


Genealogy is connected and future prospects.
Chapter 8

General discussion and future perspectives
Discussion and future perspectives

In the Netherlands, the number of patients treated with breast-conserving surgery has increased up to 76% of all breast cancer patients, amounting over 10,000 patients a year (Figure 1). With extended survival now common amongst breast cancer patients, limiting the impact of surgical morbidity is becoming an essential aspect of high-quality, long-term survivorship. Surgical precision in breast-conserving surgery at this moment is inadequate: tumors are not excised concentrically, leading to involved margins and resection of excess healthy breast tissue. These disappointing results affect patients worldwide, regardless of whether they undergo neoadjuvant therapy or adjuvant therapy and including patients who undergo oncoplastic breast surgery. This thesis has shown the negative consequences of inadequate surgery: worse cosmetic outcomes and quality of life of breast cancer patients. Fortunately, there is a widely-available, non-invasive method to improve these secondary outcomes: ultrasound-guided surgery.

Figure 1. Breast-conserving therapy, with and without neoadjuvant chemotherapy (NAC), in all patients with invasive breast cancer per year.  

1. Quality indicators

At the moment, several quality indicators of breast cancer care are available including surgical quality indicators. In the Netherlands, there are three direct surgical quality indicators: involved margins for DCIS (target <30%), involved margins for invasive carcinoma (target <15%), and the third (new) quality indicator is breast contour-saving surgery. At the general meeting of Dutch breast cancer surgeons in 2017, the number of involved margins was portrayed as excellent (<4%) and most of the surgeons present were very satisfied with this outcome. Although 4% indeed represents a low level of involved margins, this figure includes only those patients with more than focally involved margin for invasive and in situ carcinoma (>4mm in the inked margin), excludes patients with in-situ involved margins and excludes patients receiving neoadjuvant chemotherapy. The number of involved margins is lower than the target number (<15%), but as an overall reflection on breast cancer surgery these numbers actually paint a too favorable picture. The late effects of a radiotherapy boost on (focally) involved margins are not taken into account, and current numbers are not comparable to those of other European countries such as Germany, since German guidelines recommend a re-excision in patients with focally involved margins. The most important aspects are the dialog between patient and surgeon and the patient’s expectations regarding treatment outcomes. Therefore, it is not realistic to say that tumor cells will be left behind “in only 4% of cases” since irradical excised DCIS or focal irradical margins also have treatment consequences and will influence the cosmetic outcome and psychosocial wellbeing of the patient and their relatives. The correct number to be discussed should be 16.4% in patients not receiving NACT, and for patients treated with neoadjuvant chemotherapy the figure is as high as 27.3%.

The National Consortium of Breast Centers in the United States also defines secondary surgeries as a quality indicator.² The European Society of Breast Cancer Specialists (EUSOMA) criteria define the target proportion of patients undergoing a single breast operation for the primary invasive tumor (excluding reconstruction) of 90%.³

In the national pathology study presented in this thesis, figures for secondary surgeries ranged from 5.3 to 9.3%. In the United States, re-excision lumpectomies range from 0% to 70% (by individual surgeon).² Recent publications also document wide variability in Canada (17-56% by province) and England (12%-30% by National Health Service trust).⁴,⁵ Accepting tumor-involved margins or secondary surgery as a quality indicator is controversial. For example, one fear is that surgeons may become “risk-averse”, modifying their BCT eligibility criteria for patients at high-risk for tumor-involved margins and thereby increasing primary mastectomy rates. Surgeons may also potentially increase their lumpectomy excisional volume in order to obtain free margins, with a consequent negative effect on cosmetic outcome. While surgeons recognize these problems, identifying effective
alternatives is not easily incorporated, let alone introducing effective alternatives in daily practice.

