Rates and Locations of Regional Metastases in Sinonasal Malignancies: The Mayo Clinic Experience

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Abstract

Objectives The objective of this study was to identify factors that may influence the rate and location of regional metastasis in sinonasal malignancies (SNMs).

Design This is a retrospective review.

Setting This study was set at the single-institution tertiary referral center.

Participants A total of 299 patients were treated for SNMs from 1994 to 2014.

Main Outcome Measures The main outcome measures were incidence and distribution of regional metastases.

Results Several histologic subtypes were treated, with squamous cell carcinoma (28.4%), esthesioneuroblastoma (18.1%), and mucosal melanoma (12.4%) being the most common. Of the 299 patients, 59 (19.7%) developed a regional metastasis, either at presentation or during follow-up. Higher cumulative incidence of regional metastases was significantly associated with histologic type ($p \leq 0.001$) and invasion of the dura ($p = 0.005$), infratemporal fossa ($p = 0.036$), orbit ($p = 0.020$), or palate ($p = 0.016$). Ipsilateral level II lymph nodes were the most commonly involved nodes. Contralateral regional metastases were associated with higher risk histologic types ($p = 0.005$) and dural invasion ($p = 0.008$). Parotid metastases were associated with invasion of the facial soft tissue ($p = 0.028$), and retropharyngeal metastases were associated with invasion of the pterygoid plates and musculature ($p = 0.030$).

Conclusion Histologic type of SNM appears to be the most important factor in predicting the rate of regional metastases. Histologic type and invasion of certain neighboring structures may help define which lymphatic basins are at highest risk for metastasis.

Keywords
- sinonasal malignancy-
- sinonasal
- cancer
- metastasis
- regional metastases

Introduction

Sinonasal malignancies (SNMs) are both rare and aggressive. They represent approximately 3 to 5% of all head and neck malignancies and less than 1% of malignancies overall.[1,2] They are associated with a poor prognosis and tend to be locally advanced on presentation. The presence of large air spaces in the paranasal sinuses allows asymptomatic growth of tumors, and early symptoms such as nasal obstruction and epistaxis are often attributed to common nasal complaints, and therefore, overlooked.[3] The last few decades have seen advancements in endoscopic endonasal skull base surgery, microvascular reconstruction, stereotactic radiosurgery, proton beam therapy, and advances in both chemotherapy and immunotherapy. These have allowed more advanced and more complex tumors to undergo intent-to-cure treatments. Despite this, 5-year overall survival (OS) for all SNMs has remained stable in aggregate over the past 30 years, at 50 to 55%.[1]

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The most common pattern of failure for SNM is local recurrence; however, regional metastases are a significant predictor of survival.[4] Regional metastases have been estimated to occur at a rate between 3 and 33%, differing based on tumor histology, T-stage, and treatment of the primary site.[5–8] In the setting of a clinically N0 neck, elective treatment with surgery or radiation is commonly recommended when there is an occult metastasis risk of approximately 10 to 20% or more. However, one must also predict the likely location of a metastasis, which is especially challenging in SNM due to the complex lymphatic drainage pathways of the nasal cavity, paranasal sinuses, and neighboring structures. Given the heterogeneity of histologies and anatomic subsites as well as the rarity of these tumors, there is little consensus regarding the rate and location of regional metastases for SNM. To gain a better understanding of the rate and location of SNM metastases, we analyzed our experience over the past 20 years.

