Clinical Decision-making in Atypical and Suspicious Categories in Fine-needle Aspiration Cytology of the Breast

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Abstract. *Backgroud: Fine-needle aspiration cytology (FNAC) is a simple and reliable technique to assess breast lesions, although a definitive differential diagnosis (benignity vs. cancer) is achieved approximately in 60-70% of cases because an inadequate (C1), atypical (C3) or suspicious (C4) category is otherwise reported. Patients and Methods: A retrospective analysis of 763 cases with C3 or C4 reports was performed to define their positive predictive value (PPV), as well as the practical implications of clinical and imaging findings as for clinical decision-making. FNACs were collected from January 2003 to September 2012 at the Breast Unit of IRCCS "A.O.U. San Martino-IST" Genoa, with each being received later to definitive histology. The PPV for cancer of C3/C4 categories were computed to measure the accuracy of FNAC; moreover, the PPV was also stratified according to clinical, mammography and sonography data alone or by their combination. Resuls: The PPV of C3 and C4 was 21.1% (80/380) and 84.1 % (322/383), respectively. Within each C3/C4 category, a significant direct correlation ($p<0.001$) between the suspicion index of clinical, mammography and sonography data and cancer detection rate was always observed. The PPV of C3/C4 stratified by the combination of clinical and imaging findings showed satisfactory values in the C3 category only when there was an agreement between clinical and imaging findings, whereas the PPV of the C4 category was always remarkably high (ranging from 92.3% to 100%). Conclusion: the diagnostic work-up in C4 reports or in patients with a C3 report but with an high suspicion index at clinical or imaging examination should be preferably implemented by means of a core biopsy to optimize the therapeutic planning; given a C3 report with dubious clinical and/or imaging findings, an excisional biopsy (or in alternative vacuum-assisted breast biopsy with complete removal of the nodule) should be preferably performed in order to reach a definitive histological diagnosis with no further delay.*

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Fine-needle aspiration cytology (FNAC) represents a simple, cheap, quick, safe and reliable technique for the assessment of breast lesions; usually, a sensitivity >80% and a specificity close to 99% are reported, while the inadequacy rate ranges from 1% to 40% and it is strongly aspirator-dependent, with lower figures when an ultrasonography guidance is used and higher rates in the case of deep, desmoplastic lesions (1-5). As a matter of fact, a definitive differential diagnosis between benign or malignant disease can be achieved in no more than 60-70% of cases, while in the remaining cases, an inadequate (C1), atypical (C3) or suspicious (C4) category of FNAC is reported (6). Certainly, FNAC findings should be weighed in the context of clinical and imaging (mammography and sonography) findings within to so-called 'triple test'. Its diagnostic accuracy reaches 100% when there is an agreement of all three modalities (clinical, imaging, cytology) as for a malignancy, although breast examination is gradually losing its relevance due to the ever increasing rate of non-palpable breast lesions, which are detected thanks to the widespread use of screening mammography (1, 7-8).

FNAC has certainly some limitations: i) the lack of experienced cytologists in many Institutions impairs the reliability of cytological findings; ii) the distinction between the C3 and C4 classes is strictly operator-dependent so that the use of a single category has been suggested; iii) even in cases of malignancy, cytological examination cannot tell the difference between invasive and *in situ* carcinoma and, mostly, information regarding prognostic biologic factors, such as estrogen- and progesterone receptors, proliferative index and HER-2 overexpression are difficult to be determined; and iv) FNAC is preferentially indicated for the assessment of nodular lesions than ill-defined breast masses or a suspicious cluster of microcalcifications.

Table I. *Fine-needle aspiration cytology (FNAC) results in relation to final outcome.*

FNAC report	Benign	Cancer	Total	PPV (%)
C3	300	80	380	21.1
C4	61	322	383	84.1
Total	361	402	763	52.7

PPV, Positive predictive value

With these limitations in mind, a consecutive series of 763 cases of abnormal (C3-C4) FNAC, performed on equivocal or suspicious lesions detected at palpation or imaging studies, were analyzed in order to define the positive predictive value (PPV) of C3 and C4 reports and the practical implications of the combined test results as for the subsequent clinical decision-making.

Materials and Methods

The present study examined FNAC findings of 763 female patients with an age range from 24 to 83 years which were reported into the C3 or C4 category; FNACs were collected from January 2003 to September 2012 at the Breast Unit of IRCCS "A.O.U. San Martino-IST" Genoa. FNAC was always performed under ultrasonographic guidance whenever clinically detectable breast lesions dubious or suspicious/positive imaging findings were detected; it was not performed in breast lesions consisting of microcalcifications only.

