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Original article

Dose–volume histogram analysis of brainstem necrosis in head and neck tumors treated using carbon-ion radiotherapy

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ABSTRACT

Background and purpose: We aimed to evaluate the relationship between brainstem necrosis and dose–volume histograms in patients with head and neck tumors after carbon-ion radiotherapy.
Material and methods: We evaluated 85 patients with head and neck tumors who underwent carbon-ion radiotherapy and were followed-up for ≥12 months. Brainstem necrosis was evaluated using the Common Terminology Criteria for Adverse Events (version 4.0).
Results: The median follow-up was 24 months, and four patients developed grade 1 brainstem necrosis, with 2-year and 3-year cumulative rates of 2.8% and 6.5%, respectively. Receiver operating characteristic curve analysis revealed the following significant cut-off values: a maximum brainstem dose of 48 Gy (relative biological effectiveness [RBE]), D1 cm^3 of 27 Gy (RBE), V40 Gy (RBE) of 0.1 cm^3, V30 Gy (RBE) of 0.7 cm^3, and V20 Gy (RBE) of 1.4 cm^3. Multivariate analysis revealed that V30 Gy (RBE) was most significantly associated with brainstem necrosis. The 2-year cumulative rates were 33% and 0% for V30 Gy (RBE) of ≥0.7 cm^3 and <0.7 cm^3, respectively ($p < 0.001$).
Conclusions: The present study indicated that the dose constraints might help minimize brainstem necrosis after carbon-ion radiotherapy.

Head and neck tumors are the sixth most common malignancy worldwide. Most patients are diagnosed with squamous cell carcinoma and subsequently undergo multimodal therapy, including surgery and concurrent chemoradiotherapy [1]. However, non-squamous cell carcinomas are resistant to radiotherapy and chemotherapy, and treatment options are limited. Although surgery is the mainstay of curative treatment, there are no effective treatments for inoperable patients. In this context, carbon-ion radiotherapy has good dose-localizing properties because of the Bragg peak, and the dose to the surrounding normal tissue can be minimized [2]. Moreover, a carbon-ion beam offers high biological effectiveness, which results in favorable tumor control. Thus, carbon-ion radiotherapy might be a promising treatment for patients with inoperable non-squamous cell carcinoma [3,4].

Although carbon-ion radiotherapy has a sharp dose distribution, head and neck tumors are frequently located close to organs at risk and it is difficult to avoid adverse events when the tumor is close to these organs. Therefore, it is important to establish dose constraints that can be used in a meticulous treatment plan to minimize adverse events. For example, carbon-ion radiotherapy dose constrains have recently been reported for several organs, including the optic nerve, brain, and mucosa [5–7]. However, there are no reports regarding dose–volume histogram (DVH) analysis associated with brainstem necrosis after carbon-ion radiotherapy. Furthermore, radiation-induced brainstem necrosis is a rare but critical adverse event [8,9], because the brainstem plays important roles in controlling the cranial nerves, cardiac function, and respiratory motion. Therefore, we retrospectively evaluated the relationship between brainstem necrosis and DVH among patients with head and neck tumors who underwent carbon-ion radiotherapy.

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Materials and methods

Patient and tumor characteristics

Between January 2011 and June 2015, 139 head and neck tumors were consecutively treated using carbon-ion radiotherapy at the Gunma University Heavy Ion Medical Center. All patients were prospectively treated according to carbon-ion radiotherapy protocols that were approved by our Institutional Review Board. The first protocol was for non-squamous cell carcinomas, which were treated using 64 Gy (RBE) in 16 fractions over 4 weeks, although 57.6 Gy (RBE) was used when the skin and mucosa were broadly included in the treatment field. The second protocol was for malignant melanomas, which were treated using concurrent carbon-ion radiotherapy with 3 courses of dacarbazine, nimustine, and vincristine (DAV therapy). The dose and fractionation schedule policy was same as that in the first protocol. The third protocol was for bone and soft tissue sarcomas, which were treated using 70.4 Gy (RBE) in 16 fractions over 4 weeks. Patients were included in this retrospective study if the treatment field included the brainstem and the patient's follow-up was ≥12 months. However, we excluded patients if the brainstem was not included in the treatment field ($n = 16$), previous carbon-ion radiotherapy had been performed for the same disease ($n = 3$), or the follow-up time was <12 months ($n = 35$). The clinical characteristics of the 85 included patients are shown in Table 1. All patients had a biopsy-confirmed pathological diagnosis, and their pretreatment evaluations included a physical examination, laryngoscopy, computed tomography (CT), magnetic resonance imaging (MRI), and 18-fluorodeoxyglucose-positron emission tomography.

