Management of sinonasal mucosal melanomas and comparison of classification staging systems

Juan R. Gras-Cabrerizo, M.D.,[1] Xavier León-Vintró, M.D.,[1] Margarita Majem Tarruella, M.D.,[2]
Gabriel Pedemonte Sarria, M.D.,[1] Carolina Bothe Gonzalez, M.D.,[1] Joan R. Montserrat-Gili, M.D.,[1]
Katherina Kolanczak M.D.,[1] and Humbert Massegur-Solench, M.D.[1]

ABSTRACT

Objective: *The aim of this study was to describe treatment results in patients with sinonasal mucosal melanomas (SMMs) and to compare three different classification staging systems.*

Materials and Methods: *From 1988 to 2013, we performed a retrospective study of 20 patients with primary sinonasal melanomas. The median age at diagnosis was 71 years. There were 10 males and 10 females.*

Results: *Nine SMMs (45%) were originated in the ethmoidal sinus complex, four (20%) in the inferior turbinate, three (15%) in the nasal septum, two (10%) in the maxillary sinus, and two (10%) in the nasal vestibule. Local recurrence was diagnosed in eight patients (40%), and six out of 20 patients (30%) developed distant metastasis during the course of their disease. The adjusted survival rates at three and five years were 47% and 34%, respectively. The adjusted three-year survival rate according to the sinonasal staging system 7th edition for SMM (TNM-SMM) was 60% in T3 stage, 50% in T4a stage, and 34% in T4b stage (p = 0.05). According to Thompson's staging system, survival was 33% for group one, 58% for group two, and 0% for group three (p = 0.006). With the sinonasal staging system 7th edition for carcinoma (TNM-CAR) survival was 33% in T1, 100% in T2 and T3, 0% in T4a, and 34% in T4b (p = 0.006).*

Conclusions: *Our experience confirms the distribution of patients according to survival rates was better with the TNM-SMM than with Thompson's or the TNM-CAR systems.*

Melanomas from the mucosal surface are a rare entity, of which approximately 25% arise from the nasosinusal region. Sinonasal mucosal melanoma (SMM) represents less than 2% of all melanomas, between 5% and 9% of all head and neck melanomas and approximately 3.5% and 12% of all sinonasal malignancies. It has approximately an incidence of 0.05–0.1 per 100,000 cases a year.[1–6]

Around 80% of the SMM are found in the nasal cavity and 20% in the paranasal sinuses.[7,8] These tumors have been reported in all adult ages, equally common in men and women, with a higher incidence between 50 and 70 years.[5,9]

In contrast with the cutaneous melanoma, the etiology is unknown. However, some related factors have been described, such as preexisting melanosis (7%), heavy air pollution, and formaldehyde exposure.[3,6,9] Nevertheless, there does not exist a clear relationship with occupational exposure as with sinonasal carcinomas.

Endoscopically, it appears as a unilateral mass, and approximately in half of the cases, it is brown or black.[9] None of the classifications established for the cutaneous melanoma is valid for SMM, because the growth in depth is limited by bony or cartilaginous structures. Several classifications have been proposed in the last decades,[9–11] and in 2009, a specific classification for SMM in the head and neck region appeared for the first time in the international union against cancer (UICC)-TNM 7th edition.[12] The main treatment modality is surgery with postoperative radiotherapy. The overall survival rate is poor with a high rate of recurrence and metastatic disease.

The aim of our study was to analyze the main characteristics of these tumors, review the results of the treatment on patients treated in our hospital, and to compare Thompson's staging system with the UICC-TNM 7th edition, using both the sinonasal staging system for SMM (TNM-SMM) and the staging system for sinonasal carcinomas (TNM-CAR) (Table 1).

MATERIALS AND METHODS

Patients and Tumor Characteristics

The data used in this study were obtained retrospectively from a database that collects information concerning all patients with malignant neoplasm of the head and neck.

From 1988 to 2013, 206 patients with paranasal sinus malignant tumors were diagnosed and treated in our center. Out of those, 20 patients (9.7%) were diagnosed with SMM.

