SBRT in CARCINOMA PANCREAS

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Resurgence of Role of Radiotherapy in Neoadjuvant Treatment of Pancreatic Cancer

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Conclusion

Initial results of recent trials addressing the management of BRPC by using preoperative chemoradiotherapy have shown a meaningful improvement in clinical outcomes. The results are encouraging for incorporation of radiotherapy in the neoadjuvant management of PC. As there is a renewed interest in role of radiation in neoadjuvant setting, more evidence are expected to emerge in near future.

- Why SBRT in Pancreas Rationale
- Therapeutic Principle
- In whom – Primary indications
- Evidence
- Patient Selection
- Basic Requirements
- Preparation
- Process
- Basics of contouring
- Dose
- Nuances of Delivery
- ASTRO consensus guidelines
- Future Directions
- Take home message

Why SBRT in Pancreas -Rationale

- Aggressive tumor, few effective treatment modalities
- At diagnosis, only 20% of patients have resectable tumor, and about 40% present with a locally advanced tumor
- 60 % patients have local progression (MDACC ph II trial)
- Up to one third die from complications relating to local progression -Biliary, gastric obstruction and portal vein occlusion
- Previous Chemoradiotherapy results are discouraging
- Achieving local control, particularly in borderline resectable or locally advanced disease may lead to significant improvement in survival outcomes
- Enhance resectability rate and in turn survival

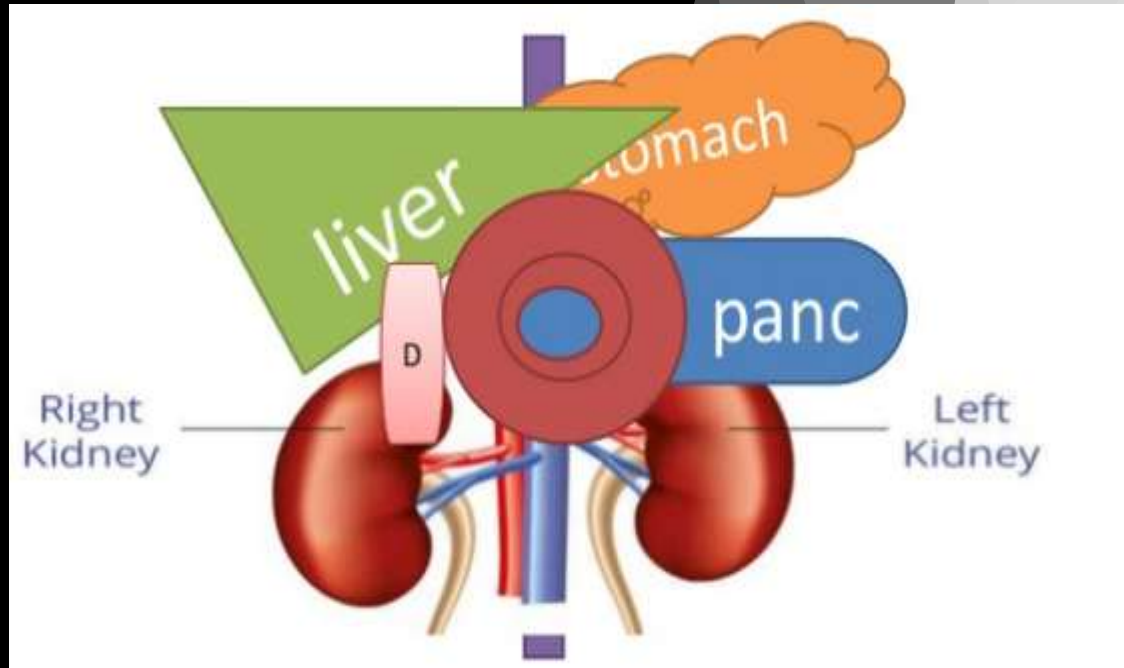
SBRT for BRPC gaining popularity

- – Does not compromise potential surgery option
- – Does not increase postoperative complications
- – Is associated with high rate of R0 resection
- – Is very well tolerated

Katz 2016

Therapeutic Principle of SBRT in Pancreas

- Intrinsic radio resistant malignancy
- To achieve high local control , high BED > 100 Gy required for tumour ablation
- Surrounding radiosensitive structures – Duodenum - Thus limitations of ablative dose delivery
- SBRT delivers a higher biological effective dose to the tumor with sharp dose escalation in a shorter treatment time course. Pancreas SBRT is a novel therapeutic option to achieve local tumor control with minimal toxicity



Optimizing technologic advancements in radiation dose delivery, image guidance, and motion management, SBRT enables the precise application of multiple high-dose radiation beams to treat the tumor plus a small margin over 1-5 days

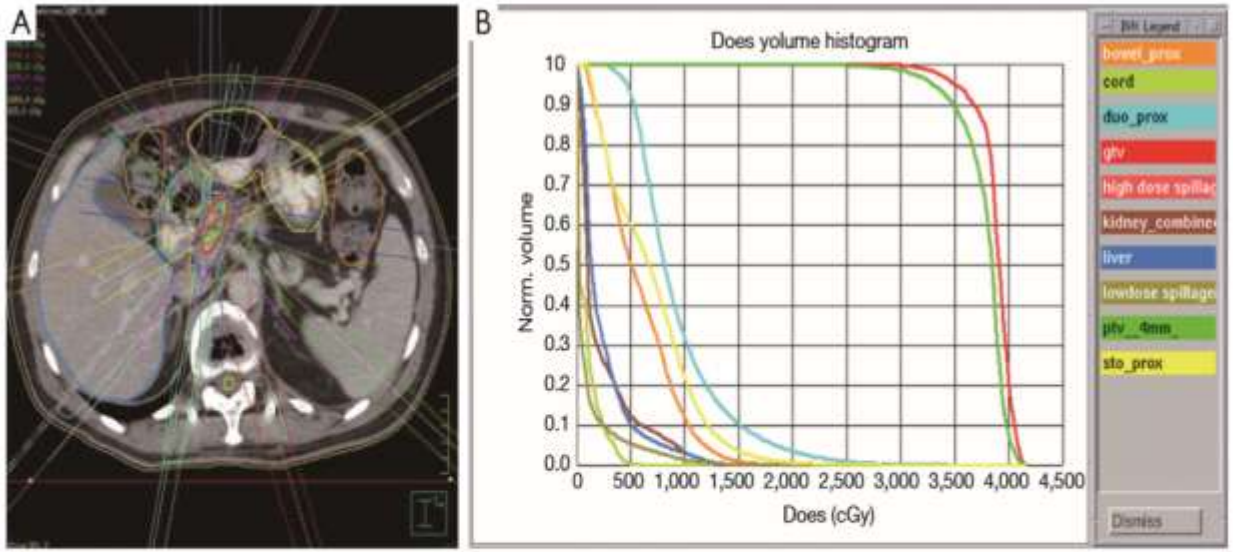
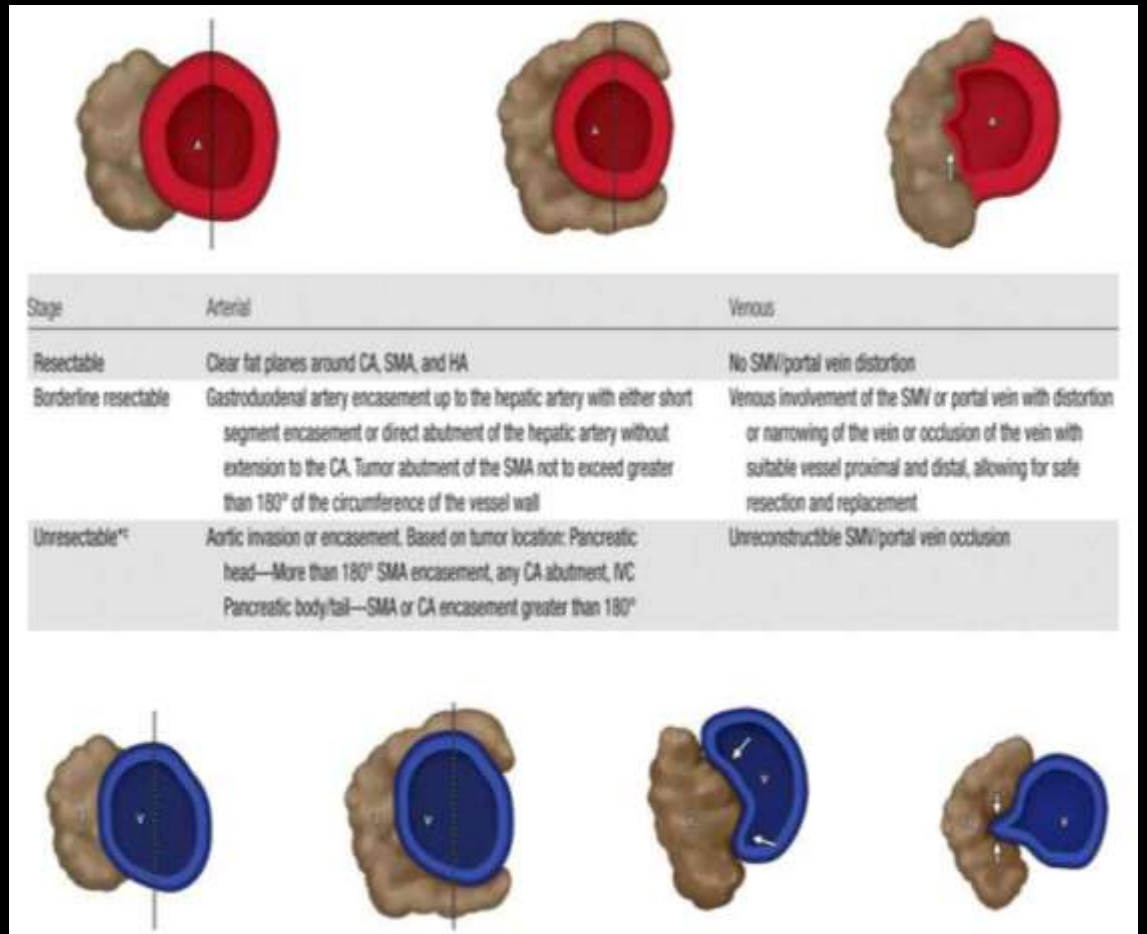


