Clinical and Translational Radiation Oncology 27 (2021) 24–31

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Dose-escalated simultaneously integrated boost photon or proton therapy in pancreatic cancer in an *in-silico* study: Gastrointestinal organs remain critical

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ARTICLE INFO

Article history:
Received 13 July 2020
Revised 28 November 2020
Accepted 4 December 2020
Available online 9 December 2020

Keywords:
Pancreatic cancer
Simultaneously integrated boost
Intensity-modulated radiation therapy
Intensity-modulated proton therapy
Robust optimization
Dose escalation

ABSTRACT

Purpose: To compare the dosimetric results of an *in-silico* study among intensity-modulated photon (IMRT) and robustly optimized intensity-modulated proton (IMPT) treatment techniques using a dose-escalated simultaneously integrated boost (SIB) approach in locally recurrent or advanced pancreatic cancer patients.

Material and methods: For each of 15 locally advanced pancreatic cancer patients, a volumetric-modulated arc therapy (VMAT), a Tomotherapy (TOMO), and an IMPT treatment plan was optimized on free-breathing treatment planning computed tomography (CT) images. For the photon treatment plans, doses of 66 Gy and 51 Gy, both as SIB in 30 fractions, were prescribed to the gross tumor volume (GTV) and to the planning target volume (PTV), respectively. For the proton plans, a dose prescription of 66 Gy(RBE) to the GTV and of 51 Gy(RBE) to the clinical target volume (CTV) was planned. For each SIB-treatment plan, doses to the targets and OARs were evaluated and statistically compared.

Results: All treatment techniques reached the prescribed doses to the GTV and CTV or PTV. The stomach and the bowel, in particular the duodenum and the small bowel, were found to be frequently exposed to doses exceeding 50 Gy, irrespective of the treatment technique. For doses below 50 Gy, the IMPT technique was statistically significant superior to both IMRT techniques regarding decreasing dose to the OARs, *e.g.* volume of the bowel receiving 15 Gy (V_{15Gy}) was reduced for IMPT compared to VMAT ($p = 0.003$) and TOMO ($p < 0.001$).

Conclusion: With all photon and proton techniques investigated, the radiation dose to gastrointestinal OARs remained critical when treating patients with unresectable locally recurrent or advanced pancreatic cancer using a dose-escalated SIB approach.

1. Introduction

Modern intensity-modulated radiation delivery techniques with photons (IMRT) and protons (IMPT) enable highly conformal and complex dose distributions to the target and relatively low doses to the surrounding organs at risk (OARs). Thus, these techniques enable hypofractionated treatment schedules, *i.e.* stereotactic ablative body radiotherapy (SABR), or simultaneously

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https://doi.org/10.1016/j.ctro.2020.12.001
2405-6308/

integrated boosts (SIB) within normofractionated volumes. These treatment concepts, which are standard of care in various solid tumors, reduce overall treatment time, increase the biologically effective dose and, thus, the local tumor control probability.

The prognosis of patients with non-metastasized, borderline resectable (BRPC) or primary unresectable locally advanced pancreatic cancer (LAPC) is still poor. Currently, intensified chemotherapy or radiochemotherapy (RCT) are part of the primary or neoadjuvant therapeutic options to downsize the BRPC and LAPC in order to enable the primary tumor resection. Followed by a surgical resection with a tumor-free margin (R0), it is the only curative treatment approach to increase the local progression free and overall survival rate [1,2]. However, even though the primary endpoint of the randomized LAP 07 study, which randomized LAPC patients to receive either neoadjuvant (RCT) or chemotherapy, namely overall survival was negative, RCT positively influenced the local tumor control rates [3]. Thus far, the radiosensitivity of the close-by organs at risk has hampered radiation dose escalation in an attempt to improve local resectability and/or tumor control. In the context of prospective trials, highly conformal photon techniques are currently being explored [4–8]. Recent clinical data suggest improvements in local control, overall survival and safety of patients receiving a SIB-based dose escalated RCT using photons [8–10].

To date, however, experience using dose-escalated proton beam irradiation in BRPC and LAPC is limited but promising [11–15]. With their lower entrance dose, their defined maximum dose deposition in the Bragg Peak as well as their steep distal dose fall-off, proton beams enable a high dose deposition in the target. Thus, intensified proton beam therapy may be a promising alternative to photon therapy opening the therapeutic window in the complex anatomical setting of LAPC and BRPC patients [16–19]. In line with this, a recent phase II clinical study comparing neoadjuvant chemotherapy with either short-course protons [5 × 5 Gy (RBE), N = 15] or photons [10 × 3 Gy, N = 12] radiotherapy, or, in case of vascular involvement, a long-course of photon therapy [28 × 1.8 Gy and with a SIB (28 × 2.1 Gy) to the vessels, N = 17] achieved a R0-resection in 65% of the patients, a 2-year overall survival of 56%, and reported grade 1 and 2 toxicities only [14]. Conversely, due to its physical characteristics, proton beam therapy is known to be highly susceptible to patient misalignment and anatomical changes, *e.g.* organ motion and filling, occurring during the course of treatment. In particular, when using pencil beam scanning techniques, these changes may lead to range uncertainties substantially affecting the dose distribution [20,21]. To overcome this, several approaches, *e.g.* image-guidance, motion mitigated approaches or robust treatment planning, have been proposed and integrated into the treatment preparation and delivery [22–24].

