Abstract: Background. We analyzed the variability and accuracy of sentinel lymph node (SLN) identification by lymphoscintigraphy performed preoperatively and repeated on the day of operation in patients with melanoma or Merkel cell cancer.

Methods. Twenty-five prospectively studied patients had lymphoscintigraphy prior to and on the day of operation. Discordance between lymphoscintigrams was defined as change in location of SLN or failure to identify a SLN by one of the studies.

Results. In 22 of 24 assessable cases (92%), SLNs were excised. Preoperative lymphoscintigraphy was correct in 19 of 22 (86%) cases. Day of operation lymphoscintigraphy was correct in 20 of 22 (91%) cases. SLN location was as classically described in 24 of 25 (96%) cases. Discordance between lymphoscintigraphy studies was 32% (8/25 patients). Half with discordant migration (8%) yielded metastases in basins not identified by day of operation lymphoscintigraphy but demonstrated by preoperative lymphoscintigraphy.

Conclusions. Head and neck lymphatic drainage patterns not only vary between patients but also can vary with time for a single patient. ©2007 Wiley Periodicals, Inc. Head Neck 29: 979–985, 2007

Keywords: sentinel lymph node biopsy; melanoma; lymphoscintigraphy; Merkel cell cancer; lymphatic drainage
the head and neck than in other parts of the body. As a result, it has been our practice to perform lymphoscintigraphy before definitive surgical counseling for patients with melanoma and Merkel cell cancer of the head and neck. The study is repeated on the day of operation to assist in intraoperative SLN identification. No interventions were undertaken on any patient during the interval between the studies; however, in some patients the second lymphoscintigram suggested a change in SLN location. This discrepancy between studies might give rise to false-negative SLN biopsies in this group of patients. Therefore, we analyzed the variability and accuracy of SLN identification by reviewing lymphoscintigraphy studies performed preoperatively and repeated on the day of operation.

**PATIENTS AND METHODS**

Between March 2000 and June 2004, a prospective database was compiled of all patients undergoing primary tumor resection of melanoma or Merkel cell cancer of the head and neck. For this study, patients that had lymphoscintigraphy performed preoperatively and repeated on the day of surgery were analyzed. Each patient had biopsy-proven disease and no clinical evidence of metastases. This cohort consisted of 25 patients. Twenty-two of the patients had melanoma, and 3 had Merkel cell tumors.

Prior to final preoperative counseling, lymphoscintigraphy was performed. Intradermal, peritumoral injections were made in quadrants with 45 to 80 μCi of technetium-99m-labeled sulfur colloid. Serial images were taken from 15 minutes to as long as 3 hours in order to identify tracer migration. No patients underwent any invasive procedures during the interval between the initial lymphoscintigraphm and the day of operation.

On the day of operation, lymphoscintigraphy was repeated with an intradermal injection of the same quantity of tracer in peritumoral quadrants. Both lymphoscintigraphy studies were reviewed prior to incision, and they were compared in order to ascertain the likely location of the sentinel node. Discordance between lymphoscintigraphy studies was defined as a discrepancy in the site of apparent SLN location that would change the incision location for the SLN biopsy or else as a failure to identify a SLN on one of two studies.

In the operating room, 0.5 mL of Lymphazurin blue dye was injected intradermally in 4 quadrants around the tumor. Intraoperatively, SLN identification was defined by gamma probe detection and staining with blue dye. If lymphoscintigraphy results differed, both sites were examined by gamma probe and incisions were made based upon elevated counts. In cases of nontransit, gamma probe examination of classically described lymphatic drainage patterns was performed, and incisions were based on the presence of increased counts. All lymph nodes that were considered blue or had counts by gamma probe >10% of the hottest node's counts were excised. Wide excision of the primary lesion was usually performed after SLN biopsy was completed, although in some cases, excision was performed first in order to reduce nearby counts in proximity to the SLN. All tissues were analyzed by histology and immunohistochemistry including S100, HMB45, and A103. Patients were followed postoperatively for recurrence and complications. Statistical analysis was performed using chi-square test.

**RESULTS**

The study group consisted of 25 patients, 18 men and 7 women, with an average age of 60 years (range, 19–86). Two patients (8%) had a prior history of melanoma. Three (12%) had a family history of melanoma. Four (16%) had a history of other skin cancers (3, basal; 1, squamous). Twelve (48%) had a history of severe sunburn or prolonged solar exposure. The average interval between the date of initial lymphoscintigraphy and the date of operation lymphoscintigraphy was 33 days, with a range of 10 to 58 days. Postoperatively, follow-up examinations were performed every 3 months. The average period of follow-up was 18 months (range, 1–52 months).

