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Scientific Article

Dosimetric Quality of Online Adapted Pancreatic Cancer Treatment Plans on an MRI-Guided Radiation Therapy System

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Abstract

Purpose: Stereotactic magnetic resonance image−guided adaptive radiation therapy (SMART) is an emerging technique that shows promise in the treatment of pancreatic cancer and other abdominopelvic malignancies. However, it is unknown whether the time-limited nature of on-table adaptive planning may result in dosimetrically suboptimal plans. The purpose of this study was to quantitatively address that question through systemic retrospective replanning of treated on-table adaptive pancreatic cancer cases.

Methods and Materials: Of 74 consecutive adapted fractions, 30 were retrospectively replanned based on deficiencies in planning target volume (PTV) and gross tumor volume (GTV) coverage or doses to organs-at-risk (OARs) that exceeded ideal constraints. Retrospective plans were created by adjusting dose-volume objectives in an iterative fashion until deemed optimized. The goal of replanning was to improve PTV/GTV coverage while keeping the dose to gastrointestinal OARs the same or lower or to reduce OAR doses while keeping PTV coverage the same or higher. The global maximum dose was required to be maintained within 2% of that of the treated adaptive plan to eliminate it as a confounding factor. A threshold of 5% improvement in PTV coverage or 5% decrease in OAR dose was used to define a clinically significant improvement.

Results: Of the 30 replans, 7 obtained at least 5% PTV coverage improvement. The average increase in PTV coverage for these plans was 11%. No plans were clinically significantly improved in terms of OAR sparing. Changes in beam-on time did not show any correlation. Statistical analysis via a linear mixed-effects model with a nested random effect suggested that both GTV and PTV coverage were improved over SMART process plans by 0.91 cc ($P = .02$) and 2.03 cc ($P < .001$), respectively.

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Conclusions: Dosimetric plan quality of at least 10% of SMART fractions may be improved through more extensive replanning than is currently performed on-table. Further work is needed to develop an automated replanning workflow to streamline the in-depth replanning process to better fit into an on-table adaptive workflow.
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Introduction

Stereotactic magnetic resonance image–guided adaptive radiation therapy (SMART) has recently been introduced clinically at several institutions.[1-4] The use of on-board magnetic resonance imaging (MRI) greatly facilitates the adaptation of radiation therapy treatment plans to accommodate daily positional variations in tumors and OARs as well as the spatial relationships between them.[5] However, SMART is subject to stringent time constraints because the patient remains on the table in the treatment position while the plan is adapted. The MRIdian MRI-guided radiation therapy machine (ViewRay, Inc, Cleveland, Ohio) provides a fast replanning workflow in which the plan is adapted by repeating the last optimization on the newly contoured anatomy without changing beam angles or dose-volume objectives. This approach is rapid but could potentially lead to suboptimal adapted treatment plans; in traditional (offline) treatment planning, trial and error adjustment of beam angles and dose-volume objectives is typically required to maximize plan quality.[6] The purpose of this work was to evaluate the extent to which our SMART program's on-table adapted plans for treating pancreatic cancer could be improved by use of an automated planning process. This clinical investigation forms an important component of a comprehensive evaluation of the on-table adaptive process.

Materials and Methods

Description of the MRI-guided radiation therapy process

This institutional implementation of the SMART process has been described in detail previously[2] and is briefly summarized here. After initial patient setup, a high-resolution volumetric MR image is acquired. The ViewRay treatment planning and delivery system (TPDS) deforms normal tissue contours from the initial plan to the newly imaged anatomy. The gross tumor volume (GTV) and/or clinical target volume (CTV) are rigidly propagated. The target and normal-tissue contours are reviewed and adjusted as needed by the physician with the assistance of the adaptive treatment planner. The automatically deformed OAR contours are then manually adjusted on the image slices within the treated volume. To save time, manual correction of the contours is limited to those slices and the organs most at risk of violating constraints: the duodenum, jejunum, and stomach.

The TPDS then predicts the dose that would be delivered to the currently contoured anatomy if the original treatment plan were delivered and displays the corresponding dose volume histograms. If the predicted dose meets constraints defined by the physician, it is delivered. If constraints are violated, the TPDS is then used to reoptimize the plan by repeating intensity modulated radiation therapy (IMRT) optimization with the same beam angles and dose-volume objectives as the initial plan but with updated contours reflecting the changed anatomy. If the reoptimized plan is deemed acceptable by the physician, patient-specific plan quality assurance is performed, followed by treatment delivery. If dose constraints are not met, adaptive planning is triggered. This involves adjustment of the dose volume objectives followed by reoptimization until dose constraints are satisfied. Large changes to the original plan are avoided because this may unreasonably increase the beam-on time or stray too far from original plan objectives for other structures.

