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Original Article

Feasibility of Re-irradiation using carbon ions for recurrent head and neck malignancies after carbon-ion radiotherapy

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ABSTRACT

Background and purpose: Locoregional recurrence after carbon-ion radiotherapy (CIRT) for primary head and neck malignancies, such as malignant mucosal melanoma, adenoid cystic carcinoma, and sarcoma, occurs occasionally. However, the treatment options are limited. We report on the toxicity and efficacy of re-irradiation using carbon ions for recurrent head and neck malignancies after CIRT.
Materials and methods: Data of 48 patients with recurrent head and neck malignancies treated with re-irradiation with CIRT at our institution (2007–2016) were retrospectively analyzed. Twenty-one patients (43.8%) had malignant mucosal melanoma, 17 (35.4%) had adenoid cystic carcinoma, six (12.5%) had bone and soft tissue sarcomas, and four patients (8.3%) had other disease types. Tumor recurrences at re-irradiation were located in the paranasal cavity (n = 18, 37.5%), nasal cavity (n = 9, 18.8%), nasopharynx (n = 4, 8.3%), orbit (n = 3, 6.3%), cavernous sinus (n = 3, 6.3%), and at other sites (n = 11, 22.9%). The median dose of initial CIRT and that at re-irradiation were 57.6 Gy and 54.0 Gy (relative biological effectiveness [RBE]), respectively. None of the patients received concurrent chemotherapy.
Results: The median follow-up period after re-irradiation was 27.1 months. Five patients (10.4%) developed Grade 3 acute toxicities and 18 (37.5%) developed Grade ≥3 late toxicities, including Grade 5 central nervous system necrosis in one patient. The 2-year local control, locoregional control, progression-free survival, and overall survival rates were 40.5, 33.5%, 29.4%, and 59.6%, respectively.
Conclusion: Re-irradiation using carbon ions may be a reasonable treatment option with tolerable toxicity for patients with recurrent head and neck malignancies after CIRT.

Carbon-ion radiotherapy (CIRT) is a high linear energy transfer radiotherapy with good dose-localizing properties that is being gradually used across Europe and Asia [1]. It delivers a high dose of radiation to the target tissue, while avoiding the adjacent critical organs-at-risk. Consequently, promising outcomes of CIRT for inoperable radioresistant malignancies such as malignant mucosal melanomas, adenoid cystic carcinomas (ACC), adenocarcinomas, and head and neck sarcomas have been reported [2–5]. Koto et al. reported 2-year local control (LC) and overall survival (OS) rates of 83.9% and 69.4%, respectively, in malignant mucosal melanoma of the head and neck treated with CIRT, with 33 patients (13%) experiencing Grade ≥3 toxicities and reportedly no Grade 5 toxicities [2]. Sulaiman et al. reported 2-year LC and OS rates of 88% and 94% for CIRT in ACC of the head and neck, respectively. They reported experienced Grade ≥3 late toxicities in 43 patients (15%) [4]. These outcomes illustrated that CIRT can achieve high LC rates with acceptable toxicity levels [2]. However, local recurrence and regional lymph node metastasis can occasionally occur after CIRT. Provided the recurrence is resectable, surgery is generally considered the first treatment of choice. However, many patients who receive CIRT are inoperable due to their locally advanced malignancies, refusal based on functional and cosmetic defects associated with surgery, or other comorbidities. The alternative treatment is chemotherapy. For malignant mucosal melanoma, new drugs such as immunologic checkpoint blockers and

Abbreviations: CIRT, carbon-ion radiotherapy; RBE, relative biological effectiveness; ACC, adenoid cystic carcinomas; LC, local control; OS, overall survival; PTV, planning target volume; MRI, magnetic resonance imaging; CT, computed tomography; PET, positron emission tomography; GTV, gross tumor volume; EQD2, the equivalent dose in 2-Gy fractions; LRC, locoregional control; PFS, progression-free survival; CI, confidence interval; CAP, cisplatin, doxorubicin, and cyclophosphamide.

