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Carbon-ion pencil beam scanning for thoracic treatment – initiation report and dose metrics evaluation

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ABSTRACT

Carbon-ion beam scanning has not previously been used for moving tumor treatments. We have commenced respiratory-gated carbon-ion radiotherapy (CIRT) in the thoracic and abdominal regions under free-breathing conditions as a clinical trial. This study aimed to investigate this treatment in the lungs in comparison with passive scattering CIRT. Five patients had thoracic tumors treated with carbon-ion scanned beams using respiratory gating. We analyzed the actual treatments and calculated passive scattering treatment plans based on the same planning CT. We evaluated tumor size until 3 months post treatment and each treatment plan regarding dose delivered to 95% of the clinical target volume (CTV-D95), mean lung dose, percentage of lung receiving at least 5 Gy (RBE) (Lung-V5), Lung-V10, Lung-V20, heart maximum dose (Dmax), esophagus Dmax, cord Dmax and skin Dmax. Obvious tumor deterioration was not observed up to 3 months post treatment. The dose evaluation metrics were similar item by item between respiratory-gated scanned CIRT and passive scattering CIRT. In conclusion, scanned beam CIRT provided treatments equivalent to passive scattering CIRT for thoracic tumors. Increased sample numbers and longer-term observation are needed.

KEYWORDS: carbon-ion radiation therapy, thoracic treatment, respiratory phase–controlled scanning beam treatment, clinical trial

INTRODUCTION

Beam delivery of carbon-ion radiation therapy (CIRT) is mainly classified into two techniques: 'passive scattering' [1] (which is conventionally used) and 'scanning' [2]. Passive scattering has already been applied to clinical treatments because of its beam stability. Although it is relatively easier to deliver shaped dosimetry, one of the disadvantages of passive scattering is the necessity for patient-oriented external equipment for adjusting beam ranges and keeping lateral beam edges sharp [3]. Owing to the size and shape of such equipment, it takes about a week to start a treatment. On the other hand, although the scanning technique itself was considered early in the development of CIRT [4], it was not applied to clinical treatments because of the technical difficulty of controlling the carbon-ion beams. Recently, with the improvement of technologies, the scanning technique has started to be used for clinical non-movable targets [4, 5]. Based on the principle of the scanning technique, namely, that it does not need any patient-oriented external equipment, it is possible to commence the treatment sooner than with the passive scattering technique.

Although the scanning technique is considered better because of modulation of the radiological dose to the target and earlier treatment commencement, irradiation of moving targets has not previously been used. To overcome the related difficulties, the combination use of 4D computed tomography (4DCT) for planning CT, respiratory-gated irradiation to reduce the field range [6, 7], and rescanning to deregulate the interplay effects was then designed and developed [8]. This is called 'respiratory-gated phase controlled rescan' (PCR) [9].

The Heidelberg Ion Beam Therapy Center in Germany has reported on the application of CIRT for the liver, using raster scanning [10], but that treatment was performed while restraining respiration. There have been no reports yet of treatments for the thoracic region. Our institute started a clinical trial for moving targets with PCR under free-breathing conditions in March 2015 [11], and observation has been under way since then.

This article reports the commencement of carbon-ion scanning beam treatment in the thoracic region with PCR under free-breathing conditions with actual tumor reactions in the acute phase, and to investigate the differences in dose parameters between scanning beam and passive scattering.

MATERIALS AND METHODS

Patient eligibility

Between March 2015 and September 2015, we treated 10 patients with carbon-ion scanning beams for moving targets. In terms of tumors in the lungs, consecutive 5 patients had their metastatic tumors. Their primary lesions were anal canal cancer, sacral chordoma, renal cancer, ocular malignant melanoma, and pancreatic cancer. We analyzed the clinical data in January 2016.

