Sentinel Lymph Node Biopsy
Indications and Technique

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KEYWORDS

• Melanoma • Sentinel lymph node • Metastasis • Staging

KEY POINTS

- Lymphatic mapping and sentinel lymph node biopsy are now standard components of treatment of intermediate-thickness melanomas (1–4 mm).
- Sentinel node status provides significant, independent staging information for patients with thick (>4 mm) melanomas.
- Sentinel lymph node biopsy provides staging information and is appropriate for selected patients with thin (<1 mm) melanomas.
- Proper performance of lymphatic mapping and sentinel lymph node biopsy requires participation or experienced clinicians in nuclear medicine, surgery, and pathology.
- Sentinel lymph node biopsy is therapeutic for regional control in most patients with regional metastases.

SENTINEL LYMPH NODE INDICATIONS
Historical Perspective

From the earliest reported clinical experience with melanoma, the importance of regional lymph node involvement has been recognized. The earliest case of melanoma reported in the English literature features a cervical lymph node metastasis in a patient with a melanoma of the face. Other similar experiences with lymphatic metastases influenced the understanding of metastasis in the disease and affected treatment recommendations including excision margins and the management of regional lymph nodes. One early treatise, delivered by the English surgeon Herbert Snow, recommended excision of regional lymph nodes immediately on diagnosis, even in the absence of clinically evident metastases.[1] He called this approach "anticipatory gland excision," which was subsequently referred to as elective lymph node dissection (ELND).

The hypothesis of ELND supporters was that regional lymph nodes functioned as filters or incubators for metastatic disease and that early removal of nodal metastases

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could interrupt a metastatic cascade and cure disease that would spread beyond the regional nodes if given time. Although experimental evidence has demonstrated that lymph nodes are not likely to be mechanical filters, their function as incubators of metastasis remains under active investigation. If this were true, ELND should improve survival in patients with melanoma. However, complete dissection of nodal basins is attended by the risk of some morbidity, leading to debate about whether the intervention was justifiable and eventually randomized clinical trials.

There were also efforts to determine which patients were candidates for early surgical intervention. Retrospective data suggested that patients with certain melanomas were more likely to benefit from surgery.[2] Patients with thin melanomas were felt to be at such low risk for both nodal and distant metastases that ELND was not warranted. Those with thick melanomas had relatively high risk for both nodal and distant disease and might not be saved by early surgery. It was the intermediate-thickness melanomas (variously defined, but often 1–4 mm) that had sufficient risk of nodal disease in the absence of distant metastases who would be most likely to benefit. Consequently, some of the randomized ELND trials focused on that population.

The ELND trials, overall, failed to show a significant survival advantage for early dissection, although most trials showed a trend in that direction, with significant benefit in some subgroups.[3–5] The debate that had started a century before might still be ongoing had sentinel lymph node (SLN) biopsy not been developed and reshaped the diagnostic and therapeutic landscape. The concept of a "sentinel" lymph node also has a long history, with several investigators suggesting specific locations of such a node for several types of tumors including cancers of the parotid and the penis.[6] However, current understanding of the SLN stems from an evolution of the ELND strategy.

In patients with primary melanomas in some locations, such as the trunk, determination of the most appropriate basin for an ELND was difficult due to variability in drainage. In the 1970s, Donald Morton and colleagues[7] evaluated lymphoscintigraphy as a means of determining the direction of lymphatic drainage. This proved to be a reliable way to identify which nodal basin was at risk. As radiotracers and imaging technology improved, it was apparent that specific lymph nodes could be seen as receiving drainage rather than an entire basin. Morton, Cochran and colleagues[8] began to explore removal of this dynamically defined lymph node as an indicator of the pathologic status of the entire basin. As initially reported in 1990, the SLN proved to be a highly reliable indicator, which quickly became a routine staging technique. Initially, completion lymph node dissection was recommended for all patients with metastases discovered in their SLNs.

