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Basic Original Report

Australasian Gastrointestinal Trials Group (AGITG) and Trans-Tasman Radiation Oncology Group (TROG) Guidelines for Pancreatic Stereotactic Body Radiation Therapy (SBRT)

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Abstract

Purpose: Nonrandomized data exploring pancreas stereotactic body radiation therapy (SBRT) has demonstrated excellent local control rates and low toxicity. Before commencing a randomized trial investigating pancreas SBRT, standardization of prescription dose, dose constraints, simulation technique, and clinical target volume delineation are required.

Methods and Materials: Specialists in radiation oncology, medical oncology, hepatobiliary surgery, and gastroenterology attended 2 consecutive Australasian Gastrointestinal Trials Group workshops in 2017 and 2018. Sample cases were discussed during workshop contact with specifically invited international speakers highly experienced in pancreas SBRT. Furthermore, sample cases were contoured and planned between workshop contact to finalize dose constraints and clinical target volume delineation.

Results: Over 2 separate workshops, consensus was reached on dose and simulation technique. The working group recommended a dose prescription of 40 Gy in 5 fractions. Treatment delivery during end-expiratory breath hold with triple-phase contrast enhanced computed tomography was recommended. In addition, dose constraints, stepwise contouring guidelines, and an anatomic atlas for pancreatic SBRT were developed.

Conclusions: Pancreas SBRT is emerging as a promising treatment modality requiring prospective evaluation in randomized studies. This work attempts to standardize dose, simulation technique, and volume delineation to support the delivery of high quality SBRT in a multicenter study.

Introduction

Pancreatic cancer (PC) is the fifth most lethal cancer, accounting for the deaths of more than 2900 Australians annually.[1] For the group of patients who have high-risk, borderline resectable (BRPC) or locally advanced pancreas cancer (LAPC), the 5-year overall survival is only 12%.[2] Furthermore, approximately half of all patients with PC will subsequently experience locoregional recurrence,[3,4] a major contributor to the substantial morbidity and mortality of pancreatic cancer.[5] Clinical trials exploring new treatment paradigms for PC including stereotactic body radiation therapy (SBRT) are recommended within international consensus guidelines.[6] The higher dose delivered per fraction with SBRT increases the biologically effective dose (BED) and extent of tumor cell kill.[7] The benefits of SBRT over conventional external beam radiation therapy (EBRT) have been demonstrated in a number of other cancers.[8,9]

There are limited published contouring guidelines for pancreas SBRT.[10] Consensus guidelines for clinical target volume delineation in postoperative, preoperative, and definitive settings do exist.[11,12] Before commencement of a randomized study, the Australasian Gastrointestinal Trials Group (AGITG) and Trans-Tasman Radiation Oncology Group identified the importance of standardizing dose and simulation technique for PC SBRT in addition to standardizing volumes for the tumor-vessel interface (TVI), planning organ-at-risk (OAR) volume (PRV), and clinical target volume. Radiation therapy quality and protocol compliance has been shown to affect important clinical endpoints.[13,14]

The intent was to reach consensus on dose and simulation technique and to develop stepwise contouring guidelines and an anatomic atlas for pancreas SBRT. Radiation oncologists will use this atlas in a large multicenter trial beginning recruitment in 2019 (NCT04089150).

Methods and Materials

Specialists in radiation oncology, medical oncology, hepatobiliary surgery, and gastroenterology attended 2 consecutive AGITG workshops in Cairns (October 4-6, 2017) and Brisbane, Australia (October 31-November 2, 2018). Before the first workshop, a literature review was performed, after which the AGITG working party (WP) drafted pancreas SBRT guidelines. These guidelines were tested on sample cases and further discussed during a dedicated pancreas SBRT contouring session at the end of the first day of the first workshop. An invited international speaker from the discipline of radiation oncology, DC, was present at the first workshop to provide feedback and assist in achieving consensus. Unresolved issues at the completion of the first workshop were then referred to the WP for further development. Their recommendations were circulated to all workshop delegates and interested individuals for comment. During September and October 2018, 2 further example cases were contoured by a broad Australian radiation oncology group before further discussion at the second workshop. Confidential group review of the 2 contoured cases occurred with issues and variations discussed. During this conference, a second overseas speaker, KG, was present to provide feedback and assist in guideline development. Feedback was incorporated, and guidelines were refined. Sample cases underwent radiation therapy planning to assist in determination of appropriate dose constraints and target coverage goals. In addition, the existent literature was scrutinized for toxicity outcomes with 5 or fewer fraction protocols. Existing pancreas SBRT studies, including the Alliance A021501 SBRT study in BRPC[15] and the Stanford SBRT Study (NCT01926197), are ongoing. The dose constraints used for these studies were evaluated and were contributory to consensus. Lastly, previous clinician experiences were used to determine achievable and safe

dose constraints to be used in the context of a national study. After the second workshop, the WP clarified any unresolved issues and completed an axial contouring atlas of an example case and published these guidelines.

Results

There were 7 and 12 delegates specializing in radiation oncology who attended the first and second workshop, respectively. The majority of attending specialists had clinical experience in SBRT, with all delegates having site-specific interest in upper abdominal radiation. In addition, hepatobiliary surgeons and gastroenterologists were in attendance to discuss the anatomic details of contouring guidelines and fiducial insertion, respectively. Consensus was achieved on most issues; however, further discussions on target volumes and dose constraints were required and further developed after workshop contact.

Discussion

It is apparent that many institutions worldwide are delivering pancreas SBRT in the absence of randomized data. The majority of experience with SBRT in the upper abdomen comes from liver SBRT. Liver SBRT has robust evidence developed over decades of phase 1 and 2 studies with local control rates in excess of 70% to 80%, and toxicity is acceptable when well-published dose constraints are respected.[16,17] Preliminary nonrandomized experiences with pancreas SBRT in addition to previous experiences with liver SBRT have informed these contouring guidelines.

