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PHYSICS CONTRIBUTION

Planning Benchmark Study for Stereotactic Body Radiation Therapy of Pancreas Carcinomas With Simultaneously Integrated Boost and Protection: Results of the DEGRO/DGMP Working Group on Stereotactic Radiation Therapy and Radiosurgery

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Purpose: The proximity or overlap of planning target volume (PTV) and organs-at-risk (OARs) poses a major challenge in stereotactic body radiation therapy (SBRT) of pancreatic cancer (PACA). This international treatment planning benchmark study investigates whether simultaneous integrated boost (SIB) and simultaneous integrated protection (SIP) concepts in PACA SBRT can lead to improved and harmonized plan quality.

Methods and Materials: A multiparametric specification of desired target doses (gross target volume $[GTV]_{D50\%}$, $GTV_{D99\%}$, $PTV_{D95\%}$, and $PTV_{0.5cc}$) with 2 prescription doses of $GTV_{D50\%} = 5 \times 9.2$Gy (46 Gy) and $GTV_{D50\%} = 8 \times 8.25$ Gy (66 Gy) and OAR limits were distributed with planning computed tomography and contours from 3 PACA patients. In phase 1, plans were ranked using a scoring system for comparison of trade-offs between GTV/PTV and OAR. In phase 2, replanning was performed for the most challenging case and prescription with dedicated SIB and SIP contours provided for optimization after group discussion.

Results: For all 3 cases and both phases combined, 292 plans were generated from 42 institutions in 5 countries using commonly available treatment planning systems. The $GTV_{D50\%}$ prescription was performed by only 76% and 74% of planners within 2% for 5 and 8 fractions, respectively. The $GTV_{D99\%}$ goal was mostly reached, while the balance between OAR and target dose showed initial SIB/SIP-like optimization strategies in about 50% of plans. For plan ranking, 149 and 217 score penalties were given for 5 and 8 fractions, pointing to improvement possibilities. For phase 2, the $GTV_{D50\%}$ prescription was performed by 95% of planners within 2%, and $GTV_{D99\%}$ as well as OAR doses were better harmonized with notable less score penalties. Fourteen of 19 planners improved their plan rank, 9 of them by at least 2 ranks.

Conclusions: Dedicated SIB/SIP concepts in combination with multiparametric prescriptions and constraints can lead to overall harmonized and high treatment plan quality for PACA SBRT. Standardized SIB/SIP treatment planning in multicenter clinical trials appears feasible after group consensus and training.

Introduction

Pancreatic cancer (PACA) is one of the most fatal solid cancers, with an incidence that has doubled globally over the past 25 years. It has a predominance in the Western hemisphere, attributed mostly to lifestyle.[1] Despite considerable therapeutic progress for other cancer types, the last major breakthrough for PACA was over a decade ago, when gemcitabine was replaced by more active chemotherapy regimens to prolong survival of patients with advanced PACA. There is still a desperate paucity of targeted therapeutic approaches for this cancer type, and second-line therapy has poor outcomes.[2,3] Local treatment approaches, such as surgery and radiation therapy, are important therapeutic elements in combination with systemic therapy, allowing for comprehensive treatment approaches to enhance overall survival.[4-6]

Stereotactic body radiation therapy (SBRT)[7] has potential advantages in PACA because most patients undergo prolonged chemotherapy with limited options for longer therapy breaks, which can be achieved with SBRT. Treatment duration for SBRT is short, recovery times are fast and local control rates appear to be at least comparable to chemoradiotherapy, because of high biological doses.[8-10] However, the pancreas is enveloped by critical organs-at-risk (OARs), predominantly the duodenum, stomach, and great vessels, which can lead to major late complications of SBRT.[11,12] This may be one of the reasons why, to date, only a few multicenter trials have been conducted.[8,13] To facilitate prospective clinical multicenter, multiplatform studies for SBRT in PACA, harmonization for motion management,[14] contouring,[15] treatment planning, and response assessment[6] are required.

Multicenter, multiplatform treatment planning benchmark studies for clinical trial and practice harmonization have been widely performed for other SBRT indications such as lung and liver tumors.[16-19] However, for PACA, the reconciliation of gross target volume (GTV), planning target volume (PTV), and OAR doses is particularly challenging and simultaneous integrated boost (SIB) and simultaneous

integrated protection (SIP) concepts are more frequently used,[20-22] for which no benchmark currently exists. We therefore conducted an international multicenter, multiplatform benchmark study to harmonize SBRT treatment planning for PACA and investigated if SIB/SIP concepts can increase treatment plan quality after crowd knowledge-based experience sharing.[23] Harmonizing treatment planning is one point to improve clinical trials on PACA SBRT through reliable reported dose parameters, which enables correlation of dose parameters with clinical outcome across different institutions and techniques.

Methods and Materials

Case selection and patient characteristics

The pancreas SBRT databases of the lead institutions of this study were screened for 3 particularly challenging cases with very close proximity of OARs. These cases were used for the combined contouring[15] and treatment planning benchmark study, after approval from the primary ethics committee (University of Kiel, reference number D 514/18). In agreement with previous studies, the number of cases was found to balance analysis power and participant workload.[17-19] Finally, 3 patients with histologically proven PACA treated with SBRT were selected for the benchmark study based on the study committee consensus decision.

For all patients, the primary planning computed tomography (CT) images were acquired head-first supine with ≤1.0 mm in-plane resolution and 1.5 mm slice thickness, as per guidelines.[14] Additional imaging information is provided in the patient descriptions below. Consensus GTV and PTV contours for these patients were derived from a prior contouring benchmark study.[15] In this contouring study, 24 experts provided 19 structure sets per patient, and from these 19 contours per patient, the expert panel derived the consensus structures. The OAR contours were provided by the radiation oncology expert group of the study committee, as per clinically accepted guidelines.[24] All participants received the same structure sets, independent from their treatment technique, to enable reliable analysis of planning results.

