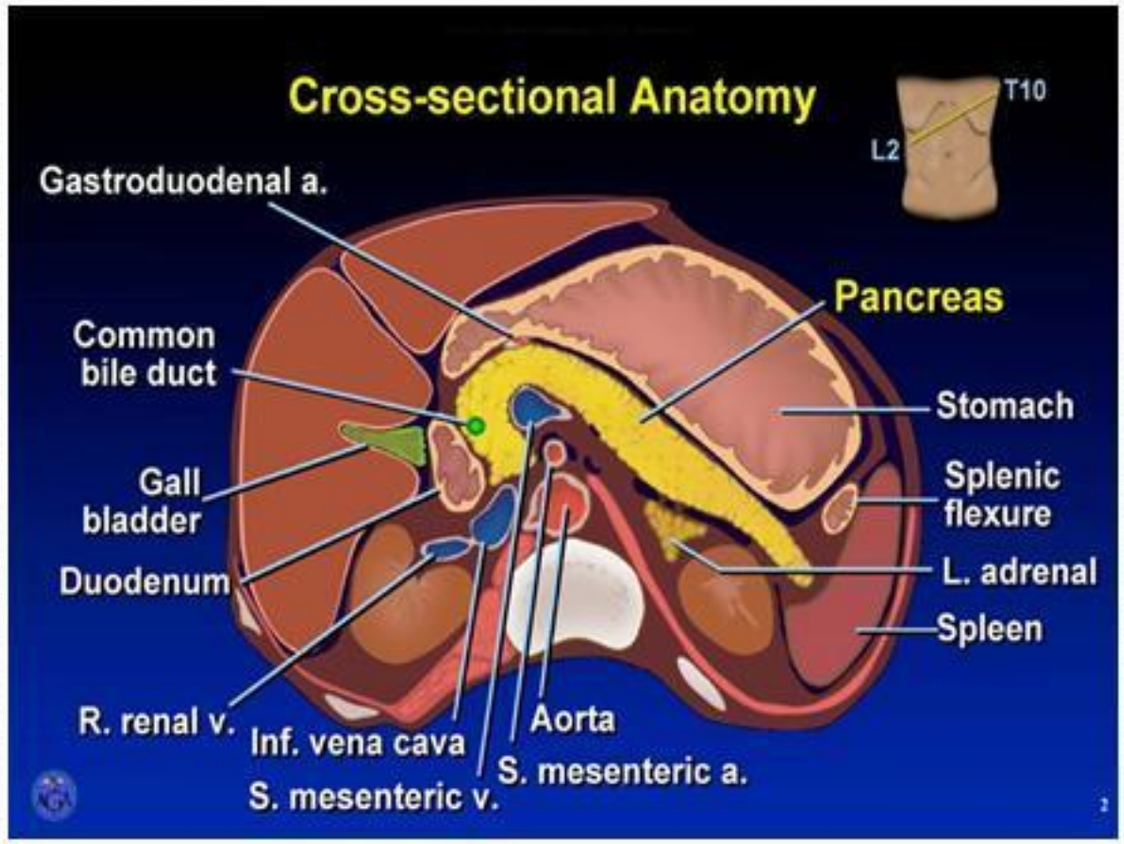
Target Volume, contouring & management of Carcinoma Pancreas

Dr Jaineet Sachdeva
Department of Radiation Oncology
CMC & Hospital, Ludhiana
Ludhiana

Anatomy

- Retroperitoneal structure
- Lies within the C of the duodenum
- Head: Ant to IVC, L2-L3
- Body: Passes obliquely to left, over the aorta, lt psoas, SA & SV
- Tail: Extends in front of Lt kidney, to hilum of spleen



Introduction

- Most lethal cancer-4th leading cause of death in US
- Usually diagnosed at an advanced stage
- >90% adenocarcinomas
- Median age at diagnosis-71yrs
- Worldwide incidence -1-10/100,000 people
- Higher in developed countries & men
- 80% patients metastatic at presentation
- Median survival : 8-14 mths

Risk factors

Low risk<5 times	Mod risk5-10 times	High risk>10 times
Alcohol use	BRCA2 gene carrier	Familial atypical multiple mole melanoma
BMI>30	Ch Pancreatitits	Family H in at least 3 I,II,III degree relatives
BRCA 1 gene carrier	Cystic fibrosis	Hereditary pancreatitis
Chlorinated Hydrocarbon exposure	Family h/O Pan Ca in 2 first degree relatives	Peutz Jeghers syndrome
DM type 2>5yrs		
FAP		
Family History in first degree relative		
HNPCC		
Polycyclic aromatic hydrocarbon exposure		
Tobacco use		

Symptoms

Symptoms	% pts(Head)	% pts(Body& Tail)
Wt loss	92	100
Jaundice	82	7
Abdominal pain	72	87
Anorexia	64	33
Dark urine	63	-
Acholic stool	62	-
Nausea	45	43
Vomiting	37	37
Weakness	35	42
Constipation	-	27
Food Intolerance	-	7

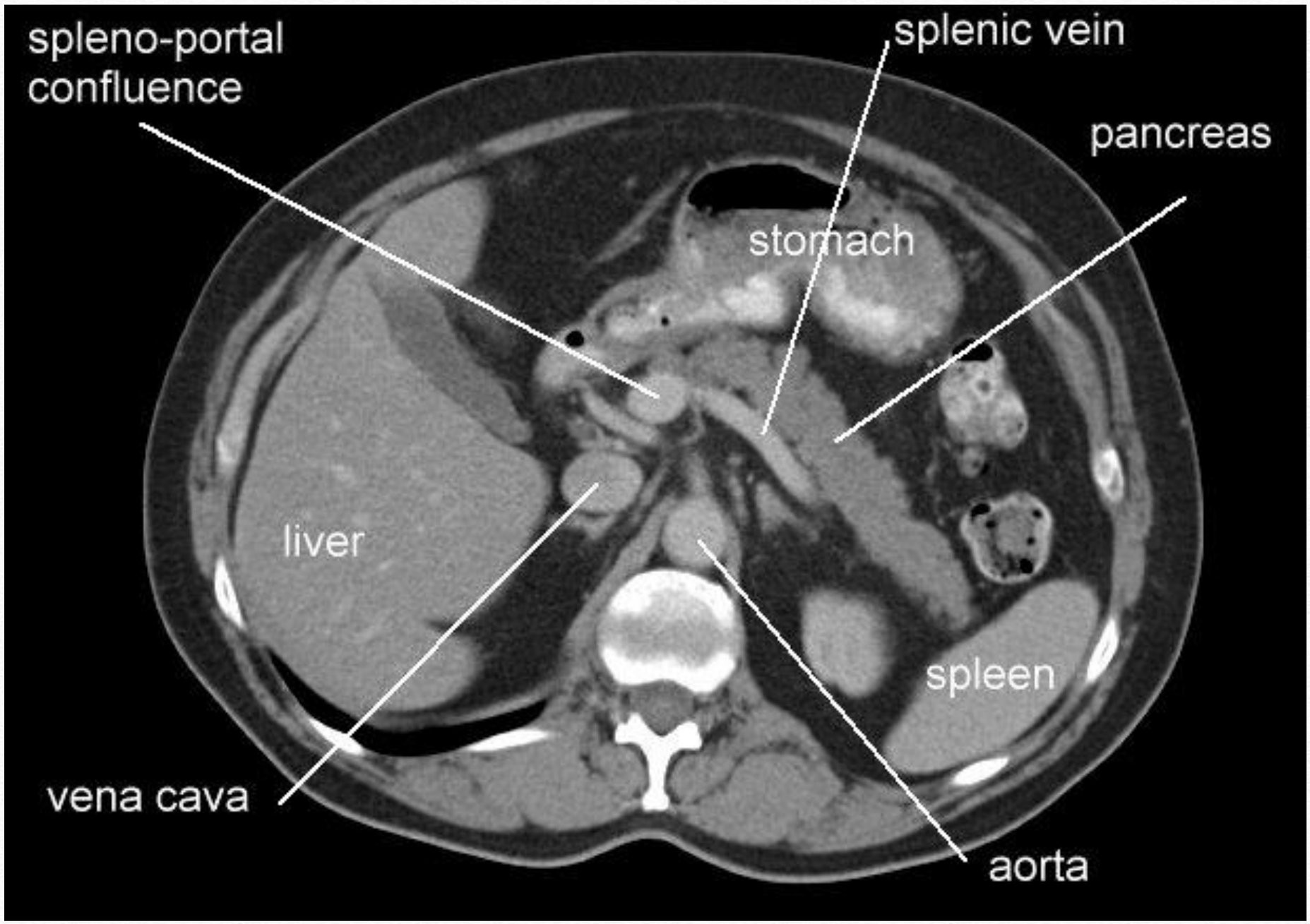
Clinical Examination

- Variable
- Normal- Early stages
- Advanced stage-Manifestations of liver involvement- abdominal tenderness, jaundice, cachexia
- Nontender distended palpable gall bladder in pt with jaundice(**Courvoisiers sign)**-83-90% specific
- **Trousseau sign**-recurrent superficial thrombophlebitis
- **Virchow node-**Lt SCN
- **Pancreatic panniculitis**- Subcutaneous areas of nodular fat necrosis