This study was implemented as a clinical trial (registration: UMIN000017134). Written informed consent was obtained from all participants, and the institutional review board approved the trial. Inclusion criteria for this study were: (i) a recognizable thoracic or abdominal tumor that could be treated with conventional passive scattering CIRT, (ii) requiring a respiratory synchronized system (gating), even if they were treated with conventional passive scattering CIRT, (iii) a thorough explanation of the clinical trial could be given and written informed consent obtained, (iv) life expectancy of more than 6 months, and (v) performance status 0–1 (WHO guidelines). Exclusion criteria were: (i) radiotherapy history in the irradiating field, (ii) active and uncontrollable infection in the irradiating field, and (iii) rejection of follow-up in our institute. Patient characteristics are summarized in Table 1, and all tumors prior to the treatment are shown in Fig. 1.

Treatment plan with scanning beams

Custom immobilization devices (Moldcare; Alcare, Tokyo, Japan; Shellfitter; Kuraray, Osaka, Japan) were prepared before taking planning CT. Planning CT was acquired in 4D mode (Aquillion One™ Vision Edition; Toshiba Medical Systems, Otawara, Japan) under free-breathing conditions. The 4DCT dataset was subdivided into 10 phases. The gating window was selected after checking its tumor displacement, and we excluded phases in which tumors located farther. For gating, we used an amplitude-based gating technique as internal signal gating [11]. For patients with a small tumor, we used commercial gold markers (Disposable gold marker; Olympus Corporation, Tokyo, Japan) for set-up registration. We inserted them near the tumor through a bronchoscope, being careful not to locate markers on the beam-line.

The clinical target volume (CTV) was defined as the gross tumor volume plus 6 mm on the reference CT (peak exhalation phase). A range-adapted internal target volume (range-ITV) was applied to account for uncertainty due to changes of the radiological path length with respiration in each beam port, using half of the 4DCT data around the peak exhalation phase. In-house 4Dtool software was used to calculate the range-ITV from the CTV by adding an interfractional margin, which was a distance of 2 or 3 mm water-equivalent path lengths (WEPLs) [12].

The range-ITV was assumed to correspond to the planning target volume (PTV) of respective beam ports. The clinical dose was calculated with the in-house treatment planning system, which was derived from Monte Carlo simulations and the relative biological effectiveness (RBE) predicted from a theoretical model [13]. After dose calculations for each phase, time-accumulated average dose distributions were constructed in a reference CT using the 4Dtool software [12].

The theoretical number of particles was calculated by the treatment planning system, and the irradiation equipment has a function for counting its actual number. Quality assurance (QA) was determined for static and dynamic states. Static QA is commonly practiced; dynamic QA was carried out with detectors moving in accordance with the target displacement. Every QA determination was confirmed to have ≤2% difference between the static and dynamic treatment plan results.

Patient set-up was based on a bony anatomic structure registration, rather than soft-tissue, because the particle beam is affected by tissue density variations, especially bone. These set-ups were implemented with a 6-axis movable treatment bed and 2D-3D registration software [5].

Table 1. Patient characteristics

Pt	Age	Sex	PS	Original disease	Location	Tumor size, mm	Dose, Gy (RBE)	Fraction	Ungated target motion, mm	Gated target motion, mm	Gating window: planning	Gating window: irradiation
1	71	F	0	Anal canal cancer	Right S1	20.2 × 14.7	60.0	4	2.4	1.0	T30–T70	T30–T70
2	59	M	1	Sacral chordoma	Right S9	43.5 × 42.3	57.6	12	9.8	9.8	T30–T60	T30–T60
3	61	F	0	Renal cancer	Right S1	23.4 × 19.4	60.0	4	0.8	0.4	T30–T70	T30–T60
4	71	M	0	Melanoma	Left S9	4.8 × 4.8	60.0	4	13.6	1.3	T30–T70	T30–T60
5	60	F	0	Pancreatic cancer	Left S6	8.1 × 7.5	60.0	4	6.7	3.2	T30–T70	T30–T60

Pt = patient.

