

ORIGINAL PAPER

The value of ultrasounds exam correlated with frozen section diagnosis in the breast tumors

ALINA VENTER¹⁾, ELENA ROȘCA²⁾, GABRIELA MUȚIU³⁾,
ADRIANA PIRTE⁴⁾, D. M. ROȘCA⁵⁾

¹⁾Department of Radiology

²⁾Department of Pathologic Anatomy

³⁾Department of Histology

⁴⁾Department of Odontology

University of Oradea

⁵⁾Clinical OMF Surgery, Cluj-Napoca

Abstract

The paper represents a parallel study regarding the harmony between the ultrasounds and the frozen section diagnosis in the breast cancer. *Patients and Methods:* We examined at an ultrasounds machine a group of 146 women aged between 16–73-year-old, which came presenting palpable formations at the level of breasts, in the Pelican Medical Centre from Oradea. The suspect lesions were subject to excisional biopsy or surgical intervention. *Results:* The elements followed at the ultrasounds exam were: echogenicity, echostructure, contour, presence and absence of posterior shadowing, microcalcification, orientation of lesion, compressibility, aspect of adjacent structures. Histopathological diagnosis of suspect lesions emphasized malignant lesions in a percentage of 64.86% of cases; the frozen section exam diagnosed invasive ductal carcinoma in 86% of the cases, invasive lobular carcinoma 8%, medullar carcinoma 2%, and benign lesions 4%. *Conclusions:* The clinical–anatomopathological collaboration is absolutely compulsory for a correct microscopic diagnosis. The ultrasounds modifications separated after the criteria taken into account allow the orientation of diagnosis to malignant–benign. At 14% of the women examined, additional lesions were identified in comparison to those palpated, the ultrasounds having a role in detecting the multifocality and muticentricity of lesions. At 29.05% from the identified lesions, malignant lesions were histopathologically identified. The frozen section diagnosis in the breast cancer allows a rapid diagnosis, correct in high percentage of cases, allowing taking an intra-surgery therapeutic attitude in only one surgical intervention, thus reducing the costs. The anatomopathologist's experience reduces the diagnosis risk in excess and/or in minus.

Keywords: breast ultrasounds, breast cancer, frozen section diagnosis.

Introduction

The breast cancer, which ranks first in the hierarchy of cancer in women, benefits from therapeutic possibilities with more favorable results when diagnosed early [1, 2]. Clinical examination, mammography and echography are methods that complement each other in order to achieve this goal [2].

The present paper is a parallel study regarding the harmony between the ultrasounds and histopathological diagnosis, through frozen section exam, in the breast cancer. We have tried to highlight the importance of ultrasounds exam by presenting two-dimensional echographic aspects that are suggestive for the malignancy of a mammary nodular lesion, the differentiation benign–malignant completed by the histopathological diagnosis of the lesion in a first step by performing frozen section diagnosis [3, 4].

Patients and Methods

We have examined a group of 146 women aged between 16–73 years, which came to ultrasounds for the existence of palpable formations at the level of breasts,

in the Pelican Medical Centre from Oradea. We have excluded from the lot patients with breast cancer diagnosed during previous exams, as well as those with breast implants. We have done the ultrasounds as a first step of exploration in women under 40-year-old, because these have the breast with dense structure. For the patients of over 40-year-old the first exam was a mammography; the ultrasounds in case of these was indicated for the additional characterization of a mammography opacity, for the assessment of mammographically dense breasts (ACR 3 or 4), for the evaluation of tumoral extension.

The ultrasounds exam was done with a Siemens Antares apparatus with linear probe of 7.5 MHz. We have explored both breasts by comparison, with attention, all the dials, making sagittal, transversal, radial, parasternal sections, including the supraclavicular and axillary regions.

The suspect lesions were subject to excisional biopsy or surgical intervention. The frozen section diagnosis includes the macroscopic description of the lesion, the microscopic description starting with the exam with small objective. The pathologist, through

inspection and palpation, localized the tumor in bioptical sample and selected the tumor fragment necessary for the examination. When from a macroscopic point of view a tumor area was not visualized, several different sections were chosen. The frozen section exam could not be done when the tumors were smaller than 5 mm and when the lesions were not palpable.

