



Original paper

Dosimetric performance of cone beam CT-guided adaptive carbon-ion radiotherapy with daily replanning for pancreatic cancer

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ABSTRACT

Purpose: We investigated whether an ultra-hypofractionated carbon-ion radiotherapy (CIRT) protocol for pancreatic cancer (PC) could produce satisfactory dosimetric results with or without cone-beam CT-guided adaptive replanning and explored the potential dosimetric advantages of the adapted protocol.

Methods: Eleven PC patients who underwent CBCT-guided online adaptive photon radiotherapy were selected. Data were imported into a CIRT treatment planning software to develop new plans for an ultra-hypofractionated CIRT protocol. Prescriptions and constraints were recalculated for a five-fraction schedule using a linear quadratic model for organs-at-risk (OARs) and targets, respectively. The biologically effective dose-equivalent prescribed dose was set at 43.2 Gy (relative biological effectiveness [RBE]). Each day, a synthetic CT (SCT) was generated from the planning CT (PCT) with the daily CBCT. A reference plan based on the PCT was compared to an adapted plan based on the SCT. Deformable image registration was used to allow summation of the daily doses.

Results: The adapted plans met the clinical goals, whereas the reference plans exceeded the constraints in 27 % (stomach), 53 % (duodenum), and 31 % (small bowel) of the fractions. The adapted plans notably decreased $V_{35.5 \text{ Gy[RBE]}}$ for all gastrointestinal OARs, while significantly enhancing the gross tumor volume (GTV) $D_{95\%}$ and planning target volume (PTV) $D_{90\%}$. The accumulated doses showed significant improvements in the duodenum $V_{35.5 \text{ Gy[RBE]}}$, GTV $D_{95\%}$, and PTV $D_{90\%}$.

Conclusion: CBCT-guided adaptive CIRT for PC demonstrated favorable dosimetric results, notably enhancing the sparing of OARs and ensuring superior target coverage compared with non-adaptive CIRT protocols.

1. Introduction

The survival rate for pancreatic cancer (PC) stands at approximately 6 % [1], which is low compared to those for most other types of cancer. Owing to its poor prognosis, PC requires multimodal therapies, including surgery, radiation therapy (RT), and chemotherapy. For photon treatment of PC, dose escalation in combination with stereotactic body RT (SBRT) has exhibited improved survival and local control

compared with conventional fractionated PC protocols [2,3]. Owing to the proximity of treatment doses to critical gastrointestinal organs-at-risk (GI-OARs), dose-escalated PC treatment comes at the expense of high-grade toxicity [4,5]. Adaptive RT (ART), which involves daily image acquisition, recontouring, and replanning, can potentially avoid toxicity in SBRT [6,7].

Recently, our group successfully demonstrated the use of a cone-beam CT (CBCT)-guided treatment machine for research involving

Abbreviations: CIRT, carbon-ion radiotherapy; PC, pancreatic cancer; CBCT, cone-beam computed tomography; OARs, organs-at-risk; RBE, relative biological effectiveness; SCT, synthetic CT; PCT, planning CT; GTV, gross tumor volume; PTV, planning target volume; RT, radiation therapy; SBRT, stereotactic body RT; GI-OARs, gastrointestinal organs-at-risk; ART, adaptive RT; TPS, treatment planning system; DIR, deformable image registration; EE-BH, end-exhalation breath-hold; CTV, clinical target volume; PRV, planning organs at risk volume; FOV, field-of-view; BED, biologically effective dose; PD, prescribed dose; LEM, local effect model; DVIs, dose volume indices; ROI, region-of-interest; std, standard deviation.

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online ART [8]. In this study, synthetic CTs generated from daily CBCTs of other patients were employed, and adaptive plans were calculated using the Ethos emulator (Varian Medical Systems, Palo Alto, CA). This approach highlights the potential of utilizing CBCT-based synthetic images for treatment planning. Furthermore, Ethos enables time-efficient image acquisition and recontouring, with the patient remaining on the treatment couch.

Carbon-ion RT (CIRT) has been shown to improve the overall PC survival compared to conventional photon therapy [9]. Better dose distributions of CIRT are due to a favorable depth-dose profile with its characteristic Bragg peak, as well as the higher local biological effectiveness of carbon ions compared with photons [10]. The abrupt falloff of the relative biological effectiveness (RBE)-weighted dose has been shown to make this treatment more sensitive to interfractional anatomical changes [11,12]. For conventional 12-fraction CIRT, this issue has been addressed through bone- and tumor matching [13] and worst-case optimization [14]. In the most closely related study, adapted plans were generated for a 12-fraction PC protocol using single-beam, adaptive passive scattering CIRT involving daily CT acquisitions and manual recontouring; however, CT was performed before each treatment and the adapted plans were generated *in silico* without being used in the actual treatment [15].

