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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.

status, presence of LVI, surgical approach (except when stratified by surgery type), and whether RT, chemotherapy and endocrine therapy was given. Adjustment was also made for DCIS margin distance as a categorical variable (≤2 mm versus >2 mm) in models examining only the invasive margin distance. No evidence of co-linearity was observed in any of the models. All analyses were carried out using Stata v11.

Results

Of the 2307 women with IBC initially eligible for inclusion in our study, seven were excluded because the margins of excision were not provided in the report or were unable to be determined by review of the slides or diagram. Therefore, 2300 women were included in the final analyses. A total of 1123 (48.8%) women had BCS whilst 1177 (51.2%) had a mastectomy (Table 1). Of the women that had BCS, 968 (86.2%) had one operation, 149 (13.3%) had two operations and 6 (0.5%) had three operations. Of the women that had a mastectomy, 297 (25.5%) had previously had BCS. Thus 452 women (19.7%) in the cohort had a re-excision or mastectomy following original BCS. A total of 288 women experienced a recurrence of BC during the follow-up period, of which 88 were LRRs. Of these 88 LRRs, 28 (31.8%) had local recurrence only, 23 (26.1%) had regional recurrence only and 10 (11.4%) had synchronous local and regional recurrence. The remaining 27 (30.7%) had recurrence in local and/or regional sites plus recurrence in distant sites. The mean follow-up was 7.9 years (range = 1.4–171 months). Mean time to recurrence for those with LRR was 4.2 years (range = 2.2–153 months). Over the first 10 years of follow-up, the average recurrence rate was 46.6/1000 per year.

Specific margin distances for each surgical approach are shown in Table 2. In general, margins tended to be closer after BCS than mastectomy, except in the case of the deep margin where there was no statistically significant difference between BCS and mastectomy.

Patient and tumour characteristics found to be associated with a higher risk of LRR in univariate analyses were age less than 50 years, premenopausal status, BC detected through self-examination, invasive tumour size larger than 20 mm, grade 2 or 3 IBC, positive nodal status at time of diagnosis and presence of LVI (Table 3). The tumour being hormone receptor positive (ER and/or PR positive) was associated with a reduced risk of LLR. Treatment factors associated with increased risk of LRR included having surgery outside the ACT, receiving chemotherapy and not having sentinel nodes examined. A trend towards a higher risk of LRR for women undergoing mastectomy rather than BCS was observed, but this did not reach statistical significance. A lower risk of LRR was observed for women that had received hormone therapy. Having any "close" margin (invasive >0–<2 mm) was associated with an increased risk of LRR (HR = 3.27, 95% CI 1.83–5.84, $p = 0.001$), but while the risk was increased for involved margins, the difference was not statistically significant at the $\alpha = 0.05$ level (HR = 2.73, 95% CI 0.84–8.77, $p = 0.092$).

Table 4 shows the results of the multivariate Cox proportional hazards regression analyses for margin distance, rounded to 1 mm increments. An involved margin or margin of 1 mm was associated with an increased risk of LRR (HR 3.24, 95% CI 1.46–7.17, $p = 0.004$; HR 2.72, 95% CI 1.30–5.69, $p = 0.008$, respectively), whilst margin distances of 2 mm and greater showed no increased risk of LRR. There did not appear to be any statistically significant reduction in the risk of LRR for margins wider than 2 mm. Adjusting for the margin distance of any additional DCIS did not make any significant difference to the overall result. Likewise, inclusion of margin distance for any DCIS component in addition to the invasive component did not alter the results significantly.

The risk of LRR by margin distance, stratified by surgical approach and RT are shown in Table 5. The risk of LRR was significantly elevated for both involved margins and margins of 1 mm in those who did not receive RT (HR = 10.4, 95% CI 1.92–56.0, $p = 0.007$; HR = 8.2, 95% CI 2.42–27.6, $p = 0.001$ respectively) in models adjusted for surgical approach. For those who did receive

Table 2
Specific margin distances according to surgical approach.