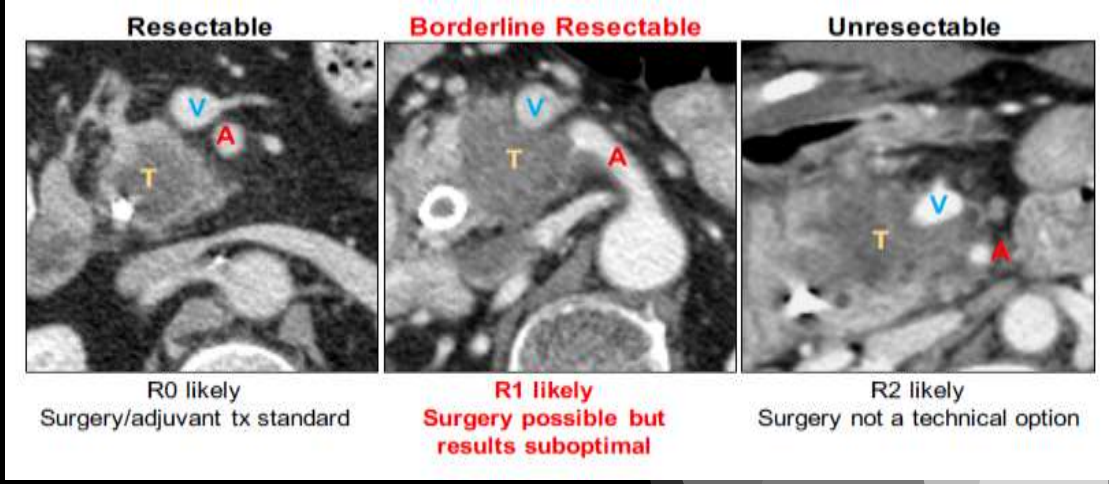
Figure 1 (A) depicts the treatment plan of a patient receiving 33 Gy in 5 fractions to treat a tumor in the head of the pancreas. Note the use of multiple high-dose beams and strict contouring of surrounding organs at risk (OARs). (B) displays the corresponding dose volume histogram (DVH). This demonstrates that dose to the planning target volume (PTV, dark green) and gross tumor volume (GTV, red) is maximized while minimizing dose to the OARs such as the duodenum (light blue), stomach (yellow), bowel (orange), liver (dark blue), kidneys (brown), and spinal cord (light green).

In Whom

- Primarily BRPC / LAPC ,
- Few other emergining indications –re-irradiation, adjuvant



Stage	Arterial	Venous
Resectable	Clear fat planes around CA, SMA, and HA	No SMV/portal vein distortion
Borderline resectable	Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery without extension to the CA. Tumor abutment of the SMA not to exceed greater than 180° of the circumference of the vessel wall	Venous involvement of the SMV or portal vein with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacement
Unresectable*†	Aortic invasion or encasement. Based on tumor location: Pancreatic head—More than 180° SMA encasement, any CA abutment, IVC Pancreatic body/tail—SMA or CA encasement greater than 180°	Unreconstructible SMV/portal vein occlusion



	Potentially Resectable	BORDERLINE RESECTABLE	Locally Advanced
SMV-PV	T-V-I < 180°	T-V-I ≥ 180° and / or reconstructable occlusion	Unreconstructable Occlusion
SMA	No T-V-I	T-V-I < 180°	T-V-I ≥ 180°
CHA	No T-V-I	Reconstructable short-segment T-V-I of any degree	Unreconstructable
Celiac Trunk	No T-V-I	T-V-I < 180°	T-V-I ≥ 180

T-V-I: tumor-vessel interface

Early Evidence

- First, dose-escalation study of pancreas SBRT by Stanford (Koong et al., IJROBP 2004)
- Escalated 15, 20, then 25 Gy x1 fraction
- 7 patients treated at 25 Gy with no GI grade 3 or greater acute toxicity.
- Median Survival only 11 months
- Most patients died of metastatic disease

Reviews

- A large review of over 14,000 patients with LAPC suggested superior survival for SBRT over chemotherapy and conventional EBRT
- The adjusted median Survival was 9.9 mo , 10.9 mo and 12 mo for EBRT , IMRT and SBRT (de Geus SW et al Cancer 2017)
- Encouraging preliminary results were also reported in a pooled analysis of 19 trials in LAPC with locoregional control rates in excess of 70 %

Conventionally Fractionated Radiation Therapy Versus Stereotactic Body Radiation Therapy for Locally Advanced Pancreatic Cancer (CRiSP): An International Systematic Review and Meta-Analysis

- **Results:** A total of 470 studies were initially screened; of these, 9 studies assessed SBRT and 11 studies assessed CFRT.
- The random effects estimate for 2-year OS was 26.9% (95% CI, 20.6%-33.6%) for SBRT versus 13.7% (95% CI, 8.9%-19.3%) for CFRT and was statistically significant in favor of SBRT. The random effects estimate for 1-year OS was 53.7% (95% CI, 39.3%-67.9%) for SBRT versus 49.3% (95% CI, 39.3%-59.4%) for CFRT and was not statistically significant

  The random effects estimate for acute grade 3/4 toxicity was 5.6% (95% CI, 0.0%-20.0%) for SBRT versus 37.7% (95% CI, 24.0%-52.5%) for CFRT and was statistically significant in favor of SBRT.

  The random effects estimate for late grade 3/4 toxicity was 9.0% for SBRT (95% CI, 3.3%-17.1%) versus 10.1% (95% CI, 1.8%-23.8%) for CFRT, which was not statistically significant.
- **Conclusion:** These results suggest that SBRT for LAPC may result in a modest improvement in 2-year OS with decreased rates of acute grade 3/4 toxicity and no change in 1-year-OS or late toxicity. Further study into the use of stereotactic body radiation therapy for these patients is needed.

SBRT in LAPC

Table 1 A summary of clinical studies of stereotactic body radiation therapy in pancreatic cancer

Study (year)	Patients (n)	SBRT dose & fraction	1-year LC	Median OS (m)	Toxicity	Chemotherapy
Koong *et al.* (15) 2004	15 LA	15-25 Gy ×1	100%	11	33% Grades 1 & 2 0% ≥ Grade 3	None
Koong *et al.* (16) 2005	16 LA	25 Gy ×1 (boost)	94%	8.3	69% Grades 1 & 2 12.5% ≥ Grade 3	5-FU with EBRT prior to SBRT
Schellenberg *et al.* (21) 2008	16 LA	25 Gy ×1	100%	11.4	19% Acute 47% Late	1 cycle induction GEM + post-SBRT GEM
Hoyer *et al.* (17) 2005	22 LA	15 Gy ×3	57%	5.4	79% Grade 2 4.5% Grade 4	
Mahadevan *et al.* (18) 2010	36 LA	8-12 Gy ×3	78%	14.3	33% Grades 1 & 2 8% Grade 3	Post-SBRT GEM
Mahadevan *et al.* (22) 2011	39 LA	8-12 Gy ×3	85%	20	41% Grades 1 & 2 0% Acute Grade 3 9% Late Grade 3	2 cycle induction GEM
Polistina *et al.* (20) 2010	23 LA	10 Gy ×3	50%	10.6	20% Grade 1 0% Grade 2	6 week induction GEM
Moningi *et al.* (23) 2015	74 LA 14 BR	5-6.6 Gy ×5	61% LPFS	18.4	3.4 % ≥ Acute Grade 3 5.7% ≥ Late Grade 2	Pre-SBRT Chemo in 77 cases
Gerka *et al.* (24) 2013	10 LA	5 Gy ×5	40%	12.2	0% Grade 3	1 cycle pre-SBRT GEM +5 cycle post-SBRT GEM
Herman *et al.* (25) 2015	49 LA	6.6 Gy ×5	83% LPFS	13.9	2% ≥ Acute Grade 2 11% ≥ Late Grade 2	GEM followed by SBRT

BR, borderline resectable; 5-FU, 5-flourouracil; GEM, gemcitibine; LA, locally advanced; LC, local control; LPFS, local progression free survival; OS, overall survival; SBRT, stereotactic body radiotherapy.

Table 2 Reported toxicities for pancreatic SBRT

Study	Grade 1 toxicities (%)	Grade 2 toxicities (%)	≥ grade 3 toxicities (%)	Main toxicities noted
Koong *et al.*, 2004	13.3	20	0	Nausea, diarrhea, abdominal pain
Koong *et al.*, 2005	43.8	25	12.5	Nausea, anorexia, duodenal ulcers
Hoyer *et al.*, 2005	42	79≥ grade 2		Nausea, mucositis, ulcers, ulcer perforation
Mahadevan *et al.*, 2010	NR	33	8	Nausea, GI bleeding, emesis
Schellenberg *et al.*, 2011	12	15	5	Pain, emesis, ulcers, perforation
Goyal *et al.*, 2012		11≤ grade 2	16	Fatigue, nausea, ulcers
Lin *et al.*, 2015	39 cases[a]	24 cases[a]	0	Anorexia, fatigue, emesis
Moningi *et al.*, 2015	NR	43 cases[a]	3.4	Duodenal ulcer, gastritis, GI bleeding, lymphopenia

[a], reported as number of cases for each toxicity, not as percentages. SBRT, stereotactic body radiotherapy; NR, not reported.

Table 2
Studies that used stereotactic body radiotherapy in the treatment of pancreatic cancer.