Emerging evidence suggests that SBRT may have a role in the treatment of PC. Despite showing improved local control, conventional EBRT has not made significant inroads toward improving survival in localized PC[4]; however, SBRT offers a number of potential advantages, including a higher BED, reduced volume of normal tissue irradiated, and reduced overall treatment time. A large institutional study by Mellon et al exploring the combination of modern chemotherapy and SBRT in BRPC and LAPC showed a median overall survival approaching 3 years, far superior to contemporary outcomes.[18] Additionally, they demonstrated that 36% of patients who received FOLFIRINOX (Oxaliplatin, leucovorin, irinotecan, 5-fluorouracil) chemotherapy and SBRT underwent surgical resection, despite having "unresectable" disease at diagnosis. A large review of over 14,000 patients with LAPC suggested superior survival for SBRT over chemotherapy and conventional EBRT.[5] Encouraging preliminary results were also reported in a pooled analysis of 19 trials in LAPC, with locoregional control rates in excess of 70%.[19] SBRT before surgical resection has been demonstrated to be safe with no increase in surgical complications compared with EBRT.[20-23] Single-center Australian data exploring SBRT in 26 patients with LAPC recorded grade 3 toxicity attributable to SBRT in 21% of patients, no grade 4 or 5 toxicity, and a local control rate of 67%, demonstrating that this treatment can be delivered safely and effectively.[24] The shorter treatment duration of SBRT has the added benefits of improved convenience for patients and improved cost-efficiency for health services. Given these encouraging preliminary outcomes, pancreas SBRT should be explored in a randomized setting.

Patient selection

Optimal patient selection for pancreas SBRT is yet to be defined. Most evidence includes patients with BRPC or LAPC. The high metastatic rate seen in all patients with pancreatic cancer has prompted recent interest in giving neoadjuvant chemotherapy in all high-risk patients.[25-27] Using neoadjuvant treatment before surgery to prevent the morbidity of surgery in patients with rapidly progressive metastatic disease is the subject of active research. More contemporary and effective systemic treatments have increased the importance of locoregional control through surgery or radiation therapy.[3,28,29] Preliminary outcomes in the LAPC cohort have been encouraging. In those patients who do not proceed to surgery, duodenal toxicity appears acceptable when published dose constraints are followed.[19] The potential for preoperative hypofractionated radiation therapy to translate into overall survival benefit was demonstrated in PREOPANC-1, and we await publication of final results.[30] These guidelines do not apply for patients with metastatic disease or large tumors or patients with gastrointestinal mucosal infiltration evident at time of diagnostic endoscopy when different dose and even conventional EBRT may need to be considered.

Dose

Published SBRT studies have utilized between 1 and 6 fractions, with 5 fraction schedules the most commonly employed.[31-33] SBRT regimens of 25 Gy in a single fraction (BED_{10} = 88 Gy, BED_3 = 233 Gy) and 45 Gy in 3 fractions (BED_{10} = 113 Gy, BED_3 = 270 Gy) have demonstrated higher toxicity in institutional studies.[31,32] Some authors have failed to correlate local control and dose, although dose has been shown to correlate with toxicity.[34] Doses of up to 50 Gy in 5 fractions (BED_{10} = 100 Gy, BED_3 = 217 Gy) to the planning target volume (PTV) have been utilized in a number of studies with acceptable toxicity.[31,35-37] In the absence of randomized evidence, the WP has recommended a dose of 40 Gy in 5 fractions (BED_{10} = 72 Gy, BED_3 = 147 Gy) to as much of the PTV as possible. To meet dose constraints to OARs, under coverage of the PTV near gastrointestinal structures is required. We recommend the dose to 90% of an evaluable PTV (PTV less gastrointestinal PRV) is greater than 100% of the prescription dose (40 Gy). Compromises to coverage may be needed when tumors are

Table 1 Suggested coverage goals for SBRT

Parameter	Per protocol	Minor variation	Major variation
PTV40_EVAL D90%, %	≥100	90-99	<90
PTV40 D99%, Gy	>30	25-30	<25
CTV D99%, Gy	>33	30-33	<30
Max dose (D0.5 cm^3), %	110-130	130-140 OR <110	>140

Abbreviations: CTV = clinical target volume; PTV40 = 40-Gy planning target volume; SBRT = stereotactic body radiation therapy. D90% = minimum dose covering 90% of volume; D99% = minimum dose covering 99% of volume; Max dose (D0.5cm) = maximum dose to volume of 0.5cm^3; PTV40_EVAL = PTV40 less the gastrointestinal structure PRV.

proximal to hollow viscous. If D90% (minimum dose covering 90% of the volume) is less than 90% of prescription dose, reduced-dose SBRT, conventional chemoradiotherapy, or chemotherapy alone should be considered (Table 1). Maximum doses (D0.5 cm^3) of 33 Gy in 5 fractions (BED_{10} = 54 Gy, BED_3 = 103 Gy) to the duodenum and small bowel have a low incidence of toxicity.[16,18] By utilizing conservative duodenal and gastrointestinal dose constraints, we aim to distinguish the areas where it is safer to deliver the prescribed dose and those where dose fall-off should be prioritized (Table 2). This is important because many patients may not proceed on to a resection and may be at risk of ongoing toxicity to structures in the treated area. This prescription ensures dose delivered is within the existing evidence and maximizes the safety and tolerability of treatment by respecting OARs with a lower dose. SBRT should be delivered as 5 fractions with a maximum of 4 treatments per week, with 2 consecutive days permitted but not 3. A minimum of 24 hours between fractions is also recommended.

Simulation

The majority of published experience to date has included the use of fiducial markers to aid with image guidance during radiation delivery.[31,38-41] The use of biliary stents as a surrogate for tumor position is controversial.[42,43] We recommend endoscopic insertion of fiducial markers 2 or more days before radiation therapy simulation. In certain circumstances (eg, patient travel), earlier simulation can be considered as the rate of fiducial migration is low.[44,45] We recommend fasting for 3 to 4 hours before radiation therapy simulation and treatment. The use of oral contrast is at the discretion of the treating radiation oncologist and may be useful before simulation and treatment in specific circumstances.[46] Similarly, water may be used to help visualize the duodenum and displace the lateral wall of the duodenum.

The WP recommends simulation and treatment during end-expiratory breath hold. Treatment during breath hold minimizes field size required compared with treatment during free breathing, with well-documented pancreas cancer amplitudes greater than 20 mm.[47-49] Treatment during end expiration is preferred over inspiration as it has superior reproducibility.[47] Treatment during end-expiratory breath hold has some disadvantages, including multiple scans to confirm reproducibility and unsuitability for some patients; additionally, some centers also may not have the technical expertise required. Nonetheless, the WP prefers treatment during end-expiratory breath hold, acknowledging it may not always be possible.

