Review Article

Axillary lymph node surgical treatment

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Abstract: Nowadays, the overall attention is focused on de-escalating treatments for breast cancer (BC) including surgery, radiotherapy and chemotherapy. The introduction of sentinel lymph node biopsy (SLNB) has led to less invasive surgical approaches for accurately staging the axilla, with axillary lymph node dissection (ALND) progressively confined to a limited group of patients. One of the goal of surgery in de-escalating approaches is to reduce surgical morbidity by restricting or avoiding axillary surgery with no effect on survival. In this context the importance of imaging study for preoperative identification of axillary metastasis, in order to reduce axillary surgery, is gradually improving while the role of intraoperative assessment of sentinel nodes is progressively becoming limited to restricted groups of patients. According to the results of the ACOSOG Z0011 and following the most important guidelines, ALND can be safely omitted in selected patients treated with breast conserving surgery (BCS) with one or two positive SLNB while the adoption of SLNB positive alone in patients undergoing mastectomy is not yet defined. The increased employment of neoadjuvant chemotherapy (NAC) and the use of SLNB in patients after NAC plays an important role in de-escalation of axillary surgery in this group of patients. However current studies on this topic are still controversial, mainly about clinically positive lymph nodes (cN+) pre NAC patients or how to manage positive SLNB in post NAC patients. Some authors have collected predictive factors of positive non sentinel lymph nodes (NSLNs) in nomograms, considered an useful tool to avoid unnecessary further surgery. Elderly women represent specific group of patients where the axillary approach needs to be properly resized. The management of axilla in BC is in continuous evolution and ongoing studies could make even SLNB useless in the next future.

Keywords: Breast cancer (BC); axillary management; sentinel node biopsy; axillary lymph node dissection (ALND); neoadjuvant therapy

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Introduction

In the last years the role of surgery in breast cancer (BC) treatment and axillary staging is gradually changing. The surgical management of BC is continuously evolving towards less extensive surgery following a new concept of "de-escalating surgery". The axillary lymph node dissection (ALND), considered for more than a century as a milestone of treatment for all BC patients, was upset-down in the last 15 years. With the introduction and worldwide spread of sentinel lymph node biopsy (SLNB) a new era began.

The use of SLNB replaced the ALND in patients with a clinically node negative status, accurately staging the axilla

without compromising regional recurrence rates and overall survival and markedly reducing the morbidity of ALND.

Actually, several studies analyzed the possibility of omitting ALND in certain patient groups with SLNB metastases with a subsequent decline in the indication for completion ALND, considering also the efficacy of adjuvant therapies to reach an acceptable local control of the disease.

In this article we review guidelines and literature regarding the current axillary management. We focused our research on main different subset as: the role of preoperative axillary evaluation; changes in intraoperative assessment of sentinel nodes; how to approach the axilla in case of positive SLNB during breast conservative surgery (BCS) or mastectomy; utilization of SLNB in neoadjuvant chemotherapy (NAC) setting; nomograms and predictive factors of additive positive non sentinel lymph nodes (NSLNs); management of the axilla in elderly women and future ongoing studies.

Preoperative axillary imaging

With the common adoption of mini-invasive axillary staging, efforts are now focusing on preoperative identification of axillary metastasis given that they may have a direct impact on surgical and medical approaches, from NAC to breast reconstructive options (1). Currently both physical evaluation and breast-directed imaging modalities are being used to test the presence and evaluate the extent of the disease. The imaging modalities run from ultrasound (US) and US guided fine needle aspiration cytology (US-FNA) to magnetic resonance imaging (MRI) (2) and 18F-Fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG-PET/CT). The ACOSOG Z0011 trial identified clinically node-negative patients by physical exams alone (3). However, given that physical examination has poor sensitivity (35% to 41%) and high false-positive rates (53%) with regards to the axilla, attention has recently shifted towards axillary imaging (4). As a result, the use of preoperative axillary US integrated with fine needle aspiration cytology (FNA) has become much more frequent in BC patients (5) as a fast, non-surgical, staging procedure associated with a low rate of complications (6-8). Several studies report of a sensitivity of US-FNA in the preoperative staging of BC of up to 80% with 100% specificity (9-11). Boland *et al.* (12) showed that the use of preoperative axillary US and US-FNA is successful in identifying a cohort of patients with a higher burden of axillary nodal disease to address directly to ALND or NAC. Despite other researches have suggested that axillary imaging with or without US-FNA may be beneficial to allocate high-risk node-positive patients directly to ALND (10,13-16), Pilewskie *et al.* (17) showed that in a population of patients meeting ACOSOG Z0011 criteria, axillary imaging (MRI, mammogram and US) did not reliably identify patients with >2 positive sentinel lymph nodes, who should undergo ALND without determination of the number of involved nodes. According to the mentioned study, if all patients with abnormal axillary imaging were triaged to ALND, the 68–73% would have been over-treated and subjected to unnecessary procedures. Y L *et al.* (18) evaluated a group of patients not fulfilling ACOSOG Z0011 inclusion criteria, demonstrating that positive US-FNA is very accurate in predicting macroscopic impacts of axillary nodes. Patients that did not fall within the ACOSOG Z0011 parameters can move on to axillary clearance without SLNB nor risk of over-treatment. Promoting the above evidence, the data of van Wely *et al.* (16) reported that patients with axillary metastases diagnosed by US-FNA have significantly more affected nodes than SLNB-positive patients and are most likely to benefit the most from further axillary treatment.

