Sentinel Lymph Node Biopsy for Sebaceous Cell Carcinoma and Melanoma of the Ocular Adnexa

Viet H. Ho, MD; Merrick I. Ross, MD; Victor G. Prieto, MD, PhD; Aisha Khaleeq, MD; Stella Kim, MD; Bita Esmaeli, MD

Objective: To provide clinical details and long-term outcome data for a series of patients with eyelid or conjunctival melanoma or eyelid sebaceous cell carcinoma who underwent sentinel lymph node (SLN) biopsy.

Design: Retrospective interventional case series with review of clinical records and pathologic specimens.

Setting: Tertiary comprehensive cancer center.

Patients: Twenty-five consecutive patients treated at 1 institution for eyelid or conjunctival melanoma or eyelid sebaceous cell carcinoma from December 2000 to October 2004.

Interventions: Surgical removal of the eyelid or conjunctival tumor and SLN biopsy.

Main Outcome Measures: Local treatment modalities; lymphatic basins in which SLNs were identified; status of SLNs; false-negative rate; and long-term patterns of local recurrence, regional and distant metastasis, and survival.

Results: Seven patients had conjunctival melanoma, 8 had eyelid-margin melanoma with a considerable palpebral conjunctival component, and 10 had eyelid sebaceous cell carcinoma. The SLNs were identified in all but 1 patient by using technetium Tc 99m sulfur colloid as a tracer. Intraoperatively, in 16 patients in whom blue dye was used in addition to technetium Tc 99m sulfur colloid during mapping, no SLN was blue. One patient with conjunctival melanoma and 1 patient with eyelid melanoma had a histologically positive SLN. Two patients with eyelid melanoma and 2 patients with eyelid sebaceous cell carcinoma had negative findings from SLN biopsy but developed recurrence in their regional lymph nodes during the follow-up period. Overall, during follow-up, 2 of 10 patients with sebaceous cell carcinoma (20%) and 5 of 15 patients with eyelid or conjunctival melanoma (33%) had regional lymph node metastasis. Four patients with melanoma who had regional metastasis also developed distant organ metastasis. Two patients with sebaceous cell carcinoma—1 with regional metastasis and 1 without—developed distant organ metastasis.

Conclusions: The detection of histologically positive SLNs in this series of patients may justify further study of SLN biopsy for high-risk patients with ocular adnexal melanoma or eyelid sebaceous cell carcinoma. The false-negative rate is higher than that reported for SLN biopsy at most other anatomic sites. Patients with negative findings from SLN biopsy still require careful long-term follow-up because they may develop regional or distant metastasis.

Arch Otolaryngol Head Neck Surg. 2007;133(8):820-826

The concept of sentinel lymph node (SLN) biopsy is based on the idea that there is an orderly and predictable pattern of lymphatic drainage from a tumor to regional lymph node basins and that the first lymph node or nodes along the drainage pathway (the SLN[s]) function as an effective filter for tumor cells. With the widespread use of SLN biopsy in the past decade, a large body of data is now available that supports sequential lymphatic dissemination and initial entrapment of tumor cells in first draining lymph nodes. Sentinel lymph node biopsy has evolved as an effective technique for identifying early subclinical regional nodal metastasis for many solid tumors throughout the body, including cutaneous melanoma and Merkel cell carcinoma. It can provide important prognostic information to the physician and patient that can help determine future treatment options. For example, identification of microscopic regional nodal metastases may indicate that more extensive therapy is warranted, and therefore patients may be eligible for enrollment in clinical trials for which they would not otherwise qualify.

With the exception of basal cell carcinoma, all cancers of the eyelid and conjunctiva have a propensity to metastasize to the regional lymph nodes, and regional metastasis commonly occurs before metastasis to distant sites. Our early experience with SLN biopsy for ocular adnexal tumors suggests that SLN biopsy for conjunctival and
eyelid lesions is feasible from a technical standpoint\textsuperscript{11,12} and can identify some microscopic metastases that would not be detected using conventional imaging techniques or via clinical examination\textsuperscript{13,14}. Herein, we present procedure-related data and long-term outcome data for patients with eyelid or conjunctival melanoma or eyelid sebaceous cell carcinoma who underwent SLN biopsy at our institution over a 4-year period.