Patients should be positioned in the supine position on a full-body vacuum bag, with arms above their head. Scans should be from the level of the tenth thoracic vertebrae (T10) to the pelvis. Diagnostic images may be fused to further assess organ motion. Diagnostic images are unlikely to be in treatment position, and this needs to be considered when utilizing information derived from these images. The WP recommends a minimum of 2 end-expiratory breath hold scans without contrast during simulation. A 4-dimensional computed tomography (4D-CT) scan should be done for all patients.

Additionally, during simulation a contrast enhanced CT scan during end-expiratory breath hold should be performed. Contrast timing should follow local diagnostic guidelines but should provide anatomic detail during late arterial (25-35 seconds post contrast injection) and portal venous phases (55-70 seconds post contrast injection) because this increases tumor-to-pancreas enhancement ratios and gross tumor volume reproducibility (Fig 1).[50] A pancreatic parenchymal phase (45-50 seconds post contrast injection) can be done as part of the portal venous phase or as a separate scan, depending on department capacity to distinguish these time points. In the event that only 1 time point for imaging post contrast injection can be performed, the WP recommends priority be given to the pancreatic parenchymal phase.

Using the end-expiratory breath hold scans (with and without contrast), an internal target volume can be created to account for variation of tumor position on multiple end-expiratory breath hold scans. The need for an internal target volume if using intrafractional imaging should be assessed on an institutional basis. The multiple end-expiratory breath hold scans and 4D-CT can be used for gastrointestinal structure PRV formation. A minimum of 3-mm expansion of the stomach, duodenum, small bowel, and large bowel to generate PRV should be employed. In patients where end-expiratory breath hold is not reproducible, a 4D data set will allow an assessment of the appropriateness of an alternative technique like free breathing or gating. The WP recommends a slice thickness of 2 mm or less. We recommend a maximum 4-week break between chemotherapy and SBRT.

Table 2 Suggested dose constraints for pancreas SBRT

Organ	Standardized name	Parameter	Constraint		
		Constraint	Per protocol, Gy	Minor variation, Gy	Major variation, Gy
Duodenum	Duodenum	Dmax (0.5 cm^3)	<33	≤35	>35
		V30	<5*	5-10*	>10*
Stomach	Stomach	Dmax (0.5 cm^3)	<33	≤35	>35
		V30	<5*	5-10*	>10*
Small bowel	SmallBowel	Dmax (0.5 cm^3)	<33	≤35	>35
		V30	<5*	5-10*	>10*
Large bowel	LargeBowel	Dmax (0.5 cm^3)	≤35 Gy	35-38 Gy	>38
Duodenum PRV†	Duodenum_PRV	Dmax (0.5 cm^3)	<38 Gy	38-40 Gy	>40
Small bowel PRV†	SmallBowel_PRV	Dmax (0.5 cm^3)	<38 Gy	38-40 Gy	>40
Large bowel PRV†	LargeBowel_PRV	Dmax (0.5 cm^3)	<38 Gy	38-40 Gy	>40
Stomach PRV†	Stomach_PRV	Dmax (0.5 cm^3)	<38 Gy	38-40 Gy	>40
Spinal cord PRV	SpinalCord_05	Dmax (0.5 cm^3)	<20 Gy	≤25 Gy	>25
Combined kidneys	Kidneys_Comb	V12‡	<25§	25-30§	>30§
Single kidney	Kidney_L Kidney_R	V10‡	<10§	10-25§	>25§
Liver	Liver	V12‡	<40§	≤50§	>50§

Abbreviations: Dmax = maximum dose; PRV = planning organ-at-risk volume; SBRT = stereotactic body radiation therapy.

* Unit is cm^3.

† Minimum PRV expansion should be 3 mm; however, larger expansions should be considered in a setting of increased organ movement or uncertainty.

‡ Unit is Gy.

§ Unit is percent.

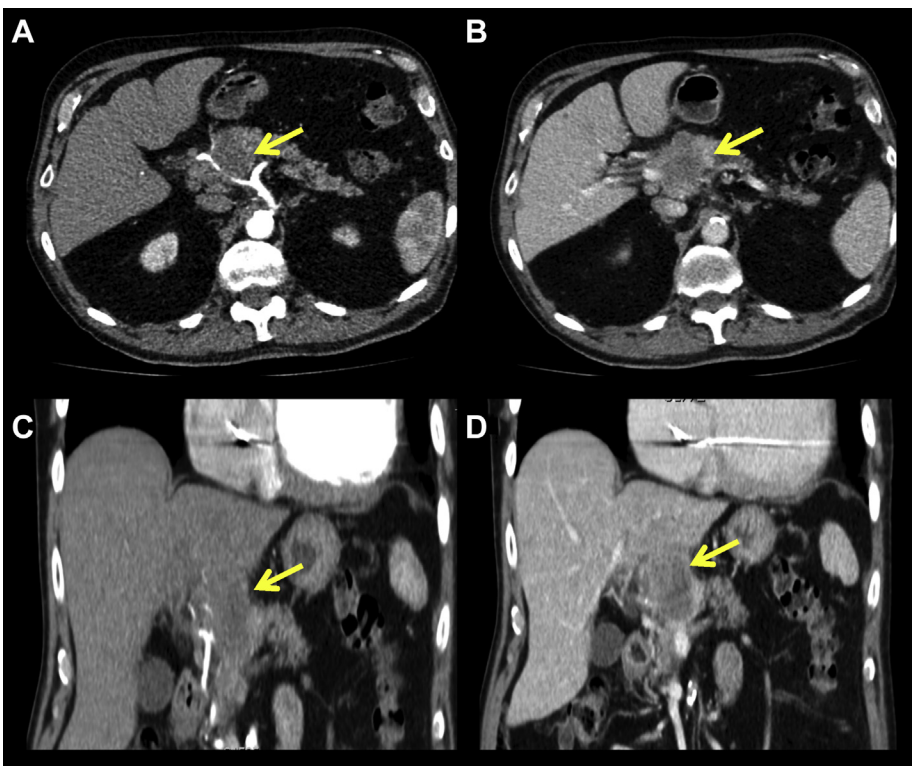

Figure 1 The value of delayed phase CT in pancreatic cancer is demonstrated in this patient with locally advanced pancreatic cancer (yellow arrow). During the portal venous or parenchymal phase, the tumor can be seen as hypodense structure within the pancreas. (A) Arterial enhanced axial CT. (B) Delayed venous phase axial CT. (C) Arterial enhanced coronal CT. (D) Delayed venous phase coronal CT. *Abbreviation:* CT = computed tomography.

