Advances in Radiation Oncology (2023) 8, 101164

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Dose Escalation for Pancreas SBRT: Potential and Limitations of using Daily Online Adaptive Radiation Therapy and an Iterative Isotoxicity Automated Planning Approach

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Received 29 November 2022; accepted 23 December 2022

Abstract

Purpose: To determine the dosimetric limitations of daily online adaptive pancreas stereotactic body radiation treatment by using an automated dose escalation approach.

Methods and Materials: We collected 108 planning and daily computed tomography (CT) scans from 18 patients (18 patients × 6 CT scans) who received 5-fraction pancreas stereotactic body radiation treatment at MD Anderson Cancer Center. Dose metrics from the original non-dose-escalated clinical plan (non-DE), the dose-escalated plan created on the original planning CT (DE-ORI), and the dose-escalated plan created on daily adaptive radiation therapy CT (DE-ART) were analyzed. We developed a dose-escalation planning algorithm within the radiation treatment planning system to automate the dose-escalation planning process for efficiency and consistency. In this algorithm, the prescription dose of the dose-escalation plan was escalated before violating any organ-at-risk (OAR) dose constraint. Dose metrics for 3 targets (gross target volume [GTV], tumor vessel interface [TVI], and dose-escalated planning target volume [DE-PTV]) and 9 OARs (duodenum, large bowel, small bowel, stomach, spinal cord, kidneys, liver, and skin) for the 3 plans were compared. Furthermore, we evaluated the effectiveness of the online adaptive dose-escalation planning process by quantifying the effect of the interfractional dose distribution variations among the DE-ART plans.

Results: The median $D_{95\%}$ dose to the GTV/TVI/DE-PTV was 33.1/36.2/32.4 Gy, 48.5/50.9/40.4 Gy, and 53.7/58.2/44.8 Gy for non-DE, DE-ORI, and DE-ART, respectively. Most OAR dose constraints were not violated for the non-DE and DE-ART plans, while OAR constraints were violated for the majority of the DE-ORI patients due to interfractional motion and lack of adaptation. The maximum

Sources of support: This work was supported by a grant from The University of Texas MD Anderson Cancer Center, Division of Radiation Oncology.

Disclosures: 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.

Research data are not available at this time.

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https://doi.org/10.1016/j.adro.2022.101164

difference per fraction in $D_{95\%}$, due to interfractional motion, was 2.5 ± 2.7 Gy, 3.0 ± 2.9 Gy, and 2.0 ± 1.8 Gy for the TVI, GTV, and DE-PTV, respectively.

Conclusions: Most patients require daily adaptation of the radiation planning process to maximally escalate delivered dose to the pancreatic tumor without exceeding OAR constraints. Using our automated approach, patients can receive higher target dose than standard of care without violating OAR constraints.

Introduction

Pancreatic cancer has poor overall survival rates owing to early metastasis and its intrinsic treatment resistance.[1] Currently, surgery is the only curative approach for pancreatic cancer, but only about 10 to 15% of patients are eligible for surgical resection at diagnosis.[2,3] Patients with locally advanced pancreatic cancer (LAPC) patients have tumors that cannot be safely resected because of excessive tumor contact with blood vessels. In some LAPC patients, stereotactic body radiation treatment (SBRT) may provide sufficient tumor control for subsequent downstaging of tumors and thus make them eligible for surgery.[4]

Although a higher biological effective dose (BED) to the primary tumor may improve LAPC outcomes,[5] the prescription dose for pancreatic SBRT is restrained by the nearby radiosensitive organs at risk (OARs) (ie, small and large bowel, duodenum, and stomach), and limitations in image guidance techniques. Furthermore, as the interfractional motion of the abdominal OARs can usually exceed a few centimeters,[6] small inaccuracies in patient positioning can result in large localization errors in high-dose gradients near the target/OAR interface, ultimately affecting outcomes. Consequently, the verification of tumor and OAR positions before each treatment becomes a standard procedure for pancreas SBRT. Therefore, the ability to achieve higher BED to pancreas tumors is dependent on precise image guidance.

One method to obtain higher tumor BED is to use daily online adaptive radiation therapy (ART), wherein a radiation treatment plan is created and treated based on the anatomy of the day.[7-9] While trials have begun to examine the efficacy of daily ART for pancreas SBRT,[10] this approach is a new concept and has not received widespread clinical adoption. Moreover, the limits of achievable dose escalation using isotoxicity approach for treating pancreas cancer, as well as patient-specific dose-escalation variations and characteristics within these cohorts, have not been elucidated.

The aim of this study was to determine the amount of dose escalation achievable using an automated daily online adaptive SBRT approach for pancreas cancer. Moreover, we aimed to examine patient-to-patient variations and effect of daily image guidance on achievable dose escalation for pancreas SBRT. To accomplish this, we used an automated approach to generate dose escalated pancreas SBRT plans using diagnostic quality computed tomography (CT)-on-rails (CTOR) imaging acquired immediately before delivery of pancreas SBRT.[11-13] CTOR is a standard diagnostic CT scanner installed in the treatment room, and it has a good image quality owing to the use of an imaging fan beam and, therefore, reduces scatter.[14] The image-guided treatment workflow with CTOR is almost identical to that with cone-beam CT (CBCT).[12] We compared our method to both standard-of-care and dose escalation without incorporating daily online adaptation to determine the amount of achievable dose escalation for pancreas SBRT as well as the effect of daily versus nondaily adaptation on target and OAR doses.

