The Utility of Sentinel Node Biopsy for Sinonasal Melanoma

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Abstract

Objective Report two positive sentinel node biopsies for sinonasal melanoma.

Design Retrospective review.

Setting Academic tertiary care center.

Participants Patients who underwent sentinel node biopsy for sinonasal melanoma between November 1, 2014 and November 1, 2015.

Main Outcome Measures Clinical course.

Results Two patients were identified. Patient 1 (83M) presented with a sinonasal melanoma anterior to the left inferior turbinate and was clinically N0 neck. Lymphoscintigraphy revealed two sentinel nodes in the ipsilateral and three in the contralateral cervical basins. The left level I sentinel node was positive for melanoma and lymphadenectomy showed no additional metastases.

Patient 2 (71F) presented after incomplete resection of a sinonasal melanoma of the left posterior maxillary sinus wall and was clinically N0 neck. Lymphoscintigraphy with single-photon emission computed tomography (SPECT/CT) localization revealed one sentinel node in the parapharyngeal space and another in the ipsilateral cervical basin. Metastatic melanoma was found in both nodes and completion lymphadenectomy was negative for additional disease.

Both patients developed distant metastasis in less than 1 year after surgical resection but responded well to adjuvant immunomodulatory chemotherapeutic agents.

Conclusion Sentinel node biopsy for sinonasal melanoma can provide crucial clinical evidence of regional metastasis prior to overt clinical signs and symptoms. This intraoperative tool has the potential to improve detection of regional metastasis and improve long-term outcomes of this aggressive malignancy.

Keywords

- ▶ sentinel node biopsy
- ▶ sinonasal melanoma
- ▶ melanoma
- ▶ mucosal melanoma

Introduction

Sinonasal melanoma is a rare malignancy derived from melanocytes of the nasal mucosa. It represents approximately 1% of all melanomas and just 4 to 8% of all malignancies of the nasal cavity and paranasal sinuses.¹ In contrast to cutaneous melanoma, the prognosis of sinonasal melanoma is extremely poor with 5-year survivals generally less than 40% despite aggressive treatment.¹

The majority of sinonasal melanomas present with localized disease, with only 5 to 20% of cases presenting with clinically detectable regional metastasis.^{1,2} Unfortunately, achieving long-term local control remains elusive with local recurrence rates of approximately 50%.^{1–3} Further, despite a relatively low rate of regional lymph node metastasis at presentation, cervical metastasis complicates the clinical course of disease in approximately 20 to 40% of cases and is often associated with local or distant recurrence.^{1–3}

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In spite of the known prognostic value of regional nodal status in cutaneous melanoma, evaluation and treatment of the cervical basin remain controversial.⁴ Some authors have questioned whether elective ipsilateral nodal dissection is warranted given the high rate of cervical metastasis at some point in the disease course; however, the lymph node basins of the sinonasal cavity are variable and posterior lesions would be expected to travel to the retropharyngeal nodes, making decisions on the extent of lymph node dissection difficult.^{3,5,6} Sentinel node biopsy offers an opportunity to perform guided lymph node biopsy for at-risk lymph node basins with minimal morbidity.^{7,8} We hypothesize that sentinel node biopsy would offer a minimally invasive approach to staging and treatment of the cervical nodal basin in sinonasal melanoma and report our initial experience of two patients with positive sentinel node biopsies.

Methods

After institutional review board approval (IRB no. 15-002683), a retrospective review was performed for all patients with sinonasal melanoma who underwent a sentinel node biopsy between November 1, 2014 and November 1, 2015. Relevant medical records were then reviewed.

Preoperative lymphoscintigraphy was performed using technetium-99m. The first patient's lesion was injected for lymphoscintigraphy by the otolaryngology service in the morning of surgery. Importantly, all injections were performed just beneath the mucosal epithelium to ensure maximal access to nasal lymphatics. Prior to injection, the nasal mucosa was anesthetized with 1% lidocaine, 1:100,000 epinephrine followed by a four-quadrant injection around the lesion with 0.39 mCi technetium-99m. The second patient underwent in office injection with 2.2 mCi of technetium-99m under endoscopic guidance followed by lymphoscintigraphy and single-photon emission computed tomography (SPECT/CT). Surgical resection was performed

the following day. Intraoperative injections with methylene blue were injected prior to the start of the case in a similar pattern and manner. A hand-held gamma probe (Neoprobe Gamma Detection System; Mammotome; Cincinnati, Ohio, United States) was used to confirm sentinel lymph nodes, and all nodes with gamma activity were removed until background activity was less than 10% of the hottest node.

Results

Two patients were identified that met the inclusion criteria.

Patient 1

The first patient was an 84-year-old male who presented with a 6-month history of gradually worsening epistaxis and was found to have a mass centered on the head of the left inferior turbinate, which was biopsied and consistent with mucosal melanoma. Clinical and radiographic evaluation with magnetic resonance imaging (MRI) did not reveal any concerning lymphadenopathy. Lymphoscintigraphy and colocalization with intraoperative methylene blue were performed as described above, which identified two sentinel nodes in the ipsilateral level 1 and level 2 cervical basins as well as three sentinel nodes in the contralateral level 2 cervical basin (►Fig. 1A).

