Breast Lymphatic Mapping and Sentinel Lymph Node Biopsy: State of the Art: 2015

Michael Reintgen [1], Lauren Kerivan [1], Eric Reintgen [1], Santosh Swaninathan [1], Douglas Reintgen [1, *]

[1] Department of Surgery, University of South Florida Morsani College of Medicine, Tampa, FL

* Corresponding Author: Douglas Scott Reintgen, MD, Department of Surgery, University of South Florida Morsani School of Medicine, MDC 52, 12901 Bruce B., Downs Boulevard, Tampa, FL 33612. E-mail contact: dreintge@health.usf.edu

Abstract. Lymphatic mapping with sentinel lymph node biopsy (SLNB) was introduced in the 1990s as a method to stage the nodal axilla in women with breast cancer. Very quickly the technique became the standard of care because pathologic staging was more accurate and sensitive and the surgical procedure resulted in low morbidity. SLNB has continued to evolve, and the applications in breast cancer have been expanded. A review of the published data was performed to update the lymphatic mapping technique and identify key issues and trends in the application of SLNB in women with breast cancer in 2015. The importance of axillary staging continues to effect the surgical treatment of patients with breast cancer. Originally described for patients with invasive cancer, the technique now plays an important role in staging women with ductal carcinoma in situ or recurrent breast cancer and patients with advanced breast cancer who are receiving neoadjuvant chemotherapy. Histologic examinations have incorporated multiple sectioning and immunostains. The morbidity has been low, and techniques for limiting lymphedema are being introduced. Lymphatic mapping will continue to play an important role in the treatment of women with breast cancer. The SLNB will evolve by eliminating the need for radioactivity in the operating room, and the technique will become more accurate and used in expanded indications by incorporating preoperative imaging and intraoperative guidance procedures.

Keywords: Breast cancer treatment and survival; Lymphatic mapping; Micrometastases; Nodal staging; Sentinel lymph node biopsy.

1. Introduction

Axillary lymph node status is the most important prognostic factor for recurrence and survival in women with early-stage breast cancer. The lymphatic mapping technique and sentinel lymph node (SLN) biopsy (SLNB) is the reference standard for staging the axilla in clinically lymph node-negative patients. It is a procedure with low morbidity and has been proved to be safe, dependable, and reproducible for nodal staging. The SLN procedure is based on the early work by Cabanas,1 who showed that tumor cells from solid malignancies migrate in a sequential fashion through the lymphatic channels to the initial nodes in the regional basin, connected by afferent lymphatic channels. Morton et al2 from the University of California, Los Angeles, and the John Wayne Cancer Institute described the use of intradermal isosulfan blue dye injection for lymphatic mapping and SLNB in patients with melanoma in the early 1990s. Shortly thereafter, the technique was applied for nodal staging in women with breast cancer. Radioguided surgery for breast cancer was introduce by Krag et al,3 Morton and Giuliano, Norman et al,4 Reintgen et al,5 and Albertini et al.6 Norman et al4 initially showed in patients with melanoma in 1989 that preoperative lymphoscintigraphy can provide a road map for the surgeon to direct the nodal dissection. Later, Reintgen et al5 and Albertini et al6 emphasized the “orderly progression of nodal metastases” and the application of the lymphatic mapping technique to breast cancer. Previous studies have demonstrated SLN identification rates of 66% to 99%, with false-negative rates of 0% to 15% and an accuracy of 95% to 100%.7, 8 and 9 The SLN procedure allows the pathologist to perform a more detailed examination of the SLN, including more sectioning and incorporating immunostains. With these

refinements, the staging of melanoma and breast cancer became more sensitive and accurate. Combined with the low morbidity of the lymphatic mapping procedure, the technique very quickly became the standard of care for nodal staging throughout the world.

2. Relevancy of Axillary Lymph Nodes

The appreciation of the axilla as the most common site of metastatic disease for patients with breast cancer has been recognized since Wilhelm Fabry (1560-1634) first described axillary nodal excision in concert with primary tumor excision.10 What has eluded investigators since then has been understanding what the presence of axillary metastases really portends for the prognosis of the patient. In the 18th century, breast cancer progression was envisioned as an orderly process beginning in the breast and spreading to regional nodal areas before systemic spread. Halstead11 was the leading proponent of the radical mastectomy that involved en bloc resection of the breast, underlying musculature, and axillary nodes. The Halstead radical mastectomy dominated surgical treatment in the 19th century. In the early 1960s, the view of axillary lymph node dissection (ALND) being standard was challenged by Devitt12 and others when they noted that retrospective data failed to show a survival advantage for radical nodal surgery. Also, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial13 confirmed in a prospective study that the addition of ALND to mastectomy did not improve distant disease-free survival (DFS) or overall survival (OS). The chief investigator for the NSABP trial, Bernard Fisher, in 1980 asserted that “breast cancer is a systemic disease, likely at its inception” and “the positive axillary node is a reflection of the interrelationship that permits the development of metastases rather than the instigator of distant disease.” Thus, identifying lymph node metastases is a simple method to identify tumor that has the phenotype to survive outside the breast in a host that is compromised and cannot prevent it. More recent studies have shown that tumor subtype (triple negative) does not independently predict nodal metastases; this finding reinforces the idea that patients can have a poor prognosis and be node negative.14 These triple-negative, basal genotype breast cancers have been associated with poor survival but with a lower rate of lymph node metastases than estrogen receptor-positive breast cancers. Triple-negative tumors possess the ability to disseminate and thrive in distant organs, but some feature of the tumor–host relationship prevents the development of nodal metastases.14

Although imperfect at best, the axillary lymph node continues to serve as an in vivo marker for determining whether tumor cells have gained access to the circulation and whether the cancer cells can survive outside the breast. Some believe that when cancer cells are found in the SLN, almost certainly they have gained access to the systemic circulation by the presence of lymphovenous shunts that are necessary to maintain low pressure and avoid lymphedema. Reaching the circulation might be a small task for a cancer cell; however, the ability to implant and grow in a distant organ requires a unique genotype and a cooperative host environment. The metastatic burden in the axillary node informs about the interaction between the tumor and host beyond what the primary tumor variables will provide. However, SLN metastasis has failed as a biomarker and is ineffective in predicting which treatments will be most successful. The status of the axillary lymph node remains a powerful predictor of recurrence and survival in the patients with breast cancer; however, it has some limitations, in particular, with the triple-negative, basal subtype of breast cancer, which results in a poor prognosis despite being more often node negative.

In fact, the distribution of axillary metastases between the SLN and non-SLNs might be an important driver of prognosis. Reintgen et al15 showed that, in patients with melanoma, the number of metastatic nodes, such as the current staging system suggests, is not nearly as important as whether the metastatic disease in the regional basin has made its way through the SLN to involve higher echelon nodes in the basin. In comparing patients with 2 positive nodes, if all the disease was confined to the SLNs, those patients will do much better than if the metastatic disease involves a SLN and a non-SLN. The SLN acts like a trap in the regional basin, and the primary site must shed a large number of metastatic cells to overwhelm the SLN and involve higher echelon nodes in the basin. Additional evidence that the SLN serves an important role in the regional basin is that if any metastatic disease is present, 70% of the time in breast cancer and 85% of the time in melanoma, the

disease will be confined to the SLN. By far the most common finding is involvement of 1 microscopically positive SLN. Similar studies are ongoing of women with breast cancer to ascertain the importance of regional basin metastasis distribution.