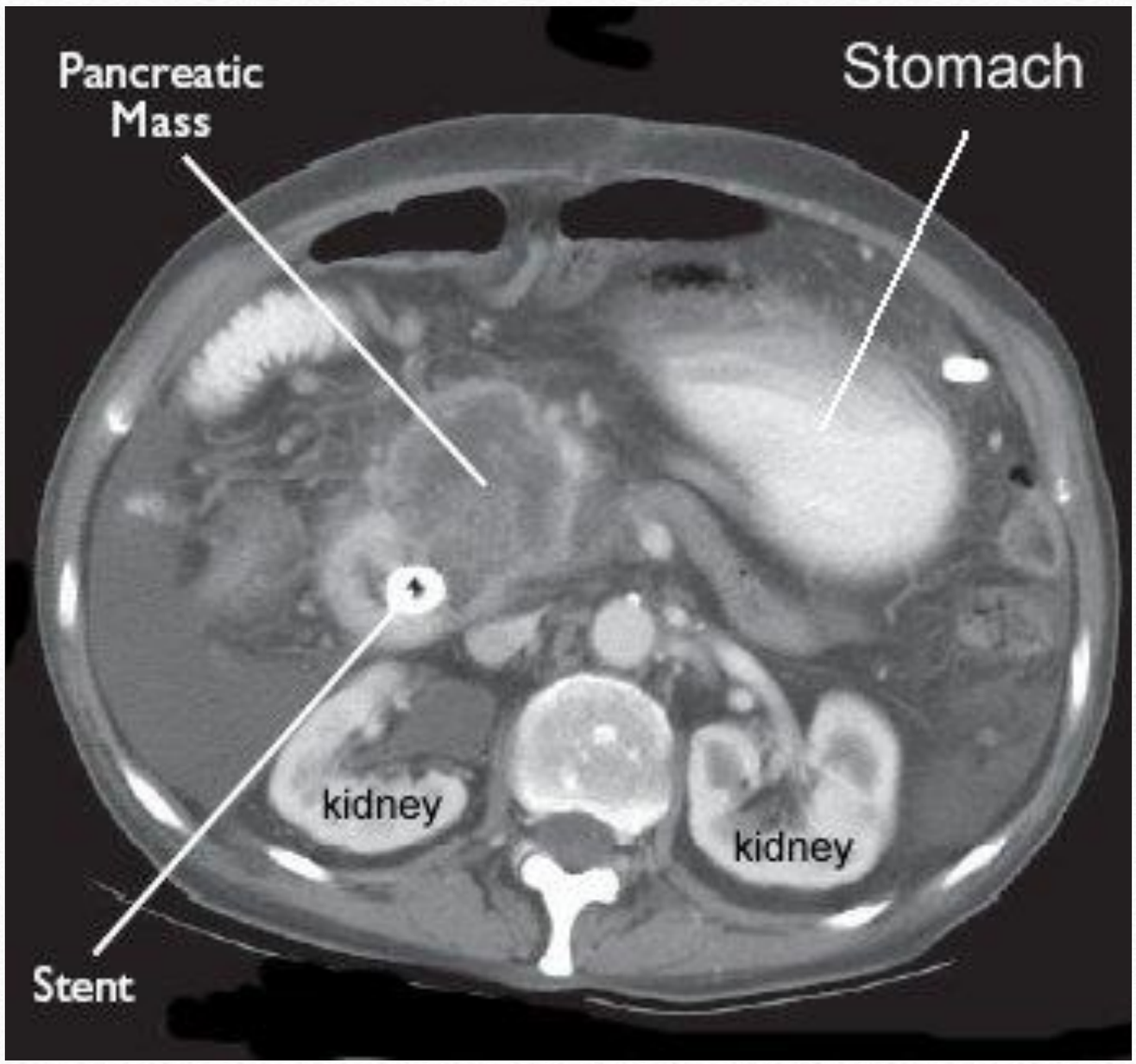
Diagnosis

- Abdominal ultrasound- first imaging
- Pancreas protocol CT- standard
- Triphasic (arterial, late & venous phase)
- Allows for enhancement between parenchyma & adenocarcinoma
- If CT not possible- MRI & MRCP recommended
- CBC, LFT, CEA,CA19.9,

CT Anatomy


spleno-portal confluence
splenic vein
pancreas
stomach
liver
spleen
vena cava
aorta

Pancreatic Mass



Tumour markers- CA19.9

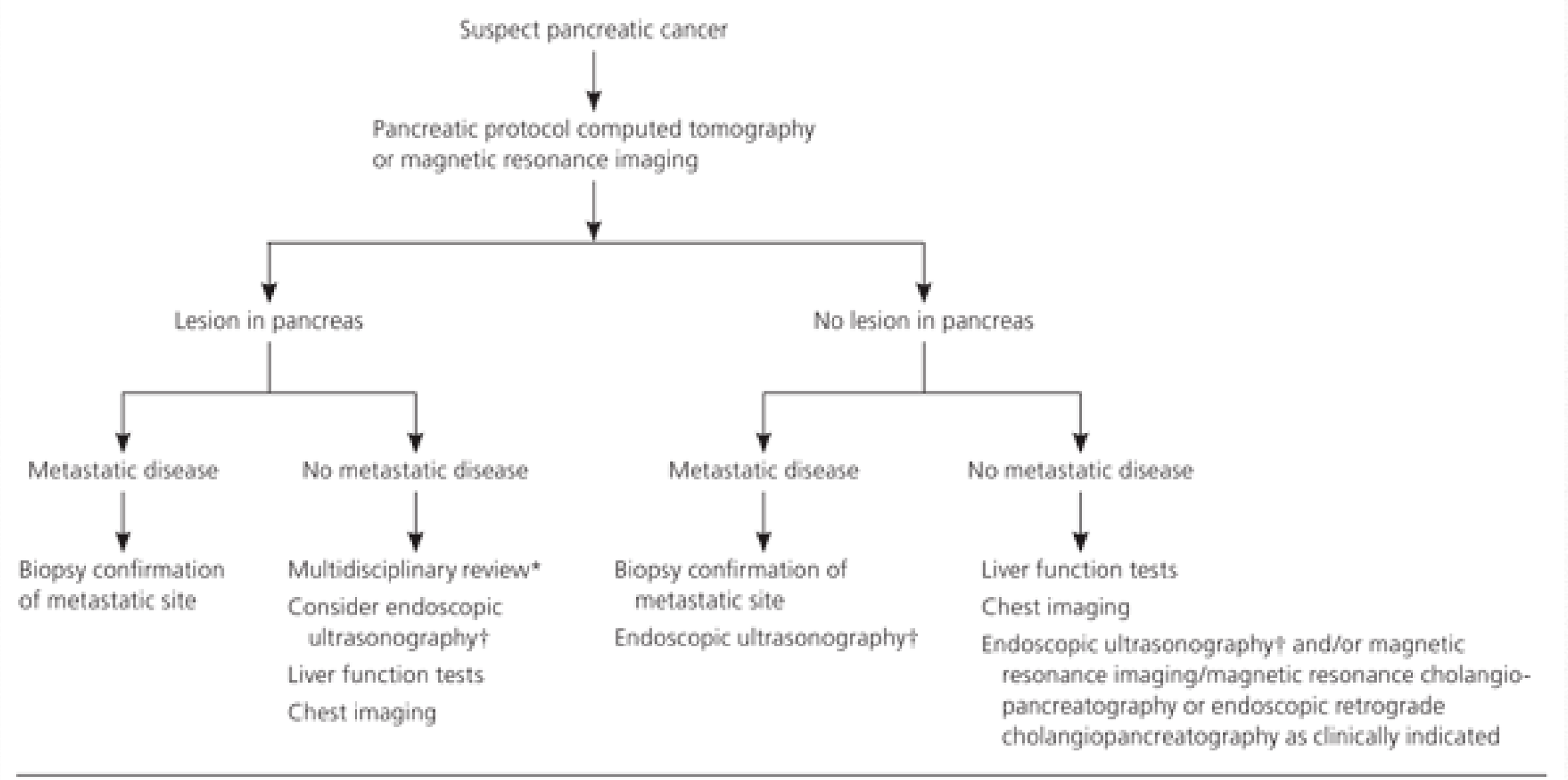
- Confirm diagnosis & predict prognosis & recurrence after resection

- Not useful for screening as it is not tumour specific

- Sensitivity-50-75% Specificity 80-85%

- Also elevated in pancreatitis, chronic inflammation

Algorithm for diagnosis



*—*Multidisciplinary review should ideally involve expertise from diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, surgery, and pathology.*

†—*Endoscopic ultrasonography–guided fine-needle aspiration if clinically indicated.*

Staging(AJCC 8th ed)

Pancreas

T1	Tumour 2 cm or less	
	T1a	Tumour 0.5 cm or less
	T1b	Tumour greater than 0.5 cm and less than 1 cm
	T1c	Tumor greater than 1 cm but no more than 2 cm
T2	Tumour more than 2 cm but no more than 4 cm	
T3	Tumour more than 4 cm in greatest dimension	
T4	Tumour involves coeliac axis, superior mesenteric artery and/or common hepatic artery	
N1	Metastases in 1 to 3 nodes	
N2	Metastases in 4 or more nodes	

M category unchanged

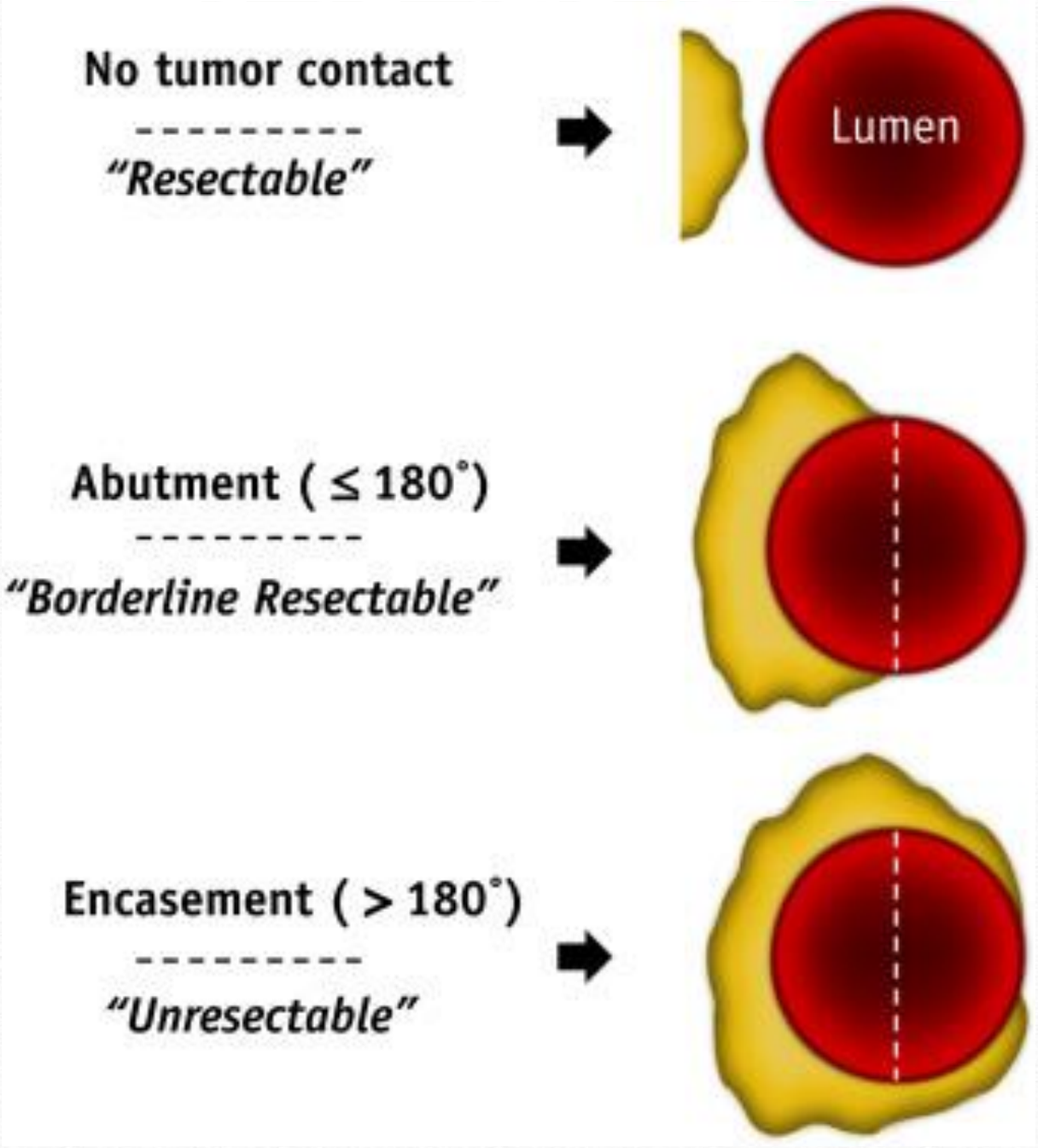
Stage

Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T1, T2, T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Overview of Treatment

