Intraoperative Margin Assessment in Breast Cancer Management

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KEYWORDS

• Breast cancer • Breast-conserving surgery • Breast-conserving therapy
• Lumpectomy • Re-excision • Margin • Intraoperative assessment

KEY POINTS

- Rates of margin re-excision vary widely in the literature.
- Efforts to reduce re-excision rates must begin at the time of diagnosis with high-quality imaging, minimally invasive breast biopsy, and multidisciplinary planning.
- A variety of techniques to reduce rates of re-excision have been described; however, careful tracking of re-excision rates and cosmetic outcomes must be undertaken when using these techniques.

INTRODUCTION: NATURE OF THE PROBLEM

Numerous trials have demonstrated equivalent survival outcomes for mastectomy and breast-conserving therapy (BCT) in early-stage breast cancer.[1–6] For patients with unifocal, early-stage breast cancer, BCT is often the preferred treatment. The goal of breast-conserving surgery (BCS) is to excise the tumor with negative margins while providing satisfactory cosmesis. Positive margins after BCS represent a significant risk factor for recurrence and patients with positive margins have rates of ipsilateral breast tumor recurrence twice those of patients with negative margins.[7] Patients who choose to undergo BCT are counseled about the possibility of having to return to surgery for re-excision of positive or close margins. The rates of re-excision reported in the literature range from less than 10% to greater than 50%.[8–15] Importantly, this variability is not explained by characteristics of either the patients or their disease.

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Achieving a negative margin at initial surgical intervention spares patients from undergoing additional operative intervention, thus sparing patients additional cost and risk. A return to the operating room for margin re-excision results in additional exposure to the risks of anesthesia, increased surgical complications including increased surgical site infections, increased health care costs, and even increased conversion to bilateral mastectomies.[16–19]

The definition of a negative margin has varied widely over time and across practices. The National Surgical Adjuvant Breast and Bowel Project B-06 trial defined a negative margin as "no ink on tumor," whereas the Milan trials required quadrantectomy with a 2-cm to 3-cm gross margin.[1,2] For patients undergoing BCS, the margin width required for a negative margin has varied widely in clinical practice.[20,21] These different definitions of margin negativity influence re-excision rates. The Society of Surgical Oncology–American Society for Radiation Oncology (SSO-ASTRO) consensus guideline on margins for BCS with whole-breast irradiation in patients with stages I and II invasive breast cancer suggest that "no ink on tumor" be considered the standard for a negative margin.[22] This guideline is based on 33 studies that included more than 28,000 patients with analysis failing to indicate an association between increased margin width and decreased risk of local recurrence. Some investigators have suggested, however, that physicians should consider each case individually, taking into account clinical, pathologic, and treatment variables to determine the need for re-excision rather than using solely margin width.[23] Soon after publication of the guideline, a survey of members of the American Society of Breast Surgeons revealed that a majority of surgeons did not perform re-excision of margins when tumor was not touching the inked margins, but for more complex margin scenarios individual surgeon judgment was used to determine if re-excision was needed.[24] The recently published SSO–ASTRO–American Society of Clinical Oncology consensus guideline on margins for BCS with whole-breast irradiation in patients with ductal carcinoma in situ (DCIS) suggested that a 2-mm margin be considered the standard for a negative margin in these patients.[25] This guideline is based on 20 studies that included 7883 patients with analysis indicating that a 2-mm margin decreased the risk of local recurrence in comparison to smaller margins.

