Fine Needle Aspiration Biopsy as Diagnostic Test in Breast Neoplasm

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Abstract - The diagnosis of breast lesions is frequently difficult and proving malignancy before treatment is of great importance. Fine needle aspiration biopsy is one of the three components of the triple test (the other two being the clinical examination and mammography or ultrasound). The present paper presents and correlates the value of ultrasound guided fine needle aspiration biopsy with the type of lesions. There are discussed the advantages of this diagnosis test performed under ultrasound guidance compared with the clinically guided fine needle aspiration biopsy and the value of the diagnosis test in reducing open surgical procedures.

Key words: Ultrasonography (US), Fine Needle Aspiration Biopsy (FNAB), Breast Neoplasm, Diagnostic Test

Introduction
Breast cancer represents a complex pathological entity that requires for diagnostic and treatment a close and tight collaboration between the oncologist, radiologist, pathologist and surgeon. A correct diagnosis needed a multidisciplinary team, the diagnosis of breast lesions having on its foundation a triple diagnostic test: clinical examination, imaging investigation (mammography and/or ultrasonography) and nevertheless the biopsy [1].

Even if the incisional or excisional biopsy remains the golden-standard in diagnosing suspicious breast lesions, it can be replaced in the majority of situations by a fine needle aspiration biopsy or by a percutaneous biopsy.

This minimum invasive method is today one of the “steps” of the triple test, contributing besides clinical and imaging examinations to the final diagnosis.

A cytological exam is often useful in confirming a clinical and/or radio-imaging suspicion of malignancy. FNAB is able to offer a fast result and thus a more rapid and correct management of the therapy, meaning for example the performance of one, instead of two surgeries, implying less costs and discomfort for the patient [2, 3, 4]. On the other hand FNAB can help in situations involving young patients with palpable lesions or patients at risk, where often is needed a simple aspiration biopsy to rule out the possibility of malignancy and to avoid unnecessary surgical interventions.

The literature data shows that the negative predictive value of FNAB is almost 100% if the other clinical and imaging investigations are also negative [5].

FNAB has numerous advantages: easy to perform, fast method requiring a minimum of supplies, with no contraindications [6]. The US guidance offers the possibility of a pre-therapeutic diagnosis - benign vs malignant- of the non-palpable lesions. The results of US guided FNAB are not dependent of the lesion’s size because any US visible abnormality can be approached under ultrasonographic guidance [7].

The main goal of the present research was to assess the role of US guided FNAB on diagnostic of malignancy breast lesions. The secondary goals were to obtain the sensibility and specificity of this diagnostic test on a sample of patients that were investigated on Breast Imaging Department of ER County Hospital from Cluj-Napoca using as golden standard the histopathological post-surgery exam.
Material and Method

Sample
The female patients with clinical and/or paraclinical suspicion of breast malignancy was the target population of the study. The women presented for an imaging breast examination (mammography or/and ultrasound) in the Breast Imaging Department of ER County Hospital from Cluj-Napoca, in the period comprised between January 2005 until December 2006 represented the available population on which the study was conducted.

All the patients that accomplished the following five-inclusion criterion were included into the study:
(1) Female patient; (2) Non-palpable lesion discovered on mammogram or/and ultrasound, classified as BI-RADS 4 or 5; (3) Non-palpable lesion discovered on mammogram or/and ultrasound, classified as BI-RADS 3, when the patient refused the follow up re-examination and desired to performs a FNAB; (4) Palpable, suspicious lesion with a non-conclusive result at clinically guided FNAB. There were excluded from the study all patients that refused to accept the FNAB.

Examination Method
The procedure was done in aseptic conditions. The transducer was cleaned using alcohol or iodine solutions. The skin above the area to be biopsied was swabbed with an iodine solution and draped with sterile surgical towels. The skin, underlying fat, and muscle were numbed with a local anesthetic (7 to 10 ml of a 1% lidocaine solution). Once the anesthesia established we performed a microincision of the skin was done in order to facilitate the needle passage through the tissues and decrease the patient discomfort.

The biopsy needle was always inserted longitudinally in order to be able to visualize through ultrasonography its entire length. The length cut of the needle was in every case of 22 mm. The number of fragments varied from case to case depending of quality of extracted tissue and the degree of the local hemorrhage.

