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Review

Refining the Performance of Sentinel Lymph Node Biopsy Post-neoadjuvant Chemotherapy in Patients with Pathologically Proven Pre-treatment Node-positive Breast Cancer: An Update for Clinical Practice

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Abstract. *Background: Neoadjuvant chemotherapy (NAC) has become the standard treatment regimen for locally advanced breast cancer and has recently been incorporated into the treatment of early breast cancer. It allows down-staging of tumors favoring breast-conservative surgery over mastectomy. Furthermore, NAC results in nodal conversion in about 40% of patients. This favorable outcome has complicated the decision-making regarding the best approach in managing the axilla post-treatment; especially in pathologically proven nodal disease prior to NAC. Axillary lymph node clearance is still the standard-of-care for this group of patients; however, it is clearly an over-treatment in a substantial number of patients. Given the high accuracy of sentinel lymph node biopsy (SLNB) post-NAC in clinically node-negative cases prior to treatment, substantial research has been carried out in order to validate the feasibility of post-NAC SLNB in pathologically proven node-positive cases. The results so far are still inconclusive, yet promising. Materials and Methods: We performed a computer-aided review of the literature for relevant articles on the performance of SLNB post-NAC in pathologically proven node-positive patients prior to chemotherapy. We also targeted studies on important factors that can refine the accuracy of SLNB in this group of patients, as well as elements favoring pathological complete response. All studies focusing on post-NAC SLNB in pre-treatment node-positive cases including randomized controlled trials, retrospective and prospective series, review articles, and two meta-analyses were included. Results: The review established a false-negative rate of 14-15.1% and an IR of 89-92.3%. Several technical enhancements, as well as imaging modalities, may be incorporated to improve the performance of SLNB. Furthermore, selected patients with more likelihood of pathological complete response represent the best candidates for this technique. Conclusion: SLNB is a valid option after NAC in patients with pathologically proven node-positive breast cancer, given the high node-conversion rate. The literature demonstrated a false-negative rate that is slightly higher than that of patients initially node-negative which although might increase the locoregional recurrence in theory, has no effect on chemotherapy-decision making, and will most probably have no impact on overall survival. We identified several measures to refine its accuracy.*

Neoadjuvant chemotherapy (NAC) has been the standard treatment strategy for patients with locally advanced, inflammatory, inoperable breast cancer, or proven lymph node metastasis. It has been recently incorporated into the management of early-stage operable breast cancer, especially triple-negative breast cancer (TNBC) (1-4). This novel approach is based on the finding that most breast tumors will decrease in size by at least 50% when exposed to three to four cycles of cytotoxic chemotherapy, thus permitting breast-conserving surgery over mastectomy. Another potential benefit of NAC is the *in vivo* assessment of the primary tumor's chemosensitivity. Furthermore, NAC may prevent recurrence by reducing the likelihood that tumor cells will be released during an upfront surgery (5). Moreover, NAC provides an opportunity for new drugs to become Food and Drug Adminstration-approved based on pathological complete response (pCR) as a criterion (6). NAC has shown survival benefits equivalent to conventional adjuvant chemotherapy. A meta-analysis combining data from more than 3,900 patients with locally advanced breast cancer demonstrated no difference in overall survival and disease progression between those treated with neoadjuvant and those with adjuvant chemotherapy (7).

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The current practice is performing axillary node clearance (ANC) in all patients presenting with biopsy-proven nodal disease prior to NAC (8, 9). However, recent studies have shown axillary lymph nodal (ALN) pCR rates of approximately 40% after NAC, with some variation based on tumor biological subtypes reaching up to 49% and 74% in TNBC and human epidermal growth factor receptor 2 (HER2)-positive disease, respectively (9-12). Thus, this subgroup of patients could be spared the ANC and all its potential complications including lymphedema, seroma formation, shoulder dysfunction, and loss of sensation in the distribution of the intercostobrachial nerve (13). Based on both the notable rate of node conversion and the success of post NAC SLNB in patients presenting with clinically node-negative axilla, the interest in SLNB post-NAC in patients who first present with clinically node-positive disease has grown (14).