Methods

Study Patients

A retrospective review of all patients with SNM treated at a single academic tertiary referral center from 1994 to 2014 was conducted. The study was approved by the Institutional Review Board (15–002683). International Classification of Diseases, Ninth Revision codes were used to query an institutional cancer database, generating a total of 373 patients to review. Patients with disease originating in the temporal bone, nasopharynx, intracranial cavity, or of the nasal skin were excluded, resulting in 299 patients with malignancy of the nasal cavity and paranasal sinuses. Medical charts were reviewed for demographic data, risk factors and symptoms identified at presentation, comorbidities, histologic and pathologic data, clinical staging, treatment, and outcomes including patterns of recurrence and survival. Histologic tumor type and grade were determined by experienced pathologists based on biopsies or surgical resections. The American Joint Committee on Cancer, 7th edition staging system was used based on tumor type and location, including histologic-specific T- and N-staging for mucosal melanoma and soft tissue sarcoma. Primary tumor anatomic subsite, extent of invasion, and nodal status were determined by evaluating radiographs, physical examinations, operative reports, and surgical pathology reports. To determine the presence of regional metastases and the affected lymphatic basin, pathologic specimen data were used when available. Rarely, radiographic criteria alone were used to determine if a regional metastasis was present, for example, in situations of overwhelming evidence of regional and/or distant recurrence and the patient underwent nonoperative or palliative treatment.

Statistical Analysis

Comparisons of descriptive variables were performed with two-sided Fisher's exact test or chi-square test. OS and disease-specific survival (DSS) were estimated using the Kaplan–Meier's method. Rates of regional metastasis were calculated as cumulative incidence to account for death as a competing risk.[9] If a patient presented with regional metastasis, then time to metastasis was set as 1 day. Comparison of rates were made using Gray's test.[10] Among patients with regional metastases, Fisher's exact test was used to see if location was related to various characteristics.

To facilitate analysis, data were selectively compressed into groups. Histologic types of tumors were grouped into low-, moderate-, and high-risk groups based on their potential for regional metastatic spread. This grouping was based on the observed rate of regional metastases in this cohort of patients. Low-risk histologic types were defined as adenoid cystic carcinoma, adenocarcinoma, and "other." Moderate-risk histologic types were defined as melanoma, squamous cell carcinoma, and sinonasal undifferentiated carcinoma. High-risk histologic types were defined as esthesioneuroblastoma, neuroendocrine carcinoma, and soft tissue sarcoma. Histologic grade was grouped into categories of low grade, moderate grade, and high grade. This final category included poorly differentiated and undifferentiated tumors. Finally, to facilitate statistical analysis, the locations of the tumors were grouped into five categories. "Midline" tumors originated from the septum or cribriform plate. "Ethmoid complex" tumors originated from the ethmoid sinus, middle turbinate, or superior turbinate. "Maxillary complex" tumors originated from the maxillary sinus or the inferior turbinate. "Frontal/sphenoid" tumors originated from the frontal sinus or sphenoid sinus. Finally, "other nasal cavity" included tumors in which the epicenter or location where the tumor began could not be identified but were clearly not tumors originating from the nasopharynx or other locations outside the sinonasal cavity that had invaded the sinonasal cavity.

Results

Patient Demographics and Survival

A total of 299 patients with malignancy of the nasal cavity or paranasal sinuses who underwent treatment at our institution met inclusion criteria. The median age of the patients was 58 years (range: 6–90), and there was a predominance of men (57.2%) and Caucasians (88.0%) in the cohort (►**Table 1**). Disclosed occupational risk factors were rare, with only 3.4% of the population reporting a history of woodworking or exposure to chemical or paint production. Approximately half (47.9%) of the population reported a history of tobacco abuse and much fewer (11.0%) reported a history of alcohol abuse. The most common presenting symptoms of SNM were nasal obstruction (57.5%), epistaxis (31.2%), headache or facial pain (31.2%), changes in vision or diplopia (13.6%), and sensory disturbances of the face or palate (12.3%).

The entire cohort of patients with SNM had 5- and 10-year OSs of 60.2 and 41.6%, respectively. The 5-year DSS was 66% and 10-year DSS was 53.9%. Patients who presented with lymph node metastases had reduced survival compared with those who did not (5-year DSS 44.6 vs. 68.6%; 10-year DSS 37.1 vs. 55.9%, $p = 0.014$).

