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Pancreatic cancer treated with SBRT: Effect of anatomical interfraction variations on dose to organs at risk

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ABSTRACT

Background and purpose: Interfraction shape and position variations of organs at risk (OARs) may increase uncertainty in dose delivery during stereotactic body radiotherapy (SBRT), potentially leading to overirradiation or concessions in planned tumor dose and/or coverage to prevent clinical constraints violation. The aim of our study was to quantitatively analyze the impact of anatomical interfraction variations on dose to OARs in pancreatic cancer (PC) treated by SBRT using a CyberKnife with integrated CT-on-rails.

Materials and methods: Thirty-five PC patients treated with SBRT (40 Gy/5 fractions) underwent a CT-scan in treatment position before each of the first three fractions using the CT-on-rails system. OARs (stomach, duodenum, bowel) were manually delineated and concatenated to one structure (Gastro-Intestinal Organ, GIO). To overlay the planned dose distribution, fiducial-based alignment of the fraction CT with the planning CT was performed. Planned DVH parameters of the OAR were compared to the parameters calculated in the fractions CTs.

Results: Compared to the treatment plan, the median V35, D2, D5, D10 and Dmax of the fraction CTs in the GIO was increased by 1.0 (IQR: 0.2–2.6), 4.4% (0.4–10.8), 2.3% (0.2–7.5), 3.3% (−0.4 to 7.1), and 12.0% (5.0–18.9) respectively. Median increase was statistically significant for all parameters in GIO and for V35 in all critical structures at Wilcoxon test.

Conclusions: Anatomical interfraction variations increase OAR dose during SBRT for pancreatic cancer daily imaging using integrated CT/CyberKnife may allow to implement strategies to reduce the risk of OAR overirradiation during pancreatic SBRT.

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Pancreatic cancer (PC) accounts for 6% of cancer-related death in Europe [1] and is expected to rank as the second cause of cancer mortality in US and Europe within a decade [2,3]. Surgery is the most effective treatment modality, resulting in a 20–25% 5-year overall survival compared to <5% in unresectable patients [4]. However, only 20% of patients are eligible for surgery at diagnosis, while chemotherapy is the only reasonable treatment option in 50% of patients showing metastatic disease at presentation [4,5]. In the remaining 30% of patients affected by border-line resectable or locally advanced disease, integration of chemotherapy with locoregional treatments such as radiotherapy has been advocated (1) to control local progression, which is responsible for one third of PC-related deaths [6] and (2) as a neoadjuvant treatment in selected patients to obtain resectability [7]. However, additional benefit of conventional radiochemotherapy compared to exclusive chemotherapy has been questioned [8]. In recent years, stereotactic body radiotherapy (SBRT) emerged as a valuable alternative to conventional radiotherapy. Theoretical advantages of SBRT include: shorter duration of treatment course (one-two weeks compared to six weeks), reducing the delay to additional chemotherapy or surgery; highly conformal ablative dose to the target; sharp dose fall-off resulting in minimal exposure of the organs at risk (OAR). Initial results from prospective phase I/II trials showed encouraging disease control rates [9]. On the other hand, anatomic proximity of dose-limiting OARs pose a serious challenge to the radiation oncologist, often resulting in a trade-off between adequate coverage of the target volume and respecting the dose constraints of the OARs. Moreover, abdominal OARs (duodenum, stomach, small bowel) may experience large intra-and interfraction physiological modifications in shape and position, adding uncertainty in the dose received by these critical structures: however to our knowledge few studies [10,11,12] investigated the effect of interfraction motion in dose delivery to OARs during standard-fractionation radiotherapy or SBRT for pancreatic cancer. It is of primary interest to address this issue in order to implement

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on line replanning strategies that allow to take into account interfraction variation of OAR position [12].

In our institution, a robotic stereotactic treatment unit (CyberKnife, Accuray, Sunnyvale CA) has been integrated with an CT-scanner on rails (Siemens Healthcare, Forchheim, Germany). This system allows the evaluation of the daily dose received by the OARs [13]. The system has been tested for clinical application in a prospective cohort of locally advanced PC patients enrolled in an ongoing phase II trial (LAPC1) evaluating systemic chemotherapy with FOLFIRINOX followed by SBRT. The aim of this study was to quantify the dosimetric impact of anatomical interfraction variations in patients who were included in the LAPC-1 study and treated with SBRT.

