Toward a Better Understanding of Sinonasal Mucosal Melanoma: Clinical Review of 23 Cases

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Background: Primary sinonasal mucosal melanoma is a rare disease, occurring far less often than cutaneous lesions. The objective of this study was to review the records of patients diagnosed with primary sinonasal mucosal melanoma.

Methods: We performed a retrospective review of the medical records of 23 patients with sinonasal mucosal melanoma who were treated at Taipei Veterans General Hospital between 1982 and 2002.

Results: Sixteen of the 23 patients were male and 7 were female; their mean age was 68.2 years (range, 39–87 years). At diagnosis, the melanoma was limited to lesions located in the sinonasal area in 20 patients, and had spread in 3 patients. Local recurrence developed in 9 patients, neck metastasis in 5, and distant metastasis in 19. The 5-year disease-specific survival and local control rates were 22.26% and 52.30%, respectively.

Conclusion: In our experience, primary sinonasal mucosa melanoma is prone to spread from the site of origin. The major obstacle in improving overall survival is achieving systemic control. [*J Chin Med Assoc* 2007;70(1):24–29]

Key Words: melanoma, nasal mucosa, nasal neoplasm, paranasal sinus neoplasm

Introduction

Primary sinonasal mucosal melanoma (SNMM) is a rare disease, occurring far less often than cutaneous lesions. Melanomas arising from mucosal surfaces constitute 0.2–8.0% of all melanomas, and 55.4% of mucosal melanomas are found in the head and neck.[1–3] Studies have estimated that SNMM comprises 3.5% of all malignancies in the sinonasal region, 6.7% of head and neck melanomas, and 1–2% of all malignant melanomas.[4,5]

In SNMM, tumors are usually diagnosed late in their course and are therefore difficult to ablate. This difficulty is likely to be compounded by the poor response of the mucosal melanoma to radiotherapy, with only a few successes reported.[6,7] Surgical excision remains the treatment of choice for localized disease with or without regional lymph node metastases. Chemotherapy is usually reserved for treatment failure or for treatment following development of distant metastases.

Still, in the absence of well-studied cases and randomized clinical trials, the appropriate treatment modalities remain controversial. More information on the incidence, progression, and treatment of SNMM is required. The few studies of SNMM have focused on patient populations in North America, primarily on Caucasian and African-American populations. A few studies have reported on Japanese patient populations, but the incidence, progression and treatment of SNMM in Asia is generally under-represented and not well understood. This is significant as the disease may display a racial discrepancy.

The present study is a retrospective review of the medical records of 23 patients who were diagnosed with primary SNMM and who were treated at Taipei Veterans General Hospital between 1982 and 2002, with the aim of furthering our understandings of the incidence, progression and treatment of the disease. To our knowledge, this is the first study to address SNMM in a Chinese patient population.

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E-mail: stapes@ms85.url.com.tw • Received: May 12, 2006 • Accepted: December 7, 2006

Methods

We performed a retrospective review of all cases of mucosal melanoma diagnosed at Taipei Veterans General Hospital between 1982 and 2002. Morphologic features of the melanomas, including histologic appearance and melanin pigmentation, were assessed in tissue sections following hematoxylin and eosin (H&E) staining. Immunohistochemical staining for melanoma markers (S-100 protein, HMB-45) were performed. Metastatic lesions arising from cutaneous melanoma, determined through direct physical examination and surveys of patients' medical histories, were excluded. None of the patients had been previously diagnosed with a malignant melanoma at any other site, or had a subsequent diagnosis of primary cutaneous malignant melanoma.

The following information was retrospectively collected from medical charts: age, sex, site of lesion, symptoms, duration of symptoms, treatment modalities, failure pattern, and survival time. Regional lymph node metastasis was identified by review of the pathology, whereas distant metastasis was recorded according to medical records and radiologic evidence.

