Needle core biopsy characteristics identify patients at risk of compromised margins in breast conservation surgery

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Selection of patients for breast-conserving surgery relies on inexact parameters such as the preoperative estimation of lesion size. This study investigates the value of needle core biopsy findings, in particular, the relative quantity of DCIS, in improving patient selection for breast conservation. Patients undergoing breast-conserving surgery for invasive ductal carcinoma from 1999 to 2004 were identified. Only patients who had a preoperative diagnosis of carcinoma (DCIS and invasive) on core biopsy were included. All core biopsies were reviewed by a breast histopathologist to document the quantity and characteristics of the DCIS component. Of a total of 281 patients, 46% ($n = 129$) had invasive disease on core biopsy (group 1) and 54% ($n = 152$) had either invasive disease with an accompanying DCIS component or DCIS only on core biopsy (group 2). The compromised margin rate for group 1 was 23% compared to 39% for group 2 ($P = 0.004$). The rate of compromised margins increased progressively as the core biopsy DCIS component increased until a rate of 75% ($n = 18/24$) was reached in patients with DCIS only on core biopsy. In patients with a DCIS component on core biopsy, the presence of necrosis ($P = 0.002$), solid type architecture ($P = 0.008$), high grade DCIS ($P = 0.007$), calcification ($P = 0.003$), and the relative proportion of DCIS present ($P < 0.001$) were associated with compromised margins on univariate analysis. On multivariate analysis of this subgroup, the proportion of DCIS in this subgroup ($P = 0.048$) was an independent predictor of compromised margins. The presence and relative proportion of DCIS on core biopsy provides important information as to whether patients are at risk of compromised margins. Documentation of these parameters may assist patient selection for breast-conserving surgery or identify patients who may benefit from wider margins at the time of initial operation.

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One of the principal drawbacks of breast-conserving surgery is that it is complicated by varying rates of compromised margins ranging from 7 to 63%.¹ Consequently, it is of particular importance that adequate selection criteria exist to identify patients who would benefit most from conserving surgery. In addition to patient and surgeon preference, the parameters according to which patients are selected for breast-conserving surgery are primarily based on the perceived size of the lesion^{2,3} and to a lesser

extent, tumour location. Attempting to gauge size of lesion preoperatively has been shown to be prone to error, with under- and overestimates of disease extent.^{4–7} Additional means of identifying those at high risk of compromised margins would be valuable in aiding the precision of patient selection for breast conservation or may identify patients who would benefit from wider margins at the time of initial operation.

There is evidence from smaller studies that the presence of DCIS in core biopsies, in addition to invasive disease, may be a marker of compromised margins.^{8,9} It is possible that those with DCIS in core biopsies may be at risk of either extratumoural DCIS or extensive intraductal component, which in turn may increase the risk of compromised margins. Although approximately 45%^{9,10} of core biopsies

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with a diagnosis of carcinoma have some element of DCIS, this is not considered to have any clinical relevance and remains under-reported.

The aim of this study was to characterise the DCIS element in core biopsies with respect to relative quantity, grade, type, presence of calcification and to determine whether this is related to the rate of compromised margins and re-operation rates in patients undergoing breast conservation for invasive ductal carcinoma.

Materials and methods

Patient Population

The study population comprised 281 patients presenting to St Vincent's University Hospital over a 5-year period (1999–2004) who had a preoperative diagnosis of breast carcinoma on core biopsy and who underwent breast conservation surgery. Only patients who had a final diagnosis of invasive ductal carcinoma on excision specimen were included. Patients were identified from a database of clinical information relating to consecutive patients presenting to the breast symptomatic service and population-based screening service at the hospital. The symptomatic clinic was attended by patients who were referred with breast abnormalities by their primary care physicians. The screening population was derived from those women attending the Irish National Breast Screening Programme (Breastcheck), which offers two-view mammographic screening every 2 years to women aged 50–64 years. Excluded from the study were any patients whose original core biopsy specimen was not available for pathological review.