3. Ultrastaging of Cancer

As nodal staging techniques for breast cancer become more accurate and sensitive, it is apparent that the patients found to be node negative in the previous 20 years using the lymphatic mapping techniques to define the node-negative population will have better survival than the node-negative population from the 1960s and 1970s. This can be attributed to the use of lymphatic mapping to identify the SLN draining the primary tumor site. The SLN can then be more closely examined for disease using more sectioning and special stains, leading to a lower false-negative rate. Thus, patients currently considered to have stage N0 using the lymphatic mapping technique are more likely to be truly node negative and will have significantly better survival than patients considered to be node negative from the 1960s and 1970s. An ancillary benefit for this more accurately staged node-negative population is that some patients will avoid systemic chemotherapy.

Lymphatic mapping was first performed in patients with melanoma in the 1990s after a number of decades of patients undergoing complete elective nodal dissection for nodal staging. In these procedures, usually 15 to 20 nodes will be removed with radical resection and each node stained with routine hematoxylin and eosin stains of the central cross section of the node. Thus, pathologists will examine < 1% of the submitted material, and low-volume disease could be missed. With the SLNB procedure, the pathologist receives 1 to 2 SLNs and can perform multiple sections of each node, using special immunostains to help identify low-volume disease. The sensitivity of the routine histologic examination has been estimated to allow identification of 1 abnormal cancer cell in a background of 106 normal lymphocytes in complete nodal dissection specimens. With the SLNB, 1 abnormal cancer cell can be identified in 107 normal lymphocytes, an order of magnitude greater in sensitivity. The survival rates for patients with breast cancer have reflected this more accurate staging accomplished with lymphatic mapping. The 10-year survival of the node-negative population in the 1970s and 1980s with axillary node dissection as the staging procedure was 80%; however, this has increased to 90% when the lymph nodes were staged with lymphatic mapping. The same phenomenon has been found in patients with melanoma16 and patients with colon cancer.17

With lymphatic mapping and a more detailed examination of the SLN, lower volume disease has been found. The question has been debated whether isolated tumor cells [pN0(i+)] and micrometastases (pN1mi) have clinical relevance. A study by Boughey et al,18 from MD Anderson and the American College of Surgeons Oncology Group (ACOSOG) Z10 trial were analyzed. In both groups, modest, but nonsignificant, differences in DFS and OS were found, and the investigators concluded that no prognostic difference was present between women with these 2 stages of minimally identified disease and that the stage groupings should be reconsidered. The study was complicated because a large percentage of the patients in both cohorts had received adjuvant chemotherapy. Others have shown different results. An Italian study analyzed the prognostic value of the pN0(i+) and pN1mi status in a consecutive series of 702 patients from a single institution.19 By performing a more detailed histologic examination, 13% of the node-negative population was upstaged to having isolated tumor cells or micrometastases. The hazard ratio (HR) for disease relapse in the upstaged population was 2.16 ($P < .001$), and this group was shown to account for 50% of the metastatic recurrences. The Micrometastases and Isolated Tumor Cells Relevant and Robust or Rubbish (MIRROR) study, with a mean follow-up period of 5.1 years for 3181 patients, showed that systemic therapy could erase the added risk associated with the micrometastases group. 20 In addition the NSABP B-32 trial detected occult metastases in 15.9% of 3887 patients, and the presence of occult metastases was shown to be an independent prognostic variable that led to a 1.2% reduction in OS at 5 years.21 The Surveillance, Epidemiology, and End Results (SEER) database was also examined for the prognostic significance of patients with breast cancer and low-volume disease in their regional basin, and the analysis found micrometastases to be important.22 The stage 1B group remains 1 of the

key parameters of response to systemic therapy,22 and arguments with these data have been made of the importance of the detailed pathologic examination of the SLN.

4. Clinical Significance of Extracapsular Invasion of SLN

After lymphatic mapping and SLNB, a certain number of patients will be identified with extracapsular invasion (ECI) in the SLN (Figure 1). ECI can be regarded as a marker of tumor migration and invasion potential. The clinical significance of this finding is unclear, and it is questionable whether the ACOSOG Z11 study results can be applied to this population such that they can avoid ALND. A study from Japan evaluated 131 consecutive SLN-positive patients who had undergone ALND from 2003 to 2008 with regard to their long-term prognosis and non-SLN metastases.23 Of the 131 patients, 46 (35%) tested positive for ECI in their SLN. Of these 46 patients, 61% had non-SLN metastases compared with 28% of the ECI-negative group ($P < .001$). Multivariate analysis showed that ECI in the SLN evaluation is a significant predictor of non-SLN metastases (HR, 3.2; $P = .005$). The 5-year DFS rate was 71.3% in the ECI-positive group and 89.9% in the ECI-negative group ($P = .001$). Cox regression analysis showed that ECI at SLNB independently predicted for lower DFS (HR, 4.5; $P = .002$). The investigators concluded that ECI in the SLN histologic findings is an independent predictor of both non-SLN metastases and poor prognosis for patients with breast cancer.

In a review of the published data concerning this topic, ECI in the SLN was associated with higher echelon nodes in the basin involved with metastatic disease, an increased rate of both axillary and systemic recurrence, and decreased survival.24 The definitive trial supporting the elimination of complete ALND in women with a positive SLN (ACOSOG Z11 study) was a practice changing trial, and the findings of that study were used to change the standard of care in treating women with breast cancer. Patients found to have ECI in their SLNs were not eligible for enrollment. Enough published evidence is available to suggest that these women will have a greater recurrence rate both in their regional basin and systemically, such that including complete ALND should still be considered the standard of care.

5 . Technical Issues of Lymphatic Mapping

5.1. Lymph Node Mapping Agents

Krag25 initially identified the SLN in breast cancer using technetium-99m (99mTc)–labelled sulfur colloid, and this was subsequently confirmed by Giuliano et al,26 using isosulfan (Lymphazurin) blue dye, with identification rates of 82% and 66%, respectively. Albertini et al6 combined these modalities, and the identification rate increased to 92%, suggesting that the use of dual localization rates were superior to single mapping agents (Figure 2). Studies performed later in the learning curve of surgeons have demonstrated that perhaps a single agent is all that is needed. A prospective randomized trial was performed by investigators from St. Vincent Healthcare Group in Dublin, Ireland, comparing the combination of radioisotope and blue dye versus radioisotope alone in 667 patients with clinically and radiologically node-negative breast cancer.27 A total of 342 patients received the combination mapping agents and 325 patients received the radioisotope alone. Their mean age was 48 years, and the mean tumor size was 24.2 mm.27 No statistically significant difference was found between the 2 groups in tumor grade, SLN identification rate, or number of lymph nodes retrieved between the 2 groups. Also, no difference was found in the number of positive lymph nodes identified in the study (23.8% vs. 22.1%; $P = .64$). 27 The study failed to demonstrate an advantage with the addition of isosulfan blue dye to radioisotope in the identification and harvesting of SLNs, as long as SLNs were visible on the preoperative lymphoscintigram (Figure 3). A meta-analysis, which examined 69 trials and > 8000 patients, seemed to confirm these findings.28 The identification rates for blue dye alone (19 studies), radiocolloid alone (16 studies), and a combination of the 2 mapping agents (34 studies) were 83.1%, 89.2%, and 91.9%, respectively. The corresponding false-negative rates were 10.9%, 8.8%, and 7%.28 The investigators concluded that although the increase in the identification rate with the combination blue dye and radiocolloid was

slight, this was not an independent predictor of false-negative SLNB rates on multivariate analysis, and, therefore, it would be acceptable to use either technique alone.28

Radiation exposure and the disposal of contamination in the surgical suite are 2 issues that have not been solved. More recent studies have reported that vital blue dye can be eliminated, which is reasonable, considering the small, albeit real, incidence of significant anaphylaxis.29 Also, one can avoid skin tattooing and any interference with pulse oximetry, as long as the preoperative lymphoscintigram shows a strong unique signal in the axilla, separable from injection site radioactivity. However, many institutions have eliminated imaging after radiocolloid injection, because surgeons will only be performing lymphatic mapping to the axilla. Although it might be helpful for identifying intramammary lymph nodes in the upper outer quadrant and keying the surgeon that these might be present, intraoperative scanning with the gamma probes should be able to find the intramammary nodes. Thus, if one is only concerned with axillary mapping, imaging becomes less useful. This policy decreases costs and still provides accurate lymphatic mapping to the axilla. However, the Holy Grail in lymphatic mapping would be to eliminate radiocolloid from the operating room.

