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Review

Role of sentinel node biopsy in breast cancer: a review

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Axillary lymph node involvement is still an important predictor of recurrence and survival in breast cancer. Axillary staging was classically done by axillary lymph node dissection (ALND), but the introduction of sentinel lymph node biopsy (SLNB) has led to a progressive and continuing de-escalation in its use. Therefore, SLNB can now be considered the standard procedure for axillary staging in clinically N0 patients. Different studies have also begun to report that a positive sentinel node does not always require ALND, reducing the morbidity derived from this technique. Fears that this sentinel node approach might not be accurate for neoadjuvant chemotherapy have been allayed by several studies showing that post-neoadjuvant SLNB in clinical N0 patients reduces the rate of ALND. This approach benefits from axillary pathological complete response with an acceptable false-negative rate. By contrast, however, cN1 disease still requires that we optimise the technique to reduce the rate of false negatives. Currently, SLNB is the best method for axillary staging in breast cancer, allowing patients to be treated according to risk of recurrence, and with good evidence that morbidity is lower than with other more radical techniques.

Keywords

Sentinel lymph node biopsy; Breast cancer; Axillary lymph node dissection; Neoadjuvant chemotherapy; Node positive; Macrometastasis; Micrometastasis

1. Introduction

The presence and extent of axillary lymph node involvement is one of the most powerful predictors of recurrence and survival in breast cancer besides tumour biology [1], making the evaluation of node status crucial to proper therapeutic management. Historically, lymph node involvement in breast cancer was determined solely by axillary lymph node dissection (ALND), which not only provided high sensitivity and accuracy of detection but also carried high morbidity (e.g., lymphedema, pain or potential injury of vascular and brachial plexus). Today, it is accepted that less radical procedures provide adequate staging.

2. Definition of sentinel node and sentinel lymph node biopsy

The sentinel node (SN) is defined as the node that first receives tumour drainage to the lymphatic system of a determined anatomical region. This definition implies a sequence in the drainage to the lymphatic system of the tumour cells. There can, therefore, be multiple SNs. The first mention of the SN in the literature dates to 1960, when Dr. Gould proposed that the SN predicts the histological state of the rest of the nodes in a determined region. However, it was Cabañas in 1977 [2] who stated that tumour cells from a primary carcinoma migrate through the lymphatic channel to a single lymph node before involving further lymph nodes within that basin [1]. In the 1990s Krag *et al.* [3] and Giuliano *et al.* [4] in identified the SN in breast cancer using a radioactive tracer and a vital dye, respectively [5].

A sentinel lymph node biopsy (SLNB) is the procedure in which the SN is identified, removed and examined to determine the presence of tumour cells. Morton *et al.* [6] first used this technique in patients with cutaneous malignant melanoma and Giuliano *et al.* [4] developed and used a modification of lymphatic mapping and sentinel lymphadenectomy to detect axillary lymph node metastasis in patients with breast cancer. SLNB predicts the axillary state in 95% of patients at low-risk of spread in breast cancer, which means that the risk of falsely staging an axillary tumour as negative is approximately 5% [7]. Therefore, lymphatic mapping by SLNB instead of systematic ALND is considered appropriate in early-stage breast cancer with clinically negative axillary lymph nodes [8]. Using this approach, the overall survival (OS), disease-free survival (DFS) and regional control for SLNB are statistically equivalent to those for ALND [9]. Nevertheless, ALND remains the standard treatment for patients with clinically positive axillary nodes who are initially treated surgically [8].

Table 1. Current indications and contraindications for SLNB of the breast.

Indications	Contraindications	Other indications (Past contraindications)
Infiltrative carcinoma T1, T2 or T3, cN0 (clinically and echographically negative) [16]	Breast cancer with N1–N2	Multifocal or multicentric tumours [17]
Intraductal or in situ carcinoma if: - indication of mastectomy - high risk of infiltration (high histological grade or comedonecrosis; Ø $\geq$3 cm; associated with a palpable or nodular lesion)	Inflammatory Carcinoma (T4d) [16]	Previous tumourectomy Previous plastic mammary surgery Previous breast or axilla radiotherapy Mammary recurrence after previous conservative surgery with SLNB [18] Before or after neoadjuvant treatment in cN0 patients [19–22] Pregnant, puerperal or lactating woman [23, 24] - Use of minimal possible dose, the same day of surgery - Vital colourants still contraindicated - Stop breastfeeding for 24 h T4b breast carcinoma in selected cases with focal changes

3. The SLNB technique in breast cancer

Several techniques are used to localise SNs during surgery. Two of the most frequently used are: vital colourant (Isosulfan Blue Dye or Patent Blue Dye) and radioactive colloid (Technetium labelled albumin). These are not mutually exclusive and can complement each other, depending on local availability and the experience and preferences of the surgical team [10].

When Blue Dye is used, 2–5 mL of blue dye is injected around the tumour periphery, avoiding intratumoral injection and/or injecting the dye into the seroma cavity secondary to breast biopsy, which could lead to a failure of mapping [11]. The time from injection to axillary incision varies from 3 to 8 minutes depending on the size of the patient and location of the tumour. Breast massage is usually performed at the site of the blue dye injection until the incision is made, theoretically helping the dye reach the SNs [12]. The axillary fascia is entered through an inferior incision in the axilla, and all blue lymphatic nodes or any at the end of a blue lymphatic channel are removed and designated as SNs. Suspicious palpable nodes are also removed. The two most common technical errors are failure to consider the node at the end of a blue lymphatic channel and failure to identify the blue node most proximal to the tumour [11].

When radiocolloid is used, close cooperation between nuclear medicine and the surgeon is essential to ensure that information is shared about changes in the injection technique [12]. The proportion of successful mappings is significantly higher in studies using radioactive colloid rather than blue dye alone [11]. The principal advantages of this approach are the provision of an anatomical map of the lymphatic drainage of every patient, finding both axillary and extra-axillary SNs, and the identification of the most adequate site to perform the surgical incision [10]. The nodes are identified by a sensitive hand-held gamma probe, and in the operating room, a small skin incision is made over the suspected nodal area and the probe is used to guide the surgeon to the labelled lymphatic nodes [11].

Other techniques for localising sentinel lymph nodes are currently being investigated, focusing on the possible benefits for centres without access to a nuclear medicine service. Two of these techniques have the greatest amount of supporting data. The first uses Indocyanine Green (ICG) injections before localising the SN with a fluorescent imaging system [13]. The second uses an injection of Superparamagnetic Iron Oxide (SPIO) and locates the sites with a magnetometer [11]. A meta-analysis has showed that using Sienna + as an SPIO and detecting it by magnetometer was non-inferior to the standard methods of SLNB for mapping [14].

4. Current indications and contraindications for SLNB

SLNB is an unstandardised procedure in continuous evolution. Indeed, many controversies remain concerning the technique and its indications and contraindications [15]. The current indications and contraindications of SLNB are summarised in Table 1 (Ref. [16–24]), together with a third column that lists past contraindications. Note that there is no evidence for SLNB to be indicated in cases of previous plastic mammary surgery or previous breast or axilla radiotherapy, and that this recommendation is only based on expert consensus.

5. Pathological examination of SNs

Frozen SN sections are examined pathologically to detect tumour cell deposits that can be classified by their size in isolated tumour cells, micrometastasis and macrometastasis. Isolated tumour cells refer to deposits $\leq$0.2 mm, designated pN0 (i+) in the Tumour, Node, Metastasis (TNM) system, and these do not worsen the prognosis compared to a negative SLNB [25]. Micrometastases are 0.2–2.0 mm clusters of tumour cells and are designated as $pN1_{mic}$ in the American Joint Committee on Cancer (AJCC) staging system [25]. These can be associated with non-SN involvement, although even then, there is not enough evidence to support ALND [26–28]. Micrometastases are associated to a worse

long-term prognosis, and evidence suggests that affected patients may benefit from systemic treatment [27]. Finally, macrometastases refer to any tumour cell cluster >2 mm and are a well-established independent predictor of a poor outcome [25].

Immunohistochemistry (IHC) staining with cytokeratin is not used routinely for pathological examination but can be useful for cases of invasive lobular carcinoma (where tumour cells closely resemble lymphoid cells). It should be used to diagnose a suspicious area on hematoxylin and eosin definitively (i.e., antibodies can uncover a small number of tumour cells that are not easily visible) [8, 25].

6. Molecular SN study

The One-Step Nucleic Acid Amplification (OSNA) test is a molecular method for detecting metastatic SNs. It relies on detecting mRNA expression of epithelial marker cytokeratin 19 (CK19), which is highly expressed in most breast cancer cells but is absent in normal lymph nodes. The sensitivity and specificity of the OSNA test has been reported for the detection of metastases, with a low rate of false positives [29, 30]. Therefore, OSNA is considered a reliable tool for intraoperative diagnosis of whole SNs and can minimise the need for secondary surgery [29].

7. SN mapping: lymphoscintigraphy and extra-axillary drainage

In many centres, lymphoscintigraphy is performed as part of the SLNB to obtain images from a gamma camera. This technique provides individual mapping for each patient and offers the possibility to visualise the SN of unexpected locations. However, controversy surrounds the technique's use, with arguments for and against. Those who defend it argue that it gives the option to mark the skin during the gamma camera imaging, making SN detection easier with a gamma probe during surgery. Although sometimes not precise enough to distinguish between SNs that are very close, it can indicate the number of nodes present. Moreover, it provides information about the extra-axillary drainage of radiocolloid to the internal mammary, intra-mammary, contralateral axillary and supraclavicular nodes. Arguments against lymphoscintigraphy include the added cost, that the handheld gamma probe may be more accurate in identifying the best side for skin incision, and that most lymph nodes draining breast cancer are in the axilla, meaning that nodes in other locations may not alter management [8, 11].

