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British Journal of Oral and Maxillofacial Surgery 58 (2020) 1097–1102

BRITISH Journal of Oral and Maxillofacial Surgery

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Survival of oral mucosal melanoma according to treatment, tumour resection margin, and metastases

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Accepted 20 May 2020
Available online 23 June 2020

Abstract

Because of the poor prognosis and of oral mucosal melanoma, and patients' short survival, large, randomised, clinical studies are difficult. We have investigated its demographic characteristics and analysed the effect of treatment, resection margins, and metastases on survival. We recorded age, sex, site of primary tumour, and types of treatment, survival, and metastases in 74 patients treated at the Department of Oral and Maxillofacial Surgery, Seoul National University Dental Hospital. Survival was analysed based on bony invasion, depth of invasion, and resection margins, and we found that it varied depending on the primary site ($p = 0.002$), and declined with liver ($p = 0.001$) or brain ($p = 0.033$) metastases. The two-year survival according to the primary site was as follows: palate 85% ($n = 32$), anterior maxillary gingiva 53% ($n = 13$), mandible 58% ($n = 13$), and posterior maxillary gingival 74% ($n = 10$) and buccal mucosa 50% ($n = 4$). The two-year survival was 34% ($n = 8$) in patients with liver metastases and 23% ($n = 7$) in patients with brain metastases. In cases of bony invasion ($p = 0.005$), depth of invasion ($p = 0.042$), unclear resection margin ($p = 0.023$), or higher T stages ($p = 0.009$), the survival declined considerably. Neck dissection did not affect survival ($p = 0.343$). Survival of the patients given chemotherapy was significantly lower ($p = 0.013$) and the two-year survival was 54.0%. The patients given radiotherapy showed no significant difference in survival compared with those not given radiotherapy ($p = 0.107$). In conclusion, primary site, bony invasion, resection margins, depth of invasion and systemic metastases were critical to predict prognosis and selection of treatment of oral mucosal melanoma.

Keywords: oral mucosal melanoma; survival rate; treatment modality; tumor resection margin; metastasis

Introduction

Melanoma that develops in the mucosa is rare, and comprises less than 2% of total melanomas diagnosed.[1] In the US, the incidence of mucosal melanoma is 2.2 cases/million/year.[2] Mucosal melanomas have different epidemiological and genetic characteristics from skin-derived melanomas,[3] and the survival for patients with mucosal melanoma is lower than that for those with skin melanoma. Among mucosal melanomas, about 33.2% originate from the mouth and pharynx.[4] Because of the low incidence, conducting extensive studies and treatment of the disease remain difficult. According to the American Joint Committee on Cancer (AJCC) Staging Manual (8th edition, 2018)[5] the criteria for T staging mucosal melanoma of the head and neck are as follows: T3 = tumours limited to the mucosa and immediately

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https://doi.org/10.1016/j.bjoms.2020.05.028

underlying soft tissue, regardless of the thickness or greatest dimension; T4a = tumour involving deep soft tissue, cartilage, bone or overlying skin; and T4b = tumour that involves brain, dura, skull base, lower cranial nerves, masticator space, carotid artery, prevertebral space, or mediastinal structure.

Despite those clear staging categories, however, studies of the clinical characteristics that affect the prognosis of head and neck mucosal melanoma have not been done, so clinicians are still not clear when to treat it, and particularly how to predict the prognosis.

In the treatment of melanoma, extensive surgical resection of the tumour mass is the first choice. Irradiation,[6,7] adjuvant chemotherapy,[8,9] and adjuvant immunotherapy are the main postoperative treatments. Some studies have indicated that irradiation does not effectively increase survival or reduce recurrence,[9,10] while patients who were given chemotherapy had prolonged survival.[11] The effectiveness of immunotherapy has not been definitively assessed, but the treatment has shown promise. However, despite these, recurrence of mucosal melanoma is common, and the lack of an established protocol has led to various treatments being used after resection.

The purpose of this study was to investigate the demographic characteristics of patients with oral mucosal melanoma and to analyse the effects of various treatments, tumour margins, and metastases on survival, with the aim of identifying strategies for predicting prognosis and selecting the best treatment for these patients.