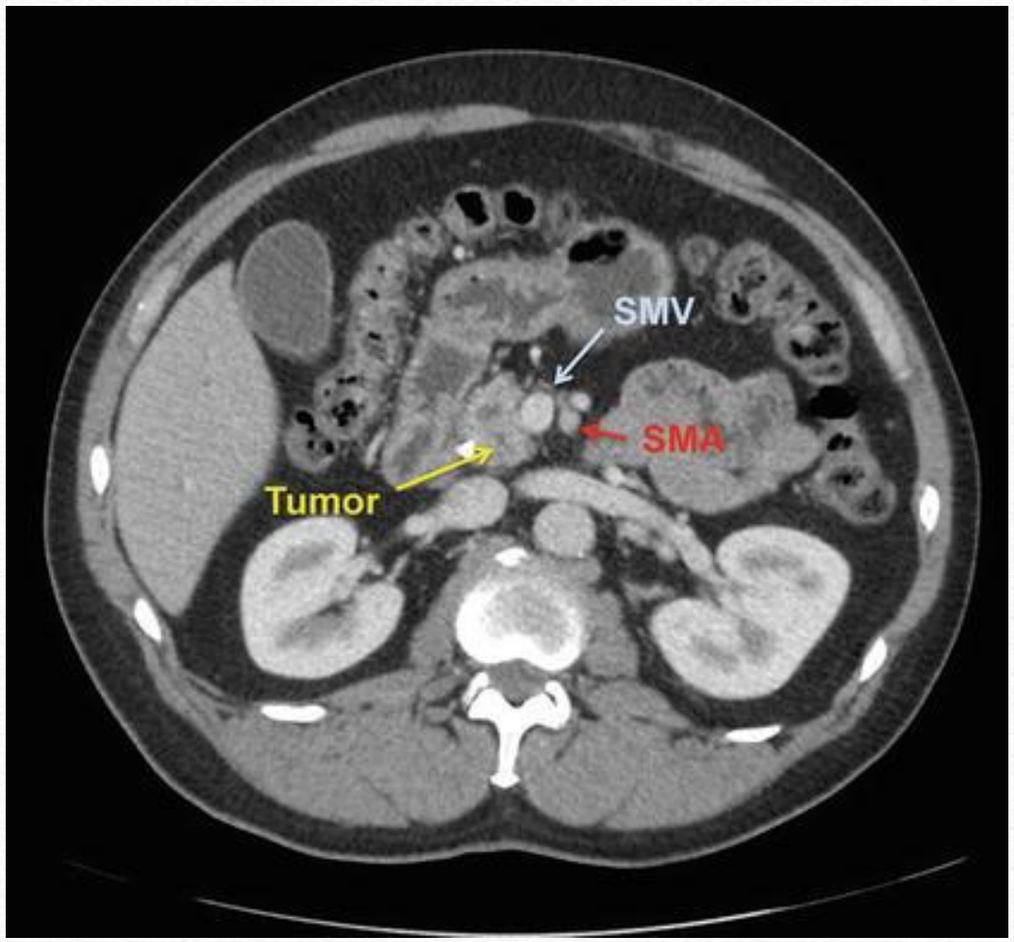
- Based on resectability
- Resection is only chance of cure of this disease
  - Resectable pts should undergo resection followed by Adjuvant therapy
  - Borderline resectable patients may benefit from neoadjuvant treatment & then surgery
  - Unresectable- CT/ CRT
  - Metastatic disease- CT/ Palliative Care

Tumour vessel attribution for resectability



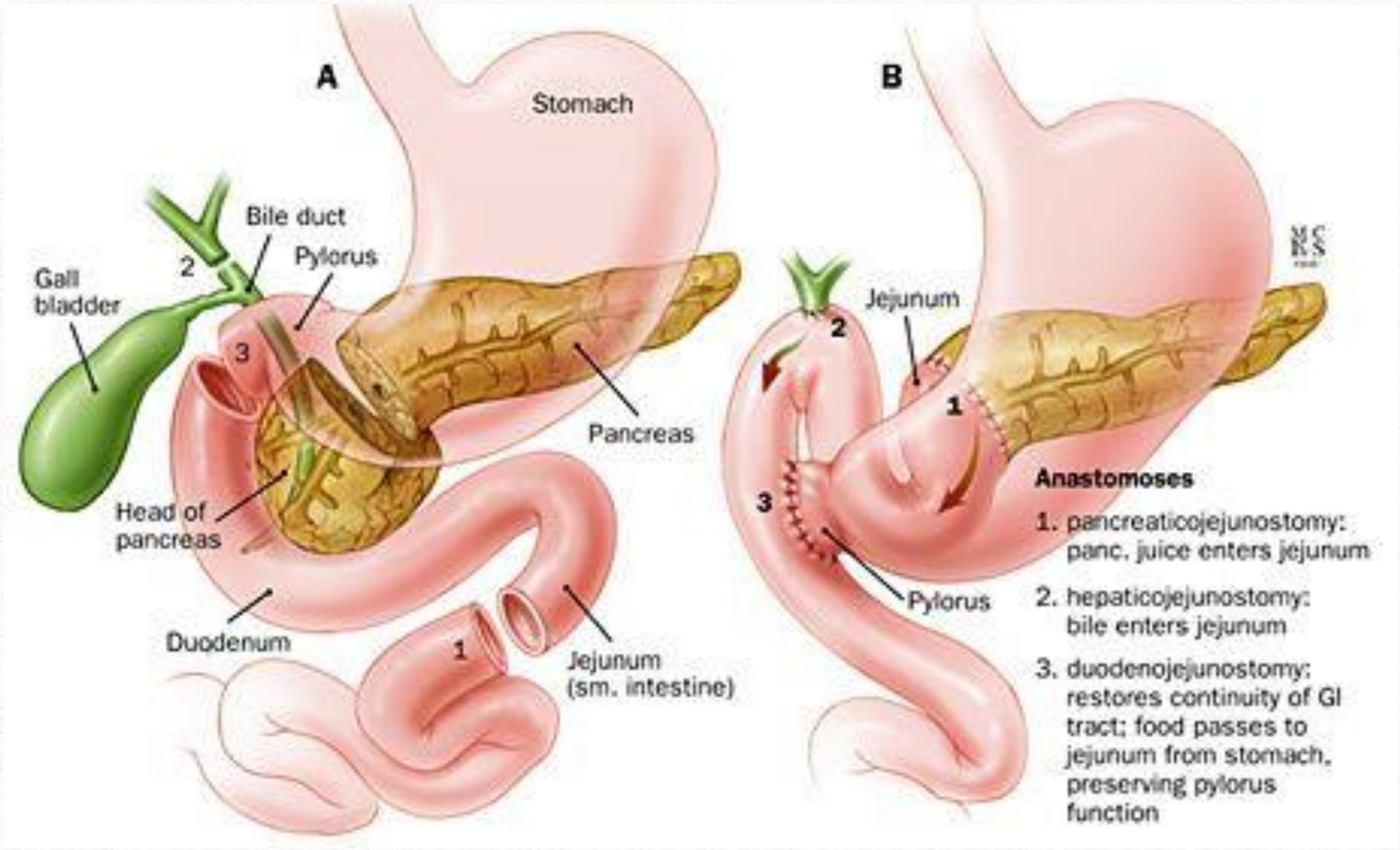
Surgery

- Mainstay of Treatment
- Feasible in only 20% cases
- Indications: T1,T2 , rarely T3
- 30% of these will actually have a R0 resection , with a resection margin of >1mm
- Also -no evidence of metastatic disease, no obstruction, Minimum PV involvement(<180 degree involvement over <1cm)
- 5 yr OS for pts with margin negative resection ~20%



Clear fat plane between tumour & SMV

Whipple Procedure



- Radical pancreaticoduodenectomy
- Removal of Pancreatic head,Duodenum, Stomach,Portion of jejunum,Gall bladder,Spleen
- Anastamoses- Gastrojejunostomy, pancreaticojejunostomy, Hepaticojejunostomy

Prognostic factors

- R0 resection
- Tumour size
- Absence of lymph nodes
- DNA Content

Role of RT

- Adjuvant RT +/- CT
- Neoadjuvant RT+/-CT
- Palliative RT
- IORT

Rationale of Adjuvant RT

- To reduce the risk of local recurrence
- Modest improvement in survival rates
- NACT/ CRT- Improves rates of resectability

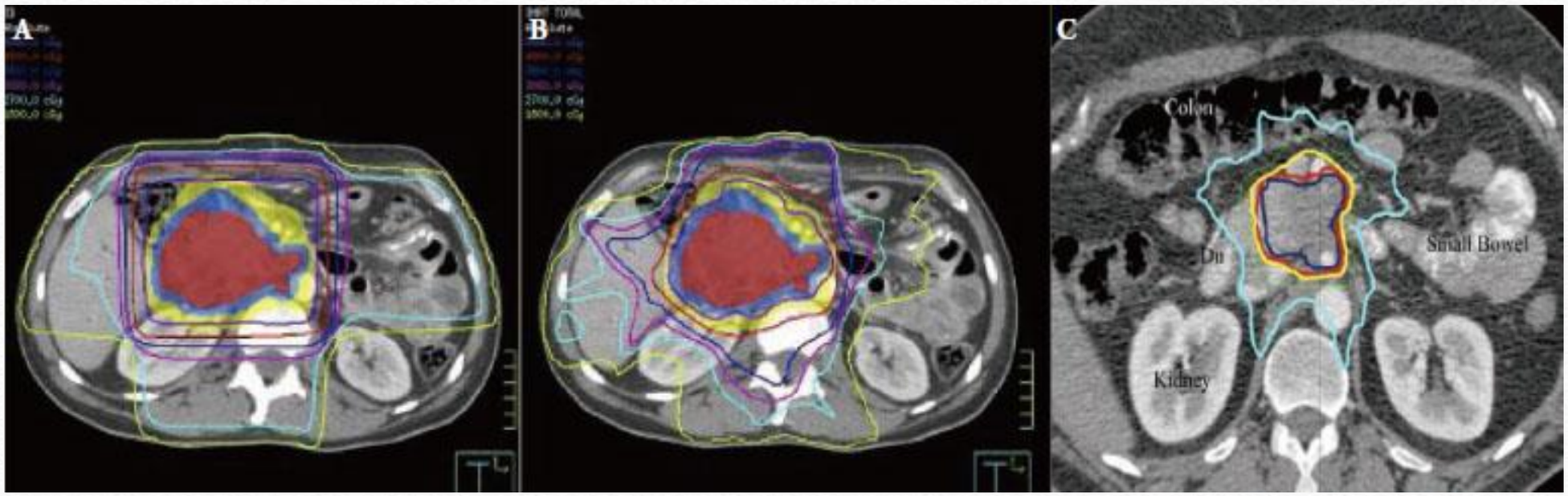
Obstacles- Conventional EBRT

- Uncertainities in true spatial extent of disease
- Inadequate knowledge of exact shape & location of normal structures
- Lack of tools for efficient planning & delivering of Radiotherapy
- Dose escalation was limited by the NTT of the surrounding structures

New planning tools

- More accurately extract in 3D , volume to be treated
- Critical normal tissues to be spared
- Direct & shape fields to achieve high conformation
- Predict dose distribution accurately
- Evaluate treatment graphically

Conformal techniques



3DCRT IMRT SBRT

- IMRT significantly reduced incidence of Gd3-4 nausea & vomiting (0%vs 11%) & diarrhoea(3%vs 18%)(*Yovino et al, 2011)*
- SBRT provides a shorter course of treatment with similar local control

RTOG Contouring Guidelines

- To ensure the adequacy of post op CTV
- Stepwise approach
- **AIM**
- To identify the Region of Interest(ROI) & margin expansion
- To create a reproducible CTV that covers the post op bed , nodal regions at risk
- Minimize inclusions of highly radiosensitive abdominal OARs

GTV

- No GTV- as post resection
- Location of pancreatic tumour prior to resection reviewed & contoured based on preop imaging
- Preop scans can be fused with postop scans to facilitate localization of tumour bed
- Surgical & pathological information must be reviewed at time of treatment planning