Although eliminating re-excisions for patients undergoing BCS is not feasible, several intraoperative margin assessment strategies are available to reduce the need for re-excision. It is important to recognize, however, that this effort must start at the time of diagnosis. High-quality diagnostic mammography must be performed with supplemental imaging when necessary, the diagnostic biopsy should be obtained in a minimally invasive manner, and multidisciplinary discussions should be undertaken especially for those patients receiving neoadjuvant therapy.[26]

PREOPERATIVE LOCALIZATION

Since the introduction of the SSO-ASTRO guideline of "no ink on tumor," attention to margin status has increased, particularly in regards to intraoperative techniques.[22] Breast cancers removed by segmental mastectomy most commonly require preoperative localization to identify the lesion to be removed. After resection, regardless of which preoperative localization modality is used, meticulous attention to proper specimen orientation is critical. It is recommended that 3 or more margins are labeled to ensure accuracy and improve results.[26] Positive margins increase the risk of local recurrence and proper preoperative localization is critical to ensuring complete excision.[22,27] A variety of techniques to localize breast lesions have been implemented, ranging from needle localization to radioguidance to electromagnetics.

NEEDLE LOCALIZATION

Stereotactic-Guided Needle Localization

On the day of surgery, the patient is taken to the radiology department. If using mammography (stereotactic approach), the breast is placed in compression paddles with an alpha-numeric grid targeting the area of concern with the shortest skin to lesion distance. A needle introducer with wire is placed into the breast parallel to the chest wall. Once placement is confirmed by medial-lateral and cranial-caudal views, the wire is deployed into the tissue. Post-placement images, typically with markers on the skin, are performed to help the surgeon determine the distance to the lesion and the best incision site (Fig. 1). After excision of the specimen, a radiograph is taken to confirm excision of the lesion (Fig. 2).[28]

Ultrasound-Guided Needle Localization

With ultrasound-guided needle localization, the patient is taken to the radiology department and placed in either a supine or lateral decubitus position. The lesion is visualized with the ultrasound probe and under direct visualization the needle and wire combination is placed into or surrounding the lesion. A post-procedure mammogram is performed. Some surgeons perform wire localization under ultrasound guidance in the operating room.

Important Considerations for Needle Localization

Needle localization is the most common and oldest method of localization. Regardless of which method is used, needle localization requires same-day placement of a wire into the lesion followed by the surgical removal of the wire and lesion. Excellent coordination between radiology and surgery is necessary. Several drawbacks occur, however, with this method. First, wire placement may affect incision location, resulting in undermining, excess removal of tissue, and poor cosmetic results compared

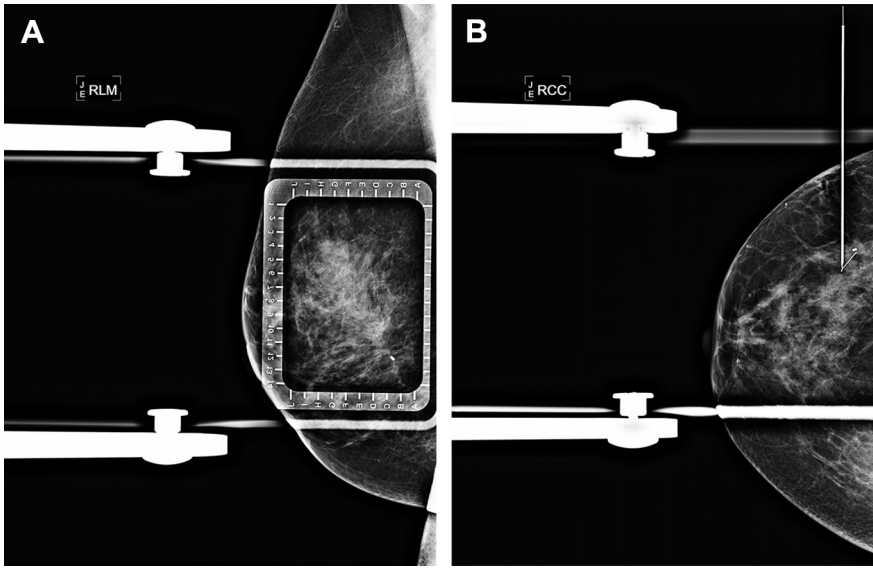


Fig. 1. (*A*) Mammographic compression for needle localization. (*B*) Mammographic compression for needle localization after wire placement.

