

Mucosal Melanoma of the Head and Neck

Predictors of Prognosis

Andrew G. Shuman, MD; Emily Light, MS; Stephen H. Olsen, MD; Melissa A. Pynnonen, MD; Jeremy M. G. Taylor, PhD; Timothy M. Johnson, MD; Carol R. Bradford, MD

Objectives: To identify significant clinical and pathological predictors of survival in mucosal melanoma of the head and neck.

Design: Retrospective case series. We reviewed cases of mucosal melanoma of the head and neck from a prospectively collected database after institutional review board approval.

Setting: A single academic institution.

Patients: Fifty-two patients with mucosal melanoma of the head and neck.

Results: With a median follow-up of 97 months, the median overall survival was 52 months, with a 5-year overall survival of 38%. The median disease-free survival was 15 months, with a 5-year disease-free survival of 22%. Younger age ($P = .02$), lower T status ($P = .003$), and lower American Joint Committee on Cancer stage ($P < .001$) were associated with better overall survival. Positive surgical margins predicted poorer overall survival ($P = .01$),

but patients who required reexcision to achieve negative margins had outcomes that were not significantly different from those with initially negative surgical margins ($P = .71$). Sex, smoking history, and primary site did not affect disease-free or overall survival. Adjuvant radiotherapy and/or chemotherapy did not predict improved outcomes. Fewer mitoses ($P = .02$) and the absence of ulceration ($P = .01$) predicted improved overall survival.

Conclusions: Our experience confirms the utility of current staging systems in predicting outcomes of mucosal melanoma of the head and neck and stresses the importance of achieving negative surgical margins. Pathologically, fewer mitoses and the absence of ulceration predict better outcomes and should be reported as part of routine histological profiles of mucosal melanoma. Further studies are necessary to change the paradigm of care for this rare and deadly disease.

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Author Affiliations:

Departments of Otolaryngology (Drs Shuman, Pynnonen, Johnson, and Bradford), Pathology (Dr Olsen), and Dermatology (Drs Olsen and Johnson), University of Michigan Medical School, and Biostatistics Unit, University of Michigan Comprehensive Cancer Center (Ms Light and Dr Taylor), Ann Arbor.

MUCOSAL MELANOMA IS A rare disease that involves the mucosa of the upper aerodigestive tract and perineum and comprises less than 1% of all diagnosed melanomas.¹ The disease has a poor prognosis and is not well understood as a distinct clinical entity owing to its rarity.² As a result, recommended management is typically based on pooled data from case reports and smaller case series. Although recurrent and metastatic disease occur frequently, most cases present solely with primary site involvement.³ Treatment is typically surgical despite the absence of prospective and/or randomized trials assessing the efficacy of treatment strategies in the primary or adjuvant setting.⁴

Mucosal melanoma has a unique staging system because traditional aspects of cutaneous melanoma staging may not apply.⁵ Histological diagnosis can be challenging owing to its rarity and variable appearance.⁶ Standard histopathological

predictors of poor prognosis that affect cutaneous melanoma staging, such as Breslow depth, ulceration, and mitoses, have not been shown to influence survival in mucosal melanoma.⁷ As a result, a salient management guideline does not exist for treatment solely based on clinical and pathological staging.

This study was designed to report the clinical characteristics of patients diagnosed as having mucosal melanoma of the head and neck, including survival, treatments received, and clinical and histopathological predictors of improved survival. We hypothesized that specific clinical and pathological factors might significantly affect survival and potentially alter the management of this challenging clinical entity.

METHODS

DESIGN

This study reports a retrospective case series approved by the University of Michigan Medi-

cal School institutional review board. The patients were identified and the data were collected from a comprehensive, prospective, single-institution, melanoma clinicopathological database from 1992 through 2009. Additional queries were made of a separate University of Michigan electronic pathology database using the terms *melanoma AND mucosa, mouth, oral cavity, lips, tongue, buccal, sinus, nose OR nasal* to ensure that all eligible patients were captured. Patients with biopsy-confirmed primary melanoma of the mucosal surface of the upper aerodigestive mucosa were included; patients who had poorly differentiated tumors that were not conclusively melanoma, primary involvement of cutaneous skin (including the lip), metastatic lesions involving aerodigestive mucosa, and primary mucosal melanoma not involving the head and neck were excluded. The demographics and clinical course as documented in the melanoma database were confirmed and cross-referenced via the electronic medical record by manual medical record abstraction.