**Calculated resection ratio**

In view of the above-mentioned disadvantages of margin involvement or secondary surgery as quality indicators, insight into surgical precision would improve when excision volume are taken into account. This thesis and other work have shown, extensively, the negative effect of excision volumes on secondary outcomes. These findings indicate that CRR would be a good additional quality indicator, in combination with margin involvement. Measuring the excision volume by standard water displacement and calculating tumor volume using an ellipsoid plus dimensions measured by the pathologist results in a uniform method. In a national survey including 65 breast surgeons, 83% answered that they always or often excise the minimal amount of healthy breast tissue. Only one surgeon answered ‘never’, and one ‘I don’t know’. The remaining 14% stated that they ‘sometimes’ excise the minimal amount of healthy breast tissue. These answers were striking: surgeons overwhelmingly regard their performance as acceptable, but actually have not quantified their own performance.

**Patient-reported outcomes**

This manuscript describes the impact of breast-conserving surgery on cosmetic outcome and quality of life and demonstrates the important correlation between these two factors. While survival and prevention of local recurrence remain the primary goals, the recent major improvements in these areas have also brought secondary outcomes to the fore. We now hope to create greater awareness among physicians of the importance of these outcomes for the patient as an individual.

Measuring patient-reported outcomes (PROMs), including cosmetic outcome and quality of life, are important for a variety of reasons:

1. Most healthcare aims to reduce symptoms, minimize disability, and improve QoL – aspects that only patients can assess. It is important to properly appreciate cosmetic outcomes and quality of life, and how they are affected by medical treatment, both for the patient’s sake and for that of the caregivers. By promoting direct feedback of this information to the care provider in the consulting room, individual patient care can be improved. For example, as we showed that quality of life will improve in the years after treatment compared to baseline, this knowledge can be used to reassure a patient during follow-up that improvements, for example in emotional wellbeing, are to be expected.

2. Being involved might lead to improved patient comfort and open-heartedness and thereby keeping direction of their own health.
3. Quality improvement through national benchmarking.

The application of PROMs allows departments, institutions and hospitals to determine the effects of care on, and compare, cosmetic outcome and patient’s quality of life.6

Recently, a pilot study implementing PROMs was initiated by the Taskforce Outcome of the NABON (Nationaal Borstkanker Overleg Nederland) Breast Cancer Audit. Three questionnaires will be used: EORTC-C30, EORTC-BR23, and the Breast-Q. The questionnaires will be filled out once during the intervention and at several time points afterwards. The goal is to monitor the experience of the implementation of PROMs for breast cancer care within several hospitals, to identify and remedy technical problems, and to create enthusiasm and support in the field. The next step will be to roll out patient feedback nationwide in all NBCA participating hospitals. This type of initiative should be encouraged, and in the future PROM’S will hopefully become standard measurements before and after breast cancer treatment.

The remaining question is: which of the available questionnaires should be used, or should a new, more modern questionnaire be developed? Clearly, it is not necessary to fill out all three of the above-mentioned questionnaires, as this would require at least twenty minutes and would probably result in reduced concentration and less willingness of a patient to complete a questionnaire. In our opinion, the current questionnaires should be individualized for every breast cancer patient. Also a more modern questionnaire should be considered, because several issues arose. Firstly, some questions in the existing questionnaires are irrelevant for breast cancer patients. For example, the EORTC-C30 was originally validated in lung cancer patients. As these patients are mostly treated with systemic therapy, specific questions such as shortness of breath, obstipation, and lack of appetite are irrelevant for breast cancer patients. Secondly, questions in the EORTC-BR23 regarding side effects of chemotherapy (nausea, vomiting, dry mouth, loss of taste, hair loss, etc.) are irrelevant when the patient did not receive (neo)adjuvant chemotherapy. A great advantage of the Breast-Q is the inclusion of separate personalized scales such as Reconstruction, Mastectomy, and Breast-Conserving Therapy scales. In addition, all modules included in these scales, for example the BCT scale (satisfaction with breasts, effect of radiation therapy, physical, psychological wellbeing, sexual wellbeing, satisfaction with the information provided and staff interactions), can be evaluated separately.

In our opinion, in addition to the overall judgment of the patient on cosmesis and their own satisfaction, a questionnaire should include separate breast-specific factors to identify the shortcomings of the (surgical) procedure. In terms of surgical outcomes, it is therefore important to at least ask questions about the scar, firmness and asymmetry of the breast.
2. The ongoing development of neoadjuvant systemic therapies - do not forget about the surgical outcomes.

