Optimising CT guided radiotherapy for breast cancer
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2010

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Download date: 20-11-2018
Minimising contralateral breast dose in post-mastectomy intensity-modulated radiotherapy by incorporating conformal electron irradiation

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Accepted for publication in
Radiotherapy & Oncology
Abstract

Purpose: To assess the potential benefit of incorporating conformal electron irradiation in intensity-modulated radiotherapy (IMRT) for loco-regional post-mastectomy RT.

Materials and Methods: Ten consecutive patients that underwent left-sided mastectomy were selected for this comparative planning study. Three-dimensional conformal radiotherapy (3D-CRT) photon-electron dose plans were compared to photon-only IMRT (IMRT$_p$) and photon IMRT with conformal electron irradiation (IMRT$_{p/e}$). The planning target volume (PTV) was prescribed 50 Gy and included the chest wall and the internal mammary and supra-clavicular lymph node regions. It was attempted to minimise dose delivered to heart, lungs and contralateral breast, while maintaining adequate PTV coverage.

Results: All plans complied with objectives for PTV coverage. IMRT$_{p/e}$ eliminated volumes receiving $\geq$70 Gy ($V_{70}$) that were present in 3D-CRT at the junction of photon and electron beams. Both IMRT strategies reduced heart $V_{30}$ significantly below 3D-CRT levels. Mean heart dose with IMRT$_{p/e}$ was lowest and equal to that with 3D-CRT. Minimising heart dose with IMRT$_p$ resulted in irradiated contralateral breast volumes much larger than with 3D-CRT. With IMRT$_{p/e}$, contralateral breast dose was only slightly increased when compared to 3D-CRT. Mean lung dose values were similar for IMRT and 3D-CRT. With IMRT, lung $V_{20}$ was smaller, whereas $V_5$ values for heart, lung and contralateral breast were higher than with 3D-CRT.

Conclusion: Incorporation of conformal electron irradiation in post-mastectomy IMRT$_{p/e}$ enables a heart dose reduction that in IMRT$_p$ can only be obtained by allowing large irradiated volumes in the contralateral breast.
Introduction

The results of a number of randomised clinical trials revealed that post mastectomy radiotherapy (PMRT) significantly improves survival in high-risk breast cancer patients as compared to surgery alone [1-3]. PMRT often involves irradiation of regional lymph nodes, such as the internal mammary nodes (IMN) and supraclavicular nodes (SCN). As the involvement of these lymph node regions often results in larger irradiation fields and larger irradiated volumes, organs at risk (OAR) can receive a considerable radiation dose. Several authors demonstrated that higher cardiac dose in loco-regional PMRT resulted in an increased risk of late cardiac mortality [4-7]. The relatively high dose delivered to OARs might explain the relatively limited benefit of PMRT in terms of overall survival [8].

Ongoing research in the field of breast cancer radiotherapy resulted in the clinical introduction of new radiation delivery techniques that improved radiation dose coverage of the designated target volumes and, at the same time, enabled improved sparing of OARs [9,10]. These techniques include: three-dimensional conformal RT (3D-CRT) [11]; intensity modulated RT (IMRT) [12]; and the use of breath-hold techniques [13,14]. Although 3D-CRT and IMRT have shown to reduce the heart dose, both techniques also have some limitations. For instance, 3D-CRT with combined photon and electron irradiation may limit the dose to the heart and the contralateral breast, but it often results in hot-spots at the junction between photon and electron beams [11,15,16]. Similarly, 3D-CRT with wide tangential photon beams and multi-beam photon IMRT have shown to increase dose delivered to the contralateral breast [17,18]. The latter is of particular concern in the light of recent reports on the increased incidence of second primary malignancies in the contralateral breast following breast cancer radiotherapy, that may be dose dependent [19-21].

From this point of view, combining the benefits of electron irradiation and photon IMRT may further improve the therapeutic ratio. The use of conformal electron irradiation already proved beneficial in 3D-CRT with regard to sparing the heart and contralateral breast [11], and comparative dose planning studies have
suggested a potential benefit of modulated and fixed electron beams incorporated in photon IMRT [22,23]. Since manufactures of treatment planning software provided the use of Monte Carlo electron dose calculation, the introduction of combining conformal electron irradiation with post-mastectomy IMRT has now become clinically feasible. This might be of particular benefit for patients that receive extensive loco-regional treatment, which often requires larger treatment fields and often results in higher doses in OARs.

