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FULL PAPER

Beam direction arrangement using a superconducting rotating gantry in carbon ion treatment for pancreatic cancer

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Objectives: Carbon ion radiotherapy provides a concentrated dose distribution to the target and has several advantages over photon radiotherapy. This study aimed to evaluate the optimal beam direction in carbon ion pencil beam scanning and compare dose distributions between the rotating gantry system (RGS) and fixed-beam port system (FBPS).

Methods: Patients with locally advanced pancreatic cancer were randomly selected. First, dose-volume parameters of 7-beam directions in the prone position were evaluated. Second, a composite plan developed using 4-beam directions in RGS was compared with that developed using FBPS, with a total prescribed dose of 55.2 Gy (relative biological effectiveness, RBE) in 12 fractions.

Results: Target coverages in the composite plan did not widely differ. For the first and second segments of the duodenum, the mean dose of D2cc was not significantly

changed (23.80 ± 11.90 Gy [RBE] and 25.63 ± 10.41 Gy [RBE] for RGS and FBPS, respectively). However, the dose-volume histogram curve in RGS showed a prominent dose reduction in the low-dose region. No significant differences were observed in the stomach, third and fourth segments of the duodenum, and spinal cord. The mean dose of the total kidney was similar between RGS and FBPS.

Conclusions: Compared with that of FBPS, the 4-beam arrangement in the prone position using RGS provides comparable or superior dose distribution in the surrounding normal organ while achieving the same target coverage. In addition, RGS allows for single-patient positioning.

Advances in knowledge: RGS is beneficial in delivering radiotherapy doses to the duodenum and allows for single-patient positioning and a simple planning process.

INTRODUCTION

Pancreatic cancer is among the most lethal cancers.¹ primarily because the majority of patients have locally advanced unresectable or metastatic disease at the time of diagnosis.^{2,3} Even after curative resection, a high proportion of patients die of local recurrence and/or distant metastasis.^{3,4} Radiotherapy (RT) in combination with chemotherapy is considered as a radical treatment for locally advanced unresectable pancreatic cancer.⁵ However, the prognosis remains poor, with a median survival time of approximately 16 months.⁶ Indeed, conventional photon RT might be insufficient to control pancreatic cancer.⁷

Moreover, pancreatic cancer is extremely hypoxic, resulting in epithelial-mesenchymal transition and resistance to apoptosis⁸; in addition, the dense tumor stroma of pancreatic cancer could be a barrier against immune response.^{7,9}

Compared with photon RT, carbon ion radiotherapy (CIRT) provides a concentrated dose distribution to the target due to a Bragg peak, lower degree of lateral scattering, and better biological effect owing to a higher linear energy transfer (LET).^{10,11} Moreover, CIRT has several other potential advantages over photon-beam RT, such as a lack of an oxygen effect, deficiency of sublethal damage repair, and less cell cycle-related radiosensitivity.^{12,13}

While most proton-beam therapy centers use a rotating gantry, CIRT facilities use a fixed-beam port system.^{14,15} The cost and difficulty of manufacturing and maintaining the much heavier rotating gantry has been a major limitation for its installation.¹⁶ Currently, commercially available rotating gantry systems have been installed in only two facilities (National Institute of Radiological Sciences (NIRS) and Heidelberg Ion Therapy Center).^{16,17} A rotating

gantry using superconducting magnets was developed in NIRS¹⁸ and has been used since 2017. A rotating gantry system offers greater flexibility in beam arrangement with a single-patient position, and better dose distribution can be expected.

To help establish optimal beam directions for the rotating gantry application, this study aimed to compare dose-volume parameters for the tumor and organs at risk (OARs) between the rotating gantry and fixed-beam port systems.

