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Pathology after neoadjuvant treatment – How to assess residual disease☆

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ABSTRACT

While systemic therapy for non-metastatic, invasive breast cancer is provided to minimize the risk of recurrence, neoadjuvant therapy (NAT) is given prior to surgery to downstage the tumor and to evaluate treatment response. Downstaging the tumor may allow for less invasive surgery on the breast and axilla, thus avoiding the need for breast reconstruction, improving cosmetic outcomes, and reducing post-operative complications. With the rising number of NAT candidates, it is becoming increasingly important to standardize how tumor response is assessed after surgery. In the post-NAT setting, macroscopic assessment of surgical samples, extent of sampling for histology, and microscopic analysis require a different approach than in the primary surgery setting. In the neo-adjuvant setting, the close collaboration of pathologists, oncologists, surgeons, and radiologists within the multidisciplinary team is essential to ensure the best possible management of breast cancer patients. Here, we provide an update on the suggested procedures for an accurate assessment of tumor response to NAT, including the evaluation of all relevant parameters that correlate with long-term prognosis and inform the subsequent adjuvant interventions.

1. Introduction

Neoadjuvant therapy (NAT) is an important tool for the treatment of selected patients with breast cancer and it aims at making operable patients with locally advanced disease, shrinking early-stage tumors -thus allowing for breast-conserving surgery (BCS)-, reducing the extent of axillary surgery, providing supplemental prognostic information based on the pathological response, and evaluating the residual tumor burden to inform the subsequent adjuvant therapy [1–5]. Patients who respond well to NAT have a lower risk of distant recurrence and better outcomes in terms of both disease-free survival (DFS) and overall survival (OS) [6,7]. Other advantages of de-escalating surgery include better aesthetic, functional, and psychosocial outcomes, lower post-surgical complication rates, shorter operating time, and cost-effectiveness [8,9].

Pathological evaluation of post-NAT surgical samples remains the gold standard for assessing treatment response [10]. The purpose is to ascertain the degree of the pathological response and to evaluate the histological and biological characteristics of any residual tumor in the breast and/or axillary lymph nodes (ALN). After NAT, approximately 40% of patients with breast cancer achieve a pathological complete response (pCR), best defined as the absence of invasive carcinoma cells both in the breast and in the examined ALN [11]. It should be noted that the degree of response may vary between the primary tumor and the ALN metastases, and among the metastases themselves [12,13].

2. Gross examination

Post-NAT surgical samples are best evaluated if received fresh because this allows for more precise identification and measurement of the “tumor bed”, i.e., the tissue encompassing the original tumor site [14]. The timing of cold ischemia and formalin fixation should be monitored, as well as the traceability, collection, transport, and storage of the surgical specimen [15]. Once the consistency of the information provided with the request form (e.g. orientation, finding) has been verified, macroscopic examination and sampling should be carried out following standard recommendations [16]. The pathologist should measure the size of the

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primary tumor bed and the size and number of any residual neoplastic foci, along with the distance of the tumor bed/residual tumor from the surgical margins in case of BCS. It is generally advisable to perform the gross examination with the support of pre- and post-NAT imaging data.

In cases with pathological partial response (pPR), the residual disease may appear nodular, partially sclerotic, or as multiple foci within an edematous and/or sclerotic area. All lesions should be described, mapped, measured, and carefully sampled. The identification of the tumor bed and the evaluation of its extent might be challenging because it appears as an area with poorly defined contours, of generally decreased consistency, with edematous and/or fibrous appearance. Since tumor-associated microcalcifications do not disappear after NAT, x-raying of the surgical specimen may improve the recognition of the area to be sampled.

According to the recommendations of the Breast International Group and the North American Breast Cancer Group (BIG-NABCG) committee, the tumor bed should be initially sampled for histology by submitting 5 blocks every 1–2 cm of the tumor bed, with a maximum of 25 blocks [17]. The Food and Drug Administration (FDA) has recommended a minimum of 1 block per centimeter of pre-treatment tumor size, or at least 10 blocks in total, whichever is greater, [18]. Hormone-receptor (HR)-positive breast cancers are characterized by a lower rate of pCR achievement [10,14]. In these cases, if there is no evidence of residual tumor, and the tumor bed has not been completely analyzed after a first round of sampling, it is advised to carry out additional sampling. ALN can be affected by a spectrum of NAT-induced fibrotic alterations that may affect their macroscopic identification, counting, and examination [19]. Standard operating procedures should be followed for ALN analysis [20]. 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 [21,22].