All SMMs were primary lesions. Median age at diagnosis was 71 years with a range between 42 and 87 years. There were 10 males (50%) and 10 females (50%). Eighty-five per cent of patients (17/20) were nonsmokers and nondrinkers.

Epistaxis was the most frequent symptom, occurring in 90% of the patients, whereas nasal obstruction, rhinorrhea, and facial pain were observed in 69%, 30%, and 23% of the patients, respectively. A history of occupational wood dust exposure was recorded only in one patient.

The extension of SMM was evaluated preoperatively in all cases by nasal endoscopy, computerized tomography, and magnetic resonance imaging to assess tumor extension. In the last cases (6/20), position emission tomography was also performed.

Ethics Statement

The Institutional Review Board of Santa Creu i Sant Pau Hospital approved all protocols used.

Statistical Analysis and Follow-Up

Survival analyses were calculated using the Kaplan Meier method, and curves were compared using the Mantel-Haenszel test (log rank). Endpoints were calculated from the date of diagnosis until recurrence. The minimum follow-up period was one year.

[1]Department of Otolaryngology/Head and Neck Surgery, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Spain, and [2]Department of Oncology , Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Spain
The authors have no conflicts of interest to declare pertaining to this article
Address correspondence to Juan R. Gras-Cabrerizo, M.D., Department of Otolaryngology/Head and Neck Surgery, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Spain
E-mail address: jgras@santpau.cat

Table 1. Classifications staging system for sinonasal mucosal melanomas

Thompson		TNM-CAR		TNM-SMM
		Maxillary	Nasal/Ethmoid	
I	Single site	Sinus mucosa	One subsite	
II	More than 1 site	Bone erosion except posterior wall and pterygoid plates	Two subsites	
III	Regional or distant metastasis	Posterior wall, subcutaneous, medial wall or floor orbit, pterygoid fossa, ethmoid	Medial wall or floor orbit, maxillary, palate, cribriform	Mucosal disease
IVa		Anterior orbital contents cribriform, pterygoid plates, infratemporal, skin, sphenoid, frontal	Anterior orbital contents, skin, pterygoid plates, sphenoid, frontal	Soft tissue, cartilage, bone, skin
IVb		Apex, dura, brain, nasopharynx, clivus, cranial nerves, middle cranial	Apex, dura, brain, nasopharynx, clivus, cranial nerves, middle cranial	Brain, dura, skull, cranial nerves masticator space, carotid

TNM-CAR = sinonasal staging system 7th edition for carcinoma; TNM-SMM = sinonasal staging system 7th edition for sinonasal mucosal melanomas.

Table 2. Sinonasal mucosal melanoma: Primary site of origin

	Number	Percentage
Nasal fossa		
Inferior turbinate		20%
Nasal septum	3	15%
Nasal vestibule	2	10%
Ethmoid sinus	9	45%
Maxillary sinus	2	10%
Total	11	55%

Table 3. Distribution of patients using the three staging systems

Staging system	Thompson	TNM-CAR	TNM-SMM
I	5	5	-
II	13	2	-
III	2	3	7
IVa	-	3	6
IVb	-	7	7
Total	20	20	20

TNM-CAR = sinonasal staging system 7th edition for carcinoma; TNM-SMM = sinonasal staging system 7th edition for sinonasal mucosal melanomas.

RESULTS

Localization and Classification Staging System

Ethmoidal sinus complex was the more frequent localization. Table 2 shows the SMM distribution according to the origin of the tumor.

According to the TNM-SMM system, the patients were classified as T3 in seven cases (35%), as T4a in six cases (30%), and seven patients (35%) as T4b.

According to Thompson's staging system, patients were classified as stage one in five cases (25%), as stage two in 13 cases (65%), and two patients (10%) as stage three.

Using the TNM-CAR the, patients were classified as T1 in five cases (25%), as T2 in two cases (10%), as T3 in three cases (15%), as T4a in three cases (15%), and seven patients (35%) as T4b (Table 3).