Patient 1 was a 70-year-old individual with PACA recurrence, after initial pancreatico-duodenectomy and adjuvant chemotherapy. The GTV was 28.0 cc and directly adjacent to the vena cava on the right and the aorta on the left. The PTV was 54.8 cc and had overlap with the vena cava (2.03 cc), the aorta (5.17 cc), and the jejunum (0.38 cc). Imaging for delineation was 4-dimensional CT, positron emission tomography (PET)-CT, and CT with intravenous contrast.

Patient 2 was a 45-year-old individual with locally advanced unresectable PACA at the pancreas head, which progressed under initial chemotherapy. The GTV was 49.4 cc and directly adjacent to vena cava and aorta posteriorly and duodenum anteriorly. The PTV was 92.9 cc and overlapped the vena cava (0.60 cc), the aorta (1.72 cc), the stomach (0.49 cc), and the duodenum (1.64 cc). Imaging for delineation was 4D-PET−CT and magnetic resonance imaging.

Patient 3 was a 61-year-old individual with chemotherapy-resistant locally advanced unresectable PACA at the pancreas head. The GTV was 38.4 cc and directly adjacent to vena cava and aorta posteriorly and duodenum on the left. The PTV was 73.2 cc and overlapped the aorta (1.34 cc) and the vena cava (0.17 cc). Imaging for delineation was 4D-CT with oral and intravenous contrast.

A graphical display of the cases is presented in Figure E1.

Beam-delivery technique planning

Anonymized planning CT and radiation therapy structure sets in Digital Imaging and Communications in Medicine standard format were distributed to all participants in this benchmark study. Beam-delivery technique selection and planning were performed with each participant's equipment, using institution-specific methods/techniques and society guidelines.[8,14,17-19] The use of a provided reference CT calibration curve (if possible) and a type-B or type-C dose calculation algorithm was required.[14] All submitted treatment plans were strongly desired to meet the predefined multiparametric dose prescriptions similar to a previous benchmark study[19] and OAR dose limitations for 2 different fractionation schemes (5 and 8 fractions). The plans had to be clinically acceptable, as judged by the participant's institutional standards:

1. Adapted from a previous study on PACA SBRT,[25] the prescription dose for 5 fractions was defined as median GTV dose ($GTV_{D50\%}$) = 5 × 9.2 Gy (46 Gy, $BED_{\alpha/\beta=10Gy}$ = 88.3 Gy_{10}). Further target objectives were as follows: (1) GTV and PTV near minimum dose (ie, $GTV_{D99\%}$ and $PTV_{D99\%}$) = 44.5 Gy and 33 Gy, respectively; (2) GTV and PTV near maximum dose (ie, $GTV_{D0.5cc}$ and $PTV_{D0.5cc}$) = 49.2 Gy, with the maximum inside the GTV; and (3) PTV median dose (ie, $PTV_{D50\%}$) = 44 Gy. A maximum possible compromise for PTV near minimum dose was allowed with $PTV_{D90\%}$ > 33 Gy.
2. Adapted from a previous study on central lung SBRT,[26] the prescription dose for 8 fractions was defined as median GTV dose ($GTV_{D50\%}$) = 8 × 8.25 Gy (66 Gy, $BED_{\alpha/\beta=10Gy}$ = 120.5 Gy_{10}). Further target objectives were: (1) GTV and PTV near minimum dose (ie, $GTV_{D99\%}$ and $PTV_{D99\%}$) = 61.5 Gy and 54 Gy, respectively; (2) GTV and PTV near maximum dose (ie, $GTV_{D0.5cc}$ and $PTV_{D0.5cc}$) = 72 Gy, with the maximum inside the GTV; and (3) PTV median dose (ie, $PTV_{D50\%}$) = 64 Gy. A maximum possible compromise for PTV near minimum dose was allowed with $PTV_{D99\%}$ = 40 Gy.
3. Based on commonly available OAR limits for pancreas SBRT in 5 and 8 fractions,[21,27-29] major OAR dose constraints for this benchmark study were: (1) duodenum/

jejunum/stomach near maximum dose (ie, $D_{0.5cc}$) <32 Gy (5 fractions) and 42.4 Gy (8 fractions); (2) aorta/vena cava near maximum dose (ie, $D_{0.5cc}$) <53 Gy (5 fractions) and 60 Gy (8 fractions); and (3) aorta V_{47Gy} <10 cc for both 5 and 8 fractions.

Further details for the multiparametric target dose objectives and OAR dose limitations are summarized in Table 1 and Table E1.

Primary dosimetric evaluation

The submitted dose distributions from all participants were imported in Digital Imaging and Communications in Medicine standard format into a common treatment planning system (Eclipse, version 15.6; Varian Medical Systems) for primary evaluation. To assess minimal dose differences between planning systems, we also asked the participants to provide relevant dose parameters (see prior section) via an online form.

The dosimetric evaluation for the GTV, PTV, and OAR dose parameters described in the previous section was based on the International Commission on Radiation Units and Measurements report 91[30] on prescribing, recording, and reporting of stereotactic treatments with small photon beams and previous studies.[17-19] Relevant dosimetric metrics were extracted using a custom-developed C# script that leverages the available Eclipse scripting application interface,[31] and dose-volume histograms (DVHs) were generated using the Python library "DVH Analytics."[32] The number of monitor units and the estimated irradiation times were also collected to investigate and compare the delivery efficiency.

