Excision margins in breast conserving therapy

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“There is a need to harmonize international guidelines on margins supported by knowledge and evidence to eliminate the intercountry and intracountry variation in margin definition that currently exists.”

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The majority of patients diagnosed with invasive breast cancer or ductal carcinoma *in situ* (DCIS) are treated by breast-conserving surgery (BCS) [1]. The aim of BCS is to achieve complete excision to clear margins, although what constitutes an adequate clear margin has been a topic of debate since BCS was first introduced. Two meta-analyses [2,3] have shown that when performing BCS in patients with invasive cancer involved margins more than double the rate of ipsilateral breast tumor recurrence (IBTR) – the odds ratio of IBTR compared with negative margins in the second meta-analysis was 2.44 (95% CI: 1.97–3.03) [3]. Close margins were also noted in this analysis to increase the odds of recurrence (odds ratio of IBTR vs negative margins 1.74 [95% CI: 1.42–2.15]). In both meta-analyses when looking at different thresholds, a negative margin clearance of 1 mm was as good as wider margins [2,3]. There were insufficient data in these analyses to compare no tumor on ink with wider margins [2,3]. A Society of Surgical Oncology – American Society for Radiation Oncology (SSO–ASTRO) consensus panel having considered the two meta-analyses and expert evidence recommended that no ink on margin be used in clinical practice as a negative margin for patients having BCS for invasive cancer [4]. One of the reasons given for choosing no tumor on ink was that this was the definition of a negative margin used in National Surgical Adjuvant Breast and Bowel Project Trial number B06 (NSABP B06) [5], a large randomized study of BCS versus mastectomy. To rely on NSABP B06 as a basis for determining that no ink on tumor is sufficient is puzzling, however, because there are no published data from NSABP B06 that provide any distances between the edge of the tumor and excision margins and review of the pathology raised concerns about margin assessment in B06 [5]. Another reason put forward for using no ink on tumor was the known difficulties of measuring distance to margins [4], in part because the process of fixing BCS specimens may result in artefactual narrowing of the *ex vivo* margin. The consensus panel authors also noted that local recurrence rates have fallen dramatically since BCS was first introduced, in large part due to improvements in systemic therapy [4]. In the meta-analysis, however, the effect of margins (estimated as odds ratios) did not change when the models were adjusted for study-level covariates including study timeframe [3]. The effect of margins thus persisted over time and the significantly higher odds ratios of IBTR for close and positive margins versus margins of 1 mm was independent of the systemic therapy given. This suggests that even for patients receiving optimal systemic therapy, margin status in BCS still matters.

Over 20% of ‘cancer’ detected by breast screening is DCIS [1] and until recently there has been no consensus on the surgical margin that was required when performing BCS for DCIS [6]. A recent systematic review investigated the association between margin width and local recurrence specifically for DCIS [7]. The authors noted significant heterogeneity of margin definitions across studies, and reported that only small numbers of studies included patients with margin widths of 1–2 mm. In their analysis, margin widths up to 2 mm were combined into one group to get sufficient numbers. Patients with margin widths ≥ 2 mm did have a somewhat lower rate of local recurrence after BCS for DCIS than patients with a margin width less than 2 mm and the authors concluded that there was weak evidence of lower odds of IBTR for margin widths ≥ 2 mm when compared with margin widths of greater than 0 (no ink on tumor) or 1 mm. They also concluded that negative margins in DCIS reduced the odds of recurrence

but that margin widths of greater than 2 mm were not associated with a further reduction in the odds of local recurrence compared with 2 mm. A subsequent consensus conference proposed that 2 mm should be the standard definition of a clear margin in DCIS for patients having BCS and whole breast irradiation [8]. The consensus group also agreed that patients with negative margins less than 2 mm after BCS should not undergo automatic re-excision but that clinical judgment should be used in determining the need for further surgery.

