

## Current status of ultrasound-guided surgery in the treatment of breast cancer

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### Abstract

The primary goal of breast-conserving surgery (BCS) is to obtain tumour-free resection margins. Margins positive or focally positive for tumour cells are associated with a high risk of local recurrence, and in the case of tumour-positive margins, re-excision or even mastectomy are sometimes needed to achieve definite clear margins. Unfortunately, tumour-involved margins and re-excisions after lumpectomy are still reported in up to 40% of patients and additionally, unnecessary large excision volumes are described. A secondary goal of BCS is the cosmetic outcome and one of the main determinants of worse cosmetic outcome is a large excision volume. Up to 30% of unsatisfied cosmetic outcome is reported. Therefore, the search for better surgical techniques to improve margin status, excision volume and consequently, cosmetic outcome has continued. Nowadays, the most commonly used localization methods for BCS of non-palpable breast cancers are wire-guided localization (WGL) and radio-guided localization (RGL). WGL and RGL are invasive procedures that need to be performed pre-operatively with technical and scheduling difficulties. For palpable breast cancer, tumour excision is usually guided by tactile skills of the surgeon performing "blind" surgery. One of the surgical techniques pursuing the aims of radicality and small excision volumes includes intra-operative ultrasound (IOUS). The best evidence available demonstrates benefits of IOUS with a significantly high proportion of negative margins compared with other localization techniques in palpable and non-palpable breast cancer. Additionally, IOUS is non-invasive, easy to learn and can centralize the tumour in the excised specimen with low amount of healthy breast tissue

being excised. This could lead to better cosmetic results of BCS. Despite the advantages of IOUS, only a small amount of surgeons are performing this technique. This review aims to highlight the position of ultrasound-guided surgery for malignant breast tumours in the search for better oncological and cosmetic outcomes.

**Key words:** Breast neoplasms; Segmental; Surgery; Ultrasonography; Mastectomy; Cosmetics; Margins; Volume status; Wire localization; Radioguided surgery

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**Core tip:** Despite improved survival and local recurrence rates of breast cancer patients in the past years, there is still much to be gained in surgical treatment. Unacceptable rates of involved margins are described, with up to 25% of the patients undergoing re-excision after breast conserving surgery. The most frequently used excision methods are wire-guided and radioguided localization for non-palpable tumours and palpation-guided localization for palpable tumours. Although ultrasound-guided surgery is a simple and non-invasive technique, it is not frequently used. This review highlights the position of ultrasound-guided surgery for breast cancer in the search for better oncological and cosmetic outcomes.

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## INTRODUCTION

### Breast conserving therapy

Breast cancer is the most commonly diagnosed cancer worldwide, including low and middle-income countries and incidence is rising with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers). In the western world, approximately 1 in 8 women (13%) will develop breast cancer over the course of their lifetime<sup>[1]</sup>.

Since disease-free and overall survival rates after breast conserving therapy (BCT) are known to be comparable with patients treated by mastectomy, BCT is established as the standard of care in women with early stage breast cancer<sup>[2-4]</sup>. BCT refers to a combination of breast conserving surgery (BCS) followed by whole breast irradiation to eradicate any microscopic residual disease. The widespread use of screening and the development of more effective treatment methods have been associated with improvement in terms of overall survival and recurrence rate, with 5 year survival rates for early stage ( I and II ) of more than 92%<sup>[5-8]</sup>.

**Primary goal:** The primary goal of BCS is to remove

the tumour with clear margins. Margins positive or focally positive for tumour cells are associated with a high risk of local recurrence and, in the case of tumour positive margins, re-excision or even mastectomy must be performed<sup>[9,10]</sup>.