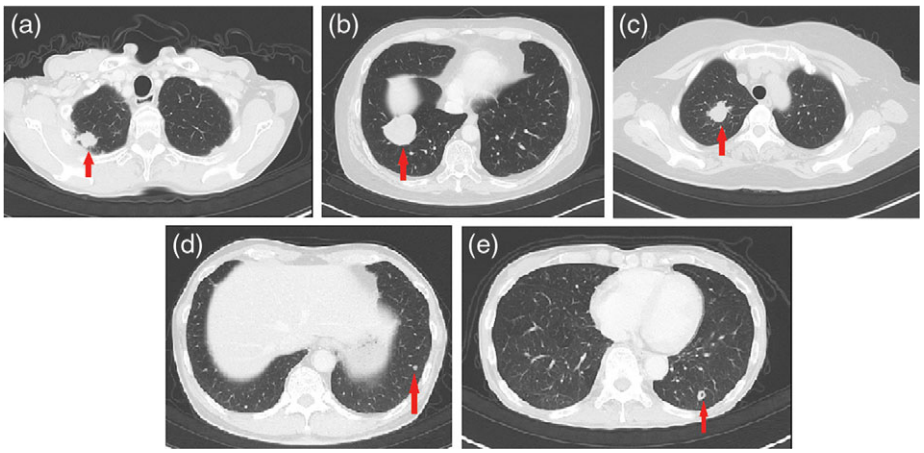

Fig. 1. Tumor locations before treatment. (a) Patient #1: right S1, (b) Patient #2: right S9, (c) Patient #3: right S1, (d) Patient #4: left S9, (e) Patient #5: left S6. Arrows indicate tumors.

Treatment plan with passive scattering beams

To simulate treatment plans with passive scattering beams, we used identical planning CTs to those used in the actual scanning treatments on this trial. Of the 10 phases of the 4DCT dataset, the reference phase was used for calculating the treatment plans with passive scattering beams. The CTV and dose/fraction were also set the same as for the plans with scanning, and the beam directions were those practiced by our institute. The treatment planning system was a heavy particle treatment planning system, version 1.0.12 (Mitsubishi electronic, Tokyo, Japan), and a pencil beam algorithm was used for calculation. The PTV was defined as the CTV plus a 5-mm margin in the craniocaudal direction, and the domain of the CTV plus the craniocaudal 5 mm was then replaced by the highest Hounsfield Units of each of the adjacent slices [14]. This process was considered to compensate for error in the evaluation of beam penetration due to respiration. Patient-oriented external equipment was used to reduce the lateral penumbra by a 5-mm lateral margin, and the range compensator was adjusted with a distal margin of a 3-mm WEPL, as is routinely used in our institute. The calculated beam data were returned to the reference CT and evaluated. These margins were determined based on using a respiratory-gating system.

Dose evaluation metrics

The dose delivered to 95% of the volume of the CTV (CTV-D95), mean lung dose (MLD), percentage of lung receiving at least 5 Gy (Lung-V5), Lung-V10, Lung-V20, heart maximum dose (Dmax), esophagus Dmax, cord Dmax and skin Dmax were evaluated. With regard to the skin, the region of interest was delineated 3 mm inside the visible skin surface.

Observation of actual scanning treatments

All patients were followed up prospectively. Acute reactions were evaluated at 3 months after the first day of irradiation. CT was performed mainly to check lung reactions and tumor size, and the largest and smallest diameters of the tumors were measured on transverse sections. Findings of skin reactions and other physical symptoms were collected by interviews and inspections. Side effects were evaluated using the Common Terminology Criteria for Adverse Events version 4.0 [15].

RESULTS

Patients were observed for a median follow-up period of 6.2 months (range 3.0–10.0 months). All patients were alive and were followed up without obvious relapse. Any symptomatic deterioration was observed at the last follow-up.

Tumor displacement

The median tumor displacement was 6.7 mm (range 0.8–13.6) without gating conditions, and 1.3 mm (range 0.4–9.8) with gating conditions. The gating window used was 40% or 50% either side of the peak exhalation phase. The details of patients are listed in Table 1.