Plan quality ranking

To evaluate the plan quality, the well-established method of relative plan ranking[17-19,33] had to be adapted as the relative scores were linearly rated, which does not reflect the SIB/SIP planning concepts with dose plateaus in PTV overlapping OAR zones.[20-22] Hence, for this benchmark study, a combination of score metrics were used for plan quality ranking, including penalty points for failing dose prescription and distant OAR requirements ($GTV_{D99\%}$, $PTV_{D99\%}$, and $OAR_{D0.5cc}$) and SIB/SIP relevant plan parameters.

For the score metric, the dosimetric values of the parameters as mentioned above were categorized into 4 relative ranks (1 = excellent, 2 = above average, 3 = below average, and 4 = poor) by using a Gaussian distribution over the achieved mean value (GTV/PTV) or over the maximum dose limit (OAR) as previously described (first-order ranking).[17-19,33] For the penalty metric, a 1-, 2-, and 3-point penalty was given for not meeting the dose prescription requirement ($GTV_{D50\%}$) by more than 1%, 2%, and 5%, respectively; a 1- and 2-point penalty was given for exceeding overlapping $OAR_{D0.5cc}$ dose limits by more than 1% and 5%, respectively; and a 1-point penalty was given for exceeding each distant OAR and GTV/PTV near maximum dose limitations.

Table 1 Dose prescriptions and clinical goals for the SBRT Pancreas study using the multiparametric method

Prescription A (5 fractions)[25]	Prescription B (8 fractions)[26]
$GTV_{D50\%}$ = 5 × 9.2 Gy = 46 Gy (100%)	**$GTV_{D50\%}$ = 8 × 8.25 Gy = 66Gy (100%)**
$GTV_{D99\%}$ = 44.5 Gy	$GTV_{D99\%}$ = 61.2 Gy
$PTV_{D50\%}$ = 44 Gy	$PTV_{D50\%}$ = 64 Gy
$PTV_{D95\%}$ = 40 Gy	$PTV_{D95\%}$ = 60 Gy
$PTV_{D99\%}$ = 33 Gy	$PTV_{D99\%}$ = 54 Gy
$PTV_{D0.5cc}$ = $GTV_{D0.5cc}$ = 49.2 Gy	$PTV_{D0.5cc}$ = $GTV_{D0.5cc}$ = 72 Gy
$Global_{Dmax}$ = GTV_{Dmax}	
Possible Compromises	Possible Compromise
$PTV_{D90\%}$ > 33 Gy	$PTV_{D99\%}$ = 40 Gy
$GTV_{99\%}$ = $PTV_{D99\%}$ = 25 Gy	

Abbreviations: $D_{0.5cc}$ = near maximum dose: dose that the volume of 0.5 cc receives; $D_{99\%}$ = near minimum dose: dose that 99% of the volume receives; GTV = gross tumor volume, PTV = planning target volume; $PTV_{D90\%}$ = dose that 90% of PTV receives; $PTV_{D95\%}$ = dose that 95% of PTV receives; SBRT, stereotactic body radiotherapy.

For the final plan score, the separate subscores and penalties were summed, and all plans were categorized again using the relative ranks method (rank 1-4) using a Gaussian distribution over the achieved mean value (second-order ranking).[17-19,33]

In short, the first-order ranking ended with a list of ranks and penalties for each plan. The second-order ranking combined this list to one "score sum," which was then ranked again to give each plan a single score rank.

This final plan quality ranking was compared against an expert panel ranking of each plan, based on the GTV/PTV dose requirements (compare Table 1), the OAR dose limitations (compare Table E1), and meeting SIP/SIB requirements as described elsewhere.[20-22] As the relative plan ranking method was adapted and used the first time for a SIB/SIP concept, the expert panel ranking was performed for validation, as described in Blanck et al.[33]

Plan quality improvement with SIB/SIP contours

In the first phase of the benchmark study, the participants were asked to plan according to their institutional best practice guidelines. After primary evaluation and results presentation at a dedicated workshop, we asked the participants to redo the planning of the most challenging case (patient 2, prescription B, compare Fig. E1 and Table 1) with dedicated SIB and SIP contours provided by the study committee. This case was judged the "most challenging" because of the largest variance in planning results for the GTV as well as for the OARs (see results section).

First, a planning risk volume with 3 mm isotropic expansion was generated for all OARs overlapping with or close to the PTV. A SIP contour was generated, defined as the overlap region between the planning risk volume and the PTV. An SIB contour was generated, defined as the GTV minus the SIP. A detailed graphical presentation of the SIB/SIP volume generation is shown in Figure E2.

In phase 2, using the SIP/SIB concept, the multiparametric prescription (Table 1) was applied for the SIB (SIB = GTV) and for the dominant PTV (PTV_{DOM} = PTV − PTV_{SIP}). Dosimetric evaluation, scoring, and expert panel ranking were performed in the same way as in phase 1. For the score function, all plans from phases 1 and 2 were computed jointly to evaluate the relative improvements of using the SIB/SIP concept.

