The accuracy of abnormal cytology report in breast fine needle aspiration alone and in combination with clinical and imaging findings – a hospital based five year study in Kuwait

R. Arora[1], A. Abd El-Hameed[1], T. Al Ajrawi[1], O. Al Harbi[2], A. A. Elbasmy[3]

Departments of Pathology[1], and Surgery[2], Al Farwaniya Hospital, Kuwait
[3]Department of Epidemiology and Cancer Registration, Kuwait Cancer Control Centre.

Abstract

Background

Abnormal cytology report (C3 – C5) is routinely used as part of the triple assessment in diagnosis of malignant breast lesions. Its value has been questioned in recent years in view of an equivocal (C3, C4) results when compared with core biopsy. The aim of this study was to find the significance of abnormal report of cytology alone and in combination with clinical and image findings; and how accurately it helps in clinical decision making.

Material and methods

We analysed 255 consecutive cases of abnormal cytology which had follow-up histopathology in our hospital from June 2002 to May 2007. The positive predictive value (PPV) was calculated alone and in combination with clinical and image findings. The PPV was also done in subsets according to patient age (< and ≥ 50 years). In addition, sensitivity, specificity, predictive values, and likelihood ratios (LRs) were determined for each broad category of triple test.

Results

The PPV of C3, C4, C5 report alone was 20%, 87.2%, and 100% respectively. C5 report is unequivocal proof of malignancy irrespective of age, clinical, and radiologic findings. Higher levels of PPV can be attained when C4 cytology is combined with suspicious clinical and radiological findings (93.8%). Patients with ≥ 50 years age with C4 cytology proved mostly malignant on histology (18/19) suggesting that an intra-operative frozen section may be more relevant in older age patients with C4 report since an additional core biopsy in these patients may still be inconclusive. C3 is the least useful and even when combined with suspicious clinical and radiological findings its PPV reached 54.6%, thus prompting a pre-operative biopsy.

Conclusion

Our study indicates that FNAC is still a valid and useful test in diagnosis of breast lesions and is critical to the surgeons in decision making. Moreover it gives outstanding results when combined with clinical and radiological findings in diagnosis and management of breast cancer.

Key words

Breast cancer, fine needle aspiration, cytology, accuracy, imaging

Introduction

The combination of clinical examination, imaging ultrasound (US) and/or mammogram and fine needle aspiration cytology (FNAC) is widely used in various parts of the world in the assessment of women with breast complaints. Sensitivity and specificity of these tests have been reported in many studies [1 – 6]. FNA cytologic diagnosis of breast lesions has been reported to be so highly specific that an intraoperative frozen section biopsy is unnecessary if a clearly positive FNA report is possible [7]. Despite this critical role of FNAC, it has been increasingly criticized

Correspondence Address: Dr. Rajan Arora, Senior Registrar, Department of Pathology, Farwaniya Hospital, P.O. Box no: 18373, Farwaniya – 81004, Kuwait. E-mail: arorarajan73@rediffmail.com.

in recent years for having suboptimal accuracy. This is particularly true with atypical (C3) or suspicious (C4) report since its positive predictive value (PPV) has been reported to be 20–50% and 90–95% respectively [8, 9]. It does not allow immediate treatment planning and usually needs histological confirmation resulting in unnecessary benign surgical biopsies. In fact some authors have proposed to abolish C3 diagnosis on FNAC [10]. Core biopsy was reported to have higher sensitivity and specificity along with lower rates of unsatisfactory results in some studies [11] and so is replacing breast FNAC in North America and United Kingdom, especially in the context of screen detected lesions. However in many centres in Asia, Middle East, Europe and Australia judicious use of FNAC and/or core biopsy continues depending on the type of lesion being evaluated and depending on FNAC result. Core biopsy is usually performed when FNAC results are inconclusive.

We evaluated 255 consecutive cases of abnormal cytology at our hospital. All of them had prior clinical and radiological results and a follow up histopathology confirmation. We calculated the positive predictive value and other relevant statistical tests of abnormal cytology alone and in combination with clinical and radiological findings with an aim to find the accuracy of these tests in our centre independently and to determine whether the results are conclusive to allow clinical decision making. The focus was on equivocal (C3, C4) results and their practical implication in view of triple test rather than simply quantifying accuracy for a single test.

