The Journal of Laryngology & Otology (2012), **126**, 147–151.

doi:10.1017/S0022215111002519

MAIN ARTICLE

Sinonasal mucosal melanoma: retrospective survival study of 25 patients

C VANDENHENDE[1], X LEROY[2], D CHEVALIER[1], G MORTUAIRE[1]

Departments of [1]Otorhinolaryngology and Head and Neck Surgery, and [2]Pathology, Huriez Hospital, University of Lille, France

Abstract

Objective: To determine potential prognostic factors for survival in patients with mucosal malignant melanoma of the sinonasal tract.

Methods: Patients managed between 1991 and 2008 were assessed retrospectively. The seventh edition Union for International Cancer Control (7th UICC) tumour-node-metastasis classification was used for tumour staging. Kaplan–Meier and log rank tests were used for survival analysis.

Results: Twenty-five patients were studied (six were tumour stage three, eight tumour stage four(a) and 11 tumour stage four(b)). Surgery was performed on 23 patients (92 per cent). Fifteen received post-operative radiotherapy. Mean follow up was 31.3 months (range, two to 99 months). Three-year disease-free survival was improved in patients with stage four tumour arising from the nasal fossa, versus other sites, and in those with stage four tumour treated with surgery plus adjuvant radiotherapy, versus other treatments.

Conclusion: Patients with melanoma of the nasal cavity have very poor survival rates. Treatment is still based on adequate surgical resection with safe margins. In this study, post-operative radiotherapy improved local control only for stage four tumours.

Key words: Nasal Cavity; Paranasal Sinuses; Malignant Melanoma; Prognosis

Introduction

Mucosal malignant melanoma of the sinonasal tract is very rare, representing less than 4 per cent of nasal fossa neoplasms.[1,2] This tumour's nonspecific clinical presentation often delays diagnosis.[3] The prognosis for patients with this tumour is dismal, with reported five-year overall survival rates ranging from 19 to 31 per cent.[4] The high incidence of sinonasal melanoma local recurrence can be attributed to submucosal lymphatic spread of the disease.[3] In the seventh edition of the seventh edition Union for International Cancer Control (7th UICC) tumour-node-metastasis (TNM) staging system, a specific classification was established for mucosal melanoma of the upper respiratory tract, comprising only stages T_3 and T_4; the tumour is designated as T_3 even when localised to the mucosa, to emphasise its aggressive behaviour.

Most studies of mucosal malignant melanoma are case reports. No consensus has yet been established on the optimal management of mucosal melanomas of the sinonasal tract. Factors affecting local control of the disease have not yet been clearly delineated.

In this paper, we report a retrospective series of 25 cases of sinonasal tract mucosal malignant melanoma managed in the same head and neck department. Our study aimed to describe the treatment of this disease, and to assess potential prognosis factors affecting local control and survival.

Materials and methods

We performed a retrospective analysis of patients with sinonasal mucosal malignant melanoma managed in the otorhinolaryngology and head and neck surgery department of the University Hospital of Lille between January 1991 and July 2008. Twenty-five consecutive patients with mucosal malignant melanoma of the sinonasal tract were identified. The following clinical data were recorded: gender, age at diagnosis, functional symptoms at presentation, and delay in aetiological diagnosis. The tumour localisation (i.e. nasal fossa, septum, lateral nasal wall or maxillary sinus) and extension (i.e. intra- or extra-nasal spread) were established from nasal endoscopy and imaging (i.e. tomodensitometry and/or magnetic resonance imaging (MRI)). The seventh edition of the 7th UICC TNM staging system for sinonasal cancers was used for tumour staging.

Accepted for publication 4 May 2011 First published online 29 September 2011

Histological diagnosis was established from biopsy specimens obtained via nasal endoscopy performed under local or general anaesthesia. Each specimen underwent specific immunostaining for vimentin, S100 protein and HMB 45.

Treatment of the tumour and any lymph nodes was recorded (i.e. surgery with or without radiotherapy, radiotherapy alone, or chemotherapy). The surgical approach was defined as endonasal or external. The surgical margins were analysed on the definitive specimen. No frozen section analyses were performed.

Patient follow up was based on repeated clinical examination (including nasoendoscopy) and imaging (i.e. sinonasal MRI) every six months. Distant metastases were investigated based on clinical signs (i.e. neurological or hepatic signs or osseous pain) and chest X-ray.