We performed a computer-aided review of the literature for relevant articles on the performance of SLNB post-NAC in patients with pathologically proven node-positive breast cancer prior to chemotherapy. We also targeted studies on important factors that can refine the accuracy of SLNB in this group of patients, as well as elements favoring pathological complete response.

Materials and Methods

Search strategy. Relevant articles were identified using electronic database searches PubMed and Ovid online databases. Articles published up to January 2016 with no upper limit were included in the study. The following free text terms were used to search for relevant literature: "breast cancer" AND "SLNB or sentinel lymph node biopsy" AND "preoperative chemotherapy OR neoadjuvant chemotherapy", AND "imaging", or "pathological complete response", or "false negative", or "identification rate", or "natural history", or "prognosis", or "recurrence", or "radiotherapy". Only articles published in English were selected. Studies identified were screened for those that were centered on SLNB post NAC in node-positive cases prior to treatment, which is the focus of this review. All randomized controlled trials, retrospective and prospective series, meta-analyses, and review articles were included. Reference articles in this review were selected to provide a balanced and representative overview of a complex subject with an extensive base of published work.

We focused our research on studies on female patients with breast cancer diagnosed with pathologically proven metastases of the axillary lymph nodes receiving NAC and undergoing SLNB followed by ALND as part of their management. Included studies had to report sentinel lymph node identification rate (IR) and false negative rate (FNR) or pCR. Our findings were then supported by more detailed research to identify practices that could refine the performance of SLNB in such cases in addition to improving pCR.

Results and Discussion

Two meta-analyses, including a total of 17 studies on the SLNB post-NAC in pathologically proven pre-NAC node-positive patients, were identified and carefully evaluated to establish the performance of SLNB in such settings. Further research was performed to provide methodologies that could enhance the accuracy of this practice and to highlight favorable factors that improve pCR yielding a total of 110 references.

The skeptics about post-NAC SLNB prefer ANC to address two concerns: Firstly, obstruction of the draining lymphatic channels by large, bulky disease which might affect the accuracy of SLNB. Secondly, the non-sequential response of involved ALNs to NAC which could lead to a false-negative SLNB, potentially leaving involved non-sentinel ALNs untreated and unstaged (15- 17). However, looking at the results of two recent meta-analyses, Fu *et al.* (18) and Van Nijnatten *et al.* (19) reported a promising pooled estimate analysis of an IR (IR) of 89-92.3% and a false-negative rate (FNR) of 14-15.1%, respectively.

An IR of 89-92.3% is certainly less than that of patients with node-negative disease prior to NAC (97.4%). This may be attributed to altered lymphatic drainage with treatment (20). However, this does not necessarily have to prohibit the practice of SLNB. Furthermore, a significantly improved IR can be achieved by the use of dual agent mapping. Boughey *et al.* reported an IR of 93.8% with dual-agent use *vs.* 88.9% with single-agent use (21). Use of blue dye alone resulted in an IR of 78.6%. The value of dual mapping was also validated by Hunt *et al.* with an IR of 99% (20). The IR can also be enhanced by performing SLNB once only. Kuehn *et al.* showed that re-operative SLNB post-NAC resulted in the lowest SLN IR (60.8%) and an exceedingly high FNR (51.6%) (22).

Regarding the FNR, it is important to note that the literature appears to be inconsistent in its definition. While some authors defined FNR as false-negative cases divided by false-negative plus true-negative cases, others defined it as false negative-cases divided by false-negative plus true-positive cases. This variation in the definition could have contributed to the inaccuracy of FNR determination (23). There is no doubt that the clinical nodal status prior to NAC is an important contributor to FNR. The literature shows lower reported FNR in pre-NAC node-negative than in node-positive cases (23-25). Takahashi *et al.* reported an FNR of 5.5% in node-negative patients before chemotherapy *vs.* a significantly higher FNR of 35.5% in node-positive patients (23). Likewise, the accuracy was significantly higher in clinically node-negative cases than in node-positive ones before NAC (97.2% *vs.* 77.1%). The low FNR observed in pre-NAC node-negative cases is similar to the reported range of FNR SLNB in the non-NAC setting (5.1%-9%) (26-28). Having said that, there are several points that we can address to refine the SLNB outcome in this group of patients.

