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Improvement of breast cancer irradiation techniques
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chapter 10

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General

The aim of the studies described in this thesis is to improve radiotherapy treatment for patients with breast cancer. Specifically, one aim was to reduce the dose to the heart and lung resulting from irradiation of the left breast, thereby reducing the chance on late cardiac mortality and radiation pneumonitis. Another aim was to improve internal-mammary and medi-supraclavicular lymph node irradiation when locoregional irradiation is indicated, thereby increasing locoregional control and maybe overall survival in this patient group. It is known that the dose to the heart resulting from irradiation of the left breast varies widely between individual patients, even with the use of modern treatment techniques. Therefore a patient selection criterion, i.e. the maximum heart distance (MHD), was introduced and explored to select patients that have a high chance of late cardiac mortality resulting from irradiation of the left breast if the commonly applied rectangular tangential field irradiation technique is used. The implications of the results presented in this thesis with respect to clinical practice and the direction of future research will be discussed in this chapter.

Target volume localization

Breast

The results presented in chapter 2 show that there is a large intra- and interobserver variation in the delineation of the breast target volume on CT scans. Using the results from this study, an improved delineation protocol has been developed which makes use of a lead wire placed around the palpable glandular breast tissue. The axial delineations should be reviewed in sagittal and coronal reconstructions and, if needed, corrections should be made to ensure the target volume surface is smooth. Preliminary results suggest that these new guidelines result in a faster and more consistent delineation of the target volume.

Delineation on CT slices of the target volume after mastectomy is not routinely performed in most institutions. The results in chapter 2 show that the largest observer variations are found in the determination of the medial and posterior borders of the CTV. The CTV in these directions is not clearly confined by anatomical borders and there is no clear and fast transition from glandular tissue to fat tissue. The observer variations in the delineation of the CTV after mastectomy might be as large as the observer variations in the delineation of the CTV after breast conserving surgery, as all glandular
tissue has been removed and its original position cannot be seen on CT slices any more to guide the delineations. However, tissue changes visible on the CT slices as a result of the mastectomy, comparison with the contralateral breast and the position of the surgical scar might provide useful information during the delineation of the CTV after mastectomy. Detailed CTV delineation studies after a mastectomy have not been performed yet.

Often it is assumed that the CTV includes the complete palpable breast after breast conserving surgery. The results presented in chapter 2 are based on this assumption. However, it could be very meaningful to study and compare the location of the glandular breast tissue with respect to the fat tissue that is not considered at risk of tumour invasion and thus could be excluded from the CTV. The distinction between fat tissue and glandular tissue is often not clear in CT images used for radiotherapy planning which are often acquired with a resolution of about 2 mm x 2 mm x 10 mm. Magnetic resonance (MR) images provide additional information on the extent of the glandular breast tissue. MR images of the breast can already be acquired with a resolution of approximately 0.5 mm$^3$ in clinical practice using breast coils. Presently, new MR image guided biopsy techniques are emerging which enable an accurate positioning of the biopsy needle. However, this position can only be determined accurately with respect to the lesion, while the absolute 3D position of the complete breast volume cannot be determined accurately because of inhomogeneities in the magnetic field due to the presence of the breast itself and the inherent inhomogeneities in the magnetic field near the breast coil. Furthermore, the MR images do not provide the necessary electron density information needed for accurate dose calculations, and thus can only be used in combination with matched CT images.

The distinction between fat tissue and glandular tissue is also much clearer on mammograms that are used to detect lesions than on CT images, because mammograms have a much higher resolution of approximately 0.05 mm$^2$. Furthermore, the contrast between glandular tissue and fat tissue is higher, due to a lower tube potential of approximately 30 kV compared to a tube potential of approximately 120 kV for CT imaging. However, mammograms are 2D images of the breast made in a non-treatment position and thus cannot easily be used for treatment planning purposes.

