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CLINICAL TRIAL

Ultrasound-guided core needle biopsy of the breast: does frozen section give an accurate diagnosis?

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Abstract Reducing the period of uncertainty between the discovery of a breast tumor and histological diagnosis alleviates the psychological impact of breast cancer to an important degree. We aimed to verify whether histological results obtained with frozen sections of core needle biopsies (CNBs) offer an accurate and reliable tool for minimising this period. In 2619 cases we compared histological diagnosis on frozen sections with those on paraffin sections of CNB and finally with the results of open biopsies. Of the cases 49% were proved malignant and 51% benign. In 99.3% of the malignant lesions preceding CNB was correctly classified as B5 ($n = 1185$, 92.9%) or at least B4 ($n = 82$, 6.4%) in frozen and in paraffin sections. There were seven false-negative cases in frozen (false-negative rate = 0.5%) and five false-negative cases (false-negative rate = 0.4%) in paraffin sections of CNB. On frozen sections complete sensitivity was 99.5% and the positive predictive value of B5 was 99.9%. There was one false-positive case in frozen sections and one in paraffin sections. False-positive rate = 0.08%, negative predictive value for B2 = 99.4% for frozen and 99.6% for paraffin sections; full specificity was 85.9 for frozen and 85.8 for paraffin sections of CNBs. Immediate investigation of CNB in frozen sections is an accurate diagnostic method and an important step in reducing psychological strain on patients with breast tumors and may be offered by specialised Breast Assessment Units.

Keywords Breast cancer · Core biopsy · Immediate diagnosis · Frozen section · Psychology

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Introduction

There are three main diagnostic procedures for pathological examination of suspicious breast lesions: fine needle aspiration cytology (FNAC), core needle biopsy (CNB) and surgical open biopsy. The latter is of second choice, as it is more invasive, more expensive [1], and requires hospitalization and anaesthesia, whereas FNAC and CNB are minimally invasive procedures that can be performed on an outpatient basis. Excellent concordance between diagnosis derived from CNB and from surgical biopsy materials for diagnosing cancer has been reported, ranging from 91–100% [2–4]. The diagnostic accuracy of CNB and FNAC has been compared in many studies, and CNB, leading to histological evaluation is generally considered to be superior to cytological results acquired by FNAC [5] especially for lesions with architectural distortion. Nevertheless, FNAC is a relevant test, especially in combination with palpation and imaging findings [6], mainly advantageous for cystic lesions, simple to perform, cheap and less invasive, and provides immediate diagnostic information. In order to rapidly obtain a diagnosis with CNB in recent years some authors have recommended core imprint cytology for better patient counselling and treatment planning [7–9]. Shortening

the period of waiting in uncertainty has great psychological impact for the patient. Several studies on breast cancer patients have shown that the time needed for diagnosis represents a major period of anxiety for the patient and that providing a definitive diagnosis within a short time reduces patient stress [10–12].

Using imprints of the cores makes a cytological diagnosis possible within a few minutes, but the diagnostic impact of this method is limited to the discrimination between ''malignant'' and ''non-malignant'' lesions without information on invasiveness or differentiation of the tumor and with the risk of missing tumor cells, especially in stroma-rich tumors (e.g. in invasive lobular carcinoma). Bauermeister recommended the investigation of core biopsies in frozen sections [13]. Thin frozen sections of excellent histological quality can be prepared from non-calcified fresh breast tissue by experienced technicians, being limited only by the fatty content of the biopsy material. This allows an accurate histological diagnosis within a few minutes, evaluating not only cytological features but also the architectural structure of the lesion, and in addition to this, the remaining tissue can be fixed and used for further investigations such as steroid receptor content and the estimation of HER-2 over expression. Bauermeister's recommendation was published in 1980. To our knowledge since then only one paper has been published on the validity of frozen sections performed on breast core biopsies: Gonzalez et al. [14] compared the results on frozen sections of Tru-cut^{R} needle biopsies with frozen sections of excisional biopsies in 162 cases. They found, that the interpretation of frozen sections of needle biopsies is reliable when performed by experienced clinicians and interpreted by experienced pathologists.