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molecular targeted drugs have been clinically introduced, though the reported response rates are low (12.0–37.1%), and sustained control is uncommon [6,7]. Effective chemotherapeutic regimens for malignancies like ACC, adenocarcinoma, and sarcoma have yet to be established. Therefore, treatment options are limited and re-irradiation with CIRT is sometimes required.

To date, only one study on re-irradiation using carbon ions for recurrent ACC of the head and neck has been published, with a short-term follow-up period of 14 months [8]. The authors reported estimated 2-year LC and OS rates of 47.4% and 63.3%, respectively, serious late toxicity incidence of 6.5%, and no radiation-induced deaths. However, the cumulative incidence of severe late toxicity is generally deemed to be higher with time from a previously reported Radiation Therapy Oncology Group analysis [9]. Therefore, the abovementioned incidence of severe late toxicity may have been underestimated. To date, the long-term safety and efficacy profiles of re-irradiation with CIRT for head and neck malignancies are unclear. In this study, we retrospectively analyzed the clinical outcomes in patients treated with re-irradiation using carbon ions for locoregionally recurrent head and neck malignancies after CIRT.

Materials and methods

Eligibility criteria

This study was approved by the Institutional Review Board of our institution and conducted in accordance with the Helsinki Declaration. This study is registered with UMIN-CTR (http://www.umin.ac.jp/ctr/index-j.htm), identification number 000038617. All patients provided informed consent, authorizing the use of their personal information for research purposes. Treatment definitions were as follows: re-irradiation, treatment with overlap between the initial CIRT planning target volume (PTV) and the second CIRT PTV; third irradiation, treatment with overlap between the first, second, and third CIRT PTVs.

We performed a comprehensive clinical trial of re-irradiation with CIRT for locoregionally recurrent malignancies, and included a wide variety of malignancies such as malignancies of the head and neck, lung, rectum, prostate, and pancreas. The common eligibility criteria were: a performance status of 0–2; measurable tumors; no systemic therapy such as chemotherapy within 1 month of commencing re-irradiation with CIRT; and an estimated life expectancy of >6 months at re-irradiation initiation.

We consulted head and neck surgeons before selecting re-irradiation with CIRT, and recommended other treatments including surgery or chemotherapy if they were deemed more suitable for the patient. When other treatments were not applicable or if the patient refused them for cosmetic or functional reasons, we administered re-irradiation. Patients with multiple metastases or other primary tumors were excluded. We conducted a retrospective survey of all patients who were treated with re-irradiation using carbon ions for recurrent head and neck malignancies after CIRT at our institution during October 2007–February 2016 using data of this comprehensive clinical trial.

Patients

Of 48 patients who met the inclusion criteria, seven (14.6%) received a third course of irradiation. Recurrent head and neck malignancies were diagnosed by biopsies and/or magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET)/CT. "In-field" and "marginal" recurrences after initial irradiation were defined as recurrent lesions inside or outside the initial PTV, respectively.

All tumors were classified according to the International Union Against Cancer tumor-node-metastasis classification (seventh edition) [10]. Acute toxicity was defined as that occurring within 3 months from the commencement of re-irradiation with CIRT. Acute and late toxicities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.0) [11]. We collected information about Grade $\geq$2 acute and late toxicities.

Carbon-ion radiotherapy

Patients were fixed using an individually tailored immobilization device (Moldcare; Alcare, Tokyo, Japan; Shellfitter; Kuraray, Osaka, Japan) and CT images were taken in the supine position.

Locoregionally recurrent head and neck malignancies were contoured as gross tumor volume (GTV) on CT images using contrast-enhanced CT, MRI, and PET/CT images as a reference. Clinical target volume (CTV) was basically defined as GTV plus 0–5 mm margin. In cases where CTV was close to the organs-at-risk, CTV was reduced. PTV was defined as CTV plus a 2 mm safety margin to account for positioning errors. Relative dose constraints at re-irradiation were as follows: brainstem, 30 Gy (relative biological effectiveness [RBE]); spinal cord, 30 Gy (RBE); and, wherever possible, optic nerve, 40 Gy (RBE).