Sentinel Lymph Node Impact on Staging

SLN biopsy has dramatically improved the accuracy of staging in melanoma due to the improved accuracy of pathologic evaluation possible with SLN relative to that performed on a full-dissection specimen. In the former, the pathologist is able to concentrate on a single or small number of nodes, allowing more sections to be evaluated and the use of immunohistochemical stains to enhance detection. Indeed, pathologic processing of SLN routinely identifies metastases with only small clusters or even individual melanoma cells.

What impact has that had on staging accuracy? The effect has been profound and repeatedly demonstrated. In one such study, Dessureault and colleagues[9] examined the outcomes of "node-negative" patients who had been staged using physical examination, ELND, or SLN biopsy. Survival among those who had only had nodal evaluation by physical examination was poor, approximately 69.8% at 5 years. Those who

were deemed node negative by ELND did better but still had only a 77.7% survival at 5 years. It was only with SLN evaluation that patients could be accurately determined to be node negative, resulting in survival of 90.5% at 5 years in that group.

It is not unexpected then that when multivariable prognostic evaluations are done in the context of large retrospective datasets and in clinical trials SLN status typically is the most powerful determinant of outcome and is independent of other variables including thickness and ulceration.[10]

The most recent and perhaps strongest indicator of this effect can be seen in a comparison of the 2 most recent American Joint Committee on Cancer (AJCC) melanoma databases.[11] The database used in the seventh edition included patients who had either not been surgically staged or who had been evaluated using ELND as well as some who had SLN biopsy.[12] The eighth edition database required patients with melanomas T1b and above to have had SLN biopsy in order to be included. For the seventh edition, 5-year melanoma-specific survival for stage IIA, IIB, and IIC were 79% to 82%, 68% to 71%, and 53%. The same stages in the eight edition had survivals of 94%, 87%, and 82%,[11] which indicates a profound change in the accuracy of prognostication and confirming the essential nature of SLN biopsy. In the era of increasingly effective adjuvant therapy, this type of accurate staging is even more critical to optimal management.

Regional Disease Control

Uncontrolled regionally metastatic melanoma can be devastating, and achieving regional disease control is an important goal in itself. With the advent of SLN biopsy, the toxicity associated with achieving this goal became markedly reduced, as SLN biopsy is associated with markedly lower morbidity than ELND, and patients with negative SLN were spared that larger procedure.[13] The first Multicenter Selective Lymphadenectomy Trial (MSLT-I) demonstrated that nodal management with SLN biopsy followed by CLND among those with SLN metastases resulted in excellent long-term disease control in the regional nodal basin.[14] Similarly, the multicenter Sunbelt Melanoma Trial demonstrated low rates of regional nodal disease recurrence for patients managed in that way.[15] In addition, it seems that early dissection, guided by SLN biopsy, is associated with lower rates of lymphedema compared with later dissection in the presences of macroscopic disease.[16]

Perhaps even more significantly, it is becoming increasingly apparent that regional disease control can also be achieved in many cases by SLN biopsy alone. This is true because in most of the cases of SLN metastases, regional nodal disease is limited to the SLN.[17] In most patients who undergo CLND after SLN biopsy, no other nodal metastases are identified in the full dissection. Similarly, in the second MSLT study, three-quarters of patients with SLN metastases who did not undergo completion lymph node dissection were free of nodal recurrence in that basin over the long term (**Fig. 1**).[18]

Survival

Perhaps the most controversial subject in regional management of melanoma is whether early nodal intervention improves survival. The answer may not be a simple yes or no. Earlier ELND trials did not show an overall benefit, as noted earlier. However, there seemed to be a consistent relationship of potential survival benefit with the thickness of the primary melanoma. Among thick melanomas (defined as >3.5 or >4 mm) there was no indication of benefit in any of the randomized trials.[4,10,19] Whereas, for intermediate thickness melanomas, there seemed to be a consistent signal of survival benefit, often to a significant degree, albeit in subgroup analyses.

