Early Experience of Tomotherapy-based Intensity-modulated Radiotherapy for Breast Cancer Treatment

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ABSTRACT:

Aims: New technology - specifically intensity-modulated radiotherapy (IMRT) - is now being applied to breast radiotherapy and a recent dosimetric analysis confirmed the advantages of IMRT over ‘wedge-only’ plans. Such application to everyday practice raises new issues and here we present the early experience of IMRT-based breast irradiation in a single centre.

Materials and Methods: We present cases of breast cancer treated by Tomotherapy®-based IMRT, where the perceived advantages of IMRT are considerable. Cases presented are bilateral disease, left breast irradiation, pectus excavatum, prominent contralateral prosthesis and internal mammary chain disease. We discuss the practicalities of such treatment and the advantages over standard breast irradiation techniques.

Results: Advantages include better conformity of treatment with lowering of dosages to underlying organs at risk, for example ipsilateral lung and heart. There is improved coverage of the planning target volume, including regional nodes, without field junction problems. Planning, quality assurance and treatment delivery are more time consuming than for standard breast irradiation and the low dose ‘bath’ is increased.

Conclusions: The standard radiotherapy tangential technique for breast/chest wall treatments has not significantly changed over many decades, whereas across many other tumour sites there have been great advances in radiotherapy technology. The dosimetric advantages of IMRT are readily apparent from our early experience. The wider spread of the lower dose zone (the low dose ‘bath’ of radiation) is a potential concern regarding late oncogenesis and methods to minimise such risks should be considered. O'Donnell, H. et al. (2009). Clinical Oncology 21, 294—301

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Key words: Breast radiotherapy, IMRT, tomotherapy

Introduction

Radiotherapy is an important part of treatment for many breast cancer patients and it accounts for a substantial proportion of a radiotherapy department’s workload — estimated at 30—40% of most UK radiotherapy department’s workload by fractionation. Adjuvant breast radiotherapy leads to improved local control rates over breast-conserving surgery alone [1]. Postoperative radiotherapy has also been shown to be associated with increased survival — the recent appreciation of this 4—5% survival gain being an impetus to optimise locoregional control in this disease; this survival advantage also extends to node-positive patients after total mastectomy [1]. The survival benefit is independent of systemic therapy and meta-analyses show that an overall survival benefit is maintained even after other deaths, unrelated to breast cancer, are taken into account [1]. Studies within the last 10 years have shown a survival advantage to node-positive patients receiving regional node radiotherapy in addition to adjuvant chemotherapy; this has fuelled renewed interest in safe regional node radiotherapy, including the internal mammary node chain [2].

Radiotherapy planning and delivery continue to evolve across most tumour sites. Standard tangential fields encompass the breast/chest wall with or without regional nodes, whereas three-dimensional conformal radiotherapy enables one to encompass the target volume using fixed, shaped radiation beams of uniform intensity across the field or with modification by devices, such as wedges. Whether assessed clinically or by computed tomography, the extent of glandular breast tissue can be difficult to localise and there is documented interobserver variability in delineation, most significantly for tumour bed boost radiotherapy [3]. The definition of the target becomes an ever more important issue as the sophistication of conformational technology increases and margins are reduced.

Intensity-modulated radiotherapy (IMRT) uses inverse planning and optimised non-uniform beam intensities with treatment plans generated using computer algorithms. As such, IMRT techniques are significantly more complex than three-dimensional conformal radiotherapy and have the
potential to achieve superior dose homogeneity and normal tissue sparing, especially for targets and organs at risk (OAR) with complex shapes, such as the breast/chest wall [4]. Tomotherapy is computed tomography-guided IMRT that delivers radiation helically, allowing precise delivery of radiation while sparing the surrounding normal tissues. The radiation source rotates around the patient and is modulated by rapidly moving micro multileaf collimators, such that the radiation is delivered using multiple tiny beamlets, thereby offering better conformity than standard LINAC-based IMRT, as illustrated by the cases described here.