Tackling the challenge of CIRT motion sensitivity, the goal of this study was to explore an approach combining CIRT and online ART using an ultra-hypofractionated schedule based on promising results from photon therapy. To the best of our knowledge, no ultra-hypofractionated CIRT protocol for PC has been applied in clinical practice. Thus, we investigated whether an ultra-hypofractionated CIRT protocol for PC could produce satisfactory dosimetric results with or without CBCT-guided adaptive replanning and explored the potential dosimetric advantages of the adapted protocol. Plans with and without replanning were generated by combining image data and contours from the treatment with an external CIRT treatment planning system (TPS). Daily dose distributions from both protocols were compared with respect to the target coverage and OAR sparing. Daily doses for the scheduled and adapted plans were summed and compared using deformable image registration (DIR).

The main novelty of our study lies in the dosimetric evaluation of a workflow that combines online ART and CIRT. Additional aspects include the exploration of an ultra-hypofractionated protocol and the use of scanning beam CIRT, which offers dosimetric advantages over passive scattering CIRT for pancreatic cancer [16].

2. Materials and methods

2.1. Patients

Eleven patients diagnosed with PC who underwent 5- or 15-fraction online ART using the Ethos system (Varian Medical Systems, Palo Alto, CA) between January 2023 and January 2024 were analyzed in this

study (Table 1). All patients had histologically confirmed pancreatic adenocarcinoma and were diagnosed with borderline resectable, locally advanced unresectable, or resectable PCs by the Tumor Board at our institution.

The study was conducted in accordance with the principles of the Declaration of Helsinki (R1446-2). The study protocol was approved by the institutional review boards of the participating institutions. Written informed consent was obtained from all patients.

2.2. Planning CT acquisition and contouring

Oral intake was stopped, except for drugs and water, for at least 3 h before planning CT (PCT) acquisition. The patients were immobilized in a head-first supine position using an individualized vacuum pillow (Body Fix; Elekta, Stockholm, Sweden). CT images (slice thickness: 2 mm) were acquired using SOMATOM Definition AS (Siemens Healthineers, Forchheim, Germany). The FOV, pixel sizes, and slice thickness were 500 mm, 0.98 mm and 2 mm for pCT, respectively. During all imaging, patients were in the end-of-exhalation breath hold (EE-BH) state. Respiratory motion was monitored with an SDX spirometric motion management system (DYN'R, Aix-en-Provence, France).

The gross tumor volume (GTV) included the primary tumor and metastatic lymph nodes. The clinical target volume (CTV) was defined as the GTV plus a 5 mm margin with the potential involvement of the *para*-aortic lymph node and neuroplexus between the celiac axis and the superior mesenteric artery (CTV_{org}). Note that overlaps between the CTV_{org} and OARs were excluded from the final CTV based on clinical judgement:

$$\text{CTV}_{\text{org}} \rightarrow \text{CTV} = \text{CTV}_{\text{org}} - \text{OARs}. \quad (1)$$

A planning target volume (PTV) margin of 5 mm was added isotropically to the final CTV (PTV_{org}). The surrounding OARs, including the stomach, duodenum, and small bowel, were contoured. Based on the institutional protocol, a 3 mm margin was added to the duodenum, while 5 mm margins were added to stomach and small bowel, and the resulting planning organs at risk volume (PRVs) were subtracted from the PTV_{org}:

$$\text{PTV}_{\text{org}} \rightarrow \text{PTV} = \text{PTV}_{\text{org}} - \text{PRVs}. \quad (2)$$

This method followed previous CIRT studies, wherein the PTV was adjusted according to the proximity to surrounding OARs to avoid excessive doses [9,15]. Board-certified radiation oncologists defined all the anatomical structures.

2.3. Daily CBCT and synthetic CT acquisition

On each day of treatment, CBCT was performed before beam delivery in the EE-BH state, using the Ethos system. The CBCT field of view (FOV) was 465 mm, and the slice thickness was 2 mm. Respiratory motion was monitored using an SDX system. The images were reconstructed using

Table 1
Patient characteristics.

ID	Age	Sex	Primary site	Stage	TNM	GTV (ccm)	CTV (ccm)	PTV (ccm)	Original fractions
1	64	M	Body	UR	T4N0M0	15.18	105.44	208.12	15
2	83	M	Body	R	T2N0M0	7.94	43.00	88.97	5
3	60	F	Body	UR	T4N0M0	11.93	70.37	134.44	15
4	81	F	Body	R	T1N0M0	5.02	24.81	55.64	5
5	57	M	Head	UR	T4N0M0	14.12	120.02	211.61	15
6	64	F	Head	UR	T4N0M0	21.66	103.79	195.33	15
7	87	F	Head	UR	T4N0M0	16.27	40.00	83.06	5
8	86	F	Head	R	T2N0M0	14.69	37.59	81.58	5
9	67	F	Body	BR	T4N0M0	3.62	104.84	185.05	15
10	66	M	Head	UR	T4N0M0	21.32	153.03	255.14	15
11	68	M	Body	UR	T4N1M1	27.17	219.31	357.88	15

Abbreviations: UR, unresectable; R, resectable; BR, borderline resectable; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume.

an iterative reconstruction algorithm with a medium noise suppression level [17].