Carbon-ion radiotherapy

All patients provided their written informed consent before undergoing treatment. The detailed techniques for carbon-ion radiotherapy and the treatment planning have been reported previously [7]. The dose of carbon-ion radiotherapy was expressed as "Gy (relative biological effectiveness [RBE])". Based on the tumor-specific protocols, 14 patients received 57.6 Gy (RBE) in 16 fractions, 65 patients received 64.0 Gy (RBE) in 16 fractions, and 6 patients received 70.4 Gy (RBE) in 16 fractions. Sixteen patients were treated using concurrent DAV chemoradiotherapy.

Table 1
Patient and tumor characteristics.

Characteristics		*N*	Percentage
Age, Median (years)		62	Range, 19–91
Sex	Male	45	53
	Female	40	47
Performance Status	0	42	49
	1	43	51
Histology	Adenoid cystic carcinoma	30	35
	Malignant melanoma	25	29
	Soft tissue tumor	8	9
	Neuroblastoma	7	8
	Adenocarcinoma	4	5
	Mucoepidermoid carcinoma	3	4
	Others	8	9
Tumor site	Nasal cavity	39	46
	Paranasal sinus	16	19
	Major salivary gland	11	13
	Pharynx	7	8
	Soft tissue	5	6
	Oral cavity	4	5
	External auditory canal	3	4
Radiation dose	57.6 Gy (RBE)/16 fractions	14	16
	64.0 Gy (RBE)/16 fractions	65	76
	70.4 Gy (RBE)/16 fractions	6	7

RBE: relative biological effectiveness.

Assessment of brainstem necrosis

Brainstem necrosis was evaluated based on central nervous system necrosis using the Common Terminology Criteria for Adverse Events (version 4.0). Grade 1 indicates only asymptomatic clinical or diagnostic observations, grade 2 indicates moderate symptoms and required corticosteroid treatment, grade 3 indicates severe symptoms and required medical intervention, grade 4 indicates life-threatening disease and an urgent need for intervention, and grade 5 indicates death. The brainstem necrosis regions were evaluated using gadolinium-enhanced MRI during the follow-up. Biopsies were not performed to diagnose the necrosis based on the risk to the patients. All DVH analyses were performed using MIM Maestro (version 6.0.2.).

Statistical analyses

The cumulative incidences of brainstem necrosis were calculated using the Kaplan–Meier method. To compare the subgroups, univariate analyses were performed using the log-rank test, and multivariate analyses were performed using Cox's proportional hazards model. Receiver operating characteristic (ROC) curves were generated to identify optimal cut-off values for the DVH parameters that were associated with brainstem necrosis. A *p*-value of <0.05 was considered statistically significant, and all analyses were performed using SPSS software (version 23.0; SPSS Inc., Chicago, IL, USA).

The Lyman–Kutcher–Burman normal tissue complication probability (NTCP) parameters [10–12] were estimated using the brainstem necrosis rate and the DVH parameters. The equivalent uniform dose (EUD) was also used to facilitate the use of the non-uniform brainstem dose distribution in the NTCP calculation [13]. The equations that we used in the analyses were as follows:

$$\mathrm{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx \tag{1}$$

$$t = \frac{\mathrm{EUD} - \mathrm{TD}_{50}}{m \cdot \mathrm{TD}_{50}} \tag{2}$$

$$\mathrm{EUD} = \left(\sum_i v_i D_i^{\frac{1}{n}} \right)^n \tag{3}$$

In these equations, n represents the parallel seriality of the organ, m represents the sharpness of the sigmoidal function, and $TD_{50,}$ represents the tolerance dose that results in a 50% probability of complications if the dose covers the organ's full volume. The subscript *i* term represents the index of each dose bin in the DVH. Python (https://www.python.org/) and its statistical module "statsmodels" (http://statsmodels.sourceforge.net/) were used to determine the maximum likelihood estimation. The log likelihood function (LLF) was calculated using the subscript *j* and *k* terms to reflect cases with or without complications, respectively:

$$\mathrm{LLF} = \sum_j \ln \mathrm{NTCP}_j + \sum_k \ln(1 - \mathrm{NTCP}_k) \tag{4}$$

The parameters m and TD_{50} were determined using the Probit regression function in statsmodels. By iteratively changing parameter n, we were able to predict the best set of n, m, and TD_{50}. The biologically equivalent doses in 2-Gy fractions (EQD_2) were converted based on an alpha/beta ratio of 2.5 Gy [14].

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