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Prospective observational study of carbon-ion radiotherapy for non-squamous cell carcinoma of the head and neck

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Key words

Carbon-ion radiotherapy, head and neck tumor, non-squamous cell carcinoma, particle beam therapy, prospective study

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To evaluate the efficacy and safety of carbon-ion radiotherapy for non-squamous cell carcinoma of the head and neck, 35 patients were enrolled in this prospective study. The primary end-point was the 3-year local control rate, and the secondary end-points included the 3-year overall survival rate and adverse events. Acute and late adverse events were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0. The median follow-up time for all patients was 39 months. Thirty-two and three patients received 64.0 Gy (relative biological effectiveness) and 57.6 Gy (relative biological effectiveness) in 16 fractions, respectively. Adenoid cystic carcinoma was dominant (60%). Four patients had local recurrence and five patients died. The 3-year local control and overall survival rates were 93% and 88%, respectively. Acute grade 2–3 radiation mucositis (65%) and dermatitis (31%) was common, which improved immediately with conservative therapy. Late mucositis of grade 2, grade 3, and grade 4 were observed in 11, one, and no patients, respectively. There were no adverse events of grade 5. Carbon-ion radiotherapy achieved excellent local control and overall survival rates for non-squamous cell carcinoma. However, the late mucosal adverse events were not rare, and meticulous treatment planning is required. Trial registration no. UMIN000007886.

The major pathological type of head and neck cancer is squamous cell carcinoma, for which the standard treatment is multimodal therapy including surgery and concurrent chemoradiotherapy.[1] Although non-squamous cell carcinoma (NSCC) is usually resistant to photon therapy and chemotherapy, carbon-ion radiotherapy is reportedly efficacious for these refractory diseases.[2,3] Carbon-ion radiotherapy provides highly concentrated dose distributions because of the Bragg peak. Furthermore, carbon-ion is classified as high linear energy transfer radiation, offering high biological effectiveness.[4] Carbon-ion radiotherapy has been applied at the National Institute of Radiological Sciences (NIRS) (Chiba, Japan) since 1994.[3,4] At NIRS, carbon-ion radiotherapy has shown excellent outcomes for inoperable patients with NSCC, such as adenoid cystic carcinoma,[5] adenocarcinoma,[6] and basal cell adenocarcinoma.[7] However, these reports have all originated from a single institution, and some clinicians have expressed concerns that reported outcomes may not be reproducible at other facilities. Therefore, we undertook a prospective trial to establish the efficacy and safety of carbon-ion radiotherapy for NSCC of the head and neck.

Materials and Methods

Patients and tumor characteristics. All patients with NSCC were prospectively treated following a protocol for carbon-ion radiotherapy approved by our Institutional Review Board. The inclusion criteria were as follows: (i) histologically confirmed NSCC; (ii) N0−1 M0; (iii) measurable tumor; (iv) age 16–80 years; and (v) performance status 0−2. The exclusion criteria were as follows: (i) history of irradiation to the head and neck; (ii) history of chemotherapy within 1 month before carbon-ion radiotherapy; (iii) uncontrolled infection; (iv) severe concomitant disease; and (v) active double cancers. All biopsy specimens were centrally re-evaluated by one pathologist (J.H.) at Gunma University Hospital (Maebashi, Japan). The current study did not enroll patients with malignant melanoma or sarcoma because they were being accrued for other prospective studies. Evaluations included physical examination, laryngoscopy, computed tomography (CT), MRI, and 18-fluorodeoxyglucose PET within 1 month before treatment. The primary end-point was the 3-year local control rate. Secondary end-points included the 3-year overall survival (OS) rate, progression-free survival (PFS) rate, health-related quality of life

(QOL), and adverse events. Acute and late adverse events were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0.

