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Sinonasal Tract and Nasopharyngeal Melanomas

A Clinicopathologic Study of 115 Cases With a Proposed Staging System

Lester D. R. Thompson, M.D., Jacqueline A. Wieneke, M.D., and Markku Miettinen, M.D.

Primary sinonasal tract mucosal malignant melanomas are uncommon tumors that are frequently misclassified, resulting in inappropriate clinical management. A total of 115 cases of sinonasal tract mucosal malignant melanoma included 59 females and 56 males, 13–93 years of age (mean 64.3 years). Patients presented most frequently with epistaxis (n = 52), mass (n = 42), and/or nasal obstruction (n = 34) present for a mean of 8.2 months. The majority of tumors involved the nasal cavity (n = 34), septum alone, or a combination of the nasal cavity and sinuses (n = 39) with a mean size of 2.4 cm. Histologically, the tumors were composed of a variety of cell types (epithelioid, spindled, undifferentiated), frequently arranged in a peritheliomatous distribution (n = 39). Immunohistochemical studies confirmed the diagnosis of sinonasal tract mucosal malignant melanomas with positive reactions for S-100 protein, tyrosinase, HMB-45, melan A, and microphthalmia transcription factor. Sinonasal tract mucosal malignant melanomas need to be considered in the differential diagnosis of most sinonasal malignancies, particularly carcinoma, lymphoma, sarcoma, and olfactory neuroblastoma. Surgery accompanied by radiation and/or chemotherapy was generally used. The majority of patients developed a recurrence (n = 79), with 75 patients dying with disseminated disease (mean 2.3 years), whereas 40 patients are either alive or had died of unrelated causes (mean 13.9 years). A TNM-type classification separated by anatomic site of involvement and metastatic disease is proposed to predict biologic behavior.

Key Words: Malignant mucosal melanoma—Sinuses—Nasal cavity—Staging—Prognosis—Histology—Immunohistochemistry—TNM classification.

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From the Departments of Endocrine and Otorhinolaryngic-Head & Neck Pathology (L.D.R.T., J.A.W.) and Soft Tissue Pathology (M.M.), Armed Forces Institute of Pathology, Washington, DC, U.S.A.

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Address correspondence and reprint requests to Lester D. R. Thompson, MD, Department of Endocrine and Otorhinolaryngic-Head & Neck Pathology, Building 54, Room G066-11, Armed Forces Institute of Pathology, 6825 16th Street NW, Washington, DC 20306-6000, U.S.A.; e-mail: lester@thompsons2.com

Malignant melanoma is a common skin neoplasm, with between 15% and 33% of these skin melanomas occurring in the head and neck. Primary mucosal malignant melanoma of the nasal cavity, paranasal sinuses, and nasopharynx (hereinafter referred to collectively as the sinonasal tract, i.e., sinonasal tract mucosal malignant melanomas [STMMMs]) is rare, accounting for between 0.3% and 2% of all malignant melanomas and about 4% of head and neck melanomas.[3–5,9,12,14,18,22,31,35,39,41,44,55,56,61] Interestingly, the head and neck represent the most common site of mucosal malignant melanoma,[11,12,41,44] with a suggested incidence of about $0.018/10^5$ to $0.051/10^5$ per year.[12,35] STMMM represents up to 4% of all sinonasal tract neoplasms.[19,22,25,31,35,38,44] Histologically, the protean manifestations of STMMM are different from their integumentary system counterparts, and diagnostic difficulties are frequently encountered in the differential diagnosis with poorly differentiated carcinoma, lymphoma, plasmacytoma, rhabdomyosarcoma, and olfactory neuroblastoma. Many cases of STMMM are reported in the literature, but the earlier literature may be dubious because of a lack of histochemical, immunohistochemical, or ultrastructural diagnostic support. Most cases are presented in the form of isolated case reports, with a few small series examining data collected on patients over many years.[2,5,7,11,12,15,16,18,21,22,27,31,34,35,38,39,41,43–45,52,55,56,58–63,65] These reports focus on a particular feature, such as the clinical, radiographic, histologic, immunohistochemical, or therapeutic outcomes, not necessarily correlating all of the findings into a thorough investigation with statistical analysis. Therefore, it is the intention of this study to provide a comprehensive analysis and suggest a staging system for STMMM incorporating the use of clinical features, histologic findings, immunohistochemical results, therapies used, and patient follow-up applied to a group of 115 patients with this tumor.

METHODS

A total of 135 cases of primary mucosal malignant melanoma were selected involving the nasal cavity, pa-

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ranasal sinuses (sphenoid, maxillary, ethmoid, and frontal sinuses), or nasopharynx. The cases were retrieved from the files of the Otorhinolaryngic-Head & Neck Tumor Registry of the Armed Forces Institute of Pathology, Washington, DC, between 1970 and 1995. However, 20 patients were excluded from further consideration because of at least one of the following reasons: 1) paraffin blocks were unavailable for additional sections or immunophenotypic analysis; 2) the original submitted case did not have sufficient demographic information supplied from which to obtain adequate follow-up information; and 3) immunophenotypic analysis confirmed a diagnosis of poorly differentiated carcinoma, lymphoma, or olfactory neuroblastoma. The cases that were reclassified were all from 1970–1978 and had all been signed out as "poorly differentiated malignant neoplasm," "consistent with," "suggestive of," or "suspicious for" malignant melanoma and had not benefitted from electron microscopy or immunophenotyping at the time of the original diagnosis. Therefore, the remaining 115 patients compose the subject of this study, chosen from a review of 20,156 (0.57%) benign or malignant primary sinonasal tract tumors seen in consultation during this time. A total of 100 cases were obtained from civilian sources, including university medical centers and foreign contributors, 11 cases from military hospitals, and 4 cases from Veterans Administration Medical Centers. None of these cases was included in the previous report by Holdcraft and Gallagher in 1969.[31]

Materials within the files of the Armed Forces Institute of Pathology were supplemented by a review of the patient demographics (gender, age, race) and symptoms at presentation (epistaxis, nasal obstruction, nasal mass, polyps, difficulty breathing, changes in breathing, discharge, pain) including duration. In addition, we reviewed the medical history (specifically noting any skin or other mucosal melanoma primary), surgical pathology, and operative reports and obtained follow-up information by direct written or oral communication with the referring pathologist, patient's physician, oncology data services and tumor registries, or the patient (patient's family member[s]). Follow-up data, available for all patients, included information regarding the exact tumor location, the specific treatment methods used, the presence or absence of recurrent or metastatic disease, and the current status of the disease and patient. Patients with primary tumors of the integumentary system or another mucosal site who later developed a sinonasal tract extension or metastasis were not considered in this study. However, patients who presented with a sinonasal tract primary and who later developed a metastatic deposit to the skin or other mucosal sites ($n = 3$) were included in this analysis. No patients in this series were part of a dysplastic nevus syndrome or xeroderma pigmentosum family. It is important to add that we are a tertiary pathology review center, conducting a retrospective review of these patients, and we did not treat the patients. This clinical investigation was conducted in accordance and compliance with all statutes, directives, and guidelines of the Code of Federal Regulations, Title 45, Part 46, and the Department of Defense Directive 3216.2 relating to human subjects in research.

Hematoxylin and eosin-stained slides from 115 cases were reviewed to confirm that the established histopathologic criteria for the diagnosis of malignant melanoma were met. A number of macroscopic and histologic observations were recorded for each tumor as follows: exact tumor location (Fig. 1); tumor size (greatest dimension in centimeters); tumor thickness (surface ulceration, submucosal origin, difficulties in extracting the specimens "en bloc," distortion of the specimen, and lack of correct orientation make accurate thickness measurements virtually impossible and impractical); polypoid mass (Fig. 2); surface epithelium (present or absent); surface origin or involvement (Fig. 3); pagetoid spread (Fig. 3); bone or soft tissue invasion by the tumor; architectural pattern of growth (epithelioid [Fig. 4A], solid, organoid [Fig. 4A], spindled [Fig. 4B], storiform [Fig. 4B], meningothelial [Fig. 4B], hemangiopericytoma-like, peritheliomatous [Fig. 4C], papillary [Fig. 4D]); melanin pigment (present or absent [Fig. 5]); regression (fibrosis, "granulation-tissue type vessels," and pigment laden macrophages); cell type (undifferentiated [Fig. 6A], epithelioid [Fig. 6B], small cell [Fig. 6B], plasmacytoid [Fig. 6C], rhabdoid, giant cell [Fig. 6D]); necrosis (present or absent); inflammatory response (lymphoid, plasmacytoid, histiocytic, acute; graded as heavy [dense continuous lymphocytic infiltrate] or light [focal or discontinuous]); perineural invasion; mitotic figures (number of mitotic figures per 10 high power fields [HPF; magnification at ×40 with a ×10 objective lens using an Olympus BX40 microscope]); atypical mitotic figures (present or absent, and defined by abnormal chromosome spread, tripolar or quadripolar forms, circular forms, or indescribably bizarre); nucleoli (present [Fig. 6D] or absent); intranuclear cytoplasmic inclusions (present [Fig. 6D] or absent), and the presence of other microscopic pathologic findings. Because of the often fragmented nature of the specimens, angiolymphatic invasion could not be adequately documented. Because we did not prosect the specimens, an accurate assessment of the margins of resection is impossible to report, and so no comment about the definitive nature of the resection can be made in this clinical report.

