Title: Modified Core Wash Cytology: a reliable same day biopsy result for breast clinics

Shortened title: Modified Core Wash Cytology for breast lesions

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Synopsis:

Core Wash Cytology can be used as an adjunct to regular Core Needle Biopsy of breast lesions to provide a reliable provisional cytological diagnosis within one hour of biopsy, and is highly conclusive in malignant lesions.

Abstract:

Background: Fine Needle Aspiration Biopsy (FNAB), Core Needle biopsy (CNB) and hybrid techniques including Core Wash Cytology (CWC) are available for same-day diagnosis in breast lesions. In CWC a washing of the biopsy core is processed for a provisional cytological diagnosis, after which the core is processed like a regular CNB. This study focuses on the reliability of CWC in daily practice.

Methods: All consecutive CWC procedures performed in a referral breast centre between May 2009 and May 2012 were reviewed, correlating CWC results with the CNB result, definitive diagnosis after surgical resection and/or follow-up. Symptomatic as well as screen-detected lesions, undergoing CNB were included.

Results: 1,253 CWC procedures were performed. Definitive histology showed 849 (68%) malignant and 404 (32%) benign lesions. 80% of CWC procedures yielded a conclusive diagnosis: this percentage was higher amongst malignant lesions and lower for benign lesions: 89% and 62% respectively. Sensitivity and specificity of a conclusive CWC result were respectively 98.3% and 90.4%. The eventual incidence of malignancy in the cytological 'atypical' group (5%) was similar to the cytological 'benign' group (6%).

Conclusion: CWC can be used to make a reliable provisional diagnosis of breast lesions within the hour. The high probability of conclusive results in malignant lesions makes CWC well suited for high risk populations.

Keywords: *breast neoplasms, diagnosis, biopsy, cytological techniques*

Introduction:

In the United states, 222 175 women were diagnosed with breast cancer in 2011[1]. Although National Comprehensive Cancer Network (NCCN) guidelines make no mention of the preferred duration of diagnostic workup[2], European guidelines encourage rapid confirmation or exclusion of cancer within 24-48 hours[3]. Especially patients with benign disease benefit from reduced duration of anxiety[4], in malignant cases a quick confirmation expedites subsequent treatment. To meet this challenge, different approaches have been developed.

Fine Needle Aspiration Biopsy (FNAB) allows a diagnosis within an hour, with sensitivity of 35-95%, specificity of 48-100% and conclusivity of 60-75%[5]. This has progressively led most clinics to adopt Core Needle Biopsy (CNB) as diagnostic tool of choice.[5-9]. Considered as the gold standard for evaluating solid breast lesions[5-9], CNB often requires more processing time. Recently, the accelerated CNB processing method has demonstrated a reliable histological diagnosis on the day of biopsy[10]. However, alternative techniques are also available.

In an attempt to combine speed and accuracy a hybrid technique, Core Wash Cytology (CWC) of a CNB specimen (CNB+CWC), combining cytology and histology, was developed. The CNB specimen and needle are 'washed' in a saline solution or special fixative which is then cytocentrifugated and pressed onto a slide. The resulting cytology specimen is interpreted using the same guidelines as used for FNAB[11]. Afterwards the Core itself provides a histological diagnosis. After an initial promising study [12], a second larger series [13] found the technique performed poorly, with a low specificity (72%) and an unacceptably high inconclusive rate (42%).

Following a successful pre-clinical pilot study[14], our breast clinic adopted a modified CWC technique for the evaluation of solid breast lesions. A review of this technique describing 229 patients showed excellent results with a sensitivity of 97%, a specificity of 100% and an inconclusive rate of 4%[15]. To our knowledge, no series validating or evaluating CWC in breast cancer have been published since.

The aim of the present study was to relate the previous pilot results to a larger consecutive daily practice series of patients diagnosed using standardized CNB+CWC in a regional breast clinic over a 3 year period.

Materials:

Patient selection, database

The prospectively filled National Pathology Database of the Netherlands (PALGA[16]) was searched to identify all CNB procedures of the breast in our clinic, between May 1, 2009 and May 31, 2012, including both symptomatic and screen detected lesions. All patients with CWC following CNB were included. We analysed baseline patient characteristics including age, referral indication and 'Breast imaging- reporting and data system' (BI-RADS)[17] classification. CWC- and CNB result, as well as information on hormone receptor- and HER2 status were recorded. Furthermore, we included post-operative pathology results and neo-adjuvant therapy in our database.

