Sentinel Lymph Node Biopsy in Melanoma and Other Cutaneous Malignancies

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Abstract

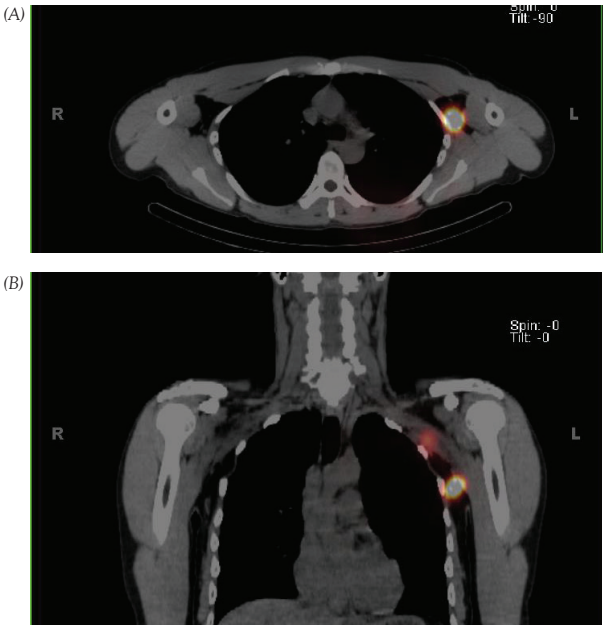
Morton and colleagues defined the sentinel lymph node as the first lymph node that drains lymph from a primary melanoma. This definition has since been expanded to apply to other cancers. Sentinel lymph node biopsy (SLNB) is a staging tool for patients with clinically node-negative primary cutaneous malignancies and no evidence of distant metastasis. It is used to determine the histologic status of the nodes of the regional nodal basin(s) draining the primary site. If the sentinel node is negative, the rest of the nodes in the basin are presumed to be negative. The status of the sentinel lymph node has been shown to be the strongest predictor of outcome in melanoma. In patients with melanomas ≥1 mm, the role of this technique is well established. For patients with melanomas ≥0.76 to 0.99 mm, there is strong evidence to support its routine use. In Merkel cell carcinoma, the preponderance of the available data supports its use. There is no role for this procedure in the management of basal cell carcinoma and dermatofibrosarcoma protuberans. In squamous cell carcinoma, the indications for the use of this modality are not clearly established and its role, if any, is likely limited to a highly selected few cases with very high-risk (as yet poorly defined) features predictive of nodal metastatic disease. In cutaneous adnexal malignancies, there are simply not enough data to determine the utility of this technique. Anecdotal evidence suggests it may be useful in some of these cases, particularly eccrine cancers.

Introduction

The modern concept of the sentinel lymph node was established in cutaneous melanoma by Morton and his colleagues.[1] They defined a sentinel lymph node as the first lymph node that drains lymph from the site of a primary melanoma. This definition has since been expanded to apply to all cancers that spread by the lymphatic route. Using vital blue dye initially and subsequently adding radioactive colloids, they were able to trace lymphatic flow from the primary tumor site to the sentinel lymph node in a very high percentage of patients, and showed that the status of the sentinel node was predictive of the status of other nodes within that basin as well as strongly correlated with prognosis.[2]

The use of sentinel lymph node biopsy (SLNB) is restricted to patients with cancers with clinically negative nodes and no evidence of distant metastatic disease, and is performed whenever possible at the time of surgical treatment of the primary tumor rather than afterward. The sentinel lymph node is carefully assessed for the presence of clinically occult disease, using serial sectioning techniques and immunohistochemical analysis that is substantially more extensive than the histopathologic analysis routinely utilized for lymph nodes harvested in a complete lymphadenectomy. If the sentinel lymph node is negative, then the rest of the nodes in the lymphatic basin in question are very likely to be negative. Fundamentally, SLNB is a staging tool that can help determine prognosis. The routine use of SLNB has not been shown to lead to a statistically significant increase in survival in any cancer type, including melanoma.[3]

FIGURE 1.