**METHODS**

Appropriate institutional review board approval was obtained for this study. A detailed retrospective medical chart review was conducted for 25 patients with eyelid or conjunctival melanoma or eyelid sebaceous cell carcinoma who underwent preoperative lymphoscintigraphy and SLN biopsy at the University of Texas M. D. Anderson Cancer Center, Houston, from December 2000 to October 2004. Because other SLN biopsy trials at M. D. Anderson Cancer Center enroll patients with other diagnoses, such as squamous cell carcinoma and Merkel cell carcinoma of the eyelid, our trial was limited to patients with conjunctival or eyelid melanoma or eyelid sebaceous cell carcinoma. The histopathologic diagnosis was confirmed by a M. D. Anderson Cancer Center pathologist in each case. Information analyzed included age, sex, location of the lesion, treatment modalities, the rate of SLN positivity, the false-negative rate for SLN biopsy findings, adverse effects of SLN biopsy, local recurrence, patterns of regional nodal and distant metastasis, and overall survival. A false-negative result on SLN biopsy was defined as recurrence in a lymph node basin in which the SLNs were previously determined to be negative.

**SELECTION CRITERIA**

For patients with conjunctival melanoma, the selection criteria for SLN biopsy were Breslow thickness of 1 mm or greater or inability to determine tumor thickness because of tangential cutting or other technical difficulties in specimen handling. For patients with eyelid melanoma, the selection criteria for SLN biopsy were Breslow thickness of 1 mm or greater, Clark level IV or greater, or presence of ulceration. All patients with a diagnosis of invasive nonmetastatic sebaceous cell carcinoma of the eyelid who were treated in our department during the study period were given the option to undergo SLN biopsy unless the tumor had been removed elsewhere prior to referral to our center.

**SLN BIOPSY TECHNIQUE**

Preoperative lymphoscintigraphy was performed 1 to 2 days prior to surgery as described previously\textsuperscript{15}. Briefly, on the day of surgery, a dose of 0.3 mCi of technetium Tc 99m sulfur colloid in 0.2 mL volume was injected in the subconjunctival space or intradermally around the eyelid lesion (to convert millicuries to megabecquerels, multiple by 37). A handheld gamma probe (RIGS model 1001; Neoprobe Corp, Dublin, Ohio) was used transcutaneously around the eyelid lesion (to convert millicuries to megabecquerels, multiple by 37). A handheld gamma probe (RIGS model 1001; Neoprobe Corp, Dublin, Ohio) was used transcutaneously around the eyelid lesion (to convert millicuries to megabecquerels, multiple by 37). A routine hematoxylin-eosin–stained section was examined from all blocks. If findings from that section were negative for disease, the block was recut and then another hematoxylin-eosin–stained section was examined, and an immunohistochemical study was performed using an antimalanocytic cocktail (HMB45 and anti-MART 1 antibodies).

**RESULTS**

A total of 9 men and 16 women with eyelid or conjunctival melanoma or eyelid sebaceous cell carcinoma underwent SLN biopsy during the study period (Table). Age at presentation ranged from 23 to 82 years (mean age, 63 years). Duration of clinical follow-up after SLN biopsy ranged from 13 to 43 months (median duration, 25 months). No patients had clinical or radiographic evidence of regional lymphadenopathy or detectable systemic metastasis at the time of SLN biopsy. Before SLN biopsy, nodal metastasis was ruled out in each patient by using magnetic resonance imaging or computed tomography of the head and neck and ultrasonography with fine-needle aspiration, if indicated.

Seven patients with melanoma involving only the bulbar conjunctiva and 8 patients with eyelid margin melanoma (5 with significant extension of disease onto the palpebral and bulbar conjunctival surface, including the caruncle in 2 patients) underwent SLN biopsy during the study period. The Breslow thickness could not be determined in 6 patients. In the remaining 9 patients, the Breslow thickness ranged from 0.62 to 12 mm (median thickness, 3.1 mm).

Fourteen patients with eyelid sebaceous cell carcinoma were seen during the study period. Only 10 of these patients underwent SLN biopsy. Of the other 4 patients, 2 elected not to have SLN biopsy, and 2 had completed their local treatment (wide local excision of the lesion with eyelid reconstruction in 1 and orbital exenteration in the other) more than 6 months prior to being seen at our center, and thus SLN mapping did not make sense.