MEASURES

The clinical variables evaluated included age at diagnosis, smoking status, clinical presentation at the time of diagnosis, site of the tumor, presence of other diagnosed neoplasms, response to and type of initial therapy, and timing and location of recurrence. Tumor staging was reported according to the guidelines set by the American Joint Committee on Cancer (AJCC).⁸

All pathological data (tissue blocks, slides, and reports) were independently reviewed by a pathologist (S.H.O.) with specific expertise in melanoma; data points were omitted in the case of missing pathological material. Specific factors assessed included tumor cell morphologic features, depth and anatomic level of invasion, growth phase (vertical vs radial), number of mitoses per square millimeter (roughly 4 high-power fields), presence or absence of ulceration, host response (nonbrisk vs brisk), presence or absence of regression, necrosis, pseudopapillomatous morphologic features, angiolymphatic invasion, and neurotropism. Depth of invasion was measured as thickness, in millimeters, from the most superficial layer of the epithelium, ulcer base, or granular cell layer, where present, and then stratified into levels based on the relationship to the submucosal lamina propria. The latter microstaging classification was derived from Prasad et al,⁹ who defined *level I* as mucosal melanoma in situ (without invasion of the lamina propria or with only microinvasion), *level II* as invasion into the lamina propria only, and *level III* as invasion into deep tissue structures, such as bone, muscle, and cartilage. *Brisk host response* is defined as at least a moderate lymphocytic inflammatory infiltrate at the base of the tumor and/or infiltrating within the tumor; *nonbrisk host response* is defined as an absent or scant inflammatory component surrounding the tumor.

DATA ANALYSIS

We calculated descriptive statistics for all variables. Frequencies and percentages are presented for categorical variables, and means (SDs) are presented for continuous variables. We analyzed associations using univariate Cox proportional hazards regression models to calculate *P* values and hazard ratios (HRs) for all the clinical and pathological variables under evaluation. For class variables, such as stage, overall Wald type III tests are reported within the text, and contrast tests across levels are reported in the tables.

We analyzed survival statistics, including median follow-up in months and median overall and disease-free survival at 2 and 5 years, using the Kaplan-Meier product-limit method. *Disease-free survival* was determined as the time from

initial treatment to the patient's last visit with no evidence of recurrent disease. *Overall survival time* was determined using a combination of electronic medical records, the melanoma database, and the Social Security Death Index and was defined as the time from the initial pathological diagnosis to death or to last known contact.

RESULTS

DEMOGRAPHICS AND TREATMENTS RECEIVED

A total of 52 patients were identified, with a mean (SD) age of 66 (13) years. Thirty-one (60%) were female. Thirteen (25%) had been diagnosed as having other cancers; 1 (2%), with prior cutaneous melanoma; and 5 (10%), with prior nonmelanomatous cutaneous malignant neoplasms. Twenty-two patients (42%) were former or current smokers. Sixteen (31%) presented with oral cavity lesions (8 of the lip; 5, gingiva; 2, hard palate; and 1, retromolar trigone), and 36 (69%) presented with sinonasal primary tumors (22 of the nasal cavity; 7, maxillary sinus; 6, ethmoid sinus; and 1, sphenoid sinus). All oral cavity tumors presented as discrete lesions. Of the 36 sinonasal tumors, 14 presented with nasal obstruction, 12 with bleeding/epistaxis, 4 with pain, and 6 with other symptoms.

Forty-six patients (88%) initially were treated surgically, of whom 42 (81% of the total) achieved complete remission. All underwent extirpation at the primary site; in 31, negative margins were achieved initially; in 13, re-excision was required to achieve negative margins; and in 2, margins remained positive despite resection (both were T4 ethmoid sinus tumors with positive margins at the skull base, 1 of which was also positive in the orbit). Five individuals (10%) underwent neck dissection for clinically evident regional metastatic disease. Ten (19%) underwent adjuvant external beam radiotherapy, and an additional 5 individuals (10%) underwent palliative radiotherapy to the primary site and/or cervical lymphatics. Three (6%) received adjuvant cytotoxic chemotherapy, and an additional 15 individuals (29%) underwent palliative chemotherapy for unresectable locoregional or distant recurrence.

Data summarizing clinical staging are provided in **Table 1**.

SURVIVAL

A flowchart summarizing patient outcomes is provided in **Figure 1**. As of the last follow-up, 17 patients were still alive. With a median follow-up of 97 months, median overall survival was 52 months (95% confidence interval [CI], 24-74 months) with 2- and 5-year overall survival of 64% and 38%, respectively. With a median follow-up of 82 months, median disease-free survival was 15 months (95% CI, 8-33 months) with 2- and 5-year disease-free survival of 43% and 22%, respectively.

