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Title

One day Core Needle Biopsy in a breast clinic: 4-years experience

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Abstract

Introduction: Many attempts have been made to combine the high diagnostic accuracy and conclusive rate of core needle biopsy (CNB) with the speed of fine needle aspiration cytology (FNAC) in evaluation of solid breast lesions. Multiple hybrid techniques have been developed to achieve this. We describe a cohort of patients for whom we used a relatively new, accelerated method of CNB processing, allowing for a definitive diagnosis the same day.

Materials and methods: all patients visiting the Radboud University Nijmegen Medical Centre breast clinic during a four year period were reviewed to identify all CNBs in this period performed in a same day diagnosis track. CNB result was compared to post-operative pathology reports, when available, and to follow-up when patients were not surgically treated.

Results: 1060 patients underwent CNB of 1383 lesions, 898 of which in a same day diagnosis track with a sensitivity of 96.9% and a specificity of 99.4%. The inconclusive rate was 9.2%.

Conclusion: For a same day diagnosis for solid breast lesions, we could give a conclusive diagnosis with accelerated CNB processing in 65% of our patients requiring CNB. This technique can be used reliably in a same day diagnosis breast clinic with a very high sensitivity, specificity and conclusive rate.

Keywords

Breast cancer, diagnosis, Core Needle Biopsy, solid breast lesion, test characteristics

Introduction

Since the first description[1] of ultrasound-guided core needle biopsy (CNB), CNB has progressively replaced fine needle aspiration cytology (FNAC) as the standard of care for evaluation of suspicious breast lesions. CNB is considered to have superior accuracy and especially a lower rate of inconclusive pathologic diagnoses[2-7] and therefore less additional biopsies. FNAC has the advantage of speed, where CNB conventionally requires overnight processing. Recently, Willems et al reviewed the evidence in the CNB vs. FNAC debate. The authors argue CNB to be preferable because of superior test characteristics and furthermore because they feel the speed advantage of FNAC is outbalanced by the fact that therapy planning requires a multidisciplinary discussion, regardless of the speed of initial diagnosis[8].

To decrease patient anxiety and improve patient satisfaction in patients with benign and malignant results alike[9-11], a number of hybrid (CNB*plus*) techniques have been developed. These allow (cytological) evaluation of CNB specimens for a provisional diagnosis. CNB*plus* techniques include core wash cytology (CWC), touch (or core) imprint cytology (TIC or CIC) and frozen section histology.

In CWC the CNB core is washed in a saline solution, the saline solution is cytocentrifugated and smeared similar to a FNAC slide[12]. In TIC, the core is rubbed onto a slide and the resulting ‘touch imprint’ is stained according to Papanicolaou or Diff-quick[13]. Frozen section histology is a regular frozen section, performed on a CNB specimen allowing for a quick histological diagnosis[14]. These procedures will provide a provisional diagnosis within the hour, whilst the traditionally overnight processed CNB specimens allows for a definitive diagnosis the next day.

Accuracy of these ‘provisional diagnosis’-techniques is less well established than it is for FNAC and CNB. TIC has been associated with a sensitivity ranging from 42 to 98%[15,16]. Specificity has ranged from 44 to 100% [17,18]. The inconclusive rate varies from 5-21%[19,16].

CWC has been less extensively studied[12,20], but the study by Uematso et al reports a sensitivity of 89%, with a specificity of 72%. This study however showed an inconclusive rate of 42%[20]. Furthermore, Wauters et al describe a ‘modified core wash’ technique, with a sensitivity of 91% and an inconclusive rate of 12%[21].

Frozen section histology has a sensitivity of 99.5% and a specificity of 86%[22].

More recently, techniques have been developed that use microwave technology to process CNB specimens quicker, thus combining the greater diagnostic power of CNB with the speed of FNAC[23]. If proven reliable, this novel processing technique could provide a same day definitive diagnosis. It also eliminates the need to perform both a cytologic and a histologic workup of biopsy specimens that hybrid techniques require. In the present study we provide the first large series of patients evaluated with this novel technique. Aims of the study were to define the accuracy of CNB using this processing technique, and to determine how effective this technique is in achieving a definitive diagnosis on the same day.

