Can intensity modulated radiation therapy reduce cardiac dose in left-sided breast patients?

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Abstract Purpose: In recent years interest has grown in the investigation and clinical application of intensity modulated radiation therapy (IMRT) for adjuvant treatment of early stage breast cancer. A review of the current literature was conducted to establish if IMRT can reduce doses delivered to the heart and potentially minimise the likelihood of cardiac toxicities for early stage left-sided breast cancer patients. Methods: A literature review was undertaken to identify recent studies (1999–2009) that compared IMRT with three-dimensional conformal radiation therapy (3D CRT) techniques for left-sided breast patients. Results: Based on the five reviewed articles, IMRT reduces the cardiac volume treated to high doses; however this is at the expense of an increase in the volume treated to low/intermediate doses. The maximum dose to the coronary arteries and left ventricle can be reduced with IMRT. Using radiobiological modelling some studies found a reduced risk of normal tissue complication probability (NTCP) for cardiac mortality with IMRT. Conclusion: The evidence provided in this review encourages the use of IMRT approaches in the treatment of early stage left-sided breast cancer in order to minimise morbidity specifically to cardiac tissue. However, in order to ensure optimal use of resources, thought needs to be given as to which women will benefit most from complex treatment approaches.

Keywords: cardiac dose, early stage breast cancer, IMRT, radiation therapy.

Introduction

The current standard of care for women with early stage breast cancer is breast conservation therapy (BCT) which includes surgical excision of the tumour and adjuvant radiation therapy to the whole breast. Results from two decades of study have conclusively shown that radiation therapy has an important role in ensuring local control for patients being treated with BCT.1–3 Despite the documented importance of radiation therapy in the overall treatment of patients with breast cancer, normal tissue toxicities can limit the potential survival advantages of this treatment modality and reduce the overall quality of life of many patients.3–4 In particular, several studies have raised concerns that cardiac morbidity and mortality may be increased by the use of left-sided breast irradiation, which often includes some of the myocardium and coronary arteries.5–7 However it has been suggested that these results were from older studies and modern tangential techniques already reduce the likelihood of cardiac toxicity. A review looking at 20 years of data has found modern techniques are not associated with a higher risk of cardiac death, but alarmingly there is an association with an increased rate of diagnoses of coronary artery disease and myocardial infarction compared with treatment to the right breast.6 Also, the more widespread use of anthracycline/ taxanes/trastuzumab chemotherapy regimens has increased the potential for cardiac toxicity.7 This supports the introduction of new measures to further reduce dose to the heart.

In recognition of the technical limitations of traditional radiation therapy techniques to provide solutions in terms of dose optimisation, three dimensional conformal radiation therapy (3D CRT) has become clinical practice in modern radiation therapy departments. Computed tomography (CT) based treatment planning gives 3D anatomical information. The information available with a CT data set and planning software allows the selection of fields and optimisation to reduce dose to the heart. 3D CRT plans usually consist of two opposed wedged tangential beams, often with field in fields to reduce any hot spots. Studies comparing two dimensional (2D) planning with 3D planning have shown that 3D CRT reduces dose to the lung and heart.8,9 3D CRT has been shown to reduce the total heart dose and to spare the left circumflex and right coronary artery, but the dose to the left anterior descending artery (LAD) remained unchanged.9 Irradiation to the LAD has been determined to have an important role in the development of cardiac toxicity.10 More complex radiation therapy techniques such as intensity modulated radiation therapy (IMRT) may have the potential to reduce the dose to this vessel. IMRT planning and treatment delivery is further improved from 3D CRT by using sophisticated computer controlled delivery to modulate the intensity of individual beamlets across the radiation beam to conform the dose more precisely to the target volume while selectively minimising dose to the surrounding healthy structures.

