Trakia Journal of Sciences, Vol. 12, Suppl. 1, pp 282-285, 2014

Available online at:
http://www.uni-sz.bg

ISSN 1313-7050 (print)
ISSN 1313-3551 (online)

HISTOPATHOLOGICAL CRITERIA OF BREAST CANCER

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ABSTRACT
Breast cancer (BC) is a heterogeneous disease, presenting with specific clinical, morphological, biological characteristics. Currently, the diagnosis and treatment of patients with BC are determined by standard clinical and morphological criteria: age, tumor size, grade and the expression of different biomarkers. (estrogen, progesterone and HER-2).
Additional difficulty arises after the differentiation of 18 histological types of invasive BC by the World Health Organization, which defined the application of immunohistochemical based surrogate panel in the clinical practice, helping in the determination of the therapeutic strategy.

Key words: Breast cancer; histopathological criteria, surgical treatment

Apart diagnostic imaging, clinical evaluation requires a preliminary histological verification of the tumour with concomitant assessment of axillary lymph nodes' status. In a number of cases, these clinical approaches precede the surgical intervention.

The consequent histological result from the core needle or excision biopsy should detect the presence of an invasive component and immunohistochemical clinically relevant biomarkers: expression of oestrogen and progesterone receptor, the HER-2 status of the tumour and proliferation (for example Ki67).

Additional examinations as abdominal ultrasound or computed tomography (CT) and bone scan should be applied and deemed necessary in patients with positive axillary lymph nodes or larger tumours (i.e. $\geq$ 5 cm of size), or when clinical signs, symptoms or laboratory parameters indicate possible metastases.

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Dual imaging combining functional and anatomical information as fluorodeoxyglucose positron emission tomography (FDG-PET)/CT could be useful when conventional methods are not convincing. Locoregional disease does not require FDG-PET/CT due to its low specificity in comparison with standard methods (1)

Pathological diagnostics should be performed with specimens obtained by core needle biopsy unlike fine-needle biopsy whose informative value is not sufficient for mammary localisations but is good enough when a positive axilla is suspected. Thus, the diagnosis of the disease is made via biopsy and the latter assists the clinical evaluation. The analysis of these parameters should be based on the 2012 WHO classification (2)

The conclusion of the pathologist should include histological type, differentiation, immunohistochemistry for oestrogen receptors using the standard method (e.g. Allred or H-score), testing for progesterone receptors, HER 2 receptors, HER 2 gene amplification – via in situ hybridization methods. (3) Markers such as Ki67 could provide additional information, especially when the analysis is standardized (4, 5) Their evaluation should be done post operatively on the surgical specimen, if a primary systemic therapy is not intended (6)

In case of tumours with negative results for ER/PgR and HER2 from the biopsy, the tests should be repeated on the surgical specimen in order to assess the heterogeneity of the tumour. (7)

For outcome prediction and therapy planning, cancers are divided into surrogate groups on the basis of histological and immunohistochemical examinations. (8In early breast cancer, routine staging is targeted at locoregional changes taking into consideration that distant metastases are very rare and not assessed as clinically positive from tumour markers assays.(9)

Post operative evaluation of tumour features of the surgical specimen should comply with TNM and is described as pTNM. Compulsory parameters include number, localisation, maximum healthy tissue diameter at tumour excision, maximum number of examined lymph nodes, number of positive lymph nodes, and metastatic involvement - isolated cancer cells, micrometastases (0.2-2 mm). The histological type, differentiation, resection margins assessment, lymphovascular invasion should be performed. The most important predictors in early-stage breast cancer are the ER/PgR and HER2 expression, number of the positive lymph nodes, tumour histological type, size, presence of peritumour vascular invasion.