As CT images and mammograms are both x-ray images, high resolution (e.g., 1 mm$^3$) and high contrast CT images are more useful than currently used CT images or mammograms to discriminate fat tissue and glandular tissue, and these images do not have the MR image disadvantages previously discussed. The contrast between glandular tissue and fat tissue increases at lower tube potentials due to an increase in the difference in linear attenuation coefficient between the two tissues at lower energy [45].
However, the signal-to-noise ratio in the images increases with lower tube potentials, which results in a decrease of the contrast. Increasing the number of photons emitted, which results in an increase of the dose to the patient, can increase this signal-to-noise ratio. Thus, the optimal tube potential is a trade-off between increased contrast between glandular tissue and fat tissue and increased dose to the patient. Without changing the tube potential, a higher CT resolution in the cranio-caudal direction can already easily be achieved by reducing the slice thickness without reducing the slice separation [35]. The image acquisition time should not be increased to prevent an increase in image distortion due to breathing. The acquisition time can be significantly reduced using spiral CT scanning, preferably on a multiple slice CT scanner.

After the optimal scan parameters are determined, a delineation study should be performed to quantify the benefit of high contrast and high-resolution CT images in combination with a lead wire placed around the palpable breast in terms of the reduction in intra- and interobserver variability in CTV delineation.

Lymph nodes

Internal mammary and medio-supraclavicular (IM-MS) lymph node localization is often performed using sonography, which is a fast, inexpensive and non-invasive technique. The normal sized lymph nodes cannot be detected directly using sonography. The location of the internal mammary vessels can be identified, and the position of these vessels is used as a surrogate for the position of the lymph nodes. However, the combined uncertainty in the position measurement of the vessels and the distribution of the lymph nodes around these vessels is large as has been shown in chapter 3. The position of the irradiation fields is often determined on the basis of sonography measurements and standard anatomical borders, leading to standard field borders. However, Bentel et al. showed that the variation in the position of the lymph nodes is wide and standard field borders may not be adequate in some cases [3,4]. These authors show that the additional localization information derived from CT images may lead to an improved positioning of the irradiation fields, which finding is confirmed by our results. Although CT is also an indirect method to determine the lymph node position, the accuracy of the lymph node position determined with CT scans is much higher than the accuracy using sonography. For centres that have limited CT scanning resources, using lymphoscintigraphy instead of sonography improves lymph node localization. Increasing the amount of technetium-99m nanocolloid injected, using smaller colloid particles, using 3D image triangularisation and usage of a medium energy collimator in combination with image filtering could further optimise the
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scintigraphy technique used in our study [24]. The increasing availability of CT scanners in radiotherapy departments, together with other treatment planning related advantages of CT scans, may lead to a growing use of CT scans for the (indirect) localization of the lymph nodes.

Conformal radiotherapy

Breast irradiation techniques

It is shown in chapter 7 that the use of conformal tangential fields to irradiate the left breast with or without intensity modulation reduces heart and lung toxicity compared to rectangular tangential treatment fields, without reducing the dose to the breast. Because the shape of the breast target volume is never rectangular, the use of rectangular treatment fields always results in the irradiation of more lung or heart than necessary to adequately irradiate the breast. It was also shown that the MHD could be used to select patients with a high chance of late cardiac mortality resulting from rectangular tangential field irradiation. For example, in order to achieve a NTCP value 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 could not be accomplished, a treatment using the IMRT technique was recommended.

However, conformal fields with only a small margin between the field borders and the breast PTV cannot easily be defined on a simulator, as the precise shape of the dorsal border of the breast near the thoracic wall cannot be visualized. One might consider introducing CT based treatment planning for all patients to define conformal fields, but this would increase the workload to an unacceptable level. Therefore, it is recommended instead to use the maximum heart distance as a patient selection criterion to select patients that have a high chance on late cardiac mortality resulting from left-sided breast cancer irradiation and patients who can be treated adequately using standard rectangular tangential fields. If a too large MHD is found, the placement of a simple block to shield the heart, maintaining a sufficient margin towards the breast should be considered. If the MHD is then still considered too high, CT based treatment planning of conformal fields is recommended. In order to verify that the amount of heart inside the treatment field during irradiation is not changed, portal imaging in the first week of treatment should be performed. Guidelines have to be developed which deviations from the intended MHD can still be accepted and which deviations should be corrected, for example by adapting the dorsal field borders.
Local control with breast irradiation