METHODS AND PATIENTS

Patient selection and image acquisition

Patients with locally advanced pancreatic cancer were randomly and retrospectively selected between June 2017 and February 2018. A total of 10 patients were enrolled. The median patient age was 62 years (range, 42–84 years). The male-to-female ratio was 7:3. The tumors were located in the pancreatic head and body in 6 and 4 patients, respectively. The median clinical target volume (CTV) was 223 cc (range, 132–337 cc). The patients were positioned in customized cradles (Moldcare®, Alcare, Tokyo, Japan) and immobilized with a thermo-plastic immobilization device (Shellfitter®, Kuraray Co., Ltd, Osaka, Japan). Treatment planning CT was performed under free-breathing conditions using a 320-detector CT (Aquilion One Vision®, Canon Medical Systems, Otawara, Japan), which obtains 16 cm images in the longitudinal direction in a single rotation. CT imaging was performed using 120-kV tube voltage, slice collimation of 270 × 0.5 mm or 320 × 0.5 mm, in cine mode, and reconstructed with a 1.0 mm slice thickness. Respiration was monitored with a respiratory gating system (AZ-733V®, Anzai Medical, Tokyo, Japan). The 4-dimension (4D) CT data sets were subdivided into 10 phases (T00 = peak inhalation; T50 = peak exhalation), with T50 used for the reference phase.

Treatment planning

We selected the prone position CT data set for this study in order to compare different beam directions for the same CTV and OARs. In addition, posterior beam directions in prone position were more stable to minimize the range uncertainty that might be caused by bowel gas or skin surface. Gross tumor volume (GTV) was delineated for the primary tumor via CT, MRI, and positron emission tomography. CTV was defined as the GTV plus a 5 mm margin plus locoregional lymph nodes and neural plexus regions. Delineated OARs were the stomach, duodenum (D1–2: first and second segments and D3–4: third and fourth segments, respectively), kidneys, and spinal cord. A radiation oncologist manually delineated the target volume and OARs in the peak exhalation reference phase (T50). CTVs were adjusted with respect to anatomical boundaries and OARs. We set a total of 7-beam directions: 315°, 340°, 0°, 20°, 45°, 90°, and 180°. Currently, the standard treatment beam directions include the left posterior oblique (340°), posterior (0°), right lateral (90°), and anterior beam (180°). Other beams (315°, 20°, and 45°) were added. A gating window was selected with a 30% duty cycle around the peak exhalation, and CTV contours were transferred from the reference phase to the other phases using B-spline-based deformable image registration (DIR).¹⁹ To account for the intrafractional beam range uncertainty, we calculated a

field-specific target volume (FTV) using 4DCT images by adding 1 mm in the setup margin.²⁰ FTV was designed as previously described,^{20–22} and 7 FTVs corresponding to each beam direction were created. Our treatment center used the HU-to-SPR table²³ the uncertainty of approximately 1% is not considered in our clinical protocol. Our paper, therefore, did not consider this uncertainty. Quadruple rescanning using carbon ion pencil beam scanning (C-PBS) and a single-field uniform dose calculation was applied. Then, 4D dose calculation was performed for the beam-on duty cycle. Accumulated dose distribution was calculated in each gating window of T40–60 and integrated for the reference phase using DIR. Dose distribution was calculated using “XiDose”, which was developed by and clinically used at the NIRS as part of our collaboration with Elekta AB, Sweden, for scanned carbon ion radiotherapy. The dose is expressed as the relative biological effectiveness (RBE)-weighted dose (Gy [RBE]), which was defined as the physical dose multiplied by the RBE.¹⁰

Dose assessments

We evaluated the dose distribution for each beam to select the best beam direction for the prone position. One fraction dose (4.6 Gy [RBE]) was administered via each beam, and the dose delivered to 95% of the CTV (CTV-D95) was adjusted to supply the same coverage. For dose optimization for OARs, the maximum dose (Dmax) was used as the dose constraint. Dmax for OARs located in the beam entry, lateral, and exit were 80%, 70%, and 60% of the prescribed dose, respectively. In the case of narrow distance or abutment between the CTV and OARs, a 10% higher Dmax to OARs was allowed to maintain similar target dose coverage. Doses for each beam were assessed with regard to CTV-D95, the dose to the most exposed two cc (D2cc) of the stomach, D1–2, D3–4, mean dose (Dmean) of the kidneys, and Dmax to the spinal cord.