Biopsies

CNB was performed using US-, stereotactic- or MRI guidance. US-guided biopsies were performed using an 18 gauge needle on a BARD® magnum® biopsy gun. The number of cores for each biopsy was at the discretion of the radiologist. Stereotactic and MRI guided biopsies were performed with a Vacuum Assisted Biopsy (VAB) system. VAB specimens were not processed using the CWC procedure, and were excluded from this study.

CWC technique

Technical details of the modified CWC procedure have been described in previous reports[14, 15]. In short: after biopsy the CNB specimen is placed in a transport solution (initially Roswell Park Memorial Institute (RPMI), later replaced with a 50% ethanol/2% polyethylene glycol solution). After removing the CNB specimen for regular processing, cells remaining in the medium are cyto-centrifugated, processed to a monolayer slide and stained according to Papanicolaou.

Pathology

The CWC specimen is interpreted within one hour following biopsy, using the same criteria as for FNAB. According to international guidelines[11], findings are categorized as 'insufficient material' (inconclusive), 'benign', 'atypical favouring benign', 'atypical' (inconclusive), 'suspicious for malignancy' or 'malignant'. CNB specimens were processed and reported on according to the Dutch national breast cancer guidelines[18]. The report includes both a classification ('benign', 'not clearly benign/suspected malignancy' or 'malignant') and a specific diagnosis. The specimen were formalin-fixed, embedded in paraffin and at least three cuts were taken. For our database, we recorded the CNB result as benign, high risk (including lobular carcinoma in situ, atypical ductal/lobular hyperplasia and complex sclerosing lesion), DCIS or invasive cancer. Post-operative pathology specimens were also processed and reported according to the Dutch national guidelines. All specimens were evaluated by experienced breast pathologists.

Follow-up

For patients with a benign biopsy result whose lesions were not resected, we performed a nationwide search in the 'PALGA'[16] database in July 2013, checking for breast related malignancy diagnosed after the biopsy procedure to identify potential false negative results.

Data-analysis

We considered benign and “atypical favouring benign” results as ‘benign’, insufficient material and inconclusive (atypical) as ‘inconclusive’, suspicious and malignant as ‘malignant’.

For descriptive purposes, we used the type of benign lesion found at CNB to describe benign lesions of patients not operated on.

For calculation of sensitivity and specificity of the CWC result, the most ‘definitive’ diagnosis available was used: post-operative pathology if available, otherwise CNB results combined with follow-up through PALGA.

Data was analysed using SPSS (IBM® SPSS® statistics version 19) (SPSS Inc., Chicago, IL, USA). Statistical significance was tested using the chi-square test, with a cut off value of 0.05.

Results:

Patients

During the studied period 1 516 patients underwent 1 820 CNB procedures for the evaluation of 1 768 breast lesions. Of these 1 253 (69%) were processed using the CWC procedure, the remaining 567 specimen were acquired using (stereotactic) VAB and thus not suitable for a 'one-stop-shop' CWC approach. General radiologists performed 53 biopsies (4.2%), dedicated breast radiologists performed 1 200 (95.8%) biopsies. Patient and lesion characteristics are shown in table 1. Of these lesions 35% were screen detected.

Of the patients analysed with the CWC procedure, 70 (5.6%) subsequently received neo-adjuvant systemic therapy, leading to a pathologic complete response in 6 patients (8.6%). For our analysis we considered the 'definitive' diagnosis in these patients to be malignant.

Final diagnosis through surgical excision was available for 894 lesions, of which 776 (87%) were malignant.

CWC results

Of the 1 253 CWC procedures 1 007 (80%) provided a conclusive result. We classified 240 as 'benign' and 767 as 'malignant' (table 2). We classified 246 specimens (20%) as 'inconclusive'. Of these, a conclusive CNB diagnosis was reached the next day in 197 (80%) cases; in 49 cases (20%) CNB remained inconclusive.

