Unresectable Pancreatic Cancer: Implications of Fractionation, Advanced Techniques, and Patient Selection

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Johns Hopkins Department of Radiation Oncology and Molecular Radiation Sciences
June 22, 2012
Disclosures

- Elekta
Unresectable/Locally Advanced Pancreatic Cancer

- Radiation Therapy
  - SBRT
    - Fractionated SBRT (>1)
    - SBRT (1 Fraction)
  - Conventional RT (+ chemo)
    - Short Course (2-3 weeks)
    - Long Course (>5 weeks)
- Chemotherapy
  - 1 or 2 Drugs
  - “Cocktail” GTX FOLFIRINOX
  - Conventional RT (+ chemo)
    - SBRT (1 Fraction)
  - Conventional RT (+ chemo)
    - Short Course (2-3 weeks)
    - Long Course (>5 weeks)
Borderline vs. Unresectable

**OPTIONS:**
- Surgery
- Chemotherapy
- Radiation
- Sequence?
Modern Treatment Devices

CYBER-KNIFE

TRILOGY

SYNERGY
Conventional Radiation Therapy

SBRT: Duodenal Sparing
Summary of Data – CRT

Table 3. Results of chemotherapy and chemoradiation treatment for patients with locally advanced pancreas cancer*

<table>
<thead>
<tr>
<th>Author, study, year (ref.)</th>
<th>Treatment</th>
<th>No. of patients</th>
<th>Median survival (months)</th>
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<tbody>
<tr>
<td>Chemotherapy alone modern phase III</td>
<td>GEM with or without bevacizumab</td>
<td>93</td>
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<td>CALGB 80303 (34, 39)</td>
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<td>ECOG 6201 (22, 35, 40)</td>
<td>GEM</td>
<td>22</td>
<td>9.2</td>
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<td>ECOG 4201 (31, 36)</td>
<td>GEM</td>
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<td>Chemoradiation classic trials: pre-CT era</td>
<td>35–40 Gy plus 5-FU</td>
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<td>Moertel et al. (34)</td>
<td>60/4 Gy plus 5-FU</td>
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<td>GITSG, 1981 (22, 35)</td>
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<td>ECOG (36)</td>
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<td>GITSG, 1988 (28)</td>
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<tr>
<td>Phase II cooperative group</td>
<td>50.4 Gy plus paclitaxel</td>
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<td>RTOG 9812 (10)</td>
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<td>RTOG PA-0020 (29)</td>
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<td>RTOG PA-0411 (30)</td>
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<td>Single institution</td>
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<tr>
<td>University of Texas M.D.</td>
<td>50.4 Gy/28fx plus capecitabine plus bevacizumab</td>
<td>47</td>
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<tr>
<td>Anderson Cancer Center, 2006 (5)</td>
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<tr>
<td>University of California</td>
<td>50.4 Gy/28fx plus capecitabine</td>
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<td>at San Francisco (38)</td>
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<tr>
<td>Memorial Sloan-Kettering</td>
<td>50.4 Gy/28fx plus erlotinib plus GEM</td>
<td>20</td>
<td>18.7</td>
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<td>Cancer Center (41)</td>
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<td>University of Michigan (42)</td>
<td>50-6-Gy/25fx plus GEM</td>
<td>27</td>
<td>23.1</td>
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<tr>
<td>University of Texas M.D.</td>
<td>50.4/28fx plus capecitabine plus cetuximab</td>
<td>69</td>
<td>18.8</td>
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<tr>
<td>Anderson Cancer Center, 2010 (43)</td>
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<td></td>
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</tr>
</tbody>
</table>

Mahadevan et al.
Locally advanced panc CA: Gem +/- Chemo/RT (ECOG 4201)

- Gem 1000 mg/m² vs. Gem 600 mg/m² (50.4 Gy)
- Improved OS with CRT
- CRT grade 4 toxicity (38% v 14%)

