ORIGINAL ARTICLE

Craniofacial Resection for Malignant Melanoma of the Skull Base

Report of an International Collaborative Study

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Objective: To report postoperative mortality, complications, and outcomes in a subset of patients with the histologic diagnosis of malignant melanoma extracted from an existing database of a large cohort of patients accumulated from multiple institutions.

Design: Retrospective outcome analysis.

Setting: Seventeen international tertiary referral centers performing craniofacial surgery for malignant skull base tumors.

Patients: A total of 53 patients were identified from a database of 1307 patients who had craniofacial resection for malignant tumors at 17 institutions. The median age was 63 years. Of the 53 patients, 25 (47%) had had prior single modality or combined treatment, which included surgery in 22 (42%), radiation in 11 (21%), and chemotherapy in 2 (4%). The margins of resection were close or microscopically positive in 7 (13%). Adjuvant radiotherapy was given in 22 (42%), chemotherapy in 3 (6%), and vaccine or interferon therapy in 2 (4%). Complications were classified into overall, local, central nervous system, systemic, and orbital. Overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) were determined using the Kaplan-Meier method. Predictors of outcome were identified by multivariate analysis.

Results: Postoperative mortality occurred in 3 patients (6%) and postoperative complications were reported in 14 patients (26%). Local wound complications occurred in 6 patients (11%), central nervous system in 7 (13%), systemic in 3 (6%), and orbital in 1 (2%). With a median follow-up of 10 months (range, 1-159 months), the 3-year OS, DSS, and RFS rates were 28.2%, 29.7%, and 25.5%, respectively. The extent of orbital involvement and adjuvant postoperative radiation therapy (PORT) were independent predictors of DSS and OS on multivariate analysis, whereas only PORT was an independent predictor of RFS. Patients treated with PORT had significantly better 3-year OS (39% vs 18%; relative risk, 2.9; $P = .007$), DSS (41% vs 19%; relative risk, 3.0; $P = .007$), and RFS (39% vs 15%; relative risk, 4.2; $P = .001$).

Conclusions: Craniofacial resection in patients with malignant melanoma of the skull base has mortality (6%) and complication rates (26%) comparable to other malignant tumors of the skull base. However, malignant melanoma is associated with a much poorer OS, DSS, and RFS. Adjuvant PORT correlated with improved 3-year OS, DSS, and RFS on multivariate analysis. These factors must be taken into account when considering craniofacial resection in a patient with malignant melanoma invading the skull base.

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MUCOSAL MALIGNANT melanoma (MM) is rare and accounts for only 1% of all melanomas.[1] Approximately 55% of mucosal melanoma arise in the head and neck, 60% of which are sinonasal in origin (SNMM).[2] The most common SNMM sites are the lateral wall and inferior turbinate of the nasal cavity, maxillary sinus, and the ethmoid sinus. Similar to other nasal and paranasal sinus tumors, these tumors often progress asymptomatically and therefore present with late-stage disease. Local extension of these tumors can result in invasion of the skull base. If the disease is localized without evidence of brain invasion, such as many other tumors of this region, the disease may be surgically encompassed by craniofacial resection (CFR). It is widely recognized that CFR for MM has a poor prognosis compared with other malignant skull base tumors.[3-5] However, to our

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Table 1. Patient and Tumor Characteristics

Characteristic	Patients, No. (%) (n = 53)
Age, y	
≤50	9 (17)
>50	41 (77)
Not reported	3 (6)
Sex	
Female	16 (30)
Male	37 (70)
Medical comorbidity	
None	47 (89)
Present	2 (4)
Not reported	4 (8)
Site of skull base invasion	
Anterior cranial fossa	53 (100)
Anterior and middle cranial fossa	0
Orbital involvement	
None	21 (40)
Periosteum/bone	18 (34)
Intraorbital contents	14 (26)
Intracranial involvement	
None	34 (64)
Bone invasion	10 (19)
Dural invasion	9 (17)
Brain invasion	0

