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Evaluation of Margin Status of a Breast Lumpectomy Specimen: What the Radiologist Should Know

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Breast Conserving Therapy (BCS) or lumpectomy has been an established treatment option for women with early-stage invasive breast cancers. Surgical margin status has a significant impact on local recurrence. However, there is much complexity in achieving a negative lumpectomy margin. There are multiple risks and predictors of positive surgical margins that the radiologist needs to be familiar with. When working as a member of a multidisciplinary team, it is important to be cognizant of the pathologist's and surgeon's roles in reducing the number of failed breast conserving surgeries. Despite the common use of imaging to help avoid positive surgical margins, it is important to remember the limitations of standard intraoperative specimen radiographs. A negative resection margin is the goal of BCS ensuring decrease of local recurrence, increased cosmesis, and improved long-term survival.

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Introduction

Breast conserving surgery (BCS) or lumpectomy is established as a standard treatment option for women with early-stage invasive breast cancers. About 60%-70% of newly diagnosed breast cancer is treated with BCS.[1] The goals of BCS are to remove the cancer with negative margins and preserve maximum cosmetic appearance of the breast. Margin status has been shown to predict local disease recurrence. In fact, a positive margin is associated with more than a 2-fold increase in local recurrence.[2] Unfortunately, approximately 1 in 4 women attempting BCS will need to undergo a re-excision due to positive specimen margin.[3,4] Re-excision procedures can potentially produce significant stress for patients and families, result in compromise of desired cosmesis, increase health care costs, and cause a delay of the adjuvant therapies.[5] In addition, re-excision procedures have shown to increase the conversion to mastectomy.[5]

Ensuring a negative lumpectomy margin requires a multidisciplinary approach. The BCS specimen margins first undergo gross inspection and palpation by the surgeon. The specimen imaging is then scrutinized by the radiologist while the patient is still on the operating table. The frozen section is then examined, and touch imprinting is performed by both the surgeon and pathologist. Finally, the specimen section and cytologic analysis are completed by the pathologist. Understanding every team member's role and the predictors of positive surgical margins improves the rate of good breast conserving therapy outcomes.

Surgical Guidelines of a Positive or Adequate Margin

Controversy has existed in the past regarding the optimal margin width in breast-conserving surgery for breast cancer. Today, the accepted guideline specifically for ductal carcinoma in situ (DCIS) is 2 mm as an optimal margin. For invasive breast cancer, the current guideline endorses no ink on the tumor.[6]

In the 2014 consensus guideline endorsed by Society of Surgical Oncology, the American Society of Breast Surgeons, and the American Society for Radiation Oncology,[7] a positive surgical margin is associated with a 2-fold increase in the risk of ipsilateral breast tumor recurrence (IBTR). They determined that more widely clear margins do not significantly decrease the rate of IBTR compared with no ink on the tumor. The consensus guideline emphasized adequate margin without ink on tumor as the standard is associated with low rates of IBTR and has the potential to decrease re-excision rates, improve cosmetic outcomes, and decrease health care costs.

How the Breast Surgeon Examines and Documents the Specimen

Documentation and correct labeling of the surgical specimen by the surgeon are essential to allow the pathologist to accurately evaluate resection margins and correlate gross findings with patient medical history.[8]

The surgeon can estimate the specimen gross margins by gross inspection and palpation.[9] Unfortunately, most early breast cancers are not palpable and need wire or seed localization before surgery (Fig 1A).[8] Intraoperative specimen radiography is often performed to identify the presence, location, number, and dimension of lesions (mass, wire, calcification, and biopsy clip) by close communication with radiologists (Fig 1B).