Results

Beam-delivery techniques

A total of 42 institutions from 5 countries participated in this study. The self-reported experience of the participants is as follows: mean SBRT experience is 8 years (range, 2-25 years); mean SBRT cases per year is 70 (range, 2-400). For all 3 patients and both phases combined, 292 treatment plans were generated using different commonly available treatment planning systems. From these 292 plans, 254 were independent plans for the first phase and evaluated as described above. Of them, 19 plans were additionally recalculated with a different dose calculation algorithm or CT calibration curve. For the second phase, 19 plans were submitted using the SIB/SIP structure set—15 plans (80%) were generated with intensity modulated arc therapy (IMAT) and 1 plan (5%) each with static field intensity modulated radiation therapy, robotic radiosurgery, helical radiation therapy, and proton therapy techniques. In first phase, 205 plans (80%) were generated with IMAT, 12 plans (5%) with static field intensity modulated radiation therapy, 18 plans (7%) with robotic radiosurgery, 7 plans (3%) with helical radiation therapy, and 12 plans (5%) with proton therapy techniques. High photon beam energies (≥10 MV) were used in 26% of the plans. Despite requirements, type-B or -C algorithms were used in only 65% for final dose calculation and the provided reference CT calibration curve by only 8 of 42 institutions. However, a spot-check validation with type-A algorithms and in-house CT calibration curves showed differences of <1% in the PTV. The total number of monitor units per fraction ranged from 609 to 12,559, and the estimated in-room treatment time ranged between 1.5 and 80 minutes and was highly dependent on the delivery system.[17-19]

Primary dosimetric evaluation

For dose prescription A (5 fractions), the $GTV_{D50\%}$ requirements (46 Gy) were met within 1%, 1% to 2%, and 2% to 5% in 62%, 14%, and 19% of the cases, respectively (median $GTV_{D50\%}$: 46.0 ± 1.2 Gy). The $GTV_{D99\%}$ goal (44.5 Gy) was mostly reached for patient 1 (median 44.6 ± 1.1 Gy) and patient 3 (median 44.8 ± 1.6 Gy), but there was a wider spread for patient 2 (median 42.0 ± 5.0 Gy). Aorta and vena cava constraints were generally not fully exploited (which means that the target structures could receive higher doses in the overlapping regions, if necessary), whereas the median $duodenum_{D0.5cc}$ for patient 2 was 34.3 ± 3.8 Gy (constraint 35 Gy).

For dose prescription B (8 fractions), the $GTV_{D50\%}$ requirements (66 Gy) were met within 1%, 1% to 2%, and 2% to 5% in 64%, 10%, and 21% of the patients, respectively (median $GTV_{D50\%}$: 66.0 ± 2.0 Gy). The $GTV_{D99\%}$ goal (61.2 Gy) was mostly reached, although the spread of the results varied considerably between patients: patient 1 (median 59.9 ± 3.4 Gy), patient 2 (median 56.1 ± 8.2 Gy), and patient 3 (median 62.7 ± 2.2 Gy). Aorta and vena cava constraints (60.0 Gy) were violated at this prescription, with median 59.7 ± 3.1 Gy and 56.5 ± 3.8 Gy, respectively. Furthermore, for patient 2 the median $duodenum_{D0.5cc}$ was 42.0 ± 7.3 Gy (constraint 42.4 Gy). Details are shown as Boxplot in Figure 1

Differences between techniques were not evaluated due to the majority use of IMAT in this benchmark study. However, other techniques did show obvious disadvantages or advantages as shown in previous studies.[17,19] Details for all cases are shown in Figure 2 and Tables E2 to E7.

Plan quality ranking

For dose prescription A (5 fractions) a total of 35, 68, and 46 penalty points were given for violating dose constraints for patients 1, 2, and 3, respectively. The expert panel ranked far fewer plans into category 1 (excellent) and more plans into category 4 (poor), with 7 and 38 plans out of 128, respectively, as compared to the score function of 27 and 12 plans, respectively. The overall absolute score difference was 29, 28, and 35 for cases 1, 2, and 3, respectively, and 11 plans were ranked 2 categories lower by the expert panel as compared to the score function. The expert panel identified 20 of 43 plans for patient 2 as already using a SIB/SIP concept for treatment planning.

For dose prescription B (8 fractions), a total of 64, 93, and 60 penalty points were given for violating dose constraints for cases 1, 2, and 3, respectively. The expert panel ranked far fewer plans into category 1 (excellent) and more plans into category 4 (poor) with 8 and 41 plans out of 126, respectively, as compared to the score function with 15 and 17 plans, respectively. The overall absolute score difference was 16, 27, and 32 for cases 1, 2, and 3, respectively, and 5 plans were ranked 2 categories lower by the expert panel as compared to the score function. The expert panel identified about 50% of plans (27/42, 26/42, and 21/42 for patients 1, 2, and 3, respectively) as already using a SIB/SIP concept for treatment planning.

Ranking details for all cases are shown in Tables E2 to E7.