Materials and methods

Patients

The prospective registry of the Radboud University Nijmegen Medical Centre breast clinic was used to identify all patients who underwent a CNB procedure between January 1st 2010 and January 1st 2012. For patients evaluated in the clinic between January 1st 2008 and January 1st 2010 the retrospective registry was used. These registries included both screen based referrals, and symptomatic patients. Patient characteristics including age, referral indication, findings on physical examination and BI-RADS classification were recorded. Data on CNB characteristics including method (ultrasound (US)/Stereotactic/magnetic resonance imaging (MRI)), number of cores taken, size of largest core, number of CNB procedures required to achieve a diagnosis and the use of additional staining techniques were recorded. Furthermore, CNB results including the type of diagnosis (benign/high risk/ductal carcinoma in situ (DCIS)/invasive carcinoma) were recorded (high risk lesions include atypical ductal/lobular hyperplasia, lobular carcinoma in situ (LCIS) and complex sclerosing lesion), as well as histologic type and doubt on representativity as mentioned in the pathology report. Preoperative findings were correlated with the post-surgical pathology report whenever surgery was performed and with follow-up when surgery was not performed.

Biopsies

Biopsies were taken by dedicated breast radiologists, using either ultrasound guidance, mammographic stereotactic guidance or MRI guidance. Ultrasound guided biopsies were performed using a 14g, or rarely a 16 or 18g needle on a true cut core needle biopsy gun (*Bard biopsy systems*). Both stereotactic, and MRI guided biopsies were performed with a 9 or a 11g needle on a vacuum assisted biopsy device (either the ‘Suros’ system

(*Hologic, Inc.*) or the ‘Vacora’ system (*Bard biopsy systems*)). The number of cores taken was determined by the radiologist.

Pathology

The 14-18g specimens in the same day diagnosis track were fixed and processed using a short, approximately 90 minute program in a ‘rapid microwave histoprocessor’ (*Pathos, Milestone Medical*) and then embedded in paraffin. Nine and 11g specimens (and 14-18g specimens not in the same day diagnosis track) were processed using the regular, overnight program of the same processor. Paraffin blocks were cut to 4 micron slides using a microtome. Slides in the same day diagnosis track were manually stained with hematoxylin and eosin (H&E) using a rapid staining protocol. All paraffin sections from specimens not in the same day diagnosis track were H&E stained in an automatic staining machine (*Prisma, Sakura Finetek Europe B.V.*). Specimens were evaluated by pathologists experienced in breast pathology. The vast majority were evaluated by a single dedicated breast pathologist (P.B.). Additional stains were performed at the discretion of the evaluating pathologist. Results were reported according to contemporary Dutch national breast cancer guidelines[24]. Whenever preliminary results were reported on the day of biopsy, and additional staining procedures were performed changing or further detailing preliminary findings only the ‘same day’ findings were analyzed. Receptor status (estrogen and progesterone receptor, and HER2neu) assessment was not routinely performed to avoid potential sampling error, but whenever neo-adjuvant systemic treatment was considered, receptor status was successfully determined on the original CNB sample.

Post-operative pathology specimens were processed and reported according to contemporary Dutch breast cancer guidelines[24].

Patient management

Treatment advice for all patients was given by the multidisciplinary breast cancer working group (MBCWG), according to contemporary Dutch breast cancer guidelines and shared decision making[24]. Provisional advice on the same day was based on the MBCWG discussion with a radiologist, pathologist, nurse practitioner and breast surgeon. The definitive treatment advice was determined during the weekly MBCWG with also a medical oncologist, radiotherapist, nuclear medicine specialist and clinical geneticist present.

Follow-up of benign lesions

For all patients a search in the Dutch nationwide pathology database (PALGA[25]) was performed, retrieving all pathology results available to date in the Netherlands for each patient. All breast-related malignancy including both regional and distant disease was recorded.

Data analyses

For descriptive purposes, the type of benign lesion found on CNB was used to describe benign lesions not treated surgically in the results section.

Data were analyzed using SPSS (PASW statistics 18) (SPSS Inc., Chicago, IL, USA).

Results

Patients

Between January 1st 2008, and January 1st 2012, 3543 patients visited our breast clinic. 1060 (30%) of these patients underwent CNB of 1383 lesions (231 patients had more than one lesion), with a range of 1-7 lesions per patient. Of 1383 biopsies, 1073 (78%) were performed under ultrasound guidance, and 898 (84%) of these were diagnosed on the same day (table 1, figure 1).

Inconclusive rate (all lesions group)

51 (3.7%) lesions required a second CNB attempt, because of an inconclusive first biopsy. Two cases required a third biopsy attempt (the results of which were still inconclusive in both cases). In a further 75 (5.4%) cases, clinical and radiographic characteristics caused doubt whether the biopsy was representative, but radiographic follow-up was preferred over a second biopsy. In 10 cases radiographic follow-up was preferred over a third biopsy. This means a total of 140 biopsies initially produced inconclusive results, a rate of 10%. Repeat biopsy yielded a definitive diagnosis in 41 of these 126 cases.