Patients and methods

A total of 76 patients were diagnosed with oral mucosal malignant melanoma based on pathological diagnosis at the department of Oral and Maxillofacial Surgery, Seoul National University Dental Hospital (SNUDH) from 2011 to 2018. Two cases with lip melanomas on non-mucosal areas were excluded. Demographic characteristics (age, sex, and primary site) were analysed in the remaining 74 patients (Table 1).

The number of patients according to the depth of invasion was analysed by dividing them into: melanoma in situ (0 mm), between 1–4 mm, 5–10 mm, and 11 mm or more. The number of patients according to the status of the resection margin was analysed by dividing them into: margin involved, close margin (between 1 and 5 mm), or sufficient margin (>6 mm). The size of tumour was divided into small (diameter less than 2 mm) and large (diameter more than 2 mm) groups. T stage was measured according to the AJCC Staging Manual.[5] Because the study was retrospective, it was granted an exemption in writing by the Seoul National University institutional review board (IRB) (IRB No. ERI19029).

Statistical analysis of survival was made, taking account of the demographic characteristics (age, sex, and primary site) and clinical features (type of operation and presence or absence of metastases) in the 74 patients. We also analysed the survival and the relation between the tumour's margin and postoperative adjuvant treatment after (radiotherapy, chemotherapy, or immunotherapy) in the 51/74 patients who were operated on at our hospital. The data of patients who were lost to follow-up were included in estimating the overall survival. Kaplan–Meier survival analysis was used for estimation of survival. For small cases, the two-year survival was calculated instead of the five-year survival. The log-rank test was used to estimate differences in survival.

Table 1
Demographic characteristics of patients with oral mucosal melanoma.

Variable	No. of cases (n = 74)
Sex:	
Female	33
Male	41
Age (years):	
<40	10
41–60	29
>61	35
Primary site:	
Palate	32
Anterior maxillary gingiva	13
Mandible	13
Posterior maxillary gingiva	10
Buccal mucosa	4
Maxillary sinus*	2

* The incidence of melanoma in the maxillary sinus was low and did not affect the significance, so it was included as an oral mucosal melanoma.

Results

There were 41 men and 33 women (mean (range) age 59 (26–87) years old. The mean (SD) follow-up period was 37 (36.5 (4.38) months) (Table 1). Supplementary Fig. 1.

Of the 74 patients, 54 had the mass resected (Table 2). The drugs used for chemotherapy were dacarbazine (n = 14), cisplatin (n = 9), vinblastin (n = 6), carboplatin (n = 3), paclitaxel (n = 2), and padexol (n = 1). The combination of cisplatin, vinblastin, and dacarbazine was used in six patients.

Fifteen patients survived, the deaths of 26 patients were confirmed, and 33 were lost to follow up by September 2018 (Table 2). Neck node metastases were found in 44 patients. Postoperative lymph node metastases were found in 11/44 patients who had not had neck dissection (Table 3). Lymph node metastases were examined according to the site of the origin of the tumour (Table 4). (Supplementary Table 1).

Further investigation was carried out in the 51 patients who had the mass resected at SNUDH OMFS to examine the relation between the results of histopathological examination and postoperative treatment (Table 5). (Supplementary Table 2).

We analysed survival depending on the demographic and clinical data for all patients. The overall two-year survival was 72% and five-year survival rate was 53%. There was no significant difference in survival according to age and sex (Supplementary Fig. 2A, B). There was, however, a difference in survival between the different primary sites

Table 2
Clinical features (treatment and survival) of oral mucosal melanoma.

Variable	No. of cases (n = 74)
Surgery	
Resection of mass	54 (51 in SNUDH OMFS)
Reconstruction (free flap):	
Yes:	31
Radial arm	22
Fibular	3
Dorsalis pedis	2
Latissimus dorsi	2
Scapular	1
Peroneal artery	1
No	23
Neck dissection:	
Yes	24
Nodal biopsy only	2
No	28
Postoperative treatment:	
AC	3
PORT	8
AI[†]	6
AC + PORT	4
AC + AI	6
PORT + AI	1
AC + PORT + AI	7
None	19
No surgery:	20
CTx.	6
RT	1
ITx. + RT	1
ITx. + CTx.	1
ITx. + CTx + RT	1
Refused treatment	10
Survival:	
Yes	15
No	26
Follow-up loss[*]	33

CTx = Chemotherapy; RT = radiotherapy, ITx = immunotherapy; SNUDH = Seoul National University Dental Hospital.