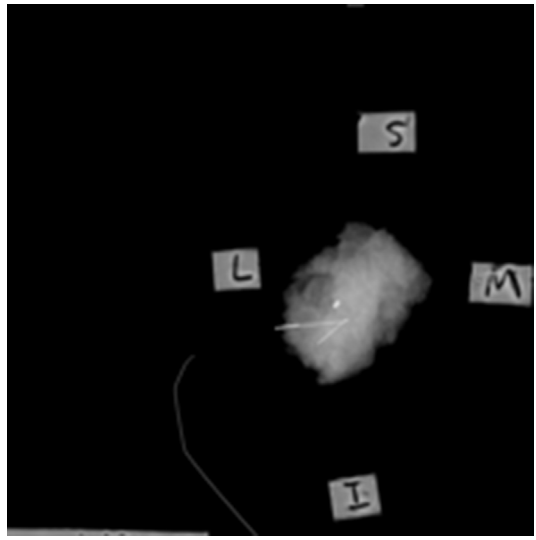


Fig. 2. Specimen radiograph after surgical excision by needle localization. A, anterior; I, inferior; L, lateral; M, medial; P, posterior; S, superior.

with other methods.[29] More importantly, needle localization has been associated with higher re-excision rates.[30] For larger lesions, needle bracketing techniques can be used, but these are associated with more residual disease and incomplete resection.[31]

INTRAOPERATIVE ULTRASOUND

Intraoperative ultrasound (IOUS) may be performed by breast imaging specialists or by surgeons. The patient is taken to the operating room and placed under anesthesia. IOUS can be performed either before the patient is prepped and draped or after the sterile field has been created. If IOUS is done in the sterile field, then an ultrasound probe cover and sterile gel are required. The lesion is identified with the ultrasound and skin markings are created on either end of the probe and a line is drawn to connect these 2 marks. The probe is then turned 90° and the lesion is identified again. The ends of the probe are marked and a second line is created transecting the previous line, which identifies the lesion. For large lesions, the edges of the lesion can be marked.[32] This technique eliminates the need for radiology involvement; however, IOUS does require the lesion to be seen under ultrasound and can be operator dependent. For lesions not visible by ultrasound, a dissolvable marker or iatrogenic hematoma may allow for use of IOUS.[33]

For DCIS patients, margin status and re-excision rates between IOUS and needle localization have been demonstrated to be equivalent.[34] A recent meta-analysis showed that for both palpable and nonpalpable lesions, localization with IOUS resulted in fewer positive margins than needle localization.[35] IOUS can also be used as an adjunct to needle localization.[36]

RADIOGUIDED SURGERY

Radioguided surgery has also become an alternative to needle localization. It consists of either radioactive seed localization (RSL) or radiocolloid injection into the lesion and

a gamma probe utilized to guide excision. RSL is used more in the United States and is focused on in this article. This technique is similar to needle localization. Under either stereotactic or ultrasound guidance, a needle is placed into the lesion. Once in place, a titanium clip containing an iodine-125 I seed is placed into the lesion. For larger lesions, several seeds may be placed for bracketing localization. A gamma probe is used to obtain a numeric response, which correlates with distance to the seed. The numbers are higher close to the radioactive seed and decrease sharply when away from the target. The excised specimen must be accurately labeled with a radioactive label and the receiving pathology team must handle and dispose of the radioactive seed properly. A specimen radiograph is obtained to ensure excision of the seed and lesion (**Fig. 3**).