	Period	N-	Chemotherapy	Median follow-up (months)	Fractions/total dose (Gy)	LC
Koong et al. [12]	2003–2004	19	Chemoradiotherapy prior SBRT	5	1/25	94%
Tozzi et al. [14]	2010–2011	30	Gemcitabine prior SBRT	11	6/45	75% (2 years)
Schellenberg et al. [15]	2004–2006	16	Gemcitabine concomitant and after SBRT	9	1/25	81%
Rwigema et al. [16]	2004–2010	24	Gemcitabine after SBRT	12	1/20–24 3/30	66% (1 year)
Chang et al. [17]	2002–2007	77	Gemcitabine after SBRT	6	1/25	84% (1 year)
Mahadevan et al. [18]	2005–2007	36	Gemcitabine after SBRT	24	3/24–36	78% (1 year)
Wild et al. [19]	2008–2012	18	83% Chemoradio-therapy prior SBRT Gemcitabine after SBRT	34.3	5/20–27	62% (1 year)
Didolkar et al. [20]	2004–2009	85	Gemcitabine after SBRT	8.65	1–4/15–30	91.7%
R. Jumeau et al.	2012–2016	21	38% chemotherapy before SBRT 29% Gemcitabine after SBRT	7	5–6/30–35	94%

24% acute post-SBRT nausea or vomiting: Grade I (2), Grade II (3) and no Grade III.
One patient - fatal hematemesis 6 months after SBRT.

SBRT in BRPC

SBRT in combination with GTX as neo-adjuvant: well tolerated with a high conversion rate from borderline resectable to resectable candidates and an increased rate of margin-negative resection

Current evidence about SBRT in BRPC is scarce, it appears that BRPC patients may benefit from neoadjuvant SBRT with impressive pathologic response and R0 resection rates

Chuong et al

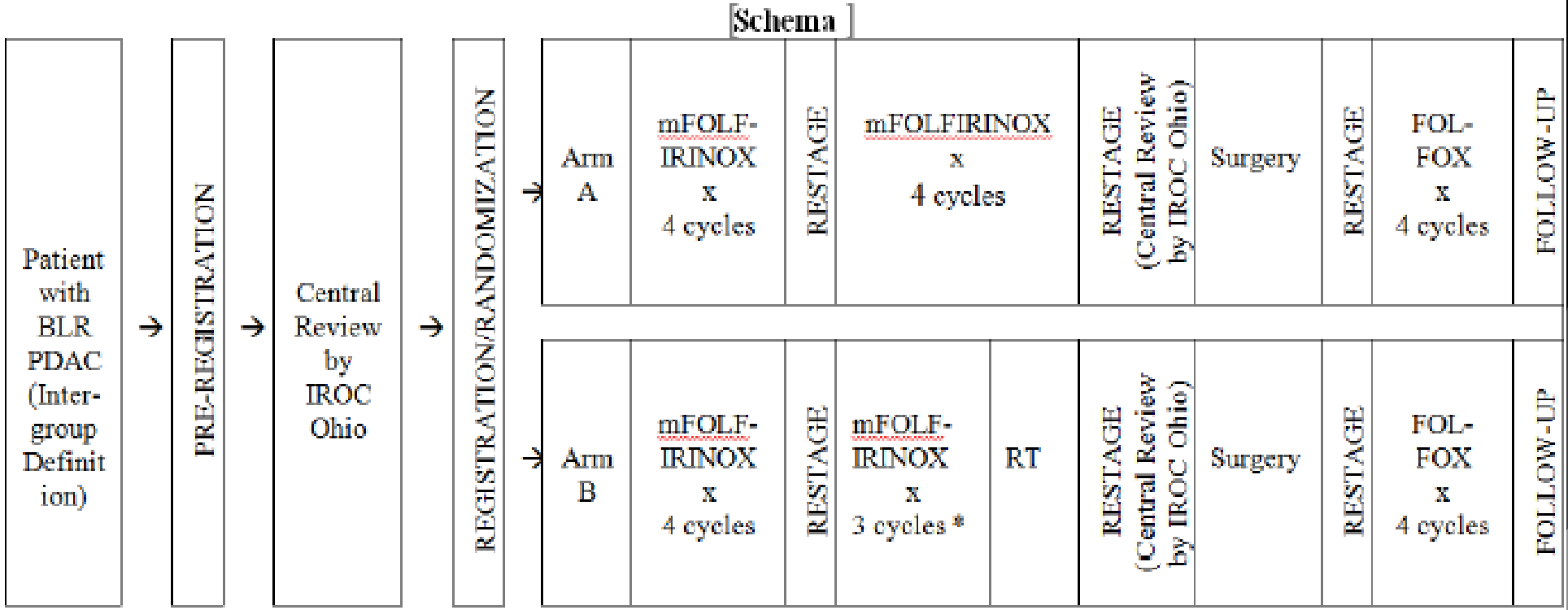
- 30 BRPC patients
- Neoadjuvant SBRT and concurrent Gemcitabine/Taxotere/Xeloda(GTX)
- 70% underwent surgery
- 90% R0 resection, 76% node negative
- Median OS 20 months
- 1-year PFS 61%
- No high-grade (>2) acute toxicity or late grade toxicity

Subsequent Retrospective study

- 57 BRPC: induction chemotherapy and SBRT.
- Median doses :35 Gy to region of vessel involvement and 25 Gy to the the tumor
- 32 (56.1%) underwent surgery, with 96.9% (31/32) R0
- 3 (9.3%) pCR and 2 (6.3%) near pCR
- Median OS 16.4 months
- No grade 3 or greater acute toxicity 5.3% grade 3 or greater late toxicity

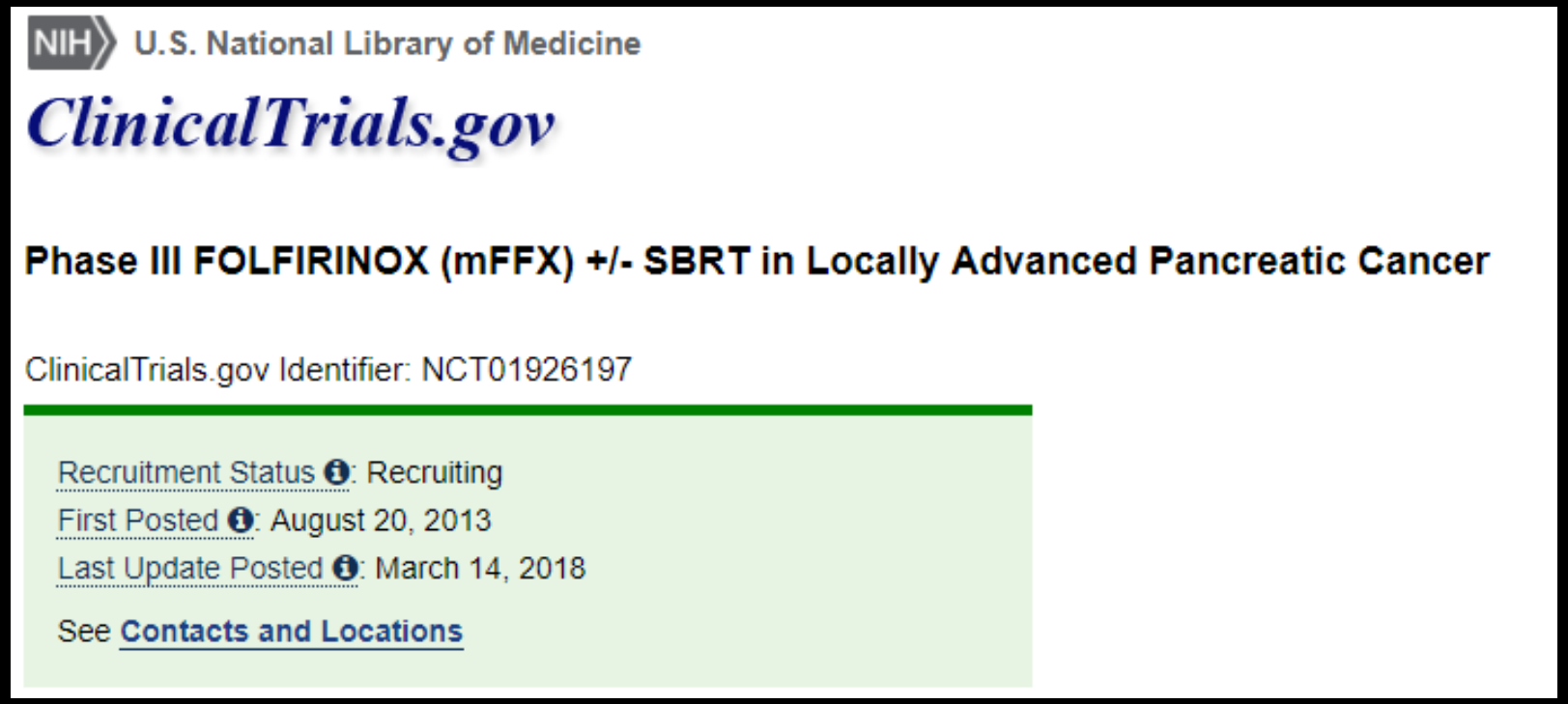
Randomised Trial (ALLIANCE)

Pancreas SBRT, A021501 Schema



Stanford Study

- Modified folfirinox alone or with addition of SBRT in LAPC
- Primary Endpoint – Metastasis free survival



NIH U.S. National Library of Medicine

ClinicalTrials.gov

Phase III FOLFIRINOX (mFFX) +/- SBRT in Locally Advanced Pancreatic Cancer

ClinicalTrials.gov Identifier: NCT01926197

Recruitment Status : Recruiting
First Posted : August 20, 2013
Last Update Posted : March 14, 2018

See **Contacts and Locations**

Patient Selection

- Good ECOG , Fit patients
- BRPC / LAPC (Proven)
- Patients with active duodenal or gastric ulcers **are not acceptable for SBRT.(**resolved previous ulcers are acceptable)
- Patients with direct tumor invasion of the bowel or stomach **are not acceptable for** SBRT (other strategies may be used) – Distance from stomach , bowel is a key factor
- Patients should not be treated with SBRT if **SBRT-specific organ at risk (OAR) constraints cannot be met.**
- Bilirubin <=2

Basic Requirements

- Patients should have 4D CT simulation / fluoroscopy to assess tumor motion
- Patients should be treated with SBRT only if tumor motion can be minimized using motion management techniques, when applicable
- Department should have the facility to do daily volumetric image guidance and appropriate image guidance
- Assessment of pre existing cardiac or lung condition to implement breath hold techniques

Preparation

- Prokinetic protocol is started 2-3 days prior to simulation.