The frequency of BCS after NACT in increasing and today more than half of all patients in the Netherlands treated with NACT subsequently undergo BCS. The first multicenter randomized controlled trials with neoadjuvant systemic therapy were initiated in the 1990’s. These well-conducted trials did not demonstrate a survival advantage in operable breast cancer when compared with conventional adjuvant therapy. Since survival and local recurrence appear comparable, other goals such as functional and cosmetic outcome are important in defining the treatment of choice. It seems that we have missed the window of opportunity to report the surgical outcomes of breast-conserving surgery after NACT in these trials. Nevertheless, NACT it is widely used in order to improve tumor resection, to increase the rates of breast-conserving surgery (BCS), to lower the morbidity of ALND and to identify patients with better prognoses, that is, patients who exhibit a pathologic complete response (pCR). The efficacy of neoadjuvant therapy to downsize or achieve pCR is improving due to more efficient targeted drug regimens, and is now up to 60% in the HR-/HER2+ and triple negative subtypes. Given the increased frequency of pCR in these subgroups, it is reasonable to ask whether surgery represents over-treatment in these patients. The omission of surgery is already current for other malignancies such as esophageal, anal, laryngeal, prostate, cervical, and lung carcinoma. The safety of surgery omission is dependent on our ability to accurately estimate pCR preoperatively. At this moment, imaging lacks sufficient sensitivity and specificity to select patients who indeed have no or only very limited residual disease. Therefore, various trials are under development that will use image-guided biopsy after NACT to test the safety of potential omission of breast cancer surgery in exceptional responders. An example is the "Minimally Invasive Complete Response Assessment (MICRA) study, initiated at the Netherlands Cancer Institute, and the recently initiated MD Anderson Cancer Center pilot study 'Identification of breast cancer patients for potential avoidance of surgery: Accuracy of image guided percutaneous sampling compared with surgery to evaluate eradication of breast cancer after preoperative chemotherapy' (Clinicaltrials.gov NCT02455791). In these studies the value of multiple biopsies of the breast in determining a pathologic complete response to NACT is evaluating. The ultimate aim is to prevent overtreatment and improve quality of life by eliminating surgery,

Although the burden of surgery can probably be reduced in the future, it is important that less surgery is not over-compensated for by more radical or unnecessary systemic therapies and/or by radiotherapy, all with their own toxicities and morbidity. Over the next decade, the
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Although the burden of surgery can probably be reduced in the future, it is important that less surgery is not over-compensated for by more radical or unnecessary systemic therapies and/or by radiotherapy, all with their own toxicities and morbidity. Over the next decade, the scope for NACT to support less (radical) surgery will be huge, and increased pCR rates will have major implications for all subsequent loco-regional treatment decisions. Since the choice for BCS after NACT in the Netherlands has increased from 400 patients in 2012 to more than 1000 patients in 2015, the unacceptable outcomes in a considerable amount of these patients must not be overlooked. In our national database study we found high rates of involved margins and our systematic review clearly shows that current evidence is insufficient to support the use of neoadjuvant chemotherapy to improve cosmetic outcomes, especially in those patients who were candidates for BCS from the beginning. We feel strongly that there is an urgent need for awareness and robust comparative studies, including both randomized controlled trials and well-designed, multicenter prospective longitudinal studies, especially in cases where NACT is used for downstaging of the breast. Until high quality evidence for the use of NACT as a treatment to optimize cosmetic outcome becomes available, patients should be thoroughly informed about alternatives and the possible risks of secondary surgery and the uncertainty of cosmetic results after BCS.
3. The successes of intra-operative ultrasonography in the elimination of surgical inaccuracy cannot be ignored any longer

