

# RADIOTHERAPY FOR BREAST CANCER: HOW CAN IT BENEFIT FROM ADVANCING TECHNOLOGY?

\*Tomas Kron,<sup>1,2</sup> Boon Chua<sup>2,3</sup>

1. Department of Physical Sciences, Peter MacCallum Cancer Centre, Melbourne, Australia
  2. Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia
  3. Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia
- \*Correspondence to Tomas.Kron@petermac.org

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## ABSTRACT

There have been significant technological and technical advances in radiotherapy over the last 20 years. This paper presents the pertinent advances and examines their application in contemporary breast cancer (BC) radiotherapy, particularly for reducing the long-term toxicity, using intensity-modulated radiation therapy, image-guided radiation therapy, and management of breathing motion. These modern technologies and techniques enable precise delivery of a highly conformal radiation dose distribution to the target volume in real-time, to optimise tumour control, and minimise treatment toxicity. They have been used for the treatment of BC in selected centres around the world. Although there is insufficient high-level evidence to support their routine application in BC at present, implementation of these technologies has been shown to be feasible, and could result in clinically meaningful long-term benefits for selected patients with BC.

**Keywords:** Breast cancer radiotherapy, intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), motion management.

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## BACKGROUND

Radiotherapy is an established adjuvant treatment for breast cancer (BC), after conservative surgery or mastectomy, to reduce the risk of local recurrence and BC mortality in selected patients.<sup>1,2</sup> The target volume for radiotherapy typically includes the ipsilateral whole breast after conservative surgery or the chest wall after mastectomy, and regional lymph nodes form part of the target volume in selected patients. Conventionally, the radiation dose used for the adjuvant treatment of BC is 45-50 Gy delivered in 25 daily fractions over 5 weeks, followed by a tumour bed boost in selected patients. Dose escalation to improve tumour control, which is often a driver for the introduction of new technology for other cancer sites, is not a critical priority for BC. The radiation doses used in adjuvant therapy for BC are relatively low compared to definitive radiotherapy for some other tumour sites, and severe acute radiation toxicity is uncommon. However, in the context

of the growing number of BC survivors, the key challenge is to minimise the risk of long-term toxicity, secondary due to the irradiation of non-targeted critical organs especially the heart, lungs, and the contralateral breast.<sup>3-5</sup> The long-term toxicities of radiation-related second malignancy and cardiac morbidity are uncommon but even low-level radiation exposure of these normal organs may be harmful.<sup>6</sup>

More recently, radiation target volumes and dose fractionation used in BC have been evolving as a result of several randomised clinical trials. These trials of adjuvant whole breast irradiation showed the non-inferiority of hypofractionated schedules, including 40.0-42.5 Gy delivered in 15-16 daily fractions to the biologically equivalent 50 Gy in 25 daily fractions in terms of tumour control and treatment toxicity.<sup>7,8</sup> The overall treatment time is further decreased to 1 week or less with the increasingly widespread use of accelerated partial breast irradiation, which also entails a

change in target volume from the whole breast to the tumour bed only, in selected patients with early BC.<sup>9</sup> Although the delivery of larger fraction sizes in a shorter overall treatment time improves patient convenience, this benefit needs to be carefully balanced against the risk of more long-term adverse effects, highlighting the importance of judicious application of radiation technical advances for reducing this risk in patients with BC.<sup>10</sup>

The evolving practice of radiotherapy for BC has brought into focus the importance and relevance of new technologies and techniques to improve its efficacy and safety. The conventional technique of whole breast radiotherapy primarily involves two parallel opposed tangential radiation beams (main picture in **Figure 1**). They are often supplemented by smaller ‘fields-in-field’ to improve dose homogeneity in the target volume by delivering additional radiation doses to the parts that do not receive the prescribed dose from the two primary tangential beams.<sup>11</sup> In comparison to the other tumour sites, whole breast radiotherapy has been delivered at many centres without contouring of the target volume and critical structures explicitly on 3D computerised tomography (CT) scans to improve dose distribution throughout the target volume and reduce treatment toxicity. Although 3D CT planning was proposed for BC treatment two decades ago,<sup>12</sup> it was not until recent years that it became more routinely used.