The use of helical tomotherapy, with the gantry rotating around the patient delivering radiation from any gantry angle, is not optimal for breast irradiation because when compared with standard tangents, use of all gantry angles results in the delivery of low doses to areas in the body that would only receive a scatter dose during conventional radiotherapy. The organs of particular concern being the contralateral breast and lung. Topotherapy, which is not yet in clinical practice, uses the tomotherapy unit in fixed gantry positions with the beam intensity modulated by the micro collimators as the patient is moved through a stationary gantry. The breast irradiation technique in use at the Cromwell Hospital is a tomotherapy-based IMRT technique designed to limit the low dose bath effect. The OAR are blocked so that beams do not enter through them in order to irradiate the target, effectively creating a tangential approach. This technique uses a more limited number and angle of beams than standard helical tomotherapy.

The introduction of such new techniques for breast radiotherapy raises new issues and here we illustrate examples from our experience to date with tomotherapy-based IMRT. The cases presented demonstrate clinical situations that pose challenges to the clinician, dosimetrist and physicist alike. They represent typical problems arising in the context of breast irradiation and we discuss some of the practicalities, advantages and the potential pitfalls of IMRT-based radiotherapy with reference to these cases. We include examples of bilateral breast radiotherapy, regional node irradiation (supraclavicular fossa and internal mammary node chain), radiotherapy after breast implantation and dose volume histogram (DVH) analyses for the OAR.

**Patients and Methods**

IMRT breast irradiation was carried out on a Hi-Art Tomotherapy® (Wisconsin, USA) apparatus at The Cromwell Hospital, London. Patients presented here were selected as they exemplified common difficulties experienced in breast irradiation and show the advantages of IMRT-based irradiation. All patients were positioned with both arms up on a MEDTEC wingboard with vacfix to immobilise the elbows. Patients were instructed on gentle breathing during (axial) scanning as per department protocol after performing an in-house study into variation with inhale/exhale techniques on computed tomography. Each computed tomography data set took about 1 min to acquire.

**Target Definition**

The aim of most radiotherapy treatments is to deliver a homogenous dose. Most centres have or are moving towards full three-dimensional planning for breast irradiation. Patient factors such as breast size, chest wall shape and incline are considered when planning the gantry angles and collimator rotations. Limiting factors are lung and cardiac tissue, as measured at the time of the simulator image, and medial and lateral borders are often compromised to reduce the extent of normal tissue irradiation. Nevertheless, tangential fields often encompass significant volumes of lung, cardiac and normal soft tissues and the amount of variation between patients can be large, as seen in Fig. 1.

With adjuvant breast treatment, the breast tissue plus or minus locoregional lymph nodes is considered the clinical target volume (CTV). This is a biological entity taking into account risk of microscopic disease in the remaining breast tissue and in the draining lymph nodes and will vary

![Conventional tangents](image-url)
between patients. The planning target volume (PTV) is a geometric entity, and includes margins added to allow for organ movement (inter-fraction and intra-fraction) and set-up error. Any potential advantages of three-dimensional conformal radiotherapy or IMRT will diminish if the target volumes are not correctly identified and the precise delineation of a target volume is critical whether for whole breast, partial breast or concomitant boost radiotherapy.

We carried out mapping of breast glandular tissue (CTV) as seen on the planning computed tomography scan. To avoid interobserver variability in contouring, the same clinician outlined all cases. Glandular tissue was visualised on computed tomography with the following boundaries: anteriorly, 0.5 cm inside skin, posteriorly, to the chest wall to include clips or deep margins if appropriate, medially, 0.5–1 cm to the ipsilateral midline to assist with contralateral breast sparing (not possible if medial tumour), laterally, the visualised breast to assist, generally excluding the axillary tail. The tumour bed was localised by use of wire placed over the lumpectomy scar at the planning computed tomography and by the appearance of a seroma on computed tomography. Nodal groups (supraclavicular fossa in case 2 and internal mammary node chain in case 4) were outlined by the same clinician on the planning computed tomography images.