Among the patients with melanoma, 12 had primary disease, and 3 had locally recurrent disease on the conjunctiva or eyelid at the time of SLN biopsy. One patient underwent orbital exenteration, and 14 patients underwent local excision of their lesion with cryotherapy to the margins and reconstruction of the eyelid or conjunctival tissue using the usual reconstructive techniques. Three of the patients who underwent wide local excision also received postoperative radiation therapy to the orbit. The patient who underwent orbital exenteration received adjuvant systemic chemotherapy (study protocol using temozolomide with pegylated interferon).

Among the patients with sebaceous cell carcinoma, 4 had primary disease, and 6 had a recurrent eyelid mass at the time of SLN biopsy. Six patients were treated with rapid transport of blue dye in the head and neck region.\textsuperscript{12} For the last 9 patients described herein, technetium Tc 99m sulfur colloid alone was used.

**HISTOLOGIC ANALYSIS OF SLNs**

All SLNs were histologically evaluated using the current protocol at M. D. Anderson Cancer Center.\textsuperscript{16} Briefly, lymph nodes were breadloafed (thin sections cut for pathologic examination) in 2-mm-thick slices. A routine hematoxylin-eosin–stained section was examined from all blocks. If findings from that section were negative for disease, the block was recut and then another hematoxylin-eosin–stained section was examined, and an immunohistochemical study was performed using an antimalanocytic cocktail (HMB45 and anti-MART 1 antibodies).
wide local excision of the mass and reconstruction, and 4 patients underwent orbital exenteration because of the advanced nature of their disease. One patient with recurrent sebaceous cell carcinoma of the lower eyelid received postoperative radiation therapy after wide local excision of the entire lower eyelid and reconstruction using a tarsoconjunctival (Hughes) flap and full-thickness skin graft.

With the intraoperative use of the gamma probe, at least 1 SLN per patient was identified in 24 of the 25 patients in the study. Patient 2 had drainage to cervical-basin SLNs on preoperative lymphoscintigraphy; however, no SLNs were found intraoperatively. She underwent a parotidectomy and selective neck dissection at the time of orbital exenteration. All the retrieved nodes were negative. A total of 64 SLNs were identified in the remaining 24 patients. Five patients had only 1 SLN identified, and 19 patients had multiple SLNs either within the same lymphatic basin or in multiple basins. The lymphatic basins from which SLNs were extracted were the parotid or preauricular basin (30 nodes [47%]), submandibular basin (cervical level I) (13 nodes [20%]), cervical level II (14 nodes [22%]); cervical level III (5 nodes [8%]); and cervical level V (2 nodes [3%]).

**ADVERSE EFFECTS**

In the first 16 patients, in whom isosulfan blue dye was used in addition to technetium Tc 99m sulfur colloid, there was no permanent blue tattooing of the conjunctival surface or the eyelid skin, and the blue dye dissipated within 24 to 48 hours after the procedure. There were no immediate postoperative complications related to the SLN biopsy procedure except for mild temporary weakness of the marginal mandibular branch of the facial nerve in 3 patients. Symptoms of lower lip paresis in these patients resolved within 6 weeks.

**SLN POSITIVITY RATE**

Two patients (patients 12 and 20) had a histologically positive SLN. One of these patients had a bulbar conjunctival melanoma with a Breslow thickness of 3.1 mm, and the other had an eyelid melanoma with a Breslow thickness of 3.1 mm.

