Summary

Worldwide, breast cancer is diagnosed in more than 1.5 million people every year. Approximately one in eight women in the Netherlands will develop breast cancer at some point in their lives. The prognosis of breast cancer patients in the western world has improved the past decades due to diagnosis of the disease in an earlier stage and due to improved treatment modalities.

Oncological outcomes, such as survival and local recurrence are the primary outcomes of breast cancer treatment. More than 90% of the patients with breast cancer are diagnosed in an early stage. In these patients, the current oncological outcomes are excellent with a 5-year survival rate of 95% and a risk of local recurrence of 2-5%.

Because of the increasing amount of breast cancer survivors living with the consequences of their (surgical) treatment, secondary outcomes such as cosmetic results and quality of life have become increasingly important in the past decades. In early stage breast cancer, surgical treatment by breast conserving surgery followed by radiation therapy has the same excellent survival as a mastectomy. Obviously, a mastectomy will result in an increased physical burden, worse cosmetic outcome and consequently, a decreased quality of life. Therefore, breast conserving therapy is in general the treatment modality of preference in early stage breast cancer. Unfortunately, unacceptable cosmetic outcomes are reported in up to half of the patients after breast conserving therapy.

The aim of the surgeon performing breast conserving surgery is to excise the tumor without tumor-involved margins while keeping the amount of excised healthy breast tissue as low as possible, since the cosmetic results improves with lower resection volumes. When tumor cells are left behind in the breast, the patient needs to get additional surgical treatment such as a re-excision or even a mastectomy, or extra radiation therapy. These additional treatments will assure oncological safety, however they will have a negative impact on cosmetic outcome.

The "Cosmetic Outcome of the Breast After the Lumpectomy Trial" (COBALT) is a multicenter, randomized controlled study from the Netherlands in 2010-2012 and was conducted in the search for an improved surgical technique to perform radical surgery...
and meanwhile lowering the amount of healthy breast tissue excised. In total, 134 breast cancer patients from six medical centers were included of which 65 patients were randomly assigned to ultrasound guided surgery (USS) and 69 patients to palpation guided surgery (PGS). During the ultrasound-guided procedure, the surgeon used an ultrasonography probe which allowed continuous tumor visualization. During palpation-guided surgery, surgeons used their fingers to palpate the tumor, retract it, and guide the dissection.

The first results of the COBALT study showed that USS leads to a reduction of positive margins and consequently, also less secondary surgery compared to PGS. Two (3%) of 65 patients assigned to USS had tumor-involved margins compared with 12 (17%) of 69 patients who were assigned to PGS. In addition, 5 patients in the PGS group (7%) received a secondary mastectomy while none of the patients in the USS group received a secondary mastectomy. The COBALT study also shows that USS is a more precise surgical method since the volume of breast tissue was lower in the USS group (38 cm³ versus 57 cm³). In the PGS group, even twice as much healthy breast tissue was removed as needed based on the tumor size. In summary, USS is a method that gives the surgeon 'eyes' leading to a more accurate removal of the tumor.

The cobalt study has earlier resulted in two theses. In the first thesis, ‘advances in breast cancer surgery – the decisive role of intra-operative ultrasound’ by Nicole Krekel, the accent was on the technique of ultrasound guided surgery and accuracy of breast conserving surgery. The second thesis ‘ Image-guided breast-conserving surgery: the dawn of a new era’ by Max Haloua – the focus was on resection volumes and cosmetic outcome. This thesis includes the last of the triology, were the focus will be on the oncological and patient reported outcomes.

In Chapter 2 we show that the excellent surgical outcomes of ultrasound guided surgery also results in improved cosmetic outcome one year after surgery. By evaluation of a three-member panel, by the computerized BCCT.core software and by patient self-evaluation with a questionnaire cosmetic outcome and patient satisfaction were measured. Time points for follow-up were 3, 6, and 12 months after surgery. The cosmetic outcomes were scored on a 4-point likert scale: perfect / good / fair/ poor. After USS, the cosmetic outcome was rated as "perfect" by 20% of the patients,
compared with 14% in the PGS group. A poor cosmetic outcome occurred in 13% after PGS and in 6% after USS. USS also showed consistently lower odds for poorer cosmetic outcomes (OR=0.55). Patient satisfaction was also higher after ultrasound guided surgery.