Same day results:

Of the 898 lesions evaluated in a same day diagnosis track, 237 (26%) were patients referred by screening programs, 571 (64%) were symptomatic, 90 (10%) were incidental radiographic lesions.

A total number of 351 lesions (39%) was found to be malignant, 547 lesions (61%) were benign. 25 (7%) of cases diagnosed with a malignancy were not treated surgically, but received palliative chemotherapy. For analytical purposes these were considered to be correct diagnoses. Patient characteristics are shown in table 2, pathology results are shown in table 3.

Of 335 cases of invasive cancer, 327 (97.6%) were correctly identified by CNB. 6 (1.8%) were incorrectly classified as ductal carcinoma in situ. Of 351 cases of malignancy (invasive cancers and DCIS), 3 (0.9%) showed benign biopsy results. Details for all surgically treated lesions are given in table 4 (same day diagnosis) and table 5 (all lesions).

In 146 (44%) of invasive carcinomas it was not possible to make a specific diagnosis on the same day, but instead a general diagnosis such as 'adenocarcinoma' or 'carcinoma' was made.

Thirty-four (10%) of invasive cancer cases received neo-adjuvant systemic chemotherapy.

Follow-up (same day diagnosis group)

Patients with a benign and/or high risk CNB result had a mean follow-up of 27.8 months, with a range of 6-54 months (sd: 13.3 months). During this period 7 patients developed a malignancy of the breast. Two of these occurred in the contralateral breast, a third location was clearly not the target of original biopsy. The remaining four cases of ipsilateral malignancy (all invasive cancers) could not be definitively established as not being the lesion originally biopsied, and were therefore considered false negatives (constituting 0.7% of all benign results). Two of these four false negative results are lesions of a single patient that developed a malignancy after 17 months during clinical follow-up because of an inconclusive CNB result (radiologic follow-up was preferred over repeat biopsy). One was a case of malignancy 33 months after a benign biopsy result of a lesion in the same quadrant. This could have been the same lesion. The final false negative result was detected seven months after the same lesion was diagnosed as benign.

Sensitivity, specificity and accuracy (same day diagnosis group)

Sensitivity for invasive cancer in our series was 96.4%. Sensitivity for malignancy (invasive cancers and DCIS taken together) was 96.9%. Specificity was 99.4%. Total accuracy (percentage of malignancies plus percentage

of benign lesions correctly identified as such) was 98.4%, or 97.9% if invasive cancers and DCIS are taken as separate diagnoses.

Discussion

Our study describes the first large cohort of patients with suspicious breast lesions evaluated using a relatively new method of accelerated CNB processing allowing for a same day definitive diagnosis in the vast majority of patients suitable for ultrasound guided biopsy. Our study shows this technique to be highly accurate, with a sensitivity of 96.9%, a specificity of 99.4%, and a total accuracy of 98.4%. Furthermore, the one day diagnosis group in our study has a low inconclusive rate of 9.2%.

Interestingly, two of the three malignancies found post-operatively that were considered benign on CNB, were phyllodes tumors (one high grade malignant, the other one borderline malignant). (Borderline) malignant phyllodes tumors are not invasive carcinomas, but should be considered malignant tumors. For simplicities sake, we therefore grouped them under invasive cancers. Since patients with benign phyllodes tumors are operated on nevertheless, their benign CNB classification did not result in malignancy remaining untreated.

The third false-negative CNB-result found in table 4 was a malignant lesion identified by concurrent cytologic cyst aspiration. As such, this malignancy did not remain untreated either.

In the same day diagnosis group, 2 (0.6%) cases showed an invasive carcinoma on CNB, whereas post-operatively only DCIS was found. 2 (0.6%) showed invasive carcinoma, and 1 (5%) a DCIS on CNB, whereas post-operatively no malignancy was found.

This phenomenon occurs regularly in literature concerning CNB. It is generally assumed that in these cases, the entire (invasive part of the) lesion was included in the biopsy core[26]. Should one assume so, specificity increases (by definition) to 100%.

In our series, one of the two lesions whose CNB showed invasive carcinoma without malignancy after resection, was actually a case of a complete response to neo-adjuvant systemic therapy. The other patient had a 7mm lesion found on MRI screening. She was surgically treated elsewhere, and the CNB diagnosis was reviewed and

confirmed by an external pathologist. The DCIS lesion that was not found post-operatively was a grade I DCIS on CNB, and post-operatively only atypical ductal hyperplasia was found.

