Radiotherapy and Oncology xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Risk factors for brain injury after carbon ion radiotherapy for skull base tumors

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ARTICLE INFO

Article history:
Received 25 December 2012
Received in revised form 5 November 2013
Accepted 9 November 2013
Available online xxxx

Keywords:
Carbon ion radiotherapy
Brain injury
Dose–volume histogram
Skull base tumor

ABSTRACT

Background and purpose: This study aimed to determine the risk factors for radiation-induced brain injury (RIBI) after carbon ion radiotherapy (CIRT) for treating skull base tumors.
Materials and methods: Between April 1997 and January 2009, CIRT at a total dose of 48.0–60.8 Gy equivalent (GyE) was administered in 16 fractions to 47 patients with skull base tumors. Of these patients, 39 who were followed up with magnetic resonance imaging (MRI) for more than 24 months were analyzed. RIBI was assessed according to the MRI findings based on the Late Effects of Normal Tissue-Subjective, Objective, Management, Analytic criteria; clinical symptoms were assessed according to the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer tables. The correlations of clinical and dosimetric parameters with incidence of ⩾grade 2 RIBI were retrospectively analyzed.
Results: The median follow-up period was 67 months. The 5-year actuarial likelihoods of ⩾grade 2 RIBI and ⩾grade 2 clinical symptoms were 24.5% and 7.0%, respectively. Multivariate analysis demonstrated that the brain volume receiving more than 50 GyE (V50) was a significant risk factor for the development of ⩾grade 2 RIBI ($p = 0.004$).
Conclusion: V50 was a significant risk factor for ⩾grade 2 RIBI after CIRT using a 16-fraction regimen.
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Ion beams, such as protons and carbon ions, provide a more beneficial dose distribution in cancer treatment compared to photons. Additionally, carbon ions are heavier than protons, providing a larger relative biological effectiveness (RBE), and thus a higher probability of tumor control, while irradiating a smaller volume of surrounding, normal tissues. At our organization, the National Institute of Radiological Sciences (NIRS) in Japan, carbon ion radiotherapy (CIRT) has been used to treat various malignant tumors since 1994. CIRT is a promising treatment for various inoperable and radio-resistant tumors [1–3].

Skull base tumors have been shown to reside adjacent to risk organs, such as the brainstem or optic nerves, and are mostly radio-resistant [4,5]. Therefore, these tumors have a good indication for particle therapy, including CIRT. We previously reported the clinical results of skull base or paracervical chordoma after CIRT. The local progression-free rate was 85.1% at 5 years, and the overall survival rate was 87.7% [6].

In the treatment of skull base tumors, however, certain parts of the central nervous system—such as the temporal lobe, frontal lobe, and cerebrum—might not be excluded entirely from the high-dose area. The incidence of radiation-induced brain injury (RIBI) with moderate-to-severe symptoms is 5–8.3% following proton radiotherapy for skull base tumors [7,8]. RIBI is one of the most critical complications for long-term survivors receiving this treatment.

In photon radiotherapy, dose–volume histogram (DVH) parameters are predictive factors for late morbidity in many organs, such as the salivary glands, lungs, and rectum. In CIRT, these are also predictive factors for the optic nerves, skin, and rectum [9–11]. However, the correlation of RIBI with DVH parameters is unclear, even in photon radiotherapy.

In this study, the correlations of clinical and dosimetric parameters with the severity and incidence of brain injury were retrospectively investigated using long-term follow-up of patients with skull base tumors treated with CIRT.

Materials and methods

Patient and tumor characteristics

Between April 1997 and January 2009, 47 patients with skull base tumors were treated with CIRT in the NIRS. All patients signed

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http://dx.doi.org/10.1016/j.radonc.2013.11.005

an informed consent form approved by the local institutional review board. Of these patients, 39 who received follow-up with magnetic resonance imaging (MRI) for more than 24 months were analyzed. Of the 8 patients who were excluded from this study, 4 died within 24 months after treatment, 3 were not followed using MRI, and 1 developed local recurrence that made it impossible to evaluate RIBI. Of the 4 patients who died within 24 months, 3 (2 with chondrosarcoma and 1 with malignant meningioma) died of distant metastases (4, 5, and 23 months after CIRT) and 1 (with chordoma) died of intercurrent causes (9 months after CIRT). None of these patients had developed RIBI as assessed by the last MRI or had any neurological symptoms. Patient and tumor characteristics are shown in Table 1.

