Management of the Axilla

Barbara Zarebczan Dull, MD, Heather B. Neuman, MD, MS*

INTRODUCTION

The status of the axillary lymph nodes is one of the most important factors impacting overall prognosis and treatment decision-making for breast cancer.1 Axillary surgery has long been an integral part of breast cancer treatment to stage the axilla and provide locoregional control. Traditionally, this has been accomplished by performing a formal axillary lymph node dissection (ALND). However, ALND is now reserved for patients with a clinically positive axilla or positive lymph nodes confirmed on needle biopsy. In patients with a clinically negative axilla, a sentinel lymph node (SLN) biopsy can be performed safely at the time of mastectomy or lumpectomy, sparing patients the morbidity associated with ALND.

KEYWORDS

- Sentinel lymph node
- Axillary lymph node dissection
- Breast cancer
- Micrometastases
- ACOSOG Z0011

KEY POINTS

- The disease status of the axilla in breast cancer remains one of the most important factors defining treatment and prognosis.
- The accuracy of SLN biopsy in staging the clinically node-negative axilla has been validated in prospective and randomized controlled trials. SLN should be considered the standard of care for patients without clinically evident axillary disease and patients with negative SLN can be spared the short- and long-term morbidity associated with ALND.
- Although micrometastases or isolated tumor cells may have a statistical association with prognosis, the clinical significance of these is uncertain. Currently, IHC should not be used to evaluate for micrometastases or isolated tumor cells in the SLN. The presence of isolated tumor cells should not be used to direct treatment decision-making.
- Controversies continue to exist regarding the use of SLN biopsies in patients who have undergone previous axillary surgery and those with multicentric breast cancer. Determining the optimal timing of SLN biopsy in patients undergoing neoadjuvant chemotherapy remains challenging.
- ACOSOG Z001 is a practice-changing trial that allows ALND to be avoided in select patients with positive SLNs undergoing breast conservation.

INTRODUCTION

The status of the axillary lymph nodes is one of the most important factors impacting overall prognosis and treatment decision-making for breast cancer.1 Axillary surgery has long been an integral part of breast cancer treatment to stage the axilla and provide locoregional control. Traditionally, this has been accomplished by performing a formal axillary lymph node dissection (ALND). However, ALND is now reserved for patients with a clinically positive axilla or positive lymph nodes confirmed on needle biopsy. In patients with a clinically negative axilla, a sentinel lymph node (SLN) biopsy can be performed safely at the time of mastectomy or lumpectomy, sparing patients the morbidity associated with ALND.

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Department of Surgery, University of Wisconsin School of Medicine and Public Health, 600 Highland Avenue, H4/726 CSC, Madison, WI 53792-7375, USA
* Corresponding author.
E-mail address: neuman@surgery.wisc.edu

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ADDRESSING THE CLINICALLY NEGATIVE AXILLA

SLN Biopsy

The sentinel node is based on the concept that breast cancers drain to a single node or nodes, the sentinel nodes, before draining to more distal nodes. It was first described in 1977 by Cabanas in work on penile carcinoma metastases. It was concluded that if the biopsied sentinel node is negative, the likelihood of additional lymph nodes being positive is low and further surgery is therefore not warranted. This concept was first applied to breast cancer in the early 1990s, with the first multicenter validation study published in 1998. Since that time, several prospective observational and randomized controlled trials have examined SLN biopsy in breast cancer, leading to SLN biopsy being considered standard of care for evaluation of the axilla in patients with clinically node-negative breast cancer.

One of the earliest randomized trials examining the use of SLN biopsy was reported by Veronesi and colleagues in 2003. They randomized 516 patients with breast cancer with tumors less than 2 cm in diameter to receive an SLN biopsy followed by routine ALND or SLN biopsy followed by an ALND only if the SLN contained metastases. The SLN was identified in 98.5% of patients with a sensitivity of 91.2%. After 10 years of follow-up, no difference was observed between the groups for local axillary recurrence (0% in the SLN biopsy group vs 2% in the ALND group) or disease-free survival (89.9% vs 88.8%).

