

Fine-needle aspiration cytology for breast lesions and cytopathologic correlations. An Italian peripheral hospital experience with 440 cases (from 2000 to 2007)

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SUMMARY: Fine-needle aspiration cytology for breast lesions and cytopathologic correlations. An Italian peripheral hospital experience with 440 cases (from 2000 to 2007).

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In the present study, we evaluate our experience with Fine-Needle Aspiration Cytology (FNAC) for the diagnosis of breast tumor. Our intent is to correlate the diagnostic accuracy of FNAC for breast lesions on the basis of their respective histopathologic results. We retrospectively examined 440 cases of breast lesions who underwent FNAC and subsequently had definitive histopathologic diagnosis. The patients were observed over a period of eight years (from January 2000 to December 2007) at the "Santo Spirito" Hospital of Casale Monferrato, a general peripheral hospital in the North-West Italy (Piemonte Region). The results of FNAC were expressed using the five diagnostic categories recommended by European Guidelines on breast tumors as follows: 159 C5 cases (36.1%), 88 C4 (20%), 51 C3 (11.6%), 42 C2 (9.5%), and 100 C1 (22.7%). The statistical analysis revealed these values: sensitivity 93.8% (C5+C4), specificity 79.6%, C5 positive predictive value 97.5%, C2 negative predictive value 83.3%, false positive fraction 2.5%, false negative fraction 16.6%, diagnostic accuracy 71.2%. In consideration to the low cost and the low discomfort for patients, we consider FNAC a safe and feasible procedure, in particular in the context of peripheral hospitals, where a sophisticated technology is not available. We remark the importance of a good selection of patients to obtain the best results from the procedure.

RIASSUNTO: Citologia da agoaspirato con ago sottile nelle lesioni mammarie e correlazioni citopatologiche. L'esperienza di un ospedale periferico italiano su 440 casi (dal 2000 al 2007).

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Nel presente studio prendiamo in esame la nostra esperienza nell'ambito della citologia da agoaspirato con ago sottile (FNAC) per la diagnosi del tumore mammario. Il nostro scopo è di correlare l'accuratezza diagnostica della FNAC per le lesioni mammarie sulla base dei rispettivi reperti istopatologici. Abbiamo esaminato retrospettivamente 440 casi di lesioni mammarie sottoposte a FNAC e con successiva diagnosi istopatologica definitiva. Le pazienti sono state osservate in un periodo di otto anni (da gennaio 2000 a dicembre 2007) presso l'Ospedale "Santo Spirito" di Casale Monferrato, un ospedale periferico piemontese. I risultati della FNAC sono stati espressi, usando le cinque categorie diagnostiche raccomandate dalle Linee Guida Europee sui tumori mammari, come segue: 159 casi C5 (36,1%), 88 C4 (20%), 51 C3 (11,6%), 42 C2 (9,5%), and 100 C1 (22,7%). L'analisi statistica ha rivelato questi valori: sensibilità 93,8% (C5+C4), specificità 79,6%, valore predittivo positivo di C5 97,5%, valore predittivo negativo di C2 83,3%, falsi positivi 2,5%, falsi negativi 16,6%, accuratezza diagnostica 71,2%. In considerazione del basso costo e del limitato disagio per le pazienti, pensiamo che la FNAC sia una procedura sicura e fattibile, in particolare nel contesto degli ospedali periferici, dove non è spesso disponibile una tecnologia sofisticata. Mettiamo infine in evidenza l'importanza di una buona selezione delle pazienti, al fine di ottenere i migliori risultati dalla procedura.

KEY WORDS: Breast Cancer - Fine-Needle Aspiration Cytology (FNAC) - Sensitivity and specificity.
Tumore mammario - Citologia da agoaspirato con ago sottile - Sensibilità e specificità.

Introduction

Fine-Needle Aspiration Cytology (FNAC) is a consolidated procedure in the diagnosis and clinical management

of breast suspected lesions. Anyway, many researchers do not agree about whether FNAC should be placed on the clinical decision tree for the diagnosis of breast cancer (1, 2). A current trend away from FNAC in breast lesions and increased use of Core-Needle Biopsy (CNB) is particularly observed in US, Canada and United Kingdom (3, 4). This trend could be due to some factors: inability to determine invasiveness, limitation in evaluation of biomarkers, possibility of overlap of benign and malignant features, high rate of insufficient results (especially for non-palpable lesions), limited number of experienced cytopathologists (5-8).

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On the other hand, the decreased application of FNAC lead to the lost of some particular advantages. FNAC is rapid, simple, minimally invasive, cheap to perform; it does not require expensive devices and can be performed even in peripheral centers, where specific technology is not available (5, 7, 9-12).