Material and methods

Study population and treatment protocol

Patients with locally advanced PC at our Institution were included in a prospective phase II single arm of a multi-center study assessing the efficacy of 8 cycles of FOLFIRINOX chemotherapy followed, in case of stable disease, by SBRT using CyberKnife. Prior to treatment initiation, fiducial markers were placed in the tumor via endoscopic ultrasonography guidance. Gross tumor volume (GTV) was delineated on a 1.25-mm sliced contrast-enhanced CT scan. Clinical target volume (CTV) included the GTV plus isotropic expansion of 5 mm to take into account microscopic tumor extension. Planning Target Volume (PTV) included the CTV plus 2 mm margin. A schedule prescribing 40 Gy in 5 fractions to the 80% isodose line of the PTV was used. It was recommended that at least 95% of the prescribed dose should cover 95% of the PTV. However, the PTV was allowed to be underdosed in order to meet the constraints of dose-limiting OARs. Dose constraints are summarized in Table 1. At the start of each treatment session, the tracking system of the CyberKnife was used for rotational alignment of the patient based on the spine. During treatment fiducial tracking was performed using the Synchrony respiratory motion tracking system to compensate for respiratory-induced target motion. Informed consent to the study procedures was signed by the patients. The study was conducted according to the principles of the Declaration of Helsinki and was approved by Institutional Review Board with the number NL49643.078.14.

System description and evaluation of daily dose

Detailed description of the system and clinical application for daily dose evaluation has been previously reported [13].

In summary, in our institution, CyberKnife has been integrated with a CT scanner on-rail. The robotic couch of the CyberKnife is used both for imaging and treatment. Geometric correspondence between CT and treatment couch rely on a relative reference system (image-based matching). At simulation and before each of the first three fractions of the treatment, an end-expiration CT scan with IV contrast was acquired in treatment position and was used for comparison. Daily CT scans were matched offline to the planning CT by applying a rigid registration that reproduces the actual tumor alignment at the CyberKnife. The rigid registration consisted of a composed transformation, including a spine-match (rotation and translation correction), followed by a translation-only match aligning the center of mass of the fiducials. The planned dose was overlaid on the daily CT using the obtained transformations for offline review. This procedure simulates the clinical procedure to align the treatment beams to the target.

Table 1
Institutional dose constraints for abdominal stereotactic body radiotherapy.

Organ	Constraint
Spine	5.5 Gy per fraction; Dmax 27.5 Gy
Liver	700 cc must receive less than 20 Gy
GIO	7 Gy per fraction; Dmax 35 Gy
Kidney	Mean Dose : inferior to 18 Gy as converted in 2 Gray/fraction equivalent dose for an $\alpha/\beta = 2.5$ Gray

Data analysis

On each fraction CT, the abdominal structures (stomach, duodenum, bowels) of the planning CT scan were overlaid using the composite transformation. Subsequently, the contours were manually adjusted to the anatomy in the fraction CT scan. All contouring was done according to the RTOG recommendations to improve reproducibility [14]. An additional structure (Gastro-Intestinal Organ, GIO) was created by concatenating stomach, duodenum, and bowel. The adjusted contours and the overlaid dose distribution were used to generate Dose Volume Histograms (DVHs). From the DVHs the following DVH parameters were extracted: the volume receiving at least 35 Gy (V35, in cc), maximum dose received by 2 cc (D2, in Gy), maximum dose received by 5 cc (D5, in Gy), maximum dose received by 10 cc (D10, in Gy), and the maximum point dose (Dmax, in Gy). Descriptive analysis was performed to compare the planned DVH parameters to the values extracted from the fraction CT scans. For each patient, the average of each DVH parameters over the three fraction CT scans was considered to represent the actual dose delivered during the treatment course. After verification that all parameters were not normally distributed using the Kolgomorov–Smirnov test, a Wilcoxon test for paired samples was performed to test the hypothesis that the median of the differences in our cohort between the planned and daily measured values is significantly different from zero; results were considered significant for a p-value <0.05 on two-tail analysis.

Results

A prospective cohort of 35 patients (19 head and 16 body tumors) underwent SBRT for the LAPC1 trial and was included in the study. Nineteen tumors were located in the head and 16 were located in the body of the pancreas; Median GTV size was 26.8 cc (range 5.1–141.0). All patients received the entire planned treatment course without interruption. Daily CT for fraction 1, 2, and 3 were available for 35 patients except for 2 patients, who underwent 2 daily CTs. In total, 138 CTs (35 planning CTs and 103 fraction CTs) were evaluated. Comparative evaluation of dosimetric parameters is reported in Tables 2, 3 and 4 and graphically shown in Figs. 1 and 2 and in Supplement Fig. 1. Tumor location and size did not statistically correlate to shift in average tumor-OAR distance and dose increment to OARs, respectively (Supplementary Table 1a and b).