Tumor Characteristics and Staging

The most common SNMs were squamous cell carcinoma (28.4%), esthesioneuroblastoma (18.1%), and mucosal melanoma (12.4%) (►**Table 1**). The primary site of the malignancy

Table 1 Demographic, tumor, and staging data for all patients

	No. of patients ($n = 299$)	Percentage (%)
Age		
Median = 58; range = 6–90		
Sex		
Male	171	57.2
Female	128	42.8
Primary site		
Maxillary sinus	74	24.7
Ethmoid sinus	63	21.1
Frontal sinus	5	1.7
Sphenoid sinus	18	6.0
Septum	31	10.3
Inferior/middle/superior turbinate	35	11.7
Cribriform plate	32	10.7
Other nasal cavity	41	13.7
Histology		
Squamous cell carcinoma	85	28.4
Esthesioneuroblastoma	54	18.1
Mucosal melanoma	37	12.4
Adenoid cystic carcinoma	30	10.0
Adenocarcinoma	27	9.0
Sinonasal undifferentiated carcinoma	24	8.0
Soft tissue sarcoma	24	8.0
Neuroendocrine carcinoma	11	3.7
Other	7	2.3
Grade		
Well differentiated	38	12.7
Moderately differentiated	74	24.7
Poorly undifferentiated	87	29.1
Undifferentiated	25	8.4
Not recorded	38	12.7
T-stage		
T1	27	9.0
T2	49	16.4
T3	70	23.4
T4a	73	24.4
T4b	80	26.8
N-stage		
N0	271	90.6
N1	9	3.0
N2	19	6.4
N3	0	0.0
M-stage		
M0	295	98.7
M1	4	1.3

was more commonly found in the paranasal sinuses than the nasal cavity (53.5 vs. 46.5%). Adenoid cystic carcinoma ($p = 0.009$) and squamous cell carcinoma ($p = 0.0001$) were more commonly found in the paranasal sinuses. Esthesioneuroblastoma ($p = 0.0003$) and mucosal melanoma ($p = 0.012$) were more commonly found in the nasal cavity. Locally advanced tumors (T3–T4) were more common than early-stage tumors (74.6 vs. 25.4%). Malignancies of the paranasal sinuses more commonly presented in locally advanced stages (T3–T4) compared with those of the nasal cavity malignancies (88.8 vs. 55.7%, $p < 0.0001$). Metastatic disease on presentation was rare, but 9.4% (28/299) of patients had regional metastases and 1.3% (4/299) had distant metastases on presentation (►**Table 1**).

Rates of Regional Metastases

The rate and distribution of regional metastases by lymphatic basin were recorded for each patient. On presentation, a total of 28 patients (9.4%) had lymph node metastases, with 3% having N1 disease and 6.4% having N2 disease. No patient presented with N3 disease. After treatment, a total of 34 patients developed regional recurrence of their disease (11.3%). A total of 59 patients (19.7%) developed regional metastases at some point, either at presentation or during posttreatment surveillance. The rate of lymph node metastases varied by histologic type, with the highest rates of regional metastases found in patients with esthesioneuroblastoma (37%) and neuroendocrine carcinoma (27%). No patients with adenoid cystic carcinoma experienced regional metastasis of their disease (►**Table 2**).

Estimated cumulative incidence of regional metastases at 1-, 3-, and 5-year intervals following primary treatment was calculated (►**Table 3**). Histologic tumor type was significantly associated with the rate of regional metastases ($p < 0.001$). Higher histologic grades of malignancies trended toward a higher cumulative incidence of regional metastases, but the difference between these models was not found to be statistically significant ($p = 0.069$). There was no significant difference in regional metastasis rate when comparing primary tumor locations within the sinonasal cavity ($p = 0.389$). However, invasion into a few neighboring structures were significantly

Table 2 Rate of regional metastases by histologic type

Histology	No. of patients	No. with Mets	Rate of Mets
Esthesioneuroblastoma	54	20	37.0%
Neuroendocrine carcinoma	11	3	27.3%
Soft tissue sarcoma	24	6	25.0%
SNUC	24	5	20.8%
Squamous cell carcinoma	85	17	20.0%
Melanoma	37	6	16.2%
Adenocarcinoma	27	2	7.4%
Adenoid cystic	30	0	0.0%
Other	7	0	0.0%
Total	299	59	19.7%

Abbreviations: Mets, regional metastases; SNUC, sinonasal undifferentiated carcinoma.

