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ORIGINAL RESEARCH

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Treatment outcomes of mucosal melanoma of the head and neck: Analysis of 190 cases from a single institution

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Abstract

Objectives: To analyze the treatment outcomes and prognostic factors of mucosal melanoma of the head and neck (MMHN) from a single institution.

Methods: From December 1989 to November 2018, 190 patients diagnosed with MMHN were included. Survival analysis was performed using the Kaplan–Meier method for univariate analysis with a log-rank test for significance and Cox regression for multivariate analysis.

Results: With a median follow-up time of 43.5 months, 126 (68.5%) patients died. The median DSS was 35 months. The 3- and 5-year disease-specific survival (DSS) rates were 48.1% and 33.7%, respectively. The median overall survival (OS) was 34 months. The 3- and 5-year OS rates were 47.0% and 32.9%, respectively. In univariate analysis, the T3 stage, received surgery, R0 resection, and combined therapy (surgery+biotherapy/biochemotherapy) were significantly associated with better survival. Multivariable Cox regression analysis revealed that the T4 stage (HR = 1.692; 95% CI, 1.175–2.438; $p = .005$) and the N1 stage (HR = 1.600; 95% CI, 1.023–2.504; $p = .039$) were strong prognostic factors for poor survival, and that combined therapy (surgery+biotherapy/biochemotherapy) was a strong prognostic factor for better survival outcome (HR = 0.563; 95% CI, 0.354–0.896; $p = .015$).

Conclusion: The prognosis of MMHN remains poor. Systemic treatment is warranted to reduce MMHN progression. Surgery combined with biotherapy may improve survival.

KEYWORDS
biotherapy, head and neck, mucosal melanoma, prognosis, survival, treatment

1 | INTRODUCTION

Mucosal melanoma (MM) is an aggressive rare malignancy arising from melanocytes in mucosal tissues lining the respiratory, gastrointestinal, and urogenital tracts. In Asia, it is the second most common subtype

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of MM, comprising 22%–25% of all melanomas.[1] Anatomically, the head and neck region is the most common area.[2]

MM is an aggressive malignancy with a very poor prognosis, with a 5-year overall survival rate of less than 30%.[3–6] High frequencies of relapse and distant metastases are responsible for the low survival probability.[2] Although MMs are distinctive from chronic ultraviolet exposure-associated cutaneous melanomas with regard to their aggressive biological behavior and unpredictable clinical course, they are currently treated in the same way.[7,8] Effective treatment modalities other than surgical resection remain unclear. Radiotherapy is shown to have a role in local control but does not improve overall survival. The treatment response of immune checkpoint inhibitors (ICIs) in MM is not as satisfactory as in cutaneous melanoma and the prognosis of patients with MM has not improved that much.[3] Moreover, understanding of this rare entity is still limited as data are scarce concerning treatment outcomes, and most of the published researches are small sample series of studies, often accompanied by low statistical testing power and conclusions that cannot be universally accepted, thus, optimal treatment regime remains undefined.

We have previously reported treatment outcomes for oral and paranasal MMs separately.[9,10] Here, we report an updated result with a large sample size from our institution.

2 | MATERIALS AND METHODS

2.1 | Data collection

One hundred and ninety patients with nonmetastatic MMHN who were treated at Sun Yat-sen University Cancer Center from December 1989 to November 2018 were included in this study. All specimens were reviewed by two pathologists including at least one expert pathologist in our center to confirm the diagnosis. TNM stage was modified based on American Joint Committee on Cancer (AJCC) staging system criteria (8th edition) for MMHN. When surgery was not available, the stage was assessed based on radiological examinations, including CT/MRI, and in a few cases, ultrasound examination as an alternative.

This study was approved by the Institutional Review Board of our institution (No. B2022-681-01), and the ethics committee review specifically waived the need for informed consent.

2.2 | Treatment details

Most patients appeared to be treated with a combination of two or more treatment modalities, of which there were four main types: surgery, radiation, chemotherapy, and biological therapy (biotherapy).

Surgical resection of the primary tumor was performed in 160 patients, and concurrent neck dissection was performed in 26 patients. Of the 160 patients, 96 underwent R0 resection.