According to the National Cancer Institute recommendations, five categories for the diagnosis of breast aspiration cytology were identified: C1, unsatisfactory; C2, benign; C3, atypical, probably benign; C4, suspicious, probably malignant; and C5, malignant (9). Clinical breast examination and imaging findings were classified into five classes with increasing suspicion, namely, i) negative; ii) benign; iii) dubious/indeterminate; iv) suspicious; and v) malignant (10-11). Each patient underwent excisional biopsy (EB) or wide excision with intraoperative histological examination, with the final outcome being classified as cancer (*in situ* or invasive) or benign disease.

The PPV for cancer for each C3 and C4 category was calculated to measure the accuracy of FNAC findings; moreover, the PPV of FNAC was also calculated in three different subsets according to clinical breast examination, mammography and sonography alone or combined together. For analysis requirements, the findings obtained at clinical breast examination and imaging (mammography and ultrasonography) were grouped into following three classes: negative/benign, dubious and suspicious/positive. The diagnostic value of cytological diagnoses, clinical and imaging studies were assessed by comparing the percentage of benign and malignant histological diagnoses in the categories C3 and C4 by using the Pearson's X-square test of significance.

Results

The PPV of C3 and C4 was 21.1% (80/380) and 84.1 % (322/383), respectively (Table I). Table II shows the association of clinical findings at breast examination to final outcome stratified by FNAC categories (C3 and C4): within each category, there was a significant direct correlation (p=0.000) between the index of clinical suspicion and the cancer detection rate. Notably, the negative predictive value (NPV), that is the likelihood of a clinically negative patient having a benign disease, was higher in the C3 category (NPV: 62/72=86.1%) as compared to the C4 category (NPV: 3/6=50%); conversely, the PPV, that is the likelihood of a clinically dubious report resulting in cancer, was higher in the C4 category (PPV: 39/45=86.7%) as compared to the C3 category (PPV: 11/32=34.4%). This means that C3 predicts a negative clinical finding more reliably than C4, while C4 implies a greater risk of finding cancer as compared to C3 when a dubious clinical finding is reported.

Tables III and IV report the corresponding figures for mammography and ultrasonography, while Tables V and VI describe the same findings stratified by the Breast Imaging Reporting and Data System (BI-RADS). Here again, there was a significant direct correlation between mammographic and cytological findings (p=0.000). The NPV of mammographic findings was greater in C3 (negative mammography: 74/98=75.5%; dubious mammography: 53/79=67.1%) as compared to C4 (negative mammography: 16/69=23.2%; dubious mammography: 29/136=21.3%) with a consequent higher PPV of C4 in the corresponding mammographic classes (negative mammography: 53/69=76.8%; dubious mammography: 107/136=78.7%). Hence, the C4 category *per se* greatly enhances the risk of finding a cancer even in the case of a negative or dubious mammography. Ultrasonographic findings, also, showed a direct correlation with cytological categories of C3 and C4 (p=0.000); the low number of cases with a negative sonography did not allow a reliable assessment of the NPV in the C3 and C4 categories. However, especially in the case of dubious sonography, a greater PPV of C4 (147/191=77%) as compared to C3 (55/332=16.6%) was observed, thus significantly increasing (p=0.001) the risk of finding a cancer in the C4 category as compared to C3. Finally, Table VII reports the PPV of different combinations of FNAC categories (C3, C4) stratified by clinical breast examination and imaging findings for cases in which all data were available; PPV was higher in the C3 category whenever there was an agreement between clinical and imaging findings, whereas the PPV of the C4 category was remarkably high (ranging from 92.3% to 100%) regardless of the type of the specific clinical or imaging combination.

Discussion

FNAC has been widely used for the diagnosis of breast lesions because it proves as a reliable, quick and low-cost procedure for obtaining very informative material. It is commonly used as part of a triple diagnostic triad that, in

Table II. *Clinical breast examination findings in 287 patients stratified by fine-needle aspiration cytology category in relation to histological outcome.*

	C3 (*n*=115)				C4 (*n*=172)				Total (*n*=287)			
	Benign		Cancer		Benign		Cancer		Benign		Cancer	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Clinical breast examination												
Negative/benign	62	86.1	10	13.9	3	50.0	3	50.0	65	83.3	13	16.7
Dubious	21	65.6	11	34.4	6	13.3	39	86.7	27	35.1	50	64.9
Suspicious/positive	1	9.1	10	90.9	3	2.5	118	97.5	4	3.0	128	97.0
Total	84	73.0	31	27.0	12	7.0	160	93.0	96	33.4	191	66.6

