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Long-term outcomes after carbon-ion radiotherapy for oral mucosal malignant melanoma

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ABSTRACT

Oral mucosal malignant melanoma (OMM) is extremely rare and has a poor prognosis. Owing to its rarity, it has not yet been possible to establish an optimal treatment modality. The objective of this study was to evaluate the long-term efficacy of carbon-ion radiotherapy (C-ion RT) for OMM. Between 1997 and 2013, 19 patients with OMM were treated with C-ion RT alone. Patient ages ranged from 44 to 84 years (median, 69 years). Nine men and 10 women were included. OMMs were restaged in accordance with the seventh edition of the tumour/node/metastasis (TNM) Staging System of the International Union Against Cancer. Before treatment, 14 patients had T3 disease and 5 had T4a disease. Three patients were classified as having N1 disease. All patients were classified as having M0. The hard palate was the most frequently involved oral subsite. All patients were treated with 57.6 Gy (relative biological effectiveness) in 16 fractions. The median follow-up period was 61 months (range, 8–190 months). The 5-year local control, overall survival and progression-free survival rates were 89.5%, 57.4% and 51.6%, respectively. For local control and overall survival, T classification was found to be a significant prognostic factor. Grade 2 and 3 osteoradionecrosis was observed in three and four patients, respectively. The presence of teeth within the planning target volume was a significant risk factor for developing osteoradionecrosis. C-ion RT was an effective treatment option with acceptable toxicity for OMM.

KEYWORDS: carbon-ion radiotherapy, mucosal malignant melanoma, oral melanoma, charged particle therapy, radiotherapy

INTRODUCTION

Oral mucosal malignant melanoma (OMM) accounts for only 0.5% of all oral malignancies, and represents ~1% of all melanomas [1, 2]. Because of this low incidence, an optimal treatment modality has not yet been established. Surgery has traditionally been the primary treatment modality for this disease. However, en bloc resection with clear margins is rarely feasible for OMM, owing to the complex anatomic structure of the oral and maxillofacial region. The prognosis of OMM remains extremely poor, despite aggressive treatment, and the 5-year overall survival (OS) is ~6.6–40% [1, 3–7]. Radiotherapy for head and neck mucosal malignant melanoma has been applied selectively because of tumor radioresistance. In a review of 815 head and neck mucosal malignant melanoma patients, Jethenamest *et al.* [8] found that the relative risk ratio of disease-specific survival for patients who received radiotherapy alone was 1.56 [95% confidence interval (CI), 1.35–1.72] as compared with patients who received surgery alone. Wushou *et al.* [9] reported a 3-year OS rate of 0% for 21 patients with OMM treated with radiotherapy alone.

In 1994, carbon ion radiotherapy (C-ion RT) was initiated at the National Institute of Radiological Sciences (NIRS). A carbon-ion beam provides a higher linear energy transfer (LET), has a unique depth–dose curve, the so-called Bragg peak, and deposits maximum energy at a designated depth [10, 11]. C-ion RT may be an effective treatment for mucosal malignant melanomas, which are known to be radioresistant, while sparing normal tissues. Yanagi *et al.* [12] reported the clinical results of 72 patients with locally advanced mucosal malignant melanoma of the head and neck treated with C-ion RT in a 16-fraction schedule. The 5-year local control (LC) rate was 84.1%, and the 3- and 5-year OS rates were 46.1% and 27.0%, respectively (median follow-up, 49.2 months). However, the study included only 7 patients with OMM and did not report detailed outcomes of these patients. To our knowledge, no clinical report has focused on patients with OMM treated with C-ion RT. The purpose of this study was to evaluate the long-term efficacy and safety of C-ion RT for OMM.