Importantly, RSL uncouples the need for radiology and surgery to be coordinated on the same day because the seed can be placed up to 5 days prior to surgery.[37] Early studies showed RSL to have fewer positive margins compared with needle localization.[29,37] Although a meta-analysis showed fewer positive margins, smaller resection volumes, and shorter operative times, only 1 of the included study addressed RSL.[38] Recent studies show that there is no difference between RSL and needle localization regarding rates of positive margins, length of operation, or excision volumes.[39] In addition, RSL is reported by patients to be more convenient and less painful.[40] RSL requires, however, onsite nuclear medicine support, a strict chain of custody, and regulations for disposal of the seeds. This may make set-up of an RSL program cumbersome for many facilities.[41]

INTRAOPERATIVE ASSESSMENT TECHNIQUES

Several intraoperative assessment techniques have been described in the literature, each of which has been used to reduce re-excision rates.

Gross Assessment

Gross examination of the whole specimen is performed by both the pathologist and the surgeon. India ink is used to define each of the 6 margins and the specimen is then serially sectioned. Margins are interpreted grossly by the pathologist as well as the surgeon. Intraoperative re-excision of any suspicious margin is performed.

Mixed results with this technique have been reported. Balch and colleagues[8] reported a 25% re-excision rate despite utilization of gross margin assessment. Another study demonstrated no reduction in the need for a second operation for re-excision.[42] Less residual disease was noted, however, within re-excision specimens collected at the time of second operation in those who had undergone gross assessment with subsequent appropriate intraoperative margin re-excision. In contrast, Fleming and colleagues[43] demonstrated that gross margin evaluation with appropriate

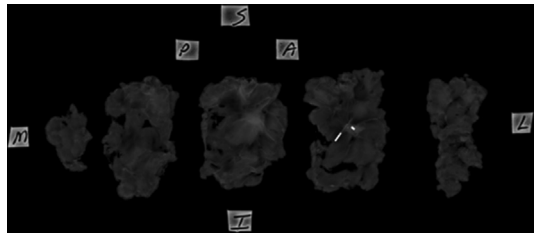


Fig. 3. Specimen radiograph confirming excision of the radioactive seed and targeted lesion.

intraoperative re-excision decreased the need for a second operation to 9.1% from 21.4%. Both lobular subtype and larger tumor size were demonstrated to be predictors of the need for a second operation for re-excision.

Specimen Radiograph

Although specimen imaging should be used for all BCS cases to document excision of the targeted lesion, some investigators have suggested use of specimen radiograph to guide intraoperative re-excision.[44] The excised specimen is oriented by the surgeon in the operating room and then delivered to the pathology suite where orientation is discussed by the pathologist and the surgeon. Specimen radiography of the whole specimen is performed to identify the targeted lesion and biopsy clip. India ink is used to define each of the 6 margins. Some investigators have reported using the whole specimen imaged from various angles to guide intraoperative margin re-excision.[45–49] Many of these studies have demonstrated poor sensitivity for this technique with 1 even reporting higher rates of positive margins with use of intraoperative specimen radiograph.[45–47] Other investigators have reported, however, decreased rates of second surgeries for re-excision of margins.[48,49]

Some investigators have advocated for additional intraoperative specimen processing with specimen radiograph.[50,51] This technique requires serial sectioning of the specimen, followed by placement of the sections on a radiograph plate based on anatomic orientation (**Fig. 4**). In addition to gross examination of the margins, the sections are submitted for specimen radiography. The specimen radiograph of the serially sectioned specimen is examined by the radiologist, pathologist, and surgeon. If tumor or suspicious calcifications are noted at or in close proximity to the margin, the pathologist, radiologist, and surgeon discuss immediate re-excision versus frozen section analysis. One series of patients with DCIS reported that use of this technique eliminated the need for a second surgery for re-excision in 28.4% of patients,[50] although another series, which included those with both invasive and in situ disease, reported that 24.2% of patients avoided a second surgery for re-excision.[51]