Other intraoperative techniques include routine resection of cavity shave margins, or additional tissue circumferentially around the cavity left by lumpectomy. This surgical technique has been shown to halve the rates of positive margins and re-excision among patients with lumpectomy.[10] Another method used in the operating room is a

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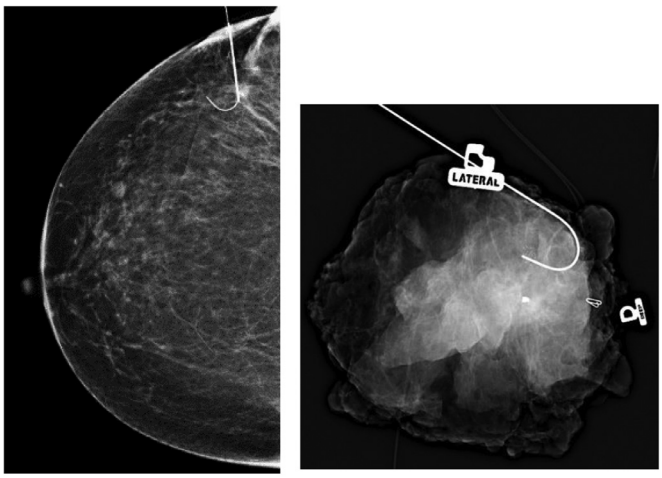

FIG 1. How the radiologist examines the specimen. (A) A radiograph demonstrating preoperative needle localization. (B) Example of an intraoperative specimen radiograph.

device that uses radio-frequency electrical fields to probe the tissue to identify any cancer that may be remaining on the surface of the tissue removed from the breast. This allows the surgeon to identify positive margins in real-time on the lumpectomy specimen to remove additional tissue from the breast at the time of surgery.[11] Cavity-shave margins and the radio-frequency electrical device both have demonstrated lower rates of positive margins but these have some potential for negative cosmetic effects.[12]

It is necessary that the specimen be submitted with appropriate clinical history and specification of anatomic site and the type of surgical specimen (total mastectomy, lumpectomy, etc.).[8] The surgeon should also accurately orient the specimen (eg, superior, inferior, medial, and lateral) with markers or sutures[8] (Fig 2A-C). The surgeon must clearly indicate any uncertainty. This will ensure precise guidance from the pathologist to the surgeon for re-excisions of additional tissue, which is crucial to achieve negative margins. Improved oncologic and prognostic outcome can then be achieved as the pathologist is then able to notify the surgeon in the event there is a positive surgical margin and additional tissue needs to be excised. This also leads to improved cosmesis as only necessary tissue is removed to achieve negative margins.

How the Pathologist Examines the Specimen

Intraoperative pathologic methods to reduce positive surgical margins include the use of permanent histopathologic section, frozen section analysis (FSA), and imprint cytology. FSA consists of freezing and sectioning the sample followed by thawing, fixation, and staining which takes about 30 minutes. Reports indicate that FSA may cause artifacts in the fatty tissue and possible tissue loss because of the process of freezing and thawing.[13] Imprint cytology is a simple and rapid method that takes about 15 minutes to provide a diagnosis. In this technique, the excised mass is oriented and pressed onto glass slides making an imprint of all 6 margins, which are then fixed and stained. The cellular surface characteristics will only allow malignant cells to adhere to the slides whereas adipose cells will not.[14] Patients who underwent BCS with intraoperative imprint cytology or FSA to assess negative surgical margins were found to have significantly fewer secondary surgical procedures for excision of their breast malignancies as opposed to permanent histopathologic section.[14]

After excision, the specimen needs to be delivered to the pathology laboratory intact, promptly, and unfixed. The size of a BCS specimen is then recorded in 3 dimensions, and the general shape (eg, ovoid, spherical) is then described. Irregular, uneven surfaces containing defects or crevices can complicate the microscopic evaluation of margins.[15] It is necessary to mark surfaces corresponding to the margins so that they can be identified microscopically. One widely practiced approach to evaluating margins histologically employs samples taken perpendicular to each of 6 inked surfaces (superior, inferior, medial, lateral, superficial, and deep), with additional samples of margins determined by the gross findings.[15] The pathologist performs the sampling of the lumpectomy specimen in a methodical approach each time to ensure diagnostic accuracy (Fig 3).

Unfortunately, the presence of negative lumpectomy margins does not provide complete assurance that all carcinoma in the region of the primary site was removed. However, negative specimen margin can predict the low likelihood of a large residual tumor burden in a patient and therefore, ensure that patient is a suitable candidate for BCT without further surgery.