Immunophenotypic analysis was performed in all cases with suitable material by a standardized Envision method using 4-μm-thick, formalin fixed, paraffin-embedded sections. Table 1 documents the pertinent, commercially available immunohistochemical antibody panel used. The analysis was performed on a single rep-

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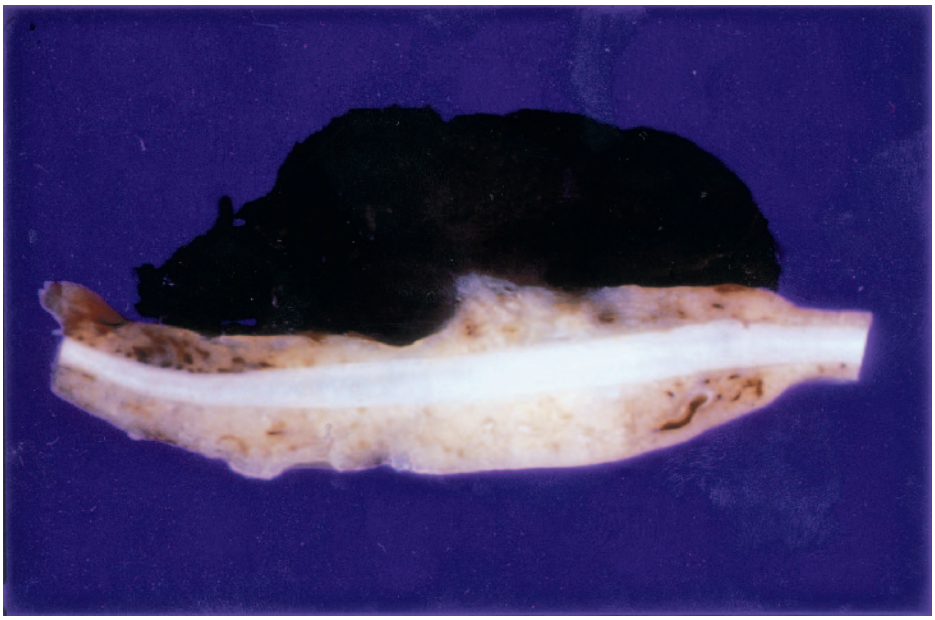

FIG. 1. This macroscopic view of a mucosal malignant melanoma of the septum demonstrates black pigment and the typical polypoid nature of the tumor. Note the well-defined border at the base of the tumor.

resentative block for each primary tumor. When required, proteolytic antigen retrieval was performed by predigestion for 3 minutes with 0.05% Protease VIII (Sigma Chemical Co., St. Louis, MO, USA) in a 0.1 M phosphate buffer, pH of 7.8, at 37°C. Heat-induced epitope retrieval was performed, as required, by using formalin-fixed, paraffin-embedded tissue treated with a buffered citric acid solution pH 6.0 (Citra, Dako Corporation, Carpinteria, CA, USA) and heated for 20 minutes in a steamer. Standard positive controls were used throughout, with serum used as the negative control. The antibody reactions were graded as absent to weak (0 to 1+), moderate (2+ to 3+), and strong (4+) staining, and the fraction of positive cells was determined by separating them into four groups: <10%, 11–50%, 51–90%, and >90%.

Our review of primary STMMM in the English literature was based on a MEDLINE search from 1966

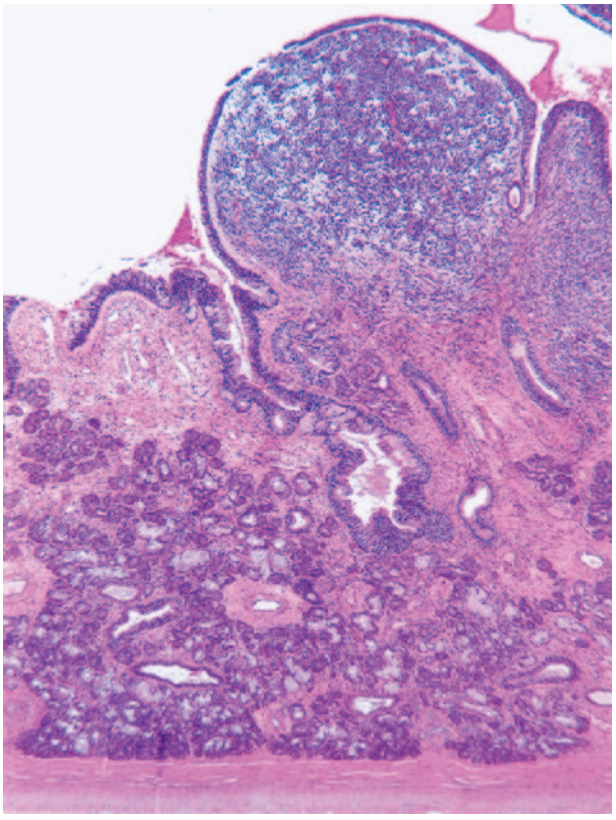

FIG. 2. A small polypoid tumor noted in the immediately submucosal area. The respiratory epithelium is intact. Good orientation permitted a "measurement" of the tumor thickness.

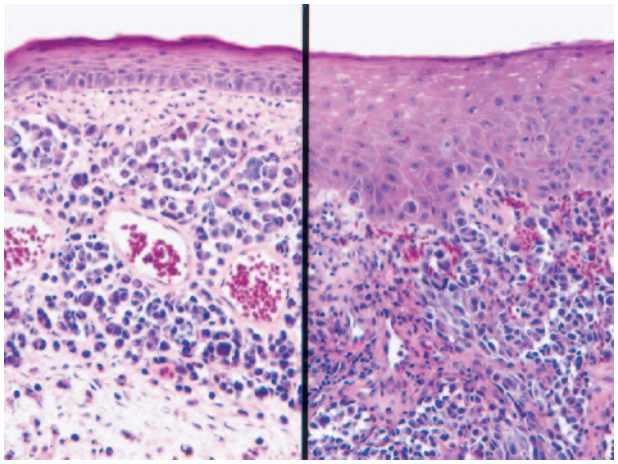

FIG. 3. Pagetoid spread and "surface epithelium" involvement are appreciated (right), although the vast majority of tumors demonstrated a "Grentz" zone of separation between the surface and the malignant infiltrate (left).

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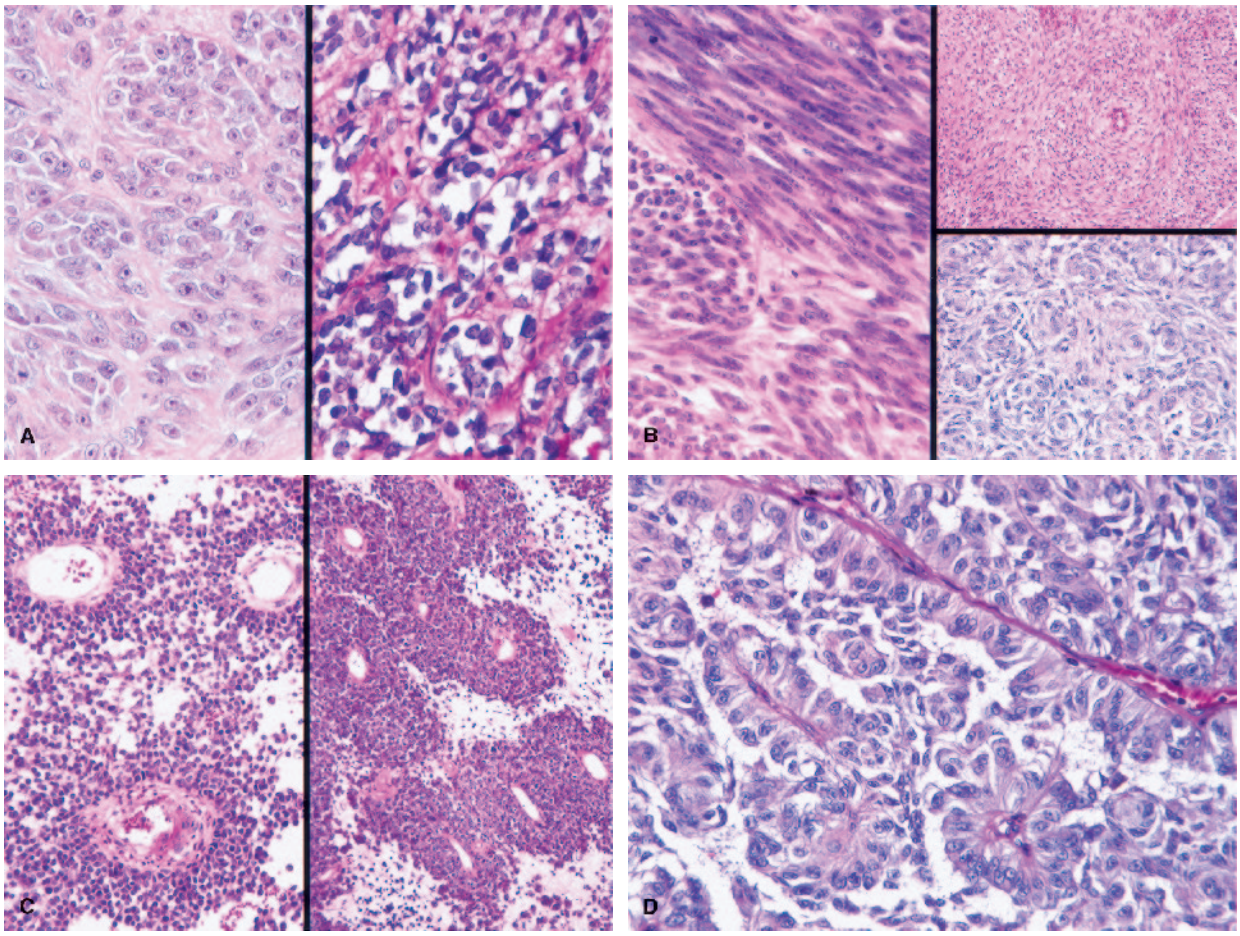

FIG. 4. (**A**) Epithelioid and nested pattern (left). An organoid or "alveolar" pattern simulated a paraganglioma, rhabdomyosarcoma (alveolar type), or an alveolar soft part sarcoma. (**B**) Interlacing fascicles (left), storiform or cartwheel (right upper), and meningothelial (right lower) patterns could be seen to a variable degree in many different tumors. (**C**) A high (left) and low (right) power illustration of the characteristic peritheliomatous growth. Areas of degeneration were noted between the vessels. (**D**) Thin fibrovascular cores lined by pseudocolumnar cells form the papillary architecture noted in a few malignant melanomas.