### Table. Clinicopathologic Characteristics and Patient Outcomes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Disease Location</th>
<th>Disease Status at SLN Biopsy</th>
<th>Initial Treatment</th>
<th>Breslow Thickness, mm</th>
<th>SLN Status</th>
<th>Duration of Follow-up, mo</th>
<th>Status at Last Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Eyelid</td>
<td>Primary</td>
<td>WLE</td>
<td>NA</td>
<td>Neg</td>
<td>18</td>
<td>Dead of heart failure; no recurrence</td>
</tr>
<tr>
<td>2</td>
<td>Eyelid</td>
<td>Primary</td>
<td>Exent</td>
<td>NA</td>
<td>Neg</td>
<td>43</td>
<td>Alive; FD</td>
</tr>
<tr>
<td>3</td>
<td>Eyelid</td>
<td>Recurrent</td>
<td>WLE</td>
<td>NA</td>
<td>Neg</td>
<td>24</td>
<td>Alive; regional nodal and distant mets (liver, lung)</td>
</tr>
<tr>
<td>4</td>
<td>Eyelid</td>
<td>Primary</td>
<td>WLE</td>
<td>NA</td>
<td>Neg</td>
<td>34</td>
<td>Alive; FD</td>
</tr>
<tr>
<td>5</td>
<td>Eyelid</td>
<td>Recurrent</td>
<td>Exent</td>
<td>NA</td>
<td>Neg</td>
<td>30</td>
<td>Alive; FD</td>
</tr>
<tr>
<td>6</td>
<td>Eyelid</td>
<td>Recurrent</td>
<td>WLE</td>
<td>NA</td>
<td>Neg</td>
<td>26</td>
<td>Alive; FD</td>
</tr>
<tr>
<td>7</td>
<td>Eyelid</td>
<td>Recurrent</td>
<td>WLE, adj XRT</td>
<td>NA</td>
<td>Neg</td>
<td>25</td>
<td>Alive; FD</td>
</tr>
<tr>
<td>8</td>
<td>Eyelid</td>
<td>Recurrent</td>
<td>Exent</td>
<td>NA</td>
<td>Neg</td>
<td>22</td>
<td>Alive; regional nodal mets</td>
</tr>
<tr>
<td>9</td>
<td>Eyelid</td>
<td>Primary</td>
<td>WLE</td>
<td>NA</td>
<td>Neg</td>
<td>17</td>
<td>Alive; FD</td>
</tr>
<tr>
<td>10</td>
<td>Eyelid</td>
<td>Recurrent</td>
<td>Exent</td>
<td>NA</td>
<td>Neg</td>
<td>21</td>
<td>Dead; distant mets (spine)</td>
</tr>
</tbody>
</table>

**Sebaceous Cell Carcinoma**

11 | Conj | Primary | WLE | Indet | Neg | 36 | Alive; FD |
12 | Conj | Primary | WLE | 3.1   | Pos | 22 | Dead; regional nodal and distant mets (liver, lung, brain) |
13 | Eyelid and conj | Primary | WLE | 1.2   | Neg | 28 | Alive; FD |
14 | Conj | Primary | WLE | 1.2   | Neg | 30 | Alive; local recurrence followed by regional nodal and distant mets (brain) |
15 | Conj | Primary | WLE, adj XRT | Indet | Neg | 24 | Alive; FD |
16 | Eyelid and conj | Primary | WLE, adj XRT | 3.5   | Neg | 25 | Alive; regional nodal and distant mets (liver, lung) |
17 | Conj | Recurrent | WLE, adj XRT | 3.5   | Neg | 19 | Alive; FD |
18 | Eyelid and conj | Primary | Exent, adj chemo | 3   | Neg | 13 | Alive; FD |
19 | Eyelid and conj | Primary | WLE, adj XRT | 12   | Neg | 24 | Alive; regional nodal and distant mets (spleen, brain) |
20 | Eyelid | Recurrent | WLE | 6     | Pos | 31 | Alive; regional nodal and distant mets (colon, lung, abdomen, contralateral orbit) |
21 | Conj | Recurrent | WLE | Indet | Neg | 32 | Alive; FD |
22 | Eyelid | Primary | WLE | 0.62  | Neg | 30 | Alive; FD |
23 | Conj | Primary | WLE | Indet | Neg | 38 | Alive; FD |
24 | Eyelid and conj | Primary | WLE | Indet | Neg | 17 | Alive; FD |
25 | Eyelid | Primary | WLE | Indet | Neg | 13 | Alive; FD |

**Melanoma**

Abbreviations: Adj, adjuvant; chemo, chemotherapy; conj, conjunctiva; exent, exenteration; FD, free of disease; indet, indeterminable; mets, metastases; NA, not applicable; neg, negative; pos, positive; SLN, sentinel lymph node; WLE, wide local excision; XRT, radiation therapy.
thickness of 6 mm with a palpebral conjunctival component. Both patients were treated with completion neck dissection, parotidectomy, and postoperative radiation therapy to the neck and parotid region. One received 12 months of adjuvant interferon therapy after neck dissection and radiation therapy, developed distant metastasis 12 months after SLN biopsy, and died 22 months after the SLN biopsy. The other developed distant metastasis with multiple organ involvement 29 months after SLN biopsy and at the time of this study was being considered for systemic chemotherapy.

