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Surgery and Sentinel Lymph Node Biopsy

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Abstract

In patients with melanoma, surgery is pivotal not only for the primary tumor but also for regional and often distant metastases. The minimally invasive technique of sentinel node biopsy has become standard for detection of occult regional node metastasis in patients with intermediate-thickness primary melanoma; in these patients it has a central role in determining prognosis and a significant impact on survival when biopsy results are positive. Its role in thin melanoma remains under evaluation. The regional tumor-draining sentinel node is also a useful model for studies of melanoma-induced immunosuppression. Although completion lymphadenectomy remains the standard of care for patients with sentinel node metastasis, results of ongoing phase III trials will indicate whether sentinel node biopsy without further lymph node surgery is adequate therapy for certain patients with minimal regional node disease.

Although this issue of *Seminars in Oncology* outlines many exciting nonsurgical developments against melanoma, surgery remains the mainstay of treatment – particularly now that surgical techniques have become less morbid for all stages of disease. At the primary site, margins of excision have been narrowed without sacrificing survival or local control. At the regional lymph nodes, sentinel lymph node biopsy can identify occult metastasis without the complications of elective standard lymphadenectomy. At distant sites, metastasectomy can significantly prolong the survival of carefully selected patients. This review considers the surgical treatment of melanoma, with a focus on sentinel node technology.

Wide Excision of Primary Cutaneous Melanoma

As early as the mid-19th century, British surgeon William Norris recognized the importance of treatment margins in primary melanoma. He recommended surgery to “not only remove the disease, but cut away some of the healthy parts. I would, after excising the part, touch the wound with caustic so as not to leave an atom of the disease, if possible, and occasionally apply the same remedy to the skin in the vicinity.”¹ Although pathologic studies have identified atypical melanocytes at a distance of 5 cm from the primary tumor,^{2–4} margins of 3 to 5 cm were often accompanied by fairly significant morbidity. As described below, subsequent clinical trials have generally supported the efficacy of narrower excisions (Table 1).^{5–9}

A prospective randomized study organized by the World Health Organization Melanoma Program examined 1-cm versus 3-cm margins for 612 patients with primary melanomas $\leq$ 2 mm in thickness.⁵ There was no advantage with the wider margin. Similarly, trials from the French Group for Research on Malignant Melanoma and the Swedish Melanoma Trial Group

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found no significant difference in survival or local recurrence between 2-cm and 5-cm margins for melanomas ≤ 2 mm thick.^{8,9} The Intergroup Melanoma Surgical Trial compared 2-cm and 4-cm margins in 468 patients with intermediate thickness (1–4 mm) melanomas of the proximal extremity or trunk.^{6,10} Again, there was no increase in local recurrence or decrease in survival with the narrower margin.

In a more recent randomized trial, 900 patients in the United Kingdom underwent excision of ≥ 2 -mm melanomas, with margins of 1 cm or 3 cm.⁷ Narrower margins were associated with an increase in locoregional recurrences (primarily nodal disease) and a trend toward decreased survival. However, there was no difference in local or intransit recurrence, and the higher rate of nodal disease might have reflected this trial's exclusion of sentinel node biopsy. Another randomized study of patients with > 2 -mm primary melanomas did not demonstrate any outcome difference with 2-cm versus 4-cm margins of excision.¹¹

As confirmed in a meta-analysis of several randomized trials (Figure 1),¹² a 2-cm margin of excision is safe and effective for intermediate-thickness (1–4 mm) melanoma, although a 1-cm margin is acceptable in anatomically restricted areas such as the face. There is no evidence-based optimal margin for primary melanomas > 4 mm. A 2-cm margin is recommended; wider margins may be considered if easily obtained. A 1-cm margin is appropriate for primary melanomas < 1 mm. Two clinical situations require special attention to margins: lentigo maligna melanoma and desmoplastic melanoma. The former is relatively common in elderly patients with severely sun-damaged skin. Because its histologic extension may exceed its clinically evident borders, a series of punch biopsies may be warranted to evaluate the adequacy of proposed margins, especially before complex reconstructive procedures. Desmoplastic melanoma may also extend for several centimeters beyond the usual 2-cm margin; its increased risk of local recurrence may merit wider margins.¹³ However, desmoplastic lesions are often on the head or neck, where very wide margins are not practical. The North Central Cancer Treatment Group is conducting a randomized controlled trial of adjuvant radiation for some patients with desmoplastic melanoma.