The definitive diagnosis of 'inconclusive' CWC specimen was benign in 157 cases (64%) and malignant in 89 cases (36%, $p < 0.001$). Of all lesions benign on final histology, 38% were inconclusive on CWC. Of the malignant lesions, 11% were inconclusive on CWC.

Malignant lesions with a Bloom-Richardson classification (BR grade) 1 were more often inconclusive on CWC than those with a BR grade 3 (15% versus 5%, $p=0.005$). CWC of invasive lobular carcinoma was more often inconclusive than that of invasive ductal carcinoma (22% versus 7%, $p < 0.001$).

CNB results

In 91 cases (7%) the CNB specimen did not reveal a definitive diagnosis. In 74 (81%) cases because of doubt on representativity of the biopsy, in 8 (9%) cases because of insufficient material and in 9 (10%) biopsies the diagnosis was formally inconclusive. In 41 of these cases repeat CNB was performed and in 29 cases a surgical excision biopsy. For 21 patients radiographic and/or clinical follow-up was preferred.

In 49 (54%) of cases with an inconclusive CNB, CWC was inconclusive as well. For 36 cases (39%) CWC correctly predicted outcome, for 6 cases (7%) CWC did not correctly predict the final result.

In 31 cases, CWC and CNB showed contradictory results. In 25 of these, CWC indicated malignancy whereas the final CNB result showed a benign lesion. A repeated CNB and/or resection was performed in 19 cases, revealing malignancy in 9 cases.

In 6 cases CWC indicated a benign lesion and CNB a malignancy. In 5 of these cases a repeat biopsy and/or resection was performed, revealing malignant disease in all 5 cases.

The PALGA search was performed for the 355 patients with a conclusive benign CNB result. Median available follow-up was 30 months, with a range of 12-49 months. Eight patients were subsequently diagnosed with breast

cancer. Three cases concerned contralateral breast lesions. The remaining five were considered false negatives (only one of these five was conclusive at initial CWC).

The percentage of 'conclusive' CWC results was 80%. Sensitivity of a conclusive CWC result was 98.3%, specificity 90.4%. Of the 'conclusive' CWC results, 38 were incorrect (3.8%).

Discussion:

This series is the largest available in the current literature on Core Wash Cytology in breast lesions. It provides clear test characteristics and guidance on interpretation of atypical, inconclusive, and suspicious results. Unlike our previous series[15] it includes many benign cases, making it more representative of daily clinical practice. The very high sensitivity of a conclusive result makes CWC particularly suitable for immediate reassurance of patients with benign disease.

The hybrid nature of the procedure means each biopsy functions as its own internal control. The resection specimen and follow up through the Dutch national pathology database PALGA provide a strong external control, making it unlikely that false positive and/or false negative results were missed. The equipment and experience required for this technique are the same as for FNA-acquired breast cytology.

As CWC is an additional rather than an alternative processing procedure, extra information is created. Most often, this information is confirmed by other sources. However, in approximately 3% of cases CNB and CWC results are contradictory. As expected, a malignant CNB result is reliable when CWC indicates benign disease. Conversely, when CNB was benign but CWC indicated malignancy about one third of cases proved malignant after resection. Thus, CWC provides a (modest) reduction in false negative CNB results. One explanation could be the presence of a very small fragment of malignant tissue in the biopsy core, completely disintegrating during transport to the pathology department. Malignant cells would then be found on CWC, though no malignant lesion is found in CNB.

Using a liquid based cytology method and processing the CWC specimen to a monolayer slide takes slightly more time (approximately 20 minutes) and effort, compared to performing a 'direct smear' technique. We believe this to be worthwhile, as previous literature shows interpretation time is reduced, cellular morphology is improved, and there are less inconclusive results[19, 20].

The most important limitation of CWC is the number of inconclusive results. In the previous series[15] in line with FNAB guidelines[11] we considered 'atypical favouring benign' to be inconclusive. This series clearly demonstrate an atypical result can be considered conclusively benign (table 4). This is remarkable, as FNAB series show a prevalence of malignancy in this category of about 37%[21-23]. The proportion of atypical results in the present series (6.4%) is somewhat higher than large FNAB series (3.9 and 4%)[21, 23] possibly indicating our pathologists reporting more atypical lesions other pathologists might have reported as benign (inter-observer variation). Furthermore, there could be a difference in population (mostly symptomatic in the present series), or an intrinsic difference between CWC and FNAB specimen.

