LYMPHOSCINTIGRAPHY AND SENTINEL NODES

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ABSTRACT

Sentinel lymph node biopsy (SLNB) has been validated to show whether a patient’s breast cancer or melanoma has spread to regional lymph nodes. As a result, management of patients with these cancers has been revolutionized. SLNB has replaced axillary lymph node dissection (ALND) as the staging modality of choice for early breast cancer and has replaced complete lymph node dissection (CLND) as the staging modality of choice for melanoma of patients whose SLNBs indicate no metastases.

Recently concluded multicenter, randomized trials for breast cancer with 5- to 10-years outcomes data have shown no significant differences in disease-free-survival rates or overall survival rates between SLNB and ALND groups but have shown significantly lower morbidity with SLNB as opposed to ALND. The lowest false negative rates (5.5%-6.7%) were seen in studies that used preoperative lymphoscintigraphy and dual mapping during surgery.

To assess survival impact of SLNB in melanoma, the Multicenter Selective Lymphadenectomy Trial (MSLT-I) was performed. Melanoma specific survival rates were not different between subjects randomized to SLNB with lymphadenectomy for nodal metastasis on biopsy versus those randomized to observation with lymphadenectomy for nodal relapse. However, the 10-year disease-free survival rates were better for the SLNB group, as compared with the observation group, specifically among patients with intermediate-thickness melanomas and those with thick melanomas.

Key Words:

lymphoscintigraphy, sentinel lymph node, breast cancer, melanoma,
INTRODUCTION

Lymphoscintigraphy is the planar or tomographic imaging of a radioisotope in lymphatics, usually Te-99m. Identification and localization of all sentinel lymph nodes (SLNs) for surgical biopsy is the goal. We discuss SLN procedures that include lymphoscintigraphy in the settings of malignancies to skin, breast, and head and neck.

LYMPHOSCINTIGRAPHY IN SENTINEL LYMPH NODE PROCEDURES

Lymphoscintigraphy for identifying and localizing sentinel lymph nodes (SLNs) has emerged over the past two decades as the staging modality of choice for breast cancers and melanomas that are clinically node negative (1-3). SLNs are regional nodes that directly receive lymph drainage from the primary tumor. If the first lymph node draining a tumor is negative for malignant cells, there is a high probability that the remaining lymph nodes in the relevant primary and subsequent basins will also be negative (4). Removing only SLNs eliminates the need for a full lymphadenectomy, reduces associated adverse effects, and usually results in better quality of life. There may be several SLNs in a patient, as there may be drainage in multiple directions from the primary lesion. In the case of multiple nodes, the nodes that demonstrate significant radiotracer uptake might all or individually also accumulate metastatic cells, therefore these should be surgically removed and tested for metastatic cells.

Cabanas, a urologist, introduced sentinel lymph node biopsy (SLNB) in the management of penile cancer (5). In the 1990s, Morton et al. developed and applied SLNB in the management of...
patients with melanoma and breast cancer. These protocols used blue-dye techniques that resulted in SLNs being visible due to the staining blue of lymph vessels and sentinel nodes (3). Also in the 1990’s, Krag et al. introduced SLNB based on radiotracer techniques. These radiotracer techniques depend on detecting the radiotracer gamma emissions using a gamma counting probe and/or a gamma camera (2). Lymphoscintigraphy is the dynamic and/or static imaging of the transit of radiotracer from tumor(s) to SLN(s). The imaging often provides a surgeon a means to easily identify and biopsy SLNs.

During the years following initial demonstrations of SLNB protocols, large numbers of investigative studies have supported SLNB as being a highly reliable method for screening axillary nodes (and extra-axillary nodes) in early (stage I, II) breast cancer. In the management of early breast cancer, SLNB has replaced the more invasive axillary lymph node dissection (ALND). In melanoma, lymphoscintigraphy provides a means of localizing SLNs to a specific regional drainage area or to multiple regional drainage areas. SLNB has undergone refinement and improvement since the first protocols were reported. SLNB is now widely accepted and used in breast cancer and melanoma (6). It has also been evaluated for potential application in other malignancies. We discuss SLNB primarily in the context of breast cancer and melanoma; however, we also remark on the status of SLNB protocols for head and neck malignancies.

