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**A two millimetre free margin from invasive cancer
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TITLE PAGE

**A TWO MILLIMETRE FREE MARGIN FROM INVASIVE CANCER MINIMISES RESIDUAL
DISEASE IN BREAST-CONSERVING SURGERY****Ward ST, Jones BG, Jewkes AJ****CORRESPONDING AUTHOR:**

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KEYWORDS:

Surgical margins; Re-excision; Breast-conserving surgery; Breast neoplasm

ABSTRACT**Aims**

In breast-conserving surgery, the width of free margin around a tumour to ensure adequate excision is controversial. The aim of this study was firstly to evaluate the frequency of residual disease in wider excision specimens in patients who undergo further surgery due to close margins of less than 5 millimetres. Secondly, the ability of demographic and tumour-related factors to predict the close margins was appraised.

Patients and methods

Three-hundred-and-three patients were included in the study. Patients undergoing wider excision were assessed for the presence of residual disease and this was tested for association with the width of the initial free margin. Various factors were studied for association with close or involved margins by univariate analysis.

Results

Fifty-three percent of patients were eligible for re-excision based on the need for a 5 millimetre clearance. With a free margin of 2 mm or more from invasive cancer, the probability of finding residual disease was 2.3%. The probability of residual disease was higher for DCIS and did not decline with increasing free margin width.

Tumour size, lobular cancer type, vascular invasion and nodal involvement, were associated with close margins.

Conclusions

We suggest that a free margin of 2 mm from invasive cancer is adequate to minimise residual disease, whereas the equivalent free margin for DCIS is unclear. Patients with large tumours and lobular cancer type should be counselled at the time of first surgery concerning the higher risk of further excision and mastectomy.

Word count: 241

What is already known about this topic?

Following breast-conserving surgery, a margin involved with tumour is associated with residual disease and an increased risk of local recurrence. The necessary width of free margin to minimise both residual disease and local recurrence is controversial. The relationship between residual disease and local recurrence is also unclear.

What does this article add?

Our department requested re-excision of margins if the free margin width was less than 5 millimetres.

Most other units aim for less than a 5 millimetre free margin and we were thus well-positioned to study the relationship between free margin width and residual disease.

INTRODUCTION

Breast-conserving surgery (BCT) followed by adjuvant radiotherapy has been validated as an alternative to mastectomy over 20 years follow-up in selected patients [1,2]. These studies have demonstrated similar survival in both groups although there is an increased rate of local recurrence in patients undergoing BCT. Local recurrence has a detrimental effect on survival with nearly 50% patients with local recurrence having coincident distant disease [3,4].

There are no defined anatomical compartments in the breast and surgeons therefore rely on a rim of normal tissue around the tumour known as the *free margin* as evidence of complete removal. The most important factor determining local recurrence is the status of the free margin of the excised specimen [5]. Local recurrence occurs more frequently when there is no margin of normal tissue around the tumour despite adjuvant radiotherapy [6]. The width of free margin necessary to conclude that the tumour has been adequately excised is controversial and may differ for invasive cancer and ductal carcinoma in-situ (DCIS) [5,7].

A survey of two hundred breast surgeons from the United Kingdom revealed a wide variation in what is considered to be an adequate margin with 24% wanting a clear margin of 1 mm and 65% wanting a margin of 2 mm or more [8]. This study highlights a disparity in practice across different units and the need for evidence-based guidelines.

Marginal involvement is an indication for further surgery in the form of either wider excision or mastectomy and is frequently associated with residual disease in the further surgical specimen [6]. Further surgery when margins are not involved has been undertaken in order to gain a free margin clearance of 1, 2 or 5 mm [8]. Further surgery is obviously desirable if it leads to a risk reduction of local recurrence but negatively impacts on cosmesis as well as patient psychology and hospital resources. The relationship between residual disease and local recurrence is unclear [6].