The prescribed dose for initial irradiation with CIRT ranged from 48.0 Gy (RBE) to 70.4 Gy (RBE) in 12–16 fractions. The most commonly prescribed dose was 57.6 Gy (RBE) in 16 fractions (29 patients, 60.4%), followed by 64 Gy (RBE) in 16 fractions (8 patients, 16.7%). Meanwhile, the prescribed dose for re-irradiation with CIRT ranged from 40.0 Gy (RBE) to 64.0 Gy (RBE) in 8–16 fractions. The most commonly prescribed dose was 52.8 Gy (RBE) in 12 fractions (21 patients, 43.8%), followed by 57.6 Gy (RBE) in 12 fractions (17 patients, 35.4%). All doses were administered four times a week for 2–4 weeks. The cumulative dose prescribed to patients was calculated as the equivalent dose in 2-Gy fractions (EQD2) based on the linear and quadratic model using $\alpha/\beta = 10$. In our cohort, the median value (minimum–maximum) for EQD2 was 136.3 (115.3–159.1) Gy (RBE). Maximum doses of OAR (optic nerve and brainstem) were calculated as EQD2 according to the linear and quadratic model using $\alpha/\beta = 2$.

The total dose was applied to the isocenter, and the PTV was enclosed conformally at the minimum by the 90.0% isodose line with the prescribed dose. Three-dimensional treatment planning was performed using the in-house HIPLAN software (NIRS, Chiba, Japan) until May 2012, and XiO-N (ELEKTA, Stockholm, Sweden; Mitsubishi Electric, Tokyo, Japan) from April 2012 onwards. Irradiation was performed in 2–5 fields with 250 or 290 MeV carbon ions. For each irradiation, the patient's position was confirmed using a computer-aided online positioning system.

Follow-up

After treatment, follow-up observations were performed every 3 months if serious complications had not occurred. During each follow-up observation, CT or MRI, or, if necessary, PET was performed.

Statistical analyses

LC, locoregional control (LRC), progression-free survival (PFS), and OS rates were calculated using the Kaplan–Meier method. All parameters were defined as intervals starting from date of re-irradiation commencement; LC was defined till the date of local tumor regrowth in the first, second, or third PTV or the last follow-up; LRC was defined till the date of local or regional relapse or the last follow-up; PFS was defined till the date of disease pro-

gression at any site, death from any cause, or the last follow-up; OS was defined till death or the last follow-up.

Univariate and multivariate analyses were performed to identify potential prognostic factors for LC, PFS, and OS among different subgroups using the log-rank test. The patients were divided into subgroups according to the median values of age, interval between initial irradiation and re-irradiation, re-irradiation dose, and GTV at re-irradiation. Multivariate analysis was performed using a Cox proportional hazards model. A two-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were conducted using JMP statistical software (version 14.0; SAS Institute Inc., Cary, NC, USA).

Results

All 48 patients completed re-irradiation with CIRT. The patient and tumor characteristics are summarized in Table 1. Twenty-one patients (43.8%) had malignant mucosal melanoma, 17 (35.4%) adenoid cystic carcinoma, six (12.5%) bone and soft tissue sarcomas, and four (8.3%) had other disease types. The recurrent tumors at re-irradiation were located in the paranasal cavity ($n = 18$, 37.5%), nasal cavity ($n = 9$, 18.8%), nasopharynx ($n = 4$, 8.3%), orbit ($n = 3$, 6.3%), cavernous sinus ($n = 3$, 6.3) and other sites ($n = 11$, 22.9%). Five patients (10.4%) had clinical stage I disease at re-irradiation, one (2.1%) stage II, 11 (22.9%) stage III, and 27 (56.3%) stage IV disease. Four patients with lacrimal gland carcinoma could not be classified because grouping by stage is not recommended by the International Union Against Cancer tumor-node-metastasis classification (seventh edition) [10]. The median interval between initial irradiation and re-irradiation was 24.2 (range, 4.5–112.5) months. The median follow-up duration after re-irradiation for all patients and survivors was 27.1 (range, 6.2–113.7) months and 49.9 (range, 11.0–113.7) months, respectively. At re-irradiation, 21 patients (43.8%) had in-field recurrence and 27 patients (56.2%) had marginal recurrence. None of the patients received with concurrent chemotherapy.