The current reference standard for the detection and targeted excision of the SLN is preoperative lymphoscintigraphy with 99mTc (Figure 3). Because surgeons are most concerned with performing accurate mapping to the axilla, the radiocolloid is injected in the ipsilateral subareolar plexus, and the time and expense of imaging is not recorded. However, there is a worldwide shortage of 99mTc; thus, alternative nonradioactive dyes for SLN labeling must be found. Indocyanine green (ICG) has been considered a possible alternative. A prospective clinical trial was performed to compare the usefulness of ICG versus 99mTc for the identification of SLNs.30 The preoperative and intraoperative SLN detection rates were compared. The study showed that SLN location was identified in all cases before surgery using 99mTc; however, visualization with ICG green before the skin incision was only possible in 17 of 80 patients (21%).30 However, SLN identification using the near infrared fluorescence technique in the operative site after skin incision and initial tissue preparation was 141 of 147 (96%), making it comparable to 99mTc. Although using ICG eliminates the need for handling any radioactive material and would be a major advantage, the new marker does not perform up to the reference standard, 99mTc, in preoperatively identifying all nodal basins at risk of metastases and providing the surgeon with the information needed to perform the dissection. This quality is less important in breast mapping, because the surgeon is most concerned with accurate mapping to the axilla. ICG has been used successfully in performing lymphatic mapping for gynecologic malignancies, with marked improvement of bilateral SLN detection rates of 96% versus 61% compared with dye and radiocolloid.31

Another novel mapping agent, [99mTc]tilmanocept, a new CD206 receptor-targeted radiopharmaceutical agent, was evaluated for its use in lymphatic mapping in a series of patients with intraoral or cutaneous head and neck cancer undergoing primary tumor resection, SLNB followed by complete lymph node dissection (CLND).32 All patients were considered clinically node negative at the time of the study. The mapping agents in use at that time, radiocolloid and vital blue dye, are characterized by a nonspecific accumulation of the agents in the SLN by macrophages and dendritic cells. The small molecular size (7-nm diameter) of tilmanocept and its specific targeting to CD206 mannose-binding receptors located on reticuloendothelial cells within the lymph node permit rapid injection site clearance and avid, stable binding within the target nodes.32 Tilmanocept identified $\geqslant$ 1 SLNs in 81 of 83 patients (97.6%). Of the 39 patients with tumor-positive regional nodes, 1 patient had a single tumor-positive non-SLN, for whom all SLNs were tumor negative, for a false-negative rate of 2.6%. The negative predictive value was 97.8%, and the overall accuracy was 98.8%.32 No differences were noted between the same-day and next-day mapping procedures. Compared with SLN mapping of head and neck cancer in published studies using blue dye and radiocolloid (false negative rate, 10%), the false-negative SLN rate appeared to be improved and could be used in this population to obviate the need for elective lymph node dissection. The specificity of tilmanocept for lymphatic tissues assessed by in vivo imaging and in vitro analysis of its receptor binding properties suggest that tilmanocept does not move downstream to distal second station lymph nodes, permitting

high confidence that the hot node found during next-day procedures will be the SLN. The ability to perform the mapping injection the day before surgery without any decrease in accuracy provides flexibility in scheduling. Recently, a study using this compound was performed in women with breast cancer.33 A total of 13 centers enrolled 148 patients, who were injected with both tilmanocept and vital blue dye. Intraoperatively, 207 of 209 nodes detected by blue dye were also detected with tilmanocept, for a concordance rate of > 99%. Of the 33 pathology-positive nodes (18.2% patient-positive pathology rate), tilmanocept detected 31 of 33 compared with 25 of 33 for blue dye (P = .03). The investigators concluded that tilmanocept identified more SLNs in more patients and a higher number of metastatic breast cancer lymph nodes than identified by blue dye. 33

The cost of technetium sulfur colloid has increased recently, and other agents are now being studied in attempts to find better specificity and eliminate radioactivity from the operating room. However, until improvements are realized, technetium sulfur colloid will remain the reference standard.

5.2. Site of Mapping Agent Injection

Multiple different sites of tracer injection have been used, with the easiest and most effective location the subareolar plexus of Sappey.34 This site has proved to be superior to other injection sites, because a high percentage of the injectate reaches the axillary more quickly as it follows the natural progression of lymph flow from the subareolar plexus. Combined with a reduction in “shine through” from injecting around tumors in the breast parenchyma located in the upper, outer quadrant and the fact that the cancer does not have to be located in the breast, the subareolar injection has proved to be the preferred injection site for breast lymphatic mapping, with the caveat that it will not light up any internal mammary (IM) lymph nodes. Most groups will not harvest any IM nodes found on preoperative lymphoscintigraphy studies; thus, this might not be an important limitation.

5.3. Intraoperative Examination of SLN

One approach in an attempt to gain intraoperative information on the status of the SLN is to perform frozen section analysis of the SLN. However, the low-volume disease in the SLN and the waste of valuable material as the sections are cut on the cryostat are significant shortcomings. Touch preparation techniques performed directly on the SLN avoids the waste of material with the cryostat; however, institutions must have good cytology interpretation for effective use. Others will submit fresh, nonfixed SLNs to the pathology laboratory for macroscopic analysis, with frozen section analysis performed on grossly suspicious SLNs.35 If positive, the surgeon has the option of completing the ALND. If negative, the SLNs are fixed, paraffin-embedded, and sectioned at 2-mm intervals for routine and immunostain examination.

6. Extra-Axillary Sites of Lymphatic Flow

Preoperative lymphoscintigraphy in women with breast cancer has imaged drainage to the SLNs in the axilla (Figure 3); however, in approximately 10% of patients, drainage has also been seen to extra-axillary sites, most commonly the IM nodes and the subclavian or ipsilateral neck nodes. These patients can be identified with preoperative lymphoscintigraphy studies if the radiocolloid is injected into the breast parenchyma around the primary tumor. The lymphatic channels that lead to the IM basin initially go deep through the pectoralis fascia to the IM chain. Injections into the skin above the tumor or the subareolar plexus will not image these extranodal sites.