Image-Guided Biopsy

Ultrasound-guided biopsy was used for the evaluation of sonographically visible lesions and was performed in the supine or decubitus position using a high resolution 12.5 MHz linear array transducer. A 14-gauge automated needle device with a 22 mm throw biopsy gun was used (Tru-Core™, Medical Device Technology, Gainesville, FL, USA). Three cores were retrieved in the case of ultrasound biopsies. The accuracy of a three-core retrieval policy had been validated in two previous studies.^{11,12} The principle indication for stereotactic-guided core biopsies was for lesions not seen on ultrasound. Stereotactic-guided core biopsies were performed in the upright position using a digital Siemens Optima machine (Solna, Sweden) and a spring-loaded biopsy device (Tru-Guide™, Bard Ltd, Crawley, UK). Fourteen gauge, and occasionally 11-gauge needles were used for stereotactic core biopsies during the study period. Our protocol was to retrieve eight cores under the stereotactic technique for each lesion in line with international

recommendations.^{12–15} Clinical core biopsies were guided by palpation and were performed using a Pro-Mag™ biopsy gun (Manan Medical Products, Northbrook, IL, USA) with a 14- or 16-gauge needle.

Pathological Assessment

Core biopsies were formalin fixed, paraffin embedded and processed according to standard protocol. Each biopsy was stained with haematoxylin and eosin and examined at a minimum of two levels. All available core biopsies, which were reported as invasive carcinoma, invasive carcinoma and DCIS, or DCIS, were subjected to systematic histological review. The reviewing histopathologist was blinded to the margin status and histopathology findings at excision. The quantity of DCIS was expressed as a percentage of the total carcinoma present in the core biopsy. The grade of the invasive carcinoma, grade of DCIS, architectural type of the DCIS component, calcification within the DCIS component and the presence of necrosis were recorded on review. The architecture of DCIS was described as solid, cribriform, micropapillary or papillary. The presence of necrosis in DCIS was recorded separately and was not used as an architectural description.

Wide local excision specimens were examined according to the United Kingdom Royal College of Pathologists Cancer Screening Programmes guidelines.¹⁶ Each specimen was orientated by the surgeon using metal clips (one medial, two anterior, three superior) and sutures (long lateral, short superior, double deep) according to standard protocol. Specimen X-ray was performed in theatre. Following fixation, the specimen was sliced at 3–5 mm intervals in the antero-posterior plane perpendicular to the medio-lateral axis. Individual slice X-rays were performed in specimens removed for calcification. Detailed macroscopic examination was carried out including documentation of tumour size, location and tumour-margin distance for all six margins (anterior, posterior, medial, lateral, superior, inferior). Tissue blocks were selected for microscopic examination from all six margins in addition to multiple tumour blocks and representative blocks from the remainder of the specimen including skin. Separate re-excision specimens taken at time of initial surgery or during a second procedure were sliced at 3–5 mm intervals, X-rayed as appropriate and blocked extensively for histological evaluation.

The tumour-margin distance was specified for each margin with respect to the presence of DCIS and/or invasive carcinoma. The margins were considered compromised if foci of DCIS or invasive carcinoma were found within 5 mm from the radial resection margin. The presence of lobular carcinoma *in situ* or atypical ductal or lobular hyperplasia was not considered to affect margin status. Patients whose radial margins (superior, inferior, medial, lateral) were compromised were candidates for

re-operation. Re-excision was not indicated for tumour-margin distances of 5 mm or greater. In addition to tumour-margin distance, other tumour characteristics such as size and grade were recorded. Tumour size was recorded both as the invasive component and whole tumour, including invasive and DCIS components. From these measurements the presence of extratumoural DCIS was inferred.

For categorical variables, statistical comparisons between groups were made using χ^2 or Fisher's Exact test, where appropriate. For normally distributed continuous variables, comparisons were made using *t*-test and Mann-Whitney *U*-test for non-normally distributed variables. Multivariate analysis was conducted using logistic regression with the presence or absence of clear margins as the outcome variables. Statistical analysis was performed with SPSS statistical software (Statistical Package for the Social Sciences, version 11, Chicago, IL, USA).