Factors that Predict an Increased Risk of a Positive Surgical Margin

There are multiple variables that have been shown to be significantly associated with an increased risk of positive surgical margins. In one study, these factors included larger tumor size, high tumor grade, lymphovascular invasion, and presence of DCIS or lobular features.[16] As illustrated in our cases (Fig. 4 and 5), the extent of DCIS and lobular feature are often very difficult to define with mammogram or ultrasound, which likely accounts for the high risk of positive margins.

In another study, a 20% positive tumor margin rate was observed for nonpalpable breast malignancies that require preoperative needle localization.[17] The variables associated with a positive resection margin in this study included presence of multifocal disease and inadequate localizations performed under mammographic guidance.[17,18] Figure 6 demonstrates how inadequate mammography guided needle

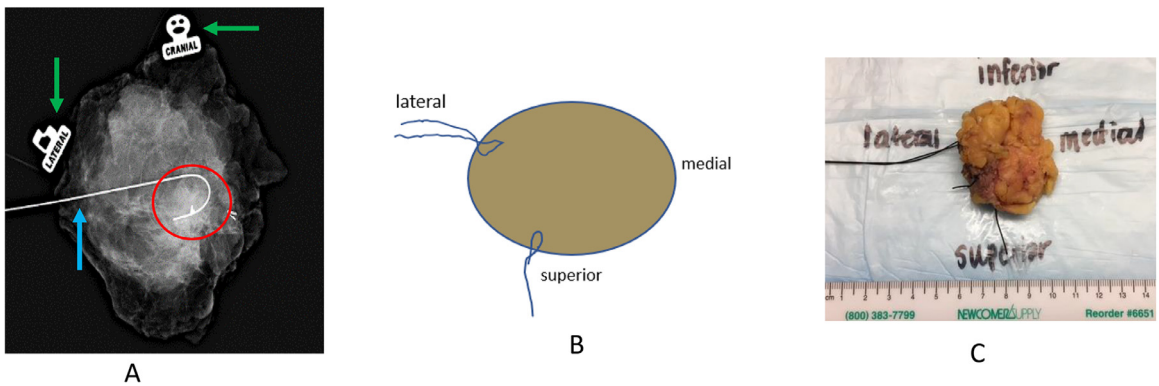

FIG 2. How the surgeon labels the specimen for the radiologist and pathologist. (A) Specimen radiography for the radiologist showing lateral and cranial markers for specimen orientation (green arrows), the mass with calcification (red circle), and the wire (blue arrow). (B) Illustration and (C) gross specimen demonstrating labeling with sutures for the pathologist for orientation. The single/short stitch corresponds to the superior margin while the double/long stich corresponds to the lateral margin. (Color version of figure is available online.)