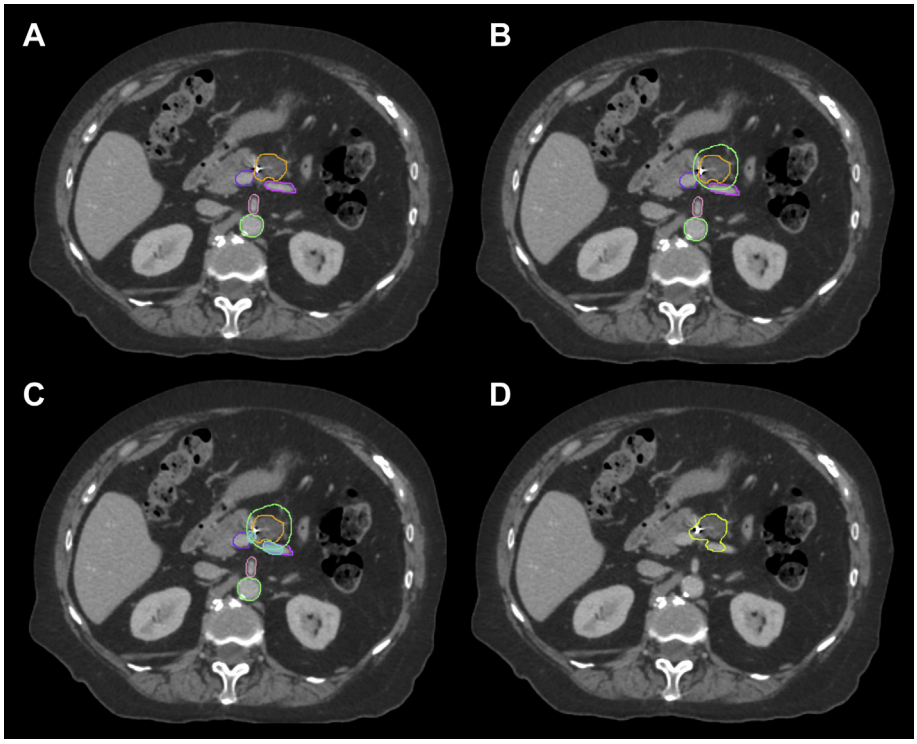

Figure 2 A patient with locally advanced pancreatic cancer and tumor involvement of the splenic vein (magenta) with close proximity to left portal vein (purple). (A) The GTV (orange) and nearby vessels are contoured. (B) A 5-mm expansion of the GTV (green) helps delineate which vessels are within 5 mm of the GTV. (C) The entire circumference of involved or proximal vessels are contoured to form tumor vessel interface (light blue). (D) GTV and tumor-vessel interface are combined to form the CTV (yellow). *Abbreviation:* GTV = gross tumor volume, CTV= clinical target volume.

The WP strongly encourages treatment during end-expiratory breath hold with an active breath hold device or with gated technology. In patients who cannot perform end-expiratory breath hold, alternative methods may need to be employed. When treating during free breathing, an internal target volume should be delineated using the 4D-CT scan (or 4D magnetic resonance imaging [MRI]). For centers that elect to treat during free breathing, if tumor or fiducial movement on respiration is greater than 5 mm, the WP recommends amplitude-reducing methods or appropriate compensation such as gating, tracking, compression, or a combination.

Volume delineation

The difficulties associated with accurate and consistent delineation of the primary gross tumor volume (GTVp) have been demonstrated previously.[51] Intravenous contrast agents are recommended for reproducible volume delineation. GTVp delineation is recommended with the assistance of a radiologist utilizing all available information including CT, MRI, positron emission tomography (PET)-CT, and endoscopy reports (Appendix A, available online at https://doi.org/10.1016/j.prro.2019.07.018). The utility of PET-CT as a prognostic biomarker in pancreas cancer is an area of interest.[52-54] In addition to tissue collection, endoscopy is essential to assess duodenal involvement. All patients undergoing pancreas SBRT should be considered for empirical antacid therapy with a proton pump inhibitor or otherwise. Ideally, MRI and PET are performed in treatment position. However, in the majority of institutions this will not be possible. When MRI is utilized, existing guidelines for GTVp delineation may be of value.[55] The GTVp should include fibrotic areas near vessels based on experienced radiologist review. This is identified as poorly defined or thickened vessel edges. It is now known that pancreatic stellate cells and the desmoplastic reaction around tumor edges is a key contributor to pancreatic cell cancer biology, including regional progression and distant metastasis.[56,57] As such, this poorly defined area around the tumor should be included in the GTVp. If it is unclear whether a vessel is involved, it should be included in the GTVp. The TVI is the area involved or in close proximity between major vessels, and the GTVp and is important as close margins and recurrences commonly occur in this area. The TVI concept has been utilized by others.[15,18] We define the TVI as the area where the GTVp is involving or within 5 mm of the major vessels in the upper abdomen, including celiac artery, superior mesenteric artery, common hepatic artery, left gastric artery, superior mesenteric