Incidences for tumour-involved margins in BCS have been reported up to 40%<sup>[11-15]</sup>. However, direct comparison of studies is difficult due to the use of varying definitions for positive margins, for instance a "close margin" is used for either a positive and negative margin. In the United Kingdom previous guidelines recommended a margin > 2 mm, however current guidelines do not encompass a clear definition on margin status and they recommend breast units to have local guidelines regarding acceptable margin width<sup>[16]</sup>. Danish National Guidelines recommend tumour-free margins  $\geq 2$  mm<sup>[17]</sup>. Other European countries such as Germany and France have BCS guidelines on margin status that indicate that patients with margins  $\leq 1$  mm should undergo additional surgery<sup>[18,19]</sup>. In the Netherlands and the United States guidelines for BCS are stating all specimens without tumour-cells at the inked margins are tumour free margins, and these specimens do not necessitate additional local treatment such as surgery or radiotherapy<sup>[10,20]</sup>.

In the recent St. Gallen International Breast Cancer Conference 2015, the majority of the panelists agreed that the minimal acceptable surgical margin was "no ink on invasive tumor" in women undergoing BCS for invasive breast cancer and proceeding to standard radiation and adjuvant systemic therapy<sup>[21]</sup>. However, two recent surveys in the United States have reported that, against the national breast cancer guidelines, 85% of breast surgeons do not accept a tumour-free margin less than 1 mm<sup>[22,23]</sup>.

In the United States, a striking number of approximately one-fourth patients who undergo initial BCS for breast cancer will have a subsequent operative intervention<sup>[24]</sup>. Evidently there remains an international controversy regarding the definition of tumour margins. It is, however, important to note that a tumour-free resection margin of > 1 mm is unrelated to local recurrence or overall survival, and the range of local recurrence rates is 2%-5%<sup>[5,25]</sup>.

**Secondary goals:** Together with increasing breast cancer incidence, the improved outcome has resulted in a growing population of breast cancer survivors and there has been considerable interest in secondary goals such as cosmetic outcome and quality of life of (QOL)<sup>[26-33]</sup>. The achievement of tumour-free margins during BCS is of great importance for local recurrence but also for the cosmetic outcome. Positive resection margins result in additional treatment, such as higher radiotherapy dose, re-excisions and even mastectomy, these additional therapies will ensure oncological safety but negatively influencing the cosmetic outcome<sup>[30,31]</sup>. Besides young age, central inner quadrant localization, axillary dissection, re-excision and complications, larger

excision volumes and secondary radiotherapy (administration of boost and whole breast irradiation dose) are the two key determinants of cosmetic outcome<sup>[29,32,33]</sup>.

Poor cosmetic outcomes are observed in up to 30% of patients after BCS<sup>[32-34]</sup>. In a large survey among 963 women treated with BCS for breast cancer, cosmetic results were scored as 3.4 on a 5-point scale with from 1 (very dissatisfied) to 5 (very satisfied)<sup>[35]</sup>.

The importance of achieving optimal oncological control may lead to an unnecessarily large resection of breast tissue. Literature shows that cosmetic failure rates are significantly higher when a lump exceeds 50-100 cm<sup>3</sup><sup>[29,32,36-37]</sup>. However, these studies dated from the 90's and recent data on volume are scarce. When the surgical accuracy of BCS is improved by a higher rate of margin clearance and smaller excision volume, this will improve not only oncological outcome, but also improves patient satisfaction and cosmetic outcome.

In many cases, an unnecessarily large volume of healthy breast tissue is excised along with the tumour, while clear margins are not assured<sup>[13,38,39]</sup>. High excision volumes are rarely related to the size of the tumour. Therefore, as a tool to define the amount of tumour and the excess healthy breast tissue in a surgical specimen, the calculated resection ratio (CRR) was introduced, indicating excess healthy tissue resection<sup>[13]</sup>. The CRR represents a comparison of the total resection volume to the optimal resection volume. This means that in an ideal situation, the specimen volume is equal or smaller than the optimal resection volume and the  $CRR \leq 1$ . For example, in a retrospective study, 10.7% of 726 patients with T1-T2 tumours still had positive or focally positive margins when the CRR was  $> 4.0$ , meaning that the tumour is often located eccentrically in the surgical specimen<sup>[13]</sup>.

Despite the ongoing development of techniques for diagnosing and treating breast cancer, the current techniques BCS in many cases do not meet primary and secondary goals and there is still much to be gained. This review aims to highlight the position of ultrasound-guided surgery for breast tumours in the search for better oncological and cosmetic outcomes.

