



Evaluation of short-term gastrointestinal motion and its impact on dosimetric parameters in stereotactic body radiation therapy for pancreatic cancer

Yusuke Uchinami^a, Takahiro Kanehira^b, Yoshihiro Fujita^a, Naoki Miyamoto^{b,c}, Kohei Yokokawa^b, Fuki Koizumi^a, Motoyasu Shido^a, Shuhei Takahashi^a, Manami Otsuka^a, Koichi Yasuda^d, Hiroshi Taguchi^d, Keiji Nakazato^b, Keiji Kobashi^e, Norio Katoh^{a,*}, Hidefumi Aoyama^a

^a Department of Radiation Oncology, Hokkaido University Faculty of Medicine and Graduate School of Medicine, North 15 West 7, Kita-ku, Sapporo, Hokkaido 060-8638, Japan

^b Department of Medical Physics, Hokkaido University Hospital, North 14 West 5, Kita-ku, Sapporo, Hokkaido 060-8648, Japan

^c Division of Applied Quantum Science and Engineering, Hokkaido University Faculty of Engineering, North 13 West 8, Kita-ku, Sapporo, Hokkaido 060-8628, Japan

^d Department of Radiation Oncology, Hokkaido University Hospital, North 14 West 5, Kita-ku, Sapporo, Hokkaido 060-8648, Japan

^e Global Center for Biomedical Science and Engineering, Hokkaido University Faculty of Medicine and Graduate School of Medicine, North 15 West 7, Kita-ku, Sapporo, Hokkaido 060-8638, Japan

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ABSTRACT

Background: The aim of this study is to quantify the short-term motion of the gastrointestinal tract (GI-tract) and its impact on dosimetric parameters in stereotactic body radiation therapy (SBRT) for pancreatic cancer.

Methods: The analyzed patients were eleven pancreatic cancer patients treated with SBRT or proton beam therapy. To ensure a fair analysis, the simulation SBRT plan was generated on the planning CT in all patients with the dose prescription of 40 Gy in 5 fractions. The GI-tract motion (stomach, duodenum, small and large intestine) was evaluated using three CT images scanned at spontaneous expiration. After fiducial-based rigid image registration, the contours in each CT image were generated and transferred to the planning CT, then the organ motion was evaluated. Planning at risk volumes (PRV) of each GI-tract were generated by adding 5 mm margins, and the volume receiving at least 33 Gy (V_{33}) < 0.5 cm³ was evaluated as the dose constraint.

Results: The median interval between the first and last CT scans was 736 s (interquartile range, IQR:624–986). To compensate for the GI-tract motion based on the planning CT, the necessary median margin was 8.0 mm (IQR: 8.0–10.0) for the duodenum and 14.0 mm (12.0–16.0) for the small intestine. Compared to the planned V_{33} with the worst case, the median V_{33} in the PRV of the duodenum significantly increased from 0.20 cm³ (IQR: 0.02–0.26) to 0.33 cm³ (0.10–0.59) at Wilcoxon signed-rank test ($p = 0.031$).

Conclusion: The short-term motions of the GI-tract lead to high dose differences.

Introduction

Stereotactic body radiation therapy (SBRT) has emerged as a new strategy for pancreatic cancer, and improved treatment outcomes have been reported in resectable and unresectable cases[1–6]. The advantages of SBRT have the potential to deliver higher doses to the tumor and

shorter treatment periods, which allow a transition to chemotherapy or surgery without long delays. One of the challenges in the treatment planning is that the tumor is usually located close to the gastrointestinal tract (GI-tract), and excess doses of a few Gy can result in severe adverse events [7,8], to ensure against this careful attention must be paid to minimize adverse events.

Abbreviations: 4DCT, four-dimensional computed tomography; CTV, clinical target volume; FFF, flattening filter-free; GI-tract, gastrointestinal tract; GTV, gross tumor volume; IQR, interquartile range; MV, mega-voltage; PRV, planning at risk volume; PTV, planning target volume; ROI, region of interest; SBRT, stereotactic body radiation therapy; SD, standard deviation; VMAT, volumetric modulated arc therapy.

* Corresponding author.

E-mail address: noriwokatoh@med.hokudai.ac.jp (N. Katoh).

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In addition to these anatomical characteristics, GI-tract motion must also be considered. Intra-fractional motion is a short-term motion in the order of seconds or minutes during the radiotherapy [9–11], mainly caused by respiration or organ peristalsis[12]. A robust treatment plan employing sufficiently large margins can account for the small intra-fractional motions, which arise as the planning CT is scanned at a single time point. With recent technological developments in respiratory motion management, dose uncertainties from respiration would be negligible during beam delivery when appropriate measures, such as respiratory gating are employed[13]. However, the influence of organ peristalsis on the dose distribution has not yet been thoroughly studied mainly as it is a continuous and irregular motion[14,15]. To avoid under- and overdoses, short-term GI-tract motion should be considered in SBRT planning for pancreatic cancer. In this study, we evaluated this motion using multiple CT images scanned in patients treated with SBRT or proton beam therapy (PBT). We also quantified the dosimetric impact of short-term motion in the simulation SBRT plan. The aim of this study is to investigate the short-term motion and its impact on the dose that the GI-tract is exposed to.