The present study compares histological diagnoses made on frozen sections of 2619 core biopsies with those made on paraffin sections of the subsequently fixed and paraffin-embedded cores and finally with the results of open biopsies or tumorectomy specimens, if available.

Methods

Between 1996 and March 2006 a total of 3109 breast lesions (screen-detected and symptomatic) were diagnosed by ultrasound guided CNB in our clinic. After written informed consent of the patient a minimum of three adequate cores were obtained from each lesion using an automated biopsy gun (Bard Magnum^{TM}) and 14 gauge needle (ULTRACORE^{TM}, inter.® Medical Device Technologies Inc., Gainesville, FL, USA) under ultrasound guidance with a 13 MHz small parts probe (Sono Line Elegra VFX13-5, Siemens Medical Solutions, Erlangen, Germany). In most cases the biopsy area was clipped with an Ultraclip® II Tissue Marker (Inrad®, Kentwood, MI, USA) to ensure later identification for excision.

Some cores ($n = 490$) were primarily fixed in formalin and paraffin-embedded, because tissue did not seem to be adequate for frozen section (adipous tissue, numerous micro-calcifications, radiologically suspect micro-calcifications without well-defined tumorous lesion). The remaining 2619 cores were immediately investigated in a hematoxilin and eosin-stained frozen section with preliminary histological diagnosis being available after a median time of 11.3 min. Occasionally, when sectioning the frozen core proved to be more difficult than expected, no further attempts were made and frozen section was deferred to save material. In all cases, immediately after taking the frozen section the remaining tissue was fixed in formalin (4%, pH 7.0), followed by routine paraffin embedding. In cases where CNB showed a malignant or suspicious lesion, where CNB did not give clear results or in cases with discordance between suspicious radiological findings (mammography or ultrasound) and benign histology, proper surgical tumor therapy or open diagnostic biopsy was performed. If histological diagnosis on CNB was clearly benign, patients were reassigned to normal radiological follow up, which was performed by either the radiologist who had referred the woman to our unit (56%) or by ourselves (44% of patients with benign lesions). In this group no subsequent carcinoma was found in the CNB area during the following years. Median follow up in the patients controlled in our unit was 2.05 years (1 month–9.22 years).

All histological results of CNB were retrospectively classified according to the B classification of the European Guidelines (Table 1; [15]). A condensed version of this classification was published in German by the Austrian Society of Pathology [16].

The following parameters were evaluated separately for diagnoses on frozen and on paraffin sections in accordance with the defined standards of quality assurance published by the European Commission [17].

Complete sensitivity

The number of carcinomas that were not definitely **negative** or were inadequate on core, expressed as a percentage of the total number of carcinomas.

Table 1 B Classification of core biopsy histology [15]

B 1: Unsatisfactory/normal breast tissue
B 2: Benign
B 3: Benign but of uncertain malignant potential for example most papillary lesions, radial scar/complex sclerosing lesion, lobular intraepithelial neoplasia, atypical ductal hyperplasie (ADH), phylloides tumour, if not obviously malignant
B 4: Suspicious of malignancy for example cores which contain probable carcinoma but cannot provide definitive diagnosis
B 5: Malignant for example ductal carcinoma in situ (DCIS), invasive carcinoma

Full specificity

The number of correctly identified benign lesions (the number of B2 results minus the number of false negatives) expressed as a percentage of benign lesions.

Positive predictive value of a B5 diagnosis

The number of correctly identified cancers (number of B5 results minus the number of false positive results) expressed as a percentage of the total number of positive results (B5).

False negative rate

The number of false negative results expressed as a percentage of the number of total carcinomas sampled.

False positive rate

The number of false positive results expressed as a percentage of the total number of carcinomas sampled.