Evidence of the attention to, enthusiasm for, and indeed success of this procedure in aiding management of various cancers is apparent from an internet search on “sentinel node”, which generated over 500,000 hits (https://www.google.com/#q=sentinel+node) and from the search (http://www.ncbi.nlm.nih.gov/pubmed/?term=sentinel+node), which generated over 10,000 investigative and educational publications on SLN topics in peer-reviewed journals.

**Procedure for SLN Lymphoscintigraphy**
There are minimal to no preparations that a SLNB patient needs to conduct for a SLNB procedure. Some centers use topical EMLA cream (lidocaine and prilocaine) to reduce the pain of needle puncture. Patients encouraged to use EMLA cream are instructed where and how to apply the cream to unbroken skin. They are asked to do this a minimum of 30 minutes prior to procedure injections (7). At the clinic, most patients wear gowns following removal of all jewelry and clothing that might negatively affect the lymphoscintigram.

Following a lymphoscintigraphy, the physician responsible for the injection/imaging procedure should communicate directly with the surgeon(s) involved. All such communications should be documented. At the time of surgery, the surgeon(s) should have access to all acquired images.

**Radiopharmaceuticals and Injection Parameters**

Radiopharmaceuticals used for lymphoscintigraphy include Tc 99m pertechnetate labeled colloids (particles range from 3nm-5000 nm and are often filtered to narrow size ranges) and Tc-99m-tilmanocept (Lymphoseek®)—mannosyl diethylene-triamine-pentaacetate (DTPA) dextran. Tc-99m-tilmanocept was approved by the United States Food and Drug Administration for SLN protocols in breast cancer and melanoma in 2013 and for SLN protocols in head and neck squamous cell carcinoma in 2014. Colloids move by lymphatic flow; their migration is dependent on particle size. Most SLN procedures to date have used radiocolloids.

Tc-99m-tilmanocept is a receptor-based radiotracer. It targets the receptor protein CD-206, found in high concentrations on the surfaces of macrophages and dendritic cells (8). Biochemically, Tc-99m-tilmanocept is a macromolecule comprising multiple units of DTPA and mannose, each covalently attached to a dextran backbone. The mannose acts as a ligand for the receptor, and the
DTPA serves as a chelating agent for the Tc-99m labeling. Tc-99m-tilmanocept demonstrates faster injection site clearance and equivalent primary SLN uptake as compared to Tc-99m sulfur colloid (9).

There are no consensus SLN protocols, and there are no consensus radiotracer activities or volumes. Practitioners implement and fully test protocols appropriate for their practice environments and patient demographics.

Injection doses range from 3.7 MBq (0.1 mCi/each intradermal injection) in melanoma to total doses of 185-370 MBq (5-10 mCi) in breast cancer. For melanoma, injections are most often intradermal. Two to four intradermal injections of 0.1 ml each injected around the tumor site (or around the site of previously excised tumor) are recommended (10). For extremities, due to rapid lymphatic flow, two injections (one medial, one lateral) near the surgical scar or the primary lesion are recommended.

In SLN protocols for breast cancer, injection techniques are more complex and varied. Injection strategies can include superficial (subdermal, periareolar, subareolar) and/or deep (peritumoral) injections (11-13). Superficial injections are easier to perform than deep injections; however, they may not provide full drainage information. Specifically, to locate extra axillary SLNs, particularly internal mammary SLNs, a protocol should include peritumoral injections (14). Administering peritumoral injections requires more information about the exact location of the tumor than does administering superficial injections. Also, if there has been an excisional biopsy, or if there is a prosthesis, care must be taken not to inject into the dead space of a seroma or into a prosthesis (10, 15).

