

Consensus Guideline on the Management of the Axilla in Patients With Invasive/In-Situ Breast Cancer

Purpose

To outline the management of the axilla for patients with invasive and in-situ breast cancer.

Associated ASBrS Guidelines or Quality Measures

1. Performance and Practice Guidelines for Sentinel Lymph Node Biopsy in Breast Cancer Patients – *Revised November 25, 2014*
2. Performance and Practice Guidelines for Axillary Lymph Node Dissection in Breast Cancer Patients – *Approved November 25, 2014*
3. Quality Measure: Sentinel Lymph Node Biopsy for Invasive Breast Cancer – *Approved November 4, 2010*
4. Prior Position Statement: Management of the Axilla in Patients With Invasive Breast Cancer – *Approved August 31, 2011*

Methods

A literature review inclusive of recent randomized controlled trials evaluating the use of sentinel lymph node surgery and axillary lymph node dissection for invasive and in-situ breast cancer as well as the pathologic review of sentinel lymph nodes and indications for axillary radiation was performed. This is not a complete systematic review but rather, a comprehensive review of recent relevant literature. A focused review of non-randomized controlled trials was then performed to develop consensus guidance on management of the axilla in scenarios where randomized controlled trials data is lacking. The ASBrS Research Committee developed a consensus document, which was reviewed and approved by the ASBrS Board of Directors.

Summary of Data Reviewed

Recommendations Based on Randomized Controlled Trial Data for Patients Treated With Surgery as the First Line of Treatment for Invasive Disease

1. ***Indications for sentinel node surgery in patients with invasive breast cancer and clinically negative axillary nodes***

Sentinel lymph node biopsy (SLNB) has replaced axillary lymph node dissection (ALND) for the staging of clinically node-negative invasive breast cancer patients, based on randomized clinical trial data that demonstrated equivalent survival between SLNB and

ALND¹, with reduced morbidity for SLNB alone.² All patients with a clinically negative axilla for whom axillary staging would provide information relevant for treatment decisions should be offered SLNB, and routine ALND should not be performed as an initial staging procedure for clinically node-negative disease. The studies which validated the use of SLNB defined a clinically negative axilla as one which was negative by physical exam and/or mammography; ultrasound and breast MRI were not routinely utilized during this time period. In patients who are discovered to have positive axillary nodes by percutaneous biopsy after an ultrasound and/or MRI, axillary surgical options of SLNB versus ALND should be considered taking into account planned breast surgery and extent of nodal disease on imaging.

2. *Indications for SLNB alone in patients with clinically negative axilla, and 1 or 2 positive sentinel nodes*

Data from the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial demonstrate that ALND may be omitted in selected patients with 1 or 2 positive SLNs.³⁻⁵ In the ACOSOG Z0011 trial, 813 patients with clinical T1-2 node-negative tumors who underwent breast conserving surgery (BCS) and were found to have hematoxylin and eosin (H&E)-positive SLNs were randomized to ALND vs no further axillary surgery. Patients with clinically palpable lymph nodes or clinical T3 tumors were not eligible for this study. The study also excluded patients receiving neoadjuvant chemotherapy, patients with >3 positive SLNs on final pathology, and patients with gross extra-nodal disease intra-operatively. Patients with microscopic extra-nodal extension found at pathologic review of the sentinel nodes were not excluded from the Z0011 study. The protocol mandated the use of standard whole-breast radiation without nodal irradiation following BCS. The trial was closed early due to lower-than-expected mortality rate and slow accrual with an enrollment of 47% of the targeted 1900 patients.

Analysis demonstrated non inferiority between ALND and SLNB-only arms. At a median follow up of 9.3 years, disease-free (78.2% vs. 80.2%) and overall survival (83.6% vs. 86.3%) were similar in the ALND and SLNB-only arms.³ Local-regional relapse-free survival was also similar (81.2% vs 83.0%), with only one regional recurrence noted in a patient on the SLNB-only arm versus none in the ALND arm between years 5 and 10 of follow-up.

Of note, the majority of women in the trial were older than 50 years (64%) and had clinical T1 tumors (68%) and ER-positive disease (77%). Per trial protocol, most women received whole-breast radiation (89%). Further, almost all women received systemic therapy (96% total: 58% adjuvant chemotherapy and 46% adjuvant endocrine therapy). The burden of nodal disease for patients participating in the trial was low, with 60% having only 1 positive SLN. Forty percent of patients had micrometastases or isolated tumor cells and 60% had macrometastases in the sentinel nodes. Additional positive axillary nodes were found in 27.3% of patients who underwent ALND.