Similar SLN identification, false-negative rates, and disease-free survival have since been demonstrated in several other large prospective and randomized controlled trials. The largest include the prospective American College of Surgeons Oncology Group (ACOSOG) Z0010 trial and the randomized National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial. ACOSOG Z0010 is a multicenter, prospective observational study designed to examine the clinical significance of SLN micrometastases; this study also identified eligible patients for the randomized ACOSOG Z0011 trial (discussed later). Patients with T1 or T2 clinically node-negative breast cancer underwent SLN biopsy. A total of 198 surgeons participated in this trial. An SLN was identified in 98.7% of patients. At a median follow-up of 3.1 years, the local recurrence rate (ie, the clinical false-negative rate) was 0.3%.

Finally, the NSABP B-32 was a randomized controlled trial of 5611 patients from 80 academic and community centers in the United States and Canada that took place between 1999 and 2004; 187 surgeons participated in the trial. The objective was to compare locoregional recurrence, morbidity, and survival of SLN biopsy alone versus SLN followed by ALND. In this trial the rate of SLN identification was 97.3% and the false-negative rate was 9.8%; tumors in the lateral region of the breast, prior excisional biopsies, and removal of less than two SLN was associated with increased false-negative rates. No difference in locoregional recurrence, overall survival, or disease-free survival was observed between the trial arms.

These multicenter trials involving hundreds of academic and community surgeons demonstrate that SLN mapping can be performed accurately in patients with early stage breast cancer. Based on these data, SLN should be considered standard of care and patients with negative SLNs spared the morbidity of an ALND (Table 1).

Technical Details

Blue dye versus radiocolloid tracer

No consensus exists regarding the optimal means of performing lymphoscintigraphy. However, most surgeons who perform lymphatic mapping report using blue dye and radiotracer. In a survey of the Fellows of the American College of Surgeons, 90% of
respondents stated that they used both methodologies. Similarly, 79.4% of participating surgeons in the ACOSOG Z0010 Trial reported using both modalities, whereas 14.8% used blue dye and 5.7% only radiotracer. No relationship between lymphoscintigraphy technique and the identification of an SLN has been observed in prospective or randomized trials. Surgeon experience is the most important factor influencing successful SLN mapping. In cases where an SLN cannot be identified, an ALND is the standard of care.

Injection site
Injection for lymphoscintigraphy can occur either subdermally around the areola or directly around the tumor. The concordance of the two injections sites was examined in a prospective study of 68 patients, reported in 1999 by Klimberg and colleagues. Patients received an injection of technetium-99 sulfur colloid in the subareolar area of the breast, and an injection of isosulfan blue around the tumor. Four patients did not have an SLN identified; however, the SLNs in 62 of the 64 patients who had successful SLN identification were identified as hot and blue, suggesting that the site of injection has minimal impact on which lymph nodes are identified as the SLNs. This observation was extended in a 2007 multicenter trial of 459 patients where the detection rate of SLNs was significantly higher in the patients undergoing periareolar injection compared with peritumoral injections. Given these findings and the ease of a subareolar injection, this technique is favored by many surgeons.

Morbidity
One of the benefits of SLN biopsy is the decreased morbidity compared with ALND. However, complications do occur. Wound infections, seromas, paresthesias, lymphedema, and decreased shoulder abduction have all been reported in the literature after SLN biopsy (Table 2).

Wound infection is uncommon after SLN biopsy. Results from ACOSOG Z0010/11 demonstrated a wound infection rate of 1% (only 0.1% requiring readmission for treatment with intravenous antibiotics). Seroma formation after SLN biopsy is similarly uncommon. Patients in the ACOSOG Z0010 trial had a 7.1% incidence of seroma formation, with only 0.4% necessitating drain placement for treatment. This trial identified increasing age, removal of greater than or equal to five lymph nodes, and use of radiocolloid-only mapping technique to be associated with increased risk of seroma formation.