CTV

Area likely to be the highest concentration of residual subclinical tumour that can be treated with RT without resulting in a treatment volume that encompasses an excessive amount of normal organs /tissues

CTV

- **Post op bed-** based on location of initial tumour from preop scans

- **Anastamoses**-Pancreaticojejunostomy

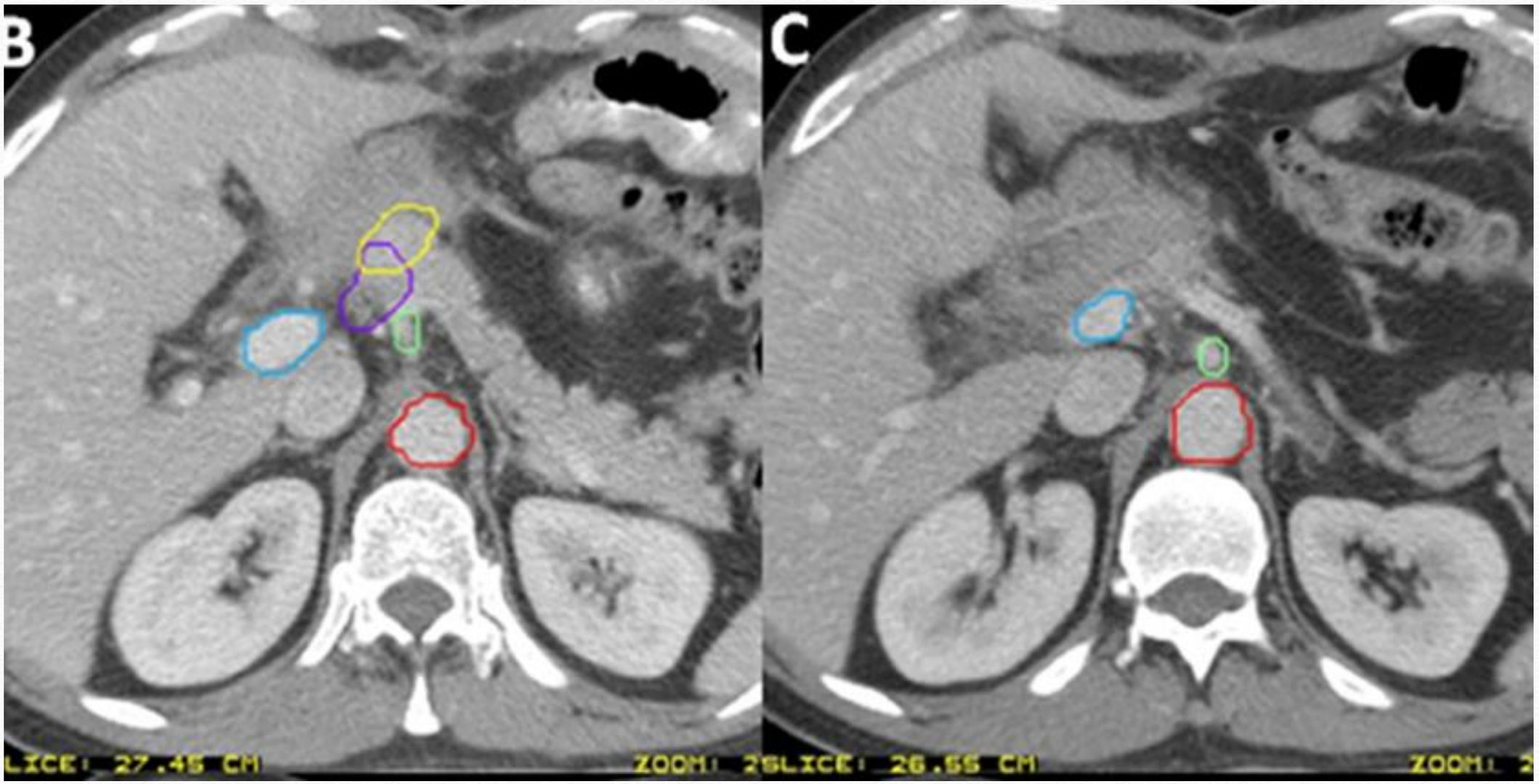
  Choledochal/ hepaticojejunostomy

- **Abdominal nodal regions**

Peripancreatic, celiac, superior mesenteric, porta hepatis, para aortic

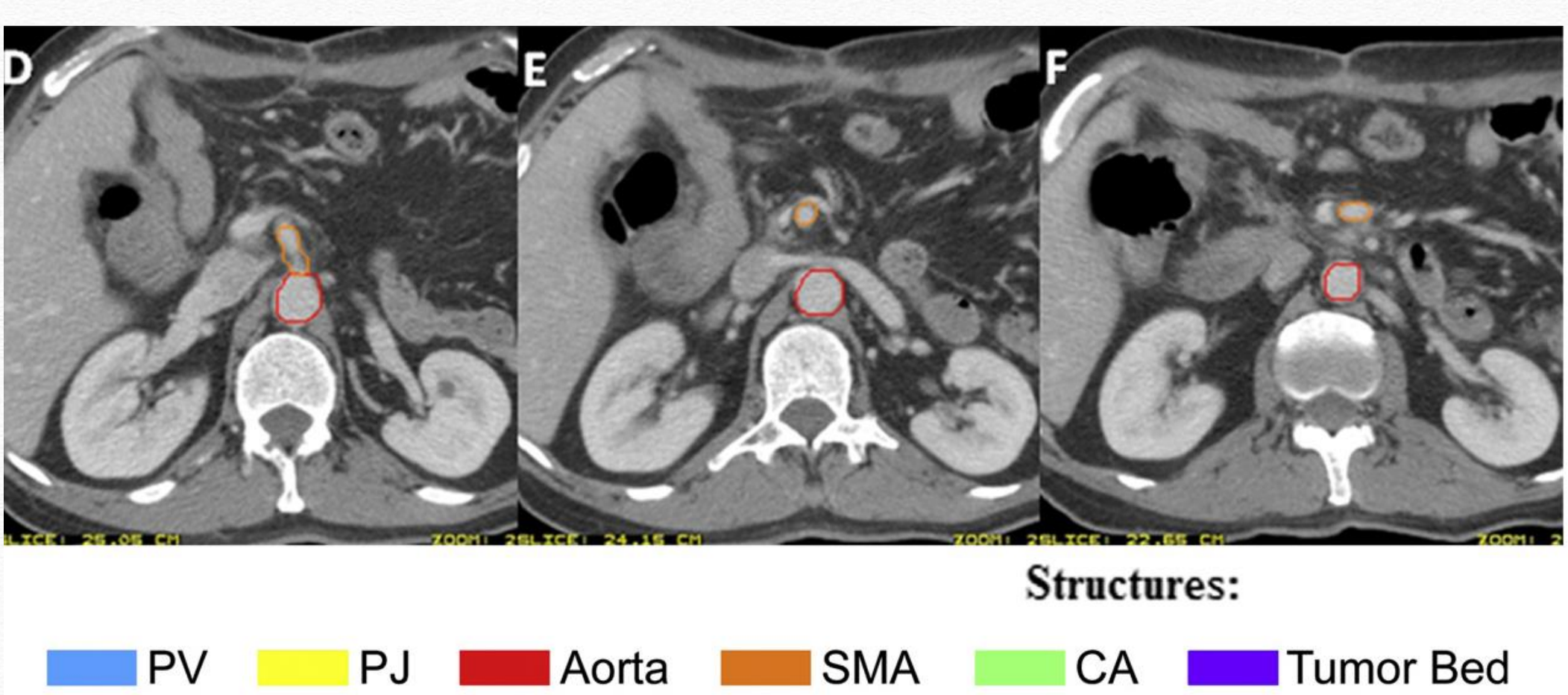
ROI delineation CA

- Most proximal 1-1.5 cm of celiac artery



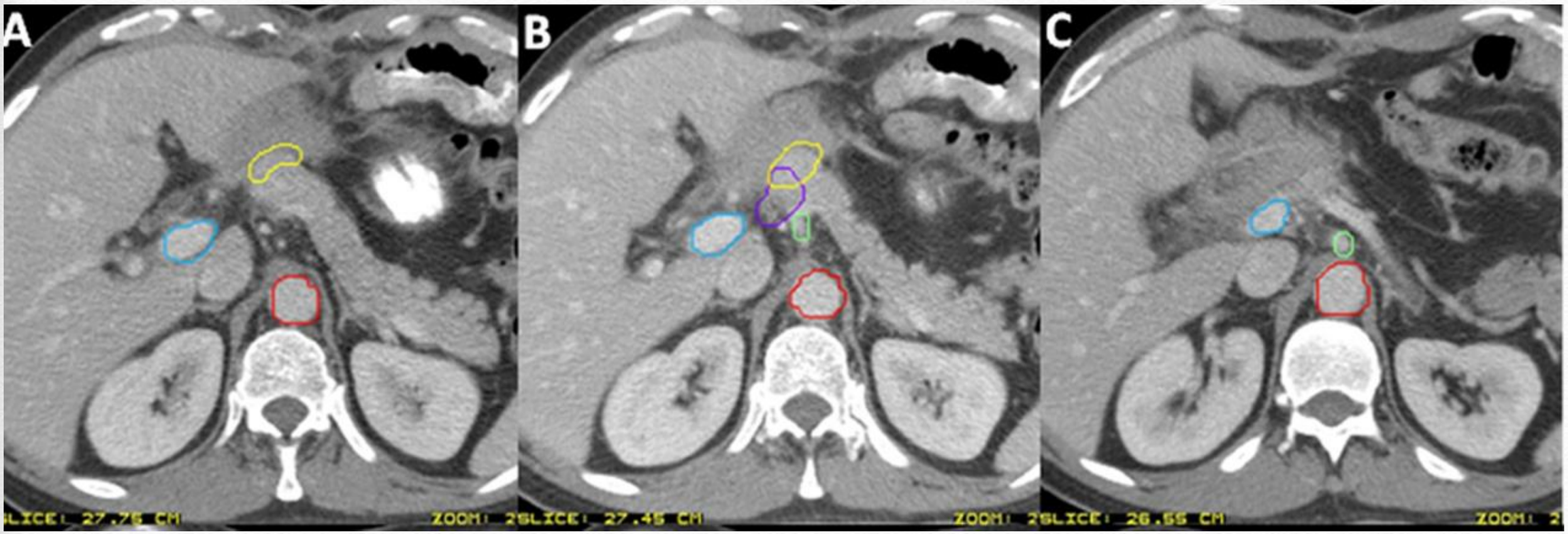
SMA

- Most proximal 2.5-3.0 cm of Superior mesenteric artery



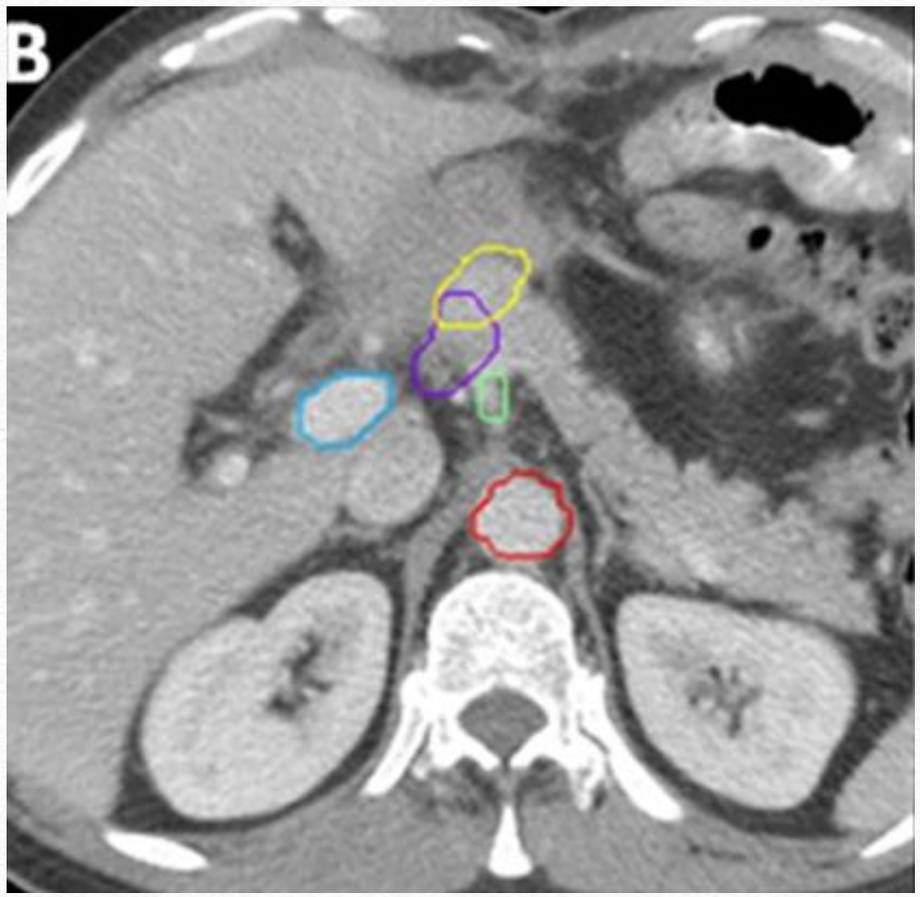
ROI delineation-PV

- Include the PV segment that runs slightly to the right of, anterior to & anteromedial to the IVC
