**The IMPORT HIGH (CRUK/06/003) Image Guided Radiotherapy (IGRT) Study (09/150/16): A
model for assessing IGRT**

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Context

Radiotherapy for breast cancer is in an exciting era. Technological improvements in radiotherapy delivery and imaging are being used to achieve dose inhomogeneity [1] complex planning within trials [2], and for cases requiring extensive nodal irradiation [3]. These complex treatments require the use of advanced verification imaging i.e. image guided radiotherapy (IGRT). IGRT is defined in many ways, and includes imaging throughout the radiotherapy process. In this Editorial IGRT is used specifically to refer to imaging at the time of treatment at levels 2c to 2e, under the National Radiotherapy Implementation Group Report on IGRT [4]. This is the highest level of inter-fraction intervention in the scheme and requires matching and analysis using target anatomy or implanted markers as surrogates.

The necessity of IGRT in complex radiotherapy raises the issue of how its impact can be tested. Randomised trials are appropriate to test many research hypotheses but not all. For example it is not ethical to set up a no imaging versus imaging study where it is clear that a new imaging technology is both superior, and required, to deliver high quality radiotherapy. We present an exemplar of how this issue may be resolved by using the IMPORT HIGH trial as a case study.

Intensity Modulation and Partial Organ Radiotherapy (IMPORT) HIGH

IMPORT HIGH (CRUK/06/003) is a Phase III randomised trial of radiotherapy dose escalation in women at higher than average risk of local cancer recurrence after breast conserving surgery [5,6]. It is funded by Cancer Research UK and coordinated by the Institute of Cancer Research Clinical Trials and Statistics Unit. Radiotherapy treatment within the IMPORT HIGH trial requires a conformal photon boost in the control arm and a simultaneous integrated boost in the test arms. There was a steep increase in the complexity of planning, treatment and imaging within the trial compared with standard UK practice. The trial changed practice in the UK by requiring surgical clips to be inserted into the tumour bed at the time of surgery [7,8]. This was crucial so that the tumour bed and partial breast volumes could be defined correctly, and to verify the tumour bed position at the time of treatment. A planning study demonstrated the complex dose distributions could be achieved and delivered with a range of planning systems and treatment units hence widespread implementation was feasible[9]. The tight (5mm) margins on the tumour bed volume and the need to maintain dose discrimination in the simultaneous boost plan means that it was not appropriate to use standard imaging based on bony anatomy for verification.

1 All participating centres use IGRT with a defined verification protocol. Although this ensures safe
2 treatment and adherence to the trial protocol it does not enable an assessment of the efficacy of
3 IGRT compared to standard imaging as no patients are imaged with standard portal imaging. This
4 raises important questions about image guidance: how can the efficacy of IGRT be tested whilst still
5 providing the highest quality treatments for the patients? and what is the variation, if any, with the
6 type of imaging equipment used?
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10 **IMPORT – IGRT Study**

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13 IMPORT HIGH provides a unique opportunity to answer these questions and the IMPORT-IGRT study
14 was created as a sub-study within it to investigate the efficacy of IGRT in breast radiotherapy. The
15 project was titled ‘Evaluation of Image Guided Radiotherapy for more accurate Partial Breast
16 Intensity-Modulated Radiotherapy: comparison with standard imaging technique’ and was funded
17 by the Medical Research Council under the Efficacy and Mechanism Evaluation programme
18 (reference 09/150/16). It was administered by the National Institute for Health Research and ran
19 from 03.2010 to 08.2013.
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28 IMPORT-IGRT had a multi-institutional observational design. Data were collected from 218 patients
29 treated within IMPORT HIGH from 5 radiotherapy centres giving a total of 1574 imaging data sets.
30 The centres used a variety of standardly-available imaging equipment allowing 2D kV, and 3D kV and
31 MV imaging information to be collected and compared. There was no change to patients’ treatments
32 or verification from that defined by the IMPORT HIGH protocol: standard imaging data were
33 obtained from the IGRT information. This design allows IGRT to be assessed in an ethical way as all
34 patients receive the best treatment and imaging.
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42 Data were collected on the daily set up accuracy and reproducibility of: (i) image guidance, (ii)
43 standard portal imaging (deduced from the IGRT data by matching to bony anatomy rather than the
44 surgical clips) and (iii) laser external set-up (using no shift from the treatment images). The primary
45 outcome of the study was evaluating the population systematic error data for IGRT, standard
46 imaging and using external anatomy for set-up (no imaging shift). From these, and the measured
47 population random error data, estimates of tumour bed planning target margin sizes were
48 calculated. These margin data were used to create a series of treatment plans for 60 patients. These
49 data informed on PTV coverage and non-target tissue doses, particularly the volume of breast tissue
50 spared high dose. Analysis of data from a range of clinical trials was used to comment on the risk of
51 late adverse effects from volume changes with the use of IGRT compared to standard or no imaging.
52 Data on the time taken to acquire and analyse images were collected from the participating centres.
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Main findings