MATERIALS AND METHODS

Patients and tumor characteristics

This retrospective study was approved by the NIRS Ethical Committee on Human Clinical Research. From April 1997 through April 2013, 19 patients with OMM were treated with C-ion RT alone. All tumors were pathologically confirmed. The patients had medically inoperable tumors or declined surgery. Tumors were restaged in accordance with the criteria listed in the seventh edition of the tumour/node/metastasis (TNM) Staging System of the International Union Against Cancer (UICC). Before treatment, 14 patients had T3 disease and 5 had T4a disease. Three patients were classified as having N1 disease. All patients were classified as having M0. Patient ages ranged from 44 to 84 years (median, 69 years). Nine men and 10 women were included in the study. The hard palate was the most frequently involved oral subsite (11 cases, 57.8%), followed by the maxillary gingiva (4 cases, 21.1%), the tongue (2 cases, 10.5%), the mandible gingiva (1 case, 5.3%) and the lip (1 case, 5.3%). All patients received C-ion RT as the primary treatment.

Carbon-ion radiotherapy

The clinical relative biological effectiveness (RBE) value was determined to be 3.0 at the distal part of the Bragg peak [10]. The dose of carbon-ions was expressed in Gy (RBE), which was calculated by multiplying the physical dose by RBE [13]. C-ion RT was delivered in 16 fractions over a 4-week period, with four treatment days per week. The prescribed total dose was 57.6 Gy (RBE) in all patients.

Patients were positioned in customized cradles (Moldcare; Alcare, Tokyo, Japan) with the face immobilized with a low-temperature thermoplastic device (Shellfitter; Kuraray, Osaka, Japan). A specialized mouthpiece was used to reproduce the position of the upper and lower jaws, and to avoid unnecessary irradiation to the oral mucosa. A set of 2.5-mm-thickness computed tomography (CT) images were taken for treatment planning. The gross tumor volume (GTV), including the melanosis and positive lymph node, was defined as the gross extent of the tumor, as observed on intra-oral examination findings using endoscopy, CT images and magnetic resonance (MR) images. The clinical target volume (CTV) was defined as the GTV with a margin of 5–10 mm. The planning target volume (PTV) was defined by adding a margin of 2–3 mm to the CTV. Prophylactic lymph node irradiation was not performed. More than two portals were used to improve dose distributions in the jawbone. Three-dimensional treatment planning was performed using original HIPLAN software (NIRS, Chiba, Japan).

Evaluation and follow-up examinations

LC was defined as no evidence of tumor regrowth in the PTV or the entire oral mucosa. Regional control was defined as no evidence of regional lymph node metastases. Acute and late toxicities were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Regarding osteoradionecrosis (ORN), the teeth within the PTV and the maxilla or mandible volumes receiving > 50 Gy (RBE) (V50) were determined to be at-risk regions. Oncological status was followed using both MRI or CT and oral endoscopic examination every 2–3 months for the first 2 years and every 3–6 months thereafter.

Statistical analysis

Survival time was calculated from the initiation of treatment to the date of death or last confirmed date of survival. Rates of LC, OS and progression-free survival (PFS) were calculated using the Kaplan–Meier algorithm. Potential prognostic factors (gender, age, tumor site, and T, N classification) for LC and OS rates were evaluated using a log-rank test. The correlation of ORN with teeth within the PTV and V50 of the maxilla or mandible were evaluated using Fisher's exact and Mann–Whitney U tests, respectively. *P*-values <0.05 were considered statistically significant, and all statistical tests were two-sided. All statistical analyses were performed using JMP® version 11.0 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

The median follow-up period was 61 months (range, 8–190 months) for all patients, and 106 months (range, 55–190 months) for the five surviving patients. No patients were lost to follow-up.

Local control and survival

The 3- and 5-year LC rates for all 19 patients were both 89.4% [95% confidence interval (CI) = 66.3–97.3%; Fig. 1]. Three patients showed local failure: 1 had T3 disease and 2 had T4a disease. All local recurrences developed in the PTV. One patient received salvage surgery and showed no evidence of disease upon last follow-up. Four patients developed regional lymph node metastases after C-ion RT. Of these patients, two received salvage neck dissection and one received re-C-ion RT. Three patients who received salvage treatments for regional recurrence did not develop re-recurrence until the last follow-up. Of the 14 patients who died, 10 died of distant metastases (lungs, 4; brain, 3; liver, 2; and skin, 1) and 4 patients died of intercurrent causes without active disease (lung cancer, 1; gastric cancer, 1; heart failure, 1; and unknown, 1). Of the 10 patients who had distant metastases, 6 had T3 disease and 4 had T4a disease.

