Definition and Management of Positive Margins for Invasive Breast Cancer

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KEYWORDS

• Breast-conserving surgery (BCS) • Negative margins • Reexcision • Margin width • Recurrence

KEY POINTS

- Final margin status at breast-conserving surgery is the critical prognostic factor for ipsilateral breast tumor recurrence (IBTR).
- Negative (clear) margins reduce the risk of IBTR; wider margin widths do not further reduce this risk. No ink on tumor is adequate for optimal oncologic control.
- Positive margins require additional surgery.
- Additional margin resection (directed or shave) at primary lumpectomy significantly reduces the rate of positive margins.
- There is a current need for improved intraoperative assessment of the margin status to aid in complete resection.

INTRODUCTION

From the Halsted radical mastectomy to transcriptomics-based personalized therapy, the management of breast cancer has witnessed a massive evolution in the past 5 decades. The adoption of routine screening mammography, improved access to care, availability of radiation therapy, and development of robust systemic therapy options have all facilitated earlier diagnosis and the transition from mastectomy to breast-conserving surgery (BCS) for a select subset of patients. BCS entails complete tumor resection with a concentric margin of surrounding healthy tissue performed in a cosmetically acceptable manner. BCS portends a distinct advantage to the patient in

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the ability to preserve their breast while maintaining adequate oncologic control. However, the success of the BCS is predicated upon the ability to obtain tumor-free (negative) margins. What constitutes adequate negative margins has been a subject of much debate. This article discusses the current understanding and recent developments in the management of invasive breast cancer using BCS.

LOCAL THERAPY PARADIGM SHIFT: LESS IS MORE

For almost a century, the Halsted radical mastectomy, which included complete removal of breast tissue, underlying pectoralis muscles, and regional lymph nodes, was the procedure of choice for invasive breast cancer.[1] Improvements in understanding of the tumor biology and significant surgical morbidity associated with radical mastectomy led investigators from the National Surgical Adjuvant Breast and Bowel Project (NSABP) to conduct the NSABP-B04 (1971–1974) trial, which compared radical mastectomy to less extensive surgery (total mastectomy with or without radiation therapy).[2] To further minimize the extent of surgery, NSABP-B06 (1976–1984) and the European Organization for Research and Treatment of Cancer 10801 (1980–1986) trials were conducted to compare the outcomes of mastectomy with those of lumpectomy with radiation therapy and lumpectomy alone. Twenty-year follow-up results of these clinical trials established equivalent long-term disease-free and overall survival in patients receiving radical mastectomy, total mastectomy, or lumpectomy for invasive breast tumors.[3,4] The results of these trials established BCS with radiation therapy as the new "standard of care" for stage I/II breast cancer with the goal of optimal oncologic control and better cosmetic outcome in order to improve overall patient quality of life. In recent years, the use of neoadjuvant systemic therapy has facilitated the use of BCS for patients previously slated for mastectomy. The American College of Surgeons Oncology Group Z1031 and NSABP-B18 trials demonstrated the role of neoadjuvant endocrine therapy and chemotherapy in substantially increased use of lumpectomy as the surgical procedure over mastectomy.[5,6] Currently, about 60% to 75% of patients diagnosed with early stage breast cancer undergo BCS as their initial surgical treatment.[7–9]

MARGINS IN BREAST-CONSERVING SURGERY

The goal of optimally performed BCS is to achieve clear surgical margins during initial tumor resection while maintaining the natural shape of the breast. The status of surgical margins is determined microscopically by applying ink to the surface of the lumpectomy specimen and analyzing the closest distance between the inked lumpectomy edge and any cancerous tissue (invasive or ductal carcinoma in situ [DCIS]). The surgical margin status is one of the strongest predictors for local recurrence and guides the decision to reexcise.[10–12] On microscopic evaluation, the status of the margin can be (a) extensively positive, (b) focally positive, (c) close, and (d) negative (**Fig. 1**).

Extensively positive margins are defined as the presence of ink at the surface of the surgical specimen on either invasive cancer cells or DCIS and are a reflection of incomplete resection. Positive margins are strongly associated with a substantial increase in local recurrence risk than those with negative margins.[12–14] Focally positive margins, defined as tumor touching the inked margin over a length of 4 mm or less, are associated with a lower residual disease burden as compared with extensively positive margins.[15] Negative margins, initially defined by NSABP-B06 as no ink on invasive carcinoma or DCIS, have been shown to substantially decrease the risk of ipsilateral breast tumor recurrence (IBTR). Traditionally, negative but close margins have been described as margin width $\leq$2 mm from invasive carcinoma or DCIS. The appropriate