Wilkinson J, Moody AM, Wilson CB, Sharma R, Klager S, *et al.* A randomised controlled trial of forward-planned radiotherapy (IMRT) for early breast cancer: baseline characteristics and dosimetry results. *Radiother Oncol* 2009;**92**:34–41. http://dx.doi.org/10.1016/j.radonc.2009.03.003

78. Poortmans P, Bartelink H, Horiot JC, Struikmans H, Van den Bogaert W, Fourquet A, *et al.* The influence of the boost technique on local control in breast conserving treatment in the EORTC 'boost versus no boost' randomised trial. *Radiother Oncol* 2004;**72**:25–33. http://dx.doi.org/10.1016/j.radonc.2004.03.007

79. Deasy JO. Comments on the use of the Lyman–Kutcher–Burman model to describe tissue response to nonuniform irradiation. *Int J Radiat Oncol Biol Phys* 2000;**47**:1458–60. http://dx.doi.org/10.1016/S0360-3016(00)00500-9

80. Gay HA, Niemierko A. A free program for calculating EUD-based NTCP and TCP in external beam radiotherapy. *Phys Med* 2007;**23**:115–25. http://dx.doi.org/10.1016/j.ejmp.2007.07.001

81. Jackson A, Ten Haken RK, Robertson JM, Kessler ML, Kutcher GJ, Lawrence TS. Analysis of clinical complication data for radiation hepatitis using a parallel architecture model. *Int J Radiat Oncol Biol Phys* 1995;**31**:883–91. http://dx.doi.org/10.1016/0360-3016(94)00471-4

82. Roberts SA, Hendry JH. The delay before onset of accelerated tumour cell repopulation during radiotherapy: a direct maximum-likelihood analysis of a collection of worldwide tumour-control data. *Radiother Oncol* 1993;**29**:69–74. http://dx.doi.org/10.1016/0167-8140(93)90175-8

83. Alexander MA, Brooks WA, Blake SW. Normal tissue complication probability modelling of tissue fibrosis following breast radiotherapy. *Phys Med Biol* 2007;**52**:1831–43. http://dx.doi.org/10.1088/0031-9155/52/7/005

84. Avanzo M, Stancanello J, Trovo M, Jena R, Roncadin M, Trovò MG, *et al.* Complication probability model for subcutaneous fibrosis based on published data of partial and whole-breast irradiation. *Phys Med* 2012;**28**:296–306. http://dx.doi.org/10.1016/j.ejmp.2011.11.002

85. Fehlauer F, Tribius S, Holler U, Rades D, Kuhlmey A, Bajrovic A, *et al.* Long-term radiation sequelae after breast-conserving therapy in women with early-stage breast cancer: an observational study using the LENT-SOMA scoring system. *Int J Radiat Oncol Biol Phys* 2003;**55**:651–8. http://dx.doi.org/10.1016/S0360-3016(02)04120-2

86. Johansen J, Overgaard J, Rose C, Engelholm SA, Gadeberg CC, Kjaer M, *et al.* Cosmetic outcome and breast morbidity in breast-conserving treatment–results from the Danish DBCG-82TM national randomized trial in breast cancer. *Acta Oncol* 2002;**41**:369–80. http://dx.doi.org/10.1080/028418602760169433

87. Offersen BV, Overgaard M, Kroman N, Overgaard J. Accelerated partial breast irradiation as part of breast conserving therapy of early breast carcinoma: a systematic review. *Radiother Oncol* 2009;**90**:1–13. http://dx.doi.org/10.1016/j.radonc.2008.08.005

88. Hurkmans CW, Dijckmans I, Reijnen M, van der Leer J, van Vliet-Vroegindeweij C, van der Sangen M. Adaptive radiation therapy for breast IMRT-simultaneously integrated boost: three-year clinical experience. *Radiother Oncol* 2012;**103**:183–7. http://dx.doi.org/10.1016/j.radonc.2011.12.014

89. van Luijk P, Delvigne TC, Schilstra C, Schippers JM. Estimation of parameters of dose-volume models and their confidence limits. *Phys Med Biol* 2003;**48**:1863–84. http://dx.doi.org/10.1088/0031-9155/48/13/301

90. Yorke ED. Modeling the effects of inhomogeneous dose distributions in normal tissues. *Semin Radiat Oncol* 2001;**11**:197–209. http://dx.doi.org/10.1053/srao.2001.23478

91. Rancati T, Fiorino C, Gagliardi G, Cattaneo GM, Sanguineti G, Borca VC, *et al.* Fitting late rectal bleeding data using different NTCP models: results from an Italian multi-centric study (AIROPROS0101). *Radiother Oncol* 2004;**73**:21–32. http://dx.doi.org/10.1016/j.radonc.2004.08.013

