



Update of the American Society of Breast Surgeons Toolbox to address the lumpectomy reoperation epidemic

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Abstract: In 2015, the American Society of Breast Surgeons (ASBrS) convened a multidisciplinary consensus conference, the Collaborative Attempt to Lower Lumpectomy Reoperation Rates (CALLER). The CALLER conference endorsed a “toolbox” of multiple processes of care for which there was evidence that they were associated with fewer reoperations. We present an update of the toolbox taking into consideration the latest advances in decreasing re excision rates. In this review, we performed a comprehensive review of the literature from 2015–2018 using search terms for each tool. The original ten tools were updated with the latest evidence from the literature and our strength of recommendation. We added an additional section looking at new tools and techniques that may provide more accurate intraoperative assessment of margins. The updates on the CALLER Toolbox for lumpectomy will help guide surgeons to various resources to aid in the removal of breast cancer, while being aware of cosmesis and decreasing re excision rates.

Keywords: Breast conservation; toolbox; re-operation rate; re-excision rate

Submitted Apr 16, 2018. Accepted for publication Nov 05, 2018.

doi: 10.21037/gs.2018.11.03

View this article at: <http://dx.doi.org/10.21037/gs.2018.11.03>

Introduction

Reoperations after initial lumpectomy for breast cancer occur in about one in five patients and range from less than 10% to greater than 70% (1-6). The NSQIP database captures that reoperations after lumpectomy appear to be a high outlier compared to other organ sites (7). Addressing these high rates in 2015, the American Society of Breast Surgeons (ASBrS) convened a multidisciplinary consensus conference, the Collaborative Attempt to Lower Lumpectomy Reoperation Rates (CALLER). The CALLER conference endorsed a “toolbox” of multiple processes of care for which there was evidence that they were associated with fewer reoperations (8). The awareness of these high re excision rates have led to the descriptors of “over surgery”, “epidemic”, “over treatment” and “disutility” (9-12). This awareness also motivated the development of lumpectomy margin guidelines, enhanced

preoperative imaging techniques, localization techniques and even novel tools at intra operative margin assessment. Our update on the toolbox takes into consideration the latest advances in decreasing re excision rates. The tools, references and strength of recommendation are described in *Table 1*.

We conducted a comprehensive review of the literature in PubMed from 2015 through 2018. We used different search terms specific for each topic as listed below.

Update on toolbox

Tool 1: preoperative diagnostic imaging should include full-field digital mammography and supplementary imaging to include ultrasound as needed

Background

There are multiple pre-operative imaging modalities, each

Table 1 CALLER Toolbox update on references and strength of recommendation

CALLER Toolbox tool	2015 strength of recommendation	2018 strength of recommendation	Resource intensiveness*	Updated references
Preoperative diagnostic imaging should include full-field digital mammography and supplementary imaging to include ultrasound as needed	Strong-moderate	Similar	Moderate	(13-21)
Minimally invasive breast biopsy (MIBB) for breast cancer diagnosis	Strong	Similar	Low	–
Multidisciplinary discussions to include radiology, pathology, surgery, and radiation and medical oncology	Strong-moderate	Similar	Low	(12,22-31)
For nonpalpable breast lesions, the use of radioactive seeds, intraoperative US, or wire localization to direct lesion excision is recommended	Strong	Similar	Moderate	(32-42)
Oncoplastic techniques can reduce the need for reoperation in anatomically suitable patients	Strong-moderate	Strong	Moderate	(3,43-60)
Specimen orientation of 3 or more margins	Strong	Similar	Low	(61-68)
Specimen radiograph with surgeon intraoperative review	Strong	Similar	Low	(13,14,69-74)
Consider cavity shave margins in patients with T2 or greater tumor size or T1 with extensive intraductal carcinoma (EIC)	Strong-moderate	Strong	Low	(75-77)
Intraoperative pathology assessment of lumpectomy margins may help decrease re-excision when feasible	Strong-moderate	Strong	Highest	(69,78-90)
Compliance with the SSO-ASTRO margin guideline to not routinely re-operate for close margins with no tumor on ink in patients with invasive cancer	Strong-moderate	Strong	Low	(4,5,8,11,91-106)

*, resource intensiveness to adopt if system not already in place.

with their own advantages and disadvantages.

Update

The addition of tomosynthesis has helped detect breast cancers, especially in dense breast tissue. It has been shown to be more accurate in detecting tumors (13,14).

Ultrasound (US) has emerged as one of the more accurate predictors of tumor size. Recent studies have compared mammogram, US and magnetic resonance imaging (MRI) to predict tumor size; concluding US was the most accurate (15). MRI overestimates tumor size. This was confirmed by Cortadellas *et al.* who found that US was the best predictor of tumor size when compared to the pathologic assessment of the surgical specimen (16).

The routine use of MRI is not standard of care. It is known to have an increased false positive rate and to be associated with the need for additional work up. Tseng *et al.* concluded that MRI provides greater accuracy for a third of patients undergoing preoperative mammogram and

ultrasound (17). Some have recommended MRI in patients with dense breast tissue as part of the preoperative work up, however Elder *et al.* found no statistically significant difference in numbers of cancers detected or recurrence rates. This questions the routine use of MRI in breast cancer patients solely based on breast density (18). MRI has not been shown to improve disease free survival and overall survival (19). A population-based study in Canada showed preoperative MRI was associated with significant increase in ancillary investigations, wait time to surgery, mastectomies and contralateral prophylactic mastectomies (20).

Contrast enhance spectral mammography has shown promise in detecting tumor extent preoperatively, showing better size measurements with histopathologic size compared to full-field digital mammography and US (21).

Conclusion

Complete preoperative imaging is necessary; the type of modality is dependent on patient factors, comfort level of

the surgeon and communication with the radiologist.

Search terms: complete diagnostic preoperative imaging breast surgery; preoperative imaging breast surgery.

- ❖ Total titles reviewed 48;
- ❖ Total abstracts reviewed 29;
- ❖ Total manuscripts reviewed 15;
- ❖ Total manuscripts used and referenced 9.

