# SUMMARY

The main advantage of BCS, when compared to mastectomy, is preservation of the breast with concomitant improvements in the cosmetic outcomes. In addition to adequate tumour excision, a secondary but important goal in BCS is therefore to obtain a satisfactory cosmetic outcome. However, BCS is associated worldwide with high rates of tumour-involved resection margins, while the rates of cosmetic failure are substantial (up to 40% of patients). The total volume of resected breast tissue has proven to be the key determinant of cosmetic outcome. The adequacy of BCS therefore depends on achieving a complete tumour excision, while removing as little healthy breast tissue as possible.

In **Chapter 2** our doubts regarding the adequacy of BCS were confirmed in a retrospective, multicentre study. BCS was shown to result in high rates of tumour-involved resection margins and excessively large excision volumes. Outcomes were evaluated in 726 consecutive patients undergoing BCS for invasive palpable (72%) or nonpalpable (28%) breast cancer, in four affiliated institutions. Excess breast tissue resection was assessed using the calculated resection ratio (CRR), which is the total resection volume divided by the optimal resection volume (tumour volume plus a margin of 1 cm healthy breast tissue). In an ideal situation, the total resection volume is equal to the optimal resection volume and CRR is 1.0. If the total resection volume is twice the size of the optimal resection volume, CRR is 2.0 and the excision volume is twice as large as it should be. Our study clearly showed that in many cases an unnecessarily large volume of healthy breast tissue is excised along with the tumour, while still not assuring clear margins. This was illustrated by the median CRR of 2.5 (0.01 – 42.93), implying that resection volumes were two and a half times as large as they should be. In over a third of all patients excision volumes exceeded 85 cm3, clearly leading to a deterioration in cosmetic outcome. A remarkable finding was that despite the large amount of normal breast tissue resected in many cases, the tumour was often located eccentrically in the surgical specimen, and the margins were positive or focally-positive for invasive carcinoma in over 20% of patients. Even in excessively large resections, corresponding to four times the optimal excision volume, 10.7% of the surgical margins were still positive or focally-positive. Interestingly, the involved margin rate was higher for the excision of palpable carcinomas than for the excision of nonpalpable carcinomas (22.5% and 17.4%, respectively; P = 0.13). We concluded that concerns about inadequate resection margins and the risk of subsequent re-excision probably lead to an unnecessarily large resection of adjacent healthy breast tissue along with the tumour. The study findings suggest that a smaller volume of breast tissue can be excised without compromising the oncological margin status. Improvement of surgical accuracy is not easily accomplished however, and surgical factors should be modified.

### CHAPTER 2
### BCS IS ASSOCIATED WITH HIGH RATES OF TUMOUR-INVOLVED RESECTION MARGINS (>20%), WHILE THE EXCISION VOLUMES ARE EXCESSIVELY LARGE (OVER 2.5 TIMES THE OPTIMAL RESECTION VOLUME)

In **Chapter 3**, the efficacy of the three most commonly used methods of BCS for nonpalpable invasive breast cancer, wire localisation (WL), ultrasound (US)-guided surgery (USS), and radio-guided occult lesion localisation (ROLL), was evaluated. Once again, the primary outcomes were excess tissue resection, defined as CRR, and the status of the surgical resection margins. A total of 201 consecutive patients undergoing BCS for nonpalpable invasive breast cancer in four affiliated institutions were retrospectively analysed. Of the 201 excisions, 117 were guided by WL, 52 by US, and 32 by ROLL. The median CRRs were 2.8 (WL), 3.2 (US), and 3.8 (ROLL) (WL versus ROLL, $P < 0.05$), representing a median excess tissue resection of 3.1 times the optimal resection volume. Interestingly, the rate of focally-positive and positive margins for invasive carcinoma was significantly lower with US (3.7%) compared with WL (21.3%) and ROLL (25%) ($P = 0.023$). It could be concluded that intra-operative guidance by US is the most efficient method of obtaining tumour-free margins in patients undergoing BCS for nonpalpable breast cancer. Most importantly, USS optimises the surgeon's ability to obtain adequate margins. Intra-operative US is strongly recommended for the accurate intra-operative assessment of all echogenic nonpalpable breast tumours, and intra-operative localisation with WL or ROLL should be fully replaced by intra-operative US.