- Contour from the bifurcation of the PV to, but not including , the PV confluence with either the SMV or the SV
- PV bifurcation can be extrahepatic/intrahepatic
- PV most often merges first with SMV, but may merge with SV



ROI Delineation- Post op bed

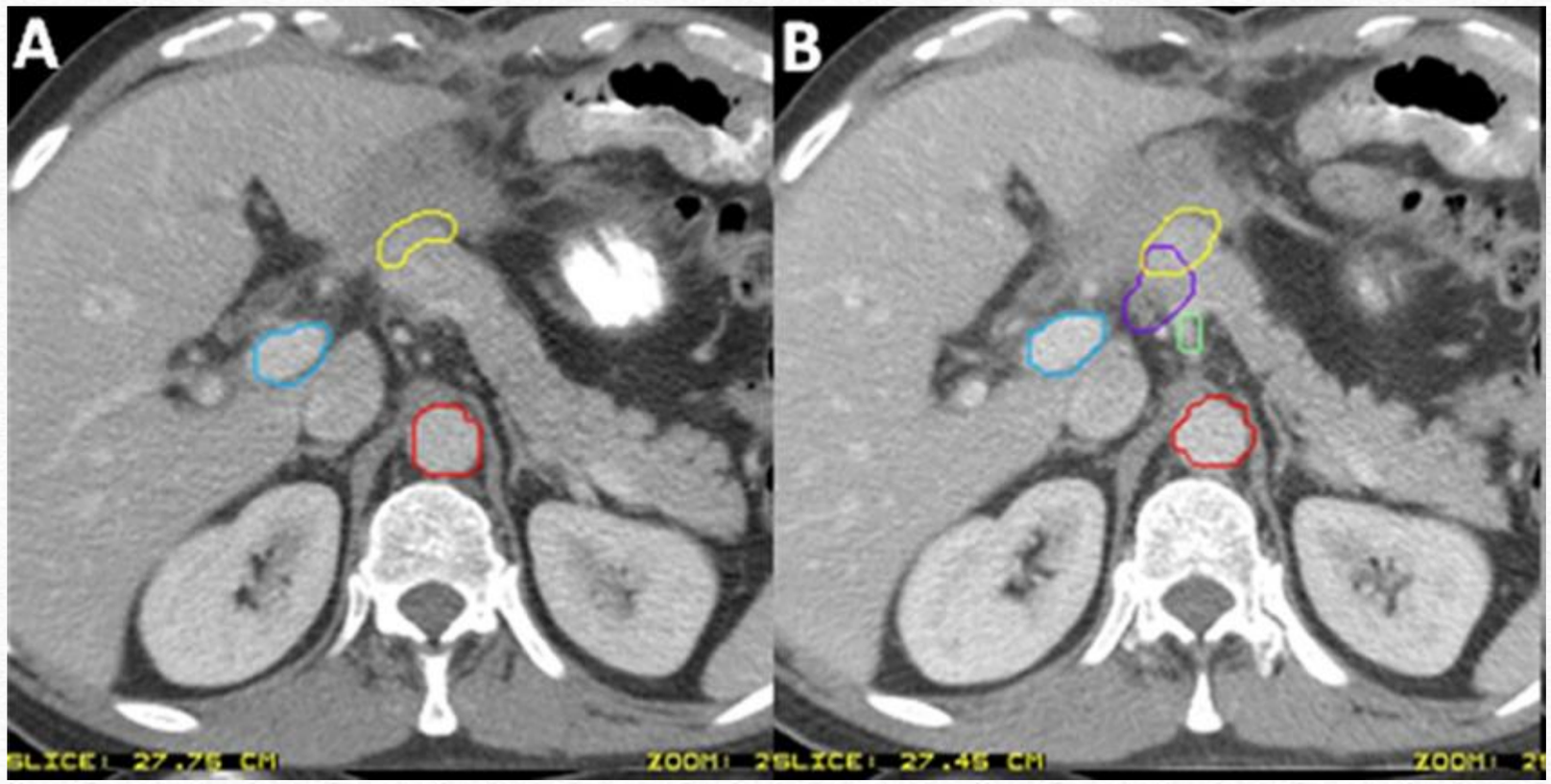
- Location of pancreatic tumour prior to resection must be reviewed & contoured based on preop imaging
- Surgical clips placed for purpose of delineating areas of concern intraop, such as close margins, uncinate margin etc must be included
- Provided there is written documentation that clips were placed for specific tumour related /RT planning related purposes



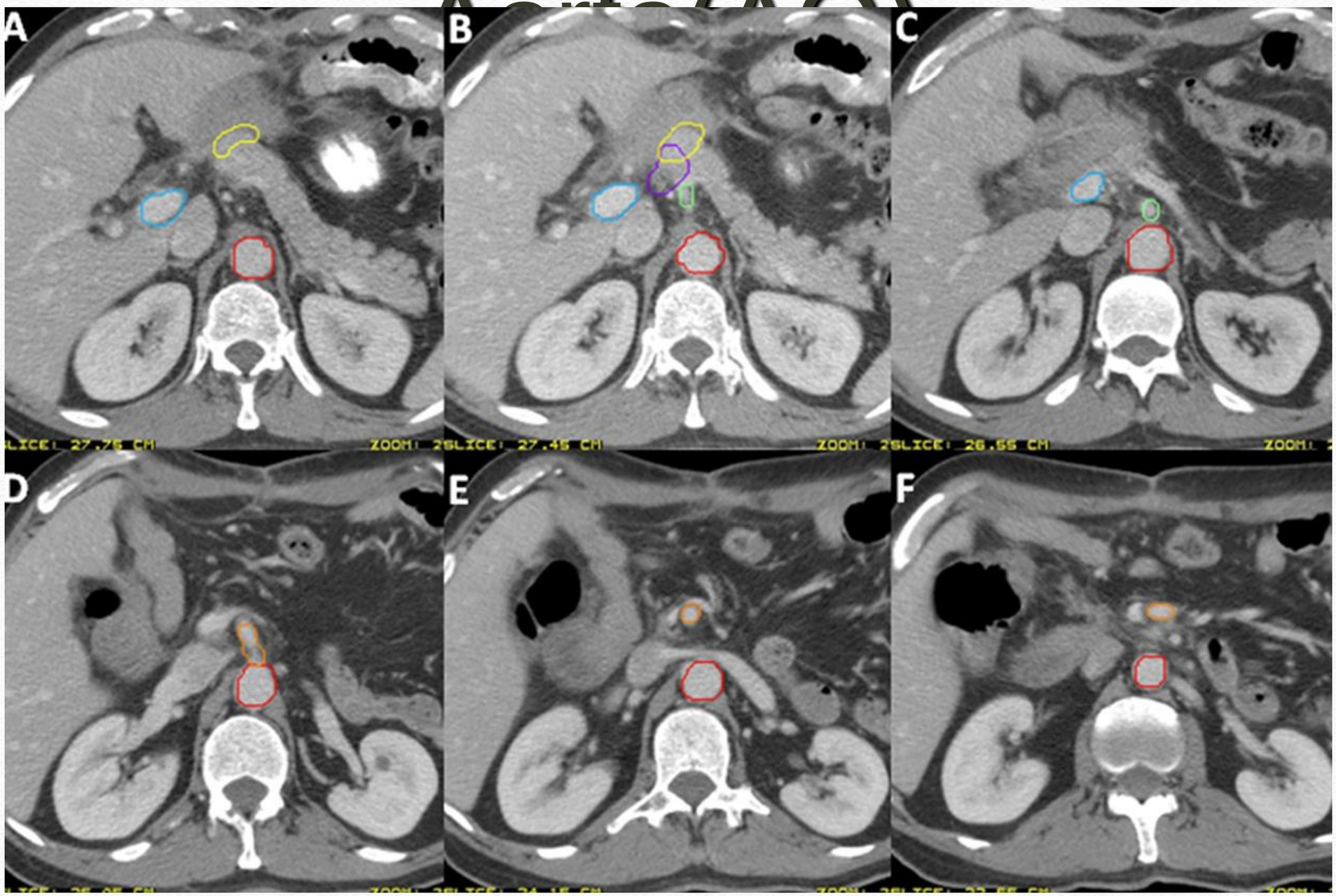
ROI delineation: PJ

Pancreaticojejunostomy identified by following the pancreatic remnant medially & antly until the junction with the jejunal loop is noted