Tool 2: minimally invasive breast biopsy (MIBB) for breast cancer diagnosis

Update

There is no new evidence to refute that minimally invasive breast biopsy for breast cancer diagnosis is appropriate. It provides definitive diagnosis that allows for preoperative treatment planning in a multidisciplinary fashion.

Search terms: breast and lumpectomy and preoperative minimally invasive breast biopsy; breast conserving surgery and preoperative minimally invasive breast biopsy; core needle biopsy for breast cancer diagnosis and breast conserving surgery; core needle biopsy and open biopsy for breast cancer and breast conserving surgery.

- ❖ Total titles reviewed—no new articles from 2015 to 2018.

Tool 3: multidisciplinary discussions to include radiology, pathology, surgery, and radiation and medical oncology

Background

All participants in the ASBrS 2015 Consensus Conference to reduce reoperations recommended pre-operative multidisciplinary discussions to include representatives from the specialties of breast imaging, pathology, surgery, radiation oncology, medical oncology, genetics, and others. These recommendations were not based on level 1 evidence. They were based on personal, professional society, and other consensus conference recommendations, because to our knowledge, there had been no prospective randomized trials that stratified patients into a “non-multidisciplinary” arm.

Update

In an updated review of the literature, no studies with a high level of evidence to confirm the importance of pre-operative multidisciplinary planning to improve the outcome of re-excision rates were identified. Anecdotally, pre-operative multidisciplinary planning is increasing, resource-intensive and of value to patients. In an effort to quantify how

often-multidisciplinary appointments were scheduled before surgery, Churilla *et al.* queried the SEER database (22). Among 88,865 patients, pre-operative multidisciplinary appointments were scheduled in only 2.9%; only 14% of these had appointments with different providers the same day. These findings ought to motivate all stakeholders to improve the percentage of patients receiving pre-operative multidisciplinary planning and to schedule these appointments according to the patients’ requests if possible.

One part of pre-operative multidisciplinary planning that may impact reoperation rates is the decision whether the patient will receive neoadjuvant systemic therapy (23,24). This provider-patient decision is discussed in more detail in the last section of this update.

In the absence of high level evidence informing surgeons of the association between multidisciplinary planning and reoperations, we refer readers to the organizations and their summary documents that describe the importance of multidisciplinary planning for many reasons, to include efforts to reduce reoperations (12,25-29).

In the strongest terms possible in a position statement, the European Union of Breast Cancer Specialists “demanded” that the countries of Europe provide sufficient funding so that all women have access to “multi-disciplinary and multi-professional” care (30).

Out of scope

Many other multidisciplinary tumor board and interdisciplinary topics of communication are emerging in the breast cancer literature. They are important for optimizing patient care and they may reduce reoperation rates by better collaboration and planning, but are out of scope for this update. One example can be found in the following reference (31).

Various other ideas to improve multidisciplinary communication include better interoperability of electronic medical and imaging records, and standardization and incorporation of a pre-operative tumor board summary into medical records with or without synoptic templates.

If complete multidisciplinary pre-operative patient planning is not possible for any reason, then communication between the breast surgeon and the breast radiologist should still occur to optimally localize the lesion to be excised, especially if it is non-palpable.

Conclusion

Pre-operative multidisciplinary planning—after a minimally invasive biopsy of the breast confirms breast cancer—is recommended for all patients prior to a planned breast

conserving procedure.

Search terms: breast and multidisciplinary, breast tumor board, breast and interdisciplinary, breast lumpectomy and multidisciplinary, lumpectomy and multidisciplinary, breast and tumor board, breast and tumor conference.

- ❖ Total titles reviewed >500;
- ❖ Total abstracts reviewed 75;
- ❖ Total manuscripts reviewed 15;
- ❖ Manuscripts used and referenced 11.

Tool 4: for nonpalpable breast lesions, the use of radioactive seeds, intraoperative US, or wire localization to direct lesion excision is recommended

Background

A significant number of breast cancers are nonpalpable at the time of diagnosis (32). Image guided localization has been shown to decrease the positive margin rate and results in fewer re excisions (33). Currently the gold standard is wire-localization, however there are several new techniques of localization including radioactive seed, and non-radioactive device placement, each with its own advantages and disadvantages.

Update

A recent Cochrane review compared new forms of guided surgical intervention against wire-guided localization. They found there was no statistically significant difference between radio-guided occult lesion localization, radioactive seed localization versus wire localization (34). One major criticism of the wire localization technique is the workflow perspective, since the wire must be placed the day of surgery. This is a suboptimal patient experience (35). Hayes provided a review on localization techniques available today. She notes some of the advantages of non-wire devices include, avoids dislodgement or migrated wires, flexible surgery schedule for on time starting the operating room, improves surgical options of cosmetic approach, advance placement decouples the radiology-surgery schedule, and continuous intraoperative reorientation with target centering specimen (36).

By using bracketed technique larger resection areas are possible while preserving cosmesis. A retrospective review looked at DCIS with radioactive seed in single versus multiple, bracketed localization. They found that the rate of positive resection margin was 47.9% with single seed, compared to 29.3% with multiple seed localization. The reoperation rate was 39.6% versus 20.7% in single versus multiple seeds (37). Bracketing is possible with radioactive

seeds, and has been shown to be superior with seeds than wire. A retrospective study showed a decrease in re excision rate with similar specimen volumes and lower rate of mastectomy for bracketed seed localization when compared with wire localization (38).

Cox *et al.* reported on the use of the SAVI SCOUT, concluding comparable re excision rates with other techniques, as well as improving the surgical approach allowing for optimal incision placement, improve operating room efficiencies and patient wait times (39). Radiolabeled seed localization has been shown to result in less pain, higher convenience rate with comparable excision volume and positive margin rates. SAVI allows for bracketing larger lesions, which can help define the borders of a more extensive area (40).

In a prospective randomized study Bloomquist *et al.* also showed higher patient satisfaction with radioactive seed localization compared to wire, resulting in less pain as well as higher convenience. As with similar studies they showed comparable excision volume and positive margin rate (41). Langhans *et al.* reported on a randomized control trial of radioactive seed localization versus wire guided for non-palpable cancers. They found no significant difference in the resection margins or duration of procedure. The main advantage was logistical (42).