Methods and Materials

Patient data

This study is a retrospective analysis of 18 retrospective patients with borderline resectable or LAPC who were treated with SBRT at the University of Texas-MD Anderson Cancer Center. Patients were treated with prescription doses of 33 to 40 Gy in 5 fractions via step-and-shoot intensity modulated radiation therapy (IMRT). Fan-beam CT scan from a CTOR system (GE HealthCare, Milwaukee, WI) was acquired at each fractionation for every patient; therefore, 6 CT scans (1 planning CT scan and 5 CTOR scans from each treatment fraction) were available for each patient. All the CTOR scans were acquired with the breath-hold technique without iodinated contrast.

Target volumes and OARs

Both the gross tumor volume (GTV) and the tumor vessel interface (TVI) were manually contoured on every CT scan and verified by an experienced radiation oncologist. The planned target volume for the dose-escalated planning target volume (DE-PTV) was defined to be the sum of the GTV and the TVI contours with a 3-mm uniform margin. We also generated the contours for 9 OARs (stomach, small bowel, large bowel, duodenum, spinal cord, left and right kidneys, liver, and skin) in the abdominal region. The OAR contours were automatically generated using an in-house deep-learning-based auto-

contouring system[15] and were subsequently reviewed and edited by experienced medical physicists. The skin contour was defined to be the 2-cm thick internal ring from the surface of the body.

We defined the hard dose constraints[16,17] for the OARs to determine whether an automatically optimized plan was clinically acceptable and if we could continue escalating the prescription dose. The dose constraints for the OARs are summarized in Table E1. Most importantly, the maximum dose (D_{max}), dose at 1 cc ($D_{1.0cc}$), dose at 10 cc ($D_{10.0cc}$), and dose at 30 cc ($D_{30.0cc}$) to the luminal OARs (large and small bowels, duodenum, and stomach) must be less than 40, 35, 30, and 20 Gy, respectively. The dose constraint for the skin was used to avoid excessively high monitor units from select few gantry angles. There were no hard dose constraints for the targets in this study; instead, the dose constraints for the targets in the IMRT objective function were increased over each optimization process if all the OAR dose constraints were satisfied.

Plan generation

Three radiation treatment plans were generated on each CT scan: the original clinical plan without dose escalation on the planning CT (non-DE), the dose-escalated plan created on the original planning CT (DE-ORI), and the dose-escalated plan created on the daily ART (DE-ART) CTOR image. Each plan generation process is demonstrated in Figure 1B. The clinical SBRT non-DE plans on the planning CT were used for actual patient treatment in the past. The DE-ORI plans were initially generated in the planning CTs using the automatic dose-escalation planning algorithm. For non-DE and DE-ORI plans, the isocenter was repositioned to match the target on the daily CTOR image, and the dose was recalculated with the updated isocenter. DE-ART plans were generated on each daily CTOR image using the automation algorithm without any prior information.

Automation algorithm for dose-escalation plans

To automatically generate the dose-escalation plans, the scripting feature was used in RayStation version 10 (RaySearch Laboratories, Stockholm, Sweden). We initially created 9 step-and-shoot IMRT beams (0, 40, 80, 120, 160, 200, 240, 280, and 320° gantry angles) and set the dose constraints for OARs described in Table A1, which are the hard dose constraints to determine plan quality. The OAR dose goals in the IMRT objective function (ie, soft dose constraints) for the optimization process were defined to be slightly tighter than the hard dose constraints. The initial prescription dose was 36 Gy for the 3 targets (GTV, TVI, DE-PTV). The weights of the D_{max} goals for the targets were lower than those for the minimum dose goals, as dose inhomogeneity within the targets was not a concern in this study.

With the templated beams and the dose constraints, the dose escalation algorithm demonstrated in Figure 1A was initiated. First, the plan undergoes an initial optimization process, and the algorithm checks if all the dose constraints are achieved. If all the dose constraints are achieved, the dose goals for the targets are increased by 100 cGy, and the plan is reoptimized with the new goals. If the dose constraints are not achieved, the 35 Gy isodose volumes within the luminal OARs (ie, small and large bowels, duodenum, and stomach) and the skin are converted into "hotspot" structures, dose goals on the hotspot structures are added to the IMRT objective function, and the plan is reoptimized. The algorithm was continued until the dose constraints were not satisfied for 3 iterations consecutively.

Plan evaluation

Once the plans were created and fractional doses were calculated on each daily CT image, we estimated cumulative dose metrics delivered to the patient. Similar to a previous study, cumulative dose metrics were estimated by accumulating the dose-volume histograms of each region of interest by summing the daily fractional dose-volume histograms and extracting the dose metric of interest.[11]

We evaluated the plans based on the following dose metrics. For target structures (GTV, TVI, etc), we assessed the minimum dose to 10, 50, 80, 90, 95, and 98% of the target volume ($D_{10\%}$, $D_{50\%}$, $D_{80\%}$, $D_{90\%}$, $D_{95\%}$, and $D_{98\%}$, respectively) as well as the D_{max}. For the luminal OARs, D_{max}, the highest dose in 1.0-cc subvolume ($D_{0.1cc}$), $D_{0.3cc}$, $D_{1.0cc}$, $D_{3.0cc}$, and $D_{9.0cc}$ were assessed. D_{max} and $D_{50\%}$ were assessed for the liver and kidneys, respectively, and $D_{25\%}$ was assessed for both liver and kidneys. D_{max} was assessed for the spinal cord and skin.

Additionally, we analyzed the variations in the dose metrics in each fractionation of the DE-ART plan because of interfractional organ motion. These variations were quantified by the maximum differences in $D_{95\%}$ of the targets and $D_{1.0cc}$ of the luminal structures of a patient during the 5-fraction treatment.

