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CLINICAL INVESTIGATION

NRG Oncology International Consensus Contouring Atlas on Target Volumes and Dosing Strategies for Dose-Escalated Pancreatic Cancer Radiation Therapy

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Purpose: Dose-escalated radiation therapy is increasingly used in the treatment of pancreatic cancer; however, approaches to target delineation vary widely. We present the first North American cooperative group consensus contouring atlas for dose-escalated pancreatic cancer radiation therapy.

Methods and Materials: An expert international panel comprising 15 radiation oncologists, 2 surgeons, and 1 radiologist was recruited. Participants used MimCloud software to contour high- and low-risk clinical target volumes (CTVs) on 3 pancreatic cancer cases: a borderline resectable head tumor, a locally advanced head tumor, and a medically inoperable tail tumor. Simultaneous Truth and Performance Level Estimation volumes were created, and contours were analyzed using Dice similarity coefficients.

Results: The contoured gross tumor volume for the borderline head, locally advanced head, and unresectable tail tumor cases were 156.7, 58.2, and 9.0 cc, respectively, and the Dice similarity coefficients (SD) for the high- and low-risk CTV ranged from 0.45 to 0.82. Consensus volumes were agreed upon by authors. High-risk CTVs comprised the tumor plus abutting vessels. Low-risk CTVs started superiorly at (tail and distal body tumors) or 1 cm above (head, neck and proximal body tumors) the celiac takeoff and extended inferiorly to the superior mesenteric artery at the level of the first jejunal takeoff. For head, neck, and proximal body tumors, the lateral volume encompassed the entire pancreas head and 5 to 10 mm around the celiac, superior mesenteric artery, superior mesenteric vein, including the common hepatic artery and medial portal vein, consistent with a "Triangle" volume-based approach. For distal body and tail tumors, the entire tail was included, along with the splenic vessels and the takeoffs of celiac artery.

Conclusions: Through multidisciplinary collaboration, we created consensus contouring guidelines for dose-escalated pancreatic cancer radiation therapy. These volumes include not only gross disease, but also routine elective coverage, and can be used to standardize practice for future trials seeking to define the role of dose-escalated radiation therapy in pancreatic cancer.

Introduction

Indications and techniques for dose-escalated radiation therapy (RT) in pancreas ductal adenocarcinoma (PDAC) have evolved over the past 2 decades. In 2004, Koong et al[1] published the first series treating patients with locally advanced pancreas cancer (LAPC) using single-fraction RT up to 25 Gy. Although toxicity in the initial cohort was minimal, additional studies showed higher rates of late effects such as ulcer and perforation of duodenum or stomach with single-fraction treatment, leading to the preferred use of multifraction regimens.[2] A multi-institutional prospective single-arm study published in 2015 popularized 33 Gy in 5 fractions,[3] and more recent data using modern techniques have suggested efficacy and safety with dose-escalation upward of 50 Gy in 5 fractions achieving a biologic effective dose (BED_{10}) of 100 Gy.[4,5] Dose-escalated RT is increasingly used off trial in PDAC; however, justification for this strategy is based upon single-arm prospective and retrospective studies, whereas[4,6] level 1 evidence remains lacking. Going forward, it is imperative to generate randomized data defining the clinical scenarios in PDAC where dose-escalated RT is efficacious and should be a standard care option.

In addition to RT dose, target delineation has evolved and remains a topic of debate. In some series, dose-escalated RT treated only areas of gross tumor due to concerns about toxicity to nearby luminal structures unable to be clearly visualized. However, studies assessing patterns of recurrence after dose-escalated RT to tumor alone have mapped local recurrences to areas of surrounding vasculature, neural tracts and nodal basins.[7-11] These data, along with improved techniques in motion management and organ visualization, have led to reconsideration of treatment volumes.

Post hoc analyses of several pivotal RT trials, including for PDAC, have shown that target volume delineation can affect study outcomes.[12] Such findings are particularly true for disease sites such as PDAC where dosimetric tradeoffs are required to optimize tumor coverage while meeting critical organ at-risk (OAR) constraints. Yet practice patterns vary widely, depending in part on evolving fractionation regimens, and there is no accepted standard for radiation volumes in PDAC. Therefore, we created contouring guidelines to standardize practices across clinical settings and in prospective trials seeking to define the role of dose-escalated RT in PDAC.

Methods and Materials

The first and senior authors (NNS and WAH) recruited an international panel of physicians with expertise in PDAC including radiation oncologists, surgical oncologists, and a diagnostic radiologist (Table E1). Next, the first author

performed a literature review on dose-escalated RT and target volume delineation in PDAC. Participants were asked to send relevant references for inclusion. Publications were presented to the group via two 1-hour video conference meetings, and further discussion regarding existing data was encouraged.

After these meetings, radiation oncologists were asked to contour target volumes for 3 representative and deidentified PDAC cases: (1) borderline resectable pancreas head tumor, (2) locally advanced, technically unresectable pancreas head tumor, and (3) medically inoperable pancreas tail tumor. For each case, a background vignette was provided with relevant clinical information, along with diagnostic magnetic resonance imaging (MRI) and computed tomography (CT) simulation scans. Contours were completed using MIM Cloud (MIM Software Inc). The gross tumor and adjacent OARs were outlined by the first author, and each participant was asked to contour a high-risk clinical target volume (CTV) with or without an additional low-risk CTV, according to their routine practice. Participants were blinded from reviewing others' contours and only the first author and physics collaborators (NNS and YZ, EP) had access to all complete contours. Contour analysis was performed using the Sorensen-Dice similarity coefficient and mean distance to agreement and maximum Hausdorff distance.[13,14] The Dice3D coefficient measures the similarity between two 3D contour volumes. It is calculated using the formula:

$$Dice = \frac{2|A \cap B|}{|A| + |B|} \quad (1)$$

where |A| is the volume of contour A, |B| is the volume of contour B. $|A \cap B|$ is the volume of the intersection of the 2 contours A and B. The Dice Score ranges from 0 to 1, with a higher score indicating a better overlap ratio. A score of 1.0 indicates perfect agreement between the 2 contour volumes (they are identical), whereas a score of 0.0 indicates no overlap between the 2 contour volumes. The mean distance to agreement measures the average distance between 2 contours, with a lower value indicating better alignment. It is calculated by averaging distances from each point on contour A to its nearest point on contour B. The maximum Hausdorff distance identifies the greatest distance between any point on one contour and its nearest point on the other, with a higher value indicating worse alignment and highlighting the largest spatial discrepancy. For each individual contours, these metrics were extracted by comparing with a "gold standard contour" created using the Simultaneous Truth and Performance Level Estimation (STAPLE). The STAPLE contour represents a probabilistic volume demonstrating the weighted global aggregated result of all participants.[15] The core idea of STAPLE is to estimate the most likely "ground truth" segmentation by considering the performance of each input segmentation. It assigns a reliability weight to each segmentation based on its agreement with the others, effectively down-weighting segmentations that are likely to be less accurate. By iteratively refining these weights and the consensus, STAPLE produces a statistically robust combined segmentation, mitigating variability and bias from different segmentations. Individual contours were also used to create a "count map," wherein each voxel value is determined by the number of participants including the corresponding image voxel within their target volume. The maximum count was 15 given 15 contouring participants. The count map therefore enabled careful analysis of controversial regions prompting further discussion by the group.

Anonymized contours of participants and STAPLE contours were reviewed at the February 2024 NRG Oncology meeting for those attending in person. Subsequently, a video conference meeting was held inviting all participants to assess volumes and discuss areas of controversy. Step-by-step contouring instructions and an atlas were prepared by the first author and circulated to the group for feedback. In addition, a consensus was reached regarding recommendations for dose/fractionation and OAR constraints. The study was approved by the Institutional Review Board at Medical College of Wisconsin.

Results

Fifteen radiation oncologists contoured all 3 cases resulting in a total of 45 volumes that were included in the STAPLE contour and final analyses. Contouring participants and observers who provided feedback at initial and subsequent stages practiced in the United States and Europe for a median for 10 years (range, 3-36 years).

The gross target volumes (GTVs) for the borderline resectable head, locally advanced head, and tail tumor cases were 156.7, 58.2, and 9.0 cc, respectively. The high- and low-risk STAPLE CTVs were 355.7/591.5, 141.5/267.89, and 32.4/182.6 cc, and the DICE3D similarity coefficients (SD) were 0.80 (0.06)/0.79 (0.11), 0.82 (0.07)/0.78 (0.10), and 0.74 (0.14)/0.45 (0.17), respectively. The mean and max distances from STAPLE volume for the high-risk CTV for the 3 cases were 4.2/12.0, 3.3/7.8, and 2.7/6.5 mm and for the low-risk CTV were 5.4/14.7, 4.8/11.2, and 15.9/51.1 mm. The proportion of radiation oncologists who included a low-dose elective CTV for each case was 80% (borderline resectable head), 67% (locally advanced head), and 80% (unresectable tail).

The count maps identified several regions of variation with regard to the low-dose elective volume including (1) coverage of the aorta (ie whether to include vessel when not invaded or even abutting), (2) extension into the porta hepatis (particularly the lateral border), and (3) in the setting of tumors centered in the distal body/tail of the pancreas, the proximal extent of elective pancreas coverage (Fig. 1). Each of these regions was discussed in detail in the context of the literature search on known patterns of PDAC spread, with emphasis on vascular and neural tract patterns of recurrence. A survey was sent out to the entire multidisciplinary group regarding these issues, after which a draft of contouring steps was circulated and then finalized with group consensus.

Before creating low-dose CTVs, the following normal anatomy structures should be identified: celiac artery, celiac

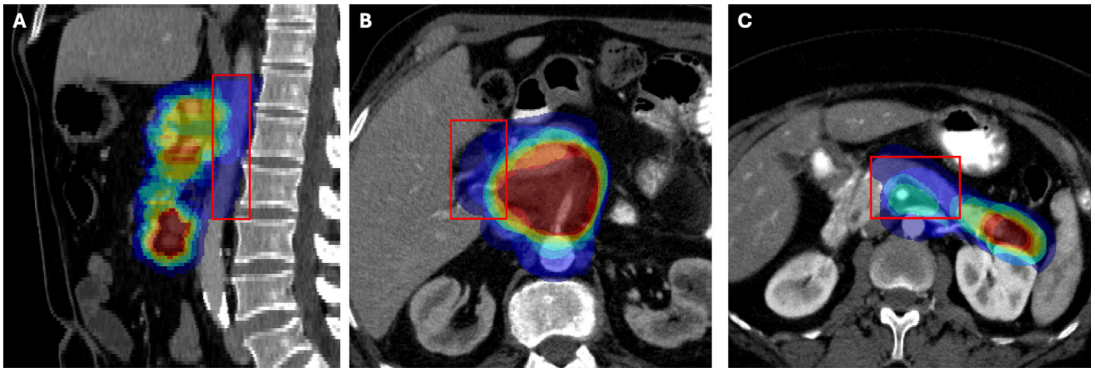

Fig. 1. Count maps showing controversial regions identified including (A) aorta, (B) porta hepatis (for head tumor cases), and (C) uninvolved pancreas (for tail tumor case).

bifurcation, splenic artery, common hepatic artery (CHA), gastroduodenal artery, superior mesenteric artery (SMA), superior mesenteric vein (SMV), portal vein, first jejunal branch of SMA. These are identified in Figures 2 and 3.