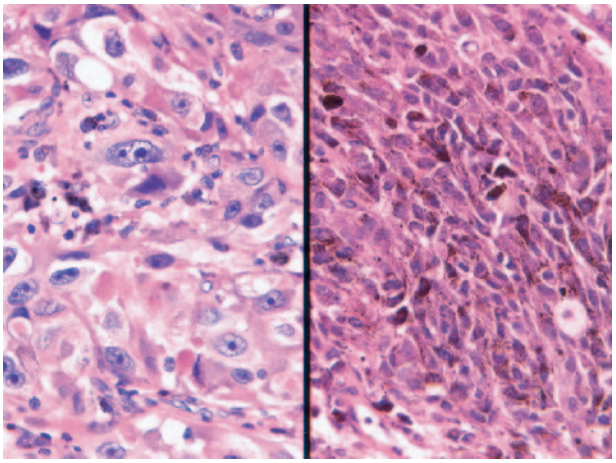

FIG. 5. Focal melanin pigment noted in an epithelioid mucosal malignant melanoma (left). The melanin pigment almost completely obscures the cytologic features of this spindle cell malignant melanoma (right).

to 2002 but was confined to reports with at least 10 cases of STMMM, which included clinical and histologic descriptions written in English.

Categorical variables were analyzed using χ^2 tests to compare observed and expected frequency distributions. Comparison of means between groups were made with unpaired t tests or one-way analysis of variance, depending on whether there were two groups or more than two groups, respectively. Multiple comparisons were analyzed using the Tukey method and log-rank analysis. Linear regression was used to investigate two measured variables, and Pearson correlation coefficients were generated to measure the strength of the association. Confidence intervals of 95% were generated for all positive findings. The alpha level was set at $p < 0.05$. All analyses were conducted using Statistical Package for the Social Sciences (SPSS) software (version 8.0 for PC; Chicago, IL, USA).

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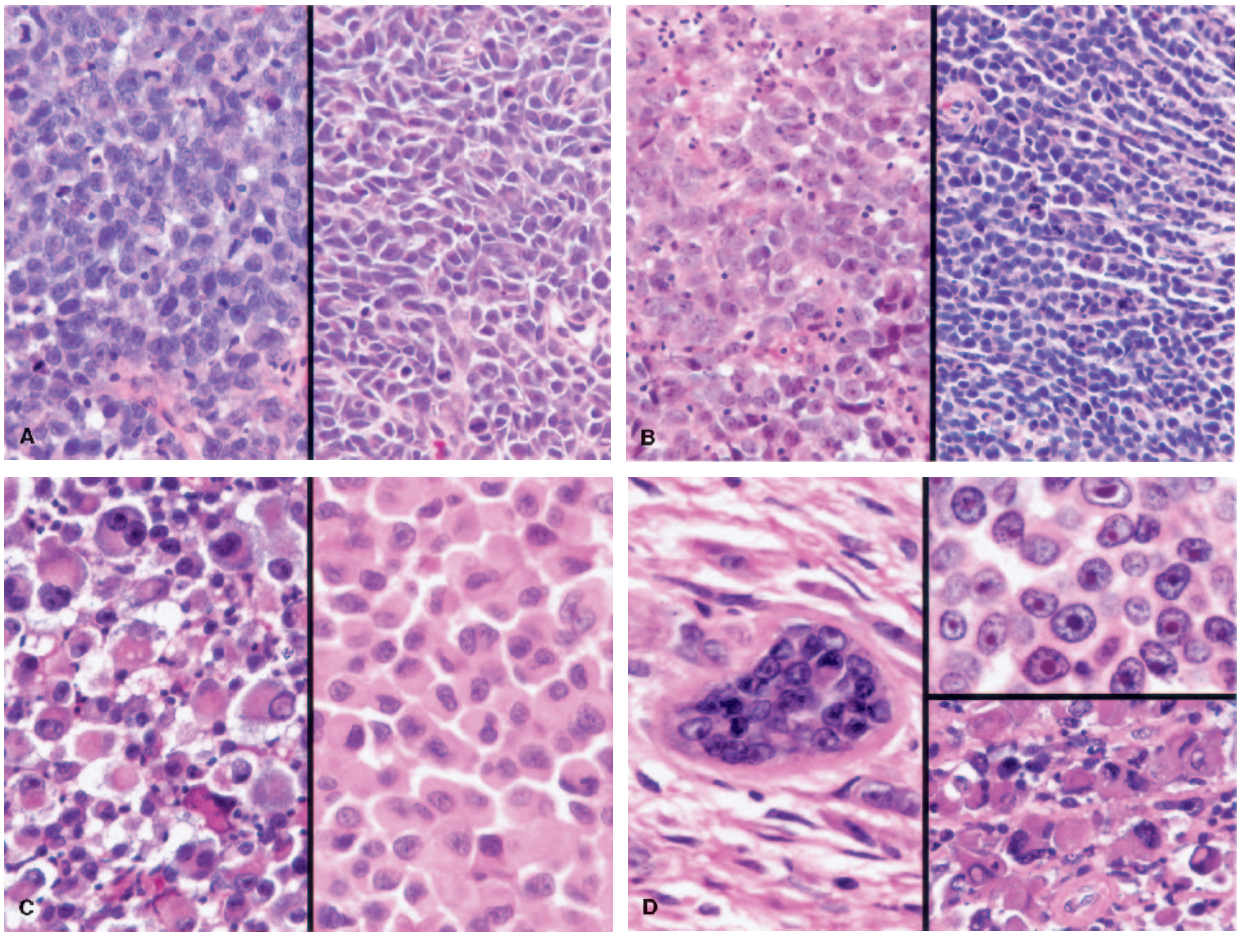

FIG. 6. (**A**) Two different undifferentiated malignant melanomas without a specific architecture, composed of small to medium irregular cells with a high nuclear-to-cytoplasmic ratio and high mitotic index. (**B**) Epithelioid cells arranged in nests demonstrate delicate nuclear chromatin with a syncytial-type arrangement (left). A small-cell infiltrate with high nuclear-to-cytoplasmic ratio (right). (**C**) Atypical plasmacytoid cells with eccentrically placed nuclei with prominent nucleoli and intranuclear cytoplasmic inclusions. A "hoff" zone is easily identified (left). A more well-differentiated plasmacytoid population shows abundant opaque eosinophilic cytoplasm arranged eccentrically from the atypical nuclei. (**D**) Tumor giant cells were frequently identified (left) containing numerous irregular nuclei with prominent nucleoli. Irregular, magenta, enlarged nucleoli (right upper) were identified in most mucosal malignant melanomas, while intranuclear cytoplasmic inclusions (right lower) were seen less frequently.

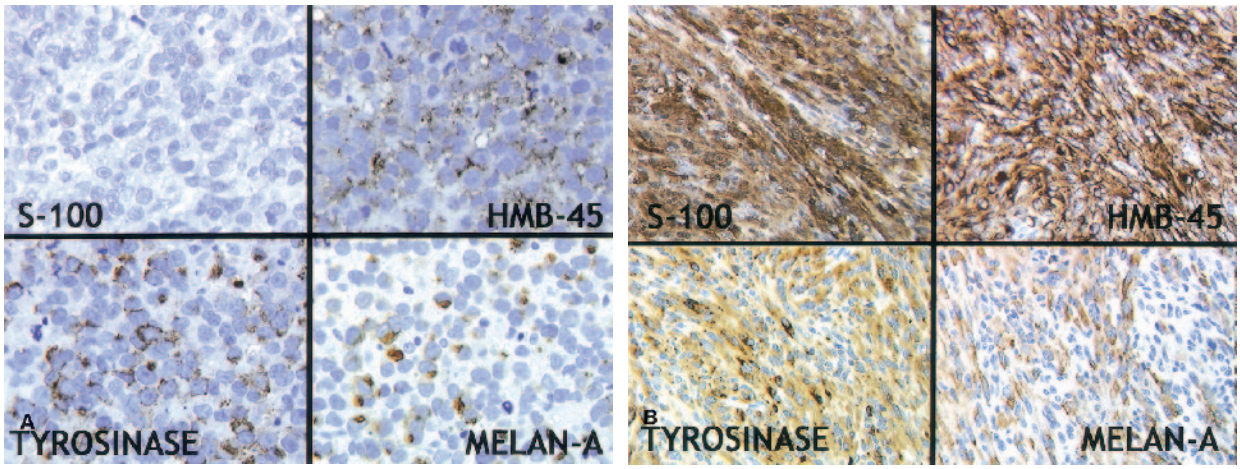

FIG. 7. (**A**) Four different epithelioid and undifferentiated tumors demonstrate the variability of expression of S-100 protein, HMB-45, tyrosinase, and melan-A in sinonasal tract mucosal malignant melanomas. (**B**) Four different spindle and storiform tumors demonstrate a similar variability of melanoma marker expressivity as shown with S-100 protein, HMB-45, tyrosinase, and melan-A.

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TABLE 1. *Immunohistochemical panel*

Antigen/antibody	Primary antibody	Company	Dilution	Cellular conditioning
S-100 protein	rp	Dako, Carpinteria, CA	1:800	N/A
HMB-45	HMB-45	Dako	1:50	N/A
Tyrosinase	T311	Novocastra, New Castle, UK	1:200	Steam
Melan A	A103	Novocastra	1:40	Steam
Microphthalmia transcription factor (MITF)	C5+D5	Neomarkers/LabVision, Freemont, CA	1:200	Steam
Vimentin	mm	BioGenex Labs, San Ramon, CA	1:400	Steam
CD56 (NCAM)	123C3	Zymed, San Francisco, CA	1:400	Steam
Synaptophysin	rp	Ventana, Tucson, AZ	Neat	N/A
CD57	HNK1	Beckon Dickinson Immunocytometry Systems, San Jose, CA	1:20	N/A
CD99	12E7	Dako	1:80	N/A
Neuron-specific enolase (NSE)	rp	Dako	Neat	N/A
Epithelial membrane antigen (EMA)	mm	Dako	1:100	Protease digestion
Cytokeratin (AE1/AE3 and LP34)	mm	Boehringer Mannheim Biochemicals, Indianapolis, IN, and Dako	1:50 1:200	Protease treatment
CAM 5.2	K8	Ventana	1:100	Enzyme digestion
CD117	C-19	Dako	1:1600	Steam
Chromogranin	rp	Dako	1:100	N/A
Glial fibrillary acidic protein (GFAP)	rp	Dako	1:2000	Protease digestion
CD45RB (LCA)	mm	Dako	1:200	N/A
Smooth muscle actin	1A4	Sigma, St. Louis, MO	1:800	N/A
Muscle specific actin	HUC1-1	Ventana	Neat	N/A
Desmin	D33	Dako	1:100	N/A
Desmin	DR11	Dako	Neat	Enzyme digestion

mm, mouse monoclonal; rp, rabbit polyclonal; N/A, not applicable.