CLINICAL PREDICTORS

Increased age was significantly associated with poorer overall and disease-free survival ($P=.02$ and $P=.07$, re-

Table 1. Staging of Mucosal Melanoma at Diagnosis

AJCC Status	No. (%) of Patients ^a	Median OS, mo	Median DFS, mo
T status			
3	38 (73)	58	30
4	14 (27)	10	3
N status			
0	45 (87)	58	22
1	1 (2) ^b	4	0
2	6 (12)	17	5
3	0
M status			
0	47 (90)	56	22
1	5 (10)	4	0
Stage			
I	13 (25)	81	33
II	18 (35)	56	38
III	6 (12)	28	19
IV	15 (29)	9	0

Abbreviations: AJCC, American Joint Committee on Cancer; DFS, disease-free survival; ellipses, not applicable; OS, overall survival.

^aBecause of rounding, percentages may not total 100.

^bThe single patient with N1 disease died at 4 months and was never free of disease.

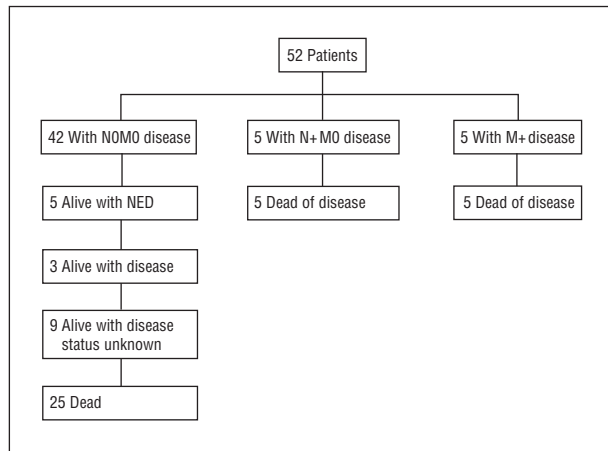


Figure 1. Clinical outcomes. NED indicates no evidence of disease; plus sign, positive.

spectively). The AJCC stage and individual T, N, and M status were all significantly associated with overall survival (Wald type III test, $P=.003$, $P=.003$, $P=.001$, and $P<.001$, respectively) (**Figure 2** and **Figure 3**). The AJCC stage and T, N, and M status also significantly predicted disease-free survival (Wald type III test, $P<.001$, $P<.001$, $P=.003$, and $P<.001$, respectively). Sex, primary site, and smoking status were not associated with overall or disease-free survival (**Table 2**).

Patients with negative surgical margins had significantly better overall survival than those who did not achieve negative margins (median, 56 vs 9 months; $P=.01$) (**Figure 4**). Of the patients with initially positive margins who underwent a second resection and achieved negative margins, there was no difference in overall or disease-free survival compared with the patients who had initially negative margins (overall, 81 vs 56 months [$P=.71$]; disease-free, 26 vs 16 months [$P=.28$]). The HR

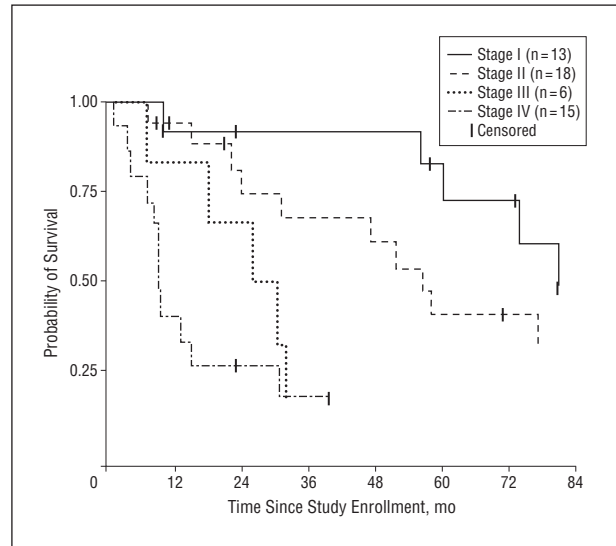


Figure 2. Kaplan-Meier overall survival curve by American Joint Committee on Cancer staging.