According to the literature, lymphoscintigraphy may be used in patients with breast cancer recurrence who have previously undergone any type of axillary procedure [25]. As detection techniques have improved, however, there has been an increase in the detection of extra-axillary lymph nodes in breast cancer. The clinical importance of these nodes detected remains unclear [31].

Concerning the internal mammary nodes, we must consider that the SN technique has limitations due to radioactivity interference from the primary tumour [32]. Lymphoscintigraphy studies suggest that approximately 30% of medial tumours and 15% of lateral tumours drain primarily to these nodes, while surgical series have indicated that there is a higher risk of their involvement in cases of medial tumours and positive axillary nodes [20]. In a population-based cohort study by Thorsen *et al.* [33], the irradiation of internal mammary lymph nodes increased the OS in patients with early-stage node-positive breast cancer. One of the most important arguments against this approach is the potential for cardiopulmonary toxicity [33]. Thus, when considering investigating internal mammary nodes, a diagnostic procedure with a complication rate of approximately 2%–6%, the surgeon should consider how the results will affect adjuvant chemotherapy or radiotherapy [34].

Intra-mammary lymph nodes may be detected in 1%–28% of breast cancers [35]. Positive intra-mammary nodes can modify disease staging but do not necessarily imply axillary lymph node involvement. In this setting, biopsy of both the axillary and intra-mammary nodes is recommended, with the completion of axillary surgery detailing the status of the axilla [36, 37]. If the intra-mammary nodes are the only draining sites detected on lymphoscintigraphy, an uncommon scenario, care should be individualised to the needs of the patient [36] but management of the axilla should be governed by axillary SN status.

8. Staging the axilla after a negative SLNB

The role of axillary surgery as a staging and prognostic procedure, rather than only as a therapeutic intervention, has been widely accepted over recent years. Several factors have contributed to the progressive decrease in the extent of axillary surgery, such as screening mammography, adjuvant and systemic therapies, radiotherapy, and the relevance of biological markers [38, 39].

Axillary recurrence after SLNB is considered a rare event [40]. In a systematic literature review by Van der Ploeg *et al.* [41], the axillary recurrence rate in SLNB-negative cases was just 0.3%. According to other studies, this recurrence rate could increase to 1.5% after 5 years [7]. Of note, neither the ALMANAC [42] nor the NSABPB-32 [9] study found statistically significant differences in OS, DFS or regional control between SLNB alone and ALND following a negative SLNB.

Given an identification rate of 98% and a predictive value for SN of 97.5%, we are confident that it is not necessary to perform ALND in patients without SN involvement [43]. Today, SLNB is considered standard care for axillary staging in cN0 breast cancer [1] because axillary local recurrence is extremely rare after a negative SLNB (0.3%), adding ALND to SLNB does not affect the DFS or OS, and the morbidity of SLNB is less than that of ALND [44, 45].

Table 2. Axillary local recurrence and relative survival in SN micrometastases, macrometastases with or without ALND. Patients: National Cancer Database (1998–2006). Adapted from Bilimoria *et al.* [46].

Surgery and micro/ macrometatasis	Axillary local recurrence (5 years)	Relative survival (5 years)
SN micrometastases		
SLNB	0.4%	99%
SLNB + ALND	0.2%	97.8%
SN macrometastases		
SLNB	1.0%	89.9%
SLNB + ALND	1.1%	89.1%

9. Overview of management after a positive SLNB

9.1 Introduction

The presence of axillary lymph metastases is still one of the most important prognostic factors in breast cancer. As outlined above, ALND has been the preferred method for assessing axillary involvement for years, allowing us to know the state of the axilla and when clinically relevant disease was present. Although this could affect axillary recurrence and local disease control, removing all axillary nodes causes anatomic disruption that may result in interstitial fibrosis and lymphedema. This is one of the most uncomfortable complications of axillary surgery, compromising quality of life. SLNB therefore aims to avoid the morbidity of ALND while preserving its prognostic utility. In the studies of validation of sentinel node biopsy, concordance between SN involvement and axillary involvement was reported in 97.5% of cases and in 95% of case of non-metastatic involvement of the axilla.

9.2 Axillary surgery after a positive SLNB

Patients with a positive SN had historically undergone ALND to assess nodal involvement. Today, however, some clinical trials have concluded that performing an ALND does not provide any survival benefits for patients with limited axillary disease.

First, we must consider that 30%–50% of patients with a positive SN have disease limited to this SN, without other involved nodes [1]. Moreover, axillary recurrence is uncommon, reported in less than 2% of cases in most studies. In a retrospective study, Bilimoria *et al.* [46] reported on 97,314 SN-positive cases, among which 23% with SN macrometastases (pN1) and 55% with SN micrometastases (pN1mi) did not undergo ALND and the remaining 22% underwent ALND. After adjusting for differences in pathological characteristics and adjuvant treatment between participating clinics, axillary local recurrence and 5-year relative survival for both pN1 and pN1mi SN disease, were the same with or without ALND (Table 2, Ref. [46]).

Similar results were reported by Yi *et al.* [47] in a retrospective study of 26,986 SN-positive cases from the SEER Database (1998–2004). Of these, 11% had SN macrometastases and 33% had micrometastases (neither group underwent ALND). Compared with the rest of the patients who underwent ALND, there were no significant differences in OS over a 50-month follow-up period. Thus, compared with SLNB alone, it was shown that ALND does not improve survival for breast cancer patients with micrometastasis at SLNB.

Another retrospective study comprising 276 SN-positive patients, treated both with and without ALND, also concluded that the omission of ALND in women with SN-positive disease did not significantly affect breast, nodal or distant recurrence, or mortality. This study also reported low rates of axillary recurrence at 28–82 months (typically, 0%–2%) [48].

The ACOSOG Z0011 study tried to answer if ALND affects the survival of patients with SN involvement [49, 50]. This prospective, non-inferiority, randomised trial closed prematurely due to poor enrolment and a low number of events. ACOSOG Z0011 included 891 SN-positive cases with clinical stage T1–T2/N0 breast cancer randomly assigned to complete ALND. These were compared with a group that received no further surgery. All patients underwent breast conserving surgery (BCS) and whole-breast radiation therapy, with most women also receiving systemic treatments. Patients were excluded if they had $\geq$3 positive SNs or matted nodes, and SLNB was studied by routine hematoxylin and eosin staining. Additional positive nodes were described in 27.3% of cases that underwent ALND, but at a median follow-up of 6.3 years, there were no differences between the ALND and non-ALND arms in local (3.6% vs. 1.9%), regional (0.5% vs. 0.9%), or overall locoregional (4.1% vs. 2.8%) recurrence [51]. Consequently, they concluded that SN alone did not result in statistically inferior survival compared to ALND. The 5-year OS rate was 92.5% in the SN group and 91.8% in the ALND group ($p = 0.25$); the corresponding rates for the 5-year DFS were 83.9% and 82.2%, respectively ($p = 0.14$).

Unfortunately, several criticisms were levelled at the ACOSOG Z0011 study. If we consider the entire population of the study, 69% of the patients were stage T1, more than 80% were had hormone receptor-positive disease and 61% had no intravascular invasion. Moreover, the patients were not stratified by important prognostic factors, such as HER2 overexpression or proliferation markers, and the follow-up was too short. The groups were also unbalanced by the size of metastasis (micrometastases: 37.5% in the ALND group and 44.8% in the SN group; $p < 0.05$). Of even greater importance was the use of poorly defined radiotherapy protocols. It was concluded that BCS followed by whole-breast irradiation could include treatment of the lower axilla, but the lack of clearly described protocols means that the results of ACOSOG Z0011 cannot be readily translated to all patients with early-stage breast cancer.

Although the Z0011 protocol required only whole-breast radiotherapy using standard tangential fields, the extent of radiotherapy coverage of axillary or upper nodes had not pre-

Table 3. Studies of SLNB after neoadjuvant treatment.