Pancreatic cancers can invade beyond the pancreas capsule via direct tumor extension, nodal extension, or perineural invasion. The low-dose CTV aims to encompass both nodal and perineural invasion, which are centered around peripancreatic vasculature. For pancreas head neck, and proximal body tumors, particular emphasis was placed on patterns of neural tract spread for informing the design of the low-dose CTV, consistent with a "Triangle" volume-based approach,[11,16] given considerable data suggesting extrapancreatic perineural invasion driving local recurrence for tumors emanating from these portions of the pancreas. Consensus was to include a low-dose/elective CTV for all cases where such volumes were felt to be dosimetrically and clinically feasible. A margin range of 5 to 10 mm around vasculature is recommended because we do not currently know the distance from the vessel wall to the edge of where at-risk extrapancreatic perineural plexi and lymphatic channels lie; however, we believe it is around 5 to 10 mm from vascular structures.

High-dose GTV/CTV—all tumors

(1) Include all gross disease (primary tumor and nodes) based upon review of diagnostic imaging (MR, CT, and positron emission tomography (PET)). Gross nodes include those >1 cm and/or with enhancement pattern consistent with metastatic cancer.
(2) Include the entire diameter (on axial slice) of the following adjacent vessels within 5 mm of gross disease and extend 5 mm along the vessel including the entire circumference: celiac artery, SMA, SMV, and portal vein. For tail tumors, also include and extend along the splenic artery.
(3) Include adjacent hazy soft tissue surrounding tumor opacifying the fat space (Fig. 4).

Low-dose CTV—pancreatic head/neck/proximal body tumors (Fig. 2)

(1) Start by creating a 10 mm isotropic expansion around gross tumor (primary and nodes). For patients treated

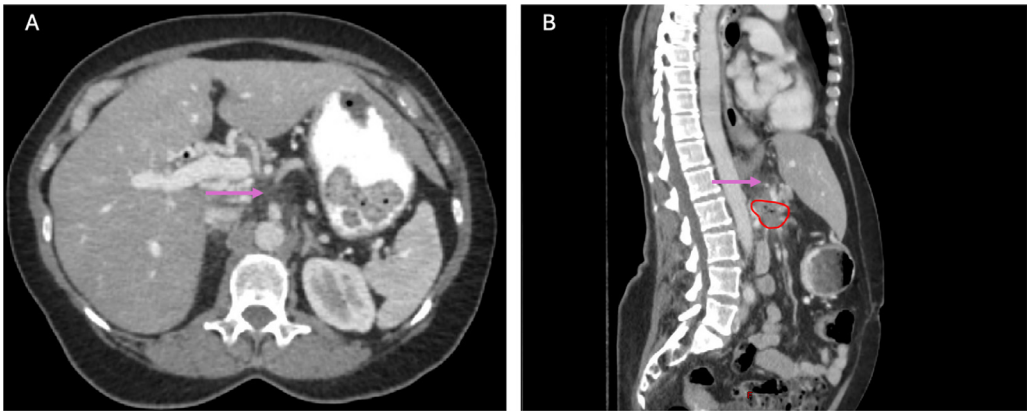

Fig. 2. CT scan for a patient with locally advanced pancreas cancer receiving dose escalated radiotherapy. The purple arrows in (A) and (B) point to area of gray haziness at level of celiac bifurcation, which is located superior to contoured gross tumor shown in red. *Abbreviation:* CT = computed tomography