For each CBCT, the GI organs (duodenum and stomach) were automatically segmented using full image deep convolutional neural networks [17]. The other OARs (small and large bowel, kidneys, and spinal cord) were automatically propagated from the initial PCT using a modified basis spline (B-spline) DIR algorithm followed by simple postprocessing and smoothing of the results. All the structures were reviewed and manually modified by board-certified radiation oncologists.

The Ethos system then generated a synthetic CT (SCT) to calculate the dose distribution by mapping the initial PCT onto the CBCT using a B-spline DIR algorithm [18]. The Hounsfield unit values of each CBCT voxel were replaced with those of the PCT. Furthermore, the PCT voxel information was propagated via rigid registration to areas outside the FOV of the CBCT to compensate for the limited scan length. To increase the registration quality for CT-to-CBCT DIR, only voxels inside the CBCT reconstruction radius were used in the cost function. This approach prevented the occurrence of registration artifacts when the reconstruction radius truncated the body. The displacement field $T_{PCT \rightarrow CBCT}$ of DIR was saved for subsequent use.

2.4. Carbon-ion treatment plan creation

The target dose, OAR constraints and field angles followed those of previous Japanese CIRT PC studies, where the dose was typically delivered in 12 fractions [16,19,20]. All doses were given as the RBE weighted absorbed dose [21]. To investigate an ultra-hypofractionated protocol, prescriptions and constraints were determined for a 5-fraction schedule using the linear quadratic (LQ) model [22] with α/β ratios of 3 Gy and 10 Gy for the OARs and targets, respectively (Table 2). If the original treatment consisted of 15 fractions, 5 fractions were randomly selected for this analysis, to minimize potential biases that could arise from systematic selection, such as using only the first five fractions. The biologically effective dose (BED) equivalent prescribed dose (PD) for the PTV and GTV was 43.2 Gy[RBE] for 5 fractions and 8.64 Gy[RBE] for 1 fraction, compared with 55.2 Gy[RBE] for 12 fractions.

A three-field setup at angles of 90°, 180°, and 270° was used. The 90° and 270° fields were accessible through a horizontal beam line, and the 180° field through a vertical beam line. A fourth field at 0° was rejected because of the potential uncertainty introduced by respiratory motion [23]. Plan generation and dose calculation were performed with the open-source research TPS matRad [24]. A generic pre-implemented CIRT beamline was used. The dose influence matrix was calculated on a 2 mm³ dose grid with a lateral spot spacing of 5 mm and a longitudinal spot spacing of approximately 2 mm, depending on the available energies. One-hundred twenty-one different energies were available for Carbon ions. These are spaced linearly between 115.23 MeV/u to 398.84 MeV/u, corresponding to peak positions from 32 mm to 294 mm in water. MatRad assumes an active spot scanning dose application, and

Table 2

Biological effective dose-equivalent clinical goals [16,19,20]. α/β ratios of 3 Gy and 10 Gy were assumed for normal tissue and tumor, respectively. These values were used to calculate the new goals and constraints.

Structure	Metric	Goal/Constraint
GTV	$V_{95\%PD}$ (%)	≥ 95
PTV	$V_{95\%PD}$ (%)	≥ 90
Stomach	$V_{35.5 \text{ Gy[RBE]}}$ (ccm)	< 1
Duodenum	$V_{35.5 \text{ Gy[RBE]}}$ (ccm)	< 1
Small bowel	$V_{35.5 \text{ Gy[RBE]}}$ (ccm)	< 1
Spinal cord	D_{max} (Gy[RBE])	< 22.2
Left kidney	$D_{50\%}$ (Gy[RBE])	< 11.9
Right kidney	$D_{50\%}$ (Gy[RBE])	< 11.9

Abbreviations: GTV, gross tumor volume; PTV, planning target volume; PD, prescribed dose; RBE, relative biological effectiveness.

the doses were calculated using a dose-to-water pencil beam algorithm [25]. The beam shape was modeled using a single Gaussian function. For modeling the RBE, matRad uses the local effect model IV (LEM IV) [26]. Two response curves for early and late responding tissue with intrinsic α/β ratios of 2 Gy and 10 Gy were available. The α/β ratio of 2 Gy was used for all OARs, while the α/β ratio of 10 Gy was used for all target volumes (GTV, CTV, and PTV).

The dose–volume histograms (DVHs) were calculated using the 3D slicer [27]. When evaluating $V_{35.5 \text{ Gy[RBE]}}$ (ccm) for GI OARs, the volumes given by matRad deviated by up to 0.02 ccm from those obtained using the 3D slicer. Thus when analyzed using the 3D slicer, plans for fractions and accumulated doses were deemed successful if $V_{35.5 \text{ Gy[RBE]}}$ (ccm) < 1.02 was achieved.