Duodenum

Median daily V35 was higher compared to the treatment plan, resulting in a median increment of 0.3 cc with an Interquartile range (IQR) from −0.2 to 3.9 cc. D2, D5, D10 and Dmax increased in median by 1.8%, 1.8%, 2.3%, and 11.2%, respectively. The median V35, D2, D5, D10, and Dmax was increased compared to the planning CT in 26 (74%), 26 (74%), 24 (69%), 21 (60%), and 29 (83%) of the patients, respectively. Daily Dmax exceeded 35 Gy in 30 (86%) and 40 Gy in 16 (46%) of the patients. At Wilcoxon test, median daily values were significantly higher than planned for all considered parameters.

Table 2
Summary of planned and daily fraction dosimetric parameters for 35 prospective patients. For each structure, contours were manually adjusted on contrast-enhanced CT acquired before every fraction and dose overlay was obtained on image-matching for offline review.

		V35 (in cc)	D2 (in Gy)	D5 (in Gy)	D10 (in Gy)	Dmax (in Gy)
Duodenum	Median planned value (IQR)	0.0 (0.0 to 0.2)	30.7 (24.3 to 32.8)	28.1 (19.5 to 31.1)	24.0 (14.2 to 27.1)	36.1 (34.2 to 37.2)
	Median average daily value (IQR)	0.4 (0.1 to1.25)	32.3 (24.7 to 34.0)	28.3 (19.9 to 31.3)	23.1 (15.8 to 28.2)	39.7 (37.0 to 43.0)
	Median difference (IQR)	0.3 (−0.2 to 3.9)	1.8% (0.0 to 9.4)	1.8% (−1.4 to 11.9)	2.3% (−1.4 to 10.0)	11.2% (3.6 to 16.0)
Stomach	Median planned value (IQR)	0.0 (0.0 to 0.3)	27.6 (21.1 to 32.7)	24.8 (17.5 to 30.8)	20.6 (14.9 to 27.2)	36.6 (32.7 to 37.7)
	Median average daily value (IQR)	0.5 (0.0 to 1.0)	29.2 (24.9 to 33.6)	25.6 (20.9 to 30.2)	21.6 (17.1 to 27.1)	38.9 (35.7 to 40.8)
	Median difference (IQR)	0.2 (−0.1 to 9.6)	2.6% (−2.4 to 12.7)	1.7% (−6.0 to 12.4)	0.0% (−7.0 to 11.2)	5.9% (1.1 to 11.6)
Bowel	Median planned value (IQR)	0.0 (0.0 to 0.1)	19.6 (14.0 to 28.7)	18.2 (12.2 to 25.2)	15.6 (10.1 to 22.5)	31.7 (21.2 to 36.3)
	Median average daily value (IQR)	0.0 (0.0 to 0.2)	20.9 (14.9 to 27.6)	17.4 (13.0 to 23.2)	16.1 (9.9 to 21.0)	32.3 (23.4 to 38.8)
	Median difference (IQR)	0.0 (0.0 to 0.2)	1.0% (−10.8 to 10.6)	−1.3% (−12.0 to 6.8)	−2.7% (−16.0 to 28.8)	2.6% (−8.7 to 21.0)
GIO	Median planned value (IQR)	0.2 (0.0 to 0.9)	33.3 (30.7 to 34.0)	31.8 (26.1 to 32.8)	29.1 (20.8 to 30.8)	37.2 (36.4 to 40.4)
	Median average daily value (IQR)	1.6 (0.6 to 3.0)	34.6 (31.1 to 36.2)	32.5 (27.2 to 33.6)	29.8 (22.6 to 31.7)	42.2 (41.0 to 44.7)
	Median difference (IQR)	1.0 (0.2 to 2.6)	4.4% (0.4 to 10.8)	2.3% (0.2 to 7.5)	3.3% (−0.4 to 7.1)	12.0% (5.0 to 18.9)

Abbreviations: GIO: Gastro-Intestinal Organ. IQR: Interquartile Range. V35: volume receiving 35 Gy, in cc. D2: dose received by 2 cc in Gy. D5: dose received by 5 cc in Gy. D10: dose received by 10 cc, in Gy. Dmax, maximum point dose, in Gy.

Table 3
Wilcoxon test for comparison between planned and daily values of D2, D5, D10 and Dmax for each OAR.