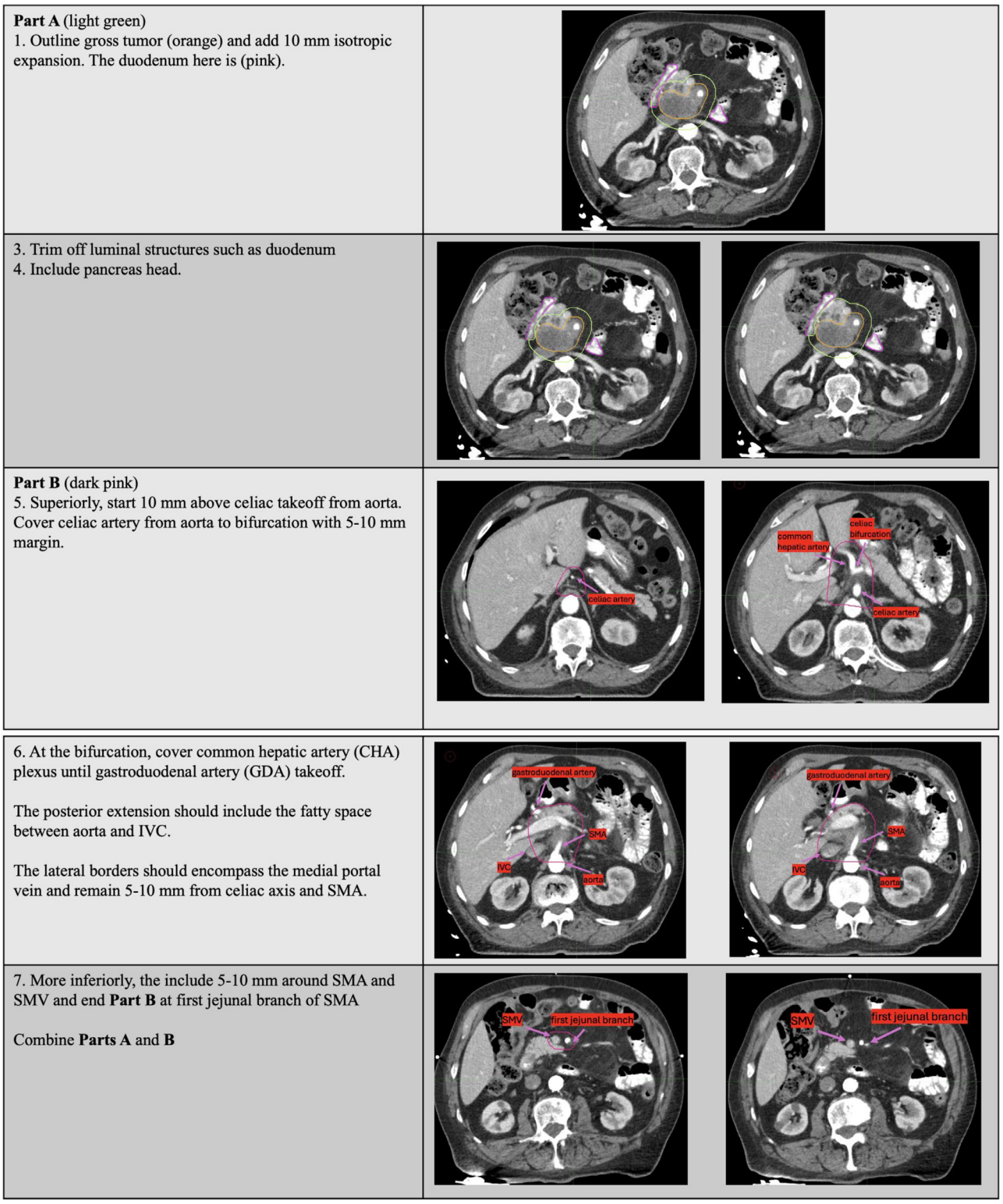

Fig. 3. Low dose CTV for pancreatic head/neck/proximal body tumors. Detailed instructions in text. *Abbreviations:* CTV = clinical target volume; IVC = inferior vena cava; SMA = superior mesenteric artery

with induction chemotherapy, consider including pre-chemotherapy disease extent. Crop this structure off adjacent luminal structures (bowel and stomach), unless they are invaded, or there is concern for microscopic regional extension.

(2) Add the entire pancreas head to step 1, completing Part A of the low-dose CTV.

(3) For Part B, commence volumes 10 mm above celiac takeoff from the aorta. To ensure coverage of the celiac

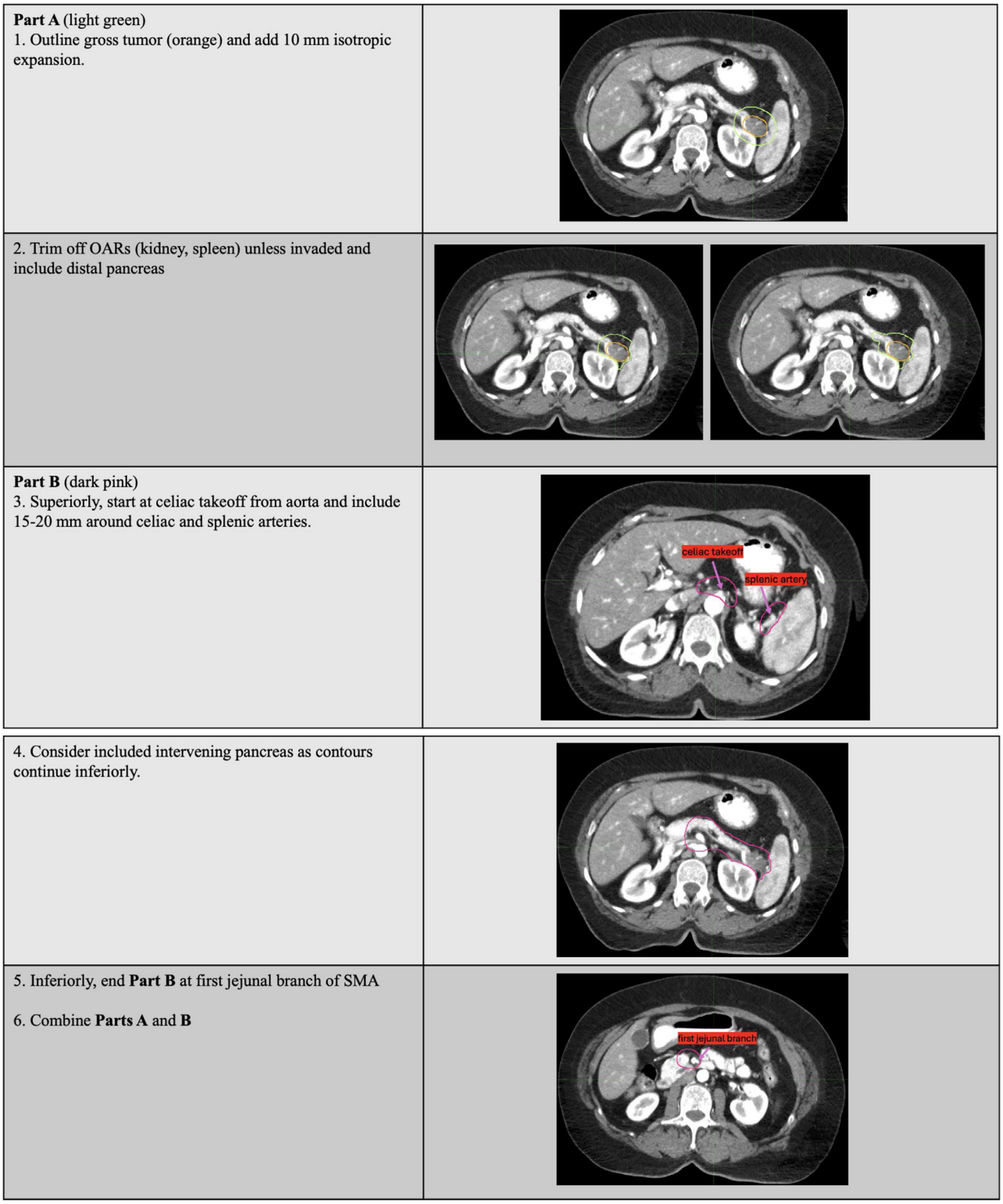

Fig. 4. Low dose CTV for pancreatic distal body and tail tumors. Detailed instructions in text. *Abbreviations:* CTV = clinical target volume; OAR = organ at-risk; SMA = superior mesenteric artery.