The aim of the present review is to examine the impact of the following technical advances of radiotherapy for BC:

1. Intensity-modulated radiation therapy (IMRT);
2. Image-guided radiation therapy (IGRT);
3. Management of breathing motion affecting the target volume and critical organs, especially the heart.

## CONTEMPORARY TECHNOLOGIES AND TECHNIQUES OF RADIOTHERAPY

The past two decades have witnessed significant technological advances in radiation oncology, enabled by the increasing availability of computer technology to improve the characterisation of target volume, precision of its localisation, accuracy of radiation delivery, and homogeneity of dose distribution in the target volume. The improvements

in target volume characterisation and localisation are beyond the scope of the present review. IMRT, IGRT, and motion management primarily concern treatment delivery. IMRT improves homogeneity of radiation dose distribution in the target volume and enables delivery of highly conformal radiotherapy. IGRT is essential for accurate and reproducible positioning of radiation beams during treatment. Motion management is related to IGRT, as the same imaging tools could also be utilised to assess movements of the target, in order to improve treatment accuracy, and critical normal organs, to minimise radiation exposure. We present a general review of the three techniques with particular reference to BC. More in-depth reviews are presented elsewhere.<sup>13-16</sup>

### IMRT

The application of IMRT in the discipline of radiation oncology is increasing rapidly. The concept of IMRT was developed in the early 1980s, and involved subdivision of radiation beams into segments of different intensity, to increase the freedom of shaping radiation dose distribution and optimise its conformity and homogeneity in the target volume.<sup>17</sup> The subdivision became easily achievable when multileaf collimators (MLCs) became a standard accessory of most linear accelerators used in radiotherapy delivery.<sup>18</sup> The MLCs consist of many thin tungsten leaves that move independently of each other to shape the radiation fields. They effectively function as variable internal blocks in the beam, and conform to the target volume of individual patients quickly and automatically during treatment to enable radiation delivery to multiple small fields in rapid succession. The leaf pattern may also be dynamically modified during treatment to further decrease the time required for delivery of each fraction. More recently, this dynamic delivery was further enhanced by the capacity of linear accelerators to dynamically modify the MLC patterns whilst rotating the radiation source around the patient, a process called volumetric modulated arc therapy (VMAT).<sup>19</sup>

The design of target volumes and sequence of delivery of IMRT or VMAT are, in most cases, not possible without computer aid.<sup>20</sup> In the process of ‘inverse treatment planning’, the required radiation dose distribution is clinically defined, and the best possible method to achieve this distribution is yielded by a computer optimisation process. This has a number of important consequences:

- Contouring of all target volumes and relevant normal organs is required for the computer optimisation process,<sup>21</sup> increasing the workload of clinicians with resource implications in individual radiotherapy centres.
- An IMRT plan typically consists of at least seven radiation fields, each of which is subdivided into multiple segments. Treatment plans of this complexity cannot intuitively be understood and verified. They require additional quality assurance measures, which could be additional calculations or physical measurements, further increasing resource requirements.<sup>13</sup>
- The overall beam-on time for delivery of IMRT is longer than in conventional radiotherapy, resulting in more radiation leakage. Improvement in conformality of radiation dose distribution to the target volume is often countered by an increase of low radiation doses to normal organs distant to the target. The potential long-term adverse effects of low radiation dose exposure of normal organs, particularly the risk of radiation-related second malignancy, are an important consideration in the application of IMRT in patients with early BC, many of whom are long-term survivors.<sup>22</sup>
- Since the margins applied around target volumes to account for uncertainties in planning and treatment delivery in IMRT are typically smaller than in conventional radiotherapy, reproducibility of patient set-up and regular verification imaging become correspondingly more important.<sup>23</sup>