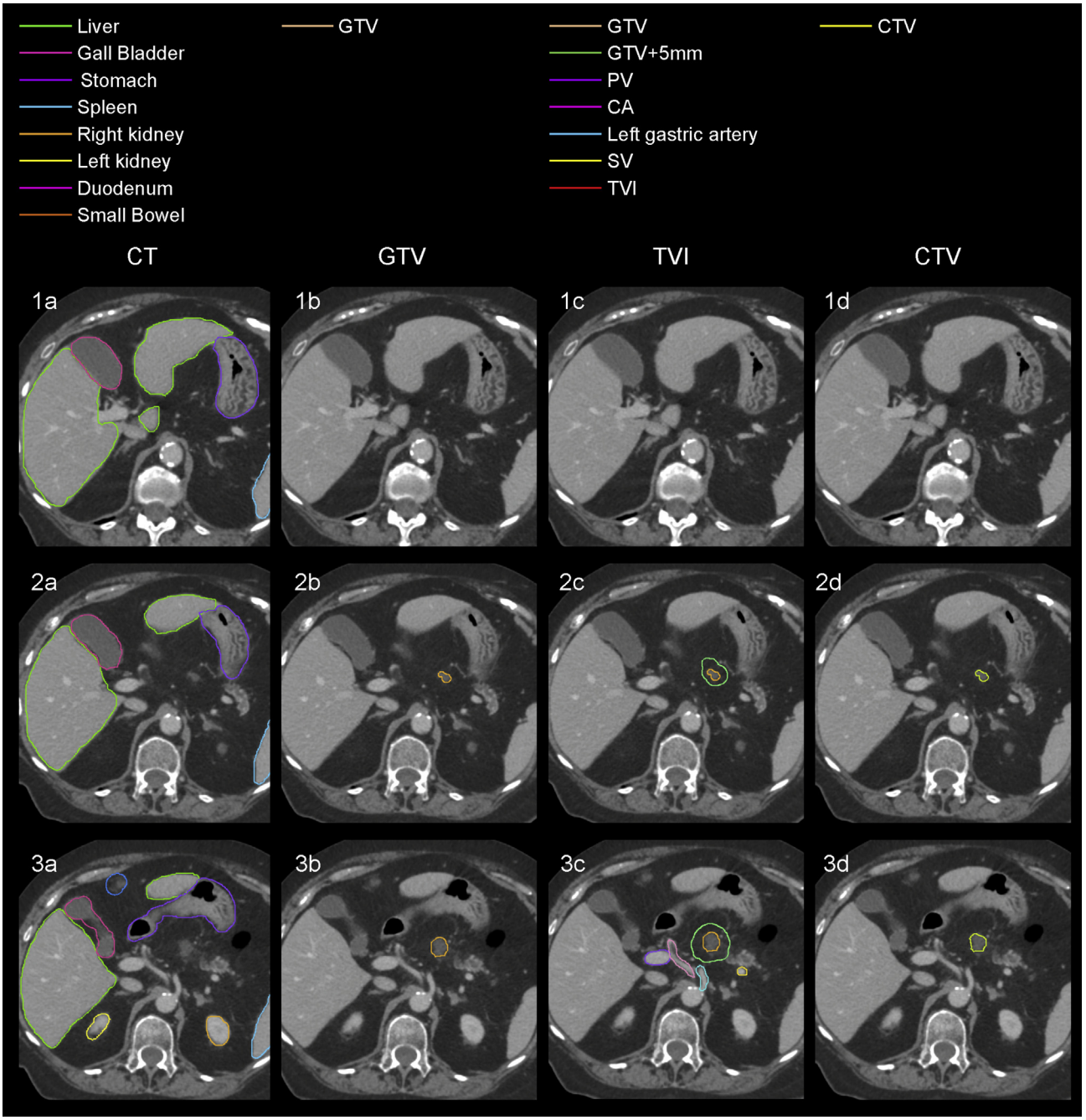

Figure 3 Contouring atlas for pancreas stereotactic body radiation therapy demonstrating formation of the tumor-vessel interface. Patient with locally advanced pancreatic cancer and aberrant left gastric artery. Abbreviations: CA = celiac artery; CTV = clinical target volume; GTV = gross tumor volume; PV = portal vein; SMV = superior mesenteric vein; SV = splenic vein.

vein, portal vein, splenic vein, or aorta. If GTVp is within 5 mm of these structures, then a TVI is defined as above and incorporated into a clinical target volume of 40. In principle, any major vessel within 5 mm of the tumor should be contoured from 5 mm proximal to 5 mm distal of the GTVp (Fig 2). This region should be defined in 3 dimensions (eg, using axial, sagittal, and coronal planes) (Fig 3, Appendix B, available online at https://doi,org/10.1016/j.prro.2019.07.018). Whole vessel circumference should be included. In the case of aorta and portal vein, only the proximal half may need to be contoured as part of the TVI as these vessels have a much larger circumference (Table 3). Accurate contouring of OARs is an essential component of pancreatic SBRT and should be verified along with target volumes by radiation oncologist peer review before radiation therapy planning.

The majority of studies have utilized a 5-mm expansion to PTV.[19] In general, a 5-mm margin is

