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Chapter 5

Cardiac and lung complication probabilities after breast cancer irradiation

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Abstract

**Purpose.** To assess for locoregional irradiation of breast cancer patients, the dependence of cardiac (cardiac mortality) and lung (radiation pneumonitis) complications on treatment technique and individual patient anatomy.

**Methods and materials.** 3D treatment planning was performed for 30 patients with left-sided breast cancer and various breast sizes. Two locoregional techniques (Techniques A and B) and a tangential field technique, including only the breast in the target volume, were planned and evaluated for each patient. In both locoregional techniques tangential photon fields were used to irradiate the breast. The internal mammary (IM) – medial supraclavicular (MS) lymph nodes were treated with an anterior mixed electron / photon field (Technique A) or with an obliquely incident mixed electron / photon IM field and an anterior electron / photon MS field (Technique B). The optimal IM and MS electron field dimensions and energies were chosen on the basis of the IM-MS lymph node target volume as delineated on CT-slices. The position of the tangential fields was adapted to match the IM-MS fields. Dose-volume histograms (DVHs) and normal tissue complication probabilities (NTCPs) for the heart and lung were compared for the three techniques. In the beam’s-eye view of the medial tangential fields the maximum distance of the heart contour to the posterior field border was measured; this value was scored as the maximum heart distance (MHD).

**Results.** The lymph node target volume receiving more than 85% of the prescribed dose was on average 99% for both locoregional irradiation techniques. The breast PTV receiving more than 95% of the prescribed dose was generally smaller using Technique A (mean: 90%, range: 69%-99%) than using Technique B (mean: 98%, range: 82%-100%) or for the tangential field technique (mean: 98%, range: 91%-100%). NTCP values for excess cardiac mortality due to acute myocardial ischaemia varied considerably between patients, with minimum and maximum values of 0.1% and 7.5% (Tech. A), 0.1% and 5.8% (Tech. B) and 0.0% and 6.1% (tangential tech.). The NTCP values were on average significantly higher (p < 0.001) by 1.7% (Tech. A) and 1.0% (Tech. B) when locoregional breast irradiation was given, compared with irradiation of the left breast only. The NTCP values for the tangential field technique could be estimated using the maximum heart distance. NTCP values for radiation pneumonitis were very low for all techniques; between 0.0% and 1.0%.

**Conclusions.** Technique B results in a good coverage of the breast and locoregional lymph nodes, while Technique A sometimes results in an underdosage of part of the target volume. Both techniques result in a higher probability of heart complications compared with tangential irradiation of the...
breast only. Irradiation toxicity for the lung is low in all techniques. The maximum heart distance is a simple and useful parameter to estimate the NTCP values for cardiac mortality for tangential breast irradiation.

Introduction

A number of large randomized trials has shown a small but statistically significant increased risk of cardiac mortality associated with locoregional irradiation of breast cancer [2,11,27,28]. It is also shown that modern treatment techniques can result in a lower cardiac dose than the older techniques used in these trials [3,10]. However, even with modern techniques a subgroup of patients with left-sided breast cancer receives a relatively high cardiac dose, which is associated with a significant increase in cardiac mortality in these earlier studies [7,28]. Recently published studies confirm an increase in mortality from myocardial infarction after irradiation [24,25]. For example, an increase of 1% was found for patients irradiated for right-sided breast cancer after lumpectomy, while an increase of 2% was found for patients irradiated for left-sided breast cancer after lumpectomy [25]. The increase in overall survival found in some trials gained by locoregional treatment for breast cancer appeared to be counterbalanced by the increase in late cardiac mortality [2,17,26].