Next, we compared the composite plans using gantry beam directions with the current treatment protocol in the fixed-beam port system in terms of dose assessment metrics. Treatment planning for the fixed-beam port system used 4-beam directions: 3 fractions at 340°, 4 fractions at 0°, 2 fractions at 90°, and 3 fractions at 180° in the prone position. Those for the gantry system were 2 fractions at 315°, 4 fractions at 0°, 3 fractions at 20°, and 3 fractions at 180° for the same prone position. A dose of 55.2 Gy (RBE) in 12 fractions was prescribed. Treatment planning was performed to cover the CTV-D95 with at least 90% of the prescribed dose. The dose constraints were as follows: 50% of the bilateral kidney volume should receive <15 Gy (RBE), and D2cc of the stomach/D1–2/D3–4 should receive <40 Gy (RBE). The dose to the spinal cord was limited to 30 Gy (RBE). Statistical significance was analyzed via the Wilcoxon signed-rank test, and $p < 0.05$ was considered significant.

RESULTS

Dose-volume parameters according to 7-beam directions

The representative dose distributions of the seven beams are shown in [Figure 1](#) and [Supplementary Figure 1](#). The dose-volume parameters of the target and OARs for each beam direction are

Figure 1. Representative carbon ion dose distributions of 7-beam directions. The images are levels of stomach and the first and second segment of the duodenum (D1-2). Red, yellow, pink, green, dark blue, and light purple isodose lines show 95%, 90%, 70%, 50%, 30%, and 10% of the prescribed dose, respectively.

shown in [Figure 2](#) (all values are listed in [Supplementary Table 1](#)). The dose constraints of OARs were assigned a lower priority than the target coverage. The CTV or GTV coverage among the seven beams ([Figure 2a and b](#)) did not widely differ; the mean CTV-D95 and GTV-D95 were 4.47–4.49 Gy (RBE) and 4.55–4.56 Gy (RBE), respectively. For D1–2 ([Figure 2c](#)), the beam angle of 0° (posterior direction) maximally reduced the dose to D2cc, whereas that of 90° (right lateral direction) showed the highest dose to D2cc; this was attributable to the beam entry location of D1–two from the right side ([Figure 1f](#)). A beam angle of 45° (right posterior oblique direction) also showed a high dose to D2cc ([Figure 1e](#)). D2cc to D3–4 ([Figure 2d](#)) was similar between most beam directions except for 180° (anterior beam direction). The inferior side-of CTV was usually located behind the third segment of the duodenum, resulting in an increased dose to D3–4 ([Supplementary Figure 1](#)). A similar phenomenon was observed in the stomach ([Figure 2e](#)), which was located closely to the anterior part of CTV ([Figure 1g](#)). From the beam angle of 340° (left posterior oblique direction) to 45° (right posterior oblique direction), the spinal cord dose was higher than that of other beam directions ([Figure 2f](#)). The 315° (left posterior oblique direction) partly avoided the spinal cord due to a left shift of the CTV location ([Figure 1a](#)). The right-side-beam direction (45° and 90°) showed a high dose to the right kidney ([Supplementary Figure](#)

[1](#), and [Fig. 2g](#)). Conversely, the left side-beam direction (315°) showed a high dose to the left kidney ([Supplementary Figure 1](#) and [Fig. 2h](#)). However, the Dmean according to beam direction was not markedly different in both kidneys (approximately ≤ 1 Gy [RBE]).

