Improvement of breast cancer irradiation techniques
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Citation for published version (APA):
Radiotherapy is an important treatment modality for patients with breast cancer. With respect to most other common cancers, a high local control rate and good overall survival can be achieved for the majority of breast cancer patients with current surgery and adjuvant radiotherapy treatment techniques. However, because the incidence of breast cancer is high, small radiotherapy treatment improvements can still have a large impact on the number of patients with locally controlled disease and prolonged survival. Radiation pneumonitis, cardiac morbidity, late cardiac mortality and a decreased cosmetic outcome are possible side effects of radiotherapy. Although the incidence of late cardiac mortality is low, the severeness of the complication justifies the continued search for better irradiation techniques. In this thesis a number of improvements of breast cancer radiotherapy techniques are described.

In chapter 1 the development of breast cancer treatment techniques is briefly discussed, with emphasis on radiotherapy techniques. The effect of radiotherapy on local control and overall survival is presented according to treatment site. The complications arising from radiotherapy are quantified, and involve skin reactions, arm and shoulder malfunctioning, pulmonary function changes, cardiac morbidity and late cardiac mortality. Although skin reactions are common, these complications are usually transient and not very severe. The other complications only arise in a few percent of all patients. However, some of these complications are much more severe.

In chapter 2 the accuracy of the delineation of the breast target volume on CT-scans is quantified. The patient averaged deviations in planning target volume (PTV) extent were larger in the posterior (range: 42 mm), cranial (range: 28 mm) and medial (range: 24 mm) directions than in the anterior (range: 6 mm), caudal (range: 15 mm) and lateral (range: 8 mm) directions. The intraobserver variation was decreased by a factor 4 on scans made with a lead wire compared to scans made without a lead wire. Consequently, if breast target volumes are to be delineated on CT-scans, lead wires should be placed on the skin around the palpable breast to reduce the intraobserver variation.

In chapter 3 the accuracy of sonography, lymphoscintigraphy and computer-tomography for localisation of the IM lymph nodes is quantified. The use of sonography is not recommended, because the accuracy of the
lateralisation is only 10 mm (1 SD) and a systematic deviation in depth of 5 mm is found which is also patient and observer dependent. Lymphoscintigraphy and computer-tomography have a comparable accuracy of 5 mm (1 SD) in depth and 6 mm (1 SD) in lateralisation, which is adequate for radiotherapy.

In chapter 4 and chapter 5 an improved technique for irradiation of the internal mammary (IM) - medial supravacular (MS) lymph nodes is presented. This technique is compared with our standard technique that consists of an anterior mixed electron / photon IM-MS field and with irradiation of the left breast only. For the latter technique, the maximum distance of the heart contour to the posterior field border, as seen in the beam's-eye view of the medial tangential fields, was measured. This value was scored as the maximum heart distance (MHD). In the improved technique, an oblique electron and an oblique asymmetric photon field are combined to irradiate the IM lymph nodes. To irradiate the MS lymph nodes, a combination of an anterior electron and an anterior asymmetric photon field is used. In all three techniques, tangential photon fields are used to irradiate the breast. Using the CT-data during treatment planning for all three treatment techniques, both locoregional treatment techniques resulted in good coverage of the lymph nodes, while the standard locoregional technique sometimes results in an underdosage of part of the target volume (mean PTV volume receiving a dose of 95% or more: 90%, range: 69%-99%). The improved and standard locoregional techniques result in a 1.7% and 1.0% higher probability of heart complications compared with irradiation of the left breast only. The normal tissue complication probability (NTCP) values for the tangential field technique could be estimated using the MHD. NTCP values for radiation pneumonitis were low for all techniques; between 0.0% and 1.0%.

