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CONCLUDING REMARKS AND FUTURE PROSPECTIVES
Concluding remarks and future perspectives

Improvements in locoregional treatment of breast cancer
The improved prognosis of breast cancer patients and consequently longer life expectancy increases the importance of keeping long-term side effects of treatment as low as possible without jeopardising cure rates and local control. Therefore, the realisation that the side effects of local and regional cancer treatment seriously affect patients’ quality of life led to an ongoing trend towards less invasive locoregional treatments, indeed with the preservation of optimal locoregional control. To further boost this trend, new diagnostic and treatment options should be investigated, and when clinically relevant, fast implementation should be encouraged.
In this thesis several strategies for improving locoregional treatment were analysed, with the aim of decreasing side effects while preserving optimal locoregional control.

Local treatment of in situ breast cancer
The first part of this thesis describes the long-term results of treating ductal carcinoma in situ (DCIS) with breast conservation by complete local excision with or without adjuvant radiotherapy in the EORTC 10853 DCIS trial. Historically, mastectomy was the standard treatment for DCIS until breast-conserving therapy was introduced for invasive breast cancer. The replacement of mastectomy with breast-conserving surgery in patients with localised DCIS and invasive cancer was an important improvement in the quality of care for these patients. The question that rose following the introduction of breast-conserving surgery was whether adjuvant radiotherapy after a local excision for DCIS was indicated. Long-term outcomes of several randomised trials addressing this issue showed that adjuvant radiotherapy halved the incidence of a local recurrence (either DCIS or invasive), but there was no demonstrable effect on survival. The 15-year results of the EORTC 10853 DCIS trial were consistent with these findings. Furthermore, the results showed that patients with an invasive local recurrence had a 5-times higher risk of mortality, and a 17-times higher risk of breast-cancer specific mortality compared to patients who did not experience a local recurrence. Therefore, the prevention of a local recurrence remains very important and for that reason radiotherapy is a standard part of the breast-conserving therapy for DCIS.
However, not all DCIS lesions treated with surgery alone will lead to (invasive) local recurrences. In this trial, 84% of the patients treated with local excision only did not develop an invasive local recurrence within 15 years, and they were spared the adjuvant radiotherapy. The challenge is to accurately identify the patients with DCIS who can safely be treated with surgery alone and those who can even safely be left untreated.
The introduction of nation-wide breast cancer screening and the implementation of digital mammography have resulted in a significant increase in the incidence of DCIS. The rise in DCIS incidence has not resulted in a decrease in the incidence of invasive breast cancer. This implies that part of the screen-detected DCIS lesions can be considered as overdiagnosis, i.e. lesions that would never have led to symptoms during the patient’s lifetime if they had not been detected.
Because clinicians do not know which patients will be overdiagnosed at the time of diagnosis, all DCIS lesions are treated alike by ablative or breast-conserving treatment, putting many women at risk of overtreatment. Not only do overdiagnosis and the resulting overtreatment contribute to the problem of escalating health-care costs, but patients can also be harmed by unnecessary treatment. The challenge for the future is to identify a subgroup of patients with localised DCIS in which (part of) the standard treatment could be safely omitted since they have a very low risk of developing an invasive tumour. With the data of the EORTC 10853 trial presented in this thesis, it
was not possible to identify a subgroup of patients with a low risk of recurrence so that adjuvant radiotherapy could be withheld. Thus, apparently other features of DCIS with a very low risk of an invasive local recurrence are required to justify local excision only, or even a wait-and-see policy. To determine for which patients with low risk proliferative in situ lesions treatment can be omitted, it is crucial to conduct a randomised clinical trial that includes women participating in a breast cancer screening program. Such a trial is currently being endorsed by the European Organisation for Research and Treatment of Cancer (EORTC 1401) in collaboration with the Dutch Breast Cancer Research Group (BOOG 2014-04): the LORD trial. The LORD trial is a randomised, international, multicenter, phase III non-inferiority trial, accruing women aged ≥ 49 years with primary low-grade DCIS detected by microcalcifications upon screening. Patients will be randomised between active surveillance and standard treatment according to local guidelines. Active surveillance comprises monitoring by annual mammography and treatment if there is progression to an invasive lesion. The aim of the trial is to investigate whether active surveillance of low-grade DCIS is as safe as the current standard treatment, and to study the effects on the quality of life of these women by sparing them from intensive treatment. New insights into the molecular biology of in situ lesions will further improve the selection of harmless versus harmful DCIS lesions and guide local treatment.\textsuperscript{7-10}

