The Effect of Positive Margins on Outcomes in Breast Cancer

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PCN16

BACKGROUND

- Breast cancer is the most common form of cancer and the second leading cause of death in women in western countries.[1] Breast-conserving therapy (BCT), consisting of lumpectomy and radiation therapy, has become the standard treatment for T1-T2 breast.[2]
- Successful breast conservation requires complete tumour excision with a "tumour-free" or "negative" margin of resection. Adequate surgical margins are recognized as a key predictor of local recurrence in breast cancer. However, there is no universal agreement on the width of the tumour-free margin.[3]

OBJECTIVE

- To review the data available on excision margins following BCT, focusing on:
  - Definitions of positive margins, close margins, and negative margins
  - Percentage of operations resulting in positive margins
  - The effect of positive margins on future treatment
  - The relationship between positive margins and disease-free survival and overall survival

METHODS

- A targeted literature search was performed in PubMed:
  - Search terms included combinations of free text and Medical Subject Headings for breast cancer, BCT, and margins.
  - Search limits:
    - Included English-language articles published since 2009 (to update a previously undertaken review)[4]
    - Restricted to studies conducted in humans
    - Excluded editorials, comments, letters, case reports, and phase 1 studies
- Targeted searches were also conducted to identify guidelines and to help address gaps in the literature.
- Articles that were cited in a recent review by Houssami et al.[4] and other recent articles considered of particular relevance were obtained.

RESULTS

- Of 473 identified articles, 45 were considered relevant to this review.

Definitions of Positive Margins

- Definitions of positive and negative margins in the identified studies were variable, but typically a clear margin of 2 mm was considered acceptable.
  - The majority of identified studies defined margins as follows:
    - Positive margin: National Surgical Adjuvant Breast and Bowel Project (NSABP) definition: presence of tumour cells at the edge of resection or inked histology section[5-9]
    - Negative margin: no tumour within 2 mm of the margin[6,8,10,11]
    - Close margin: tumour within 2 mm of the margin[5,6,8]
  - Surgeons in Europe were more likely to require a wider margin of 3 mm–10 mm, compared with those in North America.[12]
- Table 1 summarises definitions of margins provided in various guidelines.

Table 1. Definitions of Margins Provided in Guidelines

Body, Year Guidelines Issued	Recommendations Around Margins
NICE, 2002[13]	"Sufficient tissue should be removed to ensure that no tumour is found at the surgical margins, since positive or narrow (< 2 mm) margins are associated with high rates of local recurrence."
NICE, 2009[14]	"The optimum clear margin has yet to be defined [in eBC] and was not a topic identified for this guideline."
ACR, 2012[15]	"Patients with negative margins of excision (typically defined as the absence of either invasive or ductal in situ disease at an inked surface) have consistently been observed to have low rates of recurrence after treatment with BCT and radiotherapy, and patients with positive margins have been observed to have high rates of local recurrence." "There are significant technical considerations and limitations in the assessment of margins. There are variations in the use and definition of a 'close margin' with different groups using 1, 2 or 3 mm as the cut off."
BASO, 2009[16]	"All patients should have their tumours removed with no evidence of disease at the microscopic radial margins and fulfilling the requirements of local guidance."

ACR = American College of Radiology; BASO = guideline of the Association of Breast Surgery, United Kingdom; eBC = early breast cancer; NICE = National Institute for Health and Care Excellence.
[a] Only the ACR guidelines include details of the literature identified to support these statements. The methodology of the literature review used in the ACR guidelines is not presented.
Note: Guidelines for ductal carcinoma in situ differ from those for eBC; this presentation focuses on eBC.

Percentage of Operations Resulting in Positive Margins

- Rates of positive margins following surgery vary widely (Table 2). This may be a result of differences in the following:
  - Definition of positive versus negative margins
  - Approach to identification of close margins—palpable tumour or microscopic lesions
  - Presentation of data for "final margin status" or initial margin status
  - Patient characteristics impacting the likelihood of positive margins
- Most studies indicate positive margins in 20%-40% of patients after breast conserving surgery.