Regarding acute toxicities, four patients developed Grade 3 acute mucositis and one developed Grade 3 dermatitis (Table 2). Regarding late toxicities, one patient developed Grade 5 and another developed Grade 4 central nervous system necrosis (radiation-induced brain necrosis). This patient who developed Grade 5 brain necrosis underwent re-irradiation for recurrence in the petrous bone after CIRT for ACC of the right submandibular gland. Nine months later, brainstem necrosis and edema were diagnosed, and despite immediate corticosteroid administration, the patient died from central nervous necrosis. The maximum dose of brainstem in this patient was 0.96 Gy (RBE) (1.3 Gy [EQD2]) at initial irradiation and 51.7 Gy (RBE) (82.7 Gy [EQD2]) at re-irradiation.

Other toxicities included Grade 4 optic nerve disorder (loss of vision in nine patients), Grade 4 infection (meningitis in one patient), and Grade 4 arterial injury (false aneurysm rupture in the carotid artery in one patient). In total, 18 patients (37.5%) developed Grade $\geq$3 late toxicities.

Following the third irradiation, one patient developed Grade 2 acute dermatitis, two developed Grade 2 central nervous system necrosis, and one developed Grade 2 osteonecrosis. No other acute or late toxicities were observed.

The maximum doses of organs at risk are summarized in Table S1. The median values of maximum doses of the contralateral optical nerve at initial irradiation, re-irradiation, or third irradiation were 22.5, 2.9 Gy, or 1.0 Gy (RBE) (EQD2), respectively; of the chiasm 10.8, 1.4, or 3.1 Gy (RBE) (EQD2), respectively; and of the brainstem 16.6, 5.1, or 5.1 Gy (RBE) (EQD2), respectively.

Table 1
Patient and tumor characteristics.

Factors	Patients ($N = 48$)
Sex, *N* (%)	
Female	28 (58.3)
Male	20 (41.7)
PS, *N* (%)	
0	38 (79.2)
1	10 (20.8)
Primary site at initial irradiation, *N* (%)	
Carcinoma and melanoma	
Nasal cavity	18 (37.5)
Paranasal cavity	13 (31.3)
Lacrimal gland or orbit	4 (8.3)
Nasopharynx	3 (6.3)
Palate	2 (4.2)
Submandibular gland	1 (2.1)
Tongue	1 (2.1)
Bone and soft tissue sarcoma	
The first or second cervical vertebra	2 (4.2)
Temporal or occipital bone of the skull	2 (4.2)
Orbit	1 (2.1)
Maxillary bone	1 (2.1)
Clinical Stage at initial irradiation, *N* (%)	
I	0
II	4 (8.3)
III	5 (10.4)
IV	33 (68.8)
Unknown	6 (12.5)
Histology, *N* (%)	
Malignant mucosal melanoma	21 (43.8)
Adenoid cystic carcinoma	17 (35.4)
Bone and soft tissue sarcoma	6 (12.5)
Others	4 (8.3)
Age at initial irradiation	
Median, years (range)	56.5 (26–85)
Initial irradiation dose (Gy (RBE))	
Median (range)	57.6 (48.0–70.4)
Median interval between initial irradiation and re-irradiation, months (range)	24.2 (4.5–112.5)
Median follow-up from re-irradiation, months (range)	27.1 (6.2–113.7)
Site of failure at re-irradiation, *N* (%)	
In-field	21 (43.8)
Marginal	27 (56.2)
Re-irradiation dose (Gy (RBE))	
Median (range)	54.0 (40.0–64.0)
TNM classification at re-irradiation, *N*(%)	
rT1N0M0	6 (12.5)
rT2N0M0	1 (2.1)
rT3N0M0	9 (18.8)
rT4N0M0	29 (60.4)
rT4N0M1	2 (4.2)
rT0N1M0	1 (2.1)
Clinical stage at re-irradiation, *N* (%)	
I	5 (10.4)
II	1 (2.1)
III	11 (22.9)
IV	27 (56.3)
Others	4 (8.3)
Site of re-irradiation, *N* (%)	
Carcinoma and melanoma	
Paranasal cavity	18 (37.5)
Nasal cavity	9 (18.8)
Nasopharynx	4 (8.3)
Orbit	3 (6.3)
Cavernous sinus	3 (6.3)
Jawbone	1 (2.1)
Submandibular gland	1 (2.1)
Tongue	1 (2.1)
Pterygoid muscle	1 (2.1)
Frontal bone	1 (2.1)