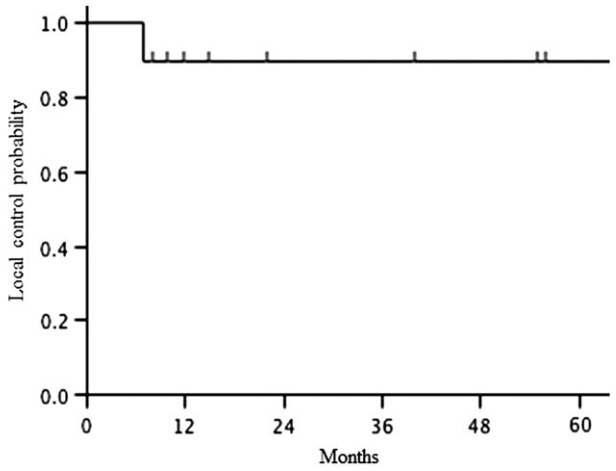

Fig. 1. Local control rate in the patient cohort ($n = 19$).

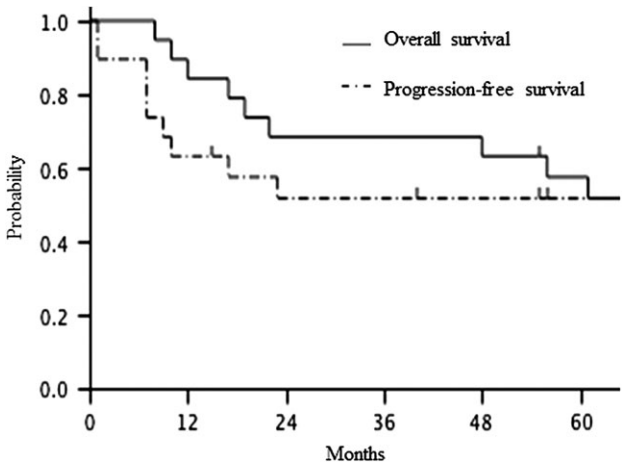

Fig. 2. Overall survival and progression-free survival rates in the patient cohort ($n = 19$).

The 3- and 5-year OS rates were 68.4% (95% CI = 45.2–85.1%) and 57.4% (95% CI = 35.0–77.2%), respectively. The 3- and 5-year PFS rates were both 51.6% (95% CI = 30.0–72.8%) (Fig. 2).

Prognostic factors for LC and OS are shown in Table 1. Univariate analysis showed that T classification was a significant prognostic factor for both LC and OS. The 5-year LC rates for T3 and T4a tumors were 100% and 60.0% ($P = 0.014$), respectively. The 5-year OS rates for T3 and T4a tumors were 71.4% and 20.0% ($P = 0.015$), respectively.

Acute and late reactions of normal tissues

With respect to acute toxicity, Grade 2 and 3 mucositis was observed in 11 and 8 patients, respectively. However, all patients completed the planned C-ion RT. A Grade 2 acute skin reaction was observed in only 1 patient; others were classified as having Grade 0–1 reactions. With respect to late toxicity, no greater than Grade 2 late mucosal and skin reactions were observed. Grade 2 ORN was observed in 3 patients (16%) and Grade 3 ORN that required sequestrectomy was observed in 4 patients (21%). All Grade 2 and 3 ORN developed from the alveolar bone and were localized in the high dose–irradiated volume. Of the 4 patients who received sequestrectomy, 3 maintained swallowing and speech functions through the use of maxillary prostheses, and 1 died of a distant metastasis shortly after developing ORN. Of the 12 patients who had teeth within the PTV, 3 developed Grade 2 ORN and 4 developed Grade 3 ORN; 7 patients without in-PTV teeth developed no greater than Grade 2 ORN. In-PTV teeth was demonstrated to be a significant risk factor for developing ORN ($P = 0.017$). The V50 of the maxilla or mandible was calculated using dose–volume histogram (DVH) data. The mean V50 of the maxilla or mandible was 12.5 ml (range, 0–23.4 ml) for patients with Grade 0–1, and 12.5 ml (range, 3.1–22.3 ml) for patients with Grade 2–3 ORN, respectively. No significant difference was detected between Grade 0–1 and Grade 2–3 ORN ($P = 0.8326$).

