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Particle beam therapy

Feasibility of carbon ion radiotherapy for locally advanced sinonasal adenocarcinoma

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ABSTRACT

Background and purpose: To evaluate the safety and efficacy of carbon ion radiotherapy (CIRT) for locally advanced sinonasal adenocarcinoma.

Material and methods: Twenty-two patients with sinonasal adenocarcinoma were treated with CIRT. CIRT was the primary treatment for 16 patients. Four patients received CIRT for local recurrence after surgery and two for residual tumour after surgery or chemotherapy. At the start of CIRT, 1 patient had T-classification (T) 2 disease, 2 had T3 disease, 5 had T4a disease, and 14 had T4b disease. Fourteen patients were treated with 57.6 Gy equivalent (GyE)/16 fractions, and 8, with 64.0 GyE/16 fractions.

Results: The median follow-up period was 43 months for all patients. The 3-year local control and loco-regional control rates for all patients were 76.9% (95% confidence interval [CI] = 56.7–97.1%) and 61.3% (95% CI = 38.5–84.1%), respectively. The 3-year overall survival and disease-specific survival rates were 59.1% (95% CI = 38.6–79.6%) and 65.6% (95% CI = 44.9–86.3%), respectively. Acute reactions of grade 3 of the skin and mucosa were observed in 2 and 4 patients, respectively. Late reactions included lateral visual loss (5 patients), mucosal ulceration (1 patient), and brain necrosis with clinical symptoms (1 patient). In the 5 patients who developed visual loss, the optic nerve was close to the tumour.

Conclusions: CIRT was effective and generally safe for locally advanced sinonasal adenocarcinoma.

Malignant tumours of the sinonasal tract are relatively rare, accounting for 3% of all head and neck malignancies. Adenocarcinomas account for 10–20% of all primary malignant tumours of the nasal cavity and paranasal sinuses [1].

Although surgery is the most important treatment for sinonasal adenocarcinoma, postoperative radiotherapy remains the treatment of choice for locally advanced sinonasal adenocarcinoma [2–4]. In a large study on sinonasal adenocarcinoma, Choussy et al. showed a significant survival advantage with surgery alone or in combination with radiotherapy, when compared with radiotherapy alone [2]. In the literature, the 5-year overall survival (OS) rate of sinonasal adenocarcinoma patients treated with surgery, with/without radiotherapy, ranged from 43% to 79% [2,3,5–8]. However, there are few reports on the clinical outcomes of radiotherapy alone for sinonasal adenocarcinoma. Waldron et al. reported on the outcome of 29 patients with ethmoid sinus carcinoma, including 9 with adenocarcinomas treated with radiotherapy alone. Of these 9 patients, 3 had T-classification (T) 1 disease, 5 had T2 disease, and 1 had T4 disease. Three patients developed local recurrence and 6 patients survived with a median follow-up period of 6.1 years [9].

Carbon ion radiotherapy (CIRT) was initiated at the National Institute of Radiological Sciences in 1994. Carbon ions exhibit high linear energy transfer and display good dose-localising properties compared to other ion species and photons [10,11].

We found that CIRT showed promising results for locally advanced head and neck cancer in a phase II clinical trial [12]. In that study, the 5-year local control (LC) and OS rates for 27 patients with adenocarcinoma of the head and neck region were 73% and 56%, respectively. Accordingly, this treatment protocol was used to treat head and neck carcinomas thereafter.

Clinical data for determining the effect of radiotherapy, including CIRT, on locally advanced sinonasal adenocarcinoma is insufficient. Accordingly, the objective of this study was to evaluate the effectiveness and safety of CIRT for patients with locally advanced sinonasal adenocarcinoma.

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Materials and methods

Eligibility criteria and ethics

The treatment protocol for head and neck cancer was reviewed and approved by the National Institute of Radiological Sciences Ethics Committee on Human Clinical Research, and all patients provided written informed consent. The eligibility criteria of the patients received definitive CIRT for head and neck cancer were as follows: (1) histologically confirmed carcinoma, (2) medically inoperable tumour as deemed by the referring surgeons or declined surgery, (3) age between 15 and 79 years, (4) Karnofsky performance status score of >60, (5) N0M0 status, (6) grossly measurable tumour, (7) no prior radiotherapy to the carbon ion treated area, (8) no chemotherapy within the past 4 weeks, and (9) no serious medical or psychological conditions precluding safe administration of treatment. Of the eligible patients, only those with sinonasal adenocarcinoma were selected and analysed in this study.

Carbon ion radiotherapy

Doses of carbon ions were expressed in photon-equivalent doses (Gray equivalent [GyE]), defined as the physical doses multiplied by the RBE of the carbon ions [10]. The biological flatness of the spread-out Bragg peak (SOBP) was normalised by the survival fraction of the human salivary gland tumour cells at the distal region of the SOBP, where the RBE of carbon ions was assumed to be 3.0. CIRT was administered on a fractionation schedule comprising 64.0 GyE/16 fractions for 4 weeks. When a wide range of skin or mucosa was included in the target volume, a dose of 57.6 GyE/16 fractions for 4 weeks was used. In cases where the tumours showed subcutaneous, nasopharyngeal, or oral cavity invasion, a lower dose was often used.