SPECT-CT lymphoscintigraphy of a 49-year-old male with a 1.8 mm nonulcerated melanoma with 1 mitosis per mm2 on the left upper back (primary site not shown). (A) Axial view through the level of the axillae showing two distinct "hot" level I lymph nodes within the left axilla. (B) Coronal view demonstrates the same 2 level I lymph nodes as well as a fainter level II lymph node higher in the left axilla. (All images and intraoperative photographs courtesy of Amod Sarnaik, MD, and Georgina Crago, PA-C.)

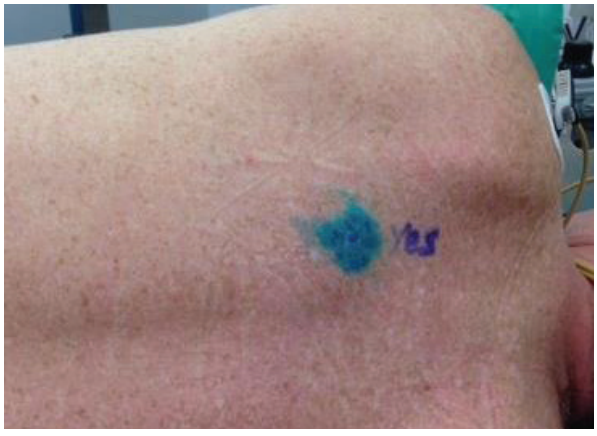
The technical aspects of SLNB in melanoma have been well described by Bagaria et al.[4] SLNB involves preoperative injection of a traceable substance, usually a colloid solution labeled with ^{99m}Technetium, in the vicinity of the tumor—intradermally around the biopsy scar in the case of melanoma. Scintillation cameras are then used to obtain dynamic images (**Figure 1**), which help in identifying the sentinel node, which may at times be located outside of traditional lymphatic basins.[5] In the operating room, a vital blue dye is injected intradermally at the primary site (**Figure 2**). Guided by the lymphoscintigraphy, the appropriate lymphatic basin(s) are explored. Senti-

Practical Application

- SLNB is recommended for patients with clinically node-negative melanomas ≥0.76 mm thick to improve prognostication, relapse-free survival, and in some cases, outcomes for node-positive patients.
- Completion lymphadenectomy is recommended for melanoma patients with a positive sentinel node for additional prognostic value, improved regional control, and decreased morbidity, and to establish eligibility for clinical trials of adjuvant therapy.
- SLNB is recommended for all patients with clinically node-negative Merkel cell carcinoma to improve prognostication. Microscopic nodal disease is often treated using radiation instead of completion lymphadenectomy.
- There is no role for SLNB in patients with basal cell carcinoma or dermatofibrosarcoma protuberans.
- The role of SLNB in patients with squamous cell carcinoma remains to be defined but is very limited at best.
- Cutaneous adnexal malignancies (especially eccrine carcinomas) have a high rate of occult nodal involvement and may be appropriate for SLNB.

nel nodes are identified by palpation, identification of radioactivity with a handheld probe, or visualization of uptake of the blue dye (**Figures 3-5**). Indications for and results of SLNB in melanoma are outlined in the next sections, followed by a discussion of the application of this procedure to other cutaneous malignancies.

FIGURE 2.



Site of left upper back primary melanoma (same patient as in Figure 1) after injection of 1 mL of isosulfan blue dye. (Patient is in lateral decubitus position.)

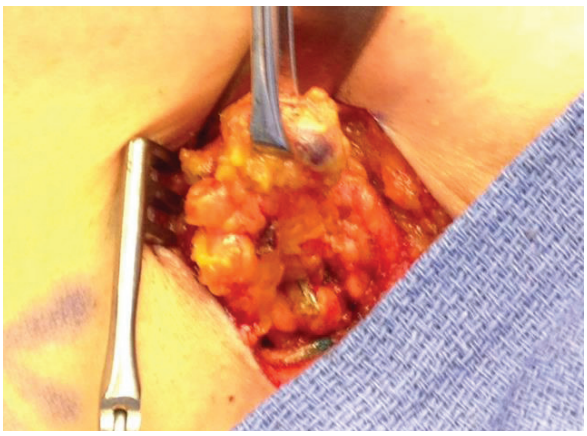
Cutaneous Melanoma

Intermediate thickness melanoma (1.00-4.00 mm)