Previous studies have demonstrated that sensitivity and specificity of FNAC for breast tumor, ranged from 82.5% to 98.2%, and from 77.4% to 100% respectively (2, 10, 11, 13-15). Akçil et al. have recently published a meta-analysis of 25 studies describing FNAC analyses performed from 1984 to 2007 on palpable breast masses. In these studies the sensitivity of FNAC ranged from 78% to 100%, and the specificity from 76% to 100% (16). The different frequency of cancer detection most likely depends on the selection of patients as well as the skill of the personnel who performed and interpreted the aspiration (17).

The aim of our study is to review our experience with FNAC for the diagnosis of breast lesions, comparing our results with other published studies.

Patients and methods

A retrospective search using a computer database from our Pathology Department was performed to identify patients who underwent Fine-Needle Aspiration (FNA) for suspected breast lesions from January 2000 to December 2007 at Casale Monferrato *Santo Spirito* Hospital, a general peripheral hospital in the North-West Italy, in the Piedmont Region. Within this group we selected the patients who had histological definitive diagnosis obtained from surgical samples. For all these cases, a comparison of the cytologic and histologic diagnosis was made to determine the sensitivity (SE), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), false positive (FP) fraction, false negative (FN) fraction and diagnostic accuracy of FNAC.

FNA was performed handmade by surgeon or pathologist for palpable breast lesions. In case of nonpalpable masses, the radiologist performed the procedure under ultrasound guidance. A 21- to 25-gauge needle was used, attached to a 20 ml syringe. Two separated passes were made into the lesion with the needle. During each pass, the needle was moved throughout the lesion several times. Samples obtained was treated in double way: a part of aspirate material was shuffled and stained with Papanicolau or May-Grünwald Giemsa stain, while a part was fixed in an alcoholic fixative to prepare monolayer slide with Cytoc ThinPrep® 2000 Processor and stained with Papanicolau stain.

FNA specimens were examined and every diagnosis was expressed using the five diagnostic categories recommended by European Guidelines on breast tumors as follows: C1 (insufficient), C2 (benign), C3 (atypia, probably benign), C4 (suspicious of malignancy) and C5 (malignant) (18,19).

Results

A total of 942 FNAs of breast lesions were performed. Among these we examined the 440 cytological cases having a corresponding surgical specimens (150 mastectomies, 171 quadrantectomies and 119 excisional biopsies). The age of the patients ranged between 20 and 85

years. The most frequently interested region in breast parenchyma was the upper outer one (200/440), while the others were equally represented.

These were the results of FNAC: 159 cases (36,1%) were positive for malignant tumor (C5), 88 (20%) resulted suspected for malignancy (C4), 51 (11,6%) presented atypical cells of undetermined significant (C3), 42 (9,5%) were negative for malignancy (C2), and 100 (22,7%) were inadequate for diagnosis (C1).

Histological evaluation of the cases has consented to detail each cytological diagnostic category. In C5 category, 155/159 cytological positive results corresponded to histological malignant tumors (ductal and lobular infiltrating carcinoma), with only 4/159 false positive cases, corresponding to intraductal atypical papilloma. In C4 cytological category, 72/88 resulted malignant; 16/88 cases classified as C4 resulted benign, corresponding to 9 intraductal papillomas, 4 fibroadematous lesions, 2 fibrocystic disease with atypical epitheliosis and one granulomatous flogistic lesion. As regards to C3 diagnostic category, 43/51 cases resulted benign lesions on histological examination, while 8/51 cases were consistent with malignant diagnosis (6 infiltrating ductal carcinoma and 2 intraductal neoplasia). In C2 diagnostic category, there were 7/42 false negative cases, corresponding to 4 infiltrating carcinoma, one breast lymphoma and 2 intraductal carcinoma. In our series, 100/440 cases resulted inadequate (22,7%). Histological examination revealed that 38 C1 patients had malignant lesions. In the remaining 62 patients a nodular pathology resulted absent on excisional biopsy, and only some alterations in normal breast tissue, such as various degree of fibrocystic disease, were found. These data are shown in Table 1.

For statistical analysis, many Authors exclude the C1 cytological diagnostic category (17, 20). Anyway, we decided to perform the analysis not only excluding the C1 cases, but also using the complete dataset (as seen in Sapino et al.) (19), in order to offer a detailed evaluation of the results. When we included the C1 findings, an interpretation of inadequate or benign on cytology with a finding of cancer on histology was considered false negative, as suggested in Park et al. (21). Moreover, we calculated the percentages considering as positive not only C5 results,

TABLE 1 - SUMMARY OF FINDINGS. FINE-NEEDLE ASPIRATION CYTOLOGY VS SURGICAL PATHOLOGY.