Table 1 (*continued*)

Factors	Patients (*N* = 48)
Bone and soft tissue sarcoma	
Temporal or occipital bone of the skull	3 (6.3)
The first or second cervical vertebra	2 (4.2)
Sphenoid bone	1 (2.1)
Operability at re-irradiation, *N* (%)	
Inoperable	39 (81.3)
Operable	9 (18.7)
GTV at re-irradiation (ml)	
Median (range)	10.4 (0.5–89.5)

Abbreviations: PS, performance status; RBE, relative biological effectiveness

Table 2
Toxicity.

Grade	2	3	4	5
Acute				
Mucositis	14	4	0	0
Dermatitis	1	1	0	0
Conjunctivitis	1	0	0	0
Nausea	1	0	0	0
Middle ear inflammation	1	0	0	0
Hearing impaired	1	0	0	0
Late				
Central nervous system necrosis	7	1	1	1
Optic nerve disorder	0	2	9	0
Infection	7	6	1	0
Arterial injury	0	0	1	0
Cataract	0	1	0	0
Osteonecrosis	7	0	0	0
Trismus	4	1	0	0
Dysphagia	1	1	0	0
Mucositis	4	0	0	0
Middle ear inflammation	2	0	0	0
Hearing impaired	1	0	0	0
Soft tissue necrosis	1	0	0	0
Central hypothyroidism	1	0	0	0

By the end of the follow-up, 10 patients survived, 29 died of cancer and eight of unrelated causes. One patient died of treatment-related causes. The 2-year LC, LRC, PFS, and OS rates following re-irradiation were 40.5% (95% confidence interval [CI]: 25.6%–57.3%), 33.5% (95% CI: 20.4%–49.7%), 29.4% (95% CI: 17.8%–44.4%), and 59.6% (95% CI: 45.1%–72.6%), respectively (Fig. 1a–d). The median PFS time was 10.0 months (0–83.4 months). At the time of first relapse, 16 local recurrences, 2 regional recurrences, 13 distant metastases, 5 local recurrences + distant metastases, 4 regional recurrences + distant metastases, and 1 local + regional recurrence were detected. In total, recurrences were observed in 41 patients.

Multivariate analysis revealed that site of failure at re-irradiation was a significant prognostic factor of LC ($P = 0.030$) and PFS ($P = 0.042$), and that the interval between initial irradiation and re-irradiation was a significant predictor of PFS ($P = 0.036$) and OS ($P = 0.002$) (Supplementary Table S2). The 2-year LC and PFS rates of in-field recurrence *versus* marginal recurrence as site of failure at re-irradiation were 52.8% *versus* 28.2%, and 38.6% *versus* 19.1%, respectively. The 2-year PFS and OS rates of an interval between initial irradiation and re-irradiation of <24 months *versus* ≥24 months were 20.8% *versus* 38.3%, and 37.5% *versus* 82.7%, respectively (Supplementary Fig. S1a–d).

Discussion

CIRT is a promising treatment option for inoperable patients who had locally advanced radioresistant malignancies such as malignant mucosal melanoma, ACC, and sarcoma [2–4]. However, patients with locoregional recurrence after CIRT are rarely candidates for surgery. Therefore, new approaches, such as re-irradiation with CIRT, are required for effective and safe treatment of these patients. To date, only one study has reported on the use of re-irradiation with CIRT for head and neck ACC, although the follow-up period was short (14 months) [8]. To the best of our knowledge, we are the first to evaluate the efficacy of re-irradiation with CIRT for locoregionally recurrent head and neck malignancies including malignant mucosal melanomas and sarcomas. We also evaluated late toxicities in our cohort (median follow-up for all patients, 27.1 months and for survivors, 49.9 months). Our findings demonstrated that re-irradiation with CIRT may achieve moderate local control and survival with tolerable toxicity.

