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Carbon ion radiation therapy

Dose–volume histogram and dose–surface histogram analysis for skin reactions to carbon ion radiotherapy for bone and soft tissue sarcoma

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ABSTRACT

Background and purpose: To evaluate the usefulness of the dose–volume histogram (DVH) and dose–surface histogram (DSH) as clinically relevant and available parameters that helped to identify bone and soft tissue sarcoma patients at risk of developing late skin reactions, including ulceration, when treated with carbon ion radiotherapy.

Materials and methods: Thirty-five patients with bone and soft tissue sarcoma treated with carbon ion beams were studied. The clinical skin reactions were evaluated. Some pretreatment variables were compared with the grade of late skin reactions.

Results: Average DVH and DSH were established in accordance with the grading of the skin reactions. Prescribed dose, the difference in depths between the skin surface and the proximal extent of the tumor, and some DVH/DSH parameters were correlated with late skin reaction (≧grade 3) according to univariate analysis. Furthermore, the area irradiated with over 60 GyE (S_{60} > 20 cm^2) on DSH was the most important factor by multivariate analysis.

Conclusions: The area irradiated with over 60 GyE (S_{60} > 20 cm^2) on DSH was found to be a parameter for use as a predictor of late skin reactions.

In 1994, clinical research trials using carbon ion beams were initiated at the National Institute of Radiological Sciences (NIRS) in Chiba, Japan [1–3]. As of February 2008, a total of 3819 patients (4053 lesions) have been treated by this modality. Some of these patients, especially those with bone and soft tissue sarcoma, had tumors located near the skin and developed severe skin reactions after treatment [3]. Among them, some progressed to grade 4 late skin reactions identified as ulcers. To allow the prediction of such skin reactions, it is useful to search for factors that are related to the skin reactions. Thus, in this study, certain factors of patients with bone and soft tissue sarcoma were assessed in terms of correlation with late skin reactions associated with the clinical use of carbon ion radiotherapy.

Materials and methods

Protocol study

From June 1996 to December 1999, 64 lesions in 57 patients (37 men and 20 women) with unresectable bone and soft tissue sarcoma were treated with carbon ion beams according to our dose escalation protocol. The patient eligibility of this protocol was described previously [3]. Briefly, they had histologically confirmed bone and soft tissue sarcomas judged unresectable by the referring surgeon. The tumor had to be grossly measurable, but its size was not allowed to exceed 15 cm. For dose escalation, at least 3 patients each were treated at the same dose level, and then, after careful observation, a 10% total-dose escalation was conducted. All patients signed informed consent forms approved by the local institutional review board.

Patient selection criteria

For the sake of accuracy and simplicity of evaluation, the following patients were excluded from the analysis: (1) those with tumor invasion into the skin, which might complicate the direct radiation effect on the skin; (2) those who died within six months (in the case of acute skin evaluation) or within 1.5 years (in the case of late skin evaluation) after treatment; (3) those treated in both supine and prone positions because they required recalculation of the total dose of both positions using a pseudo-target; and (4) those with tumors located in a limb, because skin reactions of limbs show different patterns from those of other sites, and should be dealt with separately. After these adjustments, 35 patients (35 lesions) were analyzed for acute skin reactions and 27 of these patients (27 lesions) were also analyzed for late skin reactions.

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Carbon ion radiotherapy

Carbon ion beams were generated by HIMAC (Heavy Ion Medical Accelerator in Chiba), the world's first heavy ion accelerator complex dedicated to medical use in a hospital environment [1]. The energy levels of the generated beams were 290 MeV, 350 MeV, and 400 MeV. For the treatment, the patients were positioned in customized cradles (Moldcare; Alcare, Tokyo, Japan) and were immobilized with a low-temperature thermoplastic retaining device. A set of 5-mm-thick slice CT images was taken for treatment planning with the patients retained in the immobilization device. Three-dimensional treatment planning was performed using HIPLAN software (by NIRS) [4].

In accordance with the ICRU Report [5], the visible lesion on the CT image was defined as the gross tumor volume (GTV). The clinical target volume (CTV) included the GTV and the estimated subclinical local involvement. An internal margin was added to the CTV to allow for tumor movement and tumor growth. The planning target volume (PTV) consisted of the CTV, the internal margin, and a set-up margin corresponding to the sum of the error lengths at positioning (about half the length of the CT slice thickness in our system) including the dose calculation error associated with the change from the CT value to the beam range (about 3% at our system). As a result, a margin of about 5 mm was usually added to the CTV to create the PTV. The PTV was covered by at least 90% of the administered dose.