Material and Methods

FNAC is routinely used in our centre for the last 15 years and is an established mode for assessment of women with breast problems. There is no protocol for routine breast screening in our region and all women with breast complaint irrespective of age undergo clinical evaluation (palpation) followed by US or mammogram or both depending on patient profile (mammogram is not done for patients < 35 years of age and pregnant patients). Findings at palpation and imaging are classified using standard and established scale of five categories with increasing suspicion of malignancy [12, 13] as follows: 1=negative, 2=benign, 3=dubious/ indeterminate, 4=suspicious, 5= malignant. FNAC is done for all cases if a lesion is detected by either method except when the lesion is small ($\leq$ 5 mm) and benign by palpation and imaging. FNAC is performed under US guidance using standard technique and stains. Cytology reporting is done with internationally accepted guidelines. The C1 (inadequate/insufficient) category is used when smears are too sparsely cellular or distorted to allow a microscopic diagnosis or the aspirate is inconsistent with clinical and imaging findings. The C2 (benign) diagnostic category is used when the sample is adequate and shows no evidence of malignancy. An abnormal cytology report is defined as: C3 for atypia, C4 for suspicious of malignancy and C5 for unequivocal evidence of cancer [14].

According to diagnostic and management protocols in our hospital a negative / benign (C1, C2) or positive (C5) cytology report usually doesn't warrant further investigation and management is planned accordingly keeping in view the findings of triple test. However atypical or suspicious report usually warrants histological confirmation.

To conduct the present study a consecutive series of abnormal cytology reports were retrieved from the files of Pathology Department, Al Farwaniya Hospital, Kuwait for a period of 5 years (June 2002 to May 2007). There were a total 635 cases, out of which 255 with histopathology confirmation were included. Cases without available follow up histopathology were excluded from the study. For each of these 255 cases selected for the study the following parameters were noted: age, findings at palpation, image findings, cytology report and final outcome. Final outcome was classified as cancer (invasive or insitu) or benign on histology.

We calculated the positive predictive value for cancer as our main measure of accuracy for each of the C3, C4, C5 categories. The PPV was determined for findings at palpation, imaging, palpation and imaging combined with cytology. For this purpose findings at palpation and imaging

were grouped in three classes namely negative/ benign, dubious, and suspicious/positive i.e.

P1: Negative/benign on palpation

P2: Dubious (indeterminate) on palpation

P3: Suspicious/positive on palpation

R1: Negative/benign on radiology

R2: Dubious (indeterminate) on radiology

R3: Suspicious/positive on radiology

The PPV of abnormal cytology in age groups < 50 years and ≥ 50 years was also determined. In addition sensitivity (proportion of patients with breast cancer who had a positive test), specificity (proportion of patients with benign breast disease who had a negative test), PPV (fraction of all diagnoses that were confirmed malignant by histologic examination), negative predictive value (NPV = fraction of all diagnoses that were confirmed benign by subsequent biopsy), and likelihood ratios (LR = the ratio of the probability of a particular test result in patients with malignancy to the probability of the same test result in patients without malignancy) were performed for each of the broad categories of triple test. Analysis of data were done with EpiCalc 2000 version 1.02.

Results

Patients age ranged from 18-83 with a mean of 42 ±11.98. Results are summarized in tables I-IV. Table 1 shows the PPV of abnormal cytology report (C3, C4, C5) to be 20%, 87.2% and 100% respectively. The sensitivity, specificity, PPV, NPV, LR+ve and LR- ve for FNAC alone was 82% (95% confidence interval [CI], 75-88), 95% (95% CI, 89-98), 96% (95% CI, 90-99), 80% (95% CI, 72-86), 16.4 and 0.19 respectively.

Table 2 shows the PPV of abnormal cytology in relation to age. PPV of clinical findings (palpation) and imaging to final outcome are shown in Table 3. The PPV of P1, P2, and P3 findings at palpation was 11.8%, 54.3%

	Histology		Total	PPV (%)
	Cancer	Benign		
FNAC				
C3	26	104	130	20
C4	34	5	39	87.2
C5	86	0	86	100

Table 1: PPV of abnormal cytology report

	Positive predictive value		
	FNAC-C3	FNAC-C4	FNAC-C5
Age / Years			
<50	17.1% (21/123)	85 % (17/20)	100% (49/49)
≥50	68.5% (5 /7)	94.7% (18/19)	100% (37/37)

Table 2: PPV of abnormal cytology report in relation to age

	Histology		Total	PPV (%)
	Cancer	Benign		
Palpation				
Negative/benign (P1)	6	45	51	11.8
Dubious (P2)	57	48	105	54.3
Suspicious/positive (P3)	83	16	99	83.8
Radiology				
Negative/benign (R1)	2	17	19	10.5
Dubious (R2)	30	77	107	28
Suspicious/positive (R3)	114	15	129	88.4

Table 3: PPV of clinical and radiological examination

	Positive predictive value	
	FNAC-C3	FNAC-C4
Suspicious/positive only at palpation, not imaging	22.2% (2/9)	50 % (1/2)
Suspicious/positive only at imaging, not palpation	41.7% (5/12)	91.7% (11/12)
Suspicious/positive at both palpation and imaging	54.6% (6/11)	93.8% (15/16)