RESULTS

Clinical

The patients included 59 women and 56 men (Table 2) who ranged in age from 13 to 93 years, with a mean age at presentation of 64.3 years (median 66 years). There was no significant difference in overall survival between the genders ($p = 0.688$). Whereas there seemed to be an increase in the number of black patients with STMMM (10.4%), these patients did not realize a difference in overall outcome ($p = 0.930$). Of note, there was a significant decrease in overall survival for patients who were ≥60 years of age at initial presentation than those who were younger ($p = 0.029$). The patients were stratified by state of residence at the time of diagnosis, separated into "southern" (<40°N) and "northern" (≥40°N) latitude. There were more patients with STMMM living in the south ($n = 84$) versus the north ($n = 31$), which was a statistically significant difference ($p = 0.005$); however, there was no significant difference in overall survival or patient outcome between the southern and northern dwellers ($p = 0.223$).

TABLE 2. *Clinical characteristics of 115 sinonasal tract mucosal malignant melanomas (STMMM)*

Clinical characteristics	STMMM
Gender	
Females	59
Males	56
Age	
Range	13–93 y
Mean	64.3 y
Women (mean)	65.2 y
Men (mean)	63.3 y
Race	
Caucasian	103 (89.6%)
African American	12 (10.4%)
Symptoms	
Duration (range)	0.5–96 mo
Duration (mean)	8.2 mo
Duration mean (women)	5.8 mo
Duration mean (men)	4.7 mo
Epistaxis	52
Mass	42
Obstructive symptoms	34
Difficulty breathing/congestion	8
Pain	3
Polyps	6
Nasal discharge	4

The patients presented clinically with a variety of symptoms referable to the tumor location where epistaxis (frequent and profuse; $n = 52$), a mass lesion ($n = 42$), or obstructive symptoms ($n = 34$) accounted for the most frequent presenting symptoms. When obstruction was the only symptom ($n = 19$), the patients were more likely to have a worse clinical outcome (67% dead with disease; mean 1.7 years; $p = 0.02$) versus patients who presented with epistaxis as the sole symptom ($n = 25$; 55% dead with disease, mean 2.3 years, $p = 0.127$) or a combination of symptoms ($n = 71$; 53% dead of disease;

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mean 1.5 years; p = 0.228). Patients also experienced difficulty breathing and congestion, polyps, pain and a nasal discharge, or combination thereof. The melanorrhea, "coal flecked" or brown nasal discharge, suggested the presence of melanin pigment. No patients presented with visual symptoms related to pressure effect of the mass. The duration of symptoms ranged from a few days to 96 months, with an average of 8.2 months. The overall short duration of symptoms is most likely related to the high frequency of epistaxis as the initial symptom, usually prompting earlier medical attention. There was no difference in average length of symptoms between the genders (p = 0.621). There was no statistically significance difference in patient outcome between patients who had a short duration of symptoms (<6 months) versus those with a longer duration of symptoms (≥6 months; p = 0.348). We were unable to specifically correlate the clinical presentation with the tumor location, although there was a statistically significantly shorter duration of symptoms for patients whose tumors were located in the nasopharynx (mean 4.1 months) when compared with tumors of the other specific anatomic sites (p = 0.049). Curiously, tumors of the nasopharynx were also noted to have a significantly worse clinical outcome (p <0.001).

Formaldehyde exposure was identified in nine patients in whom a work history could be elicited (direct interviews with patients were not possible in most cases because many of the patients were deceased, and so this number may be underestimated). The exposure (of an undetermined duration) occurred in two painters, two furniture and cabinet makers, three laundry workers, and two construction workers.

Three patients of the 115 in this series had a documented melanoma involving the skin: one patient was a 90-year-old woman who developed a metastatic melanoma on the chest 2 years after the nasal columella primary; the next patient was a 57-year-old man who had a melanoma of the skin of the back documented 4 years earlier, and demonstrating completely different histologic features, although there was no surface involvement or surface origin documented in the maxillary sinus neoplasm; and the final patient was a 71-year-old man who had a Clark's level III melanoma of the flank 12 months prior to the nasal cavity and palate melanoma presentation; whereas the nasal neoplasm did not have junctional activity, no metastatic foci were identified, making it highly unlikely that the nasal cavity would be the only target of metastatic disease while the rest of the body was uninvolved. Therefore, two independent primaries were considered to have occurred in these three patients. No patients in this clinical series had a history of radiation exposure, either therapeutic or environmental.

Pathologic Features

Macroscopic

The tumors occurred in the nasal cavity alone, nasal septum alone (Fig. 1), turbinate alone, nasopharynx alone, maxillary sinus alone, and in the nasal cavity and the paranasal sinuses, including ethmoid, frontal, sphenoid, and/or maxillary sinus (Table 3). Lesions described as "nasal cavity alone" or "nasal cavity and paranasal sinuses" may have had tumors that involved a specific subsite (septum, turbinate) but were not designated as such. None of the tumors in this series at initial presentation involved the orbit, cribriform plate, or cranial fossa. The tumors ranged in size from 0.5 to 6.5 cm, with a mean of 2.4 cm (median 2.1 cm). There was no statistically significant difference in the size of tumors between the genders (women, 2.4 cm; men, 2.3 cm; p = 0.186). There was a statistical difference in the mean size of tumors that involved certain sites, such as the turbinate alone (mean 1.9 cm) and the maxillary sinus alone (mean 3.4 cm; p = 0.016), but not for the other anatomic sites. Furthermore, the larger the overall size of the lesion (>3.0 cm), the more likely the patient was to have a poor clinical outcome (p = 0.005). The majority of lesions were received as multiple, irregular fragments of soft tissue, especially in the biopsy and wide excision specimens. The resection specimens were frequently received as polypoid masses (Figs. 1 and 2). The cut surface, when not submitted in multiple fragments, was composed of grayish pink to brownish, black firm masses. The majority of the nasal cavity tumors were described as polypoid masses and were frequently brown or black (n = 60).

TABLE 3. *Macroscopic findings of 115 sinonasal tract mucosal malignant melanomas (STMMM)*

	STMMM
Anatomic site	
Nasal cavity alone	34
Septum alone	20
Turbinate alone	10
Nasopharynx alone	9
Maxillary sinus alone	3
Nasal cavity and sinuses (NOS)	39
Location	
Left	57
Right	46
Bilateral	3
Midline	9
Size (cm)	
Range	0.5–6.5
Mean	2.4
Thickness (cm)	
Range	0.2–1.9
Mean	0.72

NOS, not otherwise specified.

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Microscopic

The majority of tumors demonstrated, for the most part, an intact overlying respiratory surface epithelium (n = 95) (Figs. 2 and 3), with variable degrees of ulceration in most of these cases. Technically, there is no epidermal to "dermal" interface, and so an accurate determination of the depth of invasion and tumor thickness is exceedingly difficult. Although the surface epithelium was present in most of the cases, the presence of ulceration, fragmentation, discohesion, and tangentially sectioned specimens precluded coming up with a truly accurate tumor thickness. However, with these limitations in mind, tumor thickness was measured at its greatest point in a perpendicular axis to the mucosal surface or wherever tumor was closest to the surface (Table 3). The tumors measured from 0.2 to 1.9 cm in greatest thickness, with a mean of 0.7 cm. There was a statistical correlation between the size of the tumor and the tumor thickness ($p = 0.01$), but the tumor thickness did not correlate with the patient outcome ($p = 0.561$). Junctional activity or surface derivation of the neoplasm was noted in 23 neoplasms, although invasion into versus from the surface epithelium was often difficult to accurately determine (Fig. 3; Table 4). The tumors that demonstrated a surface derivation did not have a statistically significant difference in outcome when compared with those that did not ($p = 0.366$). Pagetoid spread within the epithelium was recognized in 18 tumors, in which the neoplastic cells extended beyond the extent of the neoplastic cells in the stroma below. Tumor cell invasion into the surrounding bone was noted in a few cases (n = 14), although this feature was not statistically significant ($p = 0.594$). Curiously, we identified metaplastic bone within the tumors in six cases. Different architectures, including solid (n = 60) (Fig. 4A), spindled (n = 45) (Fig. 4B), or peritheliomatous (n = 39) (Fig. 4C) were most common, whereas storiform (Fig. 4B), pseudopapillary (Fig. 4D), and alveolar (Fig. 4A) patterns were only noted focally. Fibrosis (regressive changes) was noted in 41 neoplasms but was not correlated with a worse clinical outcome ($p = 0.805$). Whereas a plasma cell infiltrate predominated (n = 60), mature lymphocytes or a mixed tumor cell infiltrate was also identified in an additional 25 tumors. Therefore, there was a heavy infiltrate in the majority of tumors. However, we did not consider these lymphoid cells to be "tumor infiltrating" lymphocytes. Pigment-laden histiocytes were prominent in 56 tumors. Tumor cell necrosis was conspicuous in 67 tumors, particularly prominent in the tumors arranged in a peritheliomatous pattern. Tumor necrosis was not statistically significant in overall patient prognosis ($p = 0.333$). Melanin pigment was revealed in the neoplastic tumor cells' cytoplasm as brown to black granules in many cases (n = 77 tumors; Fig. 5). The tumor cells were primarily undifferentiated (small to medium cell) in appearance (Fig. 6A), but epithelioid (n = 46; Fig. 6B), spindle cell (n = 29; Fig. 4B), plasmacytoid (n = 25; Fig. 6C), and rhabdoid cells were also identified. A signet-ring and hemangiopericytoma-like patterns were not identified. Tumors with an undifferentiated histology were more likely to have an unfavorable patient outcome ($p = 0.033$). This variable cytomorphologic appearance was characteristic both between tumors as well as within tumors. The tumor cells had a high nuclear-to-cytoplasmic ratio with pleomorphic nuclei containing prominent, enlarged, magenta, and irregular nucleoli (n = 97) and intranuclear cytoplasmic inclusions (n = 76; Fig. 6D). Tumor giant cells were seen in a number of tumors (n = 49; Fig. 6D). The cytoplasm was usually eosinophilic and opaque. In general, mitotic figures were easily identified in every case (Figs. 4A, 6A, B), with a mean of 17.8 mitotic figures per 10 HPFs. Atypical mitotic figures could be found in the vast majority of tumors (n = 92), although the number of atypical mitotic figures was not specifically catalogued. Patients whose tumors had >10 mitotic figures per 10 HPFs were noted to have a worse clinical outcome ($p = 0.026$), and the higher the number of mitotic figures, the worse the patients' outcome. Because of the nature of the specimens, perineural and vascular invasion was difficult to document and was present in only a few cases in which surrounding nasal cavity or sinus submucosa was included in the biopsy material.