None of the patients with sebaceous cell carcinoma had a positive SLN on initial assessment, although a repeated review of the SLNs after same-basin recurrence in patient 8 revealed histologic evidence of sebaceous cell carcinoma in 1 of the SLNs that had been missed on the initial assessment. An interesting finding in this case was that the immunohistochemical study with the standard antikeratin antibodies was negative for metastatic tumor cells, thus resulting in the initial incorrect diagnosis of negative SLN.

FALSE-NEGATIVE RATE FOR SLN BIOPSY

Two patients with sebaceous cell carcinoma (patients 3 and 8) and 2 patients with eyelid margin melanoma with palpebral conjunctival involvement (patients 16 and 19) who had negative findings on SLN biopsy later developed regional nodal metastasis after SLN biopsy (median time period, 12.5 months; range, 1-15 months).

Clinical recurrence in the lymph node basin in which the SLNs were previously found to be negative prompted reevaluation of the SLN sections, and on reevaluation, microscopic sebaceous cell carcinoma was found in 1 of the SLNs from patient 8. Thus, this case represents a false-negative finding for an SLN owing to lack of detection of micrometastases on the original evaluation of SLNs.

All 4 patients with a false-negative finding for an SLN underwent a completion neck dissection and postoperative radiation therapy to the involved nodal basins as soon as the regional nodal metastasis was discovered. Three of the 4 patients (2 with melanoma and 1 with sebaceous cell carcinoma) developed distant organ metastasis after SLN biopsy (median time period, 23 months; range, 14-24 months) and received systemic chemotherapy.

An additional patient with melanoma (patient 14) who had a negative SLN had local recurrence of her amelanotic conjunctival melanoma on the conjunctival surface and refused a recommendation that she undergo orbital exenteration. Instead, the patient elected to have conservative surgery at another institution. A year after her local conjunctival recurrence, she developed regional nodal metastasis. Despite completion neck dissection and radiation therapy to the involved nodes, she developed distant organ metastasis in multiple organs a few months later and to date is receiving hospice care.

LOCAL RECURRENCE, REGIONAL NODAL AND DISTANT METASTASIS, AND SURVIVAL

Two patients with bulbar conjunctival melanoma had local recurrence on the conjunctival surface. One patient (patient 14), mentioned in the previous subsection, had diffuse amelanotic recurrence of her conjunctival melanoma and was treated elsewhere with plaque radiotherapy, having refused the recommendation that she undergo orbital exenteration at our institution. The second patient (patient 13) underwent orbital exenteration after recurrence of her conjunctival melanoma. Orbital exenteration was recommended because the patient had been noncompliant with respect to follow-up visits, and it was believed that further conservative surgery was not in her best interest. None of the other patients in the study had a local (orbital, eyelid, or conjunctival) recurrence during the study period.

Overall, 2 of 10 patients with sebaceous cell carcinoma (20%) and 5 of 15 patients with melanoma (33%) had regional nodal metastasis during the study period. The 5 patients with melanoma who had regional nodal metastasis also developed distant organ metastasis. One of the 2 patients with nodal metastasis from sebaceous cell carcinoma developed distant metastasis during the study period. One additional patient with sebaceous cell carcinoma developed distant organ metastasis (lung and spine) without any detectable nodal metastasis on ultrasound or clinical examination.

Two patients with melanoma (patients 12 and 19) and 1 patient with sebaceous cell carcinoma (patient 10) died of metastatic disease during the study period. Another patient with sebaceous cell carcinoma (patient 1) died of unrelated causes (heart failure) during the study period.

