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Review

Perioperative measures to optimize margin clearance in breast conserving surgery

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ABSTRACT

Margin status is one of the most important determinants of local recurrence following breast conserving surgery. The fact that up to 60% of patients undergoing breast conserving surgery require re-excision highlights the importance of optimizing margin clearance. In this review we summarize the following perioperative measures that aim to enhance margin clearance: (1) patient risk stratification, specifically risk factors and nomograms, (2) preoperative imaging, (3) intraoperative techniques including wire-guided localization, radioguided surgery, intraoperative ultrasound-guided resection, intraoperative specimen radiography, standardized cavity shaving, and ink-directed focal re-excision; (4) and intra-operative pathology assessment techniques, namely frozen section analysis and imprint cytology. Novel surgical techniques as well as emerging technologies are also reviewed. Effective treatment requires accurate preoperative planning, developing and implementing a consistent definition of margin clear-ance, and using tools that provide detailed real-time intraoperative information on margin status.

Contents

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Introduction

Screening mammography increased the incidence of ductal carcinoma in situ (DCIS) and early stage invasive breast cancer [1,2]. Previously, mastectomy was the standard treatment, but the physical and psychological morbidity associated with it led to the study of less aggressive approaches. Surgical treatment shifted from mastectomy to breast conserving surgery (BCS) in conjunction with adjuvant therapies as several major randomized clinical trials (RCTs) showed no significant difference in disease-free and overall survival between both approaches [3–8]. The treatment of DCIS underwent similar changes; although the role of adjuvant radiation therapy for DCIS is controversial [9–11].

Despite the advantages, BCS has a higher risk of local recurrence (LR) than mastectomy [3,8]. Predictors of LR include patient age, tumour stage, tumour grade, disease distribution, lymphovascular invasion (LVI) status, molecular subtype, and surgical margin status [12]. Of these, the strongest predictor of LR is surgical margin status [13,14]. The risk of LR from a positive margin is 2–3 times that with a negative margin [15].

Positive margins are managed with re-excision or mastectomy, depending on the number of positive margins and the remaining amount of breast tissue. Positive margin rates after BCS for breast cancer and DCIS are 15–47% [16–19] and 20–81% [9,20–26], respectively. Re-excision rates range from 23% to 59% depending on the treatment centre and the surgeon's practice [27–29]. The completion mastectomy rate is approximately 14% [30]. Re-excision may result in poor cosmetic outcome, increased medical cost, and patient anxiety. As the rate of patients with early invasive cancer and DCIS continues to increase, obtaining negative margins during primary BCS is essential. This review summarizes the perioperative approaches that aim to optimize margin clearance for patients undergoing BCS.

Surgical margins

Ideally BCS should consist of removing the whole tumour, a thin layer of normal tissue to absorb the margin ink, and no other normal breast tissue, but this is technically impossible; therefore several millimetres of normal tissue are excised around the tumour. Margins are measured grossly and microscopically by determining the presence of cancer cells at a fixed distance from the cut edge. Margins are negative if no invasive cancer and/or DCIS are identified microscopically at the edge of the specimen, positive if invasive cancer and/or DCIS are at the cut edge of the specimen, and close if invasive cancer and/or DCIS are between the cut margin and a distance defined as negative. The presence of lobular carcinoma in situ or atypical ductal or atypical lobular hyperplasia at the margin is not considered to be positive.

Margin size is a matter of significant debate because of the lack of a standardized definition. The landmark RCTs that established BCS as the standard-of-care treatment differed in their definition for negative margins [3–8]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 trial used microscopic criteria, specifically the absence of cancer cells at the inked edge of the specimen [3]. The other RCTs used macroscopic absence of disease at the margin [4–8]. Several groups have each proposed different definitions along with treatment algorithms [31,32]. The American Society of Breast Surgeons (ASBS) states that when all margins are ink negative and $\geq$1 mm no further surgery is recommended [31]. If the margin is close ($<$1 mm) or focally involved, re-excision is not mandatory but should be considered on a case-by-case basis. If the ink margin is positive re-excision should be performed. The National Comprehensive Cancer Network (NCCN) recommends that patients with invasive or infiltrating cancer without evidence of extensive intraductal component have a pathologically negative margin of resection if no tumour is detected on the inked margin [32]. For DCIS a margin of $>$10 mm is accepted as negative, but may also be excessive and lead to less than optimal cosmetic outcomes. A margin of $<$1 mm is considered inadequate. In cases with margins between 1 and 10 mm, wider margins tend to have lower LR rates, but close surgical margins ($<$1 mm) at the fibroglandular boundary of the chest wall or skin do not require re-excision and instead warrant higher boost dose radiation. Despite these attempts, in clinical practice variability in the definition of margin size has been well documented amongst surgeons [33].

Wide surgical margins have not been associated with a decrease in the risk of LR. A meta-analysis of 21 retrospective studies with 14,571 breast cancer patients showed no statistically significant difference in LR rates at a follow-up time of 104.4 months even when stratifying for different margin sizes and adjusting for adjuvant therapy [34]. With regards to DCIS, there is also no compelling evidence that wider margins are better. Although a recent meta-analysis pooling data from 21 studies concluded that margin widths $\geq$10 mm significantly decreased the risk of LR relative to margins $\geq$2 mm regardless of radiation therapy [35], adopting such a policy is challenging given that $<$10% of studies within the meta-analysis' dataset reported obtaining that margin size [36]. Additionally a prospective study of 671 patients with DCIS conducted by the Eastern Cooperative Oncology Group (ECOG) reported that the actuarial risk of LR at 5 years did not differ between patients with margins $\geq$10 mm and those with smaller margins, despite stratification by histologic grade [37]. Recently, a multidisciplinary consensus panel of the Society of Surgical Oncology and the American Society for Radiation Oncology developed recommendations regarding margin definition using a meta-analysis of 33 studies (n = 28,162 patients) [38]. Positive margins (ink on invasive carcinoma or DCIS) had a two-fold increase in the risk of LR compared with negative margins, which was not mitigated by favourable biology, endocrine therapy, or a radiation boost. Wider clear margins than no ink on tumour did not significantly decrease LR relative to no ink on tumour. Therefore there was no evidence that more widely clear margins reduce LR in young patients or for those with unfavourable biology, lobular cancers, or cancers with an extensive intraductal component.

Preoperative assessment of patients undergoing breast conserving surgery (BCS)

Multiple studies have evaluated clinical, pathological, and treatment-related risk factors associated with LR, all of which should be considered preoperatively. These risk factors include young age [39], positive lymph nodes [40], high tumour grade [41], comedo and lobular histology [42], microcalcifications on