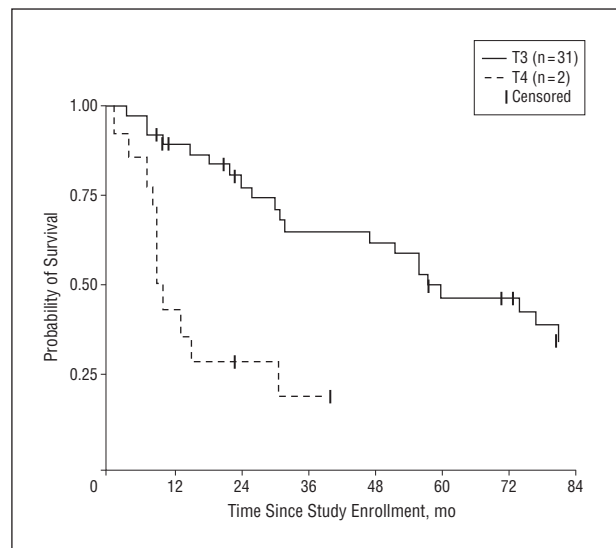


Figure 3. Kaplan-Meier overall survival curve by American Joint Committee on Cancer T status.

for margin status (6.3 [95% CI, 1.0-39.1]) remained marginally significant ($P=.05$) after controlling for T status. Surgical margins were extremely variable given the variations in extirpative technique and tumor sites, limiting analysis of this variable.

HISTOPATHOLOGICAL FINDINGS

In 16 patients, tissue was unavailable for retrospective pathological evaluation. There was no evidence of a statistically significant difference between those with and without tissue available for analysis in overall or disease-free survival (overall survival HR, 1.8 [95% CI, 0.9-3.5; $P=.11$]; disease-free survival 1.7 [0.8-3.4; $P=.15$]). Among patients whose tissue was analyzed, the following histopathological findings were less common: ulceration (51%), tumor regression (9%), radial growth (10%), necrosis (38%), pseudopapillomatous growth (25%), angiolym-

Table 2. Clinical Predictors of Survival in Mucosal Melanoma (Univariate Cox Proportional Hazards Regression Model)

Variable	No. of Patients ^a	OS		DFS	
		HR (95% CI)	P Value	HR (95% CI)	P Value
Age, decade intervals	52	1.40 (1.05-1.88)	.02	1.33 (0.98-1.79)	.07
Female sex ^b	31	0.72 (0.37-1.43)	.35	1.19 (0.59-2.40)	.64
Site					
Oral cavity	16	1.00 [Reference]		1.00 [Reference]	
Sinonasal	36	1.66 (0.77-3.57)	.20	0.69 (0.31-1.52)	.35
Smoking					
Never	28	1.00 [Reference]		1.00 [Reference]	
Ever	22	1.15 (0.58-2.27)	.69	1.29 (0.64-2.58)	.47
Stage					
I	13	1.00 [Reference]		1.00 [Reference]	
II	18	2.25 (0.80-6.47)	.13	1.27 (0.43-3.76)	.67
III	6	3.14 (0.87-11.28)	.08	2.12 (0.61-7.34)	.23
IV	15	6.79 (2.31-19.96)	<.001	6.51 (2.26-18.77)	<.001
T status					
T3	38	1.00 [Reference]		1.00 [Reference]	
T4	14	5.27 (1.89-14.70)	.002	4.97 (1.83-13.54)	.002
N status					
N0	45	1.00 [Reference]		1.00 [Reference]	
Positive	7	4.33 (1.77-10.61)	.001	4.44 (1.68-11.75)	.003
M status					
M0	47	1.00 [Reference]		1.00 [Reference]	
M1	5	18.64 (5.32-65.32)	<.001	15.67 (3.74-65.55)	<.001
Margins					
Negative	31	1.00 [Reference]		1.00 [Reference]	
Positive	2	9.54 (1.80-50.49)	.01
Reexcised	13	0.85 (0.35-2.03)	.71	0.79 (0.33-1.89)	.28

Abbreviations: CI, confidence interval; DFS, disease-free survival; ellipses, not applicable; HR, hazard ratio; OS, overall survival.

^aTotals may not equal 52 because of missing or nonapplicable data.

^bMale sex is the reference category.