Materials and Methods

Patients

This study was approved by our institutional ethics review committee (IRB-number:21–0074). Eligibility criteria were as follows: SBRT for pancreatic cancer without lymph node or distant metastases, and at least three different CT image sets available at the planning CT scan. To study a larger number of cases, we also included patients who had received PBT. Of patients treated with SBRT or PBT between January 2015 and October 2022, eleven patients with pancreatic cancer were finally included in the study (Supplementary material A). All patients received respiratory-gated SBRT or respiratory-gated spot-scanning proton therapy using the fiducial marker transarterially placed near the tumor [16,17]. Because this study included a mix of pancreatic cancer patients treated with SBRT or PBT, simulated SBRT plans were generated for all patients to reduce errors in the treatment planning.

CT data acquisition

The general protocol of the planning CT image acquisition was the same for PBT and SBRT. The CT scans were of 2–2.5 mm slice thickness and obtained using a vacuum cushion after six or more hours of fasting. Four-dimensional computed tomography (4DCT) imaging was performed using the real-time position management (RPM) system to determine the accurate respiratory phase in a patient (Varian Medical Systems, Palo Alto, CA). The obtained 4DCT images were reconstructed into ten sets of three-dimensional CT (3DCT) images based on ten respiratory phases (from 0 %, 10 %, ... to 90 %) using the RPM system. In 3DCT images, 0 % images were images of spontaneous inspiration, and 50 % images were spontaneous expiration. A non-contrast planning CT image (CT_P) and if possible a contrast enhanced CT (CT_{CE}) were acquired. Since the respiratory gating was performed at the spontaneous expiration, the CT_P and CT_{CE} were also obtained at this point in the respiratory phase. The obtained CT_P and CT_{CE} were checked to confirm whether they were appropriately scanned at the spontaneous expiration with reference to the 4DCT 50 % phase (CT_{4D}), which corresponds to a CT image at spontaneous expiration. The CT_P or CT_{CE} was determined to be properly imaged with spontaneous expiration by a board-certified radiation oncologist if the fiducial marker location was within 4 mm in the craniocaudal direction after bone-based rigid image registration with CT_{4D}. The median interval from first to last CT scan at the planning CT scan was 736 s (interquartile range, IQR: 624–986).

Target and organ contouring

Contouring was performed based on our institutional protocol. For patients treated with PBT, additional contours were generated for this study. Gross tumor volume (GTV) was defined as the tumors identified by the available images including non-enhanced CT, enhanced CT, and/or positron emission tomography (PET) images. The clinical target volume (CTV) was generated as the GTV with the tumor-vessel interface (TVI), including the major vessels within 5 mm of the GTV[18]. Planning target volume (PTV) was defined as the CTV with a margin of 5 mm considering the set-up margin and gating window of 2 mm. The planning at risk volume (PRV) of the GI-tract (GI-tract_PRV) was defined as the area encompassing the stomach, duodenum, small intestine, or large intestine plus a 5 mm margin. Here, the PTV_{eval} is defined as the PTV minus the area overlapping the GI-tract_PRV. The prescribed dose was 40 Gy in 5 fractions for 90 % of the volume of PTV_{eval}, and the 80–90 % isodose lines surrounding the dose volume. In cases where the dose of PTV_{eval} was difficult to establish accurately (e.g the GTV was surrounded by the GI-tract), an acceptable dose was targeted in the plan (Table 1). For our institutional dose constraints, the volume receiving at least 33 Gy (V₃₃) < 0.5 cm³ was used for each of the PRV (Stomach_PRV, Duodenum_PRV, Small intestine_PRV, and Large intestine_PRV) to ensure safety compared to Oar et al. as reported elsewhere [18]. Other target goals and major dose constraints are described in Table 1.

Simulation SBRT planning

Simulation treatment plans (PLAN_{sim}) were generated for all the study patients on the CT_P with the Auto-Planning module of Pinnacle³ version 14.0 (Philips, Amsterdam, Netherlands). A previous study has reported that treatment planning using the Auto-Planning module was clinically acceptable at a very high-quality level in SBRT for pancreatic cancer[19]. Simulation SBRT plans were generated by volumetric modulated arc therapy (VMAT) with two full arcs, 6 mega-voltage (MV) flattening filter-free (FFF) beams in a TrueBeam (Varian Medical Systems) (SBRT-VMAT). Gantry spacing was 2 degrees, and a dose grid of 2 mm was applied at the dose calculation. These planning parameters were the same as those used in previous studies for primary liver tumors [20]. To reduce the errors involved in simulation planning, the plan quality was checked by Y.U and T.K. The above simulation planning workflow was like the actual SBRT in that the doses were delivered by 6 MV-FFF beams using a TrueBeam, implementing a SyncTraX FX4 (Shimadzu, Kyoto, Japan) for fiducial marker-based respiratory gating.

Table 1
General dose constraints for SBRT.

Contour	Dose constraints
GTV	D _{50%} ≥ 40 Gy, (acceptable, D _{2%} ≥ 40 Gy)
PTV _{eval}	D _{90%} ≥ 40 Gy, (acceptable, D _{90%} ≥ 32 Gy)
PRV (adding a 5 mm margin to each GI-tract organ)	
Stomach_PRV	V ₃₃ < 0.5 cm ³
Duodenum_PRV	V ₃₃ < 0.5 cm ³
Small intestine_PRV	V ₃₃ < 0.5 cm ³
Large intestine_PRV	V ₃₃ < 0.5 cm ³
Kidneys, bilateral	V ₁₂ < 25 %
Liver	V ₁₂ < 40 %
Spinal cord + 5 mm	V ₂₀ < 0.5 cm ³

Vx: volumes receiving a minimum of X Gy.

Dx%: minimum dose received by X as the percent of the target volume.