plexus, cover the entire celiac artery from the aorta to its bifurcation into splenic and CHA with a 5 to 10 mm margin, excluding nearby gastrointestinal (GI) luminal organs (stomach and bowel).

(4) To ensure coverage of CHA plexus, cover the full extent of the CHA with 5 to 10 mm margin until at minimum the gastroduodenal artery. At the level of CHA coverage, also consider including the portal vein. Extend posteriorly

to the anterior surface of the aorta and the inferior vena cava (IVC) to encompass the fatty space that contains key extrapancreatic nerve plexi. The entire aorta need not be contoured but consider including the anterior portion to ensure a margin of the SMA and celiac artery and covering approximately 5 to 10 mm laterally to the aorta.

(5) Continuing inferiorly, the lateral border should encompass the portal vein through the portosplenic confluence. The (patient) left lateral border should remain 5 to 10 mm from the celiac axis and SMA, again excluding GI luminal organs (stomach and bowel).

(6) Anteriorly, the contour should encompass the SMA plus a 5- to 10-mm margin to ensure coverage of the SMA plexus. Elective coverage of the SMV can be considered at the level of the SMA and/or tumor. At this level, the posterior border can also move anteriorly and off aorta.

(7) Inferiorly, end at the first jejunal branch of the SMA. This completes Part B of the low-dose CTV.

(8) Combine Parts A and B.

Low-dose CTV—pancreatic distal body and tail tumors (Fig. 3)

(1) Start by creating a 10 mm isotropic expansion around gross tumor (primary and nodes). For patients treated with induction chemotherapy, consider including prechemotherapy disease extent. Trim this structure off adjacent OARs (kidney and spleen), unless they are invaded.

(2) Add the entire relevant parts of distal pancreas head to step 1. The distal pancreas comprises the body and tail. For tail tumors, include the entire tail and for body tumors, include the entire body. This completes Part A of the low-dose CTV.

(3) For Part B, commence contours at the level of celiac artery takeoff from the aorta. At this level, include 15 to 20 mm circumferentially around the splenic artery. Consider also a 5 to 10 mm margin around the celiac axis, depending on extent of primary tumor (50% of our group included the celiac axis in the elective volume).

(4) Continue inferiorly, as you reach the level of pancreas, consider connecting celiac and splenic artery volumes to include intervening pancreas, again depending on gross tumor including involvement.

(5) The low-dose CTV will terminate inferiorly at the first jejunal branch of the SMA. This completes Part B of the low-dose CTV.

(6) Combine Parts A and B.

Additional considerations on simulation, dosing, and treatment planning

Although not the primary focus of this contouring atlas, our group discussed the following points related to PDAC RT planning and delivery:

(1) For simulation, intravenous (IV) contrast should be used for all CT-based treatments, with consideration for triple phase protocol (arterial, pancreatic, portovenous at 25, 40, and 70 seconds from injection). However, in cases where this is not feasible (eg, with breath-hold scans with active breathing control), diagnostic multiphasic scans can be used to inform contours. If only one contrast scan is possible, then IV contrast at 40 to 50 seconds is recommended to maximize visualization. Oral contrast can be considered to aid in small bowel delineation; however, overfilling should be avoided because patients will be fasting for treatments. One option is to give a small amount ($\sim$100 cc) contrast or water when laying on simulation table, allowing at least 15 minutes for transit into the duodenum. Motion assessment should be performed in all cases, and a motion management strategy (breath-hold, compression, etc.) undertaken for $>$5 mm target movement during the respiratory cycle. Scan slice thickness should be $\leq$2 mm in target region. Fiducial markers are highly recommended; however, metal stents can be used as a surrogate as needed. Given potential for greater variability in day-to-day stent positioning, if a stent is used rather than fiducials, consideration should be given for larger margins. To aid in contouring, consider fusion with diagnostic MRI (for CT-based treatments) or PET if performed.

(2) Recommended dosing strategies for 5, 15, and 25 fraction regimens are as follows, and also shown in Table E2:

- 5-fraction: 10 Gy per fraction (high-dose)/6.6 Gy per fraction (low-dose)
- 15-fraction: 4.5 Gy per fraction (high-dose)/2.5 Gy per fraction (low-dose)
- 25-fraction: 3 Gy per fraction (high-dose)/1.8 Gy per fraction (low-dose)

(3) Suggestions for OAR metrics for various dose and fractionation schedules are displayed in Table 1. These constraints were created with nonadaptive treatments in mind. In cases where adaptation is used, consideration can be given for more permissive metrics (ie allowing a higher dose to luminal structures) and/or planning without a planning organ at risk volume (PRV) around stomach or bowel.[17-19]

(4) For dose-escalated RT in PDAC, the prescription dose may not reflect dose delivered due to proximity of target structures to OARs necessitating underdosing, and differences in planning. Given this variability, comparing outcomes across studies and understanding patterns of recurrence has been challenging.[20] As such, we recommend systematically reporting dose delivered to target structures via the following metrics as shown in Table 2.