The main objective of this planning comparative study was to test the hypothesis that photon IMRT combined with conformal electron irradiation results in a significant reduction of the radiation dose to the contralateral breast as compared to photon IMRT alone. In this study, our current standard, i.e., photon 3D-CRT combined with electrons [11], was used as a reference for both new techniques.

**Materials and Methods**

*Patients and CT acquisition*

The study population was composed of 10 consecutive patients who underwent left-sided mastectomy. A computed tomography (CT) scan was made in treatment position (supine) for the purpose of treatment planning with a slice thickness and index of 3 mm in all patients. CT-data were transferred to the Pinnacle3 treatment planning system (TPS) incorporating Monte Carlo electron dose calculation (research version 8.1y, Philips Radiation Oncology Systems, Fitchburg WI, USA).

*Regions of interest*

The clinical target volume (CTV) consisted of the chest wall, the IMN and the SCN. The chest wall CTV extended from the ipsilateral edge of the sternum medially to the mid-axillary line laterally. It excluded the anterior rib surface and the pectoral muscle. The IMN CTV was defined from the inferior aspect of the clavicular head through the fourth inter-costal space by an elliptical cylinder with a
Electron irradiation in post-mastectomy IMRT

lateral and anterior-posterior diameter of 15 and 10 mm, respectively. It was placed adjacent to the left edge of the sternum and ventral to the pleura. The SCN CTV included the supraclavicular lymph nodes regions and extended in the cranial direction until the level of the cricoid. The planning target volumes (PTVs) were obtained for each CTV by applying a 5 mm margin in three dimensions. The SCN and chest wall PTVs were restricted to 5 mm and 2 mm under the skin surface, respectively, to exclude the build up region from the PTVs (additional bolus was applied on the chest wall only). The heart was contoured until the level of the pulmonary trunk superiorly, excluding the major vessels, including the pericardium. Both lungs were contoured using the automatic contouring tool of the TPS and were edited manually when necessary. The contralateral breast was contoured excluding the skin and pectoral muscles. Regions of interest were defined in addition to the CTVs and OARs for the purpose of IMRT optimisation (Fig. 1).

Photon-electron 3D-CRT treatment planning

Treatment planning procedures for photon-electron 3D-CRT have been described previously in more detail [11]. Briefly, a total dose of 50 Gy was prescribed to each PTV in 25 daily fractions of 2 Gy. A matchline was determined at the level of inferior aspect of the clavicular head. Superior to the matchline, the SCN PTV was treated with conformal anterior-posterior and posterior-anterior photon beams, delivering roughly 75% and 25% of the prescribed dose, respectively. Inferior to the matchline, the major part of the chest wall PTV was treated with shallow tangential photon beams. These excluded the medial part of the chest wall PTV and the IMN PTV. A conformal medio-lateral beam, was used to deliver approximately 0.75 Gy per fraction to the entire chest wall PTV and the IMN PTV. All photon beams had a common isocenter that was placed on the matchline. An anterior-posterior electron beam was added to complete the remaining 1.25 Gy to the medial part of the chest wall PTV and the IMN PTV. The medial border of the electron beam was shaped by means of a lead cut-out conformal to the medial edge of the PTV, whereas the ipsilateral border of the
electron beam slightly overlapped the shallow tangential photon beams. The ipsilateral border of the electron beam was shaped in such a way that the size of the overlap area was minimal and adequate PTV coverage was maintained.

![Figure 1. Structures created for intensity modulated radiotherapy optimisation](image)