When considering atypical results as conclusively benign, 20% of CWC procedures was inconclusive. This was higher (38%) for benign lesions. Conversely, only 11% was inconclusive in malignant lesions. This is in line with literature concerning FNAB, and the previous series by Uematso[13, 24]. CWC performs favourably compared to FNAB series showing 27-42% inconclusiveness[19].

A correlation between differentiation grade and conclusivity was observed: in BR grade 3 lesions only 5% was inconclusive whereas BR grade 1 lesions are, in terms of conclusivity (15%), in between high grade malignancies and benign lesions.

More inconclusive results among lobular carcinomas mirrors previous literature[25]. Cells of invasive lobular carcinoma may be hard to distinguish from lymphocytes in cytology specimen.

The CWC procedure allows us to run a true 'one-stop-shop' breast clinic. It provides 80% of patients, suitable for ultrasound guided biopsy, a diagnosis within hours of entering our clinic. In daily practice, patients sequentially visit the radiology department and the outpatient clinic, and immediately receive a preliminary diagnosis based on cytology, combined with history, physical examination and imaging. This strategy results in 95% of patients receiving a tentative conclusion and corresponding treatment plan or reassurance the same day. It also facilitates the immediate planning of treatment and/or further analysis when required. The combination with regular CNB processing means we can provide 99% of patients with a conclusive diagnosis the following day, without the necessity of repeat biopsy. This policy limits the duration of anxiety, cost and the number of invasive procedures. Furthermore it helps to streamline treatment planning, reducing time and number of office visits between initial diagnosis and additional diagnostics or treatment. Although the relatively small decrease in time will not likely result in a survival benefit[26], in our experience it is greatly appreciated by patients.

Of all patients expecting a diagnosis within an hour of biopsy, we have to disappoint approximately 5%. Managing expectations is therefore crucial to patient-satisfaction.

This series paints a more realistic picture of CWC compared to our first clinical series. Differences can be explained by a more balanced case mix with more benign lesions in the present series. Comparison to our first series and the study by Uematso et al. points out the crucial fact that CWC is well suited for high-risk populations, but less so for low risk groups [13, 15]. With increasing numbers of benign lesions test characteristics and specifically conclusivity show a marked drop. The Uematso series contains less than 50% malignant cases, and has an inconclusive rate of over 40%. However, when conclusivity for malignant- and benign lesions is taken separately results are more similar to ours.

Interestingly, Lankford et al. provide very different results with excellent test characteristics and an inconclusive rate of only 7% even though their population was extremely low risk with only 13% malignant lesions[12]. Their population is different, as it only included non-palpable lesions. Furthermore a different, 4 point classification for CWC results was used rather than the internationally accepted criteria for FNAB cytology[11]. Another explanation could be that the increased conclusivity reported by Lankford comes at the cost of decreased sensitivity (82% versus 98% for a conclusive result in the present series).

Compared to FNAB or regular CNB, the CWC technique has clear advantages. CWC is much faster than regular CNB, whilst retaining the advantages through the additionally processed core. Unlike FNAB, the CNB specimen serves as an internal quality assurance, greatly reducing the number of repeat biopsies that accompanies an inconclusive FNAB result[24]. Processing in under one hour is superior to the 4-6 hours required for accelerated CNB, and the technique is far less logistically demanding[10].

We excluded stereotactic biopsies, because a much larger gauge needle is generally used, decreasing the surface to volume-ratio of the specimen. Moreover, stereotactic biopsies are often scheduled one to several days after initial evaluation of mostly screen-detected lesions, and these patients have a lower prevalence of malignancy and more DCIS. For these reasons we do not perform CWC for stereotactic biopsies.

Although this study was retrospective, we were able to reliably retrieve all relevant variables. Our study reflects real-life daily practice, including many benign cases, less experienced radiologists and samples of lesser quality. These unpolished results can be considered representative for the high volume breast clinic.