The freezing of biopsy sample was done with CO₂, the section was done in relation to the structure of the tumor between 20–30 µm, the staining was done with Hematoxylin–Eosin, and Nikon the microscope exam, starting the exam with a magnifier. The cytology exam through printing the tumor immediately after the section was done using May–Grünwald–Giemsa stain. The examination of the wax embedding biopsy allowed sections of 5–7 µm and the basic diagnosis was done using the classical Hematoxylin–Eosin stain.

Results

We have done the exam of those 76 women until 40-year-old, as well as of those 70 women of over 40-year-old for which, at the mammography the following were separated: opacities with dense centre, opacities with regulated contour, wiped or regular, asymmetries of focal density. The elements followed during the echographic exam were: the presence and the localization of the lesions, their dimensions, echogenicity, echostructure, shape, and aspect of the contour, the presence or the absence of the posterior attenuation, the presence or the absence of the microcalcifications, the orientation of the lesion, the compressibility, the aspect of the adjacent structures and the rapport to those.

In which concerns the presence and positioning of the lesions, this is done after the hours of the watch, taking into account the distance towards the nipple and the depth towards the tegument. The dimension measured from an ultrasounds point of view is smaller than the one measured from a mammographical and clinical point of view.

By **echogenicity**, the breast nodules may be anechoic, hypoechoic, isoechoic, hyperechoic or complex. The echogenicity of nodules from our group is illustrated in Figure 1.

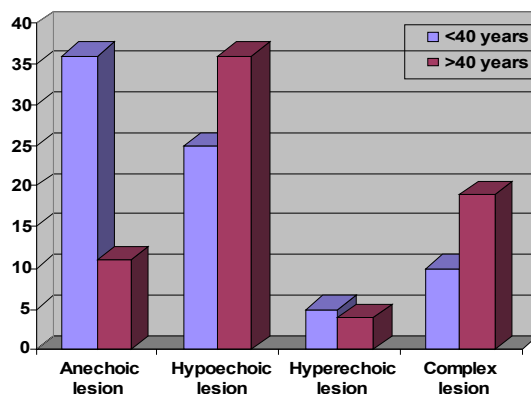


Figure 1 – Echogenicity of breast masses.

We can observe the high difference of cyst lesions in the group under 40 years of age, of the hypoechoic and complex lesions at the group over 40 years of age. Also, at 18 of the 146 women examined we have separated

additional lesions in comparison to those palpated or towards those visible on the mammography pictures.

The **echostructure** of identified nodules may be homogenous such as simple cysts, fibroadenomas, small neoplasms, well differentiated, but can also be heterogeneous complex, such as complex, fibrous fibroadenomas, the intracyst carcinoma or neoplasms.

The **transmission of ultrasounds** associated with lesions identified may be unmodified, with posterior acoustic amplification, posterior shadowing or their combination.

In the group examined, the identified lesions had the following behavior concerning the transmission of ultrasounds (Figure 2).

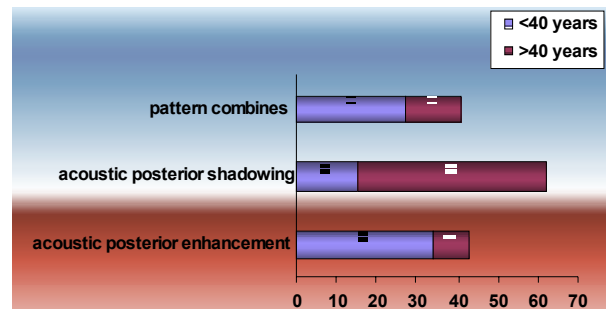


Figure 2 – Ultrasound transmission.

Another aspect tracked at the identified lesions is the **contour**, which may be circumscribed (regular or irregular) or not circumscribed; the margins of the lesions may be flou, microlobular, spiculiform or angle-shaped. The contour of identified nodules is exemplified in Figure 3.