The findings of ACOSOG Z0011 are further supported by the International Breast Cancer Study Group Trial 23-01, which compared ALND versus SLNB alone for patients with micrometastases (0.2mm-2.0mm) in the SLN.⁶ Eligible patients had clinically negative nodes defined by lack of palpable nodes, and had tumors less than 5cm. 933 patients were randomized after surgery if they had 1 or more nodes with micrometastases without extranodal extension. Patients had an average age of 53, were primarily ER positive (88-91%), 95% had only 1 positive node, and 9% had a mastectomy vs 91% breast conservation surgery. Ninety-six percent received adjuvant therapy, and 19% had intraoperative radiation therapy vs postoperative radiation therapy. No differences in overall survival or disease-free survival were observed in this trial after 5 years of follow-up.

Based on these data, the American Society of Clinical Oncology (ASCO)⁷ and National Comprehensive Cancer Network (NCCN)⁸ guidelines recommend considering omission of ALND for patients with 1-2 positive sentinel nodes undergoing breast conserving surgery with whole breast radiation for those women who meet eligibility criteria for these clinical trials.

3. *Indications for axillary radiation alone in patients with clinically negative axilla and positive sentinel nodes*

Historically, there has been interest in randomized data evaluating the use of radiation therapy alone for patients with positive axillary nodes. The NSABP B-04 study, which published 25 year follow-up data in 2002, reported no differences in local regional recurrence for patients with clinically positive nodes who underwent radical mastectomy versus simple mastectomy with axillary irradiation.⁹ In 2014, The European Organization for Research and Treatment of Cancer (EORTC) reported results from the ‘After Mapping of the Axilla: Radiotherapy Or Surgery (AMAROS) study’ which randomized patients with 1 or 2 positive SLNs to ALND vs axillary radiation, regardless of type of original surgery (mastectomy or breast conservation therapy).¹⁰ This study evaluated 1425 patients with positive SLNs and documented a 5 year axillary recurrence of 0.43% for ALND and 1.19% for radiotherapy alone. Because the event rate was low, the study was underpowered to determine non-inferiority of axillary radiation. A subset of patients in this study were treated with mastectomy (17%), and though the numbers are small and a definitive role for axillary surgery versus radiation alone in the mastectomy group cannot be provided, patients with low nodal burden on SLNB (1-2 nodes positive and/or micrometastatic disease) may consider the use of axillary radiation alone.

The majority of patients in the AMAROS trial would have been eligible to participate in ACOSOG Z11, in which patients underwent breast preserving surgery and received whole-breast radiation. ACOSOG Z11 demonstrated a similarly low event rate.^{3,5} Importantly, a review of the axillary radiation portals used in Z11 did not show greater use of expanded radiation portals for those with SLNB alone compared to those with ALND.¹¹ Therefore, the use of axillary radiation in patients with 1-2 positive sentinel

nodes undergoing breast conservation surgery is not currently recommended. Based on the AMAROS study, indications for tangents only, high tangents or inclusion of an axillary and supraclavicular field should be determined by risk of residual burden of disease, and risk/benefit analysis based on disease subtype for patients undergoing a mastectomy.

4. *Indications for immunohistochemistry (IHC) use in pathologic evaluation of sentinel nodes*

Results from two studies indicate that cytokeratin staining with IHC resulting in IHC-only positive sentinel nodes (N0i+) are not associated with clinically significant local or distant recurrence risk, and routine use of IHC is not indicated in the setting of primary surgery. In the ACOSOG Z0010¹² and National Surgical Adjuvant Breast and Bowel Protocol (NSABP) B-32¹³ trials, all patients were treated on the basis of H&E SLN staining only. To control for treatment bias, clinicians and patients were blinded to the results of IHC staining. In ACOSOG Z0010, a prospective observational study of SLN biopsy, occult metastases were found by IHC in 8.9% of 3945 patients who were SLN-negative by H&E. However, 5-year survival was not different between those patients who were H&E negative and IHC negative, and those who were H&E negative and IHC positive (95.8% vs 95.1%, $P = 0.53$).¹² In NSABP B-32, a prospective randomized study of SLNB plus ALND vs SLNB alone (with ALND limited to SLN-positive patients), occult metastases were found by IHC in 15.9% of 3887 H&E-negative patients. Although overall, disease-free and distant disease-free survival were significantly worse for IHC-positive than for IHC-negative patients, the absolute difference in overall survival was only 1.2% (94.6% vs 95.8%, $P = 0.03$).¹³ Routine use of IHC staining of SLNs is thus not recommended in the setting of surgery as first line of treatment and should be limited to selective use at the discretion of the pathologist. In the setting of neoadjuvant therapy, IHC staining of SLN should be considered for patients with biopsy proven node positive disease who undergo SLN surgery.