Statistical analysis

To compare the dose metric differences between the DE-ORI and DE-ART plans in the targets and the luminal OARs, a 2-sided paired Wilcoxon signed-rank test was used. P values of <0.05 were selected to show statistical

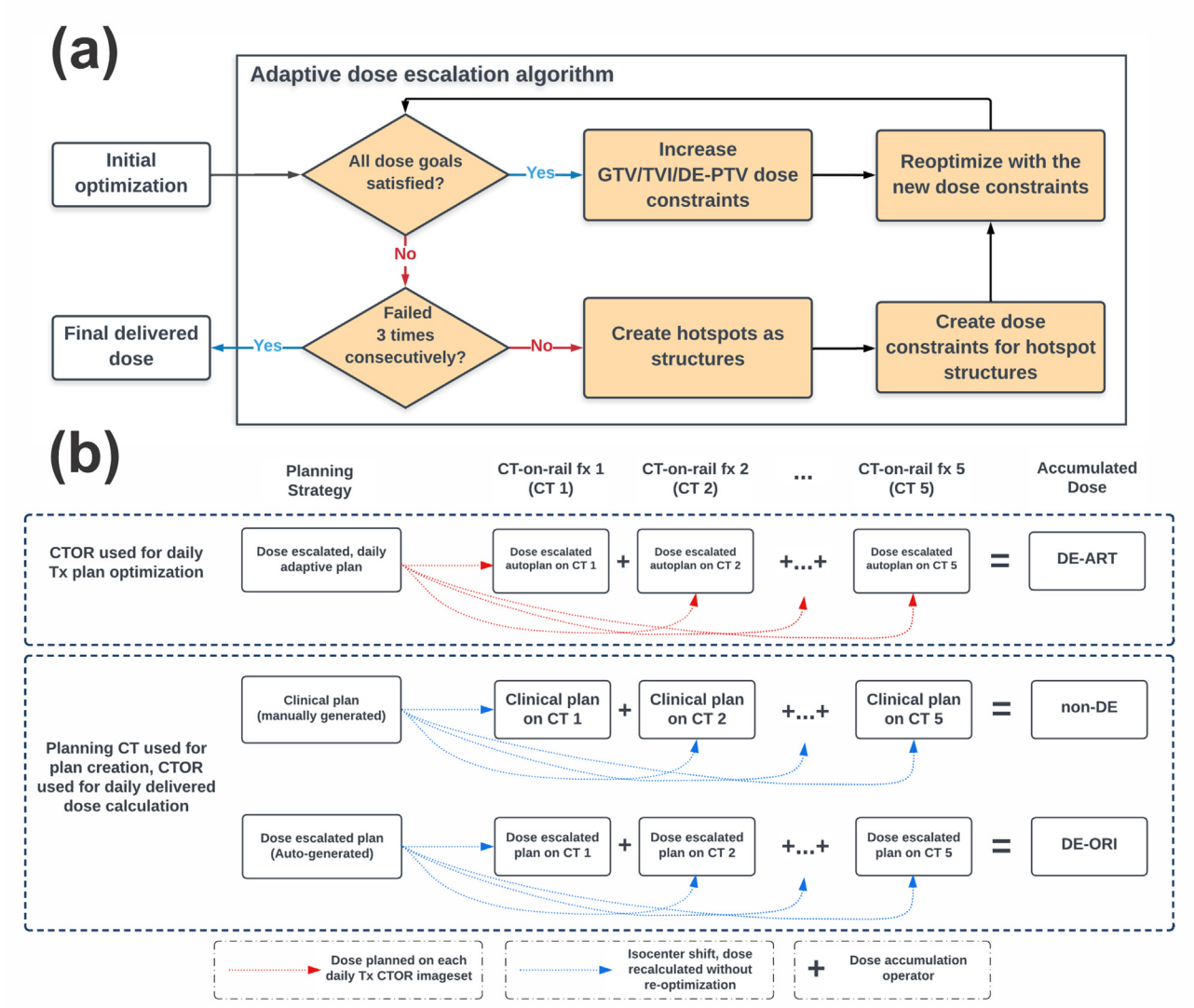

Figure 1 a, Flow chart of the automatic dose escalation plan generation algorithm. b, Flow chart of the non-dose-escalated plan (non-DE), dose-escalated plan created on the original planning CT (DE-ORI), and dose-escalated plan created on daily adaptive radiation therapy CT (DE-ART) generation process. *Abbreviations:* CT = computed tomography; CTOR = CT-on-rails; DE-PTV = dose-escalated planning target volume; GTV = gross tumor volume; TVI = target vessel interface; Tx = treatment.

significance. All statistical analysis were conducted with python SciPy package (version 1.7.3).[18]

Results

Plan comparison

The dose metrics were compared between the non-DE, DE-ORI, and DE-ART plans, as shown in the boxplots in Figures 2 and 3. The non-DE plans did not exceed the dose constraints for all the structures, as the prescription dose was initially lower than most of the dose constraints. For the DE-ORI plans, the median target coverages were substantially improved from the non-DE plans, and the dose constraints for the spinal cord, kidneys, and liver were achieved. However, the median D_{max} and $D_{1.0cc}$ to the duodenum were 50.4 and 35.9 Gy, respectively, which exceeded the dose constraints of 40 and 35 Gy, respectively. For the DE-ART plans, the median target coverages were even higher than those of the DE-ORI plans. The median $D_{95\%}$ for the GTV, TVI, and DE-PTV were increased by 5.2, 7.3, and 4.4 Gy, respectively, and the median $D_{80\%}$ for the GTV, TVI, and DE-PTV were increased by 4.3, 5.9, and 4.3 Gy, respectively. Furthermore, OAR dose constraints were achieved for all except