Most studies with 3D CT data available for dose-volume analysis were restricted to evaluation of the tangential treatment technique [3,6-8,10,22]. Little detailed information is available about cardiac doses in modern techniques including the locoregional lymph nodes in the target volume [15,23]. Pakisch et al [23] calculated dose-volume histograms of the lungs and heart for treatment techniques including the lymph nodes in the target volume. However, they did not outline the target volume, so no information about target coverage was available. Jansson et al [15] included 30 patients in a comparative treatment planning study. They presented data about heart and lung doses and target coverage, but the new technique which they studied can only be employed on an MM22 or MM50 Racetrack microtron of which only a few exist in the world. They compared their new technique with a tangential irradiation technique, which has the disadvantage that generally a considerable part of the contralateral breast has to be included to obtain adequate target coverage.

The aim of this study is to quantify cardiac and lung complication probabilities and target coverage based on 3D CT data for a tangential breast irradiation technique as well as for two widely applicable locoregional breast irradiation techniques, using perpendicular or oblique incident photon and electron parasternal fields. An additional goal was to find anatomical
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parameters from which cardiac complications can be estimated.

Methods and materials

Patient selection and treatment planning

A retrospective study was performed for 30 left-sided breast cancer patients of which CT data were available. The CT scans extended from the supraclavicular region to the most caudal part of the lungs, with a 5 or 10 mm slice separation. Treatment planning was performed using our 3D treatment planning system1 [4]. For photon beam dose calculations the octree/edge model [5] was used in combination with the ratio of tissue-air ratios algorithm to take inhomogeneities into account [12], whereas for the electron beams a 3D implementation of the MDAH pencil beam model [21] was applied.

The breast planning target volume (PTV) was outlined on each CT slice using the visible breast parenchyma. Clinical target volumes (CTVs) and planning target volumes were defined according to ICRU guidelines [13]. The breast PTV was defined to extend to 5 mm beneath the skin. Non-pathological internal-mammary (IM) medial-supraclavicular (MS) lymph nodes can hardly be seen on CT-data. With the aid of other visible structures, the IM-MS CTV was defined. The CTV of the IM lymph nodes was assumed to be located around the internal mammary vessels. There was a gradual transition of the IM lymph node CTV into the MS lymph node CTV. The IM-MS PTV was defined by expanding the CTV 5 mm in the anterior-posterior direction and 10 mm in the medio-lateral direction. A cap of half of the CT slice separation was used as expansion in the cranio-caudal direction.

The cranial limit of the heart included the infundibulum of the right ventricle, the right atrium, the right atrium auricle and excluded the pulmonary trunk, the ascending aorta and the superior vena cava. The lowest external contour of the heart was the caudal border of the myocardium. The pericardium was excluded from the heart volume. The contour of the lung was automatically outlined. The breast and IM-MS target volumes and the heart were delineated by an experienced radiation oncologist and checked by a second colleague. Only a few discrepancies were encountered, and in these cases consensus about the volume extension was always reached.

1 U-MPlan with software version V339
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Treatment techniques

Three treatment techniques were compared: two techniques (Techniques A and B, Figure 1) were used to irradiate the breast and IM-MS lymph nodes and a tangential field technique was used if only the breast was considered as the target volume. For all three techniques, two symmetric tangential photon fields (6 or 8 MV) were used to irradiate the breast. All patients were planned in a supine position. The dorsal edges of both beams were made coplanar to decrease the amount of lung tissue irradiated. For the tangential field technique, the medial beam edge of the medio-lateral beam was located at the sternum midline. For Technique B it was located 35 mm ipsilateral to the sternum midline at the level of the nipple and for Technique A it depended on the extent of the IM-MS field.

For Technique A, an anterior field was used to irradiate the IM-MS lymph nodes, which overlapped the tangential breast fields by 5 mm on the skin. For Technique B, an oblique IM field was used to irradiate the IM lymph nodes, while a separate anterior field was used to irradiate the MS lymph nodes. For Techniques A and B, 70% of the dose to the lymph nodes was given with electrons, in order to spare underlying structures and 30% with 6 MV or 8 MV photons to avoid overdosage of the skin. The width, length and electron beam energy of the IM and MS fields were chosen in such a way that the lymph node PTV received 85% of the prescribed dose or more. The value of 85% is in accordance with the requirements formulated in the EORTC 22922-10925 trial investigating the role of IM-MS lymph node chain irradiation in stage I-III breast cancer [1].