The difference in cosmetic outcomes between the two patient groups is mainly due to the secondary treatments as a consequence of involved margins and larger resection volumes after PGS. When the removed volume was more than 40cc, this resulted in a significantly worse cosmetic result, which occurred at 20% after USS and 56% after PGS.

In Chapter 3 the long-term outcomes of the COBALT study are presented. Quality of life was measured during follow up with the EORTC-QLQ C30 and QLQ-BR23. After a mean follow up of 41 months, there was no difference between the USS or PGS regarding oncological outcomes. None of the patients developed a local recurrence, and survival for USS and PGS were 94% and 97% respectively. After 3 years, USS achieved better cosmetic outcomes compared to PGS, with poor outcomes of 11% and 21% respectively. No significant difference in cosmetic outcome after one and three years was seen. The cosmetic outcome of patients in which the excised volume was larger than 40cc (more often in PGS group) still had a higher risk of a worse cosmetic outcome. The influence of excision volumes larger than 40cc were independent of breast size.

After 3 years, patient satisfaction after PGS was worse (13% dissatisfied) compared to USS (3% dissatisfied). Dissatisfied patients included those with larger excision volumes, additional local therapies and worse quality of life (QoL). After 3 years, no difference in QoL factors was seen between USS and PGS. However, a worse quality of life was shown in patients with a fair/poor cosmetic outcome regarding pain, arm-symptoms, breast symptoms, body image and sexual enjoyment compared to patients with good/excellent outcomes.

Since the cosmetic outcome is of major importance for every breast cancer patient, we investigated which breast specific factors mainly influence cosmetic outcome in Chapter 4. In the cosmetic questionnaire, the patients from the COBALT study received eight questions regarding the breast which again were also scored on a 4-point scale (perfect / good / reasonable / bad) during follow up. Six questions concerned breast specific factors: scar, size, shape, firmness, nipple position and color. In addition, there were two
questions about the overall cosmetic outcome of the breast and overall patient satisfaction. The five patients undergoing secondary mastectomy as a result of tumor-involved margins were excluded. This study shows that a questionnaire with the different breast-specific factors, provides important information about the ultimate cosmetic outcome and patient satisfaction after breast-conserving treatment. In addition, the scores on breast specific factors are a starting point for the overall outcomes and will offer the surgeons tools to improve their quality of care. There is a high correlation between all six breast specific factors and overall cosmetic outcome and patient satisfaction although the degree of influence per factor differs over time.

After three years, factors affecting symmetry (size, shape and position of the nipple) are particularly important. This underscores the importance of smaller excise volumes during the surgical procedure. The ongoing negative effect of radiotherapy resulting in more fibrosis during follow up, and thereby increasing firmness, was illustrated in the deterioration of cosmetic outcome over time. Furthermore, it is beyond dispute that there is a strong correlation between the perception of cosmetic outcome and feeling of satisfaction in breast cancer patients. However, one out of ten patients are satisfied despite a fair or poor cosmetic outcome, showing that other factors next to cosmetic outcome affect satisfaction such as expectations of the patient. By measuring patient reported outcomes as a standard postoperative procedure, the results can be of great value in counseling other similar patients and their relatives before breast cancer treatment.

In Chapter 5 we investigated the relation between cosmetic outcome and quality of life by performing a questionnaire in the COBALT study population 3,6,12 and 36 months after surgery. We found that the cosmetic outcome measured by panel and patient self-evaluation decreased during time, and this did not account for measurement by the computerized BCCT.core software. The deterioration mainly takes place in the first 12 months and the cosmetic assessment after 12 months is representative for the long term-cosmetic outcome after BCT. The deterioration of cosmetic outcome in time is mainly caused by the effects of additional radiotherapy and a larger excision volume.
We showed that in the COBALT population, the quality of life factor ‘emotional functioning’ was the only factor that improved compared to baseline (measured prior to surgery). Other factors such as general health, future prospective and pain deteriorated during follow-up. However, all factors improved after three years, showing no significant difference anymore at that moment compared with baseline. Arm symptoms was the only exception, and this is probably due to the axillary lymph node dissection, which 20% of the patients underwent. In patients with “good/excellent” cosmetic outcome, body image, pain, arm- and breast-symptoms are significantly better compared to a “fair/poor” cosmetic outcome when measured by panel and patient evaluation. For the objective measurement by the computer-controlled system, this correlation was not seen.