Conclusion

There are several methods at localization of non-palpable cancers. The non-wire localizations are becoming more popular and have now been validated by randomized trails. They have been shown to facilitate patient and physician schedules. It also allows for more flexible incision placement. There is no difference in the positive margin rate. Surgeons should perform the modality they are most comfortable with, being aware of the various options.

Search terms: localization technique for breast conserving surgery, localization technique for breast lumpectomy, specimen imaging breast conserving surgery, specimen imaging breast surgery.

- ❖ Total titles reviewed 28;
- ❖ Total abstracts reviewed 20;
- ❖ Total manuscripts reviewed 16;
- ❖ Manuscripts used and referenced in text 11.

Tool 5: oncoplastic techniques can reduce the need for reoperation in anatomically suitable patients

Background

Driven by the desire to prevent ipsilateral breast deformity

after breast conserving surgery and to improve symmetry with the contralateral breast, the use of oncoplastic techniques after lumpectomy is increasing (43-46). The focus here is to update information on the opportunity to potentially lower reoperations by receipt of oncoplastic lumpectomy compared to standard lumpectomy alone. Other oncoplastic areas of interest, such as selection of technique and cosmetic and oncologic outcomes, are out of scope for this update.

Is oncoplastic lumpectomy associated with fewer reoperations for margin reasons?

To our knowledge, there is no level 1 evidence that oncoplastic lumpectomy compared to simple lumpectomy results in lower reoperation rates. However, there are systematic reviews of the literature, comparative effectiveness studies and case series with lower levels of evidence that increasingly support the notion that receipt of oncoplastic surgery is associated with fewer reoperations (43-59).

By literature review, the unadjusted rates of reoperation with oncoplastic lumpectomy are lower than those reported recently in 3 different national patient registries. The mean lumpectomy reoperation rates reported in the National Cancer Data Base and the ASBrS patient registry in 2014 were 23.6% and 21.6% respectively (3,4). In 156 National Health Service Trusts in England, 11,032 (20%) of 55,297 patients underwent reoperation (2). In contrast, in a recent systematic review of patients undergoing oncoplastic breast-conserving surgery in the years that overlapped with the national registry data above, De La Cruz *et al.* reported on 55 studies that evaluated 6,011 patients from 1998 to 2015 (49). In 49 of these studies that reported positive margin status and reoperations, the overall rates were 10.8% (range, 0–40%) and 6% (range, 0–27%) respectively (49).

In 2017, in a different systematic review, Campbell *et al.* identified 13 studies that compared reoperation rates in those patients undergoing oncoplastic lumpectomy versus those undergoing standard lumpectomy (48). Eight studies reported a benefit regarding margin status and reoperations; five failed to demonstrate benefits. Many of these studies were limited by lack of clarity of margin status and margin definitions. Some reported reoperation rates without margin data; others reported margin status without reoperation rates and others added a comparator control group of patients undergoing mastectomy. The largest study in the review cited above had an oncoplastic lumpectomy

sample size of 1,177 patients (46). These patients were retrospectively compared to patients undergoing standard lumpectomy [3,559], mastectomy [3,263], and mastectomy plus reconstruction [2,608]. Reoperation rates were not reported but the patients undergoing oncoplastic lumpectomy had fewer positive/close margins (5.8%) compared to standard lumpectomy (8.3%, $P=0.04$).

Post-operative complications

A recent consensus panel concluded that oncoplastic lumpectomy was associated with an increased risk of post-operative complications compared to standard lumpectomy (43). Post-operative complications after oncoplastic lumpectomy to include fat necrosis, skin necrosis, seroma, hematoma and surgical site infection occurred in 14.3% of patients in a systematic review of the literature (49). In other reviews, increased complication rates have also been reported (48,51).

Radiation after oncoplastic lumpectomy

Breast tissue is re-arranged with most oncoplastic techniques. Thus, the radiation oncologist is challenged during their attempts to target the breast tissue adjacent to the patient's resected cancer. Such targeting is especially relevant for patients recommended to receive a boost dose of radiation and for patients wanting to be candidates for accelerated and/or partial breast radiation. To address these concerns, a group of radiation oncology experts systematically reviewed the literature (60). They recommended that surgeons consider the application of clips to the tumor bed. Pre-operative radiation oncology consultation was also recommended for patients wanting oncoplastic reconstruction in order to discuss radiation boost options, the "impact of surgical technique on fractionation scheme", and the likelihood that accelerated or other forms of partial breast radiation may not be possible (60).

The future

In 2017, in Basel Switzerland, the "First international consensus conference on standardization of oncoplastic breast conserving surgery" was convened. The delegates agreed that there is a need for prospective multicenter trials to "optimize patient selection and for standardized criteria to qualify and accredit oncoplastic training centers" (43).

Conclusion

In mostly unadjusted non-randomized retrospective reviews of patients undergoing initial breast conserving surgery,

the reoperation rate is lower for margin reasons in those patients receiving oncoplastic lumpectomy compared to those that undergo lumpectomy without reconstruction. Oncoplastic procedures can also improve cosmetic outcomes and expand the population of patients eligible for breast conserving surgery.

The post-operative rates of surgical site infection and reoperations for reasons other than margins may be increased.

Pre-operative consultation with radiation oncology, prior to planned reconstruction that includes tissue rearrangement, and application of marking clips to the peri-tumoral tissue should be considered.

Nearly all systematic reviews of oncoplastic lumpectomy agree there is a need for prospective multicenter comparative effectiveness studies to further evaluate patient reported outcomes, cancer recurrence rates, complication rates and reoperation rates stratified by type of procedure.

Search terms: breast and oncoplastic; lumpectomy and oncoplastic; breast conserving and oncoplastic.

- ❖ Total titles reviewed 299;
- ❖ Total abstracts reviewed 66;
- ❖ Total manuscripts reviewed 35;
- ❖ Manuscripts used and referenced 21.