Management of the Regional Lymph Nodes

Evolution of Sentinel Node Biopsy

In the late 1800s, Herbert Snow initiated a surgical controversy that would continue for over a century, by recommending elective removal of clinically normal regional lymph nodes in patients with cutaneous melanoma.¹ He believed that early removal of “infected” lymph nodes would prevent subsequent metastasis to distant sites and therefore improve patient outcomes. However, most patients with clinically localized primary melanoma do not have nodal involvement and therefore cannot benefit from nodal resection. Since complete lymph node dissection is a substantial operation and entails the risk of significant morbidity, its universal application for all melanoma patients was quite controversial. Eventually the Intergroup Melanoma Surgical Trial demonstrated evidence of a survival benefit in several subgroups, including patients with extremity melanoma, those with non-ulcerated melanoma, and those 60 years old or younger.¹⁴ However, the survival difference for the overall group comparison did not reach statistical significance ($p=0.12$).

Selective biopsy of high-risk regional nodes can eliminate blind use of complete lymphadenectomy – if the biopsy technique accurately identifies the most likely nodal targets of metastasis, the so-called sentinel nodes. The idea of tracking lymphatic drainage from a primary anatomic site had been percolating since its introduction by Virchow in the 1800s.¹⁵ In cancer, Gould et al¹⁶ in 1960 and Cabanas¹⁷ in 1977 described “sentinel” lymph nodes that drained the testicle and penis, respectively, and were the most likely to harbor metastatic disease. However, these nodes were defined by fixed anatomic standards that did not

accommodate dynamic variations in lymphatic drainage. The sentinel node concept based on functional assessment of lymphatic pathways began to realize its clinical potential about 20 years ago, with the development of cutaneous lymphoscintigraphy to identify the lymphatic basins receiving drainage from primary melanomas.

In 1977, Holmes et al¹⁸ proposed preoperative lymphoscintigraphy to guide the rational treatment of regional lymph nodes. They subsequently reported successful use of lymphoscintigraphy to identify nodal basins draining primary melanomas in 32 patients.¹⁹ As the technology improved, lymphoscintigrams often revealed one or more initial nodal targets within a drainage basin. These targets were functionally defined as sentinel nodes (SNs). If the SN is the first regional node to receive lymph from a primary tumor, then it would also be the first site of any tumor cells metastasizing via lymphatic routes. If so, then biopsy and analysis of the SN might be used to determine the tumor status of the entire nodal drainage basin. Intraoperative lymphatic mapping of the SN was initially tested by using vital blue dyes to map lymphatic channels in a feline model.²⁰ In 1985, the first clinical trials of intraoperative lymphatic mapping and sentinel node biopsy (SNB) were begun at the John Wayne Cancer Clinic. At the time of surgery, blue dye was injected at the primary site, and an incision made over the draining basin. Skin flaps were then raised toward the primary site until a blue channel was identified, which was then traced to the sentinel node. The completeness of the procedure was determined by exploration several centimeters around the initial blue node. In 1990, the first report of SNB was presented by Morton's group²¹ at the Society of Surgical Oncology. In this study, 223 patients with cutaneous melanoma underwent 237 dye-directed mapping procedures; at least one SN was identified in 194 procedures (82%). All patients underwent complete lymphadenectomy after SNB: of the 40 (21%) specimens containing tumor cells, all but two were associated with tumor-positive SNs. Although an initially skeptical response to this report delayed its publication until 1992,²² SNB was subsequently adopted by many investigators, who confirmed its accuracy and low morbidity.

Initial investigations of SNB used preoperative lymphoscintigraphy to identify the nodal drainage basin, but radioactive tracers were not used for intraoperative identification of SNs within the basin. This changed with the advent of handheld intraoperative gamma probes. Use of a probe for intraoperative mapping of the SN was described in an animal model by Alex et al,²³ and its clinical use was reported by Essner et al²⁴ at the Society of Surgical Oncology in 1994. Several radiotracers have been evaluated and are now used clinically,^{25,26} alone or in conjunction with a blue dye. In fact, dual-agent mapping (dye plus radiotracer) seems to produce the best results. The SN identification rate is approximately 82–87% for dye-directed mapping (although this increases with experience²⁷), as compared with 99% for dual-agent mapping. Use of the probe not only improves the identification of additional SNs within the drainage basin but also eliminates the need for dissection of subcutaneous flaps in the direction of the primary site.

