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THE ROLE OF THE PATHOLOGIST IN THE INDIVIDUALISATION OF THERAPY IN PATIENTS WITH BREAST CANCER

Božena Šarčević

Department of Pathology, University Hospital for Tumours,
„Sestre milosrdnice“ University Hospital Center,
Zagreb, Croatia

Summary

The diagnosis and treatment of breast cancer has rapidly evolved over the past 20 years. Starting in the 1980s, there have been important alterations in the diagnosis and treatment of breast cancer, having an important impact on the diagnostic procedure employed by pathologists. Numerous studies in recent years have identified many prognostic and predictive factors for breast cancer. Most of them have been determined pathohistologically, which resulted in a large responsibility for pathologists, therefore the pathologist has become a key person in a multidisciplinaty team of breast cancer and the person very responsible for the implementation of specific individual therapy.

Keywords: breast cancer; pathologist; personalised therapy.

Breast cancer is the most common cancer among women in both developing and developed regions in the world. Clinical cancer develops over a long period of time, requires multiple molecular alterations, and involves evolution of cellular populations with increasingly aggressive phenotypic characteristics [1]. Although the time required for the process of carcinogenesis is not well established for any human cancer, estimate suggest that this multistep process unfolds over many years and possibly several decades. Breast cancer represents a diverse collection of malignant diseases of the breast with highly variable clinical behaviors and disparate response to therapy [2].

Personalised oncology is evidence-based, individualised medicine that delivers the right care to the right cancer patient at the right time and results in measurable improvements in outcomes and a reduction on health care costs. The essence of personalised oncology lies in the use of biomarkers. The biomarkers can be from tissue, serum,urin or imaging and must be validated. Also, their have different importances: predictive, prognostic and early response biomarkers.

The diagnosis and treatment of breast cancer has rapidly evolved over the past 20 years. In the first part of the 20th century, treatment of breast cancer consisted of radical mastectomy, but adjuvant systemic treatment and adjuvant radiotherapy did not play a major role. Diagnosis of breast cancer was mostly made based on clinical presentation, later aided by mammography and often combined with frozen section pathology confirmation. Starting in the 1980s, there have been important alterations in the diagnosis and treatment of breast cancer, having an important impact on the diagnostic procedure employed by pathologists.

Histopathological features play an important role in guiding the treatment decisions. In addition, genetic research is starting to have an increasing impact on guiding therapy by providing prognostic and predictive factors [3].

To obtain optimal morphology in the histology sections, and to obtain optimal immunohistochemical staining results, the resection specimen should be cut into thin slices immediately after surgery.

For microscopic examination the pathologist should be obtained and processed for paraffin sections full diameter of the tumour and its surroundings, small part of the tumour to perform immunohistochemistry, if there are macroscopical or radiological abnormalities in the tissue surrounding the invasive tumour, these areas should be sampled. If the surrounding tissue is without abnormalities, it is necessary to take at least two sections from macroscopically normal breast tissue.

On slides stained with hematoxylin eosin (H.E.), pathologist must determine the prognostic and predictive factors for breast cancer. This includes the histological type of cancer [4], the degree of tumour differentiation [5], mitotic counts, lymphovascular invasion, estrogen and progesterone receptors [6], protein HER-2 [7] and proliferative index Ki-67 [8].

Receptors are determined by immunohistochemistry and the results are expressed as the percentage of positive cells and intensity of staining. Stai-

ning for estrogen and progesterone receptor is allways nuclear in localization and in most institutes all patients with a tumour in which more than 10% or more 1% of the tumour cells show positive staining regardless of the intensity of staining are candidates for adjuvant hormonal therapy. According to the consensus of the St Gallen 2014. cut-off of the progesterone receptors is 20%. This value best separating luminal type A from luminal type B breast cancer. Values below 20% indicate that the progesterone receptors are negative or low [9]. When negative staining for estrogen and/or progestrone receptor is seen, it is important to confirm that staining of the hormone receptor-negative case has been successful. This can usually be tested, since the majority of normal breast tissues contain some nuclei ducts and lobules that are positive for estrogen and progesterone receptor. If no normal breast epithelial cells are found to show positive staining, the hormone receptor assays should be repeated on another tumour block.

HER-2 gene amplification is observed in 15-30% of invasive breast cancers and leads to HER-2 receptor overexpression. HER-2 positive invasive breast cancers respond favourable to therapies that specifically target the HER-2 protein, therefore it is very important today to identify candidates for this type of targeted therapy. Several technologies are available for determining HER-2 status, but the two most commonly used are immunohistochemistry [IHC], which measures HER-2 protein expression and CISH [chromogen in situ hybridisation] which detects HER-2 gene amplification a method that is often used today in the pathology than FISH (fluorescence in situ hybridisation). The interpretation of the results is based on the intensity and percentage of stained cells. The most commonly used score system is 0, 1+ (negative results) , 2+ and 3+ (positive results). A 2+ is considered equivocal and should be followed by retesting by CISH. Women with IHC 3+ tumours are candidates for therapy with trastuzumab, but women with 2+ tumour should be retested and if the results show amplification of gene of those are candidates for trastuzumab. To ensure the highest possible accuracy, pathology centers must standardise methodologies and testing procedures.

Proliferative index is also very important and is determined by immunohistochemistry by monoclonal antibody Ki-67. Positive reaction is nuclear reaction and are counted positive nuclei in 1000 tumour cells on the high magnification and the results obtained is expressed as a percentage of positive nuclei. According to St Gallen consensus cut of value is 20% of positive

cells, which means that below this value is low and value above 20% is high proliferative indeks [9].

Based on the receptors, HER-2 status and proliferative index breast cancers are classified immunophenotypically into five subgroups: luminal type A, luminal type B HER-2 negative, luminal type B Her-2 positive, HER-2 positive (non-luminal type) and triple negative tumours. Based on the immunophenotype of the cancer patients receive appropriate therapy. The multigene testing remains inaccesible for the majority of women with early breast cancer, therefore is adopted clinico-pathological testing, now expressed in surrogate IHC-based classification.

Numerous studies in recent years have identified many prognostic and predictive factors for breast cancer. Most of them determined pathohistologically, which resulted in a large responsibility for pathologists. In addition, the pathologist has become a key person in a multidisciplinaty team of breast cancer and the person very responsible for the implementation of specific individual therapy.

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Sažetak

Uloga patologa u individualiziranoj terapiji bolesnica s karcinomom dojke

Unazad 20 godina dijagnostika i liječenje karcinoma dojke snažno je napredovalo. Počevši od 1980. godine kada su počele biti važne promjene u dijagnostici i liječenju karcinoma dojke, sve je to utjecalo na dijagnostički postupak i rad patologa. Brojna novija istraživanja utvrdila su većinu prognostičkih i prediktivnih čimbenika za karcinom dojke. Većina njih određuje se patohistološki a što je u konačnici rezultiralo velikom odgovornošću patologa koji je postao ključna osoba u multidisciplinarnom timu za karcinom dojke i vrlo odgovorna osoba za primjenu specifične individualizirane terapije.

Ključne riječi: karcinom dojke; patolog; personalizirana terapija.

Corresponding author:
Božena Šarčević
E-mail: bozena.sarcevic@kbcsm.hr