Sinonasal mucosal melanoma: A 12-year experience of 58 cases

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ABSTRACT: *Background.* Sinonasal mucosal melanoma is a rare malignancy with poor prognosis.

Methods. Patients with sinonasal malignant melanoma who underwent surgery by different approaches were included in this study. Overall survival (OS) and event-free survival were calculated, and statistically significant variables by univariate analysis were entered in a multivariate Cox regression model.

Results. Pathological staging was pT3, pT4a, and pT4b in 30 cases (51.7%), 17 cases (29.3%), and 11 cases (19.0%). At 3 and 5 years, OS was 43.5% and 29% and event-free survival was 23.6% and 12.4%, respectively. At univariate analysis, OS was significantly influenced by male sex, advanced pT classification, positive margins, and surgical approach; event-free survival was affected by positive margins. At multivariate analysis, the risk of death was independently associated with male sex (hazard ratio [HR] = 2.27; $p = .04$) and positive margins (HR = 2.32; $p = .03$).

Conclusion. Male sex and positive margins were negative prognostic factors. Endoscopic resection did not show an increased risk of death compared with more extensive surgical approaches. © 2015 Wiley Periodicals, Inc. *Head Neck* **38**: E1737–E1745, 2016

KEY WORDS: mucosal melanoma, endoscopic surgery, sinonasal tract, prognosis, survival

INTRODUCTION

Mucosal melanoma is a rare malignancy with an estimated incidence of 0.7 in 100,000 new cases per year.[1] Mucosal melanoma more frequently arises from melanocytes of the mucosa in the head and neck (about 50% to 55% of all lesions),[2,3] anorectal region, and vulvovaginal tract, whereas other localizations (conjunctival and meningeal) are extremely rare. In the head and neck, mucosal melanoma accounts for a small percentage (0.2% to 10%) of all melanomas.

Mucosal melanoma is one of the most aggressive tumors of the head and neck region with a very high risk of local and distant failure and a 5-year overall survival (OS) of <35%.[2,4,5] The rarity of the neoplasm, its heterogeneity in growth pattern (superficial spreading vs deep infiltration), and different sites of origin (sinonasal tract, oral cavity, and pharynx) have hampered identification of specific prognostic factors.

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Surgery is generally considered the primary treatment of choice,[6,7] but controversies exist with regard to the surgical approach; moreover, general consensus on the role of adjuvant treatments (radiotherapy [RT], chemotherapy, and biochemotherapy) is lacking.[8]

We assessed survival rates and predictive factors in a cohort of patients affected by sinonasal mucosal melanoma who were treated with curative intent over a 12-year period at 2 academic centers.

MATERIALS AND METHODS

This was a retrospective observational cohort study; data of patients who underwent surgery for sinonasal malignant melanoma at the Departments of Otorhinolaryngology at the University of Brescia and Varese from 2002 to 2013 were retrieved from clinical charts and included in a dedicated database. Patients with distant metastases at presentation were excluded from the study. Two experienced head and neck pathologists (M.L.M. and F.S.) reviewed all pathological specimens. Diagnosis of sinonasal malignant melanoma was confirmed by histological analysis and immunohistochemical profiles, including HMB-45, S-100, Melan-A, MIFT, and MART-1. In all patients, preoperative imaging assessment of the primary lesion included MRI (or CT, whenever an MRI was not feasible). The presence of nodal and distant metastases was assessed

by positron emission tomography-CT or a combination of neck ultrasonography and chest-abdomen CT. Patients underwent surgery with curative intent and were followed for a minimum of 12 months or until their death. All patients were staged according to the seventh edition of the American Joint Committee on Cancer/Union for International Cancer Control staging system for mucosal melanoma of the upper aerodigestive tract.[9]

Surgical approach

Surgery was performed according to 4 types of techniques: endoscopic resection without dural excision; endoscopic resection with transnasal craniectomy; combined cranioendoscopic resection; and transfacial external approaches. The surgical techniques for endoscopic resection, endoscopic resection with transnasal craniectomy, and cranioendoscopic resection have already been described in detail in previous reports.[10–13] The main surgical steps together with specific indications and contraindications are summarized below.

