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REVIEW

Surgical margins in breast conservation

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ABSTRACT

Breast cancer is the most common tumor affecting women worldwide. Breast-conserving therapy (BCT) followed by irradiation nowadays is the treatment of choice for early-stage disease; there is no difference in long-term survival between mastectomy and BCT combined with external radiotherapy. A positive margin is associated with increased risk of local recurrences after BCT for invasive breast cancer and ductal carcinoma in situ. The exact definition of an adequate surgical margin after breast cancer resection has long been debated among physicians and represents an area of considerable variation in clinical practice. There is a lack of standardization in the pathology methods of margin evaluation, which yields little consensus regarding what constitutes an adequate negative margin. As a consequence, patient management varies widely based on the threshold that surgeons accept for adequate margins and the subsequent need for re-excision. We analyze and discuss recent literature about this topic both from the pathological and from the surgical point of view.

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1. Introduction

Breast cancer is the most common tumor affecting women worldwide; in Italy about 41,000 new breast cancers are diagnosed yearly.¹ The adoption of screening mammography has led to the identification of smaller, often non-palpable, tumors that can be treated with breast-conserving surgical approaches as opposed to mastectomy.^{2–4} Breast-conserving therapy (BCT) followed by irradiation nowadays is the treatment of choice for early-stage disease; there is no difference in long-term survival (more than 20 years) between mastectomy and BCT combined with external radiotherapy.^{5,6} The main goal of BCT is the complete removal of cancer with clear surgical margins while maintaining the natural shape of the breast. The principal risk with the conservative option is local recurrence, ranging between 0.6% and 1.5% per year, and is directly related to the presence of residual tumor in the remaining mammary gland, since isolated local recurrence (i.e. without systemic metastases) is mainly observed in the first 2–3 years after surgery.⁷ Re-excision is a possible further procedure in women undergoing BCT in order to obtain negative margins in patients with initial positive margins. Recent reports have shown that oncoplastic surgery (OPS) was effective in reducing re-excision rate for positive margins in invasive ductal carcinoma (IDC) and ductal carcinoma in situ (DCIS).^{8,9} OPS is defined by the combination of surgical oncology principles with plastic surgery techniques, allowing

larger excision of breast tissue compared to standard BCT for the treatment of patients with DCIS and IDC.

The status of the surgical margins is assessed by applying ink to the surface of the lumpectomy specimen and determining the microscopic distance between tumor cells and the inked surface. The exact definition of an adequate surgical margin after breast cancer resection has long been debated among physicians and represents an area of considerable variation in clinical practice.^{10–12}

2. Pathological evaluation

There is no standard method of margin evaluation for breast specimens and there is no standard number of histologic sections examined from each margin surface. Margins can be evaluated (a) by a radial method, (b) by a shaved method, or (c) by shaving the walls of the lumpectomy cavity.

a. The most common method of margin assessment is the radial (or perpendicular) margin technique, which allows for a precise measurement of the distance from the tumor to the inked margin. With this method the specimen is received with at least two of the margins marked with metal clips or sutures for specimen orientation. The six margins of the specimen are then inked in six different colors by the prosector. The inked breast tissue is cut into 0.2–0.3 cm sequential sections perpendicular to its long axis so

that the perimeter of each tissue section contains few (two to four) margins identified by the different ink colors. With this technique the pathologist can report the exact microscopic distance from the tumor to each margin and can distinguish between a truly positive margin (tumor at ink) and a close margin. The disadvantages of this method include running ink, imprecise margin orientation and surface complexity of the breast specimen.