Another common morbidity is arm paresthesias in the form of numbness and tingling. Although much of the early postoperative paresthesias resolve, some persist.

Table 1
Accuracy of SLN biopsy

<table>
<thead>
<tr>
<th></th>
<th>Veronesi et al⁶</th>
<th>Sentinella/GIVOM⁷</th>
<th>ALMANAC⁹</th>
<th>ACOSOG Z0010¹²</th>
<th>NSABP B-32¹³</th>
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<tr>
<td>Study design</td>
<td>RCT</td>
<td>RCT</td>
<td>RCT</td>
<td>Prospective</td>
<td>RCT</td>
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<tr>
<td>Year</td>
<td>2003</td>
<td>2007</td>
<td>2006</td>
<td>2007</td>
<td>2010</td>
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<tr>
<td>Patient enrollment</td>
<td>516</td>
<td>697</td>
<td>991</td>
<td>5327</td>
<td>5611</td>
</tr>
<tr>
<td>SLN identification</td>
<td>98.5%</td>
<td>95%</td>
<td>98%</td>
<td>98.7%</td>
<td>97.3%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>91.2%</td>
<td>83.3%</td>
<td>93.3%</td>
<td>NR</td>
<td>90.2%</td>
</tr>
<tr>
<td>False-negative rate</td>
<td>8.8%</td>
<td>16.7%</td>
<td>6.7%</td>
<td>0.3%</td>
<td>9.8%</td>
</tr>
</tbody>
</table>

Notes:
- False-negative rate based on a median clinical follow-up of 31 months.
as long as 24 months.\textsuperscript{6,18,21} At 24 months postoperative, 9.9% of patients in the NSABP B-32 trial reported numbness, whereas 9.2% reported residual tingling.\textsuperscript{21} This contrasts with the study by Veronesi and colleagues,\textsuperscript{6} where only 1% of SLN patients reported persistent paresthesias. The varying rates of paresthesias are likely caused by the subjective nature of patient self-reporting, but demonstrate that for patients this may significantly impact quality of life.

Lymphedema is one of the most feared complications after axillary surgery. Early studies reported a 0% incidence of lymphedema after SLN biopsy.\textsuperscript{6,25} However, larger trials including ACOSOG Z0010 and NSABP B-32 (which used objective measurements of arm circumference) have demonstrated rates of lymphedema after SLN biopsy of 7% and 9%, respectively.\textsuperscript{19,21} Multivariate analysis performed on the data from ACOSOG Z0010 found that increasing age and body mass index were significantly associated with development of lymphedema.\textsuperscript{19}

It is not uncommon for patients to have decreased shoulder range of motion after axillary surgery secondary to postoperative pain. The NSABP B-32 trial found that 41% of patients had deficits in shoulder abduction 1 week postoperatively. However, most resolve and by 6 months only 6% of patients reported decreased shoulder abduction.\textsuperscript{21} These results are similar to those reported by the Sentinel Node Biopsy versus Axillary Clearance and the Sentinella-GIVOM trials.\textsuperscript{18,26}

Finally, an uncommon, but potentially life-threatening complication that can occur during SLN biopsy is an allergic reaction to isosulfan blue dye. Reactions can range from a mild rash or blue hives to more serious anaphylaxis. The NSABP-32 trial reported an incidence of 0.4% for mild grade I and II allergic reactions and 0.2% of more severe grade III and IV reactions, such as anaphylaxis and cardiac or respiratory arrest.\textsuperscript{13}

**Indications**

Based on these and other trials, the current recommendations from the American Society of Clinical Oncology state that SLN biopsy is indicated in T1 and T2 tumors without clinical involvement of the axilla.\textsuperscript{27} These indications are in accordance with the 2010 American Society of Breast Surgeons guidelines for performing SLN biopsy with the addition that SLN biopsy be performed in patients undergoing a mastectomy for ductal carcinoma in situ (DCIS).\textsuperscript{28}