The stomach and duodenum are of high priority in selecting the beam direction. The dose of D1–2 in 90° and 45° beam directions was higher than that in other directions. A 180° beam direction showed a high dose to the stomach and D3–4. The beam directions from 315° to 20° were better for the stomach and duodenum based on the dose volume parameters. In terms of LET distribution, a high LET region is located on the distal part of the beam direction. Although 180° showed a high dose to the stomach and D3–4, we selected this beam direction to stretch the high LET region. Finally, we selected 4-beam directions. The 0° beam was the best direction for OARs, except for the spinal cord. For the right side-of the patient, the 20° beam was preferred rather than 45° or 90° to reduce the dose to D1–two and the right kidney. In the left side, the 315° beam rather than the 340° beam was selected due to an undesirable increase in the spinal cord dose from the 340° beam. The difference in the left kidney dose between the 315° and 340° beam was clinically acceptable.

Figure 2. Dose-volume parameters (mean dose with standard deviation) of the target volume and organs at risk according to beam angles (4.6 Gy [relative biological effectiveness] in one fraction). The dose covering 95% of (a) clinical target volume (CTV) and (b) gross tumor volume (GTV); the minimum dose received by the most exposed two cc volume of the organ (D2cc) of (c) the first and second segments of the duodenum (D1-2), (d) third and fourth segments of the duodenum (D3-4), and (e) stomach; the maximum dose of the (f) spinal cord; and the mean dose of the (g) right kidney and (h) left kidney.

Comparison of composite plan between the gantry system and fixed-beam port system

A representative dose distribution of the composite plan (=55.2 Gy [RBE]/12 fractions) is depicted in Figure 3a and b, and the dose volume histograms and parameters of the OARs are shown in Figure 3c–3h and Table 1. The dose coverage for GTV and CTV was almost similar between the gantry and fixed-beam composite plans (Figure 3a and b). The mean D95 values of the GTV and CTV were 99 and 97% of the prescribed dose, respectively. The volume of CTV was 223 ± 59 cc. The volume of 95% isoline of gantry and fixed-beam was 219 ± 57 cc and 220 ± 57 cc, respectively. For D1–2, the mean dose to D2cc was not significantly changed (Table 1). However, the dose-volume histogram curve in the gantry system showed a prominent dose reduction in the low dose area (Figure 3c). No significant differences in the stomach and D3–four were observed between the two composite plans in either the dose-volume histogram curve or D2cc (Figure 3d and e, and Table 1). The mean Dmax of the spinal cord was slightly higher in the gantry system due to a 315° beam direction (Figures 1a and 3f, and Table 1). However, this difference was clinically acceptable. The 90° direction of the

fixed-beam port system increased the dose to the right kidney in the dose-volume histogram curve and V15 (Figures 1b and 3g). Conversely, the 315° direction of the gantry beam increased the left kidney dose (Figures 1a and 3h). However, both were low and of acceptable volume (Table 1). The mean dose to the total kidney volume was similar between the two plans (4.7 Gy [RBE] in the gantry system and 4.6 Gy [RBE] in the fixed-beam port system).

DISCUSSION

This study demonstrated that a rotating gantry system in C-PBS offered considerably greater flexibility in beam directions with a single-patient position, resulting in improved dose distribution for pancreatic cancer. Compared with the fixed-beam port system, beam arrangement using a rotating gantry is useful to safely conduct CIRT for pancreatic cancer.

Our facility installed the compact superconducting rotating gantry system with C-PBS in 2015. It has a wider range of beam angle selection (1° rotation between 250° and 110°, 225°, 200°, 180°, 160°, and 135°) compared to that of the original fixed-beam

Figure 3. Representative carbon ion pencil beam scanning dose distributions of the composite plan from (a) four gantry beam directions and (b) four fixed-beam directions in the same prone position (55.2 GyE in 12 fractions). Dose-volume parameters (mean dose with one direction of standard deviation) of OARs between two composite plans; (c) the first and second segments of the duodenum (D1-2), (d) third and fourth segments of the duodenum (D3-4), (e) stomach, (f) spinal cord, (g) right kidney, and (h) left kidney. Solid and dashed lines indicate the gantry and fixed-beam port systems, respectively.