	Fine-Needle Aspiration Cytology					Total
	C1	C2	C3	C4	C5	
Total	100	42	51	88	159	440
Percentage of total (%)	22.7	9.5	11.6	20	36.1	100
Benign histology	62	35	43	16	4	160
Malignant histology	38	7	8	72	155	280

but we also grouped together C4 and C5, and C3, C4 and C5, as suggested by Sapino et al. (19). We put in bold the results we retained more representative of our series. The data are presented in Tables 2A, 2B and 2C.

Discussion

The failure to diagnose adenocarcinoma of the breast by FNAC is a major clinical concern (22). The false-negative rate has varied widely in literature, but in experienced hands has been approximately 3-5% (23). A false-negative aspirate may be due to interpretative errors (cases of low grade malignancies, such as lobular, tubular, or papillary carcinomas). More frequently the skill of the aspirator is the most importante variable, but a less-than-optimal fixation or drying is also considered (23-25). A number of stu-

dies have shown that false-positive and false-negative rate are consistently lower when the pathologist aspirates and reads the smear. Even when a well-trained clinician performs the FNA, the cytopathologist is deprived of important informations (historical examination, nature of the nodule, its consistency and mobility) (23, 25).

In our series the false-negative rate was 16.6% (7/42 in C2 cytological category). This percentage is elevated if compared to the standard recommended in the Literature (5, 19). With the exception of the case of breast primitive lymphoma (where cytological slide is characterized by the presence of ductal typical elements associated with small lymphocytes), in the other 6 cases any figure of malignancy was absent. The reason is most likely related to samplig errors, especially when the ultrasound support was not employed. In spite of this observations, the negative predictive value of C2 was 83.3%, compa-

TABLE 2A - STATISTICAL ANALYSIS OF FNAC RESULTS IN 440 HISTOLOGICALLY CONTROLLED CASES.

	With C1		
	Diagnostic categories considered as positive		
	C5	C4 - C5	C3 - C4 - C5
SE (n) x100 = %	155/280 = 55.4*	(72+155)/280 = 81.1	(8+72+155)/280 = 83.9§
SP (n) x100 = %	(62+35+43+16)/160 = 97.5	(62+35+43)/160 = 87.5	(62+35)/160 = 60.6
PPV (n) x100 = %	155/159 = 97.5	(72+155)/(88+159) = 91.9	(8+72+155)/(51+88+159) = 78.9
FP (n) x100 = %	4/159 = 2.5	(4+16)/(88+159) = 8.1	(4+16+43)/(51+88+159) = 21.1
FN (n) x100 = %		(7+38)/(100+42) = 31.7	

* absolute sensitivity (ref. 18); § complete sensitivity (ref. 18).

TABLE 2B - STATISTICAL ANALYSIS OF FNAC RESULTS EXCLUDING C1 CASES.

	Without C1		
	Diagnostic categories considered as positive		
	C5	C4 - C5	C3 - C4 - C5
SE (n) x100 = %	155/(7+8+72+155) = 64.0*	(72+155)/(7+8+72+155) = 93.8	(8+72+155)/(7+8+72+155) = 97.1§
SP (n) x100 = %	(35+43+16)/(35+43+16+4) = 95.9	(35+43)/(35+43+16+4) = 79.6	35/(35+43+16+4) = 35.7
PPV (n) x100 = %	155/159 = 97.5	(72+155)/(88+159) = 91.9	(8+72+155)/(51+88+159) = 78.9
FP (n) x100 = %	4/159 = 2.5	(4+16)/(88+159) = 8.1	(4+16+43)/(51+88+159) = 21.1
FN (n) x100 = %		(7/42) = 16.6	

* absolute sensitivity (ref. 18); § complete sensitivity (ref. 18).

TABLE 2C - OTHER RESULTS OF STATISTICAL ANALYSIS.

Other statistics	
C3 PPV (n) x100 = %	[(159-4)/159] = 15.7
C4 PPV (n) x100 = %	(72/88) = 81.8
C5 PPV (n) x100 = %	(8/51) = 97.5
C2 NPV (n) x100 = %	[(42-7)/42] = 83.3
% of C1 (n) x100 = %	(100/440) = 22.7
C1 in cancer (n) x100 = %	(38/280) = 13.6
% of (C3+C4) (n) x100 = %	[(88+51)/440] = 31.6
Accuracy (including benign cases)	with C1: 280/440 = 63.6
(n) x100 = %	without C1: 242/340 = 71.2

nable to other published data (88% in Choi et al.) (26).