Results

CNB was performed in 3109 radiologically assessed breast lesions to ascertain histological diagnosis: 2619 (84%) cores were judged by the pathologist to be adequate for frozen section. In 490 cases the material did not seem appropriate for high quality frozen sections because of a high amount of fatty tissue and/or microcalcifications. Therefore, these cores were immediately put into formalin and frozen section was deferred to save tissue. These cases were not further analysed in this study.

Of the cases investigated in frozen and in paraffin section 1276 (49%) were malignant in open biopsy and 1343 (51%) were benign. Thus, the ratio of benign to malignant biopsies was about 1:1.

The results according to the B classification of frozen section and of the subsequent paraffin sections of the ultimately malignant lesions are shown in Table 2. The final results are defined as the histological diagnosis of the subsequent surgical procedure. The vast majority of the ultimately malignant lesions was classified B5 (n = 1185, 93%) or at least B4 (n = 82, 6.4%) in frozen and in paraffin section. Five cases were negative in frozen and in paraffin section. Nevertheless, open surgical procedure was performed because of discordance with a suspect radiological finding. Two additional cases were negative in frozen section, whereas the subsequent paraffin section revealed a focus of tumor cells and was classified as B5. A review of the slides confirmed the negative results.

For the definitely benign lesions summarized in Table 3, final results represent the histological diagnoses of subsequent open biopsies in all cases, where CNB results were >B2 or when there was a discordance between radiological and histopathological diagnosis. In cases where benign histology in CNB agreed with the radiological image, no further surgical confirmation of the diagnosis was performed, unless the woman so desired, and patients were followed at routine mammography intervals. In 14 cases frozen sections were unsatisfactory. In 1105 cases frozen as well as paraffin embedded cores were B2, 15 of which were radiologically suspect and thus subjected to open biopsy. In one case of benign adenomyoepithelioma the frozen section was classified B3 and the paraffin section B5. Moreover, B5 for frozen section was followed by B3 for paraffin section in one case of ductal hyperplasia without atypia.

Evaluation of specificity, sensitivity, positive predictive value and false positive or false negative results is listed in Table 4.

Discussion

Accurate preoperative assessment of breast cancer is crucial for treatment planning, including operative procedures as well as neoadjuvant preoperative therapies. Core needle biopsy has been shown to be an

Table 2 Lesions ultimately diagnosed as malignant

Frozen section	Paraffin section	final diagnosis (*n*)		*n*	%
B2	B2	invasive ductal carcinoma [a]		5	0·4
B2	B5	invasive ductal carcinoma		2	0·2
B4	B4	Invasive ductal Ca	20	55	4·3
		invasive lobular Ca	4		
		papillary Ca	6		
		tubular Ca	3		
		DCIS	19		
		other	3		
B3	B4	DCIS		2	0.2
B4	B5	invasive ductal Ca	16	26	2·0
		mucinous Ca	3		
		tubular carcinoma	3		
		DCIS	2		
		other	2		
B5	B4	invasive lobular carcinoma		1	0·1
B5	B5	invasive ductal Ca	895	1185	93·0
		invasive lobular Ca	117		
		mucinous Ca	15		
		tubular Ca	11		
		papillary Ca	11		
		medullary Ca	16		
		inflammatory Ca	10		
		DCIS	34		
		recurrency	58		
		Other	18		
		Total malignant lesions		1276	100

[a] Open biopsy was performed to clarify discordance between radiological finding and core histology

Abbreviations: Ca = Carcinoma, DCIS = ductal carcinoma in situ

excellent tool, working with true tissue specimens, thus permitting evaluation of both the architectural and the cytological patterns [18, 19].The diagnostic accuracy of routinely paraffin embedded CNB has been verified since the early 1990s, and in their review article Usami et al. reported good concordance between diagnosis on CNB and on surgical biopsy [4]. Dillon et al. gave their special attention to the false negative rate [20]. In their study of 2427 core biopsies the overall false negative rate was 6.1%, corresponding to false negative results in 85 patients. They reported that a ''triple assessment'' of clinical, radiological and pathological findings during the weekly multidisciplinary breast meetings allowed prompt recognition of 77 of these discordant results. Harris et al. [21] demonstrated the preoperative evaluation of prognostic factors in core biopsies.