### CHAPTER 3
### US-GUIDED SURGERY IS THE MOST ACCURATE METHOD FOR NONPALPABLE BREAST CANCER EXCISION, RESULTING IN EXTREMELY HIGH RATES (>96%) OF TUMOUR-FREE RESECTION MARGINS

In **Chapter 4**, the physical changes in breast specimens in the period from excision to pathological evaluation were recorded, taking special note of the influence of formalin fixation. Previous studies have suggested that a physical deformation ('shrinkage') of the breast specimen occurs in the period between the surgical procedure and the pathological examination, interfering with the accuracy of the final margin assessment. We conducted an observational study to test these findings, including 68 breast specimens of consecutive patients undergoing BCS for palpable T1-2 N0-1 breast cancer in three affiliated hospitals. Each specimen was weighed and its volume calculated with the specimen length, width, and height, both immediately following excision, and after





arrival at the pathology department. Volume displacement was used to measure the actual specimen volume. Pre- and post-fixation closest distances of the tumour-free margin were compared. It was shown that the surgical specimen weight was grossly similar to the actual specimen volume, and remained equal in time between the surgical and pathological measurements ($P = 0.94$). The mean (range) distance of the closest tumour-free margin did not change with formalin fixation ($P = 0.1$). We concluded that surgical breast specimens do not shrink in the time between the surgical procedure and the pathological examination, and formalin fixation does not change the size of the resection margin. The margin analysis and volume measurements as given in the pathology report are, therefore, not affected by any changes in specimen size or shape. An additional finding was that calculations of specimen volumes are unreliable, and the use of water displacement or specimen weight is recommended for accurate volume measurement.

### CHAPTER 4
### RESECTION MARGIN ANALYSIS AND BREAST SPECIMEN VOLUME MEASUREMENTS AS GIVEN IN THE PATHOLOGY REPORT ARE NOT AFFECTED BY ANY CHANGES IN BREAST SPECIMEN SIZE OR SHAPE

The efficacy of intra-operative US during the resection of nonpalpable tumours has been clearly demonstrated. USS allows real-time localisation of the breast carcinoma and subsequent planning of surgical margins. Although the surgical excision of palpable breast cancer can be performed with guidance from intra-operative palpation, the use of intra-operative US during palpable breast cancer excision may also lead to an improved surgical accuracy. **Chapter 5** described a randomised controlled trial protocol, in which it was hypothesized that the use of US during the excision of palpable breast cancer would improve the ability to spare healthy breast tissue, while maintaining or even improving the oncological margin status. This randomised controlled trial (COBALT trial) compared US-guided breast-conserving surgery for palpable breast cancers to standard palpation-guided surgery (PGS), in terms of the extent of healthy breast tissue resection, the percentage of tumour-free margins, cosmetic outcomes and quality of life.

### CHAPTER 5
### THE USE OF ULTRASONOGRAPHY FOR PALPABLE BREAST CANCER EXCISION MAY IMPROVE HEALTHY BREAST TISSUE SPARING, WHILE MAINTAINING OR EVEN IMPROVING THE STATUS OF THE RESECTION MARGINS

In **Chapter 6**, the performance of surgeons was evaluated during training for US-guided excision of palpable breast cancer. A hands-on training period was initiated in which surgeons could perform US-guided BCS for palpable breast cancer. Thirty female patients undergoing BCS for palpable T1-T2 invasive breast cancer were recruited. Three individual breast surgeons, assisted by US, targeted and excised the tumours. The main objective was to obtain adequate resection margins with optimal resection volumes. All tumours were correctly identified during surgery, and 29 of 30 tumours were removed with adequately negative margins. Only one tumour was removed with focally-positive margins. The median (range) CRR was 1.0 (0.4 – 2.8), and for all breast surgeons, the CRR improved during the training period. By the 8$^{th}$ procedure, all surgeons showed proficiency in performing intra-operative breast US. It was shown that surgeons can easily learn the skills needed to perform intra-operative US for palpable breast cancer excision. The technique proved to be simple, safe and effective in obtaining adequate resection margins. Over the training period, resection volumes improved markedly and reached optimal volumes, thereby presumably resulting in an improvement in cosmetic outcomes.

