



Long-term treatment outcomes and prognosis of mucosal melanoma of the head and neck: 161 cases from a single institution



Shiran Sun, Xiaodong Huang, Li Gao, Ye Zhang, Jingwei Luo, Shiping Zhang, Kai Wang, Yuan Qu, Runye Wu, Qingfeng Liu, Jianping Xiao, Guozhen Xu, Junlin Yi*

National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, China

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ABSTRACT

Objectives: This study aimed to evaluate the clinical features, treatment outcomes and prognostic factors of mucosal melanoma of the head and neck (MMHN) in patients who were treated at our institution.

Materials and methods: Between Jan. 1981 and Oct. 2015, 161 patients with non-metastatic MMHN were treated at our institution. The patients' clinical characteristics, treatment modalities, outcomes, prognostic factors, and failure patterns were retrospectively analysed.

Results: With a median follow-up time of 74 months, the 5-year overall survival rate (OS), local control rate (LC), distant metastasis-free survival (DMFS) were 44.4%, 59.4%, and 49.3%, respectively. Regarding the different treatment modalities, the 5-year OS was 50.0% in the surgery group and 43.1% in the surgery combined with radiotherapy group, while, the 5-year LC rate was 42.5% in the surgery group and 75.3% in the surgery combined with radiotherapy ($p < 0.001$). According to the AJCC 7th edition staging system for MMHN, the 5-year OS for patients with stage III, stage IVA, and stage IVB MMHN were 65.2%, 33.1% and 14.3%, respectively ($p < 0.001$). In the multivariate analysis, the T stage, neck lymph node involvement, and surgical margins were independent prognostic factors for OS; surgical margins and adjuvant radiotherapy were independent prognostic factors for LC.

Conclusion: The addition of radiotherapy improves the local control rate of MMHN. T stage, neck lymph node status, and surgical margins are independent prognostic factors for the OS in patients with MMHN. The AJCC 7th edition staging system for MMHN appears to effectively stage this disease.

Introduction

Mucosal melanoma is a rare malignant neoplasm, accounting for only 0.8–3.7% of all melanomas [1,2]. The most common site of mucosal melanoma is the upper aerodigestive tract, which accounts for 55% of all cases [1]. Several studies have reported that MMHN is more common in some parts of African countries and Japan than in Western countries [3,4]. The most common primary sites of MMHN are the sinonasal cavity and oral cavity. Although rare, MMHN is a very aggressive malignancy, with 5-year OS ranges from 20% to 40% [5–8]. The overall prognosis is considered to be worse than those of cutaneous and ocular melanomas. Wide surgical resection is generally considered the primary treatment for localized MMHN. Postoperative radiotherapy is often used to improve local control. The use of systemic therapies has not yet been established as a method for improving the treatment outcomes. A large cohort study of 815 patients, who were selected from

the SEER database, indicated that an age > 70 years, a primary tumour site of nasopharyngeal and paranasal sinuses, nodal metastases, distant metastasis, and a tumour size > 4 cm were independent prognostic factors of a poorer survival [5]. Other retrospective studies have identified additional prognostic variables, such as advanced T-category, positive surgical margins, deep infiltration, vascular invasion, pigmented lesions and treatment approaches [6,9–12].

Because of the rare entity of this disease, the knowledge about MMHN is gained mainly from small sample series. In our study, we report one of the largest single-institution studies of primary MMHN.

Methods

Clinical data

Between Jan. 1981 and Oct. 2015, 161 patients with non-metastatic

* Corresponding author.

E-mail addresses: cindy899@126.com (S. Sun), hxd010@hotmail.com (X. Huang), li_gao2008@outlook.com (L. Gao), drzye@163.com (Y. Zhang), nqluo202@163.com (J. Luo), zhshp1@hotmail.com (S. Zhang), kaiwang2001@vip.sina.com (K. Wang), qu_yuan01@163.com (Y. Qu), wurunye@aliyun.com (R. Wu), qingfeng1910@163.com (Q. Liu), jpxiao8@163.com (J. Xiao), guozhenxu@vip.sina.com (G. Xu), yijunlin1969@163.com (J. Yi).

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MMHN who were treated at our institute were retrospectively analysed. This study was approved by the local ethics committee. All of the patients were pathologic-proven, which was reviewed by at least two pathologists from our institution. One-hundred and fifty-three patients were restaged based on clinical documents, surgical records and imaging findings according to the American Joint Committee on Cancer (AJCC) 7th edition staging system for mucosal melanoma of the head and neck [13]. The clinical TNM classification was determined by clinical and radiological examinations, including CT, MRI, and ultrasound, but most of them were based on CT and MRI (CT in 83 patients and MRI in 58 patients).

Treatment data

The treatment modalities mainly included surgery alone, which was performed in 60 patients, surgery combined with radiotherapy, which was performed in 87 patients (preoperative in 47 patients and postoperative in 40 patients), and radiotherapy alone, which was performed in 14 patients.

The recommendations for the primary treatment were given by our multidisciplinary team. Surgery alone was suggested for tumours of an early stage. Postoperative RT (PORT) was recommended for those with positive or close surgical margins. PORT was delivered at 4–6 weeks after surgery. For the patients with a locally advanced and borderline resectable disease, preoperative RT was recommended. The planned surgery was delivered at 4–6 weeks after the completion of radiotherapy. RT alone was given to the patients with an unresectable tumour.

Surgical resection of the primary tumour was performed in 147 of the 161 patients. Overall, radical surgery with total macroscopic resections was performed in 113 patients, while the remaining 34 patients received subtotal macroscopic resections or tumour resection.

