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The value of intraoperative diagnosis in breast lesions

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Abstract

Frozen section examination is aimed at making a preoperative diagnosis, determining the benign or malignant nature of a breast lesion, but also the most suitable surgical procedure. The sensitivity and specificity of this method and the causes of discrepancies were analyzed in a retrospective study of 2 177 breast lesions. *Method*. 1 150 frozen sections from 2 177 breast lesions were performed in the interval 1999–2005. The sections made at the open door cryostat and measuring 5μm were stained with rapid Hematoxylin–Eosin. The following terms were used for describing the intraoperative diagnosis: negative, positive, and await paraffin section. After the frozen section diagnosis was made, the frozen tissue was thawed to room temperature and fixed in formalin overnight for further paraffin processing. The remaining unfrozen tissue was processed into a paraffin section. *Results*. The number of cases and the number of frozen sections increased from 1999 (341 cases, 87 frozen sections) to 2005 (441 cases, 220 frozen sections). Mean sensitivity (a/a+c) was 94%, and mean specificity (d/b+d) was 99%. The false positive cases accounted for 0.08%, while the false negative ones for 2.26%. In 7% of the cases the diagnosis could not be made on frozen section. *Conclusions*. Despite the raging popularity of aspiration cytology, frozen section still stands out as the method of choice for rapid diagnosis. Frozen section is not indicated to be performed on mammographically detected lesions, small lesions, papillary lesions, proliferating fibrocystic disease, or tubular carcinoma.

***Keywords*:** frozen sections, breast lesions.

Introduction

Intraoperative diagnosis is a rapid diagnostic method aimed at making a diagnosis when it could not be established preoperatively, determining the benign or malignant nature of a lesion, as well as at orienting the surgeon about the extent of the surgery he is about to perform. Although prevalently used in breast disorders, the intraoperative diagnosis applies also to thyroid, digestive system tumors.

The goal of this paper is to present the main steps in performing an intraoperative diagnosis for a breast lesion, its indications, usefulness, and disadvantages, based on a retrospective study on 2 177 breast lesions.

Material and methods

In the interval 1999–2005, at the Pathology Laboratory of the Târgu Mureş Emergency Hospital 2 177 breast lesions had been examined, in 1 150 of them an intraoperative diagnosis being made.

Some of these lesions were detected by mammographic screening, but most by self-palpation. That explains why most intraoperative examinations were on tumorectomy, sectorectomy or mastectomy specimens containing a tumor visible at gross examination, but also unapparent lesions represented merely by microcalcification foci detected at mammography.

Usually, microcalcifications should not be examined intraoperatively, but it was the policy of our laboratory to not follow this rule. The same pathologist performed most intraoperative examinations, but there were instances when other pathologists were involved.

For the intraoperative examination, the pathologist received together with the specimen a referral note filled out by the surgeon including patient's personal data, main investigations performed on her breast lesion and their results (breast ultrasound, mammography), as well as her personal and family history.

The breast specimen was sent unfixed in formalin and in a short time (minutes) the pathologist had to measure the specimen, grossly identify the lesion, describe it, take a tissue fragment, and then freeze it. The sample frozen at the open door cryostat at -23^{0}C was later on sectioned and stained with Hematoxylin–Eosin.

The pathologist, who then sent his histopathological intraoperative diagnosis to the operating room, interpreted this section. The diagnosis had to be either negative (or benign, when on the examined section no malignant, *in situ* or infiltrating lesion was identified), positive (or malignant, when a malignant lesion such as an *in situ* or infiltrating breast carcinoma or another malignant breast lesion – malignant lymphoma, sarcoma was identified) or await diagnosis.

When the diagnosis was positive, the pathologist had to mention if the malignant tumor was of carcinoma type or another type, and if a carcinoma whether it was invasive or noninvasive, and to assess the excision margins.

The frozen section together with the remaining tissue was fixed in formalin at room temperature for 24 hours. Later on, tissue fragments were taken and paraffin sections prepared, and the Hematoxylin–Eosin stained sections were examined by a single pathologist for a definitive histopathologic diagnosis.

The results of the intraoperative diagnosis were compared with those of the definitive diagnosis.

Results and discussions

In the interval 1999–2005 the number of breast lesion cases showed a constant increase and so did the number of intraoperative examinations (Table 1).