Table 3 Estimated cumulative incidence of regional metastases at 1-, 3-, and 5-year intervals following primary treatment of SNM

	Incidence at 1 y (%) (95% CI)	Incidence at 3 y (1%) (95% CI)	Incidence at 5 y (%) (95% CI)	*p*-Value
Histologic type				
Low risk	0.0 (0.0–0.0)	1.8 (0.1–8.6)	1.8 (0.1–8.6)	<**0.001**
Moderate risk	16 (10.6–22.5)	19.2 (13.1–26.2)	20.5 (14.1–27.8)	
High risk	20.3 (12.6–29.2)	27.6 (18.3–37.6)	33.3 (22.6–44.4)	
Grade of tumor				
Low grade	2.6 (0.2–12.0)	5.9 (1.0–17.5)	5.9 (1.0–17.5)	0.069
Moderate grade	9.6 (4.2–17.8)	16.7 (8.7–26.9)	24.4 (13.6–36.8)	
High grade	17.0 (11.4–23.5)	20.0 (13.9–26.9)	20.0 (13.9–26.9)	
T-stage				
Early T-stage	9.3 (4.1–17.2)	10.9 (5.1–19.4)	13.2 (6.3–22.7)	0.117
Late T-stage	15.4 (11–20.5)	20.4 (15.2–26.1)	22.8 (17.1–29.0)	
Location of primary				
Midline	11.6 (5.7–19.9)	17.0 (9.2–26.9)	27.1 (15.7–39.8)	0.389
Ethmoid complex	11.0 (5.1–19.4)	16.2 (8.5–26.0)	16.2 (8.5–26.0)	
Maxillary complex	18.0 (10.6–27.0)	23.1 (14.6–32.8)	23.1 (14.6–32.8)	
Frontal/sphenoid	12.0 (3.1–30.2)	12.0 (3.1–30.2)	12.0 (3.1–30.2)	
Other nasal cavity	14.9 (5.9–27.6)	14.9 (5.9–27.6)	14.9 (5.9–27.6)	
Invasion[a]				
Orbit	22.3 (14.6–30.9)	27.9 (19.3–37.2)	27.9 (19.3–37.2)	**0.020**
Skull base	13.3 (8.3–19.4)	17.7 (11.7–24.6)	21.4 (14.4–29.2)	0.730
Dura	16.4 (8.7–26.3)	25.2 (15.2–36.6)	32.5 (20.4–45.2)	**0.005**
Brain	16.7 (2.4–42.4)	29.6 (4.6–61.9)	29.6 (4.6–61.9)	0.532
Infratemporal fossa	29.2 (12.6–48.0)	34.9 (15.7–54.9)	34.9 (15.7–54.9)	**0.036**
Pterygopalatine fossa	27.6 (16.1–40.3)	29.7 (17.7–42.7)	29.7 (17.7–42.7)	0.066
Pterygoid space	24.0 (9.5–42.0)	28.9 (12.4–47.8)	28.9 (12.4–47.8)	0.204
Nasopharynx	23.1 (5.2–48.4)	23.1 (5.2–48.4)	23.1 (5.2–48.4)	0.572
Palate	27.2 (14.5–41.5)	32.9 (18.7–47.9)	32.9 (18.7–47.9)	**0.020**
Facial soft tissue	17.5 (6.2–33.6)	21.6 (8.5–38.6)	21.6 (8.5–38.6)	0.919

Abbreviations: CI, confidence interval; SNM, sinonasal malignancy.
Note: *p*-Values obtained by Gray's test.
[a]*p*-Values for this section are comparing between the presence and absence of invasion into the applicable structure.

associated with higher cumulative incidence of regional metastases (►**Table 3**). Invasion of the dura was significantly associated with higher incidence of nodal metastases compared with tumors that did not invade dura ($p = 0.005$), but invasion of the osseous skull base was not ($p = 0.730$). Other areas of invasion that were significantly associated with higher incidence of nodal spread include the infratemporal fossa ($p = 0.036$), orbit ($p = 0.02$), and palate ($p = 0.016$).