The goal was to generate and compare two treatment plans for each fraction, a reference plan P_{ref} and an adapted plan P_{adp} . Initially, P_{ref} was generated for the PCT of each patient. If it met all the clinical goals in Table 2, P_{ref} was deemed acceptable. To evaluate the dose distribution of non-adapted plans on the daily anatomy, P_{ref} was then applied to the five daily SCTs, resulting in a scheduled dose D_{sch} for each fraction. P_{adp} was generated directly on the SCT for each fraction, using the same constraints as for P_{ref} . Using P_{adp} , adapted doses D_{adp} were calculated for each fraction.

2.5. Inverse registration and dose accumulation

To compare the accumulated doses for both the scheduled and adapted methods, the doses of the fractions were mapped back to the anatomy of the PCT using a DIR displacement field. The displacement field was acquired by inverting the field originally used to map the PCT onto the CBCT:

$$T_{SCT \rightarrow PCT} = T_{PCT \rightarrow SCT}^{-1} \quad (3)$$

The registered scheduled and adapted doses (five each) were then summed to give the accumulated doses $D_{acc,sch}$ (scheduled) and $D_{acc,adp}$ (adapted).

2.6. Statistical analysis

Treatment characteristics for $P_{ref/adp}$ were calculated on the SCT for the daily fractions and on the PCT for the accumulated doses. The characteristics of P_{ref} and P_{adp} were compared using a two-sided Wilcoxon signed-rank test; p values < 0.05 were considered statistically significant. Statistical analyses were performed using SciPy software.

3. Results

3.1. Comparison of P_{ref} and P_{adp} for single fractions

The numerical results for individual fractions are listed in Table 3. Of the 55 analyzed fractions, P_{ref} exceeds the OAR constraints for the stomach in 15 fractions (27 %), duodenum in 29 fractions (53 %), and small bowel in 13 fractions (31 %). For P_{adp} , no GI constraints are exceeded, indicating that recontouring and replanning of potentially harmful toxicity to OARs near the tumor can be averted. The volumes of the stomach, duodenum, and small bowel delivered to 35.5 Gy[RBE] are reduced significantly ($p < 0.05$) for P_{adp} , with the mean reduced by 0.8 ± 1.4 ccm, 0.9 ± 0.9 ccm, and 1.3 ± 2.5 ccm, respectively.

The tumor coverage goals are missed for P_{ref} in 23 fractions (41.8 %) for the GTV and 36 fractions (65.4 %) for the PTV. P_{adp} meets the coverage goals for all fractions, with significant increases in GTV $D_{95\%}$ and PTV $D_{90\%}$. The mean GTV $D_{95\%}$, mean CTV $D_{95\%}$ and mean PTV $D_{90\%}$ were increased by 0.4 ± 0.5 Gy[RBE], 0.3 ± 0.4 Gy[RBE] and 0.5 ± 0.5 Gy[RBE] respectively, representing relative increases of 5.1 %, 4.3 % and 6.3 %. For GTV and CTV, median $V_{95\%PD}$ and $V_{98\%PD}$ were significantly improved. The differences in the individual fractions are

Table 3
Performance of P_{ref} and P_{adp} on the SCT for individual fractions (55 fractions in total).

Structure	Metric	Goal/Constraint	Number of constraint violations		P_{ref} median [IQR]	P_{adp} median [IQR]	p-value
			P_{ref}	P_{adp}			
GTV	$V_{95\%PD}$ (%)	≥ 95	23	0	96.8 [89.7–99.1]	99.9 [99.6–100.0]	<0.05
	$V_{98\%PD}$ (%)	Not specified			85.4 [68.6–94.6]	98.9 [98.1–99.7]	<0.05
	$D_{95\%}$ (Gy[RBE])	Not specified			8.3 [8.1–8.5]	8.6 [8.6–8.6]	<0.05
CTV	$V_{95\%PD}$ (%)	Not specified	36	0	97.1 [86.4–99.5]	100.0 [100.0–100.0]	<0.05
	$V_{98\%PD}$ (%)	Not specified			76.6 [59.9–91.8]	95.6 [92.3–98.2]	<0.05
	$D_{95\%}$ (Gy[RBE])	Not specified			8.3 [8.0–8.4]	8.5 [8.4–8.5]	<0.05
PTV	$V_{95\%PD}$ (%)	≥ 90	36	0	84.8 [73.8–92.7]	97.1 [95.7–98.0]	<0.05
	$D_{90\%}$ (Gy[RBE])	Not specified			8.0 [7.8–8.3]	8.5 [8.4–8.5]	<0.05
Stomach	$V_{35.5 \text{ Gy[RBE]}}$ (ccm)	<1	15	0	0.2 [0.0–1.2]	0.0 [0.0–0.3]	<0.05
Duodenum	$V_{35.5 \text{ Gy[RBE]}}$ (ccm)	<1	29	0	1.2 [0.2–2.1]	0.1 [0.0–0.8]	<0.05
Small bowel	$V_{35.5 \text{ Gy[RBE]}}$ (ccm)	<1	17	0	0.2 [0.0–1.6]	0.2 [0.0–0.4]	<0.05
Spinal cord	D_{max} (Gy[RBE])	<4.4	0	0	1.7 [1.7–1.9]	1.7 [1.6–1.9]	0.06
Left kidney	$D_{50\%}$ (Gy[RBE])	<2.4	0	0	0.1 [0.1–0.1]	0.1 [0.1–0.1]	<0.05
Right kidney	$D_{50\%}$ (Gy[RBE])	<2.4	0	0	0.1 [0.1–0.1]	0.1 [0.1–0.1]	0.59
Body	D_{max} (Gy[RBE])	Not specified			9.9 [9.8–10.2]	9.6 [9.5–9.8]	0.10