The clinical application of SLNB was first described in cutaneous melanoma by Morton et al.[1] Since that time, the use of this modality has become standard of care for clinically node-negative cutaneous melanoma.[6] Indeed, both the National Comprehensive Cancer Network (NCCN) guidelines and recently issued joint guidelines from the American Society of Clinical Oncology (ASCO) and the Society of Surgical Oncology (SSO) recommend routine use of SLNB for all clinically node-negative cutaneous melanomas 1 to 4 mm thick.[7,8]

The first Multicenter Selective Lymphadenectomy Trial (MSLT-1) established the feasibility of SLNB in the treatment of clinically node-negative melanomas.[2] In this randomized trial, 1347 patients with intermediate thickness melanoma (defined by the investigators as 1.2 to 3.5 mm but subsequently also analyzed by the more conventional definition of 1.0 to 4.0 mm) were randomized to either SLNB or nodal observation. Patients with evidence of sentinel node involvement by melanoma underwent completion lymphadenectomy (by definition, a radical lymph node dissection performed to achieve complete removal of the regional nodal basin after a positive SLNB) within a few weeks of the SLNB procedure. Any patients with a negative sentinel node and those randomized to wide excision of the primary alone who subsequently manifested clinically detected nodal disease underwent therapeutic lymphadenectomy at the time of recurrence. In this study, the rate of sentinel lymph node identification was >99%, and 19.1% of all SLNB patients in the study had positive sentinel nodes.[3] Sentinel node status proved to be the strongest predictor of outcome; patients with intermediate thickness melanoma having a positive node were approximately 2½ times more likely to relapse and die than those with a negative sentinel node. For patients with melanomas 1.00 to 4.00 mm in thickness, this corresponded to a 10-year melanoma-specific survival of 85.7% if the sentinel nodes were negative, and 63.1% if at least 1 sentinel node was positive.[3] MSLT-1 demonstrated no significant difference in melanoma-specific survival between the 2 study arms. Disease-free survival was significantly better for the SLNB arm than for the observation arm, due almost entirely to decreased nodal recurrences in the SLNB arm. For the subgroup of intermediate thickness melanoma patients who required lymphadenectomy for documented nodal involvement, there was a higher 10-year melanoma-specific survival rate in those whose nodal disease was diagnosed by SLNB compared with those who had clinically detectable recurrent nodal disease (for patients with melanomas 1.00 to 4.00 mm in thickness: 63.1% vs 41.4%; hazard ratio 0.55, P = .003). These results clearly support

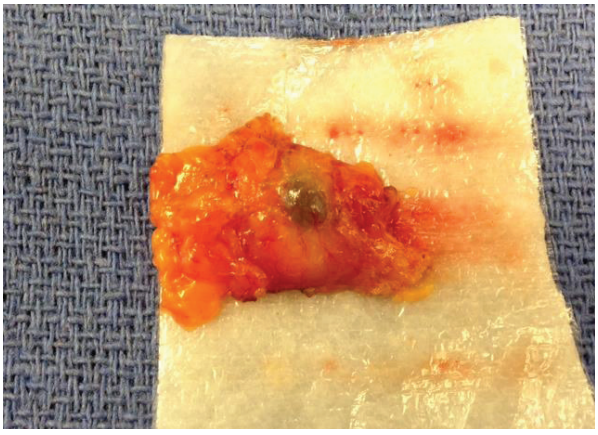
FIGURE 3.



The sentinel lymph node has been identified in the left axilla by intraoperative use of a handheld gamma detector and following a blue lymphatic channel. The node is being circumferentially dissected free and will be removed through a small axillary incision. The transected edge of the blue lymphatic channel is visible at the bottom of the dissected field.

the joint ASCO/SSO guideline that SLNB is "recommended for patients with intermediate-thickness melanomas (Breslow thickness, 1.00 to 4.00 mm) of any anatomic site."[8]

FIGURE 4.



Ex vivo picture of the dissected sentinel lymph node and surrounding axillary tissue.

FIGURE 5.