Lymphatic Basins at Risk

In patients who did have a regional metastasis ($N = 59$), the location of these metastases by lymphatic basin was recorded based on pathologic or radiologic data. These patterns were then analyzed to determine which basins were most frequently affected in patients who developed regional metastases based on tumor type, location, and invasion of neighboring structures (►**Table 4**).

Overall, level II of the neck was the most commonly affected lymphatic basin, occurring in 69% of patients with any regional metastases. Level I was the next most common (45%), followed by levels III (29%), IV (21%), V (17%), retropharynx (17%), and parotid gland (14%). Nodal spread relative to the tumor epicenter was more common in the ipsilateral nodal basins; however, 22% of the lymph node metastases occurred on the contralateral side of the tumor epicenter. Bilateral regional metastases occurred in 23 of the 59 patients (39%): 10 of the 27 patients with metastases at presentation, 10 of the 30 patients with regional recurrence after treatment, and 3 of the 4 patients with nodal disease both at presentation and in recurrence.

Table 4 Distribution of lymphatic levels affected in patients with known regional metastases

Category[a]		Ipsilateral				Contralateral
		I–IV	V	RP	PAR	Any
Histologic type						
Low risk		100.0	0.0	0.0	0.0	0.0[b]
Moderate risk		78.6	17.9	14.3	14.3	17.9[b]
High risk		89.7	13.8	10.3	13.8	55.2[b]
Location of primary						
Midline		94.7	10.5	10.5[b]	10.5	47.4
Ethmoid complex		81.8	0.0	18.2[b]	27.3	27.3
Maxillary complex		80.0	15.0	0.0[b]	10.0	20.0
Frontal/sphenoid		66.7	33.3	0.0[b]	0.0	66.7
Other nasal cavity		83.3	50.0	50.0[b]	16.7	50.0
Invasion[c]						
Skull base	Yes	90.0	16.7	20.0	13.3	53.3[b]
	No	79.3	13.8	3.4	13.8	17.2[b]
Dura	Yes	90.9	13.6	18.2	13.6	54.5[b]
	No	81.1	16.2	8.1	13.5	24.3[b]
Pterygoid space	Yes	100.0	42.9	42.9[b]	14.3	42.9
	No	82.7	11.5	7.7[b]	13.5	34.6
Facial soft tissue	Yes	33.3[b]	16.7	0.0	50.0[b]	16.7
	No	90.6[b]	15.1	13.2	9.4[b]	37.7

Abbreviations: I–IV, levels I to IV of the lateral neck; V, level V of the lateral neck; Any, any contralateral nodes; PAR, parotid; RP, retropharynx.
Note: Within a certain category, the values in this table represent how often (%) a regional basin was affected in patients who had known regional metastases. Rows do not sum to 100% due to patients having metastases in multiple lymphatic basins.
[a]Categories also included in statistical analysis but not reported in this table due to nonsignificant findings: histologic grade of tumor and T-stage.
[b]$p < 0.05$ by Fisher's exact test.
[c]Statistical testing for the invasion category is a comparison between those with and without invasion into the applicable structure. Testing was also completed for invasion of the orbit, brain, infratemporal fossa, pterygopalatine fossa, nasopharynx, and palate, and no significant differences were identified.

Based on histologic type, a high-risk malignancy was significantly more likely to be associated with contralateral regional metastases than moderate- or low-risk malignancies ($p = 0.005$). Histologic grade of tumor did not have a statistically significant association with the lymphatic basin affected by regional metastases. When considering tumor location, tumors in the "other nasal cavity" group, which were large and destructive lesions where tumor epicenter could not reliably be determined, were statistically more likely to be associated with retropharyngeal node involvement than other locations.

Invasion of certain anatomic regions was associated with metastasis to specific lymphatic basins. Invasion of facial soft tissue was significantly associated with parotid lymphatic involvement ($p = 0.028$) and invasion of the pterygoid plates and surrounding area was associated with retropharyngeal node involvement ($p = 0.030$). Contralateral metastases were significantly associated with dural invasion ($p = 0.008$), even when controlling for histologic type of malignancy.