Results

Patient Population

In total, 281 patients with invasive ductal carcinoma were identified who had a preoperative diagnosis of breast carcinoma and who underwent breast conservation. These patients were divided into two groups. Group 1 ($n=129$) had predominantly invasive disease with <5% DCIS on core biopsy. Group 2 ($n=152$) comprised patients who had a DCIS component on core biopsy, that is, patients who had invasive carcinoma with accompanying DCIS accounting for at least 5% of the total carcinoma on core biopsy and patients who had DCIS only on core biopsy. The median (whole) tumour size in group 1 was 1.8 cm, and in group 2 it was 2 cm.

Compromised Margins

The rate of compromised margins of patients in group 1 was 23% ($n=30/129$) compared to 39% ($n=60/152$) of the patients in group 2 ($P=0.004$). In those with compromised margins, DCIS was present within 5 mm of the margins in 53% ($n=16$) of group 1 and 55% ($n=33$) of group 2. All other patients with compromised margins had invasive disease, with or without DCIS within 5 mm of the margin. If a compromised margin definition of <2 mm is applied, the rate of compromised margins in group 1 was 14% ($n=17/129$) compared to 27% ($n=39/152$) in group 2 ($P=0.009$). Figure 1 more precisely demonstrates the rate of compromised margins for any given degree of DCIS component in the core biopsy. There is a clear increase in the rates of compromised margins with any given increase in the DCIS component until a rate of 75% is reached when there is a 100% DCIS component in the core biopsy.

Figure 1 Relationship between the relative proportion of DCIS in core biopsy and the rate of compromised margins on excision.

Figure 2 Effect of the presence or absence of DCIS in core biopsies on compromised margins for given tumour sizes.

Figure 2 illustrates the magnitude of the effect of the presence or absence of DCIS in the core biopsy on compromised margins in relation to given tumour sizes. The most pronounced effect appeared to be in patients whose tumours sizes were 2–3 cm. In group 1, 21% ($n=7/32$) of patients with tumours of this size had compromised margins compared to 55% ($n=23/42$) of similar patients in group 2 ($P=0.004$). Figure 3 provides examples of core biopsies with relative proportions of DCIS to invasive carcinoma.

DCIS Characteristics in the Core Biopsy (Group 2)

The characteristics of the DCIS component on core biopsy in group 2 and their relationship to compromised margins are demonstrated in Table 1. On univariate analysis, high-grade DCIS in the core biopsy was associated with a higher rate of compromised margins than low/intermediate grade ($P=0.007$). DCIS architecture that was described as purely 'solid' was associated with a higher rate of compromised margins compared to architecture that was purely 'cribriform' ($P=0.008$). The presence of necrosis ($P=0.002$), relative proportion or percent of DCIS present ($P<0.001$) and the presence of calcification in the DCIS component of the core biopsy ($P=0.003$) were associated with a higher rate of compromised margins. The presence

Figure 3 Core biopsies with varying relative proportions of DCIS to invasive carcinoma (**a**, invasive carcinoma, no DCIS; **b**, 5% DCIS; **c**, 50% DCIS; **d**, 100% DCIS).

Table 1 Characteristics of core biopsy DCIS in patients with this component on core biopsy (univariate analysis)

	Compromised margin group (n = 60)	'Clear' margin group (n = 92)	
Necrosis present	35/55 (64%)	32/86 (37%)	0.002
Calcification present	30/54 (56%)	26/86 (30%)	0.003
Grade of DCIS (high)	35/56 (63%)	35/89 (39%)	0.007
Solid architecture (vs cribriform)	30/43 (70%)	31/70 (44%)	0.008
Relative proportion/percent DCIS (median)	50%	10%	<0.001

of calcification appeared to be related to the proportion of DCIS in the core biopsy. Of patients with calcification in the DCIS component, 66% ($n = 38/58$) had $\geq 20\%$ DCIS component compared to 20% ($n = 23/117$) of those with no calcification ($P < 0.001$).

