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Carbon-ion Radiotherapy for Inoperable Head and Neck Bone and Soft-tissue Sarcoma: Prospective Observational Study

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Abstract. *Background/Aim: Bone and soft-tissue sarcomas of the head and neck have very poor prognoses. This prospective study aimed to investigate the efficacy and safety of carbon-ion radiotherapy (C-ion RT) for bone and soft-tissue sarcoma of the head and neck. Patients and Methods: The present study was a prospective clinical study that included 10 consecutive patients diagnosed with bone and soft-tissue sarcoma of the head and neck who were treated with C-ion RT between 2012 and 2018 at our institution. C-Ion RT consisted of 70.4 Gy (relative biological effectiveness) in 16 fractions. Results: The 3-year local control, overall survival, and progression-free survival rates for patients overall were 72.9%, 77.8%, and 36%, respectively. Conclusion: The present study demonstrated the efficacy of C-ion RT for bone and soft-tissue sarcoma of the head and neck; adverse events were within the expected range.*

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Bone and soft-tissue sarcomas of the head and neck (BSS-HN) account for less than 1% of all head and neck malignancies and less than 10% of all soft-tissue sarcomas (1). Treatment of BSS-HN varies depending on histological type but surgery is generally the mainstay of treatment. However, there are many cases in which resection or reconstruction is difficult because of functional or cosmetic challenges that affect the quality of life or due to the proximity of the tumor to the orbit or skull base. Therefore, radical surgery is combined with chemotherapy and radiotherapy to treat BSS-HN (2). BSS-HN has a very poor prognosis, with a 5-year overall survival (OS) rate of 21.7-59.7% with surgery, chemotherapy, and radiotherapy (2-4). Because BSS-HN is a rare tumor, there are few reports on it compared with those on squamous cell carcinomas, and a viable treatment method has yet to be established.

Carbon-ion radiotherapy (C-ion RT) provides highly concentrated radiation dose distributions with a Bragg peak and has high biological effectiveness. Locally advanced head and neck cancer has been treated with C-ion RT at the National Institute of Radiological Sciences (NIRS) (Chiba, Japan) since 1994 (5). At NIRS, C-ion RT has shown excellent outcomes with BSS-HN, with 3-year local control (LC) rate of 91.8% and OS of 74.1% (6). However, this NIRS report (6) originated from a single institution, necessitating reproducibility at other facilities. Therefore, we conducted a prospective study to confirm the efficacy and safety of an established dose and fractionation schedule of C-ion RT for BSS-HN.

Patients and Methods

Patients. The present study was a prospective clinical study that included 10 consecutive patients diagnosed with inoperable BSS-HN treated with C-ion RT between June 2012 and May 2018 at Gunma University Heavy Ion Medical Center. This study was approved by our Institutional Review Board (trial approval number: 921, trial registration number: UMIN000007938) and carried out in accordance with the Declaration of Helsinki. The target number of patients for this study was 15; however, poor accrual due to the rarity of BSS-HN resulted in only 10 patients being enrolled over a 6-year period. All patients provided informed consent prior to treatment. The inclusion criteria were as follows: (i) Histologically confirmed bone and soft-tissue sarcoma, (ii) N0-1 M0 disease, (iii) measurable tumor, (iv) age 16-80 years, and (v) performance status 0-2. The exclusion criteria were as follows: (i) History of irradiation of the head and neck, (ii) history of chemotherapy within 4 weeks before C-ion RT, (iii) uncontrolled infection, (iv) severe concomitant disease, and (v) active double cancer. All biopsy specimens were centrally re-evaluated by a pathologist at Gunma University Hospital (Maebashi, Japan). Evaluations included physical examination, laryngoscopy, computed tomography (CT), magnetic resonance imaging (MRI), and ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography (FDG PET/CT) within 1 month before treatment to rule out distant metastasis. The primary endpoint was the 3-year LC rate; LC was defined as no evidence of tumor regrowth in the planning target volume (PTV). Secondary endpoints were the 3-year OS rate, the progression-free survival (PFS) rate, and adverse events. Acute and late adverse events were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0. (ver. 4.0) (7).

