Pancreas SBRT

Rakendu Shukla, MD
KyNam Nguyen, MD
Brandon Dyer, MD

Faculty Advisor: Arta Monjazeb, MD PhD
University of California - Davis
Clinical Presentation

• 48 year old woman initially presented with RUQ abdominal pain and dark urine
• CT imaging showed a 2.3cm pancreatic head mass encasing the common hepatic artery with no regional lymphadenopathy.
• EUS/ERCP and FNA of the mass showed well-differentiated adenocarcinoma
• Staging: cT4N0M0, III (AJCC 8)
Clinical Presentation

• Started on systemic therapy, and received total of 8 cycles of FOLFIRINOX
• Response: stable disease, mass measuring 3.3cm not meeting RECIST 1.1 criteria for progressive disease
• No evidence of regional or distant disease based on CT imaging
• Biliary stent placed after first cycle of chemotherapy
• Deemed unresectable after induction chemotherapy based on encasement of the Common Hepatic Artery
• Referred to radiation oncology for evaluation of definitive chemoRT vs SBRT
Clinical Presentation

- **PMH**: GERD
- **PSH**: none
- **FHx**: ovarian cancer in mother
- **SHx**: 20py, quit 14 years ago

- **PE**
  - KPS 70
  - Vitals: BP 117/59, P 60, T 36.7°, RR 15
  - Chest: Lungs clear to auscultation bilaterally.
  - Heart: Regular rate and rhythm. No MRGs
  - Abdomen: Soft, nontender, nondistended, without organomegaly or masses. Negative Murphy’s sign, negative Courvoisier’s sign
  - Extremities: No clubbing, cyanosis, or edema. WWP
Clinical Presentation

• Labs:
  – Na 140, K 4.3, Cl 104, CO2 26, BUN 12, Cr 0.9, Ca 9.9
  – Pro 7.8, Alb 3.9, Alk Phos 136(H), AST 37, ALT 22, Bili 1.2
  – WBC 5.3, Hgb 12.9, Crit 37.9, Plt 107(L)

<table>
<thead>
<tr>
<th></th>
<th>Pre-chemo</th>
<th>s/p 4 cycles</th>
<th>s/p 7 cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA 19-9</td>
<td>13,375</td>
<td>5,455</td>
<td>2,518</td>
</tr>
</tbody>
</table>
Imaging findings
Pre-chemotherapy

December 19, 2018
Imaging findings
Post-chemotherapy
Pancreatic Cancer Epidemiology

• Approximately 55,400 diagnoses and 44,330 deaths in 2018 per ACS
• 4th leading cause of death from cancer
• Risk factors: tobacco use, high animal fat diet, radiation and chemo exposure, 2-naphthylamine, benzene, gasoline. Possible links to alcohol, coffee, chronic pancreatitis, diabetes
• Associated with BRCA1/2, PALB2, ATM, CDKN2A mutations, and Peutz-Jeghers and Lynch syndromes
Work-up

- H&P
- CT with pancreas protocol
- Endoscopic Ultrasound (EUS) for T and N staging
- Biopsy: EUS, ERCP, CT guided biopsy, laparoscopy for biopsy and rule out metastatic disease
- CBC, CEA, CA 19-9, amylase, lipase, glucose, bilirubin, alkaline phosphatase, LDH, LFTs
- Body imaging to rule out distant disease
# Staging (AJCC 8th Edition)


<table>
<thead>
<tr>
<th><strong>T Stage</strong></th>
<th><strong>Criteria</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Tumor cannot be assessed</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor limited to pancreas, ≤2cm</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor ≤0.5cm in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt;0.5cm and ≤1cm in greatest dimension</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumor &gt;1cm and ≤2cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;2cm and ≤4cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt;4cm in greatest dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor involves celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>N Stage</strong></th>
<th><strong>Criteria</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastases</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in 1-3 regional lymph nodes</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis to 4 or more regional lymph nodes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>M Stage</strong></th>
<th><strong>Criteria</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>cM0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>cM1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>pM1</td>
<td>Microscopically confirmed distant metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Stage</strong></th>
<th><strong>N0</strong></th>
<th><strong>N1</strong></th>
<th><strong>N2</strong></th>
<th><strong>M1</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>IA</td>
<td>IIB</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>T2</td>
<td>IB</td>
<td>IIB</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>T3</td>
<td>IIA</td>
<td>IIB</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>T4</td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>IV</td>
</tr>
</tbody>
</table>
# Surgical Resection Criteria

<table>
<thead>
<tr>
<th>Arterial</th>
<th>Venous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resectable</strong></td>
<td><strong>Borderline Resectable</strong></td>
</tr>
<tr>
<td>• No contact with CA, SMA, or CHA</td>
<td>• Contact with CHA without extension to CA or HA bifurcation</td>
</tr>
<tr>
<td></td>
<td>• ≤180° involvement of SMA</td>
</tr>
<tr>
<td></td>
<td>• Contact with variant arterial anatomy</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Treatment Options