Overall survival, disease-specific survival, and local control rates were calculated using the Kaplan-Meier method. Time was defined as the period from the first treatment to the target event. Target events were death (overall survival) and death due to SNMM (disease-specific survival). Patients who died of other diseases were censored for local control. If the tumor was never eradicated, the local control period was 0. Those patients who survived were followed until March 2005. Survival regarding factors such as gender, primary sites, surgical margins and clinical stages were analyzed by the log-rank test.

As there is no provision within the TNM system for staging SNMM, we employed the following arbitrary staging system: stage I was defined as primary lesion, stage II as regional lymph node metastasis and stage III as distant metastasis.

Results

Of the 294 cases of malignant melanoma diagnosed at our institution during the study period, 47 (16.0%) were from the mucous membrane. Of these, 23 were from the sinonasal mucosa, whereas 8 were from the oral cavity. Others were from the nasopharynx, eustachian tube, vagina, rectum, anus, and stomach.

Twenty-three patients were retrospectively recruited for the present study. Patient information is presented in Table 1. Sixteen patients were male and

Table 1. Patient characteristics

Patient no.	Age (yr)	Sex	Primary site	Symptoms
1	65	M	Ethmoid sinus	Headache
2	57	M	Nasal cavity	Not applicable
3	71	M	Nasal cavity	Epistaxis, nasal obstruction, postnasal dripping
4	75	M	Maxillary sinus	Epistaxis, nasal obstruction, exophthalmus
5	39	M	Nasal cavity	Nasal obstruction
6	70	M	Nasal cavity	Nasal obstruction, purulent rhinorrhea, epistaxis
7	82	M	Maxillary sinus	Epistaxis, headache
8	69	F	Maxillary sinus	Purulent rhinorrhea, epistaxis
9	71	M	Maxillary sinus	Nasal obstruction
10	62	M	Inferior turbinate	Epistaxis, nasal obstruction
11	78	F	Maxillary sinus	Foul odor, epistaxis, nasal obstruction
12	70	M	Inferior turbinate	Epistaxis
13	80	F	Maxillary sinus	Epistaxis, nasal obstruction
14	59	M	Maxillary sinus	Epistaxis
15	71	M	Nasal cavity	Epistaxis
16	60	F	Nasal cavity	Epistaxis, nasal obstruction
17	71	M	Nasal cavity	Epistaxis, nasal obstruction
18	63	M	Maxillary sinus	Nasal obstruction
19	52	F	Nasal cavity	Epistaxis, nasal obstruction
20	57	F	Nasal cavity	Epistaxis
21	78	M	Nasal cavity	Epistaxis, nasal obstruction
22	81	F	Middle turbinate	Epistaxis, nasal obstruction
23	87	M	Nasal cavity	Epistaxis, nasal obstruction

7 were female; their mean age was 68.2 years (range, 39–87 years).

The exact genesis site of SNMM was difficult to ascertain. Tumors originated in paranasal sinuses in 9 patients (the maxillary sinus in 8 and the ethmoid sinus in 1), and in the nasal cavity in 7 (specifically, the inferior turbinate in 2 patients and the middle turbinate in 1). The most common presenting symptoms were epistaxis, noted in 18 patients, and nasal obstruction, noted in 15. The initial visit to a physician ranged from 2 weeks to 1 year (mean, 3.1 months) following the appearance of symptoms.

At the time of their initial visit, tumors were limited to the local sinonasal region in 20 of the 23 patients. Three patients displayed both local and distant lesions. No patient had neck lymph node metastasis.

Treatment was varied. Surgery was the sole treatment in 5 patients. In addition to surgery, adjuvant radiation was performed in 12 patients, and adjuvant chemotherapy in 1 patient. Two patients received radiation only; 1 received chemotherapy only (dacarbazine [DTIC] + tamoxifen). All 3 strategies were employed for 2 patients.

Surgery included medial maxillectomy via the lateral rhinotomy approach, the Caldwell-Luc operation, and endoscopic excision. Postoperative radiotherapy (mean dose, 5,422 cGy; range, 2,100–6,000 cGy) was performed in 9 patients, excluding patient 10 who did not receive the full course of radiotherapy because of poor general condition. The radiation dose was 6,000 cGy for patient 7, who received radiotherapy alone as the primary treatment.