TABLE 4. *Microscopic features of 115 sinonasal tract mucosal malignant melanomas (STMMM)*

Microscopic characteristic	STMMM
Surface derivation	23
Pagetoid spread	18
Growth pattern	
Spindle	45
Peritheliomatous	39
Solid sheet	60
Meningothelial	14
Specific subtype	
Spindle cell	29
Epithelioid	46
Plasmacytoid	25
Rhabdoid	3
Undifferentiated	67
Pigmented	77
Giant cell formation	49
Mitotic figures	
Mean (per 10 HPF)	17.8
Atypical figures (present)	92
Necrosis present	67
Perineural invasion	4

HPF, high-power field.

Immunohistochemical Results

Nearly all lesions tested reacted with vimentin (97.1%) (Table 5). A variety of melanoma markers were

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TABLE 5. *Immunohistochemical panel results*

Antibody	No. of cases with positive reactions
S-100 protein	99 (91.0%)
HMB-45	82 (75.9%)
Tyrosinase	84 (77.7%)
Melan A	70 (64.8%)
Microphthalmia transcription factor (MITF)	62 (57.4%)
Vimentin	102 (97.1%)
Neuron-specific enolase (NSE)	49 (46.2%)
CD117	37 (37.8%)
CD99	24 (22.9%)
Synaptophysin	13 (13.3%)
CD56 (NCAM)	8 (7.5%)
CD57	5 (4.7%)
Epithelial membrane antigen (EMA)	0
Cytokeratins	0
CAM 5.2 (K8)	0
Chromogranin	0
Glial fibrillary acidic protein (GFAP)	0
CD45 (LCA)	0
Smooth muscle actin	0
Muscle specific actin	0
Desmin D33	0
Desmin DR11	0

tested in this clinical series with S-100 protein and tyrosinase (Fig. 7) identified more frequently than HMB-45, melan A, or microphthalmia transcription factor (MITF) (Table 5). All cases were identified by the panel of S-100 protein, HMB-45, and tyrosinase when used in combination. Of the 43 spindle-cell melanomas tested, 84% were S-100 protein immunoreactive, 72% were tyrosinase immunoreactive, and 65% were HMB-45 immunoreactive (60% each for melan A and MITF). A panel identified all cases. In the undifferentiated group, 96% of cases were identified by S-100 protein, 82% with tyrosinase, and 77% with HMB-45; this panel identifying all cases. Curiously, a number of other antibodies demonstrated reactivity in the tumor cells and included neuron-specific enolase, CD117, CD99, synaptophysin, CD56, and CD57 for a greater or lesser degree in the majority of the tumor cells, although only in a few cases. Epithelial membrane antigen, cytokeratins, and muscle markers were not expressed (Table 5).

Treatment and Follow-up

All patients were treated by partial or complete surgical excision; complete surgical removal of the tumor was not always possible as a result of the complex anatomy of the nasal cavity, paranasal sinuses, and nasopharynx. Thirty-three patients were treated by surgery alone without any additional therapy (mean follow-up, 6.7 years); 20 died with disease (mean 1.9 years), whereas 13 were either alive or had died of unrelated causes (mean 14.1 years). An additional 10 patients were managed by surgery and chemotherapy (mean follow-up, 7.2 years; 8 dead with disease, mean 2.9 years), whereas 50 patients had surgery and radiation therapy (mean follow-up, 5.9 years; 34 dead with disease, mean 2.5 years). The remaining 22 patients were managed with surgery and combination therapy (mean follow-up, 6.2 years; 13 dead with disease, mean 2.1 years). Although the overall survival for STMMM was grim (65.2% died with disease), a surprising number of patients were alive or had died without evidence of disease at last follow-up (40 patients; 34.8%). The specific type of therapy did not seem to influence the overall patient outcome, as there was no statistically significant difference between patients managed by surgery alone ($p = 0.209$), surgery with chemotherapy ($p = 0.947$), surgery with radiation therapy ($p = 0.825$), or surgery and combination therapy ($p = 0.144$). When the patients died with or from their disease (the distinction is often difficult to ascertain retrospectively), they, in general, died a mean of 2.3 years after initial presentation (Table 6). Eight patients survived for >5 years with their tumors before dying of their disease up to 15.2 years after initial presentation. In general, the 40 patients who were without evidence of disease at last follow-up had a mean follow-up of 13.9 years. These results yield a raw 5-year survival of 42.6% and a raw 10-year survival of 24.3%. This contrasts to a disease-free 5-year survival of 31.3% and a disease-free 10-year survival of 22.6% (Table 7). Seventy-nine patients had a significantly worse patient outcome ($p < 0.001$) when they developed recurrent disease, followed by development of cervical lymph node metastasis and then disseminated disease. Lung, liver, and bone were the most frequent sites affected with metastatic tumor. Curiously, the three patients with a "skin melanoma" at some point in the period of study survived 2.7, 12.1, and 0.7 years, respectively, the middle patient surviving to die of a lung adenocarcinoma, unrelated to the melanoma.

Specific clinical and histologic features have been suggested to be of prognostic significance (Table 6). Patients who were older than 60 years at initial presentation ($p = 0.029$), who developed recurrences ($p < 0.001$), presented with obstructive symptoms only ($p = 0.02$), had tumors located in the nasopharynx ($p < 0.001$), an undifferentiated histology ($p = 0.033$), and >10 mitotic figures per 10 HPFs ($p = 0.026$) were each more likely to experience a worse clinical outcome.

DISCUSSION

The value of retrospective analysis of any diagnosis is often dubious in the modern management of human disease. However inexact and incomplete these analyses may be, when a rare neoplasm such as STMMM is considered, the accumulated experience examining many cases can bring to light a number of features that the individual case study may overlook. The advantage of a referral practice, such as the Armed Forces Institute of

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TABLE 6. *Patient outcome for 115 sinonasal tract mucosal malignant melanomas (mean yr of follow-up)*

	All patients	A, NED	D, NED	D, WD
All patients with follow-up	115 (6.3)	16 (16.6)	24 (12.1)	75 (2.3)
Follow-up range	0.2–28.4	4.3–27.2	0.2–24.2	0.3–15.2
Males	56 (6.8)	8 (15.3)	13 (13.6)	35 (2.3)
Females	59 (5.9)	8 (17.8)	11 (10.3)	40 (2.3)
African American	12 (6.8)	2 (21.2)	1 (20.3)	9 (2.1)
Size				
<3.0 cm	77 (6.4)	14 (15.3)	12 (12.1)	51 (2.4)
≥3.0 cm	34 (5.8)	1 (23.4)	11 (12.3)	22. (2.0)
Histologic type				
Undifferentiated type	67 (4.9)	7 (12.8)	12 (11.6)	48 (2.1)
Spindle cell melanoma	29 (8.0)	3 (16.7)	9 (14.6)	17 (3.0)
All other melanomas	86 (5.8)	13 (16.5)	15 (10.6)	58 (2.1)
Patients with recurrence	79 (3.2)	1 (24.8)	5 (11.8)	73 (2.3)
Patients without recurrences	36 (13.1)	15 (16.0)	19 (12.1)	2 (0.5)
Tumors with regression	41 (6.5)	6 (17.8)	6 (16.0)	29 (2.2)
Tumors with surface origin	23 (6.2)	4 (12.1)	5 (10.6)	14 (3.0)
Tumors without pigmentation	38 (6.5)	6 (13.6)	9 (11.4)	23 (2.7)
Anatomic site				
Nasal cavity (NOS)	34 (7.1)	6 (16.1)	6 (15.8)	22 (2.2)
Septum alone	20 (7.5)	3 (16.1)	7 (7.2)	10 (5.2)
Nasopharynx alone	9 (2.5)	N/A	1 (7.7)	8 (1.8)
Turbinate alone	10 (8.2)	2 (12.1)	4 (13.3)	4 (1.1)
Maxillary sinus only	3 (7.2)	1 (19.7)	N/A	2 (1.0)
Nasal cavity and sinuses (NOS)	39 (5.4)	4 (19.0)	6 (13.9)	29 (1.8)

* Size was unknown in 4 cases.

A, NED, alive, no evidence of disease; D, NED, dead, no evidence of disease; D, WD, dead, with disease; N/A, not applicable; NOS, not otherwise specified.

Pathology, is to compile a multitude of important points related to clinical presentation, pathology recognition, special study application, and predictive value about prognosis, which can aid in the management of an otherwise highly lethal neoplasm. Rather than exhaustively enumerate all of the statistical data accrued in this study, we will instead try to relate the information to the questions most frequently raised when considering a diagnosis of STMMM: 1) etiology, 2) clinical demographics, 3) radiographic analyses, 4) pathology features and differential diagnosis, 5) clinical management, and 6) prognosis, including recurrence and staging.