Fifty-three patients received radiation therapy. Conventional shunt in 48 cases, low shunt in 5 cases. One patient received a reduced radiation dose (32 Gy) and the other received standard radiation doses (50–78 Gy). The median radiation dose was 60 Gy (range 32–78 Gy).

Seventy-seven patients received dacarbazine-based chemotherapy, including 59 patients who received surgery. The main regimes were: 23 cases of dacarbazine alone; 4 cases of dacarbazine combined with vindesine; 3 cases of dacarbazine combined with paclitaxel; 1 case of combined dacarbazine and carmustine; 8 cases of dacarbazine combined with cisplatin; 18 cases of combined with dacarbazine, cisplatin, and vindesine; combined application of dacarbazine, cisplatin, and paclitaxel in 7 cases; 11 cases of application of dacarbazine, cisplatin, and Me-CCNU; 2 cases of application of dacarbazine, cyclophosphamide, and vincristine; the median duration of chemotherapy was three treatment cycles, ranging from 1 to 5 treatment cycles.

Between 2000 and 2014, 45 patients received biotherapy as an important part of systemic therapy. Of these patients, 38 patients received biotherapy combined with surgery, and the remaining 7 inoperable patients received biotherapy as part of palliative care. In the combined treatment regime, biotherapy was given within 3 months after surgery. Treatment consisted of seven times subcutaneous injections of IFN-α-2b (3 million units) in 31 cases, 10 times subcutaneous injections of IL-2 (3 million units) in 12 cases, and cytokine-induced killer (CIK) therapy in 7 cases.

Eight patients refused treatment due to advanced inoperability.

2.3 | Follow-up and statistical analysis

Follow-up was performed through outpatient interviews, face-to-face communication, or telephone. The last follow-up time was January 2020. Surveillance was conducted through CT/MRI and ultrasound every 3 months for the first 2 years, every 6 months for years 3–5, then once every year. Positron emission tomography and bone scintigraphy were performed when tumor recurrence or metastasis was suspected. Disease-specific survival (DSS) was calculated from the date of diagnosis to the date of death from tumor progression. Patients last known to be alive were censored at the time of last contact. Patients who died from another cause were censored at the time of death. Overall survival (OS) was calculated from the date of diagnosis to the date of death due to any causes.

Statistical significance was conducted using the student's *t*-test, Fisher's exact test, Mann–Whitney *U* test, and chi-squared test. Survival analysis was performed using the Kaplan–Meier method for univariate analysis with a log-rank test for significance and Cox regression for multivariate analysis. All tests were two-sided. A p value <.05 was considered statistically significant. All data were analyzed using SPSS 26 software (SPSS, Chicago, IL).

3 | RESULTS

3.1 | Patients and tumor characteristics

In total, 190 patients were included in this study. All were ethnic Han Chinese. The patient and tumor characteristics were shown in Table 1.

TABLE 1 Patients and tumor characteristics.

