Improvement of breast cancer irradiation techniques
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Introduction
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Background

Breast cancer is a very common disease in western countries. The incidence in the Netherlands is approximately 130/100,000 women per year, meaning that one out of ten women is faced with the diagnosis of breast cancer during her life [55]. Currently, breast cancer is often being diagnosed at an earlier stage than in the past. This is due to the adoption of breast screening programs for women between 50-70 years of age and a bigger awareness of the risk to develop breast cancer that led to an increase of self-examination of the breast among women. This, together with improved multimodality treatment techniques contributed to a decrease in breast cancer mortality in the West-European countries. The 5-year overall survival for the complete group of breast cancer patients in the Netherlands increased from 52% in the period 1955-1969 to 76% in the period 1987-1992 [55]. It was concluded in 1997 that proper screening of women between 50-70 years of age in the Netherlands could result in an increase in overall survival of 17% [55]. Between 1989 and 1995, the incidence of in situ carcinoma among women between 50-70 years of age increased by 130%, while the incidence of stage I tumours doubled and the incidence of stage II tumours was approximately stable. The number of stage III-IV tumours in women older than 50 years of age decreased by 24% [7].

Surgery and radiotherapy are the most important modalities for locoregional breast cancer treatment. In the beginning of the previous century surgery was very extensive. Radical mastectomy (removal of the entire breast, the lymph nodes and the pectoralis major muscle) was performed in order to prevent tumour growth, local recurrences and distant metastasis [18]. Later, the modified radical mastectomy procedure was introduced: removal of the entire breast and axillary lymph nodes [42].

In the beginning of the twentieth century some types of breast cancer were already treated by breast conserving surgery removing the primary tumour plus a margin and were additionally irradiated using low-energy X-rays. The introduction of megavoltage therapy in the 1930's led to further developments in breast conserving therapy. While surgery was still used to remove the primary tumour to prevent tumour regrowth, radiotherapy was given to prevent further local recurrences. Due to earlier diagnosis and similar efficacy as modified radical mastectomy, breast conserving therapy plus whole breast radiotherapy is increasingly applied in order to avoid mutilating surgery [65]. However, in high risk breast cancer patients, mastectomy is still applied.
Introduction

Tumour control and survival

Radiotherapy after breast conserving therapy or mastectomy

In the year 2000, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published the results of a new meta-analysis of randomised breast cancer trials comparing surgery, being either mastectomy or breast conserving, with and without adjuvant radiotherapy in early stage breast cancer [1]. It was shown that 20-year overall survival of early stage breast cancer patients who received mastectomy or breast conserving surgery was 35.9%, while it was significantly increased by 1.2% to 37.1% if adjuvant radiotherapy was given. Radiotherapy fields generally included not only chest wall (or breast) but also axillary, supraclavicular, and internal mammary nodes. Although breast cancer specific mortality after 20 years was reduced, there was a significant increase of non-breast cancer related mortality after radiotherapy (Table 1). This increase was 1% after 10 years, and as high as 4.3% after a 20 years follow-up period. The increase in long-term mortality was caused by a significant increase of vascular mortality (death rate ratio 1.3). It was concluded that radiotherapy would be expected to produce an absolute increase in 20-year survival of about 2-5% without long-term hazard. The average long-term vascular mortality hazard would, however, reduce this benefit in young women and reverse it in older women. The increase in non-breast cancer related deaths in some of the older trials that were analyzed has also been associated with an increase in cardiac mortality, caused by the use of old irradiation techniques in these trials.

Table 1. Isolated local recurrences and specific survival as reported in a meta-analysis of randomized trials comparing surgery plus radiotherapy with surgery alone in early stage breast cancer [1]. Both mastectomy and breast conserving surgery are included.