A number of clinical trials compared partial breast irradiation to whole breast irradiation or no irradiation at all [10,11,30,37,44]. In a first analysis of the Christie Hospital Breast Conservation Trial comparing whole breast (WB) irradiation to tumour bed (TB) irradiation, performed at six years from first randomisation, comparable local control rates, i.e., 92% of the TB group and 96% of the WB group, were found [37]. A re-analysis after 8 years from inception revealed actuarial breast recurrence rates of 15% (TB) versus 11% (WB) for infiltrating ductal carcinoma, whereas, for infiltrating lobular carcinoma, the recurrence rate was 34% (TB) versus 8% (WB) [37]. Furthermore, a later re-analysis did show a significant decrease in local control in the TB group: 75%, compared to the WB group: 87%, expressed in actuarial terms at 8 years [30]. This shows that preliminary results from this kind of studies must be interpreted with caution. Inadequate primary surgery or the use of too small irradiation fields in combination with inadequate positioning of the treatment fields may partly explain the lower local control. Deboise et al. argue that the inclusion of better imaging techniques (e.g., MR imaging or sonography) as an aid to shape and position the treatment fields may lead to comparable local-control rates for patients which receive adequate primary surgery [9]. However, new tumours in a different quadrant or distinctly removed from the primary tumour were shown to contribute 51% of the total number of recurrences in a study comparing the incidence of new primary breast cancer tumours and local recurrences after a mean follow-up of 14 years [39]. This is consistent with the findings in a large EORTC trial comparing the impact of a boost on local control and cosmesis in patients with early breast cancer, where after a mean follow-up of 5 years, 47% of the recurrences were located only in the primary tumour bed [2].

The risk of local recurrences as a function of position relative to the primary tumour site derived from mastectomy samples might also prove to be useful for field shape definition [16]. Holland et al. estimated the expected rates of local recurrences after breast-conserving surgical procedures relative to the extensiveness of the excision and relative to the distance from the primary tumour based on mastectomy samples. If tumours smaller than 2 cm would be removed with a margin of 2 cm or 4 cm, 42% or 10% of the patients would still have tumour foci in the remaining breast, respectively. These foci could be responsible for either short- or long-term recurrence [17]. These percentages were not significantly influenced by the size of the original tumour. Thus, it can be concluded that radiotherapy to the tumour bed alone is insufficient. The influence of only a small decrease of the treatment fields to irradiate the whole breast on local control is, however, not known. All the information from trials investigating limited
radiotherapy and from pathology studies on tumour spread should be used to develop a valid tumour control probability (TCP) model or, more accurately, a local control probability (LCP) model. The model should describe the increase in local control as a function of dose and position in the breast with respect to the primary tumour. Such a model is a useful treatment plan evaluation tool that enables a more clinically relevant optimisation of conformal techniques to shield the lung and heart than using dose homogeneity constraints. In contrast to most TCP models of different organs in which a homogeneous clonogenic cell density and thus a homogeneous tumour recurrence probability is assumed in the largest part of the tumour volume, the LCP model should explicitly incorporate the inhomogeneous distribution of glandular tissue considered to be at risk of tumour recurrence.

The benefit of conformal breast irradiation with or without intensity modulation compared to standard rectangular tangential irradiation fields still has to be proven clinically, although some centres already incorporate individually shaped blocks to shield the lung or heart [31]. A clinical study investigating the exact position of local recurrences with respect to the treatment field borders is needed to establish the value of conformal breast irradiation. The study results can be used to improve future treatment techniques and to validate and improve the LCP models needed for automated optimisation of (intensity modulated) treatment plans.