GTV: gross tumor volume, PRV: planned at risk volume, PTV: planned target volume, SBRT: stereotactic body radiation therapy.

Study workflow

Details of the study workflow are shown in Fig. 1. First, the CT_{CE} and CT_{4D} were rigidly registered with respect to the vertebral bone for the CT_p , and translation-only registration was performed based on the fiducial marker position (Fig. 1A-ab). This alignment method is similar to the actual patient positioning procedure and previous inter-fractional motion studies[14]. After the rigid image registration, the GI-tract contour in CT_p was deformably transferred to the CT_{CE} or CT_{4D} . Here, we defined the region of interest (ROI) in CT_p , CT_{CE} and CT_{4D} as ROI_p , ROI_{CE} and ROI_{4D} , respectively (Fig. 1A-c). The deformed ROI were reviewed, and most of them were manually modified, then transferred back to the CT_p . Dosimetric parameters were analyzed using the planned dose distribution on the CT_p for each ROI (Fig. 1A-d). Study contouring was conducted for the entire stomach and duodenum according to RTOG recommendations[21]. The small or large intestines were contoured from the diaphragm to the lowest axial slice of the CTV with a 20 mm margin. Since it was difficult to distinguish the small intestine from the large intestine in one patient, the entire intestine other than the stomach and duodenum was contoured as the small intestine in this case. At least two radiation oncologists (Y.U and Y.F) reviewed these contours to minimize errors among physicians. The above procedure was performed by MIM maestro ver. 7.0 (MIM Software, Cleveland, OH, USA).

Data analysis

The locational difference among three ROI indicates the short-term motion (Fig. 1B-a). The sum of the ROI was generated as ROI_{all} to evaluate the minimum margin to compensate for the motion uncertainty based on the ROI_p (Fig. 1B-b). Then, the margin needed to compensate for the ROI_{all} was determined based on the ROI_p every 2 mm (Fig. 1B-c). To avoid incorrect evaluations, the boundary of the GI-tract was made the same for each of the patients and it was verified that this uncertainty did not influence the results (Supplementary material B). As standard distance metrics, Dice index and mean distance to agreement were also evaluated in each GI-tract (Supplementary material C). For more practical values, the change over time in the shortest distance was measured between the PTV and GI-tract. In this evaluation, the stomach and duodenum were evaluated as one ROI of the stomach-duodenum. All CT images used in the analysis were imaged with spontaneous expiration, and the effects of respiration were assumed to be negligible. The paired differences of dosimetric parameters were analyzed with paired Wilcoxon signed-rank tests, with the p-value < 0.05 considered to show significance. The statistical analysis was performed with the JMP Pro version 16 (SAS, Cary, NC).

