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GENERAL INTRODUCTION AND OUTLINE OF THE THESIS
INTRODUCTION

Improvements in locoregional treatment of breast cancer

Breast cancer represents the most common female malignancy in the developed world, affecting approximately one out of eight women during her lifetime. The incidence of breast cancer is still increasing. In the Netherlands, between 2001 and 2011, the incidence has increased from 144 cases per 100,000 women to 166 cases per 100,000 women.\(^1\)\(^2\) Despite this increase in incidence, the mortality rates of breast cancer have been decreasing. This decrease started in the 1990s and is mainly attributable to the increased application of systemic treatment, to the nation-wide screening programmes, and to an improved local control.\(^3\)\(^5\) Nowadays local control is excellent\(^4\) as a result of several improvements in diagnosis and treatment over the past few decades. Better imaging made possible by MRI and digital mammograms provides a more accurate pre-operative baseline assessment of the extent of the lesion and signs of microinvasion.\(^7\)\(^8\) Trends in surgical management, such as better localisation methods and oncoplastic techniques, have been shown to decrease the rate of incomplete excisions.\(^9\) More standardised margin assessment helps to better identify patients with a positive margin, who may need additional local treatment.\(^10\) Improvements in radiotherapy, in fields and dose, have improved outcome in terms of better local control and fewer side effects.\(^11\)\(^12\) Developments in systemic treatments both for early and for advanced disease should further decrease local recurrence rates.\(^5\)

The increase in incidence of breast cancer together with the decrease in mortality rates in the last decennia implies that relatively and absolutely more patients will survive their potentially life-threatening disease and will finally die of other causes. This also means that more patients will live with the side effects of the – often aggressive – cancer treatments. Side effects of loco-regional treatment of breast cancer can be acute or late-onset, they can last a lifetime, and they often have a significant effect on a woman’s quality of life. A mastectomy, for example, will induce distortion of the body image, resulting in a psychological burden. Radiotherapy as part of the breast-conserving therapy can cause fibrosis and lymphedema of the breast and it can affect cosmesis. Moreover, in case of treatment of left-side breast cancer it can also increase the risk of cardiovascular events in the long term.\(^13\)\(^14\) And although infrequently seen, radiotherapy can induce radiation pneumonitis and plexopathy.\(^15\) Local treatment of the axilla such as an axillary lymph node dissection (ALND) can cause long-term morbidity including lymphedema, dysesthesia and neuropathy of the ipsilateral arm.\(^16\)\(^18\) This too might result in distortion of the body image and impaired shoulder function.

Due to breast cancer screening and improved awareness, breast tumours nowadays are often found in an early stage. Consequently, the average size of the tumours is smaller and they have less frequently spread to the lymph nodes.\(^19\)\(^20\) This results in more patients being able to undergo breast- and axilla-conserving treatment and an overall better local control.

The high survival rates, the overall reductions in local recurrence rate and the consequences of side effects of cancer treatment on quality of life raise the issue of overtreatment. In other words, can we sustain optimal loco-regional control with more conservative treatment approaches leading to fewer side effects, while maintaining these excellent locoregional control rates?

The answer is yes. In the last few decades, surgical treatment of the breast has become more conservative. Forty years ago, the standard surgical treatment of the breast was a Halsted mastectomy, whereby not only the breast tissue was removed, but also the overlying skin, the pectoralis muscle and the ipsilateral lymph nodes.\(^21\) This type of surgery was replaced by changed into a modified radical mastectomy, which conserved the pectoral muscle. Large randomised trials
conduct in the 1970s and early 1980s showed that breast-conserving surgery with adjuvant radiotherapy was comparable to mastectomy in terms of local control and survival; thus it reduced morbidity and improved quality of life.22-27 Further developments of this conservative treatment include a more precise excision with improved pre-operative localisation methods.28 Improved cosmesis can be obtained with oncoplastic breast surgery or an immediate reconstruction after a mastectomy. Decreasing the fields of radiotherapy to the breast can be accomplished by partial breast irradiation, or by omitting radiotherapy to the breast at all in a selected subgroup of patients.12,29 Furthermore, neoadjuvant systemic treatment can decrease the size of the cancer to such an extent that breast conservation is feasible in patients who would otherwise have an indication for a mastectomy.30-32 Following more conservative treatment of the breast, more conservative treatment of the axilla became available after the introduction of the sentinel node biopsy that spared an ALND in node-negative patients.33 However, for patients in whom the sentinel node harbours metastasis, an ALND has long been the standard of care. Although an ALND provides excellent regional control, it is associated with long-term and short-term side effects.16-18 Omitting surgery of the axilla in patients with a positive sentinel node, e.g. by irradiating the axilla, could decrease these side effects. For patients who are clinically node-positive at presentation, a more conservative treatment could be a safe option, e.g. after downsizing the metastatic load in the nodes with neoadjuvant systemic treatment. Accurately identifying patients with a good response to neoadjuvant systemic treatment is crucial to select those patients suitable for more conservative local treatment. Despite these developments, conservative surgery of the breast and/or the axilla is currently not an option for all patients, e.g. patients with large tumours or metastatic lymph nodes in the axilla. Research is required to carefully select those patients for whom more conservative surgery is possible, as such surgery decreases the risk of morbidity without compromising locoregional control.