There were cases for which the ultrasound guided biopsy was performed in a region with microcalcifications. In these situations 4 to maximum 6 fragments were extracted, all of them being discharged on a Petrie plate and covered with 1-2 ml of saline solution. A mammographic control, using manual settled parameters (24 kV, 14mA) was performed in order to confirm the presence of microcalcifications in the extracted samples.

Complementary biopsies were performed in those cases with a negative mammography control of microcalcifications.

Tissular samples were conserved using a 10% formalin solution.

At the end of procedure a compressive bandage was applied for 5 to 10 minutes and the place of the microincision was wrapped with auto-adhesive, sterile bandlets (“steri-strip”).

The material used in biopsy procedure were: ethylic alcohol or iodine solution; sterile tampons; 20 ml syringe with a 21 gauge, 4 cm needle; CAMECO device; cytology platelets; and sterile gloves.

Data Analysis
There were a number of variables collected for each patient included into the study. The data were collected into an Excel database. The statistical parameters associated to the diagnostic test were computed using CATRom [8]. The 95% confidence intervals associated to frequencies were calculated with a dedicate software [9].

Results
One hundred and sixty-nine patients were included in the analysis, all of them being in accordance with the inclusion criteria. Minimal age was 22 years; maximum age was 87 years, with a medium value of 52.57 years (95%CI [50.75 – 54.39]). Age histogram of the studied population is presented in figure 1.

Figure 1. Age histogram of the studied population
The dimensions of mammary lesions varied from 3 mm (see figure 2) to 40 mm.

![Figure 2. 3 mm lesion. US guided FNAB with visualization of the extremity of the needle during the procedure (transverse insertion). Cytological result: malignant cells. Histopathological result: ductal carcinoma in situ (DCIS).](image)

A total number of 212 US guided FNAB were performed on the studied sample of patients. The distributions of the investigations (FNAB – breast, FNAB – lymph node) were as followed:
- To a number of 152 patients a FNAB from a single breast lesion was performed (71.69%, 95%CI [65.10-77.83]);
- To a number of 17 patients two breast lesions were punctured (8.02%, 95% CI [4.72-12.26]);
- To a number of 26 patients a US guided FNAB from a lymph node was also performed (12.26%, 95%CI [8.02-17.45]).

Percentage distribution of the number of US guided FNAB-s performed is presented in figure 3.

![Figure 3. Percentage distribution of US guided FNABs](image)

Thirty-eight percent of all investigated patients (95% CI [31.19-45.70]) were presented with a palpable breast mass at clinical examination. Forty-seven percent (95% CI [21.31-34.91]) of these patients had undergone a clinical guided FNAB before being referred to the Radiology Department. The patient were investigated with mammography and ultrasonography and all discovered, suspicious lesions were punctured under US guidance.

The diagnostic distribution revealed by US guided FNAB is presented in Table 1.

The diagnostic distribution revealed by a post-operative histopathology exam of the initially punctured lesions and the classification benign-malignant is presented in Table 2.

**Table 1. Diagnosis obtained by means of US guided FNAB: breast lesion**

<table>
<thead>
<tr>
<th>Lesion type</th>
<th>Absolute frequency</th>
<th>Relative frequency</th>
<th>95% CI for relative frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>69</td>
<td>37.10</td>
<td>[30.11-44.62]</td>
</tr>
<tr>
<td>Malign</td>
<td>81</td>
<td>43.55</td>
<td>[36.02-51.07]</td>
</tr>
<tr>
<td>Non-conclusive</td>
<td>36</td>
<td>19.35</td>
<td>[13.98-25.80]</td>
</tr>
<tr>
<td>Total</td>
<td>186</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Post-operative histopathology diagnosis and classification: breast lesion**

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Absolute frequency</th>
<th>Relative frequency</th>
<th>95% CI for relative frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>67</td>
<td>36.02</td>
<td>[29.04-43.55]</td>
</tr>
<tr>
<td>Malign</td>
<td>119</td>
<td>63.85</td>
<td>[56.45-70.96]</td>
</tr>
<tr>
<td>Total</td>
<td>186</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Particular forms of ductal invasive carcinoma and other types of malignant lesions are presented in figures 4-9.
Figure 4. Distribution of particular subtypes of ductal invasive carcinoma.