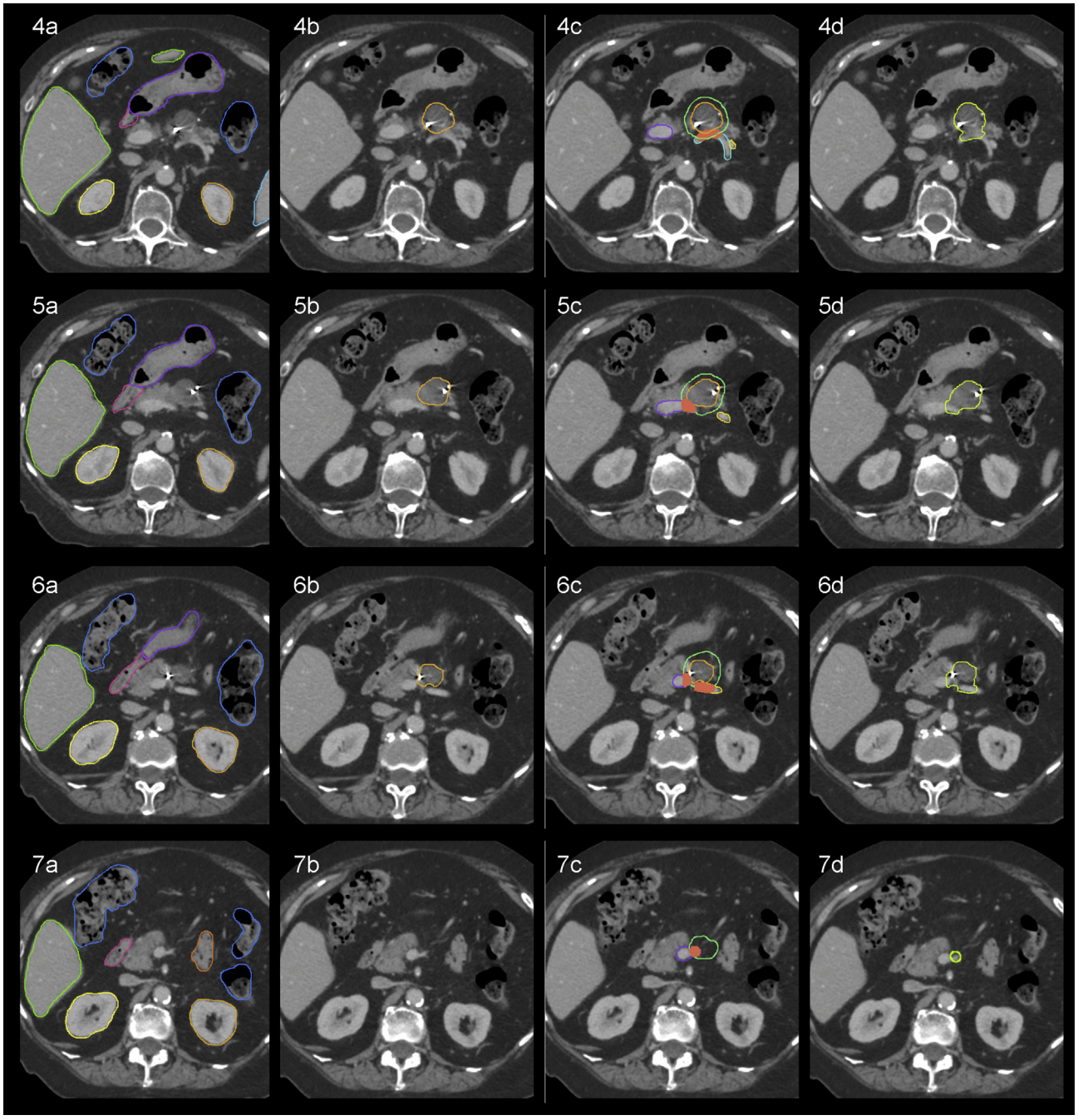

Figure 3 Continued

recommended. When a PTV of 40 crosses into or near a hollow viscous PRV, compromises need to be made to dose coverage in this area to preserve hollow viscous dose constraints. We recommend the duodenal, stomach, small bowel, and large bowel PRV be a minimum 3-mm expansion. However, if treating during free breathing or organ movement is seen to be large on multiple end-expiratory breath hold scans or 4D-CT, a greater PRV margin is required. Concessions to large bowel maximum dose (D0.5 cm^3 and D5 cm^3) may be considered to meet coverage goals.

There is controversy surrounding the treatment of an elective nodal volume during SBRT. There is no randomized evidence suggesting superiority of elective nodal radiation therapy to treatment of macroscopic disease alone in patients receiving SBRT. Some authors have suggested high locoregional recurrence rates after SBRT.[58,59] In contrast, other reviews, including a large meta-analysis, have demonstrated lower recurrence rates.[19,60] The evidence around SBRT to an elective nodal volume is unclear owing to different dose prescriptions, treatment techniques, and definitions of locoregional

Table 3 Boolean expression for generation of PTV40 for SBRT in pancreatic cancer

1	Contour GTVp and GTVn as determined with assistance of radiologist using endoscopy and all available imaging.
2	Contour superior mesenteric artery, celiac artery, common hepatic artery, left gastric artery, superior mesenteric vein, portal vein, splenic vein, and aorta that is within 5 mm of GTVp.
3	GTV40 = GTVp + GTVn
4	CTV40 = GTV40 + TVI
5	ITV40 creation using motion information from multiple end-expiratory breath hold scans and/or 4D-CT*
6	PTV40 = CTV40 (or ITV40 if generated) + 5 mm†
7	Ensure maximum dose to gastrointestinal structures (duodenum, small bowel, stomach, large bowel) is < 33 Gy (D0.5 cm^3) and to viscous PRV is < 38 Gy (D0.5 cm^3)

Abbreviations: 4D-CT = 4-dimensional computed tomography; CTV40 = 40-Gy clinical target volume; GTVn = gross tumor volume of the lymph nodes; GTVp = primary gross tumor volume; ITV = internal target volume; ITV40 = 40-Gy internal target volume; PTV40 = 40-Gy planning target volume; SBRT = stereotactic body radiation therapy; TVI = tumor-vessel interface.

* If using free-breathing technique, the ITV will need to account for motion on 4D-CT.

† Institution dependent.

recurrence and a lack of prospective data. The WP does not recommend an elective nodal field in the absence of prospective data.

Concurrent chemotherapy

Some studies have described outcomes with concurrent chemotherapy[35,39] with acceptable toxicity. Single-center Australian data describes SBRT for 26 patients with LAPC who were treated with concurrent capecitabine and experienced no grade 4 or higher SBRT toxicities.[24] The lack of data proving safety and superior outcomes has led to the authors recommending against concurrent chemotherapy during pancreas SBRT, particularly with the dose escalation recommended.

Conclusions

Pancreas SBRT is emerging as a promising treatment modality requiring prospective evaluation in randomized studies. Given the high level of precision required and the potential for significant toxicity, pancreas SBRT should be performed in a trial setting with appropriate quality assurance and prospective data collection. This project attempts to standardize dose, simulation technique, and volume delineation to support the delivery of high-quality SBRT in a multicenter study.

Supplementary Data

Supplementary material for this article can be found at https://doi.org/10.1016/j.prro.2019.07.018.