Recommendations Based on Randomized Controlled Trial Data for Patients Treated With Neoadjuvant Systemic Therapy for Invasive Disease

1. *Indications for SLNB in patients undergoing treatment with neoadjuvant systemic therapy with clinically negative axilla at diagnosis (prior to neoadjuvant systemic therapy)*

The largest published study evaluating SLNB after neoadjuvant chemotherapy came from the NSABP B-27 trial, in which 428 patients who underwent neoadjuvant chemotherapy had SLNB followed by completion ALND. In this cohort, SLN(s) were successfully identified in 85% with a false-negative rate of 11%.¹⁴ A meta-analysis of 24 published studies, which included 1799 patients who underwent SLNB with subsequent ALND after neoadjuvant chemotherapy, reported an SLN identification rate of 89.6% and a false-

negative rate of 8.4%.¹⁵ In a more recent meta-analysis of 1,456 patients across 16 studies, the SLN identification rate was 96%, and the false negative rate was 6%.¹⁶

These results can be compared with those from the NSABP B-32 trial, which compared SLNB with ALND for node-negative breast cancer patients.¹ No patients in this clinical trial underwent neoadjuvant chemotherapy, and most had T1 tumors (80%). In this study, a SLN was identified in 97.3% of patients and the false negative rate was 9.8%.¹ The long-term follow-up data show that SLN after systemic therapy does not lead to higher local regional failure rates.¹⁷ For patients with a clinically negative axilla prior to neoadjuvant systemic therapy, accuracy rates of SLNB following neoadjuvant chemotherapy are acceptable.

2. *Indications for SLNB in patients undergoing treatment with neoadjuvant systemic therapy with clinically positive axilla at diagnosis (prior to neoadjuvant systemic therapy)*

The role of SLNB in patients with a clinically positive axilla treated with neoadjuvant chemotherapy was evaluated in the ACOSOG trial Z1071.¹⁸ This study investigated SLNB after neoadjuvant chemotherapy for stage II, stage IIIA, and stage IIIB breast cancer patients who had biopsy proven axillary lymph node metastases prior to systemic chemotherapy. The primary objective of the study was to determine the false negative rate of SLNB in this setting. All patients had positive node status confirmed by ultrasound-guided biopsy, either with fine needle aspiration or core biopsy. All patients in the study had a SLNB followed by an immediate completion ALND. Patients were required to have 2 or more SLNs identified.

The results of the analysis of 694 patients with cN1 disease revealed a false negative rate of sentinel node mapping of 12.6%. If dual agent mapping was performed, the FNR was 10.8%. In a subset of 170 patients included in the primary endpoint analysis, a clip was placed at the time of the initial needle biopsy documenting metastatic disease. In 107 of these patients, the clipped node was found to be one of the SLNs. The false negative rate was 6.8% in those patients where the clipped node was one of the SLNs.¹⁹

The SENTINA trial was designed to evaluate the use of SLN in patients receiving neoadjuvant chemotherapy, before and/or after treatment. Arm C of this trial had a similar subset of cN1 or cN2 patients for which the false negative rate for SLNB in patients with clinically positive nodes at diagnosis who underwent SLNB after neoadjuvant chemotherapy was determined to be 14%. This trial did not have a subset analysis based on number of nodes, use of a clip, or dual tracer.²⁰

Based on the ACOSOG 1071 study, it is reasonable to consider SLNB in patients with a cN1 or cN2 disease at presentation and good clinical response to neoadjuvant chemotherapy. If a SLNB is performed, dual tracer is recommended, and effort should be made to remove the initially positive lymph node (often the 'clipped' node) and all sentinel nodes. If a clip was not placed or it cannot be identified, at least 2 and ideally 3

sentinel nodes are advised to be identified and removed as the false negative rate is lower with a greater number of SLNs removed.

