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Letter to the Editor

Neoadjuvant Therapy Should Be the Standard of Care for Every Node Positive Breast Cancer Patient

Omar Hamdy

Surgical Oncology Unit, Oncology Center, Mansoura University, Mansoura, Egypt

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Correspondence to
Omar Hamdy
Surgical Oncology Unit, Oncology Center, Mansoura University, Geehan Street, Mansoura 35516, Egypt.
E-mail: omarhamdy87@gmail.com

ORCID iDs
Omar Hamdy
https://orcid.org/0000-0002-2924-4207

Conflict of Interest
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To the Editor:

This letter addresses a very simple, yet crucial question. Can we adopt the practice of offering neoadjuvant therapy (NAT) as a rule, for every node positive breast cancer patient, in order to avoid harmful axillary dissection in those who achieve pathological complete response (pCR)?

Sentinel lymph node biopsy (SLNB), is considered to be the standard of care for node negative breast cancer, as it can save patients from the complications of axillary lymph node dissection (ALND). These complications include lymphedema, arm stiffness, and neuralgia, all of which significantly affect the patient's quality of life and raise healthcare costs. It also allows accurate axillary staging with minimal morbidity. In patients undergoing breast conserving surgery and whole breast irradiation, it is now even acceptable to omit axillary dissection, if one to two lymph nodes (LNs) are found to be positive on SLNB [1-4].

Till date, according to the European Society for Medical Oncology (ESMO) guidelines for early breast cancer, there are still no definite indications for NAT in early breast cancer, except for downsizing large tumors in women with large tumor to breast ratio, desiring conservative breast surgery. Many studies have investigated the management of the axilla, in node positive breast cancer patients who received NAT. However, none of them considered node positivity to be an absolute indication for NAT. NAT is still not considered as the standard of care in early breast cancer, despite there being evidence that achieving pCR after NAT improves both, overall survival (OS), and disease free survival (DFS). The National Comprehensive Cancer Network guidelines have recently considered node positivity, which is more likely to convert to node negativity, as an indication for NAT. However, it is recommended, that a dual mapping technique is applied for sentinel lymph node (SLN) localization to remove two or more LNs, and to insert a clip in positive LNs before starting NAT in these patients [1-3,5-8].

In the setting of breast cancer, NAT (including chemotherapy, endocrine, and targeted therapy) offers the same long-term outcomes as that of adjuvant therapy [9]. However, it offers the advantages of facilitating conservative breast surgery in patients who were not suitable candidates for upfront breast conservation. It also helps in downsizing inoperable tumors to make them amenable for surgery. In addition, it provides important prognostic and therapeutic data, based on the magnitude of tumor response, especially in those who achieve pCR of the primary tumor, as well as the axillary LNs. This improves both, the OS, and the DFS. The improvement in survival is more likely to occur in triple negative breast

cancer, and in human epidermal growth factor 2 (HER2)-positive breast cancer, particularly when trastuzumab is added to the treatment regimen. The patients who achieve axillary pCR, show better loco-regional and survival outcomes, irrespective of the primary tumor response [4,5,7,10-16]. NAT also provides adequate time for genetic testing, and planning for breast reconstruction, when indicated. Furthermore, it provides information to assess the *in vivo* response to therapy [2,11].

The benefit of NAT, which is the focus of this article, lies in the opportunity to offer SLNB instead of ALND in patients with node positive breast cancer that was cleared by NAT. This consequently saves patients from the harmful outcomes of ALND [2].

The cons of NAT include both, the possibilities of over- and under-treatment. This depends on the errors in correct estimation of the extent of disease prior to, or after NAT. The possibility of disease progression during therapy also exists, particularly in chemo-resistant tumors. However, there is no significant difference in 15-year distant recurrence between NAT and adjuvant treatment. Post-NAT under-treatment can be limited by a detailed pathological assessment, meticulous tumor localization, and appropriate radiotherapy [2,14,17].

In terms of prognosis, the response of the axillary nodes to NAT is known to be a more important factor, than the initial axillary status. The false-negative rates (FNRs) of SLNB after NAT range from 5% to 30%, but these FNRs can be reduced to less than 10% when the dual technique for SLN localization is used, and when more than two LNs can be dissected and examined [6,8,10,11,18-21].

At least 28% of all candidates from all breast cancer subtypes achieve pCR in both, the breast, and axillary tumor, with the highest pCR rate in hormone negative, HER2-positive breast cancer, and the lowest rate in luminal A subtype [17,22]. The rates for axillary pCR are higher, reaching up to 37% (between 5% and 75%). This rate reaches up to 21% in patients with estrogen receptor-positive/HER2-negative tumors, 60% in triple negative tumors, between 67% and 73% in HER2-positive tumors when trastuzumab is used in combination with chemotherapy, and up to 97% when dual HER2 blockage is applied [7,8,10,11,15,16,20,23,24].

Considering its significant effect on minimizing the complications and morbidities of ALND, SLNB can be considered as a goal rather than as a tool. Axillary complete pathological response can be achieved after NAT in at least 21% of luminal A, and, up to 97% of HER2-positive subtypes of node positive breast cancer. Every node positive breast cancer patient receives chemotherapy, either in the neoadjuvant or adjuvant setting. There is no significant advantage for receiving it in the adjuvant setting as compared with NAT. NAT should therefore be adopted to be the standard of care for every node positive breast cancer patient.

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