THE AMERICAN SOCIETY OF Breast Surgeons

Resource Guide

Breast Cancer Breast Conservation Surgery Margins

Purpose

To provide guidance for re-excision surgery after breast conservation (lumpectomy/ partial mastectomy/wide local excision) for breast cancer (invasive and in-situ).

Methods

Literature review inclusive of meta-analyses evaluating the impact of margin status on local recurrence rates, randomized controlled trials on rates of margin re-excision with technique, and large-sample retrospective reviews of data associated with margin re-excision. This is not a complete systematic review but a comprehensive review of the modern literature on this subject, which was completed in October 2023. The American Society of Breast Surgeons (ASBrS) Research Committee developed a consensus document which was reviewed and approved by the ASBrS Board of Directors.

Approval

Please see list of Authors and Disclosures at the end of the statement. This resource guide was developed under the direction of and approved by the ASBrS Board of Directors.

Recommendations

Tumor Margin Width	Breast Conservation Surgery‡ for	
	Invasive Cancer† **(with or without DCIS*)**	**DCIS*** **(with or without microinvasion)**
≥ 2 mm	Re-excision is **not** recommended if undergoing radiation therapy (type to be determined by radiation oncologist) Document reason if re-excision is performed	Re-excision is **not** recommended if undergoing radiation therapy (type to be determined by radiation oncologist) and other recommended adjuvant therapies as indicated Document reason if re-excision is performed
< 2 mm, no tumor on ink	Re-excision is **not** recommended May consider re-excision on a case-by-case basis, depending on number of margins with close disease, extent of disease close to margin, location of close margin, and plan for adjuvant radiation and type of radiation therapy Document reason if re- excision is performed	**Re-excision is recommended** Multi-disciplinary discussion should be performed if re-excision is not performed and Document reason in the patient's record
Tumor on Ink	**Re-excision is recommended** Multi-disciplinary discussion should be performed if re-excision is not performed and Document reason if re- excision is not performed in the patient's record	**Re-excision is recommended** Multi-disciplinary discussion should be performed if re-excision is not performed and Document reason if re- excision is not performed in the patient's record
Atypical Hyperplasia or Classic LCIS at the margin or close to a margin	Should not guide decision to re-excise	Should not guide decision to re-excise

‡Recommendations for adequate margins for both invasive cancer and DCIS apply to patients receiving whole breast radiation following breast conserving surgery. *Recommendations for DCIS apply only to pure DCIS or DCIS with microinvasion. Patients who have an invasive cancer >1 mm in size and with an intraductal component should be treated based on the invasive cancer recommendations. Specifically, a margin <2 mm for the DCIS component in a specimen also containing invasive cancer is within guideline recommendations. †Recommendations apply to invasive carcinoma both in the upfront surgery setting and following neoadjuvant chemotherapy.

Summary of Data Reviewed

Margin status

The presence or absence of malignant cells on the edge or close to the edge of a partial mastectomy specimen describes the surgical margin status. This margin status is a surrogate marker of residual disease in the breast and impacts patient risk of ipsilateral breast tumor recurrence (IBTR). There is significant variation in margin definitions, positive margin rates, and re-excision lumpectomy rates (RELR) in patients undergoing breast conserving surgery (BCS).[1-14] Surgeon opinion of a negative margin has historically ranged from "ink negative" to greater than 1 cm, providing one potential explanation for variation in surgical re-excision rates.[1-4,8-10,12,14-16] Consensus margin guidelines were published by the Society of Surgical Oncology and the American Society for Radiation Oncology (SSO/ASTRO) in 2013 for invasive carcinoma[17] and in 2016 by SSO, ASTRO, and the American Society of Clinical Oncology (ASCO) for DCIS.[18]A meta-analysis demonstrated that, after publication of these guidelines, the RELR declined from 22% to 14%.[19]

