Localization of Regional Lymph Nodes in Melanomas of the Head and Neck

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Objectives: To study the efficacy of gamma-probe radiolocalization of the first draining (sentinel) lymph node (SLN) in stage N0 melanoma of the head and neck and to evaluate its potential role in the staging and treatment of this disease.

Design: Gamma-probe radiolocalization, a new alternative to blue-dye lymphatic mapping, uses a scintillation (gamma) probe to identify radiolabeled SLNs. In a consecutive sample clinical trial, gamma-probe radiolocalization of the SLN is compared with lymphoscintigraphy and blue-dye mapping. Follow-ups ranged from 1.7 years to 4 years, with a mean follow-up of 2.5 years.

Setting: Tertiary and private care teaching hospital.

Patients: Between June 1993 and November 1995, 23 patients with stage N0 intermediate-thickness melanoma of the head and neck were enrolled in this volunteer sample.

Interventions: Twenty-four hours prior to surgery, a radioactive tracer was intradermally injected around the circumference of a primary melanoma. Twelve patients also had blue dye injected just prior to surgical resection. Using a handheld gamma probe, radiolabeled lymph nodes were identified and selectively removed with minimal dissection. In patients with nodes with histologic evidence of metastases, a regional lymphadenectomy was performed.

Main Outcome Measures: The successful identification of radiolabeled SLNs, the correlation of SLN radiolabeling to lymphoscintigraphy and blue-dye mapping, and the long-term development of regional metastases.

Results: Surgeons successfully resected the radiolabeled SLNs in 22 (96%) of 23 patients. The success rate of blue-dye lymphatic mapping was 8 (75%) of 12 patients and lymphoscintigraphy was 20 (91%) of 22 patients. One hundred percent of blue-stained lymph nodes were radiolabeled. The one patient in whom no SLN could be identified developed regional disease at 17 months.

Conclusions: Gamma-probe radiolocalization and resection of the radiolabeled SLN is a simple and reliable method of staging regional lymph nodes and determining the need for elective lymphadenectomy.


For more than 2 decades, the surgical management of regional lymph nodes with no clinical evidence of metastases (stage N0) has remained controversial. The debate centers on whether there is a subgroup of patients with melanoma in whom the incidence of micrometastases justifies elective lymph node dissection (ELND).

Proponents of ELND argue that early removal of all potential lymph node metastases reduces or eliminates a patient’s tumor burden and a source of future metastases. In addition, ELND allows the regional lymph node status to be staged and enables patients with proven lymph node metastases to enter adjuvant therapy trials earlier in their clinical course. Critics of ELND note that because the incidence of micrometastases in head and neck lymphadenectomy specimens is between 10% and 40%, approximately 60% to 90% of ELNDs and 70% of parotidectomies for patients with clinical stage N0 melanoma are performed unnecessarily on lymphatic beds without metastatic disease. In addition, the survival benefit of ELND has not been conclusively proved.

The decision to perform ELND is especially difficult in the head and neck region because the lymphatic drainage patterns are multiple and varied. Melanoma on the anterior part of the face, scalp, or ear may have lymphatic drainage to the intraparotid, preauricular, submental, and/or ipsilateral cervical nodes. The poste-
PATIENTS, MATERIALS, AND METHODS

This clinical trial was conducted in a tertiary care teaching hospital and a private practice setting in accordance with the Human Subject Protection Committee and the Radiation Safety Committee, University of Vermont, Burlington, and the respective committees of the participating institutions. Between June 1993 and November 1995, 23 patients (7 women and 16 men) with stage N0 intermediate-thickness invasive melanoma of the head and neck were enrolled in this volunteer study group. Pregnant patients were not eligible, and if clinically indicated, a pregnancy test was administered to rule out pregnancy. The range of ages was 22 to 89 years with a mean of 56 years. Preoperatively, the diagnosis of intermediate-thickness malignant melanoma was determined by biopsy (shave, 1 patient; incisional, 7 patients; punch, 5 patients; and small incisional, 7 patients) or wide resection (3 patients) of the primary melanoma. The distribution of patients according to tumor thickness was as follows: 0.76 mm to 1.50 mm, 11 patients and 1.51 mm to 4.00 mm, 12 patients. All patients who met the study criteria then underwent radionuclide localization on the morning of surgery.