The aim of this *in-silico* treatment planning study was to assess the dosimetric differences of the dose-escalated SIB-techniques between IMRT, *i.e.* volumetric-modulated arc therapy (VMAT) and Tomotherapy (TOMO), and robustly multi-field optimized (rMFO) IMPT, both regarding the radiation dose to the targets as well as to the surrounding OARs.

2. Material and methods

2.1. Patient and tumor characteristics

This study included free-breathing treatment planning CT data of 15 patients with non-resectable LAPC or locally recurrent pancreatic cancer of the pancreatic head or body having received primary or adjuvant radiochemotherapy (Table 1) [8]. The Ethics Committees of the University Hospital Carl Gustav Carus Dresden (EK 98032017) and of the Charité Universitätsmedizin Berlin (EA1/236/16) approved this study.

2.2. Definition of target volumes and organs at risk

The gross tumor volume (GTV) encompassing the primary or recurrent tumor was delineated based on additional diagnostic information (positron emission tomography and/or magnetic resonance imaging) on the treatment planning CT. The clinical target volume (CTV) included the GTV, a putative microscopic tumor extension surrounding it, and an elective volume including the regional lymph nodes [8]. For photon treatment planning, the CTV was enlarged by a 5 mm isotropic margin resulting in the planning target volume (PTV). Since range and setup uncertainties were taken into account when applying a robust optimization algorithm for the proton dose calculation, no additional PTV margin was added to the CTV for IMPT plans (see *2.4*). Moreover, the spinal cord, liver, kidneys, spleen, stomach and the intestinal cavity as bowel bag (additionally separated into duodenum, non-duodenal small bowel and large bowel) were contoured as OARs.

2.3. Dose prescription

For each patient, three different intensity-modulated techniques were planned with SIB approach: TOMO, VMAT and rMFO-IMPT. For the photon techniques, a median dose (D_{median}) of 66 Gy was prescribed to the GTV (boost) and 51 Gy to the PTV. Taking into account the higher radiobiological effectiveness of protons (RBE = 1.1), equivalent median doses of 66 Gy(RBE) and 51 Gy(RBE) to the GTV and CTV, respectively, were planned using rMFO. For comparison, all treatment plans were generated to deliver at least 95% of the prescribed doses (D_{pres}) to 95% of the GTV and CTV or PTV ($D_{95\%}\geq$95%), respectively, while keeping within the OAR dose constraints. The near dose maximum in 2% of the respective volumes ($D_{2\%}$) was not to exceed 107% of the D_{pres}. In order to avoid under- or overdosage of the elective volume, the dose coverages for the CTV or PTV minus the boost (CTV–GTV, PTV–GTV) were additionally assessed, respectively. The treatment goals for the OARs (with their priority) were chosen taking into account the institutional guidelines and QUANTEC dose constraints [25]: The maximum dose to the spinal cord (D_{max}) was set to be $\leq$45 Gy (priority 1) and the volume of the liver receiving 30 Gy (V_{30Gy}) $\leq$ 100ccm (priority 5). Each kidney should receive at most a mean dose (D_{mean}) of $\leq$18 Gy, while remaining the $V_{20Gy} \leq$ 10%, but at least $\leq$32%, for each kidney (priority 4). D_{max} of the stomach should not exceed 45 Gy; if this was not feasible the following constraints had to be met: $V_{50Gy} \leq$ 5ccm and $V_{40Gy} \leq$ 100ccm (priority 3). Finally, the constraints $V_{50Gy} \leq$ 10ccm, $V_{40Gy} \leq$ 100ccm and at least $V_{15Gy} \leq$ 120ccm were applied to the bowel (priority 2).

2.4. Treatment planning

Each treatment plan was generated using inverse optimization, whereas fluence and segments (photons) as well as energy layers, spot positions and spot distances (protons) were set by the respective treatment planning systems. For each treatment plan, the primary aim was to achieve the target coverage goals, while the objectives for the OARs were selected to minimize the dose. No simultaneously integrated protection regions (field-in-field) for OARs overlapping with the low-dose target were applied.

The VMAT plans were calculated in RayStation Research V5.99 with a collapse cone convolution algorithm (RaySearch Laboratories AB, Stockholm, Sweden) after optimizing the dose distribution using 6MV photons in a dose grid of 2 mm × 2 mm × 2 mm. Depending on the complexity of the target volumes and the sur-

Table 1
Patient, tumor and treatment characteristics.