Subsequent to diagnosis and treatment, except in 4 patients who died from other diseases, 19 patients developed distant failures. Twelve had local and/or regional recurrence with distant failures, and 7 had isolated distant failures (Figure 1). The 5-year local control rate was 52.3%. Mean interval to development of local recurrence after initial treatment was 3.4 months (range, 0.5–12 months), whereas the median interval to distant metastasis — the time from the date of first treatment to the date the distant metastasis was found — was 12 months (Table 2). The lungs and liver were the most frequent sites of dissemination (13 and 11 patients, respectively), followed by bones (8 patients), adrenal gland (4 patients), brain (2 patients), kidney (1 patient), and pancreas (1 patient).

Follow-up was performed until March 2005. Survival ranged from 3–132 months. However, death due to advanced disease was pronounced and occurred rapidly within the first 24 months following initial treatment. The 5-year overall survival rate was 15.65%, and median overall survival time was 20 months; 5-year disease-specific survival rate was 22.26%, and median disease-specific survival time was 20 months (Figure 2). The 5-year disease-free survival rate was 14.54%, and median survival time was 20 months.

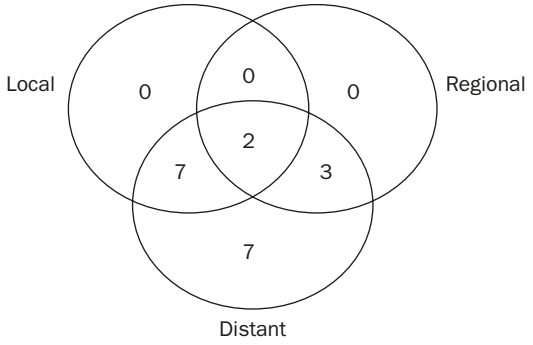

Figure 1. Patterns of treatment failure in patients with primary sinonasal mucosal melanoma, excluding 4 patients who died from other diseases. Nineteen patients developed distant failures, 12 had local and/or regional recurrence with distant failures, and 7 had isolated distant failures.

Mean 5-year overall survival time was 16 months for males and 24 months for females. Statistically significant differences in survival time were noted with respect to both primary site and clinical stage ($p<0.05$) (Table 3). For primary site, mean 5-year overall survival time and disease-specific survival time were both 24 months for nasal cavity and 7 months for paranasal sinus. For clinical stage, mean 5-year overall survival time and disease-specific survival time were both 20 months for stage I and 4 months for stage III.

Discussion

Primary SNMM occurs mainly in elderly people, and equal gender distribution has been reported.[8,9] In addition, the disease may display a racial discrepancy.[10] However, most of the reports of mucosal melanomas in the English literature are based on patient populations in the United States and describe the occurrence of mucosal melanomas in Caucasian and African-American patients,[3,4] and sometimes in Hispanic American patients as well.[2] A few reports describe the occurrence in Japanese populations,[11,12] but Asia as a whole is under-represented in the English literature with regard to mucosal melanomas.

There appears to be variable genetic predisposition for mucosal melanoma in different races. Mucosal melanomas constitute 1-quarter to 1-third of all melanomas in Japanese patients, but <2% of all melanomas in Western patients.[11,12] Melanomas in the sinonasal region constitute 7–11% of all Japanese melanomas (at all sites),