Year of publication	Study name	Period	Patients	N Axila	Identification rate	False negative rate	Mapping Method Identification rate	Mapping Method False negative rate	Number of SN False negative rate
2005	NSABP B27 [85]	1997–2000	428	N0–N1 palpation	88.9%	10.7%		Dual mapping 9.3%	
2008	French study [21]	2003–2007	195	N0–N1	90%	11.5% N0 9.4% N1 15 %		Dual mapping	
2013	SENTINA TRIAL (Arm C) [101]	2009–2012	900	N1–N2 Ultrasound	80%	14%	I: 77% I + Blue: 87%	I 16% I + Blue 8.6%	1 SN 24% 2 SN 18% 3 SN 7%
2013	ACOSOG Z1071 Alliance trial [102]	2009–2011	649	N1–N2 Cytology, Core biopsy	92.9%	12.6%		I: 20.3% I + Blue 10.8%	2 SN 21.1% $\geq$3 SN 9.1 % Multiple injection 7.1% Simple injection 13.3%
2015	FNAC [103]	2009–2012	153	N1–N2	87.6%	IHQ i+ Mic 8.4% If ypNo (i+) – 13.3%		I $\pm$ Blue	
2018	GANEA2 [89]	2010–2014	957	N0–N1	N0 97.6% N1 79.5%	11.5%			Number of nodes not predictors of complementary involvement ALNDo related

IHQ, Immunohistochemistry; I, Radiolabeled colloid mapping.

viously been described in these patients. This fact led to considerable speculation that high tangent fields, a third field of directed nodal treatment, could have explained the results in the SN group. For this reason, Jagsi *et al.* [52] reviewed the radiotherapy protocols to determine if there were differences between the two groups. Studying 605 patients with completed case report forms, they found that only 89% received whole-breast radiotherapy, and that, of these, 89 (15%) also received treatment to the supraclavicular region. Detailed radiotherapy protocols were obtained for 228 patients, of whom 185 (81.1%) received tangent-only treatment and 43 (18.9%) received nodal radiotherapy using three fields (ALND group = 22; SN group = 21). They noted that patients who received direct nodal irradiation had statistically significant greater nodal involvement. To assess the tangent height, they then reviewed 142 patients. High tangents (cranial tangent border $\leq$2 cm from the humeral head) were used in 50% of patients (33 of 66) randomly assigned to ALND and in 52.6% (40 of 76) randomly assigned to SLNB alone. It was concluded that most patients in the ACOSOG Z0011 trial received tangential radiotherapy and that there were no significant differences in the use of prohibited nodal fields between the study groups.

Recently, Giuliano *et al.* [53], the authors of the ACOSOG Z0011 report, published their results for long-term locoregional recurrence. At a median follow-up of 9.25 years, there was no statistically significant difference in local recurrence-free survival ($p = 0.13$). The incidence of nodal recurrence at 10 years was 0.5% in the ALND group and 1.5% in the SLNB group ($p = 0.28$). The 10-year cumulative locoregional recurrence rate was 6.2% with ALND and 5.3% with SLNB alone ($p = 0.36$). Despite the potential for residual axillary disease after SLNB alone, not performing axillary clearance still produces excellent regional control in appropriately selected patients.

Another important change that has come with the thorough assessment of SNs is the more frequent identification of micrometastatic foci ($\leq$2 mm in diameter) and isolated tumour cells. Currently, the significance of these findings is still unknown. The International Breast Cancer Study Group (IBCSG) 23-01 [26] is a multicentre, phase 3, randomised, non-inferiority trial designed to identify whether ALND represents overtreatment for patients who have SN micrometastases. The eligibility criteria were tumour $\leq$5 cm, non-palpable axillary lymph nodes, and one or more SN micrometastases with no extracapsular extension, resulting in 931 patients being randomly assigned to ALND or no further surgery. It should be noted that the study included patients with isolated tumour cells and that 70% of the patients had metastases smaller than 1 mm. Most patients underwent BCS, but mastectomies were performed in 9% of cases. After a median follow-up of 5.0 years, the 5-year DFS was 87.8% in the SLNB group and 84.4% in the ALND group ($p = 0.16$). In addition, axillary recurrence was 1% in the SN group despite 13% of non-sentinel positive nodes being found in the ALND group [26]. These findings were corroborated after a median follow-up of 9.7 years [28]. The considerable proportion of non-sentinel metastatic nodes was also reported in a meta-analysis [54], non-sentinel involvement in 20%–

40% of cases. Therefore, we can conclude that ALND may be avoided in cases with micrometastasis. This is why the St Gallen Consensus Statement, since 2013, has recommended avoiding axillary node clearance for metastases measuring <2 mm at SLNB in patients with early breast cancer, without this affecting survival [55].

Despite the negative and controversial opinions arising from the ACOSOG trial, its conclusions mean that 38% of SN-positive patients older than 50 years are spared complete axillary dissection [10]. What is more, the 2014 American Society of Clinical Oncology (ASCO) guidelines recommend not performing ALND in patients with one or two SN metastases who will be treated by BCS with whole-breast radiotherapy, and if needed, systemic therapy [16].

9.3 The prognostic value of ALND

Axillary dissection has historically been used to guide adjuvant treatment rather than as a treatment. In the IBCSG 23-01 study [26], the SN and ALND groups did not differ in adjuvant therapy, suggesting that more extensive surgery in the axilla did not influence systemic treatment. The AMAROS randomised, multicentre, phase 3 non-inferiority trial [56], randomised patients with T1–T2 breast cancer and non-palpable axillary nodes to receive either ALDN or axillary radiotherapy following a positive SLNB. This study aimed to assess whether axillary radiotherapy provided comparable regional control, with fewer side-effects, to that offered by ALND. After a median follow-up of 6.1 months (IQR 4.1–8.0) the study reported that there were no significant differences in 5-year axillary recurrence, DFS or OS between the two groups. Given the percentages of patients receiving any systemic treatment (90%), hormone therapy (ALND 79%, SN 77%) and chemotherapy (61%) in this trial, we can conclude that the extent of axillary surgery had no influence on systemic treatment. However, there was a significant difference in ipsilateral arm lymphedema between the two groups at 5 years, with this affecting 23% in the ALND group and 11% in the radiotherapy group ($p < 0.0001$). Axillary radiotherapy after a positive SN was thus shown to provide comparable axillary control to ALND with significantly less morbidity for patients with early-stage breast cancer.

The ACOSG Z0010 [57] study enrolled 5210 patients with T1–T2 disease who underwent BCS with whole-breast irradiation and SLNB. The researchers aimed to determine the prevalence and significance of occult metastases in SNs and bone marrow. Immunohistochemistry was used to analyse cases with an SN-negative hematoxylin-eosin stain, which revealed occult metastases in 10.5% of patients; however, these metastases were not associated with inferior survival. By contrast, occult bone marrow metastases were present in 3%, were associated with decreased OS and were unrelated to SN involvement. This trial indicated that the prognostic value of SLNB is limited, but that it sometimes cannot be improved by extending axillary surgery and adding ALND.

These data indicate that the information provided by ALND is no longer considered useful. Biological prognostic factors, such as hormone receptor status, HER2 overexpression and proliferations markers are of far greater value when determining systemic treatment than the number of nodes involved.

9.4 Locoregional recurrence: related factors and the relationship with systemic treatment

Based on several large randomised controlled trials [58, 59], BCS with whole-breast irradiation has equivalent DFS and OS to mastectomy for early breast cancer. Locoregional relapses have been correlated with conventional clinicopathological parameters, such as tumour size, grade and lymph node involvement. However, if we consider the biology of breast cancer, traditional prognostic factors provide limited information. A molecular taxonomy for breast cancer may therefore improve the prediction of locoregional recurrence. Breast cancer subtypes are associated with different risks of locoregional recurrence after breast cancer surgery. In a systematic review of 12,592 patients with breast cancer who underwent conservative or radical surgery, those with luminal subtype tumours had a lower risk of locoregional recurrence than those with triple-negative and HER2-overexpressing tumours. Consequently, breast cancer subtype should be taken into account when considering local control and may help to identify patients at increased risk of locoregional recurrence [60].

Another consideration for not performing ALND after a positive SLNB in breast cancer is that personalised systemic therapy can reduce locoregional relapse. The NSABP B-13 study [61] compared surgery alone with the use of sequential chemotherapy plus surgery in patients with oestrogen receptor-negative tumours and negative axillary nodes. At 8 years' follow-up, there was locoregional recurrence in 12.7% and 5.8% of patients in the surgery and surgery plus chemotherapy groups, respectively ($p = 0.0003$). The NSABP B-14 study [62] then examined the benefit of adjuvant tamoxifen in women with clinically node-negative, oestrogen receptor-positive breast cancer. After 10 years, the addition of tamoxifen had resulted in lower rates of ipsilateral recurrence (placebo = 10.3%, tamoxifen = 3.4%; $p < 0.001$) and regional recurrence (placebo = 2.4%, tamoxifen = 1.4%; $p = 0.02$). Furthermore, the NSABP B-31 and NCCTG N9831 [63] trials reported that the addition of trastuzumab to chemotherapy in patients overexpressing HER2 reduced locoregional relapse by 40% compared with chemotherapy alone.

For these reasons, we can conclude that appropriate targeted multimodal therapy not only increases DFS and OS but also contributes to achieving locoregional control.

9.5 Macrometastasis in patients with mastectomy

The NSABP B-04 trial [58] compared radical mastectomy, total mastectomy, and total mastectomy followed by irradiation that included the axilla. Patients were classified as having palpable or non-palpable axillary lymph nodes. Patients with clinically positive axillary nodes underwent radical mas-

tectomy or total mastectomy with postoperative irradiation, while those with clinically negative nodes underwent one of three procedures: radical mastectomy; total mastectomy without ALND but with postoperative irradiation; or total mastectomy plus axillary dissection, only if their nodes became positives. None of the women received adjuvant systemic therapy. After 25 years of follow-up, no significant differences in regional recurrence were found between the radical mastectomy (8%) and mastectomy plus radiotherapy (11%) groups for patients with palpable axillary lymph nodes ($p = 0.67$); there were also no significant differences in distant recurrence (41% and 43%, respectively; $p = 0.44$). In the group with non-palpable nodes, the comparison between axillary clearance, axillary radiotherapy and no treatment at all, revealed no differences in distant metastasis. However, there were statistically significant differences in regional recurrence between patients with no axillary treatment (6%) and those who underwent ALND or axillary radiotherapy (4%) ($p = 0.002$).