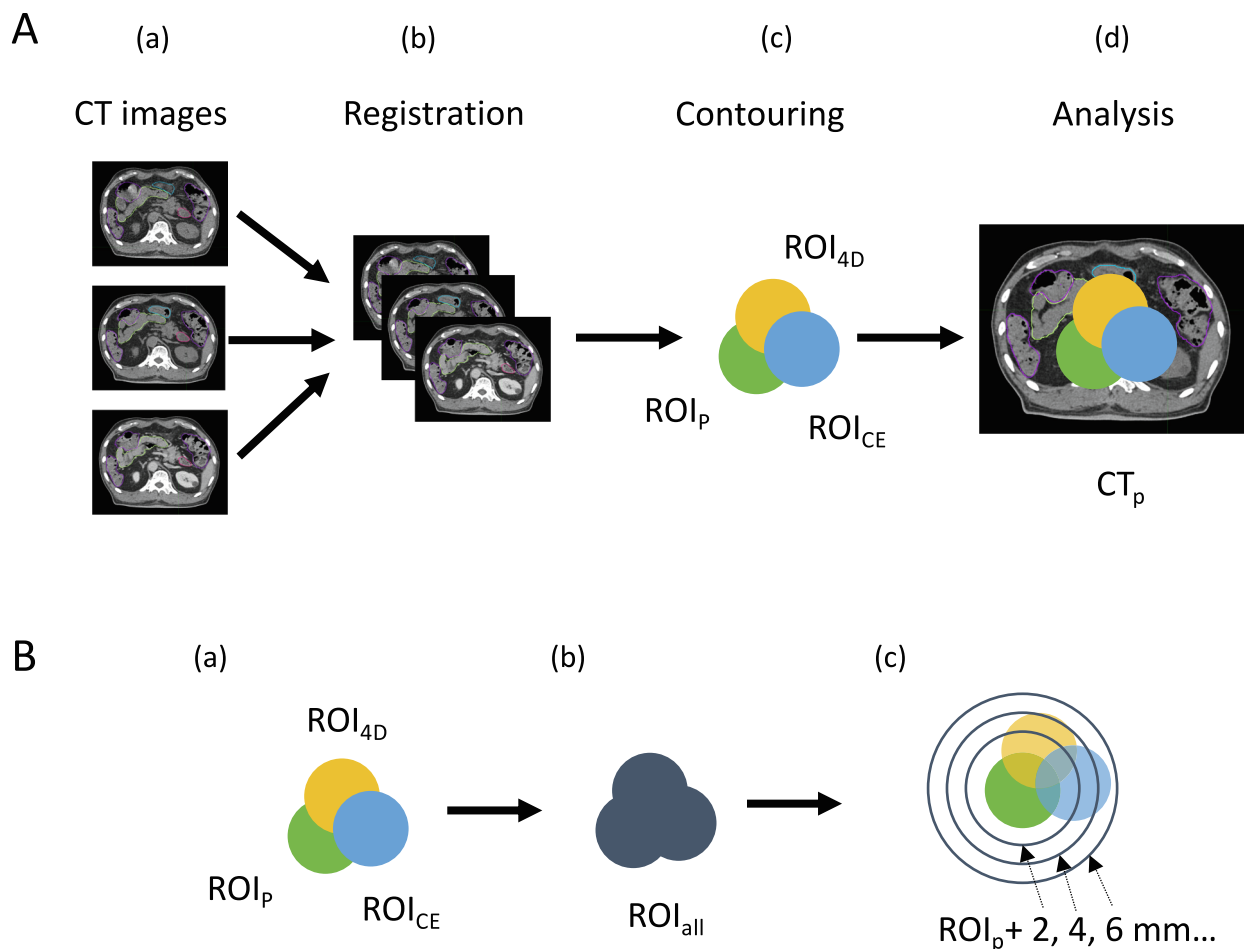


Fig. 1. (A) The method of target or organ contouring and (B) the method of quantifying the minimum margin to compensate for ROI at the planning CT scan. A (a): Three different CT images (CT_p , CT_{CE} , and CT_{4D}) were prepared. (b) The CT_{CE} and CT_{4D} images were rigidly registered based on the vertebral bone for the CT_p , then translation-only registration was performed based on the fiducial marker position. (c) Target or organ contours in CT_p (ROI_p) were deformably transferred to the CT_{CE} or CT_{4D} , then transferred back to the CT_p after review and modification of deformed contours. Each region of interest (ROI) on CT images are shown as ROI_p , ROI_{CE} and ROI_{4D} . (d) Analysis was performed on the CT_p using ROI_p , ROI_{CE} , and ROI_{4D} . B (a): ROIs in CT_p , CT_{4D} , and CT_{CE} are termed as ROI_p , ROI_{CE} , and ROI_{4D} . (b) The sum of all contours is defined as the ROI_{all} . (c) To evaluate the margin to compensate for ROI_{all} , margins were determined every 2 mm from the ROI_p to the entire circumference. In this example, the minimum margin is calculated to be 6 mm. ROI: region of interest.

Results

Contour analysis

An example of short-term GI-tract motion after fiducial-based matching (shown in Fig. 2) was established to take place within the 986 s between the first and last CT scan. The shortest distances between the PTV and each GI-tract have changed over time (Supplementary material D). Based on the shortest distance in CT_P, the median maximum change of the distance over time was 0 mm (IQR: 0–0) in the stomach-duodenum, 0 mm (-1.2 to 1.1) in the small intestine, and 0 mm (-0.9 to 2.1) in the large intestine. The minimum margin to compensate for the motion uncertainties of the GI-tract was calculated, to include an area distant from the tumor. To compensate for these GI-tract motion, the median necessary margin was 10.0 mm (IQR: 8.0–14.0) for the stomach, 8.0 mm (8.0–10.0) for the duodenum, 14.0 mm (12.0–16.0) for the small intestine, and 13.0 mm (11.5–14.5) for the large intestine (Fig. 3).

Dosimetric analysis

The short-term motion increased V₃₃ in some of the worst cases, which caused the deviation of the dose constraint of V₃₃ < 0.5 cm³ (Table 2). Because the large intestine in one patient (patient No 3) was difficult to identify, the entire intestine other than the stomach and duodenum was contoured as the small intestine.

Compared to the median V₃₃ (IQR) of PLAN_{sim}, that of the worst case, which is at the highest values among the three CT data sets, deviated in three cases in the duodenum and two in the other organs (Table 3). The absolute increase of median V₃₃ was 0.02 cm³ in the stomach, 0.13 cm³ in the duodenum, but not present in the small intestine or the large

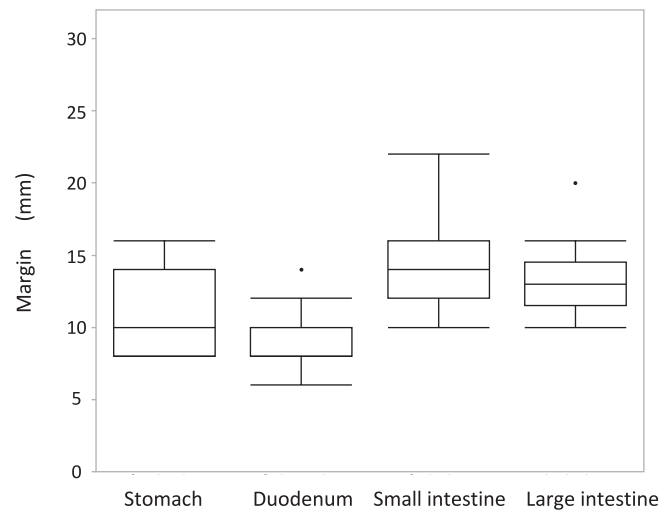


Fig. 3. Box plot of the necessary margins to compensate for motion in the contoured GI-tracts. Boxes show the interquartile range from 25 to 75 %ile. Median values and outliers are shown as horizontal lines within the box and black circles. GI-tract: gastrointestinal tract.

intestine. The median of the D_{0.5} dose increased 3.3 % (26.9 to 27.8 Gy) in the stomach, 5.5 % (30.8 to 32.5 Gy) in the duodenum, 10.5 % (28.4 to 31.4 Gy) in the small intestine, and 6.9 % (25.8 to 27.6 Gy) in the large intestine.