Acute tumor reactions

After irradiation with scanning beams, changes in tumor size were minimal. Except for Patient #2, changes in tumor size were considered to be due to the effects of tumor control or to the effects of partial volume on CT conditions. The tumor of Patient #2 presented an evanescent enlargement at 1 month, and shrinkage at 3 months post treatment, both of which were considered to be caused by inflammation and edema, respectively (Fig. 2). There were no greater than Grade 1 reactions in the skin and lungs. At the 3-month observation of Patient #5, the tumor was difficult to measure owing to radiation pneumonia, despite Grade 1 lung reaction. The tumor size courses are presented in Table 2.

Dose assessment

Figure 3 shows an example of the dose distribution for Patient #2. Figure 3a is the plan with scanning and indicates high concentration to the CTV (yellow circle). Figure 3b is the plan with passive scattering and also indicates good dose delivery to the target, but its green or blue line easily makes the range of the spread-out Bragg Peak (SOBP) recognizable.

The median CTV was 15.3 ml (range 5.7–115.6 ml). For the CTV-D95 for all patients, both of the irradiation techniques provided an excellent dose delivery, exceeding 95%. The dose to the lungs was related to the CTV quantity. The greater the increase in the

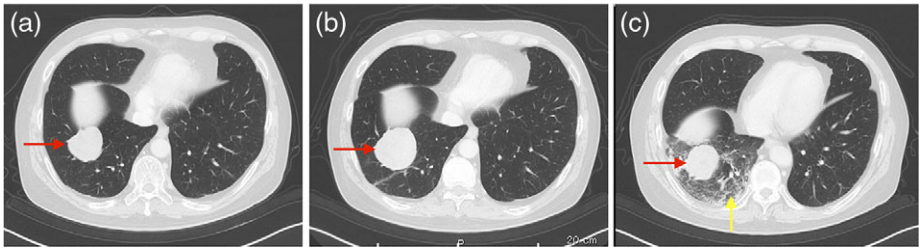

Fig. 2. Serial changes of tumor (Patient #2). (a) Pre-treatment; (b) 1 month later; (c) 3 months later. Arrows indicate tumors and acute radiation pneumonia.

Table 2. Acute reactions after irradiation with scanning method

	Pre-treatment (mm)	1 month (mm)	3 months (mm)	Skin	Lung	Symptom
Pt 1	20.2 × 14.7	16.7 × 11.9	17.5 × 12.1	Grade 0	Grade 1	None
Pt 2	43.5 × 42.3	54.0 × 53.9	46.4 × 45.4	Grade 1	Grade 1	None
Pt 3	23.4 × 19.4	22.1 × 19.0	21.5 × 18.2	Grade 1	Grade 1	None
Pt 4	4.8 × 4.8	4.7 × 4.6	5.4 × 5.4	Grade 0	Grade 0	None
Pt 5	8.1 × 7.5	8.2 × 5.8	Unmeasurable	Grade 1	Grade 1	None

Pt = patient.

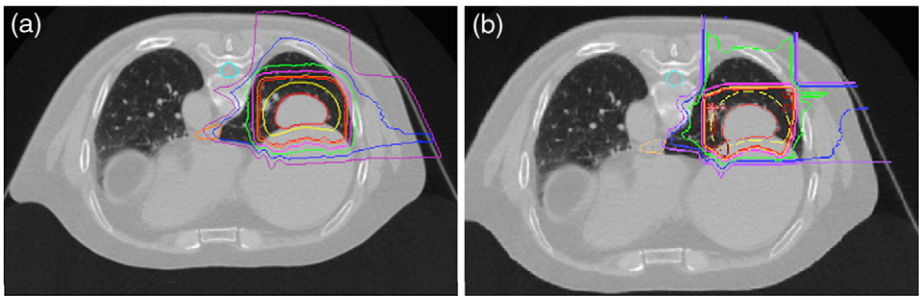

Fig. 3. Dose distributions on reference CT regarding Patient #2 in prone position. (a) Plan with scanning beam. (b) Plan with passive scattering beam. Red, yellow, cyan and orange circles indicate gross tumor volume, clinical target volume, cord, and esophagus, respectively. In regard to iso-dose values, red, orange, pink, green, blue and purple lines indicate 95%, 90%, 70%, 50%, 30% and 10%, respectively.