Structures were created for direct aperture optimisation-based intensity modulated radiotherapy (IMRT): structure A) extending from the planning target volumes (PTVs) in the medio-dorsal direction with a margin of 3 cm; structure B) extending 4 mm inside the posterior part of the PTVs; and structure C) including the tissue ventral to the chest wall PTV and ~3 cm of air to provide skin flash in IMRT beams. A bolus of 5 mm (grey) was used in each photon beam inferior to the matchline. During optimisation, objective values and weights were optimised for the various structures, including heart (maroon), lungs (teal), contralateral breast (green), chest wall PTV (red), internal mammary nodes PTV (blue) and supraclavicular nodes PTV (not shown).
Electron energy (8-14 MeV) was determined by the depth of the IMN, that did not exceed 5 cm in the patients included in this study. Wedges were used in the photon beams and a maximum total of three small manually shaped photon beams were added, when necessary, to obtain a homogeneous dose distribution. Wedge fractions and relative weights of photon beams were weighted manually, i.e., by forward planning. The plan was optimised in such a way that ≥98% of the chest wall PTV and the SCN PTV received ≥95% of the prescribed dose and ≥98% of the IMN PTV received ≥90% of the prescribed dose (a slightly lower dose was accepted in the deepest parts of the IMN PTV because with the use of anterior-posterior electron irradiation, a PTV margin of 5 mm for position inaccuracies in the dorsal direction is debatable and may unnecessarily increase the dose to the heart). It was attempted to minimise the dose delivered to heart, lungs and contralateral breast by effective use of multileaf collimator shielding and careful selection of gantry angles. A skin flash of ~3 cm was used in photon beams wherever appropriate and a bolus of 5 mm, covering the patient’s skin inferior to the matchline, was applied in all (3D-CRT and IMRT) photon beams.

**IMRT treatment planning**

Two direct aperture optimisation (DAO)-based IMRT treatment plans were constructed for each patient: one photon-only IMRT plan (IMRT\textsubscript{p}) and one with an electron beam identical to that used in the 3D-CRT plan (IMRT\textsubscript{p/e}). When used, the contribution of the electron beam was fixed in the optimisation process at a dose of 1.25 Gy. In each IMRT plan, 9 different photon beam directions were used: 300°, 330°, 0°, 30°, 60°, 90°, 120°, 150° and 180°. The actual gantry angles of the 330° and 150° beams were slightly adjusted for each patient in such a way that these were similar to that of the shallow tangential beams of the 3D-CRT plan. The photon beam isocenter of the IMRT plans was always similar to that of the 3D-CRT plan. DAO-settings were the same for each IMRT plan: segment size ≥6 cm\textsuperscript{2}; minimum leaf separation ≥2 cm; number of leaf pairs ≥3; monitor units per segment ≥4; and a maximum total of 40 segments for each plan. The IMRT optimisation process was performed on the basis of a series of structures that were
created in addition to the OARs and PTVs (Fig. 1). Objectives and weights were entered for each volume of interest. By a trial-and-error adaptive adjustment of the objectives, the doses to both lungs, heart and contralateral breast were reduced as much as possible, while attempting to preserve target coverage similar to that as achieved by the 3D-CRT plan. Although it was attempted to minimise the contralateral breast dose at all times, reducing the mean heart dose and heart V30 to levels similar or below that with 3D-CRT plan had priority. In the IMRT plans, no dose \( \geq 60 \text{ Gy} \) was accepted, with the exception of the area of overlap between electrons and photons in the IMRT\(_{p/e}\) plan, where no dose \( \geq 70 \text{ Gy} \) was accepted.

**Target coverage, dose homogeneity and OAR dose**

Target coverage and target dose homogeneity were determined for all plans by evaluating the proportions of chest wall PTV and SCN PTV receiving \( \geq 95\% \) and \( \geq 107\% \) of the prescribed dose and the proportions of IMN PTV receiving \( \geq 90\% \) of the prescribed dose. In addition, absolute volumes receiving \( \geq 60 \text{ Gy} \) and \( \geq 70 \text{ Gy} \), and the general maximum dose were determined for all plans. Heart dose was determined by calculating the proportion of the heart receiving \( \geq 5 \text{ Gy} \) (V5), \( \geq 30 \text{ Gy} \) (V30) and the mean heart dose. Lung dose (both lungs combined as one organ) was determined by calculating the proportion of lung receiving \( \geq 5 \text{ Gy} \) (V5), \( \geq 20 \text{ Gy} \) (V20), and the mean lung dose. Similarly, we determined the contralateral breast V0.05, V0.6, V1, V2 and V5 and the contralateral breast mean dose, as some of these parameters were recently proposed as maximum dose objectives in treatment planning to limit the risk of second breast cancer [19-21].