[*] Follow-up loss refers to patients who did not appear on the next appointment, and we were unable to confirm their life or death at the telephone interview.

[†] Interferon, interleukin-2 and pembrolizumab was used for immunotherapy.

Table 4
Neck lymph node metastasis of oral mucosal melanoma related to primary site of origin.

Variable	Neck lymph node metastasis (n = 69)		Total
	No	Yes	
Primary site:	25	44	69
Maxilla	19	31	50
Mandible	3	10	13
Buccal mucosa	2	2	4
Maxillary sinus	1	1	2

Table 5
Bony invasion, thickness of tumour, and resection margins of oral mucosal melanoma based on pathological result after resection of the mass.

Variable	No. of cases (n = 51)
Bone invasion:	
Yes	19
No	32
Depth of invasion (mm):	
Melanoma in situ	1
1–4	15
5–10m	11
>11	18
Non-specific[*]	6
Resection margin status:	
Clear margin	44
Invaded margin	4
Non-specific[*]	3

[*] No information about depth of invasion or resection margin in pathological report.

(p = 0.002). The two-year survival according to the primary site was: palate 85%, anterior maxillary gingiva 53%, mandible 58%, posterior maxillary gingival 74%, and buccal mucosa 50%. No patients whose primary site was maxillary sinus survived more than two years (Supplementary Fig. 2C). Survival was higher in patients who had resection of the mass than in those not operated on, but the difference was not significant (p = 0.059) (Supplementary Fig. 2D). There was no significant difference in survival between the patients who had neck dissection and those who did not (p = 0.343).

In patients with cervical lymph node metastases survival tended to decrease, although the difference was not sig-

Table 3
Cervical lymph node, local and distant metastasis of oral mucosal melanoma related to mass resection, neck dissection and pathologic diagnosis of lymph node.

Variable	No. of cases (n = 74)	Treatment		
		No surgery	Mass resection	Neck dissection (+/−)[§]
Metastasis				
Cervical lymph node	44	11	33	23 (7/16)
Local	10	1	9	6 (4/2)
Distant:	35			
Lung	20	2	18	10 (3/7)
Liver	8	1	7	4 (1/3)
Brain	7	1	6	1 (1/0)
Bone and other organs[†]	10	2	8	3 (1/2)

−; Clear lymph node on pathological report during neck dissection, which means prophylactic neck dissection.

[†] Bone and other organs include spine, sacrum, sternum, axilla, bladder, ear, adrenal gland, peritoneum, buttock, and so on.

[§] Invaded lymph node on pathological report during neck dissection, which means therapeutic neck dissection.

