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

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Key words
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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.

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) NO–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.

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Carbon-ion radiotherapy in head and neck tumor

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, stomatologist, 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

| Characteristic                              | n   | (%) |
|--------------------------------------------|-----|-----|
| Age                                        | 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)  |
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 one patient, lymph node metastasis in one, and distant 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

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\begin{array}{l|c|c|c|c|c|c|c|}
\hline
\text{Number at risk} & \text{0} & \text{12} & \text{24} & \text{36} & \text{48} & \text{60} \\
\text{Local control} & 35 & 32 & 31 & 18 & 10 & 3 \\
\text{PFS} & 35 & 29 & 26 & 17 & 10 & 3 \\
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**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.

![Representative case of nasal cavity adenoid cystic carcinoma treated with carbon-ion radiotherapy.](image)
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.5 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.6 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%.

### 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**                          |        |               |                 |               |                 |
| $\geq 59$                        | 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      | –             |                 |               |                 |
| **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            |                 |

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Changos 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.

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

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