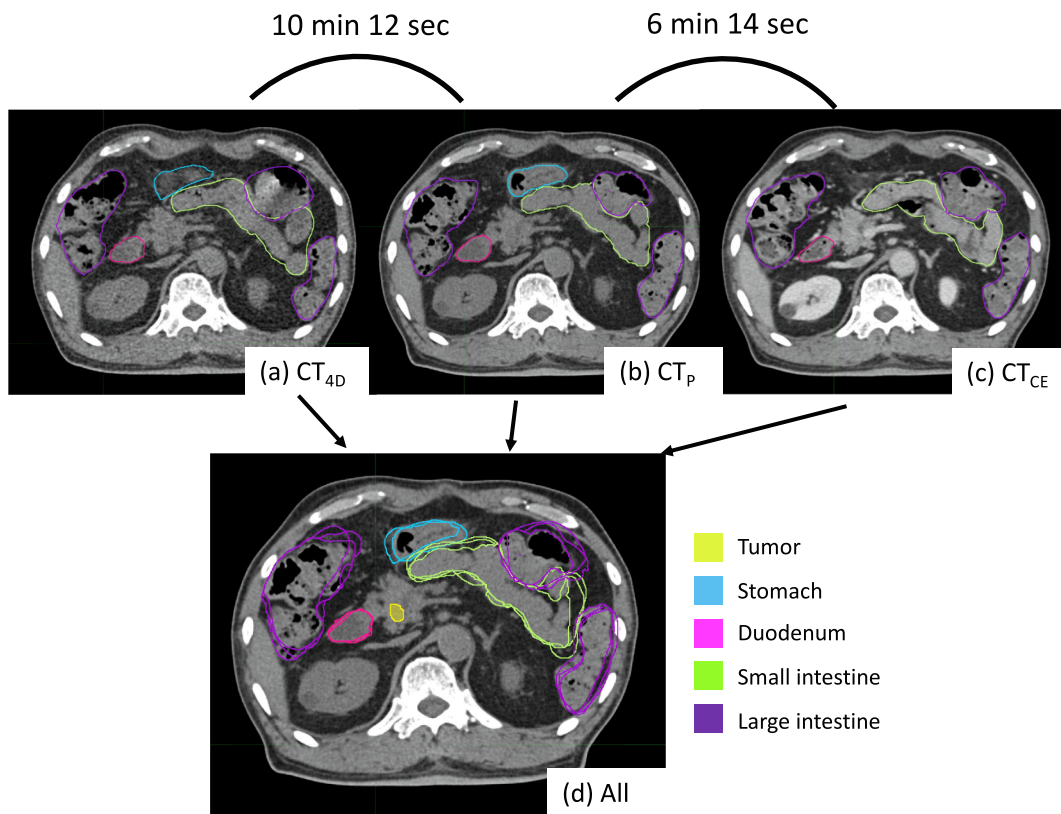


Fig. 2. The GI-tract motion of a case after fiducial-based image registration. The contour of the stomach (blue), duodenum (pink), small intestine (green), and large intestine (purple) are shown on each of the CT images (a-c). The contours of three CT images are simultaneously shown superimposed on the CT_P in panel (d), which indicates variations of GI-tract location. GI-tract: gastrointestinal tract. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Details of V₃₃ for each patient.

Patient No	Stomach_PRV* (cm ³)		Duodenum_PRV (cm ³)		Small intestine_PRV (cm ³)		Large intestine_PRV (cm ³)	
	PLAN _{sim}	Worst-case	PLAN _{sim}	Worst-case	PLAN _{sim}	Worst-case	PLAN _{sim}	Worst-case
1	0	0	0.08	0.59	0.28	0.30	0	0
2	0	0	0.02	0.91	0.14	0.43	0.01	0.75
3	0.14	0.75	0.03	0.10	0.04	1.18	**	**
4	0	0.04	0.20	0.33	0	0.04	0	0
5	0.02	0.02	0.39	0.39	0.04	0.04	0	0
6	0.36	1.25	0	0	0.19	0.19	0	0
7	0	0	0.28	0.48	0.06	0.46	0.06	0.17
8	0.27	0.37	0.20	0.31	0	0.13	0	0
9	0.06	0.06	0	0	0	0	0.34	1.07
10	0	0	0.22	0.22	0.24	1.51	0	0
11	0.02	0.08	0.26	0.94	0	0	0	0

Worst-case is the one with the highest V₃₃ among the three CT data sets (CT_P, CT_{CE}, CT_{4D}).

*PRV: Generated by adding a 5 mm margin to each GI-tract (stomach, duodenum, small intestine, or large intestine).

**Difficult to identify the large intestine in one case.

PRV: planning at risk volume.

Table 3
Dosimetric parameters at PLAN_{sim} and worst-case values due to GI-tract motion.