If needed, the caudal border of the IM-MS field was extended caudally to include the medial caudal part of the breast. A cranial match plane was created in which there was no divergence of the tangential fields (and IM fields; Technique B) by using gantry, collimator and table rotations and by placing blocks in the cranial part of the fields [19]. Applying this technique, all fields could be matched properly without using asymmetric fields.

Table 1. Breast and lymph node PTV coverage.

<table>
<thead>
<tr>
<th></th>
<th>Technique A</th>
<th>Technique B</th>
<th>Tangentials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Breast PTV: Volume (%) with dose &gt; 95%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>90 (69-99)</td>
<td>98 (82-100)</td>
<td>98 (91-100)</td>
</tr>
<tr>
<td></td>
<td>Lymph nodes PTV: Volume (%) with dose &gt; 85%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>99 (91-100)</td>
<td>99 (92-100)</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. Transversal slice through the middle of the breast for Technique A (top) and Technique B (bottom) showing the external contour, heart, lungs and field outlines. Note the low dose region present in technique A between the IM-MS fields and the tangential fields.
Dose prescription

The treatment plans were normalized at the ICRU reference point of the breast PTV [13]. The ICRU reference dose was 2 Gy per fraction, with a total treatment dose of 50 Gy. For techniques A and B, the dose of the IM and MS electron and photon fields were prescribed at the middle of the IM and MS target volumes.

![Diagram of heart contour and maximum heart distance](image)

**Figure 2.** The maximum heart distance is defined as the maximum distance of the heart contour, as seen in a beam’s-eye view of the medial tangential field, to the medial field edge.

Data analysis

Dose-volume histograms (DVHs) were computed for the breast and IM-MS target volumes and for the heart and lungs. For the breast PTV, the volume receiving at least 95% of the reference dose was computed, while for the IM-MS target volume, the volume receiving at least 85% of the reference dose was calculated.

To quantify lung and heart toxicity, the physical dose distribution was
first converted into a normalized total dose (NTD) distribution [20], using the linear quadratic model with an \( \alpha/\beta \) ratio of 3 Gy. For the heart, the normal tissue complication probability (NTCP) for excess cardiac mortality after 10-15 years was calculated using a fractionation schedule of 2 Gy per fraction and applying the relative seriality model [16] with parameter values \( (\gamma = 1.28, s=1, D_{50}=52.3 \text{ Gy}) \) derived by Gagliardi et al. [7]. These values were chosen because they were based on 3D-CT dose computations combined with the clinical results of a large patient group included in two randomized trials [11,28]. For the tangential field technique, the maximum heart distance, i.e., the maximum distance of the heart contour to the medial field end, as can be seen on a beam's eye view of the medio-lateral tangential field, was measured (Figure 2). An average differential DVH of the heart was calculated by adding all individual differential DVHs, which were expressed in percentages of the heart volume, divided by the number of patients. Thereafter, also a cumulative average DVH was calculated.

\[\text{Figure 3.} \quad \text{Correlation between breast PTV coverage and the thickness of the breast tissue in the central plane measured at the medial border of the tangential fields for Technique A (r=0.64).}\]
In the calculations of lung toxicity, the left and right lung are treated as one single organ. After the NTD calculation, the mean normalized total dose (NTD_{mean}) was calculated and used to compute the NTCP for radiation pneumonitis. Radiation pneumonitis was scored, when the complication was classified as a grade 2 or higher, according to the Southwest Oncology Group (SWOG) toxicity criteria, i.e. when the patient needed steroid treatment because of dyspnea and cough after the radiation therapy and when radiographic changes were visible on the chest X-ray film within the treatment field. This method was developed to present the clinical results of a recently published, large multi-center study of the relation between the incidence of radiation pneumonitis and DVH parameters [18].