CTV, the more exposure to the lungs, but every MLD was quite low, such as <10 Gy (RBE), which indicated that treatment with scanning beams also enabled precise exposure. Respective doses to the organs at risk (OARs; heart, esophagus, cord and skin) for the passive scattering and scanning treatment plans for each individual case were not so different, and this was dependent on whether the tumor was located near an organ or not. Each treatment plan was acceptable for clinical use. The results for each patient are shown in Table 3.

DISCUSSION

We treated five thoracic tumors using carbon-ion scanning beams and compared their dose evaluation metrics with those of the plans used by conventional passive scattering beams. The differences between the plans with scanning and passive scattering were small, and it was considered that these two techniques could provide equivalent treatment, despite some advantages for scanning due to the earlier treatment commencement and a reduction in material costs.

The reasons we selected metastatic tumors in the lungs for the clinical trial were: (i) a metastatic tumor has a recognizable, clear borderline, and (ii) a solitary metastasis is considered a stable disease with respect to localization. With regard to (i), a primary lung cancer lesion sometimes has indentations involving a part of normal and/or atelectatic lung, and it is always controversial which or how long indentations to target. As for (ii), surgical treatment would be possible if the new technique should fail.

Our institute has been treating metastases in the lungs with 60 Gy (RBE), currently only when the clinical condition is considered to be a solitary metastasis. We thoroughly explained to our patients that this treatment was not intended to prolong their prognosis, because they had metastatic diseases. Concerning Patient #2, chordoma

Table 3. Comparison of dose evaluation metrics between scanning and passive scattering

	Pt 1		Pt 2		Pt 3		Pt4		Pt5	
Volume (ml)	15.3		115.6		34.9		5.7		6.4	
	Passive	Scan	Passive	Scan	Passive	Scan	Passive	Scan	Passive	Scan
CTV-D95 (%)	98.5	95.5	99.7	99.5	98.5	99.3	99.5	99.3	97.2	99.3
Lung-V5 (%)	5.5	6.2	17.9	20.5	11.8	13.1	3.4	5.9	3.6	6.7
Lung-V10 (%)	4.9	5.4	16.9	18.8	11.3	12.1	3.0	4.9	3.1	5.6
Lung-V20 (%)	3.6	3.9	15.6	16.7	10.5	10.6	2.5	3.5	2.5	4.1
Mean lung dose (Gy) (RBE)	1.8	1.9	7.3	8.0	4.9	5.3	1.2	1.8	1.2	2.0
Heart Dmax (Gy) (RBE)	0.0	0.0	28.5	32.7	0.0	0.0	0.0	2.0	8.6	16.4
Esophagus Dmax (Gy) (RBE)	11.2	14.0	25.0	27.9	4.1	11.6	0.0	0.0	0.0	0.0
Cord Dmax (Gy) (RBE)	6.1	8.4	2.8	7.5	8.2	18.0	0.7	0.8	1.3	2.4
Skin Dmax (Gy) (RBE)	18.4	13.2	29.7	17.7	17.3	16.4	16.0	17.8	28.7	31.2

Pt = patient.

usually develops multiple metastases when it starts to progress outside of the original site; thus, we did not regard reaching such a stage as an indication for CIRT. The patient originally had a sacral chordoma and then progressed, so we did not consider that CIRT could provide any benefit for overall survival. Although it was not expected to improve survival, controlling the huge tumor had a merit in terms of relieving the coming respiratory disturbance. In the case of Patient #2, because the tumor was huge for a treatment in the lungs, we decided to prescribe 57.6 Gy (RBE) in 12 fractions, a dosage generally used for primary bone and soft tissue disease treatments.

