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Original article

Carbon-ion radiotherapy for locally advanced primary or postoperative recurrent epithelial carcinoma of the lacrimal gland

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ABSTRACT

Purpose: To evaluate the applicability of carbon ion beams for the treatment of carcinoma of the lacrimal gland with regard to normal tissue morbidity and local tumor control.

Methods and materials: Between April 2002 and January 2011, 21 patients with locally advanced primary epithelial carcinoma of the lacrimal gland were enrolled in a Phase I/II clinical trial of carbon-ion radiotherapy (CIRT) at the National Institute of Radiological Sciences. Acute radiation toxicity was the primary endpoint of this dose-escalation study and the late toxicity, local control, and overall survival were additionally evaluated as secondary endpoints. Of the 21 subjects enrolled, all patients were followed for more than 6 months and analyzed.

Results: The radiation dose was increased from the initial dose of 48.0 Gy equivalents (GyE)/12 fractions at 10% increments up to 52.8 GyE. Of the 21 patients, five received a total dose of 48.0 GyE, and 16 received a total dose of 52.8 GyE. No patient developed grade 3 or higher skin toxicity. As late ocular/visual toxicity, three patients had grade 3 retinopathy and seven patients lost their vision. Among the 10 patients treated until May 2005, five patients had local recurrence, three of whom had marginal recurrence. Therefore, the margin for the CTV (clinical target volume) was set to a range according to the orbital exenteration since June 2005. After the application of the extended margin, no local recurrence has been observed. The three-year overall survival and local control rates were 82.2% and 79.0%, respectively.

Conclusion: CIRT can be applied for primary epithelial carcinoma of the lacrimal gland, with a borderline acceptable morbidity and sufficient antitumor effect when an extended margin is adopted.

An epithelial tumor of the lacrimal gland is a very rare orbital tumor. The incidence of this disease is estimated to be 0.072 per 100,000 people [1]. In the field of ophthalmology, these tumors are associated with a poor prognosis, frequently leading to death. Adenoid cystic carcinoma histology occurs most frequently, and accounts for 20–30% of all malignant tumors of the lacrimal gland [2]. There is no current standard therapy due to the low incidence of the disease; however, surgical resection (orbital exenteration or eye-sparing surgery) and postoperative radiotherapy are generally selected. A five-year local control rate of about 50% has been reported in previous studies, and the outcomes are not satisfactory for patients with carcinoma of the lacrimal gland [3–9]. Moreover, orbital exenteration is a highly invasive treatment for patients, resulting in significant impairment of the QOL (quality of life) both physically and cosmetically. Consequently, it is hoped that a treatment allowing both preservation of the eyeball and improved tumor control rates can be established. In the present study, we evaluated the safety and efficacy of carbon-ion radiotherapy (CIRT) for locally advanced or postoperative recurrent epithelial carcinoma of the lacrimal gland.

Methods and materials

Protocol

The purpose of the present study was to establish a treatment method that can control primary epithelial malignant tumors of the lacrimal gland using carbon ion beams, and possibly to preserve the eyeball. A Phase I/II study was conducted beginning in April 2002 using the medical heavy particle accelerator (HIMAC: Heavy ion medical accelerator in Chiba) installed in the National Institute of Radiological Sciences. Regarding the CIRT, a dose escalation trial was conducted from a starting radiation dose of

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48.0 Gray equivalent (GyE)/12 fractions. A follow-up of 3 months or more was conducted in at least three of the patients that were treated with the same radiation dose, and if a reaction of Grade 3 or more was not observed in the acute normal tissue reaction score of the NCI-CTC (National Cancer Institute Common Toxicity Criteria) version 2.0 [10] regarding all cases, the radiation dose was increased by 10%. However, if a normal tissue reaction of Grade 3 or more was observed, the subsequent irradiation method and radiation dosage in these cases were investigated upon consultation with the protocol management committee.

Patient eligibility

Patients were eligible if they had pathologically diagnosed epithelial carcinoma of the lacrimal gland that was untreated or was remaining or recurring following conservative surgery, and in whom there was no lymph node or distant metastasis. The staging was performed according to the American Joint Committee on Cancer (AJCC) system, fifth edition (1997) [11]. All patients signed an informed consent form approved by the local institutional review board prior to their participation.