Table 2. Treatment modalities and outcome

Patient no.	Duration of initial symptoms before diagnosis (mo)	Initial stage	Initial treatment	Metastatic sites	Outcome	Follow-up (mo)
1		I	OP+RT	Brain	DOD	7
2		I	OP	Lung, liver, bone	DOD	19
3	4	I	OP+RT	Liver, lumbar spine, adrenal gland, kidney	ANED	132
4	0.5	I	CT	Lung, liver, bone	DOD	16
5	12	I	OP	Lung, liver, bone, adrenal gland, pancreas	DOD	20
6	3	I	OP+RT	Lung	DOD	24
7	3	I	RT	Brain	DOD	7
8	4	I	OP+RT	Retroperitoneum adrenal gland	DOD	20
9	2	I	OP+RT+CT		DOOC	10
10	1	I	OP+RT	Bone	DOD	6
11	8	I	OP+RT		DOOC	3
12	3	III	OP+RT	Lung, liver, adrenal gland	DOD	4
13	1	III	OP+RT	Lung, liver	DOD	3
14	4	I	OP+RT+CT	Liver	DOD	20
15	2	I	OP+RT	Lung, liver	DOD	45
16	1	I	OP		DOOC	65
17	3	I	OP+RT	Lung, liver, bone	DOD	84
18	4	III	OP+CT	Lung	DOD	5
19	3	I	OP	Lung, bone	DOD	36
20	2	I	OP+RT	Lung, liver, bone	DOD	24
21	3	I	RT	Lung, liver	DOD	12
22	1	I	OP+RT		DOOC	28
23	6	I	OP	Lung	DOD	25

OP = surgery; RT = radiotherapy; CT = chemotherapy; DOD = died of disease; ANED = alive with no evidence of disease; DOOC = dead of other cause.

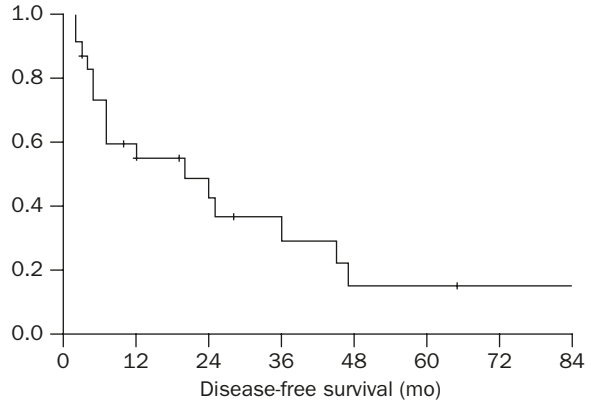

Figure 2. Five-year disease-free survival rate of 23 patients with primary sinonasal melanoma.

but <1% of all Western melanomas.[12,13] All of our patients were Chinese in race. Of the cases treated at our hospital between 1982 and 2002, 16% of lesions were from mucous membranes, while 9% of all melanoma cases were primary SNMM. Because of the lower incidence of melanoma in Asians, and because of the limited number of studies, it is still difficult to ascertain whether the incidence of mucosal melanoma actually differs from that found in other Asian races.

Symptoms and signs are generally regarded as being nonspecific. In the present study, epistaxis and nasal obstruction were the major symptoms at presentation. Most of the nasal lesions appeared as polypoid, fleshy, and friable masses with black pigmentation, and thus might have been regarded as nasal polyps.

Correct diagnosis of mucosal melanoma is not difficult when melanin-rich tumor cells can be identified on histologic examination (such as H&E stain). However, because amelanotic lesions may resemble many other tumor cell types, including those of lymphoma, sarcoma, poorly differentiated carcinoma, schwannoma and other metastatic lesions of cutaneous melanomas,[14–16] immunohistochemical staining plays an important role in diagnosis. S-100, HMB-45 and Melan-A are the most

Table 3. Overall survival and disease-free survival in patients with primary sinonasal mucosal melanoma

	Cases, *n*	Median OS (mo)	Median DSS (mo)	Median DFS (mo)	Median LCS (mo)
Gender					
Male	16	16	19	7	24
Female	7	24	24	36	
p		0.68	0.88	0.18	0.15
Primary site					
Nasal cavity	14	24	24	25	
Paranasal sinus	9	7	7	7	
p		0.001	0.003	0.099	0.721
Surgical margin					
Yes	8	20	20	5	20
No	11	36	36	36	
p		0.093	0.093	0.097	0.258
Clinical stage					
I	20	20	20	24	
III	3	4	4	4	4
p		<0.001	<0.001	0.001	0.256