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Veronesi et al\textsuperscript{6a}</th>
<th>Sentinella/GIVOM\textsuperscript{18a}</th>
<th>ALMANAC\textsuperscript{9b}</th>
<th>ACOSOG Z0010/19,20c</th>
<th>NSABP B-32\textsuperscript{21a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound infection</td>
<td>NR</td>
<td>NR</td>
<td>11%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Seroma</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>1%</td>
<td>7%</td>
<td>11%</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>0%</td>
<td>12%</td>
<td>4%</td>
<td>5%</td>
<td>7%</td>
</tr>
</tbody>
</table>

**Table 2**

Morbidity after SLN biopsy compared with ALND

Abbreviation: NR, not reported.
\textsuperscript{a} Morbidity data at 24 months.
\textsuperscript{b} Morbidity data at 12 months.
\textsuperscript{c} Morbidity data at 6 months.
\textsuperscript{d} Subjective rate of lymphedema presented.
Contraindications

Although SLN biopsy is a well-established alternative to ALND in T1 and T2 breast cancers, several contraindications to performing the procedure exist. Palpable axillary lymph nodes are an absolute contraindication to SLN biopsy and these patients should be offered an ALND if metastatic disease is confirmed. Large T4 tumors and inflammatory breast cancer are also considered contraindications to SLN biopsy because tumor deposits may decrease the reliability of lymphatic mapping.

Because isosulfan and lymphazurine blue dye have not been proved to be safe in pregnancy, SLN localization using dye is contraindicated in pregnant women. There are also limited data regarding the risk of radiotracer to an unborn fetus. A recent study demonstrated that fetal exposure to radiolabeled colloid during SLN biopsy is less than 0.3% of the Nuclear Regulatory Commission guideline for limitations during pregnancy. Although use of radiotracer is probably safe in pregnancy, data are limited and pregnancy, therefore, is considered a relative contraindication to SLN biopsy.

Areas of Ongoing Controversy

Ductal carcinoma in situ

Patients with DCIS do not undergo routine examination of the axillary lymph nodes because, by definition, DCIS has little to no metastatic potential. However, studies have demonstrated that certain DCIS patients at high-risk for microinvasive disease may benefit from an SLN biopsy. In a 2000 study by Klauber-DeMore and colleagues, it was found that 12% of their 76 patients with high-risk DCIS had metastatic disease in the SLN. Similar findings were reported in 2006 by Goyal and colleagues using the Breast Test Wales database. In their series, 38% of the 587 patients with DCIS were found to have invasive disease on final pathology. Axillary nodal staging was performed in 269 patients, with nodal metastases in 13%. In both studies, presence of a palpable or imaging-identified mass was associated with upstaging to invasive cancer.

Because of the risk of upstaging at the time of surgery, SLN biopsy should be considered in any patient with DCIS undergoing mastectomy. Furthermore, in patients undergoing lumpectomy in whom there is increased suspicion that microinvasive or invasive carcinoma will be identified, consideration of an SLN biopsy at the time of their breast surgery is reasonable.