SNB Selection Criteria

Most patients with clinically localized cutaneous melanoma are candidates for SNB. The value of SNB depends on the likelihood of nodal metastasis, which in turn can be estimated by a nomogram that considers the primary tumor's Breslow thickness, Clark level and ulceration, and the patient's age (Figure 2).²⁸ Reported rates of SN metastasis are 12–19.7% for 1–2 mm primary melanomas, 28–33.2% for 2–4 mm melanoma,^{29,30} and 28–44% for melanomas > 4 mm. As indicated by the multivariate analysis in Table 2,²⁹ almost all patients with lesions at least 1 mm in thickness have a sufficiently high risk of nodal metastasis to justify SNB. Gershenwald and colleagues³¹ noted that patients with thick (>4 mm) melanoma also appear to be good candidates for SNB. In their study of 126 patients with thick primary melanomas,

SN status and ulceration were the only independent prognostic factors in multivariate survival analysis. Patients with tumor-negative SNs had an 86.7% 3-year survival (Figure 3).

SNB for thin melanoma is somewhat more controversial. Ranieri³² demonstrated prognostic value for determination of SN status in patients with thin melanoma, but routine use of SNB for all patients with thin melanoma would not be cost-effective.³³ Clinicopathologic factors that might increase the risk of nodal metastasis from a thin primary melanoma include Breslow thickness > 0.75 mm, Clark's level IV, ulceration, young patient age, mitotic rate greater than zero, absence of tumor-infiltrating lymphocytes, male sex and primary tumor regression (Table 3).^{30,34–55} Interestingly, however, the rate of clinical nodal recurrence may be higher than the rate of positive SNs among patients with melanomas < 0.76 mm (2.3% versus 0.94%, respectively, based on mean of reported studies), and among those with primary tumors between 0.76 and 1.00 mm (8.6% versus 5.5%, respectively).^{30, 47–50} This unexpected finding suggests that the selection criteria for SNB need refinement and/or current pathologic techniques are not adequately sensitive. In either case, a better means of risk determination is needed to identify patients who should undergo SNB for a thin melanoma.

In addition to thickness, age is an important determinant of the risk of nodal metastasis. Paradoxically, although increasing age is associated with worse overall survival, it is also associated with less nodal metastasis. This relationship appears to be a continuous variable with different studies setting cut points at 45, 50 or 60 years.^{29,50,56} There is a relationship between age and lymphatic function as measured by radiotracer uptake in SNs; patients older than 50 years have significantly lower counts in the hottest SN.⁵⁷ It is possible that an age-related decrease in lymphatic function decreases the potential for nodal disease but increases the risk of systemic metastasis.

Finally, histologic subtype may play a role in determining the risk of nodal metastasis, particularly with regard to desmoplastic melanoma (DM). Studies of SN positivity in desmoplastic melanoma have shown conflicting rates of nodal metastasis. Some have demonstrated rates equivalent to those of standard melanoma⁵⁸; others reported almost no nodal involvement in DM.⁵⁹ These conflicting findings may reflect pathologic classification of DM. Recently “pure” and “mixed” types of DM have been described.^{60,61} Pure DM is characterized by prominent desmoplasia throughout the lesion and the absence of another histologic subtype. The rate of SN involvement in pure DM appears to be quite low.

SNB Technique

SNB for clinically localized melanoma is an outpatient procedure. It should be preceded by preoperative lymphoscintigraphy to identify the regional drainage basin(s) and the approximate site of SNs within that basin.⁶² Dynamic lymphoscintigraphy can distinguish true SNs, which receive direct drainage from the primary tumor site, from second-echelon non-SNs, which may be near SNs but do not receive direct drainage from the primary tumor. Preoperative lymphoscintigraphy can also identify ectopic nodes in popliteal and epitrochlear basins of patients with distal extremity lesions, in the triangular intermuscular space of patients with lesions on the back and flank, or in intercostal locations of patients with lesions on the abdomen and chest.^{26,63,64} These sites contain SNs in approximately 5–10% of cases.