<table>
<thead>
<tr>
<th>Follow-up (years)</th>
<th>Surgery alone (%)</th>
<th>Surgery plus radiotherapy (%)</th>
<th>Absolute difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrences</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>27.2</td>
<td>8.8</td>
<td>-18.5 (2p&lt;0.0001)</td>
</tr>
<tr>
<td>20</td>
<td>30.1</td>
<td>10.4</td>
<td>-19.7 (2p&lt;0.0001)</td>
</tr>
<tr>
<td>Overall mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>45.5</td>
<td>43.4</td>
<td>-2.1</td>
</tr>
<tr>
<td>20</td>
<td>64.1</td>
<td>62.9</td>
<td>-1.2 (2p=0.06)</td>
</tr>
<tr>
<td>Breast cancer specific mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>39.6</td>
<td>36.6</td>
<td>-3.0</td>
</tr>
<tr>
<td>20</td>
<td>51.4</td>
<td>46.6</td>
<td>-4.8 (2p=0.0001)</td>
</tr>
<tr>
<td>Non-breast cancer specific mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>9.8</td>
<td>10.8</td>
<td>+1.0</td>
</tr>
<tr>
<td>20</td>
<td>26.2</td>
<td>30.5</td>
<td>+4.3 (2p=0.0003)</td>
</tr>
</tbody>
</table>
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A highly significant reduction of breast cancer specific mortality of 3% after 10 years and 4.8% after 20 years was found. The reduction of locoregional recurrences with radiotherapy was also highly significant. In the EBCTCG meta-analysis it is shown that isolated local recurrences can be reduced by approximately 70% with additional radiotherapy after mastectomy or breast conserving surgery in early stage breast cancer patients (Table 1).

Radiotherapy after mastectomy

Although the EBCTCG meta-analysis results have been published after the publication of individual trial results, the meta-analysis was based on older data with a shorter median follow-up for some of the trials. The meta-analysis also included trials that made use of old irradiation techniques or trials in which no adjuvant chemotherapy was given. The results of this meta-analysis may therefore underestimate the gain that can be reached with more recent treatment techniques. The results after a median follow-up time of at least 10 years of large randomized trials using more modern radiotherapy techniques show that in high risk pre- and postmenopausal women receiving chemotherapy after mastectomy, the addition of adjuvant radiotherapy results in an improved overall survival of as much as 8%-9% at 10-years [39,40,45]. In these studies breast-cancer specific survival was not offset by an increase of non-breast cancer related deaths in the radiotherapy groups. In a more recent meta-analysis of randomized trials in which postmastectomy radiotherapy was given in combination with adjuvant systemic therapy and modern radiotherapy treatment to high risk stage III-IV pre- and postmenopausal breast cancer patients, it was concluded that overall survival was significantly improved with an odds ratio of 0.82 (95% confidence limits 0.72-0.92) [37]. The locoregional recurrence rate was reduced by a factor of 2-4 for patients receiving mastectomy, chemotherapy and adjuvant radiotherapy.

These results suggest that with the introduction of better irradiation techniques, late cardiac mortality as found in the older trials is no longer a problem. Although late cardiac mortality might not anymore be significantly increased in a large, heterogeneous population of patients, it is known that the dose to the heart varies widely between individual patients, even with the use of modern treatment techniques. This implies that there might still exist a subgroup of patients that are still at risk for late cardiac mortality.
Internal mammary and medio-supraclavicular lymph node chain

The incidence of involvement of the internal mammary medio-supraclavicular (IM-MS) lymph node chain ranges from 10% in axillary node negative patients with central or medial tumour location to about 50% in patients with axillary node invasion. In spite of this significant involvement the usefulness of irradiating the IM-MS lymph nodes remains controversial. In a large number of studies a significant decrease in locoregional recurrence was a consistent finding [12,19], although a survival benefit could not be clearly demonstrated. Some reports have even shown detrimental effects on long term survival [5,6]. In a meta-analysis performed by the Early Breast Cancer Trialists’ Collaborative Group, however, long-term breast cancer deaths were demonstrated to be reduced in irradiated patients [6]. Because of these controversies a large EORTC phase III randomised trial [62] was started in 1996 to investigate the effect of IM-MS irradiation in stage I-III breast cancer on overall survival and cause-specific mortality.

Axillary region

The presence or absence of axillary lymph node involvement is important for prognosis and staging of patients with breast cancer. Clearing the axilla improves regional tumor control and may improve survival in some cases [21,36]. Axillary lymph nodes are involved in about 40% of the patients. In the remaining 60% no therapeutic benefit is gained from axillary node dissection but these patients are exposed to the considerable morbidity associated with this procedure [27,54]. In order to reduce the associated surgical morbidity, sentinel node biopsy has been investigated as a means of axillary staging. Sentinel node biopsy is a much more limited surgical procedure with less associated morbidity. If the sentinel node biopsy is negative, then no axillary lymph node dissection is needed. A series of randomized clinical trials, in which simple mastectomy was the primary surgical procedure, have compared axillary lymph node dissection with axillary radiotherapy. With respect to the endpoint of survival generally no differences were found between the two approaches. The axillary recurrence rates varied between 3-19% for all trials and between 3-12% for those using megavoltage radiation equipment in these studies [2,11,13,31]. In clinical series on the effectiveness of axillary radiotherapy in the treatment of early stage breast cancer in the context of breast conserving therapy the axillary recurrence rates vary mostly between 0.6-3.6% [4,22,66]. A large EORTC phase III randomised trial [63] was started in 2001 to compare
complete axillary node dissection with axillary radiotherapy after positive sentinel node biopsy staging. The primary endpoint is axillary recurrence. However, shoulder function analysis, quality of life assessment and quantifying the morbidity of the treatment, are important secondary endpoints as well.