Twenty-two patients had melanoma, with an average tumor thickness of 2.33 mm. Primary T classification of melanoma patients was as follows (see Table 1): T1a, 2; T2a, 9; T2b, 3; T3a, 1; T3b, 4; T4a, 1; T4b, 2. All 3 Merkel cell patients had T1 tumors.

The distribution of the primary sites was as follows (see Table 2): upper face, 2; mid-face, 7; lower face, 1; periauricular/ear, 8; coronal neck, 1; posterior neck, 3; vertex of scalp, 2; and coronal scalp, 1. Twenty of the primary tumors were located laterally, and 5 were located near the midline of the head or neck.

The histology-confirmed success of SLN excision was 22 of 24 (92%) cases evaluated by pathology. In 1 case, the SLN was within the parotid by
Lymphoscintigraphy and by gamma probe at operation, but the patient refused any manipulation of parotid tissue. Lymphoscintigraphy images performed preoperatively accurately identified the SLN location in 19 of 22 (86%) assessable cases. Lymphoscintigraphy on the day of operation identified the SLN in 20 of 22 (91%) cases. When the images from both studies were employed, SLN sites were correctly identified in 21 of 22 (95%) cases. Fifty-two SLNs were excised from the 22 patients for an average of 2.4 SLN per patient. Fifty-one of the 52 (98%) SLNs biopsied were identified by gamma probe elevated counts. Thirty-two (62%) of the SLNs biopsied were identified by blue dye staining. The gamma probe was significantly more sensitive than blue dye in identifying SLNs (p < 0.001).

An average of 1.38 lymph node basins (total 33 lymphatic basins) were biopsied per patient studied. Eight patients (32%) had SLNs removed from multiple basins. Preoperative lymphoscintigraphy identified an average of 1.21 basins per patient (total 29). Day of operation lymphoscintigraphy identified an average of 1.17 basins per patient (total 27). Both preoperative and day of operation lymphoscintigraphy correctly identified the lymphatic basins in 5 of the 8 patients (63%) who had SLNs excised from multiple basins. The primary sites that yielded SLNs in multiple basins at operation were as follows: periauricular in 4 of 8 cases (50%), mid-face in 3 of 7 cases (43%), and scalp vertex in 1 of 2 cases (50%).

The lymphoscintigraphy results of each case were compared with classically described drainage patterns, based upon the primary tumor location and operative findings. The SLN location identified at operation (including the intraparotid SLN that was not excised) was consistent with classically described lymphatic drainage patterns in 23 of 25 (92%) cases. In 5 of the 50 lymphoscintigrams performed, there was no migration of tracer, yielding a nontransit incidence of 10%. Sixty percent (3 of 5) of midline primary lesions had bilateral drainage patterns on lymphoscintigraphy versus 5% (1 of 20) of lateral primary lesions (p < 0.025).

The incidence of discordance between preoperative and day of operation lymphoscintigraphy in this series was 32% (8 of 25 cases). In 4 cases, this was due to migration to different nodal basins, and in 4 cases, it was due to nontransit of tracer. In 2 cases, lymphoscintigraphy pointed to a different nodal basin, but the incision could be extended to allow for evaluation of both sites. In each case, SLNs were identified and removed from each basin. One case was a right ear melanoma in a 63-year-old man with a T2a primary in which the parotid SLN suggested on the day of operation study was not diagnostic for metastasis, but level III SLNs suggested by the preoperative study contained metastatic melanoma (see Figure 1). In the other case, a 73-year-old woman with a T2a melanoma on the nape of her neck, an SLN was suggested on lymphoscintigraphy in the lateral posterior triangle preoperatively. The day of operation study pointed to the submandibular triangle, but the SLN was found in the lateral posterior triangle at operation. By histology and immuno-histochemistry criteria, the node was free of melanoma.

In 2 cases, a 42-year-old man with T3a melanoma of the midline forehead and a 60-year-old man with T1 Merkel cell of the lateral mid-face, there was a change in laterality of lymphoscintigraphy was consistent with classically described patterns in 21 of 25 (84%) cases and with 21 of 25 (84%) operative findings. The SLN location identified at operation (including the intraparotid SLN that was not excised) was consistent with classically described lymphatic drainage patterns in 23 of 25 (92%) cases. In 5 of the 50 lymphoscintigrams performed, there was no migration of tracer, yielding a nontransit incidence of 10%. Sixty percent (3 of 5) of midline primary lesions had bilateral drainage patterns on lymphoscintigraphy versus 5% (1 of 20) of lateral primary lesions (p < 0.025).