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3 With a policy in place to undertake further surgery when required to gain a free margin of certain width,
4 pre-operative factors that could predict the likelihood of inadequate margins in BCT specimens could be
5 useful in both patient counselling and the selection of patients for more extensive primary surgery or
6 routine cavity shaving. Previous studies have found inconsistent associations of a wide range of factors
7 available pre-operatively with the presence of involved margins and residual disease [6,9].
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15 During the study period, our unit aimed for a free margin of 5 mm in patients undergoing breast-conserving
16 surgery for both invasive cancer and DCIS. The association between the width of free margin and residual
17 disease in wider excision specimens was evaluated to guide local policy. Various demographic and
18 tumour-related factors were also studied for an association with inadequate margins in order to establish
19 how these factors could influence the nature or extent of surgery.
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PATIENTS AND METHODS

The Good Hope Hospital Breast Cancer Database (GHHBCD) identified 310 patients who underwent breast-conserving surgery for breast cancer between 1st October 2002 and 22nd October 2008. These patients all had a pre-operative histological diagnosis of probable invasive cancer or DCIS, but seven patients were excluded due to absent or benign disease following excision, leaving a total of 303 patients in the study population.

The BCT specimens were oriented by the surgeon using sutures and in some instances, accompanied by one or more cavity shaves before submission for histopathological analysis. For ease of discussion, cavity shave specimens taken at the initial operation will be referred to as *primary cavity shaves*.

Surgical specimens were immediately placed in 10% neutral buffered formalin and transported to the pathology department. The specimens were left in formalin for a minimum period of 24 hours. BCT specimens were sliced at 5 mm intervals usually in the direction of the shortest axis. Every radial and deep margin of BCT specimens were analysed, taking at least three blocks of tumour from the closest macroscopic margins. Most or all of the tissue from cavity shave specimens were embedded for microscopic examination.

The distance between the tumour and the margin on microscopic assessment was noted for the following margins: medial, lateral, superior and inferior by analysis of pathology reports. A free margin width of less than 5 mm for either invasive cancer or DCIS was deemed to be inadequate in our unit, prompting either a wider excision or mastectomy. Anterior (superficial) and deep margins were not assessed in this study because generally wider excision was not performed if the anterior or deep free margin was less than 5 mm. The ability to perform a wider excision of the anterior and deep margins is frequently limited by the location of the tumour and there is evidence that most recurrences in relation to breast tissue occur along radial margins [10].

For those patients who underwent wider excision following BCT, the presence of residual disease was determined. Residual disease was defined as the presence of either invasive cancer or DCIS. Those

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3 patients who underwent completion mastectomy or who were treated with chemoradiotherapy between the
4 primary and further operations were excluded from the analysis. Some patients underwent wider excision
5 of two or more margins sent as separate specimens, enabling the histopathological assessment of each
6 margin and its wider excision to contribute separately to the analysis.
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13 In the second part to the study, patients were classified into two groups: *Close margins* (one or more free
14 margins of less than 2 mm at BCT) and *clear margins* (all free margins 2 mm or more). The two groups
15 were compared for differences in demographic factors (age at diagnosis, tumour laterality), pathological
16 factors (tumour grade, tumour type, presence of vascular invasion, use of a primary cavity shave) and
17 radiological factors (ultrasound-determined tumour size). Ultrasound-determined measurements were
18 chosen because they were thought to be more objective than clinical measurements and were more
19 frequently performed than mammographic measurements.
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29 The experimental protocol was approved by the Good Hope Hospital Research and Ethics Committee. All
30 breast cancer database data, pathology report data and radiology report data were tabulated using Microsoft
31 Excel 2007 and statistical analysis was performed using StatView (v5.0, SAS Inst. Inc.). The Mann-
32 Whitney U-test was used to test for statistical significant differences in age, and tumour size while Chi-
33 squared analysis was used to test for statistical significant differences in tumour grade and type and the
34 presence of vascular invasion. χ^2 and P-values were calculated to three significant figures.
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RESULTS

Of the 303 patients in the study population, 93 (31%) patients underwent a wider excision and 39 (13%) a completion mastectomy. This left 171 (56%) patients who did not proceed to further surgery. Eleven patients in the wider excision group progressed to a third operation, all mastectomies.

Based on the criteria for free radial margins of 5 mm, 161 (53%) patients were eligible for further surgery although only 132 (44%) actually proceeded to this.

Of the 93 patients undergoing a wider excision, 140 wider excision specimens (88 for invasive cancer and 52 for DCIS) were analysed, a mean of 1.5 wider margins per patient.

Width of free margin and residual disease in wider excision specimens

The percentage of wider excision specimens found to contain residual disease declined with increasing width of the free margin from invasive cancer at first surgery (see table 1). With a free margin of 2 mm or more, the probability of finding residual disease was 2.3%.