Discussion

Management of SNM presents the treating physician with several important challenges. First, treatment of the primary tumor site often risks morbidity to adjacent structures that are critical to life or quality of life. Also, there is a great deal of heterogeneity in the clinical behavior of the different histologic types of SNM, each being sufficiently rare to limit an evidence-based approach to their management. The decision of when to treat regional lymphatics is clear when evidence of nodal metastasis is present. However, in the clinically N0 neck, it is challenging to estimate the risk of occult nodal metastases and to select which basins require treatment. The presence of regional metastases, including occult disease, has been shown to have a significant effect on prognosis. In a review of 704 cases at a single institution, Cantù et al showed that survival was significantly reduced in patients with regional metastases, from 45.3 to 50.6% 5-year OS to 0 to 16.8% in those with nodal disease.[11]

The overall rate of regional metastasis in this series was 19.7% (59/299); with 28 patients (9.4%) having nodal disease on presentation and 34 patients (11.3%) suffering a regional recurrence of disease following intent-to-cure treatment. This is similar to other estimates of the rate of regional metastases from SNM in the literature. Dutta et al queried the Surveillance, Epidemiology, and End Results (SEER) database of all SNM, and identified an 18 to 27% rate of regional metastases depending on the site of disease.[2] A review of the SEER database of nasal cavity squamous cell carcinoma revealed a rate of 9.1% of patients who presented with regional metastases,[12] and another study of the SEER database found a 23% rate of regional metastases in patients with maxillary sinus squamous cell carcinoma.[4] Mirghani et al performed an excellent literature review and found rates of regional failure after treatment between 2 and 33%.[6]

In this series, several factors were significantly associated with increased rate of regional metastases. Histologic type of tumor appeared to be the most impactful factor in determining the risk for metastases, which is consistent with well-known characteristics of SNM and the heterogeneity of tumor behavior. In this series, the location of the primary tumor within the sinonasal cavity was not associated with a difference in the rate of regional metastases. Metastases were more commonly seen in advanced T-stage, but this correlation did not reach levels of statistical significance. Interestingly, when evaluating invasion of specific neighboring structures, it was found that tumor invasion into the orbit, dura, infratemporal fossa, or palate were associated with a statistically significantly increased rate of regional metastases. This finding suggests that it is the transgression of the osseous confines of the sinonasal cavity into adjacent structures that increases a tumor's risk for developing regional metastases.

Dural invasion remained a significant predictor of regional metastases even after controlling for histologic type, and eliminating esthesioneuroblastoma as a potential confounder due to its known high incidence of regional metastasis. The central nervous system was once thought to be devoid of lymphatics; however, recent findings suggest that there is a network of lymphatic vessels within the dura of the skull base along dural sinuses. These vessels have a layer of functional lymphatic endothelium, have been shown to carry interstitial fluid and cells from the CSF, exit the skull base via established foramina and the cribriform plate, and drain to deep cervical lymph nodes.[13,14] This discovery would lend credence to the finding in this series that dural invasion increased the risk for regional metastasis to the cervical lymph nodes, but skull base invasion did not. Interestingly, invasion of the brain was not significantly associated with higher rates of regional metastases. To invade the brain parenchyma, a tumor must also invade the dura. However, we suspect that the low number of patients with brain invasion, and therefore, wide confidence intervals in the estimated cumulative incidence of regional metastases influenced this statistical comparison.

There is very little literature on which lymphatic basins within the neck are at highest risk in the setting of SNM. Early studies of sinonasal lymphatic drainage by Rouviere in 1932 described anterior sinonasal tissues draining into the submental region and posterior sinonasal tissues into the lateral retropharyngeal nodes and deep jugular chain.[15] Recently, Fernández et al performed lymphoscintigraphy during sentinel lymph node biopsy for patients with sinonasal tumors and found that levels I to II most commonly contained the sentinel node, but radioactivity was identified in retropharyngeal nodes in 6.6% of cases.[16] The most common basin affected by lymph node metastases in this study was level II of the ipsilateral neck, followed by level I of the ipsilateral neck. This corresponds with data collected by Shidnia et al, who found that level II of the ipsilateral neck was the most common site of lymphatic burden, followed by level I.[17] These findings are also supported by Katz et al, who found level II to be the most common basin at risk, followed closely by level I, in a subset of patients treated with local radiotherapy for a SNM.[18]