Table III. *Mammographic findings in 499 patients stratified by fine-needle aspiration cytology category in relation to histological outcome.*

	C3 (*n*=196)				C4 (*n*=303)				Total (*n*=499)			
	Benign		Cancer		Benign		Cancer		Benign		Cancer	
	n	%	n	%	n	%	n	%	n	%	n	%
Mammography												
Negative/benign	74	75.5	24	24.5	16	23.2	53	76.8	90	53.9	77	46.1
Dubious	53	67.1	26	32.9	29	21.3	107	78.7	82	38.1	133	61.9
Suspicious/positive	4	21.1	15	78.9	4	4.1	94	95.9	8	6.8	109	93.2
Total	131	66.8	65	33.2	49	16.2	254	83.8	180	36.1	319	63.9

Table IV. *Ultrasonographic findings in 708 patients stratified by fine-needle aspiration cytology category in relation to histological outcome.*

	C3 (*n*=356)				C4 (*n*=352)				Total (*n*=708)			
	Benign		Cancer		Benign		Cancer		Benign		Cancer	
	n	%	n	%	n	%	n	%	n	%	n	%
Ultrasonography												
Negative/benign	2	50.0	2	50.0	0	0	2	100.0	2	33.3	4	66.7
Dubious	277	83.4	55	16.6	44	23.0	147	77.0	321	61.4	202	38.6
Suspicious/positive	7	35.0	13	65.0	13	8.2	146	91.8	20	11.2	159	88.8
Total	286	80.3	70	19.7	57	16.2	295	83.8	343	48.4	365	51.6

addition to FNAC, includes clinical breast examination and imaging (mammography and sonography); the diagnostic accuracy is close to 100% when all three modalities favor a benign or malignant diagnosis (1, 7-8). However, the use of FNAC varies considerably in different centers due to its controversial inadequate rates and availability of experienced cytopathologists (12-14). Moreover, the difficulty, even in the case of a malignant cytological report, to reliably distinguish invasive from *in situ* carcinoma, as well as to supply information regarding prognostic biologic factors, has justified the use of core biopsy (CB) as first-line diagnostic modality as it more often provides conclusive and adequate diagnosis. The inadequacy rates in breast lesions undergoing both FNAC and CB were of 19.1% and 1%, respectively (15). Conversely, some other centers prefer the primary use of FNAC because the PPV of a malignant report is close to 100% allowing a one-day diagnosis in 49% to 90% of breast cancer (16-19).

In our present experience, the PPV of the C3 and C4 categories was remarkably different (21.1% *vs*. 84.1%, respectively), emphasizing the need to maintain the distinction between these two classes as suggested by literature data reporting a PPV for C3 ranging between

Table V. *Clinical (palpation) or imaging findings stratified by Breast Imaging Reporting and Data System (BI-RADS) in relation to final outcome in 200 patients with C3 fine-needle aspiration cytology (FNAC) report.*

Report at	Benign		Cancer		Total	PPV
	n	%	n	%		%
Palpation						
p-/px	83	79.8	21	20.2	104	20.2
p+	1	9.1	10	90.9	11	90.9
Imaging						
E3, R3	30	76.9	9	23.1	39	23.1
E4, R3	10	58.8	7	41.2	17	41.2
E4, R4	8	66.7	4	33.3	12	33.3
E4, R5	0		0		0	n.a
E5, R3	1	100.0	0		1	0
E5, R4	1	50.0	1	50.0	2	50.0
E5, R5	4	28.6	10	71.4	14	71.4
E2, R2	0		0		0	n.a.
E2, R1	0		0		0	n.a.
E1, R3	0		0		0	n.a.

PPV, Positive predictive value; *p-*, palpation negative/bengin; px, palpation dubious; n.a., not applicable.

Table VI. *Clinical (palpation) or imaging findings stratified by Breast Imaging Reporting and Data System (BI-RADS) in relation to final outcome in 382 patients with C4 fine-needle aspiration cytology (FNAC) report.*

Report at	Benign		Cancer		Total	PPV
	n	%	n	%		%
Palpation						
p-/px	9	17.6	42	82.4	51	82.4
p+	3	2.5	118	97.5	121	97.5
Imaging						
E3, R3	3	23.1	10	76.9	13	76.9
E4, R3	2	10.5	17	89.5	19	89.5
E4, R4	15	29.4	36	70.6	51	70.6
E4, R5	0		9	100.0	9	100.0
E5, R3	2	28.6	5	71.4	7	71.4
E5, R4	4	15.4	22	84.6	26	84.6
E5, R5	3	3.6	81	96.4	84	96.4
E2, R2	0		1	100.0	1	100.0
E2, R1	0		0		0	n.a.
E1, R3	0		0		0	n.a.