Abbreviations are as in Table 2.

shown in Fig. 1.

3.2. Comparison of accumulated doses

The numerical results for the accumulated doses are listed in Table 4. The data are shown in Fig. 1. P_{ref} exceeds the stomach constraints in one patient, duodenum constraints in five patients, and small bowel constraints in one patient. P_{adp} exceeds the duodenum constraints in two cases and the small bowel constraints in one case. The mean $V_{35.5 \text{ Gy[RBE]}}$

is reduced for all GI organs with a significant reduction for the duodenum ($0.4 \pm 0.5 \text{ ccm}$, $p < 0.05$). The GTV coverage goals are missed in six accumulated reference plans and three accumulated adapted plans, whereas the PTV coverage goals are missed in eight accumulated scheduled and two accumulated adapted plans. The mean GTV $D_{95\%}$ and mean PTV $D_{90\%}$ are both increased significantly, with differences of $1.9 \pm 2.7 \text{ Gy[RBE]}$ (4.8 %) and $1.7 \pm 1.7 \text{ Gy[RBE]}$ (4.3 %). The mean CTV $D_{95\%}$ was increased, though not significantly, by $1.0 \pm 2.0 \text{ Gy[RBE]}$ (2.3

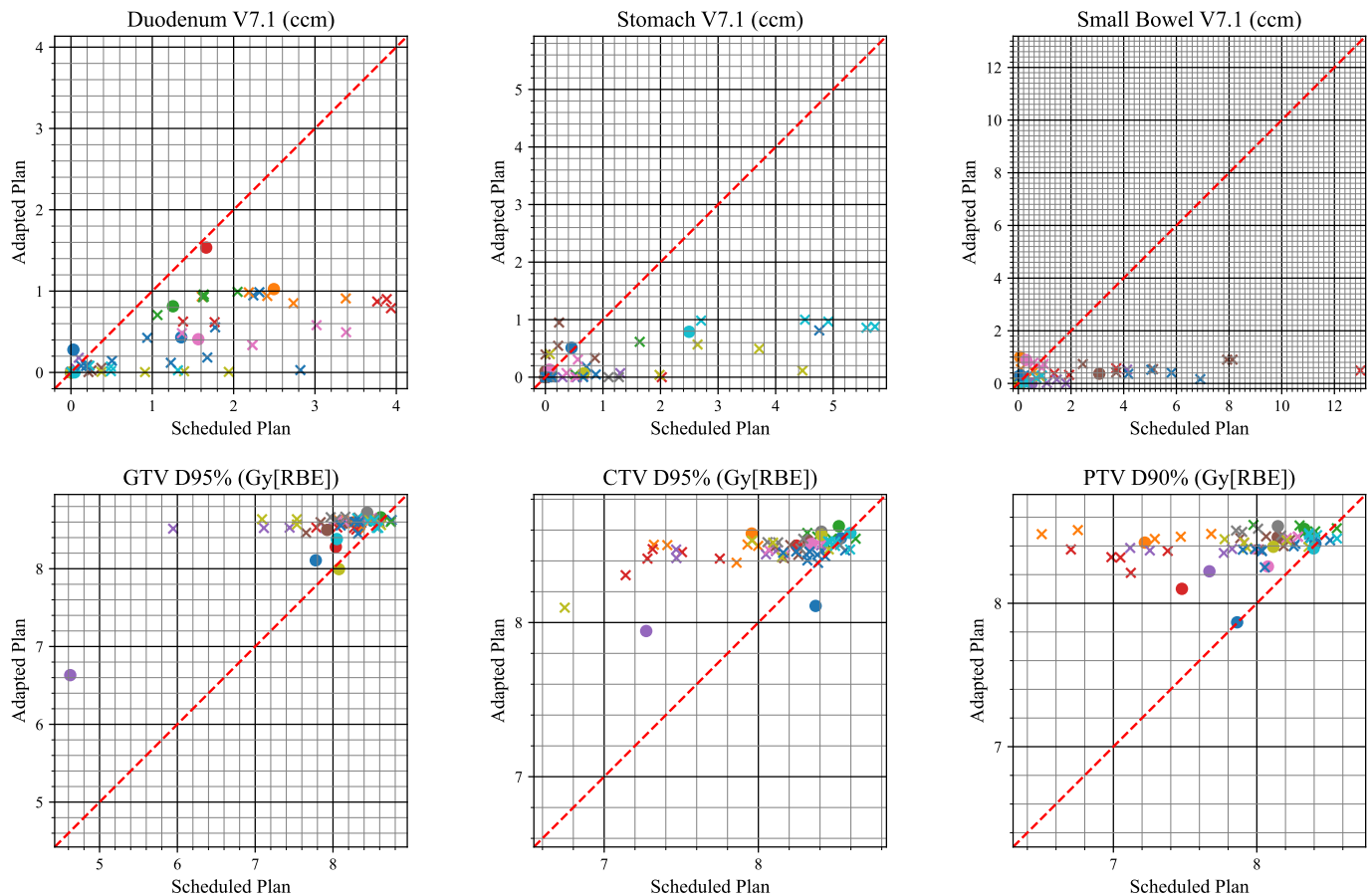


Fig. 1. Dose volume indices for D_{adp} and D_{sch} . The position along the x-axis gives the value for the scheduled plan (Volume for OARs, Dose for targets), and the position along the y-axis gives the value for the adapted plan. Each color corresponds to one patient. The crosses and circles represent the fractional and accumulated doses, respectively. The accumulated doses are normalized to a single fraction.

Table 4Performance of P_{ref} and P_{adp} on the PCT for accumulated doses (11 patients).

Structure	Metric	Goal/Constraint	Number of constraint violations		P_{ref} median [IQR]	P_{adp} median [IQR]	p-value
			P_{ref}	P_{adp}			
GTV	$V_{95\%PD}$ (%)	≥ 95	6	3	93.8 [89.6–99.3]	98.5 [94.9–99.4]	<0.05