Our institution's dose constraints for pancreatic cancer SMART are listed in Table 1. Potentially dose-limiting OARs include the duodenum, jejunum, and stomach. In evaluating the plan for delivery, the institutional dose constraints require that less than 0.5 cc each of the duodenum, jejunum, and stomach receive a dose of 35 Gy. The normal prescription used in this study was 95% of the planning target volume (PTV) covered with 40 Gy or more. Coverage of the PTV was sometimes compromised to allow for sparing of the OARs within the constraints mentioned. A lower prescription dose of 35 Gy, and in some cases, 33 Gy, was used to achieve an acceptable plan. The constraint of 35 Gy to OARs was also relaxed to 1.0 cc in other cases. Other structures that might also play a role in determining plan quality for pancreatic targets, include the kidneys, liver and spinal cord.

Table 1 Organ-at-risk constraints used in on-table adaptive treatment planning of the pancreas

Organ at Risk	Volume	Dose (Gy)
Duodenum	< 0.5 cm^3	< 35
Jejunum	< 0.5 cm^3	< 35
Stomach	< 0.5 cm^3	< 35
Liver	>1000 cm^3	< 15
Kidneys	$< 20\%$	< 17.5
Spinal cord	< 0.35 cm^3	< 23

Given the limited experience with our online adaptive program, our approach to online adaptive planning was based on established programs.[1-4] As we have gained experience in the use of SMART for the treatment of pancreatic cancer, adjustments have been made, leading to the standards we now use.

The ViewRay system is capable of more in-depth plan adaptation, including more extensive changes in dose-volume objectives, but this is rarely performed owing to the increased chance that an extended planning time would be required to achieve the same goals as the original plan. If critical structure constraints are still exceeded after fast reoptimization, the plan is often normalized to the OAR constraint, compromising target coverage to achieve acceptable critical-structure doses. Although this is a quick and simple way to achieve OAR sparing to prescribed constraints, it often results in less than ideal target coverage. Ultimately, the balance between target coverage and OAR sparing, as well as the decision to treat or not to treat, are determined by the physician.

Retrospective replanning

The adapted fractions of the first 28 consecutively treated patients with pancreatic cancer to be treated with SBRT at our institution were reviewed. The number of adapted fractions was 74, and patients were treated using the Co-60 version of the MRIdian.[1,7-10] From the 74 adaptive plans, 30 were chosen for in-depth replanning based on target coverage that was less than prescription goals. These plans were retrospectively replanned without adjusting contours and were limited to adjustment of dose-volume objectives, similar to online replanning. Objectives in the TPDS are given as threshold doses and the relative importance for each target or risk structure, which were summed over all voxels belonging to the structure to form the objective function. The importance is a weighting factor, relative to other planning objectives, to achieve the associated dose threshold. Adjustments in the importance, and sometimes the threshold, were used in attempts to achieve an improved plan. Beam-on time was also monitored and kept to within 5% of the beam-on time of the adaptive-delivered plan. Time spent replanning was 1 to 5 hours per plan by an experienced planner. Several cases required more time to plan to satisfy all required criteria for an acceptable replan.

During the adaptive process, the TPDS system allows for adjustment of several optimization parameters, including IMRT efficiency. Major adjustments like this can change the character of the plan, so these adjustments were avoided in our process. Adjusting these more complex parameters could drastically change the beam-on time of the plan, making it difficult to actually deliver in the clinic. Lowering the IMRT efficiency might improve dose distribution but could increase the beam-on time to something that could not be feasibly delivered in the clinic. The intricate balance established to achieve an acceptable beam-on time during offline planning would be difficult to re-establish during online adaptive planning.

Primary plan-evaluation metrics for this study were the same as those used in the established SMART process, namely target coverage as specified in the initial plan and the volume of the duodenum, jejunum, and stomach receiving 35 Gy (V35), as shown in Table 1. The goal of replanning was to improve one or more primary evaluation metrics without degrading any of the others. A threshold of 5% improvement in PTV coverage or 5% decrease in OAR dose was used to define a clinically significant improvement. Because OAR sparing was nearly always the limiting factor at the cost of PTV coverage, improvement in PTV coverage while keeping OAR doses the same resulted as the main goal in replanning.