The aim of this literature review is to assess whether IMRT is superior over 3D CRT in reducing cardiac dose for early stage left-sided breast cancer. The review will compare the dosimetric outcome and normal tissue complication probability (NTCP) for excess cardiac mortality. NTCP modelling involves complex mathematical calculations that estimate the probability of a heart complication for a given dose level when the heart is given a homogeneous irradiation. There are six different NTCP model/parameters for the heart, three for pericarditis and three for cardiac mortality.11
Methods
This review is based on a search of Medline, PubMed and ScienceDirect. A combination of keywords were used: “intensity modulated radiation therapy”, “radiation therapy”, “breast conservation therapy”, “normal tissue complication”, and “cardiac dose”. Recent articles published between 1999 and 2009 were included in this review. Article relevancy was based on left-sided treatment site and disease stage of patient. Included articles needed to use inverse planned IMRT. Using listed references from retrieved articles was also part of the search strategy.

Results
There were 189 articles on IMRT for breast cancer patients. This was refined to five relevant articles. All studies prescribed a target dose to 50 Gy except for Hong, et al., which prescribed to 46 Gy.

Landau, et al., restricted their study to left-sided breast patients with increased heart volume in the field. The selected 10 left-sided breast patients had a medial heart distance (MHD) of at least 1 cm. MHD is the maximum length of heart seen in the beam’s eye view of the medial tangent field. This study compared IMRT to 3D CRT that includes alloy shielding blocks. Though this study used physical compensators it was included as it is felt this could be theoretically achieved with multi-leaf collimator (MLC). For the 3D CRT, shielding blocks were designed using the beam’s eye view to either shield as much of the heart as possible without compromising the PTV, or block off the heart completely regardless of the effect on the planning target volume (PTV). These were compared to an IMRT 2-field that used the same beam orientations and a 4-field arrangement. The 4-field IMRT arrangement was optimised to deliver dose to the medial and lateral aspects of the PTV while sparing the heart. The 4-field IMRT showed the lowest amount of heart receiving high doses with reduced volume receiving 80% and 90% of the dose (V80 and V90). IMRT increased the volume receiving 60% of the dose (V60) compared to 3D CRT. PTV homogeneity as indicated by the volume between the 95% and 107% iso dose lines (V95-107) as per ICRU guidelines (ICRU report 50) increased with the IMRT techniques compared to 3D CRT. While the partial blocks had comparable homogeneity to the IMRT plans this was reduced with full cardiac blocking.

Hurvikmans, et al., completed the largest study in this analysis with a retrospective planning study using CT data of 17 randomly selected left-sided breast patients. In terms of heart dose, the volume of heart receiving 95% (V95) of the dose was 4% and 1% for the 3D CRT and tangential IMRT fields respectively. This study also used the relative seriality model to predict the normal tissue control probabilities (NTCP) for cardiac mortality. Results showed NTCP reduced from 4% to 2% with the 3D CRT and IMRT technique respectively. Homogeneity as indicated by the V95-107 was not significantly different between the two techniques.

Cho, et al., also looked at NTCP using the relative seriality model and cardiac sparing with IMRT; they designed a more simplified tangential IMRT solution using pre-defined segments and compared this with 3D CRT. The sample was restricted to patients who have a large amount of heart within the field, selecting nine left-sided breast patients with a MHD of at least 2 cm. The results found a reduced risk of cardiac mortality with IMRT with NTCP of 2.1% and 0.2% for the 3D CRT and IMRT plans respectively. The PTV homogeneity as indicated by the V95-107 was generally very low for both techniques.

A 2009 publication by Lohr, et al., compared 14 patients with left-sided breast cancer with an “unfavourable thoracic geometry”, using 3D CRT and 9-field IMRT planning techniques. Unfavourable thoracic geometry was defined as patients with minimal distance of the heart to the thoracic wall or concave thoracic wall/pectus excavatum. IMRT consistently reduced the maximum dose to the heart, as well as the volume of the heart that received more than 30 Gy or more than 40 Gy. The IMRT plan increased the mean heart dose to 8.52 Gy compared to 6.85 Gy with 3D CRT. The study also looked at the dose received by the left ventricle. By comparing the IMRT plan with the 3D CRT plan, the maximum dose to the left ventricle was reduced by an average of 30.9%. The mean dose to the left ventricle was reduced by an average of 10.7%. With NTCP modelling the mean risk of excess cardiac mortality was reduced from 6.03% to 0.25%. The coverage of the PTV was only slightly inferior.