Conversely in our series 6 of the 20 (30%) DCIS lesions diagnosed on CNB were post-operatively ‘upgraded’ to invasive ductal carcinoma. This problem is also well known in the literature, with reported underestimation rates of 26.2% to 27.1%[27,28].

Clear differences can be seen between the patient group in the same day diagnosis track, and the ‘all lesions’ group. There is also a difference in accuracy (although fairly small in absolute numbers). This is likely due to case selection, as stereotactic biopsies are not analyzed in a same day diagnosis track (the thicker cores cannot be processed in a similarly fast way as the thinner cores from ultrasound guided biopsies). This causes screen detected malignancies, especially DCIS to be underrepresented in the fast track lesion group. It thus appears that the ‘hardest’ cases are not included in the one day diagnosis group. An apparently similar effect was found by Fajardo et al in their series of 2403 non-palpable lesions either biopsied by US-guided or stereotactic CNB[29].

Inter-observer variability

For FNAC it is widely accepted that this technique has a high operator dependency, although original data on this subject seems to be somewhat limited[30-32]. For CNB, inter-observer agreement has not been extensively investigated. Two studies of considerable size conclude that there is a high inter-observer agreement, although it seems likely that all participating pathologists had an ‘above average’ experience interpreting CNB specimens[33,34].

The technique described in our study does not require any additional skills or experience compared to the classic CNB technique, and only a minor investment in equipment is required. However, to achieve a high effectiveness in terms of speed, it does require careful planning of patients, doctors and supporting staff. In our clinic, patients are scheduled for biopsy early (before 11am), with the results ready for discussion in the MBCWG (and subsequent communication to our patients) at 15.15h. Alternatively, using a *CNBplus* technique, a well organized clinic would be able to render a (less accurate) provisional cytologic diagnosis within the hour. The complex logistics involved and the four hour processing time may form a barrier to more widespread implementation of this technique.

As each biopsy specimen is only processed and evaluated once, it stands to reason it is more cost effective than previously described *CNBplus* techniques, that require both a cytologic and a histologic work up. FNAC was traditionally considered to be cheaper than CNB, but this cost advantage seems to disappear when the number of repeat-biopsies in inconclusive cases are taken into consideration[35]. Although the accelerated processing technique requires some additional investments and logistic commitment, it is probably only a little bit more expensive than regular CNB processing.

Drawbacks

Although our population consists of both screening and symptomatic patients, the fact that stereotactic biopsies are never diagnosed the same day means that our study has a tendency to select symptomatic patients.

Length of follow-up in our study was heterogeneous: our oldest cases having over 50 months of follow-up, the most recent only 6 months. Ideally all cases would have a similar, long follow-up.

Another potential drawback of our study is the used definition of an inconclusive diagnosis. We based this definition on two parameters: the biopsy being repeated (decided on by the MBCWG, which can be considered the gold standard), and doubt of representativity mentioned in the pathology report. As true representativity is a more complex combination of pathologic and radiologic observations, it is possible we over- or underestimated the true inconclusive rate.

Lastly: the fact that the majority of biopsies in our clinic are interpreted by a single dedicated pathologist (P.B.), gives our clinic a slight advantage over clinics where cases are more evenly distributed amongst multiple general pathologists. This means our results may not be fully applicable to other settings.

Comparison with other techniques

Test characteristics in this study are similar to those of regular CNB. The inconclusive rate of 9.2% falls in line with two large series reporting inconclusive rates of 4.3% and 7%[4,3], and the review by Willems et al describing a 1% inconclusive rate[8]. Sensitivity of 96.9% is similar to the 93% and 96% found by the two series[4,3]. Specificity of 99.4% is also similar to the 88% and 100% they describe[4,3]. Our results show that accelerated processing does not have a negative influence on these test characteristics. The rate of conclusiveness for FNAC in most previous literature is lower for both benign and malignant results. Willems et al calculated a conclusive rate between 60-75%[8]. When compared to *CNBplus* techniques, all test

characteristics (as described in the introduction section) including inconclusive rate are similar and/or better in our study[12,20,21,15,13,19,17,16,18].

Conclusion

We describe test characteristics for a relatively novel technique that allows for quicker processing of otherwise regular core needle biopsies, based on a series of 898 lesions biopsied in our breast clinic between January 1st 2008 and January 1st 2012. Our series demonstrates a total accuracy of 98.4%, with a sensitivity of 96.4% for invasive cancer, 96.9% for malignancy including DCIS and a specificity of 99.4%. The inconclusive rate is 9.2%.

Accelerated CNB processing can safely provide a definitive diagnosis on the same day for 65% of patients requiring biopsy.