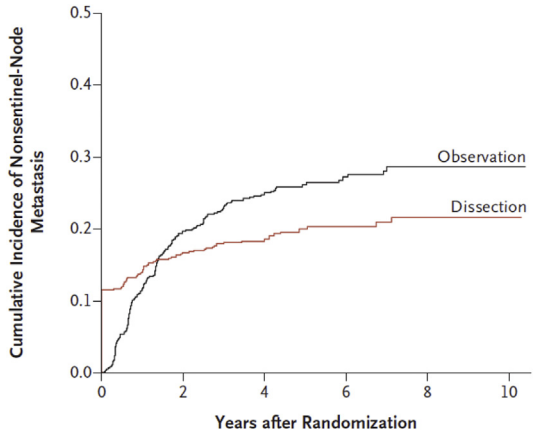

Fig. 1. Risk of in-basin nodal recurrence in the 2 arms of the second Multicenter Selective Lymphadenectomy Trial. All observation arm patients had had disease in SLN and had the remainder of their regional nodes left in place. Most do not demonstrate later recurrence in other regional nodes. (*From* Faries MB, Thompson JF, Cochran AJ, et al: Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma. N Engl J Med 376:2211-2222, 2017; with permission.)

MSLT-I was designed to evaluate the survival question as well and focused on an intermediate thickness (1.2–3.5 mm) group. In the final analysis, the number of events was lower than anticipated, making the trial underpowered, and the 3.1% increase in melanoma-specific survival seen in the SLN arm of the study was not significant ($P = .18$). However, examining the "node-positive" patients in the trial showed a marked difference in outcome (hazard ratio [HR] 0.56, 95% confidence interval [CI] 0.37–0.84, $P = .006$) for patients with nodal metastases removed with SLN-guided treatment compared with those with nodal recurrence in the observation arm. Given the risk of "ascertainment bias" with that simplistic analysis, a more statically sophisticated latent subgroup analysis was performed to try to adjust for any potential biases in the cohorts.[20,21] This also demonstrated a significant survival benefit associated with SLN management for the intermediate-thickness group but not the thicker primary patients. It is worth noting that although this statistical technique has been peer-reviewed and published in biostatistical journals, it is difficult to validate in other ways. Other retrospective series and meta-analyses also show a benefit. In the meta-analysis by Santos-Juanes and colleagues,[22] they found the melanoma-specific survival of SLN biopsy patients is better than that of wide local excision patients (HR 0.88, 95% CI 0.80–0.96).

So there remains a strong possibility that long-term survival is improved with early removal of nodal metastases and that this benefit depends on the thickness of the primary tumor. Other factors that may also play a role in the effectiveness of nodal treatment are primary tumor ulceration and patient age. However, the critical role of SLN biopsy in staging and regional control diminishes the relevance of the survival question in selecting patients for the procedure. It remains an important topic for translational research into the process of metastasis.

Selection for Sentinel Lymph Node Biopsy

The role of SLN biopsy in intermediate-thickness melanoma is now clear, and it is recommended for those patients in melanoma treatment guidelines of professional

oncology organizations such as the American Society of Clinical Oncology, European Society of Medical Oncology, Society of Surgical Oncology, and national consensus panels in Australia, German, and Netherlands.[23–29] Other nonthickness factors such as age or potentially gene-expression profiling may further refine selection for SLN biopsy in this group, but at present it is a standard component of therapy. However, it is worth considering whether the same rationales can be applied in patients with thick (>4 mm) or thin (<1 mm) melanomas.

For thick melanomas, it has generally been felt that their prognosis is poor, even in the absence of nodal disease. However, numerous series now demonstrate that there is a significant association of long-term survival with the absence of nodal metastases on SLN biopsy.[30] This prognostic information may be of great importance with the increased variety of effective, although potentially toxic, adjuvant systemic therapies. In addition, it seems that even with thick primary melanomas, most patients with SLN metastases have no additional disease found on CLND, and the SLN biopsy may be therapeutic for regional control even in the absence of a full dissection.