- Medullary carcinoma
- Metaplasic carcinoma
- Papilar carcinoma
- Tubular carcinoma
- Mastitis carcinomatosa

Figure 5. Medullary carcinoma, mammographically occult at a 32 years old patient. US guided FNAB confirmed the malignancy.

Figure 6. US guided FNAB of a ductal invasive carcinoma.

Figure 7. Cluster of microcalcifications discovered on mammography and also visualized by US. Positive US guided FNAB. Histopathology: ductal carcinoma in situ.

Figure 8. Ductal invasive carcinoma with an extended necrotic component. US guidance permitted a more peripheral approach of the lesions in order to obtain malignant cells and implicitly a real positive cytological result (the initial biopsy was clinically guided and with a non-conclusive result).

Spearman rank correlation coefficient was applied to demonstrate if there is a correlation between the results obtained by means of US guided FNAB and those revealed by a post-operative histopathologic exam. A value of 0.4523 (p < 0.001) was obtained for Spearman correlation coefficient when the test was applied on the sample if one hundred and eighty-six diagnostic interventions.
Figure 9. Clinically malignant lesion, displaying suspicious features on ultrasound (intracystic papillary lesion). The US guided FNAB allowed us to extract an amorphous material from the center of the lesion. Histopathology: fibrocystic disease of the breast.

Thirty-six out of one hundred and eighty-six cases (19.36%, 95%CI [13.98-25.80]) were classified as non-conclusive US guided FNABs. From these cases 11 had been diagnosed post-operative as benign (5.91%, 95%CI [2.69-10.21]) and 25 as malign (13.44% CI [8.61-19.35]). Cases with non-conclusive results at the US guided FNAB were not taken in consideration when computing statistical parameters regarding FNAB as a diagnostic test in tumoral pathology of the breast. The contingency table that reflect the concordance between the results obtained by US guided FNAB and the histopathological results obtained post surgery are presented in Table 3.

Table 4. US guided FNAB as diagnostic test in malignant breast pathology: 2×2 contingency table

<table>
<thead>
<tr>
<th>Result of US guided FNAB</th>
<th>Post-operative histopathological result</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Malign</td>
<td>Benign</td>
</tr>
<tr>
<td>Malign</td>
<td>80</td>
<td>1</td>
</tr>
<tr>
<td>Benign</td>
<td>14</td>
<td>55</td>
</tr>
<tr>
<td>Total</td>
<td>94</td>
<td>56</td>
</tr>
</tbody>
</table>

χ² = 94.7539 (p < 0.0001), Φ = 0.7948, Φ = dichotomial correlation coefficient

The following parameters were calculated based on data from table 4:

- Sensitivity = 0.8511 [0.7678 - 0.9111]
- Specificity = 0.9821 [0.9095 - 0.9964]
- False positive rate = 0.0179 [0.0036 - 0.0905]
- False negative rate = 0.1489 [0.0889 - 0.2322]
- Accuracy = 0.9000 [0.8432 - 0.9395]
- Negative likelihood ratio = 0.1516 [0.0938 - 0.2469]

Discussions

In the presented study, the smallest lesion had 3 mm in diameter and the US guided FNAB offered a real positive diagnostic of malignancy (malignant cells revealed by cytology, ductal carcinoma in situ at histopathologic exam). Fifty-nine patients from our studied group had palpable lesions. Forty-seven of them had initially been submitted to a clinical guided FNAB with a non-conclusive or negative result, meaning amorphous material without cells at all or with cells lacking the typical criteria for malignancy. Taking in consideration the fact that in all these cases there were strong clinical or imaging suspicions of breast neoplasia, a second cytological punctation under US guidance was performed. Sonographic guidance led us to only 10 non-conclusive results (a case of fibro-cystic disease of the breast, a philosarcoma, a benign phyllodes tumor, a ductal invasive carcinoma with extensive necrosis and 6 cases of ductal invasive carcinomas). The rest of thirty-seven US guided FNAB-s had conclusive results, as follows: 29 malignancies and 8 benign results. From these 8 situations with a benign cytological exam, 5 were false negative, including a papillary carcinoma, a phyllosarcoma and 3 invasive ductal carcinomas. There was no false positive result.