The radioactive tracer was technetium Tc 99m sulfur colloid (CIS-US, Inc, Bedford, Mass). The tracer, 0.25 mL to 33.3 mL (mean, 15.91 mL) (0.25-0.90 mCi [mean, 0.43 mCi]), was injected intradermally around the circumference of the primary melanoma. Injection volumes ranged from 0.1 to 1.0 mL (mean, 0.5 mL). Between 20 and 120 minutes after receiving the radionuclide injections, planar gamma camera images were obtained in an attempt to identify a focal area of accumulation (a “hot” spot). A mark, corresponding to the imaged hot spot, was placed on the skin for comparison to the intraoperative GPRL of the SLN. Of the 23 patients, 12 also had an intradermal, peritumoral injection of blue dye (1% isosulfan blue, Ben Venue Labs, Bedford, Ohio) immediately before surgical resection.

Measurements of the accumulated radioactivity in the radiolabeled lymph nodes were made intraoperatively with a handheld gamma probe (C-Trak, Care Wise Medical Products, Morgan Hill, Calif). Counts were obtained during a 10-second interval. A focal area of radionuclide accumulation was readily discerned by listening to the audio signal of the gamma probe, which increased pitch as the emission level increased. The point of maximal emission identified the SLN. The significance of a given emission measurement was derived from the Poisson distribution, which relates the SD to the mean number of disintegrations according to the formula below:

$$SD = \sqrt{(N_e - N_f)/(N_e + N_f)}$$

where $$N_e$$ equals the counts of the hot spot or SLN and $$N_f$$ equals the mean counts of the adjacent tissue or the lymphatic bed after biopsy of the SLN. To achieve an emission measurement precision of 98%, the counts for a given hot spot or radiolabeled lymph node must be greater than background counts by 3 SDs. In practical terms, to qualify as a hot spot, a discrete area had to have at least 15 counts in 10 seconds and a ratio 3 times that of the background.14,16

After localization on the skin surface, a small incision was made directly over the radiolabeled SLN(s) and the dissection proceeded aided by the handheld gamma probe. Elevation of skin flaps was unnecessary. Most incisions were limited to the width necessary to allow entry of the gamma probe (diameter, 19 mm). After removal of the radiolabeled SLN(s), the remaining lymphatic bed was scanned to verify that all radioactive nodes had been removed (Figure 1 through Figure 3).

Radioactive SLNs were submitted separately for routine histopathologic evaluation using hematoxylin-eosin staining and immunohistological techniques with antibodies to S100 protein and HMB-45. If the final histopathologic interpretation of the radiolabeled lymph node(s) was negative for micrometastases, no further intervention was performed. If the radiolabeled lymph node(s) was positive for metastatic melanoma, then a complete regional node resection was performed within 5 days.

rior scalp region can drain to the occipital, retroauricular, or cervical nodes. In addition, the initial drainage pathways could involve multiple regions simultaneously requiring their complete resection.7,10 The potential for cosmetic and functional morbidity in patients without regional lymphatic micrometastases is significant.7-10

If a precise method of diagnosing micrometastatic disease was available, lymph node dissections could be based on the actual, not theoretical, presence of micrometastases. In addition, studies examining the survival benefit of lymphadenectomy could limit the analysis, perhaps more appropriately, to the subgroup of patients who actually have disease.

Recently, a new method for evaluating the regional lymphatic bed of a malignant melanoma was reported.11 Blue dye injected around the tumor travels through the lymph vessels and eventually stains the first draining lymph node (the sentinel lymph node [SLN]). Morton et al13 determined that if the SLN histologic results were negative for evidence of metastases, then there was less than 5% incidence of micrometastases in the remaining lymphatic basin. Several authors12,13 have confirmed that the histologic status of the SLN accurately predicts the occurrence of regional micrometastases and can therefore minimize the expense and morbidity of unnecessary ELND.

The blue-dye lymphatic mapping technique has several drawbacks.11-14 First, it is difficult to determine the precise location of the blue-stained nodes prior to skin incision resulting in unnecessary dissection; second, substantial experience is required to achieve a high success rate of localization; third, it is difficult to verify complete removal of all first draining lymph nodes; and fourth, the blue dye characteristically causes staining of local tissues and is cumbersome to use in the head and neck region.