In recent years, several authors have tried to combine the advantages of CNB with the FNB possibility of reading smears on site immediately after the CNB procedure. They investigated core imprint cytology in order to immediately predict the histological result of the CNB. In a study of 199 symptomatic breast patients Qureshi et al. [22] conclude that this method is a reliable way of diagnosing symptomatic breast lesions in one-stop breast clinic. Farshid et al. presented a prospective study with 567 breast lesions and showed that cytological results on core imprints are a reliable predictor of core histology [7]. In a literature review they listed eleven studies with values for sensitivity ranging from 74–95.9% and for specificity from 78–98% for this method. These authors argued that immediate histological diagnosis is not possible on CNBs, and therefore core imprint cytology should be incorporated into the workflow of same day breast assessment clinics, thus offering immediate patient counselling.

We agree that reducing the waiting time for the diagnosis is very important for the patient. Several studies have shown that the period surrounding the diagnosis of breast cancer is one of the most stressful times for women and their partners [23–27]. In our series, 51% of the final histological diagnoses were benign and 49% were malignant. This means that approximately half of the patients with breast tumors requiring histological examination need not even be alarmed, as their tumor is benign. The other half with a malignant diagnosis in core histology at least does not suffer prolonged uncertainty and the sometimes paralyzing shock response is displaced by the activity of discussing therapy options and other questions with the

Table 3 Lesions ultimately diagnosed as benign

Frozen section	Paraffin section	Final diagnosis (*n*)		*n*	%
B1	B2	fibrous-cystic disease		14	1,0
B2	B2	fibrous-cystic disease	480	1090	81·1
		fibroadenoma	453		
		inflammatory lesions	50		
		fat necrosis, scar	48		
		small papillary lesions without atypia	35		
		Other	24		
B2	B2	fibrous-cystic disease	9	15[a]	1·1
		fibroadenoma	1		
		inflammatory lesions	2		
		fat necrosis, scar	3		
B2	B3	fibrous-cystic disease	17	48	3·6
		atypical ductal hyperplasia	18		
		fibroadenoma	7		
		sclerosing adenosis	3		
		papilloma	2		
		benign phylloid tumour	1		
B3	B3	fibrous cystic disease	9	153	11·4
		atypical ductal hyperplasia	40		
		fibroadenoma	38		
		papilloma	32		
		sclerosing adenosis	11		
		benign phylloid tumour	5		
		inflammatory lesions	5		
		others	8		
		biopsy refused	5		
B3	B2	fibroadenoma	6	12	0·9
		sclerosing adenosis	4		
		ADH	1		
		small papillary lesion without atypia	1		
B3	B5	Adenomyoepithelioma		1	0·1
B4	B2	ADH	2	9	0·7
		fibrous cystic disease	1		
		fibroadenoma with epithelial proliferation	1		
		papillary lesions	1		
		sclerosing adenosis	4		
B5	B3	ductal hyperplasia without atypia		1	0·1
		Total benign lesions		1343	100

[a] Open biopsy was performed to clarify discordance between radiological finding and core histology.

Abbreviations: ADH = atypical atypical ductal hyperplasia

Table 4 Summary of quality parameters for both, frozen and paraffin sections, referenced to EU quality recommendations

	Frozen section(%)	Paraffin section(%)	EU threshold [a]	
			Minimum(%)	Preferred(%)
Complete sensitivity	99·5	99·6	>80	>90
Full specificity	85·9	85·8	>75	>85
Positive predictive value of B5	99·9	99·9	>99	>99.5
Negative predictive value of B2	99·4	99·6	n.d.	n.d.
False negative cases	7	5	n.d.	n.d.
False negative rate	0·5	0·4	n.d.	n.d.
False positive cases	1	1	n.d.	n.d.
False positive rate	0·08	0·08	n.d.	n.d.

