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FAST FACTS

Width of excision margins after breast conserving surgery for invasive breast cancer and distant recurrence and survival

One premise of cancer treatment is that if a tumour is cut out but tumour cells remain present or close to the edges (of the cut), the risk of cancer returning at the same site is increased. Increased surgical focus on adequacy of margin excision would improve breast cancer survival worldwide.

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Importance of tumour removal

In many cancers, such as colorectal cancer, attention to ensuring meticulous removal of the cancer with an encompassing cuff of normal tissue (ie, no tumour at the pathological margin) results in improved outcomes. The association between margin involvement and poorer recurrence and survival outcomes^{1,2} led to studies that showed a strong association between the width of tumour from the margin in colorectal cancer and subsequent outcomes.²

Most patients with early breast cancer are treated with breast conserving surgery. Removing cancers without leaving malignant cells at a surgical margin reduces local recurrence³⁻⁷ but the effects of margin involvement on distant recurrence and mortality are unclear. How far the tumour should be from the specimen margin to ensure optimum oncological outcomes is contentious.

The definition of a clear margin matters

When cancer is surgically removed, the tumour is subject to pathological examination. The edges of the removed cancer specimens, known as the margins, can be either microscopically involved, in that the tumour is at the edge of the specimen, or not involved, that is, no tumour is seen at the edge. The distance from the edge of the margin to the tumour is measured. A close margin occurs when the tumour is not at the edge but within a given distance; usually 1 mm or 2 mm. Close margins are important because pathological assessment provides a representative sample of material examined. Involved or close margins are associated with between 39% and 85% patients having residual cancer after re-excision surgery.⁴ Occult foci of disease occur beyond the apparent edge of cancers and might not be adequately treated by adjuvant treatment.

Internationally, proportions of surgical margins involvement for breast cancer vary from 9.4% to 17.8% depending on definition of involvement.^{3,5,8,9} A meta-analysis of 14 571 patients reported findings that a 1 mm margin of normal tissue around invasive cancer after breast conserving surgery was reasonable.³ In 2009, UK British Association of Surgical Oncology guidelines⁵ did not recommend a specific width of clearance around invasive cancers, and 21% of patients had tumours with less than 1 mm from margins in a large UK study.⁹ In 2014, an

authoritative US guideline advised that avoiding the presence of cancer touching the margin (known as tumour on ink) was sufficient to minimise local recurrence.^{3,6} The National Institute for Health and Care Excellence (known as NICE) did not define a minimum margin distance but suggested that the benefits of further surgery should be discussed with the patient where margins were close but not on the edge.⁷ Differences in guidelines have led to confusion about the correct approach to surgical margins.

Local recurrence is associated with higher rates of death from breast cancer.¹⁰ Globally, local recurrence rates after breast surgery have reduced from 20% before widespread adjuvant treatment use to 5% or lower currently.⁴ The effect of both adjuvant systemic treatment and radiotherapy in reducing local and distant recurrence has probably influenced the interpretation of the significance of margin proximity.

To answer the questions of whether involved or close margins are associated with increased distant recurrence and decreased overall survival, we conducted a prospectively registered systematic review of all the available literature according to PRISMA guidelines (doi:10.1136/bmj-2022-070346).⁸ Patient pathology specimens were categorised as tumour at the margin (involved), close margins (tumour <2 mm from the margin, but not at the margin), and negative margins (tumour ≥2 mm from the margin).

We included 68 studies comprising 112 140 patients undergoing breast conserving surgery. Overall, 9.4% (95% confidence interval 6.8% to 12.8%) of patients had tumour at the margin and 17.8% (13.0% to 23.9%) had tumours at or close to the margin. The rate of distant recurrence was 25.4% (14.5% to 40.6%) in patients with tumour at the margin, 8.4% (4.4% to 15.5%) with tumours at or close to margins, and 7.4% (3.9% to 13.6%) patients with negative margins.

On multivariable analyses, importantly taking into account postoperative chemotherapy and radiotherapy, involved margins compared with negative margins were associated with increased distant recurrence (hazard ratio 2.10 (95% confidence interval 1.65 to 2.69), $P < 0.001$) and local recurrence (1.98 (1.66 to 2.36)). Compared with negative margins, close margins were associated with increased distant recurrence (1.38 (1.13 to 1.69), $P < 0.001$) and local recurrence (2.09 (1.39 to 3.13), $P < 0.001$), after

adjusting for receipt of adjuvant chemotherapy and radiotherapy.