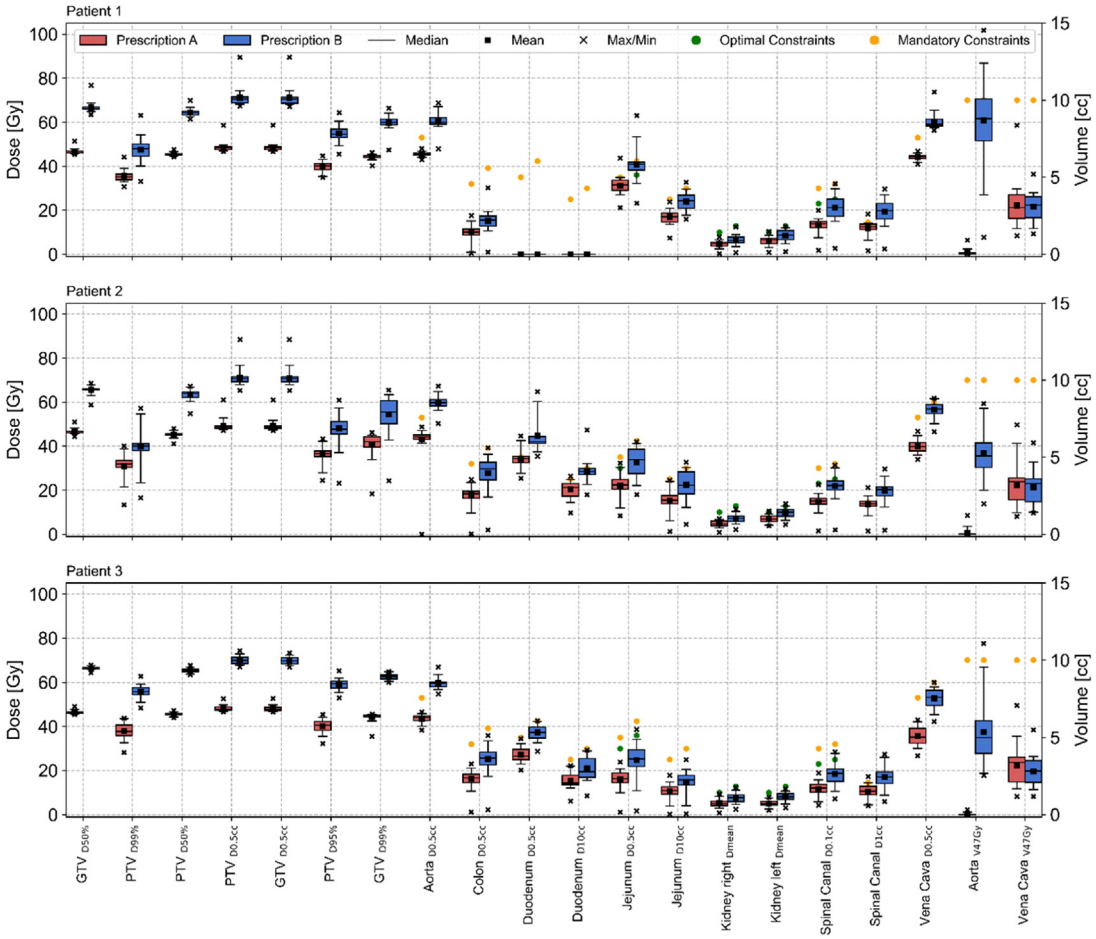

Fig. 1. This figure illustrates a box-and-whisker plot comparison of dose metrics for patients 1 to 3 under prescription A and B in phase 1. The boxplots in blue indicate the results for prescription A, whereas the boxplots in red represent prescription B. Each boxplot displays the median (central line), mean (square), and the range between the 5th and 95th percentiles (whiskers), with 42 datapoints per boxplot representing the 42 participating institutions. The "x" marks represent the minimum and maximum values.
Abbreviations used in the figure are in the following formats: Dx% (Gy) = dose received by x% of the volume; Dxcc (Gy) = dose received by x cubic centimeters; Dmean (Gy) = mean dose; and VxGy [%] = volume percentage receiving x Gy.

Plan quality improvements

For the second phase of the study (replanning), for the biologically higher dose prescription B (8 fractions) and patient 2, the $GTV_{D50\%}$ requirements (66 Gy) were met within 2% in 95% of the cases (18/19) as compared with 69% respectively 58 % (29/42 resp. 11/19) in the first phase. The $GTV_{D99\%}$ goal (61.2 Gy) was now reached in almost all cases (18/19) and was better harmonized (mean 64.2 ± 1.3 Gy) than the first phase (mean 54.4 ± 8.2 Gy resp. 52.8 Gy ± 9.9 Gy); see Figures 2 and 3. The mean $duodenum_{D0.5cc}$ was also better harmonized with 41.3 ± 3.8 Gy as than the first phase 44.6 ± 7.3 Gy resp. 43.5 ± 7.3 Gy (constraint 42.4 Gy); see Figure 3. Details are shown in Table 2 and Table E8.

For the second phase, a total of 19 penalty points were given for violating dose constraints (mean 1 per plan), as compared with 93 in the first phase (mean 2.2 per plan) for the 42 plans resp. 42 penalty points for the 19 plans (also mean 2.2 per plan); see Table E8. Of the 19 planners that participated in the second phase, 7 did not use a SIB/SIP planning concept in the first phase, and 12 improved their plan based on the expert panel ranking—5 by 2 ranks or more and 4 of those without prior SIB/SIP concept use. For the score function, 2 planners were ranked lower as compared to the first phase, whereas 14 improved, 9 of them by 2 ranks or more. Twelve of the 18 best-ranked plans were from the second phase of the study, including both plans with the lowest score sum. A graphical display of the improvement of selected cases is shown in Figure 4.

Best practice guidelines

Based on the combined expert panel and computed plan ranking used in the present study, 3 individual planners were selected to present their best practice approach for