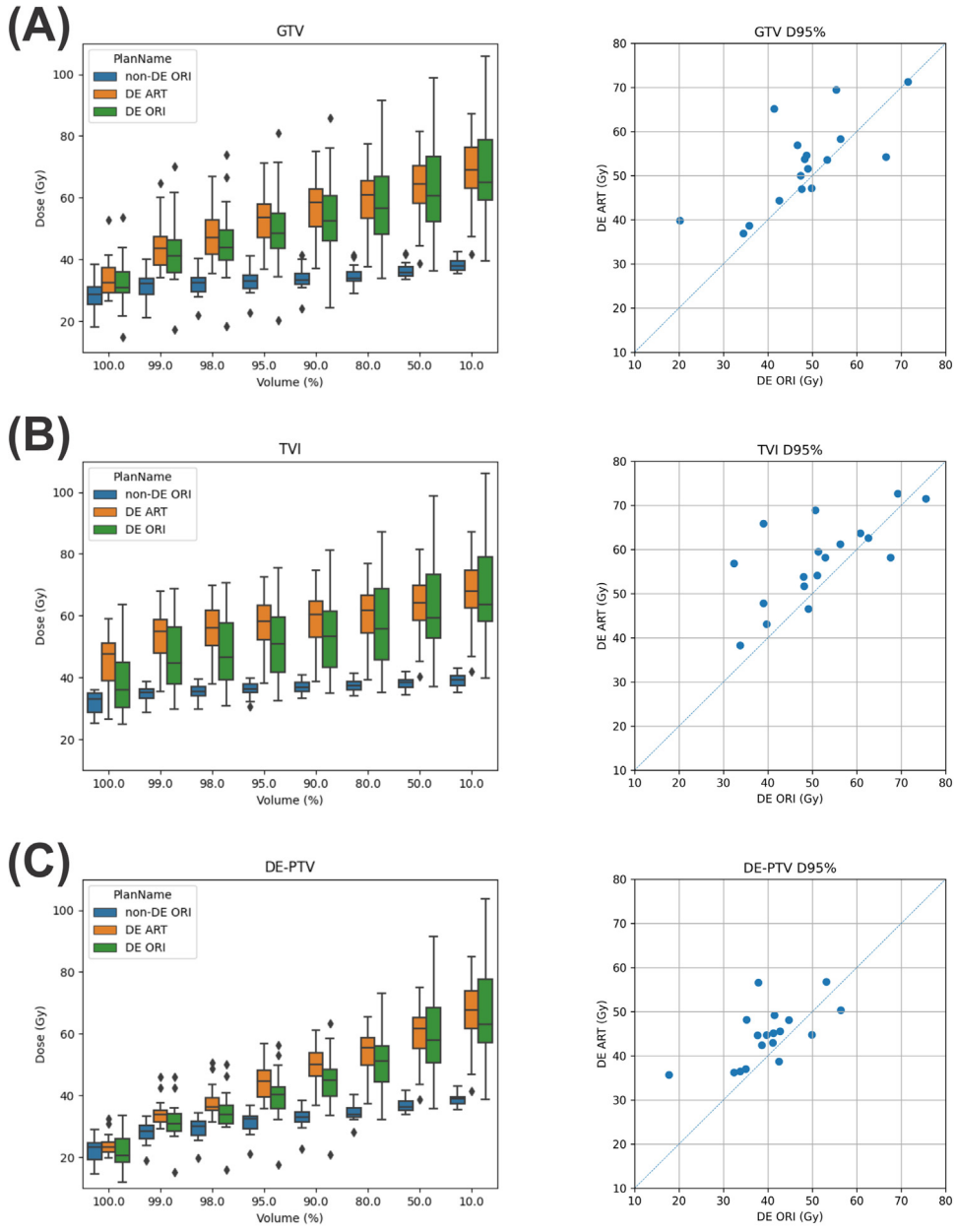

Figure 2 The cumulative dose metrics for the A, gross target volume (GTV); B, tumor vessel interface (TVI); and C, dose-escalated planning target volume (DE-PTV) for the non-dose-escalated plan (non-DE), the dose-escalated plan created on the original planning CT (DE-ORI), and the dose-escalated plan created on daily adaptive radiation therapy CT (DE-ART) are illustrated with boxplots. Right panels show scatter plots for $D_{95\%}$ of the targets from the DE-ORI and DE-ART plans.

for 1 patient who had the duodenum D_{max} of 40.6 Gy. Further details of the dose metrics of the targets and the luminal structures for the DE-ORI and DE-ART plans are demonstrated in Tables 1 and 2.

For the other OARs, the average D_{max} of the spinal cord was 17.7 ± 5.9 Gy for DE-ORI and 15.4 ± 5.2 Gy for DE-ART. The average D_{max} and $D_{50\%}$ of the liver were 34.5 ± 14.4 Gy and 0.7 ± 0.5 Gy, respectively, for DE-ORI and 33.4 ± 12.4 Gy and 0.7 ± 0.6 Gy, respectively, for DE-ART. The average $D_{25\%}$ for the kidneys was 4.81 ± 3.05 Gy for DE-ORI and 4.71 ± 2.88 for DE-ART. Lastly, the average D_{max} skin dose was 30.7 ± 6.1 Gy for DE-ORI and 31.0 ± 4.2 Gy for DE-ART.