The question remains regarding the clinical relevance of this multidirectional drainage because most patients will also receive adjuvant chemotherapy and/or hormonal therapy, and a percentage will also undergo adjuvant radiation therapy. A recent study evaluated the incidence and prognostic effect of metastatic IM SLNs.36 During a 13-year period, 3685 patients underwent breast surgery and SLNB after intratumor or peritumoral injection of radiocolloid. In 754 patients (20.5%), ipsilateral IM SLNs were visualized on preoperative lymphoscintigraphy. The harvest rate of IM SLNs was 81%. IM metastases were detected in 21.3% of the harvested SLNs and 3.5% of all patients. The presence of IM metastases was associated with axillary metastases (P < .001). With a mean follow-up period of 61 months, 10.9% of the patients had died. A multivariate analysis showed that IM

metastases did not have a significant effect on overall survival unless the patients had IM metastases alone without axillary metastases.

Most groups have ignored the IM chain or IM lymphatic flow found on preoperative lymphoscintigraphy studies because harvesting this site is technically demanding, adds another scar to the patient undergoing lumpectomy to treat her primary tumor, and the clinical relevance is uncertain because most patients will also receive total body therapies in the form chemotherapy and/or hormonal therapy and might also receive adjuvant radiation therapy to this area. Most US surgeons have confined their energy to the performance of accurate axillary SLN mapping.

7. Predicting Extent of Nodal Metastases—The Promise of Axillary Imaging

Enhanced axillary imaging is an area of active investigation as an approach toward more accurate preoperative nodal staging.37 These procedures can possibly, not only save node-negative patients from undergoing unnecessary axillary surgery, but could also help to distinguish node-positive patients who might be treated appropriately with SLN resection alone from those who would benefit from more extensive ALND. Axillary ultrasound (AUS) can be used to identify suspicious nodes, followed by ultrasound-guided fine needle aspiration (FNA). In a study by Caudle et al,38 708 patients with node-positive T1 and T2 invasive breast cancer evaluated from 2002 to 2012 underwent surgery directly after diagnosis and did not undergo neoadjuvant chemotherapy (NAC). These patients were stratified according to whether their node-positive disease was identified by preoperative AUS and FNA (190 patients) or by SLN resection (518 patients). The investigators found that those diagnosed as node-positive by preoperative AUS and FNA were substantially more likely to have $\geqslant$ 3 metastatic axillary nodes, larger nodal metastases, and extranodal disease extension compared with those deemed node-negative after AUS and FNA.38 Furthermore, the study identified significant axillary disease burden in patients with 1 to 2 suspicious lymph nodes found by AUS and a positive preoperative lymph node on FNA. In addition, the presence of infiltrating lobular histologic features, but no other clinicopathologic features, was associated with $\geqslant$ 3 positive nodes at surgery. Finally, their study found that $\geqslant$ 3 suspicious lymph nodes found by AUS among the FNA-positive patient group was associated with pathologic stage N2 or higher disease in 60% of patients.38 From these findings, Caudle et al38 concluded that AUS and FNA are useful in predicting the nodal disease burden and suggested caution in the omission of ALND for AUS-detected patients, who might not be comparable to SLN resection-detected patients in the ACOSOG Z0011 trial.37 and 38 AUS can be used as a tool to select patients with a high axillary disease burden who are likely to benefit from ALND and other more aggressive therapies.

8. Morbidity of SLNB and Avoidance of Lymphedema

The ALMANAC trial39 (Axillary Lymphatic Mapping Against Nodal Axillary Clearance) studied the morbidity associated with lymphatic mapping and demonstrated that SLNB is associated with a significant reduction in overall morbidity. This group from the United Kingdom conducted a multicenter randomized trial to compare the quality of life outcomes between patients with clinically node-negative breast cancer who had undergone SLN versus those who had undergone CLND of the axilla. A total of 1031 patients were randomly assigned to 1 of the 2 axillary procedures. Patients with SLN metastases underwent CLND or axillary radiotherapy. The relative risks of any lymphedema or sensory loss for the SLNB group compared with standard CLND of the axilla at 12 months was 5% versus 13% and 11% versus 31%, respectively. Drain usage, length of hospital stay, and time to resumption of normal day-to-day activities after surgery were statistically significantly lower in the SLNB group ($P < .001$), and the operative time was reduced ($P = .05$). Patient-recorded quality of life and arm functioning scores were significantly better statistically in the SLN group throughout all periods tested (1-12 months). These benefits were seen without any increase in anxiety level in the SLN group.

Lymphedema in breast cancer patients causes a long-term decrease in quality of life, as well as chronic pain, depression, and anxiety (Figure 4). The percentage of patients with breast cancer experiencing lymphedema after undergoing ALND has ranged from 20% to 45% and increases if the patient also receives adjuvant nodal radiotherapy.40 The significant effect on quality of life and the requirement for lifelong therapy demands that effective preventative strategies be investigated. Lymphatic mapping and SLNB resulted in the potential to avoid this complication by just removing the 1 to 2 nodes most likely to contain metastases. However, even in the best of hands, a small, albeit real, chance (1%-3%) exists of lymphedema developing after SLNB. The factors shown to increase the risk of secondary lymphedema include the number of nodes dissected, the use of extended nodal radiotherapy, and body mass index > 30 kg/m2.41 Current management involves symptom relief with manual lymph drainage with massage, compression garments, and physical therapy; however, this requires extended treatment with a complaint patient.42 Breast cancer survivors with lymphedema report long-term morbidity that includes chronic pain, depression, and anxiety. The medical costs are high and the loss of work productivity is significant.43

Axillary reverse mapping is a technique developed by Klimberg44 and others in an attempt to eliminate this complication. This procedure is performed in conjunction with the lymphatic mapping procedure. Radiocolloid is injected into the subareolar plexus for axillary lymphatic mapping, and blue vital dye is injected into the proximal ipsilateral, medial arm to identify the arm lymphatics entering the axilla. With axillary reverse mapping, an attempt is made to spare all lymphatics coming from the arm while harvesting the SLN. If the breast SLN is the same as a node receiving a blue lymphatic from the arm, the SLN is harvested, and some form of a lymphatic/venous anastomosis is performed. This technique has resulted in a decreased in the lymphedema rate after SLNB.

For patients with grossly positive nodes or women with a positive SLN after mastectomy, CLND is recommended. Techniques are currently being developed to avoid lymphedema even with this more radical procedure. The lymphatic microsurgical preventive healing approach (LYMPHA)40 for the primary prevention of lymphedema is one such procedure. Originally described by Boccardo et al45 in 2009, they reported a 4.05% rate of ongoing lymphedema in a population of 74 patients who had undergone axillary dissection with a 4-year follow-up period. Afferent lymphatic channels, identified by the injection of vital blue dye in the ipsilateral upper arm, that have been divided by the axillary dissection procedure are sutured into a branch of the axillary vein distal to a competent valve. The site of the anastomosis is necessary to prevent clotting. Pre- and postoperative lymphoscintigraphy that includes arm measurements and bioimpedence spectroscopy are performed. In a 2015 series from Columbia University, Feldman et al,40 performed LYMPHA in 37 women who were undergoing ALND during a 26-month period. Successful completion of the anastomosis occurred in 27 women (73%), with an average size of the lymphatic channels of 1 to 2 mm. The unsuccessful attempts resulted from the lack of a suitable vein, lack of a suitable lymphatic, or extensive axillary disease. The mean follow-up period was 6 months. The body mass index was > 30 kg/m2 in 37% of the women, and 63% had received axillary radiotherapy. The lymphedema rate was 12.5% in the 24 patients with a successfully completed anastomosis and 50% in the 8 unsuccessfully treated patients. No LYMPHA-related complications occurred. Comparing patients with completed and incomplete LYMPHA with $\geqslant$ 3 months of follow-up, the odds ratio for the development of lymphedema with LYMPHA versus no LYMPHA was 0.14 (95% confidence interval, 0.02-0.90, with a Fisher exact probability test for 2-tailed P = .05). These early data from a high-risk cohort of patients suggests that LYMPHA is feasible, safe, and effective as a method for the primary prevention of clinical lymphedema. 40

