

desmoplastic melanomas are characterized by a uniform desmoplasia that is prominent throughout the entire tumor (termed “pure” desmoplastic melanoma), whereas other desmoplastic melanomas appear admixed with other histologic subtypes (termed “mixed-type”).¹⁷⁶ Distinguishing the phenotypic heterogeneity of desmoplastic melanomas has been reported to be important for stratifying patients with regard to risk of lymph node metastasis and prognosis.^{176,177} Data indicate that patients with pure desmoplastic melanoma have a lower incidence of positive SLNs than do patients with mixed-type or nondesmoplastic melanoma, suggesting that SLN biopsy in patients with pure desmoplastic melanoma may not be warranted.^{166,177}

Imaging Considerations

Although imaging studies historically have represented a prominent component of the initial staging workup of patients with melanoma, there is little, if any, role for routine comprehensive imaging in patients with early-stage disease¹⁷⁸ as numerous studies have demonstrated that they are insensitive tests to identify occult regional nodal metastases.¹⁷⁸ Even among patients with positive SLNs, contemporary studies indicate that the incidence of synchronous distant metastasis in asymptomatic patients with microscopic SLN metastases is low and has not been significantly impacted by recent advances in imaging. Recent studies support that most patients (except perhaps those with thick or ulcerated primaries, or with significant SLN tumor burden) can be spared formal staging evaluation before completion lymph node dissection.^{178–180} A complete staging evaluation may then be pursued after completion lymph node dissection prior to consideration of adjuvant therapy or participation in adjuvant therapy trials.

Although one melanoma group has reported that preoperative ultrasound and fine-needle aspiration cytology (FNAC) may accurately identify up to 65% of SLN metastases in patients with primary cutaneous melanoma based on morphologic criteria,¹⁸¹ the results of a recent study by Uren and colleagues of 716 patients suggest that preoperative

ultrasound can complement but should not substitute for SLN biopsy.¹⁸² Interestingly, the proportion of ultrasound-detected SLN metastases to the neck in this study was significantly greater than the proportion of SLN metastases detected by ultrasound in other nodal regions by univariate analysis (sensitivity: axilla, 21.1%; groin, 15.6%; neck, 45.89%; $p = 0.007$), but was associated with lower specificity when compared with SLNs in the axilla and groin.

Technical Considerations

Successful sentinel lymph node biopsy requires the integration of several disciplines, nuclear medicine, surgery, and pathology. The contemporary approach consists of three main components: (1) preoperative cutaneous lymphoscintigraphy to identify the regional nodal basins at risk and the number and location of the SLNs within the basin; (2) excisional biopsy of SLNs in all regional nodal basins at risk demonstrated by preoperative lymphoscintigraphy and intraoperative localization with vital blue dye and handheld gamma probe detection of ⁹⁹Tc-labeled sulfur colloid; and (3) careful pathologic evaluation of the SLNs. Lymphatic mapping and SLN biopsy is much preferably performed at the time of wide excision of the primary tumor or biopsy site (see above). Since the introduction of lymphatic mapping and SLN biopsy, the technique has undergone several refinements that have improved detection of SLNs.

Use of a vital blue dye (isosulfan blue 1%) to help identify SLNs has been part of the lymphatic mapping and SLN biopsy procedure since its introduction. The blue dye is injected into the patient intradermally around the intact tumor or biopsy site, taken up by the lymphatic system, and carried via afferent lymphatics to the SLN. The draining nodal basin is explored, and the afferent lymphatic channels and first draining lymph nodes (the SLNs) are identified by the uptake of the blue dye. With the use of blue dye alone, an SLN is identified in approximately 85% of cases. Although this initial approach was promising, it left 15% of patients unable to benefit from SLN biopsy because no SLN was identified.

Subsequently, two additional techniques have been incorporated that have significantly improved SLN localization: (1) preoperative lymphoscintigraphy and (2) intraoperative injection of technetium-99 (^{99}Tc)-labeled sulfur colloid accompanied by intraoperative use of a handheld gamma probe. Preoperative lymphoscintigraphy using ^{99}Tc -labeled sulfur colloid (in the US) permits the identification of patients with multiple draining nodal basins and patients with lymphatic drainage to SLNs located outside standard nodal basins.^{154,183–186} For the SLN biopsy technique to be accurate, all true SLNs, regardless of location, must be identified and harvested, as the histologic status of one draining basin does not predict the status of other basins in patients with melanomas that drain to multiple regional nodal basins.^{187,188}