Loehrer et al. JCO 2011
Successful SBRT/SABR Minimizes Volume Irradiated

- Treat tumor only, typically no prophylactic nodal irradiation
- Account for organ motion
- Achieve sharper dose fall-off gradients to normal tissue
- Requires image guidance to achieve necessary precision
<table>
<thead>
<tr>
<th>Description</th>
<th>Results</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koong et al</td>
<td>Phase I dose escalation</td>
<td>25 Gy x1 results in excellent local control</td>
<td>Minimal acute toxicity</td>
</tr>
<tr>
<td>Koong et al</td>
<td>45 Gy IMRT + 25 Gy boost</td>
<td>Increased acute toxicity, 94% FFLP</td>
<td>Rapid distant progression</td>
</tr>
<tr>
<td>Schellenberg et al</td>
<td>Gem + 25 Gy x 1 (CK)</td>
<td>&gt;90% FFLP at 1 yr</td>
<td>Rapid distant progression</td>
</tr>
<tr>
<td>Chang et al</td>
<td>Pooled analysis of all 25 Gy 1 patients (n=77)</td>
<td>84% FFLP at 1 yr</td>
<td>Included palliative patients, 25% G2 or higher tox at 1 yr</td>
</tr>
<tr>
<td>Murphy et al</td>
<td>Pooled normal tissue dosimetric analysis</td>
<td>Strong correlation between duodenal dose and toxicity</td>
<td>V15&lt;9 cc, V20&lt;3cc, Dmax&lt;1cc</td>
</tr>
<tr>
<td>Schellenberg et al</td>
<td>Gem + 25 Gy x 1 (Trilogy)</td>
<td>FFLP 94% at 1 yr</td>
<td>Rapid distant progression</td>
</tr>
</tbody>
</table>

Compliments of Albert Koong MD
Universal Survival Curve

\[ \ln S = \begin{cases} 
-n \cdot (\alpha \cdot d + \beta \cdot d^2) & \text{if } d \leq D_T \\
-n \cdot \left( \frac{1}{D_0} d - \frac{D_q}{D_0} \right) & \text{if } d \geq D_T 
\end{cases} \]

\[ D_T = \frac{2 \cdot D_q}{1 - \alpha \cdot D_0} \]
Phase II Multi-Institutional Study of Stereotactic Body Radiation Therapy for Unresectable Pancreatic Cancer

Locally Advanced Pancreatic Cancer (Gemcitabine, up to 1 Cycle allowed)*

2 week break

SBRT 6.6 Gy x 5 Mon-Fri

>2 week break

Gemcitabine Chemotherapy (3 wks on, 1 wk off)
Until toxicity or progression

Primary endpoint: Late GI Toxicity > 4 months
Secondary: Tumor Progression Free Survival, pre-tx biopsy QOL, tumor markers.

N=60

Trial open at Stanford, Johns Hopkins, Memorial Sloan Kettering.
Fractionated SBRT Pancreas Protocol

- 3-D CT, Multi-D evaluation, up to 3 doses Gem
- PET/CT: Treatment planning, no metastatic dz
- Gold fiducials placed, blood/tissue obtained
- Simulation: 4D CT if <5 mm motion treat FB
- If >5mm, rescan with ABC and IV/oral contrast
- Contour GTV/PTV and prox duod/stomach
- Conduct plan
- Review plan/DVH with other physicians
- 5 days of SBRT over 1-2 weeks (30-60 min)
- Continue Gem
53 y/o male with unresectable pancreatic cancer. Gem x 3 → 6.6 Gy x 5 (protocol)
RT Plan: DVH