92. Smith RP, Bloch P, Harris EE, McDonough J, Sarkar A, Kassaee A, *et al.* Analysis of interfraction and intrafraction variation during tangential breast irradiation with an electronic portal imaging device. *Int J Radiat Oncol Biol Phys* 2005;**62**:373–8. http://dx.doi.org/10.1016/j.ijrobp.2004.10.022

93. Creutzberg CL, Althof VG, Huizenga H, Visser AG, Levendag PC. Quality assurance using portal imaging: the accuracy of patient positioning in irradiation of breast cancer. *Int J Radiat Oncol Biol Phys* 1993;**25**:529–39. http://dx.doi.org/10.1016/0360-3016(93)90077-9

94. Lirette A, Pouliot J, Aubin M, Larochelle M. The role of electronic portal imaging in tangential breast irradiation: a prospective study. *Radiother Oncol* 1995;**37**:241–5. http://dx.doi.org/10.1016/0167-8140(95)01653-8

95. British Institute of Radiology Working Party. *Geometric Uncertainties in Radiotherapy*. London, UK: British Institute of Radiology. 2003.

96. Association of Breast Surgery at BASO. Surgical guidelines for the management of breast cancer. *Eur J Surg Oncol* 2009;**35**(Suppl. 1):1–22. http://dx.doi.org/10.1016/j.ejso.2009.01.008

97. Coles C, Yarnold J. Localising the tumour bed in breast radiotherapy. *Clin Oncol* 2010;**22**:36–8. http://dx.doi.org/10.1016/j.clon.2009.08.014

98. Topolnjak R, de Ruiter P, Remeijer P, van Vliet-Vroegindeweij C, Rasch C, Sonke JJ. Image-guided radiotherapy for breast cancer patients: surgical clips as surrogate for breast excision cavity. *Int J Radiat Oncol Biol Phys* 2011;**81**:e187–95. http://dx.doi.org/10.1016/j.ijrobp.2010.12.027

99. Coles CE, Harris EJ, Donovan EM, Bliss P, Evans PM, Fairfoul J, *et al.* Evaluation of implanted gold seeds for breast radiotherapy planning and on treatment verification: a feasibility study on behalf of the IMPORT trialists. *Radiother Oncol* 2011;**100**:276–81. http://dx.doi.org/10.1016/j.radonc.2011.03.007

100. Leonard CE, Tallhamer M, Johnson T, Hunter K, Howell K, Kercher J, *et al.* Clinical experience with image-guided radiotherapy in an accelerated partial breast intensity-modulated radiotherapy protocol. *Int J Radiat Oncol Biol Phys* 2010;**76**:528–34. http://dx.doi.org/10.1016/j.ijrobp.2009.02.001

101. Kim LH, Wong J, Yan D. On-line localization of the lumpectomy cavity using surgical clips. *Int J Radiat Oncol Biol Phys* 2007;**69**:1305–9. http://dx.doi.org/10.1016/j.ijrobp.2007.07.2365

102. van Herk M, Remeijer P, Rasch C, Lebesque JV. The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;**47**:1121–35. http://dx.doi.org/10.1016/S0360-3016(00)00518-6

103. Topolnjak R, Sonke JJ, Nijkamp J, Rasch C, Minkema D, Remeijer P, *et al.* Breast patient setup error assessment: comparison of electronic portal image devices and cone-beam computed tomography matching results. *Int J Radiat Oncol Biol Phys* 2010;**78**:1235–43. http://dx.doi.org/10.1016/j.ijrobp.2009.12.021

104. Penninkhof J, Quint S, Baaijens M, Heijmen B, Dirkx M. Practical use of the extended no action level (eNAL) correction protocol for breast cancer patients with implanted surgical clips. *Int J Radiat Oncol Biol Phys* 2012;**82**:1031–7. http://dx.doi.org/10.1016/j.ijrobp.2010.12.059

105. Bogle W, Hsu YS. Sample size determination in comparing two population variances with paired-data: application to Bilirubin tests. *Biom J* 2002;**5**:594–60. http://dx.doi.org/10.1002/1521-4036(200207)44:5<594::AID-BIMJ594>3.0.CO;2-5

106. de Boer HC, Heijmen BJ. eNAL: an extension of the NAL setup correction protocol for effective use of weekly follow-up measurements. *Int J Radiat Oncol Biol Phys* 2007;**67**:1586–95. http://dx.doi.org/10.1016/j.ijrobp.2006.11.050