Endoscopic resection was planned whenever the lesion was superficially located and did not involve critical structures, such as maxillary bony walls (with the exclusion of the medial one), hard palate, or orbital content. When signs of anterior skull base invasion were detected at imaging examination, surgery included endoscopic resection with transnasal craniectomy. The resection was extended from the posterior wall of the frontal sinus to the planum sphenoidale anteroposteriorly, and from the septum to the lamina papyracea; the overlying dura with the olfactory bulb/tract was always included in the specimen. In lesions crossing the midline, resection was extended to the contralateral side. Duraplasty was performed with 3 layers of the iliotibial tract, according to a technique previously reported.[13]

The transnasal approach alone was considered to be inadequate, and was therefore combined with a classic subfrontal craniotomic approach (cranioendoscopic resection), in the presence of the frontal sinus wall involvement or extensive of the dural infiltration (especially over the orbital roof).

When the maxillary sinus was invaded beyond the medial wall, the nasal floor was eroded, and/or the orbital content was invaded, a purely external approach was planned, a term including different approaches (ethmoidomaxillectomy with or without orbital content clearance, classic anterior craniofacial resection by lateral rhinotomy, and coronal approach). In the latter group, the reconstructive strategy, when required, encompassed different options ranging from prosthetic obturators to pedicled or free-flaps. Internal carotid artery encasement, macroscopic brain infiltration, optic chiasm involvement, and distant metastases were considered contraindications for surgery.

Elective neck dissection was never performed in view of the low risk of regional lymphatic involvement at presentation. A comprehensive neck dissection was planned only in patients presenting positive neck nodes at diagnosis.

Adjuvant treatment

Adjuvant RT, with different techniques, was planned in the presence of positive surgical margins, intracranial extension, and/or nodal metastases. The gross target volume covered the primary site and the neck when nodal metastases were present. Chemotherapy was added in the presence of nodal metastases.

Statistical analysis

The main endpoints were OS and event-free survival. OS was defined as the time from surgery to the date of death of all causes, whereas event-free survival was defined as the time from surgical treatment until relapse (any site) or death of all causes. Both OS and event-free survival were determined from the date of diagnosis of sinonasal malignant melanoma to the end of follow-up, which was June 30, 2014. Vital status at the end of the follow-up and causes of death were ascertained for all subjects.

The associations among demographic, clinical, and pathological variables with pT classification and surgical approach (endoscopic resection, endoscopic resection with transnasal craniectomy, and cranioendoscopic resection with external approach) were tested by univariate analysis using the chi-square test.

Cumulative survival curves were modeled using the Kaplan–Meier method with Greenwood SE. The association of demographic, clinical, and pathological variables with patient survival was tested by univariate analysis using the log-rank test.

All variables associated with OS and event-free survival by univariate analyses were entered in a multivariate Cox-regression model. Results are shown as hazard ratios (HRs), 95% confidence intervals (CIs), and p values. A graphical check on each regressor did not detect major departures from the proportional hazard assumption of the models fitted.

All statistical tests were 2-tailed and p values were considered significant when $\leq .05$. All analyses were carried out using the STATA program, version 12 (STATA Corp, College Station, TX).

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice. The study protocol was approved by the respective local ethics committees. Informed consent was obtained from all enrolled patients.

RESULTS

Demographics

After excluding 2 patients who presented with distant metastasis, a total of 58 patients were considered eligible for the present study. Demographic, epidemiologic, and clinical findings are summarized in Table 1. The majority of patients were women (63.8%); the median age was 71 years (range, 19–87 years). Mean age at treatment was 72 years (range, 35–84 years) for men, and 70 years (range, 19–87 years) for women. Presenting complaints were nasal obstruction in 79.3% of cases, epistaxis in 70.7%, anosmia in 25.9%, headache in 12.1%, rhinorrhea in 8.6%, epiphora in 5.2%, and visual impairment, diplopia,

TABLE 1. Main demographic, epidemiologic, and clinical data of 58 patients with sinonasal malignant melanoma.

Variables	No. of patients (%)
Hospital	
Brescia	31 (53.4)
Varese	27 (46.6)
Sex	
Male	21 (36.2)
Female	37 (63.8)
pT classification	
pT3	30 (51.7)
pT4a	17 (29.3)
pT4b	11 (19.0)
N classification	
Positive	3 (5.1)
Negative	55 (94.9)
Previous treatment(s)	
Yes	12 (20.7)
No	46 (79.3)
Surgical technique	
Endoscopic resection	37 (63.8)
Endoscopic resection with transnasal craniectomy	10 (17.2)
Cranioendoscopic resection	4 (6.9)
External approach	7 (12.1)
Adjuvant treatment	
Yes	16 (27.6)
No	42 (72.4)
Surgical margins	
Positive	17 (29.3)
Negative	41 (70.7)
Dural involvement	
Yes	4 (6.9)
No	54 (93.1)
Recurrence	
Yes	39 (67.2)
No	19 (32.8)
Follow-up status	
NED	20 (34.5)
Alive with disease	5 (8.6)
Died of disease	32 (55.2)
Died of other cause	1 (1.7)
Total	58 (100.00)

Abbreviation: NED, no evidence of disease.

unilateral facial swelling, and nasal pain in 3.4% each. The lesion was serendipitously diagnosed in 5 patients (8.6%) who were asymptomatic.