Perhaps the most important development in this technique has been the introduction of intraoperative lymphatic mapping using a handheld gamma probe. Preoperative intradermal injection of 0.5 to 1.0 mCi of ^{99}Tc -labeled sulfur colloid permits its intraoperative use with a hand-held gamma probe to transcutaneously identify SLNs to be removed. The use of both blue dye and radiocolloid increases the surgeon's ability to identify the SLN (greater than 96% to 99% accuracy) compared to the use of blue dye alone (84 to 85% accuracy).³⁷ Overall, radiocolloid and vital blue dye mapping techniques are complementary; to facilitate regional nodal staging, this latter technique represents the preferred approach to SLN biopsy by large academic centers and by an international consensus panel.^{37,87,189}

In general, SLNs are subjected to enhanced pathologic analysis that includes both serial sectioning and immunohistochemical analysis. As noted, frozen section analysis of SLNs in patient with cutaneous melanoma is not routinely performed.¹²¹

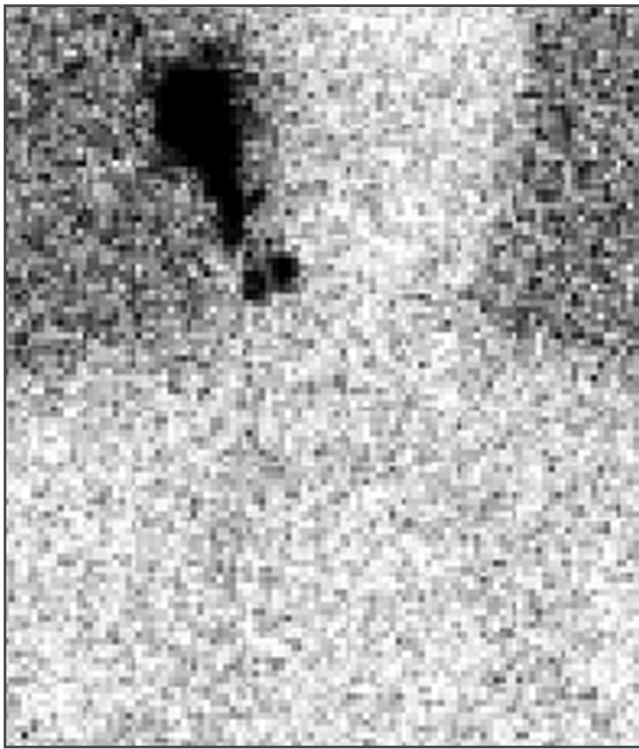
When the SLNs are histologically negative, no further surgery is performed, and the remaining regional lymph nodes are left intact. When the SLNs show evidence of metastatic disease, completion lymphadenectomy of the affected nodal basin is the current standard of care. Pathologic evaluation of completion lymphadenectomy specimens often reveals no additional disease. However, it is important to recognize that completion lymphadenectomy specimens are routinely assessed with standard his-

topathologic techniques rather than the more rigorous examination reserved for SLN biopsy specimens. As a result, additional disease in the completion nodal specimen may go undetected. This disease would represent a potential source of subsequent recurrence if it were not removed. Because such recurrences are difficult to treat surgically and may contribute to significant morbidity, completion lymphadenectomy performed for microscopic disease provides the potential for improved regional control. In addition, identifying patients with minimal disease burden by using the SLN approach may help identify the group of patients who may derive an improved survival benefit from early TLND. Furthermore, knowledge of the pathologic status of the SLNs allows proper staging and facilitates decision-making regarding adjuvant treatment.

Preoperative Lymphoscintigraphy

Preoperative cutaneous lymphoscintigraphy is used to identify the regional nodal basins at risk in patients whose primary melanoma arises in a region of ambiguous nodal drainage (eg, trunk and head and neck locations), and to determine the number and location of SLNs within a given regional nodal basin. We therefore recommend that all patients with melanomas arising in an area of potentially ambiguous drainage (ie, trunk and head and neck sites) undergo lymphoscintigraphy.