port system. In the orthogonal fixed-beam port system of vertical (0°) and horizontal (90° or 270°) beams, a 180° direction is not allowed (anterior to posterior beam direction in the prone position and posterior to anterior beam direction in the supine position). For pancreatic cancer treatment using two fixed-beam ports, 3 CT datasets (supine, prone, and prone position with 20° tilting of the couch) are acquired for 4-beam direction treatment

with a dose of 55.2 Gy (RBE) in 12 fractions in our facility. The anterior (vertical beam, 0° in the supine position, three fractions) and right lateral (horizontal, 270° in the supine position, two fractions) beam is planned on a supine CT image. Meanwhile, the posterior (vertical, 0° in the prone position, four fractions) beam and left posterior oblique (vertical, 0° in the prone position with 20° tilting of the couch, three fractions) beam is planned in

Table 1. Dose-volume parameters of the composite plan using 4-beam directions with 55.2 Gy (RBE) in 12 fractions

		Gantry system		Fixed-beam port system		<i>p</i> value
		Mean	SD	Mean	SD	
CTV	D95% (Gy [RBE])	53.55	0.12	53.65	0.13	0.09
GTV	D95% (Gy [RBE])	54.85	0.12	54.87	0.11	0.70
D1-2	D2cc (Gy [RBE])	23.80	11.97	25.63	10.41	0.72
D3-4	D2cc (Gy [RBE])	25.75	5.05	25.31	5.09	0.84
Stomach	D2cc (Gy [RBE])	36.31	4.99	35.48	4.64	0.75
Spinal cord	Dmax (Gy [RBE])	23.19	1.10	20.31	0.91	<0.01
R.kidney	V15Gy (RBE) (%)	1.18	2.69	0.65	1.35	0.58
L.kidney	V15Gy (RBE) (%)	3.63	3.15	4.08	3.58	0.76

RBE = relative biological effectiveness; SD = standard deviation; CTV = clinical target volume; GTV = gross tumor volume; D1-2 = the first two segments of the duodenum; D3-4 = the third and fourth segments of the duodenum; D95% = the dose delivered to 95% of the irradiated volume; D2 cc = the minimum dose to a two cc volume; Dmax = maximum dose; Vn = volumes receiving at least n Gy (RBE)

the prone CT image using a tilting table. Different patient positioning causes not only inconvenience, but also a change in organ location. Even in advanced image deformation and fusion techniques, radiation oncologists need to check targets and OARs on all image sets, which is time-consuming. A gantry system for CIRT solves these problems and allows a single-patient position according to the physician's preference.

Several factors should be considered in selecting the beam direction, including undesirable doses to normal tissues at the beam entry side, usage of a sharp lateral dose fall-off, and the high-density area of bilateral edge of the couch. Moreover, bowel gas in the beam pathway and high LET region between the distal edge of the tumor and nearby normal organ should be considered. Kumagai et al.²⁴ demonstrated that gas bubble position in the bowel affected dose distribution conformity to the target and caused an unnecessary dose to the normal tissues because solid organs were replaced by lower density gas. To solve this problem, it is recommended to irradiate through solid organs, such as the spinal cord and kidneys.²⁵ Omission of anterior beam direction from body could reduce irradiated dose to stomach and D3–4, while the dose of D1–2, kidney, and spinal cord increased due to relatively high dose weighting of the posterior beam direction in same total fractionations. Carbon ions exhibit a strong increase of the LET in the Bragg peak compared with that in the entrance region.²⁶ Accordingly, it should be considered that normal tissue within or nearby the tumor is also exposed to a high LET and hence receives a high biologically effective dose.²⁷ The beam directions from the posterior side (315°–20° in the prone position) showed better dose distribution for OAR while minimizing the effect of bowel gas. However, beam arrangement other than posterior directions could be considered to avoid the uncertainty of the high LET region on OARs abutting the distal edge of the beam direction.