The site of origin of the lesions was the nasoethmoidal complex in 51 patients (87.9%), the maxillary sinus in 6 patients (10.3%), and the frontal sinus in 1 patient (1.7%).

Twelve patients (20.7%) had already received some form of treatment: surgery in 6 (10.3%), exclusive chemotherapy in 1 (1.7%), and different combinations of surgery, RT, and/or chemotherapy in 5 (8.6%).

Surgery and complications

Thirty-seven patients (63.8%) underwent endoscopic resection, 10 (17.2%) underwent endoscopic resection with transnasal craniectomy, 4 (6.9%) underwent cranioendoscopic resection, and the remaining 7 (12.1%) underwent the external approach. In the latter group, 4 patients underwent radical maxillectomy with ethmoidectomy, which was extended in 1 patient to the orbital content, and 3 patients had their craniofacial resection extended to the orbital content. Only 3 patients (5.2%) with preoperative evidence of cervical node involvement underwent comprehensive neck dissection. Major postoperative complications (5.2%) included 2 cases of pulmonary embolism (1 endoscopic resection and 1 external approach), and a cerebrospinal fluid-leak in a patient who treated with craniofacial resection and orbital clearance that was managed by lumbar drainage. Minor complications (5.2%) included 2 cases of fever of unknown origin (2 endoscopic resection with transnasal craniectomy), and 1 lower limb venous thrombosis. Overall, complications were observed in 10.3% of the patients.

Pathology and staging

All sinonasal malignant melanoma were positive for HMB45, S100, Melan-A, MIFT, and/or MART. Surgical margins were involved in 17 patients (30.4%). Resection of dura was performed in 17 patients (10 had endoscopic resection with transnasal craniectomy, 4 had cranioendoscopic resection, and 3 had the external approach), but only 4 patients (23.5%; 2 endoscopic resections with transnasal craniectomy and 2 external approaches) showed positivity at definitive pathologic examination.

Pathological staging of the primary tumor was pT_3, pT_{4A}, and pT_{4B} in 30 (51.7%), 17 (29.3%), and 11 cases (19.0%), respectively. In the 3 patients (5.2%) who received neck dissection, the pathologic staging was $pT_3N_1M_0$ in 2 cases and $pT_3N_{2B}M_0$ in 1 case.

Adjuvant therapy

Postoperative treatment was delivered in 16 patients (27.6%). Fifteen received RT: in 2 patients (3.4%) with nodal metastasis, concomitant chemotherapy was added. In 1 patient (1.7%) who had already received RT before surgery, exclusive chemotherapy was administrated. Two patients, because of massive progression of the disease immediately after surgery, could not complete adjuvant treatment. The RT technique was intensity-modulated radiotherapy in 9 cases and conformal 3D in 6, with doses ranging between 50 and 68 Gy.

Follow-up, outcomes, and survival analysis

Median and mean follow-up was 30 and 20 months, respectively (range, 1–112 months). Thirty-two patients (55.2%) died of their disease, 1 (1.7%) died of other causes, 5 (8.6%) were alive with disease, and 20 (34.5%) were alive with no evidence of disease.

The recurrence rate was 67.2%. Thirteen patients (22.4%) developed a local recurrence, 10 (17.2%) developed distant metastases, and 16 (27.6%) had different combinations of local, regional, and/or metastatic relapse. Overall, local, regional, and distant metastases were found in 43.1%, 10.3%, and 39.6% of the patients, respectively.

The pT classification was associated with surgical margins ($p = .037$), with most free margins being in pT3 lesions (Table 2).

TABLE 2. Univariate analysis of pT classification and main clinical and demographic variables.