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In 2 cases, a 42-year-old man with T3a melanoma of the midline forehead and a 60-year-old man with T1 Merkel cell of the lateral mid-face, there was a change in laterality of lymphoscintigraphy.

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### Table 1. T classification of melanoma patients.

<table>
<thead>
<tr>
<th>T classification</th>
<th>No. of patients* (%, n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>2 (9)</td>
</tr>
<tr>
<td>1b</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2a</td>
<td>9 (41)</td>
</tr>
<tr>
<td>2b</td>
<td>3 (14)</td>
</tr>
<tr>
<td>3a</td>
<td>1 (5)</td>
</tr>
<tr>
<td>3b</td>
<td>4 (18)</td>
</tr>
<tr>
<td>4a</td>
<td>1 (5)</td>
</tr>
<tr>
<td>4b</td>
<td>2 (9)</td>
</tr>
</tbody>
</table>

*All 3 Merkel cell cancer patients had T1 disease.

### Table 2. Primary site location.

<table>
<thead>
<tr>
<th>Location of primary tumor</th>
<th>No. (%), n = 25</th>
<th>Discordance, frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper face</td>
<td>2 (8)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Mid-face</td>
<td>7 (28)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Lower face</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Periauricular/ear</td>
<td>8 (32)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Coronal neck</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Posterior neck</td>
<td>3 (12)</td>
<td>2 (66)</td>
</tr>
<tr>
<td>Vertex of scalp</td>
<td>2 (8)</td>
<td></td>
</tr>
<tr>
<td>Coronal scalp</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Lateral</td>
<td>20 (80)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Midline</td>
<td>5 (20)</td>
<td>1 (20)</td>
</tr>
</tbody>
</table>
raphy findings. The patient with a T3a melanoma of the midline forehead had a preoperative lymphoscintigam identify the right parotid and day of operation lymphoscintigram identify the left parotid. At operation, hot and blue lymph nodes were identified in the left parotid and found to be pathologically negative for melanoma. However, the patient was found at 18-month follow-up examination to have a clinically positive right parotid that was confirmed at operation to contain metastatic melanoma (see Figure 2).

Four cases of discordance were due to non-transit of tracer in 1 or both studies. Therefore, in 16% of cases (4 of 25) serial lymphoscintigraphy suggested differing incisions and variable nodal basins for SLN biopsy (see Table 3).

Two patients (8%), both with melanoma, had positive SLN biopsies. One patient was the previously discussed 63-year-old man with a T2a primary of the right ear with 2 positive jugular SLNs and a negative parotid SLN. This patient subsequently underwent a type I neck dissection and parotidectomy with 27 negative lymph nodes before developing in-transit metastases. The other patient was a 40-year-old woman with a T2a melanoma of the left side of the scalp. She had an

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**FIGURE 1.** Discordance in sentinel lymph node (SLN) location in a 63-year-old man with melanoma of the right ear. (A) Preoperative lymphoscintigraphy identified SLN in the right jugular chain. (B) Day of operation lymphoscintigraphy identified SLN in the right parotid. Incision was made to biopsy both nodal basins. The parotid SLN was not diagnostic, but the jugular SLN, seen on preoperative lymphoscintigraphy, was diagnostic of metastatic melanoma.

**FIGURE 2.** Change in laterality of sentinel lymph node (SLN) in a 42-year-old man with melanoma of the midline forehead. (A) Preoperative lymphoscintigraphy identified SLN in the right parotid. (B) Day of operation lymphoscintigraphy identified SLN in the left parotid. At operation, 2 SLNs were found in the left parotid and tested negative. However, on examination 18 months postoperatively, the patient had metastases in the right parotid and subsequently underwent right parotidectomy and comprehensive neck dissection.
extensive family history of melanoma, including both parents and a brother who died from melanoma. Sentinel lymphadenectomy revealed 3 microscopically positive level IV SLNs. A type I neck dissection yielded an additional 5 of 38 lymph nodes with melanoma. Subsequently, metastases developed in her lungs and bone.

The average duration of follow-up for this series was 18 months. There were 5 recurrences, all melanoma, with an average time to recurrence of 7.4 months. One patient of 25 (4%) had a “false-negative” SLN biopsy and had recurrence regionally and with bone metastases. One patient had recurrence develop in the parotid. Two patients experienced distant recurrences with metastases developed in her lungs and bone. The only complication was a drain malfunction after lateral parotidectomy that required evacuation of a fluid collection.