**Statistics**

To compare the various dose-volume parameters, the mean values were analysed with the Wilcoxon signed ranks test or the paired-samples t-test on statistical significance whenever appropriate. All tests were two-tailed, and differences were considered statistically significant at \( p \leq 0.05 \).
### Table 1. Dose-volume results with 3D-CRT\textsubscript{p/e}, IMRT\textsubscript{p} and IMRT\textsubscript{p/e}

<table>
<thead>
<tr>
<th>Target Coverage</th>
<th>3D-CRT\textsubscript{p/e}</th>
<th>IMRT\textsubscript{p}</th>
<th>IMRT\textsubscript{p/e}</th>
<th>3D-CRT\textsubscript{p/e} vs. IMRT\textsubscript{p} p-value</th>
<th>3D-CRT\textsubscript{p/e} vs. IMRT\textsubscript{p/e} p-value</th>
<th>IMRT\textsubscript{p} vs. IMRT\textsubscript{p/e} p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>**PTV receiving (\geq 95%) ((\geq 47.5) Gy)</td>
<td>(98.7 (0.3))</td>
<td>(98.5 (0.2))</td>
<td>(98.8 (0.3))</td>
<td>(0.197)</td>
<td>(0.108)</td>
<td>(0.032)</td>
</tr>
<tr>
<td>CW PTV (%)</td>
<td>(98.8 (0.3))</td>
<td>(99.3 (0.3))</td>
<td>(99.2 (0.3))</td>
<td>(0.011)</td>
<td>(0.016)</td>
<td>(0.383)</td>
</tr>
<tr>
<td>SCN PTV (%)</td>
<td>(98.5 (0.4))</td>
<td>(98.5 (0.4))</td>
<td>(98.6 (0.5))</td>
<td>(0.233)</td>
<td>(0.458)</td>
<td>(0.610)</td>
</tr>
<tr>
<td>**PTV receiving (\geq 90%) ((\geq 45) Gy)</td>
<td>(98.8 (0.5))</td>
<td>(99.3 (0.3))</td>
<td>(99.2 (0.3))</td>
<td>(0.011)</td>
<td>(0.016)</td>
<td>(0.383)</td>
</tr>
<tr>
<td>IMN PTV (%)</td>
<td>(98.5 (0.4))</td>
<td>(98.5 (0.4))</td>
<td>(98.6 (0.5))</td>
<td>(0.233)</td>
<td>(0.458)</td>
<td>(0.610)</td>
</tr>
<tr>
<td><strong>Irradiated volumes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CW PTV (%)</td>
<td>(19.0 (6.3))</td>
<td>(25.3 (8.7))</td>
<td>(27.5 (10.0))</td>
<td>(0.185)</td>
<td>(0.059)</td>
<td>(0.721)</td>
</tr>
<tr>
<td>SCN PTV (%)</td>
<td>(18.3 (8.7))</td>
<td>(4.3 (4.3))</td>
<td>(3.3 (2.1))</td>
<td>(0.007)</td>
<td>(0.005)</td>
<td>(0.609)</td>
</tr>
<tr>
<td>Volume receiving (\geq 60) Gy (cm(^3))</td>
<td>(20.3 (7.2))</td>
<td>(0.2 (0.3))</td>
<td>(5.5 (3.8))</td>
<td>(0.005)</td>
<td>(0.005)</td>
<td>(0.005)</td>
</tr>
<tr>
<td>Volume receiving (\geq 70) Gy (cm(^3))</td>
<td>(1.8 (2.0))</td>
<td>(0.0 (0.0))</td>
<td>(0.0 (0.0))</td>
<td>(0.007)</td>
<td>(0.007)</td>