		Planned value (IQR)	Daily value (IQR)	Patients receiving higher-than-planned dose	Patients receiving lower-than-planned dose	Wilcoxon test for paired samples
Duodenum	V35	0.0 (0.0–0.2)	0.4 (0.1–1-25)	26/35 (74%)	1/35 (3%)	$p < 0.0001$
	D2	30.7 (24.3–32.8)	32.3 (24.7–34.0)	26/35 (74%)	8/35 (23%)	$p = 0.0024$
	D5	28.1 (19.5–31.1)	28.3 (19.9–31.3)	24/35 (69%)	10/35 (28%)	$p = 0.0123$
	D10	24.0 (14.2–27.1)	23.1 (15.8–28.2)	21/35 (60%)	12/35 (34%)	$p = 0.0249$
	Dmax	36.1 (34.2–37.2)	39.7 (37.0–43.0)	29/35 (83%)	6/35 (17%)	$p = 0.0003$
Stomach	V35	0.0 (0.0–0.3)	0.5 (0.0–1.0)	25/35 (72%)	1/35 (3%)	$p < 0.0001$
	D2	27.6 (21.1–32.7)	29.2 (24.9–33.6)	22/35 (63%)	12/35 (34%)	$p = 0.042$
	D5	24.8 (17.5–30.8)	25.6 (20.9–30.2)	19/35 (54%)	15/35 (43%)	p = NS
	D10	20.6 (14.9–27.2)	21.6 (17.1–27.1)	17/35 (49%)	17/35 (49%)	p = NS
	Dmax	36,6 (32.7–37-7)	38.9 (35.7–40.8)	27/35 (77%)	6/35 (17%)	$p < 0.0001$
Bowel	V35	0.0 (0.0–0.1)	0.0 (0.0–0.2)	12/35 (35%)	1/35 (3%)	$p = 0.017$
	D2	19.6 (14.0–28.7)	20.9 (14.9–27.6)	19/35 (54%)	16/35 (46%)	p = NS
	D5	18.2 (12.2–25.2)	17.4 (13.0–23.2)	15/35 (43%)	18/35 (51%)	p = NS
	D10	15.6 (10.1–22.5)	16.1 (9.9–21.0)	16/35 (46%)	19/35 (54%)	p = NS
	Dmax	31.7 (21.2–36.3)	32.3 (23.4–38.8)	19/35 (54%)	16/35 (46%)	p = NS
GIO	V35	0.2 (0.0–0.9)	1.6 (0.6–3.0)	29/35 (83%)	4/35 (11%)	$p < 0.0001$
	D2	33.3 (30.7–34.0)	34.6 (31.1–36.2)	29/35 (83%)	6/35 (17%)	$p < 0.0001$
	D5	31.8 (26.1–32.8)	32.5 (27.2–33.6)	29/35 (83%)	6/35 (17%)	$p = 0.0002$
	D10	29.1 (20.8–30.8)	29.8 (22.6–31.7)	24/35 (69%)	10/35 (29%)	$p = 0.0018$
	Dmax	37.2 (36.4–40.4)	42.2 (41.0–44.7)	30/35 (86%)	5/35 (14%)	$p < 0.0001$

Abbreviations: GIO: Gastro-Intestinal Organ. IQR: InterQuartile Range. V35: volume receiving 35 Gy, in cc. D2: dose received by 2 cc in Gy. D5: dose received by 5 cc in Gy. D10: dose received by 10 cc, in Gy. Dmax, maximum point dose, in Gy.

Stomach

Daily V35 was in median 0.2 cc higher than planned V35. A median increase from planned values (by 2.6%, 1.7% and 5.9%, respectively) was observed for daily D2, D5 and DMax, but not for D10. Daily measured V35, D2, D5, D10 and Dmax exceeded the planned value in 25 (72%), 22 (63%), 19 (54%), 17 (49%) and 27 (77%) patients, respectively. Average measured Dmax exceeded 35 Gy in 27 (77%) and 40 Gy in 14 (40%) patients. A significant difference between median planned and daily parameters was found for V35, D2, and Dmax.

Bowel

In median, no increase in daily V35 was observed compared to planned value. A median increase from planned values (by 1.0% and 2.7%, respectively) was observed for daily D2 and Dmax but not for D2, D5 and D10. Daily measured V35, D2, D5, D10 and Dmax exceeded the planned value in 12 (35%), 19 (54%), 15 (43%), 16 (46%) and 19 (54%) patients, respectively. Average measured Dmax exceeded 35 Gy in 12 (34%) and 40 Gy in 7 (20%) patients. However, a significant difference at Wilcoxon test was observed only for daily V35.