Patients No	Gender	TNM stage	Tumor/recurrence localization	Previous surgical resection	Treatment intent
1	f	cTX NX M0	head	0	definitive
2	m	cT4 cN0 M0	head	0	definitive
3	m	cT4 cN1 M0	body	0	definitive
5	m	pT3 pN0 M0	head	1	definitive (recurrence)
6	m	pT3 pN1 M0	head	1	definitive (recurrence)
8	m	pT3 pN0 M0	head	0	adjuvant (individualized treatment)
9	m	pT4 cN1 M0	body	0	definitive (recurrence)
10	m	pT2 pN0 M0	head	1	definitive (recurrence)
11	f	cT3 cN0 M0	head	1	definitive
12	f	cT3 N0 M0	body	0	definitive
14	m	pT3 pN0 M0	head	1	definitive (recurrence)
15	m	pT3 pN0 M0	head	1	definitive (recurrence)
16	f	ypT3 pN1 M0	head	1	definitive (recurrence)
17	m	cT4 cN0 M0	head	0	definitive
18	m	cT4 cN1 M0	body	0	definitive

Abbreviations: f – female; m – male; T – tumor classification; N – lymph node involvement; M – metastasis; c – clinical stage; p – post-operative stage after histopathological assessment; y – tumor classification after neoadjuvant treatment; X – cannot be assessed.

rounding OARs, two coplanar arcs (182°-178°) or two coplanar arcs with a third non-coplanar, anterior arc (maximum arc of 60°, couch 270°) were chosen, respectively.

The TOMO plans with 6MV photons were created in TomoHD (Version 2.1.2, Accuray®, Sunnyvale, CA) using a convolution/superposition dose algorithm for dose calculation with a pitch of 0.25 and a field width of 2.51 cm.

The proton dose distribution was generated in RayStation Research (V5.99, RaySearch Laboratories AB) applying the Monte Carlo algorithm on a dose grid of 3 mm × 3 mm × 3 mm. Not necessitating a range shifter, the distance of the nozzle to the gantry isocenter was fixed to 50 cm. A set of three beams was chosen and robust optimization settings were applied to the optimization objectives of both targets (GTV and CTV–GTV) and the spinal cord [24]. The random setup uncertainty was set to be ±5 mm and the average range uncertainty 4.5% (systematic range uncertainty 3.5% and absolute range uncertainty 1 mm at the maximum spot energy). Of note, a treatment plan was considered robust if the $D_{95\%}$ criterion of the GTV and the CTV–GTV was fulfilled for 20 scenarios.

2.5. Treatment plan evaluation

All treatment plans were evaluated in RayStation Research (V5.99, RaySearch Laboratories AB). For this purpose, the TOMO plans were imported into RayStation Research (V5.99, RaySearch Laboratories AB). Each treatment plan was normalized to the median dose of 66 Gy or 66 Gy(RBE), while simultaneously maintaining a median dose of 51 Gy in the CTV–GTV or PTV–GTV and the dose coverage limits for both targets, respectively. Prior to dosimetric evaluation of the median values of the targets and the OARs of all patients, two radiation oncologists assessed the clinical acceptability for each treatment plan. Since in proton therapy range uncertainties are not considered in the geometrical margin approach (PTV), as is practice in photon therapy, we used the CTVs for evaluation and direct comparison for all treatment techniques. The target coverage quality was determined calculating Paddick's conformity index (CI) [26] as well as the homogeneity index [HI = $(D_{5\%}-D_{95\%})/D_{pres}$] for both targets. Furthermore, the dose gradient between the high-dose boost and the elective low-dose volume within the target was analyzed based on modified target volumes being created. For this, the GTV was isotopically enlarged (margins of 5 mm, 8 mm and 10 mm, respectively) and subsequently subtracted from the CTV or PTV, *e.g.* CTV–(GTV + 5 mm) and PTV−(GTV + 5 mm).

2.6. Statistical analyses

Dosimetric differences between the three treatment techniques were statistically assessed with the non-parametric *Friedman* test ($\alpha = 0.05$, significance at $p < 0.05$) using IBM® SPSS® Statistics (Version 25.0.0.2, IBM Corp., Armonk, NY). Subsequently, the non-parametric *post hoc* test of *Dunn* with a *Bonferroni* correction for multiple testing ($\alpha = 0.05$, significance at $p_{rMFO\text{-}VMAT}$, $p_{rMFO\text{-}TOMO}$ and $p_{VMAT\text{-}TOMO} < 0.05$) was employed in statistically significant results. A subgroup analysis for the dose to gastrointestinal organs depending on the surgical resection status (no surgical resection *versus* prior surgical resection including the duodenum) and tumor location (pancreatic head *versus* body) was performed using a non-parametric, unpaired *Mann-Whitney-U* test ($\alpha = 0.05$, significance at $p < 0.05$).

3. Results

3.1. Target coverage and inner dose fall-off

The target coverage for all treatment plans, including the robustness criteria of all proton plans, was fulfilled (Fig. 1, Table A.1). While the CI of the boost was higher for the photon techniques, the CI of the CTV − GTV was superior using rMFO (Table A.1). The homogeneity of the boost was superior for rMFO, whereas the HI of the CTV−GTV and CTV−(GTV + 10 mm) volumes was superior for TOMO (Table A.1).

The $D_{2\%}$ of the CTV−GTV or PTV−GTV was exceeded for all three treatment techniques, whereas the dose in the rMFO plans were statistically significantly higher compared to TOMO (both: $p_{rMFO\text{-}TOMO} < 0.001$) and VMAT (CTV−GTV: $p_{rMFO\text{-}VMAT} = 0.019$, PTV−GTV: $p_{rMFO\text{-}VMAT} = 0.010$) (Table A.1).