Variable	All patients *N* (%)	SMM *N* (%)	NMM *N* (%)	OMM *N* (%)	*p* Value
Sex					0.918
Male	109 (57.7)	16 (55.2)	75 (58.1)	34 (56.7)	
Female	80 (42.3)	13 (44.8)	54 (41.9)	26 (43.3)	
Age (year)	58 (7–82)	60 (7–76)	59 (26–82)	55.5 (27–78)	0.079
Cigarette smoking	46 (24.3)	7 (24.1)	33 (25.6)	13 (21.7)	0.824
Tumor site					
Nasal cavity	100 (52.6)				
Paranasal sinus	29 (15.3)				
Oral cavity	60 (31.6)				
Other sites	1 (0.5)				
T stage					0.002
T3	87 (46.0)	5 (17.2)	49 (49.0)	33 (55.0)	
T4	102 (54.0)	24 (82.8)	51 (51.0)	27 (45.0)	
T4a	77 (40.5)				
N stage					<0.001
N0	152 (80.4)	28 (96.6)	93 (93.0)	31 (51.7)	
N1	37 (19.6)	1 (3.4)	87 (7.0)	29 (48.3)	
Surgery					0.268
Yes	159 (84.1)	24 (82.8)	88 (88.0)	47 (78.3)	
No	30 (15.9)	5 (17.2)	12 (12.0)	13 (21.7)	
Resection status					0.002
R0	95 (60.1)	8 (33.3)	49 (56.3)	38 (80.9)	
R1/R2	58 (36.7)	15 (62.5)	35 (40.2)	8 (17.0)	
Unknown	5 (3.2)	1 (4.2)	3 (3.4)	1 (2.1)	
Radiotherapy					0.198
Yes	53 (28.0)	8 (27.6)	33 (33.0)	12 (20.0)	
No	136 (72.0)	21 (72.4)	67 (67.0)	48 (80.0)	
Chemotherapy					0.480
Yes	77 (40.7)	10 (34.5)	39 (39.0)	28 (46.7)	
No	112 (59.3)	19 (65.5)	61 (61.0)	32 (53.3)	
Biotherapy					0.206
Yes	44 (23.0)	4 (13.8)	22 (22.0)	18 (30.0)	
No	145 (77.0)	25 (86.2)	78 (78.0)	42 (70.0)	
Treatment regime					0.153
Surgery+bio/biochemo	38 (20.0)	3 (10.3)	18 (18.0)	16 (26.7)	
Other therapy	152 (80.0)	26 (89.7)	82 (82.0)	44 (73.3)	

Abbreviations: bio, biotherapy; biochemo, biochemotherapy; NMM, mucosal melanoma of the nasal cavity; OMM, oral mucosal melanoma; SMM, mucosal melanoma of the paranasal sinus.

There was a slight male predominance in terms of gender composition, with a male-to-female ratio of 1.4:1. The median age at diagnosis was 58 years (range: 7–82 years). HNMMs mainly consisted of MMs from four sites: MMs in the nasal cavity (NMMs, $n = 100$, 52.6%), MMs in the paranasal sinus (SMMs, $n = 29$, 15.3%), MMs in the oral cavity (OMMs, $n = 60$, 31.6%), and MMs in the oropharynx ($n = 1$, 0.5%). The median age of patients with OMMs was younger than the age of patients with NMMs ($p = .032$). Patients with MMs of the paranasal sinus (SMMs) were associated with a more advanced T stage, while OMMs were associated with a more advanced N stage. Concerning differences in surgical margins, OMMs were associated with a higher R0 resection rate (51.4%).

3.2 | Survival outcomes and prognostic analysis

Six patients who were lost after the first visit were excluded from the survival analysis. The median follow-up time was 43.5 months (range:

TABLE 2 Univariate analysis of factors predictive of disease-specific survival.

Variable	3-year DSS (%)	5-year DSS (%)	Median DSS (month)	*p* Value
Sex				0.298
Male	43.3	32.0	32	
Female	55.0	36.1	44	
Age				
Cigarette smoking				0.954
Yes	47.5	29.2	35	
No	48.5	35.6	34	
Primary tumor site				0.851
Nasal cavity	48.4	33.1	35	
Paranasal sinus	45.0	35.4	29	
Oral cavity	49.2	34.0	35	
T stage				0.003
T3	59.2	41.8	48	
T4	37.7	26.1	29	
N stage				0.067
N0	52.9	37.2	38	
N1	27.0	18.0	27	
Surgery				0.010
No	30.0	15.0	28	
Yes	51.1	36.5	37	
Radiotherapy				0.362
No	50.6	34.6	37	
Yes	42.0	32.6	30	
Resection status				<0.001
R0	61.7	44.5	50	
R1/R2	37.4	26.2	28	
Chemotherapy				0.475
No	48.2	34.4	35	
Yes	47.9	32.3	34	
Biotherapy				0.055
No	42.1	30.9	31	
Yes	66.1	43.2	50	
Treatment regime				0.017
Surgery+bio/biochemo	71.5	47.7	50	
Other therapy	41.8	30.2	30	

Abbreviation: bio, biotherapy; biochemo, biochemotherapy; DSS, disease-specific survival; NP, nasal cavity and paranasal sinus.