Intravenous contrast was not used, rather, anatomical landmarks were used, as per published computed tomography-based nodal boundaries [5]. A 0.5 cm margin was typically added to each CTV to give a PTV based on departmental calculations of systematic and random errors. The PTV remained 0.3 cm from the skin surface to ensure some skin sparing. The total time for clinician and dosimetrist outlining for CTV and OAR, respectively, was about 2–3 h. Target volumes were treated in 22–25 fractions to a dose of 45–50 Gy. In the cases illustrated, the tumour bed was boosted sequentially (8 Gy/4 fractions). There were no absolute dose constraints for the heart, lung and contralateral breast. Treatment delivery time was 8–10 min (beam on) for breast alone, 10–13 min for breast/chest wall nodes. Verification images were taken for the first three fractions, and online corrections carried out. After fraction 3, a correction for systematic set-up deviation was carried out, with images on day 4 with the correction. If all parameters were within 0.5 cm tolerance, further imaging was once weekly to minimise concomitant doses due to image-guided radiotherapy.

**Case 1: Bilateral Breast Irradiation**

Bilateral breast radiotherapy is challenging with standard radiotherapy techniques, but the use of IMRT can readily overcome the obvious difficulties while ensuring target volume conformity and lung and heart avoidance. It also eliminates the problem of overlapping fields. In Fig. 2, the conformity of the therapeutic dose (50 Gy/25 fractions) to both breasts can be appreciated. The lung doses are exceptionally low, as documented on the corresponding DVH. Inspection of the DVH in Fig. 2 shows that 20% of the combined lung volume receives <5 Gy and the volume of lung receiving 20 Gy is less than 5%. The axial computed

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**Fig. 2** — Computed tomography in axial plane (left panel) and reconstructed coronal computed tomography showing superimposed isodosimetry of the bilateral breast radiotherapy plan. The colour code represents the total dose to be received (Gy). The lower panel shows the dose volume histogram of the planning target volume and the organs at risk.
tomography images show the absence of central overlap despite bilateral irradiation.

**Case 2: Bilateral Breast and Left Supraclavicular Fossa Irradiation**

Irradiation of the supraclavicular fossa nodes is standard for patients with more than three positive axillary nodes and in the case presented below, it can be appreciated that there are obvious advantages of treating such a target volume in continuity without field junctions. Numerous methods of irradiating the axilla and supraclavicular fossa are used, such as the single isocentre technique. The side-effects of radiotherapy in this region can cause significant morbidity, making it essential to minimise excess normal tissue irradiation. In order to encompass the supraclavicular fossa with conventionally planned fields, a significant volume of normal tissues, most notably lung, is irradiated. The incidence of radiation pneumonitis in breast radiotherapy is relatively low, but when attempting to cover regional lymph nodes the risk of lung toxicity increases and the potential for lung damage increases further still where bilateral breast radiotherapy is required. Standard radiotherapy techniques, including single isocentre methods, do not overcome the issue of increased lung irradiation and the possibility of overlapping fields and potential overdosing of underlying OAR remains. Inclusion of the internal mammary chain nodes in selected cases will further increase the extent of normal tissues irradiated by standard methods, as will be discussed in case 5.

With left-sided breast radiotherapy, as shown in Fig. 3, it can be appreciated that encompassing the target volume (as it curves around the chest wall) with tangents (superimposed in yellow) would result in significant irradiation of the heart, whereas the conformity afforded with IMRT minimises the amount of heart tissue included. The DVH shows that the heart dose for this bilateral case is acceptably low: 20% of the cardiac volume receives just 15 Gy, with <3% receiving 30 Gy. The application of tangents, as superimposed in yellow on the images, highlights the contrast in the degree of cardiac irradiation with conventional radiotherapy. In order to irradiate the target volume on the left side, standard tangents would encompass a significant volume of the heart and would most probably necessitate compromise of the medial and lateral borders. The figure also shows the synchronous left regional node irradiation — to a lower dose of 45 Gy (vs 50 Gy to the chest wall) with no radiation field gap between the nodal and chest wall volumes, only a seamless transition. Also noteworthy for a case that encompasses both breast/chest walls and a unilateral regional nodal volume (axilla/supraclavicular regions) is that the combined lung DVH lies well within acceptable parameters of lung tolerance, although appreciably more than that in case 1 (Fig. 2) where there was no additional nodal radiation.