Treatment planning. All patients provided written informed consent before carbon-ion radiotherapy. Briefly, patients were positioned in customized cradles (Moldcare; Alcare, Tokyo, Japan) and immobilized using thermoplastic shells (Shellfitter; Kuraray, Osaka, Japan). A mouthpiece was created to maintain the lower jaw's position. Computed tomography simulation (thickness, 2 mm) was acquired for treatment planning, and MRI was carried out for reference imaging. The XiO-N system (Elekta, Stockholm, Sweden) was used for treatment planning. Delineation of the gross tumor volume (GTV) was based on contrast-enhanced MRI. Basically, the clinical target volume (CTV) had at least a 5-mm margin around the GTV. Clinical target volume 1 included whole anatomic sites, such as the nasal cavity and maxillary sinus, where the tumors were located, while CTV2 was limited around the GTV. Planning target volume (PTV) 1 and PTV2 had 2-mm margins around CTV1 and CTV2. Clinical target volume and PTV margins were modified as necessary when the targets were close to organs at risks (OARs). Based on previous studies, the dose constraints of OARs were defined as follows: maximum dose of 30 Gy (relative biological effectiveness [RBE]) for the spinal cord,[6] maximum dose of 57 Gy (RBE) for the optic nerve,[8] and 60 Gy (RBE) <20 cm^2 for the skin.[9] The radiation dose was prescribed at the isocenter of the PTVs. The PTVs were encompassed by the 95% isodose line of the prescribed dose. The dose of carbon-ion radiotherapy was expressed as Gy (RBE). Although 64.0 Gy (RBE) was generally administered in 16 fractions, when tumors were close to skin or mucosa, 57.6 Gy (RBE) was administered in 16 fractions. The PTV1 was irradiated with 36 Gy (RBE) and PTV2 was irradiated with the remaining dose.

Quality of life. Health-related QOL was evaluated using short form (SF)-8 questionnaires,[10] which include eight domains that are summarized by the physical components score and mental components score (MCS). Higher numerical scores indicate better QOL. The SF-8 questionnaires were completed before and at 1, 3, 6, 12, and 24 months after treatment.

Follow-up. Patients were seen every month for the first 6 months and every 3 months thereafter. Magnetic resonance imaging and CT were carried out alternately every 3 months, and 18-fluorodeoxyglucose PET was carried out every year.

Statistical analysis. The 3-year local control rate of photon therapy for NSCC was estimated to be 65%,[11] and that of carbon-ion radiotherapy was expected to be 90%. To detect a difference between these treatments by using α error of 0.05 and β error of 0.20, 23 patients were required. Considering the possibility of patient dropout and the presence of various pathologies, 35 patients were deemed necessary for this study. Local control, PFS, and OS rates were estimated using the Kaplan–Meier method and compared using log–rank tests. Differences between groups were assessed using *t*-tests. Statistical significance was defined as $P < 0.05$. Statistical analyses were undertaken using IBM SPSS Statistics for Mac, version 23.0 (SPSS, Armonk, NY, USA). Local control was defined as no evidence of tumor regrowth in the PTV. Furthermore, local control was followed until death, and patients were not censored even when they developed lymph node or distant metastasis.

Results

Between June 2010 and November 2014, 35 patients with NSCC prospectively underwent carbon-ion radiotherapy at Gunma University Heavy Ion Medical Center. Their characteristics are summarized in Table 1, and a representative case is shown in Figure 1. The median follow-up time for all patients was 39 months (range, 6–70 months). There were 21 adenoid cystic carcinomas, five olfactory neuroblastomas (ONB), four mucoepidermoid carcinomas, two adenocarcinomas, and three other pathologies (basal cell adenocarcinoma, transitional cell carcinoma, and carcinoma ex pleomorphic adenoma). There were no patients with lymph node metastasis. Fifteen patients were operable and 20 patients were surgically inoperable because of aspects of advance disease, such as invasion of the brain, basal skull, carotid artery, or base of the tongue. Operability was discussed in the Cancer Board of the hospital, including the radiation oncologist, otolaryngologist, stomatology and maxillofacial surgeon, and medical oncologist.