After SN sites have been marked on the skin by the nuclear medicine physician, the patient is taken to the operating room where blue dye is injected intradermally at the primary site. Patent V and isosulfan blue are both effective²⁰; methylene blue is less effective in highlighting lymph channels and SNs and has been associated with significant soft tissue necrosis in some cases.^{20,65}

As mentioned earlier, dual-agent mapping with dye and radiotracer is optimal: the probe facilitates identification of blue-stained SNs and it may identify further SNs that do not stain blue. However, there is no firm consensus on the level of radioactivity that corresponds to a sentinel versus nonsentinel node. Some investigators define probe-identified SNs by a radioactivity level of greater than twice background radioactivity or as more than 10% of the hottest identified node. McMasters and colleagues⁶⁶ reviewed data derived from the Sunbelt Melanoma Trial: resection of all blue-stained nodes and all nodes with >10% of the hottest node's radioactivity was associated with a estimated false-negative rate of 0.4% (Table 4). However, it is often very difficult to determine a node's true level of radioactivity until it has been removed; ex-vivo counts may be 2 or 3 times higher than in-vivo counts. A surgeon's experience with probe-directed mapping becomes a critical determinant of the number of resected nodes. In addition, nodes which are replaced by tumor may fail to take up mapping agents (dye or radiotracer). As a result, any clinically suspicious nodes found during lymphatic mapping should be removed. Complete node dissection may be recommended when an SN cannot be identified.

Excised SNs are processed for analysis as permanent rather than frozen sections. Analysis of frozen sections has a high rate of false-negative results; in addition, some diagnostic material is lost during frozen section processing. In breast cancer, touch prep analysis of SN specimens appears to be fairly accurate in selected settings.^{67–69} Data are limited in melanoma,⁷⁰ but a small study by Shidham et al⁷¹ reported good sensitivity and specificity for imprint cytology and rapid immunohistochemical staining. However, the issue may be moot because complete lymphadenectomy is usually undertaken as a separate procedure, after results of fixed-section analysis are available and after the patient has been informed. As discussed below, most patients with tumor-positive SNs have no further regional node involvement, and completion dissection may not prove to be necessary in all cases.

The SN procedure generally entails very little morbidity. Risks include wound separation (0.2–1.2%), seroma/hematoma (2.3–5.5%), wound infection (1.1–4.6%), and lymphedema (0.6–0.7%).^{72,73} Severe allergic reactions to blue dye have been reported, but these appear to be more common for lymphatic mapping of primary breast cancers, and have not been seen in large multicenter studies of melanoma. Reports of an SNB-related increase in intransit metastasis^{74,75} are not supported by results of larger retrospective studies.^{76–80} Recently published data from a prospective randomized trial confirm no increase in intransit metastasis with SN mapping, putting the question to rest (Figure 4).⁸¹

Multicenter Selective Lymphadenectomy Trial of SNB

The first Multicenter Selective Lymphadenectomy Trial (MSLT-I)^{27,72,81} included patients with clinically localized melanoma >1 mm or > Clark IV who were less than 10 weeks from their initial melanoma biopsy. Patients were randomized to either wide local excision alone (WEO) alone (40%) or to WEO with SNB (LM/SNB) (60%) and complete nodal dissection if the SN was involved. The trial enrolled 2001 patients between January 1994 and March 2002 at centers in North America, Australia, and Europe. There was good compliance with the protocol treatment assignments with small and balanced numbers of patients receiving unassigned treatments. Of those assigned to WEO, 5.0% had LM/SNB and of those assigned to LM/SNB 4.8% had WEO.

After a planned interim analysis, the Data Safety Monitoring Board recommended release of the study results, even though the two treatment arms showed no difference in the primary endpoint (overall survival). This recommendation was based on highly significant differences in disease-free survival (78.3% in the LM/SNB arm versus 73.1% in the WEO arm; hazard ratio 0.74, 95% CI 0.59–0.93). In addition, although the unexpectedly low number of metastases indicated insufficient power to detect a significant difference in overall survival,

data showed a significant melanoma-specific survival benefit for SNB among the subgroup of patients with nodal metastases (Figure 5; hazard ratio 0.51, 95% CI 0.32–0.81).⁸¹ Obviously patients with nodal metastases could not be identified at the time of randomization, but this subgroup comparison was validated by the comparable distribution of prognostic variables and similar rates of nodal positivity between those with SN metastasis and those who developed clinical evidence of nodal recurrence during observation.