Tool 6: specimen orientation of 3 or more margins

Background

Specimen orientation denotes any process used in the operating room during lumpectomy to correctly annotate the specimen's *in vivo* orientation in 3 dimensions. Orientation can be accomplished by surgical clips, commercial markers, dyes, sutures and other techniques.

Specimen orientation alone does not reduce reoperation rates. Specimen orientation was included in the 2015 ASBrS Consensus Conference Toolbox because of its efficacy to target the correct site for a focused breast re-excision in patients needing reoperation for margin reasons. If specimen orientation is omitted and a patient requires subsequent re excision for positive margins, then entire cavity re excision is necessary. As a result, higher resection volumes and worse cosmetic outcomes would be anticipated, compared to a targeted re excision.

There are many different techniques for specimen orientation. To our knowledge, they have not been tested in level 1 randomized trials for their comparative effectiveness. Despite the absence of high level evidence as to which

of many methods is best for orientation, the majority of the participants in the CALLER consensus conference recommended application of ink to at least 3 sides of the lumpectomy specimen. Other methods are acceptable. In at least one report, restricting orientation to only 2 sides limited the accuracy of identification of other sides (61). Some conference participants recommended that all sides of the lumpectomy be inked.

Is specimen orientation a measure of quality?

In 2013, the ASBrS used a modified Delphi process to rank the importance of more than 100 domains of breast surgical care. After hierarchical ranking, specimen orientation was one of nine processes of surgical care that were endorsed as a "quality measure" (62,63).

Update

In this update, we found no new studies concluding that any specific orientation method was superior to others. However, recent publications have identified some pitfalls and solutions to various orientation issues. For example, Patel *et al.* recommended a solution to the problem of "losing" orientation if a single localization method such as clipping "fails" due to accidental clip dislodgement (64). They advocated for redundancy of localization methods by using a marking board, clips and sutures. In another report, McClatchy III *et al.* described use of an organic "molecular" dye instead of standard surgical inking in cases in which surgeons wanted to employ specialized intra-operative optical imaging devices for margin assessment (65). They reported that standard inking prevented optical margin interrogation. In a different report, Taylor *et al.* described a method to better discriminate between a radioactive seed and a marking clip that were initially indistinguishable on routine specimen imaging. They recommended a change in settings to widen the window on the portable Picture Archiving and Communication System (PACS) (66). Without this maneuver, they could not confirm that the target seed was removed with the specimen. Lastly, Brice *et al.* identified a specific type of "red ink", employed for specimen orientation that created a pattern of micro-calcifications that were suspicious for cancer on specimen imaging (67). Other ink colors were not associated with this pattern. If not recognized, unnecessary cavity shaves based on specimen imaging could occur.

Other specimen topics such as intra-operative imaging of the specimen and intraoperative margin assessment techniques are updated elsewhere in this review.

How often do breast surgeons comply with recommendations to perform specimen orientation?

High levels of compliance have been achieved by American and Canadian surgeons (62,63,68). In a performance summary generated by 473 ASBrS member surgeons, specimen orientation occurred in 98.6% of 275,619 patients (range, 11–100%) after lumpectomy for cancer (62,63).

Conclusion

Specimen orientation by any technique that allows the breast pathologist to orient all sides of the specimen during margin assessment is essential. To determine the optimal method of orientation, future comparative effectiveness studies should be considered.

Search terms: breast specimen orientation, breast lumpectomy and orientation, breast specimen lumpectomy orientation, breast lumpectomy and ink, Breast AND Lumpectomy AND specimen orientation, Breast AND Specimen orientation and more margins, Specimen Orientation AND Marker OR ink OR Clip AND re excision AND re operation Specimen AND Orientation AND Marker OR Ink AND Breast cancer AND Lumpectomy. Breast AND Specimen AND Margin AND Orientation.

- ❖ Total titles reviewed 64;
- ❖ Total abstracts reviewed 24;
- ❖ Total manuscripts reviewed 12;
- ❖ Manuscripts used and referenced 8.

Tool 7: specimen radiograph with surgeon intraoperative review

Background

Intraoperative specimen radiograph review has improved with several modalities available. The surgeon should review the imaging in conjunction with a radiologist to potentially avoid re excision.

Update

Various intraoperative imaging methods exist including radiograph, ultrasound, microcomputed CT and MRI. St John *et al.* reported on a meta-analysis of 35 studies and found that frozen section and cytology had the greatest accuracy. They found there was not sufficient data on some of the newer imaging techniques to effectively make a fair comparison (69). Operating room radiograph provides immediate surgery feedback, and has been shown to not significantly impact operative time, the rate or number

of additional intraoperative margins excised or the width of final pathological margins (70). Miller *et al.* confirmed the accuracy of intra operative specimen radiograph to standard specimen mammography with a randomized trial. They found significantly reduced interpretation time, 1 minute versus 9 minutes for intraoperative mammography compared to standard specimen mammography. In addition, there was 100% concordance for target and 93% concordance for margins among the specimens (71). The use of 3D versus 2D mammography can be more accurate and was shown to reduce the re excision rate in 2.2% of patients (13). In addition, breast tomosynthesis has been shown to more accurately detect breast cancer intraoperatively (14). This has been confirmed by Amer *et al.*, showing accuracy of 40% versus 69% between full field digital mammography and digital breast tomosynthesis. Sensitivity was also significantly better at 62% versus 77% (72). The use of intra operative US is another modality for imaging specimens and margin status. It has been shown to have a 94% specificity in detecting the breast lesion as well as positive margin (73). Finally, another modality is micro-computed tomography. Tang *et al.* showed that micro-CT had the best correlation coefficient with pathologic tumor dimension, followed by MRI, US and mammography. The advantage is the ability to measure the tumor in 3D (74).

Conclusion

There are multiple modalities for intraoperative specimen review. This should be conducted with proper communication between the breast surgeon and radiologist.

Search terms: Specimen imaging breast conserving surgery, Intraoperative specimen imaging breast conserving surgery, Specimen imaging breast surgery, Intraoperative imaging breast surgery.