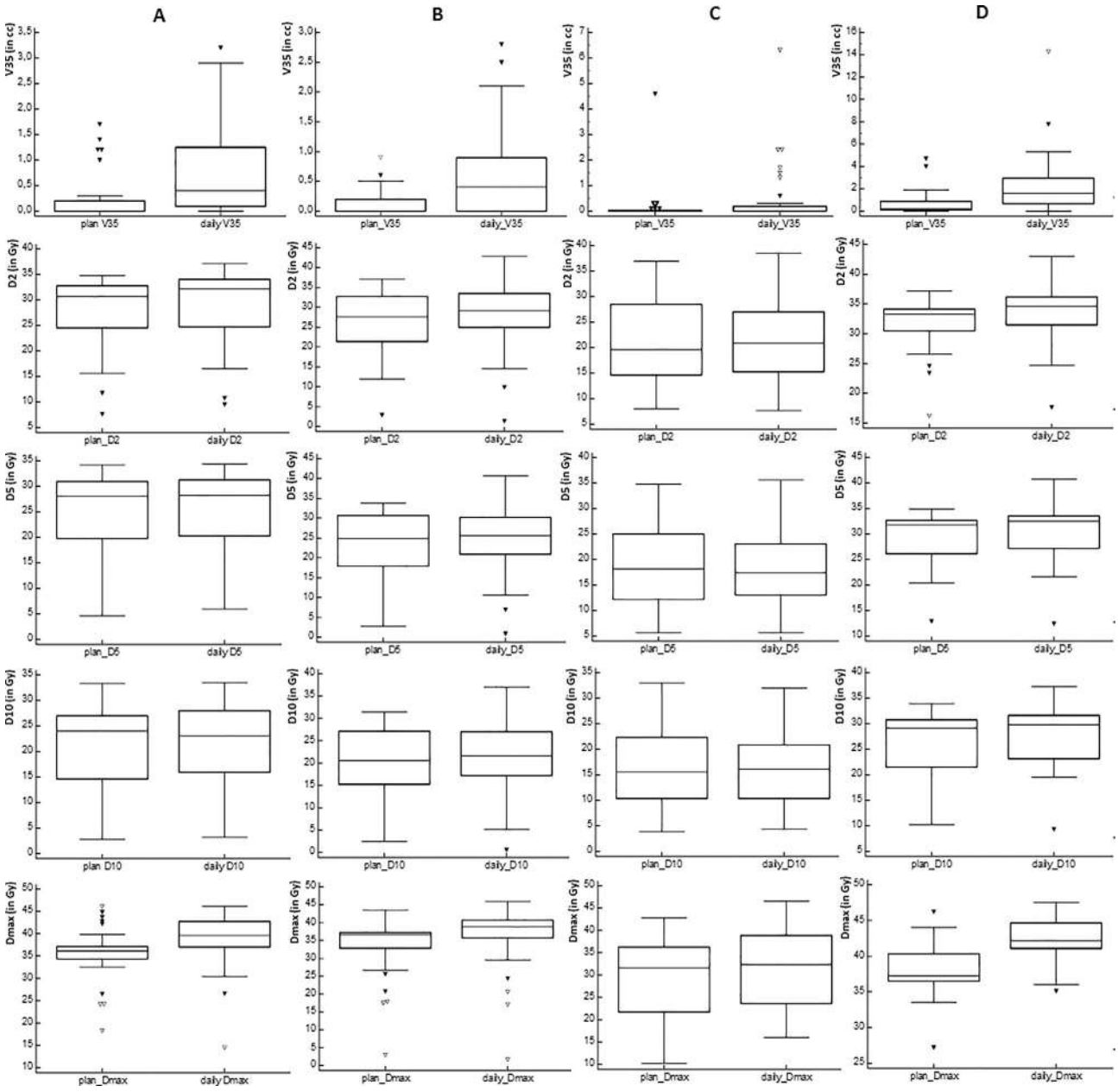

Fig. 1. Box-and-whiskers graph representing comparative evaluation of median planned (left) versus median daily (right) V35, D2, D5, D10 and Dmax (from up to down) for Duodenum (A), Stomach (B), Bowels (C) and GIO (D). Middle line represent median value; central box represent the Inter Quartile Range Error bars represent range of values excluding outside (black triangles) and far-out (white triangles) values.