**CHAPTER 6**
**SURGEONS CAN EASILY LEARN THE SKILLS NEEDED TO PERFORM INTRA-OPERATIVE US FOR PALPABLE BREAST CANCER EXCISION; THE TECHNIQUE IS NON-INVASIVE, SIMPLE, SAFE AND EFFECTIVE IN OBTAINING ADEQUATE RESECTION MARGINS.**

In **Chapter 7**, the results were reported of a multicentre, randomised, controlled trial comparing USS with standard palpation-guided surgery (PGS) for palpable breast cancer, in terms of margin status and extent of healthy breast tissue resection. A total of 134 patients with palpable T1-T2 invasive breast cancer were randomized to either USS (n = 65) or PGS (n=69). This trial clearly showed that intra-operative US guidance during palpable breast cancer excision results in a significant improvement in surgical accuracy. A dramatic difference in margin involvement was seen, with an exceptionally high rate of 96.9% tumour-free margins with USS, compared to 83.3% with PGS (P = 0.009), thereby resulting in a significantly reduced number of re-excisions, mastectomies, and irradiation boosts due to the use of intra-operative US. Even with the obvious improvement in resection margin status with USS, there were also clear benefits in excision volumes. While the PGS group showed excessively large specimen volumes of almost twice optimal, the specimen volumes with USS were significantly smaller. In fact, optimal volume resection was obtained with USS (38 vs. 58 cc and 1.0 vs. 1.7, respectively; both, P < 0.002). We concluded that USS significantly lowers the unacceptably high rate of tumour-involved resection margins following palpable breast cancer excision, thus reducing the need for further surgery or radiotherapy treatment. In addition, through the achievement





of optimal resection volumes, USS significantly reduces unnecessary healthy breast tissue resection and may therefore contribute to improved cosmetic results. Given the overwhelming advantages of USS, the results from this trial indicate that intra-operative US is an indispensible adjunct during palpable breast cancer excision. It is therefore strongly recommended that surgeons learn the skills needed to perform USS of palpable breast cancer.

**CHAPTER 7**
**ULTRASOUND-GUIDED SURGERY CAN SIGNIFICANTLY LOWER THE UNACCEPTABLY HIGH RATES OF TUMOUR-INVOLVED RESECTION MARGINS FOLLOWING PALPABLE BREAST CANCER EXCISION, WHILE REDUCING UNNECESSARY HEALTHY BREAST TISSUE RESECTION.**

A major obstacle to the use of USS is the additional expenditure required; in particular, the costs of purchasing a high-end US system and of the extra time needed for USS. On the other hand, improvements in margin clearance save the expense of subsequent re-excisions, mastectomies, or radiotherapy boosts. **Chapter 8** reports an economic evaluation, alongside the randomised trial, of the cost-benefit of USS compared to PGS for patients with palpable invasive breast cancer. On the costs side, higher costs were found in the USS group due to use of the US system (€193 [95% CI €153€233]). However, on the benefit side, higher costs were found in the PGS group due to a larger number of re-treatments. In total, the sum of the differences in costs and benefits amounted to a decrease in costs of -€154 (95% CI -€388 to €81) with USS. The return on investment was 1.80 (95% CI 0.64 to 3.01). Above a threshold of 30 patients, use of a US system in BCS is cost-saving compared to PGS. We concluded that USS is both highly effective and cost-sparing.

**CHAPTER 8**
**ULTRASOUND-GUIDED SURGERY IS BOTH HIGHLY EFFECTIVE AND COST-SPARING COMPARED WITH PALPATION-GUIDED SURGERY**