Interfractional variation for dose-escalation plans

The effect of the interfractional variation of the targets and the OARs was assessed for the targets and the

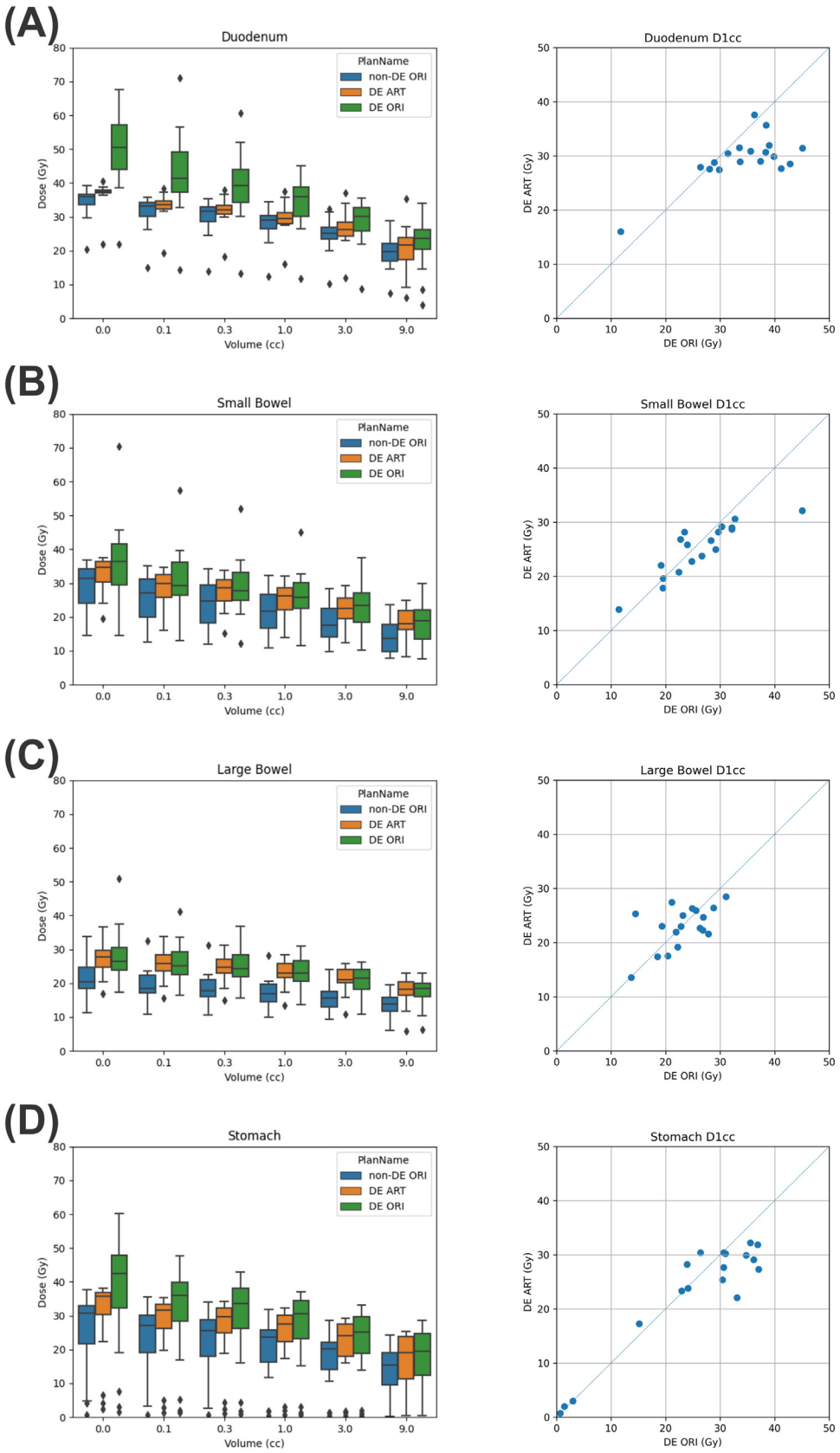

Figure 3 The cumulative dose metrics for the luminal organs at risk (OARs) including the A, duodenum; B, small bowel; C, large bowel; and D, stomach for the non-dose-escalated plan (non-DE), dose-escalated plan created on the original planning CT (DE-ORI), and dose-escalated plan created on daily adaptive radiation therapy CT (DE-ART) are visualized with box-plots. $D_{1.0cc}$ of the luminal OARs from the DE-ORI and DE-ART plans are illustrated with scatter plots.

Table 1 Dosimetric comparison of DE-ORI versus DE-ART to the targets for 18 patients