• Unresectable or borderline resectable tumors
  – Chemo alone
  – Chemo-radiation
  – Chemo + chemo-radiation
  – Chemo + SBRT + Chemo

• Re-assess resectability based on response and no distant disease
SBRT Considerations

• Advantages
  – Shortened treatment time
  – Possible improvement in local control
  – Allows integration with more intensive systemic chemotherapy
  – Cost effective
  – Smaller target volumes (no elective nodal coverage, sharp dose gradients

• Feasibility
  – Minimal or no nodal involvement
  – Well defined tumor volume
  – Favorable normal anatomy (stomach, duodenum, kidney, liver)
  – Internal markers (fiducials, stent, etc)

• Caveat: No published randomized data comparing standard chemoRT to SBRT
PANCREAS SBRT STUDIES
Stanford Experience – Single vs Multi-fraction SBRT

• Methods:
  – 167 pts with unresectable pancreatic adenocarcinoma treated 2002-13
  – 45.5% received single fraction SBRT
  – 54.5% received 5 fraction SBRT
  – 87.5% received chemotherapy
Stanford Experience – Single vs Multi-fraction SBRT

- **RT Techniques:**
  - 3-5 gold fiducial markers placed either endoscopically, percutaneously, or surgically
  - 4DCT used for simulation as available
  - Supine, arms up
  - GTV and ITV delineated using PET and 4DCT
  - 2-3mm uniform PTV margin
  - No elective nodal coverage

- **Dose:**
  - Single fraction: 25Gy
  - 5 fraction: 25-45Gy, median 33Gy
Stanford Experience – Single vs Multi-fraction SBRT

- Results:
  - Median follow up 7.9 months
  - No difference between single fraction and multi-fraction in overall survival (OS) or local recurrence (LR)
  - Median OS: 13.6 months
  - Significantly less toxicity grade ≥2 with multi-fraction. P=0.005
  - No significant difference in ≥G3 GI toxicity for single vs multi fraction. (12.3% vs 5.6%)

<table>
<thead>
<tr>
<th></th>
<th>6 mo LR</th>
<th>12 mo LR</th>
<th>6 mo OS</th>
<th>12 mo OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Fx</td>
<td>5.3%</td>
<td>9.5%</td>
<td>67%</td>
<td>30.8%</td>
</tr>
<tr>
<td>Multi-Fx</td>
<td>3.4%</td>
<td>11.7%</td>
<td>75.7%</td>
<td>34.9%</td>
</tr>
</tbody>
</table>

Fig. 3. Cumulative incidence of gastrointestinal toxicities grade ≥2 for single versus multifraction SBRT groups. SBRT = stereotactic body radiation therapy.
Phase 2: SBRT with Gemcitabine Before and After

• 49 pts with locally advanced pancreatic cancer
• Up to 3 doses of gem followed by SBRT (33Gy in 5 fxs) followed by more gem until disease progression or toxicity
• Pts assessed for toxicity and quality of life
Phase 2: SBRT with Gemcitabine Before and After

• RT
  – Gold fiducial placement
  – Respiratory motion management
  – 2-3mm PTV expansion from GTV
  – 33 Gy in 5 fractions
Phase 2: SBRT with Gemcitabine Before and After

- Results:
  - Median follow up 13.9 months
  - Median OS 13.9 months
  - Freedom from local progression at 1yr: 78%
  - ≥G2 acute and late toxicities: 2%, 11%
    - Gastritis, fistula, enteritis, ulcer
  - QOL scores stable from baseline
  - Significant improvement in pancreatic pain at 4wks

Figure 2. Kaplan-Meier estimates of the survival function for (A) overall survival and (B) progression-free survival are shown. The 95% confidence intervals are included as dotted lines.
Neoadjuvant Chemo and SBRT for Borderline Resectable Disease

– Treatment protocol:
  • Medically fit pts
  • 2-3 months chemo
  • SBRT with 5 consecutive daily fractions
  • 30 Gy in 5 fractions
  • 40 Gy dose-painting to tumor-vessel interface
  • Assessed for resection
Neoadjuvant Chemo and SBRT for Borderline Resectable Disease

– Results:
  • 159 pts: 110 borderline resectable, 49 locally advanced
  • Median follow up 14 months
  • 51% had resection among borderline pts
    – 96% had R0 resection
  • Median OS: 19.2 months for borderline; 15 months for locally advanced
    – 34.2 months for resected patients vs 14 months
  • LRC at 1 year: 78%
  • ≥G3 toxicity: 7%
NCDB Analysis

- NCDB queried for unresected non-metastatic pancreatic adenocarcinoma who received chemotherapy between 2004-2012
- 4 treatment groups found:
  - Chemo alone
  - Chemo + External beam RT (EBRT)
  - Chemo + intensity modulated RT (IMRT)
  - Chemo + SBRT

