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Original article

Surgical margins and risk of locoregional recurrence in invasive breast cancer: An analysis of 10-year data from the Breast Cancer Treatment Quality Assurance Project

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ABSTRACT

Aim: There is debate as to what constitutes an adequate excision margin to reduce the risk of locoregional recurrence (LRR) after breast cancer surgery. We have investigated the relationship between surgical margin distance and LRR in women with invasive breast cancer (IBC).
Methods: Tumour free margin distances were extracted from histopathology reports for women with IBC, treated by either breast conserving surgery or mastectomy, enrolled in the Breast Cancer Treatment Group Quality Assurance Project from July 1997 to June 2007. Cox proportional hazards regression analyses were conducted to compare the risk of LRR for involved margins compared with negative margins, measured in increments rounded to the nearest mm.
Results: 88 of 2300 patients (3.8%) experienced an LRR after a mean follow-up of 7.9 years. An involved margin, or a margin of 1 mm was associated with an increased risk of LRR (HR 2.72, 95% CI 1.30–5.69), whilst margin distances of 2 mm or greater were not. Risk of LRR with margin distances <2 mm was particularly high amongst those not receiving radiotherapy (RT).
Conclusion: Based on our findings, we recommend that a tumour free margin distance of 2 mm be adopted as an adequate margin of excision for IBC, in the setting of patients receiving standard adjuvant RT and adjuvant drug therapies as dictated by the current clinical treatment paradigms.

Introduction

Breast cancer (BC) remains a significant cause of mortality and morbidity worldwide. Despite substantial improvements in the detection and treatment of BC, the issue of what constitutes an adequate surgical margin of clearance for invasive breast cancer (IBC) remains contentious. This is particularly true for breast conserving surgery (BCS), which aims to achieve optimal clearance of IBC, whilst preserving breast cosmesis. In theory, although a wider margin of excision should result in a reduced risk of locoregional recurrence (LRR) and disease progression, wider margins may lead to a poorer cosmetic result, potentially negating the benefits of BCS over mastectomy. Similarly, aiming for wider margins than are actually needed to achieve adequate disease control may result in women undergoing unnecessary repeat surgery. Repeat surgery can impact on breast cosmesis, expose women to an increased risk of surgical complications and increase the financial and psychosocial cost of BC treatment.

Whilst the question of what constitutes an adequate margin of clearance for IBC is not new, surveys have demonstrated that divergent opinions amongst surgeons persist.[1,2] Given an example of a 60-year-old woman with an 8 mm grade III upper outer quadrant IBC, one survey of surgeons from the United States found that 11% considered absence of tumour cells at the inked margin to be adequate, 42% endorsed a margin of 1–2 mm, 25% endorsed a margin of ≥5 mm while 19% endorsed a margin of >10 mm[1]. This lack of consensus is reflected in the design of previous studies, where a 'negative' margin across different studies may be classified

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as anywhere from 'no cancer cells at the inked margin', as in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 trial, to no cancer cells at >5 mm from the cut margin in other studies.[3,4]

In Australia, the Australian Capital Territory (ACT) and South-Eastern New South Wales (SE NSW) Breast Cancer Treatment Group established the Breast Cancer Treatment Quality Assurance Project (BCTQAP), which began accruing patients in 1997.[5] Patients participating in the project gave informed consent for details of their demographic status, treatment, histopathology and results of annual follow-up to be entered into a database, with the aim of monitoring BC treatment and outcomes in the region. Over the first 10 years, the project accrued 2911 patients, providing a large cohort for further research.

The aim of our study was to investigate the relationship between surgical margin distance and LRR for women with IBC included in the 10 year BCTQAP dataset.

Materials and methods

Patient selection

Patients enrolled in the BCTQAP from July 1997 to June 2007 treated by either BCS or mastectomy for IBC and for whom at least 3 years follow-up data were available, were included in the study. Patients with Paget's disease of the breast, phyllodes tumour, IBC of special types, bilateral or metachronous BC and those with evidence of distance metastasis at the time of surgery were excluded from the study. LRR of BC during the follow-up period was considered to be local recurrence of BC in the same breast or underlying fascia/muscle, or regional recurrence in ipsilateral axillary lymph nodes that had previously been regarded as pathologically and radiologically normal.