Following the possible results of SOUND trial (19) and BOOG 2013-08 trial (20), an accurate pre-operatory axillary evaluation with US or US-FNA may also lead to avoid SLNB performance in selected groups of patients with early BC.

While US is actually the standard preoperative imaging procedure, several studies are evaluating the role of MRI in axillary staging. Assing *et al.* (21) in their study added MRI to US in preoperative staging concluding that MRI could be useful in identification of those lymph nodes not identified on US; Arslan *et al.* (22) in a recent study showed that MRI has a sensitivity of 84.7 % for detecting axillary lymph node metastases. Nevertheless, there is actually no evidence of the possibility of avoiding SLNB using MRI.

^{18}F-FDG-PET/CT is commonly applied in breast oncology imaging. However, the role of PET/CT in the regional staging of BC remains unclear, despite it being more accurate than conventional imaging modalities (23). Latest reviews reported a sensitivity and specificity that ranged from 57% to 100% and 66% to 100%, respectively (24). Several authors (23,24) showed that ^{18}F-FDG-PET/CT is not likely to replace SLNB for axillary assessment. Positive FDG uptake in the axilla does not always indicate axillary metastasis (15% false-positive). Therefore, US-FNA is useful to avoid unnecessary ALND in patients with positive

FDG uptake. On the other hand, SLNB is needed in patients with negative FDG axilla uptake and in those with negative fine-needle aspiration cytology (FNAC) of the axillary lymph nodes.

The role of the preoperative axillary imaging is in continuous evolution to help to better define the axillary management.

Axillary evaluation following NAC

Fifty-five percent of node-positive cN+ BC are down-staged by NAC (25). In order to facilitate the identification of the sentinel nodes and reduce the false negative rate (FNR), recent studies are focusing on the importance of identification of positive sentinel nodes after NAC (25-28). It is done by placing a clip in the positive node at initial diagnosis with confirmation of clipped node resection at surgery (25) or using iodine marked seed (26). The ACOSOG Z1071 trial (27) was designed to determine if SLNB was accurate in staging the axilla after chemotherapy in patients presenting with node-positive disease. The trial reported a FNR of 12.6%. In this trial, where the estimated group of patient had a clip placed in nodes after needle biopsy and who had documented removal of the clip-containing SLN, FNR was <7%. According to this data Caudle *et al.* (28) found that performing targeted axillary dissection, which involves removing SLNB with clipped node identified pre-therapy as containing metastatic disease, FNR was 2% versus 10.1% for SLNB alone. Koolen *et al.* (26) associated PET/CT before NAC with axillary lymph node marking with radioactive iodine seeds (MARI procedure) after NAC avoiding 74% of ALND in a cohort of axillary node-positive patients after NAC. The NCCN guidelines (29) have incorporated a comment that marking lymph nodes to document their removal is one method to decrease the FNR of SLNB post NAC.

Intraoperative assessment of sentinel nodes

Traditionally, intraoperative diagnosis of SLN can prevent unnecessary ALND when negative, and can allow ALND in the same surgical procedure when positive, thus avoiding a second surgery and decreasing the patient's associated discomfort (30,31). Nevertheless, according to the evolution of surgical approach in case of positive SLNB, intraoperative assessment of lymph nodes could confuse surgeons to define the better treatment planning. Moreover, there is increasing evidence that omitting ALND with or without radiotherapy in selected patients groups results in excellent and similar regional control compared to ALND. Therefore there are several reasons why the use of intraoperative assessment should be questioned. Following the results of the ACOSOG Z011 (3) and according to the American Society of Clinical Oncology (ASCO) recommendations (32), BC patients with clinically node-negative disease and one or two positive SLNs can be safely treated with BCS and radiotherapy omitting ALND. In this patient, intraoperative assessment of SLNs could not be useful nor performed.