Studying the dose gradient between the high dose and the low dose volume with the modified targets showed that the $D_{2\%}$ of the residual PTV met the dose limits for VMAT and TOMO considering an average distance of 5 mm or 8 mm from the GTV, respectively (Table A.1). Taking into account an average distance of at least 10 mm, the $D_{2\%}$ of the corresponding residual CTVs was within the limits for the rMFO plans.

3.2. Organs of the gastrointestinal tract

Not all treatment plans of the investigated techniques met the D_{2ccm} constraint to the stomach resulting in median values above the preset dose limits (Fig. 2A, Table 2). In contrast to the D_{2ccm} constraint, the median values of each technique observed the

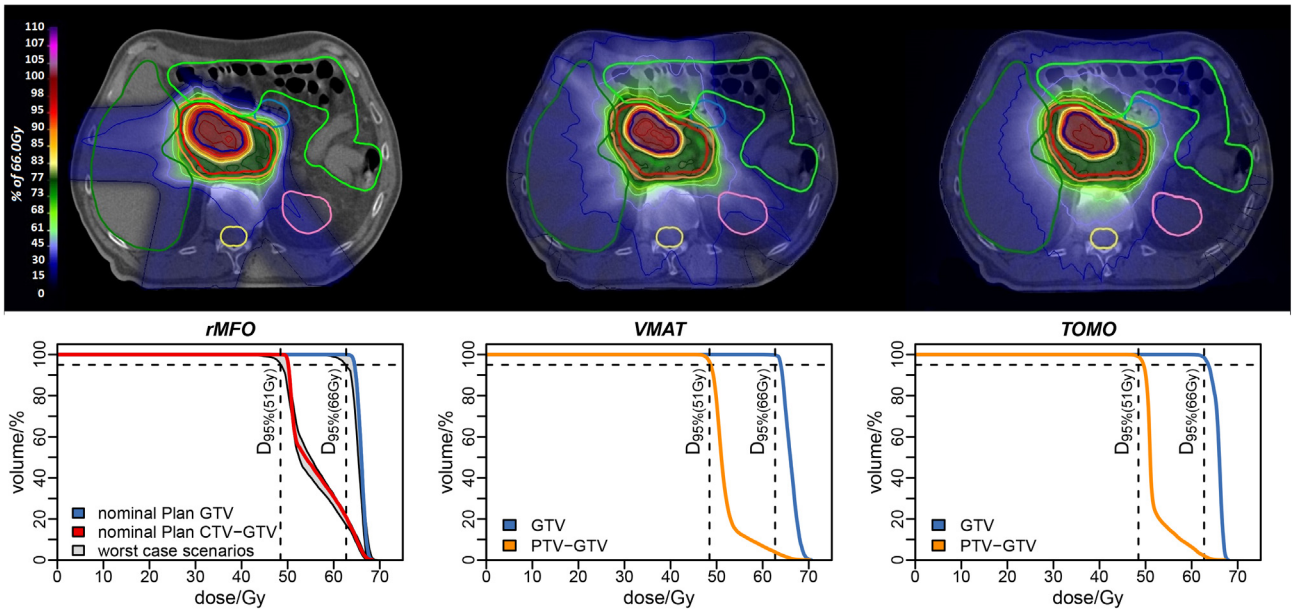

Fig. 1. Dose distribution of rMFO-IMPT (A), VMAT (B) and TOMO (C) treatment plans (upper row) showing the respective dose-volume histogram (DVH) of the target coverage in the lower row.