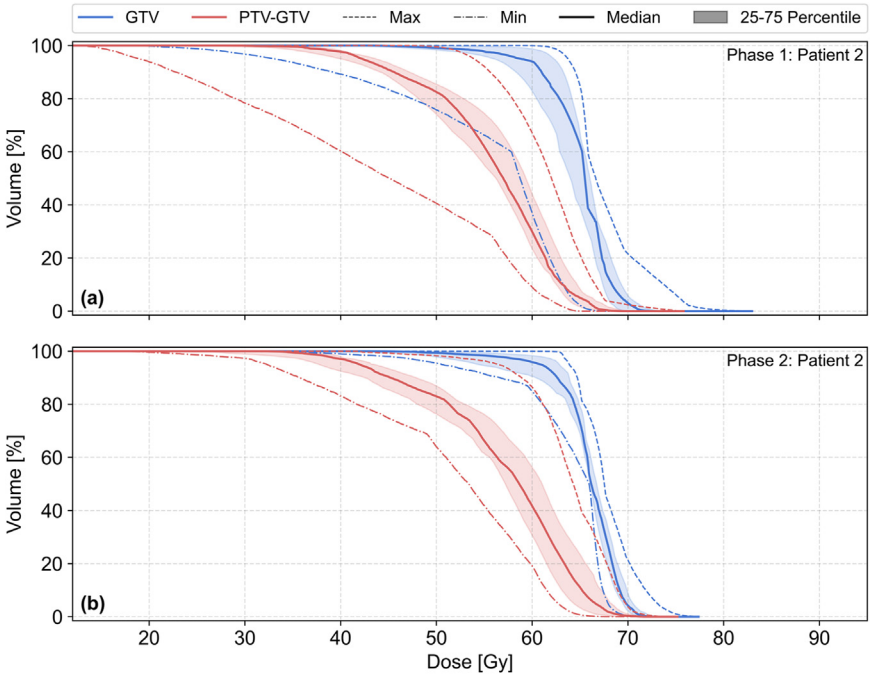

Fig. 2. Dose-volume Histograms (DVHs) for patient 2 with Prescription B over 2 study phases. Blue represents the gross tumor volume (GTV), whereas red indicates the PTV minus GTV (PTV − GTV). Solid lines represent median doses based on 19 plans from the institutions that participated in both phases. Dashed and dash-dot lines indicate the maximum and minimum doses across all plans, respectively. Shaded regions denote the interquartile range (25^{th}-75th percentile). Panel (a) illustrates the DVH for phase 1, and Panel (b) for phase 2.

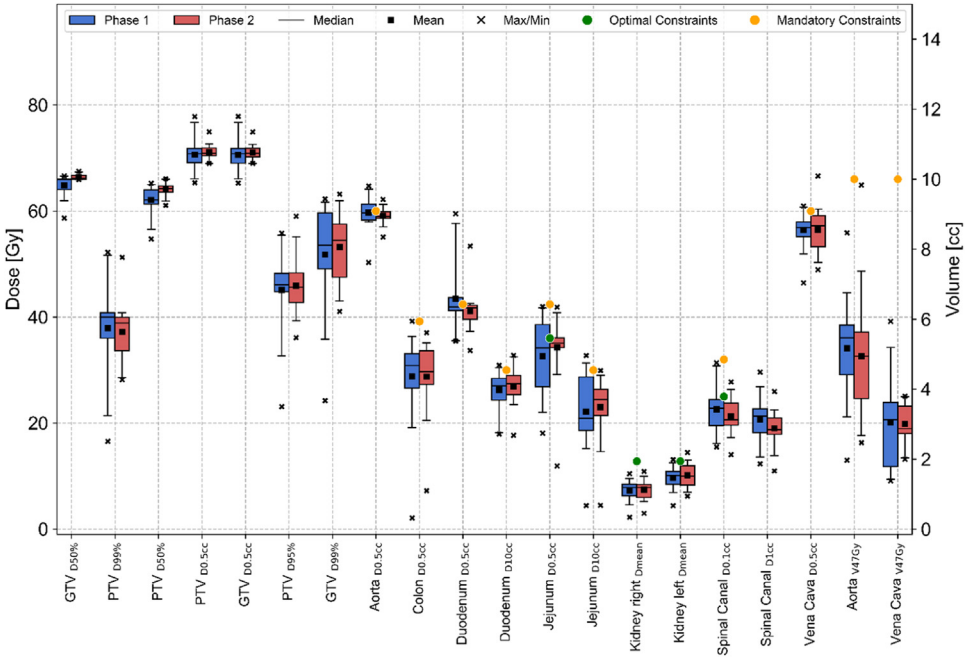

Fig. 3. This figure illustrates a box-and-whisker plot comparison of dose metrics for patient 2 under prescription B between institutions that participated in phase 1 and 2. The boxplots in blue indicate the results from phase 1 (19 cases), whereas the boxplots in red represent phase 2 (19 cases). Each boxplot displays the median (central line), mean (square), and the range between the 5th and 95th percentiles (whiskers). The "x" marks represent the minimum and maximum values.
Abbreviations used in the figure are in the following formats: Dx% (Gy) = dose received by x% of the volume; Dxcc (Gy) = dose received by x cubic centimeters.

Table 2 Comparison between phase 1 and phase 2 of the pancreas SBRT benchmark study

	Phase 1*		Phase 1†		Phase 2†		Constraint/goal
	Mean	SD	Mean	SD	Mean	SD	
$GTV_{D50\%}$ [Gy]	65.56	1.69	64.80	1.92	66.37	0.51	66.0
$PTV_{D99\%}$ [Gy]	39.96	8.01	37.93	8.97	37.45	5.53	54.0
$PTV_{D50\%}$ [Gy]	63.27	2.45	62.09	2.61	64.07	1.28	64.0
$PTV_{D0.5cc}$ [Gy]	70.97	3.55	70.62	2.99	71.04	1.41	72.0
$GTV_{D0.5cc}$ [Gy]	70.92	3.55	70.59	2.99	70.98	1.40	72.0
$PTV_{D95\%}$[Gy]	48.07	6.96	45.11	7.45	45.82	5.15	60.0
$GTV_{D99\%}$ [Gy]	54.42	8.16	51.77	9.62	64.07	1.32	61.2
$Aorta_{V47Gy}$[cc]	5.24	1.50	5.17	1.39	4.94	1.77	10.0
$Aorta_{D0.5cc}$ [Gy]	59.83	2.97	59.70	2.99	59.10	1.53	60.0
$Colon_{D0.5cc}$ [Gy]	27.76	7.76	28.76	7.93	28.22	6.86	39.2
$Duodenum_{D0.5cc}$ [Gy]	44.58	7.25	43.47	6.10	41.26	3.78	42.4
$Duodenum_{D10cc}$ [Gy]	28.24	4.38	26.21	3.62	27.23	3.60	30.0
$Jejunum_{D0.5cc}$ [Gy]	32.51	6.55	32.61	6.96	33.91	6.35	42.4
$Jejunum_{D10cc}$ [Gy]	22.32	6.31	22.13	6.72	22.74	5.70	30.0
$Kidney\_right_{Dmean}$ [Gy]	7.09	1.84	7.26	1.89	7.30	1.87	12.8
$Kidney\ \_left_{Dmean}$ [Gy]	9.77	2.12	9.64	2.03	10.05	2.19	12.8
$SpinalCanal_{D0.1cc}$ [Gy]	21.89	4.67	22.60	4.18	21.30	3.29	32.0
$SpinalCanal_{D1cc}$ [Gy]	19.83	4.55	20.66	4.11	19.00	3.23	32.0
$VenaCava_{V47Gy}$ [cc]	3.03	1.05	3.05	1.29	3.00	0.50	10.0
$VenaCava_{D0.5cc}$ [Gy]	56.56	3.47	56.37	3.26	56.52	4.01	60.0