DISCUSSION

OMM treatment remains controversial, and there is no consensus regarding the optimal therapeutic approach. Several authors have reported that radical resection is the primary treatment choice. Complete surgical resection with clear margins is the mainstay of OMM management and may provide optimal results. However, it is often difficult for oral cavity tumors to achieve a tumor-free margin of 1–2 cm, which is typically required and accepted for cutaneous melanoma, because these are usually in close proximity to complex anatomical structures, such as the pharynx and the paranasal sinus [14]. Nicolas *et al.* [3] reported that complete resection was achieved in 57% (4/7) of OMM patients who underwent surgery. Meleti *et al.* [15] reported that complete resection of the primary OMM lesion was seen in 7 (64%) of the 11 patients who underwent surgery as an initial treatment. Moreover, incomplete surgical resection might be a harbinger of distant metastasis and affect the survival rate. In a series of 52 patients with mucosal melanoma of head and neck, Shuman *et al.* [16] reported that patients with negative surgical margins had significantly improved OS compared with those who did not have negative margins (median survival time, 56 vs 9 months; $P = 0.01$). Moreno *et al.* [17] reported that the risk of death and rate of distant metastasis were much higher in patients with mucosal melanoma of the head and neck with residual tumor at the margins than in those without. Consequently, the prognosis of patients treated with surgical resection remains poor because of the high incidence of positive surgical margins.

Liu *et al.* [18] reported a 3-year OS rate of 2.97% in a review of 230 patients treated with surgery for OMM. Tanaka *et al.* [4] observed a 5-year OS rate of 15.4% for 13 patients treated with surgery for OMM. Patel *et al.* [5] reported that the 5-year disease-specific survival rate of 19 patients treated with surgery for OMM was 40%. In the present study, the 5-year LC and OS rates were 89.6% and 57.4%, respectively. Our findings suggest that C-ion RT with a high biological effectiveness may be a viable treatment option for OMM. In addition, we consider that the PTV setting was clinically acceptable because no patient developed local failure outside of the PTV, although 3 patients developed local failure within the

Table 1. Univariate analysis for the LC and OS rates ($n = 19$)

Variable	Subgroup	No. of patients	5-year LC (%)	*P* value	5-year OS (%)	*P* value
Gender	Male	9	100	0.16	53.3	0.69
	Female	10	80.0		60.0	
Age (years)	≥68	9	100	0.12	48.0	0.91
	<68	10	77.8		66.7	
Tumor site	Palate	11	91.6	0.69	58.3	0.58
	Others	8	85.7		57.1	
T classification	T3	14	100	0.01	71.4	0.01
	T4a	5	60.0		20.0	
N classification	N0	16	87.5	0.51	62.5	0.99
	N1	3	100		33.3	

LC = local control, OS = overall survival.

PTV. Therefore, C-ion RT may be a particularly promising treatment for patients with tumors that are not resected with enough surgical margins because of the tumor size or location.

Several studies have reported a much higher incidence of lymph node metastasis for patients with OMM as compared with head and neck mucosal melanoma at other sites [19, 20]. This incidence was ~25–51% [3–5]. The question of whether prophylactic lymph node dissection is of great value remains controversial. However, Tanaka *et al.* [4] reported that in 18 patients with regional metastases after primary treatment for OMM, regional metastases were controlled in 17 patients (94%) after neck lymph node dissection. Treatment of lymph node metastases might be reserved for confirmed lymph node metastases and not performed prophylactically, despite the propensity of melanoma to metastasize. In this study, prophylactic irradiation of the cervical lymph nodes was not performed. Although 4 patients had lymph node metastases after C-ion RT, 3 received salvage treatment. These patients did not develop re-recurrence until the last follow-up.