Given these results and those of the ACOSOG Z0011 study, we must evaluate if ALND can be avoided after a positive SLNB that is outside the Z0011 criteria, treated by mastectomy without radiotherapy. In a retrospective study, Milgrom *et al.* [64] compare outcomes in patients with SN-positive breast cancer treated by mastectomy or BCS without axillary-specific treatment. Most patients had hormonal receptor-positive, HER2-negative invasive ductal carcinoma and minimal nodal disease. However, compared with patients treated by BCS, those treated by mastectomy were younger, had larger tumours, had higher nomogram scores (predicting additional axillary disease) and were more likely to receive chemotherapy. Radiotherapy was used in 95% treated by BCS and 5% treated by mastectomy. At a median follow-up of 5 years, there were no significant differences in local (1.7% vs. 1.4%) or regional (1.2% vs. 1.0%) node recurrence between the mastectomy and BCS cohorts. The study concluded that patients with breast cancer who have minimal SN disease have excellent outcomes without ALND when undergoing either BCS or mastectomy.

These data and others from the MD Anderson Center [65] suggest that avoiding ALND could be reasonable for a low-risk subset of patients with SN-positive disease who will not receive postmastectomy radiotherapy. What is more, according to the AMAROS trial [56], we know that axillary radiotherapy and ALND are equally effective. This trial randomised 1425 patients with clinical T1–T2 disease and a positive SN to either ALND or axillary radiotherapy. Although 33% of the ALND group had additional positive nodes, after 5 years, local recurrence was rare in the axilla (ALND: 0.4%, Radiotherapy: 1.2%), DFS and OS were similar, and the morbidity of axillary radiotherapy was significantly lower.

Radiotherapy in patients treated with mastectomy improves survival in cases with >3 positive nodes, but some trials have reported benefit from regional node irradiation in cases with 1–3 positive nodes. Regional node irradiation improves distant DFS (78% versus 75%, $p = 0.02$) without improving the OS at 10 years follow-up [66]. The NCIC Clinical Trials Group MA.20 trial reported by Whelan *et al.* [67] produced similar results. Distant DFS at 10 years (nodal irradiation = 86.3%, control = 82.4%; $p = 0.03$), but no improvement was seen in the OS. These debated results reflect that careful treatment selection is needed for some individuals, with postmastectomy radiotherapy potentially indicated for some patients with 1–3 positive nodes.

To answer if it is time to apply the Z0011 criteria to positive SN mastectomy patients, we need to wait for new randomised trials. The UK POSNOC trial ("POsitive Sentinel NOde: adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy"), which includes Z0011 mastectomy patients [28], and the Dutch BOOG 2013-07 trial, which was designed for patients with 1–3 positive SNs [68] should be interesting.

The SINODAR ONE trial is an ongoing prospective non-inferiority randomized study designed to assess the therapeutic role of ALND in patients with one or two positive sentinel nodes, who are candidates for breast-conserving surgery or mastectomy [69].

Another very interesting ongoing study is the SENOMAC trial. This prospective and non-inferiority study includes breast cancer patients undergoing mastectomy and tumors larger than 5 cm. Specifically, the study includes clinically node-negative breast cancer patients with up to two macrometastases in their sentinel lymph node biopsy. Patients with T1–T3 as well as patients prior to systemic neoadjuvant therapy are included. Both breast-conserving surgery and mastectomy are eligible interventions. Patients are randomised 1:1 to undergo or not undergo ALND. The primary endpoint is breast cancer-specific survival at 5 years and the secondary endpoints are arm morbidity and health-related quality of life measured by questionnaires at 1, 3 and 5 years [70].

While we wait for these results to be published, we must not forget that systemic therapy reduces locoregional recurrence and that most patients with breast cancer receive systemic treatment. Moreover, local control is closely related to both the biologic subtype and the gene expression profile.

10. The SN in other scenarios

10.1 Elderly women

In women older than 65 years, performing ALND after a positive SLNB does not improve either breast-specific or all-cause survival. In the retrospective SEER study (Surveillance, Epidemiology and End Results), there were no significant differences in 5-year all-cause survival for women who underwent ALND (n = 4586; 84% survival) compared with those who did not (n = 629; 83% survival). Similar results were found for 5-year breast cancer specific survival (94.6 vs. 91.6%) [71].

A randomised trial in 2006 also demonstrated that ALND can be avoided in elderly women (age ≥60 years) with clini-

cal lymph nodes and receptor-positive tumours when treated with adjuvant tamoxifen [72]. In a retrospective study evaluating axillary treatment in 671 elderly patients (≥70 years old) with operable breast cancer and clinically clear axillas who were treated with tamoxifen, there was no significant difference in breast cancer mortality between the ALND and non-ALND groups after a median follow-up of 15 years [73].

Older women do not require axillary lymph node surgery if it will not modify adjuvant treatment choice or outcome. The NCCN 2016 guidelines affirms that "in the absence of definitive data indicating superior survival, the performance of axillary staging may be considered optional in patients who have particularly favourable tumours, patients in whom the selection of adjuvant systemic and/or radiation therapy is unlikely to be affected, the elderly or those with serious conditions" [74]. The 2008 NCCN Task Force Report on breast cancer in older women underlined the possibility of omitting biopsies in cases of oestrogen receptor-positive early breast cancer [75]. However, because of the lack of high quality evidence, this remains controversial [76].

In elderly patients (age >70 years) with small operable breast tumours that are hormone receptor-positive and HER2/neu-negative with clinically and ultrasonographically negative nodes, axillary surgery (including SLNB) can be avoided. The decision should be made in a multidisciplinary setting. By contrast, it is advisable to perform a SLNB in patients with histological high-risk types, such as triple-negative or HER2/neu-positive tumours. If SLNB is positive, the indications for ALND are the same as for young women.

10.2 Male breast cancer

Breast cancer is uncommon in men [77]. Although it shares similarities with breast cancer in women, it also presents crucial differences. As in women, it is important to assess the status of the axillary nodes. The ASCO considers that SLNB is "acceptable" in males with clinically node-negative early-stage breast cancer. The role of SLNB in such cases has been established in women, but there is a lack of large clinical trials to determine its sensitivity and specificity in men. Small reports do indicate that is feasible and accurate [8], with one literature review concluding a detection rate of 100% with no false-negatives among included studies [78]. However, the 2005 ASCO panel considered that the existing limited data precluded making any firm recommendations about SLNB for men with breast cancer. Despite the data limitations, it seems that the principles guiding SLNB in women apply to male cancer and that it is acceptable to proceed with care in the same manner [8, 25].

10.3 Pregnancy

In pregnant women, the concern about possible teratogenic effects of dyes has limited the use of SLNB. Isosulfan blue, for example, is best avoided in pregnant women due to its potential teratogenicity when absorbed systemically after subcutaneous injection. Coupled with the lack of safety data on this and other tracers [16], the 2016 clinical practice guideline update from ASCO concluded that pregnant women should not undergo SLNB [79]. However, limited data suggests that SLNB can be performed with radioactive colloid, which is not teratogenic at the dose administered for biopsy. Indeed, a study has shown that the radioactive colloid administered results in a minimal dose of radiation to the foetus. They concluded that SLNB with radiolabelled tracers was safe during pregnancy [23]. Other authors have considered both methylene blue and radiocolloid to be safe in pregnant women. In a study of 25 pregnant women with node-negative breast cancer who received methylene blue or ^{99}Tc, no fetal adverse outcomes were observed at 2.5 years' follow-up (one cleft lip was observed, but this was not attributable to the injection) [80].

The NCCN breast cancer 2016 guideline also states that blue dye is contraindicated for SLNB during pregnancy, but that radiolabelled sulfur colloid may be safe [74]. In addition, a group of specialists has reviewed the guidelines and provided guidance on the management of pregnant women with breast cancer considering recent advances. They concluded that SLNB can be safely performed during pregnancy if the risk-benefit assessment is favourable [81].

10.4 Neoadjuvant chemotherapy

Initially used for patients with advanced or inoperable breast cancer, the use of neoadjuvant chemotherapy (NAC) has been extended to women with early breast cancer. Some trials report comparable DFS and OS between patients who receive NAC and adjuvant chemotherapy [82], but the neoadjuvant approach benefits from tumour size reduction to facilitate more conservative surgery, the *in vivo* assessment of primary tumour sensitivity, and if pathological complete response is achieved, this becoming a new favourable prognostic factor. The increasing use of NAC has raised questions about what is the optimal local therapy for the axilla because this approach downstages axillary lymph nodes in 30%–40% of patients [83]. As an extension of how NAC may facilitate less extensive surgery, a proportion of patients who are initially node-positive may be spared ALND if the involved SNs become free of tumour (ycN0) after NAC. For this, we must consider two different situations: clinically node-negative (cN0) and clinically node-positive (cN1) disease.

10.4.1 Clinically node-negative disease

When considering the timing of SLNB, the identification rate before NAC was 98% and 95% after NAC in a population-based study (p = 0.032). The proportion of patients undergoing ALND was 45% in patients with SLNB before NAC and 33% for those with SLNB after NAC (p = 0.006) [84]. Performing SLNB after chemotherapy does require a simultaneous operation (breast and axilla), but it does have the benefit of possible nodal downstaging by achieving complete pathological response in the axilla, avoiding the morbidity of ALND. The feasibility and accuracy of SLNB after NAC has also been reported in multiple studies. In the NSABP B-27 study [85], the identification rate was 84.8% with SLNB and

the false-negative rate was just 10.7%. The study concluded that performing an SLNB after NAC provides comparable results to those obtained from SLNB before systemic therapy. The false-negative rate observed after NAC was similar to that for other multicentre trials of SLNB before systemic therapy, in which the false-negative rates were between 7% and 13% [51, 86, 87].