Abbreviations: D_{XXcc} = dose that the volume of XXcc receives; $D_{XX\%}$ = dose that the volume of XX% receives; $D_{50\%}$ = the median dose; D_{mean} = mean dose; GTV = gross tumor volume; PTV = planning target volume; SBRT, stereotactic body radiotherapy; SD, standard deviation; V47Gy = the volume that at least 47.0 Gy receives.

* For all 42 Institutes that participated in phase 1.

† For the 19 Institutes that participated in phase 2.

Case: Patient 2 with prescription B. Main prescription criterion: $GTV_{D50\%}$ = 66 Gy in 8 fractions.

PACA SBRT with SIB/SIP planning (Supplementary Materials).

RATING score

Recently, RAdiotherapy Treatment plannING study Guidelines (RATING) were published, along with a scoring metric to assess the quality of treatment planning studies.[34] Based on self-assessment of our study, we achieved a RATING score of 191 of 211 points (91%, Supplement Rating Score), which was validated by 2 independent reviewers.

Discussion

To our knowledge, this large multicenter, multiplatform benchmark study investigated complex treatment planning, namely SIB/SIP concepts for PACA,[20-22] for the first time. The study implemented and validated several core aspects of large-scale treatment planning studies.[16]

Primarily, we demonstrated that a crowd knowledge-based 2-stage design with replanning could remarkably increase treatment plan quality for specific complex case scenarios.[23] Although in the first phase of the study, almost 50% of the participants already used the SIB/SIP concept, we still found a very high number of constraint violations for critical organs in close proximity and underdosed GTV areas. We then provided specific SIB and SIP contours after a teaching course and allowed replanning in the second phase of the study for the most challenging case, with the higher and more challenging biological dose prescription to the target volumes in 8 than in 5 fractions. This strategy proved to be valuable as the best plans originated from the second phase, particularly from participants that did not score well in the first phase. This also demonstrates that centers with limited experience can greatly benefit from participating in multicenter studies as they can quickly learn from more experienced centers and benchmarks such as ours.

Because PACA is a rather rare indication for stereotactic radiation therapy,[8] a larger-scale multicentric approach is