Normal tissue complications

Dose-effect relationship

The benefit of breast cancer treatment using radiotherapy must always be weighted against the possible side effects of radiation treatment. The effect of radiotherapy on the normal tissues is primarily dependent on the type of organ and the dose the organ receives. In general, a higher dose will result in a higher chance on complications. Furthermore, an increase in the volume that receives a high dose will in general result in a higher complication rate. Dose fractionation is also an important factor. A radiotherapy treatment that results in a certain tumour control given with low dose per fraction will result in less complications compared to a large dose per fraction. The effect of radiation on normal tissues can be described by a three-dimensional dose-volume effect.

Figure 1. The normal tissue complication probability (NTCP) is a function of volume and dose. In this figure the NTCP for excess late cardiac mortality according to Gagliardi et al. is shown.
Other patient and treatment related factors like age, smoking, comorbid illness and adjuvant chemotherapy can also influence the radiation effect on the normal tissues. The main organs at risk in radiotherapy of the breast are the skin, shoulder including nerves and muscles, lungs and heart.

Skin, shoulder and lung

Swelling, soreness and erythema are early side effects of the skin that can already appear during external radiotherapy treatment. However, these complications are mostly transient effects that settle down after 4-6 weeks. Late cosmetic side effects of the skin (after more than 6 months) include telangiectasia and fibrosis. Total breast doses higher than 50 Gy [60,64] and a dose per fraction equal or higher than 2.5 Gy [52,64] can result in severe fibrosis. Significant dose inhomogeneity is also associated with worsened cosmetic outcome [52][60].

Arm edema (0-2%), shoulder malfunction (1%) and brachial plexus neuropathy (<1%) are observed as possible side effects of axillary irradiation [43]. Brachial plexus neuropathy seems to be a result of inappropriate field junction techniques, resulting in high fraction doses and high overall doses in the brachial plexus. For example, aggressive postoperative telecobalt therapy to the axillary, supraclavicular and parasternal lymph node regions was given to a group of 71 patients operated for breast cancer with total mastectomy and axillary clearance [25]. The prescribed dose to these lymph node regions was 44 Gy in 11 fractions. After a few years symptoms and signs of brachial plexus injury appeared in many patients. After 34 years 11 of 12 patients who were still alive had paralysis of their arms. The use of large daily fractions, which is not often used anymore, in some cases combined with hot spots from overlapping fields, was certainly the cause of the complication.

Change in pulmonary function due to partial irradiation of the lungs is another possible subacute side effect. Much work has been done to describe the pulmonary effects of radiotherapy. The normal tissue complication model developed by Lyman can be used to describe the dose-effect relationship for radiation pneumonitis [35]. It is shown that a simplification of this model, in which the lungs are assumed to be a pure parallel organ, can be used to predict radiation pneumonitis and pulmonary function loss after treatment for breast cancer [29,61].
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Heart

The EBCTCG meta-analysis showed that radiotherapy after surgery would increase the 20-year survival with 2-4% instead of the 1.2% found in the analysis if it would not be compromised by the decrease in 20-year survival due to vascular mortality [1]. Information was not collected centrally on carotid artery or cardiac exposure to radiation, so direct determination whether the increase in vascular deaths was related to such exposure was not possible in the analysis. Recently, there has been growing awareness of the possible cardiac complications of breast cancer radiotherapy. Ischemic heart disease and coronary artery disease have been recognized as 'important late manifestations of radiation' [57]. These complications can be separated according to their respective end points: mortality (ischemic heart death or myocardial infarction) and morbidity (decreases in cardiac function).

Some studies show increased symptomatic cardiac morbidity after irradiation of the heart due to treatment of Hodgkin’s disease [48]. Non-symptomatic reduction in myocardial perfusion detected by scintigraphy or left ventricular dysfunction detected by echocardiography is occasionally found for patients treated for breast cancer. However, these differences were usually temporary and not correlated with symptomatic morbidity [16,20].

A number of large randomized trials have shown an increase in late cardiac mortality for left-sided breast cancer patients treated with radiotherapy [15,17,41,51]. The importance of late side effects has grown due to the improved long-term survival for breast cancer patients. Although the risk of a fatal complication does not seem to be very high, the seriousness of this complication and the large prevalence of breast cancer justify further reduction of this complication risk.