Elsewhere, the systematic review and meta-analysis by Geng *et al.* [88], which included 1456 patients from 16 studies, revealed a pooled identification rate of 96% for SLNB after NAC in cN0 disease, with a false-negative rate of 6%. Moreover, no significant differences were found in the identification rate by the mapping method used. The large prospective multicentre GANEA 2 study [89], designed to evaluate the accuracy and safety of SLNB after NAC in 419 women with early breast cancer, also revealed that SLNB was accurate (only one axillary relapse among after a median follow-up of 3 years) in the cN0 group. Given these findings and the assertions of other authors [90], we can conclude that SLNB after chemotherapy in patients with cN0 disease has similar accuracy to SLNB performed before treatment but has the added benefit of reducing the need for ALND.

10.4.2 Clinically node-positive disease (cN1)

The main question concerning SLNB after NAC is not its feasibility but its accuracy and safety. NAC causes fibrosis and disruption of lymphatic channels and can modify the lymphatic drainage. A false-negative SLNB is drug resistant and associated with a high risk of relapse. Some studies have shown nodal pathological complete response depending reaching 49% in triple-negative breast cancer and 74% in HER2-positive disease [91]. Performing ALND in this context seems to be an overtreatment.

The application of SLNB for staging the axilla in the neoadjuvant setting is unclear for women who initially had node-positive breast cancer because of the high false-negative rates reported in some studies. The ACOSOG Z1071 (Alliance) trial [19] enrolled 663 women with N1–N2 breast cancer who received NAC, SLNB (blue dye and radiolabelled colloid), and ALND. The false-negative rate was 12.6% in patients with at least two SNs at the time of surgery, which was higher than the prespecified threshold of 10%. The false-negative rate was influenced by the use of dual- or single-agent mapping (10.8% versus 20.3%, $p = 0.05$). The presence of fibrosis after chemotherapy makes the evaluation of lymphatic drainage more difficult, and using two mapping agents with different molecular features, the false-negative rate is lower. Another factor influencing the false-negative rate was the number of SNs evaluated, it being lower when more than two SNs were evaluated (9.2%) compared with two (21.1%).

In a meta-analysis [92] of 15 studies including 2471 patients with node-positive breast cancer who underwent chemotherapy, SLNB, and then ALND, the pooled identification rate was 89%. The false-negative rate was 14% and fell lower when the SN was staged using both hematoxylin-eosin and immunohistochemistry rather than hematoxylin-eosin alone. In another meta-analysis of eight studies [93], the pooled identification rate was 92.3%, with a false-negative rate of 15.1%, and 36.8% showed axillary complete response. The false-negative rate was significantly higher when only one SN was removed (23.4%) compared with two or more (10.4%) ($p = 0.026$).

In the nodal involvement group of the GANEA 2 study [89], the overall false-negative rate was 11.2%, increasing to 19.3% for cases with one resected SN and 7.8% for cases with two or more SNs. In this work, combining blue dye and radiocolloid was recommended for SLNB, but patients with two or fewer SNs were not excluded from the trial. The multivariate logistic regression analysis of 103 patients with no SN involvement showed that lymphovascular invasion and a residual breast tumour size $\geq$5 mm after NAC remained independent predictors of complementary node involvement at ALND.

The pooled estimate for the identification rate in a systematic review of 13 studies with 1921 patients was 90% with a false-negative rate of 14% (11%–17%) [94]. Subgroup analysis revealed false-negative rates of 11% (6%–15%) with dual mapping and 19% (11%–27%) with single mapping. Considering the number of SNs, the false-negative rate was 20% (13%–27%) when one node was removed, 12% (5%–19%) when two nodes were removed, and 4% (0 to 9) when three or more nodes were removed.

Omitting further ALND in patients with clinically positive nodes and negative SLNB after NAC is not a reliable approach in the absence of an improved technique and better patient selection. The rate of identification is lower in cN1 disease than in cN0 disease, probably due to altered lymphatic drainage. However, this is not a reason to exclude SLNB in these patients, because we can improve the identification rate by dual-agent mapping. The main problem with SLNB in patients with axillary involvement is the high false-negative rate, which must be improved before this approach can be advocated.

10.4.3 Measures for reducing false-negative rates in cN1 disease

One approach that could reduce the false-negative rate in cN1 disease is to consider micrometastasis (ypN1mi) or isolated tumour cells (ypN0+) at SLNB to indicate positive lymph nodes. According to the seventh edition of the AJCC cancer staging system, these patients are considered to have residual disease, necessitating ALND [95]. For this reason, SLNB should include hematoxylin-eosin and keratin staining. Another measure to improve accuracy could be to excise the greatest number of SNs possible. The false-negative rate changed from 31.5% when one SN was removed to 21.1% when two were removed and 9.1% when three or more SNs were removed [46]. However, we know that it is not always possible to identify three or more SNs, and data do not support random sampling to identify more than two SNs. Other methods to reduce false-negative rates include the use of dual

mapping, nomograms to predict axillary response, or optimal imaging techniques to re-stage the axilla [95].

Clip placement in the involved nodes at diagnosis and removal of the clipped nodes and the SN can also reduce the false-negative rate. In the ACOSG Z1071 trial, a clip was placed in 203 patients. In 75.9%, the clip was placed in the SN and gave a false-negative rate of 6.8% [96]. A prospective study with 208 cN1 patients was performed in which a clip was placed on involved nodes [97]. After neoadjuvant treatment, patients underwent ALND and the pathologic evaluation of clipped nodes was compared with that of the SNs and the other nodes from the ALND. The authors describe a new surgical technique, targeted axillary dissection (TAD), which involves removing the SN and the clipped nodes by localisation with iodine-125 radioactive seeds. The false-negative rates when removing the SN was 10.1%, falling to 4.2% when removing the clipped nodes and 2.0% when removing the SN and the clipped nodes (TAD). The clipped node was different from the SN in 23% of the patients, including six with metastasis to the clipped nodes who had a negative SN. Straver *et al.* [98] also described a 'marking the axilla with radioactive iodine seeds' (MARI) procedure for evaluating the axillary response to neoadjuvant treatment. This involved removing the marked lymph node (I_{125}-labelled) after chemotherapy with a gamma probe and performing ALND. The identification rate was shown to be 97%, with a false-negative rate of 7% [99].

The Radioactive Iodine Seed localisation in the axilla with the sentinel node procedure (RISAS) trial assessed a combination of MARI and SLNB. This single-arm multicenter validation study sought to evaluate the accuracy of the procedure, the identification rate, false-negative rate, negative predictive value. Even though the definitive results have not been published, a high negative predictive value has been reported for the procedure [100].

Due to the lack of sufficient evidence and because of discrepancies between different countries, the EUBREAST study group has started a prospective cohort trial (AXANA Protocol- NCT 04373655). This international project compares data on axillary staging after neoadjuvant chemotherapy in cN+ patients who underwent ycN0, treated with different axillary staging techniques. The primary study endpoints are: the evaluation of 5-year invasive disease-free survival, the 3-year axillary recurrence rate and quality of life and arm morbidity in patients treated with different axillary staging techniques.

Some of the most relevant studies regarding SLNB after neoadjuvant treatment are summarised in Table 3 (Ref. [21, 85, 89, 101–103]).

In conclusion, the clinical relevance of leaving residual disease in the axilla after NAC is unclear, but there is robust evidence that axillary surgery has changed considerably over time. In patients with cN0 disease, there has been a substantial decrease in ALND and increase in SLNB after NAC, while in cN+ disease, ALND has increasingly been omitted after NAC with SLNB [104]. Persistent nodal disease could reflect chemoresistant disease, but in the neoadjuvant setting, patients have already received chemotherapy appropriate to the molecular subtype of their tumour. These patients with residual disease after NAC are candidates for new drug trials and additional systemic therapy (adjuvant after neoadjuvant). Knowing the pathological complete response in the axilla is a surrogate marker of a favourable outcome in these patients. Thus, SLNB after NAC could be an option in patients with node-positive breast cancer if we carefully select patients with the highest possibility of complete nodal response (triple-negative and HER2-overexpressed) and improve the techniques used. Future prospective trials should seek to provide more complete scientific evidence of the reliability of this technique.

10.4.4 Axillary surgery in N2–N3 patients

Although this patient group have a high axillary tumour burden, several studies have reported that we should consider evaluating SLNB and avoiding ALND when there is pathological complete response. In a study of 100 patients with breast cancer who received NAC (N2 = 59, N3 = 41), 79.3% had residual disease. However, 60% when of patients with clinical complete response also showed pathological complete response [105]. In a retrospective study of 221 patients [106] (N2 and N1 with $\geq$3 suspicions lymph nodes) ypN0 was achieved in 40% of patients: 68% in HER2-positive cases and 45% in triple-negative cases. These data indicate that it is necessary to evaluate if we can reliably perform SLNB in this set of patients by selecting those with clinical complete response and subtypes with high pathological complete response rates. Prospective studies are needed.

