High Isotope Counts and Sentinel Node Positivity in Patients With Melanoma

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Background: Radioisotope mapping is an essential technical component of sentinel lymph node (SLN) biopsy, and most authors define success by an arbitrary threshold SLN-background ratio.

Hypothesis: Few studies have examined the degree to which the relative level of SLN counts correlates with the presence of metastasis. Having removed the SLN with the highest counts, there are no data suggesting how far the surgeon should persist in removing additional SLNs that contain much lower levels of isotope.

Methods: We performed 134 SLN biopsy procedures in 132 patients with melanoma. Successful isotope localization was defined using an SLN/“hottest” SLN ratio; we defined an SLN as any node containing counts at least 10% of that of the hottest SLN.

Results: Of 83 patients with more than 1 SLN site identified, 21 (25%) had SLNs that contained metastasis. In 17 (81%) of these cases, the SLN with the highest count contained tumor, but in 4 (19%) it was benign. Among these 4 patients, the counts of the hottest benign SLNs exceeded those of SLNs positive for metastasis on histological examination by a ratio of at least 10:1, and the counts of the positive SLNs were less than 4:1 of those of the background counts or the presence of blue dye failed to identify the positive SLN. No optimum ratio of SLN/SLN or SLN/background counts identified the positive SLN in all cases.

Conclusions: Although the SLN with the highest counts contained metastasis in 81% of patients with malignant melanoma and multiple SLNs, neither a relatively high isotope count nor the presence of blue dye consistently predicted SLN positivity. For maximum accuracy, SLN biopsy requires the removal of all nodes containing isotope regardless of the relative magnitude of counts and the concurrent use of blue dye to salvage those procedures in which isotope mapping fails.

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Cutaneous melanoma is becoming an ever more common disease. For many years, elective lymph node dissection was one of the most important controversies in the management of patients with malignant melanoma. The status of the regional lymph nodes is critical in staging patients with newly diagnosed melanoma because lymph node involvement is known to be the most important prognostic factor. Most patients with primary cutaneous malignant melanoma present without clinically enlarged lymph nodes. However, it has been estimated that approximately 15% of these patients harbor occult lymph node micrometastases, and accurate diagnostic identification of such lymph node metastases is important when selecting patients to receive adjuvant therapy or enroll in experimental protocols. In an attempt to solve this problem, location of the first-echelon lymph node by means of the sentinel node procedure has gained increasing acceptance over the past decade. Morton et al, who initially used vital blue dyes to identify the sentinel lymph node (SLN), introduced the concept in 1992. Subsequent investigators have shown that failure to identify the sentinel node is greatly reduced by using radiolabeled colloids in conjunction with a small handheld gamma probe. The presence or absence of metastases in the SLN has been demonstrated to accurately reflect the histological characteristics of the remainder of the nodal basin. Preoperative lymphoscintigraphy is valuable in showing drainage to multiple lymphatic basins because the SLN may not necessarily be the lymph node closest to the injection site.

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In light of these results, many medical centers have adopted a method in which blue dye and lymphoscintigraphy are used in combination. Successful SLN mapping by blue dye, defined as the identification of a blue node or a blue lymphatic vessel leading to a non-blue node, is straightforward and unambiguous. In contrast, there is no standard definition of isotope mapping success. Some authors use node counts alone to define the SLN, and others use 1 of 3 ratios: SLN/postexcision, SLN/blue node, or SLN/non-SLN. Although each method seems to work well, the derivation of the exact count levels or ratios defining the SLN has been largely empirical and arbitrary. Therefore, the aim of this prospective study was to evaluate whether high isotope counts predict metastasis in SLNs and to determine, among patients with more than 1 SLN found during surgical treatment, the patterns of SLN metastasis and whether there is indeed a threshold level of isotope counts that ensures the identification of all SLNs containing metastasis.

### Metastasis

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### Preoperative Lymphoscintigraphy

Preoperative cutaneous lymphoscintigraphy was performed either the evening before or the morning of the operation. Patients received 0.8 or 0.4 mCi (29.6-14.8 MBq), respectively, of doubly filtered technetium Tc 99m sulfur colloid. The colloid, in 0.5 mL of isotonic sodium chloride solution and divided into 4 equal portions, was injected intradermally around the circumference of the diagnostic excision scar or the primary melanoma. Immediately after the technetium Tc 99m sulfur colloid injections, dynamic acquisition (60 frames of 10 seconds; 256 × 256 matrix) was started. Static views were obtained at 5- to 10-minute intervals for up to 60 minutes postinjection. A single-headed gamma scintillation camera demonstrated dynamic and static images of the drainage patterns and the site of the regional SLN or SLNs.