Locoregional irradiation

The widely varying target volume shape between individual patients makes it necessary to individualize the treatment technique for all patients that receive IM-MS irradiation. Based on the position of the IM-MS lymph nodes and the shape of the breast or thoracic wall, either an anterior IM-MS field or an oblique IM-MS field should be chosen if the treatment technique is defined at a simulator unit. This should be combined with tangential photon fields to irradiate the breast or thoracic wall. A direct electron field can also be used to irradiate the thoracic wall. The use of the wide split tangent technique is not recommended, because it results in a higher lung and heart dose and too high dose to the IM-MS nodes (chapter 7). If the treatment technique is defined at a simulator unit, the position of the lymph nodes should be determined by scintigraphy rather than by sonography. However, radiotherapy could be improved substantially if CT treatment planning would be routinely used for these patients. This enables a better location of the target volumes and calculation of the 3D dose distribution. On the basis of this information, a better choice between anterior or oblique IM-MS fields can be made and a more accurate choice of the electron beam energy is possible. Furthermore, the availability of CT scans is needed if
one wants to implement an IMRT technique for this target volume. Although the implementation of a tangential IMRT technique might initially increase the treatment preparation time, it might be expected that treatment preparation time eventually will be comparable to conventional simulation while the design and construction of electron moulds for the IM-MS fields and, after a mastectomy, thoracic wall electron fields will no longer be needed. The treatment execution time of a tangential IMRT technique can be expected to be less than the treatment execution time of the anterior or oblique irradiation techniques.

**Incorporation of set-up errors and organ motion**

A margin between the irradiation field borders and the CTV is needed to account for the uncertainty in the localization of the CTV as well as patient set-up errors and organ motion [21,43]. The improved techniques described in chapters 4 to 7 were developed using CT based treatment plans. The CTVs and ORs were delineated and proper margins were selected to ensure an acceptable dose distribution. The estimated adequate treatment margin depends on the size of the random and systematic errors and on the percentage of patients for which one wants to achieve a specified minimum dose to the CTV [40]. The proper margin width also depends on the beam arrangement. If several beams irradiate the same edge of a CTV, tighter margins might already result in adequate CTV coverage compared to the situation when fewer fields overlap this CTV edge [33].

Instead of using margin recipes, the effect of set-up errors, organ motion and organ deformation on the resulting dose distribution can also be incorporated in the treatment plans directly. There are now a number of studies describing techniques to incorporate organ motion and deformation and set-up errors into 3D dose calculations [8,14,15,22,29,32,46].

A simple but time-consuming method is the calculation of several treatment plans to include selected set-up errors and organ deformations [8,14]. Das et al. calculated the effects of set-up errors and treatment field gantry angle deviations on the dose distribution based on re-simulation of tangential field irradiation of the breast [8]. However, deriving the resulting overall dose distribution from selected set-up errors and organ deformations is not straightforward.

Xing et al. proposed a method to estimate the effect on the overall dose distribution by multiplying the effect of several, separately calculated effects (e.g., collimator and gantry angle misalignments and patient displacements), on the dose distribution [46].

Convolution-based methods, in which the static dose distribution is convolved with a function that describes organ motion and set-up deviations have also been used [22,29,32]. The resulting dose distribution directly
The discussion section describes the overall dose distribution. This function can be Gaussian in shape, which is often used to describe set-up errors. The method described by Lujan et al. [29] is based on the convolution of a static dose distribution with a probability distribution function that describes the nature of the non-Gaussian lung motion. Organ motion due to breathing is assumed here to be one-dimensional and is modelled using a periodic non-symmetric function (more time spent at exhalation than inhalation). Convolution methods can only be used if the dose distribution is invariant under set-up errors and organ motion or deformation. Although this may lead to adequate calculations for some sites such as pelvic and head and neck treatments, its use in lung or breast cancer treatment techniques is questionable, because the dose distribution is not invariant under set-up errors and breathing motion in this region. Future research aimed at a more accurate quantification of these influences on the overall dose distribution is needed to further improve treatment techniques of breast cancer.