Multivariate analysis, by logistic regression, was performed on this subgroup (group 2) with DCIS only on core biopsy to further evaluate factors associated with compromised margins. In this analysis, relative percentage/proportion of DCIS on core biopsy ($P = 0.048$; OR = 1.02; 95%CI 1.00–1.031) was found to be independently predictive of compromised margins.

Extratumoural DCIS

In this study, the presence of 'extratumoural DCIS' was inferred if a difference existed between invasive

tumour size and total tumour size. Extratumoural DCIS was present in 6% ($n = 8/129$) of group 1, compared to 25% ($n = 38/152$) of group 2 ($P < 0.001$). Patients with extratumoural DCIS had a compromised margin rate of 48% ($n = 22/46$) compared to a 29% ($n = 68/235$) compromised margin rate in those with no extratumoural DCIS ($P = 0.01$). Fifty-seven percent of those who had extratumoural DCIS had a DCIS component on core biopsy of $\geq 50\%$.

Re-Operation Rate

Patients in group 1 had a re-operation rate (for compromised margins) of 17% ($n = 22/129$) compared to 40% ($n = 61/152$) of patients in group 2 ($P < 0.001$). There was no difference between group 1 and 2 in the frequency of compromised margins on second operation (when re-excision of margins was the second operation performed). Twenty-nine

percent of group 1 ($n=4/14$) vs 23% of group 2 ($n=9/39$) had compromised margins on second operation ($P=0.7$).

Discussion

Needle core biopsy has been a revolutionary development in the management of breast cancer. It has a preoperative accuracy of diagnosing breast cancer of approximately 97%,^{11,17} and it also has been shown to decrease the rate of compromised margins,¹⁸ reduce the overall number of operations¹⁹ and allow for the planning of axillary surgery. In this study, it is also shown to have the additional benefit of identifying patients most suitable for breast-conserving surgery or those who would benefit from a wider excision at the time of surgery. Breast-conserving surgery has increasingly become the preferred operation for breast carcinoma. Selecting patients for breast conservation is primarily based on the perceived size of the tumour on preoperative radiology, which has frequently been shown to be unreliable in determining extent of disease.⁴⁻⁷

The results of this study on a cohort of patients who had invasive ductal carcinoma demonstrate that reporting the relative quantity of accompanying DCIS in core biopsy specimens is of considerable value in identifying patients most at risk of compromised margins. Patients with invasive ductal carcinoma and minimal DCIS in their core biopsy had a 23% risk of compromised margins compared to a 39% risk if a DCIS component of at least 5% was present in the core biopsy. If a '2 mm' definition for a compromised margin is used instead of a '5 mm' margin, the risk of compromised margins were 14 and 27%, respectively. Moreover, the greater the proportion of DCIS relative to the total quantity of carcinoma in the core biopsy, the greater the risk of compromised margins. In those with pure DCIS on core biopsy (and invasive disease on excision), the rate of compromised margins was as high as 79%. In multivariate analysis, relative proportion of DCIS was an independent prognostic indicator of compromised margins. Increased risk of compromised margins translated into higher re-operation rates. Those patients with a DCIS component on core biopsy had a re-excision rate of 40% compared to only 17% in those with invasive disease on core biopsy.

Several potential reasons may exist to explain the association between DCIS on core biopsy and compromised margins on excision. Extratumoural DCIS, where DCIS extends beyond the boundaries of the invasive component, appears to be an important factor. Certainly, other authors have shown that DCIS in core biopsies is a marker of extensive intraductal component,^{9,10} a previous relative contraindication for breast conservation,²⁰⁻²² which had been considered to increase the risk of compromised margins.^{23,24} In this study, a DCIS component on

core biopsy was associated with extratumoural DCIS on excision specimen. This relationship appeared particularly pronounced in patients who had a high percentage of DCIS on core biopsy, with 57% of patients with extratumoural DCIS having >50% DCIS component on core biopsy. Moreover, there was a clear association between extratumoural DCIS and an increased risk of compromised margins. Although this may provide part of the rationale behind the assumption that core biopsy can identify those at risk of compromised margins, this is not the entire explanation, as only a relatively small proportion of patients had extratumoural DCIS.