Variables	pT3 (%)	pT4a (%)	pT4b (%)	Total (%)	*p* value
Sex					NS
Male	9 (30.00)	7 (41.18)	5 (45.45)	21 (36.21)	
Female	21 (70.00)	10 (58.52)	6 (54.55)	37 (63.79)	
N classification					NS
Positive	3 (10.00)	0 (0.00)	0 (0.00)	3 (5.17)	
Negative	27 (90.00)	17 (100.00)	11 (100.00)	55 (94.83)	
Pretreatment					NS
No	25 (83.33)	12 (70.59)	9 (81.82)	46 (79.31)	
Yes	5 (16.67)	5 (29.41)	2 (18.18)	12 (20.69)	
Surgical technique					NS
Endoscopic resection	22 (73.33)	11 (64.71)	4 (36.36)	37 (63.79)	
Endoscopic resection with transnasal craniectomy	4 (13.33)	3 (17.65)	3 (27.27)	10 (17.24)	
Cranioendoscopic resection	1 (3.33)	1 (5.88)	2 (18.18)	4 (6.90)	
External approach	3 (10.00)	2 (11.76)	2 (18.18)	7 (12.07)	
Adjuvant treatment					NS
No	25 (83.33)	9 (56.25)	7 (63.64)	41 (71.93)	
Yes	5 (16.67)	7 (43.75)	4 (36.36)	16 (28.07)	
Surgical margins					**.032**
Uninvolved	25 (83.33)	10 (62.50)	4 (40.00)	39 (69.64)	
Involved	5 (16.67)	6 (37.50)	6 (60.00)	17 (30.36)	
Relapse					NS
No	8 (26.67)	7 (41.18)	4 (36.36)	19 (32.76)	
Yes	22 (73.33)	10 (58.82)	7 (63.64)	39 (67.64)	
Total	30 (51.72)	17 (29.31)	11 (19.97)	58 (100.00)	

Abbreviation: NS, not significant.
$\alpha = 0.05$.
The figures in bold indicate statistical significance.

No significant relationship was observed among the surgical approach and sex or previous treatment. Moreover, the technique adopted did not affect the risk of positive margins, need for adjuvant treatment, or risk of relapse (Table 3).

OS (±SE) at 1, 3, and 5 years was 75.3% (±5.9%), 43.5% (±7.5%), and 29.0% (±5.9%), respectively. Event-free survival at 1, 3, and 5 years was 58.2% (±6.7%), 23.6% (±6.4%), and 12.4% (±6.5%), respectively (Figures 1A and 1B). One, 3, and 5-year OS and event-free survival according to sex (Figure 2A and 2B), pT classification (Figure 2C and 2D), and surgical technique (Figure 2E and 2F) are summarized in Table 4.

TABLE 3. Univariate analysis of surgical approaches and main clinical and demographic variables.

	Endoscopic resection (%)	Endoscopic resection with transnasal craniectomy (%)	Cranioendoscopic resection with the external approach (%)	Total (%)	*p* value
Sex					NS
Male	11 (29.73)	6 (60.00)	4 (36.36)	21 (36.79)	
Female	26 (70.27)	4 (40.00)	7 (63.64)	37 (63.69)	
Pretreatment					NS
No	28 (75.68)	9 (90.00)	9 (81.82)	46 (79.31)	
Yes	9 (24.32)	1 (10.00)	2 (18.18)	12 (20.69)	
Adjuvant treatment					NS
No	29 (80.56)	6 (60.00)	6 (54.55)	41 (71.93)	
Yes	7 (19.44)	4 (40.00)	5 (45.45)	16 (28.07)	
Positive margins					NS
No	22 (71.0)	5 (62.5)	6 (54.5)	33 (66.0)	
Yes	9 (29.0)	3 (37.5)	5 (45.5)	17 (34.0)	
Relapse					NS
No	13 (35.14)	5 (50.00)	1 (9.09)	19 (32.76)	
Yes	24 (64.86)	5 (50.00)	10 (90.91)	39 (67.24)	
Total	37 (63.79)	10 (17.24)	11 (18.97)	58 (100.00)	

Abbreviation: NS, not significant.
$\alpha = 0.05$.