Table 1 – ***Increased number of the breast lesion and intraoperative examinations during the period 1999–2005***

Year	Total cases	Intraoperative examination
1999	341	87
2000	339	112
2001	423	157
2002	462	184
2003	498	195
2004	473	195
2005	441	220
Total	***2 177***	***1 150***

If in 1999 the intraoperative examinations were performed in 25.51% of the cases (87/341), in 2005 they reached 49.88% of the cases (220/441). This is accounted for by the increasing number of breast lesions, the lack of information from additional investigations on the given lesions, as well as by surgeons' higher confidence in the value of intraoperative examination.

It is also true that "True cut" biopsy was introduced at the Pathology Laboratory of the Târgu Mureş Emergency Hospital only in 2006.

By this method 469 malignant and 600 benign lesions were diagnosed. On paraffin embedded sections a diagnosis of malignancy was made in 468 cases and of benign lesion in 574 cases.

Sensitivity (Sb) was calculated as the percentage of patients with malignant breast lesion in which the intraoperative diagnosis was positive (malignant).

Specificity (Sp) was calculated as the percentage of patients with benign lesion in which the intraoperative diagnosis was negative (benign). In our series sensitivity was of 94% and specificity of 99% (Table 2).

Sensitivity increased from 91% in 1999 to 94% in 2005.

Specificity showed an insignificant decrease from 100% in 1999 to 99% in 2005.

The percentage of cases in which the intraoperative diagnosis was awaiting definitive diagnosis was 7%. This percentage changed from 10% in 1999 to 3% in 2005.

Table 2 – ***Results of the intraoperative examination and paraffin-embedded sections***

Results of intraoperative examination	Malignant at definitive diagnosis	Benign at definitive diagnosis
Malignant *469*	468	1
Benign *600*	26	574
Total	494	575

In the cases in which the intraoperative diagnosis was await definitive diagnosis the final diagnoses varied. The most difficult to diagnose were: proliferating fibrocystic mastopathy, multiple papillomatosis, various types of adenosis (nodular, sclerosing, tubular), solitary intracystic papilloma, malignant phyllodes tumor, inflammatory benign lesions, lipogranuloma, various types of sarcoma, intraductal carcinoma, microinvasive carcinoma, tubular carcinoma, infiltrating lobular carcinoma, preoperatively treated infiltrating breast carcinoma.

False-positive results were recorded in 0.08% and false-negative ones in 2.26% of the cases. In our study a false-positive diagnosis was made in only one case. In this young patient the intraoperative diagnosis was of malignancy (positive), and on paraffin section was sclerosing radial scar.

False-negative results were recorded in 26 cases. These cases had *in situ* or infiltrating lobular carcinoma, extensive intraductal carcinoma, malignant or benign phyllodes tumor with a focus of infiltrating ductal carcinoma, fibroadenoma associated with metastasis in an axillary lymph node (at the definitive diagnosis it was proved to be a focus of endosalpingiosis), microinvasive carcinoma, but also NOS infiltrating ductal carcinoma or medullary carcinoma.

Twenty to 35% of all intraoperative examinations are performed for diagnosing breast lesions [1].

The goal of such an investigation is to determine the type of surgery to be performed. Lately, "Tru cut" biopsy has taken over the role of intraoperative examination; the latter being performed only in those hospitals where biopsy has not been introduced yet, or when the biopsy diagnosis is inconclusive [2].

On the other hand, in the palpable lesions the role of the intraoperative examination is to establish their benign or malignant nature. Equally important with the intraoperative examination is the assessment of the excision margins, as, especially in small malignant tumors, the treatment consists in extended sectorectomy and the therapeutic success largely depends on the absence of tumor tissue in the excision margins. The presence of carcinoma *in situ* at the excision margins is associated with a higher rate of recurrences.

In our medical center, in which the "Tru cut" biopsy was recently introduced, the intraoperative examination had an extremely important role. Also, the fact that it was performed, with few exceptions, by highly

experienced pathologists in breast pathology, made the diagnostic errors a rarity. In the study interval, the sensitivity of the method was 94% and its specificity of 99%.

In a study by Bianchi S *et al.* (1995), the reported sensitivity was 92.7% and specificity 99.2%, and in a study published by Eskelinen M *et al.* in 1989, sensitivity was 97.3% and specificity 99.5% [3, 4].

The percentage of cases in which the intraoperative diagnosis was awaiting definitive diagnosis was 7%.