The excision of certain breast cancers still presents a considerable challenge, and specialized approaches combining oncological surgery and plastic surgery techniques - collectively referred to as oncoplastic breast surgery – are widely used to improve both the cosmetic and oncological outcomes of these breast cancers. The choice of the technique should rely on a well-defined algorithm that takes into account the size of the tumour in relation to breast size, location of the tumour and minimal postoperative complications. **Chapter 9** provides a summary of the various oncoplastic techniques

with their advantages, limitations and indications. Furthermore, the oncological and cosmetic outcomes of the various oncoplastic procedures, and the morbidity, quality of life and applied algorithms were systematically reviewed and evaluated. A total of 2090 abstracts on the topic of oncoplastic breast surgery published between 2000 and 2011 were evaluated, and 88 articles were identified for potential inclusion and reviewed in detail by the lead authors. No randomised controlled trials were identified. Eleven prospective observational or comparative studies fulfilled inclusion criteria and were selected. In these studies, 80% to 93% of the tumours were invasive breast cancers. Tumour-free resection margins were observed in 78% to 93% of cases, resulting in a 3% to 16% mastectomy rate. Local recurrence was observed in 0% to 7% of the patients. Good cosmetic outcome was achieved in 84 to 89% of patients. Decision-making for the indications and type of surgery often depended on surgeon preference, without the use of a uniform algorithm. Most studies also showed significant weaknesses that negatively influenced generalizability, including lack of adequate design and important methodological shortcomings. We concluded that current evidence supporting the efficacy of oncoplastic breast surgery is based on poorly designed and underpowered studies. Given the increasing importance and application of oncoplastic breast surgery, a well-defined indication algorithm should be applied, thus allowing informed decision-making on the most appropriate surgical technique for the treatment of a specific breast cancer case. In conclusion, there is a pressing need for robust comparative studies of oncoplastic breast surgery, including both randomized controlled trials and well-designed, multicenter prospective longitudinal studies.

**CHAPTER 9**
**THERE IS A PRESSING NEED FOR WELL-DESIGNED COMPARATIVE TRIALS TO EVALUATE THE RESULTS OF ONCOPLASTIC BREAST SURGERY AND ASSESS INDICATONS**

# FUTURE PERSPECTIVES

### Intra-operative ultrasonography to eliminate surgical inaccuracy

The results from this thesis clearly show that breast-conserving surgery (BCS) for both palpable and nonpalpable breast cancer is highly inaccurate. Current rates of tumour-involved resection margins are unacceptably high and lead to a huge number of re-excisions, mastectomies, or additional radiation boosts. In addition, the very high rates of excessive healthy breast tissue resection contribute to the frequently unsatisfactory cosmetic results. This inaccuracy of BCS procedures is universal and present in institutions worldwide, affecting all surgeons, and applies to both standard





BCS and oncoplastic breast surgery. Consequently, there is an urgent need for a dramatic improvement in surgical techniques.

The intra-operative use of US has been proven to significantly improve the surgical accuracy of BCS. Firstly and most importantly, the problem of tumour-involved resection margins is virtually resolved through the continuous visualisation of the breast cancer with intra-operative US. Secondly, US-guided BCS results in optimal breast volume resection. The capability to guide procedures, through real-time tumour visualisation, is a unique feature of intra-operative US for which no other localisation technique can be substituted. Given the overwhelming advantages of intra-operative US, this tool should be considered an essential adjunct during BCS for both nonpalpable and palpable breast cancer excision. All 'blind' palpation-guided procedures should be fully abandoned and replaced by US-guided surgery. In cases where US-guided surgery is impossible other localisation methods, such as wire-localisation or radio-guided occult lesion localisation should be applied.

### The future role of intra-operative ultrasonography

The future role of intra-operative US will be brought about by a combination of technological advances and surgical experience with US. Some predictable issues concerning intra-operative US include improvement in instrumentation and incorporation of new US technology. New, small probes, suitable for small mammary wounds, and more user-friendly, portable scanners will be developed (i.e. an I-phone App); the resolution of US will further improve, and the refinement of three-dimensional images will simplify the use of intra-operative US for planning and guiding tumour excision.[1] Furthermore, a wireless connection between the operating room and the radiology department should become available, enabling surgeons to consult the radiologist at any time during the surgical procedure.

### Ultrasound-training

Although the surgeon performing adequate US will clearly achieve a better surgical performance, the main obstacle to the wider use of intra-operative US among surgeons is the fact that most surgeons have little experience of the technique. Despite the clear benefits of intra-operative US in breast cancer surgery, this lack of personal experience with the US technique may cause surgeons to be hesitant in the use of US. Indeed, if intra-operative US is carried out without sufficient specific preparation qualified training, the advantages of the technique will be lost. It is also important to be aware that the surgeon should not be required to distinguish benign from malignant lesions; the surgeon's aims should be to target the breast tumour intra-operatively with US and to carry out a precise excision by delineating the tumour volume.