Two patients (10%) presented nodal metastasis at the time of diagnosis, and one of them also presented distant metastasis (5%).

Treatment

Fifteen patients (75%) received surgery followed by radiotherapy, three patients concomitant chemoradioteraphy (15%), and two patients surgery alone (10%).

In the surgery group, 13 patients were operated using the transfacial approach, and four patients by endonasal endoscopic surgery.

Recurrences and Survival

Local recurrence was diagnosed in eight patients (40%), and in the group of patients with local control, four developed distant metastasis (33%). Six out of 20 patients (30%) had distant metastasis during the course of their disease. The most frequent regions of distant metastasis were the lungs and the bone (50%).

The adjusted survival rates at three and five years were 47% and 34%, respectively.

The adjusted five-year survival rate in SMM from the nasal cavity was 38% compared with 33% in SMM from the paranasal sinuses ($p = 0.6$)

The adjusted survival at three years according to the TNM-SMM was 60% in T3 stage, 50% in T4a stage, and 34% in T4b stage ($p = 0.05$). According to Thompson's staging system, the survival rate was 33% for group one, 58% for group two, and 0% for group three ($p = 0.006$). With the TNM-CAR, survival was 33% in T1, 100% in both T2 and T3, 0% in T4a, and 34% in T4b ($p = 0.006$) (Fig. 1).

DISCUSSION

Mucosal melanoma is a different entity to skin melanoma and does not share either the risk factors, nor the staging system or the survival rates.

Several epidemiologic factors have been described. The fact that the nasal septum and the inferior turbinate are a frequent localization suggests that some inhaled carcinogen could be involved. Formaldehyde is an irritant of the upper respiratory system, and it has been considered as a risk factor for nasosinual carcinoma and for SMM [8,13].

Formaldehyde is used in a variety of jobs such as painters, furniture markers, laboratory technicians, or mortuary employees. In our series, we considered occupation, but in only one patient, a possible exposure to formaldehyde was collected.

Due to the few cases of SMM reported in head and neck and the different behavior with respect to the carcinomas, a staging system for SMM did not exist until the latest 7th TNM-UICC edition was published. Up to 2009, various SMM staging systems had been proposed with the aim of establishing systems that were simple and easy to manage.