Margin	Surgical approach	Involved (0 mm)	>0 mm–<2 mm	2 mm–5 mm	>5 mm	*p* value
Invasive						
Superficial	Breast conservation	8 (0.7)	19 (1.7)	100 (8.9)	994 (88.7)	<0.001
	Mastectomy	8 (0.7)	13 (1.1)	44 (3.8)	1108 (94.6)	
Medial	Breast conservation	1 (0.1)	11 (1.0)	24 (2.1)	1086 (96.8)	0.001
	Mastectomy	0 (0.0)	4 (0.3)	6 (0.5)	1166 (99.2)	
Lateral	Breast conservation	1 (0.1)	7 (0.6)	29 (2.6)	1086 (96.7)	<0.001
	Mastectomy	2 (0.2)	1 (0.1)	5 (0.4)	1168 (99.3)	
Inferior	Breast conservation	4 (0.4)	15 (1.3)	94 (8.4)	1009 (89.9)	<0.001
	Mastectomy	3 (0.3)	8 (0.7)	19 (1.6)	1146 (97.5)	
Deep	Breast conservation	10 (0.9)	67 (6.0)	189 (16.8)	856 (76.3)	0.227
	Mastectomy	17 (1.4)	55 (4.7)	182 (15.5)	923 (78.4)	
Superior	Breast conservation	3 (0.3)	17 (1.5)	111 (9.9)	991 (88.3)	<0.001
	Mastectomy	1 (0.1)	7 (0.6)	10 (0.9)	1158 (98.5)	
DCIS[a]						
Superficial	Breast conservation	5 (0.8)	16 (2.4)	49 (7.5)	585 (89.3)	0.001
	Mastectomy	4 (0.5)	9 (1.2)	26 (3.3)	742 (95.0)	
Medial	Breast conservation	3 (0.5)	7 (1.1)	9 (1.4)	634 (97.1)	0.141
	Mastectomy	3 (0.4)	3 (0.4)	4 (0.5)	769 (98.7)	
Lateral	Breast conservation	2 (0.3)	5 (0.8)	20 (3.1)	626 (95.9)	0.001
	Mastectomy	1 (0.1)	2 (0.3)	4(0.5)	772 (99.1)	
Inferior	Breast conservation	8 (1.2)	10 (1.5)	52 (7.9)	586 (89.3)	<0.001
	Mastectomy	6 (0.8)	6 (0.8)	15 (1.9)	754 (96.5)	
Deep	Breast conservation	5 (0.8)	40 (6.1)	106 (16.2)	503 (76.9)	0.386
	Mastectomy	13 (1.7)	41 (5.6)	119 (15.2)	609 (77.9)	
Superior	Breast conservation	5 (0.8)	14 (2.1)	65 (9.9)	573 (87.2)	<0.001
	Mastectomy	6 (0.8)	6 (0.8)	7 (0.9)	761 (97.6)	
Closest (DCIS or invasive)	Breast conservation	38 (3.4)	115 (10.2)	384 (34.2)	586 (52.2)	<0.001
	Mastectomy	39 (3.3)	95 (8.1)	226 (19.2)	817 (69.4)	

DCIS = ductal carcinoma in situ.
[a] Among those with DCIS component only.

Table 3
Relationship between demographic, clinical and treatment factors and risk of LRR.