This institution's clinical SMART protocol did not place a specific constraint on the global maximum dose, but replans in this study were constrained to have a global maximum dose that was held within 2% of the treated plan. This was done to avoid the maximum dose from becoming a confounding factor in plan quality. Initially, many plans were thought to be improved when the global maximum was allowed to increase. This was thought to be an unfair comparison. As a general rule, OAR doses can be decreased by allowing an increased global maximum dose, representing a different planning tradeoff but not necessarily a better overall plan. Our goal was to maintain as fair a comparison as possible. For this reason, beam-on time for the retrospective plans was kept within 5% of the adaptive plan from which they were derived.

Secondary evaluation metrics included doses to the kidneys, liver, and spinal cord. Replans were required to avoid increasing the dose to these organs above conservative limits used in the clinical SMART process (Table 1). A successful replan was defined as a plan with an increase in PTV coverage or a decrease in the OAR maximum dose of at least 5% without increasing duodenum, jejunum, or stomach V35 and leaving other OAR doses unchanged.

To understand the quality of the implemented plan, the relationship between the measured GTV/PTV volume and the type of radiation plan scheme (retrospective adaptive/SMART process as a reference) was assessed via a linear mixed-effects model (LMM) with a nested random effect to account for within-subject and within-fraction correlation. Similarly, the relationship between the volume change from the implementing retrospective adaptive plan and the total volume for the GTV/PTV was evaluated via LMM with the random effect to account for within-subject correlation. The significance level was set at $P < .05$. All analyses were conducted with R statistical

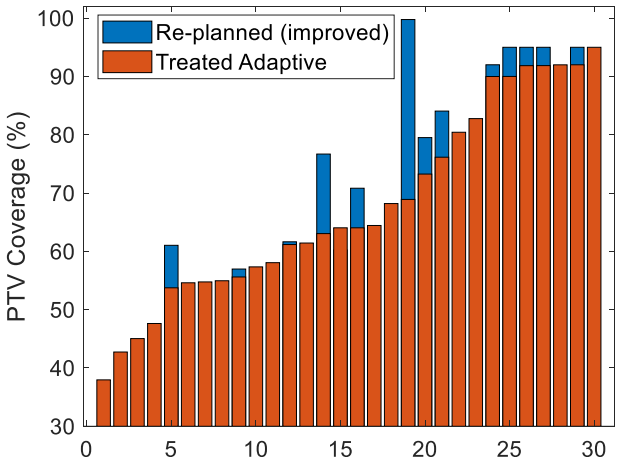

Figure 1 Histogram of planning target volume coverage of the 30 replanned cases showing improvement in coverage from the online adaptive plan. Only a small number were improved to a clinically significant degree regardless of coverage at time of treatment.

software, version 3.6.0,[11] with packages lme4[12] and lmerTest.[13]

Results

From the 30 fractions that were replanned, 7 showed an increase of at least 5% in PTV coverage (mean, 11.1%; range, 5.0%-30.9%). No replans were successful in terms of reducing OAR dose without decreasing PTV coverage. The PTV coverages of all 30 replanned fractions before and after replanning are shown in Figure 1. Overall, the PTV coverage before replanning was less than desired, with a majority of the plans achieving less than 80% PTV coverage. This was considerably less than was achieved in the original off-line pretreatment plans. The primary plan-evaluation metrics for the 7 plans that were improved by replanning are shown in Table 2. In all cases, the percentage change in volume for both coverage and sparing was calculated as a percentage of the total

Table 2 Primary plan evaluation metrics for the 7 treated adaptive plans that were improved by retrospective replanning