During follow-up, four patients had local recurrence in the parotid gland ($n = 2$) and maxillary sinus ($n = 2$). Salvage surgery was carried out in these patients, who were alive without disease progression at last follow up (1, 6, 31, and 41 months after surgery). There were no severe postoperative complications. The 3-year local control rate for all patients was 93% (95% confidence interval [CI], 84%–100%) (Fig. 2). The 3-year local control rates for T2, T3, and T4 tumors were 100%, 86%, and 94%, respectively (Table 2, $P = 0.08$). The local

Table 1. Patient and tumor characteristics

Characteristics	*n* = 35 (%)
Age	
Median (years)	59 (range: 31–77)
Sex	
Male	15 (43)
Female	20 (57)
Performance status	
0	11 (31)
1/2	24 (69)
Histology	
Adenoid cystic carcinoma	21 (60)
Olfactory neuroblastoma	5 (14)
Mucoepidermoid carcinoma	4 (11)
Adenocarcinoma	2 (6)
Others	3 (9)
Location of primary tumor	
Maxillary sinus	9 (26)
Nasal cavity	9 (26)
Parotid gland	6 (17)
Oral cavity	5 (14)
Pharynx	4 (11)
External auditory canal	2 (6)
Operability	
Operable	15 (43)
Inoperable	20 (57)
Disease	
Primary tumor	29 (83)
Postoperative recurrence	6 (17)
T stage	
T2	5 (14)
T3	8 (23)
T4	22 (63)
Radiation dose	
64.0 Gy (RBE)/16 fractions	32 (91)
57.6 Gy (RBE)/16 fractions	3 (9)

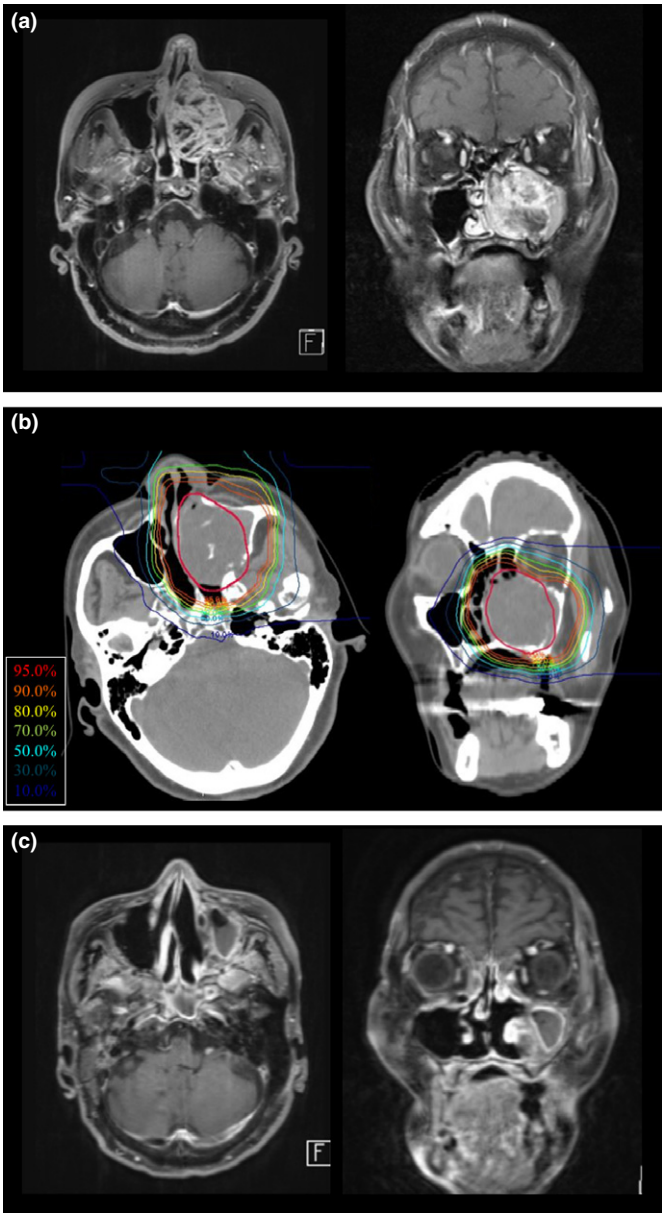


Fig. 1. Representative case of nasal cavity adenoid cystic carcinoma treated with carbon-ion radiotherapy. The 77-year-old female patient had a T4aN0M0 left maxillary sinus tumor. (a) MRI contrast-enhanced T1-weighted images revealed the maxillary sinus tumor with the extension to the nasal cavity. The patient refused surgery and hoped to receive carbon-ion radiotherapy. (b) Dose distribution of carbon-ion radiotherapy using 64.0 Gy (relative biological effectiveness) in 16 fractions. The gross tumor volume is shown in red. (c) Twenty-four months after treatment, the tumor had shrunk on MRI. There were no late adverse events of grade 2 or higher. The patient was alive at 3 years after treatment without disease progression.

control rate was 90% for patients with adenoid cystic carcinomas ($n = 21$) and 100% for all other pathologies ($n = 14$). Other clinical factors were not significantly associated with local control.