If Pancreatogastrostomy, not included, as leads to more toxicity



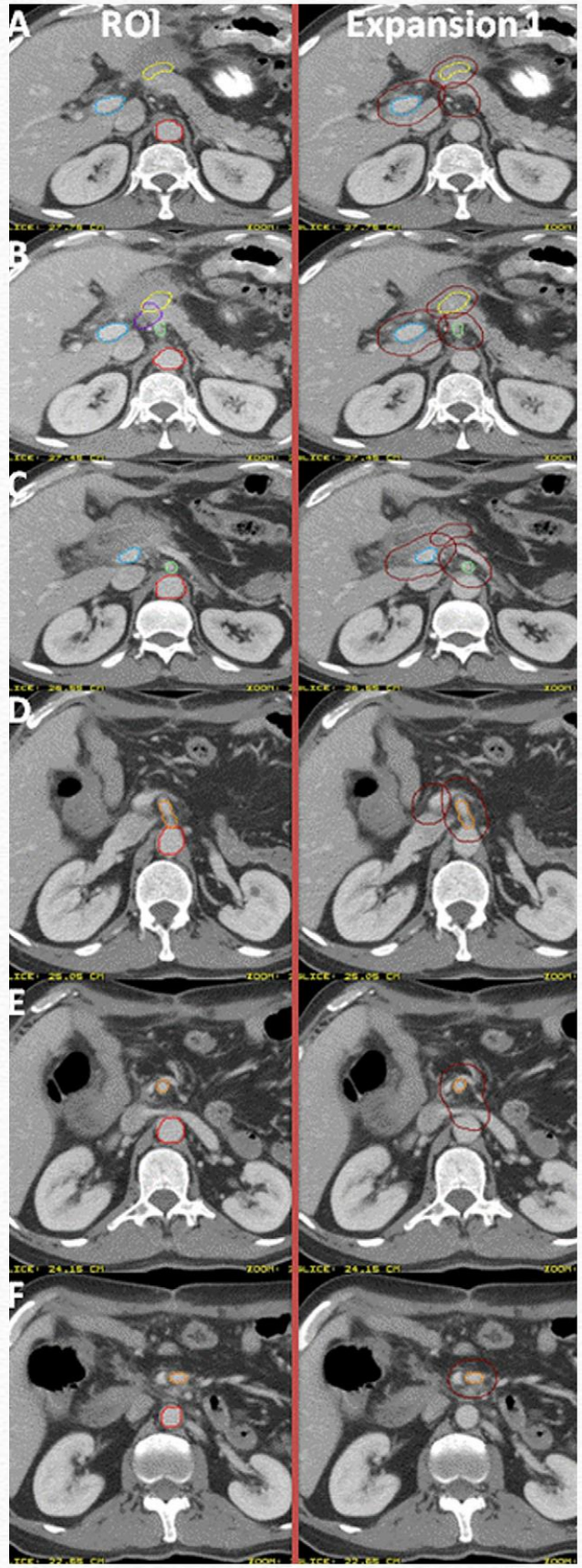
ROI Delineation: Aorta(AO)



- Aorta from most cephalad contour of either the celiac axis, ,PV or ,PJ (whichever is most cephalad) to the bottom of L2 vertebral body
- If GTV extends to/below the bottom of L2 then contour the aorta towards the bottom of L3 vertebral body as needed to cover the region of preop tumour location

ROI expansions

- The celiac axis , SMA & PV ROIs should be expanded by 1.0-1.5cm in all directions
- PJ should be expanded 0.5-1.0 cm in all directions
- Delineated clips must be expanded 0.5-1.0 cm in all directions or used without expansion
- If all these structures are expanded uniformly by 1.0 cm , they can be expanded as a single unit



ROI expansions

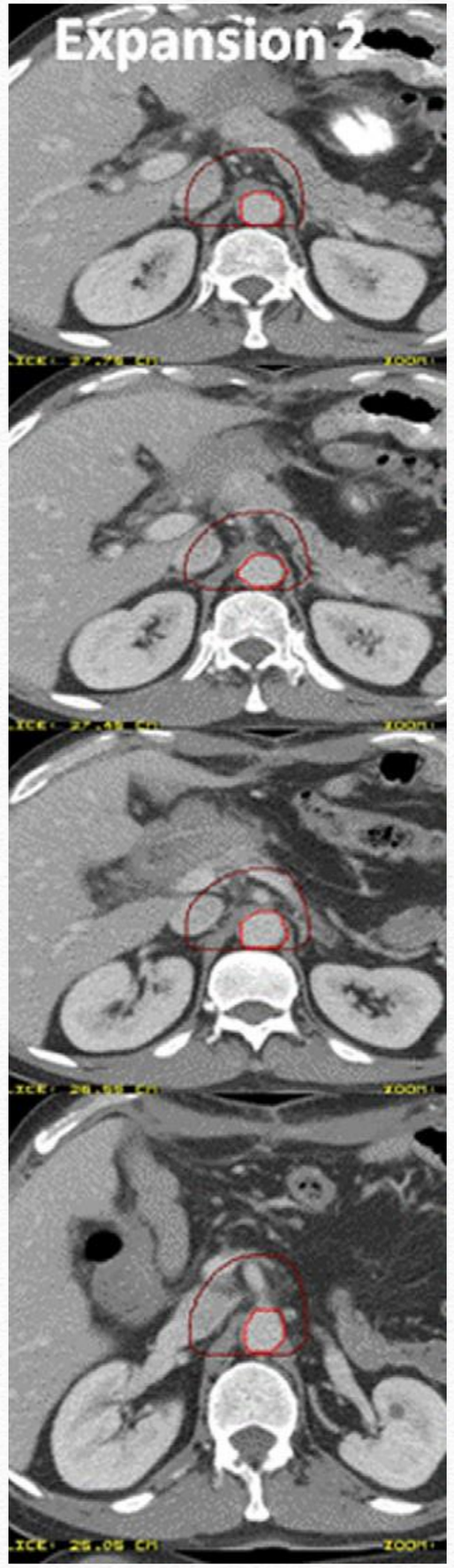
- Aortic ROI is expanded asymmetrically to include prevertebral nodal regions from top of PJ , PV or CA , to bottom of L2/ L3(if GTV location low)

- **Suggested expansion**- 2.5-3.0 cm to right,1.0 cm to left,2.0-2.5 cm antly, 0.2 cm postly towards ant edge of vertebral body

- **Goal:** To Cover paravertebral nodes latly while avoiding kidneys

- PJ or PV expansion may extend cephalad to above the level of celiac axis. The aortic expansion should then be extended cephalad to the same level as the highest CT slice of PV/PJ expansion

- This is **Expansion 2**



ROI expansion-CTV

- CTV should be created by merging these ROI/ROI expansions

- CA, SMA, PV, GTV, AO, PJ, HJ, Clips

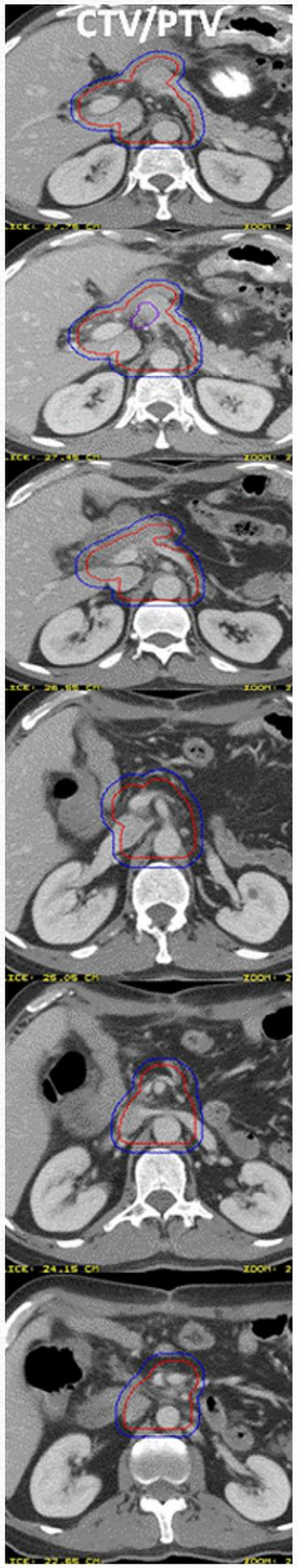
Constraints

- Post margin should follow the contour of ant aspect of the vertebral body without actually including >0.10cm ant vertebral body edge

- If PJ can’t be identified, CTV should be generated without it

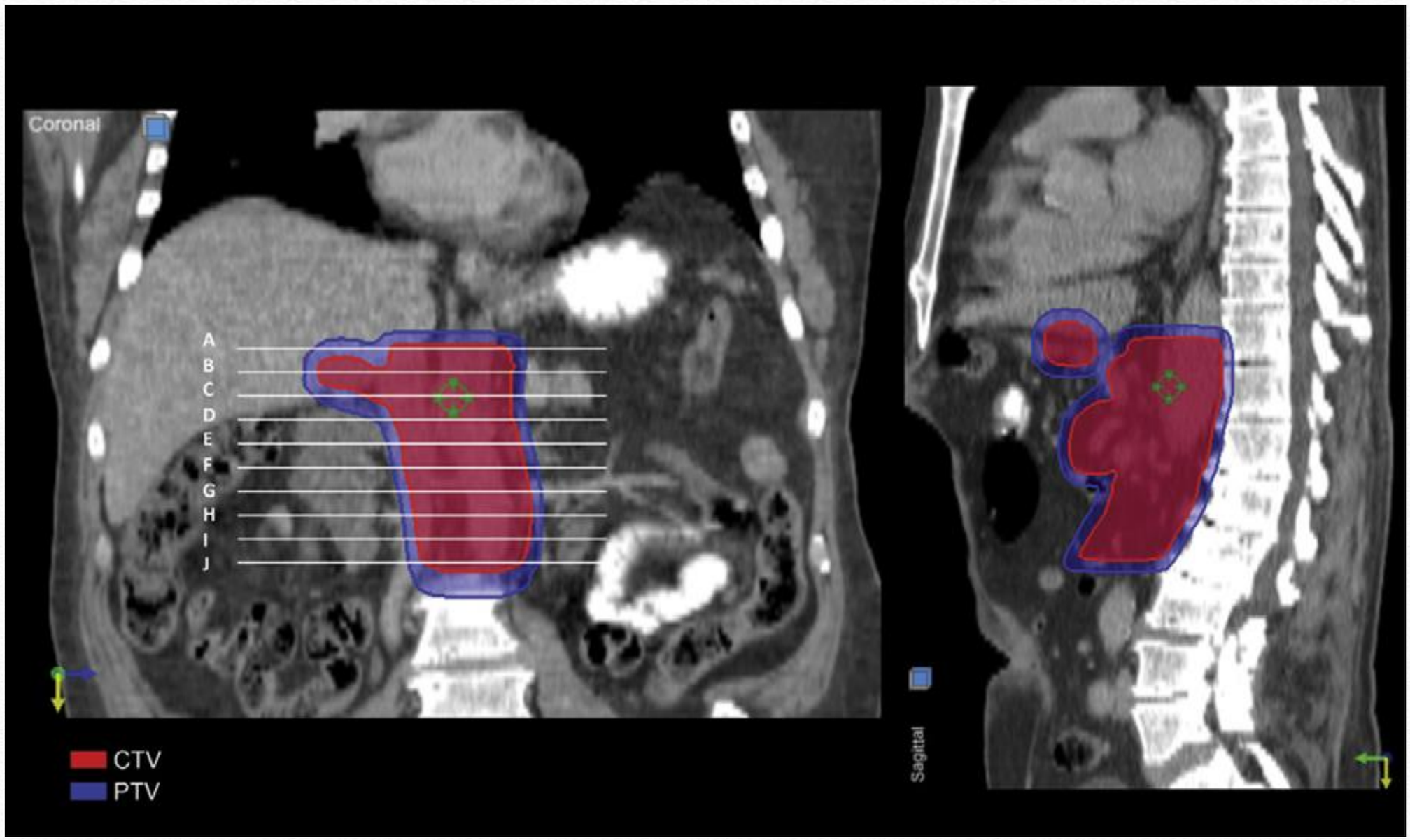
- If there is a pancreaticogastrostomy- do not include it in CTV

- If CTV with expansions, protrudes into a dose limited normal organ such as liver/stomach, CTV should be edited to be adjacent (may touch the edge) of relevant structure