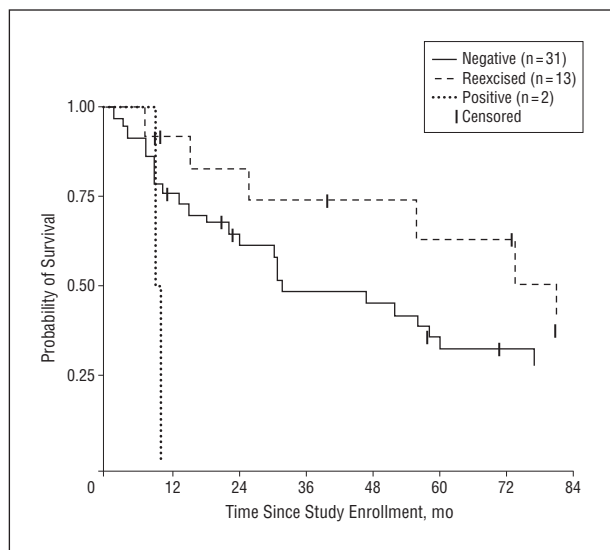


Figure 4. Kaplan-Meier overall survival curve by margin status.

phatic spread (19%), neurotropism (18%), and brisk host response (26%) (**Table 3**). The mean (SD) thickness (depth of invasion) was 6.2 (3.8) mm (range, 1.6-16.0 mm). There was a mean (SD) of 7.1 (7.2) mitoses/mm² (range, 0-25.0 mitoses/mm²). Level of invasion based on the Prasad scale (available for 36 patients) was I in 3 patients (8%), II in 13 (36%), and III in 20 (56%); these levels did not predict overall or disease-free survival in our cohort.

An increased number of mitoses was associated with poorer overall and disease-free survival ($P = .02$ and $P = .002$, respectively). Ulceration was associated with poorer overall survival (HR, 3.71 [95% CI, 1.43-9.63; $P = .01$]), with a trend toward poorer disease-free survival that did not reach clinical significance (2.23 [0.93-5.35; $P = .07$]).

COMMENT

DEMOGRAPHICS, STAGING, AND OUTCOME

Our demographic data with regard to age, sex, site, and stage are fairly similar to those reported elsewhere.⁵ Mucosal melanoma of the head and neck occurs at similar rates among both sexes, is typically diagnosed after the fifth decade of life, and is more frequent in the sinonasal cavity compared with the oral cavity. Other aerodigestive mucosal surfaces are more rarely involved. Increased age predicts worse outcomes, consistent with prior reports.¹⁰ We did not identify other demographic factors that were significant predictors of outcome, nor was primary site associated with a significantly different prognosis.

Our data corroborates the utility of the AJCC mucosal melanoma staging system. Overall stage and T, N, and M status all predict overall and disease-free survival. Our data are consistent with recent analyses with similar find-

Table 3. Pathological Predictors of Survival in Mucosal Melanoma (Univariate Cox Proportional Hazards Regression Model)

Variable	No. of Patients ^a	OS		DFS	
		HR (95% CI)	P Value	HR (95% CI)	P Value
Tumor thickness, mm	13	0.99 (0.86-1.12)	.82	1.14 (0.93-1.39)	.20
Microstaging level					
III	20	1.00 [Reference]		1.00 [Reference]	
I or II	16	0.54 (0.22-1.31)	.17	0.61 (0.26-1.43)	.25
Host response					
Nonbrisk	26	1.00 [Reference]		1.00 [Reference]	
Brisk	9	0.86 (0.32-2.37)	.78	0.76 (0.26-2.25)	.62
Regression					
No	29	1.00 [Reference]		1.00 [Reference]	
Yes	3	2.61 (0.73-9.35)	.14	1.30 (0.37-4.57)	.68
Growth					
Vertical	36	1.00 [Reference]		1.00 [Reference]	
Radial	4	0.20 (0.03-1.46)	.11	0.25 (0.03-1.83)	.17
Mitoses/mm ²	36	1.06 (1.01-1.12)	.02	1.09 (1.03-1.16)	.002
Ulceration					
No	17	1.00 [Reference]		1.00 [Reference]	
Yes	18	3.71 (1.43-9.63)	.01	2.23 (0.93-5.35)	.07
Necrosis					
No	21	1.00 [Reference]		1.00 [Reference]	
Yes	13	1.77 (0.76-4.12)	.19	1.93 (0.83-4.47)	.13
Pseudopapillomatous growth					
No	24	1.00 [Reference]		1.00 [Reference]	
Yes	8	1.05 (0.39-2.81)	.93	1.03 (0.39-2.72)	.95
Angiolymphatic invasion					
No	30	1.00 [Reference]		1.00 [Reference]	
Yes	7	1.78 (0.69-4.63)	.24	1.53 (0.60-3.89)	.37
Neurotropism					
No	27	1.00 [Reference]		1.00 [Reference]	
Yes	6	0.94 (0.27-3.28)	.92	1.22 (0.41-3.67)	.72

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

^aBecause of missing data, numbers may not total 52.

ings.^{11,12} As we demonstrate, prognosis is extremely poor among patients presenting with advanced primary disease or regional and/or distant metastases.