Display on intraoperative gamma detector showing high level of radioactivity (1215 counts per minute) in the lymph node ex vivo, confirming that it is indeed a sentinel node. Note the normal background radioactivity count of 2 counts per minute. All 3 nodes identified on preoperative SPECT-CT lymphoscintigraphy were eventually removed and confirmed to be radioactive to varying degrees.

Thick melanomas (>4.00 mm)

MSLT-1 included patients with thick melanomas, but defined as >3.5 mm instead of the more conventional definition of >4.00 mm. The sentinel node was positive in 32.9% of these patients, and the status of the sentinel node was again shown to be a powerful independent predictor of melanoma-specific survival.[3] A study by Gershenwald et al showed that in thick melanomas using the standard definition of >4.00 mm, the rate of sentinel lymph node positivity was 39% and sentinel node status was predictive of outcome,[9] substantiating the generalizability of the MSLT-1 results to the T4 population. Of note, although MSLT-1 patients with thick (>3.5 mm), sentinel node-positive melanomas had a worse prognosis (48.0% 10-year melanoma-specific survival compared with 64.6% if the sentinel node was negative), over one third of sentinel node-negative patients with thick melanomas still died from their disease. Disease-free survival was statistically significantly better for the SLNB arm than for the observation arm, and the median time to nodal recurrence among observation arm patients was only 9.2 months. Melanoma-specific survival was not different for the thick melanoma patients in the 2 arms, even when only the node-positive cases were considered.[3] Taken as a whole, the available data regarding thick melanomas support recommending routine use of SLNB for melanomas >4.00 mm to improve prognostication and recurrence-free survival.

Thin melanomas (<1.00 mm)

MSLT-1 excluded patients with melanomas <1.00 mm, so we have no prospective randomized trial data to guide decision-making in this important patient population. NCCN guidelines recommend considering SLNB for patients with melanomas ≥0.76 but ≤1.00 mm, and offering it when the primary is ulcerated or has a mitotic rate ≥1 per mm^2. These guidelines do not recommend SLNB for melanomas <0.76 mm.[7] ASCO/SSO guidelines suggest that SLNB may be considered for thin melanomas in the presence of high-risk features such as ulceration or mitotic rate >1 per mm^2.[8] A literature review by Andtbacka and Gershenwald reported positive SLNB in 6.2% of patients with melanomas 0.75 to 1.00 mm. In patients with melanomas <0.75 mm thick, the rate of positive sentinel lymph node was only 2.7%.[10] Han et al reviewed their experience with melanomas ≤1.00 mm at a center where the routine practice was to recommend SLNB for all patients with melanomas ≥0.76 mm, minimizing the selection biases inherent in most other retrospective reviews of SLNB for thin melanoma. They reported an overall positive node rate of 8.4%.[11] For T1a melanomas 0.76 to 1.00 mm, the rate of positive SLNB was 4.8%. For T1b tumors ≥0.76 mm, it was 13.0%. Ulcerated melanomas were rare among cases ≤1.00 mm, but when ulceration was present, the rate of a positive sentinel node increased significantly, while mitotic rate ≥1 per mm^2 was of borderline significance (P = .06). The authors concluded that these numbers justified routine consideration of SLNB in patients with melanomas ≥0.76 mm, utilizing a 5% threshold for detecting a positive sentinel node as sufficient to consider the procedure indicated. For patients where a higher (10%) threshold would be considered more appropriate, such as for older patients or those with some minor comorbidities not constituting a contraindication to general anesthesia, they concluded that SLNB would be indicated only for those with melanomas 0.76 to 1.00 mm with ulceration or mitotic activity.