![Cumulative average dose-volume histograms of the heart. Technique B resulted in a slightly better DVH (dashed line) than Technique A (solid line), because the internal mammary radiation fields are turned away from the heart. On average, only a small part of the heart received a high dose using the tangential field technique (dotted line).](image)

**Figure 4.** Cumulative average dose-volume histograms of the heart. Technique B resulted in a slightly better DVH (dashed line) than Technique A (solid line), because the internal mammary radiation fields are turned away from the heart. On average, only a small part of the heart received a high dose using the tangential field technique (dotted line).

**Results**

The objective to achieve an adequate dose coverage of the lymph nodes for both Technique A and Technique B was reached for most patients (Table 1). In one patient however, the posterior part of the lymph node target volume was located as deep as 6.5 cm beneath the skin and an adequate dose coverage could not be achieved with the maximum electron beam energy of 20 MeV that is available in our department. The results for this patient were excluded from the analysis.
Table 2. **Irradiation toxicity.**

<table>
<thead>
<tr>
<th>Technique</th>
<th>Technique B</th>
<th>Tangentials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NTCP for cardiac mortality (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>2.3 (0.1-7.5)</td>
<td>1.6 (0.1-5.8)</td>
</tr>
<tr>
<td>SD</td>
<td>1.7</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>NTCP for radiation pneumonitis (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>0.2 (0.1-0.4)</td>
<td>0.4 (0.1-1.2)</td>
</tr>
<tr>
<td>SD</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Mean lung dose (Gy)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>3.7 (1.7-6.1)</td>
<td>5.8 (3.3-9.9)</td>
</tr>
<tr>
<td>SD</td>
<td>1.3</td>
<td>1.7</td>
</tr>
</tbody>
</table>

The breast PTV receiving at least 95% of the prescribed dose was on average 98% for Technique B and the tangential field technique (Table 1). It was only 90% for Technique A, because part of the PTV was located in a low dose region between the tangential fields and the IM-MS fields. It was found that the volume of this low dose region in the breast PTV is correlated with the breast tissue thickness at the medial beam edge of the tangential fields (Figure 3). This correlation is weak ($r = 0.64$), but it can be seen that for patients with a large tissue thickness (e.g., more than 30 mm), there is a clearly increased risk of a cold spot.

The cumulative average DVH of the heart is shown in Figure 4. On average, both locoregional treatment techniques resulted in a significantly higher dose to the heart than the tangential field technique. The average DVH curve for Technique B is completely located below the DVH for Technique A, although the difference is small above the 20 Gy level.

The large individual differences in the differential DVHs resulted in a large variation in NTCP values for excess cardiac mortality calculated from the DVHs (Figure 5 and Table 2). The mean NTCP value was lower for Technique B than for Technique A by 0.6% with borderline significance ($p=0.05$). The average NTCP for the tangential field technique was, however, significantly ($p<0.001$) lower than the average NTCP of the locoregional irradiation techniques by 1.7% (Tech. A) and 1.0% (Tech. B).

For the tangential field technique, a good correlation was found between the maximum heart distance and the NTCP for excess cardiac mortality (Figure 6). No NTCP values above 1% were found below a maximum heart distance of 1 cm, while all NTCP values above 2% were found for maximum heart distances of 2 cm or more. Furthermore, the NTCP values increase steeply with maximum heart distances of 2 cm or more.
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The mean lung dose was on average 3.7 Gy (range 1.7 - 6.1 Gy), 5.8 Gy (range 3.3 - 9.9 Gy) and 3.8 Gy (range 0.8-8.9 Gy) for Techniques A and B and the tangential field technique, respectively. The associated NTCP values for radiation pneumonitis grade 2 or higher were all very low; of the order of 0% to 1% (Figure 7 and Table 2). The small increase in lung dose, which was sometimes found using Technique B instead of Technique A, was due to a larger contribution of the IM field to the lung dose. The part of the lung receiving a high dose due to the tangential fields was usually smaller for Technique B, partly counterbalancing the increase in lung dose due to the IM field.