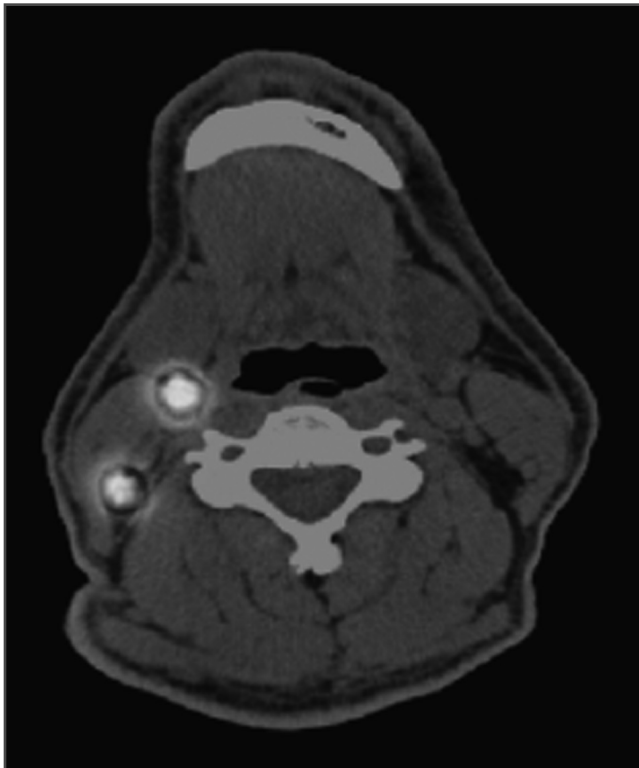
At MD Anderson Cancer Center, this procedure usually is performed days before the actual operation to permit appropriate surgical planning. Following radiotracer injection, real-time images are obtained to visualize both afferent lymphatic channels and nodal basins at risk. Although images obtained in patients whose primary melanoma is remote from the regional nodal basin are often easily interpretable, it may be difficult to discern discrete lymphatic drainage patterns in patients whose melanomas are close to potential regional nodal basins, a common challenge among patients with head and neck (or truncal) primary melanomas. In these instances, multiple views often are helpful, maximizing the ability to document drainage to the regional nodal basin (Fig 25–2).



A



B



C

Figure 25–2. Preoperative lymphoscintigraphy. A 68-year-old patient who was diagnosed with a 1.1-mm non-ulcerated melanoma arising from the posterior aspect of the pinna of the right ear. Routine transmission lymphoscintigraphic image of the head and neck (A) as well as SPECT/CT images of the head and neck (B,C) were obtained following the intradermal injection of 0.5 mCi technetium-99m sulfur colloid around the known melanoma lesion (B). Note that in the transmission image (A) it is difficult to discern whether the two lymph nodes taking up the technetium-labeled sulfur colloid in the upper neck are superficially located or found deeper within the neck adjacent to vital structures. In contrast, note clear localization of two sentinel lymph nodes (SLNs) in the axial SPECT/CT (C). Anatomic localization of the radiotracer uptake activity clearly demonstrates that one SLN is situated more posterior in the internal jugular lymph node group in the vicinity of the spinal accessory nerve, whereas the second more anterior node is more superficially located in the jugulodigastric chain. This dual modality (functional and anatomic) imaging technique greatly facilitates surgical planning and patient counseling and has become a routine practice in our center.

More recently, we have used SPECT-CT imaging to enhance anatomic visualization of the SLNs, particularly in the head and neck region (Fig 25–3). This approach provides advantages over planar imaging alone, including higher sensitivity for SLN detection; detection of SLNs in new node fields; improved detection of SLNs near injection sites (where shine-through may be a significant problem); and improved SLN location by providing detailed anatomic localization (see Figs 25–2 and 25–3).¹⁹⁰

It is clear that lymphatic drainage patterns from cutaneous invasive melanoma of the head and neck is highly complex, with multiple SLNs commonly draining to multiple regional nodal basins. Using this approach, Eicher and colleagues⁴⁵ found that head and neck primary sites drained to an average of 2.2 nodal basins per patient, with drainage to nonadjacent nodal basins in 42% of patients. In a subsequent effort to better understand “lessons

learned” from preoperative lymphoscintigraphy performed on patients with primary melanoma of the head and neck, Reynolds et al¹⁹¹ developed a three-dimensional visualization of skin lymphatic drainage patterns by employing “heat map” technology based on lymphoscintigraphy data from 929 patients with primary cutaneous melanoma on the head and neck treated at the Sydney Melanoma Unit. These data not only demonstrated inadequacies of “classical” descriptions of lymphatic drainage patterns, but also provide an important educational evidence-based tool for clinicians (Fig 25–4).