Case #		Dose (Gy)	Treated adaptive		Replanned		Change (%)
			Vol (%)	Vol (cm^3)	Vol (%)	Vol (cm^3)	
1	PTV	40	90	14.7	95	15.5	5.0
	GTV	40	100	6.6	99.5	6.6	−0.5
	Duodenum	35	1.8	1.9	2.4	2.6	0.6
	Stomach	35	0.0	0.0	0.0	0.0	0.0
2	PTV	40	64.0	53.0	70.8	58.6	6.8
	GTV	40	95.9	39.4	96.0	39.5	0.1
	Duodenum	35	0.78	1.0	0.41	0.51	−0.2
	Stomach	35	0.0	0.0	0	0	0.0
3	PTV	40	63.1	60.2	76.7	73.2	13.6
	GTV	40	87.9	49.6	94.0	53.0	6.1
	Jejunum	35	0.2	0.2	0.5	0.4	0.3
	Stomach	35	0.2	0.7	0.2	0.9	0.0
4	PTV	40	73.3	72.5	79.5	78.6	6.3
	GTV	40	91.0	57.4	91.0	57.4	0.0
	Jejunum	35	1.3	1.3	1.4	1.4	0.1
	Stomach	35	0.1	0.5	0.1	0.6	0.0
5	PTV	40	53.8	59.3	61.0	67.3	7.3
	GTV	40	90.0	45.7	93.0	47.2	8.0
	Duodenum	35	0.4	0.4	0.5	0.5	0.1
	Stomach	35	0.1	0.2	0.0	0.0	-0.8
6	PTV	33	68.9	58.6	99.8	84.8	30.9
	GTV	33	82.4	45.7	100.0	55.4	16.6
	Duodenum	35	1.4	1.0	1.0	0.4	−0.9
	Stomach	35	0.0	0.0	0.0	0.0	0.0
7	PTV	33	76.2	41.4	84.1	45.7	7.9
	GTV	33	87.5	27.4	98.5	30.8	11.0
	Jejunum	35	0.3	0.5	0.3	0.5	0.0
	Stomach	35	0.0	0.0	0.0	0.0	0.0

Abbreviations: GTV = gross tumor volume; PTV = planning target volume.

Table 3 Change in beam-on times from original (pre-treatment) plan to on-table adaptive plan on a tri-head Cobalt-60 gantry

Case #	Beam-on times, s		% Δ
	Original plan	Adaptive plan	
1	1814.0	1586.4	12.5
2	1873.5	2281.5	−21.8
3	2292.0	1702.0	25.7
4	2292.0	1764.6	23.0
5	2000.7	1983.8	0.8
6	1574.5	1344.6	14.6
7	1608.2	1802.9	−12.1

volume of the structure as contoured in the adapted plan. Overall, including all 30 plans, PTV coverage improved by a mean of 6.2%, whereas GTV coverage improved by a mean of 3.0%.

Although beam-on time was allowed to vary for on-table adaptive plans during SMART, it was not allowed to render the plan undeliverable. Changes in beam-on times showed no correlation in the 7 most improved plans (Table 3), whereas beam-on times for retrospective plans were held to 5% of the adapted plans from which they were derived.

Statistical analysis for GTV and PTV volume coverage using LMM suggested that the retrospective adaptive plan resulted in higher quality in terms of volume of coverage. For both GTV and PTV, the retrospective adaptive plan was found to correspond to greater volume than the SMART process by 0.91 cc ($P = .02$) and 2.03 cc ($P < .001$), respectively (Table 4). No significant association was identified between change in volume from the implementing retrospective adaptive plan and the total volume for GTV and PTV (Table 5).

Table 4 Linear mixed-effects model results for effect of type of plan (retrospective adaptive and SMART process as reference) on GTV/PTV volume change

	Estimate	Standard error	*P* value
GTV			
(Intercept)	38.48	4.38	<.001
Retrospective adaptive vs SMART process	0.91	0.38	.02
PTV			
(Intercept)	57.41	7.53	<.001
Retrospective adaptive vs SMART process	2.03	0.58	<.001

Abbreviations: GTV = gross tumor volume; PTV = planning target volume; SMART = stereotactic magnetic resonance imaging−guided adaptive radiation therapy.

Table 5 Linear mixed-effects model results of the effect of GTV and PTV total volume on the change in volume coverage from retrospective adaptive plan

	Estimate	Standard error	*P* value
GTV			
(Intercept)	0.95	0.81	.25
GTV total volume	0.00	0.02	.98
PTV			
(Intercept)	0.97	1.40	.50
PTV total volume	0.01	0.01	.34

Abbreviations: GTV = gross tumor volume; PTV = planning target volume; SMART = stereotactic magnetic resonance imaging−guided adaptive radiation therapy.