Table 2. Details of Craniofacial Resection and Adjuvant Treatment

Feature	Patients, No. (%) (n = 53)
Type of approach	
Anterior fossa	49 (92)
Anterior and middle fossa	0
Not reported	4 (8)
Margins of resection	
Negative	40 (76)
Positive	5 (9)
Close	2 (4)
Not reported	6 (11)
Tracheostomy	
No	35 (66)
Yes	12 (23)
Not reported	6 (11)
Reconstruction	
No	7 (13)
Yes	41 (77)
Not reported	5 (9)
Type of reconstruction	
None	7 (13)
Locoregional flap	25 (47)
Free flap	6 (11)
Autologous vascularized	6 (11)
Nonvascularized bone	3 (6)
Titanium	1 (2)
Not reported	5 (9)
Adjuvant radiotherapy	
No	30 (57)
Yes	22 (42)
Not reported	1 (2)
Adjuvant chemotherapy	
No	49 (92)
Yes	3 (6)
Not reported	1 (2)
Other adjuvant therapy	
No	49 (92)
Vaccine	1 (2)
Interferon	1 (2)
Not reported	2 (4)

knowledge there are no reports in the literature that describe a cohort of patients of sufficient number to carry out statistical analysis to report complications, mortality, and outcome for this individual histologic tumor type. The primary objective of this collaborative study was to examine a relatively large cohort of patients from multiple institutions to determine overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) as well as mortality and postoperative complications. We also wanted to identify patient and tumor-related predictors of prognosis by multivariate analysis.

METHODS

A preexisting international collaborative database of 1307 patients who underwent CFR for malignant tumors of the skull base[6] was analyzed for patients who had a histologic diagnosis of MM. A total of 53 patients (4%) were eligible for analysis. Details on patient characteristics, tumor characteristics, prior treatment, and surgical approach for CFR including extent of invasion, reconstruction and resection margins, postoperative mortality and complications, and postoperative adjuvant therapy were extracted for analysis.

Patient and tumor characteristics are given in **Table 1**. Of the 53 patients, 16 (30%) were women and 37 (70%) were men. The age range was 3 to 81 years, with a median of 63 years. More than 75% of patients were older than 50 years. Medical comorbidity was reported in 2 patients (4%). The site of skull base invasion was the anterior cranial fossa in all cases. Invasion of the intraorbital contents occurred in 14 patients (26%) and invasion of dura in 9 patients (17%). Twenty-five patients (47%) had received treatment prior to CFR, which included previous surgery in 22 (42%), previous radiation in 11 (21%), and previous chemotherapy in 2 (4%).

Details of the CFR are given in **Table 2**. The skull base tumor was resected via an anterior fossa approach in all 49 patients in whom these data were reported. Surgical margins were close or microscopically positive in 7 patients (13%). The details of reconstruction of the surgical defect were available in 48 patients (91%). The most common reconstruction was galeal-pericranial or pericranial flaps (25 patients [47%]) followed by free flaps (6 patients [11%]). Adjuvant postoperative radiotherapy (PORT) was given in 22 patients (42%) with a median dose of 5600 cGy (range, 2400-7000 cGy). Adjuvant chemotherapy was given in 3 patients (6%) and adjuvant interferon/vaccine therapy in 2 (4%).

Complications were categorized into wound (infection, dehiscence, and flap necrosis), central nervous system (CNS) (cerebrospinal fluid leak, meningitis, and pneumocephalus), systemic (myocardial infarction, urinary tract infection, pulmonary, renal, and metabolic), and orbital (nasolacrimal duct obstruction, diplopia, and blindness).

To identify patient and tumor factors predictive of recurrence and survival, the following variables were analyzed by univariate analysis using the log-rank test: age, sex, medical comorbidity, orbital involvement, intracranial involvement, sur-

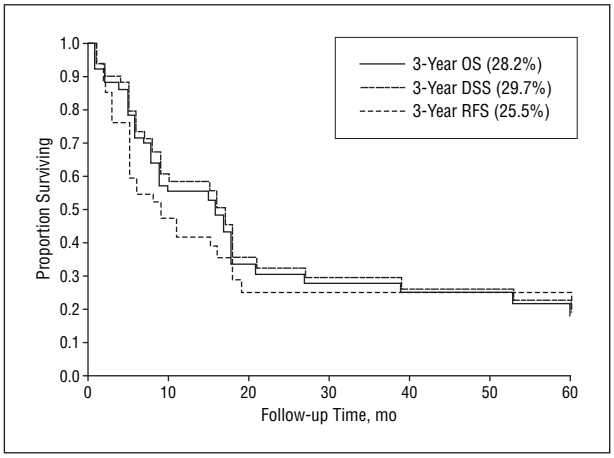

Figure. Three-year overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) for craniofacial resection for malignant melanoma invading the skull base.

gical margins, previous surgery, radiotherapy and chemotherapy, adjuvant radiotherapy, and chemotherapy. Staging information was recorded in 22 patients (48%) but was not assessed as a predictor owing to lack of a universally accepted staging system. Factors that were statistically significant on univariate analysis ($P<.05$) and showed a trend toward significance ($.05<P<.15$) were then assessed in multivariate analysis using a Cox proportional hazards model. Statistical analysis was carried out using SPSS for Windows version 11.01 (SPSS Inc, Chicago, Ill) and JMP (version 4.0; SAS Institute Inc, Cary, NC).