Although it is important to measure PROMs and other quality indicators, these will not mean anything if it does not lead to improvement of breast cancer care. Ensuring the best possible quality of breast cancer care for all our patients is our primary goal. At this moment, BCS still lacks surgical precision. While the search has been ongoing for new ways to reduce margins (shaved margins, hyperspectral optic imaging, molecular fluorescence-guided surgery), the solution has actually been available in every hospital since the 1970’s: an ultrasound. Ultrasound guided surgery allows the surgeon to combine oncologic safety with the smallest excision volumes and to provide satisfactory resection margins that result in improved cosmesis. In addition to the radiologist, many other physicians have learnt how to perform ultrasound: the urologist, gynecologist, anesthesiologist, liver surgeons and cardiothoracic surgeons. Astonishingly, there appears to be little motivation amongst surgeons to learn ultrasound-guided surgery. This could be due to the fact that many surgeons already consider their outcomes, margins and re-excisions to be acceptable (although they admittedly do not exactly know how much healthy breast tissue they excise).

In the above mentioned national survey, the most common explanations for not performing USS were:

- I have no experience with the technique but I would like to learn 45%
- I have no experience with the technique and I do not want to learn 25%
- You can’t see all tumors on ultrasound 21%
- Difficult and long learning curve 13%
- No ultrasound available 6%
- No cooperation with the radiologist 6%

Almost half of the surgeons do not feel the need to learn USS because they use palpation-guided surgery for palpable breast cancer or other techniques in non-palpable breast cancer. The use of ultrasound has repeatedly shown superiority over WGL but despite these outcomes, was not implemented by surgeons. 13-15 Wire guided localization remained the golden standard until another alternative gained popularity: radioactive seed localization (RSL), which is now one of the most commonly used method in the Netherlands today. Ultrasound guided surgery has not been compared to RSL. In an evaluation of all patients at the Netherlands Cancer Institute since the introduction of RSL in 2007, it also seems that RSL
is associated with a long learning curve since it took at least a few years to achieve low resection volumes. The median resection volumes for invasive breast cancer declined from 198cm$^3$ in 2008 to 46cm$^3$ in 2014 ($P<0.001$; figure 2a and 2b)$^{16}$

Figure 2a. Resection volumes in invasive breast cancer treated with BCS localized by radioactive seed localization.$^{16}$

Figure 2b. Resection volumes in invasive breast cancer treated with BCS after neoadjuvant therapy localized by radioactive seed localization.$^{16}$

For patients after NACT, the median resection volume declined significantly, from 119.5 cm$^3$ in 2008 to 45.0 cm$^3$ in 2014 ($P<0.001$). Involved margins were seen in 18.4% and 19.1%, with a significant improvement over time for focally involved margins in patients with invasive breast cancer only. With the exception of USS, localization techniques remain ‘blind’ procedures, are expensive, require specific protocols, a license for the use of radiation in
medical procedures, and above all, they are invasive procedures needing good planning together with the Department of Radiology and Nuclear Medicine. With a cheaper and less invasive procedure available, it is troubling that 85% of the respondents to the national survey would use WGL, ROLL or RGS seed placement in case of an ultrasound visible lesion.

There have been ongoing developments of medical ultrasound probes, the latest being the Lumify transducer®. They are developed to be the lightening eyes who guide the surgeon in the ‘dark’ breast, even in non-experience hands. They facilitate the use of USS since they can easily be directly connected to an Iphone or Ipad device, thus being is easier to handle and require less space. They claim to have a high quality vision, however, studies still have to be performed to show the quality during breast surgery. Nonetheless, the Lumify® can be leased for €200 a month or purchased for €7000 and in case of equal quality to the current ultrasound probes, this would mean an enormous cost reduction in breast cancer surgery.

Another positive development is that many surgeons would like to learn USS and this should be facilitated during surgical residencies and international courses. In 2017, the first ESSO breast cancer course on ultrasound-guided surgery took place. We would encourage all breast surgeons to invest a little bit of their time to learn USS and improve their surgical precision. In our opinion, non-palpable breast cancer excisions should always include a radiologist in the procedure.