The study described herein expands the published literature on the feasibility and safety of SLN biopsy in patients with eyelid and conjunctival cancers and provides data about the rate of positivity of SLNs, the false-negative rate for SLN biopsy, and the overall patterns of local recurrence, regional nodal and distant metastasis, and survival in a group of patients with eyelid sebaceous cell carcinoma and eyelid and conjunctival melanoma.

This study, which to our knowledge represents the largest report to date on SLN biopsy for ocular adnexal cancers, confirms our earlier experience that SLN biopsy is feasible and safe in patients with conjunctival or eyelid tumors. Sentinel lymph node biopsy, which added about 1 to 1.5 hours of surgery to the planned eyelid or conjunctival procedure for patients in our cohort, was associated with negligible risk. The occurrence of temporary weakness of the marginal mandibular branch of the facial nerve in 3 patients was the only adverse effect encountered and resulted in no long-term sequelae. However, the critical question is whether the finding of a histologically positive SLN in 2 of the 25 patients in this series justifies SLN biopsy for high-risk patients with eyelid and conjunctival melanoma or sebaceous cell carcinoma.

Both of the patients with a positive SLN in our cohort had melanoma, 1 with a Breslow thickness of 3.1 mm and the other with a Breslow thickness of 6 mm. For the purposes of this study, we allowed patients with indeterminate tumor thickness, a relatively common finding resulting from mishandling of conjunctival and eyelid melanoma surgical specimens, to undergo SLN biopsy, assuming that...
their tumors may have been greater than 1 mm thick, following the same protocol as with other skin sites. However, it is quite possible that inclusion of these patients confounded our results for rate of SLN positivity and decreased the yield of SLN biopsy findings. If we excluded patients with melanoma with indeterminate tumor thickness, the rate of SLN positivity would increase from 13% (2 of 15) to 22% (2 of 9). Similarly, most studies of series of patients with head and neck melanomas report SLN positivity rates of 15% to 21% for intermediate-thickness melanomas (1.0-4.0 mm) or melanomas less than 1.0 mm thick with other high-risk features, such as ulceration or a Clark level of IV or greater.19-22

The overall false-negative rate in our series of patients was 16% at a median clinical follow-up time of 25 months. Four patients (2 with sebaceous cell carcinoma and 2 with eyelid margin melanoma with significant palpebral conjunctival extension and Breslow thicknesses of 3.5 mm and 12 mm, respectively) had negative SLNs but developed same-basin nodal recurrence during the study period. Several studies19-22 to date have indicated that the false-negative rate for SLN biopsy for cutaneous melanoma of the head and neck ranges from 4.5% to 24% depending on the median length of clinical follow-up. Schmalbach et al19 reported a false-negative rate of 4.5% with a median clinical follow-up time of 25 months in a study of 80 patients with head and neck melanomas treated at the University of Michigan Head and Neck Surgery Department. These investigators used a small (2-3 cm) incision directly overlying the SLNs and performed selective biopsy of individual SLNs, similar to the technique used in our cohort. Chao et al22 reported a higher false-negative rate for SLN biopsy findings in patients with head and neck melanomas than in patients with extremity and trunk melanomas in the Sunbelt Melanoma Study. O’Brien et al26 from the Sydney (Australia) Melanoma Unit, reported a false-negative rate of 25% for head and neck melanomas within 12 months of clinical follow-up. Jansen et al23 reported a false-negative rate of 10.5% for their patients with head and neck melanoma after a mean follow-up period of 23 months. Technical differences and variability in length of follow-up period may account for some of the differences in the false-negative rates in these studies.

Several factors may contribute to a false-negative finding from an SLN biopsy. The lymphatic drainage in the head and neck region is more complex and variable than that in other anatomic sites. With SLN biopsy in the head and neck region, usually more than 1 SLN is radioactive, and there may be some variability as to how many of the radioactive nodes are biopsied by the surgeon. The parotid nodes are small and often located in fibroadipose tissue, making dissection more challenging, particularly given the risk of facial nerve damage. Another source for a false-negative finding from an SLN may be referred to as "biological failure"; that is, a situation in which the lymphatic channels are obstructed by malignant cells, causing rerouting of lymphatic flow through open nonrelevant lymphatic channels. This latter factor may have contributed to the false-negative SLN biopsy findings in patient 19, who had a bulky mass that likely obstructed many of the draining lymphatics. Finally, detection errors can occur during pathologic examination, such that a micrometastasis is not detected in the specimen, as was the case in patient 8, who had an initially negative SLN biopsy finding (with keratin-negative carcinoma cells) that later was deemed histologically positive on repeated review of the histologic sections. However, it is unlikely that this situation is representative of a considerable number of sebaceous carcinomas because the vast majority of such lesions express the keratins commonly detected in standard antikeratin antibodies. Careful examination and immunohistochemical evaluation of SLNs can help decrease the risk of this type of error.16,25