- ❖ Total titles reviewed 18;
- ❖ Total abstracts reviewed 16;
- ❖ Total manuscripts reviewed 11;
- ❖ Manuscripts used and referenced in text 8.

Tool 8: consider cavity shave margins in patients with T2 or greater tumor size or T1 with extensive intraductal carcinoma (EIC).

Background

Cavity shaves for margins are becoming more common practice, however is not yet the standard of care. There is now evidence to show they decrease the positive margin and re excision rate.

Update

Chagpar *et al.* conducted a randomized control trial of cavity shave margins, proving that this technique halved the rates of positive margin and re excision rates (75). Since that time there have been several retrospective studies and some randomized controlled trials demonstrating the effectiveness of this technique. It has not been shown to adversely affect cosmetic outcomes. Corsi *et al.* found that avoiding cavity shaved margins expose patients to 6.2-fold higher risk of positive margin and 5.46-fold higher risk of reintervention (76). The cost effectiveness has been looked at, and there has been no increase in cost doing cavity shaves due to significantly fewer reoperations (77).

Conclusion

Cavity shave margins reduce the positive margin and re excision rate by half without adding significant time or cost. This is an effective, precise way of decreasing the re excision rate in breast conservation patients.

Search terms: cavity shave margins breast conserving surgery, cavity shave margins breast conserving surgery re excision, cavity shave margins breast conserving surgery reoperation, cavity shave margins, cavity shaved margins, cavity shaved margins breast conserving surgery.

- ❖ Total titles reviewed 14;
- ❖ Total abstracts reviewed 10;
- ❖ Total manuscripts reviewed 7;
- ❖ Manuscripts used and referenced in text 3.

Tool 9: intraoperative pathology assessment of lumpectomy margins may help decrease re-excision when feasible

Background

In a 2012 systematic review of the literature, Esbona *et al.* identified 37 studies that measured reoperations after lumpectomy and compared those patients undergoing lumpectomy with immediate intraoperative margin assessment—either imprint cytology or frozen section analysis to those that underwent post-operative permanent histopathologic assessment (78). The final re excision rates after lumpectomy were 35%, 11%, and 10% for post-operative assessment, imprint cytology and frozen section analysis respectively ($P < 0.001$). In 2014, Boughey *et al.* compared the 30-day reoperation rates after lumpectomy for cancer between the National Surgical Quality Improvement Project (NSQIP) and the Mayo Clinic-Rochester data bases (89). Their purpose was to determine if there were differences between a national sample of institutions that

had diverse pathologic practices and a single institution that utilized frozen section analysis. In NSQIP, the reoperation rate was 13.2%. At the Mayo Clinic-Rochester, the rate was 3.6% ($P < 0.001$); on multivariate analysis, the odds ratio for the likelihood of a reoperation in facilities reporting in NSQIP compared to the reference institution that used frozen section was greater than 4 ($P < 0.0001$) (79).

On the evidence of these and other publications, the 2014 ASBrS Consensus Conference concluded that immediate methods of intra-operative margin assessment were associated with fewer reoperations compared to postoperative margin assessment. On the other hand, it was also noted that some institutions already had low rates of reoperation without intra-operative assessment. Additionally, for many institutions wanting to change their practice to one of routine frozen section, it was predicted that there would be significant, perhaps even insurmountable financial and staffing barriers to building the infrastructure for such a program.

Update

Since the 2014 Consensus Conference, multiple investigators have reviewed the association between intraoperative pathologic specimen evaluation of the lumpectomy margin and reoperation rates (69,80-88). In a meta-analysis of these techniques in 2017, St John *et al.* reviewed 838 unique studies to identify 35 with sufficient data to determine pooled sensitivity, specificity, and area under the receiver operating characteristic curve (69). The respective values per group were as follows: frozen section =86%, 96%, 0.96; cytology =91%, 95%, 0.98; intraoperative ultrasound =59%, 81%, 0.78; specimen radiography =53%, 84%, 0.73; and optical spectroscopy =85%, 87%, 0.88. The authors concluded that intraoperative frozen section and cytology had the greatest accuracy.

In a systematic review of the literature in 2017, Gray *et al.* identified 106 publications that were focused on intraoperative management of lumpectomy specimens (80). After disentangling those studies relevant to immediate intraoperative pathologic examination from those related to specimen imaging, cavity shaves and specimen imaging, they identified those studies that focused specifically on pathologic techniques. Collectively, the patient sample size for these exceeded 10,000 (80). Due to the heterogeneity of margin definitions and the outcomes measured in these studies, they did not combine data for a pooled or meta-analysis. Upon completion of their review, the authors

concluded that frozen section analysis and imprint cytology were associated with lower rates of positive margins. Using standard definitions for level of evidence and strength of their recommendation, the authors categorized frozen section and imprint cytology as 2B and 2C respectively.

In 2018, 3 breast surgeons authored chapters in textbooks that also reviewed the literature on margin assessment to include intra-operative pathologic assessment techniques (81,87,88). In each of these reviews, there was overlap of the publications already cited above. Notwithstanding this overlap, 2 of these 3 authors qualitatively concluded that the receipt of frozen section analysis and imprint cytology during lumpectomy were associated fewer reoperations (81,88). The third author cited similar studies but emphasized the “shortcomings” of immediate intraoperative pathologic maneuvers to include the dual burdens of extra time-in-the-OR and cost, as well as surface sampling errors, loss of tissue for biomarker evaluation and the inability of cytology to distinguish between invasive and *in-situ* cancer (87).

Patients with ductal carcinoma in situ (DCIS) without invasive cancer were not included in most of the aforementioned studies. In 2016, Decker *et al.* reviewed the role of intraoperative frozen section and touch prep in 8,259 DCIS patients captured in the Surveillance, Epidemiology, and End Results-Medicare data base. In this report, intraoperative assessment was not associated with any reduction in reoperations (adjusted OR 1.07; 95% CI, 0.95–1.21; P=0.293) (85).