Measures for reducing FNR. Our literature review identified the following measures for reducing FNR: i) Extending the definition of positive nodes by considering SLN

micrometastasis (ypN1mi) or isolated tumor cells (ypN0+) as positive LNs (29). Unlike the non NAC setting, the size of SLN metastases does not correlate with the rate of non-SLN metastases (30). According to the Seventh Edition of the American Joint Committee on Cancer staging system, patients who are ypN0i+ or ypN1mi at SLNB post-NAC are considered to have residual nodal disease; hence, mandating ANC (31). Therefore, examination of additional levels of hematoxylin and eosin staining and keratin staining are essential (32). ii) Excision of a greater number of SLNs: The removal of more SLNs also improved the accuracy from an FNR of 31.5% when one SLN was examined to 21.1% when two SLNs were examined, and 9.1% when three or more were examined (21). This is not unlike the conclusion drawn in the settings of cN0 prior to NAC, where FNR also decreased with more SLNs removed (20). However, it is not always possible to identify three or more SLNs (22, 30, 33). Furthermore, there are no current data supporting random sampling of nearby ALNs to replace SLN mapping and identification of at least three nodes following NAC (14). iii) Clip placement at diagnosis of node-positive disease with removal of the clipped node during SLN surgery can reduce the FNR of SLN surgery after NAC to 6.8% (34). iv) A similar technique that involves marking of the ALN with radioactive iodine seeds (MARI procedure) has been described by Straver *et al*. as an alternative to SLNB in the setting of NAC in cytologically proven axillary lymph node metastasis (35). It entails using ultrasound-guided insertion of iodine-125-labelled (I-125) seeds to localize a cytologically-proven tumor-positive node at the time of initial evaluation. After NAC, the marked node, which was indicative of the overall response, is identified using a gamma probe and selectively removed in a manner similar to SLNB. MARI is a safe, promising, and patient-friendly method for assessing post neoadjuvant ALN involvement, with reported IR and FNR of 97-100% and 0-7%, respectively (35, 36). However, a possible limitation of the above two methods (*i.e*. clip marking and MARI) is that there is a possibility of non-conformance between the ALN which was identified and marked by ultrasound and the SLN. Moreover, a negative resected clipped LN does not reflect the pathological response in the rest of the ALNs. Thus, further larger-volume prospective studies are required to assess the accuracy of these methods in predicting the pathological response in additional lymph nodes. Nonetheless, these techniques can help refine the accuracy of SLNB post-NAC (34-36). v) Avoiding repeat SLNB (22), and vi) the use of dual mapping technique have also been shown to reduce the FNR by improving the IR (29). This is contrary to the conclusion drawn by Tausch *et al*., who recommended the use of blue dye alone in the NAC setting on the basis that blue dye is much smaller in particle diameter than the radioactive tracer, thus facilitating its passage through possibly fibrosed and narrowed lymphatic vessels (25). However, the identification of more than two SLNs and the use of a dual tracer resulted in an FNR of <10% (18, 33). vii) Nomograms developed to predict axillary pCR post NAC in pN-positive cases may guide us towards those with high probability of achieving axillary pCR, thus refining SLN results and eventually sparing responders the morbidity of axillary clearance (37). viii) Serial clinical assessment is an integral part in preoperative evaluation of nodal response to NAC. Clinical examination of ALNs to determine response to NAC is inaccurate (38) with Arimappamagan *et al*. reporting sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for detecting patients with axillary pCR of 86%, 64%, 40% and 94%, respectively (39).