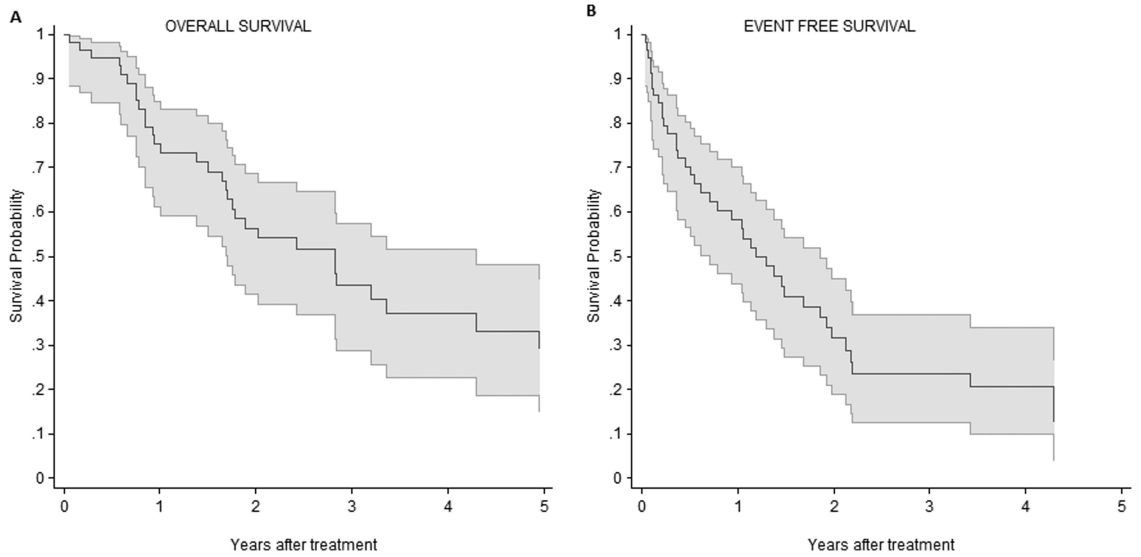

FIGURE 1. (A) Overall survival and (B) event-free survival curves obtained by the Kaplan–Meier method.

At univariate analysis, OS was significantly influenced by male sex ($p = .026$), advanced pT classification (pT4b vs pT3–4a; $p = .009$), positive margins ($p = .01$), and surgical approach (cranioendoscopic resection; external approach; and endoscopic resection with transnasal craniectomy vs endoscopic resection; $p = .007$), whereas event-free survival was significantly affected only by positive margins (Table 4). The other variables investigated, including adjuvant therapy, were not associated with either OS or event-free survival.

Multivariate analysis was performed on both OS and event-free survival, including the following: sex, pT classification, surgical technique, and surgical margins (Table 5). In both cases, age was also retained as a possible confounder.

Regarding OS, male sex and positive margins were associated with an HR for death of 2.24 and 2.32, respectively. Endoscopic resection with transnasal craniectomy and cranioendoscopic resection with the external approach were associated with an increased HR for death of 2.58 and 1.94, respectively, and of 2.10 when compared to endoscopic resection, which was of borderline statistical significance ($p = .07$) in multivariate analysis.

No variables were significant when considering event-free survival (Table 5), although surgical margin involvement was close to significance ($p = .08$).

DISCUSSION

The main findings of our study were: (1) male sex and positive margins are positively associated with risk of death; (2) endoscopic resection is associated with better OS than the other treatments at univariate analysis and possibly at multivariate analysis ($p = .07$); and (3) event-free survival does not show statistically significant difference between endoscopic resection and more aggressive techniques.

One of the strengths in the present article was that it included a series of patients with mucosal melanoma arising within a single anatomic site, the sinonasal tract; furthermore, patients were collected over a 12-year period in 2 centers where the same guidelines for clinical workup, treatment selection, surgical technique, and posttreatment surveillance were followed. The relatively short period of patient recruitment implies that there were no major changes in management policy.

The large majority of our patients (81.0%) were treated by a purely endoscopic endonasal approach (endoscopic resection or endoscopic resection with transnasal craniectomy). The surgical approach was not associated with previous treatments, pT classification, positive margins, need for adjuvant RT, or relapse. Moreover, there was no significant association among pT classification, surgical approach, risk of relapse, or need for adjuvant treatment (Table 4). On one hand, these findings suggest that the more favorable results of endoscopic procedures are not due to selection bias (ie, lower stage of lesions for less aggressive approaches), and, on the other hand, that endoscopic techniques are not associated with an increased risk of incomplete excision, as already demonstrated.[11] However, external or combined approaches remain the only reliable surgical option in sinonasal malignant melanoma massively infiltrating sinonasal bony boundaries and surrounding structures at presentation. It is worth mentioning that this recommendation is shared by many authors comparing purely endoscopic and combined external excision of sinonasal malignancies.[11]

Up to a few years ago, external surgical techniques with wide resections were considered appropriate to treat most of the sinonasal malignant melanomas. However, as emphasized in recent years, mutilating surgeries are not necessarily associated with a better outcome.[1,14–20] Our data reinforce these conclusions, as better oncologic results were obtained by a minimally invasive approach (3-year OS: 59.9% ± 9.1% vs 13.6% ± 11.7% for cranioendoscopic resection with the external approach). Indeed, as shown by multivariate analysis, patients undergoing endoscopic resection with transnasal craniectomy had a 2.6-fold greater risk of death than those undergoing

