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Original article

Four-dimensional treatment planning in layer-stacking boost irradiation for carbon-ion pancreatic therapy

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ABSTRACT

Purpose: We evaluated respiratory-gated carbon-ion beam dose distribution with boost irradiation in pancreatic therapy and compared results between the passive scattering and layer-stacking (a kind of semi-active scanning) irradiation techniques.

Materials and methods: A total of 21 patients who were treated with conventional passive carbon-ion beam for pancreatic cancer underwent 4DCT imaging under free-breathing conditions. We defined two types of clinical target volume (CTV) for the initial and boost irradiations: CTV1 included the gross tumor volume (GTV) and peripheral organs, and CTV2 included the GTV only with an added uniform 2-mm margin. Planning target volumes 1 and 2 (PTV1 and PTV2) were calculated by adding the range variation considered internal margin defined by 4DCT to the respective CTVs. The initial prescribed dose (=45.6 Gy (RBE); RBE-weighted absorbed dose) was given to PTV1, and the boost dose was increased up to 26.4 Gy (RBE) and given to PTV2. Dose assessments were compared between irradiation techniques using the paired *t*-test.

Results: D95 (GTV, CTV2) values were increased from 44.2 Gy (RBE) with the prescribed dose of 45.6 Gy (RBE) to 69.8 Gy (RBE) with the prescribed dose of 72.0 Gy (RBE) with both irradiations. Layer-stacking irradiation reduced excessive dosing to normal tissues compared with passive scattering irradiation, particularly for boost irradiation. 1st–2nd portion V20/V40, and stomach V20 values up to the prescribed dose of 48.0, 60.0, and 52.8 Gy (RBE) were smaller than those in passive scattering irradiation without boost. Kidney V15/V30 (0.6% ($P = 0.05$)/0.1% ($P > 0.20$) for right kidney, 10.4% ($P < 0.01$)/3.2% ($P < 0.01$) for left kidney), pancreas V20/V40 (88.6% ($P < 0.01$)/83.0% ($P < 0.03$)), duodenum 3rd–4th portion V20/V40 (23.6% ($P < 0.01$)/9.5% ($P > 0.06$)), and stomach V20 (16.3% ($P < 0.01$)) values in layer-stacking irradiation were smaller than those in passive scattering irradiation up to the prescribed dose of 72.0 Gy (RBE) and also smaller than those with passive scattering irradiation without boost irradiation (=45.6 Gy (RBE)).

Conclusion: In pancreatic particle beam therapy, delivery of the prescribed dose by layer-stacking boost irradiation provides a greater reduction in excessive dose to normal tissues than delivery by passive scattering irradiation.

The clinical challenge of pancreatic cancer is well known. Worldwide, more than 37,000 pancreatic cancer deaths are estimated for 2011 [1], and 5-year survival rate in patients receiving curative resection is approximately 20%. Pancreatic cancer is often resistant to chemotherapy and radiotherapy, although several treatment centers have performed external beam radiotherapy with chemotherapy.

Our center uses carbon-ion beams for pancreatic cancer with full-dose gemcitabine, with the aim of enhancing local control by increasing radiosensitization [2]. Several studies have reported that pancreatic treatment using proton beams provides superior dose conformation and greater potential for dose escalation than treatment with photon beams [3]. Carbon-ion beams provide a more conformal dose distribution to the target than proton beams due to their lower degree of lateral scattering, and better biological effects due to their higher linear energy transfer (LET), even though they produce a fragmentation tail [4]. Given that dose escalation with chemotherapy is now approaching 52.8 Gy (RBE) [5], which is the relative biologic effectiveness (RBE)-weighted absorbed dose defined in ICRU report 78 [6], this approach appears a promising way to improve local control. Another approach is boost irradiation to the primary tumor. As the abdominal region is strongly affected

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by intrafractional respiratory motion [7] and positional variation due to bowel gas [8], however, the treatment beam may cause over- or underdosage to the target and normal tissues. These factors, including residual motion, should therefore be considered in dose assessment even when the respiratory-gating technique is applied, because current treatment planning systems remain 3D-based, making it difficult to evaluate over- or under-dosing. However, treatment planning includes information on respiratory phase; in other words, the fully complete 4D dose calculation, including the time information, is particularly important for radiation oncologists and medical physicists in assisting their understanding of the results.

Here, we evaluated 4D scattered carbon-ion beam distribution with boost irradiation in the pancreatic region and compared dose distribution with passive scattering and layer-stacking irradiation using 4DCT data sets.