(5) Three- and 5-mm planning target volumes (PTVs) were recommended for adaptive and nonadaptive cases, respectively, depending on the technology, motion management and intrafraction verification.

Table 1 Constraints for consideration when delivering dose-escalated pancreas radiation therapy

	5-fraction		15-fraction		25-fraction	
Organ at-risk	**Dosimetric parameter**	**Constraint**	**Dosimetric parameter**	**Constraint**	**Dosimetric parameter**	**Constraint**
Small bowel	D0.5cc [Gy]	≤33	D0.035cc [Gy]	≤45	D0.035cc [Gy]	≤60
	D5cc [Gy]	≤30	D40cc [Gy]	≤37.5	D40cc [Gy]	≤50
Small bowel + 5 mm	D0.035cc [Gy]	≤36	D0.035cc [Gy]	≤51	D2cc [Gy]	≤60
Duodenum	D0.5cc [Gy]	≤33	D0.035cc [Gy]	≤45	D0.035cc [Gy]	≤60
	D5cc [Gy]	≤30	D40cc [Gy]	≤37.5	D40cc [Gy]	≤50
Duodenum + 5 mm	D0.035cc [Gy]	≤36	D0.035cc [Gy]	≤51	D2cc [Gy]	≤60
Stomach	D0.5cc [Gy]	≤33	D0.035cc [Gy]	<45	D0.035cc [Gy]	≤60
	D5cc [Gy]	≤30	D40cc [Gy]	≤37.5	D40cc [Gy]	≤50
Stomach + 5 mm	D0.035cc [Gy]	≤36	D0.035cc [Gy]	≤51	D2cc [Gy]	≤60
Large bowel	D0.035cc [Gy]	≤40	D0.035cc [Gy]	64.5	D0.035cc [Gy]	≤68
	D5cc [Gy]	≤33	D20cc [Gy]	47	D20cc [Gy]	≤52
Liver	Mean	≤15	Mean	≤20	Mean	≤25
Spinal cord	D0.035cc [Gy]	≤22	D0.035cc [Gy]	≤42	D0.035cc [Gy]	≤50

Abbreviation: Gy = gray.

For real-time adaptive treatments, the PTV should not be trimmed off luminal organs at-risk; OARs are contoured as visualized, and the treatment planning system will push dose away from critical structures.

(6) Outside of a clinical trial, a 1- to 5-mm PRV is recommended for gastrointestinal OARs (stomach, duodenum, and small bowel), depending upon technology and intrafraction verification strategy.

(7) Most of the group agreed that when anatomically feasible, RT should be delivered over 5 fractions, particularly in cases where technologies such as online adaptive and MR guidance are available. However, there was consensus that 5-fraction dose-escalated RT generally not be used when pancreas tumors are invading the stomach, duodenum, or small bowel (ie if ulcerating lesions visible on endoscopy). Yet most agreed that limited pancreas tumor abutment of luminal structures should not preclude 5 fraction regimens. "Long segment" abutment (>3-5 cm), particularly if >180° around gross tumor, was considered a relative contraindication. Some participants favored 5-fraction regimens in most cases (include OAR invasion), allowing for underdosing of tumor/luminal surface interface and accepting lower tumor/CTV dose coverage. Others preferred protracted regimens of 15 to 25 fractions in these cases, and in scenarios without access to MRI-guided or adaptive RT. Additional randomized data are needed in this space.

(8) A 120% to 140% maximal point dose (D0.035 cc) hotspot was recommended when dosimetric constraints can be achieved and should be located within the gross tumor exclusive of the 5 mm PRV. If this cannot be achieved, then the hotspot should at least be outside of bowel PRV.

(9) Target volume coverage (high-dose) should be optimized to be as high as possible and cover the majority of the GTV while meeting constraints for critical luminal structures. Although there was no absolute

Table 2 Dose statistics for target volumes

	Target volume			
Metric	**Low-dose CTV**	**High-dose CTV**	**Primary GTV**	**PTVoptimize***
Mean dose (Gy, % prescription)				
Maximum dose (Gy, % prescription)				
Minimum dose (Gy, % prescription)				
Proportion receiving prescription dose (%)				
Proportion receiving 90% prescription dose (%)				

Note: The table is meant to be empty, because it is an example template for reporting on target dose statistics for a treatment plan.
Abbreviations: CTV = clinical target volume; GTV = gross target volume; Gy = gray; PTV = planning target volume.
* For adaptive cases only. PTVoptimize is defined as high-dose PTV−(luminal OARs + 5 mm).

minimum coverage threshold, the group recommended aiming for at least 70% prescription dose coverage for the PTV. Alternatively, for adaptive cases, a PTV minus 5 mm PRV optimization structure can be used, and coverage of this at prescription dose should exceed 90% to 95%.

(10) For hypofractionated cases, selective adaptive replanning should be considered depending on review of daily cone beam computed tomography (CBCT) images.