Surgical specimen orientation

Indeterminate, high-risk, or confirmed breast cancer tissue specimens should have margins oriented intraoperatively by the surgeon, and orientation labelling clearly communicated to pathology and radiology.[20-23] After the surgeon orients the specimen, the surgeon or pathologist should ink the 6 margins of the excised specimen. The operative report should document whether the fascia was removed from the muscle. The removal of any skin should also be noted. Nonpalpable, image-detected lesions require radiographic confirmation of their removal by specimen imaging.[21-24] Specimen imaging findings should be communicated intraoperatively to the surgeon and should also be available for the pathologist. The pathologist should document grossly and microscopically the orientation, distance, and extent of involvement of both the invasive and in situ components for each specific margin, compliant with the College of American Pathologists breast cancer reporting protocol.[25]

Tools and techniques to aide in limiting margin positivity

Multiple techniques exist to reduce the chance of microscopically positive BCS margins. In 2015, the American Society of Breast Surgeons (ASBrS) held a multidisciplinary consensus conference entitled a "Collaborative Attempt to Lower Lumpectomy Reoperation Rates" (CALLER) and created a "toolbox".[23] An updated literature review in 2018 found continued evidence supporting the recommendations in the CALLER Toolbox.[26] Potential strategies to employ include wireless localization, specimen imaging/x-ray/tomosynthesis, routine shave

margins, and surgeon specimen orientation/inking. Emerging technologies for intraoperative margin assessment (e.g. fluorescence, radiography, advanced microscopy, bio-impedance, and mass spectrometry), are undergoing feasibility and accuracy evaluation.[27] These technologies should ideally not add too much time to the surgery and should provide cost savings and improved efficacy compared with presently available technologies.[27]

Positive margins

Patients with invasive or in situ breast carcinoma with histologic positive margins (ink-positive) after BCS have increased IBTR compared with patients with negative margins.[1,6,7,9,10,28,29] IBTR and local regional recurrence (LRR) after BCS for invasive cancer can influence patient survival. The Early Breast Cancer Trialists Collaborative Group concluded that 1 life is saved at 15-year follow-up for every 4 local recurrences prevented at 10 years after lumpectomy.[30] A meta-analysis of 68 studies with a total of 112,140 patients showed that positive, on-ink margins are associated with higher rates of distant recurrence, even after adjustment for adjuvant therapies.[29] Re-excision to achieve negative margins therefore should be performed in most patients with ink-positive margins. However, many factors, including patient age, co-morbidities, life expectancy, extent of excision, extent of margin involvement, tumor characteristics, and expected adjuvant therapies, should be considered before proceeding with re-excision. Re-excision may not be necessary for involved posterior margins if underlying muscle fascia has been removed and no gross disease was appreciated at time of surgery. Re-excision of an involved anterior margin may not be necessary if there is no residual breast parenchyma and re-excision would involve only resection of skin, as this has low-yield for identification of any residual disease.[31-33] If re-excision is not performed for a positive margin, the reason should be documented in the medical record.

Negative and "close" margins

Invasive carcinoma (with or without DCIS)

Because there has historically been disagreement regarding adequate margin width, practices vary among surgeons, pathologists, and radiation oncologists.[2,3,8,9,12,14] In the 1970s, the National Surgical Adjuvant Breast and Bowel Project B-06 study defined a negative margin as no tumor cells found on the inked edge of a surgical specimen.[34] In a meta-analysis, the effect of margin status and margin distance on IBTR in patients with early-stage invasive breast cancer was evaluated in 21 studies and identified 1026 local recurrences in 14,571 patients. The odds ratio for recurrence was 2.42 (P <.001) for positive versus negative margins. Greater radial width of a negative margin (1 mm compared with wider margins) had borderline significance for lowering local recurrence risk, but no significance when adjusted for

radiation boost or endocrine therapy.[6]

Based on these and SSO/ASTRO meta-analysis data, the SSO/ASTRO guideline (endorsed by ASCO[35]) and current National Comprehensive Cancer Network (NCCN) guidelines use "no ink on the tumor" to define a negative margin for invasive breast cancer treated with BCS with whole breast radiation.[15,35] Patients who have an invasive cancer >1 mm in size and with an intraductal component should be treated based on the invasive cancer recommendations. Specifically, a margin <2 mm but not on ink for the DCIS component in a specimen containing invasive cancer is guideline concordant. Since publication of the SSO/ASTRO guideline, there has been improved consistency in the reporting of lumpectomy margins and surgical management.[19,36]