Limitations

This review collates data from more than five times the number of patients in the 2014 US consensus guideline addressing local recurrence and surgical margins.⁶ As with previous analyses, most of these data are from cohort studies, not randomised trials, thus a causal association between margin proximity and distant recurrence cannot be proven. Given the unavoidable absence of randomised evidence on the consequences of margin proximity, these findings plausibly indicate that clearance of margins in invasive breast cancer should remain a priority to reduce both distant and local recurrence irrespective of the increased use of adjuvant treatments.

Why surgical tumour margins matter

Current international guidelines need revision to account for these findings. Recognising that wider margins might require further surgery, decisions about re-excision should be the product of an informed discussion between clinicians and patients. The issue of involved margins after breast conservation might not be routinely discussed with patients but patient advocates believed that complete surgical excision to prevent distant recurrence was more important to them than cosmesis. In multidisciplinary team meetings, opinions vary about what margin width is acceptable for invasive and in situ cancer. International guidelines on the optimal width for margin clearance should be based on the width to prevent distant recurrence as a primary aim. Wider margins should not necessarily increase mastectomy rates but might require more specific preoperative multidisciplinary team planning of surgical incisions and operations.

Conclusions

These comprehensive data indicate the likelihood that inadequate margin width results in higher risks of distant recurrence and breast cancer mortality, as well as increased local recurrence. Involving patients with cancer in discussions about margin clearance before surgery should be an essential part of informed consent for surgery. Increased surgical focus on adequacy of margin excision would improve breast cancer survival worldwide.

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- 1 McArdle CS, Hole D. Impact of variability among surgeons on postoperative morbidity and mortality and ultimate survival. *BMJ* 1991;302:5. doi: 10.1136/bmj.302.6791.1501 pmid: 1713087
- 2 Adam JJ, Mohamdee MO, Martin IG, et al. Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet* 1994;344:11. doi: 10.1016/S0140-6736(94)92206-3. pmid: 7915774
- 3 Houssami N, Macaskill P, Marinovich ML, et al. Meta-analysis of the impact of surgical margins on local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy. *Eur J Cancer* 2010;46:32. doi: 10.1016/j.ejca.2010.07.043 pmid: 20817513
- 4 Aalders KC, van Bommel AC, van Dalen T, et al. Contemporary risks of local and regional recurrence and contralateral breast cancer in patients treated for primary breast cancer. *Eur J Cancer* 2016;63:26. doi: 10.1016/j.ejca.2016.05.010 pmid: 27299664
- 5 Association of Breast Surgery at BASO 2009. Surgical guidelines for the management of breast cancer. *Eur J Surg Oncol* 2009;35(Suppl 1):22.
- 6 Buchholz TA, Somerfield MR, Griggs JJ, et al. Margins for breast-conserving surgery with whole-breast irradiation in stage I and II invasive breast cancer: American Society of Clinical Oncology endorsement of the Society of Surgical Oncology/American Society for Radiation Oncology consensus guideline. *J Clin Oncol* 2014;32:6. doi: 10.1200/JCO.2014.55.1572 pmid: 24711553

- 7 (NICE) National Institute for Clinical Excellence. NG101: early and locally advanced breast cancer: diagnosis and management. 2018.
- 8 Bundred JR, Michael S, Stuart B, et al. Margin status and survival outcomes after breast cancer conservation surgery: meta-analysis. *BMJ* 2022;378:e070346. doi: 10.1136/bmj-2022-070346.
- 9 Maishman T, Cutress RI, Hernandez A, et al. Local recurrence and breast oncological surgery in young women with breast cancer: the POSH observational cohort study. *Ann Surg* 2017;266:72. doi: 10.1097/SLA.0000000000001930 pmid: 27455160
- 10 Early Breast Cancer Trialists' Collaborative Group Darby S, McGale P, Correa C, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011;378:16. doi: 10.1016/S0140-6736(11)61629-2. pmid: 24656685