To address these drawbacks we designed a preclinical model to test the technique of noninvasive gamma-probe radiolocalization (GPRL) of radiolabeled lymph nodes. Results of this animal study confirmed that GPRL accurately identified the SLN(s) stained with blue dye 100% of the time.17 A small pilot series10 in patients with
clinical stage N0 melanoma also established that the SLN was easily identified underneath the skin surface with the handheld gamma probe and removable through a small incision. Most recently, in a study of 121 patients with cutaneous stage N0 melanoma of the trunk and extremities, SLN localization was successful in 98% of patients.

Gamma-probe radiolocalization of the SLN(s) in melanoma of the head and neck can potentially elucidate each patient’s unique pattern of regional drainage, provide a cosmetically appealing and minimally invasive method of SLN biopsy, assist in the evaluation of the remaining lymphatic basin, and help determine whether a regional lymphadenectomy would be indicated.

Unlike melanoma of the trunk and extremities, the head and neck region is concentrated with many lymphatic drainage pathways and multiple potential recipient nodes. Under these conditions, the success of GPRL is unclear. In a prospective, consecutive series study, we compared GPRL of the SLN with intraoperative blue-dye lymphatic mapping and lymphoscintigraphy (gamma camera imaging).

**RESULTS**

Of the 23 patients with intermediate-stage N0 malignant melanoma, 22 (96%) had successful radiolocalization of the SLN. In 12 of the 23 patients, blue-dye lymphatic mapping was also performed. The SLN was successfully identified using this technique in only 8 (75%) of the 12 patients. Accurate localization of those nodes that stained blue was greatly enhanced by using the gamma probe. In every case, each blue-stained SLN was radiolabeled. Lymphoscintigraphy was performed in all but 1 of the 23 patients. Lymphoscintigraphy imaged a hot node (a focal area of accumulation) in 20 patients, for a success rate of 91%.

Of the 2 patients who did not have successful gamma camera imaging, one patient had successful localization of the SLN using GPRL, while the other patient failed to have an SLN identified by any modality (blue-dye lymphatic mapping, lymphoscintigraphy, or GPRL).

Of the 23 patients with melanoma, 3 patients (14%) had SLNs positive for metastatic melanoma. One patient had a lesion (3.81 mm) on the right cheek with SLN localization to the right midcervical region. The SLN was histologically positive for micrometastases, and the patient underwent a superficial parotidectomy and neck dissection of levels I through IV. Thirty-two nodes were evaluated in the specimen, and none had evidence of micrometastases. The second patient with an SLN positive for metastatic melanoma had a primary lesion (4.00 mm) of the left lateral periorbital area. Sentinel lymph nodes were identified in the left periauricular area and the left submandibular area. The SLN in the left submandibular area was positive for metastatic melanoma. The patient underwent a left parotidectomy and neck dissection of...
levels I through IV. Of 24 nodes, none were positive for micrometastases. The third patient had a primary lesion (2.53 mm) of the right, lower, anterior neck, the level 1V region. A hot supravclavicular node was readily identified with the gamma probe. After removal of this node through a 3.0-cm incision, examination of the remaining lymphatic bed revealed continued activity. Using the gamma probe to guide the dissection, a second node was identified along the superior border of the subclavian vein near the lung surface. Both radiolabeled lymph nodes were positive for metastatic melanoma. A type III modified radical neck dissection was performed, and histologic evaluation of the lymphadenectomy specimen revealed 1 of 26 nodes positive for metastatic disease. For each of the patients, the location of each primary lesion, its thickness, its primary lymphatic drainage pathway, and the presence of micrometastases in the remaining lymphadenectomy specimen are summarized in the Table. In 2 (66%) of these 3 patients, the SLN was the only node positive for micrometastases. Of note is that the precise pattern and site of lymphatic drainage was not always accurately and precisely determined by the location of the primary lesion.

The posttreatment surveillance ranged from 1.7 to 4 years with a mean follow-up of 2.5 years. Three patients had evidence of recurrence (1 local, 1 regional, and 1 systemic) during this time. In the patient with the regional recurrence, the SLN could not be localized by GPRL, blue-dye lymphatic mapping, or lymphoscintigraphy. His lesion was 1.74-mm thick, located in the left side of the midneck region, and initially treated with wide local excision and serial examinations. Regional recurrence occurred 17 months later and was treated with a type III modified radical neck dissection. Of 21 nodes, 2 were positive for metastases. The other 2 patients with recurrence had no evidence of regional disease.