**Imaging**
In melanoma, depending on the location of the primary tumor, imaging must cover all possible drainage sites. For example, if the primary tumor is on a patient’s trunk, imaging of the left and right axillary and neck regions as well as the left and right pelvis/inguinal regions must be performed (Fig. 1). For extremity tumors, imaging of the axillary and antecubital regions (upper extremity tumors) or of the inguinal and popliteal regions (lower extremity tumors) must be performed. For head and neck squamous cell carcinoma, the entire head and neck must be imaged. In particular, all locations distal to the tumor must be imaged, as lymph drainage is generally caudal in direction. Also, for head and neck SLN procedures, practitioners should note always that many structures in the head and neck are small and vital. Drainage across the body midline is common following injections in the trunk and head and neck (16) (Fig 2). In addition, for some indications, single-photon emission computed tomography (SPECT) or SPECT/CT may be preferred.

All aspects of imaging procedures, including skin marking (see below), should be performed with the patient positioned as she/he will be positioned in surgery.

*Dynamic Imaging.* In melanoma patients, dynamic imaging is started as soon as the injections are complete. Particularly for head and neck melanomas, immediate imaging reduces the chance of missing a SLN due to rapid drainage from intradermal injections with uptake by superimposed nodes. Images at one frame per second (preferred in head and neck), or two, or five may be performed. Such imaging can provide visualization of the pathways of the radiopharmaceutical and lymph fluid.

Dynamic imaging is not performed routinely in breast cancer protocols as in that context flow is often difficult to image. Also, detection of flow may require long imaging times not generally
convenient for practitioners. That said, dynamic images can be acquired in breast cancer protocols and have been proven useful in some cases (Fig. 3).

**Planar Imaging.** Planar imaging is performed following dynamic imaging or is interspersed with dynamic imaging. Planar imaging is usually performed at 5 minute intervals until SLNs are well visualized. Images in multiple projections are acquired (anterior, lateral obliques, and lateral, as needed in breast cancer; anterior or posterior and lateral obliques and/or lateral, if needed, in melanoma). The SLNs in patients with breast cancer or melanoma or head and neck cancer are usually well visualized in 10-60 minutes; however, visualization can also take several hours.

The performance of SPECT or SPECT/CT has gained importance in SLN protocols by virtue of reports documenting increased success in identifying SLNs when compared with planar imaging (17). In melanoma of the head and neck, in which SLNs may be located very close to the primary tumor, the inclusion of SPECT or SPECT/CT may aid in localizing SLNs masked during planar imaging because of their proximity to injection sites (18). In breast cancer, SPECT/CT is an optional technique that is sometimes useful. It can be useful if there is non-visualization of a SLN, if a patient’s BMI is elevated, if extra-axillary lymph nodes are visualized, if a patient has had previous breast surgery, if a patient has contralateral uptake, if there is visualization of an internal mammary lymph node, or if contamination is suspected (19, 20) (Fig 4).

**Transmission Imaging.** In most SLN procedures, planar images are acquired using a flood source (Tc 99m or Co 57). The images acquired include both emission data (from the radiopharmaceutical within the patient) and transmission data (from the flood source). Such images include body contours that provide anatomical reference for visualized SLNs.
Skin Marking. Once SLNs are visualized, a gamma counting probe is used to locate each node and a marking pen is used to indicate locations on the skin that can be used to triangulate and locate each node during surgery. Skin markings can also be determined by superimposing a point source of activity on activity in a SLN while observing the image on a scope. Marking is done in at least two projections so that in the operating room the surgeon can use the markings to predict the depth of the node and to triangulate to the position of the node in the body.

When more than one node is visualized in a region and more than one detected at surgery using an intraoperative probe, false negatives are reduced if the surgeon excises all radioactive nodes. In melanoma studies, in which lymphatic channels are often visualized, SLNs at times are straightforward to locate, however, SLNs are not always easily identified. Surgeons are advised to excise all radioactive nodes when possible.

CANCER INDICATIONS

Breast Cancer

In breast cancer, SLNB results in lower morbidity and in mortality rates compatible to those of ALND. Additionally, SLNB renders a positive node rate similar to that of ALND.

A single “best” SLN protocol for use in the management of breast cancer does not exist; several protocols have proven to be very successful.
**False Negative Rate and Its Implications.** Typically, the aim of a SLNB is a false-negative rate below 5%. The false-negative rate is the proportion of negative sentinel nodes at biopsy when the patient actually has positive axillary lymph nodes. This is extremely important since a patient with a false negative result may have been under staged and possibly under managed. A systematic review of 69 studies performed in 2004 as part of guideline development for ASCO found that the false negative rate of the studies ranged from 0% to 15% (21). Importantly, observational studies have reported very low rates of axillary recurrence following a negative SLNB (22). Practitioners should be able to implement a breast cancer SLNB protocol that results in identification of at least one SLN in over 95% of patients whose management includes the specified SLNB protocol (22).