3–290 months). By the time of the last follow-up, 126 (68.5%) patients died, including one who died of severe postoperative bleeding and five died without evidence of tumor progression. Of the remaining 120 patients who died of tumor progression, 41 (21.6%) died of distant progression and 79 (41.6%) died of local/locoregional progression. The median DSS was 35 months. The 3- and 5-year DSS rates were 48.1%, and 33.7%, respectively. The median OS was 34 months. The 3- and 5-year OS rates were 47.0%, and 32.9%, respectively.

The results of the univariate analyses of prognostic factors for DSS are shown in Table 2, and the Kaplan-Meier survival curves for DSS are presented in Figure 1. T3 stage, received surgery, R0 resection, and combined therapy (surgery+biotherapy/biochemotherapy) were significantly associated with better survival.

Based on the univariate analysis results that surgery and biological therapy tended to improve survival ($p < .1$), we grouped patients who received combination therapy including these two treatments as one group in multivariate analysis, and multivariable Cox regression analysis revealed that the T4 stage (HR = 1.692; 95% CI, 1.175–2.438; $p = .005$) and the N1 stage

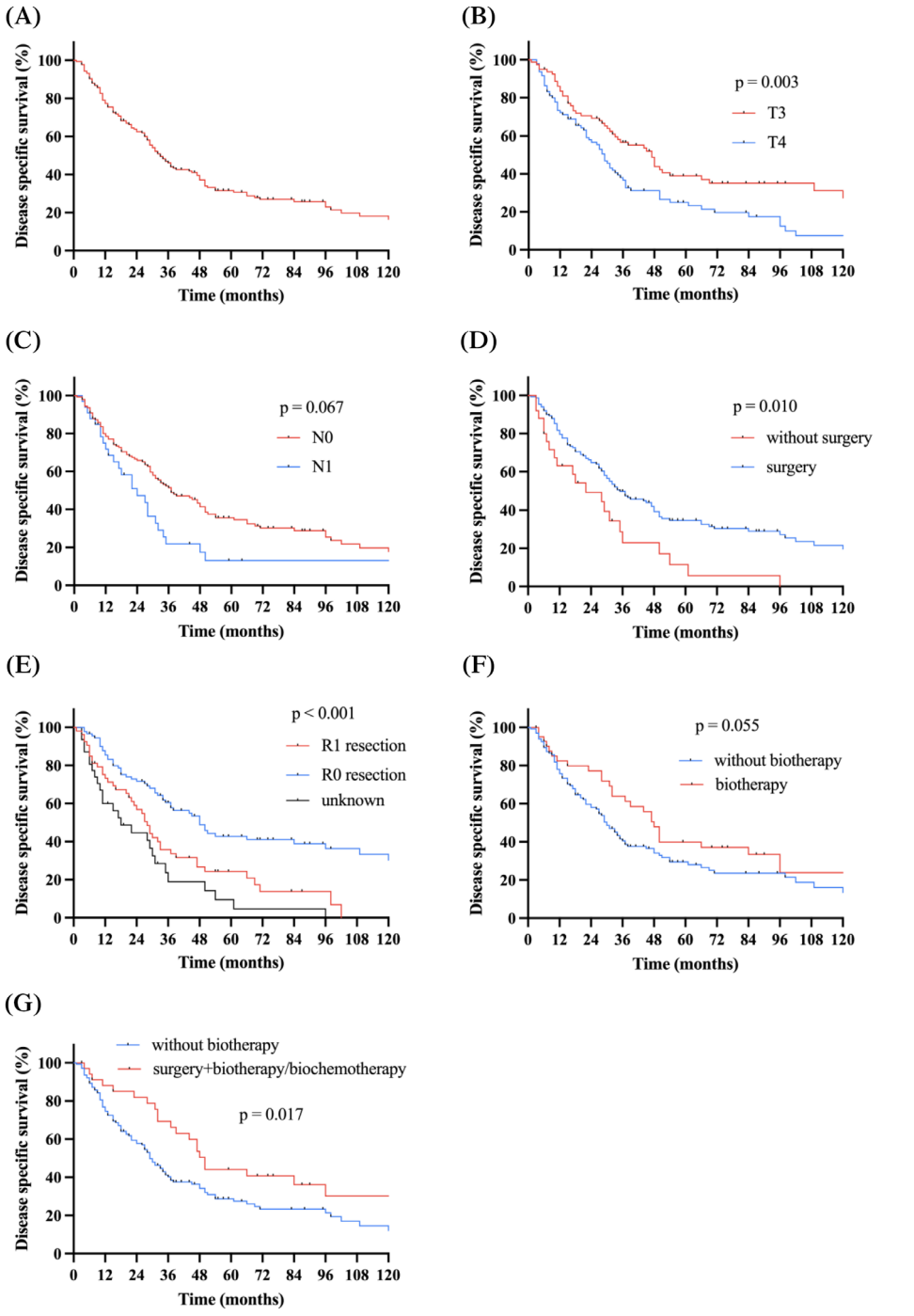

FIGURE. 1 Kaplan–Meier curves of disease-specific survival (DSS). (A) DSS for the entire cohort; (B) DSS stratified by T stage; (C) DSS stratified by N stage; (D) DSS stratified by surgery; (E) DSS stratified by resection status; (F) DSS stratified by biotherapy; (G) DSS stratified by treatment regime.

(HR = 1.600; 95% CI, 1.023–2.504; $p = .039$) were strong prognostic factors for poor survival, and combined therapy (surgery +biotherapy/biochemotherapy) was a strong prognostic factor for better survival outcome (HR = 0.563; 95% CI, 0.354–0.896; $p = .015$; Table 3).