Ballantyne[10] elaborated a more simple classification, grouping patients in three stages according to local, regional, or distant metastatic disease. In 2003, Thompson *et al.*[9] proposed a staging system with three stages grouping patients with a tumor limited to a single site in
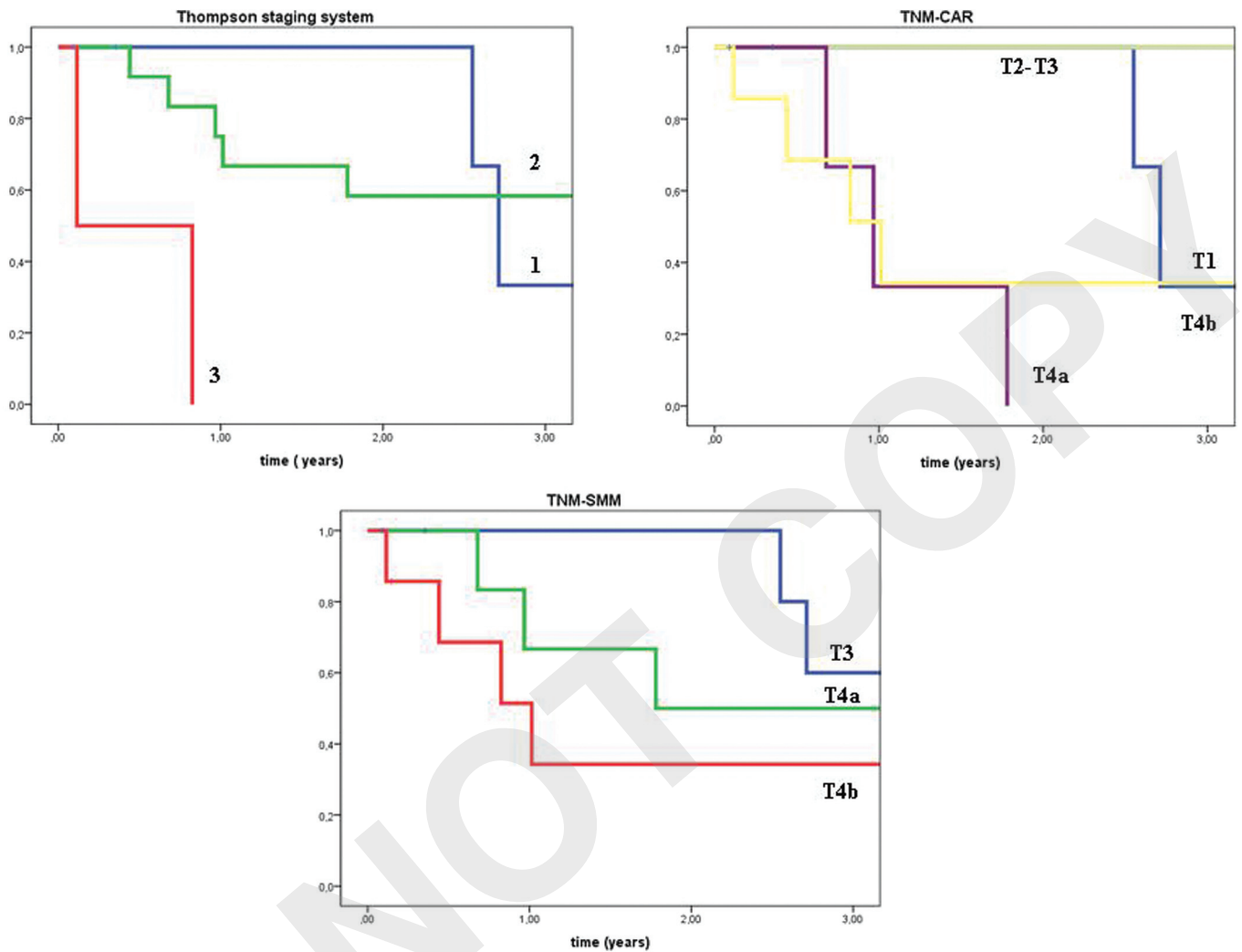
Figure 1. *Adjusted survival according to stages in the three classification systems.*

the first group, tumors involving more than one anatomic site in the second group, and patients with regional or distant metastasis in the last group. The new 7th TNM-SMM establishes T3 as the minimum category for all SMM, even if they are very small in size. Therefore, T1 or T2 categories do not exist. The reason for this is that even the SMM exclusively confined to the mucosa are considered very aggressive.

Some authors have compared the current 7th TNM edition with other alternative classifications. Gal *et al.*[5] concluded that the new staging system for SMM was more efficient and precise than the staging used for the paranasal sinuses carcinoma.

On the other hand, Michel *et al.*[14] believe that the TNM used for carcinomas in the nasosinusal region should be the primary staging system for patients with mucosal melanomas of the sinonasal tract. They demonstrated that TNM carcinoma is superior in terms of overall and disease-free survival. They showed differences between T1 and T2 respect to T3 and T4 (46% and 24% versus 28% and 0%) with the TNM carcinoma system. Regarding TNM-SMM, they did not find differences in survival between T3 and T4a. It is necessary to emphasize that they only included four patients in the T3 category and 30 patients in the T4a category, nevertheless, we present a proportional distribution of patients in the three stages. Moreno *et al.*[3] also found a better correlation with the TNM carcinoma, although they did not compare this classification with the TNM-SMM system but only with the Ballantyne's staging.

We compared the three major systems in our population based on adjusted survival rates and according to patient distribution. The first criterion suggests that the optimal staging classification system is the one in which the difference between the best and the worst stage is as wide as possible, and intermediate stages are distributed in a regular form inside the field of survivals between the extreme stages. The second criterion requires that the distribution among patients be balanced.