Demographic, clinical and treatment factors		LRR	Total	% LRR	Crude HR	95% CI	*p* value
Age group	<50 years	43	626	6.9	2.61	1.55–4.39	<0.001
	50–59 years	21	769	2.7	1.00	1.00	
	60–69 years	11	535	2.1	0.79	0.38–1.64	0.532
	70+ years	13	370	3.5	1.50	0.75–3.00	0.253
Menopausal status	Post-menopausal	40	1468	2.7	1.00		
	Pre-menopausal	41	612	6.7	2.35	1.52–3.63	<0.001
	Peri-menopausal	7	220	3.2	0.99	0.44–2.20	0.972
Family History	Average	74	1852	4.0	1.00		
	Mod. increased	8	234	3.4	0.93	0.45–1.92	0.835
	High risk	5	200	2.5	0.73	0.30–1.82	0.504
Detection	BreastScreen	15	709	2.1	1.00		
	Specialist/other	8	432	1.9	0.87	0.37–2.04	0.741
	Self	65	1159	5.6	2.93	1.67–5.13	<0.001
Tumour size[a]	≤10 mm	10	466	2.2	1.00		
	>10–20 mm	27	890	3.0	1.43	0.69–2.95	0.335
	>20–50 mm	43	805	5.3	2.76	1.38–5.48	0.004
	>50 mm	8	139	5.8	3.58	1.41–9.08	0.007
Grade[a] [b]	1	10	669	1.5	1.00		
	2	30	894	3.4	2.44	1.19–5.00	0.014
	3	48	717	6.7	5.49	2.78–10.9	<0.001
ER[b]	Negative	37	417	8.9	1.00		
	Positive	51	1870	2.7	0.27	0.18–0.41	<0.001
PR[b]	Negative	41	683	6.0	1.00		
	Positive	47	1601	2.9	0.40	0.29–0.67	<0.001
Multifocal	No	72	1916	3.8	1.00		
	Yes	16	384	4.2	1.15	0.67–1.98	0.611
DCIS present	Yes	62	1462	4.2	1.00		
	No	26	838	3.1	1.47	0.93–2.32	0.103
Nodal status	Positive	48	837	5.7	1.00		
	Negative	36	1325	2.7	2.43	1.57–3.74	<0.001
	Unknown	4	138	2.9	1.06	0.38–2.97	0.918
LVI	No	41	1661	2.5	1.00		
	Yes	44	573	7.7	3.45	2.25–5.28	<0.001
	Unknown	3	66	4.6	1.51	0.47–4.90	0.491
Surgery type	Breast conservation	35	1123	3.1	1.00		
	Mastectomy	53	1177	4.5	1.52	0.99–2.33	0.056
Surgery place	ACT	69	1991	3.5	1.00		
	SE NSW/other	19	309	6.1	1.79	1.07–2.97	0.025
Surgical revision	No	66	1848	3.6	1.00		
	Yes	22	1452	4.9	1.20	0.74–1.95	0.455
Radiotherapy	Not offered/refused	33	843	3.9	1.00		
	Yes	55	1457	3.8	0.97	0.63–1.50	0.898
Hormone therapy	Not offered/refused	37	553	6.7	1.00		
	Yes	51	1747	2.9	0.41	0.27–0.62	<0.001
Chemotherapy	Not offered/refused	28	1188	2.4	1.00		
	Yes	60	1112	5.4	2.48	1.58–3.88	<0.001
Closest margin[c]	>5 mm	48	1501	3.2	1.00		
	≥2 mm–<5 mm	22	593	3.7	1.18	0.71–1.95	0.525
	>0 mm–<2 mm	15	163	9.2	3.27	1.83–5.84	<0.001
	0 mm (involved)	3	43	7.0	2.73	0.85–8.77	0.092

LRR = locoregional recurrence; HR = hazard ratio; CI = confidence interval; ER = oestrogen receptor; PR = progesterone receptor; DCIS = ductal carcinoma in situ; LVI = lymphovascular invasion.
[a] Invasive tumour component.
[b] No LRR occurred among those with missing grade, missing ER or PR.
[c] Nearest invasive margin.

RT, there was also an elevated risk of LRR observed for involved margins, with borderline statistical significance (HR = 2.50, 95% CI 1.00–6.29, $p = 0.051$). Multivariate modelling of locoregional recurrence with or without radiotherapy were attempted for BCS and mastectomy separately. Small numbers in these analyses produced confidence intervals that were very wide and the results not considered meaningful.

Discussion

Our study, which examines the outcomes of 2300 women with a mean follow-up of 7.9 years, supports the adoption of 2 mm as the standard minimum margin of clearance required to achieve adequate local control of IBC in patients undergoing BCS or mastectomy. Whilst having a margin of ≤1 mm was associated with an increased risk of LRR, no statistically significant reduction in the risk of LRR was found for margins wider than 2 mm, even after adjusting for the margin distance of any additional DCIS. In addition, the risk of LRR with margin distances <2 mm was particularly high amongst those not receiving RT. Locoregional relapse is the outcome used in this study. Of the 88 patients that had locoregional relapse, 38 patients had relapse involving the breast or chest wall.

There have been conflicting recommendations as to what should constitute a negative surgical margin of clearance for IBC. Consensus recommendations from an international panel of experts including specialists in the fields of oncologic surgery, radiation oncology, pathology, radiology, medical oncology and epidemiology have endorsed the adoption of “tumour not touching

Table 4
Hazard ratio (HR) for LRR of BC for closest invasive margin relative to all invasive margins >5 mm (model 1), with adjustment for DCIS margin <=2 mm (model 2), and for closest surgical margin distance DCIS and invasive margins combined (model 3). $N = 2277$.