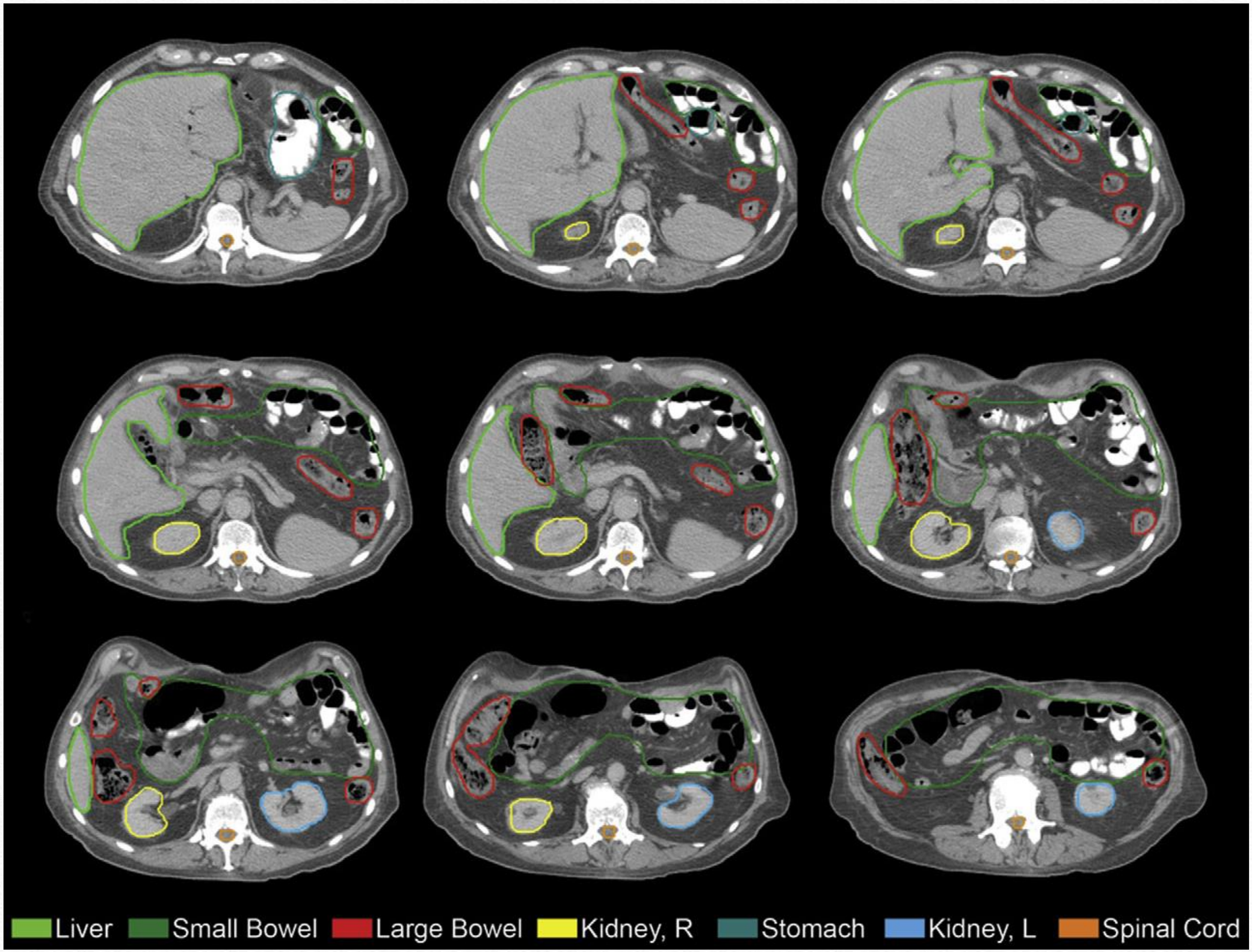


PTV

0.5 cm expansion on CTV



OARs


Liver
Small Bowel
Large Bowel
Kidney, R
Stomach
Kidney, L
Spinal Cord

OARs

- Kidneys, liver & stomach contoured completely to calculate a DVH
- Renal hilum should be excluded from kidney contourto avoid overestimating the renal parenchymal volume
- SI from jejunum to 2cm below lower extent of CTV should be contoured
- Should not include entire abdominal cavity
- Large bowel to be contoured separately
- Spinal canal defined within the cranial caudal extent of CTV

Normal Tissue Dose Constraints Adjuvant

Organs at Risk Dose Limits
Criticial Structure Variation Acceptable

Structure	Constraints
Kidney (L & R)	D50% ≤ 20Gy (no more than 50% of each kidney can receive more than 20Gy). Mean dose ≤ 20Gy. If only one kidney is present, D15% ≤ 20Gy (no more 15% of the volume of that kidney can receive more than 20 Gy
Liver	Mean liver dose must be ≤ 30 Gy
Stomach and SmallBowel	Max dose ≤ 56 Gy; D15% ≤ 50Gy (no more than 15% of the organ can receive more than 50Gy)
SpinalCord	Max dose to a point that is 0.03 cm^3 must be < 50Gy

Summary

- **Delineate ROIs**-PV, PJ, CA, SMA, AO, Tumour bed
- **Expansion 1**- 1.0 cm expansion on PV , PJ, CA & SMA
- **Expansion 2**-2.5-3.0 cm to right,1.0 cm to left,2.0-2.5 cm antly, 0.2 cm postly towards ant edge of vertebral body
- **CTV**- Merging of Expansion 1 & 2(Boolean addition)
- Confirm that CTV encompasses tumor bed & contoured clips
- **PTV** - 0.5 cm expansion on CTV

Dose Fractionation

Adjuvant RT-

- 45-46 Gy/ 1.8-2 Gy/Fraction to tumour bed surgical anastamoses & adjacent lymph nodes + additional 5-9 Gy to tumour bed & anastamoses
- Escalation above 54 Gy is avoided

Radical (with 5FU/ Gem)

- 45-50.4 Gy/ 25-28 F/ 5-5.5 wks followed by surgery 8 wks post RT

Borderline resectability

- **Marginally resectable :**Pts who have a potentially resectable cancer after preop CRT

- **Pancreatic body/tail** : Solid tumour contact ≤180 ° or >180 ° without involvement of aorta or gastroduodenal artery

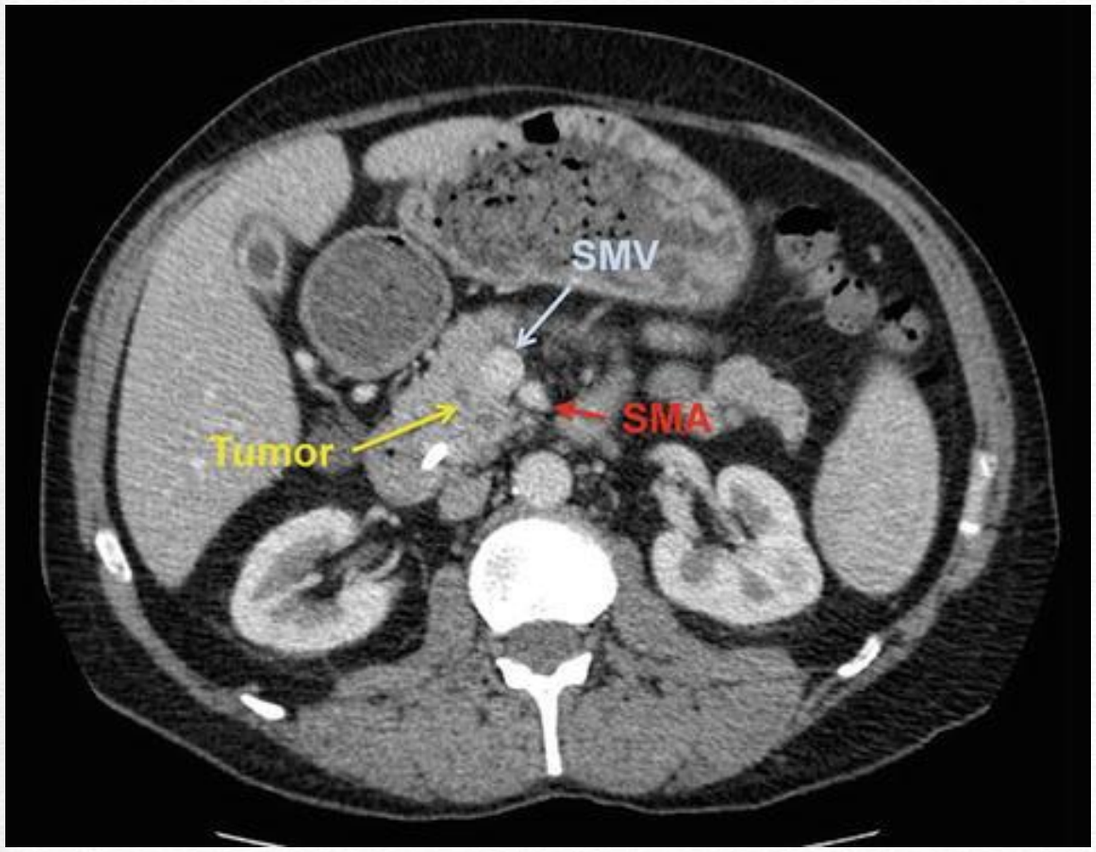
- **Head:** Solid tumour contact without extension to CA / hepatic artery bifurcation , allowing for safe & complete resection & reconstruction

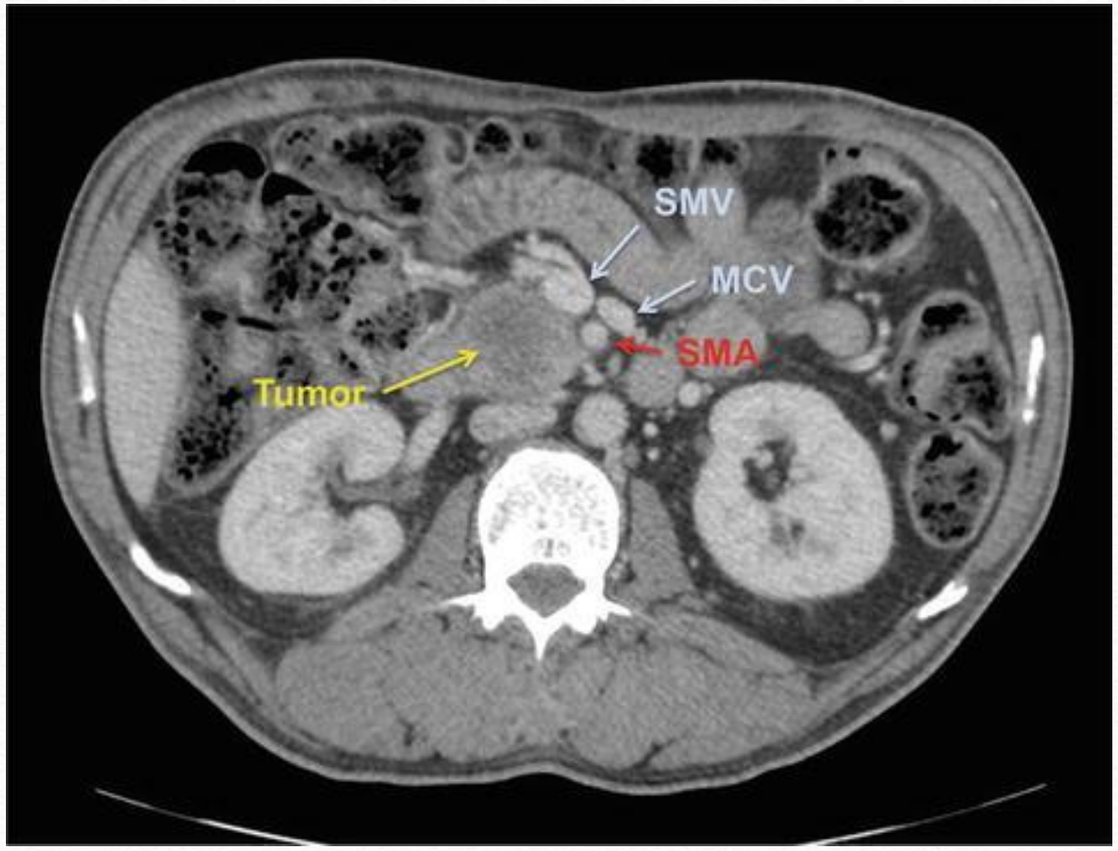
- **SMA:** Solid tumour contact ≤180 °

- **SMV/PV:**Solid tumour contact >180 ° with contour irregularity or vein thrombosis but with suitable vessel proximally & distally to site of involvement to allow safe & complete resection & vein reconstruction