Recent studies, such as CREATE-X [107] and Katherine [108], have shown that adjuvant treatment for patients with residual cancer after NAC reduces the risk of recurrence for triple-negative breast cancer or HER2-amplified cancers, respectively. Similarly, the conversion of nodes from positive to negative may allow for regional nodal irradiation to be omitted, depending on the results of trials such as NSABP B-51 [109].

Residual disease is very important because it reflects the patient prognosis and the need for adjuvant treatment after neoadjuvant treatment [110].

11. Conclusions

In conclusion, SLNB is currently the best method for axillary staging in breast cancer, allowing patients to be treated according to risk of recurrence, and with good evidence that morbidity is less than with other more radical techniques. The following statements summarise the key elements of our knowledge.

- The presence of axillary lymph metastases is still a key prognostic factor in breast cancer.
- In early-stage breast cancer with clinically negative axillary lymph nodes, SLNB is the standard method for assessing

involvement of the axilla. OS, DFS and regional control are statistically equivalent in SLNB and ALND.

• SLNB predicts the axillary state in 95% of patients, giving a false-negative rate of 5%.

• Only inflammatory breast cancer and known node involvement are contraindications to the use of SLNB to stage the axilla.

• Axillary recurrence after SLNB is a rare event, occurring at rates between 0.3% and 1.5% at 5 years.

• ALND can be avoided in patients with early breast cancer and micrometastasis on SLNB.

• In patients with limited positive nodal disease (<3 involved SNs) treated by BCS with whole-breast radiotherapy and systemic therapy, SLNB alone was non-inferior to ALND in terms of survival.

• Axillary radiotherapy after a positive SLNB provides comparable control to that after ALND for patients with early-stage breast cancer but is associated with significantly less morbidity.

• Axillary surgery can be avoided in elderly patients with operable small breast tumours and positive hormone receptors, HER2/neu-negative and clinically node-negative breast cancer.

• SLNB after chemotherapy in clinically negative nodes patients has an accuracy similar to that before treatment and reduces the need for ALND.

• SLNB after NAC in patients with clinically node-negative disease can identify 84.8% of cases with a false-negative rate of 10.7%.

• Among women with initial node-positive breast cancer, the benefit of using SLNB to stage the axilla in the neoadjuvant setting is unclear because of the high false-negative rate.

• Some measures can improve the accuracy of SLNB in patients with clinically involved nodes, such as the use of dual mapping, excising the greatest number of SNs possible or placing a clip on involved nodes at diagnosis.

Author contributions

MJPF designed the research study. MJPF and MEFM and RPC performed the research. AGT and MCD and MBL and APM, and ROM, and EMP, and SPS and JPS specifically completed the revision according their specialization. All authors contributed to the editorial changes in the manuscript. All authors read and approved the final manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

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References

[1] Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a metaanalysis. Cancer. 2006; 106: 4–16.

[2] Cabanas RM. An approach for the treatment of penile carcinoma. Cancer. 1977; 39: 456–466.

[3] Krag DN, Weaver DL, Alex JC, Fairbank JT. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. Journal of Surgical Oncology. 1993; 2: 335–340.

[4] Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Annals of Surgery. 1994; 220: 391–401.

[5] Gallegos-Hernández JF. El ganglio centinela. Concepto y aplicaciones prácticas en oncología. Revista Mexicana de Anestesiologia. 2007; 30: 193–199.

[6] Morton DL, Wen DR, Wong JH, Economou JS, Cagle LA, Storm FK, *et al.* Technical details of intraoperative lymphatic mapping for early stage melanoma. Archives of Surgery. 1992; 127: 392–399.

[7] Atalay C. New concepts in axillary management of breast cancer. World Journal of Clinical Oncology. 2014; 5: 895–900.

[8] Lyman GH, Giuliano AE, Somerfield MR, Benson AB, Bodurka DC, Burstein HJ, *et al.* American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. Journal of Clinical Oncology. 2005; 23: 7703–7720.

[9] Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, *et al.* Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncology. 2010; 11: 927–933.

[10] Benitez A, Cortés M, Bajén M, Gasén AR, Sabaté A. Ganglio centinela, ROLL y SNOLL en cáncer de mama. In Soriano, A., Martin, J., Garcia, A., (eds) Medicina nuclear en la práctica clínica (pp. 571–584). 2nd edn. Grupo Aula Médica: Madrid. 2012.

[11] Harlow SP, Weaver DL. sentinel lymph node in breast cancer: Techniques. 2016. Available at: www.uptodate (Accessed: 1 December 2016).

[12] Schwartz GF, Giuliano AE, Veronesi U. Proceedings of the consensus conference on the role of sentinel lymph node biopsy in carcinoma of the breast, April 19-22, 2001, Philadelphia, Pennsylvania. Cancer. 2002; 94: 2542–2551.

[13] Zhang X, Li Y, Zhou Y, Mao F, Lin Y, Guan J, *et al.* Diagnostic Performance of Indocyanine Green-Guided Sentinel Lymph Node Biopsy in Breast Cancer: a Meta-Analysis. PLoS ONE. 2017; 11: e0155597.

[14] Teshome M, Wei C, Hunt KK, Thompson A, Rodriguez K, Mittendorf EA. Use of a Magnetic Tracer for Sentinel Lymph Node Detection in Early-Stage Breast Cancer Patients: a Meta-analysis. Annals of Surgical Oncology. 2016; 23: 1508–1514.

[15] Manca G, Rubello D, Tardelli E, Giammarile F, Mazzarri S, Boni G, *et al.* Sentinel Lymph Node Biopsy in Breast Cancer. Clinical Nuclear Medicine. 2016; 41: 126–133.

[16] Lyman GH, Temin S, Edge SB, Newman LA, Turner RR, Weaver DL, *et al.* Sentinel Lymph Node Biopsy for Patients with Early-

Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. Journal of Clinical Oncology. 2014; 32: 1365–1383.
[17] Mosbah R, Raimond E, Pelissier A, Hocedez C, Graesslin O. Relevance of the sentinel lymph node biopsy in breast multifocal and multicentric cancer. 2015. Available at: http://linkinghub.elsevier.com/retrieve/pii/S1297958915000983 (Accessed: 12 January 2017).
[18] Maaskant-Braat AJG, Voogd AC, Roumen RMH, Nieuwenhuijzen GAP. Repeat sentinel node biopsy in patients with locally recurrent breast cancer: a systematic review and meta-analysis of the literature. Breast Cancer Research and Treatment. 2013; 138: 13–20.
[19] Boughey JC. Sentinel Lymph Node Surgery after Neoadjuvant Chemotherapy in Patients with Node-Positive Breast Cancer. Journal of the American Medical Association. 2013; 310: 1455.
[20] Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, *et al.* Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. The Lancet Oncology. 2013; 14: 609–618.
[21] Classe JM, Bordes V, Campion L, Mignotte H, Dravet F, Leveque J, *et al.* Sentinel lymph node biopsy after neoadjuvant chemotherapy for advanced breast cancer: results of Ganglion Sentinelle et Chimiotherapie Neoadjuvante, a French prospective multicentric study. Journal of Clinical Oncology. 2009; 27: 726–732.
[22] Hunt KK, Yi M, Mittendorf EA, Guerrero C, Babiera GV, Bedrosian I, *et al.* Sentinel lymph node surgery after neoadjuvant chemotherapy is accurate and reduces the need for axillary dissection in breast cancer patients. Annals of Surgery. 2009; 250: 558–566.
[23] Gentilini O, Cremonesi M, Trifirò G, Ferrari M, Baio SM, Caracciolo M, *et al.* Safety of sentinel node biopsy in pregnant patients with breast cancer. Annals of Oncology. 2004; 15: 1348–1351.
[24] Rovera F, Chiappa C, Coglitore A, Baratelli GM, Fachinetti A, Marelli M, *et al.* Management of breast cancer during pregnancy. International Journal of Surgery. 2013; 11: S64–S68.
[25] Seth P Harlow M, Donald L Weaver M. Diagnosis, staging and the role of sentinel lymph node biopsy in the nodal evaluation of breast cancer. 2016. Available at: www.uptodate.com (Accessed: 1 February 2016).
[26] Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, *et al.* Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncology. 2013; 14: 297–305.
[27] Jafferbhoy S, McWilliams B. Clinical Significance and Management of Sentinel Node Micrometastasis in Invasive Breast Cancer. Clinical Breast Cancer. 2017; 12: 308–312.
[28] Galimberti V, Cole BF, Viale G, Veronesi P, Vicini E, Intra M, *et al.* Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 trial. Lancet Oncology. 2018; 19: 1385–1393.
[29] Szychta P, Westfal B, Maciejczyk R, Smolarz B, Romanowicz H, Krawczyk T, *et al.* Intraoperative diagnosis of sentinel lymph node metastases in breast cancer treatment with one-step nucleic acid amplification assay (OSNA). Archives of Medical Science. 2016; 6: 1239–1246.
[30] Julian TB, Blumencranz P, Deck K, Whitworth P, Berry DA, Berry SM, *et al.* Novel Intraoperative Molecular Test for Sentinel Lymph Node Metastases in Patients with Early-Stage Breast Cancer. Journal of Clinical Oncology. 2008; 26: 3338–3345.
[31] Chen RC, Lin NU, Golshan M, Harris JR, Bellon JR. Internal mammary nodes in breast cancer: diagnosis and implications for patient management - a systematic review. Journal of Clinical Oncology. 2008; 26: 4981–4989.
[32] Albertini JJ, Lyman GH, Cox C, Yeatman T, Balducci L, Ku N, *et al.* Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. Journal of the American Medical Association. 1996; 276: 1818–1822.
[33] Thorsen LBJ, Offersen BV, Danø H, Berg M, Jensen I, Pedersen AN, *et al.* DBCG-IMN: a Population-Based Cohort Study on the Effect of Internal Mammary Node Irradiation in Early Node-Positive Breast Cancer. Journal of Clinical Oncology. 2016; 34: 314–320.
[34] Caudle AS, Smith BD. Do Internal Mammary Nodes Matter? Annals of Surgical Oncology. 2019; 26: 930–932.
[35] Fujii T, Yajima R, Matsumoto A, Yamaki S, Uchida N, Tsutsumi S, *et al.* Implication of an Intramammary Sentinel Lymph Node in Breast Cancer: is this a True Sentinel Node? a Case Report. Breast Care. 2010; 5: 102–104.
[36] Intra M, Garcia-Etienne CA, Renne G, Trifirò G, Rotmensz N, Gentilini OD, *et al.* When sentinel lymph node is intramammary. Annals of Surgical Oncology. 2007; 15: 1304–1308.
[37] Pugliese MS, Stempel MM, Cody HS, Morrow M, Gemignani ML. Surgical management of the axilla: do intramammary nodes matter? American Journal of Surgery. 2009; 198: 532–537.
[38] Riogi B, Sripadam R, Barker D, Harris O, Innes H, Chagla L. Management of the axilla following neoadjuvant chemotherapy for breast cancer- a change in practice. Surgeon. 2021; 19: 1–7.
[39] Magnoni F, Veronesi P. Sentinel node biopsy in conservative surgery for breast cancer: a changing role in clinical practice. Minerva Chirurgica. 2020; 75: 386–391.
[40] Naik AM, Fey J, Gemignani M, Heerdt A, Montgomery L, Petrek J, *et al.* The Risk of Axillary Relapse after Sentinel Lymph Node Biopsy for Breast Cancer is Comparable with that of Axillary Lymph Node Dissection. Annals of Surgery. 2004; 240: 462–471.
[41] van der Ploeg IMC, Nieweg OE, van Rijk MC, Valdés Olmos RA, Kroon BBR. Axillary recurrence after a tumour-negative sentinel node biopsy in breast cancer patients: a systematic review and meta-analysis of the literature. European Journal of Surgical Oncology. 2008; 34: 1277–1284.
[42] Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM, *et al.* Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. Journal of the National Cancer Institute. 2006; 98: 599–609.
[43] Veronesi U, Paganelli G, Galimberti V, Viale G, Zurrida S, Bedoni M, *et al.* Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. Lancet. 1997; 349: 1864–1867.
[44] Kell MR, Burke JP, Barry M, Morrow M. Outcome of axillary staging in early breast cancer: a meta-analysis. Breast Cancer Research and Treatment. 2010; 120: 441–447.
[45] Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, *et al.* A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. New England Journal of Medicine. 2003; 349: 546–553.
[46] Bilimoria KY, Bentrem DJ, Hansen NM, Bethke KP, Rademaker AW, Ko CY, *et al.* Comparison of sentinel lymph node biopsy alone and completion axillary lymph node dissection for node-positive breast cancer. Journal of Clinical Oncology. 2009; 27: 2946–2953.
[47] Yi M, Giordano SH, Meric-Bernstam F, Mittendorf EA, Kuerer HM, Hwang RF, *et al.* Trends in and outcomes from sentinel lymph node biopsy (SLNB) alone vs. SLNB with axillary lymph node dissection for node-positive breast cancer patients: experience from the SEER database. Annals of Surgical Oncology. 2010; 17: 343–351.
[48] Cyr A, Gao F, Gillanders WE, Aft RL, Eberlein TJ, Margenthaler JA. Disease recurrence in sentinel node-positive breast cancer patients forgoing axillary lymph node dissection. Annals of Surgical Oncology. 2012; 19: 3185–3191.
[49] Giuliano AE, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch AM, *et al.* Locoregional Recurrence after Sentinel Lymph Node Dissection with or without Axillary Dissection in Patients with Sentinel Lymph Node Metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. Annals of Surgery. 2010; 252: 426–433.
[50] Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, *et al.* Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. Journal of the American Medical Association. 2011; 305: 569–575.

[51] Krag D, Weaver D, Ashikaga T, Moffat F, Klimberg VS, Shriver C, *et al.* The sentinel node in breast cancer-a multicenter validation study. New England Journal of Medicine. 1998; 339: 941–946.
[52] Jagsi R, Chadha M, Moni J, Ballman K, Laurie F, Buchholz TA, *et al.* Radiation field design in the ACOSOG Z0011 (Alliance) Trial. Journal of Clinical Oncology. 2014; 32: 3600–3606.
[53] Giuliano AE, Ballman K, McCall L, Beitsch P, Whitworth PW, Blumencranz P, *et al.* Locoregional Recurrence after Sentinel Lymph Node Dissection with or without Axillary Dissection in Patients with Sentinel Lymph Node Metastases. Annals of Surgery. 2016; 264: 413–420.
[54] Cserni G, Gregori D, Merletti F, Sapino A, Mano MP, Ponti A, *et al.* Meta-analysis of non-sentinel node metastases associated with micrometastatic sentinel nodes in breast cancer. British Journal of Surgery. 2004; 91: 1245–1252.
[55] Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B, *et al.* Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Annals of Oncology. 2013; 24: 2206–2223.
[56] Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, *et al.* Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncology. 2014; 15: 1303–1310.
[57] Giuliano AE, Hawes D, Ballman KV, Whitworth PW, Blumencranz PW, Reintgen DS, *et al.* Association of occult metastases in sentinel lymph nodes and bone marrow with survival among women with early-stage invasive breast cancer. Journal of the American Medical Association. 2011; 306: 385–393.
[58] Fisher B, Jeong J, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. New England Journal of Medicine. 2002; 347: 567–575.
[59] Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, *et al.* Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. New England Journal of Medicine. 2002; 347: 1227–1232.
[60] Lowery AJ, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ. Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. Breast Cancer Research and Treatment. 2012; 133: 831–841.
[61] Fisher B, Dignam J, Mamounas EP, Costantino JP, Wickerham DL, Redmond C, *et al.* Sequential methotrexate and fluorouracil for the treatment of node-negative breast cancer patients with estrogen receptor-negative tumors: eight-year results from National Surgical Adjuvant Breast and Bowel Project (NSABP) B-13 and first report of findings from NSABP B-19 comparing methotrexate and fluorouracil with conventional cyclophosphamide, methotrexate, and fluorouracil. Journal of Clinical Oncology. 1996; 14: 1982–1992.
[62] Fisher B, Dignam J, Bryant J, DeCillis A, Wickerham DL, Wolmark N, *et al.* Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. Journal of the National Cancer Institute. 1996; 88: 1529–1542.
[63] Perez EA, Romond EH, Suman VJ, Jeong J, Davidson NE, Geyer CE, *et al.* Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. Journal of Clinical Oncology. 2011; 29: 3366–3373.
[64] Milgrom S, Cody H, Tan L, Morrow M, Pesce C, Setton J, *et al.* Characteristics and outcomes of sentinel node–positive breast cancer patients after total mastectomy without axillary-specific treatment. Annals of Surgical Oncology. 2012; 19: 3762–3770.
[65] Cody HS 3rd. Extending ACOSOG Z0011 to Encompass Mastectomy: what Happens without RT? Annals of Surgical Oncology. 2017; 24: 621–623.
[66] Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, *et al.* Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. New England Journal of Medicine. 2015; 373: 317–327.
[67] Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, *et al.* Regional Nodal Irradiation in Early-Stage Breast Cancer. New England Journal of Medicine. 2015; 373: 307–316.
[68] van Roozendaal LM, de Wilt JHW, van Dalen T, van der Hage JA, Strobbe LJA, Boersma LJ, *et al.* The value of completion axillary treatment in sentinel node positive breast cancer patients undergoing a mastectomy: a Dutch randomized controlled multicentre trial (BOOG 2013-07). BMC Cancer. 2016; 15: 610.
[69] Tinterri C, Canavese G, Bruzzi P, Dozin B. SINODAR one, an ongoing randomized clinical trial to assess the role of axillary surgery in breast cancer patients with one or two macrometastatic sentinel nodes. Breast. 2016; 30: 197–200.
[70] de Boniface J, Frisell J, Andersson Y, Bergkvist L, Ahlgren J, Rydén L, *et al.* Survival and axillary recurrence following sentinel node-positive breast cancer without completion axillary lymph node dissection: the randomized controlled SENOMAC trial. BMC Cancer. 2017; 17: 379.
[71] Javid SH, He H, Korde LA, Flum DR, Anderson BO. Predictors and outcomes of completion axillary node dissection among older breast cancer patients. Annals of Surgical Oncology. 2014; 21: 2172–2180.
[72] Rudenstam C, Zahrieh D, Forbes JF, Crivellari D, Holmberg SB, Rey P, *et al.* Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10-93. Journal of Clinical Oncology. 2006; 24: 337–344.
[73] Martelli G, Miceli R, Daidone MG, Vetrella G, Cerrotta AM, Piromalli D, *et al.* Axillary dissection versus no axillary dissection in elderly patients with breast cancer and no palpable axillary nodes: results after 15 years of follow-up. Annals of Surgical Oncology. 2011; 18: 125–133.
[74] Gullick WJ. Breast cancer. 2016. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (Accessed: 15 March 2016).
[75] Carlson RW, Moench S, Hurria A, Balducci L, Burstein HJ, Goldstein LJ, *et al.* NCCN Task Force Report: breast cancer in the older woman. Journal of the National Comprehensive Cancer Network. 2007; 6: S1–S25.
[76] Sun SX, Hollenbeak CS, Leung AM. Deviation from the Standard of Care for Early Breast Cancer in the Elderly: what are the Consequences? Annals of Surgical Oncology. 2015; 22: 2492–2499.
[77] White J, Kearins O, Dodwell D, Horgan K, Hanby AM, Speirs V. Male breast carcinoma: increased awareness needed. Breast Cancer Research. 2011; 13: 219.
[78] Boughey JC, Bedrosian I, Meric-Bernstam F, Ross MI, Kuerer HM, Akins JS, *et al.* Comparative analysis of sentinel lymph node operation in male and female breast cancer patients. Journal of the American College of Surgeons. 2006; 203: 475–480.
[79] Lyman GH, Temin S, Edge SB, Newman LA, Turner RR, Weaver DL, *et al.* Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. Journal of Clinical Oncology. 2014; 32: 1365–1383.
[80] Gropper AB, Calvillo KZ, Dominici L, Troyan S, Rhei E, Economy KE, *et al.* Sentinel lymph node biopsy in pregnant women with breast cancer. Annals of Surgical Oncology. 2014; 21: 2506–2511.
[81] Loibl S, Schmidt A, Gentilini O, Kaufman B, Kuhl C, Denkert C, *et al.* Breast Cancer Diagnosed during Pregnancy: Adapting recent advances in breast cancer care for pregnant patients. JAMA Oncology. 2015; 1: 1145–1153.
[82] Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, *et al.* Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. Journal of Clinical Oncology. 2008; 26: 778–785.
[83] Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A, Margolese RG, *et al.* Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. Journal of Clinical Oncology. 1997; 15: 2483–2493.