There is some inconsistency in the definition of IMRT in the literature. In whole breast radiotherapy, the use of two parallel opposed tangential radiation beams, supplemented by one or more smaller beams in the same direction (field-in-field approach; **Figure 1**), is sometimes referred to as IMRT, even if inverse treatment planning and complex field design is not a prerequisite.<sup>24</sup> This field-in-field approach was used in the IMRT arm of two randomised trials of early BC, which showed a decrease in acute radiation toxicity such as moist desquamation in the IMRT arm compared to 2D radiotherapy.<sup>25,26</sup> This was associated with an improved cosmetic outcome in the IMRT arm.<sup>26</sup> Including these results, a systematic review has found that radiotherapy for BC is one of the few areas where the benefit of IMRT is proven.<sup>24</sup>

The more contemporary definition of IMRT involves the use of more than two beam directions and inverse treatment planning. For whole breast irradiation, multi-field inverse-planned IMRT may provide additional degrees of freedom to optimise dose distribution, particularly when the target volume also includes the regional lymph nodes,<sup>27,28</sup> or to reduce radiation doses to the heart for patients with left-sided BC.<sup>29</sup> Heart sparing has been one of the main drivers for the introduction of inverse-planned IMRT in BC.<sup>28,30</sup> It is difficult to achieve in some patients using two tangential beams; in particular, if the target volume includes the internal mammary lymph nodes.<sup>31</sup> However, the inclusion of additional beam directions requires caution as it may paradoxically increase radiation doses to the contralateral breast, lung, and heart.<sup>32</sup>

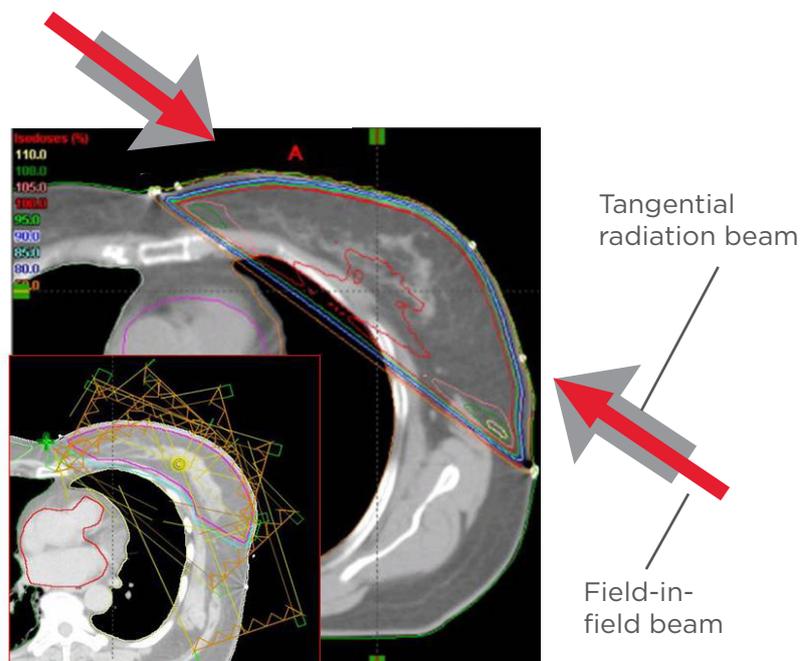
### The role of IMRT in radiotherapy for BC

The use of a field-in-field approach for whole breast irradiation is well-established as it not only reduces treatment time compared to the use of conventional wedges, but also optimises radiation dose distribution in the target volume: a key benefit of multifield inverse-planned IMRT without its disadvantage of increased doses to the distal non-targeted organs. Thus, implementation of inverse-planned IMRT and VMAT for BC is likely to be limited, with careful patient selection based on anatomy and the need for regional nodal irradiation rather than a 'one size fits all' approach informing their utilisation.

### IGRT

Verification imaging is a quality assurance measure undertaken to confirm if the target volume is accurately localised for treatment delivery. There is no uniformly accepted distinction between conventional verification imaging and IGRT.<sup>33,34</sup> However, there is general agreement that IGRT should include the following features:

- Availability of high quality imaging equipment in the treatment room;
- Ability to visualise the actual target volume (and not just the external markers or bony anatomy) with the patient in treatment position, immediately prior to treatment;
- Presence of predefined protocols to indicate the necessary corrective measures in the presence of inaccurate target volume localisation on verification images.