### Non-palpable breast cancer

Due to the development of imaging techniques and screening programs, the incidence of non-palpable breast cancer has increased with up one third of the diagnosed breast cancer being non-palpable. In this group, DCIS represents a challenging problem for breast-conserving surgery (BCS) given that it is typically non-palpable and non-contiguous. Different management procedures are used to remove the non-palpable tumour with optimal resection margins: Wire guided localization (WGL), radio guided localization (RGL) or intra-operative ultrasound-guided surgery (IOUS)<sup>[33-52]</sup>. Despite improved techniques intra-operatively, unfortunately no assessment can ensure clear lumpectomy margins during surgery.

**Wire guided surgery:** WGL has been the most com-

monly used technique for non-palpable breast cancer in the past years. Pre-operatively, a thin, hooked wire is placed into a non-palpable lesion under mammographic, sonographic, or CT guidance. When the lesion is visible on ultrasound, this is the easiest approach because the wire can directly be placed under ultrasound guidance. The mammographic approach is based on measurements of distances between the lesion and the nipple (or other reference points) performed on the two projections of the mammogram. Subsequent mammograms are then obtained to reposition the wire more accurately, and a confirmatory mammogram is finally obtained.

After WGL, positive margins are described in 10%-43% of patients with up to 40% re-excisions after initial surgery<sup>[38,42-44]</sup>. The reported CRR after WGL is 2.8-4.3<sup>[13,39]</sup>. Volumes and cosmetic outcome must be compared to other techniques in the same study groups and therefore are mentioned in the next paragraph.

Even though WGL has proven to be a useful localization tool, it is associated with several shortcomings. The wire tip gives no indication of the extent of the tumour and the amount of tissue to be excised is estimated by the surgeon intraoperatively. This could explain the high amount of incomplete tumour resections.

Additionally, the wire may migrate, become displaced or transected<sup>[45]</sup>. Also the extra pre-operative procedure is demanding for the patient pre-operatively with pain and discomfort caused by the wire.

**Radio-guided surgery:** Due to the technical and scheduling difficulties of WGL, radio-guided surgery (RGS) was developed, in the form of radio-guided occult lesion localization (ROLL) and radio-guided seed localization (RSL). ROLL uses the radiotracer which is injected intra-tumourally for the sentinel lymph node procures to guide surgical excision of the primary tumour. The gamma-detecting probe guides the localization of the lesion throughout the surgical procedure. In RSL, a radio-opaque titanium seed containing Iodine-125 is placed into the tumor under stereotactic or ultrasound guidance. The seed can be placed days to weeks preoperatively. Again, a handheld gamma probe is used to guide surgical resection of the tumor during surgery.

RGS has been prospectively compared to WGL. Overall tumour free margin rates of RGS range from 73% to 96% with a weighted average of 90%<sup>[42,47,48]</sup>. The range of re-excisions reported is 4.6%-27%<sup>[38,45]</sup>.

Sajid *et al.*<sup>[42]</sup> showed in a meta-analysis the risk of having positive resection margins following WGL was higher than ROLL. (OR = 0.47; 95%CI: 0.22-0.99;  $z = 1.99$ ;  $P < 0.05$ ). A systematic review by Lovrics *et al.*<sup>[40]</sup> demonstrates that WGL produces higher positive margins rates and more re-operations. However, Postma in their randomized controlled trial, showed WGL is comparable to ROLL in terms of complete tumour excision and re-excision rates and ROLL was leading to larger excision volumes (71 cm<sup>3</sup> vs 64 cm<sup>3</sup>). The average excision volume of five studies including 1077 patients with DCIS or invasive breast cancer was 86 cm<sup>3</sup><sup>[47]</sup>.

Further evaluation about the effect of the specimen volume on margins status demonstrated no correlation and was difficult to interpret because of varying patient populations and the fact that excision volumes were missing in most studies.