Carbon-ion radiotherapy (CIRT)

Carbon ion beams were generated by the HIMAC and were delivered to the target such that the target could be covered with a homogeneous biological effect by the spread-out Bragg peak (SOBP). The clinical radiation dose obtained by applying the relative biological effectiveness (RBE) of the carbon ion beam to the physical radiation dose was defined as the photon equivalent dose, and using units of GyE, the RBE was normalized so that it was 3.0 where the mean LET (Linear Energy Transfer) was 80 keV/μm.

To immobilize the patient, a head rest (Moldcare; Alcare, Tokyo, Japan) and a low-temperature thermoplastic shell (Shellfitter; Kuraray, Osaka, Japan) were used. A set of 2.5-mm-thick computed tomography (CT) images was taken for treatment planning with the patient in the immobilization devices. Three-dimensional treatment planning was performed with the Heavy Ion Plan software program [12]. The gross tumor volume (GTV) was determined with reference to contrast-enhanced CT, contrast-enhanced MRI (magnetic resonance imaging) and methionine PET-CT (positron emission tomography-CT). The clinical target volume (CTV) was defined by adding regions in which potential tumor was considered. Until May 2005, the CTV was generally determined to be in the range of 0–5 mm of the GTV border to spare adjacent critical organs, such as the optic nerve or retina (MM: minimal margin). Thereafter, a margin according to the orbital exenteration was set as the CTV, where the inner edge contained the lacrimal sac, the outer edge was the frontal bone configuring the outer orbit, the upper edge of the outer malar bone was the outer frontal bone containing the lacrimal gland, the lower edge was the upper maxillary bone configuring the outer orbit, and the outside (as well as the posterior edge) of the malar bone was the distal optic nerve of the affected side not containing the optic chiasm (EM: extended margin). The planning target volume (PTV) was set as the set-up margin by adding about 3 mm to the CTV. Typical dose distributions with a minimal margin and extended margins are shown in Fig. 1.

Endpoints and statistical analyses

The primary endpoint was the acute adverse reaction of the normal tissue configuring the eyelid, orbit and eyeball, while the secondary endpoints were the late adverse reactions, survival rate and local control rate. The acute adverse reactions until 3 months following treatment were evaluated based on the NCI-CTC Version 2.0, and scoring of the late adverse reactions was conducted according to the RTOG/EORTC (Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer) Late Radiation Morbidity Scoring Schema [13], with the highest grade determined for the early and late reactions, respectively. Patients were followed by the referring ophthalmologist and radiation oncologist at three-month intervals during the first three years after CIRT and at intervals of 6 months thereafter. An MRI of the head and neck, whole body CT and methionine PET scans were taken every 6 months. The visual acuity, intraocular pressure and visual field were evaluated at each ophthalmological examination with special focus on the development of blindness or neovascular

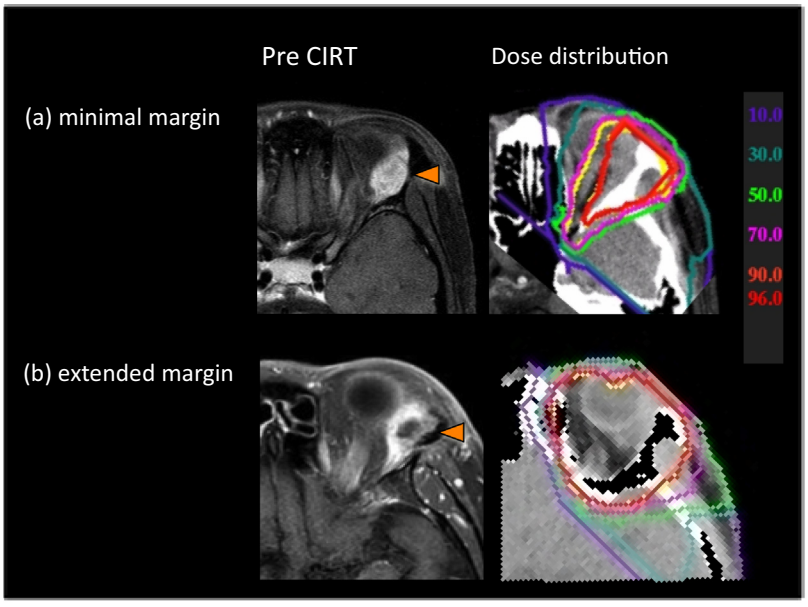

Fig. 1. (a) This MRI was obtained before carbon ion radiotherapy (CIRT) (left). The dose distribution of CIRT with minimal margin is illustrated for patients with carcinoma of the lacrimal gland (the red line indicates 96% isodose of the prescribed dose) (right). (b) The dose distribution of CIRT with extended margin is illustrated.

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