None of the patients in this series received concomitant systemic treatments. Table I summarizes the patient and tumor characteristics. The primary tumor sites were the maxillary sinus (n=3), nasal cavity (n=2), maxilla (n=2), oral cavity (n=2), and pterygopalatine fossa (n=1).

C-Ion RT. In this study, we used the C-ion RT techniques and treatment plans as were previously reported (8, 9). Briefly, patients were immobilized using thermoplastic shells (Shellfitter; Kuraray, Osaka, Japan) and positioned in customized cradles (Moldcare; Alcare, Tokyo, Japan). A customized mouthpiece maintained the position of the lower jaw (10). CT simulation (thickness, 2 mm) was performed for treatment planning and MRI 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. The clinical target volume (CTV) had at least a 5-mm margin around the GTV. CTV1 included all anatomic sites where the tumors were located, whereas CTV2 was limited to around the GTV. PTV1 and PTV2 had 2-mm margins around CTV1 and CTV2, respectively. The CTV and PTV margins were modified as necessary when the targets were close to the organs at risk. The radiation dose was prescribed at the isocenter of the PTVs. The PTVs were encompassed by the 95% isodose line of the prescribed dose. Physical dose calculations were performed using the pencil-beam algorithm. The clinical dose distribution was calculated using the physical dose and relative biological effectiveness (RBE) obtained from the responses of human salivary gland tumor cells. The C-ion RT dose was expressed as Gy (RBE) (11). Doses were delivered over 16 fractions, and the overall treatment time was approximately 4 weeks (4 fractions per week). All patients received 70.4 Gy (RBE) in 16 fractions according to the clinical protocol.

Table I. *Patient and tumor characteristics*.

Characteristic	
Age, years	
Mean (range)	51.5 (19-79)
Gender, n	
Male	5
Female	5
Histological type, n	
Chondrosarcoma	2
Undifferentiated pleomorphic sarcoma	2
Liposarcoma	1
Angiosarcoma	1
Malignant pleomorphic and spindle cell tumor	1
Malignant peripheral nerve sheath tumor	1
Rhabdomyosarcoma	1
Ameloblastic fibrosarcoma	1
Region, n	
Maxillary sinus	3
Nasal cavity	2
Maxilla	2
Oral cavity	2
Pterygopalatine fossa	1
Initial treatment	
Surgery	3
None	7
GTV, cc	
Mean (range)	66 (6-276)
>66 cc, n	6
≤66 cc, n	4
Total dose, n	
70.4 Gy(RBE)	10

GTV: Gross tumor volume; RBE: relative biological effectiveness.

Follow-up. Patients were followed-up every month for the first 6 months and every 3 months thereafter. CT and MRI were performed alternately every 3 months and FDG PET/CT, every year. LC was monitored until death, and patients were not censored despite the development of lymph node or distant metastasis.

Statistical analysis. LC, OS, and PFS rates were estimated using the Kaplan–Meier method and compared using log-rank tests. Differences between groups were assessed using *t*-tests. Differences were considered statistically significant at $p<0.05$. Statistical analyses were performed using IBM SPSS Statistics (version 26.0; IBM, Armonk, NY, USA).

Results

Between June 2012 and May 2018, 10 patients with inoperable bone and soft-tissue sarcoma prospectively underwent C-ion RT at Gunma University Heavy Ion Medical Center. Patient characteristics are summarized in Table I, and a representative case is shown in Figure 1. The median follow-up time for the whole patient cohort was 33.5 (range=16.7-81.8) months. There were two chondrosarcomas, two undifferentiated pleomorphic sarcomas, and six other pathologies. None of the patients had lymph node metastasis.