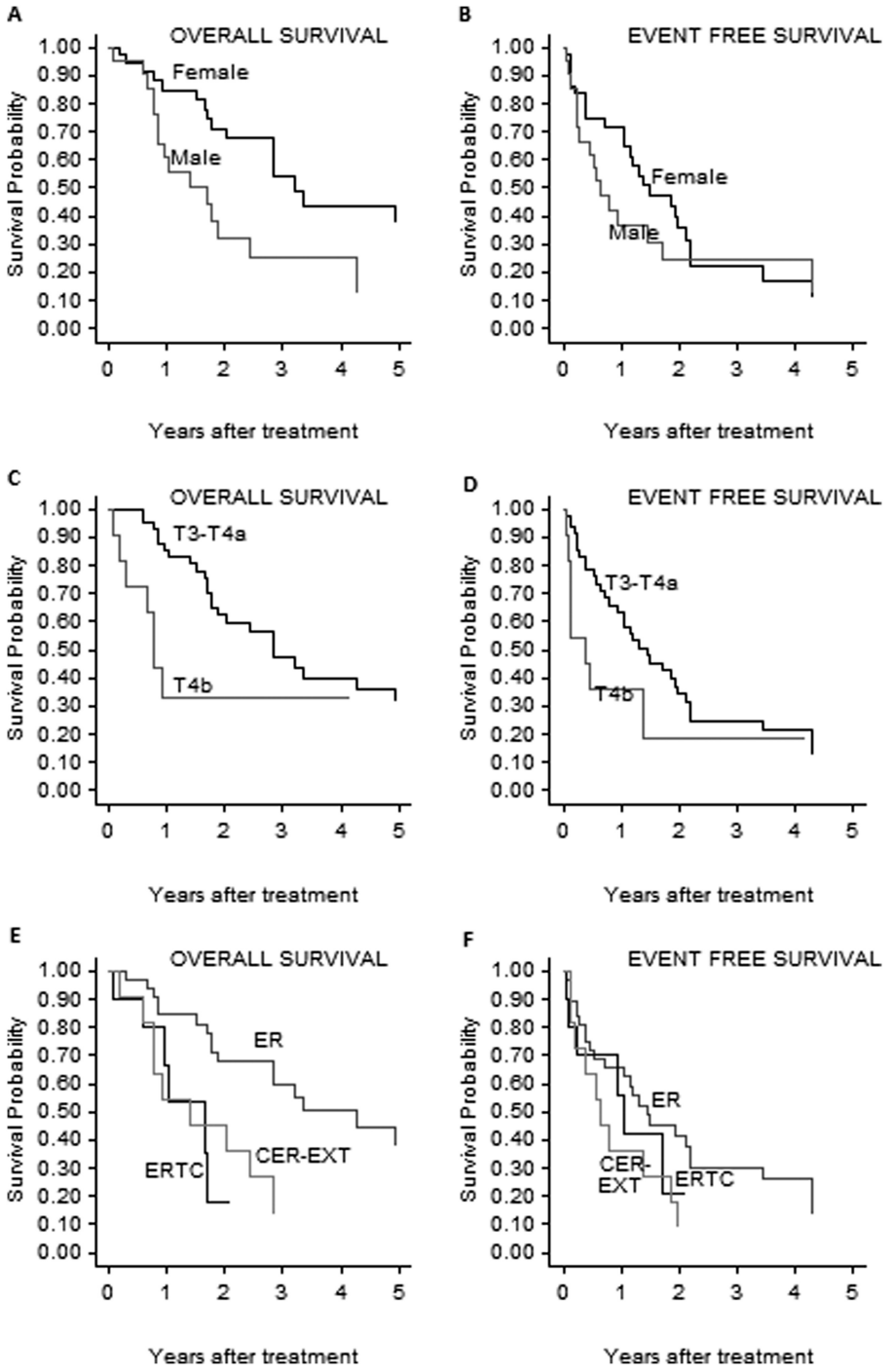

FIGURE 2. (A) Overall survival according to sex and (B) event-free survival according to sex obtained with the Kaplan–Meier method. (C) Overall survival according to pT classification and (D) event-free survival according to pT classification obtained with the Kaplan–Meier method. (E) Overall survival according to surgical technique and (F) event-free survival according to surgical technique obtained with the Kaplan–Meier method.

endoscopic resection. Moreover, cranioendoscopic resections and external approaches were associated with an increased risk of death (HR = 1.941), although the low number of patients treated by these techniques did not allow precise estimates of the effect. However, these data should be interpreted with caution. Because of the observational study design and lack of randomization, they may suggest that not only external surgical procedures, with their additional morbidity, but also a simple transnasal excision of the dura may be associated with poor outcomes. If this is the case, then the indications for endoscopic resection with transnasal craniectomy should be limited to cases with macroscopic infiltration of the dura. Some speculations may be offered to help explain outcomes in patients treated with a purely endoscopic resection: one of the most intriguing was advanced by Lund et al,[17] who hypothesized that aggressive surgery might cause severe disturbances in the immune balance and, consequently, may promote dramatic recurrence and/or explain cases with rapid systemic dissemination.