The TNM-SMM showed a progressive decrease in survival in accordance with stages (60%–50%–34%). However, Thompson and the TNM-CAR staging system did not present proportionally decreasing survival rates, and even the survival curves overlapped.

The distribution of patients in the TNM-SMM was proportional in the three stages (30%–35%), and a good balance was also found in the TNM-CAR. The main drawback for Thompson's system was that more than 60% of patients were included in a single stage two. In summary, in our population, the TNM-SMM system showed a good distribution of patients according to recurrence with an excellent distribution within each stage.

Surgery with complete excision is the main treatment. However, a satisfactory oncologic resection does not always condition a better impact on survival due to the high percentage of distant metastasis even if there is local control. Manolidis and Donald[15] and Loree *et al.*[16] showed that more than 50% of patients with local control after sur-

gery will develop distant metastasis. In our series, 33% of patients suffered from distant metastasis with good local control. The higher median age of these patients, the great aggressiveness of the SMM, and a better knowledge of endoscopic anatomy in the last decade lead us to believe that the endonasal endoscopic approach could be a good treatment for these malignancies. At present, in our center, we try to be less aggressive with the surgical resection, and we perform an endoscopic approach in all T3 tumors (mucosal disease) and as palliative treatment in patients diagnosed as T4b (very advanced disease). It is difficult to consider a standard treatment for patients with moderately advanced (T4a), and they are individually evaluated trying to improve the local control disease maintaining a good quality of life. Lund et al.[17] indicate that in selected cases, endoscopic resection does not adversely affect the outcome and may even improve survival.

The role of radiotherapy is controversial, although most reports have shown that postoperative radiotherapy improves the locoregional control but does not increase the overall survival rates.[3,5,18,19] On account of the aggressiveness of these tumors, we recommend postoperative radiotherapy in all patients, although the resection margins are free of disease.

Five-year overall survival and adjusted five-year survival ranges from 15% to 35% and from 20% to 37%, respectively, among the different series.[3,5,9,14,20] Thompson et al.[9] noted that when the patient died due to the disease, death occurred at a mean of 2.3 years after initial diagnosis. Most reports have demonstrated a better five-year survival rate in SMM from the nasal cavity compared with SMM from the paranasal sinuses,[16, 20] the nasal septum being the subsite with better prognosis.[3,17,21] Early diagnosis due to earlier symptomatology could probably explain these findings. Our survival outcomes were similar to the other reports for all SMM, although we did not observe differences between SMM from the nasal cavity and SMM originated in the paranasal sinuses.

We agree with other publications that at the time of diagnosis, lymph node metastases are present in less than 10%, and in general, neck dissection is not recommended.[19,22,23]

Distant metastases at diagnosis are also infrequent (5%–10%)[3,14] and SMMs preferentially spread to the liver and the lungs.[24] These results were similar to our findings.

Although the prognosis is poor, there are patients in our series and in the literature that surprisingly enough live free of disease for a long period of time.[6] In our series, the adjusted five-year survival was 34%, but there was one patient who lived for more than 10 years, and she developed a very late local recurrence.

CONCLUSIONS

Distribution of patients according to survival rates was better with the TNM-SMM than Thompson's and the TNM-CAR systems. Based on our outcomes, the 7th TNM-SMM could be a good staging system for SMM.