Discussion

The results imply that at a minimum, approximately 10% of treated adaptive plans could be improved at a clinically significant level by further replanning efforts that could not be afforded while the patient was on the table. The threshold of 5% improvement in PTV coverage was considered as what, to a physician, would be an acceptable improvement to justify the effort in replanning. In some cases, this improvement could be dramatic. Case 6 (Table 2) showed the most improvement. PTV coverage increased from 68.9% to 99.8%, and GTV coverage increased from 82.4% to 100%. The original plan was prescribed to 33 Gy covering 95% of the PTV. Figure 2 shows the dose volume histograms of the treated adaptive plan and the replan. It is noteworthy that our institution's clinical SMART pancreas protocol requires quantitative evaluation of gastrointestinal OAR doses exclusively in terms of the volume receiving 35 Gy. Also, overlap of the PTV and OARs was known to affect the resulting coverage of the PTV, resulting in PTV coverage of 70% or less. Time during the adaptive process was not

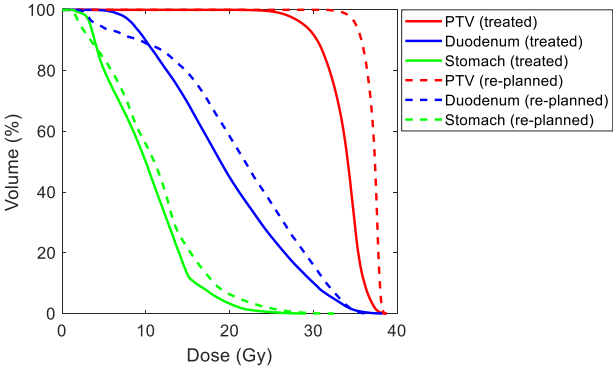

Figure 2 Comparison of dose volume histograms (DVHs) before and after replanning of the most improved case.

used to address the overlap. Instead, GTV coverage instead of PTV was considered in determining the acceptability of the adaptive plan. Although replanning improved PTV coverage and kept the OAR V35 constant, it increased the OAR mean dose in case 6. This case would still be regarded as a superior plan according to the clinical SMART pancreas protocol used. A threshold of 40 Gy covering 95% of the PTV is typically the criteria for an acceptable plan to the pancreas. Compromises to the PTV dose were made to spare the OAR adequately to 35 Gy. In some cases, the prescribed dose was lowered to 33 Gy. This was done to allow for adequate sparing of OARs that overlapped the PTV. Possible correlation was observed between these prescription-adjusted plans and the likelihood that offline replanning might improve coverage because 2 of 4 33-Gy plans improved versus 5 of the 26 40-Gy plans. However, the difference in coverage improvement between the 33-Gy and the 40-Gy plans was not statistically significant according to the 2-sample unequal variance t test (Welch test) ($P = .36$).

It is notable that given the time spent in offline replanning of the adapted fractions, it was very difficult to find occasions in which an improved quality plan was possible. This suggests that movement of anatomy between fractions may not be enough to allow an appreciable improvement in plan quality. On the contrary, changes in anatomy could also degrade the achievable quality of a deliverable plan.

Limitations of this study include the following: First, because only 30 of the 74 consecutive treated adaptive plans evaluated were replanned in-depth, efforts were only able to set a lower bound on the proportion of adaptive plans one might expect to improve with in-depth replanning. Second, patients included in this study were treated with the Co-60 version of the MRIdian. It is possible that results would be different if the LINAC version of the MRIdian were used. Third, only pancreatic cancer cases were studied. Results might be different for other anatomic sites depending on OARs and their proximity to the PTV.

This work highlights a challenge to SMART in that for a small but not negligible fraction of cases, the on-table adaptive plan produced at the time of treatment may be dosimetrically suboptimal. In-depth replanning is not feasible in the on-table adaptive environment. However, these results indicate that there is a need for a quick on-table adaptive planning method using automated planning,[14,15] knowledge-based planning,[16-23] and/or multicriteria optimization[24,25] because these techniques have been shown to reduce planning times. These future developments are beyond the scope of this work. However, it is believed this data-driven exposure of the clinical challenge presented here is of value in reiterating the need for these developments and how important they are in improving patient care.

Conclusions

On-table adaptive planning in the context of a clinical setting is restricted in that the patient must wait while adaptive planning is performed. This study showed that a number of adaptive plans, although relatively few, could be improved. Overall, statistical analysis using LMM showed increases in both PTV and GTV coverage. Improved PTV coverage of $\geq$5% was found in 10% of the on-table adaptive cases investigated. These results advance the imperative need for further developments in online adaptive planning that can perform well within the restrictions of on-table adaptive planning in real-time.

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