PRV		Value at PLAN _{sim} (IQR)	Value at worst-case* (IQR)	p-value	Deviation at worst-case
Stomach_PRV (n = 11)	V ₃₃ (cm ³)	0.02 (0–0.14)	0.04 (0–0.37)	0.121	2/ 11 cases
	D _{0.5} (Gy)	26.9 (19.8–31.9)	27.8 (19.8–32.8)	0.017	
	D ₁ (Gy)	25.5 (14.8–31.0)	26.4 (14.8–32.1)	0.010	
	D ₅ (Gy)	20.5 (5.2–24.1)	21.1 (6.6–26.2)	0.012	
	D ₁₀ (Gy)	17.6 (3.6–21.0)	17.9 (4.6–22.6)	0.017	
	V ₃₃	0.20 (0.02–0.26)	0.33 (0.10–0.59)	0.031	3/ 11 cases
Duodenum_PRV (n = 11)	D _{0.5}	30.8 (25.5–32.3)	32.5 (27.5–33.4)	0.040	
	D ₁	28.5 (22.3–31.1)	30.7 (23.3–32.3)	0.056	
	D ₅	22.0 (13.0–25.9)	23.4 (13.0–25.9)	0.027	
	D ₁₀	16.6 (9.7–22.9)	18.2 (10.1–22.9)	0.006	
	V ₃₃	0.04 (0–0.19)	0.04 (0.04–0.46)	0.060	2/ 11 cases
Small intestine_PRV (n = 11)	D _{0.5}	28.4 (24.9–31.4)	31.4 (27.4–32.8)	0.029	
	D ₁	27.0 (22.5–29.6)	29.6 (25.4–30.7)	0.032	
	D ₅	20.7 (16.1–22.6)	22.1 (17.9–22.7)	0.022	
	D ₁₀	17.8 (12.8–18.9)	17.9 (14.3–19.3)	0.008	
	V ₃₃	0 (0–0.02)	0 (0–0.31)	0.137	2/ 10 cases
Large intestine_PRV (n = 10)**	D _{0.5}	25.8 (15.7–28.6)	27.6 (18.5–31.9)	0.059	
	D ₁	24.5 (13.7–26.7)	26.1 (15.3–29.2)	0.057	
	D ₅	19.8 (10.6–20.6)	19.9 (11.4–22.8)	0.017	
	D ₁₀	17.0 (9.4–18.3)	17.4 (10.1–19.6)	0.034	

Worst-case is the one with the highest V₃₃ among three CT data sets (CT_P, CT_{CE}, and CT_{4D}). D_X shows the maximum dose delivered to a volume of X cm³ in each organ.

*PRV: Generated by adding a 5 mm margin to each GI-tract organ (stomach, duodenum, small intestine, or large intestine).

**Difficult to identify the large intestine in one case.

IQR: interquartile range, PRV: planning at risk volume.

Discussion

In this study, we report the short-term GI-tract motion other than respiration using CT images in patients treated with SBRT or PBT for pancreatic cancer. We also generated SBRT simulation plans for all cases and evaluated its impact on the dosimetric parameters. There have been several reports on inter-fractional changes [14,15], however, to our knowledge this is the first study to report on short-term motion observed within the median of 783 s from CT images. We have also evaluated the impact of the short-term motion on the dosimetric parameters. The results suggest that overdoses could occur due to the short-term GI-tract motion.

We quantified the intestinal motion during the planning CT scan and showed that the motion could not be ignored. Lens et al. analyzed the intratumoral fiducial variations with breath-holding CT in a single fraction. From 12 pancreatic cancer patients who had undergone SBRT, Lens et al. reported that the mean variation in a single fraction was – 0.2 (standard deviation; SD: 1.7) mm and – 0.5 (SD: 0.8) mm in the inferior-superior and anterior-posterior directions, respectively [22]. Grimbergen et al. analyzed patients who underwent MR-guided SBRT and reported that the mean of the maximum baseline drift of the tumor during SBRT was 1.2 mm in the craniocaudal direction, excluding respiratory motion [23]. These studies analyzed tumor motions except for respiration during treatment, but the number of studies on motions of the GI-tract is limited. Mostafaei et al. studied peristaltic motions during radiotherapy by MR-linac and reported that these motions were irregular, persistent, and comparable in magnitude to the respiratory motion [12]. They suggested that peristalsis also should be considered together with respiratory motion. From this present study, we also found that a median margin of 8.0–14.0 mm was necessary to compensate for the short-term uncertainties of each of the GI-tract organs. Our evaluations were motion in one day at the treatment planning CT scan, but such short-term motion can be suggestive of intra-fractional motion during radiotherapy.

In the worst-case scenarios, the V₃₃ of each PRV in the GI-tract was higher than the simulation SBRT plan (PLAN_{sim}), and dose constraints were violated in two or three cases (Table 3). Similar results have been reported in studies on inter-fractional [14,15] and intra-fractional motion [24] in pancreatic SBRT. Loi et al. studied inter-fractional motions of 35 pancreatic cancer patients treated with SBRT [14]. They reported a median increase of 1.0 cm³ (IQR: 0.2–2.6) in V₃₅ of the gastrointestinal tract (stomach, duodenum, and intestine) over that of the treatment plan. Niedzielski et al. also conducted a similar study using daily CT-on-rails image guidance immediately before treatment, and they reported that the dose constraints of V₃₅ in the duodenum or small intestine were violated in three out of eleven patients [15]. Alam et al. studied inter-fractional and intra-fractional motion in patients with pancreatic

cancer treated by MR-guided SBRT[24]. They reported an increased accumulated dose in the stomach-duodenum and small bowel due to intra-fractional motion, which caused deviations from institutional dose constraints in three out of five patients. Of course, it should be noted that the dosimetric analysis in the present study was based on CT images at a specific point in time. Because the GI-tract is continuously moving and deforming, a cumulative dose that accounts for organ changes over time would be closer to reality.