In the study published by Bianchi S *et al.* in 1995, in 3.3% of their cases the intraoperative diagnosis was await definitive diagnosis, and so was in 7% of the cases reported by Torp SH *et al.* in 1990 [3, 5].

The percentage of false-positive diagnoses reported in the literature ranges from 0.03 to 0.1% and of the false-negative ones from 0.5 to 1% [1, 6]. In our study, the false-positive results were only 0.08% and the false-negative ones 2.26%. On the other hand, although "Tru cut" biopsy is an excellent method for diagnosing the breast lesions; it has some limitations, including the fact that it does not allow a correct and actual assessment of some prognostic morphological factors such as the histopathological grade, microscopic type, and presence of emboli in the lymphatic vessels [6]. Also, in a solid tumor mass the "Tru cut" biopsy diagnosis is not conclusive. In such a circumstance the further investigation of the lesion is compulsory, fact requiring an intraoperative diagnosis.

The intraoperative examination also has limitations. Thus, the examination of a section processed by freezing is very quick, making the assessment of all prognostic parameters for each lesion impossible.

There are some breast lesions difficult to diagnose by intraoperative examination. Special attention should be given to the proliferating lesions of papillary type or proliferating fibrocystic disease, in which, given the artefactual changes during technical processing, the distorted appearance of nuclei may result in a misdiagnosis of carcinoma *in situ* (Figures 1 and 2).

In such circumstances, the pathologist has to inform the surgeon that he cannot make a diagnosis of certainty until the lesion is not examined on definitive sections, the more so as an intraductal carcinoma requires the presence of atypias in all structures of a lobule, so it is transformed into a ductal structure of over 2 mm in diameter. Another diagnostic problem occurs in tubular carcinoma, which can be easily confused with sclerosing adenosis (Figure 3).

Tubular carcinoma is characterized by round tubular structures with angular contours lined by a single layer of epithelial cells and a desmoplastic stroma. At periphery, the lesion has infiltrating margins. The tumor cells have few atypias, scanty mitotic figures, and the myoepithelial cells are absent. In these cases it is preferable for the pathologist to make the diagnosis on definitive sections as well as by immuno-histochemical investigations for actin, laminin, type IV collagen. Diagnostic difficulties are also encountered in the sclerosing radial scar and adenosis such as the sclerosing, microglandular or tubular adenosis (Figures 4 and 5).

A pathologist not familiar with such lesions may misinterpret them as infiltrating malignant lesions. Invasive lobular carcinoma also raises diagnostic problems. Especially in the classical pattern, characterized by a proliferation of small and uniform tumor cells which lack cohesion and are dispersed trough a fibrous stroma, the lesion may be misinterpreted as an inflammatory process (Figure 6).

The presence of pleomorphism in the tumor cell nuclei and the size of tumor cells, tumor cells being larger than inflammatory cells, make the distinction. Special care should be paid to breast lesions in young women. Such an example is juvenile papillomatosis, sometimes associated with intraductal epithelial hyperplasia.

Even though this proliferation is atypical, a conservative treatment is recommended, and thus it has not to be reported as a malignant lesion.

Diagnostic problems may also be encountered in the mesenchymal lesions, particularly fibromatosis, lesion sometimes difficult to differentiate intraoperatively from sarcoma and vascular proliferations. Also, in the malignant phyllodes tumors the nuclear pleomorphism and mitotic figures are difficult to evaluate.

In lesions smaller than 1 cm the intraoperative examination is not performed as there needs to be enough tissue left for the definitive diagnosis [7, 8].

The intraoperative interpretation of a section incorrectly performed technically, with artefacts, represents a real danger for the pathologist who can make an erroneous diagnosis.

Intraoperative examination should not be performed in the patients treated preoperatively by chemotherapy or radiation therapy as these therapies induce significant changes in the tumor tissue. Sometimes, in these cases the pathologist has to make a diagnosis examining only few placards of tumor cells, so it is preferable the diagnosis to be made by "Tru cut" biopsy before the initiation of any therapy.

The size of the tumor can be determined during intraoperative examination, but one has to take into account the fact that on a paraffin section the lesion size is 0.1 to 0.2 mm smaller, due to the fact that following paraffin fixation the tissues shrink. Also, the mitotic index can be wrongly interpreted, on paraffin section the mitotic index being usually lower.