ORN is a critical complication after C-ion RT for OMM. The hypofractionated schedule presented herein may not be the optimal strategy, particularly for ORN. In photon radiotherapy, a hypofractionated schedule generally increases the risk of late adverse effects when compared with a conventional schedule in cases for which the same total dose of radiation is administered. This principle may also be applied in C-ion RT; however, there are no clinical data for C-ion RT comparing a hypofractionated schedule with a conventional schedule. With respect to LC, Wada *et al.* [21] reported that, in a series of 31 patients with mucosal melanoma of the head and neck, a hypofractionated schedule using a dose of 3 Gy or more was effective in gaining LC. We have previously reported that the presence of teeth within the PTV [hazard ratio (HR) = 11.3] and V50 (HR = 1.15) of the maxilla were independent risk factors for the development of ORN after C-ion RT [22]. In the present study, the presence of teeth within the PTV was significantly associated with the development of ORN, although the V50 of the maxilla or mandible was not related to the degree of ORN. In conventional radiotherapy, it is generally accepted that all teeth within the PTV with a questionable prognosis, such as advanced caries, periodontal disease, impacted third molars, and teeth close to the tumor, require extraction before radiotherapy [23]. These criteria might also be applied to C-ion RT. Several patients who developed Grade 2–3 ORN in the present study had teeth with a poor prognosis within the PTV during C-ion RT.

It has previously been reported that the use of maxillary prostheses restored the functions of speech and swallowing for patients who received maxillectomy [24, 25]. Davison *et al.* [26] reported that a successful prosthesis for functional restoration of the maxillary defect utilizes the remaining palate and dentition as much as possible to maximize the support, stability and retention of an obturator bulb. An unfavorable situation for restoring oral function occurs when the size of a defect is so large that it overwhelms the remaining structures that stabilize the prosthesis over the defect. ORN after C-ion RT was limited because of its favorable dose-localized properties. Consequently, of the 4 patients with Grade 3 ORN, 3 maintained the functions of speech and swallowing through the use of maxillary prostheses.

By means of univariate analysis, a T4a tumor was found to be a risk factor for both LC and OS. The 5-year LC and OS rates for patients with T4a tumors were 60% and 20%, respectively. Dose escalation for T4a tumors may improve the LC rate because all of the local recurrences developed in the PTV. However, the delivery of a higher dose may result in frequent ORN. Of the 5 patients with T4a, 4 (80%) died of distant metastases and 1 died of unknown reasons. To improve the OS of patients with advanced disease, effective systemic therapy is necessary. Therefore, dose escalation should be carefully considered.

Recently, the focus of research for malignant disease, such as melanoma, has shifted to the immune system, which has important roles in both tumor progression and tumor elimination. Ipilimumab [a cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4)

checkpoint inhibitor] and nivolumab [a programmed death 1 (PD-1) checkpoint inhibitor] have been shown to have complementary activity in melanoma [27, 28]. Larkin *et al.* [29] found that the combination of PD-1 and CTLA-4 blockade was more effective compared with either agent alone. Immunotherapy may be a feasible treatment option for patients with metastatic mucosal melanoma [27, 30]. In the present study, no patient received these immunotherapies after developing distant metastases. These new systemic therapies may improve the survival of patients who develop distant metastases after C-ion RT. In addition, Twyman-Saint Victor *et al.* [31] reported that radiotherapy acted synergistically with anti-CTLA4 to systemically enhance melanoma response in a previous clinical trial. C-ion RT, when applied with concurrent immunotherapy, may not only show the local effect of the irradiated field but may enhance the systemic effect of immunotherapy for the potential metastases or macroscopic metastases.

This study is subject to inherent limitations owing to its small sample size and single-institution, retrospective design, although all of the patients had been enrolled prospectively and were treated using a uniform C-ion RT protocol.

CONCLUSION

C-ion RT proved promising as a local treatment with acceptable toxicity for OMM. Moreover, management for ORN might improve the quality of life of patients treated with C-ion RT. However, to clarify the efficacy of C-ion RT for OMM, further studies enrolling large numbers of patients and using carbon ion beams are necessary.

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CONFLICT OF INTEREST

There is no conflict of interest or any assistance to be disclosed for any of the authors.

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