PPV, Positive predictive value; *p-*, palpation negative/bengin; px, palpation dubious; n.a., not applicable.

Table VII. *Positive predictive value of different combinations of fine-needle aspiration cytology (FNAC) categories (C3, C4) stratified by palpation or imaging findings (M, mammography; US, ultrasonography).*

	FNAC C3	FNAC C4
Suspicious/positive only at palpation, not at imaging	80.0% (4/5)	100.0% (40/40)
Suspicious/positive only at imaging (M or US), not at palpation	50.0% (2/4)	92.3% (12/13)
Suspicious/positive at M and US	71.4% (10/14)	96.4% (81/84)
Suspicious/positive at both palpation and imaging (M or US)	100.0% (6/6)	96.1% (74/77)
Suspicious/positive at palpation, M and US	100.0% (4/4)	100.0% (41/41)

8.6% to 52%, with most of them being over 30%, and rates for C4 between 81% to 97% (2, 20-24). Regarding the apparently low PPV of C3 report, it is worth noting that finding an atypical cytological pattern in a patient, which will show at definitive histology a proliferative fibrocystic disease with or without atypia, cannot be considered *per se* as a mistake.

Of course, the diagnostic work-up cannot simply rely on cytological data. The clinical decision-making should also be based on imaging findings. From the theoretical standpoint, the definite diagnosis after a C3 or C4 report could be accomplished by means of a repeated FNAC, CB, vacuum-assisted breast biopsy (VABB) or EB. As to the former, if the primary FNAC was properly performed under sonography guidance and read by an experienced cytopathologist, a definitive diagnosis of benign or malignant disease could be rather hard to be achieved by means of a repeated FNAC. Conversely, CB may certainly increase the diagnostic accuracy of a previous FNAC having a diagnostic improvement from 54.8% with a repeated FNAC up to 78% with a CB ($p<0.001$) (6).

In our view, the greater NPV of C3 that was observed in clinically and mammographically negative breast lesions, as compared to the higher PPV of C4 in dubious clinical and mammographically detected breast findings, would suggest a different policy in these two clinical settings. On the one hand, as C3 is likely to be diagnosed as a proliferative lesion, with or without atypia, even in the case of dubious imaging findings, an EB may supply a definite diagnosis while avoiding the worthless intermediate step of a CB. As a matter of fact, a CB following a C3 report frequently gives an inconclusive diagnosis, such as B3, as suggested in many instances in our daily practice (25). An alternative to this scenario would be to use VABB with complete removal of the nodule, especially in younger women (26-27). On the other hand, a C3 report, coupled with suspicious/positive

imaging findings (BI-RADS 4-5), has a rather high PPV (over 70%) that might justify CB with the aim of defining the histological diagnosis.

Conversely, C4 should be preferably investigated by means of CB due to the consistent risk of malignancy at final histology, regardless of the imaging findings. This would allow a definite pre-operative histological diagnosis in order to better plan the therapeutic strategy with special attention: i) detailed informed consent of the patient as to the surgical program; ii) safe margins of resection to avoid an improper EB with microscopically involved (R1) surgical margins; iii) preoperative lymphoscintigraphy for sentinel node (sN) detection; and iv) cost effective selection of patients undergoing intraoperative histological examination of the sN, based, essentially, on tumor size . In fact, the selection of patients amenable to frozen section examination should be made considering the rather low rate of sN metastasis approximately 9.5% to 12.8% observed in T1a-b (<1 cm) breast cancer as compared to 35-40% in patients with greater tumor size (28-30). It is worth noting that patients with small size tumors frequently have only sN micrometastases that are likely to be missed or even destroyed at frozen section biopsies, with a consequent false-negative down-staging of the disease; moreover, such patients would hardly benefit from complete axillary lymph node dissection (31-33).

Conclusion

The FNAC C3 and C4 categories represent an indeterminate diagnostic subset with a remarkably different PPV that should be further defined on a case-by-case basis, taking into account the clinical and imaging findings. CB should be preferably used in the diagnostic work-up of patients with a previous C3 report and a rather high suspicion index at clinical or imaging examination, as well as in patients with a C4 report, due to the consistent risk of finding cancer as this procedure will allow to better planning of the therapeutic strategy. Conversely, EB should be reserved for patients with a C3 report and dubious clinical or imaging findings in order to reach a definitive histological diagnosis while avoiding an indeterminate step, such as those of B3 lesions.

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