One retrospective study mentioned CRR with a significant, and clinically relevant difference for ROLL (CRR = 3.8) compared to WGL (CRR = 2.8,  $P = 0.043$ )<sup>[15]</sup>. However, in both techniques CRR is more than one, meaning a large amount of healthy tissue is resected. Cosmetic outcomes assessed were similar after WGL and RGS in a prospective, randomized trial. Most patients rated their overall cosmesis as "excellent" or "good" (76% WGL, 80% RSL). This comparable outcome may reflect the similar reoperation rates and volumes of excision between groups<sup>[34]</sup>. An advantage of RGS compared to WGL is the fact that it can be done weeks pre-operatively. However, it still requires radioactive material being transported and attendance to the radiology department prior to surgery. Therefore, it does not overcome the scheduling conflicts between radiology or nuclear department and the surgery department. Additionally, with RGS, the borders of the tumour are not visible during surgery, there is only a diffusion zone guided by the gamma probe. The risk of seed migration and failure of seed placement ranged from 0%-0.6% and 0%-7.2% respectively<sup>[45]</sup>. Unfortunately RGS remains having an invasive component with discomfort for the patient.

**Intra operative ultrasound:** Since high-frequency real-time ultrasonography was introduced in the 1970s, technological advances have improved sensitivity and reduced the size of ultrasound scanners, making them practical and able to be used close to the bed-side or in the operating theatre. In the 1980s Schwartz *et al.*<sup>[48]</sup> were the first to describe IOUS as an effective and accurate technique for localizing non-palpable breast masses, facilitating excision and diagnosis with a minimum of patient inconvenience and discomfort as well as utilizing hospital resources efficiently. The ideal localization procedure would be non-stressful for the patient and would allow accurate targeting and removal of the lesion central in the specimen, while removing as little tissue as possible with tumour-free margins. In the current series, IOUS met these objectives better than did WGL. The rate of successful intra-operative localization in, ultrasound visible, non-palpable tumours varies between 95%-100%<sup>[49-53]</sup>. In 2002, a randomized clinical trial from Rahusen *et al.*<sup>[53]</sup> involving 49 patients with non-palpable breast cancer, demonstrated IOUS to be superior to WGL concerning margin clearance. In 2013, a systematic review and meta-analysis of patients with non-palpable breast cancer treated with IOUS vs WGL was performed. One RCT<sup>[50]</sup> and nine cohort studies with control WGL groups were identified, containing 739 patients<sup>[15,39,52-58]</sup>. The rate of involved surgical margins for IOUS varies between 0%-19%.

In the effects model there was a statistically significant difference between IOUS and WGL in terms of tumour-free margins favoring IOUS. (OR = 0.52; 95%CI: 0.38-0.71)<sup>[49]</sup>. Another meta-analysis of Pan *et al.*<sup>[59]</sup> also demonstrated a statistically significant increase in the incidence of pathologically negative margins with the use of IOUS, for both non-palpable and palpable breast cancers. A limitation of a meta-analysis by Ahmed *et al.*<sup>[49]</sup> is the heterogeneity of *in situ* cancer (DCIS) amongst the small cohorts studies. The trend is towards higher percentages of *in situ* cancer in the WGL groups within the meta-analysis, but this trend does not reach a statistically significant value ( $P = 0.65$ ). Because patients were not randomized to either cohort, more difficult cases with extensive DCIS may have been selectively approached with bracketed needle localization, whereas more "straightforward" cases of limited disease may have been chosen for ultrasound-guided excision.

Excision volumes for non-palpable breast cancer after IOUS and WGL are mostly mentioned in (retrospective) cohort-controlled studies. Different outcome of resection volume between groups were seen ranging from no difference to smaller volume in IOUS<sup>[39,58]</sup>. However, selection bias has occurred in the localization technique to assess large and clearly visible tumours without microcalcification; on average there was a larger tumour size in the IOUS group. This is indicating that, with IOUS more optimal resection volumes are obtained. The excess breast tissue resection therefore must be determined using the CRR. For example, Barentsz *et al.*<sup>[39]</sup> showed total resection volumes was similar in both groups. (56.6 cm<sup>3</sup> vs 62.8 cm<sup>3</sup>,  $P = 0.66$ ) Because of the larger tumour size in the IOUS group, the CRR was smaller. (3.3 vs 4.3) in the IOUS group ( $P = 0.018$ ). No study specifically measured cosmetic outcome after IOUS in non-palpable breast cancer compared with other techniques. However, as the volume of resection decreases and better margins are achieved, we expect cosmesis to be positively affected, as is patient satisfaction<sup>[38]</sup>.

