Guidelines

Pathological examination of breast cancer samples before and after neoadjuvant therapy: recommendations from the Italian Group for the Study of Breast Pathology - Italian Society of Pathology (GIPaM-SIAPeC)

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Summary

Neoadjuvant therapy (NAT) in breast cancer is administered to downstage the tumor, de-escalate surgery, and provide prognostic information that can be used to tailor subsequent adjuvant therapy. In this respect, the pathological evaluation of both pre-NAT biopsies and post-NAT surgical specimens is crucial to precisely assess the treatment response. With the increasing possibilities of NAT protocols and the rising number of eligible patients, it has become extremely important to standardize the pathological response assessment. Here, we provide an update on the recommendations of the Italian Group for the Study of Breast Pathology - the Italian Society of Pathology (GIPaM-SIAPeC) for the analysis of breast cancer samples before and after NAT.

Key words: breast cancer, neoadjuvant therapy, biomarkers, pathological response

Premise

Neoadjuvant therapy (NAT) consists of the administration of drugs and/or radiation before the surgical treatment of the tumor [1]. This therapeutic approach plays a key role in the clinical management of early or locally advanced breast cancers with unfavorable prognostic factors [2-6]. For these patients, the main purposes of NAT are represented by: i) reduction of tumor burden, thus allowing for surgery (in previously inoperable tumors) or surgery de-escalation, including breast-conserving surgery (BCS) and to avoid axillary dissection; and ii) detection of prognostic information to tailor subsequent adjuvant treatment [2-11].
Up to 40% of breast cancer patients achieve a pathological complete response, i.e. lack of breast cancer in surgical samples removed after NAT [12]. It is important to precisely quantify this parameter because dif-

ferent tumor(s) may respond differently to the same treatment [13,14]. The pathological evaluation of pre-NAT biopsies and post-NAT surgical samples is the gold standard procedure to assess treatment response [15,16]. In this respect, pathological complete response is associated with an improved prognosis; on the other hand, the characteristics of residual tumor deposits have a significant impact on subsequent treatment and ultimately on disease-free survival.

The evaluation of pathological response is an essential phase in clinical management of patients with breast cancer treated with NAT. The role of the pathologist starts with histopathological analysis of tumor biopsies along with biomarkers testing in potentially eligible patients and continues with assessment and characterization of pathological response and biomarkers status on the surgical sample after NAT.

Pathological evaluation before neoadjuvant therapy

Goal: To define the histological and biological characteristics of the tumor, allowing for establishment of the appropriate treatment protocol (Fig. 1).

CHECK-IN OF THE BIOPSY SAMPLES AND MACROSCOPIC EXAMINATION

The check-in criteria, as well as the methods for the macroscopic examination of pre-NAT biopsies, are the same as those for standard breast biopsies, as defined by standard operating procedures (SOPs) [17-20].

A crucial point is represented by the information provided in the request form for the pathology laboratory. Here, the clinician should clearly state that the patient is potentially eligible for NAT.

Specific information on the neoplasm(s) should also be reported:

1   localization (by imaging support, if possible);
2   size (two dimensions) and number of neoplastic foci;
3   presence of microcalcifications;
4   the number of tissue cores taken (it is desirable to take at least 2 cores per cm of tumor for a maximum of 6 total cores).

HISTOLOGICAL EXAMINATION

The histological analysis of pre-NAT biopsies should provide all the information to tailor treatment.
Therefore, the pathology report should include:

1   histological type according to the latest WHO Classification of Breast Tumors [21,22];
2   nuclear grade or grading according to the Notting-

ham Grading System [23];
3   presence of ductal in situ carcinoma (DCIS);
4   the B-classification for histopathological categorization according to EUSOMA, European Society of Breast Cancer Specialists [24];
5   estrogen receptor (ER), progesterone receptor (PgR), Ki67, and HER2 status [25].
6   additional useful information can be provided:
7   presence and percentage of tumor-infiltrating lymphocytes (TILs), particularly in HER2+ and triple-negative breast cancer (TNBC);
8   tumor cellularity;
9   presence of lymph-vascular invasion (LVI);
10 presence of tumor necrosis;
11 characteristics of the DCIS (e.g. pattern, nuclear grade).