To our knowledge, no randomized trials have been conducted to compare intra-operative to postoperative pathologic assessments of lumpectomy specimen margins for the outcomes of reoperation rates, direct costs (pathologist, technician, equipment), and indirect costs (training, time-in-OR, scheduling difficulty). Additionally, it is unclear whether the excellent results achieved by intraoperative frozen section in higher volume institutions with experienced breast pathologists would be reproducible in lower volume non-specialized centers.

Cost effectiveness of frozen section

Boughhey *et al.* built an economic model to assess annual costs associated with lumpectomy with and without frozen section. In the model, reoperation rates without frozen section were estimated from the literature at 15–50%. Reoperation rates with frozen section were based on a measured institutional performance of 3% (89). The patient population in the model was based on Medicare charge data; costs from other public and private payers were

estimated. Payer and provider costs were then calculated for differing rates of diffusion of frozen section into national practice. Limitations within this model were acknowledged. Indirect costs to providers and facilities were not included. Furthermore, total direct and indirect costs to the patient were not in the model because copays, time away from work and other costs were not known. A Monte Carlo analysis with 10,000 simulations was conducted. The simulations were of differing rates of diffusion of incorporation of frozen section into the United States and a facility’s baseline reoperation rate. The authors concluded that the incorporation of frozen section into practice offered cost savings to payers and was neutral to a slight cost saving to providers. For two specific scenarios, the estimated potential annual cost savings were \$18.2 million to payers and \$0.4 million to providers when frozen section margin analysis was used in 20% of national breast lumpectomies; savings increased to \$90.9 million and \$1.8 million if 100% of facilities adopted frozen section (89).

Arguing against the potential advantages to greater diffusion of frozen section techniques as described above, others have emphasized that the disruptions associated with its adoption, such as those associated with pathology staffing, work-flow, extra time to perform cases—coinciding with less availability of operating room access—make routine frozen section “untenable” (90). Others have emphasized the technical challenges of freezing adipose tissue, margin sampling errors, slow reporting times and logistics (87,88).

Conclusion

Reoperation rates after initial lumpectomy for cancer are significantly lower in those facilities utilizing routine intra-operative frozen section or imprint cytology for margin assessment compared to national and international average rates of reoperation.

The cost-effectiveness and reproducibility of the accuracy of frozen section techniques outside of centers that have already verified excellent results is unknown. For institutions wanting to adopt these techniques, we recommend they audit their results.

Search terms: breast lumpectomy frozen section, breast lumpectomy frozen section systematic review, breast lumpectomy touch prep, breast lumpectomy imprint cytology, breast lumpectomy intraoperative.

- ❖ Total titles reviewed 220;
- ❖ Total abstracts reviewed 64;
- ❖ Total manuscripts reviewed 27;
- ❖ Manuscripts used and referenced 12.

Tool 10: compliance with the SSO-ASTRO margin guideline to not routinely re-operate for close margins with no tumor on ink in patients with invasive cancer

Background

In 2014, the SSO-ASTRO Consensus Conference issued a Margin Statement recommending that surgeons omit re-excision lumpectomy in patients with “close” but “ink-negative” margins after an initial lumpectomy. This recommendation was based on a meta-analysis of patients with invasive breast cancer that clarified the association between lumpectomy margin status and margin width with later in-breast tumor recurrence (91,92). Soon thereafter, the ASBrS and many others endorsed the SSO-ASTRO Margin Statement (8,93).

In 2016, a second SSO-ASTRO Margin Statement that focused on patients with ductal carcinoma *in situ* was published (94). The meta-analysis that underpinned this statement found that margin widths greater than 2 mm were not associated with any further reduction in cancer recurrence compared to 2 mm (95). Since the publication of both SSO-ASTRO Consensus Statements, multiple investigators have queried patient registries to determine whether reoperation rates decreased.

Based on empirical evidence, there was much hope that avoiding re-excision in patients with close, but ink-negative margins would reduce reoperation rates in patients with invasive cancer. For example, in 2013, 328 surgeons entered information into the ASBrS Mastery patient registry on 6,725 patients undergoing initial lumpectomy for cancer. Of those patients who underwent re-excision, the primary reason for the re-excision was a close but ink-negative margin in 40% (4).

Evidence that reoperations decreased after the margin statement

Multiple investigators concluded that reoperations decreased in comparison of rates before and after the 2014 Margin Statement (5,11,96-99). Two studies utilized national registries. Among 252 surgeons entering data into the ASBrS Mastery registry on 26,102 patients undergoing initial lumpectomy, the reoperation rates decreased from 20.2% to 16.5% ($P<0.001$); there was a 13.8% decrease in reoperations performed for the reason of close margins (5). In a population-based cohort sample from the Surveillance, Epidemiology, and End Results registry, Morrow *et al.* reported a 16% ($P<0.001$) absolute reduction in reoperation rates, accompanied by a breast conserving therapy rate that

improved from 52% to 65% (11).

Most single institution studies of reoperation rates before and after the 2014 Margin Statement have similar conclusions (96-98). The University of Louisville noted a decrease in reoperation rate from 37% to 9%, $P<0.001$ ($N=237$ patients) (96). At Cedars-Sinai in Los Angeles, Chung *et al.* reported a decrease from 19% to 13%, $P=0.03$ ($N=846$ patients). At the Memorial Sloan Kettering Cancer Center, Rosenberger *et al.* reported a decrease from 21.4% to 15.1%, $P=0.006$ ($N=1,205$ patients), and at the Carolinas HealthCare System, Patten *et al.* reported a decrease from 20.4% to 16.3%, $P=0.104$ ($N=954$) (97-99).

Prediction of improvement in reoperation rates and costs of care based on retrospective application of margin statements

Multiple studies have estimated the anticipated improvement in reoperation rates if there was compliance with the Margins Statements (100-103). In the United Kingdom and Ireland, Tang *et al.* reported data on reoperations and margin status from 79 breast units during 2016 (100). The overall mean reoperation rate was 17.2% (range, 0–41%). After retrospective review of margins, the authors predicted a reduction in their overall rate to 15% if all units had consistently applied the SSO-ASTRO Statement. Yu *et al.* applied the SSO Guideline retrospectively to patients treated at a single institution and estimated a 5.6% decrease in reoperation rates and 2,360 \$ per patient cost savings (101). In British Columbia, Canada, investigators estimated their reoperation rate for invasive cancer would decrease from 25% to 16% by omitting resection in patients with close margins and Merrill *et al.*, at Massachusetts General Hospital, estimated that applying the 2014 SSO Guidelines to a 2004–2006 patient cohort would have reduced reoperations by 50% (102,103).