Gastro-Intestinal Organ (GIO)

Median daily V35 was higher compared to the treatment plan, resulting in a median increment of 1.0 cc. In median D2, D5, D10 and Dmax increased by 4.4%, 2.3%, 3.3% and 12% compared to planned values. A higher than planned value was shown for V35, D2, D5, D10 and Dmax in 29 (83%), 29 (83%), 29 (83%), 24 (69%) and 30 (86%) patients, respectively. Daily measured Dmax exceeded 35 Gy in all patients, and was equal or superior to 40 Gy in 28 (80%) patients. Significant difference between planned and measured values was observed for all dosimetric parameters.

Discussion

We report an analysis performed on a prospective cohort of 35 patients undergoing SBRT for locally advanced pancreatic cancer. The use of a combined Cyberknife-CT treatment unit allowed to obtain high-quality imaging acquired in treatment position before radiation delivery. The planned dose distribution was overlaid on the fraction CT to study the dosimetric impact of interfraction OAR variation in shape and position during the treatment course. Comparative assessment of planned dosimetric parameters with the corresponding values as recalculated on daily anatomy suggested a consistent trend toward increment in the delivered dose to critical structures compared to the original SBRT plan. In particular, median daily Dmax for the whole GIO in our population was 42.2 Gy (versus 37.2 Gy according to planned anatomy), corresponding to an equivalent dose in 2-Gy fractions of 96.2 Gy for an $\alpha/\beta = 3$. Interestingly, despite a large interpatient and intrapatient variability, OAR interfraction shifts mainly translate in overirradiation of healthy tissues rather than dose reduction. This effect was predominantly seen in critical structures adjacent to the

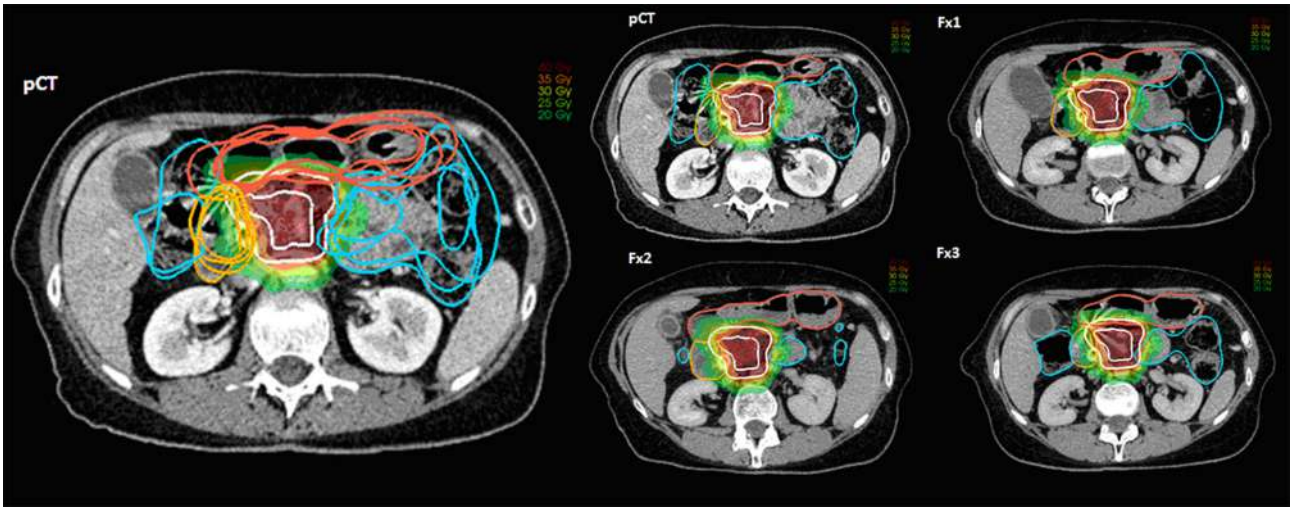

Fig. 2. Left: Dosimetric impact of anatomical variations on the treatment plan. Daily CT contours were transferred rigidly with respect to the tumor location onto the pCT scan to assess changes in the V35 region (colorwash, red). OAR variations are depicted in different colors according to each organ: the stomach (orange), the duodenum (yellow) and the bowel (blue). Right: Anatomical changes observed on each daily CT scan for a sample patient. The GTV and PTV structure (in white) were transferred rigidly from the pCT to the fraction CT scans, as well as the dose distributions of the treatment plan. It is shown the anatomical changes observed on the three critical gastrointestinal organs: stomach (orange), duodenum (yellow) and bowel (blue), with respect to a common tumor slice. Hence, we can evaluate on the daily images dosimetric changes in the V35 region (colorwash, red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
Dose conversion of median D2, D5, D10 and Dmax extrapolated from the fraction CTs for each OAR in 2 Gy equivalents according to the linear quadratic model for early ($\alpha/\beta = 10$) and late ($\alpha/\beta = 3$) toxicity.