[84] van der Heiden-van der Loo M, de Munck L, Sonke GS, van Dalen T, van Diest PJ, van den Bongard HJGD, *et al.* Population based study on sentinel node biopsy before or after neoadjuvant chemotherapy in clinically node negative breast cancer patients: Identification rate and influence on axillary treatment. European Journal of Cancer. 2015; 51: 915–921.
[85] Mamounas EP, Brown A, Anderson S, Smith R, Julian T, Miller B, *et al.* Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. Journal of Clinical Oncology. 2005; 23: 2694–2702.
[86] Tafra L, Lannin DR, Swanson MS, Van Eyk JJ, Verbanac KM, Chua AN, *et al.* Multicenter Trial of Sentinel Node Biopsy for Breast Cancer Using both Technetium Sulfur Colloid and Isosulfan Blue Dye. Annals of Surgery. 2001; 233: 51–59.
[87] McMasters KM, Tuttle TM, Carlson DJ, Brown CM, Noyes RD, Glaser RL, *et al.* Sentinel lymph node biopsy for breast cancer: a suitable alternative to routine axillary dissection in multiinstitutional practice when optimal technique is used. Journal of Clinical Oncology. 2000; 18: 2560–2566.
[88] Geng C, Chen X, Pan X, Li J. The Feasibility and Accuracy of Sentinel Lymph Node Biopsy in Initially Clinically Node-Negative Breast Cancer after Neoadjuvant Chemotherapy: A Systematic Review and Meta-Analysis. PLoS ONE. 2016; 11: e0162605.
[89] Classe J, Loaec C, Gimbergues P, Alran S, de Lara CT, Dupre PF, *et al.* Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 study. Breast Cancer Research and Treatment. 2019; 173: 343–352.
[90] Pilewskie M, Morrow M. Axillary Nodal Management Following Neoadjuvant Chemotherapy: A review. JAMA Oncology. 2017; 3: 549–555.
[91] Hennessy BT, Hortobagyi GN, Rouzier R, Kuerer H, Sneige N, Buzdar AU, *et al.* Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metastases following primary chemotherapy. Journal of Clinical Oncology. 2005; 23: 9304–9311.
[92] Fu JF, Chen HL, Yang J, Yi CH, Zheng S. Feasibility and accuracy of sentinel lymph node biopsy in clinically node-positive breast cancer after neoadjuvant chemotherapy: a meta-analysis. PLoS ONE. 2014; 9: e105316.
[93] van Nijnatten TJA, Schipper RJ, Lobbes MBI, Nelemans PJ, Beets-Tan RGH, Smidt ML. The diagnostic performance of sentinel lymph node biopsy in pathologically confirmed node positive breast cancer patients after neoadjuvant systemic therapy: a systematic review and meta-analysis. European Journal of Surgical Oncology. 2015; 41: 1278–1287.
[94] Tee SR, Devane LA, Evoy D, Rothwell J, Geraghty J, Prichard RS, *et al.* Meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial biopsy-proven node-positive breast cancer. British Journal of Surgery. 2018; 105: 1541–1552.
[95] El Hage Chehade H, Headon H, Kasem A, Mokbel K. Refining the Performance of Sentinel Lymph Node Biopsy Post-neoadjuvant Chemotherapy in Patients with Pathologically Proven Pretreatment Node-positive Breast Cancer: an Update for Clinical Practice. Anticancer Research. 2016; 36: 1461–1471.
[96] Boughey JC, Ballman KV, Le-Petross HT, McCall LM, Mittendorf EA, Ahrendt GM, *et al.* Identification and Resection of Clipped Node Decreases the False-negative Rate of Sentinel Lymph Node Surgery in Patients Presenting with Node-positive Breast Cancer (T0–T4, N1–N2) who Receive Neoadjuvant Chemotherapy. Annals of Surgery. 2016; 263: 802–807.
[97] Caudle AS, Yang WT, Krishnamurthy S, Mittendorf EA, Black DM, Gilcrease MZ, *et al.* Improved Axillary Evaluation Following Neoadjuvant Therapy for Patients with Node-Positive Breast Cancer Using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection. Journal of Clinical Oncology. 2016; 34: 1072–1078.
[98] Straver ME, Loo CE, Alderliesten T, Rutgers EJT, Vrancken Peeters MTFD. Marking the axilla with radioactive iodine seeds (MARI procedure) may reduce the need for axillary dissection after neoadjuvant chemotherapy for breast cancer. British Journal of Surgery. 2010; 97: 1226–1231.
[99] Donker M, Straver ME, Wesseling J, Loo CE, Schot M, Drukker CA, *et al.* Marking Axillary Lymph Nodes with Radioactive Iodine Seeds for Axillary Staging after Neoadjuvant Systemic Treatment in Breast Cancer Patients: the MARI procedure. Annals of Surgery. 2015; 261: 378–382.
[100] van Nijnatten TJA, Simons JM, Smidt ML, van der Pol CC, van Diest PJ, Jager A, *et al.* A Novel Less-invasive Approach for Axillary Staging After Neoadjuvant Chemotherapy in Patients With Axillary Node-positive Breast Cancer by Combining Radioactive Iodine Seed Localization in the Axilla With the Sentinel Node Procedure (RISAS): A Dutch Prospective Multicenter Validation Study. Clinical Breast Cancer. 2017; 17: 399–402.
[101] Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, *et al.* Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncology. 2013; 14: 609–618.
[102] Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, *et al.* Factors affecting sentinel lymph node identification rate after neoadjuvant chemotherapy for breast cancer patients enrolled in ACOSOG Z1071 (Alliance). Annals of Surgery. 2015; 261: 547–552.
[103] Boileau J, Poirier B, Basik M, Holloway CMB, Gaboury L, Sideris L, *et al.* Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. Journal of Clinical Oncology. 2015; 33: 258–264.
[104] Simons JM, Koppert LB, Luiten EJT, van der Pol CC, Samiei S, de Wilt JHW, *et al.* De-escalation of axillary surgery in breast cancer patients treated in the neoadjuvant setting: a Dutch population-based study. Breast Cancer Research and Treatment. 2020; 180: 725–733.
[105] Goel N, Yadegarynia S, Rodgers S, Kelly K, Collier A, Franceschi D, *et al.* Axillary response rates to neoadjuvant chemotherapy in breast cancer patients with advanced nodal disease. Journal of Surgical Oncology. 2021; 124: 25–32.
[106] Garcia-Tejedor A, Fernandez-Gonzalez S, Ortega R, Gil-Gil M, Perez-Montero H, Fernandez-Montolí E, *et al.* Can we avoid axillary lymph node dissection in N2 breast cancer patients with chemo-sensitive tumours such as her2 and TNBC? Breast Cancer Research and Treatment. 2021; 185: 657–666.
[107] Masuda N, Lee S, Ohtani S, Im Y, Lee E, Yokota I, *et al.* Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. New England Journal of Medicine. 2017; 376: 2147–2159.
[108] von Minckwitz G, Huang C, Mano MS, Loibl S, Mamounas EP, Untch M, *et al.* Trastuzumab Emtansine for Residual Invasive her2-Positive Breast Cancer. New England Journal of Medicine. 2019; 380: 617–628.
[109] Garg AK, Buchholz TA. Influence of Neoadjuvant Chemotherapy on Radiotherapy for Breast Cancer. Annals of Surgical Oncology. 2015; 22: 1434–1440.
[110] Bear HD, McGuire KP. Sentinel Node Biopsy After Neoadjuvant Systemic Therapy for Breast Cancer: The Method Matters. Annals of Surgical Oncology. 2019; 26: 2316–2318.