Regarding the relationship between the width of the free margin from DCIS and the percentage of wider excision specimens with residual disease, the overall probability of residual disease was higher for DCIS than for invasive cancer and this probability did not appear to decline as rapidly with an increasing width of free margin.

Demographic and tumour-related factors

Comparison between the *close* and *clear* patient groups revealed a statistically significant association between tumour size, the presence of vascular invasion and nodal involvement with close margins (see table 2). Despite no overall association between the various tumour types and close margins, there was a statistically significant association when comparing the frequency of only ductal and lobular invasive carcinomas. Of the above factors, tumour size (as determined by ultrasound) and tumour type would be available to the surgeon pre-operatively.

DISCUSSION

Our results clearly show a relationship between the width of the free margin and the likelihood of finding residual disease at further surgery. In order to minimise the risk of residual disease, we would recommend aiming for a free margin from invasive cancer of 2 mm. A free margin of 2 mm from DCIS was associated with a higher probability of residual disease but this analysis was based on fewer numbers.

From a logical standpoint, adequate excision should only demand a margin that is not directly involved with disease. However, the methodology employed to pathologically assess margin status is imprecise [5,7]. A single haematoxylin and eosin slide of a 2-3 mm block from a BCT specimen visualizes less than a thousandth of its surface area and therefore evaluation of margins is made by random and not complete examination of the surface [11]. A width of free margin is thus simply a marker of increased probability of adequate local excision of the tumour. A study of mastectomy specimens found that if hypothetical BCT surgery had been performed with free margins as great as 20 mm, foci of invasive tumour would remain in the breast in 14% cases [12]. This is because breast cancer is a disease of multifocality, multicentricity and discontinuous spread.

Studies have demonstrated an association between the width of the free margin and the probability of residual disease following wider excision [7,9,13,14]. A study of 211 patients treated by BCT showed residual disease in 44% cases with involved margins, 24% cases with free margins of less than 3 mm and in no cases where the free margin was greater than 3 mm [13]. In contrast to our findings, one study demonstrated residual disease in 45% patients with a free margin between 2 and 5 mm [9]. This may be due to the free margin of 2-5 mm surrounding in-situ as opposed to invasive disease.

Rationally, residual disease ought to be avoided but its importance in relation to local recurrence is unclear. The importance of the free margin width in terms of local recurrence has been corroborated by studies showing that re-excision to achieve clear margin status results in a low rate of local recurrence, equivalent to if the margins were clear initially [15]. There is also evidence that local recurrence rates are generally higher with free margins of less than 2 mm [5]. The use of routine cavity shaving in patients all treated by

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3 the same surgeon, has demonstrated a higher rate of local recurrence and lower overall survival in those
4 with positive primary cavity shaves [16] after 10 years of follow-up. This difference was however only
5 statistically significant in the patient group with node negative disease.
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11 With regard to DCIS, the full extent of disease is often non-palpable and is underestimated by
12 mammography [7] making adequate surgical margins more difficult to obtain. Our data was not able to
13 determine a free margin width associated with minimal residual DCIS due to our policy of not re-excising
14 free margins of more than 5 mm. The difficulty in obtaining a free margin around DCIS has led some
15 investigators to suggest a free margin of 10 mm to minimise local recurrence [17], although a recent meta-
16 analysis has reported no benefit from a free margin of more than 2 mm when combined with radiotherapy
17 [18].
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27 It is accepted that the most important factor leading to local recurrence after BCT and adjuvant
28 radiotherapy, and the only factor under surgical control, is the presence of involved margins, and that these
29 require re-excision [6]. The controversy over the width of free margin required to avoid re-excision has
30 been caused by conflicting results from the literature. This has probably arisen from a wide variation in
31 patient characteristics, selection criteria leading to BCT over mastectomy, inclusion of patients undergoing
32 diagnostic excisions, surgical technique, the use of radiotherapy including the use of radiotherapy boosts
33 and differences in radiological and pathological evaluation. For this reason, it is wise for every breast unit
34 to evaluate their individual rates of residual disease from wider excisions and local recurrence rates.
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44 We have shown a statistical association between tumour size and close margins. One study found
45 associations between positive margins and a variety of factors, but interestingly, only tumour size was
46 found to uphold a significant association after multivariate analysis [19]. A proportion of operations in this
47 study were diagnostic excisions as opposed to wide local clearances. However, tumour size appears to
48 consistently be associated with close or involved margins after adjusting for confounding factors [6,19,20].
49 There is also published support for the association between involved lymph nodes and vascular invasion
50 with involved margins [20], consistent with our results. A similarly-conducted study to ours [9] showed an
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3 association between close margins and pathological tumour size, an extensive intraductal component to the
4 tumour, referral from a symptomatic rather than population-based screening program and the absence of
5 pre-operative diagnosis. We did not assess all of these factors in our study and there is some evidence that
6 an extensive intraductal tumour component is associated with residual disease after adjusting for
7 confounding factors [21]. Other factors which may be important are the operating surgeon, tumour
8 multcentricity and palpability but these were not analysed in our study. In agreement with our results
9 regarding tumour type, there is evidence that lobular cancers are associated with higher rates of margin
10 involvement [22,23].