The lack of data comparing 1–2 mm with wider margins in DCIS led us to perform a detailed pathological study looking at distance to nearest radial margin versus IBTR in patients with DCIS undergoing BCS with or without radiotherapy in Edinburgh [9]. As it was a single center study, the surgery, pathology and postoperative radiotherapy were consistent and few patients received tamoxifen, so this represents a homogeneous population and removes many of the confounders that hindered the systematic review. At a median follow-up of 7.2 years, actuarial IBTR rates at 5 and 10 years were similar for margin widths of 1–2 mm and greater than 2 mm. The odds ratio of IBTR for a 1–2 mm margin width versus greater than 2 mm was 0.776 (95% CI: 0.333–1.811; $p = 0.58$). In a multivariate analysis, margin width (1–2 vs >2 mm) was not a significant predictor of local recurrence. The only significant predictor of IBTR was DCIS extent with DCIS lesions less than 15 mm having a significantly lower rate of IBTR than larger lesions [9]. While these new data from Edinburgh are not definitive because the numbers with margin widths from 1 to 2 mm was less than 100 patients, which resulted in larger confidence intervals than needed to change practice, these data do contribute to our knowledge base.

A recent study from the Memorial Sloan Kettering reported early experience following the introduction of the SSO/ASTRO guideline on margins of no tumor on ink when performing BCS for invasive cancer [10]. The authors reported that the disease present at the margin of excision in almost half the patients with ink on tumor was DCIS with the remainder having invasive cancer at the margin. When margins were close (>0 but <1 mm) in more than two-thirds of women, the disease that was close to the margins was DCIS with just over a third of women having invasive cancer close to margins. From these data, it is evident that in over 60% of patients undergoing BCS for invasive cancer that have involved or close margins, the disease that is closest to or at the margin is DCIS. This DCIS is biologically similar to the DCIS seen in patients with pure DCIS.

The study from the Memorial Sloan Kettering reported variable interpretation and application of the SSO–ASTRO consensus panel advice of no tumor on ink as an adequate clear margin for BCS in invasive cancer [10]. While nearly all the patients with tumor on ink and very few with margins ≥ 1 mm had re-excision, over 40% of patients with close margins (>0 but <1 mm) managed after adoption of the guideline had re-excision. The rate of re-excision in these patients having BCS for invasive cancer was almost 50% when the disease close to margins was DCIS. It is likely to be difficult to confirm moving forward whether no tumor on ink is sufficient for BCS in invasive cancer when the numbers who would avoid re-excision is small and there is such variability in the guideline adoption. A recent study has also raised concerns about the use of no tumor on ink as a sufficient negative margin, in that (45.7%) patients with close margins who had a re-excision had residual disease in the re-excision. This rate of residual disease was similar to patients with focally positive margins (48.7%) although not as high as the rate in patients with extensively involved margins (78.3%) [11].

A prospective study of 2858 women undergoing BCS in the UK also demonstrated that altering margin policy to follow the SSO–ASTRO guidelines would result in at most a modest reduction in re-excision rate. Most re-excisions were as a result of involved rather than close margins [12]. A concern is that IBTR is a risk factor for subsequent breast cancer death, so it needs to be avoided if possible. Given that two meta-analyses [2,3] have shown that 1 mm is the optimal margin width when performing BCS for invasive cancer and new data suggest that 1 mm may also be sufficient when performing BCS for DCIS, there is support for harmonizing the minimum margin threshold for BCS for both invasive cancer and DCIS to 1 mm. In practice in the UK, few have adopted the SSO/ASTRO guidelines and currently over half follow the UK Association of Breast Surgeons guidelines of a 1-mm margin for DCIS and over three quarters use a 1-mm margin for invasive cancer [12]. There is a need to harmonize international guidelines on margins supported by knowledge and evidence to eliminate the intercountry and intracountry variation in margin definition that currently exists. It is time for all to agree on a single margin that defines an adequate excision when performing BCS for both invasive cancer and DCIS. The evidence presented in this review suggests that margin should be 1 mm.

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