9. SLNB in Patients With Ductal Carcinoma In Situ

The incidence of ductal carcinoma in situ (DCIS) has increased dramatically in the United States and other countries with the proliferation of breast cancer screening programs. Approximately 20% of total breast cancer cases will be DCIS, and 5% to 13% of these patients will have microinvasion of the tumor cells into the surrounding stroma.46 Microinvasion is defined as a $\leqslant$ 1.0-mm extension of

tumor cells into the surrounding stroma. Furthermore, the pathologist might report findings such as "suspicious for microinvasion" or "microinvasion cannot be excluded" when tumor cell nests or single cells appear to be focally extending outside a pre-existing ductal lobular structure in a background of high-grade DCIS.46 The proper identification of microinvasion in DCIS is of high importance because the presence of microinvasion could dictate performing SLNB to evaluate the axilla for regional metastasis. For pure DCIS (no microinvasion), SLNB is not recommended, except in cases with a suspicious mass on imaging or a large area (≥ 5 cm) of calcifications without a mass. Additional factors associated with a greater risk of invasive breast cancer and subsequent nodal disease in the context of DCIS include a palpable mass, multicentric disease, high nuclear grade, necrosis, use of smaller gauge biopsy needles, and a core needle biopsy reported as DCIS with findings suspicious for microinvasion. The rate of upstaging can be as great as 91% for invasive cancer in patients with 4 of these high-risk characteristics on core needle biopsy, and DCIS with 1 high-risk characteristic has been associated with a 12% rate of SLN involvement, although > 75% of those were micrometastases. At present, SLNB is the standard of care for all invasive breast cancers. However, in a retrospective study performed by Namm et al,46 about 66% of patients with findings suspicious for microinvasion without upstaging to invasive disease could have been spared the potential morbidity of SLNB if they had not been offered SLNB until after a definitive diagnosis of invasive cancer was made. Therefore, these researchers concluded that until clinically significant lymphatic invasion can be better predicted, surgeons should consider omitting SLNB in low-risk cases (those without findings suspicious for microinvasion) until invasive ductal carcinoma has been confirmed by surgical resection to prevent the morbidity of SLNB for most patients.

However, these treatment guidelines do not address the situation of women diagnosed with DCIS on image-guided core biopsy and electing to undergo mastectomy. In these cases, if invasive cancer is found on mastectomy, nodal staging cannot be performed and lymphatic mapping cannot be offered. In a multicenter study from France, investigators sought to determine the benefit of performing upfront SLNB in these women.35 The secondary aim of their study was to determine the pathologic variables associated with finding microinvasion or invasion in the mastectomy specimen. From 2008 to 2010, 228 patients were enrolled from 14 French cancer centers, including 192 patients with pure DCIS on biopsy. The mammographic findings were either extensive microcalcifications or multicentric foci (in 2 different quadrants of the breast). ALND was avoided for 67% of the patients with microinvasive DCIS or DCIS associated with invasive breast cancer at mastectomy and found to have a negative SLN. Of the 192 patients with pure DCIS on biopsy, 39% were upgraded to invasive cancer after mastectomy. This rate was greater than other published series47 and might have resulted from the large size of the DCIS lesions in the series (mean size, 69.3 mm). The rate of positive SLNs for patients with pure DCIS on biopsy was 14%. High nuclear grade and human epidermal growth factor receptor 2/neu-amplified DCIS was associated with a greater risk of finding invasive cancer after mastectomy. The investigators concluded that underestimation of invasive components is high when DCIS is diagnosed by biopsy. Upfront SLNB for patients with extensive DCIS avoids unnecessary ALND for two thirds of patients with invasive disease found only after mastectomy.

A recent study addressed the clinical relevance of positive SLNs in women with DCIS.48 That report identified 1234 patients from a single institution with an initial diagnosis of DCIS who had undergone SLNB. Positive SLNs were defined as either isolated tumor cells (≤ 0.2 mm), micrometastases (> 0.2-2 mm), or macrometastases (> 2 mm). Positive SLNs were identified in 10.7% of the population, 66 patients with isolated tumor cells, 2.9% of patients with micrometastases, and 2.4% with macrometastases. Upstaging to microinvasive or invasive cancer occurred in 26.5% of the patients. The variables associated with a positive SLN included diagnosis by excisional biopsy, DCIS > 2 cm, > 3 interventions before the SLNB, and occult invasion. Patients with pure DCIS, independent of their SLN status, had equivalent survival that approached 100%. Patients with occult invasive cancer and positive SLNs had worse survival (91.7%). That > 3 interventions in the breast before the SLN procedure was associated with positive SLNs without an effect on survival would support the theory that benign mechanical transport of breast epithelial cells occurs with breast

manipulations. The study also concluded that except for patients at high risk of invasive disease, the routine use of lymphatic mapping for patients with DCIS is not warranted.

10. Lymphatic Mapping in Conjunction With NAC

In patients with more advanced breast cancer, NAC has been recommended in an attempt to increase the breast preservation rate without having an effect on the survival data. Although previously cases of documented node-positive disease before the advent of NAC resulted in complete ALND, the improvements in pathologic complete response rates seen with the use of targeted agents now suggest that more radical surgery might not be necessary. The ACOSOG Z1071 trial, SENTINA (sentinel-lymph-node biopsy in patients with breast cancer before and after NAC) trial in Europe49, and the Canadian Sentinel Node Biopsy Following NeoAdjuvant Chemotherapy in Biopsy Proven Node Positive Breast Cancer (SN FNAC) trial50 showed that the false-negative rate of SLNB after chemotherapy for patients presenting with node-positive disease is 8% to 14%.47, 48, 49, 50 and 51 The ACOSOG Z1071 trial reported a 12.6% false-negative rate for SLN surgery after NAC. In that study, patients with T4N1-N2M0 breast cancer underwent AUS after NAC. Post-NAC AUS images were reviewed for 611 patients, and 71.8% of the AUS-suspicious patients were node positive at surgery compared with 56.5% of the 430 AUS-normal patients. Patients with AUS-suspicious nodes had a greater number of positive nodes and a larger metastatic size ($P < .001$). However, in the setting of normal AUS findings, only 39% of the women had a complete pathologic response. The high percentage (61%) with disease remaining in the axilla after NAC and normal AUS findings underlines that some form of nodal staging remains important after NAC. AUS is operator dependent, but it has outperformed other imaging modalities such as positron emission tomography and magnetic resonance imaging. Using a strategy in which only those patients with normal AUS findings would undergo SLNB would reduce the false-negative results for SLNB from 12.6% to 9.8%. The study concluded that AUS should be recommended after chemotherapy to guide axillary surgery. A false-negative rate of 9.8% with a combination of AUS and SLNB would be acceptable for the adoption of SLNB in women with node-positive breast cancer undergoing NAC. 52 Factors that decreased the false-negative rate included the resection of $\geqslant$ 2 SLNs, the use of 2 mapping agents, the use of immunhistochemical (IHC) staining and the placement of a clip in the positive node at diagnosis with removal of the node at postchemotherapy surgery.53 Historically, patients who initially presented with clinically positive axilla would undergo CLND. Data from the ACOSOG Z1071 trial support a potential new use for AUS for the evaluation of the axilla in an increasing population of women undergoing NAC. The overall in-breast tumor response to NAC was not assessed in the trial and because residual disease in the breast indicates a poor response to chemotherapy and might indicate remaining disease in the axilla, this factor could be important in selecting women for SLNB.