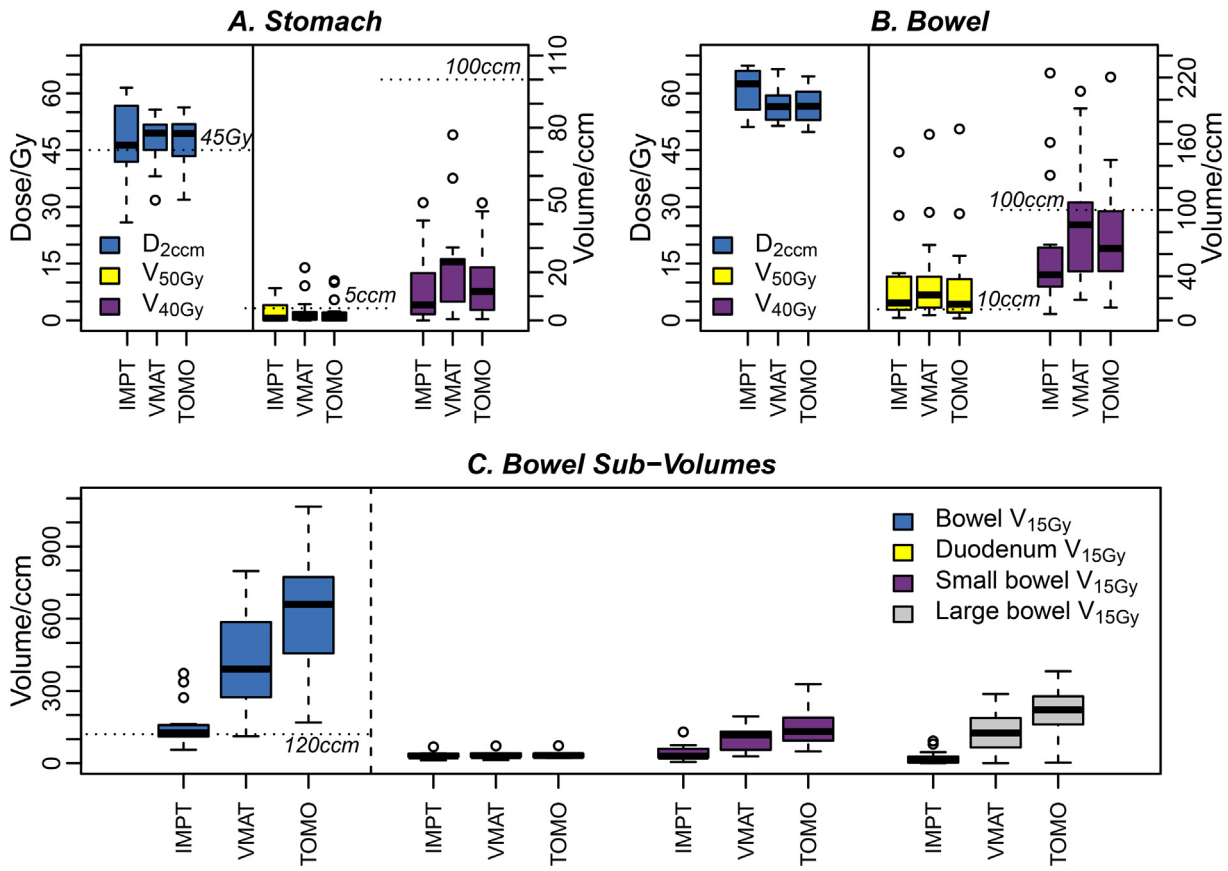

Fig. 2. Results of the dose parameters of the stomach (A), bowel (B), and its sub-volumes duodenum, small and large bowel (C) for the three treatment techniques (rMFO-IMPT, VMAT and TOMO) summarized in box-and-whisker plots.

V_{50Gy} with no statistically significant differences among the techniques. Furthermore, all treatment plans fulfilled the V_{40Gy} constraint with a statistically significant reduction of the value when using rMFO compared to VMAT ($p_{rMFO\text{-}VMAT} < 0.001$, Table 2).

For the bowel, the median value of each treatment technique exceeded the V_{50Gy}, however, the results were lowest for rMFO and TOMO (rMFO: 15.7ccm, TOMO: 14.6ccm, VMAT: 23.1ccm; Fig. 2B, Table 2). All treatment techniques met the V_{40Gy} limit, with

Table 2
Results of the dose volume histogram evaluation including the statistical analysis.