Although there is general consensus on the role of surgery as the primary treatment of choice, the role of RT

TABLE 4. Univariate analysis of overall survival and event-free survival, according to sex, pT status, surgical margins, and surgical technique.

Variables	OS ± SE				Event-free survival ± SE			
	1-y	3-y	5-y	*p* value	1-y	3-y	5-y	*p* value
Sex				.026				NS
Male	60.71% ± 10.87%	25.44% ± 10.54%	12.72% ± 10.43%		37.04% ± 10.74%	24.96% ± 10.10%	24.96% ± 10.10%	
Female	84.77% ± 6.31%	54.12% ± 9.75%	37.11% ± 10.58%		71.41% ± 7.72%	22.26% ± 8.28%	11.13% ± 6.94%	
pT classification				.009				NS
pT3–T4a	85.47% ± 5.49%	47.42% ± 8.31%	31.21% ± 8.63%		63.42% ± 7.37%	24.90% ± 7.21%	12.81% ± 3.76%	
pT4b	32.73% ± 14.97%	32.73% ± 14.97%	N.A.		36.36% ± 14.50%	18.18% ± 14.76%	N.A.	
Surgical margins				.010				.045
Free	86.06% ± 5.81%	49.22% ± 9.17%	39.48% ± 9.68%		61.97% ± 8.11%	31.51% ± 8.48%	20.26% ± 8.58%	
Involved	52.94% ± 12.11%	33.61% ± 11.80%	N.A.		47.06% ± 12.11%	6.72%% ± 6.46%	N.A.	
Surgical technique				.007				NS
Endoscopic resection	84.61% ± 6.34%	59.92% ± 9.13%	38.03% ± 10.68%		65.71% ± 8.10%	30.25% ± 8.56%	12.97% ± 7.71%	
Endoscopic resection with transnasal craniectomy	66.67% ± 16.10%	N.A.	N.A.		56.00% ± 17.06%	N.A.	N.A.	
Cranioendoscopic resection with the external approach	54.55% ± 15.01	13.64% ± 11.75%	13.64% ± 11.75%		36.36% ± 14.50%	9.09% ± 8.67%	9.09% ± 8.67%	

Abbreviations: OS, overall survival; NS, not significant; N.A., not accessible.
$\alpha = 0.05$.
See also Figures 1A, 1B, 2A, 2B, 3A, 3B, 4A, and 4B.
The figures in bold indicate statistical significance.

remains questionable.[21] Three main areas of debate exist: first, the role of adjuvant RT in improving survival is controversial; second, optimal fractionation and dose are still undetermined; and third, the role of particles, although promising, is far to being elucidated. Although, in most reports, adjuvant RT seems to improve local control of disease without affecting OS,[22–24] the indications themselves are not univocal[25]; only involved surgical margins are recognized as a factor dictating the need for adjuvant RT in head and neck mucosal melanoma[26] and sinonasal malignant melanoma.[5,27] In our experience, the main indications for adjuvant RT are the presence of involved margins, critical structure involvement (ie, dura), and nodal metastasis. Our data failed to demonstrate any impact of RT on OS and event-free survival, thus confirming the relatively high risk of failure of sinonasal malignant melanoma despite multimodal therapy. However, the intrinsic limitations of our study, including a nonrandomized treatment strategy and the lack of a specific design to assess the role of adjuvant treatment(s), should not be neglected. Moreover, it is worth mentioning that our indications for postoperative RT have been slightly modified over the years. In the early phase of our experience, we had a more conservative behavior; currently, because of a better understanding of tumor biology and a change of the staging system (entailing only T3–T4 lesions), a larger number of patients receive adjuvant RT.