Eleven patients had disease progression, and the 3-year PFS for all patients was 71% (95% CI, 56%–86%) (Fig. 2). The PFS rates for T2, T3, and T4 tumors were 100%, 63%, and 68% ($P = 0.53$). The first progressive site was local disease in three patients, lymph node metastasis in one, and distant

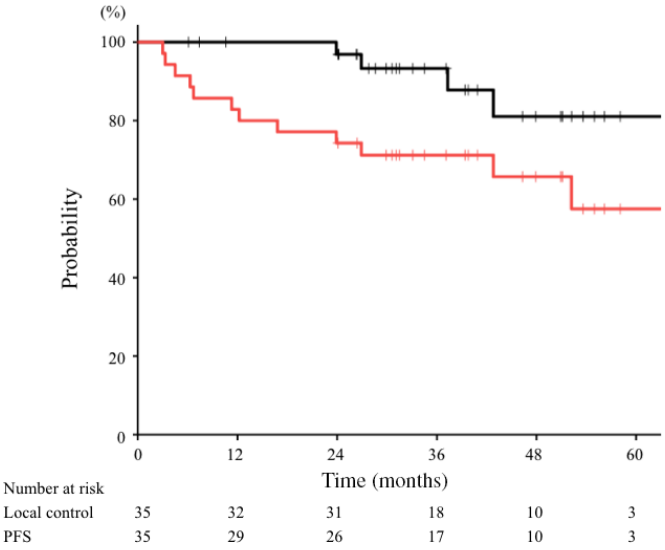


Fig. 2. Local control and progression-free survival (PFS) curves for non-squamous cell carcinoma treated with carbon-ion radiotherapy. The 3-year local control (black line) and PFS (red line) rates for all patients ($n = 35$) were 93% and 71%, respectively.

metastasis in seven (bone, $n = 3$; lung, $n = 1$; multiple sites, $n = 3$). Tumor location was significantly associated with PFS ($P < 0.01$). The 3-year PFS rate was 77% for the maxillary sinus and nasal cavity ($n = 18$), 89% for the oral cavity and pharynx ($n = 9$), 50% for the parotid gland ($n = 6$), and 0% for the external auditory canal ($n = 2$). Other clinical factors were not significantly associated with PFS.

During follow-up, four patients died of disease progression and one died of intercurrent disease (gastric cancer). Overall, the 3-year OS rate for all patients was 88% (95% CI, 77%–99%) (Fig. 3). Overall survival rates for T2, T3, and T4 tumors were 100%, 88%, and 85%, respectively (Table 2, $P = 0.95$). Regarding pathology, the 3-year OS rates were 90% for adenoid cystic carcinoma, 100% for ONB, 67% for mucoepidermoid carcinoma, and 67% for other pathologies ($P = 0.66$). Tumor location was significantly associated with OS ($P < 0.01$). The 3-year OS rates were 88% for the maxillary sinus and nasal cavity ($n = 18$), 100% for the oral cavity and pharynx ($n = 9$), 100% for the parotid gland ($n = 6$), and 0% for the external auditory canal ($n = 2$). Other clinical factors were not significantly associated with OS.