3. Histological examination

3.1. Breast surgical samples

On microscopic examination, the tumor bed may present as an area of vascularized hyalinization, with foamy macrophages, lymphocytes, multinucleated giant cells, and hemosiderin-laden macrophages, in absence of normal ductal and lobular structures. Edema, necrosis, and microcalcifications may also be present. The tumor bed area, overall cancer cellularity, percentage of in situ component, number of positive lymph nodes, and size of the largest lymph node metastasis should be assessed for the calculation of the residual cancer burden (RCB) [23]. This index has a log-linear relationship with event-free survival at 5 and 10 years, being of particular clinical value in triple-negative and HER2+ tumors. In cases of complete lack of pathological response (pNR), the pathology report should follow the standard recommendations for non-NAT samples.

In case of pPR, the pathology report should include the histological subtype, size and number of foci of residual neoplasm, presence and quantification of fibrosis, presence of lymph vascular invasion (LVI) -neoplastic emboli may represent the only identifiable residual disease-, presence, extent, and features of any intraductal component, the status of the surgical margins in case of BCS, pathologic staging according to the latest TNM edition, residual neoplastic cellularity according to the RCB system. In case of pCR, the pathology report should include the presence and amount of fibrosis, presence, extent, and features of any intraductal component, status of the surgical margins in case of BCS, pathologic staging according to the latest TNM edition. The absence of in situ tumor can be included in the definition of pCR, albeit this is of controversial clinical value.

3.2. Axillary sentinel and non-sentinel lymph nodes

Similar to primary cancer, lymph node metastases can regress partially or totally. Regression areas occur with fibrosis in which foamy macrophages and/or hemosiderin-laden macrophages may be present. Axillary lymph node dissection (ALND) leads to complications and comorbidities in up to 40% of breast cancer patients [24]. To spare an unnecessary ALND after NAT, a sentinel lymph node (SLN) biopsy (SLNB) is performed at the time of surgery [25].

According to the American Society of Breast Surgeons, SLNB is indicated for patients with a clinically negative axilla at diagnosis or with a clinically positive axilla who convert to clinically node negative following NAT [26]. To reduce the false negative rate, it is recommended that 2 or 3 SLNs are identified and removed, together with the original positive node if it had been clipped. Immunohistochemical analysis of SLNs for the expression of cytokeratins should be considered for patients with biopsy-proven node-positive disease who undergo SLNB. The pathology report should include the presence and type of residual disease (i.e. macro/micro-metastasis, isolated tumor cells), extracapsular extension, and fibrosis. In the presence of residual disease, the current standard of care requires a completion ALND (or enrolment of the patients in clinical trials evaluating the use axillary radiation in this setting). It is still debated, however, whether minimal SLN involvement (e.g., isolated tumor cells and micro-metastases) should invariably lead to additional axillary treatments. It has been reported that at variance with the primary surgery setting, low-volume disease in the SLNs does not translate to a low probability of metastases to nonsentinel ALNs [27].

Despite the implications of leaving chemotherapy-resistant tumor cells in the axilla are still unclear, the detection of these cells in the SLNs is a criteria for ALND eligibility [22,28]. Whether a subset of patients (e.g, those with a clinically negative axilla at diagnosis) with minimal SLN involvement could be safely spared additional axillary treatment is certainly worth to be investigated. In case of ALND, the pathology report should detail the number of lymph nodes examined, of those with residual disease, and of those with fibrosis in the absence of residual disease, the extent of any residual disease (e.g. macrometastases, micrometastases, isolated tumor cells), the presence and the extent of extracapsular extension, and the pathologic staging according to the latest TNM edition.