From a practical standpoint, the rare instances of failure of the radiocolloid to migrate from the injection sites may be due to subcutaneous rather than intradermal injection, especially in patients with very thin skin. Lymphoscintigraphy should be re-attempted in these patients. Preoperative lymphoscintigraphy and images also may be obtained immediately following

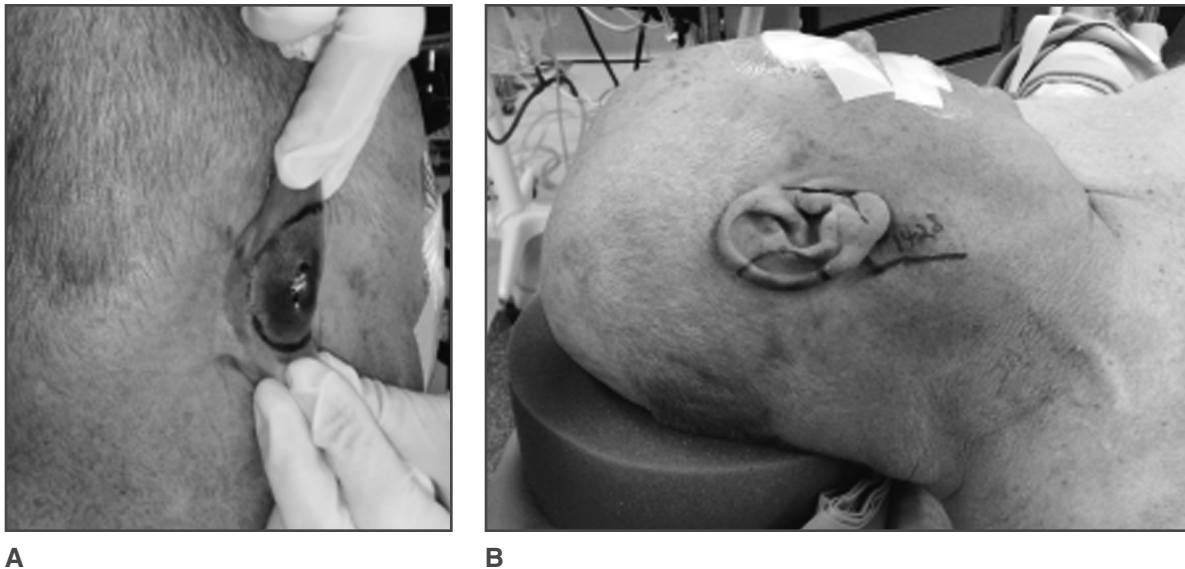


Figure 25–3. Wide local excision of a right helical rim melanoma with sentinel lymph node (SLN) biopsy. The same patient with the right auricular melanoma (Fig 25–2) returned to the nuclear medicine suite on the morning of surgery and was injected with 0.5 mCi technetium-99m sulfur colloid intradermally around the known melanoma lesion. He was then brought to the operating room where a proposed 1-cm wide local excision was outlined and an intradermal injection of 1 ml of isosulfan blue was performed (A). The patient was positioned and the incisions needed to harvest the SLNs from areas of increased focal radiotracer uptake activity were outlined based on hand-held gamma probe-guided SLN localization (B). *continues*

