ORIGINAL ARTICLE

Diagnostic accuracy of core biopsy for ductal carcinoma in situ and its implications for surgical practice

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Background: Core biopsy is considered to be a highly accurate method of gaining a preoperative histological diagnosis of breast cancer. Ductal carcinoma in situ (DCIS) is often impalpable and is a more subtle form of breast cancer.

Aim: To investigate the accuracy of core biopsy in the diagnosis of cancer in patients with DCIS.

Methods: All patients who had invasive cancer (n=959) or DCIS (n=92) that was confirmed by excision between 1999 and 2004 were identified. The diagnostic methods, histology of the core biopsy specimen and excision histology were reviewed in detail.

Results: Core biopsy was attempted in 88% (81/92) of patients with DCIS and in 91% (874/959) of those with invasive disease. Of those patients who underwent core biopsy, a diagnosis of carcinoma on the initial core was made in 65% (53/81) of patients with DCIS compared with 92% (800/874) of patients with invasive disease ($p<0.0001$). Smaller lesion size ($p=0.005$) and lower grade ($p=0.03$) were associated with increased risk for a negative or non-diagnostic core in patients with DCIS. The nature of the mammographic lesion or the method of biopsy did not affect the probability of an accurate core biopsy. Patients who had a preoperative diagnosis of DCIS by core biopsy had a reoperation rate of 36% compared with 65% of those that did not have a preoperative diagnosis ($p=0.007$).

Conclusion: Although core biopsies are highly accurate forms of obtaining a preoperative diagnosis in patients with invasive breast cancer, this is not the case in DCIS. As the number of surgical procedures can be reduced by core biopsy, it is still of considerable value in the management of DCIS.

In an era where mammographic breast screening is widespread, ductal carcinoma in situ (DCIS) is becoming more prevalent, comprising around 20% of breast cancer detected by screening.^{1–3} Breast cancer is now increasingly diagnosed preoperatively rather than at excision biopsy. Core biopsy has largely superseded fine-needle aspiration cytology in the diagnosis of breast cancer, not only because of its increased sensitivity, but also because of its ability to differentiate CIS from invasive disease. It is regarded as a highly accurate method of diagnosing breast cancer.^{4–12}

The accuracy of core biopsy as a method of diagnosing DCIS may be less reliable, having implications for patient care and treatment. In this study, we sought to analyse the sensitivity of core biopsy in diagnosing DCIS compared with invasive disease. Our secondary aim was to identify lesion characteristics in patients in whom a preoperative diagnosis was not established on core biopsy. Finally, in patients with DCIS, we evaluated the implications of core biopsy results for surgical management.

METHODS

A clinical database comprising all patients with breast cancer, presenting to the symptomatic and population-based screening service at St Vincent's University Hospital, Dublin, Ireland, over a 5-year period (1999–2004) was analysed to identify patients who were surgically treated for DCIS and invasive carcinoma. The symptomatic clinic was attended by patients who were referred with breast abnormalities by their primary care physicians. The screening population was derived from women attending the National Breast Screening Programme ("Breastcheck"), which offers a 2-yearly, two-view mammographic screening to women aged 50–64 years. Patients with phyllodes tumours were excluded from the study. Only patients with pure DCIS were included in the DCIS group.

Patients who were referred to the symptomatic service were assessed in a specialised breast surgical clinic and underwent biopsy, on the basis of clinical findings or abnormal mammograms. Patients presenting to the National Breast Screening Programme, who had abnormal mammograms, were also assessed clinically by a consultant surgeon. The clinical, radiological and pathological findings of all patients undergoing core biopsy were reviewed at weekly multidisciplinary breast screening meetings where recommendations were made to discharge, monitor clinically, further investigate or refer patients for diagnostic or therapeutic surgery.

Stereotactic-guided core biopsies were carried out with patients in the upright position with a digital Siemens Optima machine (Solna, Stockholm, Sweden) and a spring-loaded biopsy device (Tru-Guide; Bard Ltd, Crawley, UK). Fourteen-gauge needles were used for stereotactic biopsies during the study period. Our protocol was to retrieve eight cores for each lesion by the stereotactic technique. A specimen radiograph was carried out to ensure the presence of calcifications. An ultrasound-guided biopsy was used for the evaluation of lesions visible on a sonograph and was carried out in the supine or decubitus position, by using a high-resolution 12.5 MHz linear array transducer (HDI-5000 SONOCT, Bothel, Canada). Three cores were retrieved in the case of ultrasound biopsies. A 14-gauge automated needle device with a 22-mm-throw biopsy gun was used. Clinical core biopsies, guided by palpation, were carried out using a Pro-Mag biopsy gun (Northbrook, Illinois, USA) with a 14-gauge or 16-gauge needle.