**Local treatment of in situ breast cancer**

Until the 1980s, ductal carcinoma in situ (DCIS) of the breast was usually treated by mastectomy. However, following the introduction of breast-conserving therapy for early-stage invasive breast cancer, local excision of DCIS started and several trials were initiated to investigate whether adjuvant radiotherapy should be part of this breast-conserving treatment. These trials unanimously showed that radiotherapy reduced the risk of both DCIS and invasive local recurrences.34,35 However, this reduction in local recurrences has never been translated into a significant difference in survival.36 This seems to be counterintuitive since an invasive local recurrence is associated with a significantly worse prognosis in terms of overall survival and disease-free survival.37,38 Besides the decreased prognosis, prevention of a local recurrence is also very important for a patient’s well-being and medical costs. Adjuvant radiotherapy reduced the incidence of an (invasive) local recurrence by half. However, known side effects of radiotherapy such as cardiotoxicity, induction of second malignancies and contralateral breast cancer can occur.39-42 Therefore, the question has risen whether all women with DCIS should have radiotherapy as part of their conservative treatment.29 To answer this question, not only is the long-term prognosis important in terms of the risk of developing a local recurrence, but also the prognosis after a local recurrence and the possibilities of salvage treatment.

The EORTC 10853 trial analysed the effect of adjuvant radiotherapy after a local excision for DCIS on the local recurrence rate. In this thesis the 15-year outcomes of this trial are shown and salvage treatment and prognosis after a local recurrence will be analysed.
Treatment of the axilla in clinically node-negative breast cancer

A conservative method to stage the axilla is the sentinel node (SN) biopsy. This method is based on the theory of Rudolph Carl Virchow (1821–1902) who suggested that specific parts of the body drain to a common lymph node which is referred to as the SN, and subsequently to several other lymph nodes. In 1994 staging of the axilla in breast cancer patients by selectively removing the SN was first described by Giulliano. Since then, several trials have proved the accuracy of the SN in predicting the axillary lymph nodes’ status and SN-negative patients can be spared an ALND. There is some debate on the reliability of the sentinel node for certain subgroups, such as patients with large tumours or multifocal tumours. For these subgroups, as well as for patients with a macrometastasis in the SN, an ALND remained the standard practice.

The shift towards earlier breast cancer after the introduction of the screening programmes resulted in the detection of smaller tumours, with limited tumour deposit in the sentinel node. Moreover, of the patients with a positive sentinel node, 50-70% of the patients had no additional involved lymph nodes in the axilla. Therefore the question arose whether all patients with a positive sentinel node had to be treated with an ALND or whether less invasive treatment of the axilla could provide comparable locoregional control with less morbidity.

In 2001 the European Organisation of Research and Treatment of Cancer (EORTC) initiated the AMAROS trial (After Mapping of the Axilla: Radiotherapy or Surgery?). In this trial patients with a positive sentinel node were randomised between a complete ALND and radiotherapy of the axilla. The aim of this trial was to show comparable local control and survival in both treatment groups, with decreased rates of side effects in the radiotherapy-group. In this thesis the results of this trial will be presented as well as the outcomes of the sentinel node procedure in patients with multifocal breast cancer.

Furthermore, a detailed analysis of the morbidity of patients treated with an ALND or ART after a positive SN is presented, including the predictive value of treatment factors for the development of morbidity.

Locoregional treatment after neoadjuvant systemic treatment

Morbidity may be prevented not only by better selection of patients for and better tailoring of surgical and radiotherapeutical treatment, but this may also be achieved by optimising the sequence of the different treatments. The administration of systemic treatment before, instead of after surgery – the so called ‘neoadjuvant’ systemic treatment (NST) – results in an increase in the percentage of women who are suitable candidates for breast-conserving therapy, since high rates of responses – including complete pathological responses – in the breast are observed. Due to tumour shrinkage after treatment with NST, this strategy enables breast-conserving surgery in 25-30% of the patients who were originally scheduled for mastectomy. To facilitate adequate resection of residual disease in the breast after NST, the original tumour area should be marked before the start of the systemic treatment.