Most of the patients with thin melanomas have no nodal metastases. Performance of the procedure for *all* such patients cannot be cost-effective or otherwise justified.[31] However, given the very large absolute number of patients with melanoma who present with thin primaries, the small proportion of node-positive patients in that population leads to substantial morbidity and mortality and identification of higher-risk patients with thin melanomas is an important goal.[32,33] In addition, the difference in survival between node-positive patients whose metastases were detected by SLN biopsy compared with those with clinical presentation of nodal recurrences is greatest in the thin melanoma population.[34] Although a randomized trial would not be feasible in this group, this comparison adds to the incentive to identify those at greatest risk for nodal disease.

The most widely applied factor for selection with thin melanomas is tumor thickness within the 0 to 1 mm range. The AJCC now divides T1a from T1b using a 0.8 mm cutoff.[35] Several guidelines, including American Society of Clinical Oncology/Society of Surgical Oncology and the National Comprehensive Cancer Network, recommend consideration of SLN biopsy for those with melanomas at least 0.8 mm in thickness.[28,29] Within that group, patient age, comorbidities, and other tumor factors including ulceration and mitotic rate may play a role in patient selection, although standard selection variables have not been consistently validated to firmly establish standards.

For melanomas thinner than 0.8 mm, the risk of nodal involvement is quite low, broadly observed to be less than 5%, and SLN biopsy is not routinely recommended for these patients. However, patients with “high-risk” characteristics in this group may be exceptions to that practice. Defining these high-risk features, again, has been challenging. Ulceration has frequently been found to be associated with nodal metastasis in these very thin lesions, although not in every series, and is rare in truly thin melanomas. Other features that have been considered include mitotic rate, Clark level of invasion, tumor-infiltrating lymphocytes, regression, and lymphovascular invasion, but there is marked inconsistency in which characteristics are useful across different series.[36,37] One final issue in selection is the deep margin of the biopsy. When a shallow shave biopsy is performed and tumor extends through the full depth of the evaluable material, the true depth of the lesion cannot be precisely determined. Some series have associated a positive deep margin with rates of nodal involvement similar to T1b or T2 melanomas.[38] Because a small additional area of tumor may have been ablated in the biopsy procedure or lost in a subsequent inflammatory response, even rebiopsy of the same area would not resolve the uncertainty. Examination of the

biopsy slide will demonstrate the extent of margin involvement, which would also contribute to assessment of the nodal risk and recommendation for SLN biopsy.

The prognostic value of SLN staging in thin melanomas was a controversial issue early in the history of lymphatic mapping, but recent large series have now demonstrated fairly consistent findings.[39,40] Outcomes for patients with thin melanomas and SLN metastases are relatively favorable, although they are categorized as stage III. Melanoma recurrences and deaths in this group are relatively slow in appearing (few events before 2 years), but a modest decrease in survival has been consistently observed after that point. This is in contrast to the outcomes of patients with clinical nodal recurrences after local treatment of a thin primary melanoma, whose survival more closely approximates that of patients with macroscopic nodal metastases from intermediate or thick melanomas (stage IIIB/C).[34] Retrospective comparison of outcomes in patients with thin melanomas demonstrate much better survival for node-positive patients when metastases are discovered by SLN rather than recurrence, although ascertainment bias is a potential concern with such analyses.

SENTINEL LYMPH NODE PROCEDURE

Lymphatic mapping and SLN biopsy are simple in concept but require multidisciplinary expertise to be performed properly. Given the variable drainage patterns of primary melanoma sites, lymphoscintigraphy is essential to determine the location of SLNs.[41] Proper surgical technique is critical for identification, removal, and handling of the SLNs, and meticulous processing and pathologic evaluation is essential for both identification of metastases and assessment of their prognostic significance.