In 1971 Stewart and Fajardo [56] used a nominal standard dose model to quantify the radiation-induced heart disease dose-effect relationship. However, the validity of this model to predict radiation complications resulting from postmastectomy irradiation is questionable [38].

In 1996 Gagliardi et al. used the Lyman model to describe the dose-effect relationship for late cardiac mortality [14]. The clinical data from the ‘Stockholm trial’ [51] and the ‘Oslo trial’ [24] were used to derive the model parameters. Although the data of a large number of patients (Stockholm: 959 patients, Oslo: 356 patients) were used to estimate the clinical incidence of excess cardiac mortality, the confidence interval around these clinical values remains relatively wide. This is mainly due to the low absolute incidence of radiation-induced cardiac mortality and the uncertainty in the incidence of cardiac mortality in the unirradiated control groups.
The same group of investigators also estimated model parameters using the data of 157 Hodgkin's disease patients [8]. In this study a significantly increased risk of death due to ischemic heart disease following radiotherapy for Hodgkin's diseases was found. The risk increased with dose and irradiated volume. However, an unambiguous parameter set describing both the breast cancer patient group and the Hodgkin's disease patient group could not be found. This finding suggests that further possible improvements of the model should be made such as the incorporation of the enhancing effect of chemotherapy.

Radiotherapy treatment techniques

The clinical target volume (CTV) for radiotherapy is the volume that is considered to be at risk for loco-regional recurrences and should be treated to an adequate dose. Depending on the stage of the disease the clinical target volume may consist of the whole breast after breast conserving therapy or the thoracic wall after mastectomy, but may also include the internal mammary, supraclavicular and axillary lymph nodes. The surrounding organs at risk (ORs) should receive as little dose as possible. Therefore, the position and extent of the CTV and ORs should be well known. Usually the beam arrangement is determined on a simulator based on the outline of the patient and fluoroscopy images in which the bony anatomy is visible. The CTV is then assumed to lie within some predefined bony anatomy landmarks (e.g. the sternum, ribs and coracoid process).

The location of the breast CTV can also be determined with the aid of CT. Systematic quantification of intra- and interobserver variation in the delineation of CTVs has been performed for a number of treatment sites, e.g., prostate, lung and brain tumours [10,33,46,53,59,68]. Overall observer variations were relatively small for prostate tumours (approximately 3 mm, 1 SD), compared to lung tumours, where differences of several centimetres have been observed. However, such data were not available for the breast.

The location of the lymph nodes can be determined directly using lymphoscintigraphy or indirectly using sonography or CT. Because the lateralization and depth of the IM lymph nodes vary between individuals [47,58], standard field sizes are not always applicable and the lymph nodes have to be localized individually to determine the correct field borders. However, no comparison of the accuracy of these three measurement techniques has been performed previously.

In combination with the beam arrangement the proper beam modality (photons or electrons) and beam energy have to be chosen to produce a homogeneous dose in the target volume and minimize the dose to the ORs.
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There is a number of techniques developed to irradiate the breast and locoregional lymph nodes either using specifically mono-isocentric techniques [28,44,50], or multiple isocentre techniques [30,32,49,67]. These techniques all solved part of the field matching problems, but did not address the differentiation of the technique according to the location of the lymph nodes in individual patients. A comparison of techniques based on equal 3D dose calculation algorithms and equal CTV localization information has not yet been published. During the last years intensity modulated treatment techniques have been developed, mainly to provide a more homogeneous dose in the breast [3,9,23,26,34]. There are little data on the effectiveness to reduce the dose to the lung and heart using intensity modulation compared to non-intensity modulated treatment techniques.

Thesis aims

The aim of this thesis is the improvement of radiotherapy treatment techniques for breast cancer patients. The main focus was to develop conformal irradiation techniques that irradiate less heart than currently used techniques. First, studies were performed to quantify and improve target volume localization and delineation (Chapters 2 and 3). Second, new treatment techniques were developed and treatment-planning studies were performed to quantify the reduction in lung and heart dose resulting from these techniques (Chapters 4 to 7). A study comparing two different arm support devices was performed to establish which support in combination with tangential fields to irradiate the left breast would lead to the least amount of lung and heart inside these treatment fields (Chapter 8). Quality assurance procedures were implemented for a large multi-centre randomised clinical trial investigating the effect of IM-MS irradiation (Chapter 9). Finally, suggestions for future research and further treatment improvements were given (Chapter 10).

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