Prior axillary surgery

Prior axillary surgery is a relative contraindication to SLN biopsy because lymphatic drainage may be disrupted, theoretically leading to an inability to identify an SLN or an increased false-negative rate. The largest study examining this has been published from the Memorial Sloan-Kettering Cancer Center (MSKCC), looking at their experience with 117 patients with breast cancer undergoing reoperative SLN after either a prior SLN biopsy or an ALND. The SLN was successfully identified in 55% of patients. Likelihood of successful mapping was higher after a previous SLN biopsy (74%) than an ALND (38%). Of the 63 patients with successful mapping, 30% (N = 19) had a nonaxillary drainage site identified; 8 had ipsilateral axillary drainage in addition to a second site, whereas 11 had only nonaxillary drainage. At a median 2.2 years of follow-up, no axillary recurrences were observed. The authors concluded that an SLN can be identified in most patients who have had prior axillary surgery, albeit it at a lower rate than for initial SLN biopsies. However, further research is needed to define the true false-negative rate given the limited follow-up.
Multicentric breast disease
There has been concern that multiple tumors within the breast may drain to different SLNs, making an SLN biopsy unreliable. Several retrospective studies have addressed this question and found the SLN identification rate to exceed 95%.\textsuperscript{35–37} False-negative rate (confirmed by back-up ALND) was 8.8% in a retrospective review of the ALMANAC trial\textsuperscript{38} and 8% in a large single institution study.\textsuperscript{36} Two other single-institution studies have reported their clinical axillary recurrence for patients with multicentric cancer and negative SLN’s.\textsuperscript{35,37} An axillary recurrence rate of 0% was reported in a study of 142 patients at a median follow-up of 28.8 months,\textsuperscript{35} and a rate of 2.2% at 5-years in a study of 337 patients.\textsuperscript{37} Although these retrospective studies suggest that SLN could be an alternative to ALND in patients with multicentric breast cancer, larger prospective patient studies with longer follow-up are needed to confirm the efficacy of SLN biopsy in this setting.

T3 or T4 tumors
Limited prospective data exist to support the accuracy of SLN biopsy in patients with large primary tumors. Several retrospective studies examining this question have found the SLN identification rate to be more than 97%.\textsuperscript{39–41} The false-negative rate (confirmed in most cases by completion ALND after SLN) was 3%. These favorable findings need to be interpreted in the context of the overall tumor burden for patients with larger breast tumors, where 62.5% to 76.7% of patients have metastases in the SLN.\textsuperscript{39–41}

Management of Positive SLNs
ALND has been the standard of care for patients with a positive SLN. Recent research, however, has questioned whether all patients with a positive SLN require a completion ALND. In patients with clinically node-negative disease, the SLN is the only involved node in 40% to 60% of patients, which raises the question as to whether ALND offers additional therapeutic benefit for all patients.\textsuperscript{24,42}

This question was addressed prospectively in the ASOCOG Z0011 trial.\textsuperscript{43} Patients with T1 and T2 tumors undergoing lumpectomy who were found to have metastatic disease in the SLNs were randomized to undergo either completion axillary dissection or no further treatment of the axilla.\textsuperscript{43} All patients were required to have negative margins in the breast excision, and went on to have whole-breast irradiation. Low-volume nodal disease was required, with all eligible patients having less than three positive nodes and no gross extranodal disease. Adjuvant treatment was per the primary team, with 96% receiving chemotherapy and 47% endocrine therapy. The trial closed early because of low accrual and events rates, reaching only 47% of its accrual goals (891 patients enrolled). Median follow-up for the evaluable patients was 6.3 years. At 5 years, the local recurrence rate was 1.6% in the SLN biopsy group compared with 3.1% in the ALND arm.\textsuperscript{44} There was also no difference in 5-year disease-free survival (89.9% vs 88.8%).\textsuperscript{43} The authors concluded that for select patients with node-positive breast cancer and low-volume axillary disease, an SLN biopsy alone does not result in inferior survival or inadequate local control.

This trial’s eligibility criteria apply to a very select group of patients: women with low-volume breast and axillary disease undergoing lumpectomy with radiation. It is likely that some of the low axillary lymph nodes were covered by the radiation fields and therefore received treatment; this specific question is currently being examined by the study investigators. Additionally, most women received systemic therapy (either chemotherapy, endocrine therapy, or both), which impacts local recurrence and overall survival. Finally, approximately 40% of patients had only micrometastases in the SLN, emphasizing the low-volume axillary disease that was included in this trial.
Although the data cannot be widely generalized to all patients with breast cancer, this study should be considered a practice-changing trial for the subset of women with positive SLNs undergoing breast conservation.