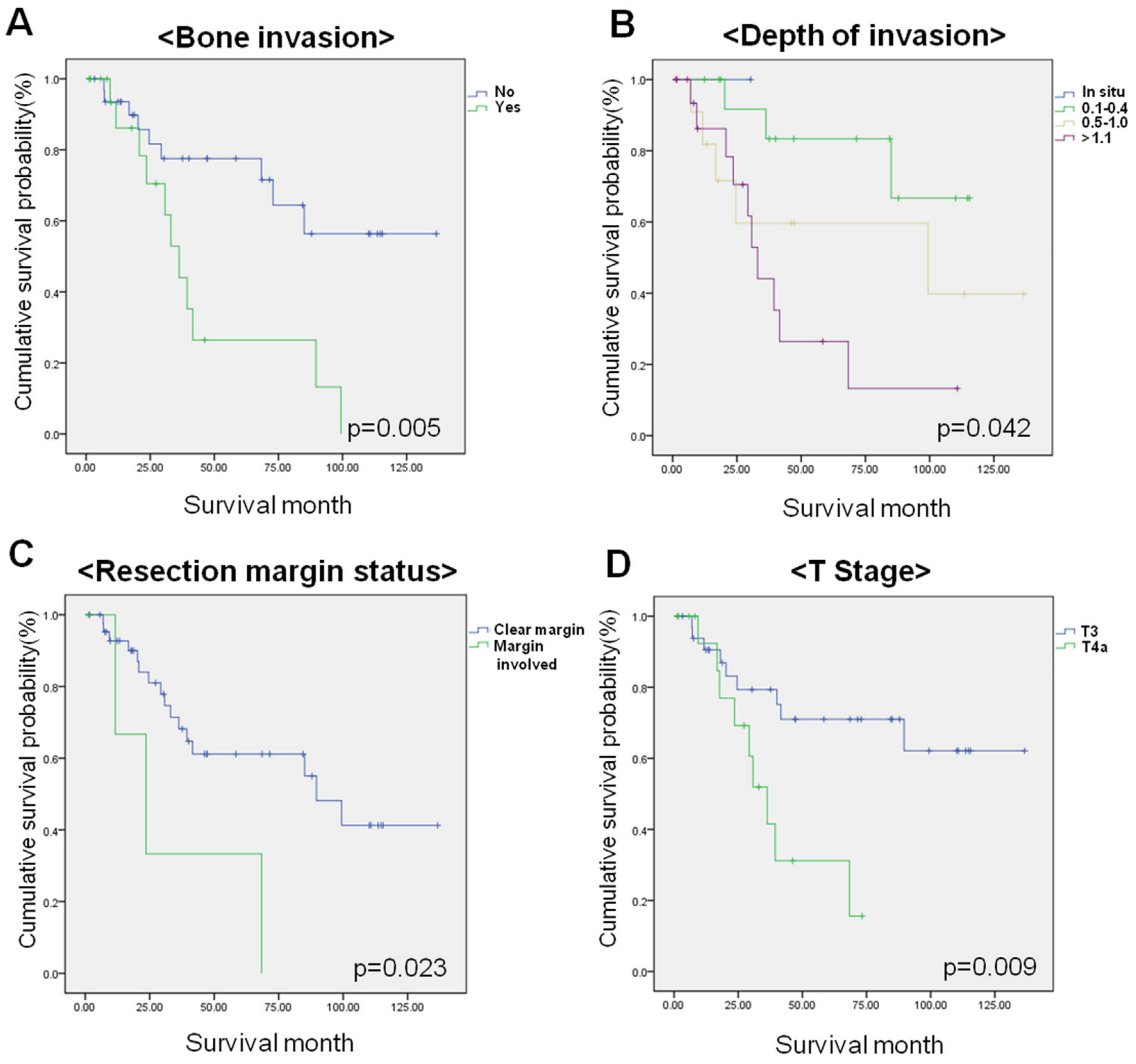

Fig. 1. Overall survival rate of patients with head and neck mucosal melanoma who underwent mass resection surgery in SNUDH OMFS, in relation to A, bone invasion of tumour; B, depth of tumour; C, resection margin clearance; D,T stage.

nificant (p = 0.139) (Supplementary Fig. 3A). Patients with local metastases and lung metastases showed no significant difference in survival, whereas those with liver (p = 0.001, Supplementary Fig. 3B) and brain metastasis (p = 0.033, Supplementary Fig. 3C) had significantly reduced survival. The two-year survival was 34% in patients with liver metastases and 23% in patients with brain metastases. The survival of patients treated with chemotherapy was significantly lower (p = 0.013), and the two-year survival was 54%. Patients given radiotherapy also had lower survival, but the difference was not significant (p = 0.107). The type of drug used for chemotherapy did not affect survival.

Based on pathological reports, patients with bony invasion by the tumour had significantly reduced survival (p = 0.005, Fig. 1A) and their five-year survival was 26%. Survival decreased as the depth of invasion increased (p = 0.042 Fig. 1B). The five-year survival according to the depth of invasion was: 0–4 mm (83%), 5–10 mm (60%), and over 11 mm (26%). A clear resection margin was associated with significantly increased survival (p = 0.023, Fig. 1C). The two-year survival was 81% for complete resection, and 33% for incomplete resection. However, the length of the healthy tissue remaining up to the resection margin of the lesion was not significantly associated with survival (p = 0.533). There was no significant association between the size of the lesion and survival (p = 0.792). The lower T stages were associated with significantly increased survival (p = 0.009).