More controversies exist for cN0 patients treated with mastectomy, ASCO recommend that patients with a SLN+ tumor who are treated with mastectomy should still be offered ALND, as radiotherapy is not routinely administered in these patients. In this group of patients the intraoperative assessment of SLNs could be performed. Several studies suggested ALND may be safely omitted in patients who are treated with mastectomy with al low tumor burden in SLNs (33,34). About patients undergoing NAC, according to NCCN guidelines (29) intraoperative assessment of axillary lymph node should be performed, since these patients are supposed to be treated with ALND in case of positive SLN. Van der Noordaa *et al.* (35) found that omitting axillary lymph node intraoperative assessment might be a reasonable option in patients presenting with limited (cN1) axillary disease and a tumor-positive lymph node while in patients with extensive nodal disease intraoperative assessment of axillary lymph nodes should be performed, since these patients should be treated with ALND in case of residual disease after NAC.

In conclusion, the use of intraoperative assessment should be limited for patients who still have an indication for ALND in case of a tumor-positive axillary lymph node. This group is made up of patients with extensive axillary disease who undergo NAC and remain node-positive after NAC and of clinically N0 patients, not treated with NAC, presenting with intraoperative unexpected extensive axillary disease.

In terms of SLN intraoperative analysis, common techniques that are used to identify tumor deposits, including touch imprint, crash, and cytological smear preparations, as well as frozen sections, all lack a sufficient degree of sensitivity (36). In this context, advances in diagnostic technology based on molecular methods for the analysis of SLN might be essential to improve therapeutic

management.

One Step Nucleic Acid Amplification (OSNA) is a highly sensitive, automated and rapid assay that analyses lymph nodes for identifying metastases by detection and amplification of the cytokeratin 19 (CK19) mRNA, an epithelial marker in BC cells (37). Several studies demonstrated that the NSLN macro-metastatic rate increased in proportion to CK 19 mRNA copy numbers (38). The findings of Banerjee *et al.* (31), Piñero-Madrona *et al.* (39), Peg *et al.* (40) were consistent with Nabais *et al.* (38), who observed that using OSNA technique to evaluate SLN, NSLN metastases can be predicted intraoperatively, supporting in decision for ALND.

Nevertheless, in current standard clinical practice, where the use of intraoperative assessment of axillary lymph nodes is decreasing, all intraoperative techniques, including OSNA, are less employed than in the past.

Breast conservative surgery and positive SLNB

As recommended by ASCO guidelines (32) about SLNB in patients with early breast cancer (EBC), a negative SLNB has not to be followed by ALND, independently from the performed surgery type. The need for ALND after positive SLNB in BCS (breast conservative surgery) was questioned. The American College of Surgeons Oncology Group Z0011 (3) trial has been a milestone in axillary treatment in EBC with clinically negative lymph nodes but positive SLNB, in patients treated with BCS, followed by whole breast irradiation (WBI) and systemic therapies. Giuliano *et al.* showed that loco-regional recurrence rates was not improved by ALND, in patients with axillary tumor burden from low to moderate, compared to SLNB alone. Several criticisms have been raised up to this trial (41), as early enrollment closure with low statistical power, no respect of inclusion criteria, lost data at follow up. Although with these limits, lots of studies have been developed reporting good results in the applicability of ACOSOG Z0011 criteria in clinical practice. It led to the inclusion of those criteria in NCCN international guidelines (29). Verheuvel *et al.* (42) have reported their experience, with an applicability in more than 51% patients. Voutsadakin and Spadafora (43) concluded to consider omitting ALND only in patients meeting ACOSOG Z0011 criteria, that means "only in post-menopausal patients, ductal invasive carcinomas, clinically negative axilla, no extranodal extension, and estrogen receptor/progesterone receptor positive disease".

Questions have been raised about the number of sentinel lymph nodes to remove to gain a predictive value on disease free survival and to guide to perform an ALND. According to retrospective and prospective studies applying ACOSOG Z0011 criteria (44-46), the ideal number of sentinel lymph nodes to be harvested is three, since the involvement of more than three nodes requires an ALND for a high risk of residual axillary disease.

Subhedar *et al.* (47) proved there was no relation between the increase of number of sentinel lymph nodes removed after ACOSOG Z0011 trial and a significant decrease of ALND. They reported a higher number of lymph node removed only in younger patients and/or with larger tumors.