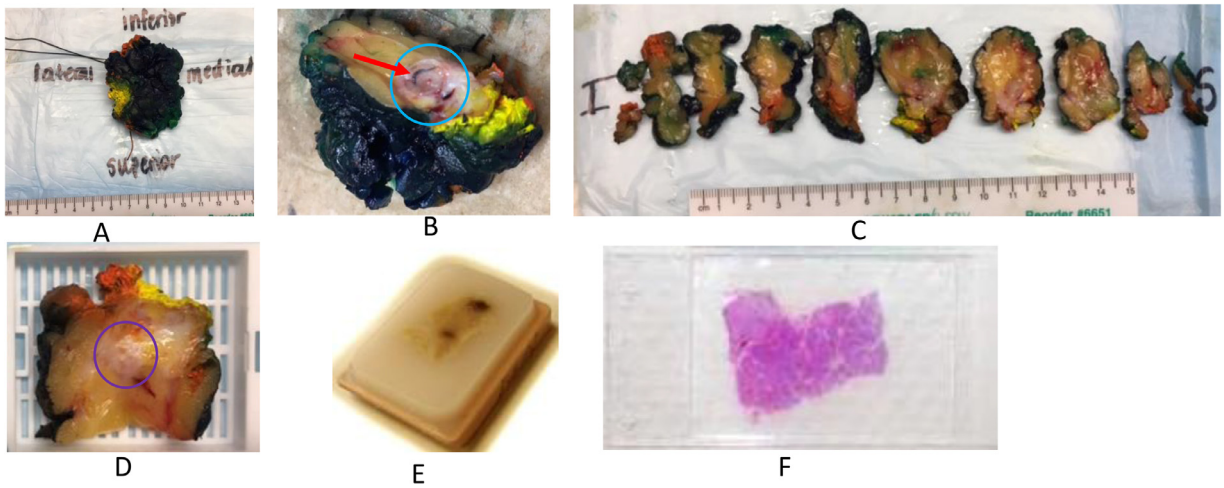

FIG 3. Orientation and sampling of a lumpectomy specimen in the pathology lab. (A) The gross specimen is inked corresponding to the sutures. Blue ink (short stitch) is the superior margin. Black is the inferior margin. Red is the anterior margin. (B) The gross specimen seen with the mass (blue circle) and biopsy clip (red arrow). (C) The gross specimens sliced in 4 mm thickness and ordered from inferior (I) to superior (S). (D) The specimen with the tumor (purple circle) is placed into a cassette for fixation anywhere from 6 to 72 hours. (E) Example of a paraffin embedded tissue block. (F) The specimen is then sectioned and mounted onto microscopic slides for analysis. (Color version of figure is available online.)

localization failed to guide the surgeon to excise the cancer. Multifocal disease is sometimes challenging to visualize on either mammogram or breast ultrasound and is associated with high risk for positive margins (Fig. 5 and 7). Breast magnetic resonance imaging is more sensitive in detection of additional lesion before surgery and defines the residual tumor in case of positive margin (Fig 7).

In addition to the tumor and imaging factors, histopathologic pitfalls including cautery artifact of the lumpectomy specimen also cause difficulty with interpretation of margins in the lumpectomy specimen (Fig 5).[19]

Conversely, previous studies have demonstrated that technical factors that can predict a negative margin include clear margins on specimen films, cavity margin dissection, and larger volumes of excision.[17]

Methods to Reduce Positive Margins

There are multiple techniques that can be utilized to reduce positive surgical margins. Preoperative multimodality imaging and mapping for adequate quantification of disease extent can be beneficial.[20] Mammogram is good for detection of cancer that is associated with calcifications and ultrasound is better for patients with dense breasts. MRI has been shown to detect additional disease in 16% of patients.[21] In addition, preoperative breast MRI has been shown to decrease the rate of positive margins and re-excision rates in women with early breast cancer.[22] However, controversy about preoperative breast MRI utilization does exist because of conflicting results on its effects on the long-term outcomes.