- b. The use of shaved (*en face*) margins allows the oriented specimen to be inked entirely in one color, as long as the prosector is able to maintain the proper orientation, and eliminates the problem of different color inks running together. The margins are shaved off parallel to the surface of the inked specimen at a tissue depth of 0.2–0.3 cm, similar to the process of peeling an orange. The sections are then embedded *en face* with the inked surface facing down so that the microscopic examination starts from the inner aspect of the breast specimen. With this technique a margin is reported as positive when tumor is present anywhere in the section, which means that malignant cells may be present within a 0.2–0.3 cm radius from the margin or at the margin, but the exact distance of the tumor to the margin cannot be evaluated by the pathologist. If no tumor is identified, the margin is reported as negative. The advantages of this method include easier and faster microscopic examination, no occurrence of ink problems and the examination of a larger portion of the specimen's surface with relatively few histologic sections. The disadvantage is that this technique is extremely problematic for surgeons since it increases the number of margins called positive.
- c. The third method, shaving the walls of the lumpectomy cavity, provides a nice solution to margin evaluation and combines the advantages of the radial and *en face* margin assessments: the surgeon resects the index lesion and then takes separate shaved margins from the cavity. The main breast specimen containing the tumor is received unoriented and does not need to be inked. Each shaved specimen represents a margin (medial, lateral, superior, inferior and posterior walls of the cavity) and is received oriented with a suture or metal clip designating the final surgical margin. The anterior margin may or may not be submitted by the surgeon. This technique allows precise margin designation and an accurate measurement of the margin width, and limits additional manipulation of the breast tissue since compression devices used for the specimen radiography may alter measurements of the margin distances. Although an increase in the number of histologic blocks and slides is the main concern for this method, a number of studies report that this method reduces the rate of re-excision for close margins.^{13–19}

3. Surgical margins

The possible scenarios of margin assessment encountered at the microscope are: broadly positive margin (Fig. 1), focally positive margin (Fig. 2), close margin (Fig. 3), negative margin (Fig. 4), and cauterized margin (Fig. 5). As previously mentioned, there is a lack of standardization in the pathological methods of margin evaluation, which yields little consensus regarding what constitutes an adequate negative margin. Patient management varies widely based on the threshold that surgeons accept for adequate margins and the subsequent need for re-excision. Morrow et al.²⁰ recently proposed that the negative margin used in the National Surgical Adjuvant Breast and Bowel Project (NSABP) trials should be adopted as the definition of an adequate margin, and the close margin, as described by pathologists and interpreted by patients and clinicians as evidence of inadequate surgery, should be replaced by the

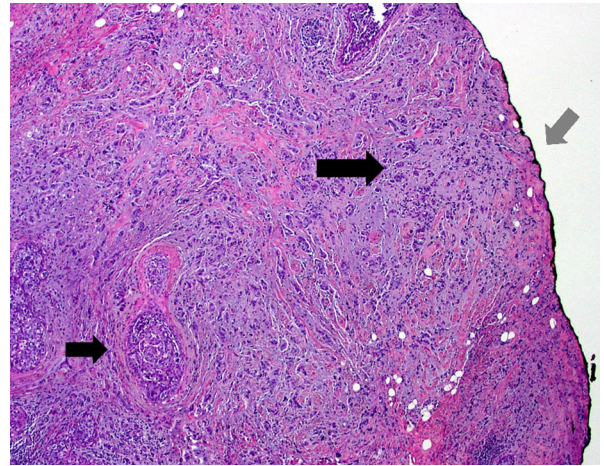


Fig. 1. Positive margin: poorly differentiated invasive ductal carcinoma (large black arrow) at ink (gray arrow) in association with high-grade ductal carcinoma *in situ* (small black arrow) (H&E, 4× magnification).

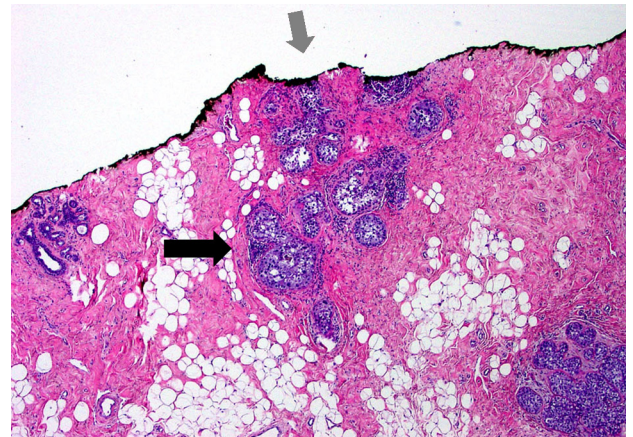


Fig. 2. Focally positive margin: high-grade ductal carcinoma *in situ* (black arrow) at ink (gray arrow) (H&E, 4× magnification).