This is the first quantitative demonstration of the benefit of IGRT in partial breast radiotherapy. The primary outcome measure was population systematic error. This was reduced by up to 2 mm with IGRT compared to standard imaging hence IGRT was superior. There was no dependence of accuracy on the type of imaging equipment used but the equipment influenced the time taken for image assessment. The difference in time between standard imaging and IGRT were small however, ranging from 12s to 67s, with 3D methods taking longer than 2D overall, but with better image quality justifying the extra time.

The magnitude of population systematic error is important and relevant because it is the main contributor to the planning target volume margin and hence to the amount of tissue irradiated to a high dose. Our work shows that 5 mm margins are sufficient where IGRT is used, 8 mm margins are required for standard bony anatomy based imaging, and 10 mm or greater, if only laser external set up is used, or if the results of imaging are not acted upon, i.e. no verification correction protocol is employed. The effect of reducing the margin size from 8 mm to 5 mm is to decrease the high dose volume by 33cm^3 (range 11 to 193 cm^3) [11]. The radiobiological implications of this reduction are still uncertain, as discussed by Mukesh *et al* [12,13]. On-going randomised trials of radiobiological effects in breast radiotherapy will produce further essential information on the dose volume effect. Work such as IMPORT IGRT will inform the quantitative understanding of this by quantifying the impact of margin sizes on irradiated volumes.

Advantages of this approach

When technological advantages in radiotherapy occur it is important to implement them in a controlled, but timely, way for patient benefit. Developments primarily involve generating dose distributions which have improved mapping to tumours and spare organs at risk more than the standard treatments they replace, and provide greater accuracy in treatment delivery. These give the potential to escalate dose to improve cure rates and to reduce adverse effects.

In some cases, the means to evaluate the benefit of a technological development in a quantitative, rigorous manner is not clear. It is not ethical to use a 'non intervention', or 'standard intervention' versus 'intervention' model where this compromises patient treatment. IGRT is a good example of this. Whilst it is obvious that the use of kV imaging or volumetric imaging at the time of treatment gives greater tissue definition, and more information with which to match imaging datasets, the size of the benefit is still a pertinent question in determining if the extra complexity, expense and time

are justified. It is difficult to quantify this improvement compared to none/standard imaging without two cohorts of patients; one cohort will then not receive the highest quality imaging available : this is inconsistent with the principle of equipoise.

IMPORT-IGRT has allowed the quantitative assessment of IGRT with no reduction in the quality of imaging and no additional interventions for the patients. It has achieved this by embedding within the IMPORT HIGH trial, maximising the use of the trial data, and being efficient and cost-effective in terms of effort. As the protocol requires the highest quality imaging data to ensure the complex dose distributions are delivered correctly, it was possible to use the information to deduce the effect of a simpler imaging approach.

Conclusion

Using this approach the benefit of IGRT has been quantified for the first time in breast radiotherapy. The IMPORT-IGRT method demonstrates a successful, efficient method of assessing a development in radiotherapy in an ethical, rigorous way by embedding within an existing trial and using complex information to determine simpler. We recommend it as an approach which can be adopted for other treatment sites and other technology.

Conflicts of Interest Declaration

There are no conflicts of interest.

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Disclaimer

The views expressed are those of the author(s) and not necessarily those of the National Health Service, the NIHR, the MRC or the Department of Health.

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