The characteristics of ONB and non-ONB head and neck NSCCs can differ substantially.[12–14] Accordingly, we compared clinical results between ONB ($n = 5$) and non-ONB ($n = 30$). The 3-year local control rates for ONB and non-ONB were 100% and 92%, respectively ($P = 0.41$). The 3-year PFS rates for ONB and non-ONB were 100% and 67%, respectively ($P = 0.13$). The 3-year OS rates for ONB and non-ONB were 100% and 86%, respectively ($P = 0.37$). Acute and late adverse events are shown in Table 3. Acute grade 2 to 3 radiation mucositis was common (65%). Grade 2 dermatitis was observed in 31% of patients, but no grade 3 dermatitis was evident. These acute adverse events improved immediately with conservative therapy. Chronic mucositis of grade 2 was observed in 31% of patients, and 1 patient (3%) suffered from grade 3 mucositis requiring hospitalization, analgesic, and gastrostoma. There were two cases of grade 2 brain necrosis requiring steroids and two cases of grade 3 cataracts requiring surgery. There were five cases of grade 2 or higher visual

Table 2. Univariate analysis for local control and overall survival (OS)

Characteristics	$n = 35$	Local control		Overall survival	
		3-year (%)	*P* value	3-year (%)	*P* value
Age					
≧59	18	93	0.45	83	0.26
<59	17	94		93	
Sex					
Male	15	94	0.85	93	0.34
Female	20	92		84	
Performance status					
0	11	91	0.69	100	0.05
1/2	24	94		82	
Histology					
Adenoid cystic carcinoma	21	90	0.64	90	0.66
Olfactory neuroblastoma	5	100		100	
Mucoepidermoid carcinoma	4	100		67	
Adenocarcinoma	2	100		–	
Others	3	100		67	
Location of primary tumor					
Maxillary sinus/nasal cavity	18	93	0.17	88	<0.01
Oral cavity/pharynx	9	100		100	
Parotid gland	6	83		100	
External auditory canal	2	–		0	
Operability					
Operable	15	93	0.85	80	0.14
Inoperable	20	93		95	
Disease					
Primary tumor	29	92	0.74	89	0.24
Postoperative recurrence	6	100		83	
T stage					
T2	5	100	0.08	100	0.95
T3	8	86		88	
T4	22	94		85	
Radiation dose					
64.0 Gy (RBE)/16 fractions	32	93	0.39	100	0.47
57.6 Gy (RBE)/16 fractions	3	100		87	

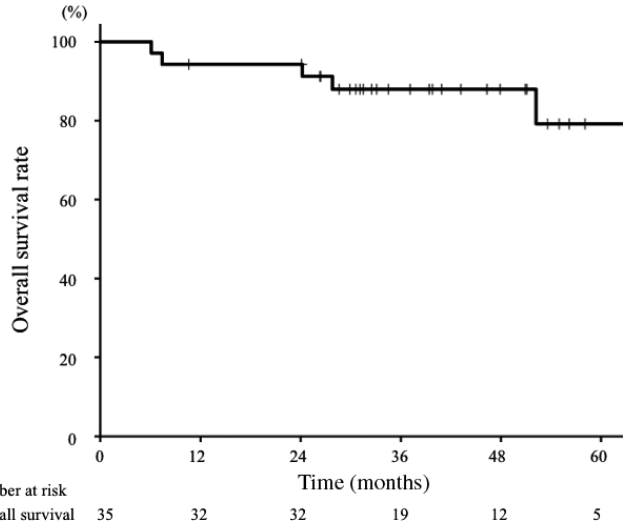


Fig. 3. Overall survival curve for patients with non-squamous cell carcinoma treated with carbon-ion radiotherapy. The 3-year overall survival rate for all patients ($n = 35$) was 88%.

Table 3. Acute and late adverse events for all patients ($n = 35$)

Acute adverse events	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Mucositis	15 (43)	8 (23)	0 (0)
Dermatitis	11 (31)	0 (0)	0 (0)
Conjunctivitis	5 (14)	0 (0)	0 (0)
Dysgeusia	1 (3)	0 (0)	0 (0)
Late adverse events			
Mucositis	11 (31)	1 (3)	0 (0)
Dermatitis	0 (0)	0 (0)	0 (0)
Conjunctivitis	1 (3)	0 (0)	0 (0)
Dysgeusia	2 (6)	0 (0)	0 (0)
Brain necrosis	2 (6)	0 (0)	0 (0)
Cataract	0 (0)	2 (6)	0 (0)
Visual imparment	2 (6)	1 (3)	2 (6)
Trismus	3 (9)	0 (0)	0 (0)
Otitis media	5 (14)	0 (0)	0 (0)
Olfactory nerve disorder	4 (11)	0 (0)	0 (0)