<td>(1.000)</td>
</tr>
<tr>
<td>Integral mean dose (Gy)</td>
<td>(9.9 (0.9))</td>
<td>(11.1 (1.1))</td>
<td>(10.7 (1.1))</td>
<td>(0.005)</td>
<td>(0.005)</td>
<td>(0.012)</td>
</tr>
<tr>
<td>Integral max dose (Gy)</td>
<td>(7.43 (3.6))</td>
<td>(60.3 (1.6))</td>
<td>(67.0 (2.4))</td>
<td>(0.005)</td>
<td>(0.005)</td>
<td>(0.005)</td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean dose (Gy)</td>
<td>(8.9 (1.8))</td>
<td>(10.1 (1.8))</td>
<td>(8.9 (2.0))</td>
<td>(0.013)</td>
<td>(1.000)</td>
<td>(0.011)</td>
</tr>
<tr>
<td>V(30) (%)</td>
<td>(8.2 (4.0))</td>
<td>(5.3 (2.8))</td>
<td>(5.2 (3.0))</td>
<td>(0.013)</td>
<td>(0.005)</td>
<td>(0.358)</td>
</tr>
<tr>
<td>V(5) (%)</td>
<td>(36.5 (6.1))</td>
<td>(77.4 (12.6))</td>
<td>(54.2 (18.0))</td>
<td>(0.005)</td>
<td>(0.007)</td>
<td>(0.005)</td>
</tr>
<tr>
<td><strong>Lungs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean dose (Gy)</td>
<td>(10.3 (1.7))</td>
<td>(10.2 (1.3))</td>
<td>(9.9 (1.7))</td>
<td>(0.341)</td>
<td>(0.041)</td>
<td>(0.138)</td>
</tr>
<tr>
<td>V(20) (%)</td>
<td>(21.3 (4.4))</td>
<td>(15.9 (3.3))</td>
<td>(17.0 (3.9))</td>
<td>(0.005)</td>
<td>(0.005)</td>
<td>(0.036)</td>
</tr>
<tr>
<td>V(5) (%)</td>
<td>(33.5 (6.0))</td>
<td>(45.4 (5.5))</td>
<td>(42.5 (6.3))</td>
<td>(0.005)</td>
<td>(0.005)</td>
<td>(0.013)</td>
</tr>
<tr>
<td><strong>Contralateral breast</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean dose (Gy)</td>
<td>(0.8 (0.2))</td>
<td>(2.7 (1.1))</td>
<td>(1.3 (0.3))</td>
<td>(0.005)</td>
<td>(0.005)</td>
<td>(0.005)</td>
</tr>
<tr>
<td>V(5) (%)</td>
<td>(0.3 (0.2))</td>
<td>(8.9 (8.0))</td>
<td>(1.0 (1.0))</td>
<td>(0.005)</td>
<td>(0.018)</td>
<td>(0.005)</td>
</tr>
<tr>
<td>V(2) (%)</td>
<td>(8.3 (4.2))</td>
<td>(47.6 (18.0))</td>
<td>(18.3 (7.8))</td>
<td>(0.005)</td>
<td>(0.005)</td>
<td>(0.008)</td>
</tr>
<tr>
<td>V(1) (%)</td>
<td>(20.1 (8.5))</td>
<td>(73.7 (19.6))</td>
<td>(53.3 (12.2))</td>
<td>(0.005)</td>
<td>(0.005)</td>
<td>(0.005)</td>
</tr>
<tr>
<td>V(0.6) (%)</td>
<td>(49.0 (10.7))</td>
<td>(88.6 (14.9))</td>
<td>(76.0 (13.9))</td>
<td>(0.005)</td>
<td>(0.005)</td>
<td>(0.005)</td>
</tr>
<tr>
<td>V(0.05) (%)</td>
<td>(95.0 (1.7))</td>
<td>(99.5 (1.0))</td>
<td>(99.0 (1.6))</td>
<td>(0.005)</td>
<td>(0.005)</td>
<td>(0.005)</td>
</tr>
</tbody>
</table>