Yao *et al.* (48) underlined in their retrospective analysis the spread of approach of SLNB without ALND (National Cancer Data Base, 1998–2011), but they also reported ALND as preferred treatment in clinical practice for high risk patients (i.e., HER2-positive disease, triple negative BC and/or age <50 years at diagnosis). In contrast with this preference, Chung *et al.* (49) focused on applicability of ACOSOG Z0011 criteria in high risk patients, showing ALND can be avoided in 84% of cases with clinically negative nodes. Wang *et al.* (50) confirmed oncological safety of SLNB only in early lobular invasive cancer (about 7% of ACOSOG Z0011 population).

In September 2016, Giuliano *et al.* (51) published an update of ACOSOG Z0011 trial after a follow up of 9.25 years. In this article, they confirmed previous results about locoregional disease control, answering critical issues and pointing out about some limits of their study.

As reported by Tsao *et al.* (52) in their comparison of spread of SLNB according to ACOSOG Z0011 trial and after diffusion of regional guideline for ALND, in the clinical practice the trend of decrease of completion axillary clearance depends on a multifactorial and individualized decision making process. Particularly, criteria not included in Z0011 trial were patient's age, presence of extracapsular invasion (ECI), lymph node ratio (defined as the total number of positive nodes/total number of nodes dissected during SLNB), size of SLNB metastasis, ER status, type of surgery.

Jagsi *et al.* (53) answered to criticism about radiotherapy (RT) lacking planning data in ACOSOG Z0011, underlining the RT contribution in control of local recurrence in positive SLNB not followed by ALND.

The AMAROS trial (54) confirmed the efficacy of axillary irradiation compared to ALND after positive SLNB, having an equivalent 5-years axillary recurrence free

survival for T1–2 primary cancer, with a significantly less morbidity in the arm treated with RT.

Some limits were ascribed to AMAROS trial, such as small recruitment, choice of tumors with low risk of recurrence, a high number of micro-metastasis and isolated tumors cells. The Hungarian OTOASOR trial (55) have proved AMAROS effectiveness applying criteria on a larger population with eight years follow up, reporting similar axillary recurrence rate, overall survival and disease free survival in patients treated with ALND or RT after positive SLNB.

ALND or RT after positive SLNB should be considered also if sentinel lymph node is affected by an ECI >2 mm .

As remembered by Gooch *et al.* (56), ECI could be present in about 19–26% of SLNB and in about 30% of cT1–2, cN0 BC. Gooch conducted analysis on a prospective database, considering ACOSOG Z0011 criteria. They found out that ECI >2 mm was correlated with a greater axillary burden, an older age, larger, multifocal and HR positive tumors, and presence of lymphovascular invasion (LVI). These evidences suggest that ECI >2 mm in SLNB should guide to perform an ALND or RT also in patients with less than three positive lymph nodes. Also for Choi *et al.* (57), an additional RT should be considered in ECI >2 mm, since it's related with N2 disease.

The first results from the German-Austrian Intergroup-Sentinel-Mamma (INSEMA) (58) trial have recently been published. This study is based on a double randomization in BCS for EBC: the first one to perform or not SLNB, the second one in patients with one or two positive SLNB to perform or not an ALND. A preoperative US evaluation is always performed as in the SOUND trial, with which primary and secondary endpoints are shared. With a good detection rate of the sentinel lymph node (99.5%), at June, 2016 the first randomization has reported only 1.3% of patients with more than three involved nodes and 12.9% of patients with one or two macro-metastasis. According to the outcome, a limited recruitment was registered till now to a second randomization, also due to patients' refusal (20% of population) and delayed recruitment by Austrian centers. A follow-on INSEMA project will be led minimizing breast irradiation in low risk patients without SLNB, while raising question is about avoiding SLNB also in patients treated to mastectomy.

As evolution of an extremely less aggressive axillary approach, great expectation are put over the ongoing prospective Italian SOUND trial (19). Authors question about role of SLNB today, since the setting of adjuvant treatment are tailored to the biological tumor characteristics, that are related to the disease prognosis more than the knowledge of axillary involvement.

All patients treated with BCS + WBI have an US axillary evaluation and a core biopsy or fine needle aspiration of suspicious lymph nodes. Population is randomized in two arms, SLNB or axillary observation. First results (59) about quality of life are about a significant less rate of disability in the observation group, more evident one week after operation (24% in SLNB arm, 10.6% in observation one).

Mastectomy and positive SLNB

ACOSOG Z011 trial has considered EBC that underwent only to conservative treatment. Nevertheless mastectomy is also another surgical option used in EBC with an unfavorable ratio breast size/tumor size or in multifocal tumors.

Current guidelines indicate ALND as standard of care after positive SLNB in mastectomy, but it starts to be a controversial issue.