False-negative SLNB

SLNB identifies most but not all patients who have nodal metastases. The Sunbelt Melanoma Trial was a prospective multicenter, nonrandomized evaluation of SLNB that provides high-quality data for estimating false-negative rates and the predictive value of

a negative SLNB. Data from 1965 patients with melanomas ≥1.00 mm thick who had a negative SLNB were analyzed, and 59 patients (3.0%) eventually developed a recurrence in the previously mapped nodal basin, after a median time of 20 months.[12] Hence, the negative predictive value of SLNB is very high (97.0%). As the authors correctly point out, the false-negative rate is calculated relative to the total number of node-positive cases, meaning the false-negative rate for the Sunbelt study was 10.8% (59 false-negative cases/[486 true-positive + 59 false-negative cases] x 100). However, some of their false-negative cases represent patients who developed local or in-transit recurrences prior to the nodal recurrence, and hence should not be considered failures of the SLNB procedure but rather recurrences attributable to residual tumor after wide excision. Adjusting the false-negative calculation to exclude these cases gives a false-negative rate of 7.6%,[12] and probably provides a truer assessment of the accuracy of the SLNB procedure. In their study, using a logistic regression model, 3 preoperative factors identified patients at increased risk of a false-negative SLNB: older age, increasing tumor thickness, and the presence of lymphovascular invasion in the primary.[12] Other authors have suggested that patients with head and neck primaries are likely at increased risk of a false-negative SLNB independent of these factors,[13] although not to the extent that the procedure should be considered differently for melanomas in this location.[14] Moreover, the increasing availability of three-dimensional preoperative localization with single positron emission computed tomography (SPECT-CT, as shown in **Figure 1**) has the potential to further decrease false-negatives.[15]

The role of completion lymphadenectomy after a positive SLNB

NCCN guidelines, strongly supported by decades of clinical experience, call for routine performance of a therapeutic lymphadenectomy in all melanoma patients with clinically positive nodes and no radiographic evidence of distant metastases.[7] The routine use of completion lymphadenectomy after a positive SLNB is more controversial,[16] although it is recommended by the ASCO/SSO guidelines in the absence of participation in a clinical trial evaluating nodal basin observation.[8] The MSLT-1 trial showed that outcomes for patients with intermediate-thickness melanoma undergoing completion lymphadenectomy were superior to those for patients who recurred in the nodal basin,[3] but by the nature of the trial the contribution of the completion lymphadenectomy over and above removal of the sentinel node could not be assessed. Non-sentinel nodes (those harvested during the completion lymphadenectomy) are only found to have tumor involvement in a minority of cases,[17] and at least some sentinel node-positive patients do well for an extended period of time even without undergoing completion lymphadenectomy.[18] On the other hand, the presence of detectable nonsentinel lymph node metastases conveys additional prognostic information.[19] The nodes in most lymphadenectomy specimens are not evaluated histopathologically to the same extent as the SLNB specimen, so there is undoubtedly some underestimation of the risk of regional recurrence if completion lymphadenectomy is omitted based solely on the incidence of observed nonsentinel node metastases. Finally, the morbidity of lymphadenectomy, especially severe lymphedema, has been shown to be less for completion lymphadenectomy after a positive SLNB than for therapeutic lymphadenectomy after nodal recurrence.[20] These facts all argue in favor of completion lymphadenectomy, but do not negate the possibility that the procedure may be safely omitted for some subsets of SLNB-positive patients. A prospective randomized trial comparing SLNB alone to SLNB plus completion lymphadenectomy for sentinel node-positive patients, MSLT-2, recently completed accrual but mature results are not expected for many years. Until these results are available, the management of the sentinel-node positive lymphatic basin will have to be individualized.[16] For now, completion lymphadenectomy remains the standard of care recommendation and is required for entry into many contemporary adjuvant therapy trials.

Special situations for SLNB in melanoma

Desmoplastic melanoma

The role of SLNB in desmoplastic melanoma (DM) is controversial. Retrospective studies have consistently reported lower rates of nodal metastasis in cases of DM, especially "pure" DMs as opposed to lesions showing mixed desmoplastic and non-desmoplastic histology.[21] Current NCCN guidelines state that patients with pure DM "have a very low incidence of nodal involvement that does not support routine use of SLNB,"[7] but the ASCO/SSO guidelines do not address DM as a separate entity.[8] The multi-institutional Sunbelt Melanoma Trial found that DMs had a positive SLNB in 17.0% of cases,[22] clearly enough to justify routine use of SLNB, but this study may have been limited by non-uniform pathologic evaluation of the primary tumors. A recent single-institution, retrospective review of SLNB in DM, with very consistent pathologic evaluation of the primary tumors, showed that the overall risk of sentinel node metastasis in DM was 13.7%.[23] For mixed tumors, the rate was 24.6%, while for pure DM it was 9.0%, statistically significantly less but still high enough to justify use of SLNB in both histologic variants of DM.