In this thesis we analyse two methods of marking the tumour bed before NST and thereby facilitating breast-conserving surgery after the NST: Radioactive Seed Localisation (RSL) and Radioguided Occult Lesion Localisation (ROLL) with technetium.

When NST does not result in a decrease in the tumour to such an extent that breast-conserving surgery can be performed, these women still have to undergo mastectomy. If immediate reconstruction is oncologically feasible, many of these women will be candidates for a combined skin-sparing mastectomy and immediate prosthetic reconstruction. Neoadjuvant chemotherapy
might have a negative influence on postoperative wound healing and thereby delay postoperative treatment.\textsuperscript{47} Consequently, such combined treatment is less likely to be offered to these patients.\textsuperscript{48} Still, the influence of neoadjuvant chemotherapy for invasive breast cancer on the rate of surgical complications after skin-sparing mastectomy with an immediate prosthetic reconstruction has seldom been studied. In this thesis we analyse the risk of short-term surgical complications after skin-sparing mastectomy with immediate reconstruction in women treated with neoadjuvant chemotherapy.

In addition to the application of more breast-conserving strategies, strategies to reduce side effects of axillary treatment should be employed. Downstaging of metastatic axillary lymph nodes is observed in patients treated with NST. The rates of complete pathological responses (pCR) in the axillary nodes vary between 22-42\%, depending on tumour subtype.\textsuperscript{49,50} If these patients with a pCR in the axillary nodes could be very accurately identified, they could be offered a more conservative therapy of the axilla that does not have the short- and long-term morbidity of an ALND.\textsuperscript{51,52}

We explore a novel minimal invasive surgical technique to provide axillary lymph node staging after NST using an \textsuperscript{125}I seed: the MARI procedure (Marking the Axillary lymph node with Radioactive Iodine seeds).\textsuperscript{53} Prior to NST, proven tumour-positive axillary lymph nodes were marked by ultrasound-guided insertion of an \textsuperscript{125}I seed. This marked node is referred to as the MARI-node. During the surgical procedure after NST, the MARI-node was selectively excised using a gamma-detection probe. A complementary ALND was performed to assess whether the pathological response in the MARI-node was indicative of a pathological response in the additional lymph nodes. The final analysis of the feasibility and predictive value of this surgical method in a prospective study is presented in this thesis.
OUTLINE OF THE THESIS

In **Part I** we describe the results of the EORTC 10853 DCIS trial. In this trial local excision of DCIS was performed with or without postoperative radiation of the breast. **Chapter 2** describes the outcome in terms of locoregional recurrence and survival in patients with a local excision of DCIS and the influence of post-operative radiotherapy on these outcomes. The effect of radiotherapy on the yearly hazard rate of local recurrences (both invasive and DCSI) is analysed. Furthermore, it describes the prognosis and treatment after recurrence in this group of patients.

**Part II** focuses on patients with early breast cancer and a clinically negative axilla treated in the EORTC 10981-22023 AMAROS trial. **Chapter 3** provides insight into the feasibility and outcome of the sentinel node biopsy in patients with multifocal breast cancer compared to patients with unifical breast cancer. **Chapter 4** presents the results in terms of locoregional recurrence and survival in patients with a positive sentinel node treated with ALND or ART. **Chapter 5** gives an overview of the incidences and risk factors of morbidity after an ALND, ART, and after the combination of both treatments.

**Part III** provides new insights into several surgical aspects of patients treated with neoadjuvant systemic treatment. **Chapter 6** describes the impact of NST on the postoperative complications of a mastectomy with immediate reconstruction with a prosthesis. **Chapter 7 and 8** describe different methods used to localise a tumour before the start of systemic treatment in order to perform breast-conserving surgery after NST. **Chapter 7** describes the radioguided occult lesion localisation with radioactive technetium (the ROLL-Tc99) in patients treated with NST. In **Chapter 8** the ROLL-Tc99 technique is compared with the radioactive seed localisation technique in which the tumour is localised with an iodine seed.

In **Chapter 9** the results of the MARI (Mapping of the Axilla with Radioactive Iodine seeds) procedure are presented. In this study, proven metastatic axillary lymph nodes were marked before the start of NST and selectively removed after completion of the systemic treatment as a method of nodal staging after NST.
REFERENCES