When excluding eight patients who did not receive any definitive treatment in multivariable Cox regression analysis, the results revealed that the T4 stage (HR = 1.621; 95% CI, 1.116–2.356; $p = .011$) and the N1 stage (HR = 1.621;95% CI, 1.019–2.580; $p = .042$) were strong prognostic factors for poor survival, and combined therapy (surgery+biotherapy/biochemotherapy) was a strong prognostic factor for better survival outcome (HR = 0.560; 95% CI, 0.348–0.901; $p = .017$; Table 4).

4 | DISCUSSION

MM of the head and neck is a rare entity with a very poor prognosis. Few published data were available with no established treatment guidelines. We retrospectively analyzed treatment outcomes of 190 cases, with a long follow-up time, from a single institution. Notably, the present study is a large series of MMHN cases to be reported.

TABLE 3 Multivariate analysis of factors predictive of disease-specific survival (including eight patients who did not receive any definitive treatment).

Variable	*p* Value	HR (95% confidence interval)
Age	0.102	1.011 (0.998–1.025)
T stage (T4 vs. T3)	0.005	1.692 (1.175–2.438)
N stage (N1 vs. N0)	0.039	1.600 (1.023–2.504)
Treatment regime (Surgery+bio/biochemo vs. other therapy)	0.015	0.563 (0.354–0.896)

Abbreviations: bio, biotherapy; biochemo, biochemotherapy; HR, hazard ratio.

TABLE 4 Multivariate analysis of factors predictive of disease-specific survival (excluding eight patients who did not receive any definitive treatment).

Variable	*p* Value	HR (95% Confidence interval)
Age	0.203	1.009 (0.995–1.022)
T stage (T4 vs. T3)	0.011	1.621 (1.116–2.356)
N stage (N1 vs. N0)	0.042	1.621 (1.019–2.580)
Treatment regime (Surgery+bio/biochemo vs. other therapy)	0.017	0.560 (0.348–0.901)

Abbreviations: bio, biotherapy; biochemo, biochemotherapy; HR, hazard ratio.

Our data showed that surgical resection with a negative resection margin, combined with biotherapy contributed to better survival outcomes.