  (advise laxative and to have soft diet devoid of gas producing food)

- Counselling , training , breathing exercises, Spirometer

- **Fiducials**

  (Ideally ≥ 3) fiducial markers (Civco, Visicoil, Gold anchor)

  In or directly at the tumor periphery and/or within 1 cm of the tumor(normal pancreas) under EUS or CT guidance done at least 3 days prior

  Fiducial > Stent > Bony landmark

Process

- Supine position with a customize immobilization device (e.g. Vac-Lok)
- Empty stomach / 4 hours fasting
- Ensure no unusual distension of stomach/duodenum/bowel. Use enema if loaded bowel
- Oral contrast: Diatrizoate Meglumine 2.5ml diluted in 50ml of water is given 20 minutes prior to the scan
- A 4DCT scan (when available) / Fluoroscopic tracking of markers - to assess respiratory motion of the tumor
    - ✓ If tumor motion > 5mm, respiratory motion management (breath hold, tracking, gating or abdominal compression etc.) required


SBRT Base plate
V Bar


Whole body Vac lock.


Abdominal compression plate


Pressure scales

Free breathing

- 4DCT: RPM or ANZAI
- Slow CT
- Internal Target Volume (ITV)-based treatment
- Gating: RPM or Calypso
- Tracking

Breath-hold

- Active Breathing Coordinator (ABC)

Process Continued

- Breath-hold technique -**deep expiratory breath-hold (DEBH) -Preferred** (End expiratory scans more reproducible)
  - other methods : comfortable breath-hold (CBH) / deep inspiratory breath-hold (DIBH).
- Slice thickness 2 mm or less
- A triphasic contrast CT scan (from diaphragm till L4-L5) at 20, 40 and 60 sec from the start of contrast infusion, with breath-hold
  - ✓ **Late arterial** (25-35 seconds post contrast injection)
  - ✓ Portal venous phases (55-70 seconds post contrast injection) because this increases tumor-to-pancreas enhancement ratios and gross tumor volume reproducibility
  - ✓ **Pancreatic parenchymal phase** (45-50 seconds) post contrast injection
- Quality assurance of the plan is must prior to starting the treatment

Pancreatic parenchymal phase

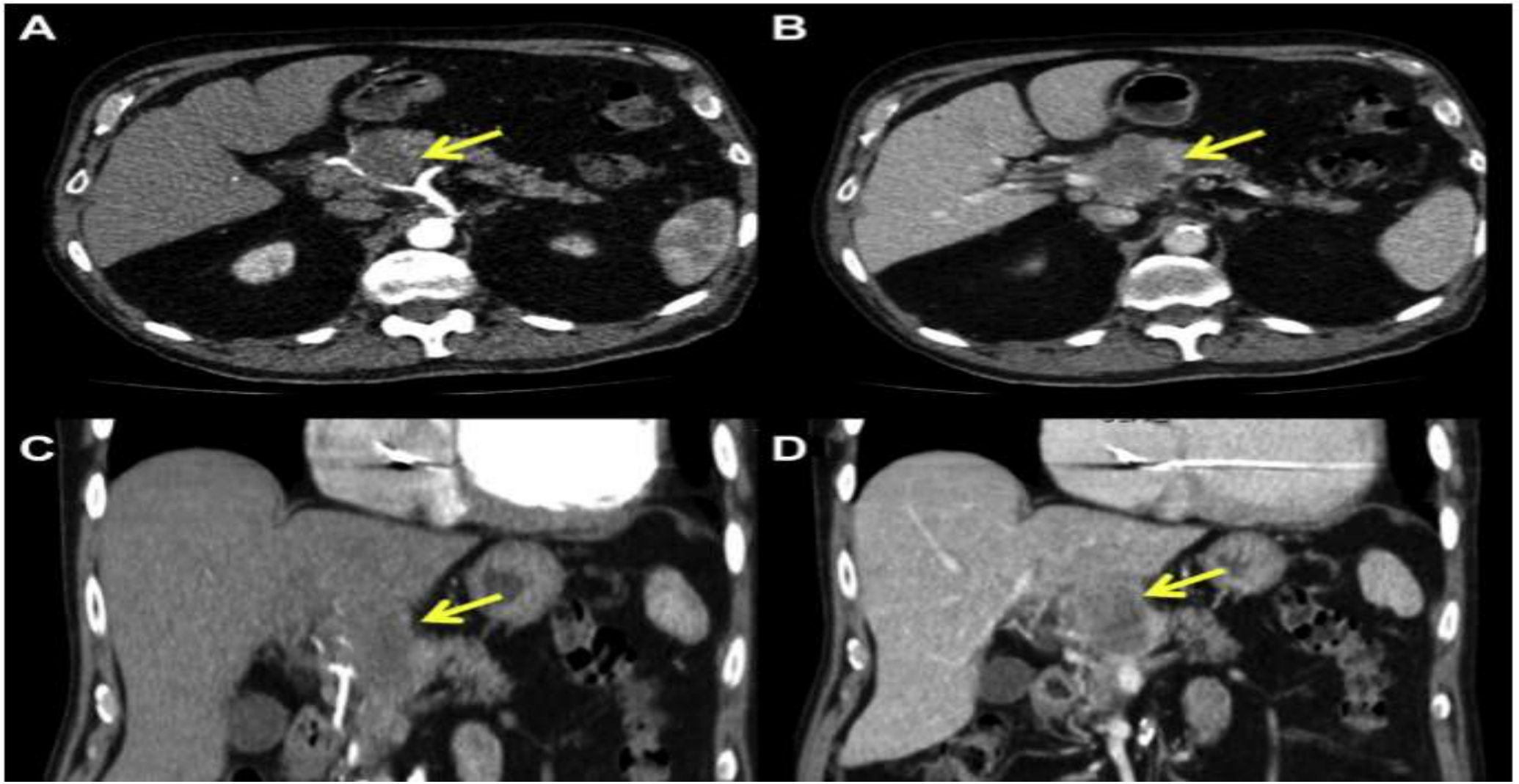


Figure 1 The value of delayed phase CT in pancreatic cancer is demonstrated in this patient with locally advanced pancreatic cancer (yellow arrow). During the portal venous or parenchymal phase, the tumor can be seen as hypodense structure within the pancreas. (A) Arterial enhanced axial CT. (B) Delayed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

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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)

TMH GI Practicum 2019

Contouring

GTVp /iGTVp

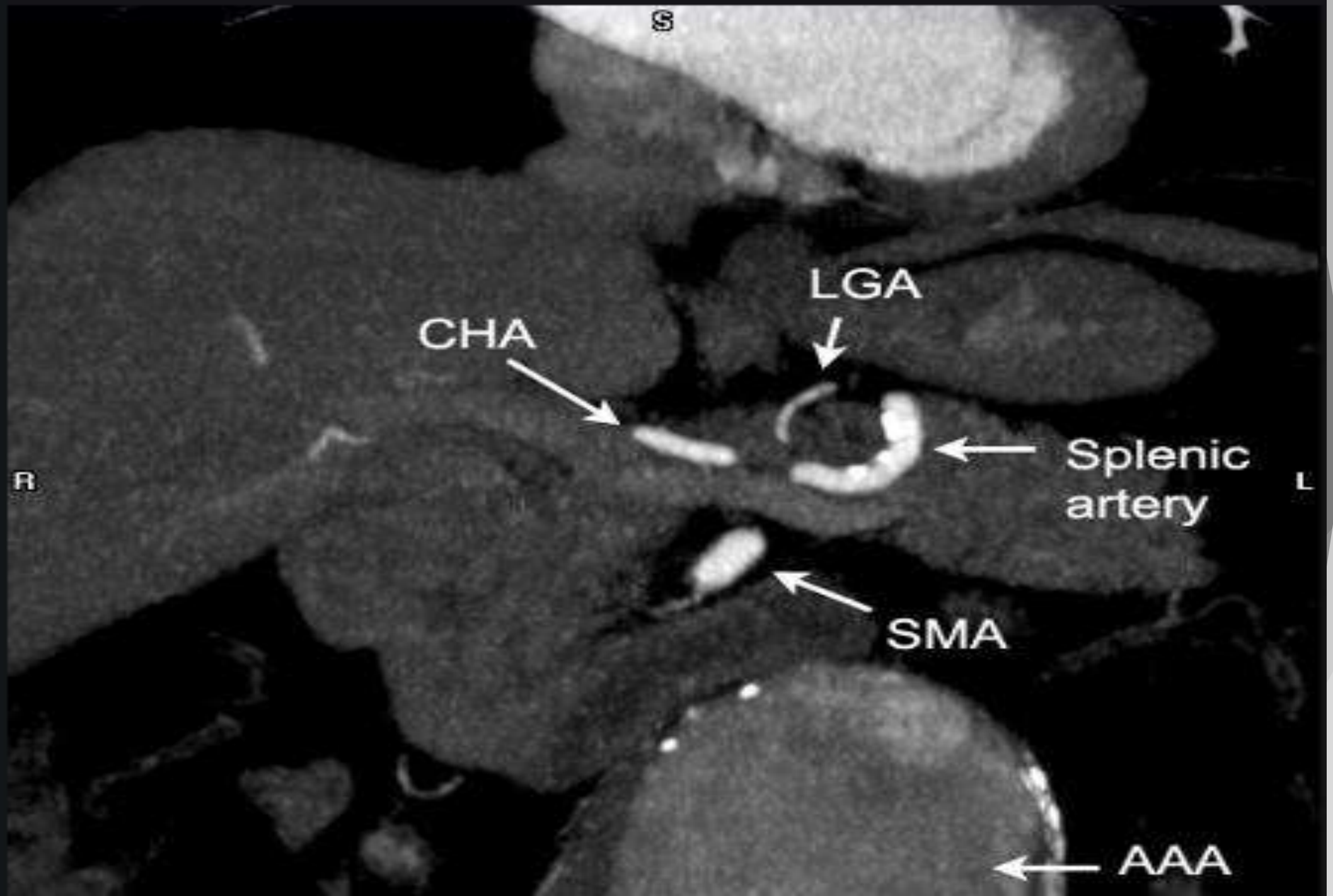
- Draw primary pancreatic tumour only. Do not include nodes or surrounding vessels