		Median daily value for 5 fractions (in Gy)	Median daily value EQD2 (in Gy, for $\alpha/\beta = 10$)	Median daily value EQD2 (in Gy, for $\alpha/\beta = 3$)
Duodenum	D2	32.3	44.1	60.9
	D5	28.3	36.8	48.7
	D10	23.1	28.1	35.1
	Dmax	39.7	59.2	86.5
Stomach	D2	29.2	38.5	51.4
	D5	25.6	32.2	41.5
	D10	21.6	25.7	31.5
	Dmax	38.9	57.7	84.0
Bowel	D2	20.9	24.7	30.1
	D5	17.4	19.7	22.7
	D10	16.1	17.7	19.9
	Dmax	32.3	44.4	61.4
GIO	D2	34.6	48.7	68.5
	D5	32.5	44.7	61.8
	D10	29.8	39.5	53.0
	Dmax	42.2	64.7	96.2

Abbreviations: GIO: Gastro-Intestinal Organ. IQR: InterQuartile Range. V35: volume receiving 35 Gy, in cc. D2: dose received by 2 cc in Gy. D5: dose received by 5 cc in Gy. D10: dose received by 10 cc, in Gy. Dmax, maximum point dose, in Gy.

tumor such as duodenum and stomach and was particularly prominent for dose received by smaller volumes (Dmax) or for the amount of tissue receiving the higher dose level related to dose limiting toxicity (V35). Conversely, dose variation was less pronounced in distant organs such as small bowel, and only a minor increase or no increase was observed in parameters related to dose received by larger volumes such as 5 or 10 cc. These observations have important implications.

First, increases in dose to the OARs reach clinically meaningful values mostly in structures in close proximity to the target and/or that are entangled in a fixed anatomic relationship with the pancreas (stomach, duodenum), while more distant structures allowed to larger variation in shape and size (bowels) are affected to a minor extent. Stomach and duodenum experience limited degrees of motion and deformation due to anatomical bounds with the abdominal cavity and the pancreas itself; by contrast the relative freedom of jejunum and ileum allow for shape variation and complex motion. Consequently, the risk of unintended overirradiation may be higher for stomach and duodenum due to the limited range of motion in regard to the region receiving the prescription dose. On the other hand, it is likely that irradiation above the planned dose occurs at different segments of the small bowel at each fraction, thus reducing the risk of delivering a higher dose to a single segment, Secondly, the dosimetric impact of interfraction variability is predominant on small volumes of tissues. Indeed, the steep dose fall-off of SBRT results in a reasonably low dose to large volumes of critical structures, thus interfractional variations are expected to be modest at this scale, while higher unplanned dose delivery to small "hot-spots" may correlate with higher risks of toxicity. It was recognized since pilot trials that administration of high doses per fraction to gastro-intestinal structures could potentially lead to severe complications. Schellenberg et al. reported excellent local control rate of 81% for single-fraction SBRT up to 25 Gy, at the expenses of an incidence of grade 2–4 toxicity of