Ethical standards

This study complies with current Dutch law.

Disclosure / conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

The authors thank Lambert Burgers for his valuable comments on the pathology section in the material and methods paragraph.

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Table 1: CNB characteristics

	Same day diagnosis (n=898)	All lesions (n=1383)
CNB method		
-US guided	898	1073 (77.6%)
-Stereotactic	0	274 (19.8%)
-MRI guided	0	36 (2.6%)
Cores:		
-mean number of cores taken	2.16 (1-6)	3.26 (1-36)
-mean size of cores in mm (range)	10.6 (2-45)	11.7 (1-60)
Invasive carcinoma:		
-subtype on same day	185/ 331 (55.9%)	283/ 432 (66%)
-subtype after additional staining	28/ 331 (8.5%)	
Invasive carcinoma and DCIS:		
-Includes Bloom-Richardson score	67/ 351 (19.1%)	162/ 533 (30.4%)

Table 2: Patient characteristics

	Same day diagnosis (n=898 ^a)	All lesions (n=1383 ^a)
Female (%)	893 (99.4)	1376 (99.5)
Age in years (mean, range, sd)	49 (17-96, 14.5)	51 (15-96, 13.8)
Lesion detected as:		
-screening abnormality	237 (26.4%)	525 (38%)
-palpable lesion	423 (47.1%)	512 (37%)
-incidental radiographic finding	90 (10%)	140 (10.1%)
-pain	44 (4.9%)	52 (3.8%)
-nipple discharge	22 (2.4%)	26 (1.9%)
-other	82 (9.2%)	128 (7.9%)
BI-RADS on mammography		
0	15 (1.7%)	26 (1.9%)
1	85 (9.5%)	109 (7.9%)
2	85 (9.5%)	109 (7.9%)
3	212 (23.6%)	291 (21%)
4	171 (19%)	408 (29.5%)
5	195 (21.7%)	244 (17.6%)
6	4 (0.3%)	4 (0.3%)
(not performed)	107 (11.9%)	140 (10.1%)
(performed but not reported)	28 (3.1%)	52 (3.8%)
BI-RADS on Ultrasound		
0	3 (0.3%)	15 (1.1%)
1	8 (.9%)	95 (6.9%)
2	37 (4.1%)	97 (7.0%)
3	384 (42.8%)	463 (33.5%)
4	225 (25.1%)	307 (22.2%)
5	205 (22.8%)	252 (18.2%)
6	1 (0.1%)	7 (0.5%)
(not performed)		96 (6.9%)
(performed but not reported)	35 (3.9%)	51 (3.7%)
Previously evaluated ^b	315 (35.1%)	512 (37%)
Previously diagnosed with malignancy of the breast	56 (6.2%)	109 (7.9%)

^anumbers representing lesions^bscreening not included

Table 3: lesion characteristics

	Lesions with a same day diagnosis (n=898)	All lesions (n=1383)
Nature of lesion ^a		
-Benign	535 (59.6%)	793 (57.3%)
-High risk	12 (1.3%)	64 (4.6%)
-DCIS	16 (1.8%)	76 (5.5%)
-Invasive carcinoma	335 (37.3%)	450 (32.5%)
Benign lesion type ^b		
-Fibroadenoma	189 (35.1%)	244 (30.7%)
-(Micro)cystic lesion	86 (16%)	152 (19.1%)
-Fibrotic tissue	78 (14.5%)	99 (12.5%)
-Other	185 (34.4%)	299 (37.7%)
Type of invasive carcinoma ^c :		
-Ductal	260 (83.3%)	349 (84.1%)
-Lobular	36 (11.5%)	45 (10.8%)
-Other	16 (5.1%)	21 (5.1%)

^apost-operative pathology results when available, definitive CNB result when no resection was performed (mostly benign lesions)

^bCNB results only

^cpost-operative results only

Table 4: lesions with a same day diagnosis (surgically treated cases only)

		Post-operative result			
		Benign	High risk	DCIS	Invasive cancer
CNB result	Benign	62	2	1	2^a
	High risk	1	2	0	0
	DCIS	0	1	13	6
	Invasive cancer	2^b	0	2	304

^aboth phyllodes tumors, one borderline malignant, one high grade malignant

^bone case of complete response to neo-adjuvant therapy

Table 5: all lesions (surgically treated cases only)

		Post-operative result			
		Benign	High risk	DCIS	Invasive cancer
CNB result	Benign	78	5	5	8
	High risk	4	11	0	1
	DCIS	11	7	63	17
	Invasive cancer	3	0	5	389