Patient 19, who had melanoma, represented an exceptional case. She had a rapidly growing eyelid and conjunctival mass of at least 12 mm in Breslow thickness (Figure). This patient developed a clinically evident nodal recurrence within 1 month after SLN biopsy. This particular patient may have had an in-transit melanoma metastasis that was missed, given that her nodal recurrence was clinically obvious only 4 weeks after SLN biopsy. Also, given her very bulky tumor, it is possible that the tumor had blocked the lymphatic channels at the time of SLN biopsy and thus did not allow for drainage of technetium Tc 99m sulfur colloid to the relevant SLNs. A large mass like this one, which involved the entire lower eyelid, much of the bulbar conjunctiva, both nasally and temporally, and part of the upper eyelid, also makes it difficult to choose the correct area(s) into which to inject the technetium Tc 99m sulfur colloid tracer for preoperative lymphoscintigraphy as well as for intraoperative localization of the SLNs.

In contrast to the SLN biopsy technique used in our cohort as well as in many other series of head and neck melanomas, Eicher et al20 advocate complete lymphatic basin dissection for all lymphatic basins that harbor an SLN. For most patients with head and neck tumors, this would entail a superficial parotidectomy as well as complete dissection of all other adjacent lymphatic basins that harbor an SLN. The authors20 also advocate dissection of all intervening basins, if the SLNs are found in noncontiguous basins, to avoid missing in-transit metastases. In the study of SLN biopsy in 43 patients with head and neck melanomas, Eicher et al20 reported a false-negative rate of zero, based not on clinical follow-up but rather on the finding that none of the non-SLN nodes in the dissected basins were histologically positive. Their approach entails a larger incision akin to that used for a standard elective neck dissection, which would require additional hours of surgery, and would be associated with higher surgical morbidity than the small-incision selective SLN biopsy used in our cohort and by several other groups.19,22,26 This approach would also produce far more lymph nodes to analyze histologically for the presence or absence of micrometastasis. We believe that given the reported low rates of SLN positivity for ocular adnexal tumors—less than 10%, according to both our own experience and population studies that predict the natural incidence of nodal metastasis in patients with conjunctival melanoma27 and in those with eyelid sebaceous cell carcinoma28-29—performing a superficial parotidectomy (plus, most likely, additional nodal basin dissection) in most patients would be unjustified. Furthermore, this would be quite a departure from the standard of care for treatment of regional lymph nodes in patients with ocular adnexal melanoma or sebaceous cell carcinoma, which at present entails observation of the nodes until overt metastatic disease is discovered.
The patients in our cohort with positive SLNs had a very poor prognosis despite the fact that they were treated with completion neck dissection and parotidectomy followed by radiation therapy to the neck and parotid region. The 2 patients in our series with conjunctival melanoma and positive SLNs developed distant organ metastasis 12 months and 29 months after SLN biopsy. Thus, although SLN biopsy helped identify those at greatest risk for nodal and distant metastasis at the earliest possible time, it did not improve the outcome for these patients. The literature on SLN biopsy for cutaneous melanoma of the head and neck or other anatomic sites corroborates our observation that patients with positive SLNs have lower survival and higher recurrence rates compared with patients with negative SLNs at the time of treatment of their primary cutaneous melanoma. Multivariate analysis involving patients with stage I and II melanoma by Gershenwald et al has demonstrated that histologic status of the SLNs is one of the most important prognostic factors for recurrence and survival.

As treatment options improve for adjuvant therapy for stage III melanoma or sebaceous cell carcinoma with nodal involvement, we may be able to select patients who might benefit from such treatments using SLN biopsy and frequent surveillance to identify microscopic metastasis at the earliest possible time after diagnosis of eyelid or conjunctival cancer.