Regarding duodenal toxicity, a high dose area on dose volume parameters has been frequently suggested as a dosimetric constraint for treating pancreatic cancer.^{28,29} For instance, Nakamura et al.²⁸ reported a 20% 1-year rate of grade ≥ 3 gastrointestinal (GI) bleeding, and V50 was the best predictor for GI

toxicity and bleeding. Similarly, Kelly et al.²⁹ reported that a duodenal V55Gy > 1 cc is an important dosimetric predictor of grade ≥ 2 duodenal toxicity. Moreover, the volume receiving low-intermediate dose has also been another concern for GI toxicity including acute nausea, vomiting, and diarrhea.^{30,31} The V25Gy was the best predictor for grade ≥ 3 GI toxicity after concurrent full-dose gemcitabine and RT. Moreover, the duodenal dose volume histogram at a lower dose (V10–20Gy) showed increased importance for late GI toxicity.³¹ In our previous report concerning CIRT, 12 patients (21%) experienced gastric ulcer, but there was no Grade 4/5 toxicity or duodenal ulcer. The GI toxicity significantly correlated with low-to-intermediate (V10–30) and high (D2cc) dose volume.³² Although the clinical significance of a reduced duodenal dose in the low-dose region should be resolved in a clinical trial, the benefit from the gantry system might potentially reduce acute and late GI toxicity.

In our current treatment strategy for pancreatic cancer, we used a respiratory cycle 4DCT data set, FTV, an accumulated dose distribution within the gating window (T40–T60), and four or more phased-controlled rescans of C-PBS, and the study was conducted using these considerations. However, interfractional variations and respiratory pattern variations during treatment were not considered. As there are several clinical variables influencing beam selection to achieve the best dose distribution, the recommendation for beam direction might not be applicable. Nonetheless, this study may serve as a reference for beam arrangement using a gantry system according to the relationships between the target volume, OARs, and bowel gas.

CONCLUSION

Compared with the fixed-beam port system, the 4-beam arrangement in the prone position using the gantry system provides comparable or even superior dose distribution in the surrounding normal organ while achieving similar target coverage to the pancreatic cancer and elective nodal area. The duodenum dose (D1–2) decreased in the low-dose range of radiation in the gantry system. Furthermore, the gantry system is beneficial for the duodenum dose and allows for single-patient positioning and a simple planning process.

REFERENCE

- Ilic M, Ilic I. Epidemiology of pancreatic cancer. *World J Gastroenterol* 2016; **22**: 9694–705. doi: <https://doi.org/10.3748/wjg.v22.i44.9694>
- Bilimoria KY, Bentrem DJ, Ko CY, Tomlinson JS, Stewart AK, Winchester DP, et al. Multimodality therapy for pancreatic cancer in the U.S.: utilization, outcomes, and the effect of hospital volume. *Cancer* 2007; **110**: 1227–34. doi: <https://doi.org/10.1002/cncr.22916>
- Esposito I, Kleeff J, Bergmann F, Reiser C, Herpel E, Friess H, et al. Most pancreatic cancer resections are R1 resections. *Ann Surg* 2008; **15**: 1651–60. doi: <https://doi.org/10.1245/s10434-008-9839-8>
- Kleeff J, Reiser C, Hinz U, Bachmann J, Debus J, Jaeger D, et al. Surgery for recurrent pancreatic ductal adenocarcinoma. *Ann Surg* 2007; **245**: 566–72. doi: <https://doi.org/10.1097/01.sla.0000245845.06772.7d>
- Balaban EP, Mangu PB, Khorana AA, Shah MA, Mukherjee S, Crane CH, et al. Locally advanced, unresectable pancreatic cancer: american Society of clinical oncology clinical practice guideline. *JCO* 2016; **34**: 2654–68. doi: <https://doi.org/10.1200/JCO.2016.67.5561>
- Hammel P, Huguet F, van Laethem J-L, Goldstein D, Glimelius B, Artru P, et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 randomized clinical trial. *JAMA* 2016; **315**: 1844–53. doi: <https://doi.org/10.1001/jama.2016.4324>
- Durante M, Tommasino F, Yamada S. Modeling combined chemotherapy and particle therapy for locally advanced pancreatic cancer. *Front Oncol* 2015; **5**: 145. doi: <https://doi.org/10.3389/fonc.2015.00145>