Measurements of tumour size and distance in millimetres of all surgical margins (lateral, medial, superficial, deep, superior and inferior) for both the invasive tumour and any additional ductal carcinoma in situ (DCIS) were extracted from the original histopathology reports for each patient. Parameters for lymphovascular invasion (LVI) (absent, limited, extensive or unknown) were also recorded. Where a patient had undergone one or more re-excision procedures or completion mastectomy, the margin measurements for the final procedure were recorded. In instances where margin distances for a specific margin were missing from the histopathology report, if available, the original glass slides were reviewed by an experienced breast pathologist or the diagram indicating the margins was sourced. If the margins could not be determined the case was excluded from subsequent analysis. For all patients with recorded margins of <2 mm, the histopathology reports were examined by a second reviewer for verification. Patients' survival status, date of death and date of first evidence of LRR or distant recurrence (if any) were collected through surveys of the treating clinicians and the patient's General Practitioner, one year after diagnosis and then every two years.

Data analysis

Data extracted for tumour size, margin distance and LVI were integrated into the existing 10-year BCTQAP dataset. Characteristics of the study group were examined using frequency distributions. Mean follow-up times were derived from dates of diagnosis, progression and death. The rate of recurrence within the study population was determined using actuarial methods.

Univariate and multivariate analyses were undertaken using Cox proportional hazards regression. The outcome of interest in these models was time to local recurrence (i.e. time from date of diagnosis to date of disease relapse). If either date was unknown, the date of the first surgical procedure and/or the date of the first treatment following progression were substituted. Time was censored at August 01 2011, or at death or at recurrence, whichever came first. For regression modelling, variables with missing data were collapsed into 'yes' or 'no/not reported'. The exception was for cases with missing grade ($n = 20$), which were excluded from multivariate analyses.

A series of models was undertaken examining the effect of the closest invasive margin distance on risk of local recurrence, for all cases and separately for those treated by BCS or mastectomy, and for those receiving radiotherapy or not.

In each of these models, margin clearance was coded as the distance of the closest invasive margin to the nearest mm (rounded) between 0 mm and 5 mm, with >5 mm as the reference category. The effect of any margin distance (rather than just the invasive margin) was also examined in separate analyses, with margin distances derived from the closest invasive or DCIS margin. In each of these models, effects were adjusted for other prognostic factors, including patient age, tumour size and grade of the invasive component, tumour hormone receptor status, nodal

Table 1
Study population characteristics.

Characteristic		N	%
Patient age	<50 years	626	27.2
	50–59 years	769	33.4
	60–69 years	535	23.3
	70+ years	370	16.1
Menopausal status	Premenopausal	612	26.6
	Perimenopausal	220	9.6
	Postmenopausal	1468	63.8
Tumour size[a]	≤5 mm	129	5.6
	>5–10 mm	337	14.7
	<10–20 mm	890	38.7
	>20–50 mm	805	35.0
	>50 mm	139	6.0
Tumour grade[b]	1	669	29.1
	2	894	38.9
	3	717	31.2
	Unknown	20	0.9
Tumour ER status	Positive	1870	81.3
	Negative	417	18.1
	Unknown	13	0.6
Tumour PR status	Positive	1601	69.6
	Negative	683	29.7
	Unknown	16	0.7
Multifocality	Yes	384	16.7
	No	1916	83.3
DCIS present	Yes	1462	63.6
	No	838	36.4
Nodal status	Positive	837	36.4
	Negative	1325	57.6
	Unknown	138	6.0
LVI	Yes	573	24.9
	No	1661	72.2
	Unknown	66	2.9
Surgery type	Breast conservation	1123	48.8
	Mastectomy	1177	51.2
Axillary surgery	None	139	6.0
	Sampling	64	2.8
	Clearance	1178	51.2
	Sentinel LNB	533	23.2
	Sentinel LNB + clearance	386	16.8
Recurrence	LRR	61	2.7
	Distant	200	8.7
	LRR + distant	27	1.2
	None	2012	87.5

LNB = lymph node biopsy; LVI = lymphovascular invasion; DCIS = ductal carcinoma in situ.

[a] Total tumour size including DCIS component.

[b] Grade of invasive tumour.