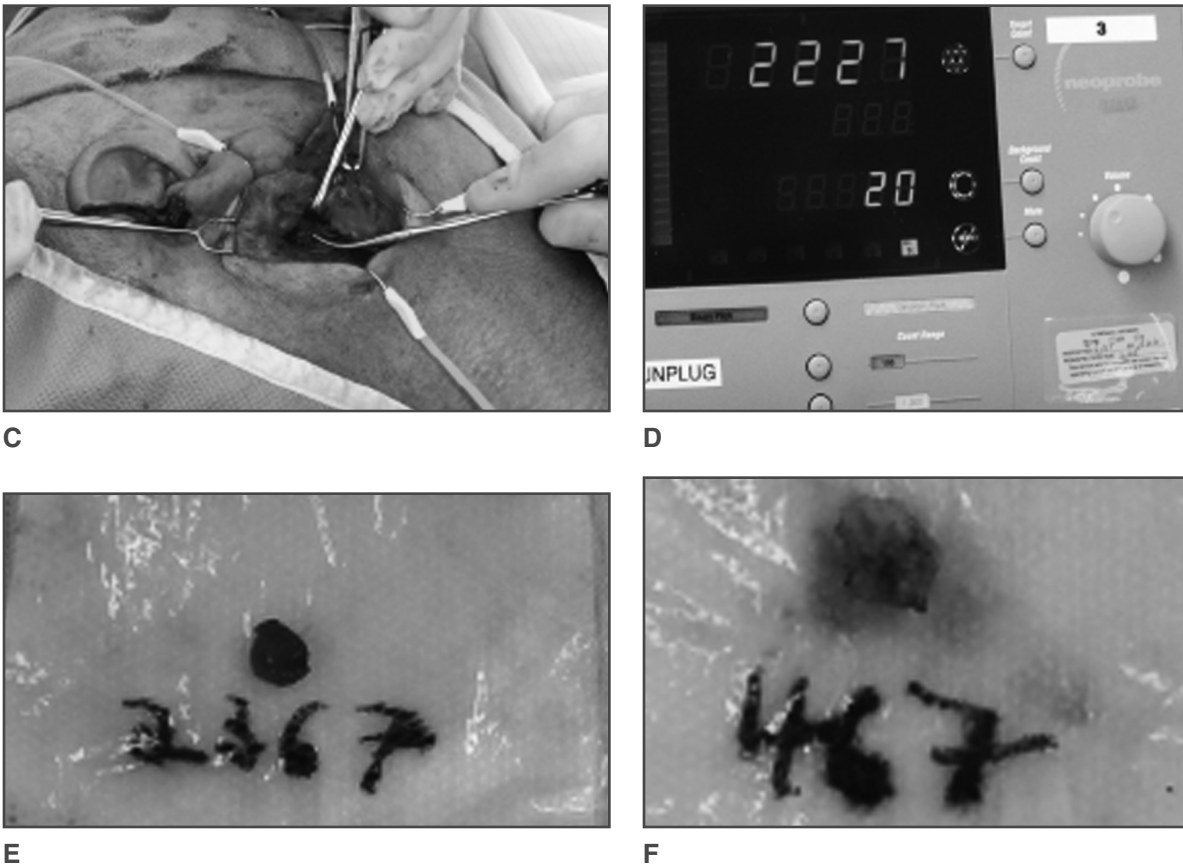


Figure 25-3. *continued* In panel **C**, a hemostat points to a SLN that had a high uptake on gamma probe evaluation (**D**) but was not stained with isosulfan blue (**E**). A second SLN had increased radio-tracer uptake activity and was stained blue; it was located just anterior to a retracting double-prong skin hook (**F**). Pathologic evaluation of both SLNs by hematoxylin and eosin staining, step sectioning, and immunohistochemistry for a panel of melanoma markers failed to reveal metastatic melanoma.

technetium-labeled sulfur colloid injection on the day of surgery, an approach preferred in some institutions. Identification of all nodal basins at risk for metastatic disease is especially important with melanomas of the trunk or the head and neck (all of which may drain to the neck), where lymphatic drainage patterns cannot reliably be predicted by clinical judgment or classical anatomic guidelines and where multiple basin drainage is common.^{192,193}

Intraoperative Considerations

Since 1994, lymphatic mapping and sentinel lymphadenectomy has been performed at MD Anderson

using both isosulfan blue dye and technetium-labeled sulfur colloid detected using a handheld gamma probe. On the day of operation, 0.5 to 1 mCi of technetium-labeled sulfur colloid is usually injected intradermally at 4 points around the melanoma site. This procedure is scheduled to be performed approximately one hour before the scheduled start of the surgical procedure, as injection immediately before the surgical procedure may not permit enough time for the colloid to travel through afferent lymphatic channels to the SLN and an interval greater than four hours may increase the likelihood that colloid may pass through some of the SLNs to second-echelon nodes, which by definition are not the nodes most likely to contain disease.