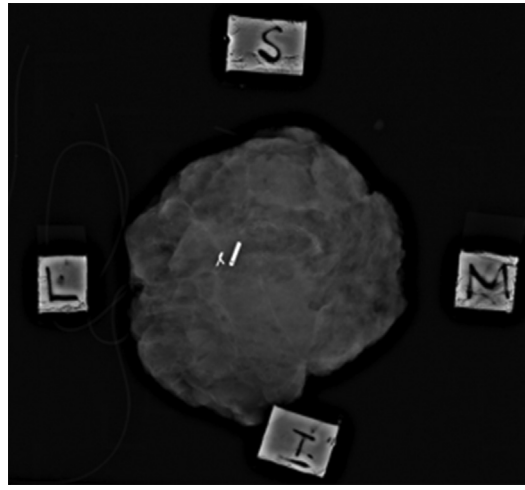


Fig. 4. Radiograph of serially sectioned BCS specimen.

Frozen Section

Intraoperative assessment with frozen section analysis has been described as a method to reduce rates of re-excision. This technique has been described as either excising tissue circumferentially from the lumpectomy specimen or excising tissue from each of the 6 margins of the lumpectomy cavity and submitting these specimens for intraoperative frozen section analysis. A recent systematic review of the literature, which included 37 studies that examined more than 3600 tumors analyzed by intraoperative frozen section, reported a decrease in re-excision rates from 26% to 4% with this technique.[52] Several studies have also demonstrated intraoperative frozen section evaluation to be cost effective.[53,54]

Cavity Shave Margins

Another intraoperative technique used to reduce the number of positive margins is cavity shaving. This technique uses removal of additional circumferential or selected tissue margins after excision of the original specimen. The number of cavity shave margins can vary from 1 (specific margin) to 6 (circumferential). Reported margin widths range from no ink on tumor to 5 mm.[55] Recently, a randomized controlled study showed that cavity shaving reduces the rates of positive margins and the rates of re-excision by up to 50%.[56] This supports previous studies that demonstrated that cavity shaved margins reduced reoperation rates.[57–60] Debate remains, however, on the overall benefit of cavity shaving. Cavity shaving makes it difficult to assess the final width of the lesion and difficult to accurately measure the final margin width. In addition, cavity shaving results in excess tissue removal, which may affect cosmesis.[61]

INVESTIGATIONAL DEVICES

As an alternative to cytology and routine cavity shaving, new intraoperative methods are being investigated, including SAVI SCOUT (Cianna Medical, Aliso Viejo, CA), Magseed (Endomag, Austin, TX), and MarginProbe (DUNE Medical Devices, Alpharetta, GA). For SAVI SCOUT and Magseed, the process is similar to RSL. The device is placed under radiologic guidance and a handheld probe is used to localize the marker intraoperatively. The SAVI SCOUT uses an infrared electromagnetic wave reflector to localize the breast lesion. A recent study shows that SAVI SCOUT is feasible for the localization and removal of breast lesions.[62] Similarly, Magseed sends a reply to the alternating magnetic fields sent from the probe creating an audible and numeric response to guide excision. Magseed can be placed into the breast up to 30 days before surgery still allowing for the uncoupling of radiology and surgery. It is undergoing clinical investigation but has been cleared by the Food and Drug Administraion for segmental mastectomies. Lastly, MarginProbe is a new technology being assessed to help intraoperative evaluation of margins. Based on radiofrequency spectroscopy, it allows intraoperative assessment with a handheld device to identify positive margins. It has been shown to identify positive margins as well as decrease positive margins rates, reducing the need for re-excision.[63,64] It has a specificity up to 70% and a false-negative rate of approximately 25%, however, based on certain studies.[64,65] It has also been found to have a high false-positive rate, which may lead to excess tissue removal.[64]

SUMMARY

Although re-excision rates have varied widely in reports of the literature, national databases have reported a range of 20% to 24%.[8–15] When institutional re-excision rates are noted to be at or above these reported national database averages, consideration

should be given to using 1 or more of these techniques and to tracking the resulting re-excision rates. It is also important to ensure that cosmetic outcomes remain appropriate when steps are taken to reduce re-excision rates for those undergoing BCS.[26]

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