



REVIEW PAPER

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Current principles underlying clinician and pathologist cooperation in pathological and genetic diagnostics in breast cancer patients in the times of personalised medicine

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ABSTRACT

Positive long-term treatment outcome in cancer patients depends mainly on the disease stage. It also depends on selection of an optimum therapeutic management. In breast cancer patients, the final treatment arrangements result, to a large extent, from a quality of cooperation of medical personnel providing cancer diagnostics and therapy. This requires knowledge of mutual expectations of doctors of different specialisations. The most common problems in interdisciplinary communication are relatively easy to notice in relations between a clinician (surgeon) and a pathologist. This paper discusses the most important aspects of that relationship.

Keywords: breast cancer, pathological diagnostics, genetic diagnostics, interdisciplinary communication.

Introduction

In breast cancer patients, a possibility to select an optimum treatment results, to a large extent, from a quality of cooperation of medical personnel providing diagnostics and therapy of neoplastic lesions in the breast gland. This also concerns full understanding of mutual expectations of doctors of different specialisations.

In patients, positive long-term treatment outcome significantly depends on a disease stage. It is also a result of a correct cancer treatment applied. Its final form is decisively influenced by a status of prognostic factors determined during a multidirectional pathological assessment (histopathological examination, immunohistochemical techniques, and molecular and genetic tests). According to classification of prognostic factors

determined to this date and used in breast cancer patients as proposed by The College of American Pathologists, they belong to one of three separate groups. The first group consists of factors of proven clinical value used in a standard way to establish a necessary treatment method for patients (including a size of a primary lesion, an axillary lymph node status, a cancer histological type and histological malignancy, and a status of oestrogen (ER) and progesterone (PgR) receptors). The second group includes factors which final prognostic value is a subject of current controlled clinical studies. The third group consists of markers currently not meeting criteria established for groups I and II [1].

As it was shown in conclusions to conducted studies, the initial classification of prognos-

tic factors became partly obsolete [2, 3]. The factors of the highest prognostic value (group I) also include a status of the human epidermal growth factor receptor 2 (HER2), a value of proliferation markers (mitotic activity index, Ki-67), and a biological type of breast cancer. Establishing the biological type of breast cancer requires determination and joint assessment of the status of ER, PgR and HER2 receptors together with the mitotic activity index, Ki-67. This way, the cancer type (luminal A, luminal B1-HER2 negative, luminal B2-HER2 positive, HER2-positive, and triple negative – basal-like) can be established unambiguously and decisions concerning planning of a required treatment scope and correct course are implied [4–12].

The tasks for pathological diagnostics for malignant breast cancer were precisely specified. Diagnostic categories for individual types of biological material were determined and introduced, to facilitate communication between different groups of specialists. The developed management standards were based on guidelines specified by scientific associations (a need to implement these standards also resulted from recommendations included in the European Commission guidelines). They concern both cytological tests, as well as pathological evaluation of tissue material (from a core needle biopsy of cancer lesions and from intraoperative samples).

The problems established in the title of this paper, concerning interdisciplinary communication, are relatively easy to notice in relations between a clinician (surgeon) and a pathologist. They may involve several interfaces of mutual communication:

- › clinician (surgeon) expectations at the disease diagnostic stage;
- › expectations associated with the treatment process (including the surgery);
- › expectations at a stage of establishing indications for more radical surgical treatment (also applies to qualification for auxiliary treatment procedures – local and systemic).

Cytological tests

It should be remembered that besides many clear advantages (low invasiveness, low cost, low difficulty of the test, and a short time of waiting for its results), the fine-needle aspiration is a diagnostic

method with numerous limitations [13, 14]. The most important of them are:

- › final disease diagnosis is not possible (concerns distinguishing between atypical ductal hyperplasias and ductal carcinomas, ductal carcinomas and invasive cancer, sarcoma and metaplastic cancer);
- › too high rate of incorrect diagnoses (an increased risk of a false negative result – when evaluating highly differentiated breast cancer, or a false positive result – when evaluating post-radiation lesions and cases of local recurrence).

The collected cell aspirate allows determination of the cancer lesion only on a basis of morphological parameters of individual cells (or their groups). To facilitate the multidisciplinary communication, diagnostic categories were introduced for obtained cytological material (from C1 – inadequate aspirate smear to C5 – malignant cell parameters) [14].