Lymphoscintigraphy and Ultrasound

In the early stages of the development of lymphatic mapping, lymphoscintigrams were performed to identify the draining nodal basins to direct ELNDs where multiple basins were at risk. Colloidal gold particles were used for this mapping, and imaging technology was somewhat rudimentary, with low-resolution images. As technology improved, it became apparent that lymphatic drainage could be traced not merely to the basin but to specific lymph nodes within the basin.

Radiopharmaceuticals used in lymphoscintigraphy vary in use around the world. In North America, sulfur colloid and tilmanocept are commonly used. Both are conjugated to ^{99m}technitium. Nanocolloid albumin is used in Europe and antimony trisulfide is used in Australia. Although there are potential functional differences in these agents, extensive experience in these different regions demonstrate that all can be used successfully.

Injection technique for the tracer is important for successful mapping. A narrow-gauge needle should be used to inject into the dermis surrounding the primary tumor site (ie, not subcutaneous). Often 4 peripheral injections are used, although the principle of injection is infiltration of lymphatic channels accessed by the primary tumor. With proper injection technique, massage of the area is generally unnecessary but may be performed to increase lymphatic flow.

Early dynamic images often identify and enumerate draining channels and document sequential or parallel drainage to SLNs. Imaging of all potential basins is also important, including minor basins such as the popliteal or epitrochlear locations in appropriate circumstances (**Fig. 2**).

In some circumstances, visualization of draining nodes by planar lymphoscintigraphy may be challenging, particularly when the primary tumor injection site is located close to or over the expected nodal location. In these instances, it is essential to

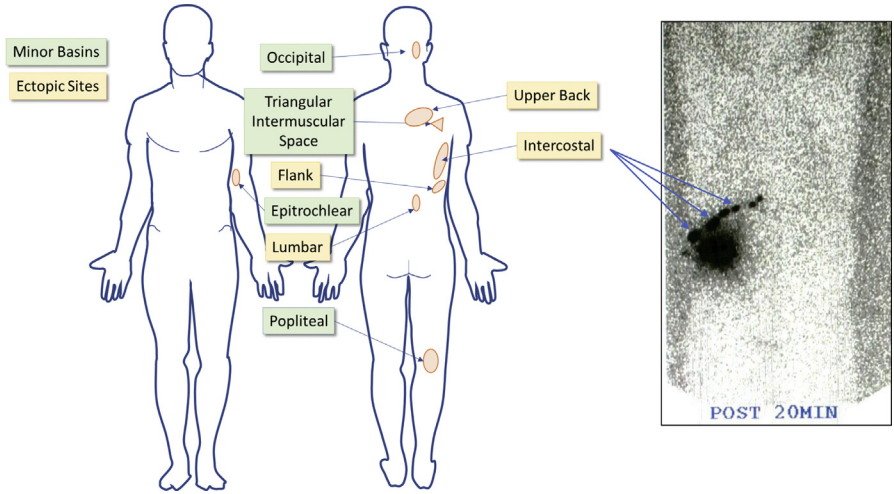

Fig. 2. Minor basins and ectopic SLN locations. Although SLNs are most often located in "standard" basin locations (cervical, axillary, inguinal) localization of SLNs outside of those areas is not uncommon. An example of intercostal SLNs is shown at right.

reevaluate the nodal basin intraoperatively with the gamma probe to verify removal of all SLNs. Three-dimensional imaging may also facilitate accurate identification of SLN in this and other complex settings. Single-photon emission computed tomography/computed tomography has been found to increase the number of detected SLNs and basins relative to planar lymphoscintigraphy alone.[42] It also provides more specific localizing information for SLNs, which may facilitate their identification and removal at the time of surgery.