Conclusion:

In the largest series currently available, we demonstrated that Core Wash Cytology can be used as an adjunct to regular Core Needle Biopsy to make a provisional diagnosis on breast lesions within one hour of biopsy. The technique has a good specificity and a very high sensitivity provided the diagnosis is conclusive. However, 20% inconclusive results means the technique is not well suited for populations with a high prevalence of benign breast disease.

Disclosure / conflict of interest

The authors declare that they have no conflict of interest.

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Table 1. Patient characteristics

Total:	1 253
• female	1 244 (99.3%)
• male	9 (0.7%)
Age in years (median, range)	55 (16-96)
Referral indication:	
• palpable breast lesion	544 (43.4%)
• screening	435 (34.7%)
• incidental radiologic finding	76 (6.1%)
• breast pain	41 (3.3%)
• follow up after malignancy	54 (4.3%)
• other	100 (8.2%)
BI-RADS ^a classification:	
• 0	1 (0.1%)
• 1	1 (0.1%)
• 2	18 (1.4%)
• 3	240 (19.2%)
• 4	392 (31.3%)
• 5	547 (43.6%)
• Unknown	54 (4.3%)
Patients previously evaluated for breast complaints ^b	501 (40%)
Patients previously diagnosed with breast cancer	128 (10.2%)

^a BI-RADS: Breast imaging – reporting and data system

^b Not including the National breast cancer screening program

Table 2. Distribution of Core Wash Cytology diagnosis

Final classification:	
• 0: not enough material	104 (8.3%)
• 1: benign	160 (12.8%)
• 2: atypia	80 (6.4%)
• 3: inconclusive	142 (11.3%)
• 4: suspicious	97 (7.7%)
• 5: malignant	670 (53.5%)

Table 3. Lesion characteristics

Nature of lesion ^a : <ul style="list-style-type: none"> • Benign <ul style="list-style-type: none"> ○ Fibroadenoma ○ (micro) cystic ○ Fibrotic tissue ○ Other • high risk^b • DCIS^c • invasive carcinoma <ul style="list-style-type: none"> ○ ductal ○ lobular ○ other 	395 (31.5%) <ul style="list-style-type: none"> • 144 (36.5%) • 5 (1.3%) • 58 (14.7%) • 188 (47.6%) 9 (0.7%) 33 (2.6%) 816 (65.1%) <ul style="list-style-type: none"> • 647 (79.9%) • 100 (12.3%) • 61 (7.4%)
Nature of invasive lesion ^a <ul style="list-style-type: none"> • Bloom-richardson classification <ul style="list-style-type: none"> ○ Grade 1 ○ Grade 2 ○ Grade 3 ○ Unknown • Estrogen receptor status <ul style="list-style-type: none"> ○ Positive ○ Negative ○ Unknown • Progesterone receptor status <ul style="list-style-type: none"> ○ Positive ○ Negative ○ Unknown • HER2 status <ul style="list-style-type: none"> ○ Positive ○ Negative ○ Unknown 	Total: 816 (100%) 161 (19.7%) 344 (42.2%) 198 (24.3%) 113 (13.8%) 677 (83%) 111 (13.6%) 28 (3.4%) 522 (64%) 266 (32.6%) 28 (3.4%) 71 (8.7%) 564 (69.1%) 181 (22.2%)

^a most definitive result: resection when available, otherwise CNB result^b e.g. atypical ductal hyperplasia, lobular carcinoma in situ^c Ductal Carcinoma in SituTable 4: Core Wash Cytology result versus most definitive result available^{ab}

	Final Histology ^{ab}				
CWC ^c		Benign	High risk	DCIS ^d	Invasive cancer
	1: benign	149	1	3	7
	2: atypia	74	2	0	4
	3: inconclusive	152	2	6	86
	4: suspicious	9	1	5	82
	5: malignant	11	3	19	637

^a most definitive result: resection when available, otherwise CNB result^b Italics signify false positive- or false negative results^c Core Wash Cytology^d Ductal Carcinoma in Situ

Figure 1: Core Wash Cytology. Resulting macroscopy of a Core Wash slide (A). Resulting microscopy of a Core Wash slide. Malignant epithelial cells with large nucleoli. Pap staining, magnification 400x (B).