The study by Hong, et al. is of particular interest as it looked specifically at dose received by the coronary arteries, a region which has been found to receive a high dose. Treatment plans for both the left and right breasts were developed using 3D CRT and intensity modulated tangential beams on five patients prescribed to 46 Gy. On average for left-sided breast patients, the dose encompassing 20% of the coronary arteries (D20) was reduced from 36.1 Gy with 3D CRT to 26.7 Gy with IMRT, and the mean dose was reduced from 21.3 Gy to 14.8 Gy. Large standard deviations of D20 and the mean dose reflect the wide variation in the position of the coronary artery regions observed for the five left-sided breast patients. The isodose level encompassing 5% of the PTV was used as an indicator of the high dose region within the PTV and was marginally lower with IMRT.

Discussion
Cardiac dose
Effects of reduction of high dose volume
All studies reported that IMRT showed a decrease in high doses to the heart (Table 1). This supports the use of IMRT as effects on cardiac toxicity are more pronounced at higher doses. Ionising radiation possibly leads to an earlier appearance of age related fibrosis of the myocardium. In the literature the median dose for myocardial fibrosis is quoted with more than 35 Gy.

Effects of increase in low/intermediate dose volume
The increase in the mean dose to the heart with IMRT reported by Lohr, et al., and V60 by Landau, et al., is a consequence of the spreading of low and intermediate dose with the multi-field technique. Questions relating to radiobiologically damaging effects of low dose to the heart are still unanswered. However some of the literature from patients treated for breast and Hodgkin’s disease supports the idea that reducing the high dose to the heart even with an increase in the amount of heart treated to low dose is still beneficial.

Dose to the coronary arteries/left ventricle
Hong, et al., demonstrate reductions to coronary arteries which is only achievable with IMRT. The anatomical position of the left coronary artery is near the left chest wall which means this area is included within the tangential irradiation volume. Treating this area to high doses can possibly result in an increased risk of the appearance of myocardial infarction in the supply area of the left coronary artery and rhythm disturbances by myocardial fibrosis.

Lohr, et al. found that with IMRT there is a reduction in the
maximum and mean left ventricle doses. Myocardial single photon emission computed tomography (SPECT) studies have shown the left ventricle irradiated volume to be the most important determinant of perfusion changes in the distribution of the left anterior descending coronary artery following radiation treatment.22,23

**Radiobiological modelling**

All studies found that IMRT reduced the NTCP for cardiac mortality. The significance of this needs to be balanced with the issues associated with the accuracy of modelling cardiac toxicity. In a review by Gagliardi, et al.12 several reasons are discussed, including inaccurate assumption of a homogeneous radiosensitivity of heart subunits, a lack of dosimetric data for the older techniques which formed the basis of the model, and a latency of symptoms of greater than 10 years.

Large variation in the literature was found between the studies for the reduction in NTCP for cardiac mortality. The percentage reduction by using IMRT varied from 1.90–5.78%. This could be explained by variation in patient selection between the studies, and by the non-linear relationship between dose and NTCP: a modest decrease in cardiac dose can result in a dramatic NTCP reduction.24 Also, although all studies used the same relative seriality model to determine NTCP there could be variation in the model parameters.