**Micrometastatic Disease**

Controversy also exists regarding the significance of isolated tumor cells and micrometastases found on SLN biopsies. The enhanced pathologic assessment associated with the SLN biopsy has resulted in the identification of increasingly small deposits of metastatic disease and subsequent upstaging of cancer. The American Joint Committee on Cancer staging system has changed to reflect this and includes three categories of nodal metastases: (1) isolated tumor cells (no cluster greater than <0.2 mm, pN0[i+]); (2) micrometastases (0.2–2 mm, pN1mi); and (3) macrometastases (>2 mm). However, the clinical significance of these very small metastatic deposits is uncertain. The Dutch Micrometastases and Isolated Tumor Cells: Relevant and Robust or Rubbish (MIRROR) trial was a retrospective analysis of 2756 patient who underwent an SLN biopsy before 2006 and were found to have isolated tumor cells or micrometastases in the regional lymph nodes. They compared outcomes for 856 patients with node-negative disease and no systemic therapy with patients with isolated tumor cells or micrometastases who did (N = 995) and did not (N = 856) receive systemic therapy. Disease-free survival was poorer in patients with either isolated tumor cells or micrometastases in the SLN (76.5% vs 85.7%; P < .001), suggesting these small tumor deposits have some prognostic significance. However, this study included contralateral breast cancer in the definition of a disease “event” (accounting for 29% of events). Because development of contralateral breast cancer is unlikely to be related to the presence of micrometastatic axillary disease, this definition makes these findings difficult to interpret.

ACOSOG Z0011 and the NSABP B-032 trials examined the significance of occult metastases in the SLN. In ACOSOG Z0010, routine immunohistochemistry was performed on SLN specimens to increase identification of isolated tumor cells and micrometastases. In this study, no difference in 5-year overall (95.7% vs 95.1%) or disease-free (92.2% vs 90.4%) survival was observed between patients with node-negative versus IHC-positive SLNs. Similarly, NSABP-B32 performed IHC staining in all SLNs found to be negative on initial processing. No difference in overall or disease-free survival was observed in patients with IHC-detected metastases versus true-negative SLNs.

Although the Dutch MIRROR study suggests that some prognostic significance may be associated with isolated tumor cells or micrometastatic disease, this has not been confirmed in large prospectively collected data. No role for the routine use of IHC staining for breast cancer SLNs exists and the presence of IHC-detected SLN metastases should not guide treatment decision-making.

**ADDRESSING THE CLINICALLY POSITIVE AXILLA**

**Axillary Lymph Node Dissection**

**Indications**

ALND is indicated in patients with clinically positive axillary lymph nodes and those that are found to be positive on needle biopsy. Completion ALND for positive SLNs, including micrometastases, is also currently recommended by the American Society of Clinical Oncology guidelines. ALND is the first-line surgical treatment in cases in which SLN biopsy is contraindicated, such as large primary tumors and inflammatory breast cancer.
Complications
Multiple studies have demonstrated that the rate of various immediate- and long-term complications is significantly increased after ALND compared with SLN biopsy (see Table 2). The more extensive dissection required during an ALND leads to increased rates of wound infection, seroma formation, and lymphedema compared with SLN biopsy.

Wound infection rates from 8% to 15% have been reported in randomized controlled trials. Postoperative seromas are also relatively common, identified in a recent meta-analysis as the most common complication after ALND. Seromas were identified in 14% of patients undergoing ALND in ACOSOG Z0011.

Seromas were identified in 14% of patients undergoing ALND in ACOSOG Z0011. In performing a thorough ALND, the surgeon often has to sacrifice sensory nerves that cross the axilla, specifically the intercostobrachial nerve. Subsequently, postoperative paresthesias are common. A report by Roses and colleagues found that 76.5% of their 200 patients who underwent ALND reported paresthesias, with only 22% achieving full resolution after 1 year of follow-up. These rates of sensory deficits are similar to those reported in studies by Purushotham and coworkers and Veronesi and coworkers, which reported 1-year rates of 65% and 68%, respectively. More recent trials, such as the ALMANAC, ACOSOG Z0011, and NSABP B-32 trials, have demonstrated a self-reported rate of paresthesias of 31%, 39%, and 44.6% after ALND.