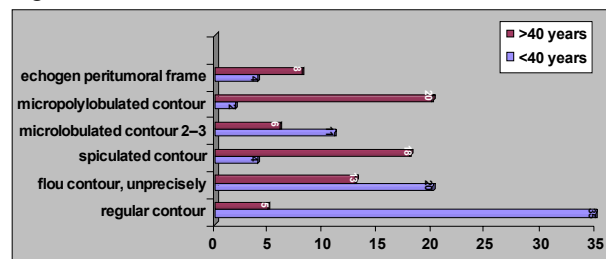


Figure 3 – Contour of the lesions.

The **orientation of the lesion** represents another aspect, which may orient towards the benign and malignant character of the lesion. For the malignant character pleads the aspect much taller than wide of the lesion. Unlike the fibroadenomas, which grow pushing the tissues around and have the axis parallel with the tegument, the neoplasms have the long axis perpendicular on the tegument (thus antiparallel orientation) following the invasion of profound and superficial plans and due to their incompressibility. This aspect is suggestive for the malignant nodules even if it appears in a single portion of the lesion. In the group explored, the identified lesions had a parallel orientation in a percentage of 50% of the cases, respectively antiparallel orientation in 22.4% of the cases.

Generally, the benign lesions are easy comprehensible, the incomprehensible ones are compatible with the malignant lesions associated or not with the fibrosis phenomenon.

We have also followed the aspect of adjacent plans,

which may be of type: diffuse or local skin thickness, tegumentary retraction, architectural distortions, interruption of anatomical plans, and growth of echogenicity of adipose tissue, which means its invasion.

At those 146 women examined, we identified 165 lesions. From an anatomopathological point of view, 74 suspect lesions were examined, these being subjected to excisional biopsy and/or surgical intervention with tumorectomy. Following the histopathological examination, 46 malignant lesions were diagnosed (four at the group age under 40-year-old, 42 at the group age of over 40-year-old) and 26 benign lesions (35.14%); the malignant lesions represents 64.86% from those subject to anatomopathological diagnosis and were: 38 ductal invasive carcinomas, one colloid carcinoma, four lobular invasive carcinoma, two medullar carcinoma, one malignant phyllodes tumor. The exam was on frozen sections, the ductal invasive carcinoma being diagnosed in a percentage of 86% of the cases, 8% lobular invasive carcinomas, 2% medullar carcinomas or 4% benign lesions, in parallel the cytological exam was also done through imprint.

The percentage of diagnosis errors was of 10% and that of lack of histological/cytological harmony of 14%.

The technical problems which represented the percentage of 10% of errors were linked to the reduced dimension of tumors, under 1 cm, lack of complete clinical data related to the preoperative medical exam, or to the difficulty of sectioning tumors with extended necrosis or with a mucoid structure.

In the suspicious of carcinomas *in situ*, papillary carcinomas, which may easily create diagnosis error, we preferred the temporization of carcinoma diagnosis until the finalization of histopathological exam at paraffin.

The histopathological diagnosis using frozen section requires complex analysis.

The diagnosis in excess was generated by the following situations.

The florid epithelial hyperplasia from a mammal fibroadenoma (Figure 4) may be mistaken for an *in situ* or invasive carcinoma (Figure 5). These errors appear when the dimension of biopsy is not sufficient, when the healthy tissue around is missing. In other cases, the fibroadenoma may be mistaken for a medullar macroscopic carcinoma (Figure 6) when the magnifying exam of the tumor is of great help. Generally, a fibroadenoma is well limited, having a capsule.



Figure 4 – Breast fibroadenoma (HE stain, 200×).

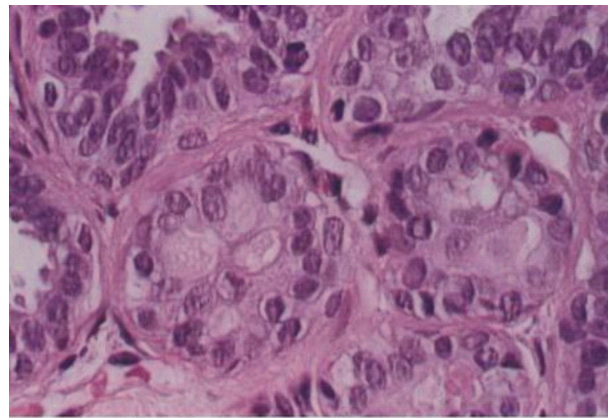


Figure 5 – Florid epithelial hyperplasia (HE stain, 400×).