OS = overall survival; DSS = disease-specific survival; DFS = disease-free survival; LCS = local control status.

frequently employed stains. S-100 has a higher sensitivity than the others, while HMB-45 can be more specific to melanoma cells. The highly specific Melan-A is used when equivocal results are obtained with the traditional immunohistochemical markers.[17]

Failure at the primary site is a frequent problem for patients with SNMM. High recurrence rates may be a result of multifocality or clinically unapparent, diffuse, submucosal lymphatic spread of melanoma cells. Therefore, even in the early clinical stage, localized lesions may need to be treated with radical excision without undue compromise of function.[18] Regional lymphatic metastasis is unusual in SNMM. A meta-analysis of 550 patients with mucosal melanoma of the head and neck documented such metastasis at initial presentation in only 18.7% of cases, with only 16.4% having regional metastasis following treatment.[8] In our study, no patient exhibited regional metastasis at initial presentation and such metastasis was noted in only 5 of 23 patients (21.7%) following treatment.

SNMM has a relatively high distant failure rate and, unlike most cancers where the risk of death decreases precipitously over time, can reappear at any time.[19] Indeed, patients with SNMM are constantly at risk of death due to the disease, and will ultimately die of it because of a combination of local recurrence and melanomatosis.[20] Consistent with this bleak outlook, the majority of patients reviewed in the present study developed distant recurrence and could not be salvaged because of advanced disease or involvement of vital organs. There was a sole exception. Patient number 3 had liver, kidney, lumbar spine and bilateral adrenal gland metastases after initial treatment. He received salvage therapy 4 times (including surgery and radiotherapy), and no residual lesion was noted during his last follow-up 132 months after the initial treatment. The reason for this patient's resilience remains elusive, but may be immune-related, with local surgical intervention acting to decrease the tumor burden and maintain the indolent state of the immune system. Similarly, Eneroth and Lundberg[21] describe 2 cases of long-term survival following repeated local and regional recurrences of a mucosal melanoma of the head and neck upon salvage treatment, which serve to highlight the value of repeated surgical procedures for recurrent diseases, and a meticulous and lifelong follow-up.

Nonetheless, the rarity of SNMM makes it difficult to determine the most appropriate treatment protocol. Surgical resection of tumor masses offers the best way for local control of mucosal melanoma, and is the only means to achieve a disease-free period in these patients.[21,22] However, the overall prognosis is generally grave.[23] In the present study, the mean 5-year overall survival rate was only 15.65%.

The value of radiotherapy in the treatment of SNMM is controversial. The use of postoperative radiotherapy has not been shown to improve survival, likely because of melanoma cells' capacity to repair sublethal damage, to the extent that it might be considered radioresistant to conventional fractionation schedules.[24,25] Therefore, high-dose-per-fraction treatment is preferred in the treatment of SNMM. Moreover, acute side effects

and long-term morbidity are less common in high-dose-per-fraction than conventional treatment schedules.[24]

Chemotherapy as an adjuvant therapy has been employed as well. However, results have been disappointing. Immunotherapy in the form of bacillus Calmette-Guérin vaccine, dendritic cell vaccine or cytokines has been used as adjuvant therapy to treat isolated cases of mucosal melanoma, but with limited success.[26,27] Gene therapy is another area of active research.[28,29] Since the majority of patients with SNMM eventually die from distant metastasis, improvements in overall survival will result from improvements in systemic therapy.

Primary SNMM is a rare disease with poor prognosis and high rates of distant metastasis. Although the majority of patients are initially seen with localized lesions, most of the 23 patients in the current study developed distant metastasis. Surgical resection offers the best method for local control and is the only means to achieve a disease-free period. Despite a variety of treatments, the outcomes in the current study remained dismal. Further studies of systemic therapy for mucosal melanoma are required to improve the overall survival rate for this disease.

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