Studies on the optimal imaging modality for post-NAC axillary restaging remain areas of great interest and controversy. Although informative, imaging like ultrasonography, MRI, and PET-CT are inadequate to preclude surgical axillary staging in breast cancer patients after NAC. The accuracy of current imaging modalities in predicting ALN response to treatment remains low at 60-72% (40). Axillary ultrasound (AUS) is commonly used at initial diagnosis of breast cancer to diagnose the presence of nodal metastasis. Sensitivity and specificity of 25-95% and 97-100%, respectively, when combined with percutaneous biopsy have been reported (41). The role of AUS in post-NAC nodal evaluation has been assessed in several studies. Sensitivity, specificity and PPV were 32-69.8%, 56-94%, and 59-89%, respectively, with better performance in detecting positive nodes rather than pCR (41-46). Boughey *et al*. reported a PPV of 71.8% in detecting residual disease post-NAC using AUS. The SLN FNR was not different based on AUS results. However, according to results from the American College of Surgeons Oncology Group Z1071 Trial using a strategy where only patients with normal AUS undergo SLN surgery, it has been shown that this methodology would potentially reduce the FNR in patients with two or more SLNs removed from 12.6% to 9.8% when preoperative AUS results are considered as part of SLN surgery (41). A a promising future for the accuracy of AUS is anticipated by enhanced sonographic technologies such as elastography and detection of blood vessel density (47, 48).

Based on the observation that a change in tumor metabolism occurs prior to its decreasing in size, fluorodeoxyglucose positron-emission tomography (FDG-PET) is expected to visualize tumor response at an earlier stage than conventional imaging modalities (48). Several studies conducted on the role FDG-PET in determining ALN status have reported high accuracy. A high specificity range of 85%-100% is consistent across studies, yet the sensitivity of this modality is lower and broader ranging from 20% to 94% (49-61). On the other hand, even though evidence exists

that FDG-PET/computed tomography (CT) can successfully monitor primary tumor response to NAC (62), limited data on serial FDG-PET for evaluating ALN response are available, and no consensus has been reached concerning the method for PET assessment (qualitative or semiquantitative) (63). Koolen *et al*. reported that the specificity and PPV were 95% and 86%, respectively, when the decrease in standardized uptake value (SUV) was greater than 60% and the area under the receiver operator characteristic curve was 0.80 (64). Likewise, early through the course of NAC Rousseau *et al*. were able to differentiate between responding and nonresponding ALNs using an SUV decrease of 50% set as threshold, with a sensitivity, specificity and accuracy of 75%, 96% and 84%, respectively. Although non-responding ALN SUV_{max} was reduced by one-third, that of responding nodes had decreased to background levels. The NPV of PET was constantly higher than for AUS even in the very early stage of chemotherapy monitoring (49). Given an axillary SUV cut-off level of 1.5, Keam *et al*. reported sensitivity, specificity, NPV, and PPV of 51.8%, 85.7%, 40.0%, and 91.3%, respectively. However, when using both serial FDG-PET/CT and chest CT, patients with an SUV>1.5 and post-NAC ALN size >10 mm on CT did not achieve pN0 (specificity 100%, and PPV 100%). Hence, patients with a post-NAC ALN SUV>1.5 and a post-NAC ALN size >10 mm on CT could avoid SLNB or minimum ALN dissection, and these patients would benefit from adequate ALN dissection (65). This is a conclusion also validated by Veronesi *et al*. (52) and Kim *et al*. (56) given the high specificity of FDG-PET. However, because of its low sensitivity and NPV, FDG-PET/CT seems inappropriate for identification of patients who would benefit from SLNB. The low sensitivity can be attributed to several factors, including relatively low spatial resolution of PET imaging not allowing the detection of micrometastases (52), and intrinsic tumor factors such as grade and type (Gil-Rendo *et al*. showed a sensitivity of 100% for detecting lymph node metastases in a group of patients with grade III malignancy and an SUV_{max} higher than 3.5 of the primary tumor) (50), and estrogen receptor (ER)-positive/HER2-negative breast carcinoma is associated with less intense ^{18}F-FDG uptake than some other tumor phenotypes such as TNBC (66, 67).

