FNAC: Its role, limitations and perspective in the preoperative diagnosis of breast cancer

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Summary

Fine-needle aspiration cytology (FNAC) was first described and performed in 1930. Thirty years later, it gained acceptance first in Europe and about a decade later in North America. The method is generally considered as a rapid, reliable, safe diagnostic tool to distinguish non-neoplastic from neoplastic breast lesions. In developed countries, in the last 20 years, mammographic screening programmes, which have been used extensively, are designed to detect the earliest possible breast cancer. The FNAC report is extremely important because it gives the necessary information for the management of patients, in order to proceed with more invasive diagnostic methods or surgical treatment, and to decide what kind of operation to perform. In the preoperative phase, FNAC has taken a fundamental role of both palpable and nonpalpable lesions, using ultrasound or stereotactic guidance. New developed techniques, breast biopsy instrumentation (ABBI) and mammotome have the advantage of complete removal of breast lesions, but this is not possible in all the examined cases. In developing countries, economical restrictions, low budget for health care and screening programmes put the patients at a disadvantage because of the high cost of sophisticated diagnostic methods, thus we recommend that FNAC be used as a routine diagnostic method because of its low cost compared with the others and this policy maximizes the availability of health care to women with breast cancer.

We conclude that FNAC plays an important and essential role in the management of patients with breast lesions and also offers a great potential for prediction of patient outcome, disease response to therapy and assessment of risk of developing breast cancer. The reliability and efficiency of the method depends on the quality of the samples and the experience of the medical staff that performs the aspiration.

Key words: Fine needle aspiration cytology (FNAC); Breast cancer; Preoperative diagnosis.

Introduction

Breast cancer accounts for 32% of all cancer cases among women and is the most common type of cancer in women [1]. Worldwide, the total number of new cases of breast cancer, which are diagnosed annually, currently exceed one million, but this figure is expected to reach approximately 1.5 million by the end of the decade [2]. There is a marked geographical difference in incidence of breast cancer, with a higher number of new cases in developed countries compared to developing countries [3]. In the United States, 215,990 new cases are expected in 2004; of these cases 59,390 are in situ carcinoma (27.8%). One in nine women will develop breast cancer in their lifetime, therefore it is considered to be the second most common cause of death after lung cancer [1, 4]. A statistically high number of incidences have been reported in Hispanic women, with 11,000 cases in 2003 [5].

Screening mammography, performed at regular intervals, is the best method for early detection of breast cancer [6]. It is used first as a diagnostic modality that seeks to answer specific questions about the character of a palpable abnormality and second as a screening test. In screening programmes approximately 15% of all lesions are found to be malignant [7]. In Europe, particularly in some institutions, fine-needle aspiration cytology (FNAC) has largely replaced excisional biopsy for the evaluation of mammographic abnormalities [8].

FNAC of both palpable and non palpable breast masses is an extremely useful diagnostic tool for the assessment of breast lesions. Studies from various countries have analysed the diagnostic accuracy of this technique. The reported values for sensitivity range from 75.8-98.7%; for specificity, 92-100%; for positive predictive value, 93.5-100%; for negative predictive value, 82.1-95.7%; for diagnostic accuracy, 88.5-94.8%; for false-positive rate, 0.6-2.5%; and for false-negative rate, 2.5-17.9% [9-12].

Missed diagnosis of breast cancer is the most common medical malpractice in the U.S. Clinicians can reduce the risk of missing diagnoses to 1% by using the Triple Test (TT) approach, which is practically based on the correlation of clinical information by breast examination, imaging and cytologic diagnosis of FNAC to direct patient management [13-17]. Women 40 years and older are likely to be diagnosed with breast cancer at the time of mammographic screening, while women younger than 40 are more likely to be diagnosed by clinical breast examination [18].

Method

In 1930, Martin and Ellis, at the Memorial Sloan-Kettering Cancer Centre in New York, were the first to report their experience with FNA biopsy [19], but in the United States, serious criticism and several problems have arisen which have practically blocked the acceptance of the method for the evaluation of mammographically detected abnormalities [20]. However in Europe, especially in Sweden, FNAC has been used routinely for several decades in the clinical management of palpable breast masses. The first stereotactic guided FNA was in 1977 at Karolinska Institute in Stockholm [21]. Sonographically guided FNAC of nonpalpable breast masses was first reported in the mid-1980s [22].

