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False-negative results of breast core needle biopsies – retrospective analysis of 988 biopsies

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Summary

Background: Breast cancer is the most common malignant neoplasm and the most common cause of death among women. The core needle biopsy is becoming a universal practice in diagnosing breast lesions suspected of malignancy.

Unfortunately, breast core needle biopsies also bear the risk of having false-negative results.

Material/Methods: 988 core needle breast biopsies were performed at the Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, between 01 March 2006 and 29 February 2008. Malignant lesions were diagnosed in 426/988 (43.12%) cases, atypical hyperplasia in 69/988 (6.98%), and benign lesions in 493/988 (49.90%) cases.

Results: Twenty-two out of 988 biopsies (2.23%) were found to be false negative. Histopathological assessment of tissue specimens was repeated in these cases. In 14/22 (64%) cases, the previous diagnosis of a benign lesion was changed. In 8/22 (36%) cases, the diagnosis of a benign lesion was confirmed. False-negative rate was calculated at 2.2%. The rate of false-negative diagnoses resulting from a radiological mistake was estimated at 36%. The rate of false-negative diagnoses, resulting from histopathological assessment, was 64%. False-negative results caused by a radiological error comprised 1.5% of all histopathologically diagnosed cancers and atypias (sensitivity of 98.5%). There were no false-positive results in our material - the specificity of the method was 100%.

Conclusions: Histopathological interpretation is a substantial cause of false-negative results of breast core needle biopsy. Thus, in case of a radiological-histopathological divergence, histopathological analysis of biopsy specimens should be repeated. The main radiological causes of false-negative results of breast core needle biopsy are as follows: sampling from an inappropriate site and histopathological non-homogeneity of cancer infiltration.

Key words: breast cancer • core needle biopsy • false negative results

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Background

Breast cancer is the most frequent malignancy and the most common cause of death in women. In highly developed countries, the incidence of breast cancer is increasing. Poland belongs to countries with a medium incidence rate. Epidemiological data of 2006 report 13322 new cases (standardised incidence coefficient of 44.2) [1]. Despite advances in the diagnostics and treatment of breast cancer, it was impossible to achieve a decrease in the number of deaths in

Tabela 1. The analysed biopsies according to the biopsy system and the guidance used.

	Vacora (MMG)	Magnum (MMG)	Magnum (USS)
Number of performed biopsies	326 (33%)	468 (47.4%)	194 (19.6%)

Poland – the number is still on the rise, and in 2006 it was 5212 (standardised death coefficient of 14.8) [1].

Advances in the field of imaging led to the development of methods that allow for breast cancer detection in a clinically silent period. This significantly improves the prognosis.

A basic method of radiological diagnostics in breast cancer is X-ray mammography. It has become a tool used in screening thanks (inter alia) to its high sensitivity, of 80–100% [2–4].

Unfortunately, the specificity of this method is substantially lower, which requires using other diagnostic methods (utrasonography, sonoelastography, MR mammography) and cytological or histopathological verification of suspicious lesions. Approximately 75% (on average) of lesions qualified for microscopic verification on the basis of mammography turn out to be benign [5].

Core needle biopsy is an increasingly more common method used in the diagnostics of breast lesions suspected of malignancy. This is the main alternative to a reference surgical biopsy [6–8] which is more expensive, carries an additional risk connected with the operation and causes a higher mental stress for the patient. Surgical biopsy is not free of false-negative results either. According to one of the studies, their rate was 2.5 [9].

Core needle biopsy allows for sampling of tissue material which can help in exact identification of the cancer type and grade. Moreover, it does not require patient's hospitalisation, it is performed under local anaesthesia and is minimally invasive. The currently used biopsy systems allow for a precise identification of the site of material sampling. Unfortunately, core needle biopsy carries also a risk of false-negative results.

Material and Medods

At the Maria Skłodowska–Curie Memorial Cancer Center And Institute Of Oncology, Gliwice Branch, 988 core needle biopsies were performed between 01 March 2006 and 29 February 2008. The examined women were aged from 25 to 85 years (mean age of 55.1 years). They were qualified for core needle biopsy on the basis of mammography and ultrasonography.

Malignant lesions were found in 426/988 cases (43.12%), atypical ductal/lobular hyperplasia in 69/988 cases (6.98%) [in 13/69 cases of atypical hyperplasia (18.84%), cancer was diagnosed after tumorectomy], and benign lesions in 493/988 cases (49.90%).

Results of 22/988 biopsies (2.23%) which showed benign lesions were found to be false-negative because further diagnostic procedures performed within maximum 3 months revealed a malignancy at the site qualified for biopsy on the basis of mammographic or ultrasound results. Cases in which the biopsy revealed atypia and further diagnostic procedures showed cancer, were treated as underestimated positive results and excluded from the analysis of false-negative results.

The time from the moment of false-negative biopsy till the onset of cancer treatment ranged from 1 month to 4 months (3.2 months on average).