Our median overall survival of 52 months and 5-year overall survival of 38% are consistent with the larger series published in the literature: Yanagi et al¹³ report 27% 5-year overall survival, and Patel et al³ report 35%. Our dismal outcomes, with particularly poor disease-free intervals despite the achievement of complete remission in 81% of patients, underscore the aggressiveness of the disease.

HISTOPATHOLOGICAL FINDINGS

One of the difficulties in diagnosing mucosal melanoma relates to its clinical rarity and variable histological presentation.⁶ Morphologically, mucosal melanoma may mimic classic pigmented cutaneous melanomas or may have a widely variable and heterogeneous appearance, with desmoplastic, epithelioid, sarcomatoid, undifferentiated, or pleomorphic components, all with or without pigmentation. Immunohistochemistry can be invaluable in making an accurate diagnosis; in general, staining patterns for mucosal melanoma parallel those seen in cutaneous melanoma. Specifically, mucosal melanomas tend to yield positive findings for S-100 and vimentin, occasionally positive findings for HMB-45 and Melan-A, and negative find-

ings for cytokeratin and epithelial membrane antigen (both of which suggest an epithelial neoplasm). In general, pathologists reviewing challenging tumors of the upper aerodigestive tract mucosa may benefit from using immunohistochemistry to help exclude or confirm a diagnosis of mucosal melanoma.

Historically, the histopathological variables that are considered part of the cutaneous melanoma profile do not apply to mucosal melanoma. Our study, to our knowledge for the first time, demonstrates a greater than 3-fold impact of the presence of ulceration with survival in head and neck mucosal melanoma. Higher mitotic indices have been suggested to correlate with poorer outcome in selected other series, and we corroborate these results.^{12,14} We did not identify any other histopathological predictors of outcome.

Case series have widely varied findings concerning the prognostic role of specific histological characteristics. Prasad et al⁷ reported that vascular invasion, polymorphous tumor cell population, and necrosis significantly affected overall and disease-free survival, whereas tumor thickness, level of invasion, ulceration, mitotic index, and neurotropism did not affect outcome. We could not confirm the utility of microstaging based on tumor depth of invasion as a predictive tool.⁹ Unlike recently published findings,¹² pseudopapillary architecture did not correlate with outcomes in our series.

As a result of our data and the varied reports in the literature, we propose that pathological analysis of mucosal melanoma should involve the formulation of a histopathological template profile of the primary lesion, which is required for most cancers, including cutaneous melanoma, and is shown in the following tabulation.

Proposed Mucosal Melanoma Histology Template

- Tumor cell morphology
- Level of invasion (I-III)
- Depth of invasion, mm
- Presence of ulceration
- Mitoses per square millimeter
- Presence of necrosis
- Presence of pseudopapillary growth
- Vascular angiolymphatic invasion
- Neurotropism
- Surgical margin status

Development of a structured primary lesion template for histopathological reports will facilitate more consistent and detailed information transfer between centers and publications to better understand clinicopathological correlation with outcomes for future studies. Specifically, ulceration and mitotic index, as well as several other variables, should be routinely reported.

TREATMENT STRATEGIES

Mucosal melanoma of the head and neck is primarily a surgical disease.¹⁵ One of our intriguing observations was the equivalent outcomes among patients treated surgically who required reexcision to achieve negative margins compared with those with initially negative margins, as well as the dramatically worse prognosis among patients for whom margins could not be cleared. This suggests the importance not only of achieving negative surgical margins but also of carefully assessing resectability preoperatively, specifically at the level of the skull base and dura. This observation is limited by the fact that larger unresectable tumors clearly have worse prognoses; this has been demonstrated in multiple series, including those that account for tumor volume.¹³ In addition, the retrospective nature of our series makes it difficult to conclude whether initial procedures that yielded positive margins were truly oncologic excisions rather than diagnostic and/or excisional biopsies; there also exists the possibility of a type II statistical error due to lack of power. Nevertheless, our data imply that aggressive surgical extirpation of positive margins is indicated when feasible, even in cases that require reoperation.