References

1. Australian Institute of Health and Welfare. *Cancer in Australia 2017*. Canberra: Australian Institute of Health and Welfare; 2017.
2. American Cancer Society. *Cancer Facts & Figures 2018*. Atlanta: American Cancer Society; 2018.
3. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): A multicentre, open-label, randomised, phase 3 trial. *Lancet*. 2017;389:1011-1024.
4. Hammel P, Huguet F, van Laethem J-L, et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: The LAP07 randomized clinical trial. *JAMA*. 2016;315:1844-1853.
5. de Geus SW, Eskander MF, Kasumova GG, et al. *Stereotactic body radiotherapy for unresected pancreatic cancer: A nationwide review*. Cancer; 2017.
6. Khorana AA, Mangu PB, Berlin J, et al. Potentially curable pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2016;34:2541-2556.
7. Brown JM, Carlson DJ, Brenner DJ. The tumor radiobiology of SRS and SBRT: Are more than the 5 Rs involved? *Int J Radiat Oncol Biol Phys*. 2014;88:254-262.
8. Ball D, Mai T, Vinod S, et al. MA 13.07 A randomized trial of SABR vs conventional radiotherapy for inoperable stage I non-small cell lung cancer: TROG09. 02 (CHISEL). *J Thorac Oncol*. 2017;12:S1853.
9. Foote M, Letourneau D, Hyde D, et al. Technique for stereotactic body radiotherapy for spinal metastases. *J Clin Neurosci*. 2011;18:276-279.
10. Russo S, Hoffe S, Kim E. *Gastrointestinal Malignancies: A Practical Guide on Treatment Techniques*. New York: Springer; 2018.
11. Goodman KA, Regine WF, Dawson LA, et al. Radiation Therapy Oncology Group consensus panel guidelines for the delineation of the clinical target volume in the postoperative treatment of pancreatic head cancer. *Int J Radiat Oncol Biol Phys*. 2012;83:901-908.
12. Caravatta L, Sallustio G, Pacelli F, et al. Clinical target volume delineation including elective nodal irradiation in preoperative and definitive radiotherapy of pancreatic cancer. *Radiat Oncol*. 2012;7:86.
13. Fairchild A, Straube W, Laurie F, Followill D. Does quality of radiation therapy predict outcomes of multicenter cooperative group trials? A literature review. *Int J Radiat Oncol Biol Phys*. 2013;87:246-260.
14. Weber DC, Tomsej M, Melidis C, Hurkmans CW. QA makes a clinical trial stronger: Evidence-based medicine in radiation therapy. *Radiother Oncol*. 2012;105:4-8.
15. Katz MH, Ou F-S, Herman JM, et al. Alliance for clinical trials in oncology (ALLIANCE) trial A021501: Preoperative extended

chemotherapy vs. chemotherapy plus hypofractionated radiation therapy for borderline resectable adenocarcinoma of the head of the pancreas. *BMC Cancer*. 2017;17:505.
16. Lee MT, Kim JJ, Dinniwell R, et al. Phase I study of individualized stereotactic body radiotherapy of liver metastases. *J Clin Oncol*. 2009;27:1585-1591.
17. Wahl DR, Stenmark MH, Tao Y, et al. Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. *J Clin Oncol*. 2016;34:452-459.
18. Mellon EA, Hoffe SE, Springett GM, et al. Long-term outcomes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma. *Acta Oncol*. 2015;54:979-985.
19. Petrelli F, Comito T, Ghidini A, Torri V, Scorsetti M, Barni S. stereotactic body radiation therapy for locally advanced pancreatic cancer: A systematic review and pooled analysis of 19 trials. *Int J Radiat Oncol Biol Phys*. 2017;97:313-322.
20. Blair AB, Rosati LM, Rezaee N, et al. Postoperative complications after resection of borderline resectable and locally advanced pancreatic cancer: The impact of neoadjuvant chemotherapy with conventional radiation or stereotactic body radiation therapy. *Surgery*. 2018;163:1090-1096.
21. Dholakia AS, Hacker-Prietz A, Wild AT, et al. Resection of borderline resectable pancreatic cancer after neoadjuvant chemoradiation does not depend on improved radiographic appearance of tumor−vessel relationships. *J Radiat Oncol*. 2013;2:413-425.
22. Chuong MD, Springett GM, Freilich JM, et al. Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated. *Int J Radiat Oncol Biol Phys*. 2013;86:516-522.
23. Palta M, Czito B, Abbruzzese J, et al. Interim acute toxicity analysis and surgical outcomes of neoadjuvant gemcitabine/nab-paclitaxel and hypofractionated image guided intensity modulated radiation therapy in resectable and borderline resectable pancreatic cancer (ANCHOR) study. *Int J Radiat Oncol Biol Phys*. 2016;96:S204-S205.
24. Kim L, Nguyen N, Singhal N, Phan VA, Iankov I, Le H. Application of stereotactic body radiotherapy in advanced pancreatic cancers in Australia. *J Med Radiat Sci*. 2019;66:54-61.
25. Chatterjee D, Katz MH, Foo WC, et al. Prognostic significance of new AJCC tumor stage in patients with pancreatic ductal adenocarcinoma treated with neoadjuvant therapy. *Am J Surg Pathol*. 2017;41:1097-1104.
26. Marchegiani G, Andrianello S, Malleo G, et al. Does size matter in pancreatic cancer?: Reappraisal of tumour dimension as a predictor of outcome beyond the TNM. *Ann Surg*. 2017;266:142-148.
27. Motoi F, Kosuge T, Ueno H, et al. Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP05). *Jpn J Clin Oncol*. 2019;49:190-194.
28. Conroy T, Hammel P, Hebbar M, et al. Unicancer GI PRODIGE 24/CCTG PA. 6 trial: A multicenter international randomized phase III trial of adjuvant mFOLFIRINOX versus gemcitabine (gem) in patients with resected pancreatic ductal adenocarcinomas. *J Clin Oncol*. 2018.
29. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364:1817-1825.
30. Van Tienhoven G, Versteijne E, Suker M, et al. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC-1): A randomized, controlled, multicenter phase III trial. *J Clin Oncol*. 2018.
31. Pollom EL, Alagappan M, von Eyben R, et al. Single versus multifraction stereotactic body radiation therapy for pancreatic adenocarcinoma: outcomes and toxicity. *Int J Radiat Oncol Biol Phys*. 2014;90:918-925.
32. Hoyer M, Roed H, Sengelov L, et al. Phase II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. *Radiother Oncol*. 2005;76:48-53.
33. Parekh A, Rosati L, Chang D, et al. Stereotactic body radiation for pancreatic cancer: Results of an international survey of practice patterns. *J Radiat Oncol*. 2017;6:273-278.
34. Brunner TB, Nestle U, Grosu A-L, Partridge M. SBRT in pancreatic cancer: What is the therapeutic window? *Radiother Oncol*. 2015;114:109-116.
35. Lin J-C, Jen Y-M, Li M-H, Chao H-L, Tsai J-T. Comparing outcomes of stereotactic body radiotherapy with intensity-modulated radiotherapy for patients with locally advanced unresectable pancreatic cancer. *Eur J Gastroenterol Hepatol*. 2015;27:259-264.
36. Song Y, Yuan Z, Li F, et al. Analysis of clinical efficacy of CyberKnife® treatment for locally advanced pancreatic cancer. *Onco Targets Ther*. 2015;8:1427.
37. Su T-S, Liang P, Lu H-Z, et al. Stereotactic body radiotherapy using CyberKnife for locally advanced unresectable and metastatic pancreatic cancer. *World J Gastroenterol*. 2015;21:8156.
38. Boone BA, Steve J, Krasinskas AM, et al. Outcomes with FOLFIRINOX for borderline resectable and locally unresectable pancreatic cancer. *J Surg Oncol*. 2013;108:236-241.
39. Gurka MK, Kim C, He R, et al. Stereotactic body radiation therapy (SBRT) combined with chemotherapy for unresected pancreatic adenocarcinoma. *Am J Clin Oncol*. 2017;40:152-157.
40. Goyal K, Einstein D, Ibarra RA, et al. Stereotactic body radiation therapy for nonresectable tumors of the pancreas. *J Surg Res*. 2012;174:319-325.
41. Herman JM, Chang DT, Goodman KA, et al. A phase II multi-institutional study to evaluate gemcitabine and fractionated stereotactic body radiotherapy for unresectable, locally advanced pancreatic adenocarcinoma. *J Clin Oncol*. 2012;30, 4045-4045.
42. Pepin E, Olsen L, Badiyan S, et al. Comparison of implanted fiducial markers and self-expandable metallic stents for pancreatic image guided radiation therapy localization. *Pract Radiat Oncol*. 2015;5:e193-e199.
43. Huguet F, Yorke ED, Davidson M, et al. Modeling pancreatic tumor motion using 4-dimensional computed tomography and surrogate markers. *Int J Radiat Oncol Biol Phys*. 2015;91:579-587.
44. Sanders MK, Moser AJ, Khalid A, et al. EUS-guided fiducial placement for stereotactic body radiotherapy in locally advanced and recurrent pancreatic cancer. *Gastrointest Endosc*. 2010;71:1178-1184.
45. Choi J-H, Seo D-W, Do Hyun, Park SKL, Kim M-H. Fiducial placement for stereotactic body radiation therapy under only endoscopic ultrasonography guidance in pancreatic and hepatic malignancy: Practical feasibility and safety. *Gut Liver*. 2014;8:88.
46. Herman JM, Chang DT, Goodman KA, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. *Cancer*. 2015;121:1128-1137.
47. Heerkens HD, van Vulpen M, van den Berg CA, et al. MRI-based tumor motion characterization and gating schemes for radiation therapy of pancreatic cancer. *Radiother Oncol*. 2014;111:252-257.
48. Bussels B, Goethals L, Feron M, et al. Respiration-induced movement of the upper abdominal organs: a pitfall for the three-dimensional conformal radiation treatment of pancreatic cancer. *Radiother Oncol*. 2003;68:69-74.
49. Feng M, Balter JM, Normolle D, et al. Characterization of pancreatic tumor motion using cine MRI: Surrogates for tumor position should be used with caution. *Int J Radiat Oncol Biol Phys*. 2009;74:884-891.
50. Godfrey DJ, Patel BN, Adamson JD, Subashi E, Salama JK, Palta M. Triphasic contrast enhanced CT simulation with bolus tracking for pancreas SBRT target delineation. *Pract Radiat Oncol*. 2017;7:e489-e497.
51. Hall WA, Heerkens HD, Paulson ES, et al. Pancreatic gross tumor volume contouring on computed tomography (CT) as