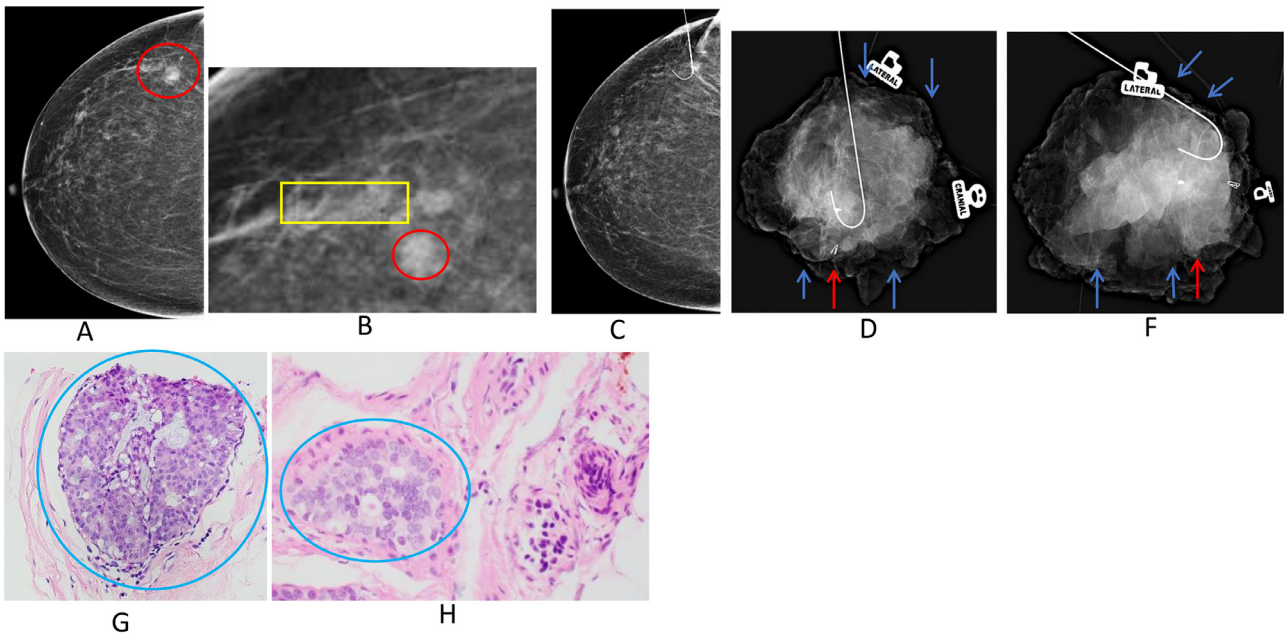

FIG 4. High grade DCIS and microcalcifications as risk factors for positive margins. (A) craniocaudal and (B) magnetization views demonstrate a 6 mm mass (red circle) and 9 mm adjacent microcalcifications (yellow rectangle) on mammogram. (C) Mammogram demonstrating needle localization. (D) and (E) Two orthogonal lumpectomy specimen radiograph. The pin clip from the initial biopsy demonstrated benign breast tissue. The hat clip from the repeat biopsy demonstrated invasive ductal carcinoma. The blue arrows show the histologically positive margin while the red arrows correspond to the suspicious radiographic margins. The lateral margin that appears negative on specimen radiography was histologically positive for DCIS. (F) and (G) Photomicrographs showing DCIS (blue circles) in the medial and lateral margins *enface*, deemed as positive margins. DCIS, ductal carcinoma in situ. (Color version of figure is available online.)

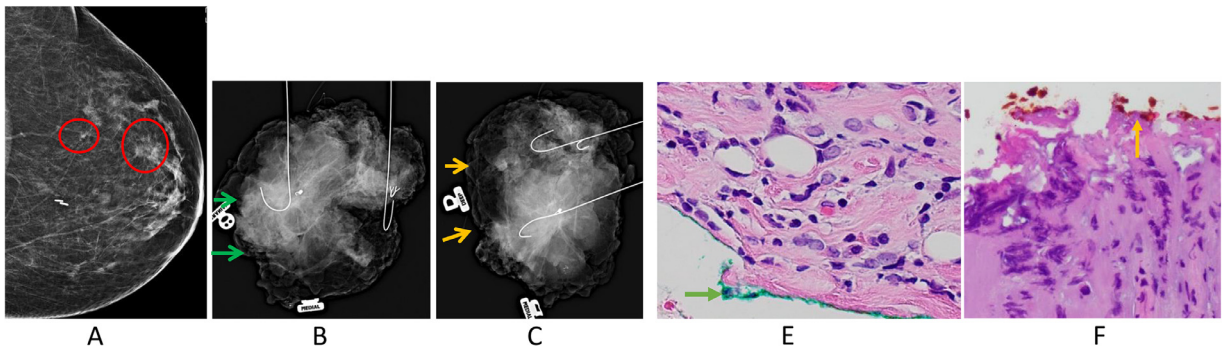

FIG 5. Invasive lobular carcinoma (ILC) and multifocal and large tumor size as risk factors for positive margins. (A) Craniocaudal view demonstrates a 12 mm mass (anterior) and a 5 mm mass (posterior) at 3 o' clock left breast (B, C) Specimen radiographs show superior (green arrows) and posterior (orange arrow) margins that are focally histologically positive for ILC. (D) Photomicrograph shows ILC on the inked superior margin (green arrow). (E) Photomicrograph demonstrates ILC on the inked and cauterized posterior margins (orange arrows). (Color version of figure is available online.)