![Conventional tangent](image1)

**Fig. 3** — Computed tomography in axial plane (left panel) and reconstructed coronal computed tomography showing superimposed isodosimetry of the bilateral radiotherapy plan plus unilateral regional nodal radiotherapy. The colour code represents the total dose to be received (Gy). The lower panel shows the dose volume histogram of the planning target volume and the organs at risk — the comparison of the combined lung dose, c.f. that in Fig. 2 is noteworthy, as is the heart avoidance. The arrowed yellow line shows the volume encompassed by conventional tangents if standard techniques were used to treat the left chest wall.
Case 3: Pectus Excavatum

Anatomical variation between patients necessitating individualised therapy is commonplace in breast radiotherapy—most often due to variation in breast size and shape and in chest wall curvature. In some instances, the chest wall curvature poses a particular challenge, such as in the case of pectus excavatum. This can be appreciated in Fig. 4, where right breast radiotherapy (45 Gy/22 fractions) was delivered to a lady with marked concavity of her anterior chest wall. When a typical tangent is applied (as shown in yellow) to ensure coverage of the target volume, the degree of underlying lung irradiated would be considered unacceptable and medial and lateral borders would be altered as a result—potentially compromising the target volume coverage. Also noteworthy is the minimal contralateral breast dose—10% receiving just 5 Gy and <5% receiving 7.5 Gy.

Fig. 4 — Computed tomography in axial plane (left panel) and reconstructed coronal computed tomography showing superimposed isodosimetry of the right breast radiotherapy plan in a patient with pectus excavatum. The colour code represents the total dose to be received (Gy). The lower panel shows the dose volume histogram of the planning target volume and the organs at risk—the combined lung dose is noteworthy, as is the conformity to the chest wall curvature. The arrowed yellow line shows the volume encompassed by conventional tangents if standard techniques were used to treat the right chest wall.

Case 4: Bilateral Implants and Breast Irradiation

The use of primary reconstructive surgery after breast cancer surgery is becoming increasingly common. The clinical indications for adjuvant breast radiotherapy remain unchanged, but the practicalities of delivering the radiotherapy are altered. The axial computed tomography images in Fig. 5 show the dose (45 Gy/22 fractions) conformity to the right breast treated with IMRT. From the corresponding DVH it is apparent that the contralateral breast dose is minimal (15% receiving 5 Gy and <5% receiving 7.5 Gy). Given the altered anatomy it can be appreciated that to encompass the target volume with conventional tangents while avoiding the contralateral breast would not be possible. With IMRT the left breast is successfully avoided, as shown in Fig. 5, with no compromise on the target volume.

Case 5: Internal Mammary Chain Nodal Irradiation

The ability to include the internal mammary lymph node chain in adjuvant breast radiotherapy without overdosing the underlying structures (notably the heart) is a challenge to which IMRT is tested. Although uncertainty remains regarding the effectiveness of irradiating the internal mammary nodes, increased interest has been generated by reports of a survival benefit in selected women whose postoperative radiation therapy portals often included the internal mammary chain [2].

OAR, such as the brachial plexus, are difficult to outline, especially on non-contrast planning computed tomography and clinicians need to become familiar with the cross-sectional anatomy of the thorax. IMRT can overcome the complexities of the target volume and spare dose to the normal tissues. In the case shown in Fig. 6, the treatment aim was to encompass the breast, supraclavicular fossa and internal mammary node chain for adjuvant radiotherapy. As before, the breast dose was 50 Gy and the locoregional nodes 45 Gy.
Discussion

Conventional radiotherapy techniques for the treatment of breast cancer have produced impressive locoregional control and overall survival rates with little change in methods over many years. With advances in imaging, treatment planning and delivery we now have new radiotherapy techniques that should offer advantages while maintaining the high rates of local control and overall survival. IMRT represents one of the most important technological advances in radiotherapy since the advent of the linear accelerator. It is an evolving field showing significant potential for improving radiotherapy treatment for many patient groups and tomotherapy IMRT is probably the most sophisticated form of IMRT in clinical practice [6].