Given the rarity of ocular adnexal melanomas and sebaceous cell carcinomas, large-scale natural history studies or population studies of these tumors are scarce. However, the literature, based on experiences at referral centers, suggests that the risk of regional lymph node metastasis may be as high as 20% to 40% for conjunctival melanoma, 30% for eyelid melanoma, 10% to 15% for sebaceous carcinoma of the eyelid, and 25% to 60% for Merkel cell carcinoma. 10% to 30% for periorcular squamous cell carcinoma, and 5% to 10% for conjunctival squamous cell carcinoma. In the cohort described herein, the overall incidence of nodal metastasis in the patients with conjunctival and eyelid melanoma was 33%. This is slightly higher than the incidence of regional nodal metastasis reported in a recent population study from Finland that estimated the maximum 10-year cumulative incidence of initial lymphatic metastasis for conjunctival melanoma to be 29%. To date, that report represents the closest attempt to a population study of patterns of metastasis associated with conjunctival melanoma without the usual inherent biases of a tertiary care center experience.

The overall rate of lymph node metastasis for patients with sebaceous cell carcinoma was 20% in our cohort, even though none of the patients with sebaceous cell carcinoma in this cohort had a positive SLN. The 20% rate in our cohort is slightly higher than that reported in other retrospective series to date, which points to about a 10% incidence of regional nodal metastasis and an overall combined rate of regional nodal and distant metastasis of 20% associated with sebaceous cell carcinoma. The higher rate of nodal and distant metastasis in our cohort is probably a function of the more advanced and recurrent nature of sebaceous cell carcinomas treated at our center during the study period. Six of the 10 patients in our cohort had recurrent disease at the time of SLN biopsy, and 4 required an orbital exenteration to achieve complete surgical resection because of the advanced nature of their disease at presentation.

In conclusion, SLN biopsy for ocular tumors is feasible and safe and can be done with a slight modification of the usual injection technique. Our data suggest that SLN biopsy can identify some patients with clinically occult microscopic metastases in their lymph nodes. The false-negative rate for ocular tumors needs to be monitored in larger studies but seems to be higher than the...
rates for most other anatomic sites. Continued improvement in identification and histologic analysis of SLNs may decrease the false-negative rate for SLN biopsy for ocular tumors. Given the minimal morbidity associated with SLN biopsy, it should be considered as an adjunct procedure for better staging of ocular adnexal cancers in high-risk patients. In future studies, melanosomas of undeterminable thickness should probably be excluded because including such tumors may subject some patients with thin tumors to unnecessary SLN biopsy and may decrease the overall yield of the procedure. For sebaceous cell carcinomas, tumors that are recurrent or large, with involvement of postseptal structures requiring an orbital exenteration, are those at greatest risk for metastasis and should be considered for SLN biopsy. Given the possibility of a false-negative finding for an SLN biopsy, patients with high-risk melanomas or sebaceous cell carcinoma of the eyelid and conjunctiva should be carefully followed up for the first 5 years following the diagnosis of their cancer even if SLNs are negative.

Submitted for Publication: July 15, 2006; final revision received November 11, 2006; accepted February 14, 2007.

Correspondence: Bita Esmaeli, MD, Section of Ophthalmology, M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Unit 441, Houston, TX 77030 (besmaeli@mdanderson.org).

Author Contributions: Drs Ho, Ross, Prieto, Khaleeq, Kim, and Esmaeli had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Ross and Esmaeli. Acquisition of data: Ho, Prieto, Khaleeq, and Esmaeli. Analysis and interpretation of data: Ho, Prieto, Khaleeq, Kim, and Esmaeli. Drafting of the manuscript: Ho, Prieto, Khaleeq, Kim, and Esmaeli. Critical revision of the manuscript for important intellectual content: Ross, Prieto, Khaleeq, Kim, and Esmaeli. Statistical analysis: Esmaeli. Obtained funding: Esmaeli. Administrative, technical, and material support: Ho, Ross, Khaleeq, and Esmaeli. Study supervision: Esmaeli.

Financial Disclosure: None reported.

REFERENCES