E14. Free margins

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The vast majority of ipsilateral breast cancer recurrences (IBCRs) following breast-conserving surgery (BCS) appear in the same quadrant as the index primary, and close to the scar of the prior surgery. This implies that regrowth of tumour cells that remained in the breast at the time of the original surgery because of incomplete removal might play a major role in the occurrence of local recurrence, despite administration of adjuvant radiotherapy. Accordingly, the status of the resection margins at BCS has been viewed as an important determinant of the risk for subsequent relapse at the site of the primary tumour. There is a general consensus that a successful BCS requires margins clear of invasive and *in situ* tumour and acceptable cosmetic results. Positive margins are significantly associated with local recurrence. Radiotherapy and systemic therapies may reduce the risk of recurrent disease but not to the same levels as for patients with negative margins. [1,2]

The likelihood of recurrence in patients with positive margins is dependent on the definition of margin status, the extent of margin involvement, the duration of follow-up and whether margins are involved by *in situ* or invasive cancer. Unfortunately, however, the definition of what constitutes a negative margin or a "close" margin is still controversial, as it is a question of what is the most accurate method for the assessment of margin status. Adequate pathologic examination of the surgical specimen requires specimen orientation and accurate inking. In general, the detection of invasive or intraductal cancer at an inked surface dictates a re-excision. The impact of focally (e.g. less than one histological field at 4× magnification) involved margins on the risk of IBCR, however, is still uncertain. Lobular intraepithelial neoplasia (lobular carcinoma *in situ*, LIN) at the margin is not considered an indication for further surgery, with the possible exception of the high-grade, pleomorphic variant of LIN (LIN3), that is currently considered a true precursor of invasive carcinoma. [3] The adoption of 'tumour not touching ink' as the standard definition of an adequate negative margin in patients with invasive cancer has been recently endorsed by an International Expert Panel in its recommendations for loco-regional treatment of primary breast cancer. [4]

The clinical implications of tumour "close" to margins are much less clear, and we lack consistent evidence that "close" margins increase IBCR. [2] On the other hand, if larger margins are routinely requested, more re-excisions and mastectomies will be performed, with an obvious psychological impact on the patients and an increased financial burden.

The assessment of margin status is more commonly performed by the histopathological examination of the inked margins of the surgical specimens, or by the examination of "cavity shavings". [5]

The intraoperative examination of margin status by frozen section analysis is a commonly applied technique to allow additional shavings of the surgical cavity at the time of lumpectomy or quadrantectomy, thus avoiding the need for a second surgery in case of positive margins. [6] Due to the time constraints of an intraoperative diagnosis, and to the increased difficulty of the histological assessment of morphological features indicative of malignancy in frozen tissue sections, the reported sensitivity rates for detecting residual disease range between 65% and 78%, whereas specificity rates ranged between 98% and 100%. [7–9]

Despite the relatively high variance in the sensitivity of frozen section assessment of margin status, which might be explained by differences in experience between pathologists, this approach has been documented to influence BCS. Indeed, some 24% to 27% of the patients will undergo additional tissue excision based on the intraoperative detection of positive margins, whereas 5% to 9% required a second re-excision procedure after definitive histopathological examination. [9–11]

Intraoperative touch preparation cytology or "imprint cytology" is sometimes used as an alternative to the examination of frozen tissue sections. [12,13]

To overcome the limitations of the intraoperative cytological or histological techniques, it has been suggested that standardised surgical cavity shaving, by removing any residual disease after excision of the primary tumour, could be effective in reducing the rates of positive margins. The rate of positive margins is inversely correlated to the volume of breast tissue removed by shaving, so that cosmetic outcome of BCS may eventually be compromised by extensive shavings. [14,15]

Irrespective of the method used for margin assessment, it is important to emphasise that a negative margin does not imply *per se* that there is no residual tumour after surgery. Indeed, the histopathological assessment of the margins cannot be extensive enough to exclude

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any minimal involvement by the tumour. It has been calculated that to scrutinise extensively the margins of a 2 cm lumpectomy, the pathologist should prepare some 30 paraffin blocks and cut and examine under the microscope more than 10,500 sections, an enterprise that is not likely to be undertaken by many. In addition, it is well known that many breast cancers (with special reference to invasive lobular carcinomas and also to low-grade intraductal carcinomas) are multifocal at the histopathological level, and the neoplastic foci may be separated by 2 or more cm of uninvolved breast tissue. [16] In all these circumstances, a surgical margin that is negative at the histopathological assessment does not imply that the surrounding breast parenchyma does not harbour residual tumour.

In conclusion, margin status should be considered in the context of multiple factors known to influence local control and the obsession about margin status ignores both the uncertainties of pathologic processing and the differences in tumour biology.

Conflict of interest statement

None declared.

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