Data were recorded using Microsoft® Excel software, and statistical analysis performed using Medcalc® software. The Kaplan–Meier method was used for actuarial survival analysis. End-points included time to local relapse, regional recurrence, distant metastasis and death. Survival curves were compared using the log rank test. The accepted degree of significance was $p < 0.05$.

Results

Epidemiological data

From 1991 to 2008, 25 patients were referred to our institution for mucosal malignant melanoma of the sinonasal tract. The sex ratio was 0.9:1 (12 men and 13 women). The median age was 68 years (range, 29 to 90 years). We detected no recurrent environmental or occupational factors. At presentation, the main symptoms were unilateral nasal obstruction (77 per cent) and intermittent epistaxis (68 per cent). The mean delay to diagnosis was 3.5 months (range, one to 17 months). The nasal endoscopy was nonspecific in all patients. More than half of the mucosal melanomas were exophytic, polypoidal lesions; the remaining were sessile, pigmented lesions with or without ulceration.

Local extension

The tumour was located in the lateral nasal wall (i.e. nasal turbinates, intersinonasal septum or ethmoid sinus) in 11 cases (44 per cent), in the maxillary sinus in four cases (16 per cent), in the nasal septum in five cases (20 per cent) and in the floor of the nasal fossa in one case (4 per cent). It was located outside the nasal fossa and sinuses in four cases (16 per cent).

Patients' tumour staging was T_3 in six patients (24 per cent), T_{4a} in eight (32 per cent) and T_{4b} in 11 (44 per cent). One patient was N_1. No patients had distant metastasis.

Treatment

A surgical procedure with curative intent was performed in 23 patients (92 per cent). An external approach was used in 12 patients (52.2 per cent) and an endonasal endoscopic approach in 11 patients (47.8 per cent). Two of these 23 patients had neck dissection performed as part of the initial treatment (Figure 1).

Of the 23 patients who received surgery, 15 received post-operative radiation therapy (to the tumour site in 13 cases, and to both the tumour site and the neck in two cases due to positive lymph nodes on dissection). Adjuvant chemotherapy was never performed. One patient was treated with radiotherapy only, and one patient was managed symptomatically for advanced local tumour (Figure 1).

Follow up and survival analysis

The mean patient follow up was 31.3 months (range, two to 99 months). The three-year overall patient

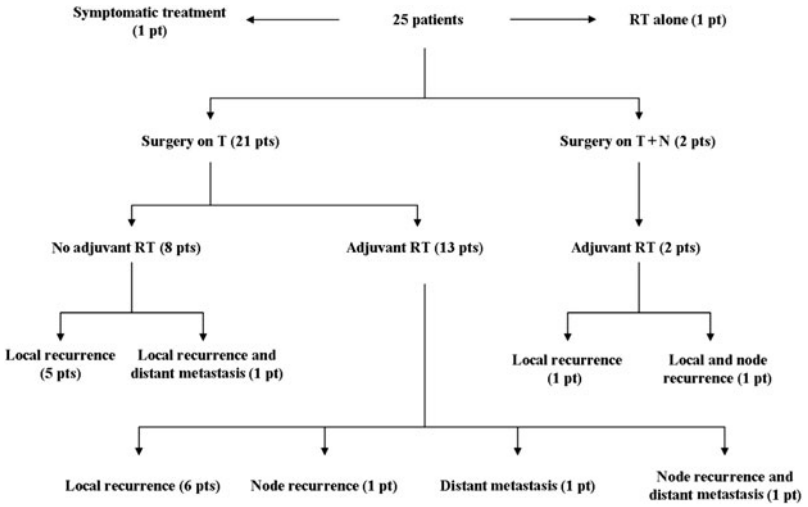

FIG. 1

Flow diagram showing treatment and follow up of the 25 patients. Surgery was the first line of treatment. Local recurrence occurred regardless of external radiotherapy (RT) of the tumour site. T = tumour; N = node

https://doi.org/10.1017/S0022215111002519 Published online by Cambridge University Press

survival was 100 per cent for T_3 patients and 52.1 per cent for T_4 patients; this difference was not statistically significant ($p = 0.14$). Disease-free survival was 75 and 27.5 per cent for T_3 and T_4 patients, respectively; this difference was not statistically significant ($p = 0.15$).