IOUS is accurate, simple and it carries a minimal risk of procedure-related complications<sup>[50,51,60]</sup>. It overcomes the issues associated with WGL and RGS because it does not require preoperative localization at the radiology or nuclear department and being a less invasive procedure. IOUS can also be used *ex vivo* to verify the presence of a tumour in a resected specimen. Downsides of IOUS include the need for or visibility of the breast lesion on ultrasound. IOUS is not very accurate for lesions presenting as clustered microcalcifications. Patients with DCIS and multifocal invasive cancer will be at increased risk for a positive margin and at increased risk for re-excision or mastectomy, also after IOUS. However, to overcome this problem, a marker which is visible on ultrasound could be placed intra-tumourally. Additionally, the availability of a surgeon with ultrasound experience or a preoperative assisting radiologist is mandatory in performing IOUS.



### Palpable breast cancer

In palpable tumours, surgeons are performing blind surgery trusting on pre-operative imaging and their tactile skills, which can be problematic, especially in dense breasts<sup>[61]</sup>. A high incidence of positive margins after palpation guided surgery (PGS) up to 40% is described<sup>[13,61-63]</sup>. Moreover, it has been shown that many surgeons tend to overexcise volumes of healthy tissue in an effort to obtain adequate margins. Median excision volume of PGS is over two times too large<sup>[13]</sup>.

Only a few reports have been published of the use of ultrasound-guided surgery in palpable breast cancer. In 2001, Moore and colleagues were prompted to prospectively evaluate IOUS in women with palpable breast cancer because of poor results obtained with PGS. They compared 27 patients undergoing IOUS with 24 undergoing PGS and their findings were striking. Only 3% positive tumour margins were noted in the ultrasound-guided surgery group compared with 29% in the palpation-guided surgery group ( $P < 0.005$ )<sup>[61]</sup>. After this, other retrospective studies showed IOUS of palpable breast cancers to be associated with markedly reduced rates of involved margins and re-excisions<sup>[59,61-64]</sup>. The COBALT-trial was the first multicenter randomized controlled trial for palpable cancer comparing IOUS with the PGS, in order to improve both oncological and cosmetic outcomes. The primary results of this trial showed a dramatic difference in margin involvement with 3% of tumour-involved margins for the invasive component in the IOUS-group compared to 17% in the PGS-group, and thus a significant decrease in additional treatment required in the IOUS group [2% re-excision and 9% boost in IOUS (total, 11%) vs 7% mastectomy, 4% re-excision and 16% boost in the PGS group (total, 27%)]<sup>[65]</sup>. Moore *et al.*<sup>[61]</sup> found that the volume of the lumpectomy specimen was smaller in the IOUS group (104 cm<sup>3</sup>) vs their palpation-guided group (114 cm<sup>3</sup>). In the COBALT study, IOUS results in significantly reduced excision volumes and CRR compared with PGS<sup>[65]</sup>. A CRR greater than 2.0 was seen in only three (5%) women in the ultrasound-guided surgery group vs 20 (29%) patients in the palpation-guided surgery arm ( $P < 0.0001$ ). Minor lesions of additional ductal carcinoma *in situ* (DCIS) were found inside or within several millimeters of the invasive tumour by the pathologist in 73 (55%) of the 132 palpable tumours in the COBALT trial. Despite the fact that United States cannot always detect DCIS, the rate of tumour-free margins was high, even in cases with additional *in situ* carcinoma (11% in the IOUS group compared with 28% in the PGS group). It could be explained by the increased accuracy with IOUS in the localization of the central point of the tumour, which allowed complete resection of the additional DCIS. Earlier studies have mentioned IOUS to improve the cosmetic results and patient satisfaction in palpable breast cancer<sup>[61,63]</sup>. The COBALT-study clearly showed IOUS resulting in better cosmetic outcome than PGS; 21% of the overall responses were excellent and 6% were poor with IOUS, while 14% and 13% of

responses were excellent and poor, respectively, with PGS. Consistently, IOUS had smaller odds of having worse cosmetic outcome than PGS (OR = 0.51,  $P = 0.045$ )<sup>[66]</sup>.