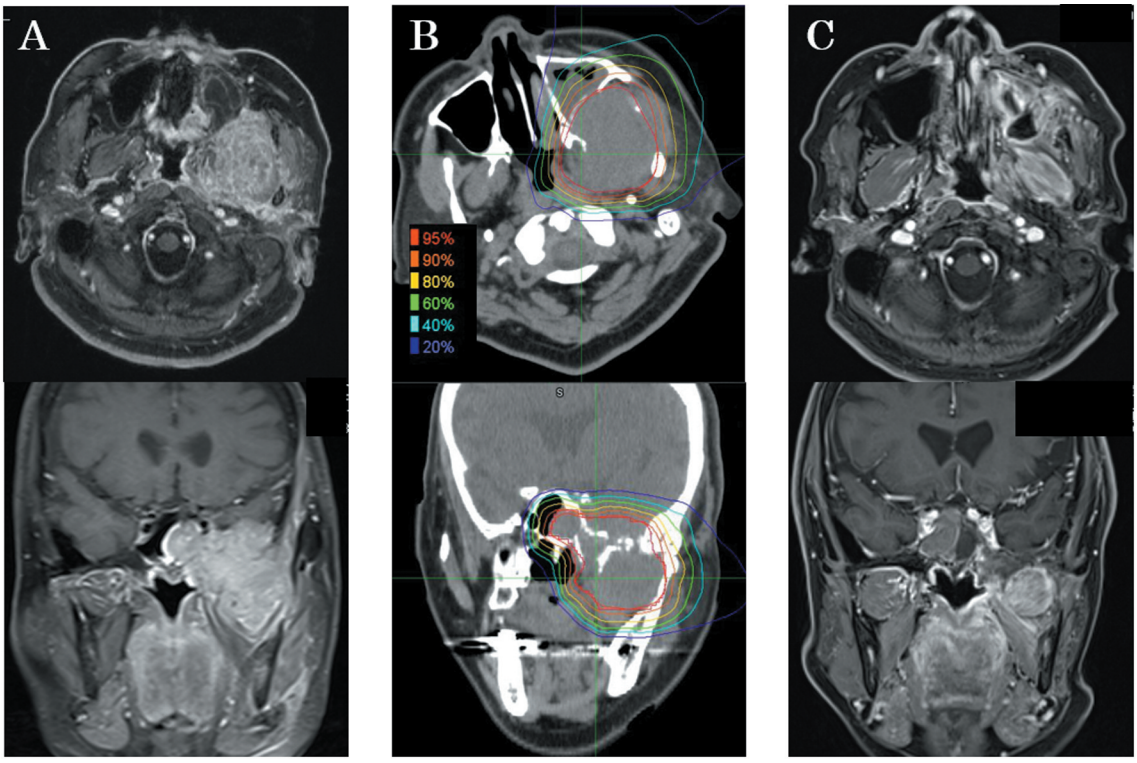

Figure 1. *Representative case of undifferentiated pleomorphic sarcoma of the pterygopalatine fossa treated with carbon-ion radiotherapy (C-ion RT). A 60-year-old female patient had tumor invasion of the pterygopalatine fossa. A: Contrast-enhanced T1-weighted magnetic resonance imaging revealed the area around the pterygopalatine fossa. The patient was diagnosed with inoperable bone and soft-tissue sarcomas of the head and neck and treated with C-ion RT. B: Dose distribution of C-ion RT using 70.4 Gy (relative biological effectiveness) in 16 fractions. The gross tumor volume is shown in red. C: Twenty-four months after treatment, magnetic resonance imaging showed the tumor had shrunk. The patient has grade 2 trismus and is still alive more than 3 years after treatment. The patient additionally underwent surgery for recurrence of the lymph node at the neck 28 months later.*

Follow-up after C-ion RT for all 10 patients is summarized in Table II. During follow-up, two patients had local recurrence in the maxilla (n=1) and oral cavity (n=1); salvage surgery was performed on these patients, and they survived without disease progression or severe postoperative complications at the last follow-up (16.8 and 62.5 months, respectively, after surgery). The 3-year LC rate was 72.9% [95% confidence interval (CI)=35.1-62.0%] (Figure 2). The 1-year LC rate was 100%, regardless of the size of the GTV (n=10) (Figure 2 and Table II). The mean GTV was 66 cc (Table I). There was no significant difference between the 3-year LC rates for those with GTV ≤66 cc and GTV >66 cc, which were 100% and 53.3%, respectively (Figure 3A; p=0.209).