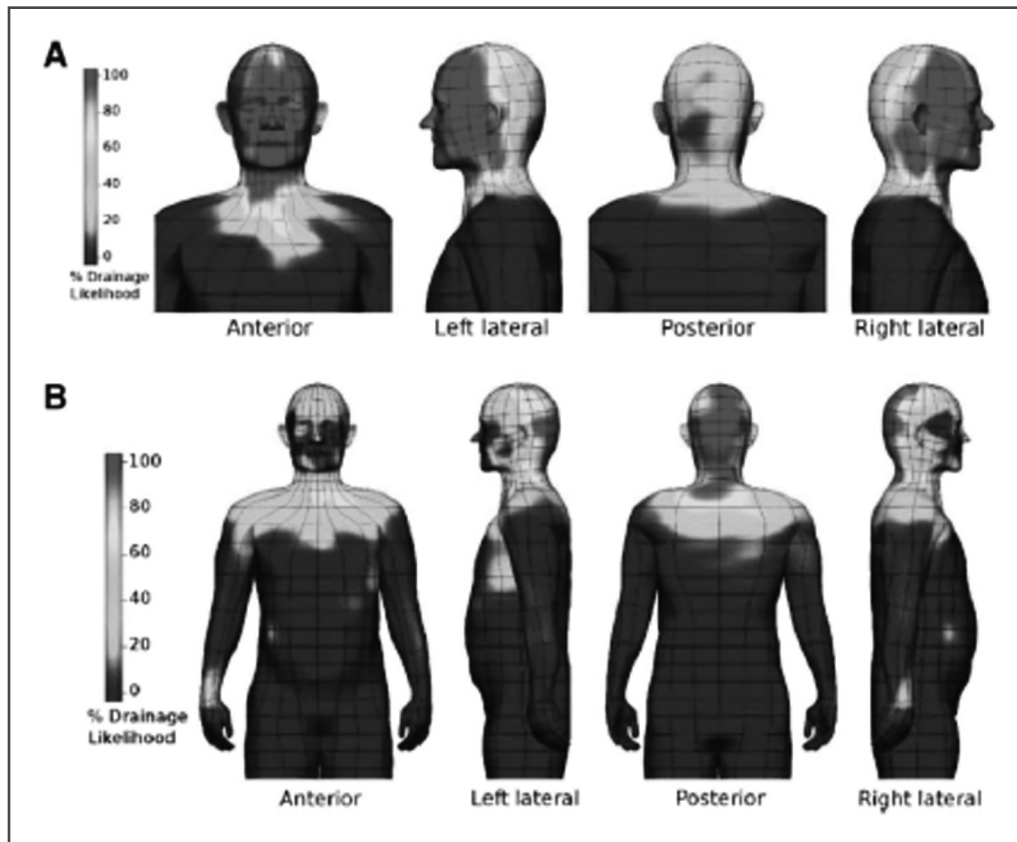


Figure 25-4. Head and neck lymphatic drainage patterns. Reynolds and colleagues from the Sydney Melanoma Unit collected lymphoscintigraphy data from 929 patients with cutaneous melanoma of the head and neck region and mapped the sentinel lymph node drainage patterns from multiple primary melanoma sites using a 3-dimensional computer model. In this example, modeling demonstrates the likelihood that a primary melanoma site will show lymphatic drainage to sentinel nodes in the (A) anterior node fields: preauricular, submental, cervical levels I, II, III, and IV, or (B) posterior node fields: postauricular, occipital, cervical level V, and supraclavicular fossa. Although posterior head and neck node fields are seen to drain the skin of the posterior head and neck region, the skin of the anterolateral neck tends to drain to nodes that are more anteriorly or laterally located. Source: Reynolds HM, et al, *Head Neck*. 2009;31:1316–1325.¹⁹¹

Immediately before the planned surgical procedure, it is helpful if the handheld gamma probe is used to localize areas of increased focal radiotracer activity transcutaneously in regional nodal basins. Areas of increased focal radiotracer activity are marked on the skin (see Fig 25-3B). Positioning the patient as he or she will be positioned for the actual procedure facilitates the most accurate documentation of the sites of SLNs.

Once adequate anesthesia is achieved and depending in part on the site of the primary, approx-

imately 1 to 3 mL of isosulfan blue dye is administered intradermally, and the injection sites massaged for approximately 1 to 2 minutes to encourage uptake by the cutaneous lymphatics. Injection is usually performed using 1-mL syringes and 25- or 27-gauge needles (see Fig 25-3A).

After injection of the isosulfan blue dye, the patient is positioned and appropriately prepped and draped. Whenever possible, intraoperative lymphatic mapping and sentinel lymphadenectomy is

performed before the wide local excision. If shine-through from the injected radioactivity at the primary site is a significant problem, wide local excision of the primary may be performed first. This approach often is used for head and neck primary sites given the proximity of some primary sites to draining regional nodal basins. With the patient prepped and draped, areas of increased focal radiotracer uptake in the first basin are confirmed with the handheld gamma probe.

A small incision is then made overlying the area of increased focal radiotracer activity; care is advised in making this SLN biopsy incision to ensure that it can subsequently be incorporated into a CLND incision should the SLN contain metastatic melanoma. Once identified, the blue-stained and/or highly radioactive node is secured with a suture and gently elevated (Fig 25–5). Surrounding fatty tissue is dissected with the electrocautery, and all vascular and lymphatic structures are identified and ligated to facilitate harvest of the lymph node.

In certain anatomic regions within the head and neck, longer SLN biopsy incisions may be required to decrease the risk of injury to vital neurovascular structures. As shown in Figure 25–2C, the SLN at the posterior-superior aspect of level IIb of the right neck would be difficult to excise without potential significant risk of injury to the spinal accessory nerve and jugular vein without a large enough incision to expose landmarks that help the surgeon to safely identify and protect those important structures.