Atypical Spitzoid tumors

Atypical Spitzoid tumors are skin lesions usually but not exclusively found in children, which have histologic characteristics of both typical benign Spitz nevi and melanomas. These lesions are notoriously difficult to classify and even expert pathologists can disagree on the specific diagnosis of these lesions, as demonstrated in a study of 30 atypical melanocytic tumors reviewed by 10 internationally renowned pathologists. There was only 1 case in which the majority of the pathologists agreed on the diagnosis. In 17 of the cases, there was no agreement among the pathologists as to the diagnosis, and some lesions that proved fatal were categorized by most observers as either benign Spitz nevi or atypical Spitz tumors.[24] This degree of diagnostic uncertainty has led to a lack of consensus regarding how to treat these tumors. One school of thought holds that these patients should all undergo SLNB. Su et al looked at patients with Spitzoid melanocytic lesions who underwent SLNB at a major US cancer center.[25] Eight of 18 patients (44%) had sentinel node metastasis. They all underwent regional lymphadenectomy and 1 was found to have an additional involved lymph nodes. Murali et al looked at the use of SLNB in patients with atypical Spitzoid tumors at a major

Australian center.[26] Twenty-nine percent of the patients had positive sentinel lymph nodes. Five of these patients underwent completion lymphadenectomy, with no further positive lymph nodes found. They found that greater tumor thickness, incomplete maturation of the nevus cells in the primary tumor, higher dermal mitotic rate, and the presence of deep dermal mitoses and/or expansile dermal nodules were associated with positive sentinel nodes. However, the only feature that reached statistical significance was tumor thickness. Conversely, others have argued that the sentinel node metastases reported in these and other studies may be false positive findings and concluded that atypical Spitzoid tumors were not associated with metastatic potential and hence SLNB was not justified.[27,28] In a very comprehensive review article, Busam and Pulitzer review the arguments in favor and against the use of SLNB in atypical Spitzoid tumors.[29] Our own experience is that SLNB is of value in both atypical Spitzoid tumors and unequivocal melanoma of childhood,[30,31] and we continue to use it routinely for atypical tumors in which the possibility of melanoma cannot be excluded.[32] In the future, it is hoped that molecular analysis may help discriminate those atypical Spitzoid lesions that represent malignant lesions, but for now this approach remains in its infancy.[33]

Merkel cell carcinoma

Of all cutaneous malignancies, Merkel cell carcinoma is second only to melanoma in terms of widespread use of SLNB. NCCN guidelines recommend the use of SLNB in Merkel cell carcinoma patients with clinically negative regional lymph nodes as an important staging tool, but note that its impact on overall survival is unclear.[34] Unlike melanoma, no prospective trials of SLNB have been conducted in Merkel cell carcinoma. Gupta et al in a literature review reported that SLNB in patients with Merkel cell carcinoma identified 32% who had occult nodal disease not identified by clinical and radiologic criteria. Furthermore, they found that recurrence rates at 3 years were 3 times higher in patients with positive sentinel nodes (60%) compared with patients with negative sentinel nodes (20%).[35] Another single-institutional study of 161 patients showed that SLNB identified occult nodal disease in 33% of Merkel cell carcinoma patients. The recurrence rate for sentinel node-positive patients was 65% compared with 39% for sentinel node-negative patients.[36] Warner et al, in a smaller study, did not see a benefit of SLNB in Merkel cell carcinoma. They retrospectively looked at 11 patients treated at their institution who underwent SLNB. Only 3 had a positive SLNB and, despite receiving adjuvant radiation, 2 of them developed recurrent regional nodal disease. Of the 8 patients with negative sentinel nodes, 5 had recurrent disease. They concluded that SLNB may not be an accurate predictor of locoregional recurrence.[37] This experience is so inconsistent with the rest of the available literature,[38] as well as our own clinical experience, that we continue to advocate routine use of SLNB for all cases of clinically node-negative Merkel cell carcinoma, in the absence of clear contraindications to general anesthesia. Nonetheless, substantial questions remain about the optimal management of both node-negative and node-positive Merkel cell carcinoma.[39]