Although MSLT-I data confirm SNB as standard of care for intermediate-thickness melanoma, they do not indicate whether completion lymphadenectomy is always necessary when the SNB specimen contains evidence of tumor. The current standard of care is removal of the remaining nodes from the basin containing an involved SN, but only about one in five such basins will yield additional involved nodes. Studies suggest that the risk of nonsentinel metastasis in a patient with a tumor-positive SN depends on the thickness of the primary melanoma, the amount of melanoma in the SN (measured by a number of methods), and the immune status of the SN.^{82–86} Another uncertainty is the clinical impact of removing tumor-involved nonsentinel nodes in a patient population that has a high risk of occult distant metastasis. The second MSLT (MSLT-II) addresses these issues by randomizing patients with tumor-positive SNs to immediate completion lymphadenectomy or to observation. Patients in the observation arm undergo periodic nodal ultrasonography. The trial is ongoing at sites in North America, Australia and Europe.

Ongoing SNB Research

Researchers are developing new radiocolloid agents for lymphatic mapping. One of these, [99mTc]diethylenetriamine pentaacetic acid (DTPA)-mannosyl dextran (Lymphoseek, Neoprobe Corp., Dublin, OH), is a radiopharmaceutical which binds to mannose receptors on antigen-presenting cells of lymph nodes.⁸⁷ Preclinical studies suggest specific binding to nodes and relatively rapid clearance from the primary injection site. It is currently being evaluated in clinical trials. Another mapping agent under investigation is carbon dye. Unlike blue dyes and radiotracers, which eventually move through the SN to nodes further along the lymphatic chain, carbon dye is relatively inert; it tends to remain within the SN – and it tends to localize within a particular portion of this node (Figure 6).³⁰ These characteristics suggest that carbon might not only confirm a node as sentinel but also indicate which areas within the SN are most likely to harbor tumor cells. Preclinical and clinical studies of lymphatic mapping with carbon dye have confirmed the presence of carbon within SNs and its co-localization with tumor foci in SNs.³⁰ Further studies will determine if the use of carbon dye as an adjunctive mapping agent can help decrease false-negative results of SNB by facilitating pathological evaluation.

Another potential refinement to the pathologic evaluation of SN is the incorporation of RT-PCR and molecular staging to detect submicroscopic evidence of melanoma. In the multicenter Sunbelt Melanoma Trial, a portion of each SN was analyzed by PCR assay for the presence of tyrosinase, MART-1, MAGE-3 and gp100 mRNA.⁸⁸ Samples that were positive for tyrosinase and at least one other marker were considered positive. Although PCR analysis significantly increased the number of SNs with evidence of tumor, it did not impact disease-free survival or overall survival. However, melanogenesis antigens such as tyrosinase are not specific for melanoma; they can also be expressed in benign nodal nevus cells. Subsequent studies have evaluated marker panels that are more specific for melanoma. Also, this study used frozen portions of the SN, sacrificing tissue from pathologic analysis; subsequent introduction of technology for RT-PCR analysis of paraffin-embedded nodes⁸⁹ has allowed complete standard pathologic evaluation prior to performing molecular assays.

Takeuchi et al⁸⁹ used multimarker RT-PCR to examine SNs from 215 patients whose SN analyses were negative for tumor by standard pathology. The markers examined were MART-1

(antigen recognized by T cells-1), MAGE-A3 (melanoma antigen gene-A3 family), GalNAc-T (β 1–4-N-acetylgalactosaminyl-transferase), and Pax3 (paired-box homeotic gene transcription factor 3). These markers are from non-overlapping biologic pathways and are not present in normal melanocytes. As shown in Figure 7,⁸⁹ marker expression had a marked impact on disease-free and overall survival; in addition, prognosis was inversely correlated with the number of positive markers. This multimarker RT-PCR assay is being prospectively evaluated as a clinical decision-making tool in MSLT-II.