The American Society of Breast Surgeons has published guidelines on credentialing criteria and recommends a minimum of 20 procedures proctored or with full axillary dissection before a surgeon should perform SLNB on her/his own (23).

**Indications for Lymphoscintigraphy in Breast Cancer.** The general indication for use of SLNB in breast cancer is early-stage biopsy-proven breast carcinoma without clinically apparent axillary lymph node metastases. Early stage implies the cancer has not spread beyond the breast.

There are several established clinical circumstances in which SLNB is used. They are the primary tumor is T1 or T2 or ductal carcinoma in situ (DCIS), the patient management includes mastectomy, the patient is a male, and the patient is to receive preoperative systemic therapy (10).

**Ductal Carcinoma in Situ.** DCIS is considered the earliest type of breast cancer; its initial diagnosis is made by core biopsy. By definition, DCIS does not metastasize to lymph nodes. However, there are several high-risk features, which if present in the pathologic specimen, may
suggest more invasive aspects, signaling metastatic potential. The risk for metastatic disease in DCIS is low; however, higher risk histopathologic features can be missed in up to 40% of cases which have high-risk features (24). Only 0.1-3% of DCIS cases have high-risk histopathologic features (24). After surgical resection (lumpectomy or mastectomy) and histopathologic analysis of the specimen, tumors previously diagnosed on core biopsy as DCIS are sometimes reclassified correctly as invasive cancer (25-27). Such reclassification is an upstaging of the patient’s diagnosis. If a more invasive cancer is found and there is no clinical evidence of metastasis in the axilla, SLNB is indicated. The SLNB should be performed in patients with DCIS if lumpectomy or mastectomy is planned. This should be done so that if the final pathology renders a diagnosis of a more invasive cancer, a second operation or a difficult SLNB after the lumpectomy or mastectomy can be avoided (28).

**Multicentric Breast Cancer.** The use of SLNB in the management of multicentric breast cancer has been and continues to be a controversial topic. While there is growing evidence that SLNB may become routine in the management of patients with multicentric breast cancer (28), there are questions about the mechanisms of how the tracer gets to the SLN and how the procedure should best be performed.

According to ASCO guidelines, it is acceptable to perform SLN procedures in multicentric breast cancer if the primary tumor measures less than 5 cm. In this case superficial injections should be performed and peritumoral injections should be avoided (28). By utilizing superficial injections in multicentric breast cancer, the SLNB performance in this context is similar to that for unifocal disease (28).

**Neoadjuvant Chemotherapy.** In locally advanced breast cancer (cancer that includes at least one large tumor), neoadjuvant chemotherapy may be offered for the purpose of reducing the
cancer and thus for the purpose of down staging the cancer prior to surgery. This approach is sometimes used even in cases with confirmed axillary metastasis. Such disease has been successfully down staged in up to 40% of cases in populations of such patients (29).

In early stage breast cancer, SLNB is being performed before neoadjuvant chemotherapy in clinically node negative patients for staging purposes. This means the patient will undergo a second surgical intervention (15, 29).

Staging of breast cancer after neoadjuvant chemotherapy can also be an important prognostic factor; therefore, SLNB may be considered after neoadjuvant chemotherapy. In that context, one should recognize the results obtained represent a new baseline, one different from the baseline prior to neoadjuvant chemotherapy, even if a pre therapy baseline was not obtained. Multiple meta-analyses suggest SLN identification can be more than 90% and false negative rates less than 12% in SLNBs following neoadjuvant chemotherapy (15, 30-32). Each neoadjuvant chemotherapy patient must be evaluated individually as to whether a SLN procedure is appropriate and as to when it should be performed if one is warranted.