Radiotherapy as a part of the treatment strategy was performed in 101 patients: 47 patients with preoperative RT, 40 patients with postoperative RT, and 14 patients with RT alone. Sixty-four patients were administered 2D radiotherapy, and 37 patients were administered intensity-modulated radiotherapy. The radiation doses varied among the treatment modalities: in the RT alone group, the median dose was 52 Gy (range: 28–80 Gy), while only one patient received 80 Gy; in the preoperative RT group, the median dose was 47 Gy (range: 32–79 Gy); and in the postoperative RT group, the median dose was 62 Gy (range: 36–76 Gy). The dose fractionation of radiotherapy ranged from 2 to 8 Gy. In this analysis, we defined a dose fractionation of 3 Gy/fraction or more as hypofractionated radiotherapy ($n = 37$) and a dose fractionation less than 3 Gy/fraction as conventional fractionated radiotherapy ($n = 50$). More than half of the patients (26/47) in the preoperative RT group received hypofractionated RT. Chemotherapy was given to 78 patients (48%). The regimens generally consisted of the following: a combination of dacarbazine, vindesine, and cisplatin. The median duration of chemotherapy was 2 courses (range: 1–4 courses). Forty-seven patients (32%) received biotherapy, which mainly included subcutaneous injections of IL-2 and IFN- α -2b.

Therapeutic neck dissection/radiation was performed in all of the N + patients. Because of the lack of a proven benefit of elective neck treatment, the decisions were mostly dependent on the location of the primary tumour, its lymphatic drainage, and its clinical stage. Nine patients (50%) who had oral mucosal melanoma underwent elective neck dissection. Only four patients (4.4%) who had sinonasal mucosal melanoma underwent elective neck dissection. In the postoperative group, 25 patients received elective neck radiation: 3 patients (100%) who had oral mucosal melanoma and 22 patients (62.8%) who had sinonasal mucosal melanoma.

Statistical analyses

All events (including local failure, regional failure, distant failure

and death) were measured from the date of treatment until the documented first failures. The statistical evaluation of the data was done using SPSS 23.0. The categorical variables were compared using the chi-square test. The survival estimation was calculated using the *Kaplan–Meier* method, while the survival curve comparisons were performed using the *log-rank* test. A Cox model was applied for the multivariate analysis to detect the prognostic factors.

Results

Patient characteristics

Of the 161 patients, 94 (58%) were male and 67 (42%) were female, and the patients had a median age of 54 years (range: 19–83 years). All of the patients were Chinese. The primary sites of the tumour were: the nasal cavity, which was observed in 88 patients (55%), the oral cavity, which was observed in 49 patients (30%), and the paranasal sinus, which was observed in 9 patients (6%). Other sites of the tumour included the palpebral conjunctiva, nasopharynx, pharynx, and larynx. The presentation of symptoms varied among the primary sites, with most patients who had sinonasal primary tumours presenting with nasal obstruction or epistaxis and most patients who had oral mucosal melanoma primary tumours presenting with a pigmented lesion, sometimes with tooth mobility. The average duration of the symptoms before a diagnosis was made was 5 months (range: 1–47 months). Clinically, lymph node metastases were present in 23% of the total number of patients (36/161). The primary tumour sites of the patients with nodal metastases included: the oral cavity, which was observed in 29 patients, the nasal cavity, which was observed in 2 patients, the nasopharyngeal, which was observed in 2 patients, the oropharyngeal, which was observed in 2 patients, and the hypopharyngeal, which was observed in 1 patient. The most common site of nodal metastases at diagnosis in patients with oral mucosal melanoma was level I (involved 20 of 29 patients), followed by level II (10 patients) and level III (5 patients). In the two patients who had sinonasal mucosal melanoma, one had nodal metastases at level I–III, the other one had nodal metastases at level I–II. In the two patients who had nasopharyngeal mucosal melanoma, one had a lymph node metastasis at level II, the other one had nodal metastases at level I–III. Two patients with oropharyngeal mucosal melanoma had involvement of level II lymph node metastases. One patient with hypopharyngeal mucosal melanoma had involvement of level II–III lymph node metastases. Patients with oral mucosal melanoma had a higher incidence of nodal metastases at diagnosis compared with those with sinonasal melanoma (59.2% vs. 2.1%, $p < 0.001$). One-hundred and fifty-three patients were restaged according to the AJCC 7th staging system and based on the clinical documents, surgical records and imaging findings. Among them, 61 patients were of stage III, 85 patients were of stage IVA, and 7 patients were of stage IVb (Table 1).

Treatment outcomes

With a median follow-up time of 74 months (range: 6–272 months), the 5-year overall survival rate (OS), local control rate (LC), and distant metastasis-free survival rate (DMFS) were 44.4%, 59.4%, and 49.3%, respectively. According to the new staging system of MMHN, the 5-year overall survival rates for stage III, stage IVA and stage IVb were 65.2%, 33.1% and 14.3%, respectively ($p < 0.001$) (Fig. 1). The 5-year OS and LC according to the different treatment modalities were as follows: surgery alone: 50.0% and 42.5%, respectively; surgery combined with radiotherapy (both preoperative and postoperative): 43.1% and 75.3%; and primary RT: 28.1% and 55.9% (Fig. 2). The addition of radiotherapy to surgery elicited superior local control but did not significantly improve the overall survival rate.

With the limitation that biases existed among the various approaches, patients with positive surgical margins and stage IV were

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