One patient died of disease progression and one of intercurrent disease (renal failure). The 3-year OS rate was 77.8% (95% CI=50.8-84.8%) (Figure 4). There was no significant difference between the 3-year OS rates for patients with GTV ≤66 cc and those with GTV >66 cc, which were 100% and 66.7%, respectively (Figure 3B, p=0.259). During follow-up, six patients had disease progression; the 3-year PFS for the whole cohort was 36% (95% CI=14.8-45.1%) (Figure 4). There was no significant difference between the 3-year PFS rates for those with GTV ≤66 cc and GTV >66 cc, which were 50% and 22.2%, respectively (Figure 3C, p=0.884). The first site of progressive disease was local disease in two patients, lymph node metastasis in three, and distant metastasis in three (bone in one, lung in two, multiple sites in one).

Acute and late adverse events are shown in Table III. Acute grade 2-3 mucositis and dermatitis were the most common adverse events, which improved immediately after conservative therapy. Grade 3 chronic mucositis was observed in one patient, who required analgesia. Grade 3 trismus was observed in one patient, who required gastrostoma because the tumor invaded almost all the muscles of mastication. There were three cases of grade 3 osteoradionecrosis that required analgesia and hyperbaric oxygen therapy, and these tumors had a tendency for widespread invasion of the maxilla and mandible. There was a case of grade 3 olfactory nerve disorder and a case of grade

Table II. *Patient characteristics and therapeutic outcomes.*

Patient no.	Age, years	Gender	Histological type	Region	Initial treatment	GTV, cc	Local recurrence	Distant metastasis	Additional treatment*	Status at study end
1	48	Male	Liposarcoma	Oral cavity	Surgery	12.07	No			Alive
2	58	Male	Chondrosarcoma	Maxilla	None	124.05	Yes		Salvage surgery	Dead
3	79	Female	Undifferentiated pleomorphic sarcoma	Maxillary sinus	None	67.67	No	Lung	None	Dead
4	24	Male	Malignant pleomorphic and spindle cell tumor	Oral cavity	Chemotherapy (HD-MTX, CDDP, ADR)	225.82	Yes	Axillary lymph node	None	Alive
5	19	Male	Rhabdomyosarcoma	Nasal cavity	None	53.59	No	Bone	Radiotherapy, VAC	Alive
6	44	Female	Angiosarcoma	Maxillary sinus	None	62.09	No	Lung	Chemotherapy (PTX)	Alive
7	27	Male	Malignant peripheral nerve sheath tumor	Maxillary sinus	None	276.31	No			Alive
8	55	Female	Chondrosarcoma	Nasal cavity	Surgery	5.63	No			Alive
9	60	Female	Undifferentiated pleomorphic sarcoma	Pterygopalatine fossa	None	90.35	No	Cervical lymph node	Salvage surgery	Alive
10	68	Female	Ameloblastic fibrosarcoma	Maxilla	None	70.63	No			Dead

ADR: Adriamycin; CDDP: cisplatin; HD-MX: High-dose methotrexate; PTX: paclitaxel; VAC: vincristine, actinomycin D and cyclophosphamide. *After local recurrence/distant metastasis.

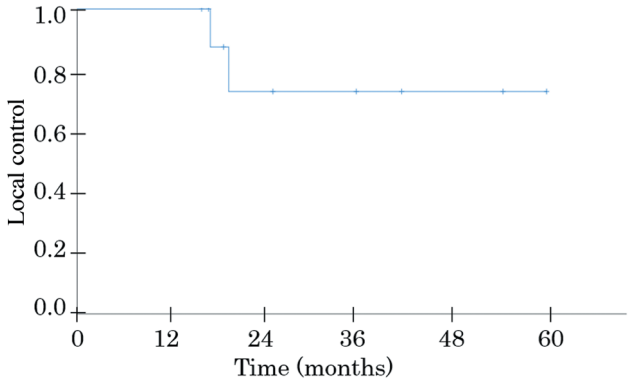

Figure 2. *Local control curve for bone and soft-tissue sarcoma treated with carbon-ion radiotherapy. The 3-year local control rate for patients overall (n=10) was 72.9%.*