Abbreviations: 3D-CRT\textsubscript{p/e} = photon-electron three-dimensional conformal radiotherapy; IMRT\textsubscript{p/e} = photon-electron intensity modulated RT; IMRT\textsubscript{p} = photon-only IMRT; IMN = internal mammary nodes; CW = chest wall; SCN = supraclavicular nodes; PTV = planning target volume; V\textsubscript{x} = proportion of organ at risk receiving \(\geq x\) Gy.

Data presented as mean values with standard deviation in parenthesis.

**Results**

**Target coverage and target dose homogeneity**

Each dose plan complied with the minimum objectives for target coverage (Table 1). Dose levels \(\geq 70\) Gy in a mean volume of 1.8 cm\(^3\) were found in the 3D-CRT plans at the level of the overlap between photon and electron beams. With IMRT\textsubscript{p/e}, no such high dose values were found, and V\textsubscript{60} was significantly reduced.
when compared to 3D-CRT. With both IMRT<sub>p</sub> and IMRT<sub>p/e</sub>, doses up to 60 Gy were accepted in the chest wall PTV in an attempt to minimise the dose delivered to OARs [24,25]. This may also explain why the proportion of chest wall PTV receiving ≥107% of the prescribed dose with IMRT was roughly comparable to that with 3D-CRT. While with 3D-CRT, the chest wall PTV volumes receiving ≥107% were located primarily in the vicinity of the beam junctions, with IMRT they were found scattered in the chest wall PTV (Fig. 2). The proportions of SCN PTV receiving ≥107% of the prescribed dose were largest with 3D-CRT because, in contrast to IMRT, only two 3D-CRT beams were used superior to the matchline.

Figure 2. Axial representation of dose distributions with three techniques

Axial representation of dose distributions with photon-electron three-dimensional conformal radiotherapy (3D-CRT<sub>p/e</sub>), photon-electron intensity modulated radiotherapy (IMRT<sub>p/e</sub>) and photon-only IMRT<sub>p</sub>.
Figure 3. Mean dose-volume histograms
Mean dose-volume histograms (DVHs) of the heart, contralateral breast and lungs with photon-electron intensity modulated radiotherapy (IMRT), photon-only IMRT and photon-electron three-dimensional conformal RT (3D-CRT).
Dose to OAR

With both IMRT\textsubscript{p} and IMRT\textsubscript{p/e}, heart V\textsubscript{30} could be reduced below values obtained with 3D-CRT (Fig. 3). However, only with IMRT\textsubscript{p/e}, mean heart dose values could be reduced to the levels obtained with 3D-CRT and both IMRT techniques resulted in larger volumes of the heart receiving a low dose. With IMRT\textsubscript{p}, attempts to reduce the intermediate and high heart dose values resulted in volumes of the contralateral breast receiving a low to intermediate dose that were much higher than that with 3D-CRT (Fig. 2). With IMRT\textsubscript{p/e}, the mean heart dose was similar to that with 3D-CRT (Table 1), and the dose delivered to the contralateral breast was only slightly higher than that with 3D-CRT (Fig. 3). Values for mean lung dose were comparable for 3D-CRT and IMRT. With both IMRT strategies, lung V\textsubscript{20} was significantly smaller, and V\textsubscript{5} was significantly larger than with 3D-CRT.

Discussion

In the current study, we showed that with post-mastectomy IMRT\textsubscript{p/e}, the heart dose could be reduced without increasing the dose to the contralateral breast, in contrast to IMRT\textsubscript{p} that only allowed for a reduced heart dose at the cost of a higher dose to the contralateral breast. As treatment outcome in terms of survival has been improved through the years [8], prevention of late radiation-induced side effects become increasingly important, in particular among young patients [26].

It has already been demonstrated that the risk of breast cancer is closely associated with breast tissue dose. It appears that a linear dose relationship is maintained at lower radiation doses and there exists no low-dose threshold, below which there is no excess risk [27]. More recently, a number of reports proposed a series of contralateral breast dose-volume thresholds (V\textsubscript{0.05 Gy}, V\textsubscript{0.6 Gy}, V\textsubscript{2.0 Gy}, and a mean dose of 1.0 Gy) that could serve as maximum dose objectives in treatment planning to limit the risk of second breast cancer [19-21]. In the current study, compliance with these dose-volume metrics was significantly better with IMRT\textsubscript{p/e} and 3D-CRT\textsubscript{p/e} than with IMRT\textsubscript{p}. However, when evaluating low dose
values such as V0.05 and V0.6 it should be realised that inaccuracies may be present in the values calculated by the planning system and reported in this study. Research should therefore be aimed at increasing the accuracy of treatment planning systems in calculating the volumes receiving such very low doses as these dose parameters are becoming increasingly important.

In addition to the increased low dose volumes in the contralateral breast with IMRT, the low dose volumes in heart and lung were also larger with IMRT. This is commonly regarded as a downside of IMRT, as it may increase the risk of secondary malignancies or impair the repair mechanisms of normal tissue. However, little is currently known of the actual effect of these low doses and future research should therefore be aimed at collecting clinical data from patients that received IMRT, in order to clarify this issue.