Closely associated with the false-negative rate is the unsatisfactory rate for FNA (C1 rate) (23). The range of non-diagnostic/inadequate rate reported in Literature is wide (<1-32%) (5, 8, 12, 27, 28). In our series we reported 22,7% of inadequate samples. Histological evaluation revealed that 38/100 cases corresponded to malignant lesions. In the remaining 62 cases, a nodular lesion was absent on histology, being the final diagnosis a fibrocystic disease with microcalcifications in 30 patients, lipomatous parenchymal involution in 5 and miscellaneous tissue alterations of none significant pathological importance in 27. FNA should not

have been performed in these 62 patients, due to the absence of palpable or non-palpable nodules. Patients with microcalcifications on X-ray examination should have undergone biopsy with Mammotome technique in preference. In the remaining C1 cases with negative histological corresponding samples, a clinical and instrumental follow-up should have been just recommended. The real cytological inadequate samples corresponded to the 38 cases with histological definitive diagnosis of malignancy, so we retain that the real rate of C1 in our series is 8.6% (38/440), according to the minimal standard recommended in Sapino et al. (<25% of the total of FNACs, and <10% of FNACs in cancer patients) (18).

A 2.5% rate of false positive cases in C5 class (4/159) was justified by the nature of the lesions (intraductal atypical proliferations). For this reason the PPV of C5 resulted satisfactory (97.5%), such as the PPV of C4 (81.8%), comparable to the values suggested by Wells (29).

As regards to cytological diagnoses included in C3 category, the 8 malignant lesions (6 infiltrating and 2 *in situ*) corresponded to well differentiated ductal carcinoma on histological slides. This report justified the mild cytological atypia of ductal cells and the lack of discohesion figures in cytological preparations. The low PPV of C3 in our series (15.7% vs 20-40% suggested by Wells) (29) is a reasonable consequence of the high PPV of C4 class, and it is related to the correct trend to include the malignant diagnoses in C4 class rather than in C3.

Excluding the C1 findings and considering as positive C4 and C5 categories, our sensitivity and specificity were respectively 93.8 and 79.6%. These results confirm that we are performing well within recently published ranges of 75.8-98.7% for sensitivity and 60-100% for specificity of breast FNAC (5,12). The accuracy rate in the whole study was 71.2%, including benign lesions (54.8% in Feichter et al.) (30).

Conclusions

In our opinion FNAC is an acceptable procedure in the diagnostic approach to suspected breast lesions. In consideration to the low cost and the low discomfort for patients, we consider FNAC a safe and feasible procedure, in particular in the context of peripheral hospitals, where a sophisticated technology is not available (31). We remark the importance of a good selection of patients to obtain the best results from the procedure. The indications should be discussed collectively by surgeon, radiologist and pathologist, and a pathologist should be present during the sampling to decide the quality of the smear at the same moment of the FNA. This practice should reduce false negative cases and above all inadequate results. The patients referred individually to our hospital for breast palpable lesions or they were sent from the screening programme. For te-

chnical reasons in the retrospective analysis of our series, it was not possible to separate these patients, but the different indications to FNA in these two groups could explain the high rate of inadequate and false negative findings. In particular our opinion is that in a number of cases the surgeon performed the FNA on poorly defined areas, in absence of a nodular lesion. Similarly to our experience, Takei et al. (31) have found that poorly defined indurated areas are more likely to yield unsatisfactory specimens, compared with well-defined breast lesions. Anyway the Authors suggest to employ FNA also in case of poorly defined areas, in consideration of the possibility of finding a substantial number of malignant cases. The employment of ultrasound-guided FNA should be generally intensificate, with particular attention to patients with poorly defined lesions.

In our experience, we usually do not repeat the FNAC in case of C1 or C3 result, but when the lesion is strongly suspicious on the basis of the clinical and radiological examination, we directly perform a surgical biopsy with intraoperative frozen section and in case of positivity we complete the operation at the same time. In the other C1 and C3 cases, when neoplasia is less probable we perform a simple open biopsy and send the specimen for definitive diagnosis. We retain that the "biopsy-frozen section-quadrantectomy/mastectomy" sequence is reliable also in those C5 cases which are not convincingly positive on clinical palpation and mammography. This approach will avoid unuseful mutilating surgery.

In conclusion, we retain that it is possible to perform definitive treatment on the basis of FNAC diagnosis if it is used in conjunction with clinical and imaging examination.

List of abbreviations

CNB – Core-Needle Biopsy
FN – false negative
FNA – Fine-Needle Aspiration
FNAC – Fine-Needle Aspiration Cytology
FP – false positive
NPV – negative predictive value
PPV – positive predictive value
SE – sensitivity
SP – specificity
TN – true negative
TP – true positive

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