**DISCUSSION**

This appears to be the first series analyzing serial lymphoscintigraphy in head and neck melanoma and Merkel cell cancer. We demonstrate that lymphatic drainage patterns of the head and neck may vary with time in a single patient, so that some SLN basins harboring metastases are not recognized by a single lymphoscintigraphy study. Thirty-two percent of cases had discordance between lymphoscintigraphy studies, half due to differing nodal basins identified and half due to failure of lymphoscintigraphy to identify a SLN.

Compared with other sites, melanoma of the head and neck is associated with higher rates of atypical lymphatic drainage patterns, false-negative SLN biopsies, and recurrences.\textsuperscript{1,8–11} Our confirmed success rate of 92% in identifying the SLN is consistent with results from other experienced centers. The 2 unsuccessful cases included 1 in which both the preoperative and day of surgery lymphoscintigraphy images failed to identify a SLN and another in which gamma probe–positive, blue-stained tissue grossly consistent with a lymph node was removed, but no lymphatic tissue was found on histology. Our incidence of complications is consistent with that reported in the Sunbelt Melanoma Trial (2.4% of 370 patients who underwent SLN biopsy for melanoma of the head and neck).\textsuperscript{12} The low false-negative SLN rate of 4% (one of 25 cases) is consistent with that reported by others.\textsuperscript{9,13,14}

Merkel cell cancer is an uncommon malignancy involving neuroendocrine cells of the epidermis. The most frequent site of occurrence is the head and neck. There is a high frequency of lymphatic metastasis, with reported incidences of 20% at presentation and 50% during follow-up.\textsuperscript{7} The role of lymph node dissection in these patients is controversial. SLN biopsy was proposed by Medina-Franco et al\textsuperscript{7} to assist in determining which Merkel cell patients might benefit from lymphadenectomy. In our series, each of the 3 patients was stage I (no regional lymphatic metastases) with SLN biopsy negative for tumor. One of the 3 cases had discordant drainage.

Lymphoscintigraphy in this series correctly identified SLN location in 76% of cases preoperatively and 84% of cases on the day of operation. When both studies were used, the SLN removed at operation was identified by at least 1 lymphoscintigraphy study in 95% of cases. In the 1 case not correctly identified by lymphoscintigram, an SLN was suggested in the upper cervical chain by preoperative LS. None were identified on the day of surgery lymphoscintigraphy, but SLNs were found with the gamma probe and excised from the parotid and level V at operation.

The nontransit rate of 10% (5 of 50 lymphoscintigraphy studies) is consistent with previously reported experiences of 2% to 10%.\textsuperscript{8,14} Nontransit of tracer can sometimes be related to lymphoscintigraphy technique. Precise injections of judicious quantities of radioactive tracer without spilling at the primary site may limit the problem. Serial images over time from multiple angles may limit the possibility of missing delayed migration or a nearby SLN due to lymphoscintigraphy imaging technique. Excision of the primary tumor, thus reducing cutaneous counts, sometimes permits detection of an underlying SLN. An SLN close to the primary tumor site may render radionuclide migration undetectable. This has been reported as a common confounding factor in SLN biopsy in the head and neck.\textsuperscript{15}

Bilateral lymphatic drainage on lymphoscintigraphy was found in 3 of 5 cases (60%) with mid-
Midline primary sites were significantly more likely to yield bilateral SLNs by lymphoscintigraphy than yield lateral lesions ($p < .025$). Two patients, 1 with melanoma on the tip of the nose and 1 on the scalp vertex, had bilateral SLNs on both lymphoscintigraphy studies. One patient with melanoma of the midline forehead had a change in laterality between studies. Only 1 case in 20 (5%) involving a lateral lesion (a Merkel cell of the lateral mid-face) had bilateral drainage patterns by lymphoscintigraphy (with a change in laterality between the 2 studies).

Multiple nodal basins were found to contain SLNs in 32% of cases (8/25) at operation. Lymphoscintigraphy was useful in identifying cases with multiple lymphatic basins. Lymphoscintigraphy identified multiple nodal basins in 7 cases (28%) preoperatively and 6 cases (24%) on the day of operation. However, the accuracy of both preoperative and day of operation lymphoscintigraphy studies in correctly identifying multiple lymphatic basins was 63%, 5 of the 8 cases that were confirmed at operation. The primary tumor locations that most frequently yielded multiple basins at operation were the ear/periauricular (4/8; 50%), the scalp vertex (1/2; 50%), and the mid-face (3/7; 43%). Multiple nodal basins were found to contain SLNs in 3 of the 8 discordant cases (38%).