Ultrasound seems to be the most sensitive modality for nodal evaluation before the biopsy procedure, frequently detecting disease before it is apparent on either physical examination or other imaging tests.[43–45] Suspicious nodal ultrasound characteristics include "rounding" of the node (length: width ratio <2), loss of hilar vascular echoes, thickening of the cortex, and particularly increased peripheral vascularity on Doppler imaging. The use of a high-frequency probe is necessary for accurate evaluations, and the experience of the operator is likely critical as well. However, even with optimal conditions, the sensitivity of ultrasound is low. The MSLT-II trial examined pre-SLN ultrasounds in its screening phase.[46] Ultrasound in this clinical context, at experienced melanoma centers, had a sensitivity of only 6.6%. Although this was higher in patients with thicker primary melanomas, the sensitivity never achieved a level that would enable observation of nodes that were negative by ultrasound. In addition, the principal rationale for pre-SLN ultrasound had been avoidance of SLN biopsy when the node was positive and proceeding directly with complete nodal dissection. Given the results of MSLT-II, this treatment pathway is no longer justified.

Operative Technique

The surgical portion of SLN biopsy must be completed with care and attention to detail to obtain the most accurate and least morbid results. The first step is confirmation of the draining basins. Review of the lymphoscintigram images and interrogation of the basins with the gamma probe before incision is important and allows appropriate adjustment in patient positioning if necessary (see **Fig. 2**). Planning of the SLN incision

location should take the site of the primary tumor and reconstruction of that defect into account. In addition, the possible eventual need for a complete dissection should be considered, even though such dissections are becoming less common in current practice. In some locations, particularly the head and neck, understanding the likely location of nodes relative to surrounding structures may affect incision location to attempt to minimize dissection needed to reach the nodes.

Vital blue dye is injected before prepping the operative field. These dyes include lymphazurin, patent V, and methylene blue. Choice of dye is regional to some extent, with lymphazurin and methylene blue most commonly used in North America. Lymphazurin has been associated with allergic reactions, although these seem to be extremely uncommon in mapping for melanomas (relative to breast cancer).[13,47] Methylene blue has been associated with skin necrosis at the injection site, making it unacceptable if the entire injection site is not to be removed in the wide excision of the primary.[48] Similar to the technique for the tracer, using a small gauge needle vital blue dye is injected in small amounts around the primary lesion with care to inject the dermis (**Fig. 3**A, B).

Once an SLN has been identified using radiotracer and vital blue dye, dissection of the node requires considerable care. The node's capsule should not be grasped with forceps or clamps, as it is likely to tear (**Fig. 3**C, D). Because metastases are frequently located just beneath this capsule, its disruption may compromise the accuracy of the evaluation. The node may be pushed in the dissection and adjacent fibrous tissue may also be manipulated to isolate the node. Lymphatic channels entering the SLN can be controlled with clips or ligated, but all reasonable efforts should be made to preserve channels that are not entering the SLN.

Once the node has been removed, it should be examined again with the gamma probe to confirm its radioactivity. The surgeon may also consider marking the node at the site of highest activity or deepest blue staining, as this is likely to be the most