GTV n

- Only gross nodes , no prophylactic nodes

Vessels to be delineated entire length

- **Arteries**
  - Common hepatic artery (CHA)
  - Left Gastric Artery
  - Celiac artery (celiac artery)
  - Superior mesenteric artery (SMA)
- **Veins**
  - Portal vein
  - Superior mesenteric vein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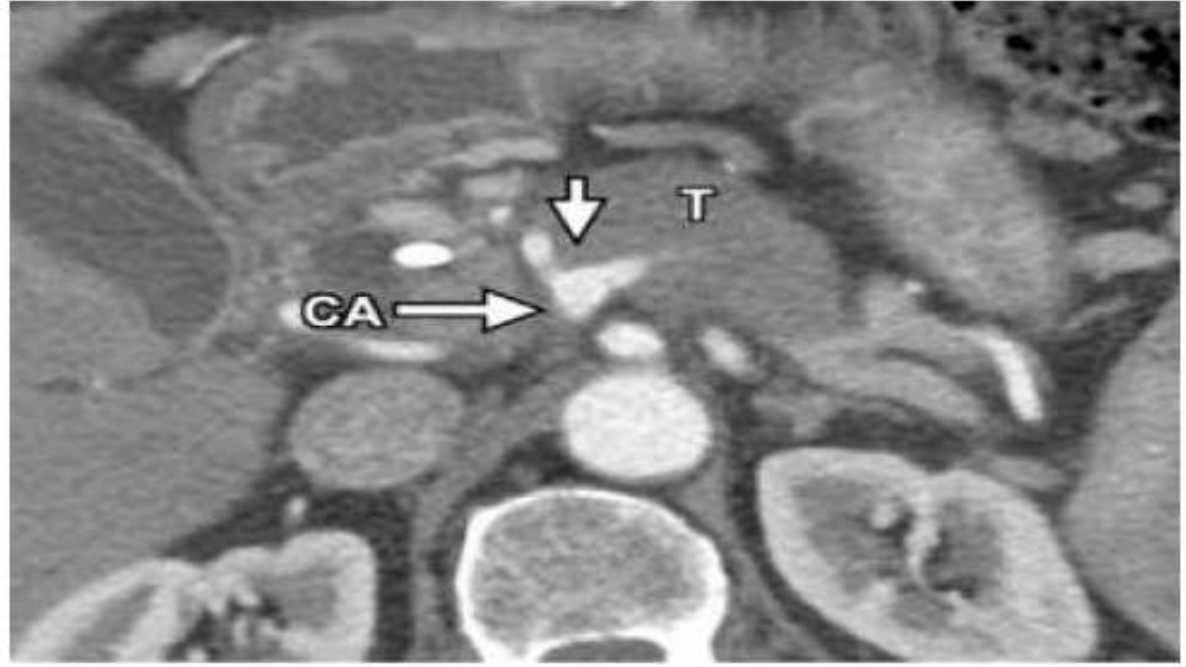
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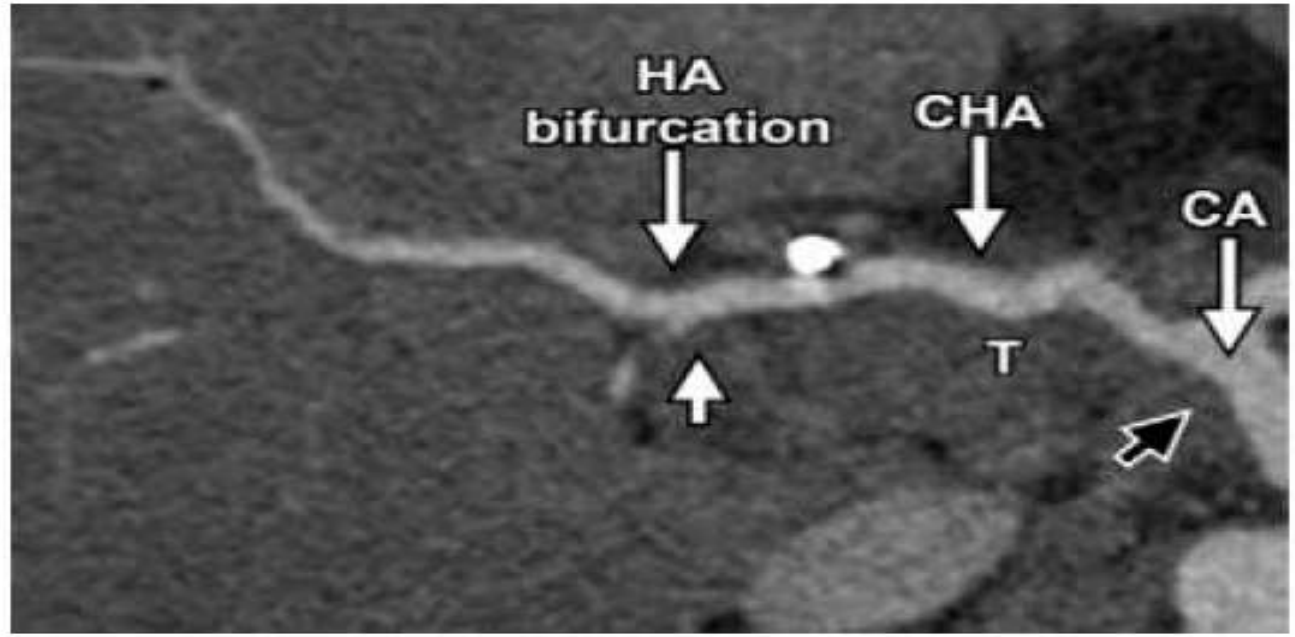
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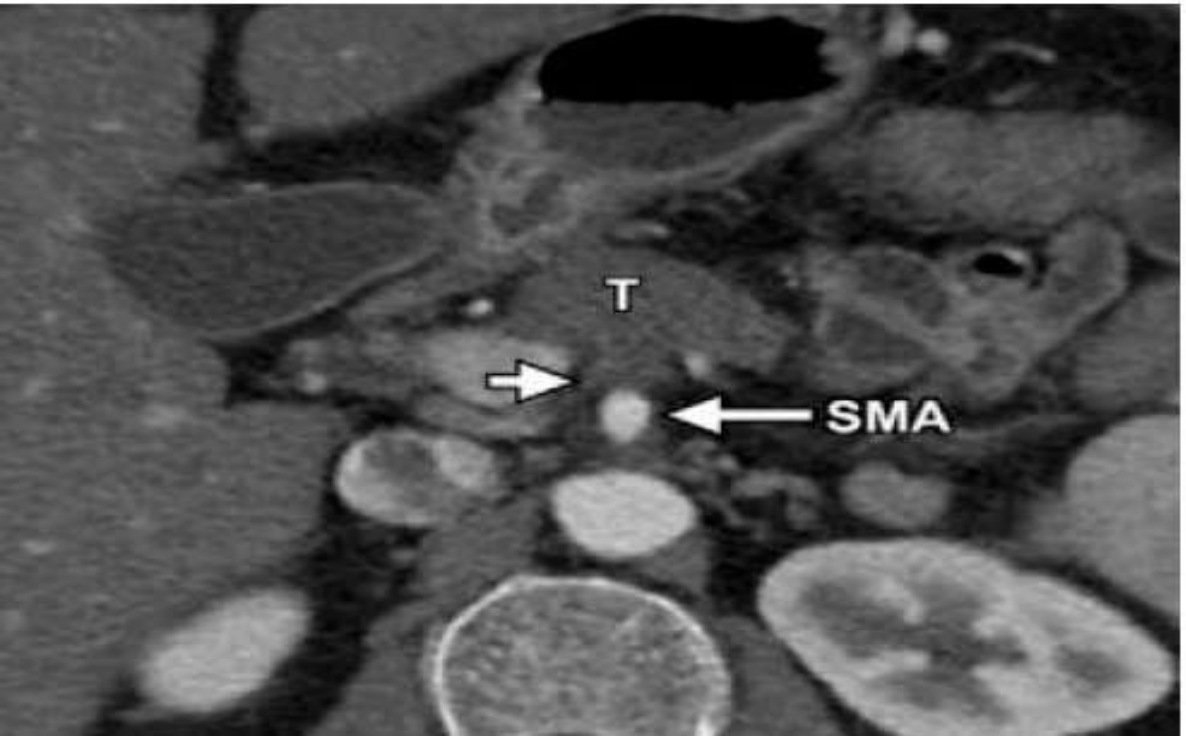
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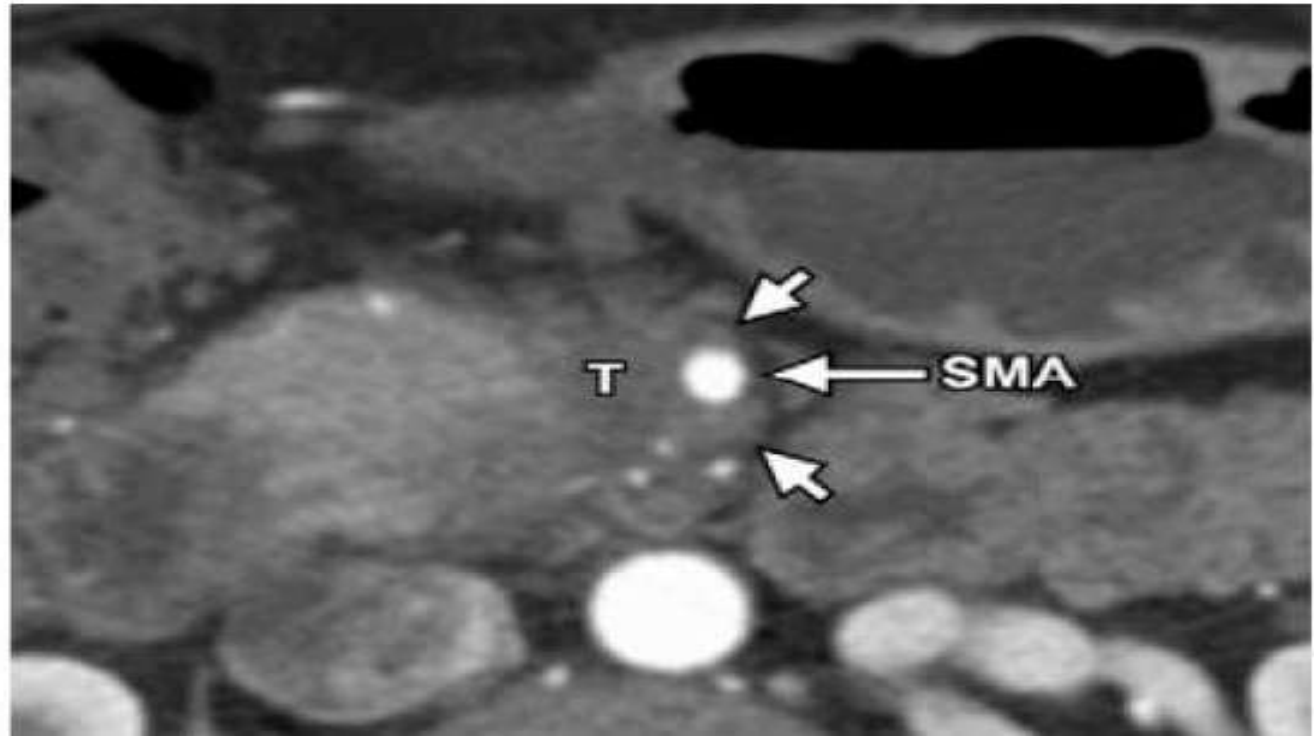
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Tumour Vessel Interphase (TVI)