US guided FNAB has a lesser number of non-conclusive results because sonography can enable...
us to visualize the necrotic areas (and thus allows us to avoid them during the procedure) and also directs us to extract samples from the actual lesion, and not from the surrounding desmoplastic tissues which are frequently those palpable and punctured by the clinician.

On the entire studied population the fine needle aspiration biopsy led us to 150 conclusive results (69 benign results and 81 malignancies) and 36 non-conclusive results. Among conclusive cases there was only a false positive result (a tubular adenoma) and 13 false negative results (8 ductal invasive carcinomas, a case of carcinomatous mastitis, a tubular carcinoma, a papillary carcinoma, a malignant fibrous histiocytoma and a philosarcoma). Although the predominant false negative results resulted from ductal invasive carcinomas, we emphasize that false negatives can also be obtained when confronting with other types or particular forms of breast cancers.

Among the non-conclusive situations we had two invasive ductal carcinomas with extensive necrosis, two ductal carcinomas in situ, two lobular carcinomas, a medullary carcinoma, two phyllodes tumors, three cases of fibro-cystic disease of the breast and five cases of ductal hyperplasia (three atypical and two typical). All mentioned cases were difficult to diagnose from a histopathologic point of view, posing problems regarding either the extraction of the biological material, either the interpretation [10].

Analyzing the obtained data for the US guided FNAB a sensibility of 85.11% and a specificity of 98.21%, with a diagnostic accuracy of 90%.1.79% were false positive results and 14.89% were false negative results (13 cases). These results are comparable with literature data where could be a sensibility of the method comprised between 82% - 99% [11, 12, 13], the higher values being in accordance with a more extensive experience of the radiologist [10, 14]. Also, the number of non-conclusive results diminishes with an increased breast experience of the cytopathologist. Note that there was only one false positive result and thus a single patient was submitted to an unnecessary intervention. Also we would like to mention that all situations with false negative cytological results had eventually a positive triple test, the clinical and the radio-imaging exams showing suspicious or even clearly malignant lesions.

We have to mention that the main limitation of our study was the small number of the patients considering both the fine needle aspiration biopsy and the histological biopsy. This limited number doesn’t relate to a small number of patients that had an indication for biopsy, but to a refusal of the majority of the women having most probably benign lesion to submit to a biopsy (most of them preferred a surgical intervention with a consecutive histopathological exam). There were also excluded from the study those patients who did not have a histopathological confirmation of biopsied lesions. Patients with a benign result were being followed during one year interval using clinical and radio-imaging examinations. We did not include in our study patients that had been followed less than a year. This one year follow-up is another limitation of our study, considering the fact that most literature recommendations suggest a minimum 2 years follow-up. Unfortunately it was difficult to apply this strategy due to a series of socio-economic factors regarding our patients.

Conclusions
1. Fine needle aspiration biopsy has an important value in diagnosing breast lesions, both in screening strategies and diagnostic ones too.
2. Although being a controversial procedure, FNAB maintains its place and value when it comes to a diagnostic algorithm, especially in correlation with the other two components of the triple test-clinical and radio-imaging (mammography and/or ultrasound) examinations.
3. Any time possible it should recommend a US, not clinical guided FNAB, taking in consideration the smaller rate of non-conclusive results of FNAB under sonographic guidance.
4. In cases with malignant lesions where surgery is considered as the first option, a positive FNAB permits a proper planning of the type of the intervention.
5. Whenever exists discordance between a cytological exam and the clinical and/or radio-imaging examination, there should be an indication for a histological biopsy and not a repetition of the FNAB.
6. In cases of malignant lesion when it is necessary to first have a neoadjuvant chemotherapy it is indicated a percutaneous biopsy.
7. Fine needle aspiration biopsy has a particular value in clearly proving the benignancy of a
lesion, avoiding unnecessary surgeries, especially in those situations with a negative triple test.

8. Nevertheless the sensibility and specificity of FNAB very much depend on the ability and the experience of the radiologist and cytopathologist.

References