OAR	Constraint	rMFO Median [range]	VMAT Median [range]	TOMO Median [range]	Friedmann p (α = 0.05)	$p_{rMFO\text{-}VMAT}$ (α = 0.05)	$p_{rMFO\text{-}TOMO}$ (α = 0.05)	$p_{VMAT\text{-}TOMO}$ (α = 0.05)
Stomach	Volume (ccm)	296.8 [138.9–901.1]			–	–	–	–
	D_{max} (Gy)	56.7 [44.2–68.4]	56.2 [45.4–68.5]	53.5 [45.3–66.3]	0.057	–	–	–
	D_{2ccm} (Gy)	46.3 [25.9–61.5]	49.5 [31.8–55.7]	49.4 [31.9–56.3]	0.936	–	–	–
	V_{50Gy} (ccm)	0.9 [0.0–13.4]	1.5 [0.0–21.9]	1.7 [0.0–16.5]	0.353	–	–	–
	V_{40Gy} (ccm)	6.4 [0.0–48.9]	24.3 [0.5–77.1]	12.0 [0.5–48.8]	**<0.001**	**<0.001**	0.204	0.053
Bowel	D_{2ccm} (Gy)	62.5 [51.1–67.3]	56.5 [51.4–66.4]	56.6 [49.8–64.5]	**0.001**	**0.010**	**0.001**	1.000
	V_{50Gy} (ccm)	15.7 [2.2–152.6]	23.1 [4.7–168.6]	14.6 [1.9–173.4]	**0.011**	0.134	1.000	**0.010**
	V_{40Gy} (ccm)	41.3 [5.7–224.2]	86.6 [18.6–264.0]	65.2 [11.6–278.3]	**<0.001**	**<0.001**	0.053	0.204
	V_{15Gy} (ccm)	126.0 [55.4–373.6]	391.2 [111.6–797.8]	659.4 [168.7–1065.8]	**<0.001**	**0.003**	**<0.001**	0.301
Duodenum	Volume (ccm)	43.0 [25.0–95.5]			–	–	–	–
	D_{2ccm} (Gy)	60.8 [31.8–65.9]	55.3 [38.3–63.0]	55.6 [36.9–63.1]	0.197	–	–	–
	V_{50Gy} (ccm)	10.8 [0.0–32.1]	12.2 [0.0–35.3]	10.4 [0.0–37.2]	0.089	–	–	–
	V_{40Gy} (ccm)	18.7 [0.1–44.9]	22.0 [1.6–53.6]	24.9 [1.0–58.7]	**0.034**	0.073	0.073	1.000
	V_{15Gy} (ccm)	29.9 [12.1–68.8]	31.4 [13.4–72.4]	32.2 [21.9–72.7]	0.882	–	–	–
Small bowel	D_{2ccm} (Gy)	56.3 [26.0–66.1]	51.5 [29.1–63.6]	51.4 [35.9–62.8]	0.282	–	–	–
	V_{50Gy} (ccm)	3.9 [0.0–68.9]	3.7 [0.0–81.3]	3.7 [0.0–82.9]	0.062	–	–	–
	V_{40Gy} (ccm)	9.7 [0.0–98.0]	21.7 [0.0–111.8]	23.4 [0.1–115.8]	**0.001**	**0.001**	**0.010**	1.000
	V_{15Gy} (ccm)	28.9 [5.4–129.9]	117.2 [28.8–194.2]	131.4 [48.8–327.9]	**<0.001**	**0.003**	**<0.001**	0.301
Large Bowel	D_{2ccm} (Gy)	26.5 [1.1–65.0]	43.4 [11.3–61.5]	41.1 [15.1–60.6]	0.247	–	–	–
	V_{50Gy} (ccm)	0.0 [0.0–22.3]	0.0 [0.0–21.7]	0.0 [0.0–21.7]	0.084	–	–	–
	V_{40Gy} (ccm)	0.1 [0.0–41.5]	8.0 [0.0–59.7]	3.4 [0.0–66.9]	**0.002**	**0.008**	0.301	0.513
	V_{15Gy} (ccm)	11.5 [0.0–92.2]	125.2 [0.0–287.2]	221.5 [2.2–381.9]	**<0.001**	**0.010**	**<0.001**	0.204
Spinal cord	D_{max} (Gy)	33.4 [8.1–42.4]	39.7 [29.7–43.5]	41.7 [26.9–44.8]	**<0.001**	**0.006**	**<0.001**	1.000
	D_{2ccm} (Gy)	26.4 [3.1–38.8]	35.4 [25.7–40.8]	37.4 [24.4–40.4]	**<0.001**	**0.002**	**0.001**	1.000
Kidney left	Volume (ccm)	225.0 [133.1–349-4]			–	–	–	–
	D_{mean} (Gy)	11.0 [1.7–16.9]	12.7 [4.9–18.1]	10.4 [5.5–13.3]	**0.038**	0.053	1.000	0.134
	V_{20Gy} (%)	18.2 [1.1–31.7]	10.9 [0.0–38.2]	3.5 [0.0–9.2]	**<0.001**	0.134	**<0.001**	0.134
Kidney right	Volume (ccm)	196.4 [130.9–384.1]			–	–	–	–
	D_{mean} (Gy)	9.8 [1.4–17.1]	12.1 [4.0–16.9]	10.6 [4.4–13.7]	0.155	–	–	–
	V_{20Gy} (%)	13.5 [0.2–31.9]	10.4 [3.7–25.9]	6.2 [0.01–9.1]	**0.002**	1.000	**0.003**	**0.019**
Liver	Volume (ccm)	1689.0 [1130.8–3510.6]			–	–	–	–
	V_{30Gy} (ccm)	30.1 [0.0–107.8]	79.6 [0.1–320.4]	62.1 [0.0–255.4]	**0.001**	**0.003**	**0.003**	1.000
Spleen	Volume (ccm)	204.8 [85.1–334.0]			–	–	–	–
	D_{mean} (Gy)	1.6 [0.0–5.7]	4.2 [0.7–14.1]	4.7 [1.2–15.6]	**<0.001**	**0.003**	**<0.001**	0.980
Body	V_{50Gy} (ccm)	278.3 [170.0–611.5]	304.3 [195.0–713.8]	292.0 [196.6–711.0ccm]	**0.038**	**0.032**	0.604	0.604
	V_{40Gy} (ccm)	453.9 [339.3–1001.1]	538.4 [372.1–1336.3]	574.3 [341.8–1321.9]	**<0.001**	**<0.001**	**0.006**	1.000
	V_{30Gy} (ccm)	646.1	916.0	938.3	**<0.001**	**<0.001**	**0.003**	0.301

Table 2 (*continued*)

OAR	Constraint	rMFO Median [range]	VMAT Median [range]	TOMO Median [range]	Friedmann p (α = 0.05)	$p_{rMFO-VMAT}$ (α = 0.05)	$p_{rMFO-TOMO}$ (α = 0.05)	$p_{VMAT-TOMO}$ (α = 0.05)
		[486.0–1326.2]	[592.7–2258.6]	[563.8–2213.2]				
	V_{20Gy} (ccm)	1069.8 [766.7–1983.2]	1762.9 [1086.5–4071.5]	1914.9 [1202.7–4497.6]	**<0.001**	**<0.001**	**<0.001**	1.000
	V_{10Gy} (ccm)	2191.0 [1539.1–4457.4]	3906.1 [2808.5–7590.8]	4511.1 [2727.1–8066.3]	**<0.001**	**0.006**	**<0.001**	0.134
	V_{5Gy} (ccm)	2757.4 [1886.8–5379.8]	5608.0 [3504.0–10165.3]	5645.3 [3375.8–10109.4]	**<0.001**	**0.001**	**<0.001**	1.000
	$V_{0.01Gy}$ (ccm)	17704.3 [22329.3–24375.9]	25456.6 [16526.8–35015.5]	32872.8 [10097.4–48580.6]	**<0.001**	**0.019**	**<0.001**	0.085