The method for histological diagnosis was identified in all patients. Specimens for core biopsy were fixed in formalin,

Abbreviations: AIEP, atypical intraductal epithelial proliferation; DCIS, ductal carcinoma in situ

Table 1 Biopsy method undertaken

	No diagnosis of DCIS on initial core, n (%)	Diagnosis of DCIS on initial core, n (%)
	n = 28	n = 53
Stereotactic core	18 (64)	36 (68)
Ultrasound core	6 (21)	12 (22)
Clinical core	4 (14)	5 (9)

DCIS, ductal carcinoma in situ.

embedded in paraffin wax and processed according to standard protocol. Each specimen was stained with haematoxylin and eosin and examined at a minimum of two levels. Specimens were reported as inadequate/non-diagnostic (B1), benign (B2), atypical (B3; AIEP, lobular hyperplastic, radial scar, papilloma), suspicious but not diagnostic of malignancy (B4) or malignant (B5), according to the non-operative B classification system.¹³ Malignant lesions were classified as in situ or invasive carcinoma. When atypia was identified on core biopsy, but a subsequent diagnosis of malignancy was made on excision, the core biopsy findings were considered to be "underestimates".

Wide local excision specimens were examined according to the United Kingdom Royal College of Pathologists Cancer Screening Programmes guidelines.¹⁴ The surgeon oriented each specimen by using metal clips (1, medial; 2, anterior; 3, superior) and sutures (long, lateral, short, superior, double deep), according to standard protocol. A specimen radiograph was taken in theatre and a copy sent with the specimen to the pathology laboratory. The specimen was weighed, measured in three dimensions and inked using alcohol, India ink and Bouin's fluid-marking regimen. After fixation, the specimen was sliced at 3–5-mm intervals in the anteroposterior plane perpendicular to the mediolateral axis. Individual slice radiographs were taken in specimens that were removed for calcification. Detailed examination was carried out, including documentation of tumour size, grade and tumour margin distance.

Data were statistically analysed with SPSS V.11 (Chicago, Illinois, USA). Categorical variables were compared by χ^2 analysis and continuous variables with the Mann–Whitney U test.

Table 2 Lesion characteristics of patients with ductal carcinoma in situ (DCIS) who had a diagnosis of DCIS on initial core compared with those patients who did not

	No diagnosis of DCIS on initial core, n (%)	Diagnosis of DCIS on initial core, n (%)	p Value
	n = 28	n = 53*	
Median age (years)	53	55	0.36
Tumour size (mm)			
≤ 15	17 (61)	12 (23)	
15–40	10 (36)	36 (69)	
>40	1 (4)	4 (8)	0.002†
Median size	1.5	2.5	0.005
Grade			
Low	6 (21)	2 (4)	
Intermediate	11 (39)	22 (42)	
High	10 (36)	28 (53)	
Unknown	1 (4)	1 (2)	0.03†

*The measurement of one patient's lesion was unrecorded.

† χ^2 test for trend.

RESULTS

The invasive carcinoma group had 959 patients compared with 92 patients in the DCIS group. Of the patients with DCIS, 53% (49/92) were diagnosed through a population-based breast cancer screening programme and 47% (43/92) were diagnosed through the symptomatic service. All patients had their diagnosis confirmed surgically. Core biopsy was attempted in 91% (874/959) of patients with invasive disease and in 88% (81/92) of those with DCIS.

Of the total patient population with invasive breast cancer, 83% (800/959) had a preoperative diagnosis of carcinoma on initial core biopsy compared with 58% (53/92) of those with DCIS ($p < 0.0001$). Analysing only patients who underwent core biopsy, a diagnosis of carcinoma on initial core was made in 92% (800/874) of patients with invasive disease compared with 65% (53/81) of patients with DCIS ($p < 0.0001$). The histology of the initial core biopsy in patients with DCIS was DCIS ($n = 53$), underestimated disease ($n = 22$) and benign histology ($n = 6$). Twelve patients with underestimated disease had to B4 biopsies, where findings were deemed suspicious but not diagnostic of DCIS.