The cytological test allows final determination of the oestrogen and progesterone receptor status (a nuclear reaction using immunohistochemical techniques). However, this does not apply to reliable determination of the HER2 receptor status (a membrane reaction), particularly, when a negative test result is obtained (during fixing of the obtained biopsy specimen cell membranes can be damaged resulting in an incorrect reading). For correct evaluation of this prognostic factor, immunohistochemical determinations on histological material are recommended [14].

Histopathological examinations (core needle biopsy material)

The main source of problems in relations of a clinician and a pathologist is a possibility that material was collected from a fragment of the studied mass that has not been not fully representative. In the event of inconsistencies between the obtained results and a radiological image of the mass (particularly, when radiological diagnostic of malignant neoplasm is possible), the biopsy must be repeated.

In accordance with the clinician's expectations, a histopathological evaluation of specimens allows determination of the mass nature (primary lesion, mass of a metastatic origin),

forms (invasive, in situ), and a histopathological type of the cancer. This also applies to determination of the cancer histological malignancy grade and receptor tests (to evaluate prognostic and predictive factors). However, this way the size of the lesion and its surgical margins cannot be determined [15–17].

Analogically to the system of diagnostic categories specified above, and used to describe the cytological tests, similar rules apply to verification of material obtained in the core needle biopsy. Introduced categories of lesions include diagnoses coded with symbols starting with B1 (denominating presence of the normal tissue) to B5 (diagnosed malignant lesion, with its type specified, marked with a–d) [15].

Histopathological examination (post-surgery specimens)

Of main issues concerning interdisciplinary communication in this area, limitations associated with the intraoperative examination must be mentioned. Furthermore, a need for ordering histopathological evaluation of tissue specimens in this mode is also an issue. For detailed discussion, these issues need to be analysed, taking into account specific characteristics of each histopathological presentation of malignant lesions in the breast gland:

1. Invasive breast cancer forms:

- an ad hoc test allows an evaluation of margins for mass resection; however, for multiple lesions (particularly, in a presence of additional cancer microfoci), it may be of limited value;
- in a selected group of patients with macrometastatic lesions present in the sentinel node (in accordance with the inclusion criteria for the study ACOSOG Z0011) [18], conservative treatment can be selected (auxiliary axillary lymph node dissection is not necessary); therefore, in such cases, it is justified not to perform the routine ad hoc evaluation of lymph nodes sampled during the surgery [19, 20];
- it should be remembered that the ad hoc examination of the sentinel node reduces the amount of tissue material to be used for routine tests (this applies, of course, to all cases when intraoperative tests are used);

- data that the clinician expects to be provided in the pathological examination report from evaluation of material collected during biopsy of the sentinel node includes information on the total number of nodes resected, number of nodes with metastases and sizes of these lesions (macrometastasis, micrometastasis, isolated tumour cells, with dimensions of the largest metastasis specified); the presence and type of the node capsule infiltration must also be specified (focal or massive infiltration) together with information on test methods used (routine tests, serial sectioning, use of immunohistochemical reactions or molecular methods) [14];
- cancer treatment failure (in form of a local recurrence or metastatic lesions) may concur with a conversion in a status of initially determined receptors; thus in the event of the above-mentioned recurrence, reassessment of ER, PgR and HER2 is required, it is also recommended following neoadjuvant therapy [21, 22].

2. Pre-invasive cancer – ductal carcinoma in situ (DCIS):

- concerning the common DCIS presentation in form of multiple lesions, lack of palpable lesions, as well as a frequently found characteristic mammographic picture (groups of suspected microcalcifications without accompanying “mass” symptoms), intraoperative pathological verification of the specimen is not recommended; for reasons described above, the result of ad hoc histopathological evaluation is frequently unreliable, this concerns, in particular, difficulties in assessment of the resection margins, as well as significant problems with diagnosing microinvasion foci [23, 24];
- as it was noted, DCIS lesions are characterised by a possibility to develop in one of two separate differentiation directions (low-risk DCIS – indolent disease vs. high-risk DCIS – “*extensive pure ductal carcinoma in situ*”); thus, a very important expectation of a clinician is a precise determination of the mass type by a pathologist (diagnosis of cancer of the second type requires surgical procedures used for treatment of invasive breast cancer) [25];