The benefits of decreasing reoperation rates by adoption of the margin statement include reducing the cost burdens for patients and payers (104).

No improvement

At the University of Colorado School of Medicine, Gladden *et al.* noted re-excision rates of 11.9% before and 10.9% ($P=0.65$) after the 2014 Consensus Statement (105).

College of American Pathology (CAP) protocols for margin assessment

In 2018, Guidi *et al.* surveyed more than 700 pathologists

enrolled in a breast pathology performance improvement project (106). They reported that there were opportunities to improve compliance with CAP protocols for lumpectomy specimens. Twenty-three percent of 791 respondents performed en face instead of perpendicular margins and 12% did not ink separate cavity shave margins; both actions might preclude compliance. Thus it behooves surgeons to discuss margin processing techniques with their pathologists.

Conclusion

There is strong evidence that compliance with the SSO-ASTRO Margin Guidelines will reduce reoperation rates.

Search terms: margin statement and breast; SSO margin statement and Morrow; SSO margin statement and reoperations; SSO margin statement and re excision; SSO margin statement and lumpectomy; SSO margin statement and trends; breast and reoperations; and all the previous replacing “statement” with “guideline”.

- ❖ Total titles reviewed 189;
- ❖ Total abstracts reviewed 42;
- ❖ Total manuscripts reviewed 30;
- ❖ Manuscripts used and referenced 19.

Are there other opportunities for reducing reoperations after lumpectomy that were not endorsed by the ASBrS Consensus Conference in 2015?

Background

The participants in the 2015 consensus conference on reoperations were asked to nominate any processes of care or adjuncts that had the potential to reduce reoperations and improve cosmetic outcomes. The final consensus statement endorsed eleven. Other processes and adjuncts were considered, such as margin devices, but not endorsed. The following discussion provides an update of margin devices.

In addition, two other processes of care are discussed for which there is some evidence of their efficacy to reduce reoperations. The processes of care discussed below have not been endorsed by the ASBrS; they represent the authors' perspective only.

Margin devices

There has been encouraging progress in the development of intraoperative devices to aid in the assessment of lumpectomy margins. The goal is to rapidly interrogate the lumpectomy specimen as well as the lumpectomy cavity to evaluate for residual cancer. Ideally, technology that would

allow conservative lumpectomy with sequential assessment of shave margins and the cavity are being optimized. This would be analogous to the MOHS method which is used to assess margins for cutaneous malignancies. Some of the emerging modalities have the added benefit of evaluating nodal disease. The MarginProbe (MP) has the largest body of data and has approval from the US Food and Drug Administration (FDA). It uses radiofrequency spectroscopy and has demonstrated a significant relative reduction (23–56%) in reoperation rates in 2 randomized clinical trials (107,108). Kupstas *et al.* in a retrospective review of 240 patients demonstrated a 50% reduction in re-excisions using the MP (109). Coble *et al.*, compared 137 MP cases to 199 full cavity shave cases. The re excision rate was reduced by 57% ($P=0.026$), from 15.1% to 6.6%. The overall tissue volume removed was reduced by 32% ($P=0.0023$), from 115 to 78 cc (110). Sebastian *et al.* reported on the use of MP in 165 patients with a margin re-excision rate of 9.9% compared to 25.8% in their historical controls (111). There has been the clinical observation that the false positive rate for the MP is higher in the setting of dense breast tissue. Blohmer *et al.* reported a prospective clinical study of 150 patients. They report an overall reduction in re-excision rates of 14.6% compared to historical controls; which included some patients with DCIS, lobular histology and dense breast tissue (112). Another technology, the ClearEdge system evaluates the bioimpedance of breast tissue. Dixon *et al.* have reported sensitivity 84–87% for involved margins and specificity to confirm negative margins at 76–85% using this system (113).

Another approach uses optical coherence tomography (OCT) which enables real-time high-resolution imaging of tissue microstructure. In a translational study by Erickson-Bhatt *et al.* involving 35 patients, a handheld surgical OCT imaging probe was developed for *in vivo* use to assess margins both in the resection bed and on excised specimens for the microscopic presence of cancer. The *ex vivo* images were compared with standard postoperative histopathology to yield sensitivity of 91.7% and specificity of 92.1%. This study demonstrates *in vivo* OCT imaging of the resection bed during lumpectomy has the potential for real-time microscopic image-guided surgery (114). Zysk *et al.* reported a multicenter, prospective, blinded study of 46 patients performed to test the feasibility of using handheld OCT probe with analysis the interpretation of 2,191 images from 229 shave margin specimens with promising results (115). Additional optical imaging modalities for intraoperative use are in development. Wang *et al.* have

developed a Raman-encoded molecular imaging (REMI) technique in which targeted nanoparticles are topically applied on excised tissues to enable rapid visualization of a multiplexed panel of cell surface biomarkers at surgical margin surfaces (116). Thomas *et al.* describe automated 3-dimensional scanner using Raman spectroscopy (117). Mondal *et al.* have described the feasibility of an optical goggle augmented imaging and navigation system (GAINS) for near-infrared, fluorescence-guided surgery using indocyanine green (118). Unkart *et al.* describe the use of a novel, ratiometric activatable cell-penetrating peptide (AVB-620) in breast cancer surgery. Their study involving 26 patients demonstrated the safety and dose optimization with Intraoperative imaging with an optical camera of surgical lumpectomy and nodal specimens after infusion with AVB-620 allowed for real-time tumor detection based upon fluorescence (119). Clinical trials of this method are currently in progress. An emerging unique approach is being investigated by Takats and Leff investigating the role of rapid evaporative ionization mass spectrometry through online chemical analysis of electrosurgical aerosol toward real-time margin assessment as an “intelligent knife”. Here as the lumpectomy is being performed the electrocautery smoke is collected and rapidly analyzed for cancer related by products which would indicate an involved surgical margin (90).