FNAC is a method of obtaining cellular material which utilizes a 22-25 gauge needle; smaller gauge needles are superior for highly fibrous lesions, while very small (26 or 27 gauge) needles are useful for intracutaneous lesions and sometimes for very small targets. A 2-inch-long needle may be necessary for a deeply located lesion and/or large breast. If a needle guide is used, a longer needle (a spinal needle) must be used. Informed consent is obtained. The skin is prepared with rubbing alcohol. Local anaesthesia is rarely necessary for FNAC. Adequate sampling is the first essential step for cytological diagnosis. The average number of FNAC passes recommended for adequate sampling of most palpable and nonpalpable breast lesions is two to four. Specimens may be considered satisfactory when there is appropriate labelling, identifying information, relevant clinical information and adequate numbers of well-preserved epithelial cells. FNAC sampling is highly operator-dependent and is better if performed by a cytopathologist who then interprets the specimen. A quick stain can evaluate specimen adequacy.

Complications

Complications include needle track seeding, vasovagal reactions or local haematomas, and occasionally very light discomfort. Multiple specimens can be obtained with an obvious lower risk of tumour seeding than in core biopsy [23]. The fact that every breast cancer will be treated after the diagnosis has been established still reduces the risk of dissemination.

FNAC and core needle biopsy

A consensus statement on FNAC for palpable and nonpalpable breast lesions was developed and approved from the US National Cancer Institute (NCI) in 1996 (24, 25). The recommendation stated that one may use FNA in women with mammograms that are *"highly suggestive of malignancy, suspicious for malignancy, and some lesions at low risk for malignancy but for which the recommended follow-up with imaging is not feasible or accepted by the patient"*. It is important to recognize the difference between FNAC and core needle biopsy (CNB). The latter consists of using a 14-gauge needle and yields tissue fragments for histological evaluation. Despite the recommendations of the NCI, the use of CNB versus FNA as the primary diagnostic method for the evaluation of breast lesions remains controversial [26-28]. Studies have shown that FNAC is more accurate, has a lower false-negative rate, and is a less painful procedure than CNB [29-32]. The small size of the tissue fragments obtained by core biopsy does not allow a more reliable diagnostic distinction compared to FNA in "borderline" lesions (hyperplasia without atypia, atypical hyperplasia vs small cell neoplasias) where FNAC diagnosis is limited. In contrast Britton *et al.*, state that sensitivity and specificity are higher for CNB than for FNAC (33). A meta-analysis of large core needle biopsy (LCNB) showed that infiltrating carcinoma was found in 15% of the surgically treated and removed specimens which were diagnosed as ductal carcinoma in situ (DCIS) on LCNB [34]. As far as the cost of the method is concerned published data found that FNAC provided sufficient pathologic diagnosis to obviate open surgical biopsy in 63-85% of cases, estimation of cost savings on the basis of the distribution of cases and indications for surgical management suggested a savings of $250,000 to $750,000 per 1,000 FNA [35].

Advantages

The advantages of the method which is a simple technique include: a) rapid accurate diagnosis that requires no anaesthesia and can be performed on an outpatient basis, b) cost effective triage in the treatment of breast masses [36-38], c) differentiation of cysts from solid tumours and a therapeutic procedure when a cyst is encountered [39-43], d) involvement of the patient in the decision-making process when malignancy is encountered [44-48], e) psychological help in the relief of anxiety for a patient with a benign breast lesion, f) evaluation of local chest wall recurrence, lymph node metastases, inoperable conditions [49, 50], g) ancillary studies [51-59], h) genomic and proteomic profiling for identification of patients at high risk for breast cancer development, tumour characterisation and prediction of patient outcome and disease response to therapy [60].

Disadvantages

False-positive cases have usually been diagnosed as the result of interpretive error [24, 61]. A false-positive diagnosis of breast cancer may prove disastrous for the patient, her clinical doctor, and ultimately the cytopathologist. Therefore it must be avoided at all costs. It is absolutely essential that the pathologist interpreting breast aspirates be familiar with conditions that create significant cytologic atypia. These include: changes induced by radiation, chemotherapy, pregnancy, epithelial hyperplasia in phyllodes tumours, ruptured tension cysts, fibrocystic changes or with reparative

atypia, fat necrosis, organizing haematoma, gynecomastia, benign papillary lesions and sclerosing adenosis with radial scarring [11, 62-66]. When the FNAC, is interpreted by an experienced pathologist, the rate of false positives is reduced to 0.1% to 0.2 % [66, 67].

It must also be recognized that a negative diagnosis on FNAC does not necessarily rule out carcinoma. Causes of false negative diagnoses are tumours larger than 4 cm due to extensive necrosis, fibrosis, cystic degeneration [15, 68-71] and malignant lesions that measure less than 1 cm. Also frequent problems of error for false-negative diagnoses are missed targets, aspiration of the wrong lesion if multiple, a mass deeper or overlying a cyst, dilution of sample by local anaesthetic, carcinomas located adjacent to benign lesions and last, but not least, lack of experience [72-74]. Other causes of false negative reports are well differentiated malignancies such as: tubular, colloid, papillary, lobular and the monomorphic type of ductal carcinoma in elderly patients [75].