	Model 1			Model 2			Model 3			
	HR	95% CI	*p* value	HR	95% CI	*p* value		HR	95% CI	*p* value
Invasive Margin							Any Margin			
>5 mm	1.00			1.00			>5 mm	1.00		
5 mm	1.18	0.53–2.64	0.686	1.16	0.52–2.61	0.714	5 mm	0.85	0.33–2.17	0.738
4 mm	0.64	0.16–2.66	0.542	0.63	0.15–2.62	0.526	4 mm	0.63	0.15–2.61	0.523
3 mm	1.66	0.80–3.44	0.169	1.65	0.80–3.41	0.178	3 mm	1.45	0.67–3.12	0.343
2 mm	1.14	0.45–2.90	0.786	1.05	0.40–2.77	0.926	2 mm	0.98	0.38–2.48	0.958
1 mm	2.72	1.30–5.69	0.008	2.44	1.09–5.49	0.030	1 mm	2.30	1.17–4.51	0.016
0 mm	3.24	1.46–7.17	0.004	3.05	1.34–6.91	0.007	0 mm	2.48	1.26–4.88	0.008
DCIS margin										
>2 mm or nil	–	–	–	1.00	–	–		–	–	–
≤2 mm	–	–	–	1.25	0.65–2.40	0.509		–	–	–

All models adjusted for age, total tumour size, invasive tumour grade, oestrogen/progesterone receptor status, lymphovascular invasion, lymph node involvement, surgical approach and whether radiotherapy, chemotherapy and hormone therapy were given. Missing grade excluded, CI = confidence interval; DCIS = ductal carcinoma in situ.

ink" as the standard definition of an adequate negative margin in patients with IBC undergoing BCS.[6] This recommendation appears to have largely been based on the results of the NSABP trials with node negative protocols,[7] which used this definition of a negative margin and a review that found a lack of consistent evidence that wider margins decrease ipsilateral breast tumour recurrence.[8] In contrast, the surgical guidelines for the management of BC, published by the Association of Breast Surgery at the British Association of Surgical Oncology, note that there are no randomised trials of margins of excision and recommend that if, after discussion at a multidisciplinary team meeting, the margin of excision is deemed to be inadequate then further surgery to obtain clear margins should be recommended. Similarly, the National Institute for Health and Clinical Excellence (NICE) guidelines for the diagnosis and treatment of early and locally advanced BC, whilst recommending a margin of 2 mm for DCIS, note that the optimum clear margin for IBC has yet to be defined.[9] It is also worth noting that in our study, the highest rates of involved or close (<2 mm) margins were observed for the superficial and deep margins. Whether further surgery or post-operative RT should be performed when these margins are involved represents another controversial issue in breast cancer treatment.[10–12]

Houssami et al. found that although margin status (that is, tumour cells present at an inked margin) was associated with an increased odds of LRR in women with early stage IBC treated with BCS, only a weak trend towards a reduced odds of LRR was observed for threshold distances of 1 mm, 2 mm or 5 mm and after adjusting for the proportion of subjects receiving a radiation boost or endocrine therapy, this effect was rendered insignificant.[13] Similarly, Groot et al. compared 201 'narrow but negative margin' cases (≤2 mm) with 500 'wide margin' cases (>2 mm), all of whom received RT, and found no statistically significant increase in LRR for narrow margins.[14]

Consistent with our results, previous studies have shown that younger age, premenopausal status, BC detected through self-examination, invasive tumour size larger than 20 mm, high grade IBC, positive nodal status at time of diagnosis and presence of LVI are associated with a higher risk of LRR in univariate analyses.[15–17] Similarly, a decreased risk of LRR with positive oestrogen and/or progesterone receptor status and the use of hormonal therapy has been demonstrated previously.[15–17] Multifocal IBC has been associated with a higher risk of LRR in patients that have not received RT.[3,18–20] We found no association, but only 16 patients with multifocal IBC were diagnosed with LRR. Patients with multifocal IBC were far more likely to have had a mastectomy rather than BCS, so the lack of an association between multifocal IBC and LRR may reflect more aggressive surgery in these patients. Other factors that have been associated with an increased risk of LRR, but were not examined in our study, include triple-negative IBC subtype[15,17] and technical factors such as method of tumour localisation.[21]