Figure 5. NTCP values for excess late cardiac mortality. The NTCP values for the tangential field technique (gray bars) were significantly lower than the NTCP values for Technique A (black bars) and Technique B (open bars).
Figure 6. NTCP for excess late cardiac mortality versus maximum heart distance for the tangential fields irradiation technique.

Discussion

The radiation toxicity for the heart and lung has been quantified for 30 left-sided breast cancer patients for two breast and adjacent lymph node irradiation techniques and one technique including only the breast in the target volume. Gagliardi et al. [7] have calculated mean heart DVHs and NTCP values for excess cardiac mortality for the breast treatment techniques applied in the Oslo and Stockholm breast cancer trials [11,28]. No increase in late cardiac mortality was found for patients who were treated for right-sided breast cancer using a $^{60}$Co tangential irradiation technique and for patients who received a mastectomy followed by chest wall and lymph node irradiation with electrons. An increase was found using a left $^{60}$Co tangential irradiation technique (6.8%) or a left (7.9%) or right (3.3%) anterior $^{60}$Co field to cover the lymph nodes. The mean NTCP values of 2.3% and 1.6% found in our study for left-sided breast cancer irradiation using Technique A or Technique B, respectively, are substantially lower. Gynes et al. [10] calculated that the volume of heart receiving a dose of
50% or more of the prescribed dose of 50 Gy using a 6 MV tangential irradiation technique to treat the left breast, was on average 5.7%. This is much more than the value of 2.3% found in our study, which is probably caused by different target definitions, leading to the more medially located medial border of the tangential fields used in their study.

Fuller et al. [6] showed that the volume of heart receiving a low dose was significantly decreased using a $^{60}$Co technique compared with orthovoltage techniques to irradiate the breast or the breast and the lymph nodes. However, the volume of heart receiving a high dose was higher using the $^{60}$Co technique. The results were not compared with more modern (linear accelerator) treatment techniques. Therefore, their conclusion that modern treatment techniques, which employ tangential fields, reduce the dose to the heart has to be placed in the proper perspective, as also argued by Janjan [14].

![Graph](image)

**Figure 7.** NTCP values for radiation pneumonitis grade 2 or higher. The NTCP values for Technique A (black bars), Technique B (open bars) and the tangential field technique (gray bars) were generally below 0.5%.
In contrast to the large trials in which an increase in cardiac mortality was found [2,11,27,28], some studies did not reveal this increase [9,22,29]. No increase in late cardiac mortality was found for patients treated for left-sided breast cancer compared with right-sided breast cancer in a recent study including 745 patients, of which some were irradiated using large tangential fields to include the parasternal lymph nodes [22]. However, this study had insufficient statistical power to detect the small relative risk of about 1.1 for left versus right-sided breast cancer treatment as found in the larger trials. A study by Gustavsson et al. [9] also showed no late cardiac mortality in a group of 90 patients with stage II breast cancer receiving postmastectomy radiotherapy with or without chemotherapy. It was concluded that this group of patients had no serious sequelae, despite the use of out-dated irradiation techniques for some of the patients. However, one cannot extend this conclusion to a large population, because a clinically very significant number of only a few percent of excess late cardiac deaths cannot be detected in such a small population of patients. Rutqvist et al. [29] did not find an increase in cardiac mortality with irradiation in a group of 684 patients who received tangential breast irradiation, compared with a control group of almost 5000 patients [29]. They also concluded that the patient group was too small to rule out an increased risk for some patients. In general, the absence of a significant increase in late excess cardiac mortality in studies with few observations, does not imply that there is no increase to be found.