There are several disadvadantages inherent in the FNA: to distinguish typical or atypical hyperplasia, inability to make a definitive benign diagnosis in histological terms, and finally to distinguish carcinoma in situ from invasive breast carcinoma. In these cases confirmatory tissue biopsy before definitive surgery is necessary.

Masood *et al.*, believe that it is possible to differentiate between proliferative and non-proliferative breast lesions and in the majority of cases atypical hyperplasia from malignant neoplasia [76, 77]. Using strict cytologic criteria (cellular arrangement, the degree of pleomorphism, anisonucleosis, the presence of myoepithelial cells, nucleoli and finally chromatin pattern) it is possible to define the continuous spectrum of changes in breast lesions and distinguish hyperplasia from neoplasia.

Also the differential diagnosis between ductal carcinoma in situ microinvasive (DCISM) and invasive carcinoma is not feasible. A confident diagnosis of malignancy of NHGDCIS (non high-grade ductal carcinoma in situ) lesions in smears can be difficult, but a major proportion can at least be suspected. Discriminating features are: cell discohesion, absence/presence of bare bipolar, bare atypical nuclei and necrosis [78]. Cytological features of NHGDCIS can be troublesome and features can overlap with benign lesions [79-81].

Increased cellularity, loss of cellular cohesion, pleomorphism, anisonucleosis, coarse chromatin pattern and absence of myoepithelial cells in the smears are the predominant features of malignant lesions. The value of smooth muscle actin immunostaining is essential to identify myoepithelial cells, which maximize the diagnostic accuracy of FNA and resolve diagnostic dilemmas in borderline cases with suspicious invasion in the examined material [82]. A new promising marker is p63 which can be used in identification of myoepithelial cells in problematic breast lesions [83]. The presence of myoepithelial cells within clusters of atypical cells is a significant finding that can separate hyperplasia from neoplasia. In cases diagnosed cytologically as atypical hyperplasia or suspicious for carcinoma a confirmatory biopsy is necessary [84].

Distinguishing proliferative breast disease from fibroadenoma and papillary lesions remains difficult. The majority of benign breast lesions yield characteristic cytologic findings that allow their subclassification, when sufficiently sampled by FNAC. The distinction between proliferative and nonproliferative fibrocystic changes is less reliable [85].

Published data [86-88] support the hypothesis that hyperplasia and atypical hyperplasia diagnosed in cellular material obtained from nipple aspirates of breast fluid or random FNA of the breast are associated with an increased risk of breast cancer. Women with atypical hyperplasia and a first degree family history of breast cancer are six times more likely to develop breast cancer than are women with atypical hyperplasia but without a family history of breast cancer [89]. It must be emphasised that any cytological diagnosis that is contrary to the clinical findings must be carefully evaluated by personal consultation between the physician or surgeon and the cytopathologist.

Prognostic and predictive factors

Assessment of prognostic and predictive factors in FNA smears may become an important part of the clinical management of patients. It should be emphasised, however, that the limit between prognostic and predictive factors is not well defined and most predictive factors are also prognostic. First, mention has to be made of the established prognostic factors. These are the TNM stage, the histological tumour grade, the nuclear grade and estrogen (ER) and progesterone (PR) receptors. ER and PR represent efficient factors which define response to hormonal therapy. The use of other objective prognostic factors is mandatory because we can not score mitoses on FNAs and another problem is the relative inexperience and lack of standardization of cytologic/nuclear grading as well as inter-observer variability for cytologic/nuclear grading [90-92].

According to the 1996 National Cancer Institute (NCI), sponsored consensus conference the recommendations are: a) evaluation of prognostic and predictive factors in FNA smears of primary breast cancer in patients who receive neoadjuvant chemotherapy before surgery, b) in cases of metastatic breast disease, assessment of ER and PR is clinically useful because metastatic sites can be negative for hormone receptors when the primary tumour is positive or positive when the primary tumour is negative, c) in women who are at high risk of developing breast cancer due to family history or proliferative breast disease, ductal lavage or FNA provides an excellent source of cells that may be used for risk assessment as well as for the monitoring of response to therapy. Accurate analysis of predictive factors, such as ER, PR and HER-2 is critical for assessing patient therapeutic management [93].

Numerous reports have been published documenting the reliability of evaluation of FNA smears in the assessment

of ER, the concordance rate with histological section findings ranges from 80% to 90% [94-96]. The assessment of HER-2 can be done in cytology specimens (archival Diff-Quik-stained smears that have been set with FISH fixatives and touch preparations) are suitable for FISH analysis. FISH testing is more reliable than IHC analysis [97].