Stereotactic core needle biopsies were performed with the use of Lorad Multicare Platinum (Hologic) table. Depending on the type of lesion, a different biopsy gun was used: Magnum (Bard) for automatic biopsy with 14 G needle if the mammography showed mammography showed a suspicious density/module, or a vacuum-assisted core needle biopsy set, Vacora (Bard) with 10 G needle, in case of microcalcifications.

During procedure, X-rays were taken to: 1. locate the lesion (3 mammograms), 2. check the location of the needle in the lesion (2 mammograms), 3. monitor the lesion after sampling (2 mammograms), and in case of sampling of microcalcifications also to: 4. check the location of the marker that was left at the site of previous sampling (2 mammograms).

US-guided biopsy used a 13-MHz linear probe. Procedure was carried out with the use of automatic biopsy gun Magnum (Bard) with 14G needle.

A typical tissue section collected during vacuum-assisted biopsy weighed approx. 150–170 mg and was from 10 to 20 mm long. At least 12 and maximally 20 samples were collected. The section obtained with the automatic biopsy gun was much smaller, weighed about 20 mg and its length depended on the position of the gun – from 15 to 22 mm. At least four of them and maximally 12 such samples were collected (Table 1).

The collected material was fixed in a 10% buffered formalin solution and sent for microscopic evaluation.

Results

From among 988 biopsies, 22 (2.23%) were found false-negative. They were histopathologically reexamined. Serial sectioning of paraffin blocks was performed. The blocks included the sampled tissues. Next, primary and additional samples were assessed.

In 14/22 cases (64%), a previous histopathological diagnosis of benign lesion was changed:

- In 2/14 cases, cancer was found – Ca lobulare infiltrans, DCIS (previously, no cancer cells were found) and Papilloma intraductale.
- In 12/14 cases, atypia was found, with indications to remove the lesion.

Tabela 2. False-negative biopsy results caused by a radiological mistake.

Age	First symptoms	BI-RADS	ACR	Type of lesion	Size of lesion	Type of biopsy	First histopathological diagnosis	Diagnosis following repeated histopathological evaluation	Type of the next biopsy	Final histopathological diagnosis – cancer type	Time to treatment onset (months)
38	Orange peel skin	4	4	MC[a]	5 cm	Vacora mmg	Laesio fibrosocystica	Columnar cell changes (CCC). Mastitis	FNAB	Ductal	4
48	Nodule	6	3	A[b]	–	Magnum mmg	Laesio fibrosa	CCC. Fibrosclerosis. Fat necrosis with fibrosis	FNAB	Ductal	Treated
48	MMG without indications	5	4	D[c]+MC	4×3.5 cm	Magnum mmg	Scarce material: a few ducts, sclerosing stroma, fragment of muscle tissue	CCC. Muscle tissue	Vacora	DCIS	4
68	Screening	5	1	D	1.5 cm	Magnum mmg	Laesio fibrosocystica	CCH. CCC. Scarce material	Surgical	Ductal	3
55	Follow-up examination	3	1	D	0.8 cm	Magnum usg	Laesio fibrosa	FA. CCC.	Surgical	Ductal	3
61	Follow-up examination	5	2	D+MC	3 cm	Magnum mmg	Granulomatous mastitis	Granulomatous mastitis. MC	Magnum	Ductal following from inflammation	4
49	Presented with FNAB result	6	2	D	2×2 cm	Magnum mmg	Fibrosclerosis. Adenosis sclerosans	CCC. CCH. HD. Adenosis sclerosans. Fibrosis	Surgical	Ductal	Treated
74	Nodule	3	1	D	3.4×2.3 ×4 cm	Magnum usg	Fragments of adipose tissue without calcifications. Scarce material	Scarce material	Surgical	Ductal	1

[a] Microcalcifications; [b] asymmetry; [c] densification.

In 6/12 cases, flat epithelial atypia was diagnosed (primary diagnosis: adenosis (2 cases), fibrous lesion (1 case), fibrocystic lesion (1 case), fibrosclerosis (1 case), and inflammatory infiltrations (1 case)):

- In 2/12 cases – Atypical ductal hyperplasia (primarily: fibrous lesions and fibrous lesion).
- In 3/12 cases – Flat epithelial atypia and atypical ductal hyperplasia (primarily: Adenosis sclerosans in 2 cases and fibrous lesion in 1 case).
- In 1/12 case – Radial scar. Atypical apocrine metaplasia in adenosis (primarily: only adenosis sclerosans).

In 8/22 cases (36%), a repeated histopathological examination confirmed the primary result of no cancer cells in the sample or the presence of benign lesion (in 6 cases, columnar cell changes were found as well) (Table 2).