4. Re-testing of tumor biomarkers

Changes of HR and HER2 phenotype is not uncommon after NAT due to intra-tumor heterogeneity, NAT-related selective pressure, and technical issues, including both pre-analytical and analytical variables [29–31]. Estrogen receptor (ER) conversion (more often from negative to positive) has been reported in 13%–18% of cases, and progesterone receptor (PgR) conversion (more often from positive to negative) in 26%–32% of cases. HER2 change from positive to negative has been reported from <10% up to 47.3% (63.2% with pertuzumab) of the cases, and conversion from HER2 negative to positive in 3%–4% of the cases [32–35]. A conversion of HR status may have prognostic implications and cause uncertainty in the choice of the post-surgical systemic treatment [36–38].

Re-evaluation of HR and HER2 status (and of Ki67 labeling index) is particularly recommended in case of triple negative status of the primary tumor or an equivocal result on pre-NAT core biopsy, if the biopsy sample had insufficient invasive tumor cells, if core biopsy was performed in another Institution, if a heterogeneous tumor or multiple tumors with different morphology are seen on

resection, and in case of pNR. It is imperative to ensure accuracy in the assessment of ER, PgR and HER2, and to double-check any apparent conversion by re-staining the previous core biopsy and the residual tumor in the same run, thus minimizing technical artifacts.

For patients who have received NAT for early-stage HER2+ breast cancer, response after HER2-directed NAT is also informative for optimization of adjuvant therapy [39]. The KATHERINE phase II study (NCT01772472) compared the efficacy of adjuvant T-DM1 (an antibody-drug conjugate consisting of trastuzumab covalently linked to the cytotoxic agent DM1) versus trastuzumab in patients with HER2+ breast cancer and residual disease in the breast and axilla after taxane-based NAT and trastuzumab [40]. The primary endpoint of better invasive DFS was met for patients subjected to T-DM1 adjuvant therapy, indicating that for patients who achieve a pCR, adjuvant treatment should consist of continuing the HER2-targeted regimen of the neoadjuvant phase, while failure to achieve a pCR would imply switching to T-DM1.

Ki67 labeling index of tumors at diagnosis is associated with higher rate of pCR to chemotherapy and it is correlated with long-term outcome in case of residual disease [41–43]. Post-neoadjuvant Ki67 labeling incorporated into the RCB index in the so-called residual proliferative cancer burden index provides a more robust prognostic estimate than either the RCB or Ki67 measurements alone [44]. Ki-67 change between pre- and post-neoadjuvant chemotherapy is an independent prognostic factor in patients with Luminal B, triple negative, and HER2-positive breast cancer subtypes, with patients who achieve a high reduction (>80% compared with that prior to NAT) of Ki67 having a favorable prognosis similar to that of patients with pCR [45,46].

Finally, the morphological evaluation of tumor-infiltrating lymphocytes (TILs) in the post-NAT residual disease setting, albeit debated, is acquiring increasing importance [47]. At present, however, this analysis is investigated in clinical trials but it is not yet applied in the clinical setting.

5. Tumor staging after NAT

In the last 30 years, more than 15 different systems for categorizing NAT response have been proposed [48]. Overall, a number of parameters associated with distant disease-free survival and overall survival have been variably included in the staging systems, including size of tumor after NAT, number of positive lymph nodes and size of the lymph node metastases, histologic grade before and after NAT, lymphovascular invasion, hormonal receptor status, and overall cellularity of residual tumor. The anatomical stage grouping endorsed by the 8th edition of AJCC is based on the TNM staging system, and includes only the size of residual tumor, the number of positive lymph nodes and size of the lymph node metastases (and any distant metastasis if present). More comprehensive systems include clinical (pre-NAT) and pathological (post-NAT) stage, tumor grade, ER status, and HER2 status (i.e. neo-bioscore staging system) [49], or tumor bed area, cellularity of residual invasive cancer, Ki67 labeling index, number of positive nodes, and size of the largest metastasis (i.e. residual proliferative cancer burden) [44].

6. Epilogue

With the steady increase of the number of candidate patients for NAT, it is more and more important to harmonize how tumor response is assessed at surgery. Macroscopic evaluation of surgical samples in the post-NAT setting, 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. In the neo-adjuvant setting, the close collaboration of pathologists, oncologists, surgeons, and radiologists within the multidisciplinary team is essential to ensure the best possible management of breast cancer patients.

Founding source

None.

Declaration of competing interest

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