- TVI is 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 vein, portal vein, splenic vein, or aorta. If GTVp is within 5 mm of these structures

- TVI (Tumour vessel interface)-Boolean all the vessels and label as Vessels combined. Erase the vessels and the part of the vessels which are not in direct contact of the GTV to generate TVI

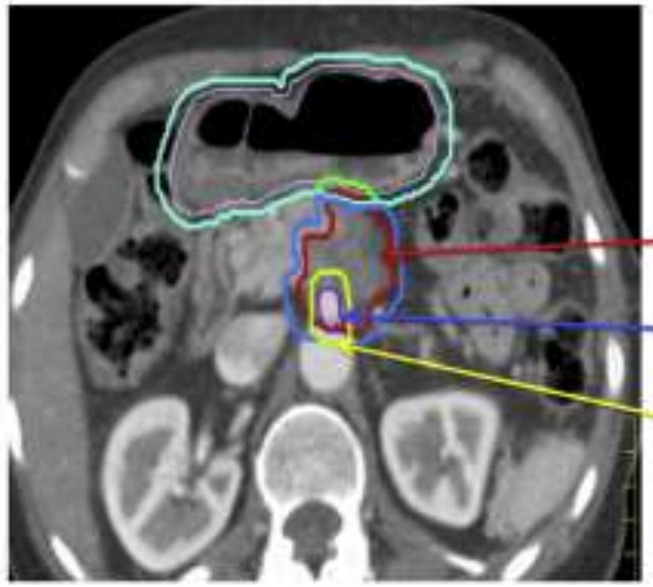


Fig. 1. Computed tomography image illustrating the gross tumor volume (GTV, in red) and tumor vessel interface (TVI, in neon green) contours. The tumor vessel interface will be treated to 36 Gy (maximum 40 Gy), the planning target volume (gross tumor volume plus margin, in blue) will be prescribed 33 Gy except for the region adjacent to the bowel (the region in green will be treated to 25 Gy). (A color version of this figure is available at www.redjournal.org.)

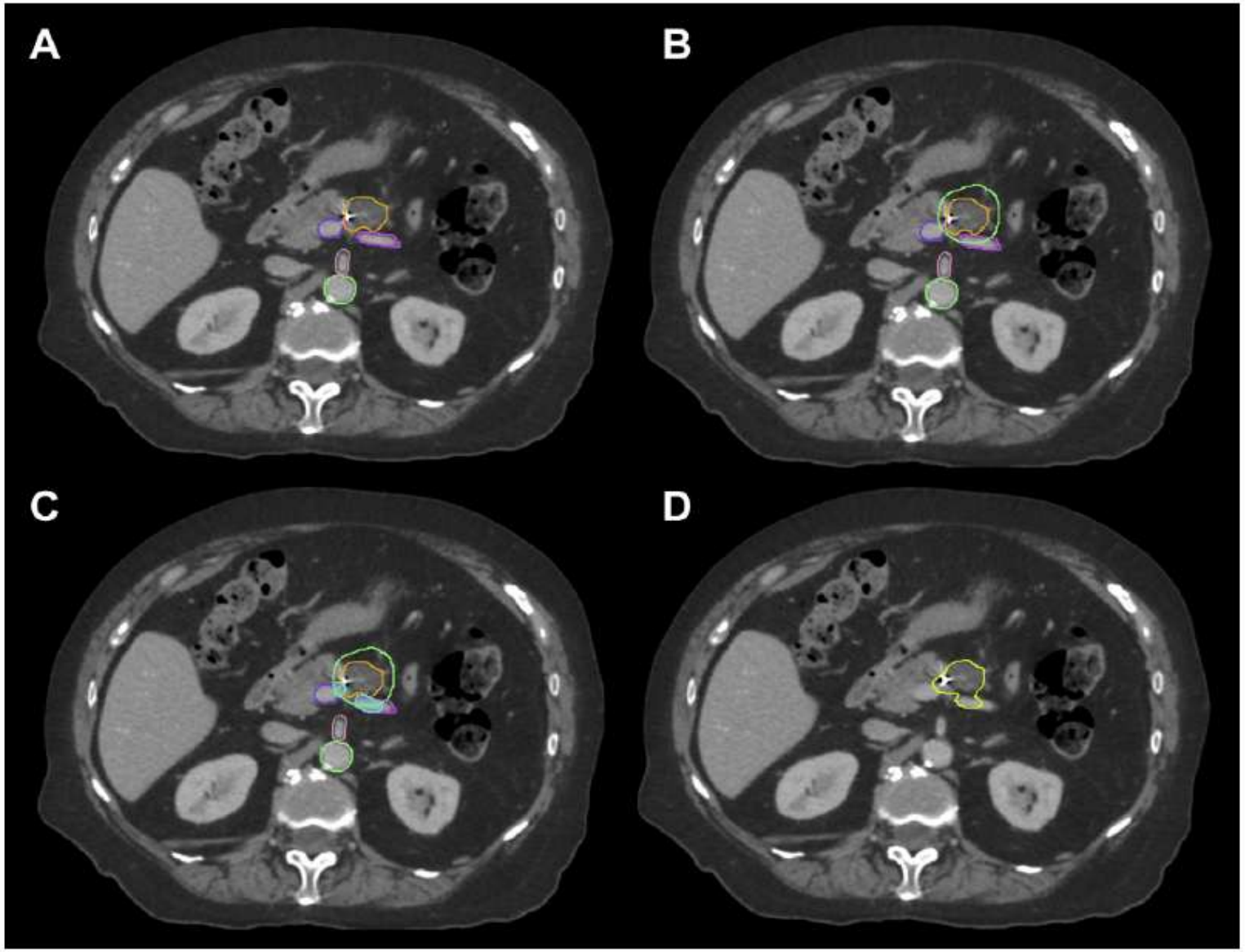


Figure 2 A patient with locally advanced pancreatic cancer and tumor involvement of the splenic vein (magenta) with close proximity to left portal vein (purple). (A) The GTV (orange) and nearby vessels are contoured. (B) A 5-mm expansion of the GTV (green) helps delineate which vessels are within 5 mm 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.