8. Koong AC, Mehta VK, Le QT, Fisher GA, Terris DJ, Brown JM, et al. Pancreatic tumors show high levels of hypoxia. *International Journal of Radiation Oncology*Biophysics* 2000; **48**: 919–22. doi: [https://doi.org/10.1016/S0360-3016\(00\)00803-8](https://doi.org/10.1016/S0360-3016(00)00803-8)
9. Olive KP, Jacobetz MA, Davidson CJ, Gopinathan A, McIntyre D, Honess D, et al. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. *Science* 2009; **324**: 1457–61. doi: <https://doi.org/10.1126/science.1171362>
10. Kanai T, Endo M, Minohara S, Miyahara N, Koyama-ito H, Tomura H, et al. Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. *International Journal of Radiation Oncology*Biophysics* 1999; **44**: 201–10. doi: [https://doi.org/10.1016/S0360-3016\(98\)00544-6](https://doi.org/10.1016/S0360-3016(98)00544-6)
11. Durante M, Loeffler JS. Charged particles in radiation oncology. *Nat Rev Clin Oncol* 2010; **7**: 37–43. doi: <https://doi.org/10.1038/nrclinonc.2009.183>
12. Ohno T. Particle radiotherapy with carbon ion beams. *Epma J* 2013; **4**: 9. doi: <https://doi.org/10.1186/1878-5085-4-9>
13. Mori S, Shinoto M, Yamada S. Four-dimensional treatment planning in layer-stacking boost irradiation for carbon-ion pancreatic therapy. *Radiother Oncol* 2014; **111**: 258–63. doi: <https://doi.org/10.1016/j.radonc.2014.02.014>
14. Bouchard M, Amos RA, Briere TM, Beddar S, Crane CH. Dose escalation with proton or photon radiation treatment for pancreatic cancer. *Radiother Oncol* 2009; **92**: 238–43. doi: <https://doi.org/10.1016/j.radonc.2009.04.015>
15. Kozak KR, Kachnic LA, Adams J, Crowley EM, Alexander BM, Mamon HJ, et al. Dosimetric feasibility of hypofractionated proton radiotherapy for neoadjuvant pancreatic cancer treatment. *International Journal of Radiation Oncology*Biophysics* 2007; **68**: 1557–66. doi: <https://doi.org/10.1016/j.ijrobp.2007.02.056>
16. Haberer Th, Debus J, Eickhoff H, Jäkel O, Schulz-Ertner D, Weber U. The Heidelberg ion therapy center. *Radiother Oncol* 2004; **73 Suppl 2**(Suppl 2): S186–S190. doi: [https://doi.org/10.1016/S0167-8140\(04\)80046-X](https://doi.org/10.1016/S0167-8140(04)80046-X)
17. Iwata Y, Fujimoto T, Matsuba S, Fujita T, Sato S, Furukawa T, et al. Beam commissioning of a superconducting rotating-gantry for carbon-ion radiotherapy. *Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment* 2016; **834**: 71–80. doi: <https://doi.org/10.1016/j.nima.2016.07.050>
18. Iwata Y, Shirai T, Noda K. Design of superconducting magnets for a compact carbon Gantry. *IEEE Transactions on Applied Superconductivity* 2016; **26**: 1–4. doi: <https://doi.org/10.1109/TASC.2015.2509187>
19. Shackleford JA, Kandasamy N, Sharp GC. On developing B-spline registration algorithms for multi-core processors. *Phys Med Biol* 2010; **55**: 6329–51. doi: <https://doi.org/10.1088/0031-9155/55/21/001>
20. Knopf A-C, Boye D, Lomax A, Mori S. Adequate margin definition for scanned particle therapy in the incidence of intrafractional motion. *Phys Med Biol* 2013; **58**: 6079–94. doi: <https://doi.org/10.1088/0031-9155/58/17/6079>