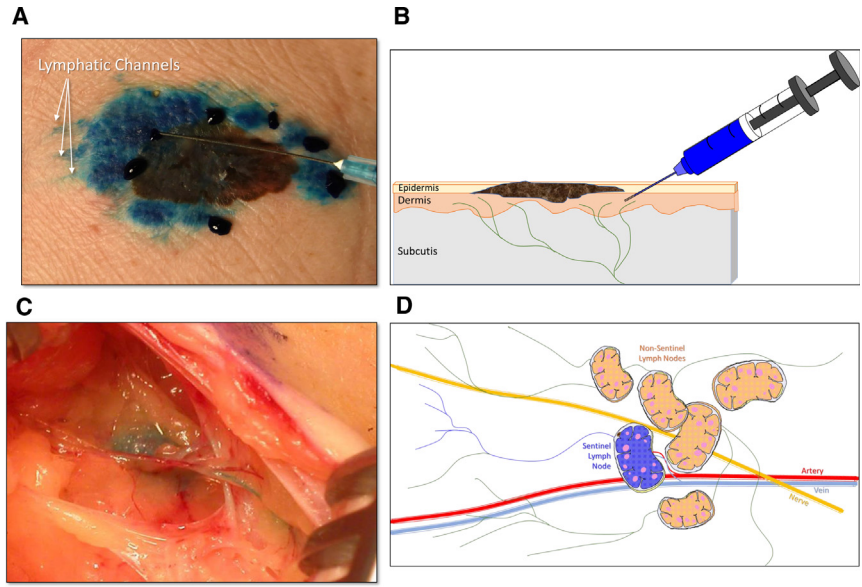

Fig. 3. (*A*) Injection of isosulfan blue should be intradermal and will often demonstrate peritumoral lymphatic channels. (*B*) Schematic of proper injection location, (*C*) View of SLN *in vivo* with undisturbed adjacent structures, (*D*) Schematic view of SLN *in vivo*.

common location of metastasis within the node, and communicating this with the pathologist. Surrounding lymph nodes within 10% of the highest tracer counts or with blue dye in them should also be excised.[15,49] Closure of the wound should include reapproximation of the lymphatic layer, while avoiding injury or entrapment of vessels or nerves in the process.

The decreased morbidity of SLN biopsy relative to complete dissection is one of the advantages of the technique, and efforts to minimize morbidity are essential, including preserving lymphatic tissue and vessels when possible. Although lymphedema is uncommon compared with CLND, it can occur. Injury or transection of motor or sensory nerves should be avoided. This is especially true in the head and neck region where the facial nerve is often close to parotid lymph nodes, the greater auricular nerve is often in the field of submandibular and jugulodigastric nodes, and the spinal accessory nerve is frequently close to nodes in Level V (**Fig. 4**).

Pathologic Processing

SLNs are sent for "permanent" pathologic evaluation. Frozen section should not be performed for several reasons.[50] First, the sensitivity of frozen section is substantially lower than with fixation, as small nodal metastases can be challenging to identify. In addition, freezing may introduce artifacts that make subsequent interpretation challenging and the tissue processing for frozen sections sacrifices potentially diagnostic material. Finally, because identification of an SLN metastasis no longer mandates immediate completion lymph node dissection, the main clinical rationale for rapid identification of nodal disease no longer exists.

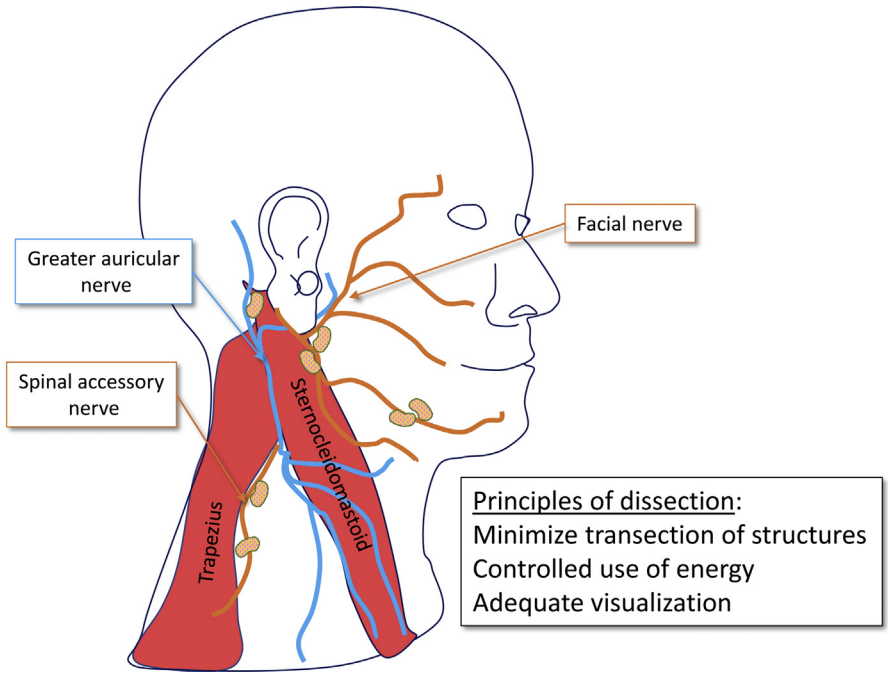

Fig. 4. SLNs are frequently located close to nerves. This is particularly true in the head and neck region. Care should be taken to avoid unnecessary transection of structures, indiscriminate use of energy devices, or operating through an incision that does not provide adequate visualization.