Discussion

Dose-escalated pancreas RT has been increasingly utilized in the borderline resectable, LAPC, and high-risk adjuvant settings. The recent increasing adoption of this strategy is in part due to improvements in technology facilitating safer and more precise treatments as well as reported improvement in clinical outcomes.[21] Despite these advancements, there has not been a North American cooperative group consensus guideline for delivery of RT in PDAC since the RTOG 0848 trial, which assessed the addition of conventional, low-dose chemoradiation after surgery.[22] Important to realize is that RTOG 0848 was designed nearly 20 years ago, and the delivery of RT has changed over the last 2 decades. Today, dose-escalated RT is mostly given in the preoperative or definitive setting but without standardized guidelines, although individual studies such as the Alliance A021501 borderline resectable PDAC trial have provided tutorials to aid in the contouring, planning, and delivery of RT. Yet off trial, radiation oncologists treat PDAC via a wide range of volumes and doses, precluding rigorous assessment of outcomes and complicating clinical trial design. As an example, in the recently reported Stereotactic MRI-guided Adaptive Radiation Therapy (SMART) trial, elective volume use and target volume delineation was left to the discretion of participating sites, which resulted in significant variation in practice, with 54% of treatment plans including a CTV.[4] To address this gap, we created expert consensus-based guidelines with input from an international and multidisciplinary panel to standardize future delivery of dose-escalated RT in PDAC and to inform treatment planning for an upcoming NRG trial assessing the role of ablative RT in LAPC. Such an atlas was also created for RTOG 0848 and is essential for consensus on prospective clinical trials.

Following a similar step-by-step process used to develop standards for contouring in prostate cancer,[23] our group's method involved first a comprehensive literature review and presentation. This was followed by contouring of 3 representative cases with quantitative and qualitative assessment, and additional discussions for guideline review including adjudication of areas of controversy. Overall, agreement levels were high among our group for high-risk areas; however, there was greater variation with regard to low-risk volumes, reflecting different attitudes toward including more or less generous elective coverage. Our recommendations presented here incorporate recent data, particularly with regard to patterns of recurrence.[7-11] However, we necessarily relied on expert consensus in areas where evidence is lacking such as coverage of elective target volumes, dosing, and constraints to critical adjacent organs.

There were several questions identified by the expert group that were felt to have been poorly discussed by the current literature. These included the following: What does it mean to deliver "dose-escalated" RT? Is the term "dose-escalated" synonymous with ablative? How do dose levels relate to the definitions for stereotactic body RT (SBRT) or stereotactic ablative RT? In centering on the terminology "dose-escalated" for our contouring atlas, we wished to distinguish our proposed RT strategy from historical conventional chemoradiation using low doses intended for delivery preoperatively or postoperatively. In contrast, dose-escalated RT is given with the goal of eradicating macroscopic tumor particularly in cases where surgery is not feasible. At the same time, we acknowledge that an ablative threshold for PDAC remains unknown, and likely exists on a continuum dependent on tumor biology and size. Some retrospective series have reported on 80.5 Gy BED as a potential dose cut point, whereas more recent data have used a 100 Gy BED level.[4,6,24] Lastly, we wished to emphasize that target BEDs can be achieved through a range of RT regimens with published data suggesting promising outcomes via 5, 15, or 25 fractions. Therefore, we did not use the term SBRT as this, by definition, mandates 5 or fewer fractions in the United States.

Most (not all) members of our group favored including elective targeting of at-risk tissue for all 3 cases, acknowledging lack of level 1 evidence supporting this strategy. Notably, this opinion represents a difference from currently published guidelines including from Australian Gastrointestinal Trials Group/Trans-Tasman Radiation Oncology Group (AGITG/TROG) (2020)[25] and to some extent the ASTRO clinical practice statement (2019).[26] Whether elective coverage should be pursued in either the preoperative or definitive setting has been unclear to-date, as has the definition of what should be included in such a volume. In the preoperative setting, although the primary goal is margin sterilization, elective coverage may be particularly important for the more important endpoint of local recurrence risk reduction. However, practice patterns with respect to elective coverage have varied among recent prospective studies. For example, in Alliance A021501, elective coverage only included the full circumference of involved vasculature.[27] On the other hand, the Alliance A021101, PREOPANC, and PREOPANC studies did not have an anatomically defined elective volume but used generous isotropic expansions to create a CTV.[27-29] Although no large, multicenter prospective studies have incorporated standardized anatomically defined elective target volume delineation, there have been signals from institutional experiences suggesting value to doing so. As an example, investigators from Massachusetts General Hospital conducted a single-arm, phase 2 study in which patients

with borderline resectable PDAC were treated with a CTV defined by not only a 1-cm isotropic margin off of GTV but also inclusion of at-risk elective nodal basins.[30] Among 32 patients who underwent resection, only 3 patients experienced local failure. Similarly, a small prospective study conducted at the University of Cincinnati showed improved local control after the protocol, which initially was designed to target gross disease only, was later modified to include elective targeting of the SMA and celiac regions.[31]

Moreover, patterns of local failure have further shed light on both the value of elective coverage in the preoperative setting as well as the at-risk tissue that should be included in such a volume. Investigators at Johns Hopkins, for example, reviewed outcomes among patients treated with preoperative SBRT from 2016 to 2019 with an approach similar to Alliance A021501 in which only gross disease and the full circumference of involved vasculature were targeted.[32] Although a high rate of margin negative resection was achieved, locoregional recurrences were frequent, with 1- and 2-year locoregional progression-free survival rates of only 70.9% and 54.2%, respectively. Although the reason for this discrepancy between margin status and locoregional control is not clear, it may reflect the fact that pathways of local spread can be discontinuous in nature along extrapancreatic neural tracts and/or lymphatic channels. Furthermore, although elective nodal irradiation has garnered more attention in the literature to-date, elective neural tract irradiation may be more important in reducing locoregional failure. Indeed, although generally not characterized due to lack of available tissue, extrapancreatic neural invasion is highly common and may in fact occur more frequently than lymphatic spread.[33-38] Furthermore, analysis of surgical specimens from a prospective phase 2 study from Japan in which patients were treated with neoadjuvant gemcitabine-based chemoradiation showed that extrapancreatic neural tract involvement was the strongest pathologic predictor of locoregional recurrence, whereas lymph node involvement was more closely tied to distant failure.[39]