Pathological evaluation after neoadjuvant therapy

Goal: To define the presence and degree of pathological response along with the biological characteristics of any residual tumor (Fig. 1).

CHECK-IN OF THE SURGICAL SAMPLES

The check-in criteria are the same as those for standard surgical samples, as defined by SOPs [17-19].
In the request form for the pathology laboratory, the clinician should report specific data:

1   NAT protocol adopted;
2   clinical staging before and after the treatment;
3   pre-NAT diagnosis and biomarkers status;
4   size and location of any residual lesion and/or presence of metastatic lymph nodes;
5   location and type of marks on the tumor (i.e. surgical clips, charcoal, gel);
6   presence of microcalcifications;
7   orientation of the surgical sample.

MACROSCOPIC EXAMINATION

Breast samples

The surgical material should be managed according to ministerial guidelines regarding the traceability, collection, transport, and storage of cells and tissues for diagnostic investigations of Pathological Anatomy Laboratories [18,26-28]. In particular, the cold ischemic time (i.e. time from the post-surgical tissue cooling for storage/transportation to the start of formalin fixation of the specimen) and formalin fixation should be monitored. The macroscopic examination and sampling should be carried out only after the consistency has been double-checked, following SOPs. It is essential to macroscopi-
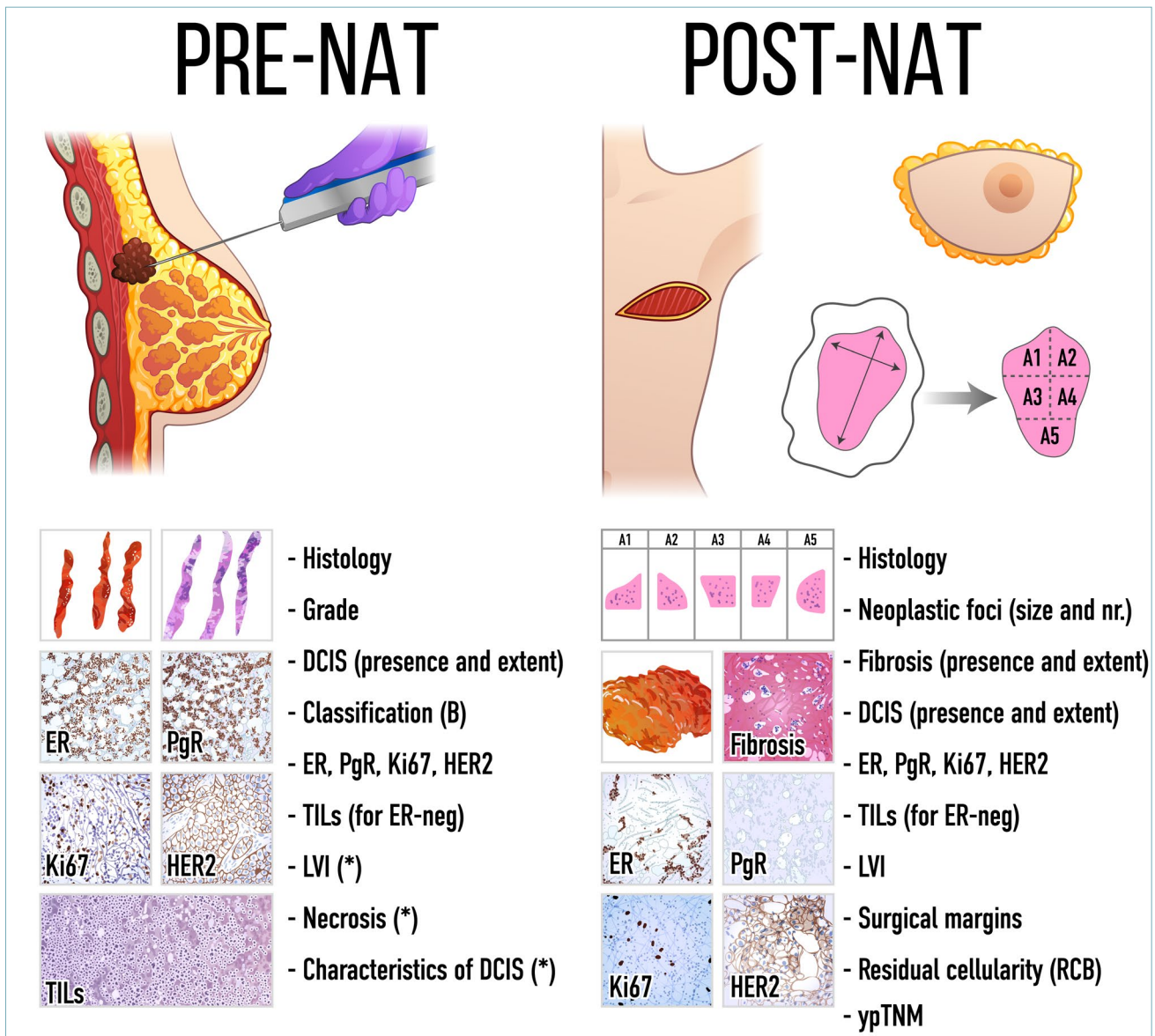
Figure 1. Schematic representation of the different tasks for the pathological handling of pre- and post-NAT breast cancer samples. NAT, neoadjuvant therapy; DCIS, ductal carcinoma in situ; ER, estrogen receptor; PgR, progesterone receptor; TILs, tumor-infiltrating lymphocytes; neg, negative; LVI, lymphovascular invasion.