Perhaps the most challenging area of SNB research is the immunology of the SN and its microenvironment. The SN is emerging as a potential site to study melanoma-induced immunosuppression.⁹⁰ In theory, interleukin-10, cyclooxygenase (COX-2), TGF- β and other immunosuppressive factors produced by a primary melanoma^{91–94} will have their most profound effects in the closest immune organ, in this case the regional lymph node. Early studies suggested that lymph nodes closest to the primary tumor site were downregulated as evidenced by lower density, frequency and dendrite formation of antigen-presenting cells.^{94, 95} However, after lymphatic mapping showed that the closest regional lymph node is not always the direct target of lymphatic drainage from a primary tumor, investigators started to compare immune parameters of sentinel and nonsentinel nodes. They found that SNs have fewer high-endothelial venules (HEV) as demonstrated by CD105 staining.⁹⁶ These vessels are important for trafficking of lymphocytes to the node for interaction with antigen-presenting cells. In addition, decreases in dendritic cell frequency, density and dendrite formation seen in earlier anatomic studies were confirmed in comparisons of SN and non-SN.⁹⁷ These decreases in paracortical dendritic cells have been confirmed by staining for S100, CD1a, MHC class II, CD40, CD80, CD86, CD207 and DC-LAMP. In addition, DC meshworks (visualized by fascin staining), which are potentially important for effector cell-antigen-presenting cell interactions, are markedly diminished in SNs relative to non-SNs. These immune changes appear to affect the likelihood of non-SN metastases.⁹⁷ RT-PCR analysis of SNs has also demonstrated relative increases in IL-10 and IFN- γ , and these changes correlated with changes in the immunosuppressive enzyme indoleamine 2,3-deoxygenase (IDO).⁹³ Taken together, these findings suggest not only the mechanisms by which melanoma evades immune recognition, but also potential methods to counteract these effects for clinical benefit.

Resection of Distant Metastatic Melanoma

Surgery is not often considered when a solid tumor metastasizes to distant sites. However, the immunogenic/immunosuppressive nature of melanoma, its pattern of metastasis, and its poor response to nonsurgical interventions make surgery a reasonable consideration in properly selected patients in stage IV melanoma.^{98–100} Retrospective series have demonstrated long-term survival in patients with melanoma metastatic to the lung,^{101,102} liver,¹⁰³ adrenal glands,¹⁰⁴ gastrointestinal tract,¹⁰⁵ or soft tissue sites. A recent international phase III trial evaluated adjuvant vaccine immunotherapy in patients with resected stage IV disease.¹⁰⁶ Although the trial did not demonstrate significant survival differences between treatment arms, overall 5-year survival rate reached about 40%. This impressive result, which probably reflects patient selection and possibly nonspecific immune stimulation in the placebo arm, compares very favorably with the reported long-term survival rates of 5–15% for systemic chemotherapy in stage IV disease.^{107,108}

Conclusions

Surgical treatment at the site of primary tumors has become less morbid without loss of efficacy through the use of narrower excision margins. Treatment of regional nodal disease has also become less morbid through the use of SNB. This technique is generally considered the standard treatment for clinically localized, intermediate thickness melanoma. It has become a

standard procedure for patients with breast cancer, eliminating unnecessary axillary lymph node dissections.¹⁰⁹ Groups around the world have also demonstrated the effectiveness of the concept in colorectal, thyroid, lung, stomach, vulvar, prostate, penile, uterine, squamous cell and Merkel cell carcinomas.^{110–112} The International Sentinel Node Society recently held its 5th Biennial Congress where over 180 abstracts were presented regarding sentinel node research in a wide array of tumor types.

However, although the SN concept is simple, its implementation requires expertise in multiple disciplines. Both the SN identification rate and false-negative rate are significantly influenced by the surgeon's experience.^{22,27} In MSLT-I, the rate of in-basin nodal recurrence (false-negative) at each center was 10.3% for the first 25 patients versus 5.2% for subsequent patients (Figure 8).⁷² Since all centers were required to accurately perform 30 SN procedures prior to enrolling patients in the trial, this suggests a fairly long learning curve of about 50 cases.

As SNB becomes standard practice for clinically localized melanoma, long-term studies will further evaluate the clinical impact of SN micrometastases, particularly those identified by molecular techniques. These studies will be facilitated by the use of paraffin-embedded specimens; archived specimens can be used to examine the prognostic importance of a positive molecular test, without the loss of diagnostic material. In addition, the SN will continue to serve as a model for melanoma-induced immunosuppression.