Lymphedema is one of the most commonly recognized lifelong complications following ALND. The rates among studies and trials vary widely (6%–70%) depending on whether the lymphedema is self-reported or objective measurements of the arm are performed. Lymphedema most commonly develops within the first year of surgery, but may develop as long as 20 years after surgery. The extent of axillary surgery, postoperative wound infection, and postoperative axillary radiation have all been found to increase risk of lymphedema.

Range of motion deficits can occur as a result of ALND. In the NSABP B-32 trial, 75% of patients reported difficulties with shoulder abduction after ALND in the immediate postoperative period; this decreased to only 9% by 6 months. These findings are similar to those of the ALMANAC trial.

OVERALL AREAS OF CONTROVERSY
Neoadjuvant Chemotherapy and Timing of SLN Biopsy
Neoadjuvant chemotherapy is an accepted initial treatment of patients with large breast cancers who wish to undergo breast conservation and for those with locally advanced breast cancer. Down-staging of the tumor occurs in most patients, with 26% to 50% achieving a pathologic complete response to neoadjuvant chemotherapy. Because this response occurs in the primary tumor and the nodal basin, it makes the timing of SLN mapping for patients undergoing neoadjuvant chemotherapy controversial.

The pros and cons of preneoadjuvant versus postneoadjuvant chemotherapy SLN biopsy are listed in Table 3. The greatest benefit to performing SLN biopsy before neoadjuvant chemotherapy is to allow for accurate staging of the axilla at the time of diagnosis. This information provides not only prognostic information, but can be used to inform decisions for adjuvant radiation. However, this approach requires patients to undergo two separate surgical procedures and, if the pretreatment SLN if found to be positive, commits them to an ALND regardless of their response to neoadjuvant therapy. In contrast, postneoadjuvant SLN biopsy accounts for patients’ response to chemotherapy and theoretically can spare patients with a good response...
an ALND. However, lower rates of SLN identification and increased false-negative rates make the accuracy of postneoadjuvant therapy SLN biopsy uncertain.

ACOSOG Z1071, a prospective multi-institution phase II study designed to validate the postneoadjuvant chemotherapy SLN false-negative rate in patients who presented with pathologically confirmed axillary lymph nodes, has completed accrual and results are pending. Until these results are available, the merits of preneoadjuvant and post-neoadjuvant chemotherapy SLN biopsy should be considered when making decisions for SLN timing for an individual patient.

FUTURE DIRECTIONS

AMAROS Trial

Axillary radiation therapy has been evaluated as an alternative to ALND. Previous small studies have demonstrated low axillary recurrence and no difference in survival in patients with clinically negative lymph nodes. The After Mapping of the Axilla: Radiotherapy or Surgery? (AMAROS) study is a prospective, randomized control comparing ALND with axillary radiation therapy in patients with early breast cancer with positive SLNs. The trial began accruing patients in 2001 and completed accrual in April of 2010. The results of this study have not yet been published, but the results may change the management of axillary lymph node metastases.

Endoscopic Axillary Surgery

To decrease the morbidity of SLN biopsy and ALND, the concept of endoscopic axillary surgery has been introduced. Few studies have demonstrated significant benefits of endoscopic axillary surgery when compared with traditional operative techniques. In one of the first studies to evaluate this technique, Kuehn and colleagues published a study of 53 patients undergoing endoscopic ALND. In this study they found that postoperative seroma formation and lymphedema were not significantly reduced compared with conventional surgery, but operative time was greatly increased. In a similar prospective study by Langer and colleagues, a 15% rate of seroma formation requiring drainage was reported and 4% of patients developed port site