**COMMENT**

The theory that involvement of certain lymph nodes within a regional lymphatic basin are prognostic of regional tumor spread has several precedents. One of the more colorful descriptions was made by Raymond H. Randal, a fourth-year medical student at Harvard University, Cambridge, Mass, in 1948. Under the tutelage of J. H. Means, Randal noted the potential relationship between a prelaryngeal node and the clinical behavior of laryngeal tumors. He creatively dubbed this node the delphian node after the prophetic oracle at Delphi.

In similar fashion, the concept of the SLN is critical to understanding the relationship of a primary melanoma to its regional lymph nodes. As first described by Cabanas in 1977, only a limited number of lymph nodes (SLNs) are the recipients of micrometastases. As they leave the primary tumor, metastatic melanoma cells move sequentially down the lymphatic ducts to the first draining lymph nodes (SLNs), then to second and third draining lymph nodes. The SLN, being the initial recipient of metastatic tumor cells, predicts the histologic features of its remaining lymphatic basin. These SLNs accurately reflect whether regional metastases have occurred with a demonstrated false-negative rate of 4% and a predictive value of an SLN negative for metastatic melanoma of 98.5%.

Biopsy of an SLN can achieve complete staging information with minimal morbidity. It also limits ELND to patients with documented lymphatic spread of cancer and provides the physician with the staging information necessary to determine if patients would benefit from early adjuvant therapy.

The survival advantage for patients treated with this strategy will need long-term evaluation before wide acceptance can occur. Currently, the Multicenter Selective Lymphadenectomy Trial of the National Cancer Institute, Bethesda, Md, a multi-institutional prospective randomized study, is investigating this question.

Nevertheless, given the power of the relationship between the SLN and its remaining lymphatic basin, it has been the goal of several investigators to find the least invasive method of localizing and removing the SLN for histologic evaluation. Recently, SLN retrieval was described using a blue-dye lymphatic mapping technique. However, the problems associated with this method led us to develop GPRL.

In our series, in 22 (96%) of 23 patients the SLN was successfully removed. This was independent of the location or depth of the primary tumor, the presence of regional metastases, or the type of biopsy performed on the primary melanoma prior to injection of the radioactive tracer. Blue-dye lymphatic mapping and lymphoscintigraphy had localization success rates of 75% (8 of 12 patients) and 91% (20 of 22 patients), respectively.
Although the sample size of this study is small, these percentages are consistent with those reported in the literature\textsuperscript{11-14} for truncal and axial melanoma. The only failure to identify the SLN occurred in a patient in whom GPRL, blue-dye lymphatic mapping, and lymphoscintigraphy were unsuccessful.

Although blue dye as a tracer was invaluable for establishing the SLN concept for melanoma, it is not an ideal agent for precise surgical localization of the SLN. In our study, it was difficult for the surgeon to know the exact location of the blue-stained nodes prior to incision using the blue-dye lymphatic mapping technique. As a result, the dissection was more extensive than when the surgeon could precisely locate the SLN with the handheld gamma probe. Lymphoscintigraphy (gamma camera imaging) successfully imaged a hot spot approximately 90\% of the time. However, its ability to accurately guide the surgeon to the SLN was limited because the lymphoscintigrams were 2-dimensional static images. In addition, the skin mark, which identified the SLN and was based on gamma camera imaging, was commonly several centimeters from the actual radiolabeled node. Similar to a Geiger counter, when the handheld gamma probe was used prior to incision, the exact location of the radiolabeled SLN was identified dynamically and in 3 dimensions to within 1 cm. This significantly minimized the extent of tissue dissection required.

A secondary benefit of GPRL was the immediate verification that all radiolabeled SLNs had been removed. Unlike blue-dye lymphatic mapping, which required additional dissection to verify that all SLNs had been excised, GPRL verified complete SLN removal simply by moving the gamma probe over the skin surface. If the level of radiation in the remaining lymphatic basin equaled background levels, complete SLN resection was confirmed. The importance of this capability was underscored in patient C. The second hot node, which was subclavicular and abutting the subclavian vein, would not have been removed with a traditional neck dissection and may have been overlooked with blue-dye lymphatic mapping.