RESULTS

Postoperative mortality was reported in 3 patients (6%). Postoperative complications occurred in 14 patients (26%). Wound complications occurred in 6 patients (11%); CNS complications, 7 (13%); systemic complications, 3 (6%); and orbital complications, 1 (2%).

With a median follow up of 10 months (range, 1-159 months), the 3-year OS and DSS rates calculated using the Kaplan-Meier method were 28.2% and 29.7% (**Figure**). The RFS interval was not available for analysis in 5 patients (9%). The median time to recurrence was 6 months (range, 1-82 months). The 3-year RFS rate was 25.5% (Figure). Data on the patterns of recurrence were not available for analysis.

The extent of orbital involvement and use of adjuvant PORT were independent predictors of DSS and OS on multivariate analysis, whereas only PORT was an independent predictor of better RFS (**Tables 3**, **4**, and **5**). Patients treated with PORT had significantly better 3-year OS (39% vs 18%; relative risk, 2.9 [95% confidence interval, 1.3-6.3]; $P=.007$), DSS (41% vs 19%; relative risk, 3.0 [95% confidence interval, 1.3-6.7]; $P=.007$), and RFS (39% vs 15%; relative risk, 4.2 [95% confidence interval,1.8-9.8]; $P=.001$).

COMMENT

Craniofacial resection for MM was associated with an overall mortality of 6% and a complication rate of 26%. These figures are comparable to reports for CFR for other malignant skull base tumors.[3,7-11] However, in contrast to other malignant skull base tumors, the survival for MM is poor. The 5-year OS and DSS for all malignant skull base tumors treated with CFR reported previously by the International Collaborative Study was 48% and 53%, respectively.[6] Histologic subtypes such as esthesioneuroblastoma have 5-year survival rates of 80% to 90% at 5 years,[6,12] whereas squamous cell carcinoma has a 5-year survival rate of 44%. In our study, the 3-year OS and DSS rates for MM were only 28.2% and 29.7%, respectively. This is also poorer than the 5-year DSS of 47% reported by Patel et al[2] (2002) on 35 patients with SNMM, most of whom did not have skull base invasion. The impact of histologic tumor type on outcome of CFR is therefore clearly illustrated by our analysis, and this observation highlights the importance of considering the influence of tumor type in therapeutic decision making in the patient in whom CFR may be technically feasible.

Table 3. Prognostic Factors of Overall Survival (OS)

Covariate	No. of Patients	3-Year OS, %	Univariate Analysis* *P* Value	Multivariate Analysis, RR (95% CI); *P* Value
Age, y				
≤50	9	25.9	.76	–
>50	41	24.5		–
Sex				
Female	16	27.5	.52	–
Male	37	30.3		–
Medical comorbidity				
None	47	25.3	.72	–
Present	2			–
Orbital involvement				
None	21	43.0	.004	Reference
Periosteum/bone	18	0		5.6 (2.0-15.3); .001
Intraorbital contents	14	31.0		2.2 (0.8-5.8); NS
Intracranial involvement				
None	34	34.6	.44	–
Bone	10	0		–
Dura	9	25.4		–
Surgical margins				
Negative	40	30.1	.10	–
Positive/close	7	14.3		–
Previous surgery				
No	31	26.6	.95	–
Yes	22	31.8		–
Previous radiation therapy				
No	42	28.0	.51	–
Yes	11	33.7		–
Previous chemotherapy				
No	50	23.2	.15	–
Yes	2	100		–
Adjuvant radiation therapy				
No	30	17.8	.01	2.9 (1.3-6.3); .007
Yes	22	38.5		Reference
Adjuvant chemotherapy				
No	49	28.4	.15	–
Yes	3	0		–

Abbreviations: CI, confidence interval; NA, not applicable; NS, not significant on multivariate analysis; RR, relative risk; minus sign, not included in multivariate analysis.
*Log-rank test.