The early detection of cancer in asymptomatic individuals has always been the expectation of the scientific community involved. Cancer is a heterogeneous group of diseases composed of a complex sequence of genetic alterations leading to progression and metastasis. Each genetic change and the consequent molecular marker for the identification of this change may be useful in early diagnosis and management.

Due to the evolution of technology there are new advances in molecular cytologic studies. Ductal lavage specimens, nipple aspirate fluid and random periareolar FNA are valuable materials which have been used for the identification of markers for high risk of cancer evolution or early cancer development [98, 99].

At the protein level, Kuerer *et al.* [100] evaluated bilateral nipple aspirate fluid specimens and found substantial qualitative differences in the protein expression patterns between breasts with cancer and breasts without cancer. Using FISH in ductal lavage specimens, King *et al.* found chromosomal alterations (1, 8, 11, 17) to be more sensitive than morphology in the categorization of abnormal lesions [101]. Using PCR, Evron *et al.* found methylated alleles of cyclin D2, retinoic acid receptor-β, and twist genes in women with endoscopically visualized carcinoma, ductal carcinoma in situ and rarely in ductal lavage fluid from healthy ducts [102]. Comprehensive gene expression can be obtained using cytopuncture (single passage FNAC). Symmans et al. indicated that transcriptional profiles from FNA more purely represent cancer cells, whereas profiles from CNB contain additional transcriptional information about stroma [103]. The same group found significant results for the future selection of appropriate therapeutic management, evaluating predictors of response to chemotherapy, gene expression associated with complete pathologic response to paclitaxel or fluorouracil, doxorubicin, and cyclophosphamide in 80% of cases [104].

New procedures in the diagnosis of dubious breast lesions and costs

Needle-localised open breast biopsy (NLBB) is considered to be the gold standard procedure for the diagnosis [105], but is an invasive and traumatic experience with poor cosmetic results, especially in cases of benign disease [106]. Azavedo *et al.* in 2,594 mammographically detected nonpalpable lesions used stereotactic fine needle biopsy and found that a combination of mammography and stereotactic aspiration of the breast is a reliable method for the early diagnosis of cancer when performed by competent hands. On the basis of combined evaluation of these samples, 2,005 cases were judged as benign and only one of these turned out to be a malignant tumour 14 months later. Out of 567 cases recommended for surgical removal, 451 cases were carcinomas and 116 benign lesions [8]. In the past, nonoperative image-guided techniques, such as FNAC and LCNB have been advocated as valid alternatives to surgery in order to diagnose these lesions. In the literature it has been mentioned that the primary use of FNA is essential because it avoids surgery at a rate from 49.5 to 77.3% [107]. A published study analytically gives the economical cost of FNAC [108]. In Nigeria, FNAC costs N250.000 ($2.00), while the cost of a surgical tissue biopsy can vary from N5000.00 to N10000.00 ($35.00 to $70.00), depending on the site or whether anaesthesia is required. In recent years microinvasive bioptic procedures such as vacuum-assisted core biopsy (VACB; Mammotome) and breast biopsy instrumentation (ABBI) have been introduced for the management of suspicious, nonpalpable mammographic lesions and achive targeting of radiographic lesions to ± 1 mm. It is important to emphasise that all these new techniques are diagnostic and not therapeutic. Sometimes excisional biopsies with ABBI were therapeutic for 30-40% of the patients who were diagnosed with cancer and in that percentage no residual tumour was found at the time of their subsequent procedure [109]. Mammotome is considered by Mariotti et al. the system of choice to obtain a fast (average operative time 10 min) and definitive diagnosis with minimum discomfort for the patient, especially in lesions located in the axillary extension, near the pectoral muscle or in subareolar lesions [110]. Published data evaluated that the average charge for a stereotactic breast biopsy ranges from $1,000.00 to $2,378.00, and for an open excisional needle localized biopsy from $2,500.00 to $3,028.00. This considerable difference can be attributed to the fact that the new stereotactic biopsy method is performed in an outpatient department with the use of local anaesthesia. Thus, the fee for preoperative testing, anaesthesia, operating room and recovery room is eliminated [111-113]. Surgical biopsies maintain precise indications: multiple lesions and clusters of microcalcifications with the greatest diameter of 2 cm.

Conclusion

Fine needle aspiration biopsy in experienced hands is an efficient tool, yields a definitive diagnosis and contributes to guided treatment if its limitations are clearly understood by the clinicians and the potential causes of false-positive diagnoses are kept in mind by the cytopathologist. With a dedicated team, the use of FNAC can help improve the management and cost of care in patients with palpable breast masses. A positive diagnosis should be reliable as a frozen section, but a negative one must be followed by an open biopsy if there is a clinical suspicion of malignancy. Under the above rule its use for routine diagnosis must be encouraged in developed and developing countries.

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