<table>
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<tr>
<th>Table 3</th>
<th>Pros and cons of preneoadjuvant and postneoadjuvant chemotherapy SLN biopsy</th>
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<tr>
<td><strong>Proneoadjuvant SLN Biopsy</strong></td>
<td><strong>Postneoadjuvant SLN Biopsy</strong></td>
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<tr>
<td><strong>Pros</strong></td>
<td><strong>Cons</strong></td>
</tr>
<tr>
<td>Accurate staging of the axilla at initial diagnosis</td>
<td>Direct additional treatment based on response to chemotherapy</td>
</tr>
<tr>
<td>Provide prognostic information by documenting response to treatment</td>
<td>Identify patients with response to chemotherapy that can be spared an ALND</td>
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<tr>
<td>Increase ability to inform adjuvant radiation therapy decisions</td>
<td>Uncertainty regarding initial nodal status (loss of prognostic information)</td>
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<tr>
<td>Requires two surgical procedures</td>
<td>Higher false-negative rate</td>
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<tr>
<td>Complications of SLN biopsy may delay chemotherapy</td>
<td>Increased rates of mapping failure</td>
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<tr>
<td>Delayed ALND may be technically more difficult</td>
<td>Chemotherapy may make SLN biopsy technically more difficult</td>
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</table>
metastases. A more recent study reported decreased drainage and operative blood loss with endoscopic axillary dissection, but found that the number of lymph nodes removed was significantly lower than with ALND.\(^7\) Based on these and other studies, the risks of port site metastases and missed axillary lymph nodes outweigh the benefits of endoscopic axillary surgery.

**Axillary Reverse Mapping**

The concept of axillary reverse mapping (ARM) is based on the hypothesis that the lymphatic channels draining the breast are different from those draining the upper arm.\(^7\) Therefore, if the upper arm lymphatics can be mapped and visualized during an ALND, then they can be preserved thereby minimizing lymphedema. In one of the first studies describing ARM, Thompson and colleagues\(^8\) successfully identified blue lymphatics draining the upper arm in 61% of patients. They removed the ARM nodes in 64% of patients in which they could be identified and found them to be negative for breast cancer. Similar results were found by Nos and colleagues,\(^8\) with identification of ARM nodes in 71% of their patient population. A 2009 study by Klimberg and colleagues\(^8\) was the first to demonstrate that lymphedema may be reduced by preserving the ARM nodes. This study included 220 patients and found that in 2.8% of patients the SLN shared a common lymphatic channel with the ARM lymphatics and 40.6% of patients had ARM lymphatics adjacent to the SLN, which were at high risk of injury. Overall, at 6-month follow-up, no patients in whom the ARM nodes were preserved had lymphedema. Additional prospective randomized trials need to be performed to validate the true impact of ARM on minimizing the development of lymphedema.

**Use of Axillary Ultrasound**

In the absence of clinically palpable lymph nodes, ultrasound of the axilla has been found to be a useful adjunct in determining preoperatively which patients may have axillary metastases. Established criteria for evaluating a lymph node as suspicious for malignancy include cortical thickening greater than 3 mm; absence of the fatty hilum; and presence of nonhilar blood flow (increased vascularity).\(^8\) Suspicious lymph nodes can then be biopsied before surgery, facilitating surgical planning. Sensitivity rates of axillary ultrasound with needle biopsy have been reported to range from 20% to 80%\(^8\) and varies based on the population evaluated. Based on these data, the American Society of Breast Surgeons recommends that preoperative axillary ultrasound be performed if the surgeon or radiologist has experience in performing the study, thereby increasing the cost effectiveness of SLN biopsy.\(^2\)

**Nomograms**

To determine which patients may benefit from further axillary surgery after the identification of a positive SLN, researchers at several institutions have developed nomograms to calculate the likelihood of additional non-SLNs being positive.\(^8\) One of the first nomograms was developed at MSKCC and uses tumor size, type, and grade, number of positive and negative SLNs, method of detection of those SLNs, and estrogen receptor status in determining the risk of additional positive non-SLNs.\(^8\) The most recent nomogram from MD Anderson Cancer Center includes many of the variables in the MSKCC nomogram, but additionally included the size of SLN metastases.\(^9\) Based on this research, nomograms can be used to inform patient discussion as to whether to proceed with completion ALND, but should not be the only determining factor.
REFERENCES