### Learning curve

Hands-on ultrasound education for surgeons and the ongoing improvements in imaging technology have made surgeon-performed breast ultrasound an effective method of identifying palpable breast lesions. With proper teaching, adequate practice, and close supervision leading to progressive independence, breast surgeons can acquire comprehensive skills that will enable them to successfully incorporate breast ultrasound and ultrasound-guided breast procedures into their clinical practice<sup>[50,51,67-72]</sup>. A weekly half-day training minimally invasive breast biopsy for breast fellows with hands-on, "live-patient" breast ultrasound training, showed proficiency in performing breast ultrasound by the 12<sup>th</sup> week<sup>[69]</sup>. In the study by Krekel *et al.*<sup>[70]</sup> surgeons underwent an ultrasound-training program performing ten cases, under the strict supervision of a breast radiologist. The learning curve for surgeons to develop the adequate skills was short, after the first two supervised cases, resections reached optimal volumes. After eight procedures, surgeons acquire the expertise to perform IOUS.

Despite the good results of IOUS, the utilization of this technique amongst breast surgeons remains consistently low, with surveys of American and Australasian breast surgeons suggesting figures between 2.8%-17%, respectively<sup>[73,74]</sup>. The main reasons for the low amount of American surgeons performing IOUS were related to their radiology department with almost half stating that radiologists had prohibited them from scanning, the remainder being due to a combination of a lack of time, hospital restrictions, lack of confidence and reimbursement as well as medico-legal liability<sup>[71]</sup>. The lack of performing IOUS by breast surgeons gains more relevance with the increasing evidence of improving outcome of BCS in palpable and non-palpable breast cancer.

### Cost-effectivity

With experienced surgeons, excision time is similar between IOUS and other guidance techniques, although there is extra time for the pre- and post-surgical use of the United States system which will account for 5-10 min<sup>[53,57]</sup>.

In the ROLL-study, QOL effects between ROLL and WGL were similar (difference 0.00 QALYs 95%CI: -0.04-0.05). Total costs were also similar for ROLL and WGL<sup>[73]</sup>. In palpable breast cancer, a cost-benefit analysis applied to IOUS vs other localization techniques for invasive breast tumours evaluating costs in terms of reoperation and complication-related costs as well as the procedural costs themselves has been performed by Haloua *et al.*<sup>[74]</sup> Although the cost of IOUS is more expensive, the overall cost of performing an IOUS procedure vs palpation only was €154 cheaper per patient

due to a reduced rate of tumour involved margins and thereby the avoidance of cost of additional treatments. Above 30 patients, use of the USS system leads to cost savings.

### Future directions

Because most of the current operative techniques for BCS in palpable and non-palpable breast cancer result in a high rate of positive margins, re-excisions and resection volumes with impact on cosmetic results, surgeons have been proactive in searching for better surgical techniques of BCS in two ways.

Firstly, surgeons have continually used ways to decrease the amount of positive margins and rate of re-excisions such as cavity shaves and touch-prep or intraoperative frozen section assessment of the margins. There is still much debate about the usefulness of these methods and their influence on re-excisions and volume resected<sup>[75-80]</sup>. These methods are potentially useful as additional methods to decrease the overall volume of excised tissue and re-excisions. However, it is preferable to perform a small lumpectomy with adequate CRR and the tumour centrally in the specimen in the first place.