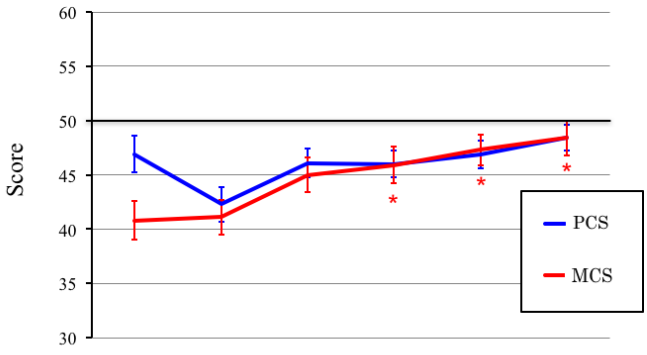
impairment (one glaucoma, one optic nerve disorder, one vitreous hemorrhage, and two retinal hemorrhages), and these tumors invaded the orbital space and were close to the eye.

Health-related QOL scores are shown in Figure 4. Radiotherapy resulted in temporary, non-significant MCS impairment at 1 month, but MCS returned to baseline levels at 3 months after treatment. In contrast, the physical components score was improved by radiotherapy, with significance improvements observed at 6, 12, and 24 months after treatment, compared with pretreatment scores ($P < 0.05$).

Discussion

The primary end-point of this study was the 3-year local control rate, which was 93% (95% CI, 84%–100%). This value is higher than our estimated value of 65% in photon therapy. Our results are comparable to previous studies of carbon-ion radiotherapy at NIRS.[2,6] In a phase II study, Mizoe *et al.*[2] reported that the 5-year local control rate was 73% for adenoid cystic carcinoma. A retrospective study of 22 patients with adenocarcinoma showed a 3-year local control rate of 84%.[6] Recently, Jensen *et al.*[15] studied intensity-modulated radiotherapy plus carbon-ion boost therapy, observing a 3-year local control rate of 84% for adenoid cystic carcinoma at Heidelberg. Our prospective study showed that the favorable outcomes of carbon-ion radiotherapy were reproducible for NSCC.

The standard treatment for NSCC, especially adenoid cystic carcinoma, is considered to be radical surgery and postoperative radiotherapy.[14] van Weert *et al.*[16] reported the clinical results of surgery for 105 adenoid cystic carcinoma patients. Postoperative radiotherapy was undertaken in 93% of the patients, and the 5-year local control and OS rates were 82% and 68%, respectively. Shen *et al.*[17] reported 101 adenoid cystic carcinoma patients treated with surgery. Twenty-four percent of patients had T4 disease, and postoperative radiotherapy were carried out in 62% of patients. The 5-year local control and OS rates were 71% and 91%, respectively. Our study showed 3-year local control and OS rates of 93% and 88%,



Mean ± SE	Before treatment	After treatment				
		1 month	3 months	6 months	12 months	24 months
PCS	46.9 ± 1.7	42.3 ± 1.6	46.1 ± 1.3	46.0 ± 1.2	46.9 ± 1.3	48.4 ± 1.2
MCS	40.8 ± 1.8	41.1 ± 1.6	45.0 ± 1.6	45.9 ± 1.7*	47.3 ± 1.4*	48.4 ± 1.6*

Fig. 4. Changes of short form-8 health survey values in patients with non-squamous cell carcinoma, before and after carbon-ion radiotherapy. *$P < 0.05$ for the comparison of values before and after treatments. MCS, mental component summary; PCS, physical component summary.

which are comparable to the previously reported results of surgery because 63% of patients had T4 disease in our study.

Our study included five patients with ONB, and their outcomes were excellent, with 3-year local control and OS rates of 100% and 100%, respectively, which are comparable to previous results of carbon-ion radiotherapy.[2] Olfactory neuroblastoma has been reported to be sensitive to chemotherapy,[13,18] due to different characteristics compared to other NSCCs, such as adenoid cystic carcinoma. Because of its distinct features, ONB should generally be distinguished from other forms of NSCCs. There have been few reports on the efficacy of photon therapy for ONB. Therefore, carbon-ion radiotherapy, with its superior dose distribution, could be a promising treatment because the diseases are close to OARs, such as the brain.