NCCN Guidelines

Borderline resectable





Approx 180 degree contact between tumour & SMV & subtle haziness post to SMA

Locally Advanced

- **Goal of RT**:To prevent/ delay local progression which may result in pain / local obstructive symptoms
- Induction CT Followed by CRT/SBRT
- **SBRT**:30-45 Gy/3F or 25-45 Gy/5F
- SBRT: Clinical trial

Rationale of NACRT

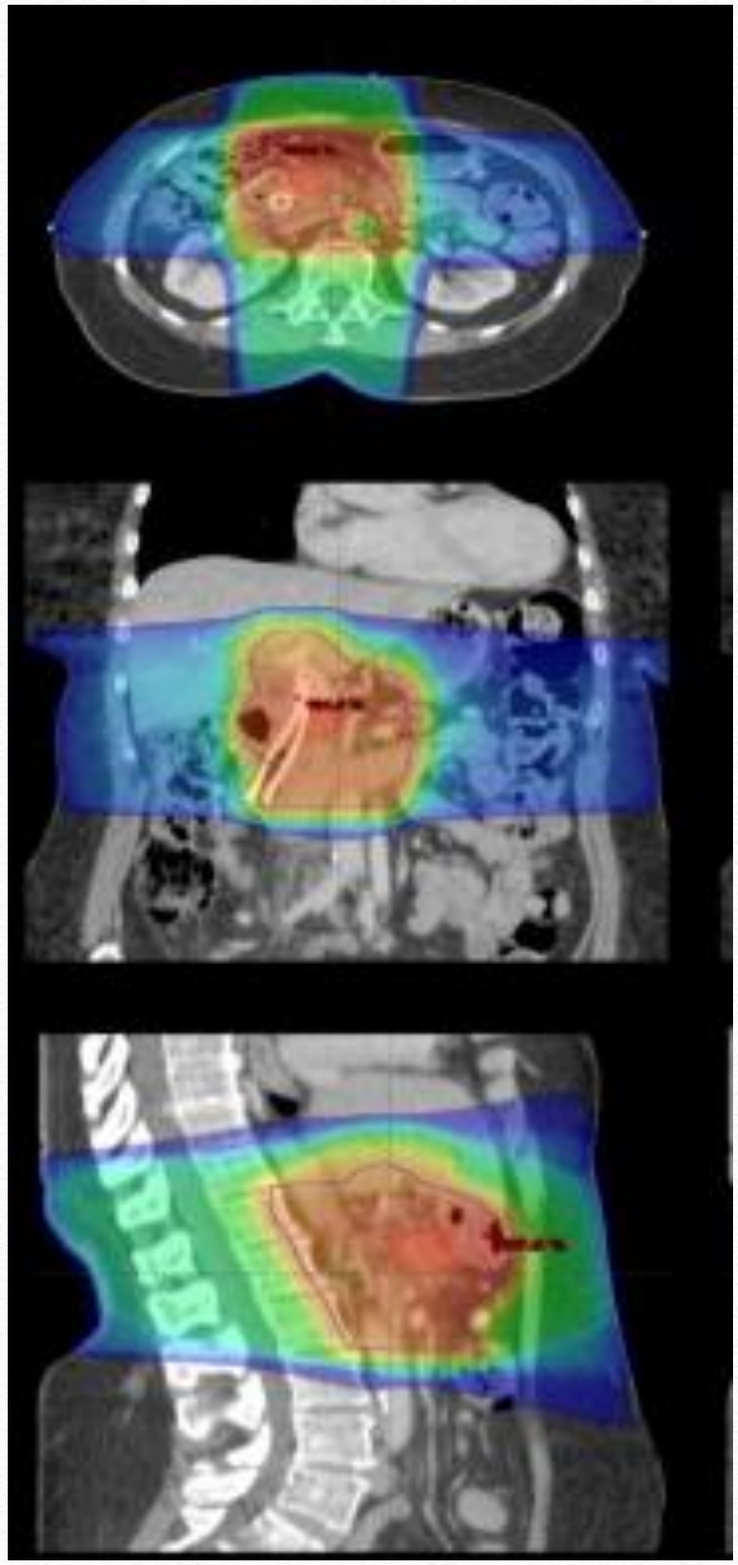
- Improvement in surgical resctability & OS seen in pts with unresectable tumour treated with NA CRT + Resection
- Median survival-16-32 mths
- 5 yr survival-18-41%(median 36%)
- No consensus on elective nodal irradiation, but high frequency of lymphatic spread seen in Ca head of pancreas
- High rate of local & nodal failure-75%
- ENI reduces the failure rate from 25% to 0-13%

Target volume

- Location of primary disease
- Status of lymph node involvement
- ENI-Nodal region with a probabilty of involvement ≥ 3% is considered at clinically significant risk

CTV

- Primary mass(GTV)
- SMA & PV adjacent to pancreatic head
- Enlarged lymph nodes
- Celiac axis depending on tumour location
- Aorta
- Primary GTV +10mm margin (Primary CTV)+ CTV ELN expanded by 0.5cm & merged together
- Alternative - Primary tumour + margin

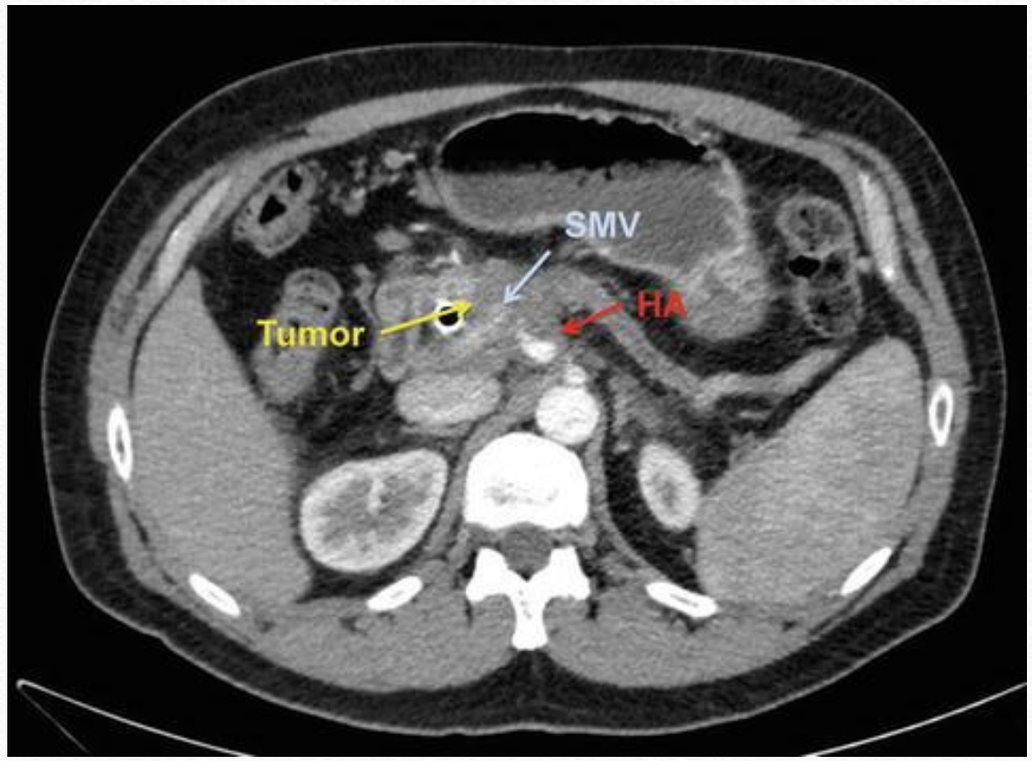


Normal Tissue Dose Constraints

Structure	Unresectable/Preoperative Recommendations[b]
Kidney (right and left)	Not more than 30% of the total volume can receive ≥ 18 Gy. If only one kidney is functional, not more than 10% of the volume can receive ≥18 Gy.
Stomach, duodenum, jejunum	Max dose ≤55 Gy; not more than 30% of the volume can be between 45 and 55 Gy.
Liver	Mean dose cannot exceed 30 Gy.
Spinal cord	Max dose to a volume of at least 0.03 cc must be ≤45 Gy.

Unresectability criteria

- Extrapancreatic involvement
- Metastatic disease in liver, peritoneum , omentum or any other extraabdominal site
- Encasement or occlusion of SMV or SMV- PV confluence
- Direct involvement of SMA , IVC, Aorta or celiac axis



Encasement of SMV & CHA

Palliative RT

- Goal: To relieve pain & bleeding &/ ameliorate local obstructive symptoms , in pts with metastatic & non metastatic disease

- Non Metastatic disease: Elderly pts

- Not candidates for definitive therapy due to poor performance status / comorbidities

Palliative - Metastatic disease

- Palliation of mets: short course RT(1-15 F)

- RT alone to primary tumour with small margin reasonable

- Local palliation for obstruction/pain refractory to analgesic therapy/ Bleed

Dose Fractionation

Unresectable/ Locally advanced

- 45-50.4 Gy/25-28 F/5-5.5 weeks (CRT)

Palliative

- 30Gy/10F/2wks

IORT

- HDR Brachytherapy/ Electrons
- Alternative to delivering high radiation doses
- High single dose of RT
- Enables healthy tissues to be displaced & shielded from radiation
- No clear survival benefit added , but used in unresectable disease
- Very limited indications in the era of High dose conformal SBRT & IG/IMRT

Adjuvant CT

- **CONKO-1:** Significant improvement in DFS & OS(21%vs 10%) with use of post op Gemcitabine vs observation

- **ESPAC 3**: No difference in OS between 5FU/LV Vs Gemcitabine following surgery. Med survival 23.0 vs 23.6 mths. More gd 3-4 toxicity with 5FU/LV

- **ESPAC 4**: Support use of Gemcitabine +Capecitabine vs Gem alone Gd 3/4 toxicity more in combined arm . Med OS 28 vs 25.5 mths. 5yrOS: 29 vs 16%

- **PRODIGE 24**: Benefit of FOLFIRINOX vs Gem alone Med DFS- 21.6 vs 12.8mths. Med OS 54.4 vs 35 mths

Locally advanced & Metastatic Disease CT

- Depending on Performance status , can plan for single agent/ multiagent CT

- Considered as initial therapy prior to RT

- **Options** : FOLFIRINOX

  Gemcitabine+ Alb Bound Paclitax

  Gem + Erlotinib

  Gem + Capecitabine

  Gemcitabine alone

  Capecitabine alone

  CI 5FU

Conclusion

- Adjuvant CRT is viable & rational for pancreatic cancer
- Neoadjuvant CRT is viable for locally advanced disease
- Dose escalation is possible with conformal techniques

Thank you