Table 4. Prognostic Factors of Disease-Specific Survival (DSS)

Covariate	No. of Patients	3-Year DSS, %	Univariate Analysis,* *P* Value	Multivariate Analysis, RR (95% CI); *P* Value
Age, y				
≤50	9	25.9	.64	–
>50	41	30.6		–
Sex				
Female	16	32.1	.25	–
Male	37	30.3		–
Medical comorbidity				
None	47	26.9	.77	–
Present	2	50.0		–
Orbital involvement				
None	21	43.0	.02	Reference
Periosteum/bone	18	0		4.8 (1.7-13.6); .004
Intraorbital contents	14	31.0		2.2 (0.8-6.0); NS
Intracranial involvement				
None	34	36.1	.40	–
Bone	10	0		–
Dura	9	28.6		–
Surgical margins				
Negative	40	32.2	.06	–
Positive/close	7	14.3		NS
Previous surgery				
No	31	27.5	.99	–
Yes	22	34.6		–
Previous radiation therapy				
No	42	29.8	.38	–
Yes	11	33.7		–
Previous chemotherapy				
No	50	24.5	.16	–
Yes	2	100		–
Adjuvant radiation therapy				
No	30	18.5	.008	3.0 (1.3-6.7); .007
Yes	22	40.7		Reference
Adjuvant chemotherapy				
No	49	30.1	.12	–
Yes	2	0		–

Abbreviations: See Table 1.
*Log-rank test.

Table 5. Prognostic Factors of Recurrence-Free Survival (RFS)

Covariate	No. of Patients	3-Year RFS, %	Univariate Analysis,* *P* Value	Multivariate Analysis, RR (95% CI); *P* Value
Age, y				
≤50	6	16.7	.25	–
>50	39	25.1		–
Sex				
Female	16	26.9	.34	–
Male	32	25.4		–
Medical comorbidity				
None	46	23.8	.64	–
Present	2	50.0		–
Orbital involvement				
None	18	33.8	.57	–
Periosteum/bone	16	0		–
Intraorbital contents	14	31.2		–
Intracranial involvement				
None	30	30.7	.47	–
Bone	9	0		–
Dura	9	30.0		–
Surgical margins				
Negative	39	29.5	.14	–
Positive/close	7	14.3		–
Previous surgery				
No	28	23.8	.83	–
Yes	20	28.6		–
Previous radiation therapy				
No	38	26.5	.51	–
Yes	10	26.7		–
Previous chemotherapy				
No	46	20.8	.06	–
Yes	2	100		NS
Adjuvant radiation therapy				
No	26	15.3	<.001	4.2 (1.8-9.8); .001
Yes	22	39.1		Reference
Adjuvant chemotherapy				
No	45	28.2	.39	–
Yes	3	0		–

Abbreviations: See Table 1.
*Log-rank test.

The 3-year RFS rate in this cohort was only 25.5%. This high rate of recurrence for MM has been documented before by Patel et al,[2] who reported local, regional, and distant failure rates of 50%, 20%, and 50%, respectively, for SNMM. The high incidence of local failure is thought to be due to occult diffuse submucosal lymphatic spread and is the primary reason for recommending radical surgery in these patients. In the paranasal sinus and skull base area, the surgical resection margins are limited owing to the constraints of the anatomical location. Nevertheless, in the present study, 87% of patients had negative margins of surgical resection. Despite this, more than 75% of patients developed recurrence. This supports the need for adjuvant therapy in addition to surgical treatment of melanoma invading the skull base. The influence of adjuvant PORT on outcomes is difficult to assess in a retrospective analysis, and we recognize the limitations of such an approach. An obvious drawback of our data is the lack of precise staging information, but there is no universally accepted staging system for MM at the present time. We were, however, able to use other anatomic descriptors of tumor extent such as orbital or intracranial involvement to account for the influence of tumor volume in our analysis. Using multivariate analysis, we have shown that the use of PORT was an independent predictor of OS, DSS, and RFS. In our study, patients who did not receive PORT had a 3-fold increased risk of poorer OS and DSS compared with those who received PORT. The risk of recurrence was 4-fold in patients who did not receive PORT. It may be argued that these observations are a result of selection bias: patients who were selected for PORT may have been better candidates in terms of both host and tumor attributes. **Table 6** presents a comparison of patient, tumor, and treatment characteristics for these 2 groups of patients in our study. Patients who were not treated with PORT