In addition to incorporation of the effect of set-up errors, organ motion and deformation on the overall dose distribution in one single treatment plan designed at the start of the treatment, it is also possible to adapt the treatment plan based on information obtained during the actual treatment series. Based on individually measured set-up errors, the beam shapes and directions can also be adapted after each fraction [15,20,27]. These methods do not only lead to a better quantification of the effects of set-up errors on the dose distribution, the methods actually enable the use of an individually determined treatment field margin that leads to an improved treatment technique. However, all methods mentioned above increase the treatment preparation and execution time. A much more efficient method could be to clinically implement a set-up error correction protocol for conformal breast cancer treatment techniques [19]. This method enables the use of smaller margins because the set-up errors are reduced, and the method does not increase treatment preparation time. The effect of set-up errors, organ motion and deformation on the overall dose distribution should be quantified in research studies using further improved methods to quantify these effects.

Increase of distance between the breast and the lung and heart

Usually, breast cancer patients are treated in a supine position. This position is comfortable for the patient and enables the selection of a wide range of beam directions. Generally, set-up errors in this position are acceptable [19].

The use of fixation devices or various arm rests influence the set-up error and can also influence the volume of the organs at risk inside the treatment fields, as shown in chapter 8 and confirmed in a study by Canney
et al. [6]. In chapter 8 it is shown that, by using a forearm support instead of a ‘L-bar’ support, the central lung distance and maximum heart distance in tangential field irradiation of the breast can already be reduced by on average 3 and 5 mm, respectively. In some institutions, a lateral decubitus or prone position irradiation is used for patients with large breasts [1,12,13,34]. This may reduce the amount of lung and heart inside the fields if the distance between the breast CTV and the ORs can be increased.

Breath hold or respiration gated breast irradiation is another method to reduce the amount of lung and heart inside the treatment fields [25,28]. These methods can reduce the volume of heart inside the field with as much as 86% [28]. Although these methods can only be implemented at the cost of some patient discomfort and an increase in workload at the treatment unit, the significant reduction of heart volume inside the treatment fields validates introduction of this technique for specific patients. Shirato et al. have already demonstrated the feasibility of gated radiotherapy for lung tumours where the gating was triggered by the position of gold markers implanted in the tumour [38]. They used a real-time tracking-tracking system consisting of four sets of diagnostic X-ray systems. Technologies such as gated radiotherapy may significantly increase the treatment time, while breath-hold techniques may be poorly tolerated by pulmonary compromised patients. A solution proposed by Keall et al. in which the target motion is synchronously followed by adapting the X-ray beam using a dynamic multileaf collimator (MLC) does not suffer from these drawbacks. However, this technique does not increase the distance between the CTV and ORs during irradiation and is therefore not as effective as gating techniques [23]. The most promising treatment technique might be to combine gated radiotherapy with set-up position verification and correction using an amorphous silicon EPID [26]. The beam could be triggered by a predefined maximum amount of lung inside the treatment fields using the same amorphous silicon imaging device that is fast enough to track breathing motion.

QA of radiotherapy trials

In the previous sections possible methods for improving radiotherapy treatment techniques for breast cancer patients were discussed. The improvement gained by the implementation of such techniques is often estimated on the basis of treatment planning studies. The actual clinical benefit of new treatment techniques can only be adequately assessed by performing a large randomised prospective trial in which the results of a standard treatment technique are compared with a new treatment
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technique. Quality assurance of such trials is needed to reach a high compliance with the trial protocol [5,18,36,41,42]. A phase III randomised EORTC trial (the AMAROS trial) comparing radiotherapy with surgery after mapping of the axilla was started in the beginning of 2001 [7]. Preliminary results of the radiotherapy dummy run procedure of this trial show that a wide variety of treatment techniques are used to treat the axillary region. In some techniques, the dose variation is greater than 20%, which is not compliant with the trial protocol and may influence the trial results. In such cases, suggestions for treatment technique modifications are send to the individual participating institutions. Even if a trial quality assurance program is performed, it is important to quantify the effect of protocol violations on the outcome of the trial, as this factor may confound the true results of the trial [36].