[a] Threshold for CNB performance suggested by the European guidelines for quality assurance in breast cancer screening and diagnosis [35] (n.d. = not defined)

breast surgeon and other persons. Therefore we are challenged to offer a reliable technique for immediate diagnosis with high sensitivity and specificity. Although the histological investigation of frozen sections of CNBs was recommended by Bauermeister in 1980 [13] and first encouraging results on 162 cases were published in 1985 (Gonzalez et al.) [14]. Our study with more than 2600 CNBs is the first we know since then, dealing with this method.

This is hard to understand because intraoperative evaluation of breast lesions in frozen tissue was routine practice for several decades, years before CNB was established for preoperative diagnosis, thus permitting individual treatment planning. Furthermore, immediate histological investigation of the cores gives clear cut information on the adequacy of the biopsies and, if specimens do not correspond to the radiologically suspected lesion, additional CNB can be performed during the same session. One argument against making frozen sections from CNBs is that it reduces the amount of tissue for paraffin embedding and in small cores the amount of remaining tissue might be too small for adequate paraffin diagnosis and subsequent immunohistochemistry. We avoided this specific problem by handling the cores very carefully: very small cores (<5 mm in diameter) were primarily excluded from immediate diagnosis on frozen sections, and in CNBs of ''normal'' size (14 gauge, about 2 cm long) the frozen sections were performed by experienced technicians only. In rare cases, when sectioning proved to be unexpectedly difficult, no further attempts were made and frozen section was deferred in order to save material. The decision whether cores are appropriate for immediate diagnosis was made by the responsible pathologist taking into account the radiologists information on microcalcifications and adipose tissue content, as well as the macroscopical appearance, in all cases.

There are reports showing a relation between the number of cores and diagnostic accuracy [28–30]. On the other hand, O'Leary et al. found that in cases of invasive breast cancer the amount of tissue obtained by CNB does not influence the level of concordance between histopathology from the preoperative CNB and the definitive excision specimen [31]. These authors reported that doubling or tripling the number or length of CNBs provides only a tiny increase in the sample as compared to the total volume of even a small tumor, such as 1 cm^3. Taking this into account one can assume that taking tissue for one or two frozen sections reduces the material by such a minimal amount, that the remaining CNB tissue is sufficient for subsequent paraffin sections and evaluation of immunohistochemical parameters. In our database immunohistochemical determination of estrogen- and progesterone receptor content and evaluation of HER-2 overexpression assessed by Hercep-Test™ (Hercep-Test™, DAKO Cytomation, Glostrup, Denmark) was possible in 93% of the CNBs frozen before paraffin embedding (data not shown). In a relatively small study we compared immunohistochemical HER-2 results achieved at core biopsy and whole tumor sections from 64 breast cancers, and the overall concordance was 92% (K = 0.8) [32]. In addition, some pathologists argue that freezing could produce artefacts, which could influence the accuracy of histological as well as immunohistochemical results. In our study, there is only one case, where nuclear irregularity caused a false positive diagnosis of low grade ductal carcinoma in situ on cryosection and overinterpretation as ADH on subsequent paraffin sections. Final diagnosis on an open biopsy specimen was ductal hyperplasia without atypia. Rereading the slides one must admit that nuclear irregularity caused by cryoartefacts was misinterpreted as atypia in this case. If immunohistochemical results seem to be doubtful because of cryoartefacts, one could easily overcome this problem by taking an additional core, which is immediately fixed in formalin for immunohistochemistry in cases where neoadjuvant therapy is based on the CNB result.

Our data indicate that selection of tissue for frozen section is very important. It is well known that it is nearly impossible to make frozen sections of reliable quality for example from material containing a higher degree of adipose tissue or with predominant microcalcifications. Therefore, we do not investigate cores obtained by stereotactic biopsy of non-tumorous lesions in frozen sections. Pijnappel et al. concluded that ultrasound-guided CNBs can be performed in a large percentage of nonpalpable lesions, but areas consisting of only microcalcifications on mammography need special attention [33].