DCIS (with or without microinvasion)

A meta-analysis from trials evaluating BCS and radiation therapy for DCIS in 4,660 patients concluded that a 2 mm margin was not associated with decreased IBTR compared with >2 mm.[7] Based on these data, recent SSO/ASTRO/ASCO consensus and current NCCN guidelines recommend that margins for pure DCIS (or DCIS with microinvasion) treated with BCS and radiation should be at least 2 mm.[15,18,30] Decreased rate of 10-year IBTR with >2mm margin after BCS for DCIS has been confirmed since publication of these guidelines, including recently by the PRECISION international cohort of 32,638 women underwent BCS for DCIS.[37] The study demonstrated a 10-year ipsilateral invasive recurrence in 5.8% of patients with <2mm margins versus 3.9% with ≥2mm margins (p=0.02). Ipsilateral DCIS recurrence occurred in 4.5% of those with <2mm margins versus 2.5% with ≥2mm margins (p=0.03). Of note, adherence to the 2 mm guideline for DCIS (in BCS with WBRT) seeks to minimize the risk of local recurrence but there is no evidence for survival improvement.[18]

Once a 2mm margin is obtained, there is insufficient evidence to support re-excision of DCIS to obtain a margin wider than 2 mm in patients receiving radiation therapy. In patients not receiving adjuvant radiation after BCS for DCIS, there are retrospective data which demonstrate that the local recurrence rate is lower with margins greater than 2 mm,[38] but no current guidelines exist for the appropriate margin status if adjuvant radiation therapy is omitted.[39]

Exceptions to margin guidelines

If re-excision is performed outside these guidelines, the reason should be documented in the medical record.[9] Justifiable reasons could include but are not limited to (1) residual adjacent malignant-appearing calcifications identified on post-lumpectomy mammography, (2) an ink-negative margin but proximate "large" volume cancer involvement within 1-2 mm of the margin, and (3) fragmented

lumpectomy specimens, causing uncertainty of margin status. Additional consideration for re-excision outside these guidelines may also be necessary after multi-disciplinary discussion in patients undergoing accelerated partial breast irradiation (APBI); the current ASTRO APBI guidelines recommend negative surgical margins, defined as "no tumor on ink," although there are no randomized controlled trials evaluating margin status for APBI.[40]

For individuals over the age of 65 undergoing breast conservation for an invasive cancer; clinical trials (CALGB 9343 and PRIME II) have indicated that radiation therapy may not be recommended after surgery. For these two trials the margin recommendations were either no tumor on ink (CALGB 9343) or ≥ 1mm (PRIME II). If the individual will not undergo radiation therapy it is recommended that the treating surgeon consider margins at least 1mm or discussion at multi-disciplinary conference.

Breast conservation after neoadjuvant chemotherapy

Margin status for BCS following neoadjuvant chemotherapy has been controversial due to concern that some patients have multifocal residual disease; these patients have worse rates of IBTR compared with those with a solitary residual mass or a pathologic complete response.[41] However, multiple large retrospective cohort studies have shown no difference in rates of local recurrence by margin status following neoadjuvant chemotherapy.[41-45] In a retrospective study of 582 patients who underwent BCS after neoadjuvant chemotherapy, rate of 4-year IBTR was 2% in those with a >2 mm margin and 3% in those with a ≤2 mm margin, despite there being a higher rate of multifocal residual disease in the ≤2 mm margin cohort (59% versus 37% of those with >2 mm margins), and 73% of those in the ≤2 mm cohort having a final margin ≤1 mm.[43] These data support using the SSO/ASTRO Consensus Guideline of "no tumor on ink" for invasive carcinoma as an acceptable margin for BCS following neoadjuvant chemotherapy.