Another available method of intraoperative margin evaluation is the MarginProbe (Dune Medical Devices, PA, United States). This device allows for *ex vivo* evaluation of the resected specimen and is especially useful in detecting DCIS. Adjunctive use of the Margin Probe device during BCS improved surgeons' ability to identify and resect positive lumpectomy margins in the absence of intraoperative pathology assessment, reducing the number of patients requiring re-excision<sup>[81-82]</sup>. Due to the *ex vivo* use of the margin probe, we think this method could be used alongside IOUS but should not be seen as a replacement method.

Additionally, the search for improving ultrasound-guided surgery is ongoing. Technical aspects are improved, such as the development of a portable three-dimensional ultrasound systems<sup>[83]</sup>. Also, IOUS is combined with other techniques such as needle localization or intraoperative margin assessment<sup>[75,77,84]</sup>. Combined techniques are especially useful in those tumours who are non-palpable and not visible on ultrasound. Ivanovic *et al.*<sup>[75]</sup> recently showed a technique of excising palpable and non-palpable breast cancer by intraoperative ultrasound with an especially constructed marking needle, being placed while the patient is anesthetized. Preliminary results showed this technique to be feasible with good oncological safety with only one patient with a positive resection margin (3%).

Secondly, the volume of normal breast tissue excised at the time of BCS must be minimized by centralizing the tumour in the surgical specimen and, in cases where a larger excision volume is necessary for oncological reasons, volume displacement and replacement techniques are utilized. This last mentioned approach is referred to as oncoplastic breast surgery (OPBS) and combines oncological resection with plastic surgery techniques in a single procedure. The term may refer

to simple volume-displacement techniques or to more complex techniques of volume replacement by using local or regional flaps. The proposed benefit of OPBS is the ability to achieve wide surgical margins, with a higher chance of obtaining tumour-free resection margins than with standard BCS. A recent study showed 11.9% positive margins and a 91% breast conservation rate<sup>[85]</sup>. Additionally, it is surprising to notice in a systematic review on OPBS that tumour-free margins ranged in the included studies from 78% to 93% with OPBS, resulting in a conversion to mastectomy in 3% to 16% of all OPBS cases. However, most studies showed significant weaknesses including lack of robust design and important methodological shortcomings, negatively influencing generalizability<sup>[86]</sup>. Therefore there is a need for well-designed comparative studies to create high quality guidelines, ensuring uniform indications for OPBS in breast cancer patients.

Considering the outcomes of studies performing IOUS, the results of OPBS may also be improved with the use of ultrasound-guidance. In patients with large tumours, a high amount of volume must be resected, even with IOUS. In these cases, by performing IOUS a safe margin with minimal volume of healthy breast tissue will be excised while achieving a good cosmetic outcome. We do think that if the tumour volume to mammary volume ratio is low, IOUS could be sufficient to achieve both tumour-free surgical margins and a good cosmetic result without concomitant reconstruction techniques.

As mentioned earlier, IOUS is not applicable in every patient. However, when applicable, IOUS is an accurate, non-invasive and technically feasible method. Although we embrace new studies to improving surgical outcome and reducing the need for re-excision in BCS, it does not seem necessary to develop new and expensive techniques for patients already suitable for IOUS. Despite advances and usability of ultrasound, the main problem remains that the use of ultrasound by breast surgeons is consistently low, as is the presence of a radiologist in the operating theatre. Surgeons who wish to provide optimal, state-of the art care for patients with breast cancer should embrace IOUS. Adequate ultrasound training should be included in the surgical curriculum for breast surgical trainees.

## CONCLUSION

The best evidence available demonstrates the benefits of IOUS in BCS with a high proportion of negative margins and optimum resection volumes compared with other localization techniques in palpable and non-palpable breast cancer visible on ultrasound. With intraoperative United States guidance, surgeons can more accurately delineate the tumour by direct feedback and thereby achieving a centrally localized tumour in the specimen. Next to this, IOUS is shown to be a method which can be learned easily by surgeons and being cost-effectiveness because of less additional therapy

applied as a result of negative margins. The oncological, cosmetic and logistical advantages of IOUS for patients with breast cancer have to be recognized by every surgeon performing BCS.

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