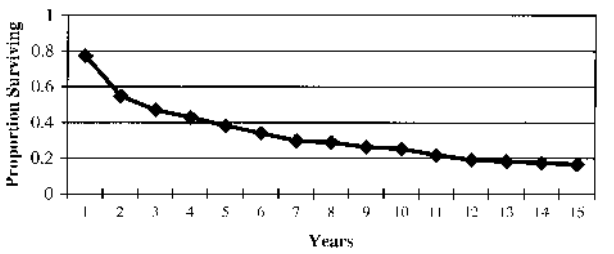
Etiology/Embryogenesis

Primary STMMMs without any evidence of an association with an integumentary primary or another mucosal primary tumor are rare, and most of the reported cases were written before modern immunophenotypic techniques were available to exclude other undifferentiated tumors. As noted in this series, the 115 STMMMs made up only 0.57% of the benign or malignant primary sinonasal tract tumors seen in consultation at the Armed Forces Institute of Pathology.

Melanocytes, derived from neural crest tissue, are distributed throughout the upper respiratory tract and oral cavity where they are found in the mucosa and stroma of adults of nearly all races, although to a greater degree in blacks.[66] Preexisting melanosis (pigment in the mucosa) in the sinonasal tract is quite uncommon, seen in eight patients (7%) in this series, thought to be a genetically determined, inducible, and reversible phenomenon.[7,17] Therefore, whether arising from the surface epithelium or from melanocytic cells in the stroma, primary STMMM arises de novo rather than from a preexisting nevus or as a metastasis from a cutaneous primary. The absence of sunlight as a causative agent implies a strong genetic influence or other environmental factor, but there are not many studies addressing this quandary.[7,30,63]

Formaldehyde exposure was identified in nine patients in whom a work history could be elicited. It is well known that formaldehyde is used for a variety of purposes, including as a preservative in paints, adhesives used to make pressed wood products (used in shelving, furniture, flooring, and paneling), adding permanent-press qualities to clothing, as foam insulation, as well as

TABLE 7. *Overall actuarial survival of sinonasal tract mucosal malignant melanoma*



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being more ubiquitously found in tobacco smoke, cosmetics, and textiles. Therefore, although a specific epidemiologic link between occupational exposure to formaldehyde and the development of STMMM has not been absolutely established,[7,32] the 7.8% of patients in this series with possible occupational exposure to formaldehyde suggests it may be an etiologic factor. This apparent association warrants further investigation.

Another epidemiology factor considered was the geographic place of residence at the time of diagnosis. We identified a significantly increased number of STMMM submitted from patients living in southern latitudes rather than northern latitudes ($p = 0.005$); nevertheless, this finding is exactly opposite of another study.[12] We did not have a greater number of referral cases from southern states during the period of consideration. We do not have an explanation because a relationship to increased sun exposure in these mucosal sites seems unlikely. This argument notwithstanding, there is no difference in patient outcome based on geographic latitude ($p = 0.223$).

Clinical Information

In our series, STMMMs were equally common in men and women. This is different from cutaneous melanomas in which men tend to predominate, reflecting increased sun exposure generally related to hair distribution and occupation. Female patients with cutaneous melanomas tend to have a better prognosis than men ($p < 0.0001$),[9,11] but no such statistical difference was found for STMMM ($p = 0.688$). A higher proportion of black patients was identified in this study (10.4%) than usually reported, but there was no difference in patient outcome when race was analyzed ($p = 0.930$).[11,31,47] In general, the mean age for STMMM (64.3 years) is later in life than cutaneous malignant melanomas. However, STMMM is a more lethal disease in patients older than 60 years ($p = 0.029$), a finding similar to cutaneous melanoma ($p < 0.0001$).[11] This may be partially accounted for by a decline of immunologic forces in general, that standard therapy could not be instituted because of their frail physical condition, or because of refusal by the patient to undergo an extensive procedure.[3,35]

Symptoms were, for the most part, nonspecific, failing to prompt patients to seek immediate medical attention. The lesions are hidden from view and are therefore more difficult to identify. In this study, patients who had obstructive symptoms alone suffered a worse prognosis when compared with those who presented with epistaxis alone ($p = 0.02$). This suggests an earlier detection of the disease attributable to seeking medical attention early on when bleeding is the presenting symptom.[18,44] Symptoms were of a shorter duration (mean 4 months) for patients who had nasopharyngeal primaries ($p = 0.049$) when compared with other locations, similar to previous reports.[5,11,23]

Pathology

Most of our patients' tumors involved the nasal cavity alone (site was not further specified) followed by a combination of the nasal cavity with the paranasal sinuses, a finding similar to the literature.[4,5,7,15,21,22,31,35,39,43,44,47,53,55,56,58,59,61,62,65] Whereas individual sinuses were solely involved in only a few cases, the majority of cases tended to involve more than one sinus by direct extension of a large, expansive mass. When specifically stated, the nasal septum and turbinates were the most frequently identified subsites,[4,5,7,15,22,31,56,65] possibly suggesting an inhaled carcinogen. When the nasopharynx is affected it portends a worse clinical outcome (88% dead in this clinical series; mean 1.8 years, $p < 0.001$).[44,47] Other than the nasopharynx specifically, a single site did not change the prognosis, although mixed sites or subsites trended toward a poor clinical outcome (74% dead of disease at 1.8 years, $p = 0.06$).[19,22,43,44,55]

The vast majority of cases typically presented as a polypoid, fleshy, bulky mass that may or may not be pigmented. The overall size (not thickness) of the lesion was of clinical import, with tumors >3 cm portending a worse clinical outcome than smaller sizes, a finding different from those of previous authors.[31,56] However, many authors do not comment on the overall size but rather on the "thickness." Meaningful measurements of tumor thickness were fraught with a host of technical difficulties: surface ulceration, submucosal origin, distortion of a "polypoid" specimen, and a lack of orientation all contributed to a tumor thickness that was an estimate at best. With these difficulties in mind, our average tumor thickness (0.7 cm) is similar to the findings of others.[25,37,40,44,45,55,56,62] Perhaps axiomatic, STMMMs are much thicker than their cutaneous counterparts. However, despite these efforts, tumor thickness failed to correlate with or predict patient outcome ($p = 0.561$).

Surface involvement defines local disease, whereas metastatic disease to this site would not demonstrate junctional activity or surface origin. However, because melanocytes can normally be found in the stroma, the identification of surface derivation or junctional activity in only 23 cases does not raise the specter of metastatic tumors in the remaining cases.[18] Pagetoid spread (epidermal migration, intramucosal spread), when present, is diagnostic of STMMM.[7,47,49]

Regression, defined by scarring and fibrosis with granulation tissue-like vessels, has been used in cutaneous melanoma as an indicator of poor prognosis. However, the presence of these features in STMMMs did not affect the clinical outcome ($p = 0.805$).[37] There was a

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brisk, heavy inflammatory infiltrate in the majority of the tumors in this clinical series, a finding discordant with a few series.[4,22,53] An absent or diminished lymphoid response is usually considered a sign of diminished immunity.[4,22] Lymphocytes at the periphery may just be reactive, rather than the "tumor infiltrating" lymphocytes, which suggest more of a immune response.[37] In this clinical series, a lymphocyte and/or plasma cell response was identified in 85 of our cases, although we could not specifically separate "tumor infiltrating" from "peripheral" as fragmentation artifacts and orientation issues seem to make such a distinction artificial. Of this group, nine (8%) patients developed metastatic disease >5 years after an initial disease-free period, and 40 patients (35%) had no evidence of disease at the last follow-up (mean follow-up, 13.9 years). These findings strongly support an immunologic control of the disease by a competent immunologic system. Few patients had immunotherapy in this series, but perhaps immunotherapy in the management of STMMM should be further studied.

Melanin pigment was seen in the majority (67%) of cases, a finding similar to the cases reported in the literature.[4,7,18,27,31,37,47] It has been suggested that cases without pigment tend to have a worse clinical outcome, but the absence of pigment in this clinical study did not predict a worse clinical outcome ($p = 0.439$). Another parameter of known prognostic significance in cutaneous melanoma is mitotic rate. Mitotic figures are usually easily identified, with >6/10 HPF considered a poor prognosticator.[53] We were unable to confirm this finding, although when using a cutoff of 10 mitoses/10 HPF (as defined in *Methods*), a significantly worse patient outcome was confirmed ($p = 0.026$).

The identification of osteoid and metaplastic bone in 5.2% of cases was unexpected, although it is a finding previously reported.[33] It may be caused by repeated trauma, mesenchymal metaplasia, reparative reaction secondary to bone invasion, and induction of bone formation of the surrounding tissues.

Like their dermatologic counterparts, STMMM is the great imitator histologically. We found the peritheliomatous growth to be particularly distinctive. Whereas the spindle cell type in cutaneous malignant melanomas seems to portend a worse outcome, only the undifferentiated type had a worse clinical outcome than the other types ($p = 0.033$) in our series. Despite the fact that focal undifferentiated cells were seen in 67 cases, it was the sole pattern in only 23 patients. It was this subset of patients who had worse clinical outcome. We are uncertain that the seemingly high number of cases with an undifferentiated type really reflects the true incidence in STMMM given that the referral cases sent into the Armed Forces Institute of Pathology may be biased toward the "undifferentiated" type.