Recurrence was observed in 17 of the 23 patients who received curative treatment (73.9 per cent), with a median delay of 24.6 months (range, 1.5 to 97 months). Local recurrence occurred in 14 cases. Of these, one patient had concomitant lymph node metastases and one patient was found to have distant metastasis on follow up. There was one case of regional recurrence with hepatic metastasis but without local relapse. There was one case each of nodal recurrence and distant metastasis (Figure 1).

Of the six T_3 patients, five had melanoma of the nasal fossa (either lateral nasal wall, nasal floor or septum) treated via an endoscopic approach, while one had melanoma of the maxillary sinus treated with a sublabial transfacial procedure. The small size of the T_3 group did not allow survival analysis based on tumour location, treatment or surgical margins.

Of the 17 T_4 patients treated with curative intent, data were available on 16 for actuarial survival analysis. Three-year disease-free survival was significantly better for patients with tumours of the nasal fossa, versus tumours elsewhere ($p = 0.012$), and for patients treated with surgery and adjuvant radiotherapy, versus other treatments ($p = 0.05$), without impacting on three-year overall survival. The surgical approach and the quality of the surgical margins did not affect the three-year disease-free and overall survival rates (Table I).

TABLE I
3-YEAR SURVIVAL ANALYSIS FOR T_4 SINONASAL MELANOMA PATIENTS

Parameter	Pts (*n*)	OS (%)	*p**	DFS (%)	*p**
Location					
– Nasal fossa	11	61.4	0.49	40.9	0.012
– Sinus	5	33.3		0	
Treatment					
– Surgery alone	4	60	0.45	0	0.05
– Surgery + RT	12	53.5		38.1	
Surgical approach					
– Endoscopic	5	80	0.06	26.7	0.66
– External	11	42.4		27.3	
Surgical margins					
– Positive	4	25	0.15	25	0.63
– Negative	12	64.8		27.8	

Data for 17 patients were analysed. *Log rank test. T = tumour stage; pts = patients; OS = overall survival; DFS = disease-free survival; RT = external radiotherapy

Discussion

The aetiopathology of mucosal malignant melanoma of the sinonasal tract is not yet well understood. In contrast to cutaneous melanoma, no risk factors have been identified.[5,6] Our study identified no likely environmental or occupational factors. This tumour generally occurs after 50 years of age, and has no sex predominance.[1,2,7]

Macroscopic examination of mucosal melanoma is not very helpful for aetiological diagnosis. Furthermore, histopathological diagnosis is difficult, not only because of the low prevalence of the tumour but also because the tumour lesions can be amelanotic, with negative Fontana staining.[6] Thus, immunostaining with specific markers is widely used.[2,8] Usually, melanoma reacts positively to antivimentin antibodies, and strongly positively to antibodies to S100, a calcium-binding protein found in neural tissue. It also reacts strongly to HBM 45 and Melan-A, which are specific monoclonal antibodies prepared using malignant melanoma extract.[5,7,9]

Regardless of sinonasal mucosal melanoma treatment, studies have reported high rates of local recurrence (31–85 per cent) and distant metastasis (25–50 per cent), and poor three- and five-year survival rates (19–31 per cent).[1,2,10] The limited size of most reported series and the heterogeneity of available data make it difficult to assess the effectiveness of different treatment modalities, as regards tumour location and survival rate.[11] Our study, performed over 17 years, identified only 25 mucosal melanoma cases with available data.

Complete surgical resection is generally accepted to be the best treatment approach for sinonasal mucosal malignant melanoma, in order to achieve prolonged survival and cure.[1,2,9] Precise delineation of the tumour extent is required, using nasal endoscopy and imaging, in order to ensure appropriate surgical intervention.

Tumour stage classification is frequently cited as a factor associated with poor prognosis.[4] In a retrospective study of 46 sinonasal mucosal melanoma cases managed between 1979 and 1997, Temam *et al.* identified T classification as an independent factor associated with local control.[12] In our study, patient survival tended to be better for T_3 cases compared with T_4 cases, although this difference was not statistically significant.