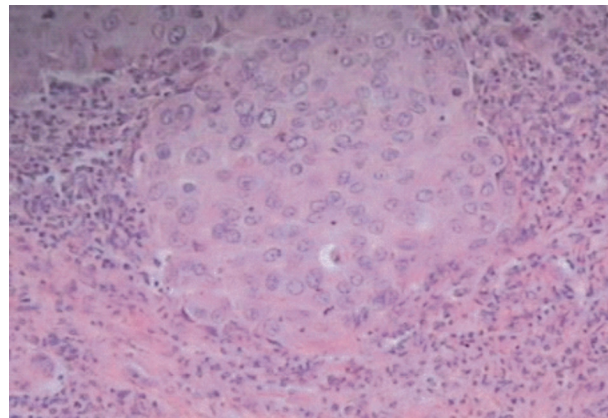


Figure 6 – Medullary carcinoma (HE stain, 400×).

The inflammatory reaction, acute or chronic, raises diagnosis issues. The bursting of a cyst may generate an inflammatory reaction in which the epithelium cells will be positioned in a stripe over a fibrous wall, which may be better visualized through metachromatic color (methylene blue). An infiltrate chronic inflammatory is not usually positioned in trabeculae as carcinoma cells and this aspect helps us to differential diagnosis. Easily a chronically inflammatory infiltrate may be mistaken for an infiltrative lobular carcinoma (Figure 7); here the experience of anatomopathologist's experience is essential, as well as the correct macroscopic exam of the tumor.

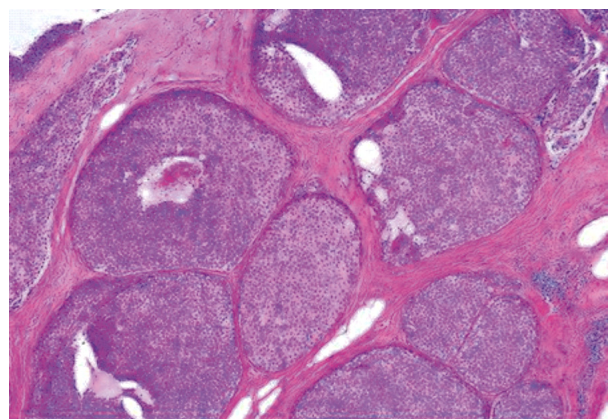


Figure 7 – Invasive lobular carcinoma (HE stain, 200×).

In the sclerosing adenosis (Figure 8) the diagnosis

error with a carcinoma may be avoided through a correct and pertinent exam from a macroscopic point of view. The presence of calcifications may generate the diagnosis excess with a carcinoma. In these lesions, the mammography exam is of great help.

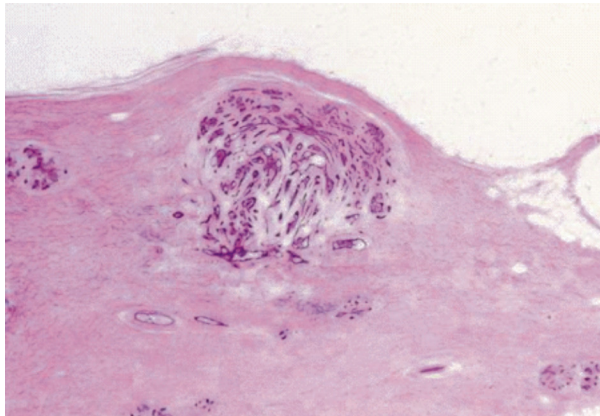


Figure 8 – Sclerosing adenosis (HE stain, 200×).