**PTV coverage**

Variation in the PTV homogeneity reported in the reviewed studies may be mainly due to differences in the methods and goals of optimisation. Most of the studies show that IMRT reduces dose inhomogeneity as supported by Cho, et al.17 Landau, et al.14 and Hong, et al.13 However, there were no differences found from the investigations of Hurkmans, et al.16 Lohr, et al.18 found a slightly inferior PTV coverage. Of particular interest are the results of Cho, et al.17 which had a significantly lower proportion of the PTV within 95–107% isodose lines compared to the other studies. The reason for this was the goal of the optimisation to have NTCP less than 2%. The authors suggest that more PTV dose heterogeneity allows better heart sparing and PTV coverage. In comparison, the study by Hurkmans, et al.16 which had higher rates of cardiac NTCP maintained acceptable PTV homogeneity. This suggests that a compromise needs to be made between PTV dose uniformity and heart sparing. The rationale for dose conformality is especially important in reducing the likelihood of a negative cosmetic result. A dose–effect relationship has been found between breast fibrosis and doses more than 50 Gy.19

**Effects on lung dose**

Though not specifically reviewed in this paper, IMRT often increased the mean dose to the lung.14,16 This is due to the low density of lung and effects of spreading of low/intermediate dose with IMRT. Cho, et al.17 and Hurkmans, et al.16 found no significant change in NTCP of radiation pneumonitis using IMRT; however there is still debate about the effects increased volume receiving low dose has on risk of pneumonitis.24

**Issues with implementation of IMRT**

**Effects of motion**

The effects of breathing motion are also an important consideration in the delivery of IMRT. Jain, et al.20 used daily cone beam CT imaging to assess the inter-fraction motion during breast IMRT and found daily PTV volume varied by up to 23%. Reductions in the effects of organ motion in IMRT delivery have been reported by the use of respiratory gating26 and breath-hold techniques.27

**Secondary malignancy**

Another concern about implementation of IMRT is the risk of secondary malignancy from the increased integral dose and dose to the contralateral breast and left lung. IMRT may increase the risk of secondary cancer for long-term survivors because of a combination of increased monitor units and increased low dose distribution from the use of multiple fields.28 Certain subgroups of women are at an increased risk. In women aged less than 40 years, those who received greater than 1 Gy of radiation to the contralateral breast had a 2.5 times greater risk than unexposed women, whereas no excess risk was observed for women aged over 40 years treated with radiation.28

**Which patients will benefit?**

A study on irradiation of intramammary node (IMN) involvement and chest wall with IMRT suggested that it was in these cases and not tangential breast irradiation that IMRT is most

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**Table 1**: Dosimetric effects of intensity modulated radiation therapy on cardiac dose compared to 3D CRT.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Year</th>
<th>Patients</th>
<th>IMRT technique</th>
<th>High dose to heart</th>
<th>Intermediate/low to heart</th>
<th>Coronary arteries</th>
<th>Left ventricle</th>
<th>NTCP 3D CRT/IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landau, et al.14</td>
<td>2001</td>
<td>10</td>
<td>Multi-field 4 beams</td>
<td>▼V80% &amp; V90%</td>
<td>▲V60%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hurkmans, et al.16</td>
<td>2002</td>
<td>17</td>
<td>Tangential</td>
<td>▼V95%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>▼4.0%–&gt;2.0%</td>
</tr>
<tr>
<td>Cho, et al.17</td>
<td>2004</td>
<td>9</td>
<td>Tangential</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>▼2.1%–&gt;0.2%</td>
</tr>
<tr>
<td>Lohr, et al.18</td>
<td>2009</td>
<td>14</td>
<td>Multi-field 9 beams</td>
<td>▼Max dose V30Gy &amp; V40Gy</td>
<td>▲Mean dose</td>
<td>–</td>
<td>▼Max dose Mean dose</td>
<td>▼6.0%–&gt;0.25%</td>
</tr>
<tr>
<td>Hong, et al.13</td>
<td>1999</td>
<td>5</td>
<td>Tangential</td>
<td>–</td>
<td>–</td>
<td>▼D20</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

V%: volume receiving #%dose
V#Gy: volume receiving #Gy
D20: dose encompassing 20% of the coronary arteries
NTCP: normal tissue control probability
IMRT: intensity modulated radiation therapy
3D CRT: three dimensional conformal radiation therapy
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References