107. Sijtsema NM, van Dijk-Peters FB, Langendijk JA, Maduro JH, van 't Veld AA. Electronic portal images (EPIs) based position verification for the breast simultaneous integrated boost (SIB) technique. *Radiother Oncol* 2012;**102**:108–14. http://dx.doi.org/10.1016/j.radonc.2011.10.007

108. Burnet NG, Adams EJ, Fairfoul J, Tudor GS, Hoole AC, Routsis DS, *et al.* Practical aspects of implementation of helical tomotherapy for intensity-modulated and image-guided radiotherapy. *Clin Oncol* 2010;**22**:294–312. http://dx.doi.org/10.1016/j.clon.2010.02.003

109. Gierga DP, Riboldi M, Turcotte JC, Sharp GC, Jiang SB, Taghian AG, *et al.* Comparison of target registration errors for multiple image-guided techniques in accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys* 2008;**70**:1239–46. http://dx.doi.org/10.1016/j.ijrobp.2007.11.020

110. Fatunase T, Wang Z, Yoo S, Hubbs JL, Prosnitz RG, Yin FF, *et al.* Assessment of the residual error in soft tissue setup in patients undergoing partial breast irradiation: results of a prospective study using cone-beam computed tomography. *Int J Radiat Oncol Biol Phys* 2008;**70**:1025–34. http://dx.doi.org/10.1016/j.ijrobp.2007.07.2344

111. Harris EJ, Donovan EM, Yarnold JR, Coles CE, Evans PM. Characterization of target volume changes during breast radiotherapy using implanted fiducial markers and portal imaging. *Int J Radiat Oncol Biol Phys* 2009;**73**:958–66. http://dx.doi.org/10.1016/j.ijrobp.2008.10.030

112. Lee G, Fyles A, Cho J, Easson AM, Fenkell LL, Harnett N, *et al.* Evaluation of variability in seroma delineation between clinical radiation therapist and radiation oncologist for adjuvant breast irradiation. *Prac Rad Oncol* 2012;**2**:114–21. http://dx.doi.org/10.1016/j.prro.2011.07.002

113. Mukesh M, Barnett G, Cumming J, Wilkinson JS, Moody AM, Wilson C, *et al.* Association of breast tumour bed seroma with post-operative complications and late normal tissue toxicity: results from Cambridge breast IMRT trial. *Eur J Surg Oncol* 2013;**38**:918–24. http://dx.doi.org/10.1016/j.ejso.2012.05.008

114. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, *et al.* Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;**368**:987–98. http://dx.doi.org/10.1056/NEJMoa1209825

115. National Institute for Health and Care Excellence. *Early and Locally Advanced Breast Cancer: Diagnosis and Treatment*. Cardiff: National Collaborating Centre for Cancer; 2009. URL: www.nice.org.uk/guidance/cg80/resources/cg80-early-and-locally-advanced-breast-cancer-full-guideline2 (accessed 19 September 2012).

116. Harrington KJ, Harrison M, Bayle P, Evans K, Dunn PA, Lambert HE, *et al.* Surgical clips in planning the electron boost in breast cancer: a qualitative and quantitative evaluation. *Int J Radiat Oncol Biol Phys* 1996;**34**:579–84. http://dx.doi.org/10.1016/0360-3016(95)02090-X

117. Machtay M, Lanciano R, Hoffman J, Hanks GE. Inaccuracies in using the lumpectomy scar for planning electron boosts in primary breast carcinoma. *Int J Radiat Oncol Biol Phys* 1994;**30**:43–8. http://dx.doi.org/10.1016/0360-3016(94)90517-7

118. Hurkmans C. Radiation therapy using a simultaneously integrated boost for early-stage breast cancer. *Future Oncol* 2007;**3**:509–13. http://dx.doi.org/10.2217/14796694.3.5.509

119. Harris EJ, Donovan EM, Coles CE, de Boer HC, Poynter A, Rawlings C, *et al.* How does imaging frequency and soft tissue motion affect the PTV margin size in partial breast and boost radiotherapy? *Radiother Oncol* 2012;**103**:166–71. http://dx.doi.org/10.1016/j.radonc.2012.03.015

120. Donovan EM, Ciurlionis L, Fairfoul J, James H, Mayles H, Manktelow S, *et al.* Radiotherapy planning with IMRT and tomotherapy to modulate dose across the breast to reflect recurrence risk (the IMPORT-HIGH trial). *Int J Rad Oncol Biol Phys* 2011;**79**:1064–72. http://dx.doi.org/10.1016/j.ijrobp.2009.12.052

EME
HS&DR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

Published by the NIHR Journals Library