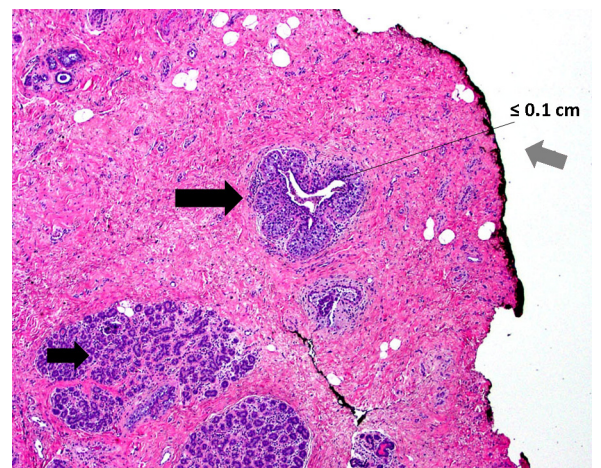


Fig. 3. Close margin: high-grade ductal carcinoma *in situ* (large black arrow) ≤ 0.1 cm from the inked edge, but not at ink (gray arrow); surrounding unremarkable breast lobules (small black arrow) (H&E, 4× magnification).

measurement of the distance of the tumor from the inked resection margin, without any additional qualifications. It is also important to recognize that a reported negative margin does not confirm that there is no residual tumor in the breast; rather it indicates that the residual

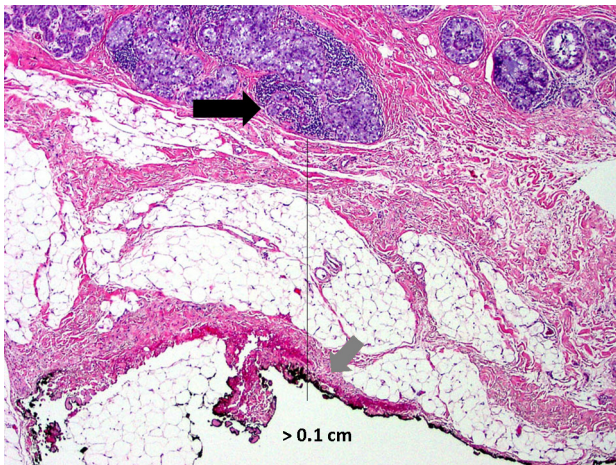


Fig. 4. Negative margin: high-grade ductal carcinoma *in situ* (black arrow) >0.1 cm from the inked edge (gray arrow) (H&E, 4× magnification).

tumor burden is low enough to be likely controlled by radiotherapy. In recognition of the multiple factors impacting local control of breast cancer, a consensus conference concluded that the only negative margin width for all patients with invasive carcinoma was tumor not touching the inked margin.²¹

In the case where there is an extensive intraductal component (EIC; ≥25% of tumor mass) in association with the invasive carcinoma it may be more appropriate to obtain a margin of at least 0.2 cm if large amounts of ductal carcinoma *in situ* (DCIS) are in proximity to the margin, since it has been shown that 70% of low-grade DCIS, 55% of intermediate-grade DCIS and 10% of high-grade DCIS may grow discontinuously within the ducts.²² Also the presence of residual calcifications at the lumpectomy site is a strong predictor of residual DCIS and even when margins are reported negative, residual suspicious calcifications should be an indication for re-excision.^{23,24}

The criteria for surgical re-excision by mastectomy after BCT, according to the Standards, Options and Recommendations (SOR) guidelines are positive resection margins, the extension of intraductal lesions extending beyond 3 cm, and the presence of multifocal lesions.^{25,26} However, according to the literature, 30–65% of mastectomies performed after BCT are free of residual tumor, which therefore casts doubt on the validity of these procedures providing no therapeutic benefit, impairing cosmesis and increasing morbidity and costs.^{27,28} In daily clinical practice it is important to know

predictors of the risk of residual cancer in the presence of positive or close margins in order to identify patients in whom unnecessary re-excision(s) or mastectomies could be avoided. Young age, tumor size, nodal status, number of involved margins, multifocality and extent of the tumoral lesion, presence of an extensive intraductal component have been found to be associated with the risk of residual cancer in the tumor cavity.^{29–33} In any case, no predictive factor has yet been proven to be reliable enough to exactly identify patients with involved margins in whom re-excision(s) or mastectomies could safely be omitted. However, it is also important to establish the exact anatomical situation of the positive margins; the absence of re-excision in the case of positive margins, whether anterior (close to skin) or posterior (close to pectoral muscle), does not appear to significantly increase the risk of recurrence, whereas positive margins are a risk factor for local recurrence when in contact with the remnant gland.³⁴