The side-effects of breast radiotherapy include lung and cardiac toxicity, lymphoedema, brachial plexopathy, soft tissue fibrosis and its cosmetic sequelae, as well as second malignancies. Patients accepting adjuvant radiotherapy should be counselled on the potential benefits of local treatment along with the side-effects, including late toxicity, particularly as many patients have a good long-term prognosis — it is with these considerations in mind that IMRT must be evaluated.

Irradiation of the left breast in particular brings its own concerns of cardiac toxicity. Randomised trials and overviews have shown an increased incidence of late cardiac mortality after breast radiotherapy, due largely — it is

Fig. 5 — Computed tomography in axial plane (left panel) and reconstructed coronal computed tomography showing superimposed isodosimetry of right breast radiotherapy after bilateral reconstructive surgery and breast implantation. The colour code represents the total dose to be received (Gy). The lower panel shows the dose volume histogram of the planning target volume and the organs at risk. The arrowed yellow line shows the volume encompassed by conventional tangents and the degree of contralateral breast irradiation incurred in doing so.

Fig. 6 — Axial computed tomography showing superimposed isodosimetry of left breast radiotherapy and unilateral regional nodes, including the internal mammary chain irradiation.
accepted — to encompassment of the left ventricle within the tangential left breast/chest wall portals. With the increasing use of anthracyclines and herceptin and their potential cardiac toxicities there could be a summation with radiation, and the relevance of cardiac avoidance, particularly when treating left-sided breast cancers, with radiotherapy has never been greater. In the cases illustrated here we exemplify the improvements that tomotherapy IMRT brings in this regard.

The incidence of invasion of the internal mammary chain nodes ranges from 4% in axillary node-negative patients to 72% in axillary node-positive patients — the tumour location within the breast also being of relevance [2]. Since the European Organization for Research and Treatment of Cancer (EORTC) trial publication [2], the internal mammary chain may also be included in the desired CTV (after a two to three decade embargo on this practice). One EORTC study (22922—10925) is currently investigating whether elective irradiation of the internal mammary and medial supraclavicular node chain has a positive impact on survival. A common problem noted from the EORTC trial is the matching of field junctions [2]. Methods of matching fields vary between institutions and such problems are inevitable with standard radiotherapy, so the benefits of conformal and IMRT become apparent. With tomotherapy-based IMRT it is possible to treat the breast/chest wall and regional nodes, including the internal mammary nodes, in continuity, thereby overcoming the issue of overlap or gaps and their resultant sequelae.

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Several investigators have described potential advantages of IMRT in breast radiotherapy, such as decreasing the dose to the ipsilateral lung and heart, particularly for internal mammary nodal radiotherapy, and reducing breast reaction and fibrosis through improved dose homogeneity [7–11]. Other studies have looked at the role of IMRT in breast cancer, addressing differing IMRT techniques, target definition and interobserver variation in outlining, the inclusion of the regional lymph node areas for treatment, and DVH analysis [7,9,10]. Donovan et al. [12] recently confirmed that most of the IMRT treatment planning methods studied offer advantages over the conventional wedge pair. However, IMRT does increase the dose to other organs not normally considered in conventional breast radiotherapy, such as the contralateral lung, contralateral breast, thyroid, humoral head and oesophagus. This low dose 'bath' almost exclusively extends only between the upper and lower axial limits of the PTV and the combined lung DVH graph in Fig. 2 demonstrates well the avoidance of intermediate dose to OAR, but at the price of a long low dose 'tail' to the curve.

The advantages of improved conformity have to be weighed against the 'low dose bath' effect. The increased dose (albeit low dose) to other surrounding normal tissues not previously considered as OAR is a potential disadvantage of IMRT for breast irradiation. The significance of low dose irradiation to these surrounding tissues is as yet unknown. For conventional methods, a small increase in lung and oesophageal cancer incidence has been reported in a population of patients with overall good long-term survival prospects [1]. However, a large-scale, single-institution, retrospective study of 16 705 patients treated for non-metastatic breast cancer suggested that standard radiotherapy did not increase the incidence of second primary cancers other than sarcomas and lung cancer [13]. The subject of late oncogenesis must be studied assiduously, with particular reference to IMRT.