Abbreviations: D_{max}: maximum dose; D_{mean}: mean dose; D_{xccm}: dose D in Gy applied to x-volume; V_{xGy}: volume receiving x-Gy.

a significantly lower value for rMFO compared to VMAT ($p_{rMFO-VMAT}$ < 0.001; Fig. 2B, Table 2). Compared to IMRT, rMFO statistically significantly reduced the V_{15Gy} ($p_{rMFO-VMAT}$ = 0.003, $p_{rMFO-TOMO}$ < 0.001). Of note, the median dose to D_{2ccm} of the bowel exceeded 56 Gy in all treatment techniques, however, with statistically significantly lower values for both IMRT techniques compared to rMFO ($p_{rMFO-VMAT}$ = 0.010, $p_{rMFO-TOMO}$ = 0.001; Fig. 2B, Table 2).

Evaluating the intestinal sub-volumes, the D_{2ccm} to the duodenum (rMFO: 60.8 Gy, VMAT: 55.3 Gy, TOMO: 55.6 Gy, Table 2) was highest compared to the small (rMFO: 56.3 Gy, VMAT: 51.5 Gy, TOMO: 51.4 Gy) or large bowel (rMFO: 26.5 Gy, VMAT: 43.4 Gy, TOMO: 41.1 Gy). Furthermore, more than 20% of the median duodenal volume (43.0ccm) was covered by 50 Gy, irrespective of the treatment modality (Table 2). The V_{40Gy} and V_{15Gy} of the non-duodenal small bowel were statistically significantly reduced with rMFO compared to both photon techniques ($p_{rMFO-VMAT}$ = 0.001, $p_{rMFO-TOMO}$ = 0.010; and $p_{rMFO-VMAT}$ = 0.003, $p_{rMFO-TOMO}$ < 0.010, Table 2, Figure 2C). Neither of the techniques reached a dose of 50 Gy in the large bowel, whereas, rMFO-IMPT statistically significantly reduced the V_{40Gy} when compared to VMAT ($p_{rMFO-VMAT}$ = 0.008), and the V_{15Gy} compared to both photon techniques ($p_{rMFO-VMAT}$ = 0.010, $p_{rMFO-TOMO}$ < 0.001).

3.3. Other organs at risk

The preset dose constraints to the liver, spinal cord and kidneys were met by all treatment techniques (Table 2). The V_{30Gy} of the liver, the D_{max} for the spinal cord, and the D_{mean} dose to the spleen and the integral body dose were statistically significant reduced when using rMFO. Conversely, TOMO achieved the lowest V_{20Gy} for each kidney and statistically significantly reduced the dose to both kidneys when compared to rMFO.

3.4. Subgroup analysis regarding surgical status and tumor localization

When separating the results in the patients' subgroups receiving primary RCT (N = 8) or RCT for local recurrence after surgery (N = 7), rMFO-IMPT reduced the V_{50Gy} to the gastrointestinal organs for both patients' subgroups in comparison to IMRT (Figure A.1.I, Table A2). Interestingly, the gastric dose in primary treated patients was significantly higher than in patients treated for local recurrent disease (*e.g.* D_{2ccm}: p_{rMFO} = 0.008, p_{VMAT} = 0.008, p_{TOMO} = 0.005).

Irrespective of the primary tumor location, rMFO (statistically) significantly reduced the low and intermediate dose to the OARs for both, pancreatic head (N = 11) and body (N = 4) patients, compared to VMAT and TOMO, *e.g.* the median V_{15Gy} for bowel of pancreatic head patients ($p_{rMFO-VMAT}$ = 0.009, $p_{rMFO-TOMO}$ < 0.001). Generally, in pancreatic head tumors of the dose to the stomach was reduced, whereas a dose reduction in the duodenum and small bowel tended to be only possible for tumors of the pancreatic body (Figure A.1.II, Table A.2).

3.5. Treatment plan approval

Taking into account the target coverage and the OAR dose constraints, the radiation oncologists each accepted twelve rMFO and TOMO treatment plans for clinical application, whereas only nine of the VMAT treatment plans. Moreover, for one patient it was not possible to obtain a clinically acceptable treatment plan.

4. Discussion

In our *in-silico* treatment planning study, we assessed whether dose-escalation using a SIB approach with VMAT, TOMO or rMFO-IMPT would be clinically feasible in LAPC and locally recurrent pancreatic cancer while maintaining the dose to OARs. In this study, rMFO-IMPT did not prove to be of particular benefit compared to both VMAT and TOMO. Even though the current standard dose prescription of 51 Gy was applied to the elective volume the radiation dose to several gastrointestinal OARs exceeded 51 Gy. So far, only a limited number of comparative dosimetric studies using moderate hypofractionated photon or proton dose-escalation have been published [19,27–29]. Of note, none of them have reported on a comparison using IMRT or IMPT techniques with a dose-escalated SIB approach to 51 Gy/66 Gy.