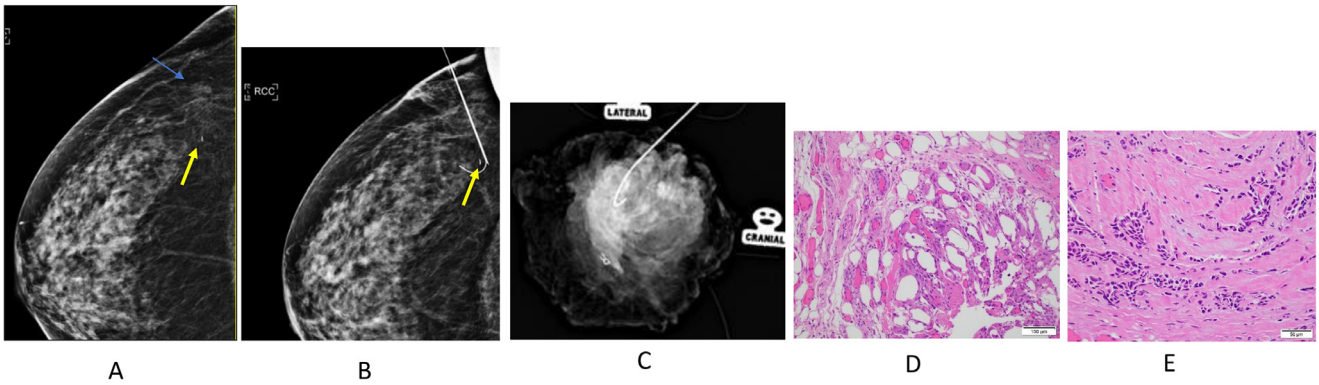

FIG 6. Inadequate needle localization as a risk factor for positive margin (A) Post-biopsy mammogram demonstrate a small 5 mm mass (ILC, blue arrow) with medially displaced ribbon biopsy clip (yellow arrow). (B) Clip displacement was overlooked and clip instead of the cancer was targeted for needle localization (yellow arrow). (C) Intraoperative specimen radiograph show a 4.5 cm specimen with clip and wire without the mass. Additional superior tissue was removed due to the uncertain clip migration. (D) Photomicrograph of the primary 4.5 cm specimen showed biopsy changes without tumor. (E) Photomicrograph of the additional tissue shows 5 mm ILC. (Color version of figure is available online.)

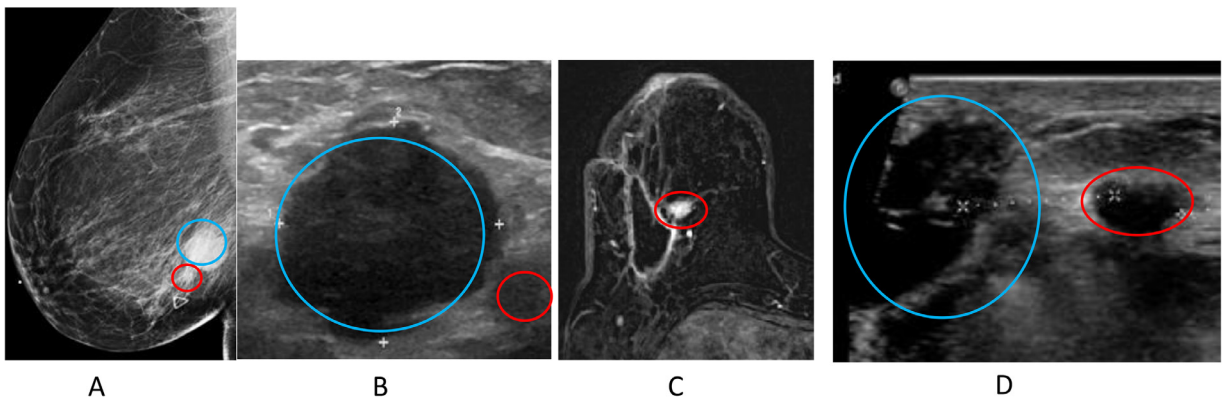

FIG 7. Multifocal disease with positive margin and MRI detected more cancer for re-excision. (A) Mammogram (B) ultrasound show a 2 cm mass (triple negative medullary carcinoma). The satellite lesion (red circle) was overlooked on both modalities.(C) MRI demonstrates a satellite mass (red circle) after re-excisional surgeries for positive margins.(D) Subsequent second look ultrasound shows a 14 mm correlate (red circle) close to the lumpectomy bed (blue circle). Repeat biopsy of the satellite lesion was found to be invasive ductal carcinoma. (Color version of figure is available online.)