The factors that contribute to an intraoperative misdiagnosis are: the poor quality of the performed sections, not grossly identified lesion focus, detection of some lesions difficult to interpret (papillary lesions, proliferating fibrocystic disease, infiltrating lobular carcinoma).

Conclusions

Intraoperative examination remains a diagnostic method when the mammographic screening for the detection of the small lesions and biopsy are not performed. As a rule, it should be used only when the other diagnostic methods failed to determine preoperatively the benign or malignant nature of the tumor.

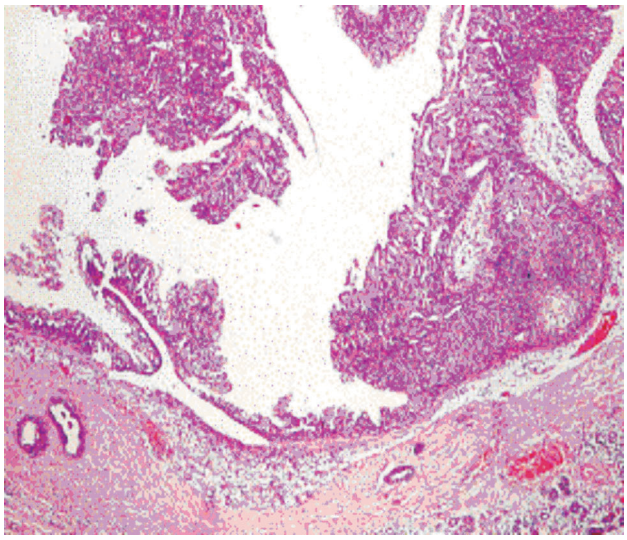

Figure 1 – ***Papillary in situ carcinoma***
(HE staining)

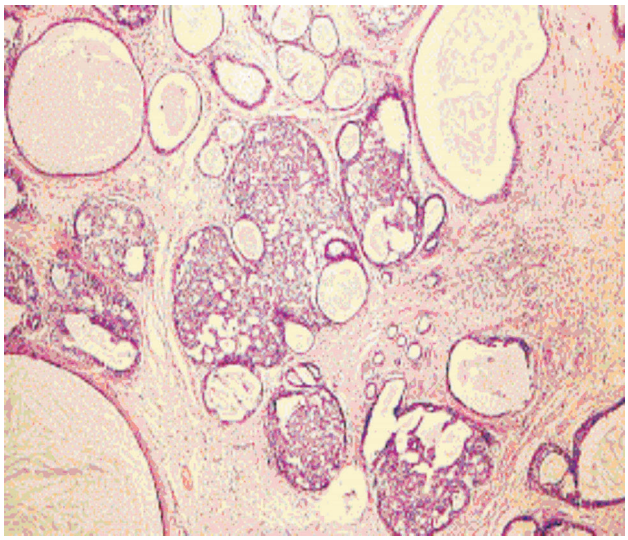

Figure 2 – ***Proliferating fibrocystic disease***
(HE staining)

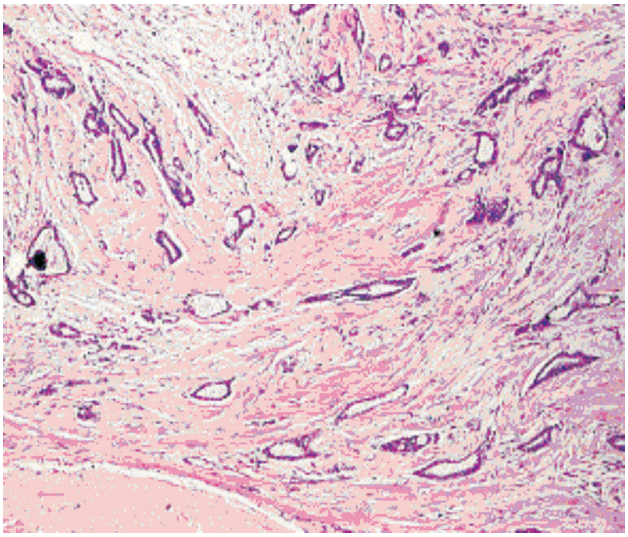

Figure 3 – ***Tubular carcinoma***
(HE staining)