Other groups have used pretreatment tattooing (sterile black carbon suspension) of biopsied axillary lymph nodes to later remove them.54 Choy et al54 showed that the tattooed nodes are visible intraoperatively months later, obviating the need for additional localization during axillary staging. The National Comprehensive Cancer Network guidelines now recommend performing the SLNB as an option for women receiving NAC. Increasingly nationwide, patients with node-positive breast cancer treated with NAC can undergo SLNB to evaluate the nodal response to chemotherapy and reserve axillary dissection for those patients with residual nodal disease. A recent report used preoperative, ultrasound-directed wire localization to improve the accuracy of axillary lymph node surgery after a previous node had been biopsied and proved to harbor metastases.55 Wire localization of the positive node or previously placed biopsy clip resulted in a 97.3% surgical removal rate compared with 79.4% if no wire localization was used and resulted in more accurate staging and a decreased false-negative rate for SLNB after neoadjuvant therapy.

11. Do Older Women With Breast Cancer Need SLNB?

Women aged > 65 years are the fastest growing subset of the American population in terms of breast cancer diagnoses and death rates, and both these factors increase with increasing age.56 Moreover, the National Cancer Institute has reported that 41.2% of newly diagnosed breast cancer cases and 57.6% of deaths occur in women aged > 65 years. A study by Sun et al56 found that older women with early-stage breast cancer were also more likely to forgo radiation and lymph node staging than their younger counterparts. This might be because of the perceived reduced benefits of radiation and lymph node staging; however, the investigators showed that forgoing these treatments was associated with a negative effect on overall survival and breast cancer-specific survival.56 After controlling with propensity score matching, patients who received radiation had a 7.4% greater survival rate, and patients who underwent lymph node staging had a 16.8% greater survival rate. For breast cancer-specific survival, the mortality rate with receipt of radiation and lymph node biopsy was 1.3% and 2.6% lower, respectively. Therefore, it is important to follow the standards of care when treating older patients, despite the perceived reduced benefits of radiation therapy and lymph node staging.56

12. SLNB for Breast Cancer Recurrence

With the widespread use of breast-conserving surgery (BCS) and the increased accuracy of diagnostic imaging techniques, the rate of ipsilateral breast tumor recurrence within 10 years after BCS has ranged from 5% to 10%.57 and 58 However, the standard treatment for these women remains controversial. In a recent update of the American Society of Clinical Oncology, the indications for lymphatic mapping were broadened to include those women with previous nononcologic axillary surgery. However, the guidelines did not address those women who had undergone previous SLNB. In cases of breast cancer involving local ipsilateral recurrences in which SLN dissection has already been performed, the standard of care is to perform ALND. The main argument against a second SLNB procedure is that the lymphatic channels have been disrupted by scarring from the initial surgery and that any postoperative radiation therapy would affect efforts to perform a second SLN procedure. However, it is possible that the use of SLN dissection can be further extended to locally recurrent breast cancers to spare the morbidities associated with ALND.59 Criticisms of this procedure include that these patients already have lymphatic pathways damaged by the first operation and possibly by adjuvant radiotherapy, which serves to lower the feasibility and accuracy of the procedure in such cases. In a study by Caspara et al,59 147 patients with locally recurrent breast cancer were examined. All patients were negative for metastatic lymph nodes on preoperative ipsilateral AUS. One half of the patient population had undergone SLN dissection and one half, ALND; 124 patients (84.4%) had previously undergone radiotherapy. Lymphoscintigraphy was performed before SLNB after breast cancer recurrence in 82% of patients—77% in the case of previous SLN dissection and 88% in the case of previous ALND. In approximately one half of these patients, a SLN was identified, and 55 of the 72 patients (76.4%) with successful SLN dissection after breast cancer recurrence were node negative. In 14 of the 17 patients with positive SLNs, metastases were located in the ipsilateral axilla, 9 of whom had undergone previous SLN dissection and 5, previous ALND. Other sites of metastases included intramuscularly in the pectoral muscle, ipsilaterally and intramammary in another, and the contralateral axilla in another patient who had undergone ALND.59 The study by Caspara et al59 has demonstrated that SLN dissection after breast cancer recurrence is a feasible procedure, with a detection rate of approximately 50%. In patients who had previously undergone SLN dissection, 37 of 73 (51%) were node negative, and these patients could thus be spared the morbidity associated with ALND. In addition, 11 patients had only micrometastases or isolated tumor cells in the SLN at recurrence. None had non-SLN involvement and thus could also be spared ALND. Eight percent of the patients had macrometastases in the SLN at recurrence compared with patients with primary breast cancer, and only 1 of these patients had non-SLN metastases and might have benefited from ALND. In 6 patients (8%), who had previously undergone ALND, the treating physicians persisted and examined the axilla for draining nodes and, when found, performed axillary dissection. Metastases were found in all 6 patients. This disease would have been overlooked if the current guidelines that state that no additional lymph nodes should

be removed if ALND has already been performed were followed. Finally, the study by Caspara et al59 reported that a substantial number of patients had drainage to aberrant SLNs, and this number was even more prevalent after previous ALND or mastectomy. Metastases in aberrant SLNs would not be removed by surgery according to the current guidelines.59

In another study addressing this issue from the European Institute of Oncology in Milan, Italy,60 212 patients with the diagnosis of operable local breast cancer recurrence were studied. All these patients had previously undergone lumpectomy and an initial negative SLNB. The results showed that preoperative lymphoscintigraphy demonstrated ⩾ 1 new SLN in 207 patients (97.7%). One or more SLNs were surgically removed from 196 of the 207 patients (92.5%). Extra-axillary drainage pathways were seen in 8%. The annual axillary recurrence rate after a median follow-up period of 48 months was 0.8%, and the cumulative incidence of axillary recurrence at 5 years was 3.9%. They concluded that a second SLNB should be considered for women with operable local breast cancer recurrence to stage the axilla after recurrence, identify extra-axillary sites of drainage, and remove all signs of local and regional spread of disease.60 They hypothesized that a postoperative collateralization of lymphatics occurs as a physiologic compensatory mechanism and that the new lymphatic pathways will allow the identification of new SLNs.60 Because the percentage of aberrant lymphatic drainage pathways outside the ipsilateral axilla in patients with previous BCS was 2.2% to 47%,60 a central role exists for preoperative lymphoscintigraphy in these patients to identify all possible routes of spread.

A recent meta-analysis of 26 studies regarding repeat SLNB for 692 patients with locally recurrent breast cancer showed high success rates for SLNB used for lymphatic mapping and identification of SLNs and acceptable identification of extra-axillary drainage for patients with previous axillary surgery.61

13. Health Care Disparities

Black women with early-stage breast cancer are significantly less likely than their white counterparts to undergo SLNB. In a study from MD Anderson Cancer Center,62 with a review of 31,274 women aged ⩾ 66 years diagnosed with early-stage breast cancer from 2002 to 2007, significantly fewer black patients than white patients underwent a SLN procedure (62% vs. 74%; $P < .001$). The SLNB rate increased in both groups during the study period, only less so in the black population. The retrospective analysis from the SEER database showed that black women were also more likely to develop lymphedema, with a 5-year risk of 12.3% for black women compared with 8.2% for white women ($P < .001$). That study was the first to demonstrate that the lower frequency use of SLN procedures in the black population had an adverse clinical outcome resulting in more lymphedema.