Reports on conformal electron planning in breast cancer are scarce [11]. Although the use of electron irradiation has proven beneficial in loco-regional RT, this often concerned electron beams with fixed size and shape or electron beams determined on the basis of exterior patient anatomy [28,29]. Application of electron irradiation in those studies may therefore not have been optimal. Electron irradiation may not have been used at its full potential also because support for electron dose calculation in planning software has been limited so far. Only recently, availability of Monte Carlo electron dose calculation has increased as more manufacturers included it in their planning software. Therefore the opportunity is now given to use the benefits of conformal electron irradiation also in post-mastectomy IMRT.

As oblique electron beams demonstrated to result in poor coverage of the IMN PTV [12,14], an anterior-posterior electron beam was employed in the present study. It was accepted that this resulted in an overlap between the electron beam and the shallow tangential photon beams. However, IMRT_{p/e} was capable to eliminate the so called hot-spots that were present in this region with 3D-CRT_{p/e}. As a result, the risk of subcutaneous fibrosis in this region might be reduced by means of IMRT_{p/e}.
In reports on loco-regional radiotherapy for breast cancer, various IMRT methods were used with regard to beam directions and optimisation methods. Some authors decided to use IMRT beam directions that specifically avoided the contralateral breast [30]. Others concluded that a 4-beam IMRT set-up optimally spared the contralateral breast, while a 9-beam IMRT set-up improved sparing of heart and lung [13]. Other authors reported that with multi-beam IMRT, substantial dose was delivered to the contralateral breast [18], while others succeeded in reducing contralateral breast dose by means of 9-beam IMRT [24].

We believe that apparent differences in outcome do not necessarily correspond to the choice of beam directions, but rather to the choice of optimisation method. While some authors use similar dose-volume objectives and weights for each patient and each technique [14,17,30], we found, similar to others, that the choice of objectives and weights, may have different effects when using different techniques [24]. For example, adjusting specific objective weights in IMRT_p/e could substantially reduce contralateral breast dose without violating other objectives, whereas similar adjustments of objective weights in IMRT_p could result in decreased PTV coverage and increased heart dose. We feel that for a fair comparison of different techniques, it should be attempted to minimise dose with each technique and for each OAR.

Many papers have focussed on comparing various techniques for loco-regional RT, in particular with regard to the ability to reduce the heart dose. There appears to be a striking discrepancy in the conclusions drawn by the various authors. When comparing 3D-CRT_p/e and 3D-CRT_p, some concluded that heart dose was lowest with 3D-CRT_p [17,31,32], while others concluded the opposite, i.e., that heart dose was lowest with 3D-CRT_p/e [11,12,14,33]. The differences may be explained by the definition of the PTVs and the criteria for coverage of the PTVs, because these varied across the different studies and across the various techniques. It seems that the lowest heart dose values were found with 3D-CRT_p/e when it was attempted to have similar PTV coverage and similar OAR shielding in each technique. We feel this is essential when comparing OAR dose and therefore complied to this concept in the current study.
Further reductions in heart dose and contralateral breast dose might be obtained by simultaneous use of breath-hold techniques and IMRT$_{p/e}$. With breath-hold techniques, the heart is displaced further outside the radiation fields and the absence of breathing motion allows for smaller PTV margins. It was demonstrated that as a result both heart dose and contralateral breast dose could be reduced [14]. Further reductions in OAR dose may also be obtained by the use of new treatment modalities such as proton irradiation. Experimental dose planning studies with protons have shown favourable dose distributions in breast cancer patients [24,34]. Unlike proton irradiation, however, electron irradiation is currently a standard treatment modality and commonly available to the majority of patients. Implementation of conformal electron dose planning in both 3D-CRT and IMRT might be the next step forward in reducing the probability of radiation induced side effects in patients receiving loco-regional post-mastectomy RT.

**Conclusions**

By combining the benefits of both conformal electron irradiation and photon IMRT, hot-spots at the photon-electron junction present in 3D-CRT are minimised and volumes of heart and lung receiving intermediate and high doses are significantly lower than with 3D-CRT. IMRT$_{p/e}$ enables a heart dose reduction that in photon-only IMRT$_{p}$ can only be obtained by allowing large irradiated volumes in the contralateral breast. Implementation of IMRT$_{p/e}$ might therefore reduce the probability of second primary malignancies in post-mastectomy radiotherapy together with a reduced risk on long term cardiac morbidity and mortality.
References