Patients with MMs are often asymptomatic in their early stages and are usually diagnosed late. Generally, OMMs often have nodular or macular appearances and present as hyperpigmented lesions. Their anatomical position offers greater accessibility for inspection.[11] Therefore, OMMs can be diagnosed earlier. In the present study, OMMs were detected at earlier ages compared with NMMs. In addition, the anatomical surgical constraints and multifocal growth pattern significantly limit the ability for wide negative margins and must be heavily weighed on the patient's quality of life.[7] In the present study, we observed that in SMMs, the R0 resection rate (51.4%) was relatively low.

In recent years, the survival rate of HNMMs has significantly improved compared with the data we reported before, and the survival gains are more pronounced in OMMs. The 3- and 5-year OS of OMMs were 49.2% and 34.0% in this study, while the 3- and 5-year OS rates were 35.0% and 20.7% in our previous study.[9,10] These improvements are mainly due to the early detection and diagnosis of MMs, and the improvement of treatment techniques in recent years.[12] More patients received complete tumor resections due to the advances in free flap reconstruction in recent years. More patients received effective combination treatments, including surgery and biotherapy, which improved survival rates. The surgical outcome in this study is worse than that in the multicentric REFCOR cohort,[13] with a 5-year survival rate of 36.5% versus 49.4% in the surgery/M0 group. The local, regional, and distant recurrence rates in the REFCOR cohort are 16.9%, 12.6%, and 57.7%, respectively. We observed that patients in the present study were more likely to have advanced disease. The proportion of patients with T4 stage (54.0%) and N1 stage (19.6%) seemed to be higher than previously reported,[13] and patients in this study had a high proportion of local and regional failure. The 5-year DSS rate in this study is comparable with that in the SEER cohort,[14] while a little better than The National Cancer Data Base cohort,[15] in which the median survival is 29.3 months, and the 5-year survival is 27.4%.

In the present study, the proportion of patients with treatment failure (63.2%) was very high. Consistent with previous studies, we did not find a survival benefit from radiotherapy.[13] Our results indicated that surgery combined with biotherapy or biochemotherapy correlated with better survival. Biotherapy has been shown to improve patient outcomes in several studies. Interferon has been shown to significantly improve both disease-free survival and overall survival in patients with cutaneous melanomas despite the significant toxicity that leads to poor patient compliance with therapy and is recommended for the adjuvant treatment of cutaneous melanomas on type 1 evidence as an individualized option.[14] In the Phase II Randomized Trial, Bin Lian et al reported that both temozolomide-based chemotherapy and high-dose IFN-α-2b were effective and safe adjuvant therapies for resected MM. Significant improvements in RFS and OS have been observed in the high-dose IFN-α-2b group and the temozolomide plus cisplatin group.[15] However, further validation of this efficacy from high-quality data, such as prospective randomized controlled phase III trials, is lacking.

It seems that the excellent treatment effect of ICIs yielded in CM may be unlikely to occur in MM, given that MM has been reported to show a lower mutation burden and poor lymphocyte infiltration.[8,16] The low mutation burden, which results in the poor generation of a tumor neoantigen, may be involved in the poor proliferation of tumor-specific T cells in MM.[8] The significantly lower number of CD8+ TIL may be associated with the poorer response to ICIs, as the anti-PD-1 antibody is reported to be dependent on CD8+ T cells to exert antitumor immunity in vivo.[17] ICIs did not perform well in MMs. The response rate (RR) of single-agent anti-PD1 therapy is around 25%, and the progression-free survival (PFS) is 3–6 months. The RR of combined immunotherapy is around 37% and the PFS is around 6 months.[18–21] It is noteworthy that the RR of ICIs in Chinese populations is lower, and the influence of race on the treatment effect of ICIs is still unclear.[22,23] Therefore, the efficacy of ICIs treatment in MMs needs further validation.

Our study has some limitations. It was a retrospective study of a single institutional data across a long time interval. Second, we did not perform further analysis of factors correlated with relapse or metastasis as the exact timing of relapse and metastasis is uncertain in some patients. Nonetheless, the present report with 190 cases of MMHN was one of the largest sample series studies from a single institution and we believed the results still provided valuable information from existing data.

5 | CONCLUSION

The prognosis of MMHN remains poor. Systemic treatment is warranted to reduce MMHN progression. Combined surgery with biotherapy may improve survival.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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