Resistance to performing USS ‘due to the long learning curve’ is based on incorrect assumptions. Studies have shown that surgeons who apply USS achieve tumor-free margins in their very first procedure and require only 8 procedures to obtain a CRR of 1. It is correct that IOUS is not especially accurate for all lesions, especially not those presenting as clustered microcalcifications. However, almost all palpable lesions are visible and the majority of non-palpable lesions. In case of breast cancer is not visible on ultrasound, a marker that is visible on ultrasound could be placed intra-tumorally to guide the excision.

In the COBALT study, ultrasound-guided surgery was shown to have high accuracy in localization of a central point, highlighted by the good outcomes in patients with tumor-associated intraductal component which is non-palpable and mostly invisible with ultrasonography.17
4. Other treatment methods for breast cancer: combine with ultrasound

Neoadjuvant chemotherapy

The goal of BCT after NACT is to remove all residual invasive or in situ cancer with negative margins. Therefore, it is essential to mark the tumor before treatment and after completion of chemotherapy, and repeat imaging must be performed to assess the response to therapy and extent of expected resection. Since the successes of ultrasound as ‘the eyes of the surgeon’ in palpable and non-palpable tumors, the use of USS in patients after NACT is self-evident. Successful use of USS after NACT has been reported in two retrospective studies. In the first, Ramos et al. reported the use of IOUS-guided lumpectomy after NACT in 58 patients with a US-visible marker. Four patients (6.8 %) required a re-excision and three patients (5.2%) received a secondary mastectomy due to tumor-involved margins.18 The mean specimen weight was very low, at 26.4 grams (6–84). In a second study, Rubio et al. reported no significant differences for involved margins between wire-guided (6.6%) and USS-guided surgery (4.4%) after NACT. The excision volumes (49.51cm³ versus 34.86cm³) were higher after wire localization in patients with a complete response.19 The precision of ultrasound-guided surgery is promising in lowering resection volumes after NACT can be achieved, even in patients with a complete pCR.

Other studies have reported acceptable outcomes, including excision volume, with the use ROLL and RGS.16,20 However, these are invasive methods requiring input from the nuclear department and require more perioperative planning. Localization techniques other than USS can be seen as ‘blind surgery’ since the tumor isn’t visualized.

Oncoplastic surgery

Although oncoplastic breast surgery is increasingly performed and shows considerable promise, no uniform algorithm yet exists and decision-making often depends on surgeon preference. Oncoplastic surgery has not yet been proven to be a superior technique in terms of improved oncological and cosmetic outcomes.21,22 USS could reduce the need for oncoplastic surgery since lower excision volumes are achievable. Nevertheless, in the case of very large tumors (>5cm) in which OPBS is indicated according to the surgeon, USS can be simultaneously used to achieve accurate margins and imaging of the exact tumor location, while still aiming to excise the minimal amount of healthy tissue.
Conclusion

In conclusion, improvements in breast cancer care will require the implementation of modern quality indicators such as the evaluation of surgical outcomes by excision volume, CRR and patient-reported outcomes, including for those patients treated with neoadjuvant systemic therapy. The role of ultrasound in optimizing the accuracy of breast-conserving surgery cannot be overlooked any longer. Perioperative imaging by ultrasound, either by a surgeon or by a radiologist must become the standard approach in breast-conserving surgery for ultrasound-visible lesions. The benefits of increasing surgical accuracy and lower excision volumes due to USS are also relevant to patients with indications for neoadjuvant systemic therapy or oncoplastic breast surgery.
In conclusion, improvements in breast cancer care will require the implementation of modern quality indicators such as the evaluation of surgical outcomes by excision volume, CRR and patient-reported outcomes, including for those patients treated with neoadjuvant systemic therapy. The role of ultrasound in optimizing the accuracy of breast-conserving surgery cannot be overlooked any longer. Perioperative imaging by ultrasound, either by a surgeon or by a radiologist must become the standard approach in breast-conserving surgery for ultrasound-visible lesions. The benefits of increasing surgical accuracy and lower excision volumes due to USS are also relevant to patients with indications for neoadjuvant systemic therapy or oncoplastic breast surgery.

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1. Dutch Institute for Clinical Auditing.