Tumour location has also been cited as a factor affecting disease control. In our study, five of our six T_3 melanomas were localised; in our T_4 patients, local control was better in patients with tumours involving only the nasal fossa, compared with other sites. Tumours occurring in the sinuses may grow asymptomatically and be detected late in the disease course, while tumours arising in the nasal cavity are usually diagnosed at an early stage, with less local infiltration. The latter tumours are more easily accessible, theoretically resulting in better outcomes. Our findings agree with those of Dauer *et al.*, obtained from a review of 61 cases.[10]

When planning surgical treatment of sinonasal mucosal malignant melanoma, the exact tumour size and location must be established in order to ensure

https://doi.org/10.1017/S0022215111002519 Published online by Cambridge University Press

complete resection. The transfacial approach is widely used for oncological resection. Due to recent technical advances allowing improved surgical view, the endoscopic endonasal approach is also relevant in skilled hands and for appropriate indications. In our study, this method was used for T_3 melanoma of the nasal fossa, and for T_4 melanoma accessible for resection and for endoscopic drilling of bony borders. We found no difference in local control of T_4 lesions, comparing external versus endoscopic approaches. Endoscopic resection may be used in lesions without extension to the glabella area and the lateral wall of the maxillary sinus.

The quality of the surgical specimen resection margins is thought by many to be associated with local control. However, in our study we observed no impact of this parameter on survival. However, given the small number of patients with positive margins in our study (five), this result should be taken with caution. Moreover, the intricate, three-dimensional nature of the nasal cavity and adjoining structures makes margin interpretation difficult.[3,4]

The effect of neck lymph nodes is not clear, particularly in N_0 patients. The reported incidence of positive lymph nodes in sinonasal mucosal malignant melanoma patients is 10 to 30 per cent.[1] Some authors have recommended systematic selective neck dissection (e.g. supraomohyoid dissection), on the basis of evidence showing poorer overall survival and distant metastasis free survival in the presence of pathological neck lymph nodes.[2,12] Our study included only two cases involving neck dissection, so the impact of this on survival was not measurable. Other authors have reported that systematic neck dissection in N_0 patients is not significantly associated with survival.[13] The role of sentinel lymph node biopsy has not been evaluated.[13]

- **Sinonasal mucosal malignant melanoma is rare**
- **Diagnosis may be delayed by presentation with nonspecific nasal symptoms mimicking chronic rhinosinusitis**
- **Treatment consists of radical excision (endoscopic or external approach) guided by magnetic resonance imaging and tomodensitometry**
- **Adjuvant radiotherapy seems to improve local control, but does not affect overall survival**

External radiotherapy has been reported as an adjuvant treatment for sinonasal mucosal malignant melanoma, but its effect has not been systematically investigated. Mucosal malignant melanomas were previously thought to be radioresistant.[1] However, recent radiobiological studies have demonstrated wide variation in the radiosensitivity of melanoma cell lines.[2,14] Temam *et al.* found that radiotherapy appeared to increase the local control rate of mucosal melanoma of the head and neck, independent of primary tumour stage, albeit with no impact on overall survival.[12] However, distant metastasis occurred earlier and more frequently in patients with locally advanced tumours, and this could explain why the authors observed no effect of post-operative radiotherapy on overall survival.[11,12] The same result was described by Owens *et al.*, who studied 48 head and neck mucosal melanoma cases and observed improved locoregional tumour control after the addition of radiotherapy to surgical treatment.[5] In our study, the same result was observed for patients with T_4 lesions. In other studies, the impact of external radiotherapy on local control has not been established.[3,14–16] Because disease is usually localised at presentation, and local disease recurrence often precedes distant metastasis, many centres have introduced adjuvant radiotherapy into their mucosal melanoma treatment protocol, even in the absence of a demonstrated survival benefit.[7,10,12] Adjuvant radiotherapy has been used more frequently when the margins of resection are invaded, or when neck dissection lymph nodes are histologically positive.[2,17]

Conclusion

Mucosal malignant melanoma is a rare but aggressive type of sinonasal tumour. Treatment aims to achieve radical resection with safe margins; however, this is often difficult due to the anatomical constraints of the nasal cavity. Thus, overall survival and local control rates are still poor. No adjuvant therapy has yet been shown to improve prognosis, although radiotherapy appears to enhance local control. Patients with sinonasal mucosal malignant melanoma are at high risk of local recurrence, and require frequent and regular follow up.