- a detailed pathological report allows making a decision whether a patient with DCIS should be qualified for a surgical verification of the regional lymph node drainage (a biopsy of the sentinel node); the so-called “poor prognostic factors” concerning a risk of coexistence of in situ and invasive forms of cancer, on a basis of data included in the description of the histopathological result, the high histological malignancy grade, multifocal nature, significant size, presence of necrosis (*comedonecrosis*), and steroid resistance can be confirmed (or excluded) [23, 24].
3. Pre-invasive cancer – lobular carcinoma in situ (LCIS):
- similarly as for DCIS-type lesions, the pathologist must specify a histopathological type of LCIS (analogically to DCIS masses, they are characterised by a different course of the disease, thus they require planning and implementation of a different treatment type); the histopathological evaluation should determine a presence of the classic LCIS type (with a minimum risk for co-existence of other breast cancer forms) or of any other type of this cancer (a *comedo* type with necrosis, *florid* LCIS, or a pleomorphic type) requiring radical resection of the diagnosed lesion [26, 27];
 - the histopathological LCIS type diagnosed also determines further management in the event of non-radical resection of the mass that underwent a surgical biopsy (the classic form does not require a radical operation) [28, 29];
 - contrary to breast cancer types described above, a diagnosis of isolated LCIS lesions does not require patients to undergo surgical procedures involving the axillary lymph nodes [26–29].

Molecular tests, genetic diagnostics

Regardless of the valid determination of the “classic” prognostic and predictive factors, increasingly often patients with breast tumours undergo tests of gene expression patterns. The breast cancer molecular signatures obtained this way allow to determine a likelihood of the disease recurrence and benefits of chemotherapy in spe-

cific clinical cases [30–39]. This concerns, in particular, patients in whom a need for this form of the systemic treatment was excluded following the “standard” assessment of the cancer type. In accordance with reported data, use of the Oncotype DX test may change qualification for chemotherapy or hormone therapy in about 30 % of patients evaluated with this validator [30, 31, 34, 35]. Use of the gene expression test (a consensus of the expert panel at the St. Gallen conference, Vienna 2017) is not justified solely in breast cancer of a low clinical risk. This concerns, in particular, patients with a tumour of pT1a/b size, of a low histological malignancy grade (G1), with a simultaneous high expression of ER receptors and no metastatic lesions in lymph nodes (pN0) [4].

As it was proven in the results of randomised clinical studies (including MINDACT [40], NSABP B-14 [41], NSABP B-20 [41], TransATAC [42], SWOG 8814 [42], TAILORx, and RxPONDER [43]), analysing usefulness of most commonly used multi-gene tests (MammaPrint 70-gene test, Oncotype DX 21-gene test), their use provides additional information about the disease, they are a valuable supplement of data obtained by evaluation of “classic” clinical and histopathological factors. A main obstacle for a general use of tests determining the expression levels for selected gene panels in breast cancer is their high price (ca. EUR 3–4 thousand).

Of the tests determining a status of single genes, the test for mutation of BRCA1 and BRCA2 genes still remains an irreplaceable diagnostic standard, in particular, for members of families with an increased rate of breast cancer occurrence [4, 44, 45]. It should be remembered that when a person is found to be a carrier of a clinically significant mutation of BRCA1 gene (mainly founding mutations and recurring mutations), the risk of them having the breast cancer is 56–84%. Of all mutations in the BRCA1 gene found so far, the most commonly determined in the Polish population (of clinical significance) are genome changes of 85delAG (ex2), 300T > G (ex5), 3819del5 i 4153delA (ex11), and 5382insC (ex20) type [46]. Its diagnosing in the breast cancer patient is also more frequently associated with a presence of disease with poorer prognosis (triple negative cancer) [47].

Other genetic anomalies predisposing to breast cancer development are mutations involving genes TP53, PTEN, ATM, BRIP1, CHEK2, and

PALB2 [48–50]. A need to determine their presence has a clinical importance comparable to cases of other malignant neoplasms [51, 52].

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Conflict of interest statement

The authors declare no conflict of interest.

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