Thus for instance, when organ sparing surgery for breast cancer is performed, the ipsilateral recurrence is determined by the resection margins status and the presence of extensive intraductal component. Clinical parameters (age, tumour stage, oestrogen expression and differentiation) have been integrated in scoring systems allowing for evaluation of recurrence probability and the odds for fatal outcome in breast cancer patients. Such systems are the Nottingham Prognostic Index (NPI) or the PREDICT score (10, 11, 12) Gene expression profiles such as MammaPrint® (Agendia, Amsterdam, the Netherlands) or Oncotype DX® Recurrence Score (Genomic Health, Redwood City, USA) could also be useful as predictors, completing the pathological evaluation and providing a prognosis to the adjuvant therapy. This is especially valid for ER-negative patients, positive early-stage breast cancer, but their real clinical relevance is still evaluated inn large-scale randomized studies like MINDACT, TAILORx and RxPONDER .

Subtype	Clinicopathological features	Notes
Luminal A	**'Luminal A-like'** • ER-positive • HER2-negative • Ki67 low* • PgR high**	Threshold values for Ki67 vary between laboratories
Luminal B	**'Luminal B-like (HER2- negative)'** • ER-positive • HER2-negative • and either • Ki67 high or • PgR low	
	'Luminal B-like (HER2- positive)' • ER-positive • HER2-positive • any Ki67 • any PgR	
HER2 overexpression	**'HER2-positive (nonluminal)'** • HER2-positive • ER and PgR absent	
Basal-like	**'Triple-negative (ductal)'** • ER and PgR absent • HER2-negative	There is a ~ 80% overlap between "triple-negative" and Basal-like types, but the triple-negative one includes also some special histological types as (typical) medullary type and adenoid cystic carcinoma, which are at lower risk for distant metastasis

Surrogate endpoints of breast cancer subtypes according to the 2013 St Gallen International Expert Consensus and the ESMO clinical practice guidelines (13)

Subtype Luminal A. Present in more than 50% of subtypes. More frequent in lobular neoplasms – all in situ and most invasive lobular carcinomas. Highly differentiated invasive ductal carcinoma of tubular and cribriform histological types also belong to this subtype. The prognosis is good (14, 15)

Subtype Luminal B. Its prevalence is between 10% and 20%, has a more aggressive clinical course and poorer prognosis than Luminal A. Histologically, it is presented with lower grade of differentiation (G2, G3) and a high proliferative index, This subtype could be manifested with overexpression of HER-2 as well, and up to 6% of cases could possess ER/HER-2 – negative phenotype (15). The differentiation of the two molecular subtypes is not completely defined especially when the lack of a precise standard for immunohistochemical detection of Ki-67 is considered (16).

Subtype HER2 positive. Histologically, these are mainly moderate- to low-differentiated invasive ductal carcinomas (G2, G3) with focal tumour necroses and overexpression of HER-2 (ICC 3+ and/or detected HER-2 gene amplification via in situ hybridization) with negative hormonal receptors.

Subtype Basal-like. Its incidence is between 10% and 20%. This group is determined on the basis of genetic and ICC features. Develop at an younger age as rapidly growing tumours and at the time of diagnosis are presented with large tumour volume and high frequency of regional lymph node metastases. Morphologically, invasive ductal carcinomas with high mitotic index and low differentiation grade (G3) are predominating (15, 17)The prognosis is very guarded regardless of the initial good response to chemotherapy. Metastases are visceral and affect mainly the lungs and the central nervous system. Immunohistochemically, expression of high-molecular cytokeratins (CK5 and CK6), P-cadherin, nestin, CD44 and EGFR is detected. The group is identified through six primary markers: ER, PgR, HER-2, EGFR, CK5 and CK6. These markers define 100% specificity and 76% sensitivity (18, 19).

At present ER/PgR and HER2 are determined as predictors of patients eligible for endocrine therapies (CTE) and anti-HER2 treatment. The strong ER expression is usually associated with lower absolute efficacy of chemotherapy.

After neoadjuvant therapy, the tumour response and the residual disease are important predictors. There is need to standardise clinical practice.

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