cally identify and describe the extension of the tumor bed and possibly the number of any residual neoplastic foci [15,29]. X-ray of the surgical specimen may be of help because tumor microcalcifications are not eliminated by chemotherapy [30]. It is advisable to carry out sampling with the help of radiograms and/or pre-and post-therapy magnetic resonance imaging (MRI) data. The residual disease may macroscopically appear as a nodular sclerotic area or as multiple foci within an edematous and/or sclerotic area. All lesions should be described, mapped, measured, and sampled; if the sur-

gical sample is small, it should be wholly included and analyzed. The identification of the tumor bed and the evaluation of its extent might be challenging, appearing as an area with poorly defined contours, of generally decreased consistency, centrally of edematous and / or fibrous appearance [31]. Extensive sampling and mapping of the area are required, using standard sections or macro-sections, providing a correlation with imaging features, and recording the topography of the samples within the tumor bed [29,32]. In case the tumor bed has not been completely analyzed after initial examination,

it is recommended to carry out additional sampling [12,33]. In the case of BCS, the surgical margins should be carefully examined and sampled. If present, the nipple-areola complex should always be examined. For cT4b tumors, the skin should be analyzed and included (with multiple samples for cT4b).

Axillary lymph nodes

Axillary lymph nodes (ALN) may develop NAT-induced alterations, with possible numerical reduction and/or fibrotic involution [34]. For this analysis, it is recommended to follow SOPs [35-37]. The eventual presence of marks on pre-NAT pathologic lymph nodes in case of targeted axillary dissection (TAD) should be reported by the clinician in the request form for the pathology laboratory [34]. This procedure consists of the selective localization and removal of marked nodes [38].