**Figure 1: Conventional whole breast radiation treatment plan using a two tangential, parallel-opposed beam arrangement supplemented by field-in-field.**

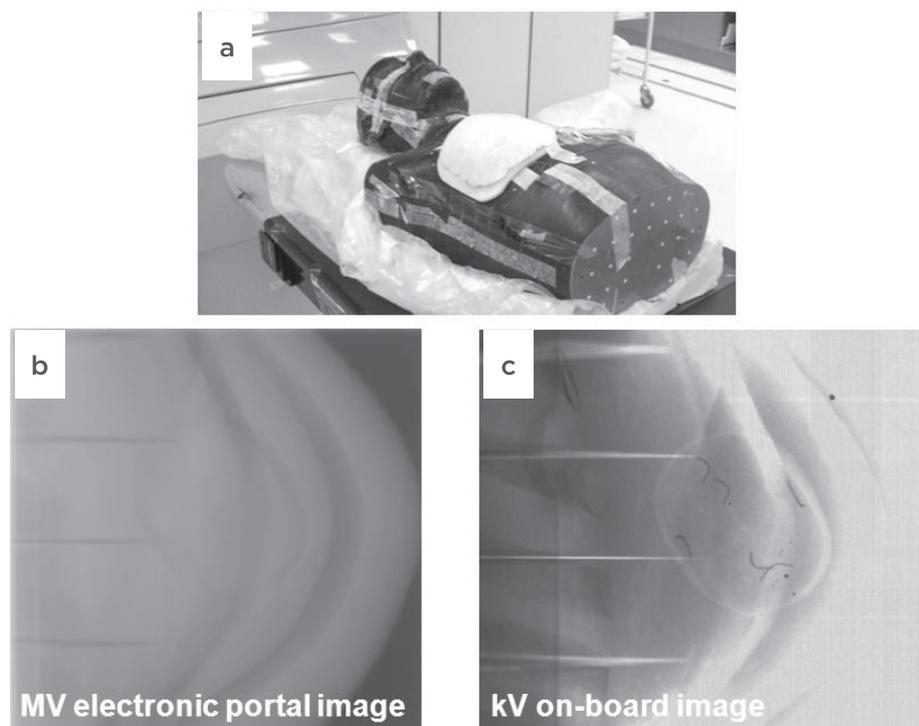
The insert demonstrates a treatment plan for multifield, inverse-planned, intensity-modulated radiation therapy.

Most modern linear accelerators are equipped with imaging equipment. A commonly available piece of equipment is the electronic portal imaging (EPI) device, which uses the megavoltage treatment beam to generate an image in a detector system, built into the gantry of a linear accelerator on the opposite side of the beam, without exposing patients to additional radiation doses.<sup>35</sup> Figure 2b shows an EPI of an anthropomorphic phantom which is depicted in Figure 2a. EPI uses megavoltage X-rays, a radiation quality optimised for treatment and not imaging. A dedicated diagnostic imaging unit using kilovoltage X-rays is now available on high-end linear accelerators to deliver high quality images as shown in Figure 2c.<sup>36</sup> The figure shows the surgical clips implanted in the phantom clearly. This can enable more precise targeting of the tumour bed, delineated by surgical clips, for the delivery of additional radiation doses to this site, to improve tumour control in patients undergoing breast conserving therapy.<sup>37,38</sup>

Projection images from many different directions, generated by the integrated diagnostic imaging unit of a linear accelerator, can be combined to form a reconstructed 3D cone beam CT (CBCT) image set prior to treatment delivery.<sup>39</sup> Comparison of this image set to the image acquired during the

preceding treatment planning process verifies not only correct positioning of the patient but also the target volume and critical organs.<sup>40,41</sup> However, the following disadvantages of CBCT may limit its application in BC:

- A CBCT delivers approximately 1 Gy of radiation dose to the imaged site. Over the course of 25 fractions, the total additional dose to the heart, lungs, and contralateral breast is of the order of 0.25 Gy, which is approximately 100 times higher than the annual radiation exposure from natural sources.<sup>42</sup>
- A CBCT is acquired over approximately 1 minute during which motion artefacts may be introduced. Digital tomosynthesis may be a faster low-dose alternative in the future.<sup>43</sup>
- CBCTs from different manufacturers have different fields of view, some of which may not cover the entire region of interest.
- Shifting of the patient to a different position on the treatment unit may be necessary to acquire a CBCT with sufficient clearance of the linear accelerator's gantry in its rotation around the patient, potentially introducing positioning errors.



**Figure 2: Image guidance in an anthropomorphic phantom with customised breast attachments.**

A) The phantom on a radiation treatment couch. Customised breast attachments were made from wax. B) Electronic portal image of the breast attachment acquired using megavoltage (MV) treatment beam. C) Image of the breast attachment acquired using diagnostic X-ray equipment integrated into the gantry of a linear accelerator. The surgical clips implanted into the phantom are visible only in this image.

*Taken from Willis et al.<sup>48</sup>*

The other modalities that may be used for IGRT of BC are ultrasound<sup>44</sup> and, most recently, magnetic resonance imaging.<sup>45,46</sup> However, these modalities require new skill sets and are not widely available at present.

### The role of IGRT in radiotherapy for BC

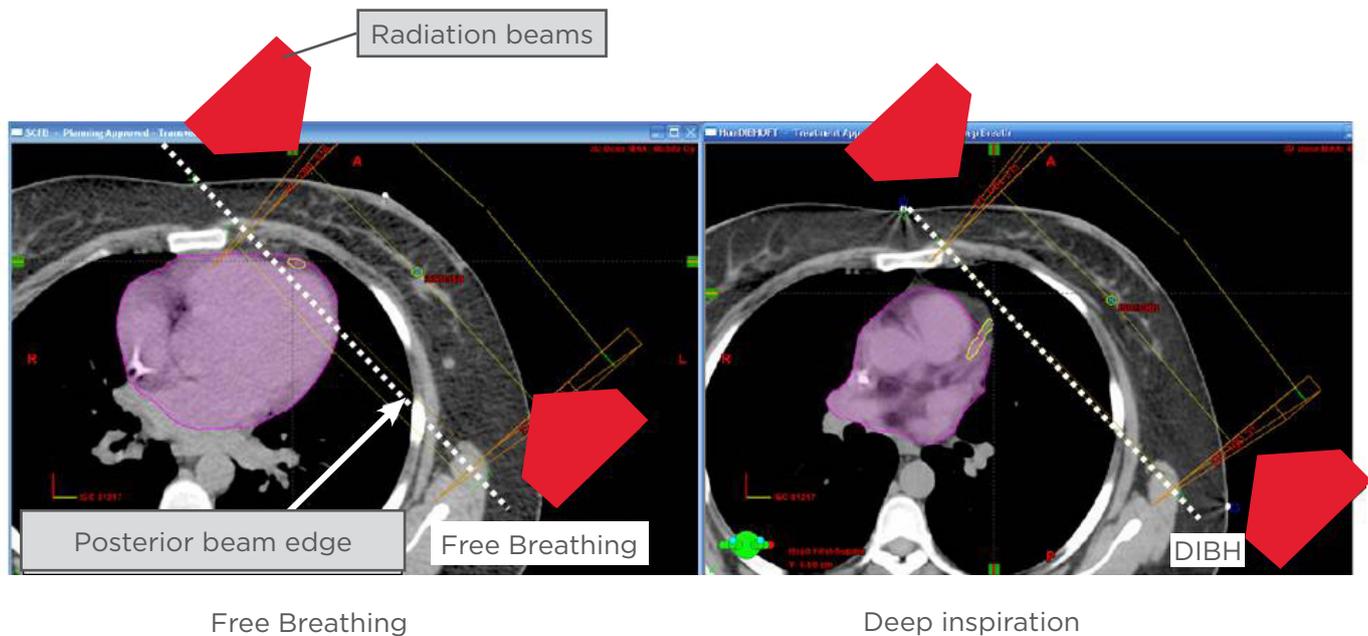
Although CBCT offers high quality verification images, this benefit needs to be balanced against the potential harm of additional radiation exposure to normal organs of patients and introduction of motion artefacts during its acquisition. Its application will likely increase if complex IMRT<sup>47</sup> and partial breast irradiation<sup>48</sup> become more widely used. However, EPI is currently the preferred option for verification imaging in most patients undergoing radiotherapy for BC.