The SLN should be thoroughly sampled to ensure identification of metastases. Typically, nodes are bivalved along their long axis and the 2 faces placed in a single block. Sections are then obtained for staining with hematoxylin and eosin and immunohistochemical markers. These include combinations of S100, HMB45, Melan-A (MART-1), and Sox-10. Specific pathologic protocols vary around the world with regard to the exhaustiveness of sectioning and the specific stains used, but a combination of markers is recommended.

Pathologic Interpretation

Pathologic evaluation of the SLN provides the most valuable prognostic information for patients and clinicians, and an SLN free of metastasis indicates a much more favorable outlook for patients. However, the relative and absolute impact of SLN status varies to some extent for different patients and primary tumors. For example, older patients have a somewhat more guarded prognosis even in the absence of nodal metastases. This is particularly true for patients with thick or ulcerated primary tumors, who may have a substantial risk of recurrence. Adjuvant systemic therapies are currently being evaluated in those Stage II patients. At the other end of the spectrum, patients with SLN metastases from thin primary melanomas have a more favorable outlook. Melanoma recurrences in that group take longer (>2 years) to occur, and the long-term outlook is more favorable. However, for both thick and thin primary melanoma patients, SLN status provides independent and significant prognostic information.

Nodal tumor burden is also an important consideration in interpreting SLN results. Factors used to rate the seriousness of a metastasis include size, which is most commonly measured as the longest diameter of the largest metastatic focus, but which can also be measured by the absolute or relative area occupied by the metastasis. Other features include the number of metastatic foci, the penetrative depth into the node, and the location of the metastasis within the node (subcapsular, intraparenchymal, or both). The effect of tumor burden is likely a continuous variable with larger metastases being worse, but a cut off of 1 mm in most frequently used in maximal diameter.[51,52] This measure has been used for several retrospective analyses and as a cutoff for eligibility in clinical trials of adjuvant therapy.

Areas of Future Interest

Despite the extensive research that has been completed so far, there is more to be done. One area that needs to be further explored is in the immunobiology of the SLN. The SLN is the first organ encountered by tumor when traveling in the lymph system and first site where tumor antigens interact with the immune system. This subsequently plays an immunostimulatory role as it primes T cells specific to these tumor antigens. However, simultaneously, there is immunosuppressive interaction occurring in the SLN from immunosuppressive cytokines and regulatory T cells present. The complicated interaction of these 2 competing mechanisms is not fully defined and will be an important area of research into the future.[53,54]

There is also an interest in improving the technical aspects of SLN biopsy, which may improve the ease or accuracy of mapping. Examples include the use of fluorescent tracers, such as indocyanine green as a mapping agent with near-infrared detection techniques. These may be most helpful in the head and neck region, in which the target SLNs are relatively close to the surface (or in nonmelanoma cancers such as gastrointestinal malignancies).[55] These tracers also have the advantage of avoiding the use of radioactive tracers.[56] Another nonradioactive tracer is supermagnetic iron oxide.[57,58] These tracers are also detectable with MRI. The feasibility of their use

has been demonstrated prospectively in breast cancer, with potential use in other malignancies including melanoma.

SUMMARY

SLN biopsy is now firmly established in the treatment of patients with melanoma, having documented irreplaceable benefits in staging and regional disease control. It should be routinely offered in intermediate and high-risk melanomas and considered in appropriately selected patients with thin melanomas. Additional refinements in our understanding of SLN biology and melanoma progression and in technical aspects of the procedure can be anticipated in coming years.

DISCLOSURE

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