Intraoperative frozen section of the ipsilateral level 1 sentinel lymph node was positive for metastatic melanoma (►Fig. 1B, ►Fig. 2). Level 1–4 neck dissection was then performed and was negative for additional metastatic disease. All other sentinel lymph nodes were negative for malignancy and the primary site of melanoma was resected to negative margins. Final pathology showed a depth of 3 mm and a mitotic rate of 2 per mm².

Initial postoperative positron emission tomography/computed tomography (PET/CT) showed no evidence of residual disease or distant metastasis, and the patient underwent adjuvant radiation therapy with 6,000 cGy in 30 fractions to the primary site and ipsilateral neck. PET/CT scan 1 year after

Fig. 1 Sentinel node biopsy for patient 1 with sinonasal melanoma centered on the head of the left inferior turbinate. (A) Lymphoscintigraphy shows multiple ipsilateral and a single contralateral sentinel node. (B) Gross appearance of the left level 1 sentinel node with 2.5-mm positive focus of melanoma.

Fig. 2 Histological section of positive sentinel node biopsy stained with hematoxylin and eosin (H&E) at magnification $\times 20$.

surgical resection showed liver metastasis, which proved to be metastatic melanoma. Patient is currently alive with disease 14 months after initial resection and has clinically responded to vemurafenib. No locoregional recurrence has occurred to date.

Patient 2

The second patient was a 71-year-old female who presented to an outside institution with 4 months of gradual onset of unilateral nasal obstruction and nasal congestion. A left-sided nasal mass was found centered on the posterolateral portion of the left maxillary sinus extending onto the middle turbinate. This was partially resected and thought to be an esthesioneuroblastoma. Subsequent pathologic review at our institution was consistent with sinonasal melanoma. Clinical and radiographic evaluation with MRI and PET/CT did not reveal any concerning areas for cervical or distant metastasis.

Lymphoscintigraphy was performed as described above and localized with SPECT/CT scan (**Fig. 3**). This revealed two sentinel nodes, one in the left parapharyngeal space and the other in the ipsilateral level 2 cervical basin. Intraoperative

frozen section analysis revealed metastatic melanoma in the parapharyngeal and level 2 cervical lymph node. Select neck dissection of the ipsilateral level 1 to 4 nodal basins were completed and no additional metastatic nodes were identified. Transnasal endoscopic resection was performed to beyond all gross disease with negative frozen section margins. Permanent sections revealed a focally positive margin at the base of the sphenoid sinus. Patient went on to receive adjuvant radiation therapy with 6,600 cGy in 33 fractions to the base of the sphenoid as well as 6,000 cGy in 30 fractions to the tumor bed, bilateral retropharyngeal nodes as well as the ipsilateral cervical basin. Clinical follow-up 7 months after surgical resection showed evidence of multifocal distant metastasis. Patient was started on pembrolizumab with a complete response of all metastatic sites. Last clinical follow-up 13 months after definitive resection demonstrated no locoregional recurrence and complete response of distant disease.

Discussion

In this study, we reported two successful sentinel node biopsies in patients with sinonasal melanoma. This technique facilitated identification of occult metastasis in the cervical basin that would otherwise have gone undetected. Because subsequent completion cervical lymphadenectomy did not identify additional foci of disease, this suggests that lymphatic mapping was accurate in these cases. Prior to this study, experience in sentinel node biopsy for sinonasal melanoma was limited to two case reports: In 2006, Starek et al reported the first successful identification of a true positive sentinel node in a case of nasal septal melanoma and subsequently, in 2008, Baptista et al reported a single case report of a true negative sentinel node biopsy in a nasal cavity melanoma^{7,8} (**Table 1**). Unlike prior reports, we utilized colocalization with methylene blue for both cases; in our first patient, the positive sentinel node was both gamma active and blue although in the second patient, methylene blue was not identified in the sentinel nodes. In addition, because our second patient's lesion was posterior in the nasal cavity and

Fig. 3 Patient number 2 with lymphoscintigraphy and single-photon emission computed tomography (SPECT/CT) scan. (A and B) show sentinel node in the ipsilateral parapharyngeal space (arrow), which was found to harbor metastatic melanoma. (C) Second sentinel node in the ipsilateral level 2 cervical area (arrow) was also positive for metastatic melanoma.