The success rates of SLNB after neoadjuvant chemotherapy may be low and the false negative rates high due to histological changes in the breast and draining lymphatics due to chemotherapeutic agents. The ACOSOG Z1071 trial was conducted to clarify this controversial issue. The primary end point was the false negative rate of SLNB after chemotherapy in women who presented with N1 disease. The false negative rate found on ALND was 12.6%, which is considered high (33).
SLN Clinical Trials in Breast Cancer. Several randomized clinical trials investigating SLNB in the management of breast cancer have been conducted over the last 15 years to compare SLNB and ALND. The outcomes of these trials include results on morbidity, mortality, false negative rate, identification rate, and quality of life.

There are four multicenter randomized clinical trials with published five- to ten-year outcome data. No significant differences have been found in disease-free survival rates (28, 34-38) or overall survival rates between SLNB and ALND groups in any of these studies (28, 35-37, 39).

All the trials showed fewer arm and breast complications and better quality of life in the SLNB groups than in the respective ALND groups. Fewer doctor visits, less medical care related to morbidity, and increased patient satisfaction are associated with SLNB. Arm and breast morbidity evaluation included the rates of lymphedema, pain, neuropathy, and reduced range of motion in the ipsilateral arm. All these outcomes were found at 6-12 months post-surgery to be less frequent in SLNB patients than in ALND patients (34, 40-45).

Table 1 summarizes the framework and results of the most important randomized controlled trials comparing SLNB and SLNB+ALND SLNB in the management of breast cancer. Results included are the overall survival rate, disease-free survival rate, identification rate, and false-negative rate. For each trial, noted is whether its protocol included dual mapping and/or lymphoscintigraphy (45-51).

In the American College of Surgeons Oncology Group Z0011 (ACOSOG Z0011) trial, patients with one or two positive SLNs were randomized intraoperatively to ALND or no ALND. Patients with three or more positive lymph nodes were excluded from the study. The main outcome of this study was overall survival. This study used blue dye alone and no radiotracer.
As seen in Table 1, the lowest false-negative rates were observed in the Sentinel Node Biopsy versus Axillary Clearance (SNAC) trial and the Axillary Lymphatic Mapping against Nodal Axillary Clearance (ALMANAC) trial. The combination of preoperative lymphoscintigraphy and dual mapping during surgery were used in these trials. Sentinella-GIVOM trial (Gruppo Interdisciplinare Veneto di Oncologia Mammaria) is the trial, among those included, with the highest false negative rates. It was conducted in small communities, where the surgeons may not have had significant experience with the procedure prior to start of the study. The ALMANAC trial employed a formal training course for all participating surgeons and included attempts to standardize the surgical procedures. Trial data suggest high tumor burdens in SLNs may be a cause of false negative SLN procedures.

**Melanoma**

There is significant risk of lymph node metastasis in cutaneous invasive melanoma--risk that increases as Breslow thickness increases (Table 2) (46). If all SLNs are negative for metastasis, it is likely there are no metastases; if one or more SLNs are positive, there may be additional metastases.

*Staging.* Staging of invasive melanoma is based on lesion characteristics including thickness (Breslow measurement) and level of skin invasion (Clark’s level); both are determined by the pathologist from a biopsy sample. The most updated guidelines from the National Comprehensive Cancer Network (47) and the American Joint Committee on Cancer have eliminated Clark’s level from staging because it is not an independent prognostic factor when mitotic rate is included in the analysis (48). It is also less predictive of outcome, less reproducible, and more subjective than
the Breslow depth (49). Clark’s levels are still used to predict prognosis in patients with thin (less than 1.0 mm) melanomas.

SLNB is recommended in melanomas of Clinical Stage T1b-T4b without clinically evident loco regional or distant metastasis. SLNB may be offered for lesions of uncertain metastatic potential. According to the most updated guidelines form the American Society of Clinical Oncology (ASCO), there is insufficient evidence to offer SLNB for thin melanomas; however, if high risk features are present, such as positive deep margins, ulceration, lymphovascular invasion, age < 40 years, significant vertical growth phase, and/or increased mitotic rate, the procedure is acceptable. If there is a positive SLN, CLND is recommended (50-53).