If residual disease is identified in the sentinel nodes following neoadjuvant therapy, the current standard of care is to perform a completion ALND given the high risk of additional disease in non-sentinel nodes. Patients should be considered for any open clinical trials evaluating the use of ALND and axillary radiation in this setting. Immunohistochemistry staining of the SLNs should be considered in the setting of node positive disease treated with neoadjuvant systemic therapy, as this decreases the FNR of SLN surgery.

Z1071, SENTINA and other trials evaluating SLN after neoadjuvant therapy were limited to patients treated with neoadjuvant chemotherapy. While extrapolation to patients treated with neoadjuvant hormonal therapy may be considered, there are no clinical trial data in this setting and nodal pathologic response rates to neoadjuvant hormonal therapy are lower.

Recommendations for Scenarios Where Randomized Controlled Trial Data are Unavailable

1. *Role of SLN biopsy in women with Inflammatory Breast Cancer*

Currently, SLN is not recommended for women who present with inflammatory breast cancer. This is based on the pathophysiology of inflammatory breast cancer, where the subdermal lymphatics may be partially obstructed and drain abnormally resulting in a high false negative rate. In a recent prospective feasibility trial conducted to determine the false negative rate of SLN biopsy in women with inflammatory breast cancer, 16 women underwent post-neoadjuvant SLN biopsy followed by ALND.²¹ A SLN was identified in only 4 of 16 patients; this low mapping rate precluded calculation of a false negative rate. This feasibility trial supports continued recommendation for ALND in women presenting with inflammatory breast cancer.

2. *Role of SLN biopsy in women with multi-focal and multi-centric disease*

The rationale for performing SLN biopsy in women with multi-focal and multi-centric disease is based on the observation that results of lymphatic mapping are similar regardless of whether a peritumoral or subareolar injection is performed.²¹ A prospective validation study of SLN biopsy was performed in patients with multicentric breast cancer; all patients underwent a SLNB followed by completion ALND. Of the 30 patients enrolled, the SLN was identified in 100% of patients with a false negative rate of 0%. These findings are supported by a recent systematic review including twenty-six studies. A SLN was successfully identified in patients with multi-focal tumors in 86-94% of cases, with a low false negative rate.²³ Reported rates were higher for patients with multicentric disease (identification rate 92-100% and false negative rate of 4-8%). Based on these studies along

with other single institution series reported in the literature, SLN biopsy is recommended for women with multi-focal or multi-centric cancer.

3. *Role of SLN biopsy in women with prior breast or axillary surgery*

Women who have had prior breast or axillary surgery may have disrupted lymphatics, which alters their lymphatic drainage. The time interval between the prior surgery and the current breast event (ie, new primary cancer, recurrence after lumpectomy, or chest wall recurrence after mastectomy) is a critical consideration in determining the role of SLN biopsy. If there has been a relatively long time interval, “new” lymphatic drainage patterns will have developed and may be able to be accurately mapped. If the time interval has been short, it is unlikely that lymphatic mapping will be accurate, and an ALND should be considered if axillary staging would influence clinical decision making. Preoperative lymphoscintigraphy with delayed imaging may be particularly useful in this setting. Determination of whether an interval is “short” or “long” is somewhat subjective and relies on the judgement of the surgeon.

Studies reporting experience with SLN biopsy in the setting of prior breast or axillary surgery generally report a lower mapping rate (29%-65%). The extent of prior breast surgery and extent of prior axillary surgery impact the likelihood of SLN identification. Additionally, reoperative lymphatic mapping more commonly identifies extra-axillary drainage.^{24,25} However, if mapping is successful, reoperative SLN biopsy is accurate with low false-negative rates.²⁴⁻²⁷ Overall, repeat SLN is feasible and should be considered if the information obtained from performing a SLN biopsy would influence clinical treatment decisions.²⁵

4. *Role of SLN biopsy in women during pregnancy*

The potential concern regarding the role of SLN biopsy in women during pregnancy relates to the use of the radiolabeled colloids and the blue dye. Limited safety data is available. Blue dye (lymphazurin and methylene blue dye) should not be used during pregnancy due to the risk of anaphylaxis for the former and limited data on fetal toxicity for the latter. However, use of radiolabeled colloids is most likely safe, with limited fetal exposure to radiation reported in the literature.^{28,29} Low dose is recommended (ie, morning of surgery injection rather than day prior to surgery injection).