Although there were an insufficient number of patients and lymph node metastases in this study to compare each lymphatic level to another, the vast majority of metastases did occur in the lateral neck (levels I–IV)—which is often treated as a single unit either with neck dissection or radiotherapy. For this reason, our statistical analysis grouped the lateral neck (levels I–IV) into a single category, and sought to understand what tumor characteristics may be associated with regional metastases to additional basins, such as level V, retropharyngeal, or parotid lymph nodes.

The identification of facial soft tissue invasion and pterygoid invasion being associated with parotid and retropharyngeal metastases, respectively, should alert the treating clinician of the potential for metastatic spread to these basins that are not always addressed when a decision has been made to treat an N0 neck. The "other nasal cavity" location group was also significantly associated with retropharyngeal nodal disease compared with other tumor locations; however, this is difficult to interpret as this group included tumors that were too large to determine where they had originated. High-risk histologic types and tumors with dural invasion more commonly spread to the contralateral neck, and therefore, either neck dissection or radiotherapy of the contralateral neck should be considered in these situations. In this cohort, none of the tested factors had an association with increased involvement of the posterior neck (level V). The information presented in this study allows us to better understand the risk factors for regional spread of SNM, which in turn may provide important information when considering management of the neck.

This study has some important differences and strengths compared with the currently available literature. Due to the relative scarcity of SNM, much of the available data in the literature relies on large population-based databases such as the SEER database. This allows conglomeration of large numbers of patients to increase statistical power, but comes at the expense of heterogeneity and loss of detail about patient care. Many of these databases contain missing data and are pooled from many institutions with widely variable treatment and follow-up patterns and protocols. In contrast, this study contains

a large number of patients treated in a single institution in a modern cohort. This allows more careful collection of data points and more thorough analysis, such as the ability to identify which lymphatic basins were affected by regional metastases or the specific structures invaded by a tumor and not simply the overall T-stage or N-stage. There are some inherent weaknesses in this study, as well. Compared with a larger population study, there are relatively few events of regional metastases, which limit the statistical power to detect factors that may be associated with the location of regional metastases. As an example, we grouped levels I to IV of the neck into one clinically relevant category and set aside from other, less commonly treated basins of the neck. With a larger cohort of patients with metastases, analysis of individual levels of the lateral neck may be possible. Because of the heterogeneity of tumor histologies studied, there are relatively smaller numbers of each tumor type, and a larger cohort may have more statistical power to identify other associations based on histologic type. Also, this study does not report outcomes after elective treatment of the lymphatic basins or evaluate the method of local tumor treatment. In further projects, we hope to evaluate the impact of elective or therapeutic neck dissection or radiation of regional lymphatics on regional failure patterns and survival.

Conclusion

This single-institution retrospective review of patients with SNM identified a regional metastasis rate of 19.7%. The histologic type of malignancy appeared to be the most significant factor in determining the risk for regional metastases, with esthesioneuroblastoma and neuroendocrine carcinoma having the highest propensity for nodal disease and adenoid cystic carcinoma and adenocarcinoma the least. Invasion of the orbit, dura, infratemporal fossa, and palate was associated with an increased rate of regional metastases, but tumor location was not. This study also identified several factors that may clarify the nodal basins at highest risk. High-risk histologic types were associated with higher rates of contralateral neck involvement, as were tumors with invasion of the skull base and dura. Invasion of the facial soft tissues was significantly associated with higher incidence of parotid metastases, and invasion of the pterygoid plates and musculature was significantly associated with retropharyngeal metastases. Close attention to these tumor factors may help identify which clinically N0 patients would benefit from treatment of regional lymphatics, and which basins should be included in that treatment.

Level of Evidence
The level of evidence is Level IV—retrospective case series.

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Conflict of Interest
The authors have no conflict of interest to disclose.

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