Carbon ion radiotherapy

Each patient was positioned in a customized cradle (Moldcare; Alcare, Tokyo, Japan), with the face immobilized by a low-temperature, thermoplastic device (Shellfitter, Kuraray, Osaka, Japan). A set of 2.5-mm-thick CT scans was obtained for treatment planning. Three-dimensional treatment planning was performed using our original HIPLAN software. The clinical target volume (CTV) had minimum margins of 5 mm added to the gross tumor volume. Furthermore, a margin of 3–5 mm was added as an internal and setup margin around the CTV to create a final planning target volume (PTV). The CTV and PTV margins of the area in proximity to critical organs, such as the brain, brain stem, or optic nerve, were reduced as necessary. At the beginning, 2 portals were used for several patients. However, more than 3 portals were used in principle to improve dose distributions.

Dose was expressed as gray equivalent (GyE), calculated by multiplying the physical dose by the RBE. The clinical RBE of the carbon beam was determined according to the RBE for acute skin reaction, which was assessed to be 3.0 at the distal part of the spread-out Bragg peak [12].

CIRT was given in 16 fractions over 4-week periods, at 4 treatment days per week. The overall treatment time was 25–30 days (median, 28 days). The prescribed total dose ranged from 48.0 to 60.8 GyE. Twenty-seven patients were treated with 60.8 GyE (3.8 GyE/fraction), 5 with 57.6 GyE (3.6 GyE/fraction), 5 with 52.8 GyE (3.3 GyE/fraction), and 2 with 48.0 GyE (3.0 GyE/fraction).

Follow-up and RIBI evaluation

Patients received follow-up at 3-month intervals for the first 2 years after CIRT and at 3-to-6-month intervals thereafter. MRI examination of the skull base was performed at 3-to-6-month intervals. The diagnosis of RIBI was based on MRI findings of a high-intensity area on T2-weighted images and enhancement on post-contrast images, appearing within the irradiation field after CIRT. If the changes as assessed by MRI showed direct continuity with the primary lesion, MRI was performed again for an accurate diagnosis of RIBI.

RIBI severity was evaluated on the basis of MRI findings according to the analytic scale of the LENT-SOMA (late effects of normal tissue-subjective, objective, management, and analytic scales) criteria: grade 1, change in focal white matter, focal contrast enhancement, and surrounding edema; grade 2, non-enhanced area or cystic lesion in the enhanced lesion; grade 3, focal necrosis with mass effect; and grade 4, mass effect requiring surgical intervention. Clinical symptoms were scored according to the toxicity criteria of the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG/EORTC) (Table 1S in the Supplementary file). The maximum grade was used for the analysis.

DVH analysis

DVH analysis was performed to identify risk factors for the occurrence of RIBI. The brain volume considered included the brain parenchyma of the temporal lobes, frontal lobes, and cerebellum, without the tumor itself. Based on DVH data obtained from the HIPLAN software, brain volumes receiving in excess of 10–50 GyE in 10 GyE increments were expressed as V10–V50 (ml).

Statistical analysis

The follow-up time was calculated from the first date of irradiation. To compare the irradiated brain volumes, the Mann–Whitney *U* test was used. Cumulative incidents of RIBI were evaluated using the Kaplan–Meier method and compared by the log-rank test as a univariate analysis among the different subgroups. Furthermore, some factors with significance ($p < 0.05$) in univariate analysis were applied to multivariate analysis using Cox's proportional hazard model. Differences were considered significant if the p value fell below 0.05. Statistical analysis was performed with SPSS software version 11 (SPSS Inc., Chicago, IL).

Results

Incidence of RIBI

The median follow-up period was 67 months (range, 24–152 months).

Incidences of RIBI and clinical symptoms are summarized in Table 2. Grade 1 RIBI was observed in 7 patients, grade 2 in 8, grade 3 in 6, and grade 4 in 1. Representative images scored as grade 2 are shown in Fig. 1. The median interval between the beginning of treatment and initial and maximum RIBI was 26 months (range, 5–103 months) and 39 months (range, 16–132 months), respectively. Of the 22 patients who developed RIBI, 17 did so in the ipsi-

Table 1
Patient and tumor characteristics.

Gender	
Male	20
Female	19
Age (years)	
Median	47
Range	16–76
History of operation	
Yes	32
No	7
Hyper tension	
Yes	7
No	32
Histology	
Chordoma	25
Chondrosarcoma	5
Olfactory neuroblastoma	4
Meningioma	4
Giant cell tumor	1

Table 2
Incidence of radiation-induced brain injury and clinical symptoms.

Grade of symptoms (RTOG/EORTC)	Grade of brain injury (LENT-SOMA)					Total
	0	1	2	3	4	
0	17	5	2	1	0	25
1	0	2	5	4	0	11
2	0	0	1	1	0	2
3	0	0	0	0	0	0
4	0	0	0	0	1	1
Total	17	7	8	6	1	39

Please cite this article in press as: Koto M et al. Risk factors for brain injury after carbon ion radiotherapy for skull base tumors. Radiother Oncol (2013), http://dx.doi.org/10.1016/j.radonc.2013.11.005