### Intraoperative Lymphatic Mapping

The location of lymphatic channels and SLNs was confirmed using a handheld gamma probe (Navigator GPS; US Surgical, Norwalk, Conn) and marked on the skin with indelible ink. When 2 or more drainage patterns were identified for the primary melanoma, each was considered separately with respect to lymphatic mapping. Isotope counts were measured over the primary melanoma and along the lymphatic channels draining to the lymphatic basin. These counts were compared with a background measurement at a neutral site away from the primary melanoma and the lymphatic basins to avoid confusion with radioactivity emitted from these regions. Measurements were recorded over the hottest node in the lymphatic basin prior to skin incision. The skin was incised in such a way that the incision could be incorporated into a subsequent lymphadenectomy scar. The first SLN was identified, and isotope counts were measured before (in vivo) and after (ex vivo) its excision. The gamma probe was used to measure residual counts in the lymphatic basin and to identify any additional SLNs. After all SLNs were removed, the residual radioactivity in the lymphatic basin was measured (postexcision). The primary melanoma was then excised (if not previously done) using margins of 1 to 2 cm, depending on the depth of invasion and the site of the lesion. In cases where the primary melanoma and the SLN were in close proximity, the primary excision was performed first to facilitate detection of the SLN.
HISTOPATHOLOGICAL EXAMINATION OF SLN SPECIMENS

Each SLN was bisected from hilum to periphery. It was then fixed in 10% neutral buffered formalin, embedded in paraffin, and sectioned. It was processed for routine hematoxylin-eosin staining and for immunoperoxidase staining using an antibody to HMB-45 and melan-A protein. Both negative and positive control stains were run simultaneously with the specimens to confirm the sensitivity and specificity of the immunohistochemical method. The SLNs were level-sectioned for routine hematoxylin-eosin staining 3 times and HMB-45 and melan-A immunohistochemical analysis 2 times. Nonsentinel lymph nodes were studied in the same manner.

RESULTS

DISTRIBUTION OF MAPPED BASINS

One hundred thirty-two patients were referred for 134 lymphatic mapping and sentinel lymphadenectomy procedures, and 155 lymph node basins were mapped in 134 patients. Axillary, inguinal, and cervical nodal basins composed 52%, 28%, and 20% of the total basins evaluated, respectively. One hundred thirteen (84%) underwent lymphatic mapping of 1 regional nodal basin, and 21 patients (16%) underwent synchronous lymphatic mapping of 2 regional nodal basins. Basins were distributed equally between the left and right sides. At least 1 SLN was identified in all of the 155 basins mapped. The mean number of SLNs identified within a basin was 2.

HISTOLOGICAL STATUS OF SLNs

By histological analysis, an SLN positive for metastasis was identified in 31 (23%) of 132 patients. The status of SLNs stratified by patient characteristics is presented in the Table. Of the 31 patients who had a positive SLN, there were 8 women (26%) and 23 men (74%) with a mean age of 53 years (range, 22-79 years). Mean Breslow thickness was 3.4 mm (range, 0.7-11.88 mm). Primary locations were trunk in 18 patients (58%), extremity in 10 patients (32%), and head and neck in 3 patients (10%). Of these patients, 28 (90%) underwent therapeutic lymphadenectomy: 16 axillary, 9 inguinal, and 5 neck (2 patients underwent 2-site lymphadenectomy). The 3 patients who did not undergo therapeutic lymphadenectomy refused the operation. No further evidence of nodal disease was detected in 26 (87%) of 30 lymphadenectomy specimens. The Figure presents the clinical outcomes of all patients who underwent SLN dissection.

RECURRENCE AND PROGRESSION OF DISEASE

One of the 103 patients who had an SLN negative for metastasis had a recurrence 9 months later. Her primary tumor was an ulcerated 7.05-mm superficial spreading melanoma of the head. Two SLNs were identified in her neck, and both were negative for metastatic melanoma. She was seen 9 months after her original operation with a palpable mass near her previous excision site as well as palpable neck nodes. She underwent a re-excision and radical neck dissection. Pathological analysis revealed recurrent malignant melanoma with 1 of 16 SLNs positive for metastasis.

Of the 24 patients who underwent therapeutic lymphadenectomy and had no further evidence of nodal disease, 4 patients had progression of their disease; 3 patients had nodal recurrence at their therapeutic lymphadenectomy site (axillary, inguinal, and neck), and 1 patient who had a therapeutic axillary lymphadenectomy had lung metastasis 1 year later.