This chapter endorses the importance of a good cosmetic outcome for quality of life and therefore attention during follow up should not only be on the loco-regional recurrence of the disease but also on cosmetic outcome. When an inadequate cosmetic outcome is seen by patients or physician in the consulting room, the cosmetic outcome and quality of life must get the attention that they deserve. Pro-active communication of the physician could lead to more understanding and acting based on the outcomes instead of waiting until the patient dares to initiate these delicate topics.

The use of chemotherapy prior to breast surgery, or neoadjuvant chemotherapy (NACT), has increased in the last decade. NACT could possible improve cosmetic outcome and quality of life by minimizing the tumor and possible reduction in the amount of excision volume or avoidance of a mastectomy. However, for a surgeon performing breast conserving surgery after BCS is more difficult since the tumor is less visible by the previous therapy. The goals of the surgeon performing BCS after chemotherapy are the same as without chemotherapy: remove the tumor with negative margins and minimize the amount of healthy breast tissue excision. In Chapter 6, we investigated the current surgical outcomes in the Netherlands including margin status and excision volumes in patients with and without neoadjuvant chemotherapy. Using PALGA (a national network and registry of histology and cytopathology in the Netherlands) we investigated patients who underwent BCS for primary invasive carcinoma during 2012-2013. Of the 9901 breast cancer patients, 626 underwent neoadjuvant chemotherapy and 9275 underwent primary BCS. Margins for invasive carcinoma and in situ carcinoma combined were
more often tumor-involved in the neoadjuvant chemotherapy group (27.3% vs. 16.4%). The number of patients with a close margin of <1 mm was another 17.4% and 17.7%, which means that in more than one third of patients unfortunately the tumor was not centrally in the excised specimen. We showed a three-time higher risk of involved margins after chemotherapy compared with the group without chemotherapy. Patients with a lobular response or a poor response to therapy, do even have an increased risk of involved margins and secondary local treatments. The mean excised volume after neoadjuvant chemotherapy was 50 cc. In this chapter, we show that that a larger amount of excision volumes gives absolutely no guarantee for free resection margins. Overall, the unacceptable amount of inadequate resection margins in one out of three women, and the increasing risk after neoadjuvant chemotherapy is disturbing. Most likely, it also results in poor cosmetic results.

Since the worrying national results of Chapter 6 regarding breast conserving surgery after neoadjuvant chemotherapy, the next step was to study the results on an international level. Therefore, in Chapter 7, we studied the effects of neoadjuvant chemotherapy on surgical outcomes (margins and secondary local treatment, excision volume and cosmetic outcomes) in international literature.

We scanned abstracts of articles with 2 independent researchers and found 27 useful researches. There are well-established randomized studies available comparing pre- and postoperative chemotherapy with regard to oncological outcomes. However, none of these studies reports about the surgical outcomes. The studies that were included in this systematic review were almost all retrospective with high heterogeneity and high risk of bias. We found a very wide range of tumor-involved margins, namely 5-40%, which were followed by secondary surgery in 0-33%. Excision volumes after neoadjuvant chemotherapy were unacceptably high in most studies, ranging from 43-268 cm3, which most likely led to a poor cosmetic outcome. To date, there are only two studies that describe cosmetic outcomes after neoadjuvant chemotherapy, these outcomes were good.

In conclusion, currently there is insufficient evidence that neoadjuvant chemotherapy improves surgical outcomes in breast-conserving surgery. Especially in node-negative patients with tumors less than 5cm we should be reticent with offering neoadjuvant
chemotherapy and at least adequately inform the patients about the possible surgical
disadvantages. There should be good, comparative studies that include patient-reported
outcomes as is done in the COBALT study.