The main reason for the different radiation doses to OARs in our study is the variation in radiation technique. While for the photon plans, no additional PTV margin around the boost was considered in order to adhere to the treatment plans delivered in a prospective clinical study [8], in proton therapy, (beam-specific) planning margins or robust optimization are indispensable, since this technique is highly susceptible to anatomical changes. In this study, the robustly optimized IMPT plans therefore showed an increased volume around the GTV receiving 95% of the prescribed boost dose. Thus, there was an enlarged dose fall-off region within the small volumes of the CTV-GTV leading to an increased dose deposition in overlapping and adjacent OARs. This fact influenced not only the high dose to the OARs but also the conformity of the GTV and the homogeneity of the dose in the CTV-GTV of the rMFO-IMPT in comparison to the IMRT plans. When including a 5 mm margin for the boost in the VMAT plans, resembling a GTV-to-PTV margin and ensuring a robust boost coverage, also similar or higher doses to the gastrointestinal OARs were found (data not shown, [30]). Contrarily, with rMFO, a significant reduction of large volume irradiation with doses $\leq$ 50 Gy to the gastrointestinal and remaining OARs was reached, which is in line with findings by other groups [16–19]. These volumes irradiated to low or intermediate doses may in turn be important causes of acute and late gastrointestinal toxicities after radio(chemo)therapy [8,31,32].

In order to exclude a bias due to the inhomogeneous patient cohort, two subgroup analyses were performed. The separation of the patients into sub-cohorts regarding previous surgical resection and primary tumor location emphasized the superiority in the low and intermediate exposure of the rMFO-IMPT approach among the techniques. Comparing the anatomical sites, no primary tumor location was found to be more suited for dose-escalated SIB irrespective of the treatment techniques. Hence, only a sufficiently large distance between the target volume and the OARs may allow for dose-escalation approaches, as already suggested by Krishnan *et al.* [10]. One such solution may be the insertion of a spacer [33,34]. Since our results are based on a limited number of patients in each subgroup, however, the analyses should be treated with caution.

Our treatment plan comparison holds several particularities. First, the robustly optimized concept employed in protons contrasts to the conventional geometric margin approach in photon therapy, since the proton range uncertainties are not considered in the PTV. Thus, the resulting treatment plans cannot be directly compared and adequate approaches to nonetheless do so are currently being explored [35]. In order to obtain an appropriate dose comparison, we used the CTVs for evaluation and comparison among the treatment technique. Second, as described before, two treatment planners conducted the dose calculations. Even though a protocol was in place, we cannot rule out that the resulting plans and thus the dosimetric results were influenced by individual decisions of the treatment planner. Third, the bowel sub-volumes were combined to a single objective "bowel" for treatment planning, thus, the dose depositions to those OARs were not independently taken into account during the inverse optimization process. A separation of the bowel into individual objectives and the utilization of a field-in-field technique to minimize the dose to overlapping structures may prevent enable more selective sparing of bowel sub-volumes. Fourth, rather conservative constraints were chosen for the gastrointestinal tract, since tolerance doses for (hypofractionated) RCT regimes are still being investigated [8,31,32]. Nichols *et al.* [17] reported doses up to 54 Gy(RBE) to <5% of the stomach and the small bowel to be well tolerated with at prescribed total median, normofractionated dose of 59.4 Gy(RBE) even when combined with capecitabine, while QUANTEC recommends a dose maximum of 45 Gy [25]. Finally, this study lacks 4D-CT data in order to take into account an internal target volume margin (ITV) for target definition. In future studies on proton beam treatment for patients with pancreatic cancer, anatomical changes, organ motion or weight loss should be considered in order to avoid inhomogeneous dose distribution during the treatment course. These may be discovered using the ITV approach, 4D treatment planning approaches or (online) adaptive treatment combined with gated proton beams.

5. Conclusion

Neither of the photon- or proton based highly conformal intensity-modulated radiation techniques enabled sparing of radiation-sensitive (gastrointestinal) organs at risk in pancreatic cancer patients when applying dose escalation with a SIB approach. Thus, in the future, carefully designed prospective, randomized trials are necessary to verify the potential benefit of a dose-escalated SIB with neoadjuvant IMPT both regarding tumor control as well as acute and late toxicity.

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.

Acknowledgement

The authors thank Prof. Dr. Peter Wust and Prof. Dr. Pirus Ghadjar (both Charité Universitätsmedizin Berlin, Germany) for kindly providing the CT data-sets of their treated patients in an anonymous manner for this study.

Funding statement

Not applicable.

Clinical trial information

The *in silico* treatment planning study was approved by the Ethics Committees of the University Hospital Carl Gustav Carus Dresden of the Technische Universität Dresden (EK 98032017) and of the Charité Universitätsmedizin Berlin (EA1/236/16).

Availability of data and materials

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2020.12.001.

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