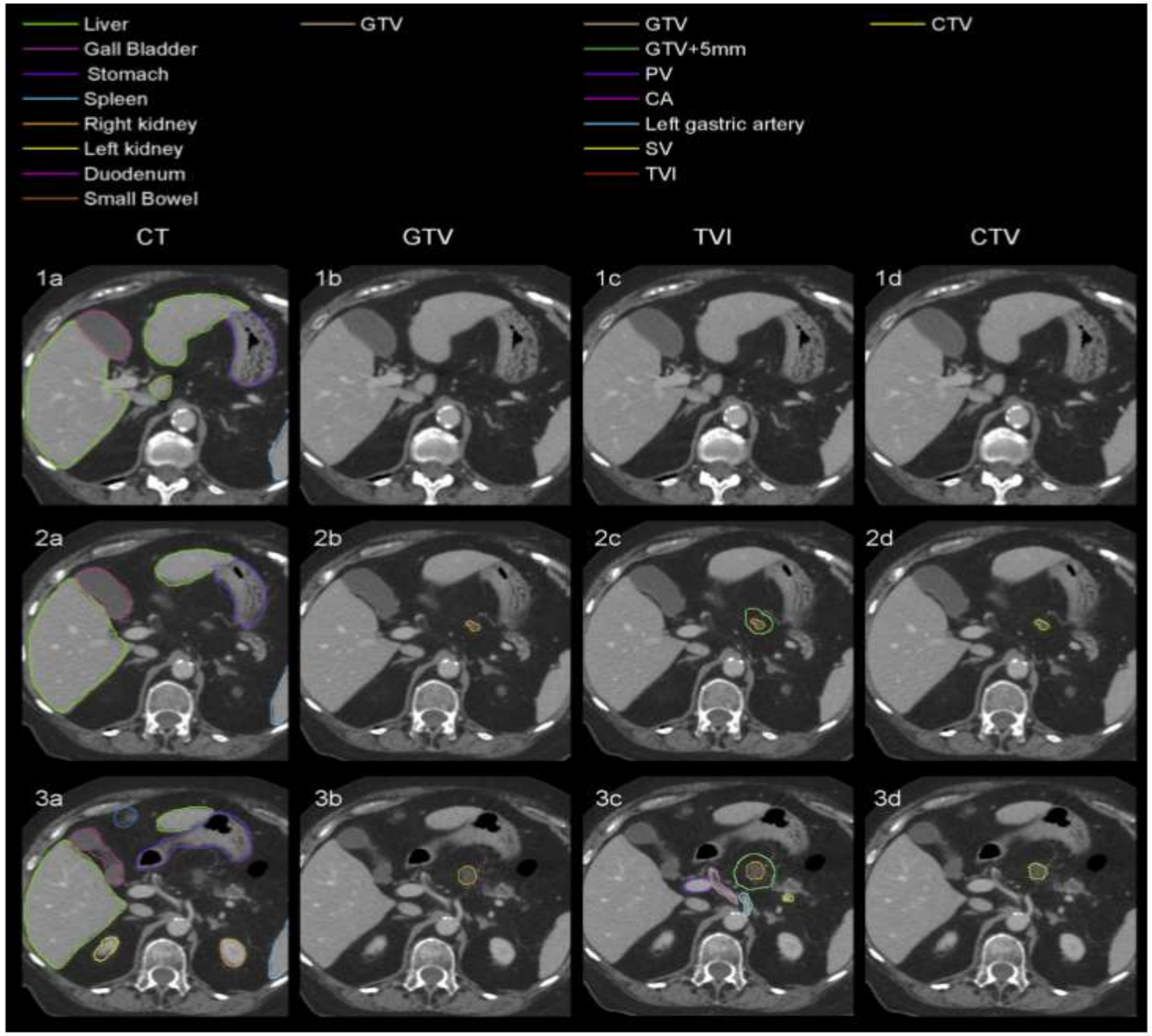


Figure 3 Contouring atlas for pancreas stereotactic body radiation therapy demonstrating formation of the tumor-vessel interface. Patient with locally advanced pancreatic cancer and aberrant left gastric artery. Abbreviations: CA = celiac artery; CTV = clinical target volume; GTV = gross tumor volume;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

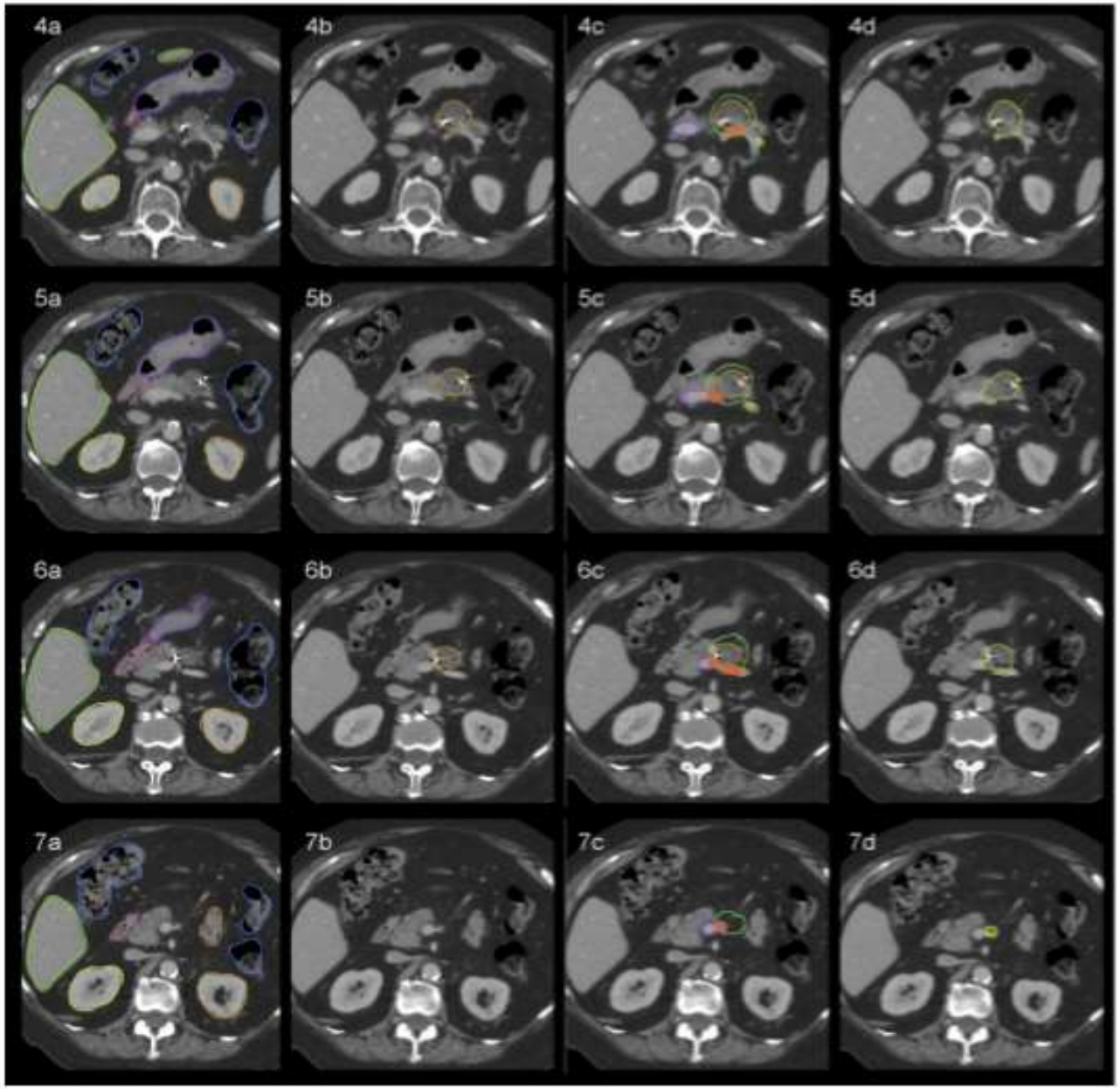
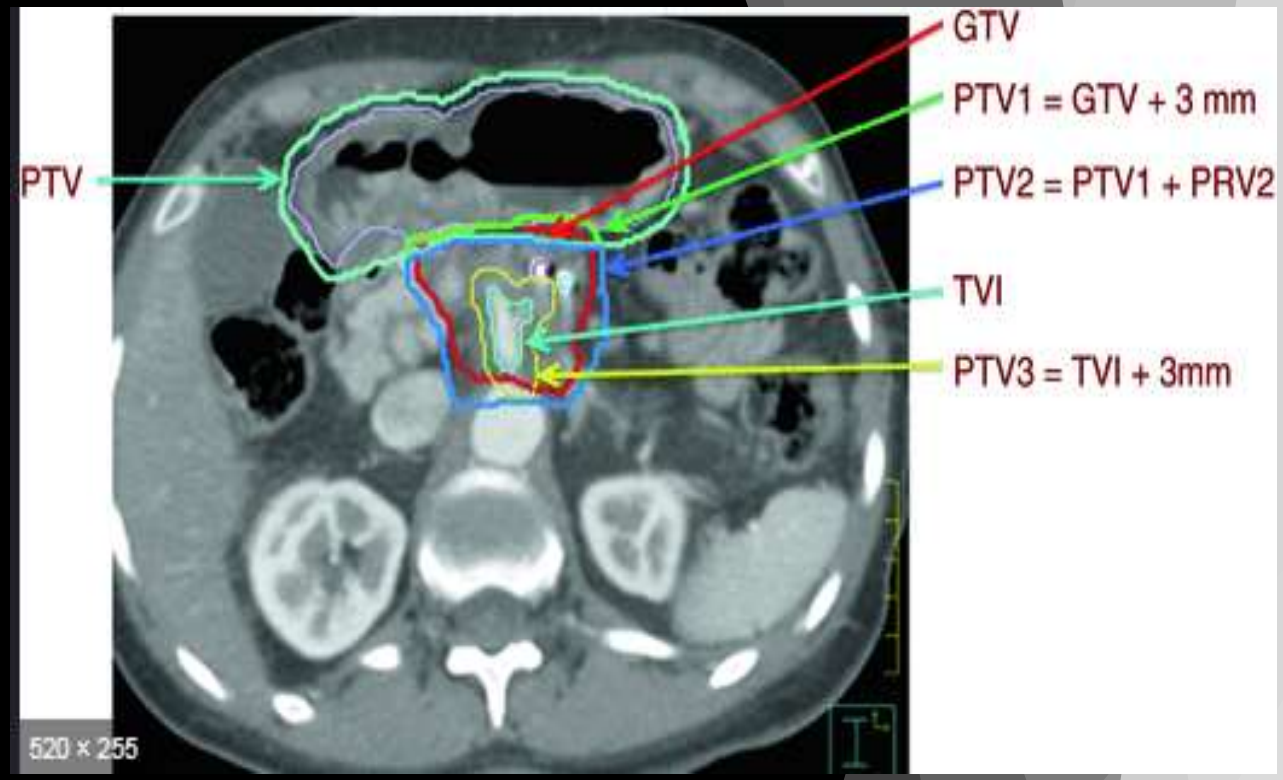


Figure 3 Continued

- TVI (Expansion) -give margin of 3mm all around the TVI to generate TVI expansion
- Contour OAR's -Stomach, Duodenum and small bowel (individual loops).
- Give margin of 3mm to each of the above OAR and label as Stomach_3mm, Duodenum_3mm and Small bowel_3mm
- PRV_GI -Boolean all the above OAR having 3mm expansion and label as PRV_GI



- PTV1: 42Gy/6# (Tumor Volume Interface (TVI)+ 3 mm)
- PTV2: 36Gy/6# (TVI + 3 mm AND GTV + 3 mm edited from PRV GI)
- PTV3: 30Gy/6# (TVI + 3 mm AND GTV + 3 mm unedited)

Volume Delineation

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Basic Original Report

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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.

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.

Dose constraints

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.

Delivery of Treatment

Principles

- Advanced organ motion management,
- Image guidance,
- Adaptive planning techniques

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ASTRO Guideline

Radiation Therapy for Pancreatic Cancer: Executive Summary of an ASTRO Clinical Practice Guideline

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Indications for conventionally fractionated RT or SBRT

In patients with pancreatic cancer, what are the appropriate indications for regimens that include conventionally fractionated RT or SBRT as:

- Adjuvant therapy?
- Neoadjuvant therapy?
- Definitive therapy?