Squamous cell and basal cell carcinoma

Basal cell carcinoma has an exceedingly low rate of metastatic spread, hence there is no role at present for SLNB in this form of skin cancer. Squamous cell carcinoma of the skin, on the other hand, has a higher but still small risk of nodal spread. As SLNB has become more accepted for other cutaneous malignancies, some have sought to define a cohort of high-risk patients with squamous cell carcinoma who would benefit from SLNB. As with Merkel cell carcinoma, no prospective evaluations of SLNB have been conducted in squamous cell carcinoma of the skin. Reports to date of SLNB in cutaneous squamous cell carcinoma have involved small and highly selected groups of patients, and none of them have had enough statistical power to elucidate high-risk factors that would justify routine use of SLNB. Renzi et al did a literature review on the use of SLNB for cutaneous squamous cell carcinoma.[40] They identified a total of 83 patients. The rate of positive sentinel nodes in the literature surveyed was between 12.5% and 44%. In the authors' own institution, however, they had a positive rate of only 4.5% (1/22 patients). Their aggregated data review indicated that a positive sentinel node was found in no patients with tumors ≤2 cm, in contrast to 15.8% of patients with tumors 2.1 to 3 cm and 30.4% of patients with tumors >3 cm. Risk factors for nodal metastasis included large size, local recurrence, poorly differentiated histology, perineural invasion, depth >4 mm, immunosuppression, squamous cell carcinoma arising in chronically inflamed skin, or penetration of tumor into the reticular dermis or deeper. A more recent series also found that size >2 cm identified a subset of cutaneous squamous cell carcinoma patients with a high risk of nodal involvement.[41] The incredible degree of selection inherent in decision-making about SLNB is evident in this report: despite the many thousands of cutaneous squamous cell carcinomas diagnosed in this country every year, the authors identified only 116 patients in the literature with lesions >2 cm and not fixed to the underlying fascia, muscle, or bone (T2 in the AJCC staging system for non-melanoma skin cancer) who had undergone SLNB, with 13 cases (11.2%) having a positive sentinel node. At present, until improved selection criteria for cutaneous squamous cell carcinoma patients can be defined, we do not perform SLNB for any patients with this tumor type, regardless of tumor size.

Other forms of skin cancer for which sentinel node biopsy should be considered

Cutaneous adnexal malignancies are a decidedly uncommon group of malignancies, arising from hair follicles, sebaceous glands, and/or eccrine or apocrine sweat glands within the skin. These multiple histologic subtypes have varied clinical behavior, but tumors can be broadly subdivided by the adnexal structure of their origin: apocrine, eccrine, sebaceous, and pilar groups. Within the eccrine group, in particular, multiple histologic subtypes have been classified, the most common being microcystic adnexal carcinoma, porocarcinoma, and hidradenocarcinoma. Of all these cutaneous adnexal malignancies, eccrine carcinomas appear to have the highest rate of regional lymph node metastasis, and we and others have advocated SLNB for all or some patients in this category.[42,43] How-

ever, there is only anecdotal evidence to support this position. Dermatofibrosarcoma protuberans (DFSP) is an uncommon low-grade sarcoma of fibroblast origin.[44] Lymphatic spread of this tumor type is exceedingly rare, and SLNB has no role in the treatment of DFSP or other cutaneous sarcomas.

Conclusion

The role of SLNB in the management of intermediate and thick melanoma of the skin is now well defined, thanks to 2 large prospective trials—MSLT-1 and the Sunbelt Melanoma Trial. We advocate its routine use for otherwise healthy patients with clinically node-negative melanomas ≥0.76 mm in thickness, as well as for patients with Merkel cell carcinoma. On the other hand, we do not recommend or utilize SLNB for cutaneous squamous cell carcinoma, basal cell carcinoma, or sarcomas. Rare neoplasms in which we have found SLNB useful include atypical Spitzoid tumors in children and young adults and eccrine carcinomas of the skin.

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