Surgical resection of distant metastasis has been associated with very favorable outcomes in both single-institution and multicenter studies; 5-year survival rate is about 40%. The use of surgery to treat distant metastases appears to have merit in properly selected patients.

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Figure 1A

Figure 1B

Figure 1.

A: Comparison of mortality at 8 to 11 years between wide and narrower excision in the 3 follow-up trials of melanoma of the extremities. **B:** Comparison of local recurrence at 8 to 10 years between wide and narrower excision in the 3 follow-up trials of patients with melanoma of the extremities. Reprinted with permission from Haigh et al.¹²

Figure 2.

Nomogram to predict positive sentinel lymph nodes. How to use the nomogram: The patient's values on each axis are located, and a line is drawn upward to determine how many points the patient receives for each variable value. The points are summed; that number is located on the "total points" axis. A line is drawn downward to then determine the predicted probability of sentinel node positivity. Reprinted with permission from Wong et al.²⁸

Figure 3.

Kaplan-Meier survival for patients with thick (>4 mm) melanoma by SN status. Disease-free and overall survivals were significantly better for patients with a negative SN biopsy ($P<.03$ and $P=.006$, respectively). Reprinted with permission from Gershenwald et al.³¹

Figure 4.

Time to local or intransit metastasis according to the type of treatment (wide excision alone or wide excision plus SNB) shows no significant difference. Reprinted with permission from Morton et al.⁸¹

Figure 5.

Melanoma-specific survival among patients with nodal metastases. Subgroup 1 comprised patients with a tumor-positive sentinel node; subgroup 2, the patients in subgroup 1 plus those in subgroup 4 with a nodal recurrence after a negative result on biopsy; subgroup 3, those with nodal recurrence during observation; and subgroup 4, those with nodal recurrence after a negative result on biopsy. Reprinted with permission from Morton et al.⁸¹

Figure 6.

Compartmentalization of intranodal lymph flow as detected in the operating room by radiopharmaceutical, blue dye, and carbon dye (left) and confirmed in the pathology department by carbon dye (right). Reprinted with permission from Morton et al.³⁰

Figure 7.

(**A**) Kaplan-Meier curve analysis of overall survival (OS) according to multiple marker quantitative realtime reverse transcriptase polymerase chain reaction and histopathology status in 215 patients; (**B**) Kaplan-Meier curve analysis of OS according to number of molecular markers in 162 SN histopathology-negative patients. H&E, hematoxylin and eosin; IHC, immunohistochemistry. Reprinted with permission from Takeuchi et al.⁸⁹

Figure 8. Relationship between nodal recurrence after a tumor-negative lymphatic mapping and sentinel node biopsy procedure and volume of cases at 10 MSLT-1 centers. Minimum duration of follow-up was 36 months. Reprinted with permission from Morton et al.⁷²

Table 1

Randomized excision margin trials

Study	N	Primary Thickness	Arms (cm)	Recurrence		Hazard Ratio for Survival (95% confidence interval)	
				Local	Nodal	Disease-Free	Overall
Veronesi et al ⁵	612	≤ 2 mm	1 vs. 3	NS		NS	NS
Cohn-Cedemark et al ⁸	989	≤ 2 mm	2 vs. 5	NS	NS	1.02 (0.80–1.30)	0.96 (0.75–1.24)
Khayat et al ⁹	337	≤ 2.1 mm	2 vs. 5	NS	NS	NS	NS
Balch et al ⁶	486	1–4 mm	2 vs. 4	NS			NS
Thomas et al ⁷	900	>2 mm	1 vs. 3	NS	NS	1.26 (1.00–1.59) *	1.21 (0.99–1.46)

* locoregional recurrence

Table 2

Multivariate analysis of prognostic factors for predicting sentinel node metastases (N = 1351). Reprinted with permission from Rousseau et al. ²⁹

Prognostic factor	OR	95% CI	P value
Tumor thickness	3.42	2.54–4.61	<.0001
Ulceration	2.21	1.57–3.13	<.0001
Age ≤ 50 y	1.81	1.31–2.51	.0003
Axial location	1.45	1.05–2.02	.026
Clark level IV/V	1.34	.94–1.92	.107
Male sex	1.09	.78–1.52	.629