	$V_{98\%PD}$ (%)	Not specified			84.3 [72.2–93.2]	95.6 [90.3–98.5]	<0.05
	$D_{95\%}$ (Gy[RBE])	Not specified			40.4 [39.9–42.2]	42.5 [41.0–43.2]	<0.05
CTV	$V_{95\%PD}$ (%)	Not specified	8	2	99.0 [96.9–99.7]	100.0 [99.2–100.0]	0.27
	$V_{98\%PD}$ (%)	Not specified			89.4 [74.8–94.2]	99.7 [97.2–100.0]	<0.05
	$D_{95\%}$ (Gy[RBE])	Not specified			41.9 [41.4–42.3]	42.7 [42.5–42.9]	0.16
PTV	$V_{95\%PD}$ (%)	≥ 90	8	2	87.2 [77.0–90.6]	94.8 [90.7–95.7]	<0.05
	$D_{90\%}$ (Gy[RBE])	Not specified			40.6 [38.8–41.2]	42.0 [41.2–42.2]	<0.05
Stomach	$V_{35.5 \text{ Gy[RBE]}}$ (ccm)	<1	1	0	0.0 [0.0–0.3]	0.0 [0.0–0.1]	0.86
Duodenum	$V_{35.5 \text{ Gy[RBE]}}$ (ccm)	<1	5	2	0.0 [0.0–1.5]	0.3 [0.0–0.6]	<0.05
Small bowel	$V_{35.5 \text{ Gy[RBE]}}$ (ccm)	<1	1	1	0.1 [0.1–0.3]	0.2 [0.0–0.3]	0.68
Spinal cord	D_{max} (Gy[RBE])	<22.2	0	0	8.8 [8.0–9.0]	8.5 [7.9–9.0]	0.32
Left kidney	$D_{50\%}$ (Gy[RBE])	<11.9	0	0	0.1 [0.1–0.1]	0.1 [0.1–0.1]	0.49
Right kidney	$D_{50\%}$ (Gy[RBE])	<11.9	0	0	0.1 [0.1–0.1]	0.1 [0.1–0.1]	0.95
Body	D_{max} (Gy[RBE])	Not specified			46.9 [46.3–47.4]	45.5 [44.7–46.6]	0.40

Abbreviations are as in Table 2.

%). The GTV $V_{95\%PD}$ and $V_{98\%PD}$, as well as the CTV $V_{98\%PD}$, improved significantly. Additionally, while the CTV $V_{95\%PD}$ improved, the difference was not significant. An example of patient 3 (light blue in Fig. 1) is shown in Fig. 2. In the case of $D_{acc,sch}^{(3)}$, the $V_{35.5 \text{ Gy[RBE]}}$ isoline intersects with large parts of the stomach, whereas the 95 % PD line (41.05 Gy [RBE]) does not cover the entire PTV. In the case of $D_{acc,adp}^{(3)}$, the stomach is largely avoided by the $V_{35.5 \text{ Gy[RBE]}}$ isoline, whereas the 95 % PD line closely follows the PTV edge. The median DVHs for all patients are shown in Fig. 3.