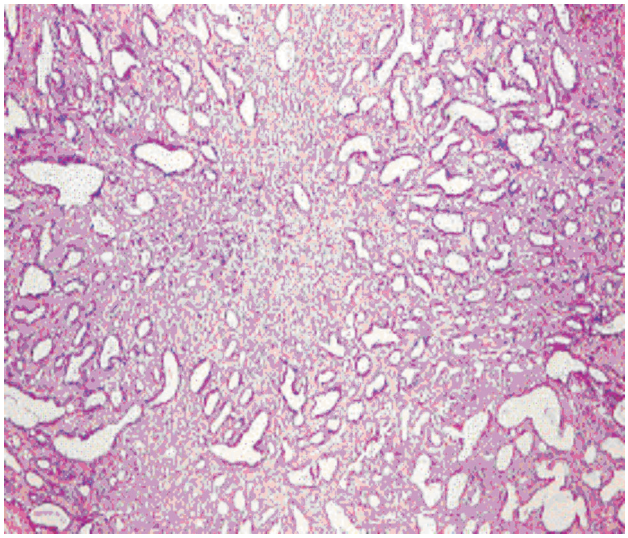

Figure 4 – ***Sclerosing adenosis***
(HE staining)

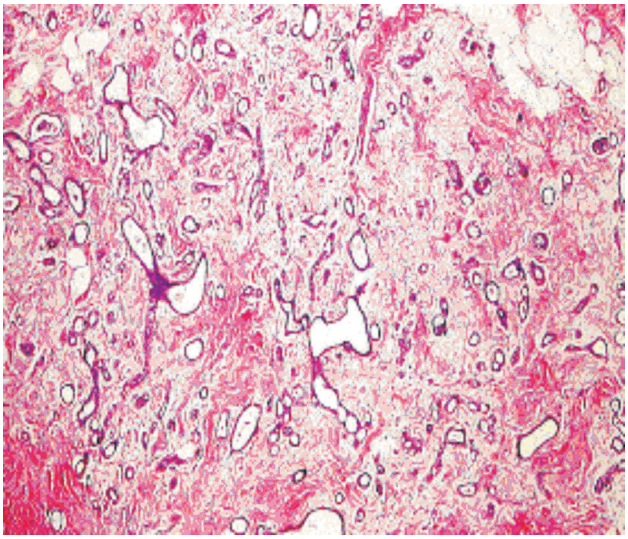

Figure 5 – ***Tubular adenosis***
(HE staining)

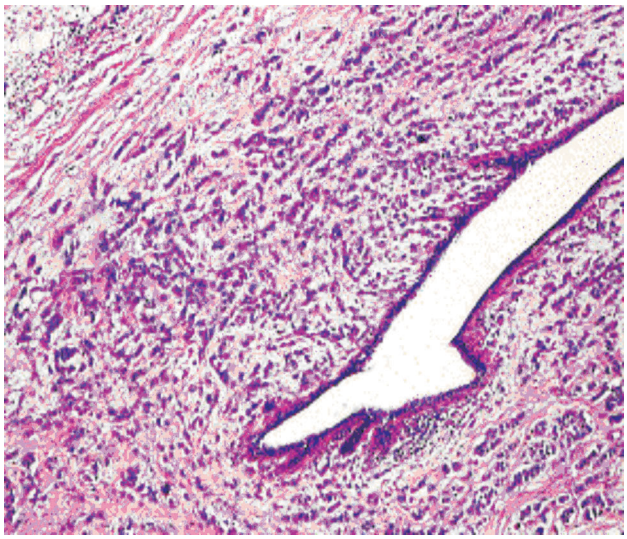

Figure 6 – ***Invasive lobular carcinoma***
(HE staining)

Even in the centers in which mammographic screening and "Tru cut" biopsy are a common practice, the intraoperative examination is of great help when these two methods failed to make a preoperative diagnosis.

It is preferable that a pathologist specialized in breast pathology make the intraoperative diagnosis, as it is familiar with breast lesions and their differential diagnosis.

In our series of patients, the presence of experienced pathologists in our team led to a very small percentage of false-positive and false-negative results. Also, in only 7% of our cases there was an await diagnosis.

The diagnosis made intraoperatively has to be followed by a definitive examination based on embedding the fragment from the intraoperative examination together with other fragments from the breast tissue in paraffin.

Generally, when not all criteria of microscopic diagnosis are present, a diagnosis that does not require a radical intervention is more indicated.

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