US-guided BCS is a relatively new technique for most surgeons, and requires a combination of knowledge and judgment of US images in order to be able to translate the US images into the technical ability of tumour excision. Intensive education of surgeons in the use of US will help to alleviate problems, and studies have shown that, with appropriate instruction and experience, surgeons can easily learn the skills needed to perform USS.[2-9] Educational issues will undoubtedly be quickly resolved when surgeons become convinced of the value of intra-operative US and are sufficiently interested in performing intra-operative US themselves.

In the coming years, both surgeons and patients should therefore be actively informed of the benefits of US-guidance during BCS. Furthermore, increased formal training and credentialing in US of surgeons will emerge as an important issue. US-training could be considered as early as in medical school, while training and credentialing in US should be introduced for surgical residents and surgeons, as these are essential aspects for the worldwide implementation of intra-operative US. Only through an active educational program will the intra-operative use of US by surgeons steadily increase to become an everyday tool for acquiring intra-operative information, and eventually US will lead to surgeons being able to 'see' in a new dimension

**Improvement of cosmetic results**

Although oncological safety remains the primary concern, breast cancer surgery today is increasingly focusing on improved cosmetic outcomes. The goal of BCS is therefore to provide a treatment as effective as mastectomy, with the added benefits of a preserved breast and an improved cosmetic result. BCS is increasingly used for ductal carcinoma in-situ and for larger breast cancers following neo-adjuvant chemotherapy. In patients with these large, ill-defined, or poorly situated tumours, even a highly accurate US-guided excision may not result in a satisfactory outcome. For this reason, - next to the introduction of intra-operative US - the emerging role of oncoplastic breast surgery offers promise, although many questions on the field of oncoplastic surgery remain unanswered, the first of which is the current lack of clarity surrounding the indications for oncoplastic surgery. No uniform algorithm yet exists for oncoplastic surgery, and decision-making often depends on surgeon preference. This is an important issue, as oncoplastic procedures indicate more extensive surgery with additional operative time and costs. The ability to identify patients at risk for poor cosmetic outcome at the time of consultation may allow for informed choices prior to surgery. A uniform management algorithm should be developed for this purpose, allowing surgeons to inform patients at the time of consultation on the type of surgery that will produce the best cosmetic result and the highest patient satisfaction possible. However, the introduction of US-guided surgery can be expected to reduce need for oncoplastic surgery, particularly because most invasive breast cancers present as relatively small (<2.5 cm) tumours.





The second issue is that more attention should be paid to adequate tumour resection. It is more even more imperative to minimise the incidence of positive margins in oncoplastic breast surgery, as positive margins often prompt a subsequent mastectomy. Intra-operative US could therefore also be very helpful during oncoplastic excisions for breast cancer.

Most importantly, prior to the worldwide introduction of oncoplastic surgery, reliable randomised clinical trials should be performed in which the oncological and cosmetic outcomes of standard US-guided surgery are compared to those of oncoplastic surgery.

In addition to oncoplastic breast surgery, delayed plastic reconstruction can be used in patients with poor cosmetic results following BCS. Indeed, many patients consult plastic surgeons for surgical correction subsequent to BCS, sometimes years after their initial treatment. The techniques of delayed reconstruction following BCS include scar revision, contralateral reduction mammaplasty, or volume displacement procedures such as local tissue rearrangement, lipofilling, implants, or fasciocutaneous or musculocutaneous flaps. The decision for a specific type of reconstruction is made following expert opinion at the outpatient clinic, and depends on a variety of factors such as the size and shape of the breast, the availability of tissues at other sites, and complicating factors such as surgery on an irradiated breast. Because of the wide variety of surgical procedures for delayed reconstruction, it would also be helpful to develop surgical guidelines or algorithms for surgical reconstruction of the breast following breast-conserving therapy. This is an important issue to be addressed in the coming years.

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