4. Discussion

The goal of this study was to evaluate whether the application of a workflow incorporating adaptive planning and ultra-hypofractionated CIRT can achieve satisfactory dose distributions and whether an adapted protocol offers dosimetric advantages over a non-adapted protocol. For each GI-OAR considered, at least 27 % of P_{ref} violated the essential constraints, whereas no constraints were breached for P_{adp} . The target coverage for the GTV, CTV and PTV also increased significantly for P_{adp} , with 41.8 % and 65.4 % of P_{ref} missing the clinical goals for the GTV and PTV, respectively. In reference to the accumulated doses, the target coverage increased significantly for GTV and PTV, whereas the critical $V_{35.5 \text{ Gy[RBE]}}$ decreased significantly for the duodenum. Considering the $V_{95\%PD}$ passing rate, better results were obtained for the CTV than for the GTV for both individual fractions as well as for accumulated doses. This can be explained by several cases where there was an overlap between OARs and the GTV. Due to OAR constraints, these overlapping regions received a lower dose, decreasing GTV $V_{95\%PD}$. These overlap regions, however, were not included in the CTV, leading to better results relative to the GTV. Compared with the six cases for $D_{acc,sch}$, the GI constraints were exceeded in three cases for $D_{acc,adp}$ with a maximum $V_{35.5 \text{ Gy[RBE]}}$ of 1.54 ccm. These results indicate that ultra-hypofractionated plans, which would otherwise lead to excessive GI-

OAR doses and unsatisfactory target coverage, can be reliably adapted to a clinically acceptable level using online ART. In some accumulated dose cases, the deviations between $D_{acc,sch}$ and $D_{acc,adp}$ were reduced, likely due to the interfractional organ motion that shifted the relative position of the dose hotspots within the OARs for D_{sch} , as reported in previous studies [11].

Strong evidence has emerged that both hypofractionation [6,7] and CIRT [9,10] improve the clinical outcomes of PC. Given the physical properties of carbon ions and technical limitations, these approaches have not yet been combined in a clinical context. Recently, many scholars have reported the successful implementation of CBCT- or MR-guided ART for numerous tumor sites, including the PC, indicating that following the emergence of improved software, recontouring, and replanning have been sufficiently optimized for widespread clinical use [28,29]. Hardware limitations remain to be overcome, as only a few CIRT centers exist worldwide with varying on-couch image-guiding systems. However, based on the results of this study, we encourage further exploration of CBCT-guided adaptive CIRT as a potential path for better local control and survival in patients with PC.

Several limitations of this study warrant discussion. A first limitation of our study is the usage of LEM IV for evaluating RBE. Dose prescriptions and recalculations are based on a microdosimetric kinetic model (MKM), as used by most Japanese centers. For pancreatic cancer, Japanese protocols assume α/β ratios of 3 Gy and 10 Gy, while European centers mostly use 2 Gy and 5 Gy [30]. However, in addition to variations in the radiobiological parameters, the MKM and the LEM are known to produce differing RBE weighted dose distributions [31]. While attempts have been made to find LEM-based prescribed dose that minimize differences to MKM-based prescribed dose [32], it remains difficult to assess dosimetric differences across targets and OARs [33].

Another limitation of this study were its small patient cohort size and the inconsistent number of fractions in the original treatment. Thirdly, changes in Hounsfield units, such as those caused by gas in the GI tract, as well as variations in the axial body shape, were not fully captured in

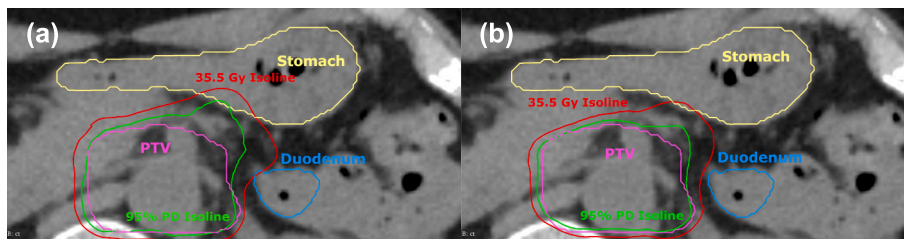


Fig. 2. Example of constraint violation when applying a scheduled plan (patient 3, accumulated dose). (a) $D_{sch}^{(3)}$ with isolines, and (b) $D_{adp}^{(3)}$ with isolines.