Fu *et al.* (60) and Kenny *et al.* (61) retrospectively investigated about the applicability of ACOSOG Z0011 in patients with positive SLNB and mastectomy. Kenny *et al.* showed the increasingly trends to avoid ALND also in mastectomy in the post ACOSOG Z0011 era in EBC with low burden axillary disease.

Fu *et al.* concluded overall survival and systemic relapse free survival rate were the same between groups treated with ALND or RT after SLNB, and reported fewer side effects with RT than with ALND.

Miller *et al.* (62) reported the potential benefit in terms of sequelae of applying ACOSOG Z0011 criteria to mastectomy patients. The two years lymphedema incidence was of 2.19% after SLNB, 10.0% after SLNB + RT, 19.3% after ALND, 30.1% after ALND + RT.

To avoid complete axillary clearance and considering ALND in mastectomy as standard of care after positive SLNB, Cowher *et al.* (63) elaborated a mixed technique, called Conservative Axillary Regional Excision (CARE). With a median of 8 nodes removed and a 0.5% of local recurrence at 5 years follow up, they considered their CARE a safety conservative treatment of axilla.

More recently, FitzSullivan *et al.* (64) verified retrospectively outcomes of positive SLNB in mastectomy underwent to ALND or axillary RT or simple observation. At a follow up of 10 years, the higher axillary recurrence was registered in patients without treatment (3.8%), the less

one in the ALND group (1.6%), the lower in patients had made axillary RT after SLNB (1.8%). These differences were not statistically significant. The authors suggested to consider SLNB not followed by ALND only in low risk groups, such as elderly patients, with small tumor size and/or small metastasis node size, with fewer positive lymph nodes and absence of LVI or ECI.

Future knowledges from trial ongoing

Further knowledges on axillary management could be available in future from results deriving from randomized controlled trials that are now ongoing:

(I) The Italian SINODAR ONE (65), and the English POSNOC (66) trials were both design to understand if ALND could be avoided in patients with one-two positive SLNB, including mastectomy; a preoperative US evaluation of axillary is mandatory in both studies;

(II) The Dutch BOOG 2013-07 trial (67) is a randomized multicentric study that analyzes cT1-2 cN0 BC, with maximum three positive sentinel lymph nodes; the aim of this study is to confirm the safety due to avoiding axillary treatment (i.e., ALND or axillary irradiation) in mastectomy after positive SLNB, comparing one group of patients treated with only SLNB with the other group undergone to axillary treatment;

(III) The Swedish SENOMAC (68) trial includes in the randomization to ALND or no further surgery after positive SLNB also T3 tumors, patients undergone to neoadjuvant systemic treatment and male patients.

Role of sentinel node biopsy in neoadjuvant setting

Usually, NAC is provided with the aim of down-staging. The main objective is to reduce the tumor volume both in breast and axilla making breast and axillary conserving surgery feasible and safe (69).

Mamounas and colleagues in 2016 described the axillary pathological complete response (pCR) in triple negative (TN) and Her2 positive BCs. They showed a pCR rate of 30% with anthracycline and 40% with taxane. In case of Her2 positive BCs, the addition of Trastuzumab is related to axillary pCR rates up to 70% (70). However, performing ALND when a pCR is documented, so without active axillary disease, should be considered as a failure of treatment planning and a kind of overtreatment (71). In addition to the debate on feasibility and safety of SLNB in neo-adjuvant setting, the timing is still a topic of discussion with pros and cons (72).

Ozmen *et al.* (73) suggest that staging the axilla before NAC let surgeons overcome the effects of systemic therapy, reducing the number of patients referred to ALND after treatment. Furthermore, many authors (27,70,72,74) described how the accuracy of SLNB may be potentially influenced by chemotherapy.

Pilewskie and Morrow (74) indicated how in several studies the most frequent concerns were related to fibrosis of lymphatic system and to the risk that a variability in axillary response may determine a FNR higher than that usually accepted. They showed the accuracy of this procedure was mostly reduced in case of bulky nodes or poor axillary response. Clearly came out how a better patients' selection is associated with the feasibility of the technique after NAC.

In fact, Mamounas and colleagues (75) examined the role of NAC analyzing the most relevant trials. The NSABP-B27, comparing NAC to adjuvant treatment and GANEA study which evaluated the role of SLNB followed by ALND in neoadjuvant setting showed encouraging data as a global identification rate of 86.5% and FNR of 10.9%. These results are substantially comparable with SLNB up front.

Furthermore, two meta-analyses confirmed the accuracy of SLNB post NAC with identification rates of 90% and 89.6% or FNR of 12% and 8.4% respectively (73).