References

1 Enée V, Houliat T, Truilhé Y, Darrouzet V, Stoll D. Malignant melanoma of the nasosinal mucosa [in French]. Retrospective study a propos of 20 cases. *Rev Laryngol Otol Rhinol (Bord)* 2000;**121**:243–50
2 Huang SF, Liao CT, Kan CR, Chen IH. Primary mucosal melanoma of the nasal cavity and paranasal sinuses: 12 years of experience. *J Otolaryngol* 2007;**36**:124–9
3 Ganly I, Patel SG, Singh B, Kraus DH, Bridger PG, Cantu G *et al.* Craniofacial resection for malignant melanoma of the skull base: report of an international collaborative study. *Arch Otolaryngol Head Neck Surg* 2006;**132**:73–8
4 Bhattacharyya N. Cancer of the nasal cavity: survival and factors influencing prognosis. *Arch Otolaryngol Head Neck Surg* 2002; **128**:1079–83
5 Owens JM, Roberts DB, Myers JN. The role of postoperative adjuvant radiation therapy in the treatment of mucosal melanomas of the head and neck region. *Arch Otolaryngol Head Neck Surg* 2003;**129**:864–8
6 Prasad ML, Busam KJ, Patel SG, Hoshaw-Woodard S, Shah JP, Huvos AG. Clinicopathologic differences in malignant melanoma arising in oral squamous and sinonasal respiratory mucosa of the upper aerodigestive tract. *Arch Pathol Lab Med* 2003;**127**:997–1002
7 Lee SP, Shimizu KT, Tran LM, Juillard G, Calcaterra TC. Mucosal melanoma of the head and neck: the impact of local control on survival. *Laryngoscope* 1994;**104**:121–6

https://doi.org/10.1017/S0022215111002519 Published online by Cambridge University Press

8 Pomar Blanco P, San Román Carbajo J, Bouso Montero M, Martín Villares C, Fernández Pello M, Tapia Risueño M. Sinonasal mucosal melanoma [in Spanish]. *An Otorrinolaringol Ibero Am* 2007;**34**:349–58
9 Trapp TK, Fu YS, Calcaterra TC. Melanoma of the nasal and paranasal sinus mucosa. *Arch Otolaryngol Head Neck Surg* 1987;**113**:1086–9
10 Dauer EH, Lewis JE, Rohlinger AL, Weaver AL, Olsen KD. Sinonasal melanoma: a clinicopathologic review of 61 cases. *Otolaryngol Head Neck Surg* 2008;**138**:347–52
11 Meleti M, Leemans CR, de Bree R, Vescovi P, Sesenna E, van der Waal I. Head and neck mucosal melanoma: experience with 42 patients, with emphasis on the role of postoperative radiotherapy. *Head Neck* 2008;**30**:1543–51
12 Temam S, Mamelle G, Marandas P, Wibault P, Avril MF, Janot F *et al*. Postoperative radiotherapy for primary mucosal melanoma of the head and neck. *Cancer* 2005;**103**:313–19
13 Stárek I, Koranda P, Benes P. Sentinel lymph node biopsy: a new perspective in head and neck mucosal melanoma? *Melanoma Res* 2006;**16**:423–7
14 Lund VJ, Howard DJ, Harding L, Wei WI. Management options and survival in malignant melanoma of the sinonasal mucosa. *Laryngoscope* 1999;**109**:208–11
15 Mendenhall WM, Amdur RJ, Hinerman RW, Werning JW, Villaret DB, Mendenhall NP. Head and neck mucosal melanoma. *Am J Clin Oncol* 2005;**28**:626–30
16 Wu AJ, Gomez J, Zhung JE, Chan K, Gomez DR, Wolden SL *et al*. Radiotherapy after surgical resection for head and neck mucosal melanoma. *Am J Clin Oncol* 2010;**33**:281–5
17 Wagner M, Morris CG, Werning JW, Mendenhall WM. Mucosal melanoma of the head and neck. *Am J Clin Oncol* 2008;**31**:43–8

Address for correspondence:
Dr Geoffrey Mortuaire,
Service d'ORL de Chirurgie Cervico-faciale,
Pr Chevalier,
CHRU Lille, 59000, France

Fax: +33 320446220
E-mail: g-mortuaire@chru-lille.fr

Dr G Mortuaire takes responsibility for the integrity of the content of the paper
Competing interests: None declared