In this study, tumor location was significantly prognostic for PFS and OS; worse outcomes (OS, 0%; PFS, 0%) were observed for the two patients with external auditory canal tumor (adenoid cystic carcinoma and mucoepidermoid carcinoma). Although both patients died of disease progression with rapid distant metastasis, the small number of patients makes the outcomes of these tumors unclear. Previously, retrospective research on 13 patients with squamous cell carcinoma in the external auditory canal and middle ear showed a poor prognosis (3-year OS, 40%).[19] Further studies of this extremely rare disease are necessary.

Although carbon-ion radiotherapy provides sharp dose distributions, it is difficult to avoid adverse events when tumors directly invade normal tissues. Acute dermatitis and mucositis were common in our study, and improved with conservative therapy. Because skin dose was strictly based on a previous dose constraint, 60 Gy (RBE) <20 cm^2,[9] severe late dermatitis was not observed. However, consideration should be given to chronic mucositis, particularly because 34% of patients had grade 2 or higher. In a previous phase II study by Mizoe *et al.*[2] at NIRS, 4% of patients had grade 2 or higher late mucositis. The comparative rarity of severe late mucositis might relate to differences in total radiation doses. Based on a phase I/II study, 64 Gy (RBE) was defined as a maximum tolerated dose.[4] Both our study and Mizoe *et al.*'s used similar criteria for 64 Gy (RBE), and selected 57.4 Gy (RBE) for tumors that were close to the skin or mucosal. Nonetheless, 64 Gy (RBE) was given to 90% of patients in our study and 8% in the previous study. Although lower doses generally reduce adverse event rates, local control can be affected. In fact, local control rates were 93% at 3 years in our study and 73% at 5 years for adenoid cystic carcinoma in Mizoe *et al.*'s study. Further studies are warranted to evaluate relationships between radiation doses and tumor control in NSCC of the head and neck. Recently, dose constraints have been established for several organs (including the optic nerve, brain, mucosa, and maxilla) in carbon-ion radiotherapy of head and neck tumors.[8,20–22] Dose constraints need to be determined for late mucositis, to allow careful carbon-ion radiotherapy planning.

Quality of life and functional status are important relative to clinical outcomes in patients with head and neck cancer. Although QOL studies of surgery and chemoradiotherapy have become more common for head and neck cancers,[23,24] no QOL study has examined carbon-ion radiotherapy. Here, QOL was prospectively evaluated using SF-8 questionnaires, which showed that mental status gradually improved after treatment. This suggests that pretreatment fears and anxiety may have disappeared following successful treatment. Physical scores temporally decreased after treatment, but rapidly improved to baseline levels during the 2 years after treatment. This suggests that acute adverse events had temporary effects, and late adverse events did not harm patients' physical conditions. Additional study is required to assess QOL during longer follow-up.

This study had several limitations. The median follow-up period of 39 months was relatively short. Therefore, additional follow-up is required to evaluate local control, OS, and late adverse events. Furthermore, the evaluation of individual pathologies was not robust because of the small number of enrolled patients. However, NSCC of the head and neck is rare, and we think it is important to evaluate outcomes prospectively. Each anatomical site and disease pathology should ideally be evaluated as a distinct disease, and an optimal strategy should be established for each of these diseases separately. Although the primary end-point of this study was 3-year local control, there was a concern that local control overestimates the treatment efficacy because of competing risk. However, in this study, local control was followed until death, and patients were not censored even when they developed metastasis. Furthermore, the patients survived well, with a 3-year OS rate of 89%, indicating that the 3-year local control was considered evaluable in this study.

In conclusion, this prospective study showed excellent local control and OS outcomes for NSCC. The outcomes were similar to those previously reported for carbon-ion radiotherapy, showing that it has reproducible efficacy. Late adverse events are not rare; therefore, dose constraints for OARs are required to establish safer treatment planning in carbon-ion radiotherapy and prevent adverse events such as late mucositis.

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Disclosure Statement

The authors have no conflict of interest.

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