OR, odds ratio; CI, confidence interval

Table 3

Previous studies of SN mapping or clinical recurrence in thin (<1.00 mm) melanoma

Study	<0.76	0.76–1.00	≤ 1.00	Factors
Sentinel node				
Bedrosian et al ^{35*}	1/40 (2.5%)	3/31 (9.7%)	4/71 (5.6%)	VGP, no other
Bleicher et al ³⁴	2/118 (1.7%)	6/154 (3.9%)	8/272 (2.9%)	Age, incomplete biopsy
Jacobs et al ⁴⁴	1/NR	1/NR	2/63 (3.2%)	MR, Br, gender
Kesmodel et al ⁴³	1/91 (1.1%)	8/90 (8.9%)	9/181 (5.0%)	Clark ≥ III
Lowe et al ⁴⁵	2/NR	1/NR	3/46 (6.5%)	ulceration, MR, VGP
Nahabedian et al ⁵¹	0/NR	2/NR	2/24 (8.3%)	None predictive
Oliveira Filho et al ⁴⁶	NR	NR	6/77 (7.8%)	None predictive
Puleo et al ⁴¹	NR	20/409 (4.9%)	NR	None predictive
Wong et al ³⁹	0/109	8/114 (7.0%)	8/223 (3.6%)	Age
Stitzenberg et al ³⁶	3/NR	3/NR	6/146 (4.1%)	
Hershko et al ³⁷	2/NR	3/NR	5/64 (7.8%)	
Morton et al ³⁰	NR	NR	34/465 (7.3%)	
Subtotal	3/325 (0.94%)	42/767 (5.5%)	83/1561 (5.3%)	
Clinical recurrence				
Morton et al ³⁰	NR	NR	238/1979 (12.0%)	TIL
Kalady et al ⁵⁰	NR	NR	38/1082 (3.5%)	male, <60, axial
Massi et al ^{52**}	8/174 (4.6%)	17/113 (15%)	25/287 (8.7%)	Median TTR 52mo
Karakousis et al ⁴⁹	21/684 (3.1%)	17/198 (8.6%)	38/882 (4.3%)	male, ALM or LMM
Corsetti et al ⁴⁸	0/NR	5/NR	5/68 (7.4%)	TTR 49.8mo
Schmid-Wendner et al ⁵³	37/2301 (1.6%)	NR	NR	2.8% total recur
McKinnon et al ⁵⁴	NR	NR	NR	male, regression
Woods et al ⁴⁷	5/400 (1.3%)	NR	NR	
Naruns et al ⁵⁵	28/649 (4.3%)	NR	NR	
Subtotal	99/4208 (2.35)	17/198 (8.6)	319/4011 (8.0%)	
TOTAL	102/4533 (2.3%)	59/965 (6.1%)	402/5572 (7.2%)	

VGP, vertical growth phase; MR, mitotic rate; Br, Breslow; NR, not reported; TTR, time to recurrence; TIL, tumor-infiltrating lymphocytes; ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma

* These patients also in Kesmodel et al,⁴³ not duplicated in total figures.

** up to 1.5 mm included, not included in total figures.

Table 4Impact of sentinel node definition on false-negative results. Reprinted with permission from McMasters et al.⁶⁶

Criteria for removal of SN	No. of false negatives/no. of basins with positive nodes	False-negative rate ^a
A. Only hottest node removed	40/288 ^b	13.9%
B. Hottest node and all obviously blue nodes removed ^{c,d}	19/285 ^e	6.7%
C. Hottest node and all blue nodes removed	6/285	2.1%
D. 1 st or 2 nd SN identified	5/288	1.7%
E. All blue nodes and all nodes >10% of hottest node	1/285	0.4%

^aThe actual false-negative rate can be determined only by long-term follow-up for recurrent nodal metastases in basins with negative SNs

^bAll results are statistically different from category A and reduce the risk of false-negative results (P<.02).

^cThis assumes that the faintly blue or obviously blue nodes would have been identified without the gamma probe, or that blue dye staining could be established prior to removing the node.

^dCases in which blue dye was not used have been excluded

^eCategory B is statistically different from categories C, D, and E (P<.01)