Two more meta-analysis, cited by Rubio (72) (conducted by van Deurzen and Tan) confirmed FNR comparable to SLNB performed without NAC (10.5% and 7.4%). Regarding the identification rate, in clinically node negative patients who underwent NAC values are similar to SLNB up front (92.7% from 5 studies, 266 patients and 94.3%) (72).

Given the several data available in literature, in the UK guidelines the surgeons are allowed to perform a post NAC SLNB if axillary lymph nodes were considered negative by US and/or FNA before starting treatment.

The decision on the opportunity to perform the SLNB should be taken in a multidisciplinary meeting at the time of the treatment planning (71). What remains unclear is the appropriate behavior in case of pCR to treatment. Therefore, SLNB in case of significant axillary burden before NAC should not be considered. Moreover, Ollila *et al.* (76) showed the great variability in the approach among different surgeons.

Usually patients with pre NAC node positive disease undergo ALND with the associated risks in terms of comorbidities and with an unclear benefit in terms of survival. Due to the upcoming data on the high rate of pCR in specific molecular subtypes as triple negative breast cancer (TNBC) and Her2 positive, ALND is starting to be considered as an overtreatment, justifying the use of the SLNB (71,73,77).

These considerations are supported by three prospective clinical trials: (I) the ACOSOG Z1071 trial (27); (II) SLNB in patients with BC before and after NAC (SENTINA) (78) and; (III) sentinel node biopsy after NAC in biopsy-proven node-positive BC: the SN FNAC Study (79).

The first study, involving 2,471 patients, investigated the feasibility of SLNB after NAC in clinically axillary node positive patients with a good response to treatment (73). The authors found an axillary pCR of 41% with a FNR from 10.8% to 12.6% related to the chemotherapy regimen administered. This value became lower if more than one sentinel node were excised and with the use of immunohistochemical (8.7%). Only in a subgroup of patients a clip was placed in the positive node before treatment; when the node with the clip corresponded to the sentinel node the FNR reported by authors was 6.8%.

Moreover, a meta-analysis including 3,398 patients, showed a similar pCR (39.2%) with a FNR of 13%, substantially overlapping the results of the previous study (73).

Another European multicentric study conducted in Sweden, enrolled 195 node positive patients who underwent NAC showing a FNR of 4% in case of more than one sentinel node excised (80).

The number of sentinel node removed was associated with treatment effect detected (88% in case of 3 nodes excised). Also an UK study, the ROSCO trial, showed an advantage of removing more than one axillary nodes after NAC in patients clinically positive when treatment started.

To reduce the FNR, many authors tried to identify and excise the pre-NAC positive nodes. Rubio showed how marking the pre-treatment positive nodes and removing them is associated with a lower FNR of SLNB. Conversely, Barrio *et al.* described how identifying post treatment changes in the nodes at pathological report is a proof that previous positive nodes were removed. They found treatment changes in 94% of the previous positive nodes with post NAC pCR (81). The subgroup analysis related to molecular subtypes showed treatment effect in 96% of TNBC and HER2 positive tumors compared to 83% of hormone receptor positive disease.

In summary, performing SLNB with double tracer (blue dye and 99 Technetium), removing more than one node, marking with a clip the positive node to check the presence during SLNB seem to make this technique accurate (73). In fact, Caudle *et al.* described how with all these recommendations the FNR of SLNB can reach 2% (28).

Usually, the FNR considered acceptable in the adjuvant setting is 10% and the same value was borrowed as the cut off reference for SLNB after NAC (72).

To assess this item, Galimberti *et al.* (82) retrospectively analyzed the outcome of 396 BC patients cN0 or cN + prior to NAC, cN0 after NAC and who received SLNB. ALND was performed only in case of positive sentinel node. After a median follow-up of 61 months, the five-year OS was 90.7%: 93.3% in patients cN0 before treatment, and 86.3% (P=0.12) in initially cN1/2 patients. The authors showed a similar axillary disease rate in initially cN0 patients and in initially cN1–2 became cN0 after treatment with no statistically significant outcome differences. These data are concordant with those from IBCSG 23-01 (83) and ACOSOG Z001119 (3) trials in which no outcome differences were observed between the ALND and no-ALND.

In conclusion, the presenting nodal stage is not a limit for SLNB. In case of positive axillary nodes pre-NAC the addition of double tracer technique, the removal of more than two nodes and marking the pretreatment positive nodes may be advisable to reduce the FNR.

Actually NCCN current guidelines support the option to perform a SLNB in patients with positive axillary lymph nodes before treatment and cN0 after chemotherapy (29,74,84).