21. Graeff C, Durante M, Bert C. Motion mitigation in intensity modulated particle therapy by internal target volumes covering range changes. *Med Phys* 2012; **39**: 6004–13. doi: <https://doi.org/10.1118/1.4749964>
22. Mori S, Inaniwa T, Miki K, Shirai T, Noda K. Implementation of a target volume design function for intrafractional range variation in a particle beam treatment planning system. *Br J Radiol* 2014; **87**: 20140233: 20140233. doi: <https://doi.org/10.1259/bjr.20140233>
23. Kanematsu N, Matsufuji N, Kohno R, Minohara S, Kanai T. A CT calibration method based on the polybinary tissue model for radiotherapy treatment planning. *Phys Med Biol* 2003; **48**: 1053–64. doi: <https://doi.org/10.1088/0031-9155/48/8/307>
24. Kumagai M, Hara R, Mori S, Yanagi T, Asakura H, Kishimoto R, et al. Impact of intrafractional bowel gas movement on carbon ion beam dose distribution in pancreatic radiotherapy. *International Journal of Radiation Oncology*Biophysics* 2009; **73**: 1276–81. doi: <https://doi.org/10.1016/j.ijrobp.2008.10.055>
25. Shiomi M, Mori S, Shinoto M, Nakayama Y, Kamada T, Yamada S. Comparison of carbon-ion passive and scanning irradiation for pancreatic cancer. *Radiother Oncol* 2016; **119**: 326–30. doi: <https://doi.org/10.1016/j.radonc.2016.04.026>
26. Jäkel O. Medical physics aspects of particle therapy. *Radiat Prot Dosimetry* 2009; **137**(1-2): 156–66. doi: <https://doi.org/10.1093/rpd/ncp192>
27. Karger CP, Jäkel O. Current status and new developments in ion therapy. *Strahlenther Onkol* 2007; **183**: 295–300. doi: <https://doi.org/10.1007/s00066-007-1645-x>
28. Nakamura A, Shibuya K, Matsuo Y, Nakamura M, Shiinoki T, Mizowaki T, et al. Analysis of dosimetric parameters associated with acute gastrointestinal toxicity and upper gastrointestinal bleeding in locally advanced pancreatic cancer patients treated with gemcitabine-based concurrent chemoradiotherapy. *Int J Radiat Oncol Biol Phys* 2012; **84**: 369–75. doi: <https://doi.org/10.1016/j.ijrobp.2011.12.026>
29. Kelly P, Das P, Pinnix CC, Beddar S, Briere T, Pham M, et al. Duodenal toxicity after fractionated chemoradiation for unresectable pancreatic cancer. *International Journal of Radiation Oncology*Biophysics* 2013; **85**: e143–9. doi: <https://doi.org/10.1016/j.ijrobp.2012.09.035>
30. Yovino S, Poppe M, Jabbour S, David V, Garofalo M, Pandya N, et al. Intensity-modulated radiation therapy significantly improves acute gastrointestinal toxicity in pancreatic and ampullary cancers. *International Journal of Radiation Oncology*Biophysics* 2011; **79**: 158–62. doi: <https://doi.org/10.1016/j.ijrobp.2009.10.043>
31. Huang J, Robertson JM, Ye H, Margolis J, Nadeau L, Yan D. Dose–Volume analysis of predictors for gastrointestinal toxicity after concurrent full-dose gemcitabine and radiotherapy for locally advanced pancreatic adenocarcinoma. *International Journal of Radiation Oncology*Biophysics* 2012; **83**: 1120–5. doi: <https://doi.org/10.1016/j.ijrobp.2011.09.022>
32. Shinoto M, Shioyama Y, Matsunobu A, Okamoto K, Suefuiji H, Toyama S, et al. Dosimetric analysis of upper gastrointestinal ulcer after carbon-ion radiotherapy for pancreatic cancer. *Radiother Oncol* 2016; **120**: 140–4. doi: <https://doi.org/10.1016/j.radonc.2016.04.040>