**Treatment of the axilla in clinically node-negative breast cancer**
The second part of this thesis focuses on the treatment of the axilla in patients treated with primary surgery and who are found to have a positive sentinel node. The introduction of the sentinel node biopsy (SNB) has been a major step towards more conservative axillary surgery, thereby preventing the morbidity of an axillary lymph node dissection (ALND) in patients with a negative sentinel node (SN).\textsuperscript{11-14} However, performing a SNB is not possible in all breast cancer patients. Current contra-indications for performing a SNB are lymphangitis carcinomatosa, large tumour burden and clinically positive lymph nodes. Relative contra-indications include recurrent breast cancer and multifocal breast cancer. Multifocal breast cancer is associated with a higher risk of nodal involvement compared to unifocal breast cancer and the drainage pattern from multifocal localisations may be different. For this reason, the value of the SNB in patients with multifocal breast cancer is debated. The EORTC AMAROS trial showed that with a 96% detection rate the sentinel node biopsy procedure was highly effective in patients with a multifocal tumour. Although the tumour-positive rate of the sentinel node was twice as high in the group of patients with a multifocal tumour, compared to the patients with a unifocal tumour, the location of the sentinel nodes and further nodal involvement after a positive sentinel node were similar in both groups. This suggests that a sentinel node biopsy is safe in patients with multifocal breast cancer. The AMAROS trial investigated the optimal local treatment of patients with a positive sentinel node. The trial showed that axillary radiotherapy (ART) as well as ALND provides excellent axillary control in these patients. At a median follow up of 6.1 years, the 5-year recurrence rate in both groups was very low (0.43% after ALND versus 1.19% after ART). Additionally, no significant difference was found in disease-free survival and overall survival. When analysing morbidity, post-operative complications and lymphedema were significantly higher in the group of patients treated with ALND compared to ART. Combining ALND and ART further increased the risk of lymphedema. Patient-related factors contributed to a higher risk of lymphedema, but not to reduced shoulder mobility. The latter was influenced by the type and extent of the axillary treatment. Therefore we conclude that, for patients in whom axillary treatment is indicated, ART can be considered a validated alternative to an ALND.
Since the results of the AMAROS have shown that the type of axillary treatment (ALND or ART) does not significantly influence survival, the next question would be whether any axillary treatment in patients with a positive sentinel node would significantly influence the prognosis. In other words: Is axillary treatment always indicated after a positive sentinel node? The additional value of axillary treatment (ALND or ART) has been questioned, since the ACOSOG Z0011 trial and IBCSG 23-01 trial showed that patients with early breast cancer and limited metastases in the SN, who were treated with breast-conserving therapy, could be spared an ALND without compromising locoregional control or survival outcome.15,16 In 13-27% of the patients treated with an ALND, additional metastases were found. In the group of patients not treated with an ALND, leaving those metastatic nodes in situ seemed not to influence the locoregional recurrence rate or the survival rate. It is suggested that the adjuvant systemic therapy and the tangential breast irradiation, covering a substantial part of the axillary content, contributed to these results.17 However, a recent planning study, evaluating dose distribution and coverage of the axilla levels I–II and the SN area, has indicated that the current tangential radiation does treat part, but certainly not all, of the axillary levels I–II of the axilla.18 Therefore, the results of these trials cannot simply be extrapolated to all early breast cancer patients with a positive SN. It is important to prevent overtreatment, but it is not yet clear in which subgroup of patients treatment of the axilla can be omitted.

Of special interest in this issue are patients who are not treated with whole breast irradiation, e.g. patients treated with a mastectomy or partial breast irradiation. One study designed to address this question is the BOOG 2013-07 trial, which is currently accruing patients in the Netherlands.19 In this prospective randomised trial, patients with cT1-2No breast cancer and 1-3 axillary SLN metastases treated with a mastectomy will be randomised between complementary axillary treatment or no further local treatment of the axilla.