REFERENCES

1. Mallone S, De Vries E, Guzzo M, et al. Descriptive epidemiology of malignant mucosal and uveal melanomas and adnexal skin carcinomas in Europe. Eur J Cancer 48:1167–1175, 2012.
2. Harbo G, Grau C, Bundgaard T, et al. Cancer of the nasal cavity and paranasal sinuses. A clinico-pathological study of 277 patients. Acta Oncol 36:45–50, 1997.
3. 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 116:2215–2223, 2010.
4. Chang AE, Karnell LH, and Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer 83:1664–1678, 1998.
5. Gal TJ, Silver N, and Huang B. Demographics and treatment trends in sinonasal mucosal melanoma. Laryngoscope 121:2026–2033, 2011.
6. Jangard M, Hansson J, and Ragnarsson-Olding B. Primary sinonasal malignant melanoma: a nationwide study of the Swedish population, 1960–2000. Rhinology 51:22–30, 2013.
7. Chiu NT, and Weinstock MA. Melanoma of oronasal mucosa. Population-based analysis of occurrence and mortality. Arch Otolaryngol Head Neck Surg 122:985–988, 1996.
8. Lentsch EJ, and Myers JN. Melanoma of the head and neck: current concepts in diagnosis and management. Laryngoscope 111:1209–1222, 2001.
9. Thompson LD, Wieneke JA, and Miettinen M. Sinonasal tract and nasopharyngeal melanomas: a clinicopathologic study of 115 cases with a proposed staging system. Am J Surg Pathol 27:594–611, 2003.
10. Ballantyne AJ. Malignant melanoma of the skin of the head and neck. An analysis of 405 cases. Am J Surg 120:425–431, 1970.
11. Prasad ML, Patel SG, Huvos AG, et al. Primary mucosal melanoma of the head and neck: a proposal for microstaging localized, Stage I (lymph node-negative) tumors. Cancer 100:1657–1664, 2004.
12. Sobin LH, Gospodarowicz MK, and Wittekind CL (Eds). TNM Classification of Malignant Tumors. 7th ed. New York, NY: John Wiley & Sons, 2009.
13. Holmstrom M, and Lund VJ. Malignant melanomas of the nasal cavity after occupational exposure to formaldehyde. Br J Ind Med 48:9–11, 1991.
14. Michel J, Perret-Court A, Fakhry N, et al. Sinonasal mucosal melanomas: the prognostic value of tumor classifications. Head Neck 36:311–316, 2014.
15. Manolidis S, and Donald PJ. Malignant mucosal melanoma of the head and neck: review of the literature and report of 14 patients. Cancer 80:1373–1386, 1997.
16. Loree TR, Mullins AP, Spellman J, et al. Head and neck mucosal melanoma: a 32-year review. Ear Nose Throat J 78:372–375, 1999.
17. Lund VJ, Chisholm EJ, Howard DJ, and Wei WI. Sinonasal malignant melanoma: an analysis of 115 cases assessing outcomes of surgery, postoperative radiotherapy and endoscopic resection. Rhinology 50:203–210, 2012.
18. Wada H, Nemoto K, Ogawa Y, et al. A multi-institutional retrospective analysis of external radiotherapy for mucosal melanoma of the head and neck in Northern Japan. Int J Radiat Oncol Biol Phys 59:495–500, 2004.
19. Lund VJ, Stammberger H, Nicolai P, et al. European Rhinologic Society Advisory Board on Endoscopic Techniques in theManagement of Nose, Paranasal Sinus and Skull Base Tumours. European positionpaper on endoscopic management of tumours of the nose, paranasal sinuses and skull base. Rhinol Suppl (22):1–143, 2010.
20. Bradley P. Primary malignant mucosal melanoma of the head and neck. Curr Opin Otolaryngol Head Neck Surg 14:100–104, 2006.
21. Dauer EH, Lewis JE, Rohlinger AL, et al. Sinonasal melanoma: a clinicopathologic review of 61 cases. Otolaryngol Head Neck Surg 138:347–352, 2008.
22. Gal TJ, Silver N, and Huang B. Demographics and treatment trends in sinonasal mucosal melanoma. Laryngoscope 121:2026–2033, 2011.
23. Harvey RJ, and Dalgorf DM. Chapter 10: sinonasal malignancies. Am J Rhinol Allergy 27(suppl. 1):S35–S38, 2013.
24. O'Regan K, Breen M, Ramaiya N, et al. Metastatic mucosal melanoma: imaging patterns of metastasis and recurrence. Cancer Imaging 13:626–632, 2013. □