Several studies have demonstrated that the majority of BC LRRs occur within five years of primary treatment,[22–24] consistent with this, the mean time to LRR in our study was 4.2 years. Therefore, we believe that, with a mean follow-up of 7.9 years, our study should have had sufficiently long follow-up for the majority of LRR in the study cohort to be detected. Our 10-year local recurrence rate of 4.7% is similar to the NSABP trials, where rates ranged from 3.5 to 6.5% for patients receiving BCS.[25]

Interestingly, the risk of LRR amongst women receiving BCS was significantly higher for those with margins of 1 mm or less, although a statistically significant increase in risk was not observed for women with involved margins. A similar effect was not

Table 5
Hazard ratio (HR) for locoregional recurrence of BC for nearest invasive surgical margin distance stratified according surgery type and whether radiotherapy was given.

Invasive margin	Surgery						Radiotherapy					
	BCS ($n = 1113$)			Mastectomy ($n = 1164$)			No ($n = 828$)			Yes ($n = 1449$)		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
>5 mm	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–
5 mm	1.13	0.32–3.96	0.852	1.36	0.47–3.91	0.565	1.10	0.25–4.85	0.900	1.13	0.43–2.97	0.803
4 mm	0.53	0.07–4.15	0.546	0.73	0.10–5.37	0.757	–	–	–	0.94	0.22–4.01	0.938
3 mm	1.39	0.46–4.21	0.551	1.57	0.54–4.56	0.403	2.78	0.91–8.52	0.073	1.40	0.53–3.70	0.495
2 mm	1.55	0.44–5.47	0.493	0.79	0.19–3.39	0.755	1.77	0.22–13.1	0.610	0.99	0.34–2.83	0.980
1 mm	4.35	1.67–11.4	0.003	1.26	0.29–5.41	0.753	8.18	2.42–27.6	0.001	1.77	0.67–4.67	0.245
0 mm	1.92	0.41–8.89	0.405	3.63	1.36–9.70	0.010	10.4	1.92–56.0	0.007	2.50	1.00–6.29	0.051

Models adjusted for age, total tumour size, invasive tumour grade, oestrogen/progesterone receptor status, lymphovascular invasion, lymph node involvement, whether hormone therapy and chemotherapy was given, DCIS involvement and surgical approach or whether radiotherapy given (where relevant), BCS = breast conserving surgery, CI = confidence interval.

observed for women undergoing mastectomy, for whom only those with involved margins had a significantly increased risk of LRR. When these results were stratified according to the use of RT and adjusted for the surgical approach, women who did not receive RT and had either involved margins or margins of 1 mm or less had an elevated risk of LRR, whilst for those who did receive RT neither involved nor margins of 1 mm or less were associated with a significantly increased risk. This reiterates previous findings that RT reduces rates of LRR[24] and suggests that for women treated with BCS in our study, RT may have masked the effect of involved margins on the risk of LRR.

Limitations of our study were the fact that central histopathology was not performed and data were extracted from reports prepared by multiple histopathologists from several different laboratories. This meant our study lacked standardised histopathology reporting, and consequently precise measurements for each margin distance were not always available for every patient. Therefore, some margin distances were determined based on size of the tumour, distance of the specified margins and macroscopic dimensions of the specimen. These margins were generally described as 'well clear' in the microscopic report. In a few reports the margins of excision could not be determined and these cases were excluded from the analysis. Although the use of non-standardised histopathology reports may have affected the precision of our data for wider margins, it is unlikely to have impacted on the validity of our findings with respect to margins of 2 mm or less. A structured breast cancer histopathology reporting protocol has been recommended and is currently being adopted in Australia, which should facilitate standardised reporting in future studies.[26,27]

Overall, our results suggest that a reduction in the risk of LRR following BCS or mastectomy for IBC can be obtained by aiming for margins that are wider than simply 'no cancer cells at the inked margin', with a margin of 2 mm achieving local control comparable to a margin of 5 mm or greater.

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 radiotherapy and adjuvant drug therapies as dictated by the current clinical treatment paradigms.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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