Regarding the treatment plans, we changed the principle of thoracic irradiations, meaning that the beam directions of the plan with scanning beams for the first patient of the trial were the same as the conventional one: four orthogonal beams at ±20° rotations [16–18]. Although conventional beam directions were used to avoid a high dose to the skin, we used the same beam directions (four beams) because we considered treatment should be equal to the previous technique. However, after a review of the first treatment, we concluded that the conventional ±20° rotated orthogonal beams were not always necessary, and that two orthogonal beams without couch rotation could offer sufficient treatment. In addition, patient position without rotations had advantages in reducing the time needed to calculate portal beams and fix patient stability.

In respect to the beam direction, dose to the skin is one of the major concerns in particle radiotherapy. The scanning method is said to reduce the proximal dose to the surface because of its physical characteristics, and this was expected in our study as well. In spite of such an expectation, Table 3 shows that this is not always applicable in principle. Doses to the skin of Patients #4 and #5 were higher by the scanning method. It was considered that these two patients had peripheral tumors, and the distance from the surface to the target was too short, even when the scanning method was used (Fig. 1). On the other hand, the skin dose of Patient #3 was almost the same between the two techniques. It was considered that the tumor of Patient #3 was located sufficiently far from the surface, minimizing the effect on the skin by the SOBP. It is generally considered that the scanning method provides reduced dose to the skin, but of course this also depends on the target location.

One of the remarkable features of making a plan with scanning beams is the difference in targeting. Conventionally, the PTV is generated from the CTV by adding margins fully considered mechanically, as based on ICRU reports [19–22]. Two or more PTVs are sometimes used in the course of treatment when a tumor would be shrinking, but it is rare to change PTVs by a beam port. To adjust scanning beams to a moving target, it is necessary to consider a range-ITV because an organic movement is generally not linear, and a change of radiological beam length can vary widely when an adjacent, quite different density structure (rib and lung/diaphragm/liver) intrudes into its beam line.

With regard to cost, scanning technique has the advantage of reducing the cost of external devices (patient customized boluses ± collimators). In addition, by virtue of not needing to construct these devices, treatment can be started sooner. The earlier commencement allows a higher turnover of patients, which is also considered a financial benefit.

This study had some limitations. First, the number of patients was very small, as the aim of this clinical trial was to establish the technical aspects of PCR. All we could learn from this study concerned the following:

(i) The tendencies of how to irradiate, and this was not based on statistics;
(ii) (This was related to the first limitation.) The dose to OARs varied according to location. Ordinarily, if OARs are nearer a target, they are more difficult to spare. Particle therapy has the merit of more efficient avoidance of OARs than radiotherapy by X-ray, although the present study could not show sufficient examples because of the small sample size.
(iii) An exhaustive comparison of plans with a scanning beam and plans with a passive scattering beam was impossible due to their respective technical aspects. As mentioned,

plans with the scanning method were evaluated based on the actual treatment (meaning that the dosimetry was determined by the accumulation of dose resulting from timing of the respiratory phases), whereas passive scattering beam plans were evaluated on the basis of the reference CT, and deliberation of moving targets was based on certain suppositions. This contributed to reduction in the dose to OARs for passive scattering beam plans. Evaluating plans with scanning beams merely based on the reference CT is one method for making an even comparison, but it retrogresses with respect to the technical improvements and may actually prove to be worthless. To evaluate plans with passive scattering beams based on a 4D calculation (such as actual treatments with scanning beams would present) would be another way of making a complete comparison, but it would be technically difficult because the 4D tool software was programmed for planning with scanning beams and not for this study. Calculation using time-accumulated average dose distributions with passive scattering beams might be notionally possible, but such a function is not used for a practical treatment because we could not afford the reprogramming. Although every calculation contains some uncertain factors, the similar results obtained from both techniques might be considered as pointing close to the truth.

In conclusion, treatments with scanning beams were able to irradiate as well as conventional treatments using a passive scattering beam with respect to the CTV. The differences in dose to OARs between the two techniques were not considered important in the clinical setting.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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