Dose was expressed in Gray equivalent (GyE), which was calculated by multiplying the physical dose with the Relative Biological Effectiveness (RBE). The RBE was estimated to be 3.0 at the distal part of the spread-out Bragg peak (SOBP) based upon radiobiological studies. The details of the RBE value used at NIRS were discussed by Kanai et al. [6].

Skin evaluation

Four radiation oncologists score-rated all the skin reactions of each patient in the maximum phase by checking the photo-slides captured during the follow-up durations, using the RTOG Scoring System for assessing acute reactions and the Late Radiation Morbidity Scoring Scheme of RTOG/EORTC for evaluating the late skin reactions [7].

Dose–volume histogram (DVH) and dose–surface histogram (DSH)

DVH was calculated for the region of interest (ROI). ROI was defined as all the organs inside the body covered by the skin at the irradiated area. DSH was calculated by the following procedure. First, the skin contours were carefully outlined with a thickness of one pixel for each CT slice. Then, the contours of the skin surface on each CT slice were divided into small (5 mm) compartments, and multiplied by the thickness of the CT slice (5 mm). In this manner, a number of 25-mm^2 square-shaped compartments with one-pixel-sized-thickness volume were made. The next step was to calculate the radiation dose delivered to each of these compartments. The equal-dose compartments were then summated to determine the cumulative area irradiated with each discrete dose level so as to obtain the cumulative DSH. The calculation of DVH and DSH was performed using HIPLAN software [4].

Evaluation of pretreatment variables

Some of the pretreatment variables thought to be relevant to late skin reactions were assessed using Fisher's exact test in univariate analysis. The variables contained sex, patient age, primary tumor site, difference in depths between the skin surface and the proximal extent of the tumor, planning target volume, prescribed dose, neoadjuvant chemotherapy, and adjuvant chemotherapy. Furthermore, some factors with significance in univariate analysis and the representative values derived from DVH/DSH parameters were applied to multivariate analysis using Cox's proportional hazard model.

Results

Patient and tumor characteristics

All 35 patients with acute skin reactions and 27 patients with late skin reactions were analyzed. The number of lesions and patients was the same. Table 1 shows the patients' and tumor characteristics. The numbers of patients at each total-dose level were 3 (52.8 GyE), 6 (57.6 GyE), 6 (64 GyE), 5 (70.4 GyE), and 15 (73.6 GyE) for acute skin reactions, and 3 (52.8 GyE), 3 (57.6 GyE), 5 (64 GyE), 4 (70.4 GyE), and 12 (73.6 GyE) for late skin reactions. All the patients were treated in fixed 16 fractions. In the patients analyzed for late skin reactions, more than one-third of the tumors were located in the sacral region.

Follow-up and skin reactions

After the treatment, the patients were examined on a regular basis throughout the follow-up period. Maximum follow-up time in these patients ranged from 29.5 to 71.7 months (median 44.7 months).

Table 1
Patients' and tumor characteristics.

	Acute evaluation	Late evaluation
Numbers	35	27
Age/median (years)	15–85/47	15–85/51
Gender		
Male	22 (62.9%)	18 (66.7%)
Female	13 (37.1%)	9 (33.3%)
Tumor site		
Sacrum	11 (31.4%)	10 (37.0%)
Spine	10 (28.6%)	8 (29.6%)
Iliac bone	6 (17.1%)	3 (11.1%)
Pubic bone	4 (11.4%)	3 (11.1%)
Others	4 (11.4%)	4 (11.1%)
Target volume/median (ml)	49–1829/714	49–1665/701
Target dose		
52.8 GyE	3 (8.6%)	3 (11.1%)
57.6 GyE	6 (17.1%)	3 (11.1%)
64.0 GyE	6 (17.1%)	5 (18.5%)
70.4 GyE	5 (14.3%)	4 (14.8%)
73.6 GyE	15 (42.9%)	12 (44.4%)
Histologic diagnosis		
Bone		
Osteosarcoma	9 (25.7%)	8 (30.0%)
Chordoma	9 (25.7%)	9 (33.3%)
Chondrosarcoma	3 (18.6%)	2 (7.4%)
Others	3 (18.6%)	0 (0%)
Soft tissue		
MPNST[a]	4 (11.4%)	2 (7.4%)
MFH[b]	1 (2.9%)	0 (0%)
Liposarcoma	1 (2.9%)	1 (3.7%)
Others	5 (14.3%)	5 (18.5%)
Chemotherapy		
Neoadjuvant (+)	19 (54.3%)	14 (51.9%)
Neoadjuvant (−)	16 (45.7%)	13 (48.1%)
Adjuvant (+)	8 (22.9%)	6 (22.2%)
Adjuvant (−)	27 (77.1%)	21 (77.8%)

[a] Malignant peripheral nerve sheath tumor.
[b] Malignant fibrous histocytoma.