In an SBRT for pancreatic cancer, a highly optimized treatment plan is generated to achieve an adequate dose to the target and maintain sophisticated dose constraints of the GI-tract. Several studies have reported an increased incidence of adverse events when high doses are administered to part of the GI-tract. From a dose-escalation study of SBRT, Courtney et al. reported that a higher dose to the GI-tract was shown to be associated with late gastrointestinal hemorrhage[25]. They also summarized increased duodenum dose-volume parameters (V_{35} , V_{40} , or V_{45}) in the patient group with higher-dose prescription. Moreover, Kopek et al. found a maximum dose to 1 cm^3 (D_1) of duodenum was important to predict late duodenal complications in cholangiocarcinomas treated with SBRT[26]. Our study did not show a significant increase in D_1 of the duodenum_PRV in the worst case ($p = 0.056$), but there was a median increase of 1.7 Gy (5.5 %). Given these findings, even slight uncertainties in the GI-tract location, especially in the proximity of the GI-tract, can lead to serious adverse events. Online adaptive therapy has become clinically applied to cope with the daily anatomical changes of patients, but some articles have reported that it takes several tens of minutes from the initial CT acquisition to beam-on [27,28]. Because our study observed the short-term GI-tract motion with a median period of 736 s, such motion should also be considered in an online adaptive strategy.

The limitations of our study include the following. Because peristaltic motion in the GI-tract is continuous, the analyzed CT images alone may not adequately reflect the organ motion. Moreover, the short-term GI-tract motion may vary among the days the images were obtained. To address these issues, obtaining multiple CT images over multiple days is ideal, but would be impractical given the burden on patients and medical staffs. Another limitation is that the dose distribution was not recalculated on different CT images. One reason for this is that the CT image data used in this study were obtained from the same body position, at spontaneous expiration, and at intervals of several minutes. Therefore, we assumed that the variations in the dose distribution due to anatomical changes are negligible in different CT images. Another reason is that the differences in CT scan conditions (enhanced, non-enhanced, or 4DCT) may lead to the slight uncertainties in the dose distribution, as also suggested in several reports [29,30]. Future studies require an increased number of patients, and CT images should be taken under the same conditions.

In conclusion, the short-term motion of the GI-tract was observed, and these uncertainties may lead to unexpectedly high dose exposure in parts of the GI-tract. To reduce adverse events of the GI-tract, it is necessary to quantify these motions and reflect them appropriately in the SBRT plan.

Declaration of Competing Interest

K.K. is an employee of the research institute of Hitachi, Ltd., currently working at Hokkaido University, under a secondary agreement. K.K. declares that this research has no relationship with Hitachi, Ltd. All other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctro.2023.100576>.