Given the potential importance of extrapancreatic neural tract involvement in driving locoregional recurrence, investigators at Heidelberg University have described and advocated for the "Triangle" operation, in which surgeons aim to clear the fatty tissue that sits in the triangular space between the celiac artery, CHA, SMA, and portal vein/SMV. This region specifically contains neural tracts at greatest risk for microscopic involvement in pancreas cancer: pancreatic head plexus I, pancreatic head plexus II, celiac plexus, SMA plexus, and CHA plexus.[40] Importantly, when investigators at John Hopkins assessed the location of locoregional recurrences among 31 patients in the aforementioned preoperative SBRT data set from 2016 to 2019 who received RT to gross tumor and involved vasculature alone and who thereafter developed a locoregional recurrence, >90% of the locoregional recurrences mapped to the "Triangle."[32] This finding was validated by investigators at Cedars Sinai, who also reported nearly all locoregional failures occurring in the "Triangle" in a cohort of their patients who were treated with preoperative SBRT.[41] Notably, there are now clinical data,[42] albeit retrospective, that support this approach, and several institutions now routinely include a Triangle volume in their target. For example, investigators from Johns Hopkins modified their preoperative SBRT treatment volumes at the end of 2020 to include the "Triangle" volume in addition to gross disease and involved vasculature and found an improvement in 2-year locoregional progression-free survival from 48% to 78% since making this change.[16] Although prospective data are ultimately needed to validate the impact of targeting the "Triangle" on locoregional control, these findings suggest that some type of elective volume coverage is critical for optimizing locoregional control and that targeting the extrapancreatic neural tracts encompassed by the "Triangle" volume may serve as a basis for volume delineation, as reflected in these consensus guidelines. Importantly, optimal dosing to this elective volume remains a point that requires further clarification and for which no consensus was achieved among this group. Furthermore, although the "Triangle" volume is likely relevant for tumors centered in the pancreatic head, neck, and proximal body, the distribution of extrapancreatic perineural invasion for distal body or tail tumors may differ, leading to the modified recommendations for elective coverage for tumors centered in the distal body or tail of the pancreas. Additionally, the true margin around vasculature structures that is required to encompass at-risk neural tracts remains unclear, which was the reason that a range of margin around vascular structures, namely 5 to 10 mm, was provided as opposed to a specific value. Moreover, whether coverage of the entire pancreatic head and tail is needed for head/neck/proximal body and distal body/tail tumors, respectively, is also unclear and would benefit from additional data on parenchymal failure rates in the setting of RT delivered with preoperative or definitive intent.

Whether similar elective coverage should be applied to the definitive setting represents another unanswered question but was favored among this group. Certainly, for unresectable disease, which remains incurable for most, prevention of morbidity and mortality related to uncontrolled local progression of gross disease is the primary goal of RT; thus, it could be argued that targeting only gross disease would be consistent with this aim.[43] However, if excluding an elective volume could lead to complications from marginal recurrences, then more generous coverage could be justified. Additionally, time off systemic therapy represents an important endpoint, and if prevention of marginal recurrence could also decrease chemotherapy use without adding treatment time, then achieving this endpoint may be a reason to incorporate elective coverage. Ultimately, however, more prospective data will be needed to clarify these questions.[11] Moreover, we also acknowledge that larger target volumes increase the risk of toxicity particularly to adjacent mucosal structures and lymphopenia.[44] As such, volume expansions should be judiciously undertaken. Although inclusion of a lower dose elective volume was not unanimous among our group, the consensus was to recommend as part of the contouring atlas with goal of

standardizing practice such that outcomes and toxicity can be better assessed.

Dose-escalated RT in PDAC can cause severe toxicity, even death when there is overlap with bowel and/or stomach, and especially in cases of direct tumor invasion into these structures with/or without existing ulceration and/or bleeding. Fortunately, these instances are rare due to patient selection, technologic advances in target visualization, and rigid immobilization. However, predicting which patient will experience a high-grade toxicity can be challenging, and tradeoffs are required between tumor coverage and dose to critical adjacent luminal organs. Reflecting these toxicity concerns, in pancreas cancer, the proportion of tumor receiving prescription dose can drop below 70% or 80%, less than what is generally accepted in other sites such as liver and lung.[45] Achieving the optimal balance between dose to tumor versus normal tissues is a key challenges in PDAC RT, and some have argued that radiation oncologists have erred on the side of excessive caution, leading to higher rates of local recurrence and persistent disease that itself represents a morbid toxicity possibly contributing to mortality.[46] Through standardizing treatment volumes and dose constraints, we can gain a better understanding of the benefits of dose-escalated RT and side effect profiles of various dose-fractionation regimens, allowing us to further optimize the therapeutic ratio in pancreas RT.

The main limitation is that our guidelines are based upon expert consensus along with a literature review of retrospective or single-arm series. Such a limitation was unavoidable because there are no prospective randomized trials assessing RT volumes in PDAC. As such, we acknowledge our atlas will evolve over time as our collective understanding of dose-escalated RT in PDAC improves. Furthermore, the volumes and metrics presented here are meant to provide guidance on the delivery of dose-escalated RT. Radiation oncologists should use their own clinical judgment to incorporate volumes that may be more or less generous.

In summary, our multidisciplinary and international pancreatic cancer experts have created an NRG consensus contouring guidelines for dose-escalated PDAC RT that reflects current knowledge of recurrence patterns with novel treatment techniques. Prospective incorporation of this atlas with assessment of clinical outcomes is needed to further optimize RT in this disease. The proposed volumes can be used to standardize practices across prospective clinical trial settings worldwide and in future trials seeking to define the role of dose-escalated RT in PDAC.

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