Although some surgeons may question need for blue dye, most surgeons believe that blue dye provides an invaluable and complementary adjunct, and remains a critical component of the lymphatic mapping technique.³⁷ The dye provides a visual aid that not only confirms that the lymph node is an SLN but also facilitates localization of SLNs when transcutaneous localization of colloid is unsuccessful and helps minimize dissection even when gamma probe localization is achieved. At MD Anderson, use

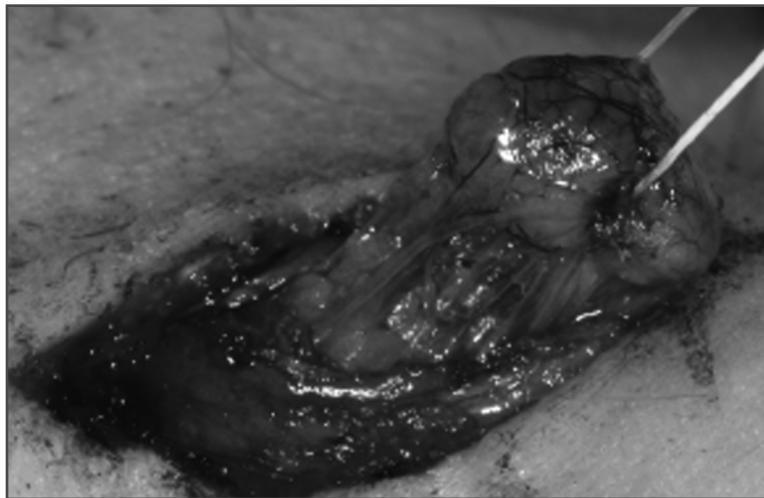


Figure 25–5. Intraoperative identification of a sentinel lymph node (SLN). Intradermal injection of a vital blue dye around the intact melanoma or biopsy site leads to uptake of the dye by the lymphatic system and transport of the dye to the draining regional nodal basins, thereby allowing for identification of SLNs. Note isosulfan blue-stained afferent lymphatic vessel leading to blue-stained SLN. (Courtesy of Jeffrey E. Gershenwald, MD. Copyright retained by the author and the University of Texas MD Anderson Cancer Center.)

of the combined-modality approach (dye and colloid) resulted in an SLN identification rate of over 99%, compared with 87% when only blue dye was used³⁷; this has been cited as the preferred approach to SLN biopsy by large academic centers^{37,189} and by an international consensus panel.⁸⁷

The SLN is visually inspected for evidence of gross metastatic disease. If it has none, no frozen section analysis of the lymph node is performed. If, however, the lymph node appears grossly suspicious (eg, obvious melanin pigment and/or tumor), a frozen section examination may be performed to confirm the diagnosis if concomitant completion lymph node dissection is considered *and* has been discussed with the patient in advance. At MD Anderson and the Sydney Melanoma Unit, frozen section analysis of sentinel lymph nodes is rather uncommon, and is reserved only for highly suspicious nodes, and only if plans for possible concomitant lymph node dissection was discussed preoperatively with the patient. The "abnormal" appearance of SLNs often simply represents reaction to a previous diagnostic biopsy procedure. If frozen section analysis were performed routinely, optimal tissue for careful permanent section analysis might be lost in processing, limiting the diagnostic yield of subsequent serial section and immunohistochemistry.¹²¹ Some investigators have employed intraoperative evaluation of sentinel lymph nodes for metastatic melanoma by imprint cytology.¹⁹⁴

After removal of the SLN, the basin is rescanned using the gamma probe. If an area of increased focal radiotracer activity is again identified, the procedure is repeated in an effort to identify additional SLNs until no nodes with greater than 10% of the radiotracer uptake activity of the "hottest" SLN remain. All additional SLNs are harvested, and their uptake of blue dye and *ex vivo* counts are documented. The lymph nodes are numbered sequentially by order of their removal and submitted for permanent-section pathologic analysis.

Operating Room Positioning Strategies

Whereas the surgical approach to patients with melanoma arising on an extremity is relatively straightforward, the surgical approach to patients with melanoma arising in a region of potentially

ambiguous lymphatic drainage (eg, trunk, head, or neck) often requires careful planning. Careful attention to patient positioning in the operating room is necessary to ensure that all components of lymphatic mapping and SLN biopsy are achievable.¹⁹⁵ Proper patient positioning must take into account not only the location of the primary melanoma and the regional nodal basins, but also potential in-transit or ectopic sites at risk for metastatic disease and potential donor sites for skin grafting. Careful study of the preoperative lymphoscintigram often provides most of the information necessary to develop an operative positioning strategy, incision design, and surgical plan.