Repeat biopsy was carried out in 4 of the 28 patients with DCIS who had an inaccurate core biopsy result, with a resultant diagnosis of DCIS in two patients. Therefore, only 7% (2/28) of patients with DCIS who had an initial negative or underestimated disease on core biopsy had a diagnosis of carcinoma by repeat core compared with 64% (37/62) of those with invasive disease ($p < 0.0001$). A repeat core specimen increased the total preoperative diagnosis by core biopsy to 60% (55/92) of patients with DCIS compared with 87% (837/959) of patients with invasive disease ($p < 0.0001$).

Table 1 shows the method of core (stereotactic in 54, ultrasound in 18 and clinical core in 9 patients) used in the initial core biopsy of patients with DCIS. An inaccurate diagnosis was made in 33% (6/18) of the ultrasound cores compared with 33% (18/54) of the stereotactic cores ($p = 1$).

Table 2 shows the characteristics of those patients with DCIS who did not have a diagnosis after initial core was analysed. Smaller lesion size ($p = 0.005$) and lower grade ($p = 0.03$) were associated with increased risk of a negative or non-diagnostic core in DCIS. The nature of the mammographic lesion did not affect the likelihood of an inaccurate core (table 3). An inaccurate diagnosis was made in 35% (7/20) of those patients with a lesion other than calcification compared with 32% (18/57) of those with pure calcification (not significant). Source of referral (population-based screening programme v symptomatic clinic) had no effect on accuracy of core biopsy in patients with DCIS.

Table 3 Mammographic findings in patients with ductal carcinoma in situ (DCIS) who had a positive diagnosis on initial core compared with those who did not

	No diagnosis of DCIS on initial core, n (%)	Diagnosis of DCIS on initial core, n (%)
	n = 28	n = 53
Calcification	18 (64)	39 (74)
Calcification with associated lesion	3 (11)	4 (7.5)
Architectural distortion or asymmetrical density	3 (11)	3 (6)
Mass or density	1 (3.5)	6 (11)
Normal	1 (3.5)	1 (2)
No mammogram or mammogram after biopsy	2 (7)	

Of the 55 patients who had a preoperative diagnosis, 40 underwent surgery for breast conservation and 15 underwent mastectomy. Of those who had a preoperative diagnosis, 36% (20/55) had a second operation. In contrast, 65% (24/37) of those with no preoperative diagnosis underwent a second procedure ($p = 0.007$).

DISCUSSION

Core biopsy is a highly accurate method of obtaining a preoperative diagnosis of breast cancer. Its sensitivity is typically cited as being 90–99%.^{4–12} In the meta-analysis by Verkooijen *et al*,⁴ the pooled sensitivity of stereotactic core biopsy was 97%. With the ability to obtain accurate preoperative histological diagnosis, a diagnostic operation is no longer necessary and early and appropriate management of breast lesions is ensured. Furthermore, one of the principal advantages of core biopsy over fine-needle aspiration cytology is its ability to distinguish between in situ and invasive disease.

In this study, our results have shown that core biopsy is considerably less reliable in patients with DCIS. A diagnosis of carcinoma was made on initial biopsy in only 65% of those who underwent a core biopsy for DCIS compared with 92% of those with invasive disease. For most patients in whom DCIS was not diagnosed preoperatively, the core biopsy findings were reported as B3 (atypia, probably benign) or B4 (suspicious for malignancy). In these patients, the role of core biopsy in preventing a diagnostic excision biopsy had not been realised, with most patients proceeding to open excision biopsy for diagnosis.

Although the association of atypical intraductal epithelial proliferation (AIEP) with carcinoma is well known, the sensitivity of core biopsy for diagnosis of DCIS is not well documented. AIEP is acknowledged as a lesion with high risk and most centres now advocate excision of these lesions rather than monitoring patients with these lesions.¹⁵ Although as many as 40% of AIEP lesions are upgraded to either DCIS or invasive cancer,^{4 16–20} it is often difficult to extrapolate from studies what proportion of patients with DCIS actually had a definitive preoperative diagnosis. AIEP is not classified as a false negative result, but usually as an underestimate. The studies that publish data on the accuracy of diagnosing DCIS report a preoperative diagnosis of DCIS in 55–95% of patients.^{21–25} Fajardo *et al*²⁴ reported, in a multi-centre study on 138 cases of DCIS, that 14.5% had atypical ductal hyperplasia on core and 3.6% were benign. In the study on 72 patients by Leifland *et al*²⁵ 78% of patients were correctly diagnosed with DCIS on core biopsy, whereas in the study by Liberman *et al*,²³ 17 of 43 (40%) of excision specimens from patients with DCIS had a diagnosis of atypical ductal hyperplasia or benign disease on their preoperative core biopsy. Cheng *et al*,²¹ reporting on the results of an Australian screening programme, recently showed that only 55% of patients with DCIS who underwent core biopsy had a preoperative diagnosis of DCIS.