Table 2. Percentage of Operations Resulting in Positive Margins: Evidence from RCTs and Observational Studies

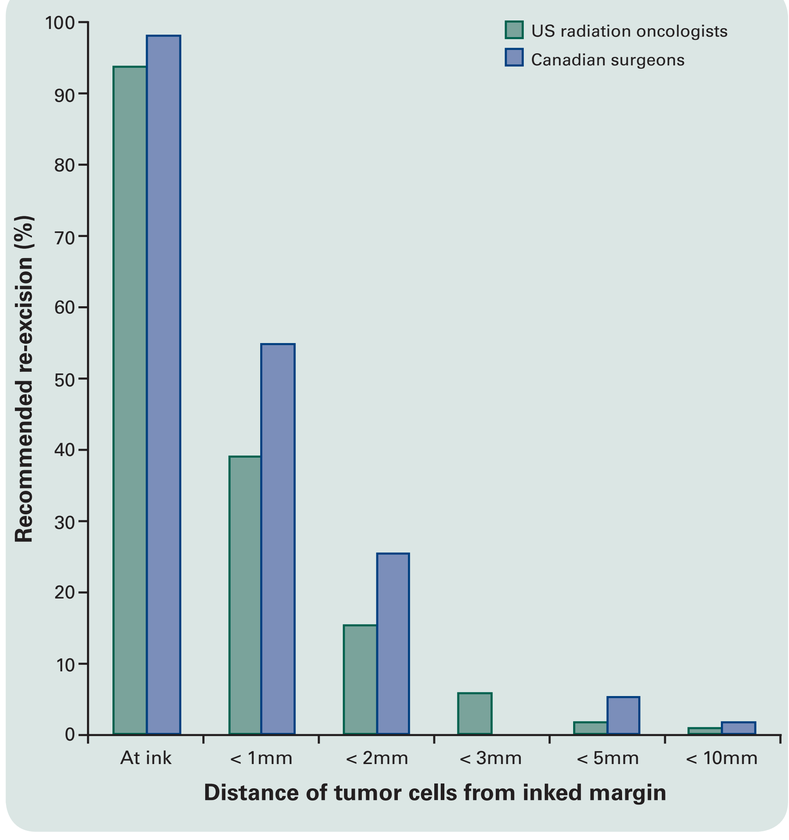
Reference (Study Type)	Study Description and Findings
Fisher et al., 2002[17] (RCT, NSABP	▪ Between 1976-1984, 2,163 women with invasive breast tumours measuring 4 cm or less were randomised to total mastectomy (n = 589), lumpectomy (n = 634), or lumpectomy followed by radiotherapy (n = 628) ▪ Lumpectomy only arm: 10.1% positive marginsa ▪ Lumpectomy + radiotherapy arm: 9.7% positive margins
van Dongen et al., 2000[18] (RCT, EORTC)	▪ Between 1980-1986, 902 patients with stage I or II invasive breast tumours were randomised to total mastectomy (n = 448 eligible) or BCT (440 eligible) ▪ "Microscopic margin involvement" observed in 48.4% patients in the BCT arm
Pleijhuis et al., 2009[2]	▪ Review of observational studies ▪ Studies have found that between 5%-82% of patients have positive or close margins following BCT, with the majority of studies indicating positive marginsa in 20%-40% of patients
Morrow et al., 2012; McCahill et al., 2012[19,20]	▪ Reviews of observational studies ▪ 20%-60% of women who undergo breast-conserving surgery require additional breast surgery after the initial lumpectomy

EORTC = European Organisation for Research and Treatment of Cancer; RCT = randomised controlled trial.
[a] Positive margins = tumour cells at inked margin.

The Effect of Positive Margins on Future Treatment

- Guidelines recommend that patients with positive margins after BCT undergo repeat surgery.[13,14,16]
  - Re-excision is still the most effective treatment in patients with positive margins, and radiotherapy cannot be used in its place.[9]
- In two surveys identified, the majority of surgeons would recommend re-excision in cases where there is a tumour within 1 mm of the inked margin (Figure 1).[12,21]