References

- [1] Chuong MD, Springett GM, Freilich JM, Park CK, Weber JM, Mellon EA, et al. Stereotactic Body Radiation Therapy for Locally Advanced and Borderline Resectable Pancreatic Cancer Is Effective and Well Tolerated. *International Journal of Radiation Oncology*Biophysics* 2013;86(3):516–22.
- [2] de Geus SWL, Eskander MF, Kasumova GG, Ng SC, Kent TS, Mancias JD, et al. Stereotactic body radiotherapy for unresected pancreatic cancer: A nationwide review. *Cancer* 2017;123(21):4158–67.
- [3] Herman JM, Chang DT, Goodman KA, Dholakia AS, Raman SP, Hacker-Prietz A, et al. Phase 2 Multi-institutional Trial Evaluating Gemcitabine and Stereotactic Body Radiotherapy for Patients With Locally Advanced Unresectable Pancreatic Adenocarcinoma. *Cancer* 2015;121(7):1128–37.
- [4] Hoyer M, Roed H, Sengelov L, Traberg A, Ohlhuis L, Pedersen J, et al. Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. *Radiother Oncol* 2005;76(1):48–53.
- [5] Jiang W, Haque W, Verma V, Butler EB, Teh BS. Neoadjuvant stereotactic body radiation therapy for nonmetastatic pancreatic adenocarcinoma. *Acta Oncol* 2019; 58(9):1259–66.
- [6] Witt JS, Kuczmarska-Haas A, Lubner M, Reeder SB, Cho SY, Minter R, et al. A Phase 1 Dose Escalation Study of Neoadjuvant SBRT Plus Elective Nodal Radiation with Concurrent Capecitabine for Resectable Pancreatic Cancer. *Int J Radiat Oncol Biol Phys* 2021;109(2):458–63.
- [7] Murphy JD, Christman-Skieller C, Kim J, Dieterich S, Chang DT, Koong AC. A Dosimetric Model of Duodenal Toxicity After Stereotactic Body Radiotherapy for Pancreatic Cancer. *International Journal of Radiation Oncology*Biophysics* 2010;78(5):1420–6.
- [8] Miften M, Vinogradskiy Y, Moiseenko V, Grimm J, Yorke E, Jackson A, et al. Radiation Dose-Volume Effects for Liver SBRT. *International Journal of Radiation Oncology*Biophysics* 2021;110(1):196–205.
- [9] Lee M, Simeonov A, Stanescu T, Dawson LA, Brock KK, Velec M. MRI evaluation of normal tissue deformation and breathing motion under an abdominal compression device. *J Appl Clin Med Phys* 2021;22(2):90–7.
- [10] Uchinami Y, Suzuki R, Katoh N, Taguchi H, Yasuda K, Miyamoto N, et al. Impact of organ motion on volumetric and dosimetric parameters in stomach lymphomas treated with intensity-modulated radiotherapy. *J Appl Clin Med Phys* 2019;20(8): 78–86.
- [11] Watanabe M, Isobe K, Takisima H, Uno T, Ueno N, Kawakami H, et al. Intrafractional gastric motion and interfractional stomach deformity during radiation therapy. *Radiother Oncol* 2008;87(3):425–31.
- [12] Mostafaei F, Tai An, Omari E, Song Y, Christian J, Paulson E, et al. Variations of MRI-assessed peristaltic motions during radiation therapy. *PLoS One* 2018;13(10): e0205917.
- [13] Campbell WG, Jones BL, Scheffer T, Goodman KA, Miften M. An evaluation of motion mitigation techniques for pancreatic SBRT. *Radiother Oncol* 2017;124(1): 168–73.
- [14] Loi M, Magallon-Baro A, Suker M, van Eijck C, Sharma A, Hoogeman M, et al. Pancreatic cancer treated with SBRT: Effect of anatomical interfraction variations on dose to organs at risk. *Radiother Oncol* 2019;134:67–73.
- [15] Niedzielski JS, Liu Y, Ng SSW, Martin RM, Perles LA, Beddar S, et al. Dosimetric uncertainties resulting from interfractional anatomic variations for patients receiving pancreas stereotactic body radiation therapy and cone-beam CT image guidance. *International Journal of Radiation Oncology*Biophysics* 2021.
- [16] Shimizu S, Miyamoto N, Matsuura T, Fujii Y, Umezawa M, Umezaki K, et al. A proton beam therapy system dedicated to spot-scanning increases accuracy with moving tumors by real-time imaging and gating and reduces equipment size. *PLoS One* 2014;9(4):e94971.
- [17] Shirato H, Shimizu S, Kitamura K, Nishioka T, Kagei K, Hashimoto S, et al. Four-dimensional treatment planning and fluoroscopic real-time tumor tracking radiotherapy for moving tumor. *Radiation Oncology Biology* 2000;48(2):435–42.
- [18] Oar A, Lee M, Le H, Hruby G, Dalftsen R, Pryor D, et al. Australasian Gastrointestinal Trials Group (AGITG) and Trans-Tasman Radiation Oncology Group (TROG) Guidelines for Pancreatic Stereotactic Body Radiation Therapy (SBRT). *Pract Radiat Oncol* 2020;10(3):e136–46.
- [19] Wang S, Zheng D, Lin C, Lei Yu, Verma V, Smith A, et al. Technical Assessment of an Automated Treatment Planning on Dose Escalation of Pancreas Stereotactic Body Radiotherapy. *Technol Cancer Res Treat* 2019;18:1533.
- [20] Uchinami Y, Katoh N, Suzuki R, Kanehira T, Tamura M, Takao S, et al. A study on predicting cases that would benefit from proton beam therapy in primary liver tumors of less than or equal to 5 cm based on the estimated incidence of hepatic toxicity. *Clinical and Translational Radiation Oncology* 2022;35:70–5.
- [21] Jabbour SK, Hashem SA, Bosch W, Kim TK, Finkelstein SE, Anderson BM, et al. Upper abdominal normal organ contouring guidelines and atlas: A Radiation Therapy Oncology Group consensus. *Pract Radiat Oncol* 2014;4(2):82–9.
- [22] Lens E, van der Horst A, Versteijne E, Bel A, van Tienhoven G. Considerable pancreatic tumor motion during breath-holding. *Acta Oncol* 2016;55(11):1360–8.
- [23] Grimbergen G, Eijkelenkamp H, Heerkens HD, Raaymakers BW, Intven MPW, Meijer GJ. Intrafraction pancreatic tumor motion patterns during ungated

- magnetic resonance guided radiotherapy with an abdominal corset. *Physics and Imaging in Radiation Oncology* 2022;21:1–5.
- [24] Alam S, Veeraraghavan H, Tringale K, Amoateng E, Subashi E, Wu AJ, et al. Inter- and intrafraction motion assessment and accumulated dose quantification of upper gastrointestinal organs during magnetic resonance-guided ablative radiation therapy of pancreas patients. *Physics and Imaging in Radiation Oncology* 2022;21: 54–61.
- [25] Courtney PT, Paravati AJ, Atwood TF, Raja N, Zimmerman CT, Fanta PT, et al. Phase I Trial of Stereotactic Body Radiation Therapy Dose Escalation in Pancreatic Cancer. *Int J Radiat Oncol Biol Phys* 2021;110(4):1003–12.
- [26] Kopek N, Holt MI, Hansen AT, Høyer M. Stereotactic body radiotherapy for unresectable cholangiocarcinoma. *Radiother Oncol* 2010;94(1):47–52.
- [27] Byrne M, Archibald-Heeren B, Hu Y, Teh A, Beserminji R, Cai E, et al. Varian ethos online adaptive radiotherapy for prostate cancer: Early results of contouring accuracy, treatment plan quality, and treatment time. *J Appl Clin Med Phys* 2022; 23(1):e13479.
- [28] Tyagi N, Liang J, Burleson S, Subashi E, Godoy Sripes P, Tringale KR, et al. Feasibility of ablative stereotactic body radiation therapy of pancreas cancer patients on a 1.5 Tesla magnetic resonance-linac system using abdominal compression. *Physics and Imaging. Radiat Oncol* 2021;19:53–9.
- [29] Xiao J, Zhang H, Gong Y, Fu Y, Tang B, Wang S, et al. Feasibility of using intravenous contrast-enhanced computed tomography (CT) scans in lung cancer treatment planning. *Radiother Oncol* 2010;96(1):73–7.
- [30] Choi Y, Kim J-K, Lee H-S, Hur W-J, Hong Y-S, Park S, et al. Influence of intravenous contrast agent on dose calculations of intensity modulated radiation therapy plans for head and neck cancer. *Radiother Oncol* 2006;81(2):158–62.