Chemotherapy, immunotherapy, or biochemotherapy (defined as systemic administration of a chemotherapeutic agent and at least 1 biologic agent, such as interferon-α or interleukin-2) have been used prevalently for the treatment of unresectable or metastatic lesions.[21,28] It is worth mentioning, however, that in 2 recent articles,[21,29] the role of systemic therapy seems to gain relevance. Gore and Zanation,[21] in a meta-analysis on sinonasal malignant melanoma, found that an increase in survival may be obtained by combining surgical resection of the primary lesion with systemic therapy, whereas Sun et al[29] identified administration of biological agents as an independent positive prognostic factor. These articles reinforce the concept that only the introduction of agents able to prevent systemic spreading of the disease can significantly improve prognosis. At present, unfortunately, there is no consensus on the drugs or combination of drugs to be recommended as adjuvant treatment.

Our series of patients confirms that sinonasal malignant melanoma is an aggressive neoplasm, with a very high propensity to relapse, regardless of the radicality of resection and adjuvant treatment(s) administered. Recurrence occurred in 39 cases (67.2%), with overall local, regional, and metastatic recurrence rates of 43.1%, 10.3%, and 39.6%, respectively. The recurrence rate in studies on sinonasal malignant melanoma may be as high as 81.8%,[30] with a similar distribution among local, regional, and distant failures, which may present in combination in a nonnegligible number of patients. The high probability of recurrence intuitively translates into poor survival; our rates of 3-year (43.5%) and 5-year (29%) OS are in agreement with the results reported in the literature, with figures generally not superior to 50% at 3 years[29,31,32] and between 26.9% and 38.7% at 5 years.[8,23,29–33] OS was significantly affected in univariate analysis by male

TABLE 5. Age-corrected multivariate analysis on variables influencing overall and event-free survival.

	OS			Event-free survival		
	HR	*p* value	95% CI	HR	*p* value	95% CI
Sex	**2.270**	**.036**	1.056–4.879	1.400	.315	0.726–2.698
Surgical margins	**2.320**	**.031**	1.078–4.991	1.790	.079	0.935–3.426
Surgical technique						
Cranioendoscopic resection-external approach-endoscopic resection with transnasal craniectomy vs endoscopic resection)	2.095	.068	0.948–4.631	1.616	.150	0.840–3.107
Endoscopic resection with transnasal craniectomy vs endoscopic resection	2.588	.102	0.829–8.082	1.389	.527	0.501–3.846
Cranioendoscopic resection-external approach vs endoscopic resection	1.941	.265	0.811–4.643	1.526	.294	0.693–3.359
Age, y	1.021	.230	0.987–1.057	1.010	.471	0.983–1.038

Abbreviations: OS, overall survival; HR, hazard ratio of death; 95% CI, 95% confidence interval.
$\alpha = 0.05$.
The figures in bold indicate statistical significance.

sex, advanced pT classification (T4b vs T3–T4a), external surgical approaches, and positive surgical margins; at multivariate analysis, OS was independently influenced only by male sex (HR = 2.27) and involved surgical margins (HR = 2.32). These 2 factors have already been found to have a negative predictive impact on survival in series of mucosal melanoma of the head and neck.[5,26] Regarding sinonasal malignant melanoma, to the best of our knowledge, the negative prognostic role of positive margins has been identified only in a small series of patients analyzed exclusively by univariate analysis,[34] whereas the association between male sex and worse prognosis was already reported in a retrospective analysis of the Swedish Cancer Registry.[35] The presence of clear margins was significantly associated with pT3, but not with the surgical approach, thus reinforcing the concept that higher T classification lesions are associated with an inherently greater risk of incomplete resection, regardless of the surgical approach. Even the finding that endoscopic resections do not entail a significantly higher risk of positive margins compared with external approaches has been already reported.[18]

According to our results, there was no statistically significant association between T and N classification and the risk of death. This observation, somewhat surprising, confirms the relatively high risk of failure for sinonasal malignant melanoma even in apparently less aggressive lesions (superficial growth, no critical structure involvement, and no regional spreading). Advanced T classification of the lesion[5] and presence of nodal metastases[5,36] have been associated with poorer outcome, but these associations were not consistent and, more importantly, some differences have been depending upon the staging system adopted.[30,32,37]

CONCLUSIONS

Prognosis of sinonasal malignant melanoma remains dismal. Our data confirm that endoscopic resection, whenever technically feasible, has outcomes similar to and possibly better than those seen with more mutilating and aggressive surgical approaches. Achievement of negative surgical margins is a key element for the definitive outcome. Only multi-institutional, prospective studies can help to define the value of adjuvant treatments. Basic research should be directed to identify effective agents and inhibitors that could prevent progression of disease. In this perspective, our efforts should be directed to sequencing tumor nucleic acids, discovering effective targets for therapy, and obtaining cell lines to perform in vivo and in vitro experiments.

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