- EBRT included: external beam not otherwise specified, orthovoltage, cobalt-60 or cesium-137, photons alone or mixed energies, or 3-dimensional conformal radiotherapy
NCDB Analysis

• Results – Pt Characteristics:
  – 14,331 pts met inclusion criteria
  – Chemo alone: 38.1%
  – Chemo + EBRT: 44.8%
  – Chemo + IMRT: 14.8%
  – Chemo + SBRT: 2.3%

• Treatment:
  – 45-50.4 Gy for EBRT and IMRT in 25-30 fractions
  – 24-35 Gy for SBRT in 3-5 fractions
NCDB Analysis

- Median Survival: 10.8 mo
  - Unmatched analysis:
    - Chemo alone: 9.9 mo
    - EBRT: 10.9 mo
    - IMRT: 12 mo
    - SBRT: 13.9 mo (p<0.0001)
  - Matched analysis:
    - SBRT improved survival when compared to chemo alone, EBRT, and IMRT

- Caveats: small n for SBRT pts, possible selection bias despite propensity matching
Italian Pooled Analysis

• Systematic review and pooled analysis of 19 trials regarding SBRT for pancreatic cancer
• Survival, loco-regional control (LRC), and toxicity outcomes aggregated for multi-variate analysis
• Inclusion:
  – Prospective trials and retrospective case series
  – Locally advanced pancreatic adenocarcinoma
  – Treated with SBRT with or without chemotherapy
Italian Pooled Analysis

• Results:
  – 6 prospective trials, 13 retrospective case series
  – Treated with linear accelerator and CyberKnife
  – Dose: 18 to 50 Gy in 1-8 fractions
  – 18 studies gave chemotherapy before and/or after SBRT
  – Median follow up ranged from 6 to 21 months
Italian Pooled Analysis

- Results:
  - Median OS: 17 months after multi-variate analysis
  - 1 year OS: 51.6%
  - 1 year LRC: 72.3% (see figure below)
- Toxicity:
  - Only 3 studies exceeded 10% for acute grade 3 and 4 effects (range 0-36%)
  - Chronic grade 3 and 4 effects did not exceed 11% (range 0-11%)

![Fig. 2. Pooled analysis and forest plot of locoregional control rate. Abbreviation: CI = confidence interval.](image-url)
Ongoing Trial – Pancreatic Cancer Research Study (PanCRS)

Induction Chemotherapy: mFOLFIRINOX x 4 cycles

Stable or Better Disease

Randomize

Arm 1
mFOLFIRINOX

Arm 2
SBRT+mFOLFIRINOX

Progression

Restage

Participating Institutions:
Stanford, MDACC, UCSF, Loyola, PMH, UTSW, MUSC, Swedish
RT Techniques

• Internal Markers:
  – Place >2 fiducials within tumor, wait 4-5 days for markers to settle
  – Can use biliary stent as internal marker
    • Stent more accurate than bony anatomy, though stent can deviate up to 8-9mm in relation to tumor
  – Fiducials>stent>bony anatomy

• Simulation:
  – IV/PO contrast
  – Thin slices
  – NPO 2-3 hr prior
  – Free-breathing 4DCT
  – Consider abdominal compression or gating if movement is >3mm
  – Supine with immobilization device

* Van Der Horst et al. IJROBP 2014
RT Techniques

• Target Volumes:
  – GTV: based on CT and PET findings
  – No elective coverage
  – ITV: based on 4DCT
  – PTV: 3-5mm uniform margin based on set-up confidence
  – Can use fiducial excursion to guide non-uniform PTV, without creating ITV

• Dose:
  – 30-35 Gy in 5 fractions
  – Consider dose-painting to 40-45 Gy over vessel involvement for borderline resectable tumors

• Constraints:
  – Stomach: Dmax <33Gy, V25<5cc
  – Liver: Mean<15Gy
  – Duodenum: V30<0.5cc, V25<5cc
  – Kidneys: Mean <10Gy
  – Cord: Dmax<23Gy

* Adapted from Hanna et al. Clin Oncol 2017
Back to the Case

- RT Plan: 35 Gy to tumor and 45 Gy to vessel encasement in 5 fractions, biliary stent used as internal marker
Dose Constraints

*Constraints deemed acceptable given that Dmax points likely to migrate with organ variability*
Take Home Points

- SBRT feasible for unresectable tumors and can have significant advantages
- May help make borderline tumors resectable
  - Dose escalation around vessels
- No published randomized data available...yet
- Consistent and acceptable OS, LC, and toxicity rates with SBRT in retrospective and prospective studies
- RT techniques crucial for target localization and minimizing dose to OARs
- Multi-fraction favored over single fraction
Please provide feedback regarding this case or other ARRO cases to arrocase@gmail.com