Table 2 Recommendations for indications for conventionally fractionated RT or SBRT

KQ 1 recommendations	Strength of recommendation	Quality of evidence	Consensus
1. Following surgical resection of pancreatic cancer, adjuvant conventionally fractionated RT with chemotherapy in select high-risk patients is conditionally recommended. Implementation Remark: High-risk clinical features would include positive lymph nodes and margins regardless of tumor location within the pancreas.	**Conditional**	**Low**	**92%***
2. Following surgical resection of pancreatic cancer, adjuvant SBRT is only recommended on a clinical trial or multi-institutional registry.	**Strong**	**Very low**	**100%***
3. For patients with resectable pancreatic cancer, neoadjuvant therapy is conditionally recommended.	**Conditional**	**Low**	**92%***
4. For patients with borderline resectable pancreatic cancer and select locally advanced pancreatic cancer appropriate for downstaging prior to surgery, a neoadjuvant therapy regimen of systemic chemotherapy followed by conventionally fractionated RT with chemotherapy is conditionally recommended.	**Conditional**	**Moderate**	**85%***
5. For patients with borderline resectable pancreatic cancer and select locally advanced pancreatic cancer appropriate for downstaging prior to surgery, a neoadjuvant therapy regimen of systemic chemotherapy followed by multifraction SBRT is conditionally recommended.	**Conditional**	**Low**	**77%***
6. For patients with locally advanced pancreatic cancer not appropriate for downstaging to eventual surgery, a definitive therapy regimen of systemic chemotherapy followed by either (1) conventionally fractionated RT with chemotherapy, (2) dose-escalated chemoradiation, or (3) multifraction SBRT without chemotherapy is conditionally recommended.	**Conditional**	**Low**	**85%***

Abbreviations: KQ = key question; RT = radiation therapy; SBRT = stereotactic body radiation therapy.

* The medical physics representative abstained from rating these recommendations.

Dose fractionation and target volumes

In patients with pancreatic cancer receiving RT, what are the appropriate dose fractionation schemes and target volumes for: conventionally fractionated RT and chemotherapy? SBRT?

4. For patients with borderline resectable pancreatic cancer selected for SBRT, 3000-3300 cGy in 600-660 cGy fractions with a consideration for a simultaneous integrated boost of up to 4000 cGy to the tumor vessel interface is conditionally recommended.	Conditional	Moderate	100%↑
5. For patients with locally advanced pancreatic cancer selected for SBRT, 3300-4000 cGy in 660-800 cGy fractions is recommended.	Strong	Moderate	100%↑

8. For patients with borderline resectable pancreatic cancer selected for SBRT, a treatment volume including the gross tumor volume with a small margin is recommended. Implementation Remark: SBRT does not routinely treat elective nodes.	Strong	High	92%↑
9. For patients with locally advanced pancreatic cancer selected for SBRT, a treatment volume including the gross tumor volume with a small margin is recommended.	Strong	High	100%↑

Sequencing of chemotherapy and RT In patients with pancreatic cancer receiving RT, what is the appropriate sequencing of chemotherapy with RT as:
adjuvant therapy?
neoadjuvant therapy?
definitive therapy?

Table 4 Recommendations for sequencing of chemotherapy and RT in patients receiving RT

KQ 3 recommendations	Strength of recommendation	Quality of evidence	Consensus
1. For patients with resected pancreatic cancer receiving adjuvant therapy, delivery of chemoradiation following 4-6 months of systemic chemotherapy is recommended.	**Strong**	**Moderate**	**92%***
2. For patients with borderline resectable pancreatic cancer receiving neoadjuvant therapy, delivery of RT following 2-6 months of systemic chemotherapy is recommended.	**Strong**	**Moderate**	**92%***
3. For patients with unresectable or locally advanced pancreatic cancer without systemic progressionfollowing 4-6+ months of chemotherapy, definitive RT is recommended.	**Strong**	**Moderate**	**85%***

Abbreviations: KQ = key question; RT = radiation therapy.
* The medical physics representative abstained from rating these recommendations.

Simulation considerations

In patients with pancreatic cancer receiving RT, how do the following impact target and normal tissue delineation, treatment planning techniques, and treatment delivery accuracy for conventionally fractionated RT and SBRT:

motion management

image guidance

CECT simulation

Table 5 Recommendations for simulation considerations

KQ 4 recommendations	Strength of recommendation	Quality of evidence	Consensus
1. For patients with pancreatic cancer receiving conventionally fractionated pancreatic RT or SBRT without breath-hold, a patient-specific respiratory motion assessment (eg, 4-dimensional [4-D] CT simulation) is recommended. Implementation Remark: For palliative or postoperative RT, motion assessment and management may not be required.	**Strong**	**High**	**100%***
2. For patients with pancreatic cancer receiving conventionally fractionated RT for whom free-breathing target motion is significant (>1 cm), a respiratory motion reduction technique is conditionally recommended. Implementation Remarks: • For palliative or postoperative RT, motion assessment and management may not be required. • For respiratory motion management techniques, the end-exhalation position may be more reproducible than inhalation positions.	**Conditional**	**Moderate**	**100%***
3 For patients with pancreatic cancer receiving SBRT, a respiratory motion management technique is recommended.	**Strong**	**High**	**100%***

(*continued on next page*)

Table 5 (*continued*)

KQ 4 recommendations	Strength of recommendation	Quality of evidence	Consensus
Implementation Remarks: • For palliative or postoperative RT, motion assessment and management may not be required. • For respiratory motion management techniques, the end-exhalation position may be more reproducible than inhalation positions.			
4. For patients receiving conventionally fractionated RT for pancreatic cancer, daily image guidance is recommended. Implementation Remarks: • Bony anatomy and surgical stents are each poor surrogates for pancreas target positioning; if used for image guidance, large internal target volume margins are necessary. • Where possible, the cine (fluoroscopic) imaging is useful, in addition to 2-D or 3-D image guidance, to confirm that the ITV adequately accounts for respiratory motion variations or intra–breath-hold drift.	**Strong**	**Moderate**	**100%***
For patients receiving SBRT for pancreatic cancer, daily image guidance with fiducial markers and volumetric imaging is recommended. Implementation Remarks: • Bony anatomy and surgical stents are each poor surrogates for pancreas target positioning; if used for image guidance, large internal target volume margins are necessary. • Where possible, the use of cine (fluoroscopic) imaging is suggested, in addition to 2-D or 3-D image guidance, to confirm that the ITV adequately accounts for respiratory motion variations or intra–breath-hold drift.	**Strong**	**Moderate**	**100%***
6. Unless there is a contraindication to IV contrast, patients with pancreatic cancer treated with RT should receive IV contrast at CT simulation; multiphasic CT with a high contrast flow rate and injection volume and patient-specific scan timing is recommended.	**Strong**	**High**	**100%***

Abbreviations: CT = computed tomography; ITV = internal target volume; IV = intravenous; KQ = key question; RT = radiation therapy; SBRT = stereotactic body radiation therapy.

* The surgical oncology representative abstained from rating these recommendations.

Prophylactic medications for toxicity In patients with pancreatic cancer receiving RT, how do prophylactic medications affect the incidence and severity of acute and late toxicities?

Table 8 Recommendations for prophylactic medications for toxicity

KQ 7 recommendations	Strength of recommendation	Quality of evidence	Consensus
1. For patients with pancreatic cancer undergoing RT, prophylactic use of antiemetic medications to reduce the rate of nausea is recommended.	**Strong**	**Low**	**100%***
2. For patients with pancreatic cancer undergoing RT, prophylactic use of medications to reduce acid is conditionally recommended.	**Conditional**	**Very Low**	**100%***

Abbreviations: KQ = key question; RT = radiation therapy.

* One task force member was recused from voting on this KQ based on his disclosures.

Advances of SBRT as adjuvant therapy in PCA

Postoperative local recurrence rates in resectable PCA 20% to 60%

Rwigema et al

- 12 patients following a margin-positive resection.
- FFLP rate at 1 year was 70.7%
- 1-year OS was 81.8%
- median OS of 20.6 months

Subsequent Rwigema et al.

- 24 resected patients with close or positive margins received adjuvant SBRT
- FFLP at 1 year was 66%
- 1-year OS 80.4%
- median OS of 26.7 months
- No patients suffered from acute grade 3 or greater toxicity

Re-irradiation with SBRT after previous conventional CRT

Wild et al. Stanford and Johns Hopkins

- Re-IR with SBRT for isolated local recurrence or progression of PCA after previous conventionally fractionated CRT.
- 18 locally recurrent or PD
- SBRT dose 20-27 Gy (median, 25 Gy) in 5 fractions
- Rates of FFLP at 6 and 12 months 78% (14/18) and 62% (5/8)
- Median OS of 8.8 months
- Effective symptom palliation was achieved in 57% of patients
- 5 (28%) had grade 2 acute toxicity; none experienced grade 3 or greater acute toxicity
- 1(6%) experienced grade 3 late toxicity in the form of small bowel obstruction

Lominska et al.

- SBRT for salvage or boost treatment after conventional EBRT
- 28 patients
- 11 SBRT boost, 17 patients underwent salvage SBRT
- 20 to 30 Gy was delivered in 3 to 5 #
- FFLP rate 86% (12/14)
- Median OS was 5.9 months (1-27 months) from the date of SBRT
- 11 (39%) had 9 months or greater OS
- OS at 1yr was 18%
- 1 patient had acute grade 2 nausea and vomiting, 2 late grade 3 gastrointestinal complications were reported

Future Directions

- Prospective study of pancreas SBRT ,randomised trials

  On sequencing / dose escalation / with newer agents

- Adaptive planning

- Exploration of biomarkers and imaging technology in order to adopt a personalized management paradigm

Research Letter

Dose escalation for locally advanced pancreatic cancer: How high can we go?

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Take Home

- SBRT Pancreas has opened up new ray of hope in the treament paradigm of Borderline Resectable Pancreatic Cancers
- Short Duration , High BED , Strategic sequencing with systemic therapy are the key to its potential success
- Precise contouring , good image guidance and motion management
- Strict quality assurance and multidisciplinary spatial cooperation are crutial

Thank you!