Structure and dose metrics	Median dose for non-DE, Gy (range)	Median dose for DE-ORI, Gy (range)	Median dose for DE-ART, Gy (range)	DE-ART minus DE-ORI	*P* value
GTV					
$D_{100\%}$	28.7 (18.1-38.5)	30.9 (15.0-53.7)	32.4 (26.7-52.8)	1.5	.212
$D_{99\%}$	32.2 (21.3-40.1)	41.1 (17.4-70.0)	43.6 (34.1-64.8)	2.5	.167
$D_{98\%}$	32.6 (21.8-40.4)	44.0 (18.5-73.8)	47.0 (35.6-66.7)	3.0	.154
$D_{95\%}$	33.1 (22.9-41.1)	48.5 (20.2-81.1)	53.7 (36.9-71.3)	5.2	.074
$D_{90\%}$	33.4 (24.2-41.4)	52.5 (24.5-85.7)	58.4 (37.2-75.1)	5.9	.048
$D_{80\%}$	33.8 (29.1-41.6)	56.7 (33.8-91.4)	61.0 (37.6-77.5)	4.3	.081
$D_{50\%}$	35.8 (33.5-41.9)	60.6 (36.3-98.9)	64.4 (38.7-81.4)	3.8	.347
$D_{10\%}$	37.9 (35.5-42.7)	64.9 (39.5-106.0)	69.1 (41.7-87.2)	4.2	.865
V35Gy	0.66 (0.19-1.00)	1.00 (0.80-1.00)	1.00 (0.99-1.00)	0.0	.148
V40Gy	0.00 (0.00-0.99)	0.99 (0.06-1.00)	0.99 (0.30-1.00)	0.0	1.000
TVI					
$D_{100\%}$	33.2 (25.2-36.1)	36.1 (24.9-63.6)	47.6 (26.7-58.9)	11.5	.008
$D_{99\%}$	35.3 (28.8-38.8)	44.6 (29.8-68.8)	55.0 (35.6-68.0)	10.4	.003
$D_{98\%}$	35.6 (29.8-39.4)	46.6 (31.0-70.8)	56.2 (38.0-69.9)	9.6	.005
$D_{95\%}$	36.2 (30.7-39.9)	50.9 (32.4-75.5)	58.2 (38.3-72.7)	7.3	.008
$D_{90\%}$	36.8 (33.3-41.0)	53.3 (34.9-81.1)	60.3 (38.6-74.6)	7.0	.018
$D_{80\%}$	37.5 (34.0-41.4)	55.8 (35.3-87.2)	61.7 (39.2-77.0)	5.9	.099
$D_{50\%}$	38.5 (34.5-42.1)	59.4 (37.2-98.7)	64.1 (40.3-81.5)	4.7	.369
$D_{10\%}$	39.3 (35.3-43.2)	63.7 (39.8-106.2)	67.8 (42.1-87.2)	4.1	.766
V35Gy	0.99 (0.24-1.00)	1.00 (0.88-1.00)	1.00 (1.00-1.00)	0.0	.011
V40Gy	0.02 (0.00-0.98)	0.99 (0.08-1.00)	1.00 (0.55-1.00)	0.1	.272
DE-PTV					
$D_{100\%}$	23.3 (14.7-29.1)	20.5 (12.1-33.7)	23.4 (19.9-32.4)	2.9	.108
$D_{99\%}$	28.3 (19.0-33.3)	31.0 (15.1-45.9)	33.9 (29.3-46.0)	2.9	.067
$D_{98\%}$	30.1 (19.8-34.4)	34.0 (15.7-50.0)	36.4 (31.5-50.7)	2.4	.043
$D_{95\%}$	32.4 (21.3-36.8)	40.4 (17.7-56.4)	44.8 (35.7-56.8)	4.4	.018
$D_{90\%}$	33.2 (22.9-38.3)	45.1 (20.8-63.4)	50.2 (36.9-61.3)	5.1	.014
$D_{80\%}$	34.0 (28.1-40.4)	51.2 (32.3-73.2)	55.5 (37.4-65.6)	4.3	.030
$D_{50\%}$	36.3 (33.8-41.8)	58.0 (35.9-91.4)	61.8 (38.8-75.0)	3.8	.284
$D_{10\%}$	39.0 (35.4-43.0)	63.1 (38.8-103.6)	67.7 (41.5-84.9)	4.0	.832
V35Gy	0.67 (0.24-0.98)	0.98 (0.73-1.00)	0.98 (0.96-1.00)	0.1	.023
V40Gy	0.02 (0.00-0.83)	0.95 (0.32-0.99)	0.96 (0.28-1.00)	0.1	.142

Abbreviations: DE-ART = dose-escalated plan created on daily adaptive radiation therapy computed tomography; DE-ORI = dose-escalated on the original planning computed tomography; DE-PTV = dose-escalation planning target volume; D_{max} = maximum dose; $D_{x\%}$ = minimum dose to *x* % of volume; GTV = gross target volume; non-DE = non-dose-escalated plan; TVI = tumor vessel interface.

luminal OARs. On average, the maximum difference in daily dose metrics of a patient by interfractional motion was 2.5 ± 2.7 Gy for TVI $D_{95\%}$, 3.0 ± 2.9 Gy for GTV $D_{95\%}$, and 2.0 ± 1.8 Gy for DE-PTV $D_{95\%}$. For the luminal OARs, the maximum differences in $D_{1.0cc}$ were 1.3 ± 0.8 Gy for the small bowel, 1.5 ± 1.0 Gy for the large bowel, 1.3 ± 1.1 Gy for the stomach, and 0.7 ± 0.4 Gy for the duodenum.

Table 2 Dosimetric comparison of DE-ORI versus DE-ART to the luminal organs at risk for 18 patients