Although a major goal of any CNB program is to reduce the number of open surgical biopsies, we follow the argumentation of Jacobs et al. [34] that there are benign lesions which should be handled very cautiously and that if there is any doubt about whether or not the CNB findings are completely representative of the targeted lesion an open surgical excision should be performed. This is why we recommend open biopsy in benign lesions like ADH and papilloma (except very small lesions without atypia, or radial scars). For this reason we have final histology for most of the B3 cores, as indicated in Tables 2 and 3.

Our results on CNB as compared with final diagnosis show a very high reliability for frozen sections as

well as for paraffin sections. The difference in complete sensitivity on frozen sections (99.5%) and on paraffin sections (99.6%) is only marginal and both values are far above the preferred threshold recommended by the EU guidelines for quality assurance (minimum >80%, preferred >90%) [35]. The values for full specificity, namely 85.9% and 85.8% for frozen and for paraffin sections, respectively, are clearly above the minimum threshold of >75% and slightly above the preferred level of >85%. These encouraging results are substantiated by the positive predictive value of a B5 diagnosis on CNB (99.9% for both frozen and paraffin sections) and the negative predictive value of a B2 diagnosis at 99.4% for frozen and 99.6% for paraffin sections (Table 4). The false negative cases (Table 2) were reread and the negative diagnoses confirmed: in two cases the tumor was seen in paraffin sections only. Superficial frozen sections missed the area with tumor cells. In five additional cases the carcinoma was not included in the CNB, neither in frozen nor in paraffin sections. These tumors were diagnosed, because open biopsy was indicated after discussion between the pathologist and the radiologist based on the discordant results with highly suspicious radiological findings. In 15 cases B2 diagnoses on cores was followed by open biopsy, which was also indicated by the discordant radiological aspect, but final histology was benign (Table 3).

Our study contains one false positive case (B5) in paraffin section (diagnosed as B3 in the frozen section) of the CNB. Final histological diagnosis on the tumorectomy specimen, however, was adenomyoepithelioma of the tubular type, a very rare lesion known to be easily misinterpreted as a carcinoma [36].

Comparing sensitivity, specificity, positive predictive value and negative predictive value, our results on paraffin sections are better than those of other groups, especially in the worlds largest series from a single institution, published by Ciatto et al. [19]. This might have several reasons. Above all, their series is a continuous one, including both, automated and directional vacuum-assisted CNBs, performed under stereotactic or sonographic guidance. In our study we restricted the cases on those, which could be localized and biopsied under ultrasound guidance. Our aim was to investigate the reliability of frozen sections, therefore lipid rich tissue and specimen with a lot of microcalcifications were excluded, as these conditions lead to bad results on frozen sections. Another important factor is the experience of the team members. Ciatto et al. [19] describe impressingly the improving sensitivity over the timeframe of the study and with greater operator cumulative caseload. In their study, biopsies were taken by one of 13 radiologists and interpreted by one dedicated breast pathologist. In our center, all 2619 cases were handled by two specialized radiologists and one pathologist.

From our data obtained on a large number of well documented cases, revealing no significant difference between results on frozen and on paraffin sections, we conclude that frozen section of CNBs is an accurate diagnostic method permitting immediate histologic diagnosis. It offers a valid tool for optimal patient counselling and further treatment planning within a very short time. From our experience patients highly appreciate the one step procedure in our multidisciplinary breast assessment unit, because they are spared the psychological distress associated with not knowing. However, in order to avoid false diagnosis cautious upfront selection of specimens is needed to identify those that are appropriate for frozen section examination. Optimal assessment of breast lesions requires dedication and experience and the best results are obtained when only experienced personnel perform and interpret CNB and their performance is audited as a matter of routine [37].

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