Sentinel Lymph Node Biopsy and the Parotid Gland

One area of lymphatic drainage within the head and neck region worthy of additional consideration in surgical planning is the parotid gland. In one study, 44% of cutaneous lesions of the scalp, ear, face, and neck were found to drain to lymph nodes within the parotid.⁴⁵ Although several groups have shown the safety and feasibility of removing SLNs from the parotid without formal superficial parotidectomy and facial nerve dissection, there are situations in which removal of a portion of the gland may be advisable.^{196,197} For example, when the SLN is deep within the substance of the gland rather than superficially located along the branches of the superficial temporal vessels, it may be worthwhile to identify the facial nerve and remove the superficial lobe of the parotid gland to avoid re-operation around the previously dissected nerve if this SLN is positive. In some centers, this approach is more readily applied if the primary tumor is thicker (>2.5 mm) and/or ulcerated.

SPECT/CT has been very helpful (compared to conventional lymphoscintigraphy) in identifying patients in whom this scenario may be likely, enabling appropriate preoperative counseling about the potential need for a more comprehensive resection of the parotid versus simple SLN removal. SPECT/CT also is particularly useful in distinguishing whether SLNs are situated within the parotid tail or in the superior external jugular lymph node chain just deep to the parotid tail.

Complications and Morbidity

Overall, SLN biopsy is associated with low morbidity.^{105,138,198,199} There are substantially fewer postoperative complications after SLN biopsy than after ELND,^{199,200} and the rate of lymphedema, pain, numbness, and loss of active range of motion are lower after SLN biopsy than after full anatomical dissection.^{57,105,199,201,202} In addition, recent data have shown that SLN biopsy does not increase the incidence of in transit recurrence.^{138,203–205}

Investigators from the Sunbelt Melanoma Trial reported overall low complication rates following SLN biopsy alone in more than 1,202 trial patients compared to the 277 patients who required a complete lymph node dissection.¹⁹⁹ This observation has been reiterated by others, as well as in the Multicenter Selective Lymphadenectomy Trial, whereby overall complication rates of 10% after lymphatic mapping and SLN biopsy increased to 32.7% after completion lymph node dissection.^{105,138,206,207} Strategies to reduce the incidence of lymphedema, more common following formal lymphadenectomy, are also helpful.

Risk of In Transit Metastasis

Although the SLN biopsy technique has gained widespread acceptance for a number of reasons: accurate nodal staging, enhanced regional control, possible survival benefit, and limited surgical morbidity compared to formal lymphadenectomy, some authors have suggested that SLN biopsy may increase the risk of in transit metastasis (ITM), thereby reducing, eliminating, or reversing any potential survival advantage associated with the SLN biopsy technique.²⁰⁸ The hypothesis that the SLN biopsy technique and subsequent completion lymph node dissection in SLN-positive patients may disturb lymph flow by mechanical disruption and lead to increased rates of ITM, if accurate, is of particular concern as SLN biopsy has been widely adopted as a standard of care. The collective experience at several large academic centers,^{203,204,209} including the MSLT-1 trial,¹⁰⁵ provides strong support that the technique of SLN biopsy itself does not

increase the risk of in transit metastasis.^{105,203,204,209} Instead, the risk of in transit melanoma metastasis depends on tumor biology and not the surgical approach to regional lymph nodes.²⁰⁵

Complications Associated with Vital Blue Dye

Although allergic reactions, including anaphylactic reactions, have been reported on rare occasions following use of vital blue dye, they have occurred only rarely in large melanoma populations.^{138,210} Blue dye can be retained at the primary site for more than a year. Although the color generally gradually fades with time, patients may be left with a permanent tattoo if the injected dye is not removed with WLE of the primary site. Careful attention to injection technique is particularly important in patients whose melanomas arise in cosmetically sensitive areas such as the head and neck. A small amount of residual dye may also persist for several months after WLE.

Role of Radiotherapy in the Clinically N₀ Neck

Although SLN biopsy represents a standard of care for patients with early stage melanoma at risk for regional lymph node metastasis, there are some patients with significant medical comorbidities for whom such regional nodal staging and prognostic assessment is of little relevance and for whom enrollment in a clinical trial is unlikely. For this small subset of patients otherwise at risk for occult nodal metastasis, elective cervical nodal irradiation may be superior to nodal observation with the attendant unacceptable risk of regional recurrence.^{211–213}

In a retrospective analysis from MD Anderson, Bonnen and colleagues reviewed 157 patients with stage I or II cutaneous melanoma of the head and neck who received elective regional irradiation instead of lymph node dissection (in the pre-SLN biopsy era) after wide local excision of the primary site.¹⁰⁴ Indications for regional irradiation included primary thickness of 1.5 mm or greater or Clark