SENTINEL LYMPH NODE

The sentinel lymph node(s) (SLN) procedure after NAT is standard practice, irrespective of the clinical status of the lymph nodes [14,39,40]. It should be noted, however, that the rate of false-negative results is significant, ranging from 5% to 16% using double and single marking of the nodes, respectively [41]. For this reason, it is advised to examine the SLN on formalin-fixed paraffin-embedded (FFPE) samples [42]. Molecular examination using the One-Step Nucleic Acid Amplification (OSNA) method is not recommended because this assay is not designed to identify minimal lymph node involvement and does not give any information on histology [43,44]. Data regarding presence and type of residual disease (e.g. macrometastasis, micrometastasis, isolated tumor cells), presence and extent of extranodal extension of the metastasis, presence, and extent of fibrosis should be provided in the report because they are relevant for the evaluation of the pathological response according to different classification systems [45-48].

HISTOLOGICAL EXAMINATION

Breast samples

On microscopic examination, the tumor bed may present as an area of vascularized hyalinization, with deposits of foamy macrophages, lymphocytes, and hemosiderin-laden macrophages, in absence of normal ductal and lobular structures. Edema, necrosis, and calcifications may be present. In cases of complete absence of pathological response, the report is made following the standard recommendations for non-NAT samples.

In cases of partial pathological response, the pathology report should include:

1 histological type;
2 size and possibly the number of residual cancer foci;
3 presence of fibrosis;
4 presence of LVI, which might be the only residual disease in some cases;
5 presence, extent, and features of any DCIS component;
6 status of the surgical margins;
7 pathological staging according to the most recent TNM edition;
8 residual tumor cellularity according to different classification systems [45-48];
9 pathologic staging according to the latest TNM edition.

Re-testing of ER, PgR, Ki-67, and HER2 status is recommended in case of TNBC or an equivocal result on pre-NAT core biopsy, pre-NAT biopsy performed in another Institution, heterogeneous tumor, or multiple tumors with different morphology, and absence of pathological response. Additional useful information includes TILs in HER2+ or TNBC, presence of perineural invasion, and grade. In particular, cytotoxic therapy can induce cellular and nuclear atypia; therefore, assessment of post-NAT tumor grade can be performed only if pretreatment biopsy samples are available for comparison [49].

In cases of pathological complete response, the pathology report should include:

1 presence and amount of fibrosis;
2 presence and features of any DCIS component;
3 status of the surgical margins;
4 pathologic staging according to the latest TNM edition.

Axillary lymph nodes

In lymph nodes, regression areas occur with fibrosis in which foamy macrophages and/or hemosiderin-laden macrophages may be present [44,50-52]. Immunohistochemical staining for cytokeratins might help the identification of any residual lymph node disease. The following information should be reported:

1 the number of lymph nodes examined;
2 the number of lymph nodes with residual disease and extent of residual disease (e.g. macrometastases, micrometastases, isolated tumor cells);
3 the presence and the extent of extracapsular invasion;
4 the presence of lymph nodes with fibrosis in the absence of residual disease;
5 pathologic staging according to the latest TNM edition.

Final remarks

With the steady increase in the number of patients eligible for NAT, it is more and more important to harmonize how tumor response is assessed by pathologists [15,16]. Macroscopic evaluation of surgical samples in the post-NAT setting, the extent of sampling for histology, and microscopic examination require a different approach compared to that after primary surgery. Pathologists must be fully aware of the recommended procedures for an accurate assessment of tumor response to NAT, including the evaluation of all the relevant parameters that correlate with long-term prognosis and inform the subsequent adjuvant interventions. Another important aspect that warrants particular attention is the role of BCS in these patients [4,53,54]. Indeed, this approach leads not only better overall prognosis, but also to improvement of the esthetic result, reduction of psychological burden, lower incidence of post-surgical complications, reduction in time of execution of the intervention (and anesthesia), cost-effectiveness for the National Health System, and ultimately improving the health-related quality of life of breast cancer survivors [7,8,55-59]. In the NAT setting, close collaboration of pathologists, oncologists, surgeons, and radiologists within the multidisciplinary team is essential to ensure the best possible management of breast cancer patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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