14. Can ALND Be Omitted in Patients With a Positive SLN?—the ACOSOG Z0010-11 Study

The ACOSOG set out in their initial clinical trial effort to establish the clinical significance of SLN and bone marrow (BM) micrometastases. A total of 5539 patients were entered in the study, with a SLN identification rate of 94.5% in the national multi-institutional study. Hematoxylin and eosin staining detected metastases in 23.9% of the patients. Using IHC staining, an additional 10.5% of patients were identified with SLN metastases. BM metastases were identified in 3% of the patients. A multivariate analysis showed that SLN or BM metastases, estrogen and progesterone receptor negativity, larger tumor size and higher grade were associated with poorer survival. IHC metastases in the SLN ($P = .66$) or BM ($P = .08$) were not independent predictors of overall survival. The study concluded that IHC examination of the SLN identified disease that might not be clinically relevant, although a strong trend was found that IHC-detected BM metastases were clinically important. 63

The ACOSOG Z0011 trial64 was a randomized trial of axillary dissection in women with clinical T1-T2N0M0 disease with a positive SLN, who had undergone lumpectomy and adjuvant radiation therapy as their primary breast cancer treatment. A total of 891 patients were randomized to observation versus CLND after a positive SLNB. With a median follow-up period of 6.2 years, no

trend was found for clinical benefit of ALND for patients with limited nodal disease (Figure 5). These findings were practice changing for surgeons and significantly changed the surgical management of the axilla. The ACOSOG Z0011 trial found that omitting ALND did not lead to inferior survival or local recurrence if the patients met the following criteria: undergoing BCS with radiation therapy, favorable low T stage, no more than 2 involved SLNs, and no gross extracapsular extension in the involved nodes. The American Society of Clinical Oncology later updated their practice guidelines to incorporate the findings of the ACOSOG Z11 trail, stating that those women who met these criteria should not undergo ALND. The results of the ACOSOG Z11 trial has resulted in a significant decline in women receiving CLND nationally. The question remains regarding the standard of care for women undergoing mastectomy and SLNB to treat their breast cancer. Because these women might not be receiving adjuvant chest wall radiation postoperatively, a treatment that probably also incorporates level 1 and 2 lymph nodes in the radiation fields, they would still be candidates for CLND after a positive SLNB.

15. Conclusion

Lymphatic mapping and SLNB will continue to play an important role in the treatment of women with breast cancer. Although some controversy exists in determining the effect of nodal staging on the treatment and prognosis of women, the knowledge gained from the technique continues to be used to guide therapy and determine the prognosis. The SLN procedure will evolve by eliminating the need for radioactivity in the operating room, and the technique will become more accurate and used in expanded indications by incorporating preoperative imaging and intraoperative procedures.

References

1. Cabanas RM. An approach for the treatment of penile carcinoma. Cancer 1977; 39:456-66.
2. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg 1992; 127:392-9.
3. Krag DN, Weaver DL, Alex JC, et al. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. Surg Oncol 1993; 2:335-9.
4. Norman J, Cruse W, Ruas E, Beatty E, Reintgen DS. The expanding role of lymphoscintigraphy in malignant melanoma. Am Surg 1989; 55: 689-98.
5. Reintgen DS, Cruse CW, Wells K, et al. The orderly progression of melanoma nodal metastases. Ann Surg 1994; 220:759-67.
6. Albertini JJ, Lyman GH, Cox C, Reintgen DS. Lymphatic mapping and sentinel lymph node biopsy in the patient with breast cancer. JAMA 1996; 276:1818-22.
7. Boolbol SK, Fey JV, Borgen PI, et al. Intradermal isotope injection: a highly accurate method of lymphatic mapping in breast carcinoma. Ann Surg Oncol 2001; 8: 20-4.
8. Cody HS, Frey J, Akhurst T, et al. Complementarity of blue dye and isotope in sentinel node localization in breast cancer: univariate and multivariate analysis of 966 procedures. Ann Surg Oncol 2001; 8:13-9.
9. Hill AD, Tran KN, Akhurst T, et al. Lessons learned from 500 cases of lymphatic mapping for breast cancer. Ann Surg 1999; 299:528-35.
10. Yalom M. A history of the Breast. New York: Alfred A. Knopf; 1997.
11. Halstead W. The results of operation for cure of cancer of the breast performed at John Hopkins Hospital. Johns Hopkins Hosp Bull 1894; 4:497.
12. Devitt JE. The influence of conservation and radical surgery on survival of patients with breast cancer. Can Med Assoc J 1962; 87:906-10.
13. Fisher B, Montague E, Redmond C, et al. Comparison of radical mastectomy with alternative treatments for primary breast cancer: a first report of results from a prospective randomized clinical study. Cancer 1977; 39:2827-39.
14. Euhus DM. Are axillary lymph nodes still relevant in breast cancer? Ann Surg Oncol 2014; 21:4051-3.
15. Reintgen M, Murray L, Akman K, et al. Evidence for a better nodal staging system for melanoma: the clinical relevance of metastatic disease confined to the sentinel lymph nodes. Ann Surg Oncol 2014; 20:668-74.
16. Dessureault S, Soong SJ, Ross MI, et al. AJCC Melanoma Staging Committee. Improved staging of node-negative patients with intermediate to thick melanomas (>1 mm) with the use of lymphatic mapping and sentinel lymph node biopsy. Ann Surg Oncol 2001; 8:766-70.
17. Protic M, Stojadinovic A, Nissan A, et al. Prognostic effect of ultra-staging nodenegative colon cancer without adjuvant chemotherapy: a prospective National Cancer Institute-sponsored clinical trials. Ann Surg Oncol 2015; 22:3296-301.
18. Boughey JC, Ballman KV, Hunt K, et al. Axillary ultrasound after neoadjuvant chemotherapy and its impact on sentinel lymph node surgery: results from the ACOSOG Z1071 trial (Alliance). J Clin Oncol 2015; 33:3386-93.
19. Mittendorf EA, Ballman KV, McCall LM, et al. Evaluation of the stage IB designation of the American Joint Committee on Cancer staging system in breast cancer. J Clin Oncol 2015; 33:1119-27.
20. Querzoli P, Pedriali M, Rinaldi R, et al. Axillary lymph node nanometastases are prognostic factors for disease-free survival and metastatic relapse in breast cancer. Clin Cancer Res 2006; 12:6696-701.
21. de Boer M, van Deurzen CH, van Dijck JA, et al. Micrometastases or isolated tumor cells and the outcome of breast cancer. N Engl J Med 2009; 361: 653-63.
22. Weaver DL, Ashikaga T, Krag DN, et al. Effect of occult metastases on survival in node-negative breast cancer. N Engl J Med 2011; 364:412-21.
23. Shigematsu H, Taguchi K, Koui H, Ohno S. Clinical significance of extracapsular invasion at sentinel lymph nodes in breast cancer patients with sentinel lymph node involvement. Ann Surg Oncol 2015; 22:2365-71.
24. Swaminathan S, Reintgen M, Kerivan L, Smith J, Reintgen D. Extracapsular extension in the sentinel lymph node: recommendations for therapy. Clin Breast Cancer (in press).
25. Krag D, Weaver D, Ashikaga T, et al. The sentinel lymph node in breast cancer—a multicenter validation study. N Engl J Med 1998; 339:941-6.
26. Giuliano AE, Kirgan DM, Guenther JM, et al. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg 1994; 220:391-8.