This study also demonstrated that the DCIS characteristics in the core biopsy, in addition to the DCIS quantity, also proved to be of value in identifying patients at increased risk of compromised margins. In patients with a DCIS component, the presence of necrosis and solid type architecture and high-grade DCIS were associated with compromised margins on univariate analysis, but not in multivariate analysis. High-grade DCIS on core biopsy in the study by Mai *et al*⁸ was also associated with compromised margins. The presence of calcification in the core biopsy of those that had a DCIS component was also associated with a higher rate of compromised margins on univariate analysis. The presence of calcification appeared to be related to the proportion of DCIS in the core biopsy, being typically present if a higher DCIS component was recorded. A high proportion of DCIS on core biopsy is in turn an independent predictor of compromised margins on multivariate analysis. Although it could be argued that calcified DCIS may have a greater likelihood of being visualised radiologically and therefore removed, we have previously demonstrated that the use of radiology in determining the extent of DCIS is particularly unreliable.²⁵ In our recent series, 40% of patients with DCIS who had compromised margins had a >1 cm underestimation of disease extent by mammography.²⁵

The studies that have examined DCIS in core biopsy and the potential effects on margin status are conflicting, but have generally shown an association with the presence of DCIS in core biopsy and compromised margin status.⁸⁻¹⁰ These studies have been small in nature and can be difficult to compare given their varied and frequently complex method of quantifying DCIS in core biopsy. In the present study, we quantified DCIS as a percentage of total carcinoma in the core biopsy. This appeared the most straightforward and reproducible method of quantifying DCIS. Other studies, using different methods, have supported our findings. Dzierzanowski *et al*¹⁰ demonstrated a trend towards increased margin positivity when DCIS was present in the core biopsy. This relationship was strongest in those who had a particular pattern of DCIS—when DCIS or invasive carcinoma was separately found in different cores taken from a patient, compared to a mixture of DCIS and invasive disease within a core.

Mai *et al*'s⁸ initial study on 51 lumpectomies showed that patients with higher amount or grade of DCIS on core biopsy were more at risk of compromised margins compared to those with only 1–2 foci of DCIS on core biopsy. In a subsequent study, Mai *et al*²⁶ did not demonstrate a significant difference between patients who had DCIS and invasive disease on core biopsy compared to invasive disease alone. Finally, Jimenez *et al*'s⁹ study of 50 lumpectomies demonstrated an association between DCIS in the core biopsy with margins compromised by DCIS but not margins by invasive carcinoma. It is likely that the much larger patient cohort in the current study allows clearer associations to emerge demonstrating not only that the presence of DCIS in core biopsy has an effect on compromised margins but also that the actual quantity of DCIS present correlates with the rate of compromised margins.

The results of this study have identified a number of factors that categorise patients as being at higher risk of compromised margins. Principally, the presence of DCIS in the core biopsy, particularly in large proportions, correlates with a higher risk of compromised margins in those patients. This information is useful in patients who have larger tumours, where there is debate as to whether breast conservation or mastectomy would be indicated as the initial procedure. In patients with smaller tumours, particularly in the 2–3 cm category, identifying patients at high risk of compromised margins may alert the surgeon that wider margins may be beneficial in that instance.

Conclusion

Previously, radiology and clinical examination have been the principle preoperative tools used to select patients for breast conservation. The results of the present study have demonstrated that preoperative histology in the form of core biopsies can also identify patients at high risk of compromised margins and reoperation. In particular, the presence and relative quantity of DCIS provide valuable information regarding the likelihood of compromised margins. This is an important finding, given that the presence of DCIS is identified in approximately 45% of core biopsies.^{9,10} In this study, presence and amount of DCIS were significant factors associated with compromised margins. Given the clinical value of determining the extent and nature of DCIS in core biopsies, routine reporting of this level of detail in core biopsies should be encouraged, as an aid to more precisely gauging the suitability of patients for breast conservation or the need for wider margins in patients undergoing breast conservation.

Conflict of interest

The authors state that there is no conflict of interest.

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