47% [15]. Adjacent organs proved eminently sensitive to severe radiation-related adverse events, consisting of 5 gastric ulcers, 1 duodenal stenosis and 1 duodenal perforation [15]. Following experience with this single fraction regimen, a dose response model based on Lyman NTCP model for duodenum toxicity was proposed, though a risk of overestimation of radiation effects for larger fraction sizes was suggested [16]. The dose-limiting character of proximal critical structures led to the use of fractionated radiation regimens and to a more cautionary tolerance-based approach. In the study by Mahadevan et al. a three-fraction schedule was prescribed using fiducial-based respiratory motion tracking on a robotic radiosurgery system. Dose escalation up to 32 Gy was allowed according to tumor location in relation to the stomach and duodenum, resulting in limited grade 3 toxicities and no grade 4 events [17]. Multiple reports from various institutions corroborated the feasibility and efficacy of this approach: in a meta-analysis from 19 trials, Petrelli et al. reported an overall occurrence of severe adverse events inferior to 10%, while promising 1-year local control was correlated to total dose and number of fractions [9]. It can be argued that optimal disease control after SBRT can be obtained only if the delivery of the highest dose to the tumor is achieved. Therefore, all strategies that enable to reduce uncertainty in dose exposure to the OARs may prove beneficial to improve tumor coverage, and vice versa. It is noteworthy that effective tumor tracking may to some extent prove beneficial in reducing toxicity. In a recent paper by Goldsmith et al. use of multiple fiducials for pancreas SBRT had one-fifth the incidence of grade 3 toxicity as compared to a single fiducial or spine tracking, provided that duodenal D1cc was inferior to 30 Gy in 3 fractions [18]. Hence, management of tumor motion might be sufficient to reduce dose to healthy tissue as a result of accurate dose delivery. This strategy implies the assumption the mutual relation between fiducials and OARs do not significantly change between planning CT and treatment course. However, this mutual relation can be significantly altered over time due to OAR motion and deformation. For this reason, analysis of delivered (rather than planned) dose to OARs is an important research topic. Multiple in-room imaging systems have been tested for this purpose, but currently available modalities show several limitations. For example, despite widespread use in modern treatment platforms for patient setup, Cone-Beam KvCT (CB-CT) provide insufficient reliability for contour delineation [19] and requires correction of the Hounsfield Unit for dose recalculation in case of replanning. Recent technical advances allowed for the development of MRI-guided linear accelerators, whose first clinical applications have been recently reported in abdominal stereotactic treatments [20]. This solution provides unquestionable advantages in terms of improved image quality, real-time tracking of both tumor and OARs and lower radiation exposure compared to CT-based modalities; on the other hand, integration of CT is an active area of research that allow to combine the versatility of a robotic-arm treatment unit with interfraction diagnostic-quality imaging. Integration of diagnostic-quality CT in a robotic linear accelerator might be a valuable and cost-effective solution for the determination of actual delivered dose to the OARs, enabling the use of strategies to mitigate the risk of additional toxicity such as pretreatment evaluation prior to treatment delivery, selection of a plan of a day from a library, or daily replanning.

There are some limitations in our study. In first instance, dose overlay can be influenced by number of variables, in particular patient motion during couch shift and uncertainty in reproducibility of image coregistration and contour delineation. Inconsistencies can be mitigated through rigorous control of patient setup with use of appropriate immobilization frames (i.e. vacuum matrass), placement of fiducial markers for correction of image matching and use of validated consensus guidelines for OAR outlining that allow inter-operator agreement. Secondarily, study of intrafraction motion (in particular respiratory motion) was not integrated in our dose distribution study, though use of real-time tumor tracking with the Synchrony system and, in future, implementation of our model with the use of daily 4D CT might compensate for additional variations in dose estimate to the OARs. Additional uncertainty in data interpretation derives from exact determination of tissue volumes receiving higher than planned dose on consecutive treatment fraction and its implication with tissue damage. It is accepted that volumes receiving higher planned doses are more likely to be injured: in a recent paper by Verma et al. a correspondence was found between volume receiving 20–35 Gy and histo-pathologic tissue damage in duodenum on surgical specimen of duodenocephalopancreatectomy for pancreas cancer following neoadjuvant SBRT [21]. However, in multiple fractions SBRT, it is debatable whether radiation induced-tissue damage may result from repeated irradiation of a same segment all over the radiotherapy course or from a single constraint violation due to unintended dose delivery as a consequence of interfraction organ motion. Moreover, as discussed by Goldsmith et al. [18], current data do not allow to determine if complications are attributable to the Dmax doses alone, or if volume and other factors may have a role. Finally, despite measurable variations in dose distributions, the impact of interfraction OAR motion assessed with daily in-room CT needs further clinical validation: an ongoing secondary analysis on our prospective cohort will correlate onset of acute toxicity with daily shifts in dose distribution to the OAR.

In conclusion, anatomical interfraction variations led to increase in measured dose to the OARs compared to planned dose in patients receiving SBRT for pancreatic cancer. This consisted of a significant median increase in all the dosimetric parameters for stomach and duodenum while only small volumes of bowel experienced higher-than-planned dose delivery. Daily imaging using integrated CT may allow to implement future strategies to reduce the risk of OAR overirradiation during pancreatic SBRT.

Conflict of interest statement

All the authors listed below (Mauro Loi, Alba Magallon-Baro, Mustafa Suker, Casper van Eijck, Aman Sharma, Mischa Hoogeman, Joost Nuyttens) report no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.01.020.

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