Few data are available on the ability of breast magnetic resonance imaging (MRI) to evaluate ALN status either prior to the start of therapy or after completion of preoperative therapy (68). Studies evaluating MRI are limited by mixed patient populations, including those with metastatic nodes removed by pre-NAC SLNB, and small sample size (40). Javid *et al*. demonstrated a moderate sensitivity (64.7%) and a high specificity (100%) for predicting ALN involvement prior to NAC, with NPV and PPV of 77.8% and 100%, respectively. In patients with positive ALN involvement pre-NAC, MRI had a moderate sensitivity (85.7%) and specificity (89%), with NPV and PPV of 80.9% and 92%, respectively (68). Likewise, Hieken *et al*.'s results on the accuracy of post NAC MRI to detect ALN involvement were not encouraging, with sensitivity, specificity, NPV, PPV and accuracy of 61%, 58.6%, 42.5%, 75% and 60.2%, respectively. The utility of breast MRI may also be constrained by inadequate visualization of the axilla in some patients (40). Hence, the low accuracy of MRI in detecting ALN post-NAC renders it inadequate for replacing post-NAC surgical staging modality.

Markers such as superparamagnetic iron nanoparticles (ultrasmall superparamagnetic iron oxide: USPIO) have been developed as contrast agents for MR lymphography to enable identification of metastatic lymph nodes by their inability to take up these iron-containing nanoparticles (69-71). The results, so far, have been promising. Harada *et al*. suggested that the use of superparamagnetic nanoparticle-enhanced MRI confers superiority over contrast-enhanced and non-contrast-enhanced MRI in detecting ALN metastases. The authors reported sensitivity, specificity, PPV, NPV and accuracy of 84.7%, 96.8%, 88.5%, 95.6% and 94% respectively (69). However, all studies were limited by a small number of patients, and all evaluated lymph node metastasis in the non-neoadjuvant setting; larger prospective studies should be performed to evaluate the accuracy of this diagnostic tool and its utility in detecting residual lymphatic disease in pre-neoadjuvant pathologically proven node-positive cases.

Likewise, Schipper *et al*. in their small study of 10 patients showed that gadofoseveset-enhanced MRI could be used for axillary staging, with a sensitivity and specificity of 86% and 94%, respectively. It correctly staged eight out of the 10 patients, compared to three out of 10 with AUS. Although promising, larger studies are needed in order to increase the reliability of these preliminary results (72).

Technetium 99m-sestamibi (MIBI) for identifying residual lymph node disease after NAC has been described. However, this method is characterized by low sensitivity and specificity of 55% and 75%, respectively (73).

Although multidetector CT scans have a limited role in breast cancer staging, Cheung *et al*. reported sensitivity, specificity, PPV, NPV and accuracy of 72%, 40%, 85.7%, 22.2% and 66.7%, respectively, in diagnosing ALN metastases after NAC. They also suggested that multidetector CT can potentially serve the role of alerting radiologists or clinicians to the possibility of false-negative nodal micrometastases on post-chemotherapy multidetector CT, especially in patients with node-positive disease on the initial multidetector CT examination (74).

Timing of SLNB. The timing of the SLNB in the NAC setting has always been a subject of controversy (75). While pre-NAC SLNB allows an accurate initial assessment of ALN

status by more established techniques, post-NAC SLNB obviates the need for two separate surgeries, allows the assessment of nodal response to treatment, may possibly reduce the number of removed ALNs in responders, and avoids the delay of NAC (76). Moreover, as discussed earlier in our review, the SLNB should preferably only be performed once (22).

Consequences of false-negative SLNB and resultant residual nodal disease. Leaving residual nodal disease carries several implications.

i) Effect on survival: There is no doubt that lymph node status after NAC is still the single-most important prognostic factor in determining breast cancer-specific and disease-free survival (77), irrespective of the primary tumor response (78). Patients who have ypN-positive disease after NAC have high rates of locoregional recurrence (79) and worse disease-free survival (80). However, in all the previous studies, ALN dissection was performed in all patients. Therefore, we do not have clear information regarding the clinical significance of leaving residual disease behind after NAC. Persistent nodal involvement post NAC means that this is potentially a chemoresistant disease. Hence, the outcomes might not be as those associated with upfront surgery (81-83). Nonetheless, the NSABP B-04 trial showed no difference in disease-free nor overall survival in cases where delayed ANC was performed when clinical adenopathy developed. Therefore, one could extrapolate that regional lymphadenopathy is an indicator rather than an instigator of distant disease (84).