Table III. *Acute and late adverse events for all patients (n=10).*

		Grade, n				
Adverse event		0	1	2	3	4
Acute	Mucositis	0	1	3	4	0
	Dermatitis	0	2	6	2	0
	Xerostomia	7	2	1	0	0
	Dysgeusia	8	2	0	0	0
	Conjunctivitis	8	1	1	0	0
Late	Mucositis	7	2	0	1	0
	Dermatitis	2	7	0	1	0
	Xerostomia	8	2	0	0	0
	Dysgeusia	7	2	1	0	0
	Conjunctivitis	8	2	0	0	0
	Trismus	4	2	3	1	0
	Osteoradionecrosis	6	1	0	3	0
	Brain necrosis	8	2	0	0	0
	Brainstem necrosis	10	0	0	0	0
	Nasal congestion	7	3	1	0	0
	Chronic sinusitis	9	0	1	0	0
	Olfactory nerve disorder	8	1	0	1	0
	Middle-ear infection	8	0	1	1	0
	External otitis	9	0	1	0	0
	Cataract	10	0	0	0	0
	Optic nerve disorder	9	0	0	0	1

3 middle ear infection. There was a case of grade 4 visual impairment (optic nerve disorder) in which the tumor invaded the orbital space and was close to the eye.

Discussion

The present study analyzed a prospective clinical study of patients diagnosed with inoperable BSS-HN and treated with C-ion RT. Previous historical results of C-ion RT with a total dose of 57.6 or 64 Gy (RBE) from NIRS showed 3-year LC and OS rates of 23.6% and 42.9%, respectively (5). However, when the total dose was increased to 70.4 Gy (RBE), the 3-year LC and OS rates improved to 91.8% and 74.1%, respectively (6). In this study, we used a total dose of 70.4 Gy (RBE), and the 3-year LC and OS rates were 72.9% and 77.8%, respectively.

