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Clinical Investigation

A Multicenter Study of Carbon-Ion Radiation Therapy for Head and Neck Adenocarcinoma

Jun-ichi Saitoh, MD, PhD,* Masashi Koto, MD, PhD,† Yusuke Demizu, MD, PhD,‡ Hiroaki Suefuji, MD, PhD,§ Tatsuya Ohno, MD, PhD,* Hiroshi Tsuji, MD, PhD,† Tomoaki Okimoto, MD, PhD,‡ Yoshiyuki Shioyama, MD, PhD,§ Kenji Nemoto, MD, PhD,‖ Takashi Nakano, MD, PhD,* and Tadashi Kamada, MD, PhD†, the Japan Carbon-Ion Radiation Oncology Study Group

**Gunma University Heavy Ion Medical Center, Maebashi, Japan; †Hospital of the National Institute of Radiological Sciences, National Institutes for Quantum and Radiological Sciences and Technology, Chiba, Japan; ‡Department of Radiology, Hyogo Ion Beam Medical Center, Tatsuno, Japan; §Ion Beam Therapy Center, SAGA-HIMAT Foundation, Tosu, Japan; and ‖Department of Radiation Oncology, Yamagata University Faculty of Medicine, Yamagata, Japan*

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Summary

In this large, retrospective, multicenter study, carbon-ion radiation therapy was a safe and effective treatment in patients with head and neck adenocarcinoma. Carbon-ion radiation therapy resulted in good local control and overall survival with acceptable toxicities.

Purpose: Head and neck (HN) adenocarcinoma is rare, and to date, there have been no reports of prospective studies. We retrospectively evaluated the efficacy and safety of carbon-ion radiation therapy (C-ion RT) for HN adenocarcinoma in institutions in Japan.

Methods and Materials: HN adenocarcinoma patients with N0M0 or N1M0 disease who were treated with C-ion RT at institutions in Japan between November 2003 and December 2014 were analyzed retrospectively. We enrolled 47 patients (30 male and 17 female patients; median age, 60 years) with HN adenocarcinoma.

Results: Primary sites included the nasal and paranasal sinus in 21 patients, orbit in 11, salivary grand in 7, oral cavity and pharynx in 6, and acoustic organ in 2. Thirty-two patients had T4 tumors, 6 had T3, and 6 had T2. Forty-five patients received a diagnosis of N0 disease, whereas 2 had N1 disease. The median total dose of C-ion RT and the number of fractions were 64.0 Gy (relative biological effectiveness) and 16 fractions, respectively. The median follow-up period was 51 months (range, 6-118 months). The 2- and 5-year overall survival rates were 87.9% and 60.4%, respectively, and the 2- and 5-year local control rates were 83.3% and 79.3%, respectively. Multivariate analysis showed that operability (patients with operable tumors) ($P = .045$) and fractionation (16 fractions) ($P = .010$) were significant

Reprint requests to: Jun-ichi Saitoh, MD, PhD, Gunma University Heavy Ion Medical Center, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan. Tel: +81-27-220-8383; E-mail: junsaito@gunma-u.ac.jp

Conflict of interest: none.

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independent prognostic factors for better overall survival. No grade 5 late morbidities were observed. Grade 4 late morbidities were observed in 4 patients, and all of these grade 4 morbidities were visual impairments. All 4 patients with grade 4 visual impairment had T4 tumors in the nasopharynx or paranasal sinuses, which implied inoperable tumors with orbital or brain invasion.

Conclusions: C-ion RT resulted in excellent local control. C-ion RT could become a curative treatment option for HN adenocarcinoma with acceptable toxicities.

Introduction

In addition to local tumor control, morphologic preservation and functional preservation are the most important objectives in the treatment of head and neck (HN) malignancies. In particular, radiation therapy alone or in combination with chemotherapy plays an important role in HN cancer treatment and is considered a curative treatment choice in the treatment of HN squamous cell carcinoma. However, a treatment strategy for HN non-squamous cell carcinoma has not yet been established because HN non-squamous cell carcinoma is extremely rare. HN adenocarcinoma is a type of HN non-squamous cell carcinoma. Surgery is considered a radical treatment for HN adenocarcinoma, and postoperative radiation therapy remains the treatment of choice in locally advanced cases (1-3). In a large retrospective study on sinonasal adenocarcinoma, Choussy et al (1) showed a significant survival advantage with surgery alone or in combination with radiation therapy when compared with radiation therapy alone. In the literature, the 5-year overall survival (OS) rate of HN adenocarcinoma patients treated with surgery, with or without radiation therapy, ranged from 43% to 79% (1-7). However, there are few reports on the clinical outcomes or effectiveness of definitive x-ray radiation therapy for HN adenocarcinoma.

Carbon-ion radiation therapy (C-ion RT) was initiated in 1994 in Japan. Compared with photons, carbon-ions provide a higher linear energy transfer and larger relative biological effectiveness (RBE). Therefore, carbon-ions provide a higher probability of tumor control for the treatment of x-ray−resistant tumors. The physical characteristics of carbon-ions, such as the Bragg peak and small lateral scattering, are theoretically superior to those of photons because carbon-ions can allow a more localized delivery of the radiation dose. As for the treatment results of HN adenocarcinoma by definitive C-ion RT, Koto et al (8) reported that after treatment in 22 patients with locally advanced sinonasal adenocarcinoma, a 3-year local control (LC) rate of 76.9% and a 3-year OS rate of 59.1% were achieved.

In November 2003, following a clinical trial, the Ministry of Health, Labor and Welfare in Japan approved C-ion RT as a highly advanced medical technology. We conducted a retrospective multicenter study to assess the clinical outcomes of C-ion RT for HN malignancies. This article reports the results of the subgroup analysis of patients with HN adenocarcinoma treated with C-ion RT.

Methods and Materials

Eligibility

A retrospective multicenter study was conducted across carbon-ion facilities in Japan. Patients provided informed consent authorizing the use of their personal information for research purposes. This study was approved by the institutional review board of each institute and was carried out in accordance with the Declaration of Helsinki.

Patients with HN malignancies, including ophthalmic tumors, who received C-ion RT as a highly advanced medical technology between November 2003 and December 2014 were included. The inclusion criteria were: (*1*) histologically confirmed malignancy (except choroidal melanoma); (*2*) no bone or soft tissue tumors; (*3*) N0M0 or N1M0 status; (*4*) medically inoperable tumors or surgery refusal; (*5*) definitive intent; (*6*) measurable tumors; and (*7*) an Eastern Cooperative Oncology Group performance status of 0 to 2. Patients who previously underwent irradiation for the same lesion were excluded.

Nine hundred eight patients were enrolled. Of these, 47 had a pathologic diagnosis of adenocarcinoma.

Evaluation of clinical outcome

LC was defined as no evidence of tumor regrowth in the planning target volume (PTV), including the PTV margin. Regional control was defined as no evidence of regional lymph node recurrence. Tumor progression was defined as any event of local tumor regrowth, regional lymph node recurrence, or distant metastasis. In normal tissues, acute and late reactions after C-ion RT were reclassified according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analyses

All survival times were calculated from the first day of C-ion RT. LC, OS, and progression-free survival rates were