Given the poor prognosis regardless of treatment modality, the role of aggressive surgical extirpation must be critically weighed against expected surgical morbidity. Acceptable functional outcomes are often achievable—even with extensive skull base and oral cavity surgery—by judicious attention to preservation of cranial nerves, meticulous reconstruction of surgical defects, and avoidance of brain retraction during skull base exposure by using an endoscopic and/or subcranial approach. Moreover, in many cases, the consequences of uncontrolled tumor progression may outweigh expected postoperative morbidity, even when the possibility of locoregional or distant recurrence is accounted for,

especially given the absence of efficacious nonsurgical treatment options. In all cases, patient input and preferences are instrumental in deciding on appropriate treatment modalities, and a frank and open preoperative discussion concerning oncologic outcomes and perioperative expectations is crucial.

With regard to the role of neck dissection, our practice has been surgical extirpation of clinically evident regional metastatic disease, without treatment of N0 disease. Our data demonstrate the uniformly poor prognosis of all node-positive patients. Some authors advocate elective neck dissection in a subset of patients with N0 disease.¹⁶ In general, although there are no conclusive data, in our experience few patients have recurrences in the neck without accompanying local or distant disease, thereby calling into question the role of surgical management of the neck in these cases. Sentinel node biopsy is an intriguing concept for mucosal melanoma of the head and neck and may merit further consideration.¹⁷

Our study was not powered or designed to study the role of adjuvant or palliative radiotherapy or chemotherapy; given these limitations, we did not identify a significant difference in outcome among the patients treated in the adjuvant or palliative setting. The data to date remain inconclusive concerning the role of radiotherapy; multiple series have reported on external beam radiotherapy as the initial and adjuvant treatment.¹⁸ Although a consensus is difficult to achieve from a small case series, Temam et al¹⁹ and Moreno et al¹² suggest that adjuvant radiotherapy may improve locoregional control despite the absence of significant improvement in overall survival. Carbon ion radiotherapy has undergone trial as well, with acceptable rates of achievement of clinical remission and initial locoregional control, but recurrences were frequent and long-term survival was rare.¹⁹ Although the data on chemotherapy are generally poor, M. D. Anderson Cancer Center, Houston, Texas, has pioneered “biochemotherapy,” involving combined cytotoxic and immunomodulatory regimens, with a small series demonstrating optimistic results that merit further investigation.²⁰ Encouraging studies of therapeutic targets based on specific gene mutations found in a subset of melanomas may also merit application to mucosal melanoma.²¹

Mucosal melanoma is a neoplasm with a nefarious course despite aggressive treatment. Given this fact, surgical procedures that yield significant functional morbidity must be weighed against the prognosis and the patient’s own choices. Further strategies to stratify patients according to risk and more efficacious treatment modalities remain elusive. One intriguing study²² reports on the loss of heterozygosity in free DNA circulating in plasma as a method of identifying subclinical metastasis in this patient population, but clinical utility remains to be defined.

STRENGTHS AND WEAKNESSES

Our report constitutes one of the larger case series of mucosal melanoma of the head and neck, which facilitates valid statistical analyses that are less prone to sampling error and confounding variables. Our data are strengthened by long follow-up and the use of a prospective clinical

copathological database to limit recall bias. The independent review by a pathologist with expertise in this clinical realm also fortifies the weight of the data.

As with any retrospective review, our conclusions and recommendations are limited by the absence of more definitive prospective data; however, this is unlikely to emerge given the rarity of the clinical condition. In addition, the small numbers of patients and inherent selection bias among those undergoing nonsurgical therapy and the variable courses of adjuvant and palliative chemotherapy and radiotherapy limit our ability to make conclusions concerning their role and efficacy in this disease and create the risk of type II errors in our analysis. Missing histopathological data points associated with the absence of a standardized template could not be obtained in some cases. Moreover, the number of variables studied and the ensuing dearth of statistical power limited the role for a multivariate analysis.

In conclusion, mucosal melanoma is an aggressive disease with a poor prognosis despite aggressive treatment. Our experience confirms the utility of current staging systems in predicting outcomes of mucosal melanoma of the head and neck. The data stress the importance of achieving negative surgical margins and suggest that adjuvant radiotherapy and/or chemotherapy may not yield improved survival. Pathologically, fewer mitoses and the absence of ulceration predict better outcomes. Further studies and incorporation of standard histological profiles will be necessary to change the paradigm of care for this rare and deadly disease.

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Correspondence: Carol R. Bradford, MD, Department of Otolaryngology, University of Michigan Hospitals, 1904 Taubman Center, Ann Arbor, MI 48109 (cbradfor@umich.edu).