Immunohistochemical Studies

The immunohistochemical profile of STMMM is identical to dermatologic lesions.[18,21,29,37,52,53,64] S-100 protein seemed more sensitive, followed by tyrosinase and HMB-45. However, only 91% of our cases were S-100 protein immunoreactive, suggesting that the application of a panel of melanoma markers is necessary to avoid misdiagnosing an occasional case. Even when the tumors are spindled or undifferentiated types, a panel of S-100 protein, tyrosinase, and HMB-45 would correctly identify all tumors. Therefore, it is our practice in an achromatic neoplasm to obtain a panel of markers that include, among other antibodies, S-100 protein, tyrosinase, and HMB-45 to accurately diagnose an STMMM. HMB-45 is more specific than S-100 protein as it recognizes the melanosomal oligosaccharide side chain of a glycoprotein (gp100). Spindle cell melanomas are frequently negative, suggesting premelanosomes may not be in abundance in this subtype. However, tyrosinase (and not HMB-45) was the most sensitive melanocyte differentiation marker. Vimentin is also useful in the differential diagnosis because olfactory neuroblastoma and sinonasal undifferentiated carcinoma are usually nonreactive. Microphthalmia transcription factor (MITF), identified by nuclear positivity, is usually identified in about 30% of nuclei in about 90% of metastatic melanomas.[48] No cases in this clinical series were uniquely identified by a positive MITF. MITF is relatively specific for melanoma, but not as sensitive as S-100 and not as specific or sensitive as tyrosinase.[48,52]

Differential Diagnosis

STMMMs may morphologically masquerade as a variety of benign and malignant neoplasms. When junctional activity and melanin pigment are present, it is pathognomonic of STMMM. If melanin alone is seen, other neural tumors must be excluded. In the past, a special stain triad was required to confirm the diagnosis of melanoma: a Fontana stain for melanin was positive, the pigment was bleached by permanganate-oxalate, and an iron stain was negative.[23,27,31] In modern times, an immunohistochemical panel is more easily interpreted and used. Depending upon the growth pattern or histologic features and the size of the biopsy, the repertoire of potential microscopic differential diagnoses can be divided into "small blue round cell," (olfactory neuroblastoma, primitive neuroectodermal tumor, Ewing's sarcoma, melanocytic neuroectodermal tumor of infancy, pituitary adenoma, lymphoma, plasmacytoma, small cell or neuroendocrine carcinoma, mesenchymal chondrosarcoma), pleomorphic (sinonasal undifferentiated carcinoma, angiosarcoma, anaplastic large cell lymphoma, rhabdomyosarcoma), or spindle cell lesions (malignant peripheral nerve sheath tumors, fibrosarcoma, malignant fi-

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brous histiocytoma, leiomyosarcoma, synovial sarcoma).[7,20,21,31,42,49,50,64] It seems that STMMMs tend to be more capricious than their cutaneous counterparts. It is when the tumors are amelanotic and/or show surface ulceration that errors in diagnosis are the most likely. The difficulty in making an accurate diagnosis was confirmed in this clinical series, in which 68% of cases were misclassified by the contributing pathologists. Rather than enumerate all of the features in each tumor type that can be used to make an accurate diagnosis, suffice it to say that clinical, histologic, histochemical, and immunohistochemical features need to be used in aggregate. Phenotypic infidelity or anomalous immunoreactivity (S-100 protein, neuron-specific enolase, CD117, CD99, synaptophysin, and CD56 are expressed in many different tumors), suggests the use of a panel of antibodies when evaluating SNT neoplasms. It is our practice to include a keratin cocktail (AE/AE3, CK1), vimentin, S-100 protein, tyrosinase, HMB-45, CD45RB, desmin, muscle specific actin, chromogranin or synaptophysin, and CD30, tailored to the histologic appearance. Metastatic melanoma must always be excluded, although highly unlikely when melanoma is seen in the sinonasal tract. Less than 1% of patients with cutaneous melanomas will develop metastatic disease to the sinonasal tract.[6,21] Isolated metastasis to the mucosa of the head and neck is vanishingly rare. Instead, metastasis is usually part of widely disseminated disease.

Treatment

STMMM has been considered a highly lethal disease for which treatment was considered a fruitless therapeutic exercise with a never-ceasing death risk. No authors question that surgery is the cornerstone of therapy and offers the only possible treatment for cure. It is important to perform surgery with wide margins of resection. However, it is nearly impossible to carry out a truly radical resection because of the almost inaccessible recesses of the nasal passages, vital structures of the region, and a desire to achieve local control without cosmetic disfigurement and loss of function.[2,18,19,22,24,27,35,39,44,51,58–62] This decision should be considered individually and proposed with circumspection in light of the size of the tumor and its anatomic location, and whether or not lymph node or distant metastasis is present at the time of initial workup (by clinical or radiographic examination). In general, because of the limited number of patients who have cervical lymph node metastasis at the time of initial presentation (5.2%), a neck dissection is not recommended. It is agreed that radiotherapy does not change the overall patient survival ($p = 0.825$).[2,9,15,18,19,21,22,24,27,28,39,43,44,51,55,59,61,63] However, we hasten to add that patients with unresectable local disease, elderly patients who are poor surgical candidates, or patients who refuse surgery should be considered for radiotherapy alone as definitive therapy. Specific immunologic therapy was documented in only six patients in this clinical series, which shows promise but remains investigational.[54]

Local recurrence is a major factor in failure of treatment and is related to several mechanisms, such as incomplete removal (anatomic relationships are complex), multifocal tumor, diffuse submucosal lymphatic spread, transformation of melanocytes at the periphery of the excision into melanoma, failure to remove nodes containing melanoma, and local implantation during surgery.[3,27,34,39,44,46,51,56] High local recurrence rates may be a manifestation of an unstable mucosa, already susceptible to whatever carcinogen may have incited the development of the melanoma initially. By whatever mechanism they develop, local recurrences can be controlled by further surgical attacks when technically feasible. Frequent (every 2–4 months) postoperative follow-up of patients, especially by history and physical examination, is paramount in achieving the best local and distant tumor control, and ultimately, patient outcome. Until there is improvement in systemic therapy, it can be inferred that the overall patient outcome will remain guarded.

Prognosis

In general, the prognosis of primary STMMM is poor, although the outcome is frequently unpredictable. There are patients in this series and in the literature who live for a reasonable period completely free of disease, until suddenly up to 12 years after the initial successful treatment, the tumor abruptly reappears and metastasizes to multiple organs and results in their death a short time later. The poorer prognosis for STMMM has been related to the tumor bulk (size), delay in diagnosis resulting from the nonspecific nature of the presenting symptoms, difficult visual examination (vs the conspicuous skin of the face), and technical inaccessibility of the primary tumor.[7,16] Other factors have been considered, but without statistical validation.

As greater experience has accumulated and as both clinicians and pathologists have refined their skills and added special techniques to their armamentarium, the prognosis may no longer be as grim as formerly thought. Although often difficult to determine from the reports, a <25% raw 5-year survival is expected.[2,3,5,7,10,14,15,18,19,21–25,27,31,35,39–41,44,45,51,55,56,58–62] This survival differs from the 5-year cancer-related survival rate of 88% for cutaneous malignant melanoma,[11,26] although reported to be slightly lower for head and neck cutaneous melanomas (65%).[3] Our raw 5-year survival of 42.6% and a raw 10-year survival of 24.3% reflect the overall prognosis for this disease. However, we calculated a disease-free 5-year survival of 31.3% and disease-free 10-year survival of 22.6%.

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TABLE 8. *Stage-based outcome for 115 sinonasal tract mucosal malignant melanomas (mean years of follow-up)*

	All patients	A/D, NED	D, WD
All cases	115 (6.3)	40 (13.9)	75 (2.3)
Stage 1	40 (11.4)	30 (13.2)	10 (5.9)
Stage 2	16 (11.6)	10 (15.9)	6 (4.4)
Stage 3/4	59 (1.5)	0	59 (1.5)

A/D, NED, alive or dead, no evidence of disease; D, WD, dead, with disease.

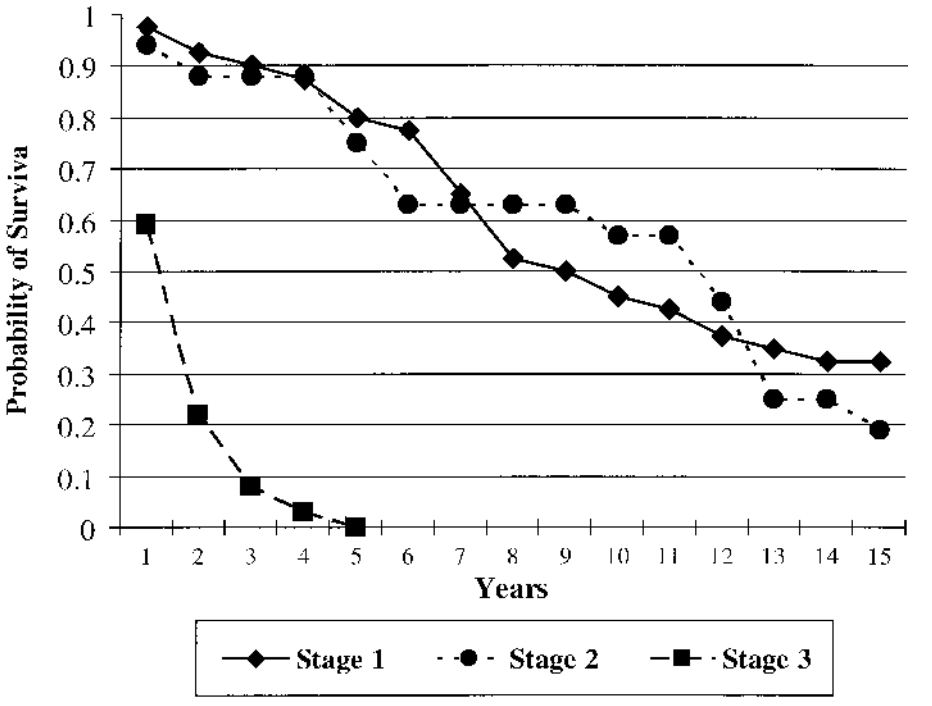
Twenty-seven patients in this clinical series survived for longer than 10 years (22.6%), with only one of these patients (3.7%) dying of disease (at 15.2 years). This finding supports the suggestion to follow patients for a minimum of 10 years.[16,21,27,43,57,62]

Staging

Improvement in diagnosis, treatment, and patient outcome can be enhanced by a central registration, treatment, and follow-up, standardized terminology and staging, standardized clinical workup and treatment protocols, and controlled clinical multicenter studies.[35] To this end, a variety of staging systems have been proposed for melanoma in general. McNeer and Cantin,[46] Clark et al.,[13] and Breslow[8] have all identified integumentary system parameters that have yielded statistically significant prognostications about patient outcome. Unfortunately, the mucosal sites within the sinonasal tract do not lend themselves to the application of these systems because of an absence of histologic landmarks identifiable as a papillary and reticular dermis and a lack of orientation to accurately determine a penetration thickness.