Jansson et al. [15] included 30 patients in a comparative treatment planning study. Their new locoregional technique resulted in a mean lung dose of 7.5 Gy (estimated on the basis of the data presented in their study) which is higher than the values of 3.7 Gy and 5.8 Gy using Technique A or Technique B, respectively. They also calculated the heart volume receiving a dose of 40 Gy or more, which is equivalent to 74% of the prescribed dose of 54 Gy. To compare their results with our data, we also calculated the heart volume receiving a dose of 74% of the prescription dose. This volume was similar (average 7%, range 0%-20% (Technique A); average 5%, range 0%-17% (Technique B)) compared with the data for their technique (average 5%, range: 2%-12%). Pakisch et al. [23] reported average lung doses of 10.6 Gy, 15.2 Gy and 16.1 Gy (scaled to a total dose of 50 Gy at the 100% isodose) for a tangential field technique adjacent to an anterior field covering the lymph nodes, a tangential field technique adjacent to an oblique field covering the lymph nodes and a technique using deep tangentials, respectively. The increased lung dose using oblique fields compared to anterior fields was also found in our study, although the absolute dose values they reported are much higher. Their average cumulative DVHs of the heart are very similar to the results presented here for the two locoregional techniques. However, as they did not outline the target
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volumes, no conclusions can be drawn from their data about which technique gives the best target coverage.

The low NTCP values found for the incidence of radiation pneumonitis for all three techniques included in our study indicate that the lung complications using these techniques may not be very important clinically. The mean lung dose varied between 0.8 and 9.9 Gy. In a study of Kwa et al. [18] including 540 patients, no radiation pneumonitis was observed for 64 patients who received a mean lung dose up to 8 Gy. In the dose range from 8 Gy to 12 Gy, 8 out of 81 patients (10%) developed radiation pneumonitis.

Our results show that the maximum heart distance is a good parameter from which the NTCP for excess late cardiac mortality can be estimated for the tangential irradiation technique. This can be expected, because the parameters used in the NTCP model for cardiac mortality indicate that the NTCP value depends on the volume contained in the high dose region. This volume is correlated with the maximum heart distance, resulting in a good correlation between NTCP values and the maximum heart distance. If CT-data and full 3D calculations are available for a patient, the direct calculation of the NTCP value is of course recommended. Das et al. [3] found a correlation between the central lung distance and the percentage of irradiated heart volume. However, this correlation was relatively weak (r=0.58). They also found a weak (r=0.64) correlation between gantry angle and percentage irradiated heart volume. Both measurements (i.e. central lung distance and gantry angle) are only an indirect method to quantify the amount of heart within the primary beam, while the maximum heart distance is a direct and simple method to determine the amount of heart within the high dose region. Based upon a maximum acceptable NTCP value, and thus the highest allowable maximum heart distance, each individual tangential irradiation set-up can be evaluated very quickly, e.g. using the beam’s-eye view option during virtual simulation or a simulator film. Proper modifications of the irradiation technique should be made if needed; i.e. by shielding part of the heart or by using intensity modulated beams [8].

The choice whether or not to irradiate the lymph nodes depends on the expected benefits of the irradiation, balanced against the irradiation toxicity for the heart and lung. Therefore, detailed data is needed about the heart and lung doses resulting from different locoregional irradiation techniques. This data can also be helpful to analyze the future results of a large EORTC study investigating the role of IM-MS irradiation [1]. Our results showed a significantly increase of the average NTCP of excess cardiac toxicity from 0.6% when only the breast is irradiated to around 2% when also the locoregional lymph nodes are included in the target volume.

In summary, Technique B results in a good coverage of the breast and locoregional lymph nodes, while Technique A sometimes results in an underdosage of part of the target volume. Both techniques result in a higher
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Heart dose compared with tangential irradiation of the breast only. Irradiation toxicity of the lung is low in the three techniques studied, while high NTCP values of cardiac mortality are found for some patients in all these three techniques. The maximum heart distance is a clinically useful parameter to predict NTCP values of excess cardiac mortality for the tangential breast irradiation technique.

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