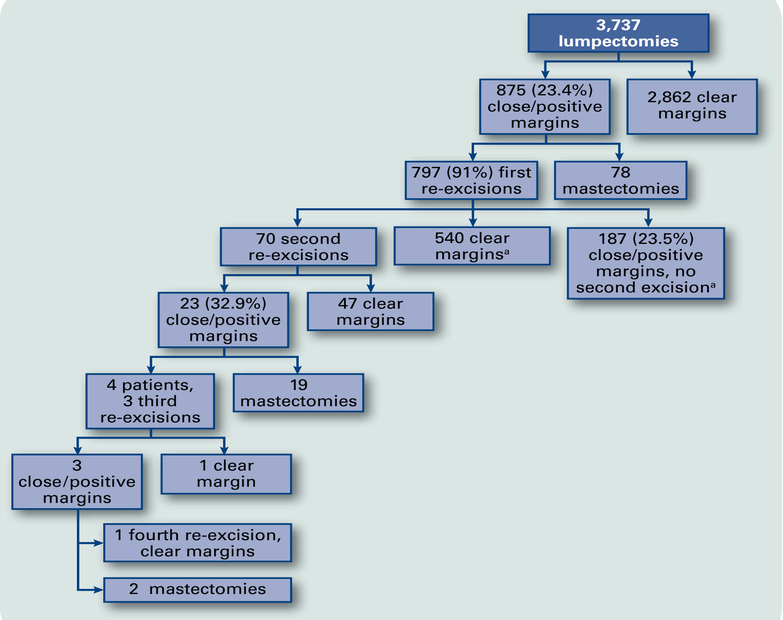
Figure 1. Percentage of Oncologists or Surgeons Who Always Recommended Re-excision According to Distance of Tumour Cells From Inked Margin



Sources: Taghian et al., 2005; Lovrics et al., [201212,21]

- In the identified studies that were designed to assess rates of re-excision following lumpectomy:
  - 20%-30% of patients required re-excision
  - ~2% of patients had multiple re-excisions (2 or more)
  - 10%-15% of patients who had lumpectomy required mastectomy subsequently
- Figure 2 presents re-excision data from one of the identified studies.

Figure 2. Surgical Outcome for Patients Undergoing Lumpectomy: Rates of Repeat Surgery



[a] Coopey et al.[10] states that "of the [797] patients who had one re-excision, 257 (32.2%) continued to have close or positive margins. Seventy of these patients underwent additional re-excisions and form the basis of this study." Therefore, the treatment path of the 187 patients who did not undergo a second re-excision is not clear. From the data provided, we can impute that 540 patients had clear margins after the first re-excision.

- The effect of positive margins on the proportion of patients undergoing repeat surgery is a result of what physicians believe, what patients are willing to accept, and what the health care system will support doing, and all of these could vary by country, region, even hospital, level of patient education, and potentially many other factors.

The Relationship Between Positive Margins and Disease-Free Survival and Overall Survival

- The identified studies consistently found a significant relationship between positive margins and local disease-free survival.
  - In a systematic review and meta-analysis by Houssami and colleagues, odds ratio for local recurrence was 2.42 for positive versus negative margins (95% confidence interval, 1.94-3.02; $P < 0.001$).[4]
  - However, among patients with a clear margin, width was not clearly related to risk of local recurrence.
- Three of four studies that assessed the effect of margin status on overall survival reported a significant association:
  - For example, in a retrospective review of data from 607 consecutive invasive breast carcinomas in 583 patients treated at a US centre between 1980-1996, overall survival and cause-specific survival at 12 years were significantly associated with margin status ($P = 0.0032$ and $P < 0.001$, respectively [Table 3]).[22]

Table 3. Association Between Margin Status and Survival

Margin Status	12-Year Overall Survival (%)	12-Year Cause-Specific Survival (%)
Negative (> 2.1 mm)	78	92
Close (0.1–2.1 mm)	70	86
Positive (cancer cells at inked margin)	65	71

Source: Goldstein et al., 2003.[22]

CONCLUSIONS

- Definition of adequate margins remains controversial.
- Nonetheless, final margin status is a key prognostic factor following BCT.
- The data identified suggest that an intervention that reduces the rates of positive margins during BCT may have the potential to improve outcomes and reduce the burden on patients and health care providers.

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Presented at ISPOR 16th Annual European Congress; November 2-6, 2013; Dublin, Ireland