Structure and dose metrics	Median dose for non-DE, Gy (range)	Median dose for DE-ORI, Gy (range)	Median dose for DE-ART, Gy (range)	DE-ART minus DE-ORI	*P* value
Small bowel					
D_{max}	31.4 (14.4-36.8)	36.4 (14.6-70.4)	34.6 (19.5-37.5)	-1.8	.018
$D_{0.1cc}$	27.0 (12.6-35.1)	29.3 (13.0-57.5)	30.0 (16.2-34.7)	0.7	.043
$D_{0.3cc}$	24.7 (11.9-34.3)	27.7 (12.3-52.1)	28.5 (15.1-33.8)	0.8	.108
$D_{1.0cc}$	21.8 (11.0-32.3)	25.7 (11.4-45.1)	26.2 (13.9-32.1)	0.5	.304
$D_{3.0cc}$	17.5 (9.9-28.5)	23.5 (10.3-37.6)	22.5 (12.3-29.3)	-1.0	.325
$D_{9.0cc}$	13.8 (7.8-23.6)	18.8 (7.7-29.9)	18.0 (8.3-25.0)	-0.8	.551
Large bowel					
D_{max}	20.3 (11.2-33.8)	26.5 (17.4-50.9)	27.7 (16.9-36.5)	1.2	.609
$D_{0.1cc}$	18.5 (10.8-32.5)	25.1 (16.5-41.1)	25.9 (15.7-33.8)	0.8	.369
$D_{0.3cc}$	17.9 (10.5-31.1)	24.3 (15.7-36.8)	24.7 (14.9-31.1)	0.4	.347
$D_{1.0cc}$	16.8 (10.0-28.1)	23.0 (13.7-31.1)	23.0 (13.6-28.5)	0.0	.523
$D_{3.0cc}$	15.6 (9.3-24.0)	21.4 (10.8-26.2)	21.1 (10.8-25.9)	-0.3	.580
$D_{9.0cc}$	13.9 (6.1-19.4)	18.5 (6.3-23.0)	18.1 (5.9-23.1)	-0.4	1.000
Duodenum					
D_{max}	35.9 (20.4-39.2)	50.4 (21.8-83.1)	37.4 (22.0-40.6)	-13.0	.000
$D_{0.1cc}$	33.1 (14.9-35.8)	41.4 (14.3-71.1)	33.6 (19.3-38.4)	-7.8	.000
$D_{0.3cc}$	31.7 (13.9-35.2)	39.3 (13.3-60.8)	32.0 (18.1-38.0)	-7.3	.001
$D_{1.0cc}$	29.0 (12.3-34.4)	35.9 (11.7-45.1)	29.4 (16.0-37.6)	-6.5	.002
$D_{3.0cc}$	25.2 (10.2-32.4)	30.2 (8.7-35.5)	26.1 (11.9-37.1)	-4.1	.021
$D_{9.0cc}$	19.8 (7.4-28.8)	23.6 (4.0-34.0)	21.6 (6.0-35.3)	-2.0	.027
Stomach					
D_{max}	30.8 (0.7-37.7)	42.5 (1.5-60.2)	35.8 (2.4-38.2)	-6.7	.005
$D_{0.1cc}$	27.2 (0.6-35.4)	35.9 (1.3-47.6)	31.6 (1.4-35.3)	-4.3	.009
$D_{0.3cc}$	25.6 (0.6-33.9)	33.6 (0.8-43.0)	29.7 (1.0-34.3)	-3.9	.024
$D_{1.0cc}$	23.7 (0.5-31.9)	30.5 (0.7-37.1)	27.5 (0.7-32.2)	-3.0	.074
$D_{3.0cc}$	20.2 (0.4-28.5)	25.2 (0.5-33.1)	24.2 (0.6-29.2)	-1.0	.108
$D_{9.0cc}$	15.5 (0.3-24.3)	19.6 (0.4-28.6)	19.1 (0.4-25.4)	-0.5	.119

Abbreviation: DE-ART = dose-escalated plan created on daily adaptive radiation therapy computed tomography images; DE-ORI = dose-escalated plan on the original planning computed tomography image; D_{max} = maximum dose; D_{xcc} = maximum dose to *x* cc volume; non-DE = non-dose-escalated plan.

Discussion

In this study, we demonstrated that the prescription dose of pancreas SBRT plans can be significantly escalated using a fully automated daily adaptive planning algorithm. Dose escalation was achieved by gradually escalating the prescription dose with OAR constraints being the limiting factor in target dose; using this isotoxicity approach, we can achieve the maximum prescription dose in every fraction based on the target and OAR positions for the given day of treatment. We also automated the dose-escalation planning to make this process efficient, streamlined for clinical implementation, and eliminated interobserver variance in the planning process to determine maximum achievable prescription doses for each study patient.

Currently, the estimated time to generate a dose-escalated adaptive plan using the automation algorithms is less than 30 minutes (8 minutes for our autocontouring algorithm from our previous study[15] and 14.8 $\pm$ 6.5 minutes [mean $\pm$ 1σ] for the dose-escalated daily adaptive planning algorithm). The process time for the autoplanning algorithm might be further reduced if we can quickly predict the achievable prescription dose with given patient

images[19-22] and use the predicted value as the target dose constraints instead of using the iterative algorithm described in Figure 1A. In this scenario, the clinical implementation of the online-adaptive dose-escalation approach would be more feasible and practical in the clinical setting; however, this will have to be elucidated in future work. Moreover, the automated process allowed us to reduce inter- and intra-planner variabilities in plan quality, as the quality of the plan is largely dependent on the planner's background, experience, the amount of time they spend on each plan, or any other unexpected factors. By automating the planning process, we were able to collect more consistent plans and easily scale up the size of the study.

A key finding of this study is the necessity of daily adaptation to achieve safer dose-escalation in pancreas SBRT. From the automatically generated plans, the mean $D_{95\%}$ of the GTV, TVI, and DE-PTV were 53.7, 58.2, and 44.8 Gy, respectively. The target coverage ($D_{95\%}$) is on average higher by 5 Gy when the dose-escalated plan was generated on a daily basis instead of delivering the dose-escalated plan by simply adjusting the treatment isocenter with daily image guidance (Table A2). Moreover, the dose to the luminal OARs, especially the duodenum, small bowel, and stomach, would violate the OAR dose constraints if patients were not treated with daily adaptive plans (Fig. 3). For example, if daily adaptation was not used, the $D_{1.0cc} < 35$ Gy constraint would have been violated for 10, 1, and 4 patients for the duodenum, small bowel, and stomach, respectively (Table A3). We also demonstrated that the prescription dose can be maximized by introducing the concept of a daily prescription dose, which represents the maximum achievable target dose on a daily CT image. The variations in $D_{95\%}$ to the targets can be up to 3 Gy (37.5% of the 8 Gy per fraction prescription dose) for the same patient with different daily CT images. Therefore, to try to increase the dose to the pancreas as much as possible, the prescribed dose may be adjusted based on daily images and OAR isotoxicity rather than being the same for every treatment session.

In this work, we found that the amount of achievable dose escalation not only varies on a daily basis for a given patient, but also that the total delivered target dose is highly patient specific. For example, daily adaptive dose escalation achieved a GTV and TVI $D_{95\%}$ greater than 60 Gy for 4 and 7 patients, respectively. Conversely, 6 and 4 patients had GTV and TVI $D_{95\%}$ less than 50 Gy, thereby indicating that these patients may not be suitable for daily adaptive dose escalated pancreas SBRT (Table A2). Since daily online adaptive SBRT is inherently resource intensive, the ability to prospectively identify patients who are suitable for this treatment approach would add great value to clinic. Therefore, future work is warranted to determine the patient-specific limiting factors in dose escalation (OAR to target distances, patient-specific OAR and target motion, etc) as well as models to identify which patients should receive daily adaptive SBRT.