The diagnostic difficulties associated with DCIS are due to several factors. DCIS typically presents as calcifications and evidence suggests that stereotactic core biopsies are not as accurate for calcifications as mass lesions. This was not the finding in the present study, where the nature of a mammographic lesion did not relate to accuracy of findings on core pathology. Arguably, in patients with calcifications on mammography, the number of core biopsies retrieved needs to be considerably higher to increase the sensitivity of diagnosis.^{26–29} It has been recommended in these patients that the number of biopsies should be at least five,^{26–28} or even ten.²⁹ When carrying out stereotactic-guided biopsies in this study, the retrieval rate was typically eight core biopsies; yet, this resulted in a low rate of diagnostic accuracy.

Take-home messages

- Core biopsy diagnosed malignancy in 65% of patients with ductal carcinoma in situ (DCIS) as compared with 92% of patients with invasive disease.
- Smaller tumour size and lower grade were associated with increased risk for a negative or a non-diagnostic core in patients with DCIS. Mammographic features were not.
- No method of core biopsy currently available is sensitive enough to reassure surgeons that an excision biopsy is not required if atypical intraductal epithelial proliferation is found on core.
- Patients with a diagnosis of DCIS on core biopsy had a reoperation rate of 36% compared with 65% for those who did not.

Of equal importance to retrieving an adequate number of cores is the adequate targeting of calcification; however, evidence suggests that this in itself is not sufficiently reassuring. Liberman *et al*²³ documented retrieving calcifications when carrying out biopsies on DCIS lesions; yet, despite this, only 60% of their patients had a preoperative diagnosis of DCIS. Finally, gauge size of the needle may also have an important role in the sensitivity of core biopsy. The use of 11-gauge vacuum-assisted needles holds considerable promise as a method of increasing the accuracy of diagnosis,^{20 22} although this is still an issue of controversy.¹⁶ Rao *et al*¹⁶ found that 35% of those who had AIEP on 11-gauge vacuum assist still had malignancy on excision, emphasising that even with larger gauge, the diagnosis of DCIS is likely to remain challenging. At present, no method for core biopsy is available, which is sensitive enough to reassure surgeons that an excision biopsy is not required if AIEP is found on core biopsy.^{30 31}

Another important issue is the considerable interobserver variation among pathologists in the diagnosis of atypical hyperplasia versus low-grade DCIS.^{32–34} The limited tissue available in core biopsy specimens may result in the qualitative changes in DCIS being represented, but insufficient quantity of change for a definitive diagnosis. For non-high-grade DCIS, the qualitative changes must be present over at least 2 mm, excluding intervening stroma. AIEP often has many of the features of DCIS, and the volume of tissue may simply be insufficient for confirming the presence of cancer. In addition, AIEP and DCIS constitute a spectrum of disease and have similar mammographic features. Therefore, the sampling error associated with core biopsy may result in a non-diagnostic specimen. Our study showed that patients with low-grade lesions were most likely not to be diagnosed at core biopsy, emphasising the difficulty that pathologists have in distinguishing between AIEP and borderline DCIS. Alternatively, low-grade lesions may be more difficult to visualise. We also showed that small lesions were less likely to be diagnosed accurately, possibly indicating the coexistence of AIEP and DCIS as a spectrum of disease or the early progression of DCIS from an area of atypia.

The low sensitivity of core biopsy in DCIS may lead clinicians to question whether it may be more appropriate, particularly in the case of smaller lesions, to decide on a wire localising wide local excision as the initial diagnostic tool. Against this, the finding that a diagnosis by preoperative core biopsy statistically reduced the number of surgical operations from 65% to 36% shows that core biopsy is still of considerable value in the management of DCIS. This study

also reinforces that benign or atypical findings on core biopsy in the presence of radiological or clinical suspicion of DCIS should prompt further investigation.

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