27. O'Reilly EA, Prichard RS, Azawi DA, et al. The value of isosulfan blue dye in addition to isotope scanning in the identification of the sentinel lymph node in breast cancer patients with a positive lymphoscintigraphy: a randomized controlled trial (I; 127:SRCTN98849733). Ann Surg 2015; 262:243-8.
28. Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a meta-analysis. Cancer 2006; 106:4-16.
29. Bezu C, Coutant C, Salengro A, et al. Anaphylactic response to blue dye during sentinel lymph node biopsy. Surg Oncol 2011; 20:55-9.
30. Intraoperative fluorescence imaging for sentinel lymph node detection: prospective clinical trial to compare the usefulness of indocyanine green vs. technetium Tc99m for identification of sentinel lymph nodes. JAMA Surg 2015; 150:617-23.
31. de Boer M, van Dijick JA, Bult P, et al. Breast cancer prognosis and occult lymph node metastases, isolated tumor cells and micrometastases. J Natl Cancer Inst 2010; 102:410-25.
32. Agrawal A, Civantos FJ, Brumund KT, et al. [99mTc] tilmanocept accurately detects sentinel lymph nodes and predicts node pathology status in patients with oral squamous cell carcinoma of the head and neck: results of a phase III multiinstitutional trial. Ann Surg Oncol 2015; 22:3708-15.
33. Wallace A, Han LK, Povoski SP, et al. Comparative evaluation of [99mTC] tilmanocept for sentinel lymph node mapping in breast cancer patients: results of two phase 3 trials. Ann Surg Oncol 2013; 20:2590-9.
34. Pelosi E, Bello M, Giors M, et al. Sentinel lymph node detection in patients with early stage breast cancer: comparison of periareolar and subdermal/peritumoral injection techniques. J Nucl Med 2004; 45:220-5.
35. Seradour B. Breast cancer screening in France: an overview in 2009. Rev Prat 2010; 60:191-9.
36. Francis A, Haugen C, Grimes LM, et al. Is sentinel lymph node dissection warranted for patients with a diagnosis of ductal carcinoma in situ. Ann Surg Oncol 2015; 22:4270-9.
37. Hieken T. The promise of axillary imaging in individualized surgical management of breast cancer patients: another step forward. Ann Surg Oncol 2014; 21:3369.
38. Caudle A, Kuerer H, Le-Petross H, Yang W, Yi M. Predicting the extent of nodal disease in early-stage breast cancer. Ann Surg Oncol 2014; 21:3440-7.
39. Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel lymph node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC trial. J Natl Cancer Inst 2006; 98:599-609.
40. Feldman S, Bansil H, Ascherman J, Grant R, Borden B. Single institution experience with lymphatic microsurgical preventive healing approach (LYMPHA) for the primary prevention of lymphedema. Ann Surg Oncol 2015; 22:3296-301.
41. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral lymphedema after breast cancer: a systematic review and meta-analysis. Lancet 2013; 14:500-15.
42. Vignes S, Porcher R, Arrault M, Dupay A. Long-term management of breast cancer-related lymphedema after intensive decongestive physiotherapy. Breast Cancer Res Treat 2007; 101:285-90.
43. Yah-Chen T, Ying XU, Cormier S, et al. Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: a 2-year follow-up study. J Clin Oncol 2009; 27:2007-14.
44. 44. Klimberg VS. A new concept towards the prevention of lymphedema: axillary reverse mapping (ARM). J Surg Oncol 2008; 97:563-4.
45. Boccardo F, Casabona F, De Cian F. Lymphedema microsurgical preventive healing approach: a new technique for primary prevention of arm lymphedema after mastectomy. Ann Surg Oncol 2009; 16:703-8.
46. Namm J, Mueller J, Kocherginsky M, Kulkarni S. The utility of sentinel lymph node biopsy in patients with ductal carcinoma in situ suspicious for microinvasion on core biopsy. Ann Surg Oncol 2015; 22:59-65.
47. Tunon-de-Lara C, Chauvet MP, Baranzelli MC, et al. The role of sentinel lymph node biopsy and factors associated with invasion in extensive DCIS of the breast treated by mastectomy: the Cinnamome prospective multicenter study. Ann Surg Oncol 2015; 22:3853-60.
48. Imboden S, Papadia A, Nauwerk M, et al. A comparison of radiocolloid and indocyanine green fluorescence imaging, sentinel lymph node mapping in patients with cervical cancer undergoing laparoscopic surgery. Ann Surg Oncol 2015; 22: 4198-203.
49. Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol 2013; 14:609-18.
50. Boileau JF, Poirier B, Basik M, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. J Clin Oncol 2015; 33:258-64.
51. Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA 2013; 310:1455-61.
52. Chin-Lenn L, Mack LA, Temple W, et al. Predictors of treatment with mastectomy, use of sentinel lymph node biopsy and upstaging to
53. Boughey JC, Ballman KV, Le-Petross HT, et al. Identification and resection of the clipped node decreases the false negative rate of sentinel lymph node surgery in patient presenting with node positive breast cancer (T0-T4, N1-2) who receive neoadjuvant chemotherapy-results from ACOSOG Z1071 (Alliance). Ann Surg (Epub ahead of print).
54. Choy N, Lipson J, Porter C, et al. Initial results with preoperative tattooing of biopsied axillary lymph nodes and correlation to sentinel lymph nodes in breast cancer patients. Ann Surg Oncol 2015; 22:377-82.
55. Madsen EV, Aalders KC, van Der Heiden M, et al. Prognostic significance of tumor-positive internal mammary sentinel lymph nodes in breast cancer: a multicenter cohort study. Ann Surg Oncol 2015; 22:4254-62.
56. 56. Sun S, Hollenbeak C, Leung A. Deviation from the standard of care for early breast cancer in the elderly: what are the consequences? Ann Surg Oncol 2015; 22:2492-9.
57. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002; 347:1233-41.
58. Wapnir IL, Anderson SJ, Mamounas EP, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol 2006; 24:2028-37.
59. Caspara C, Christensen M, Holmqvist M, Kjaer C, Garne J. Sentinel lymph node dissection in locally recurrent breast cancer. Ann Surg Oncol 2015; 22:2526-31.
60. Intra M, Viale G, Vila J, et al. Second axillary sentinel lymph node biopsy for breast tumor recurrence: experience of the European Institute of Oncology. Ann Surg Oncol 2015; 22:2372-7.
61. Maaskant-Braat AJ, Voogd AC, Roumen RM, Nieuwenhuijzen GA. Repeat sentinel node biopsy in patients with locally recurrent breast cancer: a systematic review and meta-analysis of the literature. Breast Cancer Res Treat 2013; 138: 13-20.
62. Black DM, Jiang J, Kuerer HM, Buchholz TA, Smith BD. Racial disparities in adoption of axillary sentinel lymph node biopsy and lymphedema risk in women with breast cancer. JAMA Surg 149 2014:788-96.
63. Cote R, Giuliano A, Hawes D, et al. ACOSOG Z0010: a multicenter prognostic study of sentinel node (SN) and bone marrow (BM) micrometastases in women with clinical T1/T2N0M0 breast cancer. 2010 ASCO Meeting. J Clin Oncol 2010; 28(suppl), abstract CRA504):18s.
64. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastases: a randomized clinical trial. JAMA 2011; 305:569-75.