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REFERENCES

1. Chang AE, Karnell LH, Menck HR; American College of Surgeons Commission on Cancer and the American Cancer Society. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: summary of 84,836 cases from the past decade. *Cancer*. 1998;83(8):1664-1678.
2. Manolidis S, Donald PJ. Malignant mucosal melanoma of the head and neck: review of the literature and report of 14 patients. *Cancer*. 1997;80(8):1373-1386.
3. Patel SG, Prasad ML, Escrig M, et al. Primary mucosal malignant melanoma of the head and neck. *Head Neck*. 2002;24(3):247-257.
4. Owens JM, Roberts DB, Myers JN. The role of postoperative adjuvant radiation therapy in the treatment of mucosal melanomas of the head and neck region. *Arch Otolaryngol Head Neck Surg*. 2003;129(8):864-868.
5. Mendenhall WM, Amdur RJ, Hinerman RW, Werning JW, Villaret DB, Mendenhall NP. Head and neck mucosal melanoma. *Am J Clin Oncol*. 2005;28(6):626-630.
6. Kilpatrick SE, White WL, Browne JD. Desmoplastic malignant melanoma of the oral mucosa: an underrecognized diagnostic pitfall. *Cancer*. 1996;78(3):383-389.
7. Prasad ML, Patel S, Hoshaw-Woodard S, et al. Prognostic factors for malignant melanoma of the squamous mucosa of the head and neck. *Am J Surg Pathol*. 2002;26(7):883-892.
8. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer-Verlag; 2010.
9. Prasad ML, Patel SG, Huvos AG, Shah JP, Busam KJ. Primary mucosal melanoma of the head and neck: a proposal for microstaging localized, stage I (lymph node-negative) tumors. *Cancer*. 2004;100(8):1657-1664.
10. Kim HS, Kim EK, Jun HJ, et al. Noncutaneous malignant melanoma: a prognostic model from a retrospective multicenter study. *BMC Cancer*. 2010;10:167.
11. Loree TR, Mullins AP, Spellman J, North JH Jr, Hicks WL Jr. Head and neck mucosal melanoma: a 32-year review. *Ear Nose Throat J*. 1999;78(5):372-375.
12. Moreno MA, Roberts DB, Kupferman ME, et al. Mucosal melanoma of the nose and paranasal sinuses, a contemporary experience from the M. D. Anderson Cancer Center. *Cancer*. 2010;116(9):2215-2223.
13. Yanagi T, Mizoe JE, Hasegawa A, et al. Mucosal malignant melanoma of the head and neck treated by carbon ion radiotherapy. *Int J Radiat Oncol Biol Phys*. 2009;74(1):15-20.
14. Thompson LD, Wieneke JA, Miettinen M. Sinonasal tract and nasopharyngeal melanomas: a clinicopathologic study of 115 cases with a proposed staging system. *Am J Surg Pathol*. 2003;27(5):594-611.
15. Lund VJ, Howard DJ, Harding L, Wei WI. Management options and survival in malignant melanoma of the sinonasal mucosa. *Laryngoscope*. 1999;109(2, pt 1):208-211.
16. Medina JE, Ferlito A, Pellitteri PK, et al. Current management of mucosal melanoma of the head and neck. *J Surg Oncol*. 2003;83(2):116-122.
17. Stárek I, Koranda P, Benes P. Sentinel lymph node biopsy: a new perspective in head and neck mucosal melanoma? *Melanoma Res*. 2006;16(5):423-427.
18. Krengli M, Jereczek-Fossa BA, Kaanders JH, Masini L, Beldì D, Orecchia R. What is the role of radiotherapy in the treatment of mucosal melanoma of the head and neck? *Crit Rev Oncol Hematol*. 2008;65(2):121-128.
19. Temam S, Mamelle G, Marandas P, et al. Postoperative radiotherapy for primary mucosal melanoma of the head and neck. *Cancer*. 2005;103(2):313-319.
20. Bartell HL, Bedikian AY, Papadopoulos NE, et al. Biochemotherapy in patients with advanced head and neck mucosal melanoma. *Head Neck*. 2008;30(12):1592-1598.
21. Smalley KS, Sondak VK. Melanoma: an unlikely poster child for personalized cancer therapy. *N Engl J Med*. 2010;363(9):876-878.
22. Takagi R, Nakamoto D, Mizoe JE, Tsujii H. LOH analysis of free DNA in the plasma of patients with mucosal malignant melanoma in the head and neck. *Int J Clin Oncol*. 2007;12(3):199-204.