Neo-adjuvant therapy can also be used to shrink the primary tumor prior to surgery. Studies have shown that neoadjuvant chemotherapy can downstage breast cancer in patients and increase the rate of breast-conserving surgery.[23] In fact, patients that undergo breast-conservation after neoadjuvant therapy have better survival than patients undergoing mastectomy without radiation.[23]

Other methods to reduce positive margins include intraoperative specimen assessment with frozen section.[12] Use of frozen section of the specimen margins during the surgery with shaving of additional margins about the specimen at the closest aspects grossly or on all 6 surfaces can increase the likelihood of negative margins. It has also been shown that removing 3-5 mm of normal breast about the margin of T1-2 tumor may be beneficial.[20] Thorough examinations of the in situ walls of the remaining breast and careful orientation of the specimen margins after the primary excision are also associated with a higher rate of negative margins.[20]

In addition, localization techniques also affect the margin status. Ultrasound-guided lumpectomy for palpable tumors, can lower

positive margin rates, when compared to palpation guidance.[12] In multiple smaller studies, localization techniques such as radioactive seed localization and radio-guided occult lesion localization were found to lower positive margin rates.[12] However, with both radioactive seed localization and radio-guided occult lesion localization, the largest randomized trials did not show a difference with wire localization for rate of positive margins.[12] Although bracketing wires can assist the surgeon in achieving complete excision of calcifications, the bracketing technique has not been shown to ensure clear histologic margins of resection.[24]

Limitations of Radiographs in Margin Evaluation

Intraoperative 2 orthogonal radiograph views of the specimen are most commonly used to evaluate the specimen margins.[25] This intraoperative mammogram is convenient, easy, and cost-effective, and several studies have demonstrated that intraoperative margin assessment using x-ray image of the surgical specimen has been useful.[26]

However, there has been concern that radiologic assessment alone is insufficient for accurate evaluation of margin status. One study demonstrated that margins that appear negative on specimen radiography were shown to be histologically positive in up to 44% of cases.[27] One of the main downsides to a radiograph is that 2-dimensional radiography is used to evaluate a 3-dimensional specimen leading to underestimation of the true size of the lesion.[28] In addition, radiographs can only detect a mammographic abnormality as opposed to sonographic abnormalities.

New technologies have been devised to assist in specimen assessment during surgery. Intraoperative Optical Coherence Tomography is an evolving high-resolution imaging technique involving real-time ex-vivo microscopic images up to 2 mm beneath the tissue surface. In an initial analysis the method demonstrated a sensitivity of 100% and a specificity of 82% in evaluating disease at margins.[15] Micro-CT is another technique to rapidly assess breast tumor size in 3 dimensions in intact lumpectomy specimens providing quantitative imaging parameters, image rotation, and virtual “slicing.”[29] This real-time analysis of tumor location in breast lumpectomy specimens or shaved cavity margins has shown promise in guiding surgical excision.[29] Tomosynthesis is an emerging technique that has been used in clinic to evaluate the specimen margins. Studies have showed that tomosynthesis is superior to conventional 2 dimensional mammogram in evaluation of the specimen margins.[30]

Conclusions

The breast surgeons, pathologists, and radiologists all play very important roles in achieving the negative margin of BCS to prevent tumor recurrence. Positive margins of a lumpectomy are associated with multiple tumor and technical factors. There is limitation of the current specimen mammography. Familiarity with the complexity of this process will further advance the radiologist's role in achieving a negative lumpectomy specimen margin through a multidisciplinary approach.

Disclosures

Author Karen Tran-Harding declares that he/she has no conflict of interest, grants, disclosures, or other assistance.

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IRB Statement

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Supplementary materials

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