Target Volume, contouring & management of Carcinoma Pancreas

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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

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

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>% pts(Head)</th>
<th>% pts(Body &amp; Tail)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt loss</td>
<td>92</td>
<td>100</td>
</tr>
<tr>
<td>Jaundice</td>
<td>82</td>
<td>7</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>72</td>
<td>87</td>
</tr>
<tr>
<td>Anorexia</td>
<td>64</td>
<td>33</td>
</tr>
<tr>
<td>Dark urine</td>
<td>63</td>
<td>-</td>
</tr>
<tr>
<td>Acholic stool</td>
<td>62</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>45</td>
<td>43</td>
</tr>
<tr>
<td>Vomiting</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Weakness</td>
<td>35</td>
<td>42</td>
</tr>
<tr>
<td>Constipation</td>
<td>-</td>
<td>27</td>
</tr>
<tr>
<td>Food Intolerance</td>
<td>-</td>
<td>7</td>
</tr>
</tbody>
</table>
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,
Pancreatic Mass

Pancreatic Mass

Stomach

kidney

kidney

Stent
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

Suspect pancreatic cancer

Pancreatic protocol computed tomography or magnetic resonance imaging

Lesion in pancreas

Metastatic disease

Biopsy confirmation of metastatic site

No metastatic disease

Multidisciplinary review

Consider endoscopic ultrasonography†

Liver function tests

Chest imaging

No lesion in pancreas

Metastatic disease

Biopsy confirmation of metastatic site

Endoscopic ultrasonography†

Liver function tests

Chest imaging

No metastatic disease

Endoscopic ultrasonography† and/or magnetic resonance imaging/magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography as clinically indicated

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*—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

<table>
<thead>
<tr>
<th>T1</th>
<th>Tumour 2 cm or less</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>Tumour 0.5 cm or less</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumour greater than 0.5 cm and less than 1 cm</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumor greater than 1 cm but no more than 2 cm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T2</th>
<th>Tumour more than 2 cm but no more than 4 cm</th>
</tr>
</thead>
</table>

| T3   | Tumour more than 4 cm in greatest dimension |

| T4   | Tumour involves coeliac axis, superior mesenteric artery and/or common hepatic artery |

<table>
<thead>
<tr>
<th>N1</th>
<th>Metastases in 1 to 3 nodes</th>
</tr>
</thead>
</table>

| N2   | Metastases in 4 or more nodes |

**M category unchanged**

**Stage**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1, T2, T3</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T1, T2, T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T1, T2, T3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
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.

- **No tumor contact**: "Resectable" → Lumen
- **Abutment (≤ 180°)**: "Borderline Resectable" →
- **Encasement (> 180°)**: "Unresectable"
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

- Uncertainties 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

- 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
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
- 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

Pancreateicojejunostomy 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 1.0-1.5 cm 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
OARs

- Kidneys, liver & stomach contoured completely to calculate a DVH
- Renal hilum should be excluded from kidney contour to 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

<table>
<thead>
<tr>
<th>Structure</th>
<th>Constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney (L &amp; R)</td>
<td>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)</td>
</tr>
<tr>
<td>Liver</td>
<td>Mean liver dose must be ≤ 30 Gy</td>
</tr>
<tr>
<td>Stomach and SmallBowel</td>
<td>Max dose ≤ 56 Gy; D15% ≤ 50Gy (no more than 15% of the organ can receive more than 50Gy)</td>
</tr>
<tr>
<td>SpinalCord</td>
<td>Max dose to a point that is 0.03 cm³ must be &lt; 50Gy</td>
</tr>
</tbody>
</table>
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 anastomoses & adjacent lymph nodes + additional 5-9 Gy to tumour bed & anastomoses

- 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 resectability & 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 probability of involvement $\geq 3\%$ 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

<table>
<thead>
<tr>
<th>Structure</th>
<th>Unresectable/Preoperative Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney (right and left)</td>
<td>Not more than 30% of the total volume can receive $\geq 18$ Gy. If only one kidney is functional, not more than 10% of the volume can receive $\geq 18$ Gy.</td>
</tr>
<tr>
<td>Stomach, duodenum, jejunum</td>
<td>Max dose $\leq 55$ Gy; not more than 30% of the volume can be between 45 and 55 Gy.</td>
</tr>
<tr>
<td>Liver</td>
<td>Mean dose cannot exceed 30 Gy.</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Max dose to a volume of at least 0.03 cc must be $\leq 45$ Gy.</td>
</tr>
</tbody>
</table>
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
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 12.8 mths. 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
  - Gemcitabine alone
  - Gem + Capecitabine
  - 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