ii) Effect on decision-making regarding further treatment with chemotherapy: False-negative SLNB leads to understaging of the disease, with consequent possible omission of appropriate chemotherapy, hence increasing the risk of locoregional or systemic recurrence. However, in the NAC setting, patients have already received upfront chemotherapy based on tumor characteristics (83). Nevertheless, we should consider that these patients with persistent positive ALNs have some level of chemoresistance. Hence, it is crucial to determine any residual nodal disease as these patients are candidates for future trials of new agents and additional adjuvant systemic therapy following their poor response to NAC (14, 77).

iii) Effect on decision-making regarding further treatment with radiotherapy: There is no doubt that NAC has complicated decision-making with regards to postoperative radiotherapy. Knowing that the presence of pathological residual disease (especially ypN-positive) post-NAC is one of the factors determining the need for postoperative radiotherapy (in addition to the clinical extent of the disease at presentation pre NAC), the presence, and the response to NAC help guide this decision. It is unfortunate that some patients might be deprived radiotherapy on the basis of false-negative SLNB leading to worse breast cancer-specific survival (79). On the other hand, Clarke *et al*. demonstrated no survival benefit with postmastectomy radiotherapy (PMRT) in patients with early breast cancer (85). The concern is the lack of detailed data on locoregional radiation therapy in this population of patients with biopsy-proven nodal metastases (86, 87). A recent study by Liu *et al*. demonstrated no survival benefit between patients with ypN0 who received PMRT and those who did not. However, in a subgroup analysis, an overall survival benefit was observed in patients with clinical T3/T4 tumor or stage IIIB/IIIC disease at presentation, and in those with residual invasive breast cancer post-NAC (88). Likewise, Huang *et al*. reported a reduction in the locoregional recurrence rate from 22% to 11% with PMRT, with the greatest benefits seen in patients with cT3 and cT4 tumors, stage IIB disease or greater, residual pathological tumor size >2 cm, and four or more residual involved ALNs (89). The advantage of PMRT in decreasing the locoregional recurrence was also validated by Wright *et al*. in a similar subgroup of patients (in addition to those with hormone-positive cancer) (90). Nonetheless, these features will mostly not be affected by a false-negative SLNB. Hence, we conclude that careful patient selection can be made to decide on PMRT after careful multidisciplinary decision. Moreover, although the preliminary results seem promising, we emphasize the importance of enrolling patients presenting with node-positive disease in randomized trials to further assess and establish the benefits of PMRT. Currently, there are two ongoing trials investigating the optimal locoregional therapy in this setting. The ALLIANCE A011202 trial randomizes patients with persistent ypN+ post-NAC into ANC followed by regional nodal irradiation *vs*. SLNB followed by regional nodal irradiation to see if ANC can be omitted in favor of nodal radiotherapy in patients with persistent nodal disease post-NAC (91). On the other hand, the NSABP B51/Radiation Therapy Oncology Group 1304 trial studies the need for further regional nodal irradiation in patients with node conversion post-NAC. Women who undergo mastectomy will be randomized to chest wall irradiation plus regional nodal radiotherapy *vs*. observation, whereas women who undergo lumpectomy will be randomized to whole-breast irradiation plus regional nodal radiotherapy *vs*. whole-breast radiotherapy alone (92).

Histological perspective. From a histological point of view, chemotherapy induces characteristic histological changes at the sites of both the primary tumor and involved regional ALNs with partial or complete pathological response. These changes include generally marked fibrosis, often accompanied by a foamy histiocytic infiltrate, calcifications, fat necrosis, and hemosiderin deposition (93-95). If post-NAC SLNB show treatment-induced changes in cytologically proven pN+ prior to NAC, treatment-induced lymphatic fibrosis or tumor debris may have altered the normal

lymphatic draining pattern. In this event, skeptics would question the necessity for performing ANC as this is not the true SLN (95). Moreover, if SLNB does show evidence of treatment, then this is most probably the true SLN with an easy decision for proceeding with ANC where it is positive. However, if no residual disease is identified, the doubt again arises with the possibility of non-sequential response of ALNs to NAC (32, 95). Nonetheless, we did address the fact that false negativity will not affect the chemotherapy decision since these patients have already received NAC upfront (83), and although locoregional recurrence risk is increased with residual disease (79), a delay in ANC will not affect survival (84). However, there is still some controversy regarding radiotherapy decision (79).