Materials and methods

Treatment beam irradiation techniques

Our center presently uses the passive scattering carbon-ion beam irradiation technique in the existing facility (Fig. 1a). This is laterally broadened by a pair of wobbler magnets and a scatterer, and the sharp Bragg peaks are broadened along the beam direction by a ridge filter. The spread-out Bragg peak (SOBP) length is fixed within the beam field by the maximum SOBP length, however, such that if the target is spherical, for example, a harmful high dose is given to normal tissues around the proximal aspect of the target. To reduce this harmful dosing, we use the layer-stacking irradiation technique, which uses passive particle beams to achieve higher dose conformation, and thereby provides similar dose conformity to active scanning irradiation (Fig. 1b) [9]. Layer-stacking irradiation basically delivers a uniform dose within the target by combining a finite number of small 2.5-mm SOBPs along a depth direction by using a fine ridge filter, a range shifter, and a multi-leaf collimator (MLC). The small SOBP position is shifted from the distal target position to the proximal position by changing the range shifter thickness. Beam field size is defined to fit the respective subdivided regions by changing the MLC opening width. The lateral penumbra is minimized using the patient collimator (PTC), which provides a lateral penumbra approximately half the size of that obtained using an MLC. Nominal dose rate is 5 Gy (RBE)/min for a 10-cm $\times$ 10-cm beam field with a 6-cm SOBP volume, and irradiation times for the 1st layer (most distal side) and 24th layer (most proximal side) are approximately 2.4 s and 0.5 s, respectively. For other SOBP values, we recalculated dose rates using the above values.

Patients

21 patients with pancreatic tumors were randomly selected from among inpatient pancreatic cancer patients (adenocarcinoma; mean age ± SD, 62.7 ± 9.1 years) undergoing conventional passive carbon-ion beam treatment with gemcitabine (dosage of 1000 mg/m^2 in the current protocol) at our hospital (Table 1). All gave informed consent to participate in the study, which was approved by the Institutional Review Board (IRB) of our center. Respiratory cycles for all patients are listed in Table 1. Patients refrained from eating and drinking for 3 h before CT and treatment.

Imaging

4DCT images were acquired under free-breathing conditions using a rapidly rotating cone-beam CT (CBCT), which provide a scan range of approximately 12 cm in a single rotation [10]. Since this scan range is insufficient for pancreas treatment planning, we acquired a second 4DCT scan after completion of the first by moving the couch to the next position, with an overlap region of approximately 2 cm. A total scan region of approximately 22 cm was acquired with a slice collimation of 128 $\times$ 1.0 mm and rotation time of 0.5 s. 4DCT data sets were subdivided into 10 phases (T00, peak inhalation; T50, peak exhalation) based on the amplitude of the respiratory signal. We selected an amplitude-based phase assignment method because of the greater accuracy of amplitude-based over phase-based gated treatment in clinical situations [11].

Treatment planning

A certified radiation oncologist input the target and normal tissue contours on the peak-exhalation CT data manually. We defined two types of clinical target volume (CTV), one for the initial prescribed dose and the second for boost. The first CTV (CTV1) included the gross tumor volume (GTV) plus a 5-mm margin and the locoregional elective lymph node and neuroplexus region. The locoregional elective lymph node region included the celiac, superior mesenteric, peripancreatic, portal, and para-aortic region

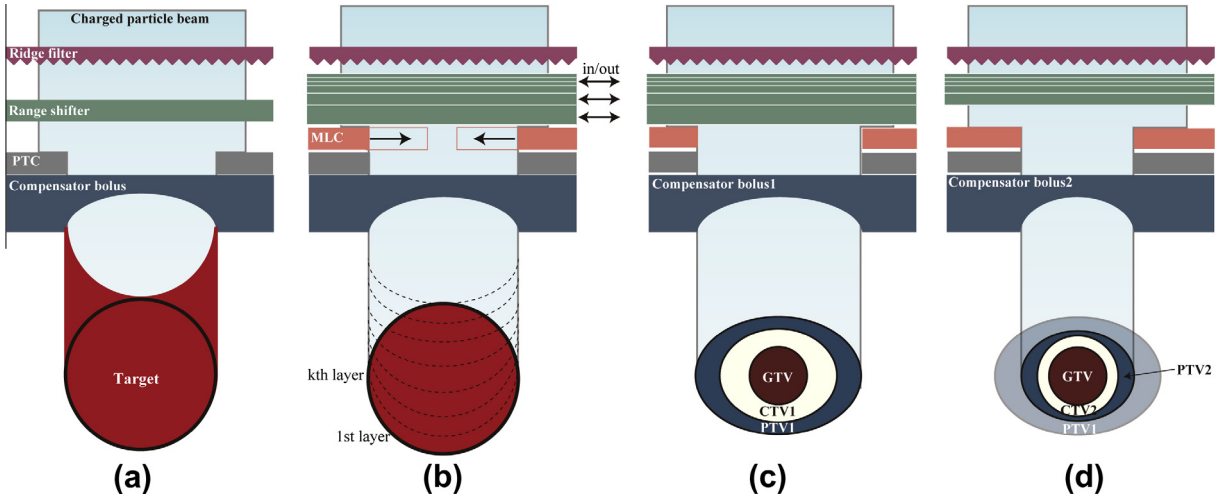

Fig. 1. Schematic drawing of layer-stacking irradiation methods. (a) Passive scattering irradiation. (b) Layer-stacking irradiation. Dotted curved lines show the distal edge of respective mini peaks. (c) Initial dose irradiation to PTV1 with compensator bolus 1. (d) Boost dose irradiation to PTV2 with compensator bolus 2. *Abbreviations:* GTV = gross tumor volume; CTV = clinical target volume; PTV = planning target volume; MLC = multi-leaf collimator.

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