Following the outcome of these trials, one could argue whether every breast cancer patient with a clinically negative axilla needs to undergo an SNB. Although the SNB is a less invasive procedure compared to an ALND, it is still associated with morbidity.12,14,20 Several trials are currently initiated to address the question of whether the SNB can be omitted in a selected group of patients. One of these is the Italian multi-centre randomised SOUND trial.21 In this trial, patients with cT1N0 disease are randomised to SNB or no axillary staging. As of June 2014, this trial has accrued over 500 patients (personal communication Dr Viviana Galimberti). The results of this trial are awaited. A similar Dutch randomised phase III trial (the BOOG 2013-08 trial) is currently being initiated for patients with unilateral cT1-2No (clinically and by ultrasound) tumours treated with breast-conserving therapy including whole breast radiotherapy.22

Another way to select a group of patients in whom an SNB can be omitted, is to find predictive factors that can accurately predict nodal involvement. The Memorial Sloan Kettering Cancer Center has developed such a model.23 Since several predictive factors of this nomogram are only known after surgery of the primary tumour (e.g. lymphovascular invasion, multifocality), this nomogram has only limited clinical utility. Ideally, it should be possible to obtain all prognostic factors for such a model from a core needle biopsy. We are currently developing a model for predicting a positive sentinel node, based on the pre-operative variables assessed at diagnostic biopsy of the primary tumour of patients included in the AMAROS trial. The molecular biological aspects of the primary tumour may further enhance the clinical criteria to select patients who do not need invasive axillary staging. If the nodal status could be predicted with a high accuracy, a patient group could be identified with such a low risk of clinically relevant macroscopic nodal involvement that an SNB could be safely withheld.
Locoregional treatment after neoadjuvant systemic treatment

The third part of this thesis focuses on treatment of the breast and the axilla after neoadjuvant systemic treatment (NST). In general, systemic treatment is given prior to surgery with the main goal of reducing the tumour load. In a substantial proportion of the patients, the tumour volume may decrease to such an extent that breast-conserving surgery can be performed in patients who were originally scheduled for a mastectomy.24,25

When after NST a mastectomy is still indicated and if oncologically safe, this mastectomy can be performed in a skin-sparing manner and combined with an immediate reconstruction with direct subpectoral implantation of a temporary tissue expander or permanent endoprosthesis. Due to a fear of more postoperative and long-term complications, reluctance exists to treat patients with a skin-sparing mastectomy with immediate reconstruction after neoadjuvant chemotherapy 26, although the effect on post-operative complications has hardly been studied. In this thesis the prospectively gathered data of 37 women undergoing a skin-sparing mastectomy with immediate reconstruction after neoadjuvant chemotherapy are presented. The post-operative complications within the first six weeks after surgery of these women were compared to an unmatched group of 176 women treated with skin-sparing mastectomy with immediate reconstruction without prior systemic treatment.

In this analysis NST did not increase the prevalence of postoperative complications. Thus, NST should not be a contra-indication for skin-sparing mastectomy with immediate prosthetic reconstruction. Ideally, this observation should be confirmed in a prospective, randomised trial in which patients with an indication for systemic treatment and who were scheduled for an SSA would be randomised to pre-operative or post-operative systemic treatment. However, since it would be not ethical to withhold the pre-operative systemic treatment from women when it is deemed indicated, such a trial is not an option. Therefore, results of case control studies will be the highest evidence that can be achieved for this clinical question.

For patients with a favourable response to the NST resulting in the option of breast-conserving surgery, identification of the initial tumour-bearing area in the breast after NST can be challenging. Therefore, localisation of the original tumour bed prior to the systemic treatment is crucial. In this thesis, both radio-guided occult lesion localisation with technetium (ROLL-Tch) and radioactive seed localisation (RSL) have been shown to be adequate procedures with comparable outcomes when used to perform breast-conserving surgery after NST. There were no significant differences between the two groups in the median weight of the resected breast specimen (53 vs. 48 g), in the median smallest margin from the residual tumour to the edge of the specimen (3.5 vs. 3.0 mm), or in the risk for additional surgery for incomplete resections (7 vs. 8%). Due to the 60 day half-life of the 125I seed, RSL does not require additional radiological localisation shortly before surgery, as opposed to ROLL-Tch where a twist marker is inserted before the systemic treatment, and technetium is injected shortly before surgery. Thus, RSL simplifies surgery scheduling and it is therefore an attractive localisation procedure, also in the neoadjuvant setting.