Severe toxicities, of Grade 5 and Grade 4 central nervous necrosis developed in one patient each. In both patients, the disease presented in the base of the skull (petrous bone or the orbit); the target volume was thus close to the brain, and high dose re-irradiation to the brain was unavoidable. It is difficult to compare the acute and late toxicity outcomes of the present study with those of previous studies of photon radiotherapy, because of differences in the sites of re-irradiation [12,13]. There was one study on re-irradiation with proton therapy in 61 patients with recurrent cancer in the orbital, nasopharyngeal, and ethmoidal regions. The median follow-up was 15.2 months and the study reported acute and late Grade ≥3 toxicity incidences of 14.7% and 24.6%, respectively, including three treatment-related deaths (Grade 5) [14]. Meanwhile, Jensen et al. reported on the use of carbon ions re-irradiation for recurrent ACC of the head and neck after CIRT [8]. During the 14-month follow-up period, they observed no Grade ≥3 acute toxicity and eight serious radiation late toxicities (15.4%) in the 52 patients, although the grading scale of the late toxicities in that study was not completely available. In the present study, five patients (10.4%) developed Grade 3 acute toxicity and no patient developed Grade ≥4 acute toxicity. Eighteen patients (37.5%) developed Grade ≥3 late toxicities including nine anticipated vision losses, who had experienced tumor recurrence abutting or surrounding the optic nerve. All were properly informed about potential re-irradiation-induced vision loss prior to obtaining consent for treatment. These acute and late toxicity profiles are comparable to those of proton therapy. They may be higher than that reported by Jensen et al. who had also used carbon ion. Such difference might be due to a longer follow-up period in our study (median follow-up for all patients, 27.1 months and for survivors, 49.9 months *versus* 14 months), and a shorter interval between the initial irradiation and re-irradiation our cohort compared to that reported by Jensen et al. (median interval: 24.2 months *versus* 61 months). In the future, newer techniques such as scanning irradiation or intensity-modulated particle therapy may improve dose distribution and reduce the doses of organs-at-risk (brain and cranial base), leading to a decreased incidence of severe toxicity [15–17]. Additionally, patients with recurrent lesions adjacent to the brain, optic nerve, or internal carotid artery that have already been treated with CIRT are considered as being at high risk for re-irradiation with CIRT. In patients with the recurrent lesions adjacent to the optic nerve or the brain, except the brainstem, their adaptation must be determined cautiously. In case where the recurrent tumor is located at the base of the skull and is adjacent to the brainstem or internal carotid artery, any adaptation should be avoided because of the high risk of extensive bleeding or treatment-related death.

For patients with inoperable recurrent head and neck malignancies after CIRT, systemic therapy can be administered as salvage therapy. Although our study included various histologic types of head and neck cancer, the most common type was malignant mucosal melanoma (43.8%), followed by adenoid cystic carcinoma (35.4%). D'Angelo et al. reported that in 86 malignant mucosal mel-