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21 Pre-operative factors such as tumour size and type could be used to counsel patients about the increased
22 risk following BCT of wider excision or mastectomy to obtain clear margins. It is possible that routine
23 cavity shaving, used selectively in patients with large tumours, may prove a useful adjunct to increase the
24 proportion of patients with clear margins.
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30 31 **CONCLUSION**

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33 This study has demonstrated that in patients undergoing BCT, a free margin of 2 mm from invasive cancer
34 is associated with a low risk of residual disease. A free margin of up to 5 mm from DCIS is associated with
35 residual disease in one third of patients. Large tumour size, as determined pre-operatively by ultrasound,
36 and lobular cancer type are associated with close margins and these patients should be counselled at the
37 time of first surgery concerning the higher risk of further excision and mastectomy.
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45 **Word count: 2394 (excluding abstract)**

46 47 48 **Acknowledgements:**

49
50 The authors would like to acknowledge Dr T Salim for informing us of the processes involved in
51 histopathological assessment of the specimens.
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TABLE 1

The percentage of wider excision specimens containing residual disease by width of free margin from the tumour at first surgery

INVASIVE CANCER				
Free margin (mm)	Residual disease	No residual disease (clear)	Total	% Residual disease
Involved	6	11	17	35.3
0.1 to 0.9	2	4	6	33.3
1.0 to 1.9	2	17	19	10.5
2.0 to 4.9	1	40	41	2.4
> 5.0	0	4	4	0.0
Total	11	76	87	
DCIS				
Free margin (mm)	Residual disease	No residual disease (clear)	Total	% Residual disease
Involved	8	10	18	44.4
0.1 to 0.9	4	3	7	57.1
1.0 to 1.9	3	6	9	33.3
2.0 to 4.9	6	11	17	35.3
> 5.0	0	1	1	0.0
Total	21	31	52	

TABLE 2

Univariate analysis of various factors between patients with clear margins of 2 mm or more against those with at least one close margin less than 2 mm. * P-values considered to be statistically significant.

Factor	CLEAR MARGINS All margins \geq 2 mm (n=202)		CLOSE MARGINS One or more margins < 2 mm (n=101)		P value
Mean age (years)	59.3		57.0		P=0.166
Laterality					P=0.685
Left	101	(50%)	53	(53%)	
Right	101	(50%)	48	(47%)	
Tumour type:					P=0.134 (P=0.0214 * Ductal vs Lobular only)
Ductal	166	(82%)	78	(77%)	
Lobular	8	(4%)	11	(11%)	
DCIS only	11	(6%)	5	(5%)	
Other	17	(8%)	7	(7%)	
Grade					P=0.431
1	49	(24%)	18	(18%)	
2	67	(33%)	36	(36%)	
3	85	(42%)	47	(46%)	
Unknown	1	(1%)	0	(0%)	
Mean size (mm)	16.2		18.2		P=0.0097 *
Lymphovascular invasion					P=0.034 *
Yes	80	(40%)	53	(52%)	
No	119	(59%)	47	(47%)	
Unknown	3	(1%)	1	(1%)	
Nodal involvement					P=0.0079 *
Yes	66	(33%)	48	(48%)	
No	136	(67%)	51	(51%)	
Unknown	0	(0%)	2	(1%)	
Use of primary shave					P=0.721
Yes	58	(29%)	31	(31%)	
No	144	(71%)	70	(69%)	
Unknown	0	(0%)	0	(0%)	