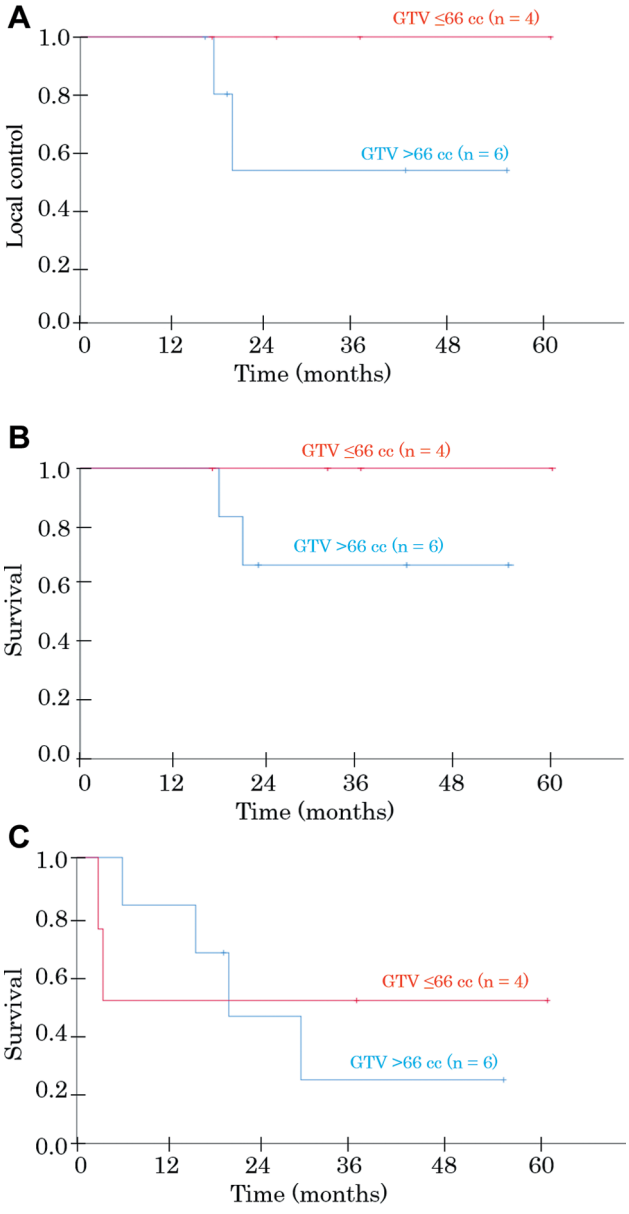

Figure 3. *A: Local control curve for bone and soft-tissue sarcoma treated with carbon-ion radiotherapy. The 3-year local control rates for gross tumor volume (GTV) ≤66 cc and GTV >66 cc were 100% and 53.3%, respectively (p=0.209). B: Overall survival (OS) curves for patients with bone and soft-tissue sarcoma treated with carbon-ion radiotherapy according to GTV. The 3-year OS rates for patients with GTV ≤66 cc and GTV >66 cc were 100% and 66.7%, respectively (p=0.295). C: The 3-year PFS rates for those with GTV ≤66 cc and GTV >66 cc were 50% and 22.2%, respectively (p=0.884).*

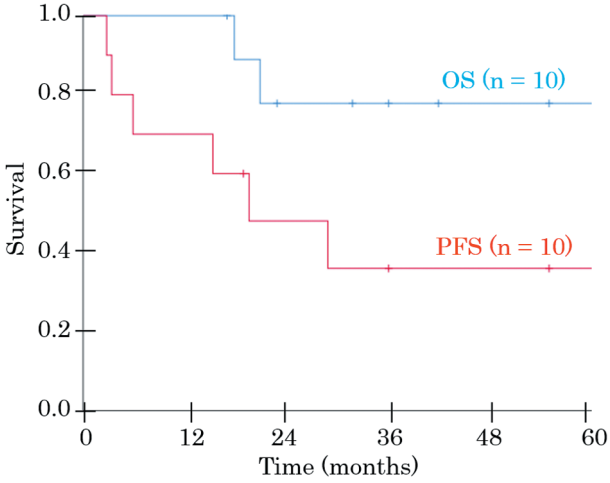

Figure 4. *Overall (OS) and progression-free (PFS) survival curves for patients with bone and soft-tissue sarcoma treated with carbon-ion radiotherapy. The 3-year OS and PFS rates for patients overall (n=10) were 77.8% and 36%, respectively.*

The results of the present study were similar to those of the previous NIRS study on treatment outcomes (6), although the LC of our study was slightly inferior (6). Therefore, the effect of C-ion RT on inoperable BSS-HN was reproduced (Table IV).

The standard treatment guidelines for BSS-HN are radical surgery, neoadjuvant and adjuvant chemotherapy, and radiotherapy. However, the literature shows the prognosis for BSS-HN was poor, with a 5-year LC rate of 21.0-47.0% with surgery, chemotherapy, and radiotherapy (2, 4) (Table IV). Moreover, the 5-year OS rates were 21.7% and 36% for those treated with chemotherapy and radiotherapy, and 50% and 59.7% for those treated with surgery, chemotherapy, and radiotherapy, respectively (2, 4) (Table IV). For bone and soft-tissue sarcomas located in regions other than the head and neck treated with C-ion RT, the GTV was considered a significant prognostic factor for OS and LC (12-14), and a previous study also reported that a GTV higher than 100 cc is a significant factor associated with worse OS for BSS-HN treated with C-ion RT (6). However, the GTV was not significantly correlated with OS, PFS, or LC in the present study. Another recent treatment study reported on craniofacial osteosarcoma treated with protons and a C-ion boost. This study reported 2-year PFS and OS rates of 45% and 68%, respectively (15) (Table IV). Most adverse events were grade 2 or lower, and the reasonably high OS suggests particle beam therapy (carbon and proton) for BSS-HN might be a possibility in the future. However, despite the proton and C-ion boost intervention, the OS in the previous study (15) was slightly lower than that of our study. Lower OS might be related to lower LC and PFS. It may be important to irradiate the target with a high dose of C-ions, which has excellent biological effects for BSS-HN.