Clinical Trials in Melanoma. Routine elective complete lymph node dissection (CLND) reveals metastases in 20 % of patients. Therefore, approximately 80 % of patients are subject to surgical morbidity with no clinical benefit. The approach of observation is not satisfactory because it leads to anxiety over uncertain prognosis. The Multicenter Selective Lymphadenectomy Trial (MSLT-I) was designed to evaluate if the SLNB with intraoperative lymphatic mapping can detect the 20% of cases with occult nodal metastasis (54).

The MSLT-I is a phase 3 trial that enrolled 2001 patients with cutaneous melanomas (predominantly of thin or intermediate thickness). The trial’s primary goal was assessment of the survival impact of SLNB. Patients were randomly assigned to undergo SLNB with lymphadenectomy for nodal metastasis on biopsy or to be observed with lymphadenectomy for nodal relapse. The results of the study show that melanoma specific survival rates were not different between the two groups. However, the 10-year disease-free survival rates were better for the SLNB group than for the observation group. This was among patients with intermediate-thickness melanomas and patients with thick melanomas (54). Many authors do not think this
study has proven conclusively the effectiveness of SLNB; however, the results are interpreted by some as indicating SLNB is standard of care (55). A meta-analysis in 2010, which included non-randomized studies with 2633 patients total, reported SLNB was associated with better survival and suggested SLNB and CLND might prolong survival in one of five treated patients after five years (56).

MSLT-II opened in 2005. The investigators plan to enroll 1925 subjects with sentinel node metastases. If a subject has a positive SLN and meets study requirements, the subject is randomized to receive either completion lymphadenectomy or observation with nodal ultrasound. Subjects are to be followed for 10 years (57). This trial is designed to answer the question “Do patients with a positive sentinel node need to undergo a completion lymph node dissection?”. The need to answer this question stems from the observation that 80% of patients with a positive sentinel node have no additional disease and do not need CLND (58).

**Head and Neck Malignancies**

Head and neck squamous cell cancer is an area in which use of SLNB is promising. Oral cavity, oral pharyngeal and supra glottic squamous cell carcinoma can reveal occult metastasis in 15-60% of cases (59). Multiple studies have validated the procedure with overall good results (60).

Patients with oral squamous cell cancers should have SLNB if they present as stage T1/T2 and as clinically neck negative by palpation, CT, MRI or PET/CT (61). Mapping is performed using preoperative lymphoscintigraphy and a gamma counting probe (62). Imaging procedures are similar to those used for breast cancer and melanoma patients, included are dynamic and planar imaging and skin marking.
Use of SPECT/CT is optional. Adequate lymph node localization can often be attained with planar imaging alone (62, 63). However, the anatomic complexity of the head and neck and the proximity of some primary lesions to SLNs and other important structures suggest SPECT/CT should be included in some cases (64, 65).

Injection of radiotracer is performed using small volumes, up to 0.2 ml containing 0.5 mCi (20 MBQ) per injection in the healthy mucosa surrounding a malignant lesion. Contamination can be avoided if the patient is asked to and does use a mouthwash or rinse before swallowing (61, 62).

Tc99m tilmanocept has been approved for SLNB in the management of oral squamous cell carcinomas. Experience with various labeled colloids has been satisfactory and several are routinely used (61).

Other mapping techniques, such as some using near-infrared fluorescence tracers (indocyanine green fluorescence navigation, for example), have also been validated in feasibility studies (66, 67). The most commonly reported limitation of this approach in this context is the tracer travels rapidly to second tier nodes.

**RADIATION RISKS**

Radiation doses to patients for all SLN procedures discussed here are small—well below limits specified by the International Commission on Radiological Protection (ICRP). The annual radiation doses to medical professionals (nuclear medicine technologists, nuclear medicine physicians/radiologists, surgeons, surgical support staff, and pathologists) routinely involved in
the performance of SLN procedures are acceptable—that is, below occupational annual limits specified by ICRP (10).

The absolute need of a pregnant woman to have a SLNB should, of course, be confirmed prior to performance of the procedure. If the procedure is warranted, it should be performed; the dose to patient and fetus are small—again within guideline limits (10).