The use of IMRT for breast irradiation is not as clear cut as for other tumour sites and the most dramatic improvements may only truly be appreciated for the more complex treatments. Accurate target volume localisation by the physician is fundamental and is undoubtedly more time-consuming for IMRT than clinical localisation by palpable breast tissue as for the tangential portals’ technique. The CTV delineated as glandular breast tissue for a conformal/IMRT plan will probably differ from a clinically marked target volume and the volume growth CTV—PTV. However, target definition apart, the superior dose homogeneity and sparing of OAR with IMRT is apparent.

Planning and quality assurance is more time-consuming for IMRT, as is daily treatment time for the patient, and this must be balanced against the advantages discussed above. Conventional tangential radiotherapy is relatively insensitive to organ motion and set-up error, but tighter set-up requirements are necessary for IMRT. During breathing, the IMRT-defined PTV may move outside the external contour (as defined on planning computed tomography) and result in geographical miss of the target. Methods such as application of virtual bolus for planning and dosimetry calculations can be used to compensate for this [8]. Methods used to account for breathing in LINAC-based breast radiotherapy include active breathing control and real-time position management, aiming to deliver treatment during phases of the breathing cycle that correspond to those when the planning scan was acquired, e.g. in deep inspiration when the heart is at maximum distance from the chest wall or breast. Image-guided techniques were not used in the cases illustrated here, rather the patients were instructed on gentle shallow breathing for planning and treatment. Future application of IMRT to sites susceptible to breathing motion, such as the breast, will require further consideration.

In addition to the improvements of IMRT over standard radiotherapy for target coverage, therapeutic homogeneity, and normal tissue avoidance, IMRT also offers assistance in current areas of study, such as partial breast irradiation and the use of concomitant boost radiotherapy. There is as yet no consensus for partial breast radiotherapy or for tumour bed concomitant boost treatment. Clinical data have documented that most in-breast failures after breast-conserving therapy are in the immediate vicinity of the tumour bed [14]. The frequency of these recurrences is greatly reduced with adjuvant radiotherapy, and the pattern of in-breast failures remote from this site (<5%) is unaltered by radiotherapy [14]. This supports that the benefit of radiotherapy is at the site of the original lesion and that the risk of new primary disease arising elsewhere in the breast is unaltered. As a result, much work is
currently being conducted to investigate the role of partial breast irradiation, concomitant boost treatment and dose escalation to the tumour bed. Dose-escalated IMRT, giving higher doses per fraction to high-risk areas, may offer a benefit in terms of recurrence risk and also prove to be cost-effective. This theory is being examined in the current IMPORT HIGH and IMPORT LOW phase III clinical trials. Tomotherapy-based IMRT should be well suited to concomitant boost radiotherapy. However, practitioners of such a concomitant boost approach must be mindful of possible compromise to late cosmetic appearance due to larger fraction sizes. Our experience to date has been with cases in whom late cosmesis was not paramount; in such cases, boosting the originally involved quadrant (with skin sparing) shortened treatment time and has been well tolerated.

The absence of any gaps/junctions between radiation fields when irradiating the chest wall and regional nodes is a perceived advantage of IMRT and we have examples of patients in whom there has been heavy axillary involvement in the gap/junction region where this advantage is, we believe, important.

The potential advantages of IMRT are easy to demonstrate qualitatively in treatment planning exercises, but careful comparative studies and clinical trials with long-term follow-up are needed to show that IMRT may also offer advantages not yet fully appreciated. The selected cases presented here exemplify problems in breast radiotherapy where IMRT is advantageous and we have anecdotally seen that the potential is recognized.

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The potential advantages of IMRT are easy to demonstrate qualitatively in treatment planning exercises, but careful comparative studies and clinical trials with long-term follow-up are needed to show that IMRT may also offer advantages not yet fully appreciated. The selected cases presented here exemplify problems in breast radiotherapy where IMRT is advantageous and we have anecdotally highlighted others. Although accepting the argument that breast radiotherapy should be made as simple as possible in order to rationalise departmental resources for this frequently employed usage, we believe that the cases presented here demonstrate some of the merits of IMRT. The technique should be further explored while being mindful of its potential disadvantages.

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