In the present study, acute adverse events improved immediately; however, a few late adverse events, such as

Table IV. *Comparing outcomes for bone and soft-tissue sarcomas of head and neck by treatment modality.*

Author (Ref)	Treatment strategy	Endpoint				
		Number of patients	Time point	Local control	Overall survival	Mean follow-up, months
Eeles *et al*. (2)	Surgery±radiotherapy±chemotherapy	103	5-Year:	47.0%	50.0%	50.0
	Radiotherapy±chemotherapy	17	5-Year:	21.0%	36.0%	
Kepka *et al*. (3)	Surgery±radiotherapy±chemotherapy	112	5-Year:	45.0%	35.0%	139.0
Smith *et al*. (4)	Surgery±radiotherapy±chemotherapy	496	–	–	59.7%	–
	Radiotherapy±chemotherapy	71	–	–	21.7%	–
Mizoe *et al*. (5)	Carbon-ion radiotherapy 57.6 or 64 Gy (RBE)/16 fr	14	3-Year:	23.6%	42.9%	54.0
Jingu *et al*. (6)	Carbon-ion radiotherapy 70.4 Gy (RBE)/16 fr	27	3-Year:	91.8%	74.1%	37.0
			5-Year:	80.4%	57.6%	
Seidensaal *et al*. (13)	Proton radiotherapy 54 Gy (RBE)/27 fr + Carbon-ion radiotherapy 18 Gy (RBE)/6 fr	18	1-Year:	–	75.0%	34.5
			2-Year:	–	68.0%	
Current study	Carbon-ion radiotherapy 70.4 Gy (RBE)/16 fr	10	2-Year:	72.9%	77.8%	33.5
			3-Year:	72.9%	72.9%	

Fr: Fractions; RBE: relative biological effectiveness.

trismus and osteoradionecrosis, were not alleviated by conservative therapy. The incidence of adverse events was generally comparable to the acute and late adverse events reported in a previous study (6). Late adverse events have a large impact on patients and should be prevented. However, because the grade 3 or higher late adverse events in this study were very close to each organ, it is the likely their onset could not be suppressed. Additionally, therapeutic C-ion doses for bone and soft-tissue sarcomas are higher than those for other pathological types, such as non-squamous cell carcinoma and malignant melanoma. Because of the small number of cases in the present study, the relationship between the onset of adverse events and treatment outcomes is unclear; however, reducing acute adverse events, which should be achieved as far as possible, will also reduce late adverse events (16-18). Onset doses for adverse events such as oral mucositis (19) and dermatitis (20) from C-ion RT for the head and neck have been reported. According to these reports, preventing the onset of acute adverse events is essential. Furthermore, preventing acute adverse events can also reduce the occurrence of late adverse events (14-16). Late adverse events such as osteoradionecrosis (21, 22), trismus (23), nasolacrimal duct obstruction (24), tooth loss (25), brainstem necrosis (26), brain injury (27), and optic nerve injury (28) have been reported. In the future, we intend to develop a C-ion RT plan considering these dose indicators of onset; thus, the incidence of adverse events is anticipated to be reduced compared with that of the present study.

This study had a few limitations. Firstly, it involved patients enrolled at a single institution. There are few institutes that administer C-ion RT; future prospective studies should increase the number of patients enrolled and include more institutes. Secondly, bone and soft-tissue sarcomas have various pathological types. Because the therapeutic effect of C-ion RT depends on the pathological tissue type, further research is important.

In conclusion, the present study reproduced the effect of C-ion RT on inoperable BSS-HN. Adverse events were also within the expected range, but the dose to organs at risk should be considered for further mitigation of adverse events.

Conflicts of Interest

None to be declared.

Authors' Contributions

Conceived and designed the research: AM, KS and JS; performed the research, analyzed the data, and contributed materials/analysis tools: AM, NK, HK, NaokoOkano, HS, KO, Naoto Osu, HY, AA and TO; planned the treatment: AM, NK, HK, Naoko Okano, KS, JS and TO; analyzed the treatment and contributed to the final draft of the article: AM, NK, HK, Naoko Okano, HS, KO, Naoto Osu, HY, AA and TO; All Authors read and approved the final article: AM, NK, HK, Naoko Okano, HS, KO, Naoto Osu, HY, AA, YT, MS, ON, SI, KS, JS, SY, KC and TO.

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