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

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Scientific summary

Image-guided radiotherapy for breast cancer

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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.

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