Management of atypical hyperplasia and lobular carcinoma in situ margins with concurrent breast cancer

In the setting of invasive breast cancer or DCIS, there continues to be significant variability in management of concurrent atypical ductal or lobular hyperplasia (ADH/ALH) and lobular carcinoma in situ (LCIS) at the BCS margin.[46] However, recent retrospective cohort studies provide guidance.

Atypical hyperplasia (ADH/ALH)

Although there are data demonstrating that ADH at a lumpectomy margin in the setting of early stage breast cancer is associated with residual ADH and sometimes DCIS,[47] multiple studies have shown that ADH at the lumpectomy margin does not

impact IBTR.[48-50] In a retrospective study of 391 patients with stage 0-II breast cancer who underwent BCS and radiation, 233 had either ADH/ALH at the lumpectomy margin but at 5- and 8-year follow-up had equivalent rates of local recurrence to those without ADH/ALH at the lumpectomy margin.[48] Based on these data, the decision to re-excise after a lumpectomy should be based on the margin status of the invasive cancer or DCIS and not the presence of ADH or ALH at or close to a margin.

Classic lobular carcinoma in situ (LCIS)

While there are no meta-analyses evaluating the impact of LCIS at a lumpectomy margin on recurrence in the setting of invasive cancer or DCIS, there are multiple retrospective, single institution studies with follow-up of at least 5 years that have shown that a positive or close margin with classic LCIS does not increase local recurrence risk.[51,52] Based on these data, the decision to re-excise should be based on the margin status of the invasive cancer or DCIS and not the presence of classic LCIS at or close to a margin.

Non-classic lobular carcinoma in situ

Management of non-classic subtypes of LCIS (including pleomorphic and florid LCIS) at the lumpectomy margin remains controversial. Small retrospective studies with heterogenous patient cohorts show that there may be an association between local recurrence and non-classic LCIS close to a BCS margin.[53,54] Recently a large retrospective single institution study of 511 patients with concurrent non-classic LCIS and stage 0-III breast cancer demonstrated that non-classic LCIS margin status was not associated with risk of local recurrence, although median follow up was relatively short at 3.4 years (interquartile range 2.0-5.9 years).[55] These data are encouraging that re-excision of a lumpectomy margin based on non-classic LCIS at or close to a margin is not necessary, although longer follow-up is needed. Currently, neither the NCCN nor other expert consensus panels have felt these data were sufficient to provide formal recommendations on non-classic LCIS margin status.[15,56]

Using re-excision lumpectomy rate a measure of quality

The use of margin status and RELR as a quality measure is controversial and the ASBrS advises caution.[4,9,13,14] RELR ranges from 0% to 70% (by individual surgeon) in the United States.[4] Recent publications also document wide variability in Canada (17-56% by province) and England (12%-30% [tenth to ninetieth percentiles] by National Health Service trust).[13,14] The European Society of Breast Cancer Specialists, the National Consortium of Breast Centers, and multiple institutions use RELR as a quality measure.[4,57-61] Arguments against using RELR as a quality measure include (1) lack of evidence defining the minimum or optimal quality

threshold for RELR, and (2) concern that unintended adverse consequences may occur if the importance of RELR is over-emphasized. For example, surgeons may demonstrate "risk aversion," changing their criteria for BCS eligibility in patients at high risk for positive margins, increasing mastectomy rates in their effort to lower RELR. Surgeons may also increase their excised lumpectomy volume, worsening cosmesis. Despite these concerns, RELR as a quality measure is already in use.[4,57-61] If RELR is used as a quality measure tool, then it should be incorporated into a program that measures other aspects of BCS quality, such as cosmetic outcome, patient satisfaction, IBTR, and breast conserving therapy rate, and incorporates tools and approaches to reduce the re-excision rate by a breast program and individual surgeons.[14,60-62] International variability of RELR deserves investigation, but RELR should not be used as the singular determinant of the quality of BCS.

The resource guide was reviewed by the Research Committee and approved by the Board of Directors on June 26, 2024.

Lead Authors: Anna C. Beck, MD (no relevant author disclosures) and Lee G. Wilke, MD (Elucent Medical – minority stock owner and founder)

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