The definition of acceptable margin width is similar for invasive cancer and for DCIS with RT; in DCIS treated without RT larger margins are favored. The case is different for lobular carcinoma *in situ* (LCIS) which is known to be a marker for breast cancer and not necessarily a precursor. A larger recent study has shown classic LCIS near the margin does not increase local recurrence.^{10,35}

Neoadjuvant chemotherapy (NACT) allows removal of a smaller amount of breast tissue than if initial surgery was performed. Shrinkage of the locally advanced breast tumor in response to NACT has been shown to occur in two different ways: concentrically and in a honeycomb or buckshot pattern. In patients with a pathologic complete response or concentric tumor shrinkage, consideration of margin width does not differ from that in a non-NACT setting. In contrast, in patients with the buckshot pattern of tumor shrinkage, determination of the appropriate extent of resection may be problematic perhaps due to the biologic features of the tumor, suggesting that if viable residual tumor is present scattered throughout the lumpectomy, even if it is not at the inked margin, re-excision should be considered.³⁶

In patients with positive margins, radiotherapy with a boost dose to the tumor bed could be an option if re-excision is likely to compromise the cosmetic outcome or is technically not feasible.

A new technique recently proposed for intraoperative margin assessment is optical coherence tomography (OCT) – a high-resolution microscopic optical imaging technique that yields real-time multidimensional images of subsurface tissue structure.³⁷ OCT is the optical analogue of ultrasound imaging but uses light waves

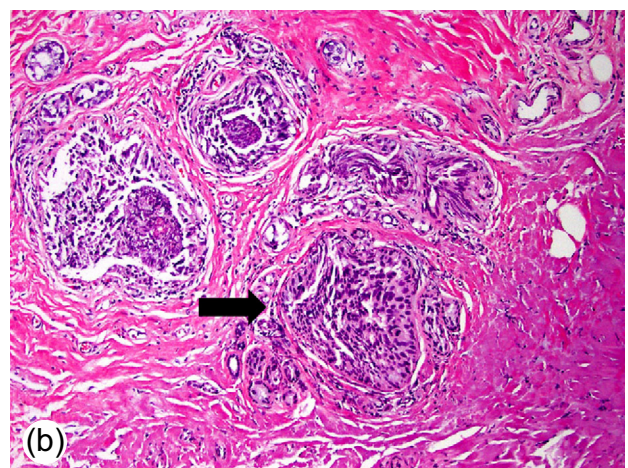
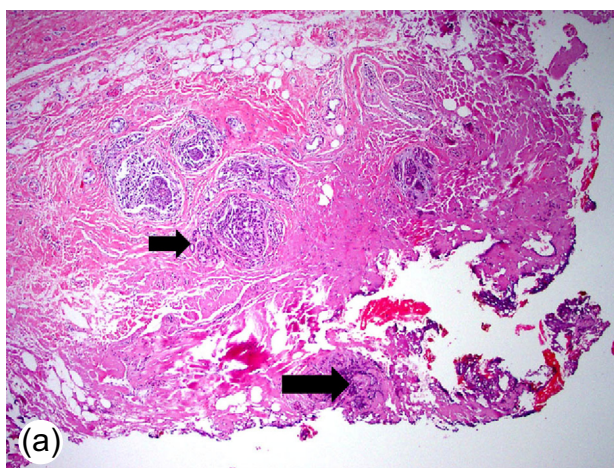


Fig. 5. (a) Cautery artifact (large black arrow; H&E, 4× magnification) limits the interpretation of the specimen margin in relation to the *in situ* carcinoma (small black arrow). (b) Cautery artifact may preclude the morphologic appreciation of the *in situ* ductal carcinoma (black arrow, H&E, 10× magnification).

instead of sound waves to create images. The penetration depth in breast tissue is about 1–2 mm, making OCT a suitable technology for intraoperative tumor margin assessment and suitable also for DCIS. The validity of this new technique must be confirmed by other data.

4. Conclusion

A positive margin is associated with increased risk of local recurrences after BCT for invasive breast cancer and DCIS. There is no cut off for the margin width, and the significance of a close margin remains controversial. The surgeon needs to balance the risk of local recurrence against cosmesis in planning BCT so that prognosis is not compromised.

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