### Motion Management

Motion management could improve the precision of radiation delivery to targets that move, particularly with the breathing cycle.<sup>16,49</sup> As chest wall motion is typically relatively limited during

quiet breathing,<sup>50</sup> the aim of motion management in whole breast radiotherapy is to reduce radiation doses to normal structures; in particular, the heart, which moves with breathing in relation to the target volume.<sup>51,52</sup> Motion management can be achieved using a variety of approaches, ranging from increasing the target volume to take motion into account, to immobilisation, gated delivery, and deep inspiration breath hold (DIBH).<sup>16</sup> In gated delivery the radiation beam is turned on only during predetermined phases of the breathing cycle to effectively 'freeze' the organ motion during radiation delivery and decrease treatment set-up uncertainty.<sup>53</sup> Its application in BC is predicated on the movement of the heart away from the high dose region of the target volume during inhalation.<sup>50,54</sup> DIBH capitalises further on this movement during deep inhalation, as illustrated in [Figure 3](#).<sup>55-59</sup>

An additional benefit of DIBH radiotherapy is that lung density is reduced and, as such, there is less healthy lung tissue in the radiation field, potentially reducing the probability of lung toxicity.



**Figure 3: Planning computerised tomography scans of a patient with left-sided breast cancer after breast conserving surgery, demonstrating the decrease in cardiac volume in the target volume during deep inspiration compared with free breathing. The heart moved inferiorly on the diaphragm and out of the radiation field during deep inhalation.**

DIBH: deep inspiration breath hold.

It is also important to note that DIBH, in the commonly used supine treatment position but not in the prone position, confers benefit to patients irrespective of the treatment technique used. In addition, a recent review of heart sparing approaches indicated that different techniques could complement each other.<sup>30</sup> For example, IMRT may further improve heart sparing in patients treated using DIBH.<sup>59</sup> However, as with other new techniques, DIBH must be implemented in practice carefully as treatment planning needs to be aligned with the DIBH state, and the breathing cycle of the patient should be monitored to ensure reproducible treatment set-up.

### The role of motion management in radiotherapy for BC

Cardiac toxicity is an important consideration for patients undergoing left-sided breast radiotherapy, particularly with the increasing use of potentially cardiotoxic systemic therapeutic agents, including anthracyclines and trastuzumab (Herceptin®).<sup>60</sup> Motion management using DIBH can be an effective method of reducing radiation dose to the heart to decrease the risk of cardiac toxicity. It is anticipated that DIBH will become increasingly used in radiotherapy for BC.

### CONCLUSION

New radiation technologies and techniques have the potential to improve the efficacy and safety of radiotherapy for patients with early BC. However, the maxim of '*primum non nocere*' is particularly relevant in these patients as the majority of them are long-term survivors. Thus, implementation of new radiation technologies and techniques must be scientifically rigorous and measured with patient safety as a key consideration. As IMRT and IGRT involve the delivery of additional low radiation doses to normal organs distal to the target volume, identification of patients who would derive the most benefit from the techniques is critical. An important consideration in implementing new radiation technologies and techniques is that they are often complementary to each other. For example, motion management would not be possible without high quality image guidance, and delivery of the highly conformal radiation dose distribution of IMRT is dependent on IGRT. Thus, it is necessary that new technological and technical advances in radiation oncology are not examined in isolation from each other. A multidisciplinary approach is key to their successful implementation to improve patient outcomes.

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