The patients were positioned in customised cradles (Moldcare; Alcare, Tokyo, Japan) and immobilised using a low-temperature thermoplastic shell (Shellfitter; Kuraray, Osaka, Japan). A set of computed tomography (CT) images of 2.5-mm thickness was obtained for treatment planning with the immobilisation devices. Magnetic resonance imaging (MRI) was routinely performed for the identification of the tumour, after planning CT image fusion. Determination of the gross tumour volume (GTV) was based on contrast-enhanced MRI. The clinical target volume (CTV) had a minimum margin of 5 mm added around the GTV. In case of possible tumour invasion to adjacent sites, CTV1 included whole anatomical sites and CTV2 was limited to the GTV. The planning target volume (PTV) 1 and PTV2 had margins of 3–5 mm added around the CTV1 and CTV2, respectively. The PTV1 was irradiated initially with 36 GyE/9 or 10 fractions, and thereafter, PTV2 was irradiated to a total dose of 64.0 or 57.6 GyE/16 fractions. The target reference point dose was defined as the isocentre, and the PTV was encompassed by the minimum 90% dose line of the reference point dose.

The limiting doses for critical normal tissues were defined as a maximum point dose of 30 GyE for the spinal cord and brain stem and 40 GyE for the chiasm and optic nerve. A limiting dose was not established for the brain. The CTV and PTV margins of areas close to critical organs such as the brain, brain stem, and optic nerve were reduced as necessary. When the ipsilateral optic nerve was located near the GTV, the dose limitation for optic nerve was ignored. Multi-portal irradiation was planned fundamentally to avoid severe normal tissue reactions. Three-dimensional treatment planning was performed using original HIPLAN software. A representative dose distribution is shown in Fig. 1.

During the CIRT, patients received no concomitant therapy, and after completion, patients received no adjuvant therapy such as surgery or chemotherapy. In cases of local recurrence and/or distant metastasis, treatment methods for these tumours had no limitations.

Evaluation and follow-up examinations

All patients were re-staged according to the seventh edition TNM staging system (International Union Against Cancer; UICC, 2009). All patients underwent a CT and MRI examination before treatment to determine the TNM stage. Acute reactions in normal tissues were classified according to the Radiation Therapy and Oncology Group (RTOG) scoring system. Late reactions were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Effect version 3.0. LC was defined as no evidence of tumour re-growth in the PTV1. Regional control was defined as no evidence of recurrence in both the sinonasal region outside of the PTV1 and regional lymph nodes. The oncological status was followed using both clinical nasal endoscopic examinations and CT or MRI every 2–3 months for the first 2 years after CIRT and every 3–6 months thereafter.

Statistics

LC, loco-regional control (LRC), OS, disease-specific survival (DSS), and disease-free survival (DFS) rates were determined using the Kaplan–Meier method, and the different subgroups were compared using the log-rank test. All analyses were calculated from the first day of CIRT. Differences were considered significant if the P value was less than 0.05. Statistical analysis was performed using SPSS software version 11 (SPSS Inc., Chicago, IL).

Results

Patient and treatment characteristics

A total 22 patients with sinonasal adenocarcinoma were enrolled in the study between June 1997 and January 2010. The characteristics of the patients and treatment are summarised in Table 1. All patients had N0M0 status. Four patients were diagnosed as having intestinal type and 18 as having non-intestinal type adenocarcinoma. Of the 8 patients with intracranial invasion, 6 had brain invasion and 2 had dura invasion.

Local control and survival

The median observation period was 43 months (range, 4–126 months) for all patients and 58 months (range, 36–110 months) for the 9 surviving patients. No patients were lost to follow-up.

The 3-year and 5-year LC rates were 76.9% (95% confidence interval [CI] = 56.7–97.1%) and 68.4% (95% CI = 44.5–92.3%), respectively (Fig. 2). The 3-year and 5-year LRC rates were 61.3% (95% CI = 38.5–84.1%) and 54.5% (95% CI = 30.7–78.3%), respectively. Five patients developed local recurrence. Of the 3 patients who developed regional recurrence, 2 had marginal recurrence and 1 had both marginal and lymph node recurrence (Table 1S). Of the 5 patients with local recurrence, 1 received salvage surgery and 1 re-CIRT. These 2 patients were alive without disease. Of the 5 patients who had distant metastasis, 3 patients remained without local recurrence.

The 3-year and 5-year OS rates were both 59.1% (95% CI = 38.6–79.6%) (Fig. 2). The 3-year and 5-year DSS rates were both 65.6% (95% CI = 44.9–86.3%). The 3- and 5-year disease-free survival rates were 45.5% (95% CI, 24.6–66.3%) and 40.4% (95% CI, 20.0–61.1%), respectively. The median survival period for all patients was 68.1 months. Of the 13 patients who died, 10 died of original disease and 3 of intercurrent causes without active disease.

Table 2S shows the results of univariate analysis for LC and OS risk factors. None of the factors evaluated correlated with LC. However, intracranial invasion significantly correlated with OS ($P < 0.05$; Fig. 3). The median survival periods for patients with and without intracranial invasion were 32.5 months and 126.4 months, respectively.