To improve the rate of negative margins in breast-conserving surgery, several new strategies are being developed, for example the use of near-infrared fluorescence and Methylene Blue for real-time identification of breast cancer using Methylene Blue.27 With this technique, Methylene Blue is administered before surgery. During surgery, the mini-FLARE imaging system is used to identify the near-infrared fluorescent signal in the surgical field, resected specimen and wound bed after resection. With this technique, positive resection margins can be identified intra-operatively, making an immediate resection of the remaining tumour feasible.27 However, with initial complete resection rates
of over 90%, it is unlikely that new localisation techniques will have a big impact on the percentage of patients treated with NST and who have negative resection-margins after the first excision. Other developments related to breast-conserving therapy are in the field of minimally invasive ablation techniques that aim to be as effective as breast-conserving therapy, but with better patient outcome in terms of cosmesis and morbidity, and reduced health care costs. Five different techniques are currently being investigated in clinical trials.\(^{28}\) (1) With cryoablation cell-death is achieved by freezing breast tumour tissue with a percutaneous probe. (2) Microwave ablation accomplishes heating by electromagnetic agitation of tissue. (3) With focused ultrasound surgery (FUS) or high-intensity focused ultrasound (HIFU), transducers are used for highly conformal delivery of heat to a target within the breast. (4) With radiofrequency ablation (RFA) heat is delivered within the breast tumour via interstitial placement of a metal electrode, which is attached to a radiofrequency generator. (5) And finally, laser ablation is an interstitial technique in which an applicator is used to deliver a high-power density of light, resulting in very high temperatures near the laser applicator. All of these techniques are still in an experimental phase and their appropriateness for use in patients treated with NST is not yet clear.

Using an \(^{125}\)I seed as a guide not only simplifies surgery of the breast, but it can also facilitate axilla-conserving surgery. In the MARI-procedure (Marking Axillary Lymph nodes with Radioactive Iodine seeds) one of the proven metastastic lymph nodes was marked with an \(^{125}\)I seed before the NST, and selectively removed afterwards.\(^{29}\) An additional ALND was performed in all patients to analyse the accuracy of the MARI-node in predicting the response in all lymph nodes. With this method the marked MARI-node could be identified in 97% of the patients and resulted in a false-negative rate of 7%. Thus, this MARI technique is technically feasible, it is applicable for patients who present with clinically N1-3 disease and it is an accurate staging method for the response of all axillary nodes after systemic treatment. With this method, patients with a complete pathological response of the lymph nodes can be spared the morbidity of an ALND. This MARI procedure is now used in our clinic for all patients who present with pathologically confirmed node-positive breast cancer and who are treated with NST. So far, an ALND is omitted for patients in whom the MARI-node shows a complete pathologic response. However, since the false negative rate was 7% and because the clinical effect of leaving nodes with residual metastatic disease in situ in this population is unknown, the patients for whom an ALND is omitted will receive adjuvant radiotherapy to the axilla. The next step forward would be to carefully select a group of patients with a complete pathological response in the MARI-node for whom axillary treatment could be completely omitted. To improve this selection of patients, we are currently investigating whether staging with an 18-FDG PET/CT scan prior to the start of the NST could help identify this subgroup of patients. The 18-FDG PET/CT has been shown to be an accurate staging procedure of regional lymph node involvement before the start of NST.\(^{30}\) In addition, the 18-FDG PET/CT has been shown to be useful for axillary response monitoring in patients treated with NST.\(^{31}\) We are currently analysing the combined data of the 18-FDG PET/CT performed before the NST and the MARI-procedure performed after NST, to see whether the combination of these two staging modalities could improve the selection of patients for whom axillary treatment could safely be omitted.

In conclusion, there is a continuous trend towards more conservative treatment in the locoregional treatment of breast cancer patients. Since the overall prognosis of breast cancer patients has been improving over the years, there is an increasing need for the prevention of long-term side effects. This thesis describe several developments in breast cancer treatment towards a more conservative treatment that preserves optimal locoregional control and reduces side effects.
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