If on one hand, we haven't yet data regarding regional recurrence after SLNB, on the other the presence of lymph nodal disease in the sentinel node (from ITC to macro-metastasis) still requires ALND.

Two ongoing randomized trials will clarify the recommendations regarding ALND after NAC: (I) the NSABPB-51 (85) on patients with axillary positive nodes before treatment converted to clinically node negative; all the enrolled patients will be randomly assigned to lymph node radiation; (II) the Alliance A11202 trial (https://clinicaltrials.gov/ct2/show/NCT01901094) on patients with biopsy proven axillary positive nodes before NAC and a positive SLNB after surgery; patients are assigned randomly to ALND or not and all of them will undergo nodal radiation.

Table 1 Variables considered in more used nomograms

Variables	MSKCC	Cambridge	Turkish	Stanford	MDACC	Tenon	MOU	GUR	Saidii
Age					•				
Tumor size	•			•		•	•		•
Palpable mass									•
Multifocality	•				•		•		
Location of tumor					•				
Tumor type	•								
Mixed histology							•		
Lobular histology							•		
Histologic grade	•	•							
Detection method of SLNs mts	•								
Size SLN mts		•	•				•	•	
Micro- or macromts				•		•			
No of SLNs removed									
No of positive SLNs	•								
No of negative SLNs	•								
SLN ratio		•	•			•		•	
LVI	•		•	•	•		•	•	•
ECI							•		•
ER	•								
Triple negativity					•				

MSKCC, Memorial Sloan Kettering Cancer Center; MDACC, University of Texas MD Anderson Cancer Center; MOU, Masarykuv Onkologicky Ustav; SNLs, sentinel lymph nodes; mts, metastasis; SLN ratio, number of positive SLNs/total number of SLNs removed; LVI, lymphovascular invasion; ECI, extracapsular invasion; ER, estrogen receptor.

With the increasing spread of neoadjuvant treatment, the greater rates of pCR and the trend towards more customized treatment planning, it is becoming crucial to have specific guidelines regarding loco-regional surgical treatment in this specific setting of patients.

Nomogram and predictive factors of additive positive NSLNs

Over the years, the parameters related to NSLNs metastasis risk after positive SLNB have been collected in nomogram, to recommend ALND and prevent local recurrence or to avoid unnecessary further surgery (*Table 1*).

Nowadays, some authors have tried to find out which nomogram may be more predictive.

Nadeem *et al.* (86) have compared the currently in use nomograms: Memorial Sloan Kettering Cancer Center (MSKCC), Masarykuv Onkologicky Ustav (MOU), university of Texas MD Anderson Cancer Center (MDACC), Cambridge, Turkish, Standford, Tenon. They constructed a ROC curve, calculate the AUC, finding in the MOU model the highest AUC value (0.74) and the lesser FNR for ≤10% probability (0%, but there were no patients in this low probability group).

Also Yildiz *et al.* (87) investigated the accuracy of nomogram and scoring system (MSKCC, MDACC, Tenon, Standford). They shared Nadeem's difficult to validate the MSKCC nomogram for the absence of size of SLNs

metastasis, and found in no one of the five nomogram a good AUC discrimination. Instead, despite the limitation of a single and small population, a statically significant correlation was identified between multifocality and size of primary tumor and SLN metastasis in a multivariate logistic regression analysis.

In conclusion, Nadeem and Yildiz agree that nomograms lose their accuracy and good discriminatory power when performed in other centers, having different population from those from institution where they were developed. An accurate nomogram should include the most possible variables, including size of metastasis in SLNs that is not yet usually documented in the pathologic data sets.

Van den Hoven *et al.* (88) compared nine nomograms: MSKCC, Stanford, Mayo, Cambridge, GUR, MOU, SAIDI, Tenon, MDACC. They considered not only AUC but also calibration as an important parameter in predictive tool evaluation, finding best value for MSKCC nomogram, followed by Mayo model.

The authors specified that an individual approach in decision making is needed, since the allowed percentage of missing NLSNs metastasis differs from patient to patient, and predictive models of high probability of having more than three positive SLNB have to be developed.

Including its limitation, MSKCC nomogram is to date the more applied and supported in its validation by different retrospective analysis from single different institution (89,90).

To date only Meretoja *et al.* (91) elaborated a nomogram based on multicentric international experience. They elaborated a formula that considers principal variables associated with additional positive NSLNs: percentage of patients with positive NSLNs, LVI, multifocality, HER2 status, number of negative and positive sentinel nodes, size of tumor, size of metastasis, EIC. This model has a good accuracy and calibration, both in internal and external applications, but it needs to be more validated before use it in clinical practice.