The diagnosis in minus, rarer than in excess, appears in the following situations:

The lobular carcinoma *in situ* is diagnosed with difficulty on frozen section; when it was suspected, we preferred to wait for the histopathological examination in order to avoid the mutilant surgical interventions through an error of diagnosis.

In comparison to the lobular carcinoma *in situ*, the ductal *in situ* carcinoma (Figure 9) is diagnosed easily on frozen sections. The errors quoted in literature are in a percentage of 55%. The ductal carcinoma *in situ* with ductal ectasia puts problems of differential diagnosis. It is preferred to wait for the exam at paraffin when there are doubts in the frozen section exam.

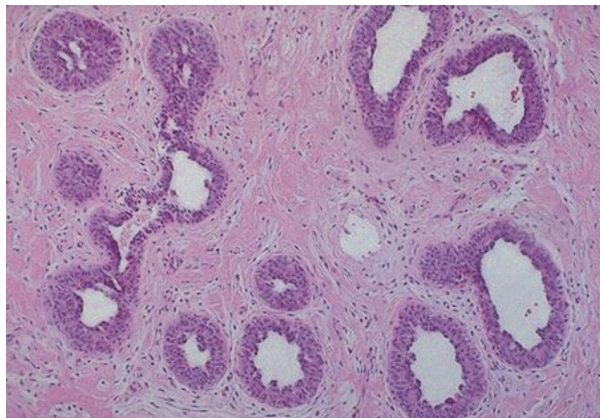


Figure 9 – Ductal carcinoma in situ (HE stain, 200×).

Discussion

The ultrasounds exam emphasizes the palpable nodules, as well as the non-palpable lesions [2, 5]; in our study, the ultrasounds separated additional lesions at 14% of the women examined. In which concerns the echogenicity of nodules, the transonic lesions are compatible with the simple cysts [6, 7]. The hypoechogenicity marked comparatively with adipose tissue suggests the malignant character, but 1/3 of the malignant lesions

may be isoechoic masses or just easily hypoechoic in comparison to the glandular parenchyma [5, 6]. Also, the atypical complex cysts are hypoechoic lesions, with thick wall, imprecise delimitation, with echoic sediment inside [7].

The acoustic enhancement is characteristic to cysts, simple fibroadenomas, medullar or colloid carcinoma. The acoustic strengthening is missing in the case of cysts with reduced dimensions, of those situated near the breastplate muscle or those with thick walls [6, 7].

The posterior shadow appears due to the elements inside the malignant lesions; this aspect is frequently encountered in scirrhous neoplasm and rarely in those with a high degree of cells (such as medullar carcinomas) [5, 6, 8]. Its presence indicates the suspicion of malignancy; its absence does not exclude the malignancy. The old fibroadenomas, calcified are very difficult to apply, are masked by an important posterior shadow, and practically makes the lesion invisible [5, 8].

The flou contour is characteristic to irregular cysts, inflamed or complex fibroadenomas, which may have this aspect only on one portion of the contour [6, 7].

The spiculiform contour is given by the appearance of parenchymous prolongations from the lesions to the surrounding parenchymous [5, 9].

In which concerns the margins with microlobulations, unlike the fibroadenomas presenting 2–3 large lobulations, in case of neoplastic lesions multiple lobulations may be observed, with reduced dimensions [6, 9].

Also, in case of the malignant lesions, the angle formed by the lesion with the surrounding parenchyma may be pointed, straight or obtuse and presents abrupt margins [5, 6, 8].

The echogene peritumoral frame is given by the perilesional edema, as well as the desmoplastic reaction of adjacent tissues; it is frequently associated with malignant lesions (especially in the intracystic or papillary carcinoma) but there are also neoplasms without echogene frame. This frame may appear also in abscesses or in some forms of fibrocystic mastosis [3, 5, 6].

From a histopathological point of view, we analyzed the connection between the clinical, imagistic, histopathological diagnosis through frozen section. Each exam by frozen section of a breast tumor was followed by a cytological exam through impression and followed by diagnosis through exam of tumor by inclusion in paraffin. We appreciated the difficulties to make the frozen section linked to the lack of clinical–anatomopathological collaboration or technical difficulties.