compared with magnetic resonance imaging (MRI), results of an international contouring conference. *Pract Radiat Oncol*. 2018;8:107-115.
52. Dholakia AS, Chaudhry M, Leal JP, et al. Baseline metabolic tumor volume and total lesion glycolysis are associated with survival outcomes in patients with locally advanced pancreatic cancer receiving stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys*. 2014;89:539-546.
53. Mellon EA, Jin WH, Frakes JM, et al. Predictors and survival for pathologic tumor response grade in borderline resectable and locally advanced pancreatic cancer treated with induction chemotherapy and neoadjuvant stereotactic body radiotherapy. *Acta Oncol*. 2017;56:391-397.
54. Schellenberg D, Quon A, Minn AY, et al. 18Fluorodeoxyglucose PET is prognostic of progression-free and overall survival in locally advanced pancreas cancer treated with stereotactic radiotherapy. *Int J Radiat Oncol Biol Phys*. 2010;77:1420-1425.
55. Heerkens HD, Hall W, Li X, et al. Recommendations for MRI-based contouring of gross tumor volume and organs at risk for radiation therapy of pancreatic cancer. *Pract Radiat Oncol*. 2017;7:126-136.
56. Apte MV, Wilson JS, Lugea A, Pandol SJ. A starring role for stellate cells in the pancreatic cancer microenvironment. *Gastroenterology*. 2013;144:1210-1219.
57. Apte M, Park S, Phillips P, et al. Desmoplastic reaction in pancreatic cancer: role of pancreatic stellate cells. *Pancreas*. 2004;29:179-187.
58. Kharofa J, Mierzwa M, Olowokure O, et al. Pattern of marginal local failure in a phase II trial of neoadjuvant chemotherapy and stereotactic body radiation therapy for resectable and borderline resectable pancreas cancer. *Am J Clin Oncol*. 2019;42:247-252.
59. Zhu X, Ju X, Cao Y, et al. Patterns of local failure after stereotactic body radiation therapy and sequential chemotherapy as initial treatment for pancreatic cancer: implications of target volume design. *Int J Radiat Oncol Biol Phys*. 2019;104:101-110.
60. Baine MJ, Sleightholm R, Lin C. Incidence and patterns of locoregional failure after stereotactic body radiation therapy for pancreatic adenocarcinoma. *Pract Radiat Oncol*. 2019;9:e29-e37.