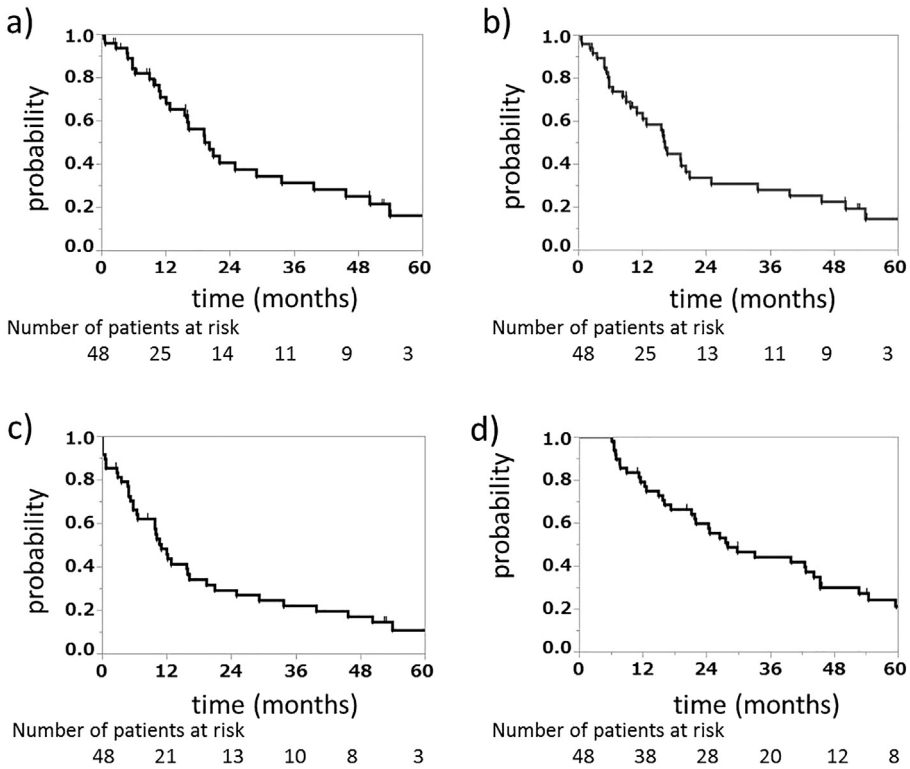

Fig. 1. Kaplan–Meier's curves of (a) local control, locoregional control (b), progression-free survival (c), and overall survival (d) following carbon-ion radiotherapy for re-irradiation of locally recurrent head and neck tumors.

anoma patients treated with nivolumab alone or combined with ipilimumab, the median PFS was 3.0, 5.9, and 2.7 months for those who received nivolumab monotherapy, combination therapy, and ipilimumab monotherapy, respectively [7]. The most effective regimen for ACC is a combination of cisplatin, doxorubicin, and cyclophosphamide (CAP), although the standard regimen has not been determined [18]. Licitra et al. showed that CAP regimen provided an overall response rate of 27% (LC, PFS, and OS not reported) [19]. Meanwhile, Jensen et al. reported on the use of re-irradiation with carbon ions for recurrent ACC of the head and neck after CIRT, and reported estimated 2-year LC and OS rates of 47.4% and 63.3%, respectively [8]. The present study illustrated that the median PFS time was 10.0 months and the 2-year LC and OS rates were 40.5% and 59.6%, respectively. These findings indicated that re-irradiation with CIRT may be superior to salvage systemic therapy.

Several studies have shown that a shorter interval between initial irradiation and re-irradiation using photon radiotherapy for head and neck cancers was a poor prognostic factor of OS [13,20]. Similarly, our multivariate analysis showed that an interval between initial irradiation and re-irradiation of <24 months was a significantly poor predictor of PFS and OS after re-irradiation with CIRT. This may be because patients with aggressive head and neck malignancies with early locoregional recurrence were included into the group with an interval between initial irradiation and re-irradiation of <24 months. Additionally, we also found that patients with marginal failure at re-irradiation showed significantly poor prognosis for LC and PFS. This may signify a tumor with a tendency to invade and spread locoregionally.

Total dose and fractionation in this study were varied, and were chosen in consideration of the proximity of the organs-at-risk, the tumor size, and the patient's condition.

Our study has several limitations. First, our study was a single-center retrospective analysis with a small sample size. Therefore, there remains the possibility of selection bias. However, our study is one of few studies on re-irradiation with CIRT for radioresistant malignancies such as ACC or malignant mucosal melanoma. Second, various radiation doses and fractions were used in our study, which may have influenced tumor control and the occurrence and severity of toxicities. We are now performing a prospective registry study of a 16-fraction schedule re-irradiation procedure using carbon ions for recurrent head and neck malignancies.

In conclusion, our findings suggest that re-irradiation with CIRT is a reasonable treatment option with tolerable toxicity for recurrent head and neck malignancies after initial CIRT. In future, large-scale multicenter trials are warranted.

Declaration of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.04.007.

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