False-negative results constituted 2.2% of all biopsy results. As much as 36% of them resulted from the course of the radiological procedure, and 64% appeared during histopathological evaluation. False-negative results caused by a radiological failure constituted 0.8% of all biopsy results and 1.5% of histopathologically diagnosed cancers and atypias (sensitivity of 98.5%). In the analysed material, there were no false-positive results, and the specificity of the method amounted to 100% (Tables 3, 4).

Discussion

False-negative result of the core needle biopsy can lead to a delay in diagnosis and treatment of breast cancer [10–12]. In the analysed material, i.e. 988 biopsies, they constituted 2.23% (22 lesions).

After an additional histopathological evaluation, the diagnosis was changed in 64% of these patients (14/22) and remained unchanged in 8/22 patients (36%).

Thus, histopathological evaluation of the sampled material could not lead to a right diagnosis in 0.8% of all biopsies and 1.5% of histopathologically diagnosed cancers and atypias. This result falls in the range reported in the literature – rate of false-negative results ranges from 0% to 6% [6,7,8,11,13–19].

In the studied group of patients, it was striking that as much as 64% of false-negative results were obtained during histopathological evaluation, which was frequently considered

Tabela 3. False-negative results caused by radiological procedure, presented according to the biopsy system and the guidance used.

	Vacora (MMG)	Magnum (MMG)	Magnum (USS)
False-negative results	1 (12.5%)	5 (62.5%)	2 (25%)
False-negative results/number of procedures	1/326 (0.3%)	5/468 (1.07%)	2/194 (1.03%)
Sensitivity of the method	99.2%	97.9%	98.6%
	98.3%		

Tabela 4. Causes of radiological errors.

	Sampling at a wrong site (the lesion was not hit correctly)	Sampling at the correct site – histopathological heterogeneity of the lesion
Number of false-negative biopsies	7	1

to be unquestionable and definitive. These data confirm the significance of consensus between the radiological and histopathological results. In case of no conformity between the radiological image and histopathological results, it should be aimed to analyse the sampled material one more time, and then to repeat the radiological or surgical biopsy – this opinion is in accordance with opinions of other authors [8,11,12].

In our material, the highest sensitivity (99.2%) was found in case of stereotactic vacuum-assisted biopsy. When comparing core needle biopsies performed with an automatic gun, US-guided biopsy was found slightly more sensitive (98.6%). The sensitivity of stereotactic biopsy was 97.9%. In the studies by other authors, the sensitivity of vacuum-assisted biopsies was similar: in case of US-guided core needle biopsies, it was from 92% [20] to 100% [21], and in case of stereotactic biopsies – over 91% [11].

The radiological causes of false-negative results of core needle biopsies in the analysed material were divided into 2 groups:

I. Sampling of the material from a wrong site (the lesion was not hit correctly)

The most common causes include:

- Selection of a wrong imaging method guiding the course of the biopsy. Most of the sampled lesions are guided by US [11] which, in comparison to stereotactic guidance, shows many advantages, allowing for a better control of the sampling process [11]. US-guided biopsies are performed in real time [11]; they allow for a direct visualisation of the needle [11,12], the time of the procedure is shorter [11,12,22], the method is more comfortable for the patient [11,12,22], and does not expose the patient to ionising radiation [11,12]. In the analysed material, 3/8 of false-negative cases would probably be better monitored under US than under stereotactic guidance (due to the characteristics of the lesions).
- Choice of a wrong biopsy system. The precision of biopsies performed with automatic guns is lower for microcalcifications than for tumours [6,10,11,21]. It was probably the cause of one false-negative result.
- No monitoring of needle location in US-guided biopsies in the orthogonal position of the probe [12], disadvantageous location of the lesion (deeply, next to the chest wall [11,12]), poor visualisation of the lesion or needle [12] due to e.g. wrong contrast parameters, haematoma, local anaesthesia at the site of the lesion. In our material, these were the probable causes of 3 false-negative results.

II. Histopathological nonhomogeneity of the lesion

Breast cancer may include not only neoplastic cells but also regions of fibrosis, necrosis, typical and atypical intraductal or intralobular proliferations or inflammatory components. This histopathological heterogeneity of the lesion (coexistence of cancer and inflammation), despite collection of 10 sections, was the probable cause of one of our false-negative results. This problem was probably also the cause of underestimation of biopsy results (i.e. situation in which atypia was diagnosed, and then, intraoperatively, cancer was found). Cases in which atypia was found in the first or the second stage of histopathological evaluation, and then, intraoperatively, cancer was diagnosed, constituted 10.4% of all diagnosed cancers. Underestimation has also been reported by many authors [7,10,11,12]. It's frequency is close to 12.8% in stereotactic biopsies [12].

Conclusions

Histopathological interpretation is a significant cause of false-negative results of core needle biopsies of the breast. In case of divergence between radiological and histopathological findings, the material sampled during biopsy should be reanalysed.

The main radiological causes of false-negative results of core needle biopsy of the breast include sampling at a wrong site, and histological heterogeneity of the tumour.

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