The ability to successfully perform GPRL of the SLN is quickly acquired.\textsuperscript{19} In fact, the results reported herein are from surgeons who began to accrue cases after participating in a 1-day training workshop at the University of Vermont. This is in sharp contrast to blue-dye lymphatic mapping, which requires considerable experience before achieving proficiency.\textsuperscript{12}

The concomitant use of a radionuclide tracer and the blue dye, although not essential for localization, did aid in distinguishing the SLN from contiguous unstained tissue. This visual check for blue dye can also reassure the surgeon who is inexperienced in using the technique of GPRL.

A total of 3 patients (14\%) had SLNs that were histologically positive for metastatic melanoma. In 2 (66\%) of these 3 patients, the SLN was the only node with micrometastases. Despite the relatively small size of this study, these percentages are representative of those reported in the literature\textsuperscript{11-14} for truncal and axial melanoma.

The posttreatment surveillance ranged from 1.7 to 4 years with a mean follow-up of 2.5 years. Of the 3 occurrences of malignant growth that became evident during this time, only 1 was regional. Since localization of the SLN failed using all modalities (the only GPRL failure), no additional insight regarding the predictive value of the SLN can be gained from this particular patient. Approximately 90\% of regional nodal recurrence occurs within the first 3 years\textsuperscript{3,4}; therefore, careful follow-up of the patients in this clinical trial continues to be important and is ongoing.

A high incidence of “skip” metastases in facial melanoma has been reported previously\textsuperscript{5-7,20} and raises the question of whether the SLN is truly prognostic of regional micrometastases. In one study,\textsuperscript{2} 40\% of patients whose primary lymphatic drainage should have been to the parotid region according to traditional anatomic charts, instead had skip metastases to the cervical region.

The apparent contradiction between the prognostic success of the SLN clinically and the clinical occurrence of skip metastases can be explained by the fact that the first draining lymph node—the SLN—is not necessarily the same as the first-order lymph node as predicted by anatomic charts. Recent studies\textsuperscript{21,22} using lymphoscintigraphy have demonstrated that the lymphatic drainage patterns as determined by lymphoscintigrams can be discordant from accepted anatomic charts in 40\% to 60\% of cases. The study by Eberbach et al\textsuperscript{23} documented that in the head and neck region the lymphatic flow proceeded to multiple nodal groups or was unpredictable (according to anatomic charts) in 75\% of patients. Therefore, it is quite possible that the SLN does not represent the first-order lymph node of a generalized lymphatic drainage map but rather the first recipient lymph node unique to each patient. For a given patient, this first recipient node may be superficial, deep, cephalad, or caudal. Thus, skip metastases may in fact represent nonstandard but sequentially draining lymphatic pathways and/or multiple draining lymph node groups in parallel array.

Finally, GPRL can be consistently performed using local anesthesia through a small, minimally invasive incision. As a result, suitable patients can undergo excision of the primary lesion and biopsy of the SLN as an outpatient at considerable savings.\textsuperscript{24} Regional lymphadenectomy under general anesthesia is reserved for approximately 10\% to 30\% of patients with micrometastases identified on permanent histopathologic sections of the SLN.

\begin{table}

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tumor Site</th>
<th>Depth, mm</th>
<th>Site of Sentinel Lymph Node</th>
<th>Elective Lymph Node Dissection</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Right cheek</td>
<td>3.8</td>
<td>Right midcervical</td>
<td>No</td>
</tr>
<tr>
<td>B</td>
<td>Left lateral periorbital side</td>
<td>4.0</td>
<td>Left submandibular</td>
<td>No</td>
</tr>
<tr>
<td>C</td>
<td>Right lower part of the neck</td>
<td>2.5</td>
<td>Right supraclavicular</td>
<td>Yes</td>
</tr>
</tbody>
</table>

\end{table}
For the past 3 years, we have successfully used the algorithm displayed in Figure 4 for clinical stage N0 melanoma of the trunk and extremities. The application of this approach in the head and neck region has been tempered by this area’s concentrated and complex regional lymphatic drainage patterns. Results of this study, which specifically examined the effectiveness of GPRL in melanoma of the head and neck, strongly suggest that use of radioisotopes and biopsy of the SLN can be consistently achieved with minimal invasiveness. Although more experience with this technique in a larger number of patients is required, we envision that such management approach will be able to minimize the time, cost, and morbidity of patients with clinical stage N0 melanoma of the head and neck region. This approach also identifies a new subgroup of study patients in whom the question of the survival benefit of early lymphadenectomy may be answered.

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