were more likely to have received preoperative radiotherapy (33% vs 15%; $P = .02$). This may be indirect evidence to suggest that patients who were treated with initial preoperative radiotherapy may have had larger, more aggressive tumors and hence had poorer outcome after CFR compared with their counterparts whose tumors were suitable for primary CFR without the need for preoperative radiotherapy. Unfortunately, our data lack details on patient selection, dose and delivery, and the intent of prior radiotherapy (ie, whether subsequent CFR was indicated for residual disease or was planned irrespective of response to prior therapy). Therefore, our findings of PORT must be interpreted with caution, particularly because previous reports on MM have shown no definitive evidence that PORT improves outcomes. Indeed, Patel et al[2] have previously reported that patients with MM of the head and neck treated with PORT had a poorer survival rate compared with those who did not require PORT. Gilligan and Slevin[13] reported that the use of radiotherapy for SNMM as the primary modality of therapy resulted in a survival rate of only 18%. These reports have been explained by the apparent high capacity that melanoma cells have to repair radiation-induced damage as reported by Bentzen et al.[14] However, despite these observations, it is important to point out that there is some evidence that PORT is efficacious in treatment of melanoma when given as a high-dose-per-fraction regimen.[15-17] Considering the relatively mild adverse effects of high-dose-per-fraction radiotherapy, especially when given as intensity-modulated radiotherapy, and the technical difficulty in achieving wide surgical margins in this anatomic location, it seems prudent to consider this option in most patients undergoing CFR for MM involving the skull base.

Our multivariate analysis also showed that the extent of orbital invasion was another important predictor of OS, DSS, and RFS. Previous studies for other malignant skull base tumors have shown that orbital involvement correlates with a poorer survival outcome.[3,10,18,19] However, in contrast to these reports, patients in our study who had invasion of the intraorbital contents actually had a better outcome compared with those with only periosteum/bone invasion. This may be explained by the fact that patients with intraorbital invasion would almost certainly have had orbital exenteration as part of the CFR, whereas orbital preservation may have been attempted in those with only periosteum/bone invasion. Owing to the high tendency for local recurrence in mucosal melanoma,[2] patients with periosteum/bone involvement treated without orbital exenteration may be expected to have a higher rate of recurrence and therefore poorer outcome. Unfortunately, these assumptions cannot be resolved owing to limitations of retrospective analysis; the patient numbers are small, and surgical operative decisions are often subjective and influenced by a multitude of factors. Nevertheless, our observation underscores the importance of a wide resection in these patients, especially when one recognizes the high tendency for local recurrence.

In conclusion, although the surgical operation of CFR has similar mortality and complication rates for MM compared with other malignant skull base tumors, it is very important that these patients be evaluated for treatment by a multidisciplinary team and be well informed of the significantly poorer prognosis of MM before surgical resection is performed. The use of adjuvant PORT should be seriously considered in most patients following CFR. The high incidence of recurrence despite adequate surgical resection suggests that major improvements in outcome for this disease will not occur until more effective adjuvant therapies for melanoma are developed.

Table 6. Comparison of Patient, Tumor, and Treatment Characteristics for PORT vs No PORT

Characteristic	No. (%) PORT	No. (%) No PORT	*P* Value
Age, y			
≤50	3 (14)	6 (22)	.49
>50	19 (86)	21 (78)	
Sex			
Female	7 (32)	9 (30)	>.99
Male	15 (68)	21 (70)	
Medical comorbidity			
None	21 (95)	26 (96)	>.99
Present	1 (5)	1 (4)	
Orbital involvement			
None	8 (36)	12 (40)	.79
Periosteum/bone	7 (32)	11 (37)	
Intraorbital contents	7 (32)	7 (23)	
Intracranial involvement			
None	14 (64)	19 (63)	>.99
Bone/dura invasion	8 (36)	11 (37)	
Margins of resection			
Negative	19 (90)	21 (81)	.44
Positive	2 (10)	5 (19)	
Previous surgery			
No	12 (55)	18 (60)	.78
Yes	10 (45)	12 (40)	
Previous radiotherapy			
No	21 (95)	20 (67)	.02
Yes	1 (15)	10 (33)	
Previous chemotherapy			
No	20 (91)	29 (100)	.18
Yes	2 (9)	0	
Adjuvant chemotherapy			
No	19 (86)	30 (100)	.07
Yes	3 (14)	0	

Abbreviation: PORT, postoperative radiation therapy.

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