If our automated dose-escalated daily adaptive algorithm was to be clinically adopted, we could potentially improve clinical outcomes of patients with pancreatic cancer. In previous studies, doses of 70 to 100 Gy BED_{10} (ie, BED with α:β ratio of 10) are required for an ablative effect and increase overall survival.[23-25] Current SBRT dose regimens of 35 to 40 Gy in 5 fractions (59.5-72 Gy BED_{10}) do not achieve this dosimetric threshold, but increasing BED without increasing normal structure toxicity could be achieved with our approach because of the inter- and intrafraction bowel and target motions,[6] although intrafraction tumor motion can be managed by adapting the breath hold technique with a more generous CTV-to-PTV margin,[26] as well as utilizing OAR margins to generate planning organ-at-risk volume. We have shown that DE-ART can achieve 110 to 125 Gy BED_{10} for the GTV and TVI, and DE-PTV can achieve 85 Gy BED_{10}. The pancreas HyTEC report showed that 12-month local control increases around 10% if the prescription dose increases from 35 to 45 Gy in 5 factions.[27] As the $D_{95\%}$ of the PTV can be increased by an average of 12.4 Gy with the proposed DE-ART approach (from 32.4 to 44.8 Gy, as shown in Table 1), we anticipate a similar increase in 12-month local control for the patient being treated with the DE-ART method.

Several prospective studies on magnetic resonance imaging-guided daily adaptive radiation therapy have been conducted for pancreatic cancer,[9,10,28,29] The SMART trial used prescription doses of 50 Gy in 5 fractions, and plans were manually adjusted every fraction based on daily magnetic resonance images.[10] While PTV coverage in these studies appear higher than our study ($D_{95\%}$ 47.5 Gy from the SMART trial vs 44.8 Gy from our study), we note that the PTV definitions between each study differ in an important manner; the DE-PTV in our study was defined to be the summation of the GTV and the TVI, with the TVI often being a large contribution to the PTV, whereas the PTV of the SMART trial did not include a TVI target. Since the TVI is the most common location of recurrence and tumor control near the TVI sometimes results in restaging of unresectable tumors being resectable, an extra dose to the TVI through a simultaneous integrated boost technique can reduce local recurrence[30,31] and improve the probability of a negative surgical margin.

An important point to note with this study is that our estimation of patient-specific dose escalation using our approach is inherently conservative for several reasons. First, we used $D_{95\%}$ as the target optimization parameter, which is a stricter constraint then $D_{90\%}$ or using an 80% isodose line prescription; using either of these target coverage parameters as the dose value for optimizing the dose escalation algorithm could potentially achieve greater target doses. Second, the TVI was included as a simultaneous integrated boost target, as well as part of the DE-PTV, in our planning approach. Dholakia et al demonstrated the necessity of including the TVI as a target structure because 90% of LAPC recurrence occurred in

this region;[32] however, this is not standard-of-care practice. For example, the SMART trial did not incorporate a TVI in the PTV.[9,10] Therefore, not including the TVI target in the PTV could lead to higher dose escalation for many patients due to a smaller PTV size. Finally, the isotoxicity approach used a conservative skin dose constraint of $D_{max} < 35$ Gy. The median skin dose was 32.8 Gy for the DE-ART plans, and the skin dose constraint was the biggest factor limiting further dose escalation. On the other hand, a skin dose constraint of $D_{max} < 39.5$ Gy was used for the SMART trial.[10] This demonstrates that our skin dose constraint is too conservative, thereby allowing our approach to achieve higher target doses in a future trial.

The limitation of this study is that the dose accumulation over the course of treatment was not performed precisely in this study, as we accumulated dose through the point dose metric. We initially tested the intensity-based deformable image registration algorithm in RayStation to register the daily CT images to the planning CT image. However, because the algorithm cannot precisely register 2 images as shown in Figure A1, the resulting summed dose was not reliable. Instead, we used the point dose summation method for dose metric analysis. We believe that the point dose summation was more suitable and reliable for our study to not underestimate the normal tissue toxicities. The failures in achieving OAR dose constraints were mostly from D_{max} or dose at small volume (eg, $D_{1.0cc}$) of the luminal structures, and the point dose summation method almost always overestimates these metrics as the method assumes that the hotspots in the OARs were located at the same spot in every fraction.

The results of our study indicate that the effectiveness of dose escalation varies among patients and is dependent on factors such as initial organ configuration and interfractional organ motion. While some patients may benefit greatly from the dose-escalated adaptive replanning approach, others may not see significant improvement. Implementing this approach can be time-consuming, with the need to spend at least 30 minutes generating a dose-escalated adaptive plan in addition to the regular image-guided radiation therapy procedure. To address this challenge, we are currently training a convolutional neural network to predict the achievable amount of dose escalation for each CT image. With that prediction model, we would be able to quickly determine whether a patient will benefit from a dose-escalated adaptive plan based on their daily organ configuration and apply the technique accordingly.

Conclusions

We demonstrated that our automated adaptive dose-escalation technique for pancreas SBRT has potential to increase target prescription dose without exceeding OAR dose constraints for many patients. Moreover, the amount of dose escalation achievable for daily adaptive pancreas SBRT is highly patient specific. Furthermore, daily treatment adaptation is required for most patients to safely achieve dose escalation of pancreas tumors using SBRT. The automation algorithm could contribute to the clinical adoption of the daily adaptive dose-escalation treatment of pancreas cancer.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2022.101164.

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