COMMENT

Malignant melanoma is the most rapidly increasing cancer in the United States, and experts estimate that up to 1 in 75 white Americans will develop malignant melanoma. When diagnosed early, it can be cured surgically in the majority of patients, but 20% will eventually develop distant metastases. It has long been recognized that involvement of the regional lymph nodes is the most important prognostic factor for patients with melanoma. Indeed, the presence of lymph node metastases decreases the 5-year survival of patients by approximately 40%, independent of other prognostic factors of the primary tumor.

The SLN biopsy has become widely accepted as a method of staging the regional lymph nodes in patients with melanoma. It can be performed on an outpatient basis at the same time as wide local excision of the primary melanoma. There is less morbidity than with an elective lymph node dissection, and the procedure is cost-effective. The advantage of SLN biopsy in patients with melanoma is that it spares 75% to 80% of patients the need for complete regional lymphadenectomy while identifying those patients at highest risk. The presence of an SLN positive for metastasis has been shown to be the single most important prognostic factor for recurrence and survival. Those patients with positive SLNs are appropri-
ate selected for therapeutic completion lymph node dissection and adjuvant therapy.

Despite increasing worldwide acceptance of the procedure and convincing validation of the SLN hypothesis, the optimum technique for SLN biopsy remains a matter of debate. An emerging international consensus supports the use of dye and isotope counts in combination, as do other large series from both academic and community settings. Although the identification of a blue-stained SLN is usually unequivocal, there are, to date, no standard criteria that define successful SLN identification by isotope count. Some authors report the absolute level of isotope counts in the SLN, with the definition of success ranging from 25 counts to as high as 2000. Because of wide variation in the absolute level of counts, most authors have chosen to use 1 of 3 count ratios to define the SLN: SLN/background, SLN/non-SLN, or SLN/hottest SLN. These conflicting definitions are the result of differences in the type, amount, and timing of radiopharmaceutical agents and the distance from the primary site to the draining lymphatic basin. Most investigators have used count ratios rather than absolute isotope counts to account for these variations in factors. In contrast, the intralymphatic kinetics of isosulfan blue dye are well established, and its definition of the SLN is universally accepted. When using isosulfan blue dye as the lymphatic mapping agent, the SLN is simply defined by the blue-stained afferent lymphatic channel leading from the primary melanoma to the blue-stained node. Thus, until the intralymphatic kinetics of the various radiopharmaceutical agents are established, these agents should serve as an adjunct to the blue dye.

There is, in fact, some scientific precedent for defining isotope count success. Nathanson et al have used a mouse model to determine that 2% to 10% of injected radiocolloid traverses the SLN and lodges in adjacent non-SLNs. Based on these results, McMasters et al devised their 10% rule and are the only investigators to date who have made a correlation between count ratios and the histopathological characteristics of the SLN. They demonstrated a reduction in the potential SLN false-negative rate from 13% (if only the hottest SLN was removed) to 5.8% (by following the 10% rule and removing all SLNs with isotope counts at least 10% of that of the hottest SLN). No other studies have validated this concept or given a convincing rationale for another definition of isotope mapping success.

In our current experience, we demonstrate that there is no single count ratio that reliably identifies SLNs positive for metastasis in all patients. Like McMasters et al, we used the SLN/hottest SLN 10% rule and defined an SLN as any node containing isotope counts of at least 10% of the hottest SLN. Among patients with SLNs positive for metastasis, the hottest SLN indeed proved positive in 81% of cases, but no single ratio of counts reliably identified the remaining 19% of SLN-positive patients whose hottest SLN was benign. Although most SLNs containing metastasis were identified by blue dye regardless of isotope count ratios, blue dye also failed to identify a substantial proportion (14%) of positive SLNs. Neither the presence of blue dye nor isotope ratios of any particular threshold level consistently identified the positive SLN in all patients.

In conclusion, SLN biopsy is a highly accurate test, if not a perfect one, that is performed within a biological system subject to variation. We would argue that the challenge for the surgeon is to maximize the accuracy of the procedure with a technique that can reliably encompass this biological variation. In our institution, all focally hot SLNs and all blue-stained nodes are removed. Isotope counting is an essential technical element of SLN mapping, and it complements blue dye, but there is no particular isotope count ratio that identifies the positive SLN in all cases. It is recommended that all blue-stained lymph nodes and all nodes that have 10% or higher of the ex vivo radioactive count of the hottest SLN should be harvested for optimal detection of nodal metastases.

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