The intraductal papilloma, the solitary cyst is problematic in which concerns the diagnosis when the conjunctive–vascular axis is not visualized at frozen section exam and may be mistaken for carcinoma [10, 11]. These lesions claim an experienced pathologist, a good microscope and compulsory the exam with small objective of the section. In the cyst–papillary lesions it is preferred to exam the sections from paraffin block, in order to avoid the excess of diagnosis [7, 11, 12].

The lobular invasive carcinoma also puts diagnosis issues when examined on frozen section exam, especially when the macroscopy does not help us; an area where the margins cannot be distinguished is palpated

[11, 13]. When at the microscope exam appear carcinoma cells positioned in an isolated manner it is difficult [14, 15].

The tubular carcinoma may be mistaken for the sclerosing adenosis at frozen section exam; this is why in these cases it is preferred to wait for the paraffin examination [11, 16].

Sometimes the gynecomasty in men with suspect cytology presents diagnosis issues and that is why the paraffin exam is preferred [14, 16].

The frozen section exam of a breast tumor may present diagnosis issues linked to the lack of experience of the pathologist, which may generate firstly an excess of diagnosis, which is even more dangerous than the minus of diagnosis, lack of clinical-pathological collaboration, as well as technical difficulties, linked to the dimension of tumor and its structure [4, 17, 18]. The temporization of diagnosis is preferred until the finalization of exam at paraffin when one of the aspects enumerated generates uncertainty of microscope diagnosis [12, 16].

A very important aspect for the success of frozen section exam is that of good *clinical-pathological collaboration* [12, 16]. For the pathologist it is very important to know the clinical data linked to the age, place of the lesion, clinical symptomatology, size of the tumor, mobility, adherence, consistency, presence or absence of a pregnancy in antecedents, surgical and therapeutic oncological antecedents, etc. [1, 4, 19, 20].

In order to avoid as much as possible the diagnosis errors in frozen section exam of a breast tumor *a certain protocol must be followed*: scheduling of extratemporaneous exam (the patient must be examined in full before surgery), the macroscopic exam of tumor, beginning of magnifying exam [11, 12, 19]. Not the last we have to remember the pathologist's experience. The lack of experience leads more frequently to an excess of diagnosis, which is more dangerous than the minus of diagnosis. When there are discrepancies between the macroscopic and the microscopic exam, we recommend waiting for the paraffin exam [21].

✉ Conclusions

The clinical-anatomopathological collaboration is absolutely compulsory for a correct microscopic exam. The ultrasounds modifications separated after the criteria followed allow the orientation of diagnosis towards malignant-benign.

The benign ultrasounds aspects are: hypoechogenicity, inhomogeneous echostructure, the presence of posterior shadow, the irregular contour, which is vaguely limited, spiculiform or microlobulate. The presence of a single sign of malignity raises suspicion. At 14% of the women examined, additional lesions were palpated in comparison to those already felt, the ultrasounds having a role in detecting the multifocality and multicentricity of lesions. At 29.05% from the lesions identified malignant lesions were histopathologically distinguished (four at the group under 40-year-old, 42 at the group over 40-year-old).

The frozen section exam in the breast cancer is

important because it allows a rapid diagnosis, correct in a high percentage of cases, allowing taking an intra-surgery therapeutic attitude in one single surgical intervention, reducing the medical costs and reducing the risk of tumor metastases. The frozen section exam in the breast cancer may be made in the pathologic anatomy labs modestly equipped, with reduced costs.

The pathologist's experience reduces the risk of diagnosis in excess and/or minus. The cytological examination through tumoral imprint is useful and is recommended to be made in the same time with the frozen section exam.

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Corresponding author

Alina Venter, Assistant Professor, MD, PhD, Department of Radiology, Faculty of Medicine and Pharmacy, University of Oradea, 10 1 December Square, 410073 Oradea, Romania; Phone +40724–243 934, e-mail: alinaventer@gmail.com

Received: June 15th, 2010

Accepted: October 10th, 2010