In chapter 6 the possible reduction of cardiac and lung dose by applying conformal tangential beam irradiation of the intact left breast with and without intensity modulation, instead of rectangular tangential treatment fields is quantified. Furthermore, the extension of the applicability of the MHD to conformal tangential fields as a simple patient selection criterion, identifying patients during conventional simulation for which rectangular and conformal tangential fields without intensity modulation will result in unacceptable NTCP values for late cardiac mortality (e.g., > 2%), was investigated. The NTCP for radiation pneumonitis was on average below 0.6% for the three techniques. The NTCP for late cardiac mortality was 5.9% (SD: 2.2%) for the rectangular field technique. This value was reduced to 4.0% (SD: 2.3%) with the conformal technique. A further reduction to 2.0% (SD: 1.1%) could be accomplished with the IMRT technique.
The NTCP for late cardiac mortality could be described with a high accuracy as a second order polynomial function of the MHD and was independent of the technique for which the MHD was determined. In order to achieve NTCP values for late cardiac mortality below 1%, 2% or 3%, the MHD should be equal to or smaller than 11 mm, 17 mm or 23 mm, respectively. If such a maximum complication probability cannot be avoided by placing a block to shield the heart without shielding of the planning target volume, a treatment using the IMRT technique should be considered.

In chapter 7 intensity modulated (IMRT) and non-intensity modulated radiotherapy techniques in the treatment of the left breast and upper IM lymph nodes are compared and evaluated. Three different treatment plans were created: 1) tangential photon fields with oblique IM lymph nodes electron-photon fields with manually optimised beam weights and wedges, 2) wide split tangential photon fields with a heart block and computer optimised wedge angles, and 3) IMRT tangential photon fields.

The average standard deviation of the differential dose-volume histogram of the breast PTV was 4.6, 3.9 and 3.5% and the average mean dose to the IM lymph nodes was 97.2, 108.0 and 99.6% for the oblique electron, wide split tangent and IMRT techniques, respectively. The average NTCP value for the heart and lungs were comparable between the oblique electron and IMRT techniques (≤ 0.7%). The wide split tangent technique resulted in higher NTCP values (≥ 2%) for the heart.

In chapter 8 the effect of the use of two different arm positioning devices on the amount of lung and heart inside left-sided tangential treatment fields was studied. This comparison was based on simulator images of medial tangential fields taken in two positions: 1) with the ipsilateral arm abducted, holding a 'L-bar' armrest and 2) with both arms extended above the head in a forearm support. The average MHD as well as the central lung distance (CLD) decreased significantly, by 3.4 (SE = 0.9) and 4.7 (SE = 1.1) mm, respectively, when the new forearm support was used. For some patients, a greater amount of the axilla was included in the field. The use of the forearm support during breast cancer treatment with tangential fields is recommended to decrease the amount of heart and lung inside the fields. The use of the forearm support also enables CT scanning of patients in treatment position.

In chapter 9 the results of the quality assurance 'dummy run' procedure of a large EORTC radiotherapy trial investigating the role of IM-MS irradiation in stage I-III breast cancer have been described. The dose in the IM-MS region deviated significantly from the prescribed dose in 10% of the cases without IM-MS irradiation and in 21% of the cases with IM-MS
Summary

irradiation. The dummy run detected a number of potential systematic protocol deviations and recommendations were sent to the participating institutions that improved interinstitutional consistency.

In chapter 10 the implications of the results presented in the previous chapters with respect to clinical practice and directions of future research are described:

- The maximum heart distance should be used to select patients during conventional simulation for which standard left-sided breast irradiation will result in unacceptable NTCP values for late cardiac mortality. These patients should be treated using conformal fields.

- Intensity modulated tangential fields should be used to treat left-sided breast of patients for which the use of conformal fields does not result in a sufficient decrease in NTCP values for cardiac mortality. Before clinical implementation, the influence of set-up errors on the dose distribution should be quantified. The use of high-resolution CT imaging might be useful to decrease the uncertainty in the localization of the breast clinical target volume.

- The irradiation technique to treat the breast and IM-MS lymph nodes should be based on individual localization of the lymph nodes using lymphoscintigraphy or CT.

- Further, clinical studies investigating the exact position of local recurrences with respect to the primary tumour and the treatment field borders are required to assess the value of conformal breast irradiation. The results can be used to further optimise breast cancer radiotherapy.