For the purposes of this study, lymphoscintigraphy results were described in terms of regions. Lymphoscintigraphy images are seldom precise enough to identify specific levels within the jugular chain. By describing lymphoscintigraphy results in terms of regions (anterior triangle, posterior triangle, submandibular/submental, parotid, or occipital), we can confidently state that our reported discordance in lymphoscintigraphy results between studies resulted from a true change in lymphatic flow rather than from interpretation of low-resolution studies. The findings at operation further confirmed our observations on lymphoscintigraphy.

In 16% of cases (4/25), serial lymphoscintigraphy suggested different incisions and different nodal basins for SLN excision (see Table 3). Half of those cases yielded metastatic melanoma in lymphatic basins that were not identified by the day of operation lymphoscintigraphy.

Two cases involved different ipsilateral nodal basins. In 1 case, a T2a melanoma of the ear demonstrated parotid versus level III SLNs on serial lymphoscintigraphy (see Figure 1). At operation, an SLN was found in level III that was shown on the preoperative but not the day of operation lymphoscintigraphy. The SLN was positive for metastatic melanoma. The other case involved a T2a melanoma on the nape of the neck that demonstrated lateral level V versus submandibular SLNs on lymphoscintigraphy. At operation, the SLN (negative for tumor) was found in lateral level V, which was shown on the preoperative lymphoscintigraphy.

The other 2 cases of discordant nodal drainage basins involved changes in laterality of SLN of patients. In 1 case, a T3a melanoma of the midline forehead demonstrated right parotid preoperatively and left parotid on the day of operation lymphoscintigraphy (see Figure 2). At operation, SLNs were found in the left parotid and tested negative. However, the patient presented 18 months later with right parotid metastatic melanoma. The other case was a T1 Merkel cell tumor involving the right cheek that demonstrated right cervical SLNs preoperatively versus left cervical and midline SLNs on the day of operation lymphoscintigraphy. At operation, left cervical and level I SLNs were found (negative for tumor), consistent with the day of operation lymphoscintigraphy.

The source of the observed discordance is uncertain. The same technique of intradermal injection of technetium in quadrants around the tumor was used in each patient and performed in the same nuclear medicine department. Previous biopsy of the primary lesion does not affect the reliability of SLN biopsy using blue dye or radiotracer in melanoma of the head and neck, extremities, and trunk.16 None of the patients in this study underwent any surgical procedures during the interval between studies. The average interval between lymphoscintigraphy studies in patients with discordance was 28 days, with a range from 10 to 36 days, which was not significantly different from the study group as a whole. Patient age and tumor thickness did not vary significantly between patients with discordant lymphoscintigrams and the study group as a whole.

As shown in Table 2, the primary tumor locations of patients with discordance on lymphoscintigraphy were evenly distributed between the upper face ($n = 2$), mid-face ($n = 2$), posterior neck ($n = 2$), and periauricular ($n = 2$) regions. However, the incidence of discordance was greater among primary lesions of the upper face (2/2, 100%), and posterior neck (2/3, 66%), versus the mid-face (2/7, 29%), and periauricular (2/8, 25%).
Seven of the 8 patients with discordant studies had lateral primary lesions.

Fifty percent of the patients with discordant migration on lymphoscintigraphy had SLNs that could be found at operation by elevated gamma probe counts in basins that were not identified on the day of surgery lymphoscintigraphy but were recognized (and thus explored) on the basis of preoperative lymphoscintigraphy. Of the 7 patients with lymphoscintigraphy discordance who had an SLN identified at operation, 3 required excisions from multiple basins. Our technique of utilizing the gamma probe prior to incision to examine multiple nodal basins in cases of discordant lymphoscintigraphy findings and nontransit was useful in guiding the successful excision of all SLNs.

Lymphatic drainage patterns in the head and neck not only vary between patients but also can vary with time for a single patient. Some basins with SLNs are not shown consistently on lymphoscintigraphy. This is a potential source of regional recurrences in patients who have apparently negative SLN biopsies. The incidence of regional recurrence was 8% in this series and has been reported to be from 5% to 25%.8,13,14 For institutions not employing serial lymphoscintigraphy, assessing classically predicted drainage basins with the gamma probe prior to incision, and appreciating the increased likelihood of bilateral and multiple drainage basins may help to reduce the possibility of missing an SLN not identified on a day of operation lymphoscintigraphy.

REFERENCES