5. *Role of SLN biopsy in women with ductal carcinoma in situ (DCIS)*

In the modern era of screen-detected breast malignancies, the risk of upgrade from core biopsy identified DCIS to an invasive cancer is approximately 10-20%. Historically, the use of SLNB has been recommended for patients with “extensive” DCIS, which has been variably defined as those with extensive microcalcifications, high grade disease and/or palpable disease. An evaluation of the UK National Health Service Breast Screening

Program identified 26,696 women with core biopsy identified DCIS (2003-2011). For patients with a final pathologic diagnosis of DCIS the risk of a positive SLN was 0.2%. Twenty one percent were upgraded to invasive disease at final pathology with 12% of these patients being node positive. The authors concluded that patients undergoing surgery for DCIS should only undergo SLN biopsy if a mastectomy is the planned initial surgical approach.³⁰ Similarly, The National Comprehensive Cancer Network (NCCN) recommends that patients undergoing surgery for DCIS have nodal evaluation with sentinel node surgery only in the setting of a mastectomy or if the anatomic location of the DCIS and initial surgery will compromise future sentinel node mapping if an invasive cancer is identified.³¹

Recommendations

1. *Indications for SLN surgery in patients with clinically negative axilla*

All patients with a clinically negative axilla for whom axillary staging would provide actionable or relevant information should be offered SLN biopsy. An example of a patient population for whom the results of SLNB may not impact systemic management are those with a high burden of comorbidities; in such patients, the decision to omit SLNB may be considered.

2. *Indications for omission of ALND in patients with positive sentinel nodes*

Based on randomized clinical studies, axillary dissection can be omitted for patients with 1-2 positive sentinel nodes undergoing breast conserving surgery who meet the following inclusion criteria:

- a. T1-2 tumors
- b. One to two positive SLNs without gross extracapsular extension (microscopic extracapsular extension is allowed)
- c. Patient acceptance and completion of standard whole-breast radiation therapy
- d. Patient acceptance and completion of recommended adjuvant systemic therapy (endocrine, cytotoxic, or both)

3. *Indications for axillary radiation in patients with positive sentinel nodes*

Based on ACOSOG Z0011 and the AMAROS study, there are no clear indications for directed axillary radiation in patients with 1-2 positive sentinel nodes who undergo breast conserving surgery. Based on the subset of patients enrolled in IBCSG 23-01 and AMAROS who underwent mastectomy with 1-2 positive sentinel nodes (either micrometastatic or macrometastatic disease), axillary radiation alone without completion ALND may be considered.

4. *Indications for the use of IHC cytokeratin staining of sentinel nodes*

IHC should be used at the discretion of the pathologist based on an inability to resolve an area of concern for metastatic disease in the node. Routine use is not recommended in patients with surgical resection as first line of treatment. It should be considered in patients treated with neoadjuvant chemotherapy with node positive disease at presentation.

5. *Indications for SLN surgery in patients undergoing neoadjuvant systemic therapy*

- a. SLNB prior to neoadjuvant systemic therapy is discouraged, as this prevents assessment of nodal response to systemic therapy.
- b. In patients who present with a clinically negative axilla, SLNB is recommended following neoadjuvant therapy.
- c. In patients with biopsy proven axillary nodal metastases prior to systemic therapy, the option of SLN surgery is left to the discretion of the surgeon after a shared decision-making discussion with the patient, taking into account the false-negative rates from ACOSOG 1071 and the SENTINA trial.
 - i. If SLN biopsy after neoadjuvant therapy is attempted, dual tracer should be used. At least 2 and ideally 3 sentinel nodes are advised to be identified and removed as the false-negative rate is lower with a greater number of SLNs removed.
 - ii. The false-negative rate is also lower if a clip was placed in the lymph node at the time of initial biopsy, and this clipped node is confirmed to be removed at the time of SLN biopsy.
 - iii. If a SLN and/or the clipped node (if clipped) is not identified, an ALND is recommended.

6. *Role of SLN biopsy for clinical scenarios where there is no supporting randomized controlled trial data*

There are a number of clinical scenarios for which randomized controlled trial data remain limited. Observational data suggests that SLN may be considered for women with multifocal or multicentric cancer, those with prior breast or axillary surgery, and during pregnancy. At present, SLN biopsy is not considered to be an acceptable method of staging the axilla for patients with inflammatory breast cancer. For patients undergoing surgery for DCIS only, those having an initial mastectomy or those for whom the breast conservation surgery may prevent future sentinel node mapping should have a simultaneous SLN biopsy.

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This statement was developed by the Society's Research Committee and on September 24, 2019, was approved by the Board of Directors.

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