Freedman *et al.* (92), Gülben *et al.* (93) and Houvenaeghel *et al.* (94) have underlined there is a subgroup of patients that may need of ALND completion (about 15% of patients in Fredman's analysis). Parameters not included in the ACOSOG Z0011 criteria and in MSKCC nomogram could reveal these population: age, HR status, HER2 status, ki67 level, presence of LVI and/or ECI .

Also Fujii *et al.* (95) highlighted the importance of presence of ECI, finding a relation between ECI in SLNs and positive NLSN while disease recurrence is associated to ECI only if is present in NLSN.

The European OSNA Users Committee (96) developed a new nomogram to predict, during operation, the risk of positive NLSN based on the CK19 mRNA copy determined by OSNA assay and tumor size (the other predictive factor, LVI, is unreliable in a preoperative core biopsy). According to this nomogram, an ALND is to perform for values higher than 31%.

Axillary management in elderly women

The prime risk factor for BC is ageing, mostly affecting women age >65 years, 20% of which being over 75 (97). Despite the significant impact of this disease on the worldwide population, existing data supporting BC management during elderly are limited. The available information is often based on broad and randomized clinical trials that specifically exclude patients over 65 years of age (98). The lack of dedicated relevant data resulted in the actual unclear roadmap for an appropriate management of elderly BC (99). Elderly women are thought to have biologically more favorable tumors. The actual approach sees younger women more likely to be treated with BCS and SLNB, opposed to older patients most often treated with mastectomy and ALND (100). Some of the reasons why aggressive treatment of such patients are not often subscribed include extensive comorbidities, patients' preference, lack of social support, a declining functional and mental status, a minimal estimated life expectancy and physician preference (99). SLNB staging in elderly women is frequently omitted (101-104). Nodal staging by ALND, in the setting of positive SLNB, can influence both systemic adjuvant chemotherapy and loco-regional radiotherapy decisions. However, its impact on cancer specific survival and on the receipt of adjuvant therapy among older patients remains unclear (105) and cannot be so clear-cut, also considering the significant potential side effects associated with the ALND. Martelli *et al.* (106) found no differences in overall or breast-specific cancer survival at the 15 years follow-up stage between ALND and no-ALND groups, within older patients who had T1N0 breast-cancer, with a lower risk of axillary recurrence in the no-ALND group. Similarly, Javid *et al.* (105) found that 5 years all causes survival and BC specific survival did not differ between positive SLNB older patients who underwent SLNB only compared to the treatment SLNB + ALND. In the mentioned reference it has been identified a panel of factors such as higher age, advanced tumor size, undifferentiated

historical grade, macro-regional nodal disease, negative hormone receptor status and mastectomy versus BCS, associated with a significantly higher risk of BC-specific mortality. The number of comorbidities was not associated with the receipt of ALND suggesting that age may play an independent role in surgical decision making. Aziz *et al.* (107) found a trend toward survival benefit among patients >70 years old who underwent ALND, becoming non-significant upon propensity analysis adjusting for receipt of ALND predictors. Several studies suggest that omitting completion of ALND not only in elderly patients with clinically N0 tumors (108), but also in positive SLNB patients (107) may be reasonable as it would have no impact on DFS and OS (104). Given the lack of direct benefits in the literature in terms of survival and local recurrence of the tumor, surgeons may choose to stage older women only when they have high suspicions of positive lymph nodes because many fragile elderly women may not benefit from lymph node staging, especially when their axilla is clinically normal (99). ALND in older patients may be reserved for cases in which data from ALND would clearly impact adjuvant therapy decisions.

Conclusions

Our review of the latest literature has confirmed the recent trend of de-escalation in the axillary surgical approach in BC with the goal of sparing unnecessary ALND even in the categories of patients traditionally subjected to ALND and reducing the associated morbidities. The indications and issues regarding the positive SLNB approach during conservative surgery and during mastectomy have become clearer, ongoing studies on these topics will provide more accurate information. In the positive SLNB setting, the adoption of the RT, according to the most important parameters, still remains a significant element in local control. About patients treated with NAC, the use of SLNB even in cN + pre-NAC patients appear to be useful and reliable in avoiding ALND in case of negative SLNB. Important studies are ongoing to evaluate the possibility of not performing ALND even in presence of positive SLNB.

Furthermore, the relevance of a more accurate evaluation of the preoperative axillary staging has been demonstrated while the SLNB intraoperative study is losing significance.

The axillary approach must therefore be re-evaluated in all categories of patients including the elderly who represent an ever increasing group of patients.

The aim of reducing surgery in axillary treatment is expressed by the presence of current studies that are considering the possibility of omitting every axillary approach in selected patient groups.

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