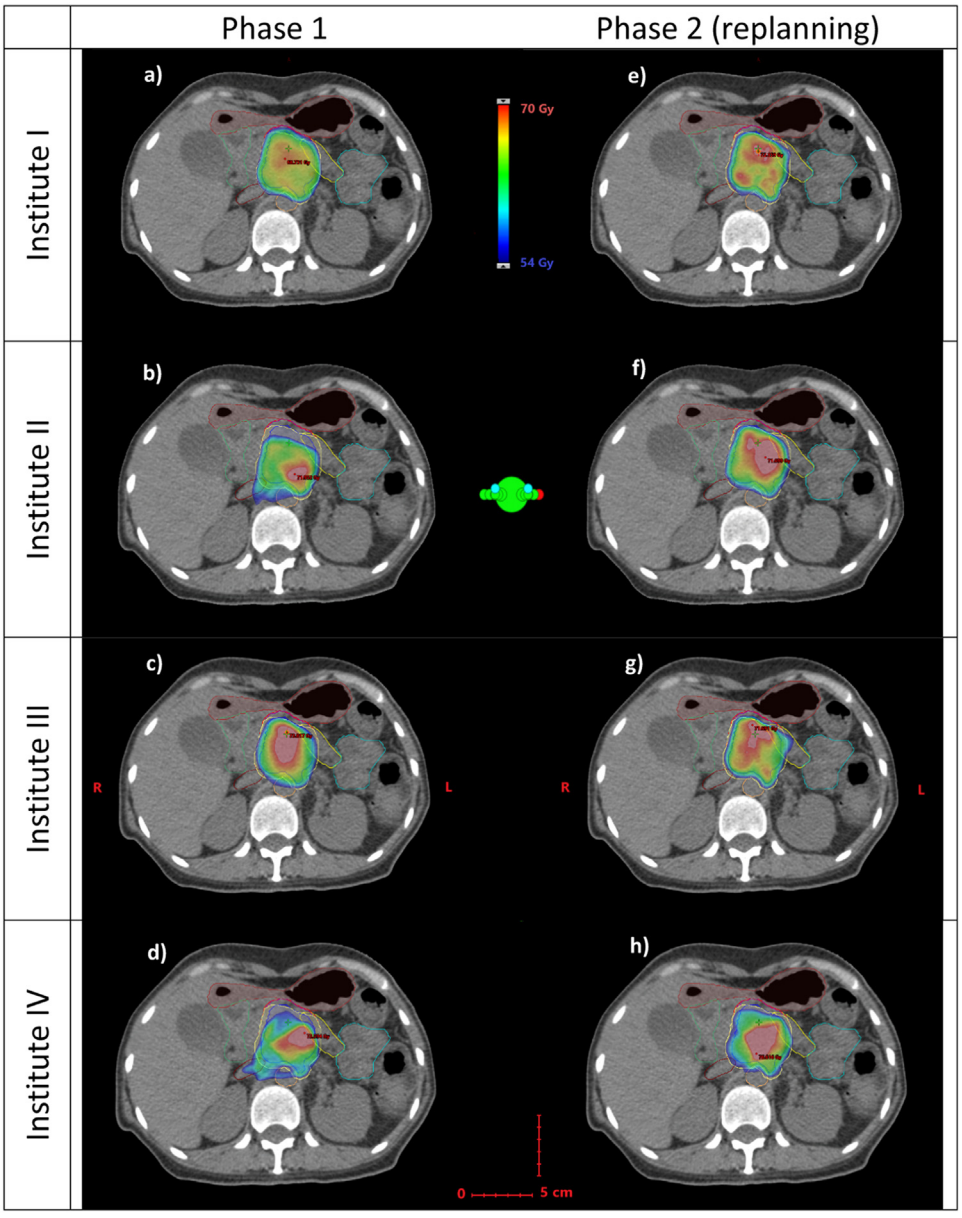

Fig. 4. Illustration of the 54 Gy isodose area of planning target volume near minimum dose ($PTVD_{99\%}$) in phase 1 (left, a-d) and in phase 2 (replanning, right, e-h) for prescription B and patient 2. Images on the same line are from the same institution. At phase 2 (right row) the colored isodose areas (>54 Gy) are clearly more conformal surrounding the PTV, and both plan quality and final score are remarkably better.

required to investigate its benefit. Benchmarking and training are essential to allow for harmonized treatment plan quality within multicenter, multiplatform clinical trials,[13,26] and this is even more important for the complex treatment approaches required for PACA, where close critical organs are radiosensitive.[11,12] SIB/SIP treatment concepts have demonstrated themselves to be valuable for PACA to reduce toxicity and maximize local efficacy,[20-22] but they require different planning strategies as compared with regular stereotactic radiation therapy. To share knowledge, we provide a detailed description of the SIB/SIP concept and best practice guidelines in the supplement, as in previous studies.[17,19]

Although our benchmark study provides the basis for joint trials with SIB/SIP concepts, several issues were highlighted requiring further work and effort to be resolved. Most notably, the $GTV_{D50\%}$ dose prescription requirement was not met within 2% in more than 25% of the cases in the first phase. This is remarkably more than in our previous study on liver SBRT, in which we demonstrated that a GTV median dose ($GTV_{D50\%}$) prescription can harmonize treatment plans slightly better than a PTV surrounding isodose ($PTV_{D98\%}$) prescription.[19] Although there was some recent discussion on the possibility to use this concept in clinical practice,[35,36] for PACA treatment planning with a SIB/SIP concept, a strict $PTV_{D95\text{-}98\%}$ prescription appears to be

impractical, or rather unfeasible, due to overlapping OARs. Because maximum dose prescriptions lead to large plan variability,[19] either a surrounding isodose prescription to the PTV without SIP to fulfill the International Commission on Radiation Units and Measurements report 91 requirements[30] or a GTV median dose prescription may be applied. This requires further investigation. We strongly believe that the GTV median dose may be a better indicator of clinical outcome,[36-40] and hence our benchmark study may also impact clinical practice, even for other indications in which critical organs in close proximity overlap the PTV.

Another issue within our study was noted with the scoring metric that was successfully applied in previous studies.[17-19,33] Although the expert panel's plan ranking generally agreed well with the computed score, some plans were ranked significantly lower by the panel due to underexplored dose in the SIP area and hence comparably lower dose in the nearby GTV part. We tried to overcome the problem that a linear score function cannot properly map this situation by introducing additional penalties; however, the dose sparing in the overlapping organs was still weighted higher than the dose to the GTV, resulting in better scores for plans with low dose in the SIP and SIB areas. A modification of the score function to handle a situation in which dose to specific parts of close OAR is not penalized needs to be investigated in the future. On the other hand, we did not notice any difference in the scores based on equipment similar to previous studies.[17,19] Furthermore, the As Low As Reasonably Achievable concept for distant OARs seems to have been followed more rigorously, yet still not for all cases. We can only once again highlight the As Low As Reasonably Achievable concept as standard clinical practice.

Limitations to this study come from the limited case numbers in the second phase of the study, as only one patient and one prescription was used and not all planners participated in replanning. Furthermore, different treatment delivery and motion monitoring techniques and accuracies, and hence different PTV margins, were not considered. Although it would be highly interesting to investigate the impact of different PTV margins on the SIB/SIP concept for PACA, it would counteract our method of plan evaluation for benchmarking treatment planning. Online adaptive replanning, which may further lead to clinical outcome improvement,[41] was also not considered but may be worth investigating. We investigated 2 fractionation schemes commonly used in our working group, but these are only examples, and the described harmonization method can be applied to all desired fractionation schemes. Lastly, delivery quality assurance and plan robustness[42] for SIB/SIP planning requires future investigation to harmonize complex stereotactic radiotherapy treatments within multicentric, multiplatform clinical trials.

In conclusion, the use of dedicated SIB/SIP concepts in combination with multiparametric prescription requirements and strict dose constraints can lead to overall harmonized and high treatment plan quality for PACA SBRT. The use of standardized SIB/SIP treatment planning in multicenter clinical trials appears to be feasible after benchmarking with study group consensus and training.

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