**SUMMARY**

SLNB is now the gold standard for lymph node staging in breast cancer and melanoma offering reduced morbidity and similar mortality rates to those of more invasive lymph node dissections. Consistent use of a chosen technique that includes Tc-99m-labelled tracer, blue dye, at least two injection sites (superficial and deep), and preoperative imaging is likely to yield a high identification rate and low false negative rate in breast cancer. In multicenter randomized trials, the lowest false negative rates (5.5%-6.7%) were seen in studies that used preoperative lymphoscintigraphy and dual mapping during surgery.

Multicenter, randomized trials for melanoma have shown that specific survival rates were not different between patients randomized to SLNB with lymphadenectomy for nodal metastasis on biopsy and patients randomized to observation with lymphadenectomy for nodal relapse. However, for patients with intermediate-thickness melanomas and patients with thick melanomas, the trials have shown the 10-year disease-free survival rate is better for the SLNB group than for the observation group.
SLNB protocols for other cancers are applied and are routine in some centers; however, such protocols are not yet widely or routinely used.
REFERENCES


17. van der Ploeg IM, Valdes Olmos RA, Nieweg OE, Rutgers EJ, Kroon BB, 


51. Karakousis GC, Gimotty PA, Czerniecki BJ, et al. Regional nodal metastatic disease is the strongest predictor of survival in patients with thin vertical growth


Figure 1. Lymphoscintigraphy images of a 43 y/o male with a melanoma on the right midback.

Lymphatic channels are seen arising from the tumor site (and injection site) (green arrow) and draining to the bilateral axillary spaces as seen on the planar posterior, right lateral and left lateral views. Visualization of lymphatic channels defines each SLN. A lymphatic channel (blue arrow) terminates on a SLN (yellow arrow). Anterior view of the pelvis demonstrates no significant activity. No foci of uptake were seen on the neck.
Figure 2. Lymphoscintigraphy images of a 67 y/o male with a melanoma of the nose, 3 mm

Breslow thickness. The site of injection of Tc-99m sulfur colloid is visualized on the nose on the anterior and lateral views (blue arrow). One right (green arrow) and two left submandibular lymph nodes were negative for metastasis.
Figure 3. Lymphoscintigraphy images of a 62 y/o female with breast cancer. Oblique views demonstrate: A. a well-defined lymphatic channel (blue arrow), which was first identified on dynamic images; B. drainage of the channel into a SLN; and C. a SLN (green arrow) and a lymphatic channel. A secondary node adjacent to the SLN is visualized; it was visualized after the SLN was visualized.
**Figure 4.** SPECT/CT images of a 72 y/o male with breast cancer. **A.** Radiotracer uptake at the peritumoral injection site in the right breast (green arrow). **B.** Two foci of radiotracer uptake corresponding to sentinel nodes in the right axilla (blue arrows).
Table 1. Results of trials comparing SLNB and SLNB+ALND in breast cancer (45-51).

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<td>91.80%</td>
<td>5</td>
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<td>N/A</td>
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<tr>
<td>ALMANAC (UK)</td>
<td>1031</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>96.10%</td>
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<td></td>
<td></td>
<td>6.70%</td>
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<td></td>
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</tr>
<tr>
<td>SNAC (Australia &amp; New Zeland)</td>
<td>1088</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>95%</td>
</tr>
<tr>
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<td></td>
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<td></td>
<td></td>
<td>5.50%</td>
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</tbody>
</table>
Table 2. Risks of lymph node metastases for melanomas of specified thicknesses (11).

<table>
<thead>
<tr>
<th>Melanoma Thickness</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thick (&gt; 4 mm)</td>
<td>40%</td>
</tr>
<tr>
<td>Intermediate (1-4 mm)</td>
<td>8-30%</td>
</tr>
<tr>
<td>Thin (&lt; 1 mm)</td>
<td></td>
</tr>
<tr>
<td>• 0.76-1.00 mm</td>
<td>5%</td>
</tr>
<tr>
<td>• &lt; 0.75</td>
<td>1%</td>
</tr>
</tbody>
</table>
LYMPHOSCINTIGRAPHY AND SENTINEL NODES
Valeria M. Moncayo, John N Aarsvold and Naomi P. Alazraki

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