Table 4: PPV of combinations of equivocal FNAC and palpation and/or radiology

and 83.8% respectively (X^2 for trend 70.1, P < 0.0001). Similarly PPV of R1, R2 and R3 report on imaging was 10.5%, 28% and 88.4% respectively (X^2 for trend97.3, P < 0.0001). The sensitivity, specificity, PPV, NPV, LR+ve, and LR-ve for clinical findings alone was 57% (95% CI, 48-65), 85% (95% CI, 77-91), 84% (95% CI, 75-90), 60% (95% CI, 51-67), 3.9, and 0.51 respectively. Similarly the sensitivity, specificity, PPV, NPV, LR+ve, and LR-ve for imaging alone was 78% (95% CI, 70-84), 86% (95% CI, 78-92), 88% (95% CI, 81-93), 75% (95% CI, 66-82), 5.6, and 0.26 respectively.

Table 4 shows PPV of equivocal (C3, C4) cytology report in combination with suspicious/positive findings on palpation and radiology. For C3 report PPV was 22.2%, 41.7% and 54.6% when it was combined with suspicious/positive palpation, imaging, and palpation plus imaging findings respectively. Similarly for C4 category PPV was 50%, 91.7% and 93.8% when it was combined with suspicious/positive palpation, imaging and palpation plus imaging findings respectively.

Discussion

FNAC was established decades ago as a vital part of assessment of breast lesions. [15] It continues to be an important pre–operative assessment tool along with clinical and radiological findings for both palpable and impalpable lesions. The benefits of this multidisciplinary approach are well recognized internationally [16, 17, 18].

We evaluated and analysed abnormal cytology report alone and in combination with clinical and radiological findingsto find its ability to help clinical decision making in our centre independently since diagnostic criteria drawn only from literature may be unreliable and varying degree of predictivity between different centres is expected.

Our study confirms that PPV of C5 cytology report is 100% as seen in an audit by Moyes and Dunne [19]. C5 cytology alone was sufficient to diagnose malignancy irrespective of age, palpation, or radiological findings and so surgical management can be planned accordingly with no risk of overtreatment. An additional core biopsy may only be done for further studies like hormone receptor status.

The baseline PPV of C4 report alone in this series was found to be low and suboptimal (87.2%) and histological confirmation should be considered prior to planning treatment in order to avoid unnecessary or excessive surgery in about 13% of cases. In addition if C4 cytology is combined with negative/benign findings on imaging its PPV is reduced significantly (50%). However, when it is combined with suspicious/positive findings at imaging and suspicious/positive clinical plus image findings, higher levels of PPV can be achieved (91.7% to 93.8%) as also shown by Bulgaresi et al [20]. This leads to significantly lesser false positive results. Only two out of 28 cases which were radiologically suspicious and had C4 report turned out to be benign. High PPV (94.7%) was also noted in patients ≥ 50 years of age with C4 cytology alone, only one false positive case was detected out of nineteen C4 cases. These results indicate that C4 cytology combined with old age and suspicious/positive radiology may allow clinical decision making. A more eager approach e.g. intraoperative frozen section rather than routine protocol of biopsy makes sense in these patients since biopsy result can still turn out to be inconclusive and may lead to management delay.

C3 is the least predictor of abnormal cytology category (PPV of 20% alone) as previously reported [19]. When associated with suspicious/positive report at palpation, imaging or both its

PPV at best was 54.6% making it inappropriate for planning surgical management and should prompt core biopsy as a routine further procedure in keeping with previous study [21]. However, we observed that 5 out of 7 patients with C3 cytology who were ≥ 50 years of age had cancer. At the same time only 21 out of 123 were malignant in < 50 years age category, thereby stressing the importance of C3 cytology in old age which usually arise due to low grade malignant lesions. Abolishing C3 cytology [10] would lead to increase in false negative rate as there is real risk that most if not all, would be classified as C2.

Higher sensitivity (82%), specificity (95%), PPV (96%), NPV (80%), and LR+ve (16.4) of broad category of abnormal cytology alone when compared with these values for clinical and radiology alone (corresponding values being 57%, 85%, 84%, 60%, 3.8, and 78%, 86%, 88%, 75%, 5.6 respectively) confirms that cytology is of paramount importance in triple test, clinical examination although significant is least useful alone and imaging remains a powerful adjunct to cytology.

Conclusion

We conclude that FNAC remains a simple, rapid, efficient and relatively inexpensive test relative to core biopsy. Genuine consideration should be given to its role in clinical decision making of breast lesions. The decision on how to manage a breast lesion should not be taken on the basis of FNAC alone, but should be based on clinical, imaging and cytology report since the accuracy of abnormal cytology report at FNAC may be substantially altered when combined with age and suspicious findings at palpation and/or imaging, allowing immediate treatment decisions with a reduced false positive risk.

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