Discussion

Mucosal melanoma is common in the head and neck (55%), and anorectal (24%) and vulvovaginal (18%) regions,[12] and typically arises in patients in their 70s,[12,13] which is 10 to 20 years later than cutaneous melanoma.[14] This may be the result of the late detection of mucosal melanomas, particularly those in the vulvovaginal and anorectal regions, because of their unusual site.[15] Mucosal melanomas of the head and

neck develop in the sinonasal area (55%) and oral cavity (40%), mainly around the age of 40,[16] with a mean age of about 61 years.[17,18] A previous study showed that oral mucosal melanoma commonly develops in the maxilla, maxillary palate, and maxillary gingiva (80%),[19] which is similar to the 74% (n = 55) in our study. While two patients with melanoma of the maxillary sinus were included in the data, we designed this study to examine melanoma of the oral mucosa. Because there were only two melanomas in the maxillary sinus, the number did not affect data processing. The age of onset of oral mucosal melanoma ranged from 26-87 years and the patients' mean age was 59 years, which is similar to previous reports.[12,17,18,20]

Prophylactic lymph node dissection is recommended by some research workers because lymph node metastases often develop from oral mucosal melanoma, but not from sinusoidal melanoma.[12] However, other people argue that neck dissection does not conclusively contribute to improved survival.[21] In this study, lymph node metastases often developed, being found in 44 /69 cases. Distant metastases were seen regardless of whether the patient had had a neck dissection. In addition, neck dissection did not significantly improve survival.

Resection of primary lesions is the gold standard of the treatment of mucosal melanoma. However, for neck dissection, the situation is different. While most people agree that therapeutic neck dissection is reasonable for clinically apparent, large, and symptomatic disease,[12] some studies have shown that neck dissection does not contribute to the patient's survival because of the rapid progression and metastatic nature of the tumour.[21] Lymph node metastases are common in oral mucosal melanoma, but neck dissection does not affect the development of future distant metastases or overall survival.

Morbidity at the primary site should rely on complete removal of the tumour, rather than the safety margin.[22] In this study the survival tended to decrease when there was bony invasion, when the resection margin was not clear, and when the depth of invasion was deep. However, no difference in survival was found when the extent of the safety margin was considered. Complete removal of the tumour is important, but the size at which to abstain and leave the safety margin has not been confirmed.

According to the AJCC Staging Manual,[5] the T stage does not take into account the size of the tumour, but depends on the type of underlying tissue invaded. We tried to confirm the relation between the size of the lesion and the survival, but we could find no significant difference. In addition, in many cases the data are missing from the histology results because of the difficulty in measuring diameters of widely-spread lesions. On the other hand, according to T staging of the AJCC Staging Manual,[5] it is classified as T3, T4a, and T4b, and T4b is unresectable. Based on the results of the biopsies of the patients who were operated on, therefore, T staging could be divided into T3 and T4a, and the results similar to the data measured based on bony invasion.

Postoperative radiotherapy and chemotherapy are considered when the lesion is large and invades the adjacent anatomical structures or extracapsular region of the lymph node, which indicates a serious risk of recurrence. This study suggests, therefore, that the survival decreases when radiotherapy or adjuvant chemotherapy is used. This may indirectly indicate that survival is reduced even in the case of serious disease, despite the perioperative treatment.

Immunotherapy known to be effective in treating mucosal melanoma includes immunomodulatory cytokines such as interferon (IFN) -α or interleukin (IL) -2 and vaccines that target immunological checkpoints such as anticytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or anti–programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1).[22]

Many studies have shown that immunotherapy is more effective than conventional chemotherapy or radiotherapy in mucosal melanoma immunotherapy.[23–27] Immunotherapy should therefore be widely used as a perioperative treatment option.

Conclusions

Survival for patients with oral mucosal melanoma varies depending on the site of origin, and decreases when there are liver or brain metastases. Survival tended to decrease when there was bony invasion, when the resection margin was not clear, or the depth of invasion was deep. Neck dissection did not affect survival (p = 0.343).

In conclusion, primary site, bony invasion, resection margins, depth of invasion of the tumour and systemic metastases were the critical factors for predicting prognosis, and have to be considered when selecting the treatment of oral mucosal melanoma.

Ethics statement/confirmation of patients' permission

I have IRB approval for this paper, and the number is IRB No. ERI19029. The personal information of patients included in some of the papers has been removed.

Conflict of interest

We have no conflicts of interest.

Acknowledgements

This study was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI15C1535).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bjoms.2020.05.028.

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