Another novel approach intraoperatively to reducing margin re-excision has been reported by Klimberg *et al.* using radiofrequency ablation (RFA). This approach treats a 1 cm zone of breast tissue with RFA around the periphery of the lumpectomy cavity during surgery (120). The concept is that if margins are close or involved that re-excision can be avoided since the adjacent tissue has been ablated by the RFA. This approach may also allow selected patients who undergo intraop RFA to forego adjuvant radiation. The ABLATE 1 trial accrued 100 patients. During the study mean follow-up period of 62±24 months (68-month median follow-up) in patients not treated with XRT, there were 2 in-site tumor recurrences treated with aromatase inhibitor, 3 biopsy entrance site recurrences treated with excision and XRT to conserve the breast, and 2 recurrences elsewhere and 1 contralateral recurrence; all 3 treated with mastectomy. A larger multicenter trial (ABLATE 2) has favorable results (personal communication-Klimberg) which will be published in the near future.

Pursuit of a triple aim of breast conserving surgery (BCS): higher BCS rate, fewer reoperations and better cosmetic outcome with “extreme” oncoplastic lumpectomy and

neoadjuvant chemotherapy.

The primary aim of oncoplastic lumpectomy is to improve the cosmetic outcome of the breast compared to standard lumpectomy. A potential secondary gain—as described earlier—may be fewer reoperations. An international consensus conference and others have described an additional advantage to oncoplastic lumpectomy. Patients with larger or multifocal tumors—initially deemed ineligible for breast conservation—can be offered larger volume oncoplastic resection techniques to extend the indications for breast conservation (43-45). Silverstein *et al.* have termed this “extreme” oncoplasty and have reported low reoperation rates even in patients with tumor extent exceeding 5 cm (44,45). In 2017, the “First international consensus conference on standardization of oncoplastic breast conserving surgery” concluded that oncoplastic techniques can “broaden” the indication for breast conserving surgery (BCS) towards larger tumors, potentially increasing the BCS rate.

Neoadjuvant chemotherapy (NAC), compared to post-operative adjuvant chemotherapy, may be able to achieve similar objectives (24). In the National Cancer Data Base (NCDB), patients with receipt of NAC, compared to those that did not, had a higher BCS rate (121). In a separate investigation of the NCDB, 71,627 stage I-III breast cancer patients were identified that received chemotherapy. In this cohort, the receipt of chemotherapy before instead of after surgery was associated with fewer reoperations after initial lumpectomy for breast cancer (24). After propensity score matching of patients and multivariate analysis, the relative odds of reduction in reoperation rates were almost halved [0.53 (0.49-0.57), $P < 0.001$]. The odds of reduction in reoperation rates were even higher in patients with triple negative and HER 2 overexpression status.

A recent systematic review of the literature also assessed reoperation rates (and other surgical outcomes) in patients with receipt of NAC compared to those that did not. In 26 publications (N=15,489 patients), Volders *et al.* identified mixed results insofar as the effectiveness of NAC to reduce reoperations after lumpectomy (23). This systematic review was limited by heterogeneity of performance by facility and publication dates. During these dates, adjuvant therapies were changing and there was wide variability of performance. Other limitations included non-uniform margin definitions, a wide range of reoperation rates between institutions and small sample sizes per facility.

Supporting the adoption of NAC and oncoplastic techniques to improve the care of selected patients

undergoing breast conserving surgery, Broecker *et al.* recently reported using both in patients with higher stage cancers and reported acceptable cosmetic results, reoperation rates and cancer recurrence rates (122).

In 2017, the National Comprehensive Cancer Network and the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017 have endorsed the option of neo-adjuvant systemic therapy to increase breast conservation rates (25,29). The St. Gallen panel recommends NAC as “preferred” first treatment, instead of primary surgery, in patients with Stage II and III triple negative and HER 2 amplified cancers. The St. Gallen Conference also recommended that the breast excisional volume be limited to only the perceived residual tumor bed after NAC; a “de-escalation” of treatment that potentially could result in a better cosmetic outcome, regardless of receipt of an oncoplastic technique (25).

Conclusion

In eligible patients, oncoplastic lumpectomy, even in patients with large tumors, and/or neo-adjuvant chemotherapy, may help to achieve higher rates of breast conservation, lower rates of reoperation, and improvements in cosmetic outcomes.

Conclusion and future directions

The economic burden of margin re excision has been estimated to be about \$18.8 million per year (123). This impact of cost should help drive breast surgeons at using all modalities possible to decrease this cost. One method might be widespread use of frozen section margin analysis. Boughey *et al.* looked at the economic impact of this and found that if feasible, intraoperative frozen section analysis to guide the surgical management would be beneficial not only to patients but also financially for health care payers and providers (89).

The concept of over treatment in surgical management has been addressed by several authors. After the 2014 consensus statement endorsing a margin of “no ink on tumor” one study showed a decrease in surgery after initial lumpectomy by 16%. This is encouraging to see positive results in a surgeon led initiative to address potential overtreatment (11). There is a focus to reduce re-excision rates. There are multiple factors, non-tumor related that lead to a positive margin including inadequate assessment of macroscopic disease extent at diagnosis,

inaccurate impalpable disease localization and limited use of intraoperative specimen radiograph. Ultimately what constitutes an acceptable margin must be individualized within the context of the tumor size, biology, stage, and planned treatments (10).

The updates on the CALLER Toolbox for lumpectomy will help guide surgeons to various resources to aid in the removal of breast cancer, while being aware of cosmesis and decreasing re excision rates.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: McEvoy MP, Landercasper J, Naik HR, Feldman S. Update of the American Society of Breast Surgeons Toolbox to address the lumpectomy reoperation epidemic. *Gland Surg* 2018;7(6):536-553. doi: 10.21037/gs.2018.11.03