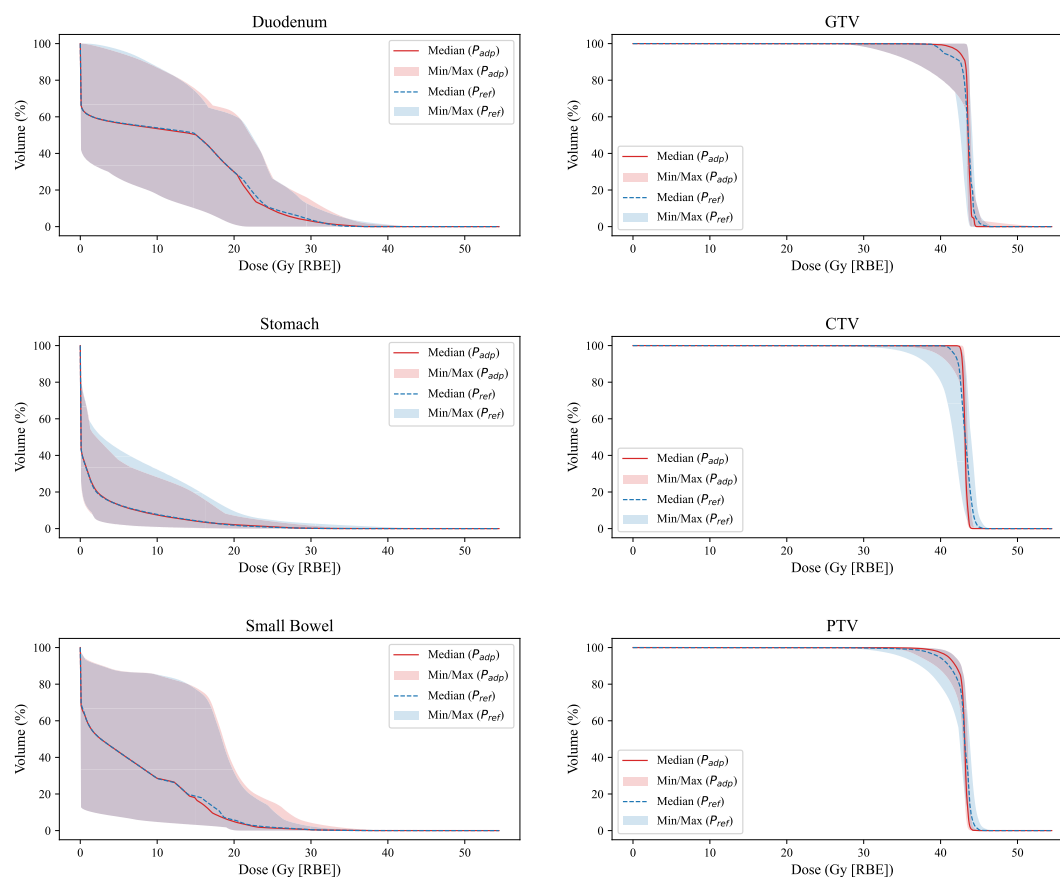


Fig. 3. DVHs for accumulated doses. At each dose, the median as well as the range across all 11 patients are shown. The solid and dashed lines refer to $D_{acc,adp}$ and $D_{acc,sch}$ respectively. The shaded region corresponds to the range.

the SCT generated in this study. These limitations may affect the accuracy of dose calculations in CIRT. In addition, dose accumulation relies heavily on the quality of the Ethos DIR algorithm. However, in contrast to the previous study by Ziegler et al. [34], in the absence of markers, no straightforward method exists to assess the registration quality.

In addition, although LQ models are commonly used to inform ultra-hypofractionated schedules in photon therapy [6,7], their accuracy in this regime is often questioned [35]. The 55.2 Gy[RBE] in the 12-fraction protocol upon which this study was based corresponds to a BED of 80.6 Gy, which was lower than the 100 Gy associated with improved local control in ultra-hypofractionated photon SBRT for PC. Increasing the effective dose of CIRT requires further investigation of the adapted GI-OAR constraints.

Finally, although image acquisition and recontouring were acquired during treatment, replanning for CIRT was performed in silico. Thus, the time efficiency demonstrated for photon CBCT-guided RT may not apply to a hypothetical setup involving a CIRT machine.

5. Conclusions

This study evaluated the dosimetric potential of ultra-hypofractionated CBCT-guided online adaptive CIRT for pancreatic cancer. For individual fractions, adapted plans met all the clinical goals, whereas they significantly reduced the OAR dose and increased the target dose. For the accumulated doses, the adapted plans exceeded some OAR constraints but still provided improved OAR sparing, whereas the target doses increased significantly. Based on this analysis, we demonstrated that ultra-hypofractionated CBCT-guided online adaptive CIRT for PC produces satisfactory dosimetric results. We anticipate that online adaptive radiotherapy holds promise for practical application, not only in photon therapy, but also in the context of CIRT.

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CRediT authorship contribution statement

Lukas Fabrizio Klassen: Conceptualization, Software, Formal analysis, Investigation, Writing – original draft. **Hideaki Hirashima:** Data curation, Writing – review & editing. **Hiraku Iramina:** Data curation, Writing – review & editing. **Takahiro Iwai:** Data curation, Writing – review & editing. **Michio Yoshimura:** Data curation, Writing – review & editing. **Hiroki Tanaka:** Writing – review & editing. **Takashi Mizowaki:** Writing – review & editing. **Mitsuhiro Nakamura:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

There is no usable data to share.

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