The TNM classification for the nasal cavity, paranasal sinuses, and nasopharynx applies only to histologically confirmed carcinomas and does not apply to melanoma, sarcoma, or olfactory neuroblastoma. The division into maxillary sinus and naso-ethmoid sinus, with orbital extension, skin invasion, or middle cranial fossa involvement, does not encompass the biologic behavior of melanoma.[1] The TNM classification of melanomas is only available for skin and ocular lesions. Further, STMMMs are frequently polypoid rather than being deeply invasive, belying the true "extent of the disease." Freedman et al. proposed a modification to the TNM but only took into consideration direct extension of the disease from the nasal cavity into the surrounding structures.[22] Kadish et al. proposed a classification for olfactory neuroblastoma based on anatomic location and extent of disease,[36] and Ballantyne considered local disease (no size or extent), lymph node metastasis, and distant metastases in his STMMM staging proposal.[3] Regional lymph node metastasis alone without distant metastasis is not a common finding: six patients in this clinical study. Conversely, when widely disseminated disease was present, regional lymph node metastasis was very common. When patients develop distant metastasis they will

TABLE 9. *Actuarial survival based on TNM staging classification*



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also frequently have locally recurrent disease.[63] Lymph node metastasis is generally noted in about one third of mucous membrane head and neck melanomas at initial presentation, imparting a worse prognosis.[11,22,24,27,31,35,39,44,51,55] Chang et al.[11] suggested that lymph node status was an important prognostic factor and should be incorporated into any formal staging system. The very rich lymphatic drainage of the sinonasal tract and nasopharynx gives a foundation for the very high incidence of lymph node and distant metastases. Therefore, although a number of staging proposals have been submitted, a comprehensive analysis using tumor location, tumor extent, tumor "size" or "thickness," and metastatic disease (lymph node or disseminated) compared with patient outcome has not been considered.

The results of this clinical study lend themselves to stratification in an attempt to yield statistically significant information by incorporating features of size (Clark's level and Breslow's thickness), sites of anatomic involvement (T category, Kadish et al.[36] and Freedman et al.[22]), and the importance of distant spread (Ballantyne[3] and Chang et al.[11]) into an easy-to-apply staging system, similar to the TNM concept.[1]

After extensive analysis, the presence of metastatic disease was the most important factor in predicting patient outcome. Table 8 demonstrates the patient outcome based on the presence of single versus multifocal disease and the presence of metastatic disease. Each of these stages has a statistically significant difference in patient outcome: stage 1 (T1N0M0): 75% without evidence of disease (mean follow-up, 13.2 years), $p < 0.001$; stage 2 (T2N0M0): 62.5% without evidence of disease (mean follow-up, 15.9 years), $p = 0.002$; stage 3 (any T, any N, M1): 100% dead with disease (mean 1.5 years), $p < 0.001$. Table 9 demonstrates the actuarial survival based on this proposed staging. This staging is a clarification of the those presented by others[3,11,22,36] but analyzed statistically with a large group of only sinonasal tract/nasopharynx-based tumors. The proposed staging system (Table 10), separated into tumor (T), lymph node (N), and distant metastasis (M) groups, has further tumor separation based on location. The T-category is then combined with the lymph node status and distant disease status into a staging group. This staging system was then applied to our patients, with resultant survival curves generated for these stages (Table 9). With only six N1M0 patients, all of whom died with disease, we combined stage 3 and 4 patients into a single curve. This proposed staging did have a statistically meaningful predictive value in suggesting which patients are more likely to die from their disease ($p < 0.001$).

Although this proposed staging system accurately predicted patient behavior in this clinical study, it in no way implies a "cookbook" recipe for success when applying this staging. It is important to recognize that there will inevitably be individual variations in therapy and natural history that may confound the results of classification. In any staging system, there will always be a small group of patients who do far better or far worse than would be expected on statistical grounds. There is a degree of subjectivity in the application of the criteria, such as anatomic site of involvement and how to determine the presence of metastatic disease (regional or distant). This proposed staging will need to be applied to a larger number of

TABLE 10. *Proposed staging for sinonasal tract and nasopharynx mucosal malignant melanoma*

Nasal cavity, paranasal sinuses, and nasopharynx histopathology staging	
Primary tumor	
T1	Single anatomic site
T2	Two or more anatomic sites
Regional lymph node	
N1	Any lymph node metastasis
Distant metastasis	
M1	Distant metastasis
Stage grouping	
Stage I	T1, N0 M0
Stage II	T2, N0 M0
Stage III	Any T, any N, M1
Stage IV	Any T, any N, M1

T, primary tumor.
TX, primary tumor cannot be assessed.
T0, no evidence of primary tumor.
T1, tumor limited to a single anatomic site. A single anatomic site is defined as one of the following: nasal cavity, maxillary sinus, frontal sinus, ethmoid sinus, sphenoid sinus, nasopharynx. Subsites, such as septum, lateral wall, turbinate, nasal floor, or nasal vestibule are not separately considered.
T2, tumor involving more than one anatomic site. More than one anatomic site is defined by tumor involvement of more than one anatomic site (although not subsite) as cited above, including any extension into subcutaneous tissues, skin, palate, pterygoid plate, floor, wall, or apex of the orbit, cribriform plate, infratemporal fossa, dura, brain, middle cranial fossa, cranial nerves, clivus.
N, regional lymph nodes (cervical lymph nodes).
NX, regional lymph nodes cannot be assessed.
N0, no regional lymph node metastasis.
N1, metastasis in regional lymph node(s) of any size, whether ipsilateral, bilateral, or contralateral (midline nodes are considered ipsilateral nodes).
M, distant metastasis.
MX, distant metastasis cannot be assessed.
M0, no distant metastasis.
M1, distant metastasis.
pTNM, pathological classification.
The pT, pN, and pM categories correspond to the T, N, and M categories. From a practical standpoint, documentation of metastatic disease (lymph node or distant) is based on findings within 90 days peri-diagnosis (ie, a lymph node is the initial presentation and a mucosal primary is documented within 3 months; a STMMM is diagnosed and then CT, MR or other studies are performed over the ensuing 6 weeks and identify metastatic disease).
pN0, histologic examination of a selective neck dissection specimen will ordinarily include 6 or more lymph nodes. Histologic examination of a radical or modified radical neck dissection specimen will ordinarily include 10 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

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TABLE 11. *Factors influencing patient outcome in sinonasal tract mucosal malignant melanoma*

Factor	Variable	No. of patients	Percent dead with disease (mean follow-up)	Univariate analysis
Age	<60 yr	38	50% (2.2 years)	p = 0.029
	≥60 yr	77	73% (2.3 years)	
Gender	Females	59	68% (2.3 years)	p = 0.688
	Males	56	63% (2.3 years)	
Ethnicity	Caucasian	103	64% (2.3 years)	p = 0.930
	African American	12	75% (2.1 years)	
Geographic region	North (≥40°N)	31	74% (2.2 years)	p = 0.223
	South (<40°N)	84	62% (2.4 years)	
Symptoms	Epistaxis alone	25	55% (2.3 years)	p = 0.127
	Obstruction alone	19	67% (1.7 years)	**p = 0.020**
	Combination of symptoms	71	53% (1.5 years)	p = 0.228
Symptom duration	<6 mo	72	75% (2.2 years)	p = 0.348
	≥6 mo	39	64% (2.5 years)	
Anatomic site	Nasal cavity	34	65% (2.2 years)	p = 0.337
	Nasopharynx	9	89% (1.8 years)	**p <0.001**
	Mixed	39	74% (1.8 years)	p = 0.059
Tumor size (cm)	<3.0	77	65% (2.4 years)	**p = 0.005**
	≥3.0	34	74% (2.0 years)	
Tumor thickness (cm)	≥0.5	47	66% (2.2 years)	
	0.6–1.0	45	60% (2.2 years)	p = 0.561
	1.1–1.9	23	74% (2.5 years)	
Pigment (microscopic)	Present	77	68% (2.1 years)	p = 0.439
	Absent	38	61% (2.7 years)	
Dominant histology	Undifferentiated only	23	72% (2.1 years)	**p = 0.033**
	Spindled only	29	59% (3.0 years)	p = 0.634
Mitotic index	<10/10 HPF	51	63% (2.9 years)	**p = 0.026**
	≥10/10 HPF	64	57% (1.9 years)	
Necrosis	Present	67	66% (1.5 years)	p = 0.333
	Absent	48	65% (3.4 years)	
Recurrence	Yes	79	92% (2.3 years)	**p <0.001**
	No	36	5% (0.5 years)	
Treatment	Surgery alone	33	58% (1.8 years)	p = 0.209
	Surgery + radiation	50	66% (2.5 years)	p = 0.825
	Surgery + chemotherapy	10	80% (2.9 years)	p = 0.947
	Surgery, radiation, + chemotherapy	22	59% (2.1 years)	p = 0.144
Stage (as proposed)	Stage 1	40	25% (5.9 years)	**p <0.001**
	Stage 2	16	38% (4.4 years)	**p = 0.002**
	Stage 3/4	59	100% (1.5 years)	**p = 0.001**

cases to determine its clinical utility and validity. Table 11 presents a summary of the variables and factors analyzed in an attempt to suggest prognostically significant features, taking into consideration the attributes of malignant melanoma in general, and mucosal melanoma in specific, suggested by others[3,4,6–8,11–13,16,18,19,21,22,24,25,32,37,45,51,53,56,58–60,62] and by this clinicopathologic series.

In summary, STMMMs, although rare, are distinct mucosal tumors. They occur in older patients of both genders and are frequently associated with a poor prognosis. The natural history is capricious, with local recurrence or distant metastasis developing unexpectedly. The clinical and radiographic features of these tumors are nonspecific; consequently, an accurate diagnosis requires histologic evaluation. The welter of morphologic features and an absence of melanin pigment bring a diverse group of sinonasal tract neoplasms into the differential diagnosis. An awareness of these factors combined with appropriate immunohistochemical analysis should allow distinction of these neoplasms from other sinonasal tract tumors. Diagnostic accuracy coupled with the size, tumor location, and presence of metastatic disease should allow for better prognostication, thereby tailoring patient management to achieve the longest possible patient survival. □

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