Finally, pCR, which is a surrogate for a favorable treatment outcome as it reflects the clearance of residual disease on histological analysis, could also be used as a marker for better survival (96-98). As a matter of fact, a recent study by Mongolian *et al*. demonstrated that patients with axillary pCR have better 10-year overall survival and recurrence-free survival of 84% and 79%, respectively *versus* 57% and 50%, respectively, in those with residual axillary disease. Patients with both axillary and breast pCR after NAC had even superior long-term survival outcomes. Patients undergoing HER2-targeted therapy for HER2-positive disease with axillary pCR had excellent 10-year overall survival of 92% (99).

The high ALN conversion reported in the literature confirms that SLNB post NAC in this subset of patients is a valuable option. There are several factors which can affect axillary nodal pCR. It is important to state that the pathological responses vary between the breast and nodal regions (100). Spanheimer *et al*. demonstrated that patients with stage II disease are more likely to convert to negative nodal status compared to stage III (101). Moreover, studies have shown lower tumor response to NAC in terms of pCR in locally advanced invasive lobular carcinoma than in invasive ductal carcinoma (102-104). TNBC and HER2-positive breast cancer, although having the characteristics of aggressive clinical behavior, rapid growth and a poor prognosis, are more sensitive to NAC; thus, more likely to achieve nodal pCR. As a matter of fact, Straver *et al*. reported that patients with TNBC or HER2-positive disease and a pCR of the primary tumor had nodal pCR of 57% and 68%, respectively. On the other hand, a low pCR in those with ER-positive tumors was reported, suggesting the possibility of the need for ANC in those patients (105). Likewise, a poorer nodal pCR was reported in cases of lymphovascular invasion (106). Moreover, nodal pCR maybe largely attributed to the type of NAC administered. Studies have shown that cyclophosphamide-containing regimens have increased the conversion rate to around 40% (107, 108). Al Mushawah *et al*. also demonstrated that the only factor associated with a difference in the rate of a complete nodal response was the type of neoadjuvant therapy used, as nodal conversion was seen with the use of systemic chemotherapy rather than endocrine therapy (109). Furthermore, Denkert *et al*. have suggested that new biomarkers such as poly(ADP-ribose) polymerase might be useful for the prediction of response to conventional and new targeted therapies (110). Finally, given the tumor subtypes with the most likelihood of achieving node conversion, we can use this information to help stratify patients according to risk and therefore decide who would benefit the most from SLNB rather than complete axillary dissection.

Conclusion for Clinical Practice

SLNB is a valid option after NAC in patients with pathologically proven node-positive breast cancer, given the high node-conversion rate. An FNR of 14-15.1%, although possibly increasing the locoregional recurrence risk in theory, has no effect on chemotherapy decision-making, and will most probably have no impact on overall survival. However, there are several measures to help refine its accuracy:

Addressing patient selection:

Those with the highest possibility of nodal pCR to NAC (most notably HER2-positive and TNBC)

Those with normal post-NAC AUS

Taking advantage of specific imaging modalities with high PPV:

FDG-PET/CT with pre-set SUVmax threshold >1.5 and lymph node size >1 cm

USPIO MRI

Improving SLN IR and reducing the chance of false negativity, for example:

Marking with MARI/ clips

Dual mapping techniques

Resection of >2 SLN when possible

Following proper pathological evaluation and broadening the definition of SLN positivity to include micrometastases and isolated tumor cells

Encouraging patients and junior doctors to enroll patients in future research programs.

Conflicts of Interests

The Authors report no conflicts of interest.

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