A multidisciplinary approach is needed for further improvement of breast cancer radiotherapy. Tools for improved target volume localization, delineation and delivery should become commercially available according to the suggestions from clinical test sites, and guidelines for their safe use in clinical practice should be developed. Based on clinical trial results and new insights in the development and progression of breast cancer, the radiation oncologist should refine the objectives of radiotherapy, for the individualized optimisation of the radiotherapy treatment. Collaboration between radiation oncologists, clinical physicists and radiation technologists is needed if a proper implementation of these new techniques is to be accomplished. Thereafter, new clinical trials supported by radiotherapy collaborative groups are needed to test the effects of the use of these new techniques on the treatment outcome.

Conclusions

The results presented in this thesis indicate that significant improvements of commonly used breast cancer irradiation techniques are possible. These improvements include better localization of the IM-MS and breast target volumes, better patient treatment positioning and implementation of conformal treatment techniques with or without intensity modulation. These conformal techniques can be introduced clinically without a considerable increase in workload if the maximum heart distance is used as a patient selection criterion.

Variations in the delineation of breast target volume on CT scans can be as large as several centimetres at the medial and caudal edges of the CTV. These variations can be decreased by using CT scans with lead wires placed on the skin around the palpable breast and by making corrections to
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the axial delineations using sagittal and coronal reconstructions. Future research should be aimed at the development of a better clinical target volume definition, e.g., by using the results from trials comparing whole breast irradiation to partial breast irradiation, by using the results from pathology studies and by using high-resolution CT imaging of the breast.

Localization of the IM nodes is often performed using sonography, which was shown to have an unacceptably high inaccuracy of 10 mm (1 SD). Localization can be improved when lymphoscintigraphy or computer-tomography are used. Both techniques have an acceptable accuracy of approximately 5 mm (1 SD).

A 6-field technique making use of oblique IM fields matched to tangential fields is developed which results in better target coverage than a commonly used technique using anterior IM fields. Intensity modulated tangential fields to irradiate the breast and upper IM nodes were also shown to result in acceptable target coverage. Such an approach might be more efficient with respect to treatment delivery than the 6-field oblique technique.

The use of standard rectangular tangential fields to irradiate the left breast without the IM-MS lymph nodes leads to the irradiation of a large amount of lung and heart for some patients. It is demonstrated that the use of conformal or intensity modulated tangential fields to irradiate the left breast can result in a decrease of the NTCP for excess cardiac mortality of 30% and 65%, respectively, compared to the standard technique. However, the use of these techniques for all patients is not needed and would be too labour intensive. By using a forearm support instead of a 'L-bar' support, the central lung distance (CLD) and maximum heart distance (MHD) in tangential field irradiation of the breast can already be reduced by on average 3 and 5 mm, respectively. Therefore, the use of the forearm support is recommended.

The MHD was introduced to select patients during conventional simulation that have a high NTCP for late cardiac mortality resulting from tangential field irradiation of the left breast. A good correlation between the MHD and NTCP calculated on the basis of 3D CT data was found. If a too large MHD is found, the placement of a simple block to shield the heart, maintaining a sufficient margin towards the breast, should be considered first, as this is a very efficient method to reduce the dose to the heart. However, if the MHD is then still too large, CT based treatment planning of conformal intensity modulated fields is recommended.

The treatment planning studies presented in this thesis did not include calculations of the influence of set-up errors and organ motion on the dose distribution. More research is needed if one wants to quantify this influence in detail. A clinical protocol for the use of intensity modulated tangential fields will be developed in the near future.
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