Table 1 Literature review of all known cases of sentinel node biopsy for sinonasal melanoma

Literature review of sentinel node biopsy for sinonasal melanoma							
Study	Number of patients	Location of primary	SN identified	SN positive	Location of SN	Completion SND	Additional N+
Current	2	1. L Inferior turbinate 2. L posterior nasal cavity	Y ^a	Y ^a	1. L level 1, 2; R level 2 2. L parapharynx; L level 2	Y ^a	N ^a
Baptista et al ⁸	1	R nasal vestibule	Y	N	R level 2,3	Y	N
Starek et al ⁷	1	L nasal septum	Y	Y	L level 2; R level 2	Y	N
Fernandez et al ⁵	1	NS	N	–	–	–	–

Abbreviations: L, left; N+, positive nodes; NS, not specified; R, right; SN, sentinel node; SND, select neck dissection.
^aBoth cases.

at risk for retropharyngeal nodal involvement, we utilized SPECT/CT technology to assist in the localization of nodes that would be challenging using gamma probe alone (► Fig. 3). These techniques may also offer a unique perspective for other sinonasal malignancies in which treatment of the N0 neck is still highly debated.⁹ In a recent review, Dooley et al advocated for elective treatment of the neck in T3–T4 sinonasal squamous cell carcinoma (SCC) secondary to higher rates of nodal involvement; however, in T1–T2 tumors, no treatment was recommended.⁹ These early stage sinonasal SCCs as well as other histologies with relatively low rates of nodal metastasis such as adenocarcinoma, undifferentiated carcinoma, and adenoid cystic carcinoma may be appropriate to stage using sentinel node biopsies though further study is needed prior to widespread application.

To undertake sentinel node biopsy in cases of sinonasal malignancies, it is essential to understand the lymphatic drainage pathway in the nasal cavity. Though most of the initial work in lymphatic drainage patterns was completed in the late 1800s and early 1900s, renewed interest has provided novel insight into nasal lymphatic channels.¹⁰ On histologic examination, nasal lymphatic channels are predominately found in the mucosa just deep to the epithelial lining and less commonly in the submucosa.¹¹ Pan et al reported on using novel cadaveric imaging technique to map lymphatic channels in the nasal cavity and found a robust, valveless interconnected network of lymphatic channels that follow two distinct pathways from the nasal cavity and nasopharynx to the retropharyngeal and the level 2 cervical chain nodes.¹⁰ Fernandez et al performed a clinical evaluation of drainage patterns after injection of radiocolloid into the head of the inferior turbinate and demonstrated that the majority of the drainage was to level 1 and level 2 cervical lymph nodes and less commonly to the retropharynx.⁵ In cases of sinonasal melanoma, though in general more anterior lesions will drain into the submandibular and jugulodigastric nodes and the more posterior lesions will drain into the retropharyngeal area, these neoplasms are often large and span multiple subsites, putting several drainage pathways at risk for regional metastasis. Though the rate of the regional spread at presentation is reported to be 5 to 20%,

approximately 20 to 40% of patients will have a regional recurrence that complicates their disease course.^{1,3} This discrepancy could indicate that there is a subset of patients who have undetected occult metastasis that manifest later in the disease course. Highlighting the impact of nodal metastasis on oncologic outcome, Chan et al reviewed 35 patients with mucosal melanoma of the head and neck and found a significant difference in overall survival in patients with nodal disease on presentation with a 5-year survival of less than 20% for node positive patients and approximately 40% for node negative patients ($p < 0.05$).¹² The most recent National Comprehensive Cancer Network (NCCN) Guidelines for mucosal melanoma recommend treatment of the nodal basin only in patients with clinical nodal disease based on physical exam and imaging studies. However, in our study, we identified two patients who had occult metastasis at presentation that would not have been detected using these guidelines. Early detection using sentinel node biopsy allowed for immediate therapeutic neck dissection and adjuvant radiation therapy. Further, the mapping and biopsy may allow additional precision of adjuvant radiation therapy to the at risk nodal basins, potentially limiting the morbidity of radiation therapy. In our series, both patients demonstrated the development of distant metastasis in less than 1 year after surgical resection; however, they responded well to immunomodulatory chemotherapeutic agents. Early identification of cervical metastasis could help stratify patients who are at a high risk for distant metastasis to allow for closer surveillance or earlier treatment with adjuvant chemotherapy and potentially improve the dismal outcomes of this disease entity.

There are several potential challenges in sentinel node biopsy for sinonasal malignancy. First, the ability to inject into the nasal cavity is somewhat dependent on the local tumor burden. Both patients in our series had relatively small, accessible tumors, or those located in more isolated areas such as within the ethmoid sinuses or frontal recess may present challenges in adequate injection. Second, considerable cost, time, and coordination are required by the nuclear medicine physicians to perform this technique in a timely manner. In addition, given the risk of retropharyngeal nodal spread,

SPECT/CT should be a readily available imaging modality, furthering the burden of cost, time, and coordination. Despite these challenges, there is a large percentage of patients who would be potential candidates for lymphoscintigraphy.

The authors wish to acknowledge several limitations of this study. Because bilateral neck dissections were not performed, we cannot definitively say that the lymphoscintigraphy accurately identified all involved lymph nodes, and the use of adjuvant radiation therapy to some of the lymphatic beds will prevent us from knowing the answer to this question based on regional nodal recurrence. In addition, this study is a small case series with limited follow-up; thus, the impact of early detection of occult nodal metastasis is unknown and requires further investigation and long-term follow-up.

Conclusion

This study reports on two patients with sinonasal mucosal melanoma who underwent successful sentinel lymph node biopsy. We were able to identify and treat occult micrometastatic disease in both the cervical basin and the parapharyngeal space. Further evaluation into the reliability and clinical benefits of this technique is required prior to its widespread adaptation.

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None.

Conflict of Interests
None.

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