Dose Volume Histogram

Prox Duodenum
# RT Plan: Beam arrangement

## Beam Setup

<table>
<thead>
<tr>
<th>Beam</th>
<th>Machine</th>
<th>Energy</th>
<th>Modality</th>
<th>Prescription</th>
<th>Isocenter</th>
<th>SSD (cm)</th>
<th>MU Per Fraction</th>
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</thead>
<tbody>
<tr>
<td>200</td>
<td>INFINITY1</td>
<td>15 MV</td>
<td>Photons</td>
<td>33Gy</td>
<td>isocen...</td>
<td>83.18 / 83.18</td>
<td>316.8</td>
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<td>240</td>
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<td>15 MV</td>
<td>Photons</td>
<td>33Gy</td>
<td>isocen...</td>
<td>81.33 / 81.33</td>
<td>423.9</td>
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<tr>
<td>280</td>
<td>INFINITY1</td>
<td>15 MV</td>
<td>Photons</td>
<td>33Gy</td>
<td>isocen...</td>
<td>82.04 / 82.04</td>
<td>189.5</td>
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<tr>
<td>320</td>
<td>INFINITY1</td>
<td>15 MV</td>
<td>Photons</td>
<td>33Gy</td>
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<td>84.52 / 84.52</td>
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<tr>
<td>0</td>
<td>INFINITY1</td>
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<td>Photons</td>
<td>33Gy</td>
<td>isocen...</td>
<td>85.08 / 85.08</td>
<td>110.7</td>
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<tr>
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<td>INFINITY1</td>
<td>15 MV</td>
<td>Photons</td>
<td>33Gy</td>
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<td>83.28 / 83.28</td>
<td>279.9</td>
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<tr>
<td>70</td>
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<td>15 MV</td>
<td>Photons</td>
<td>33Gy</td>
<td>isocen...</td>
<td>81.00 / 81.00</td>
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<td>90</td>
<td>INFINITY1</td>
<td>15 MV</td>
<td>Photons</td>
<td>33Gy</td>
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<td>79.47 / 79.47</td>
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<tr>
<td>160</td>
<td>INFINITY1</td>
<td>15 MV</td>
<td>Photons</td>
<td>33Gy</td>
<td>isocen...</td>
<td>82.75 / 82.75</td>
<td>399.8</td>
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</tbody>
</table>
**RT Plan: Dose Constraints**

- **PTV-** V33Gy = 95.2% (Goal 95%)
- **Proximal Duodenum—** V15Gy = 8.97cc (Goal <9cc)
  - V20Gy = 2.56cc (Goal <3cc)
  - V33Gy = 0.02cc (Goal <1cc)
- **Proximal Stomach—** V15Gy = 5.32cc (Goal <9cc)
  - V20Gy = 0.26cc (Goal <3cc)
  - V33Gy = 0.00cc (Goal <1cc)
- **Stomach—** V12Gy = 7.1% (Goal <50%)
  - V33Gy = 0.00cc (Goal <1cc)
- **Liver—** V12Gy = 16.5% (Goal <50%)
- **Kidney combined—** V12Gy = 8.8% (Goal <75%)
- **Cord—** V8 Gy = 0.06cc (Goal <1cc)
Use of ROI Shapes in Oncospace

Overlap Volume Histogram
- Shape Relationship Descriptors

DB of prior patients

OVH for similar patients to predict expected DVH

Decisions:
- Plan Quality Assessment
- Automated IMRT
- Expected Toxicities
- Dosimetric Trade-offs

DVH predict toxicity?
Clinical Release

- Tool is easily adapted to any site
- Release for Pancreas first
- Standardization of ROI Names
- Standardization of technique to some extent
- Query DB for predicted dose level for each objective function
- Completed new plans push to DB

Green boxes queried from DB
Orange if failed
Plan Quality Assessment

- Checks plan against protocol values
- For each objective, highlights those outside of specification
- Quickly allows for assessment of protocol during treatment planning and plan evaluation
The Active Breathing Coordinator at Johns Hopkins

A brief introduction
Schematic of ABC control (@ Hopkins)

- ABC control
- KVM transmitter
- KVM receiver
- ABC control PC
- Dummy monitor
- CAT5 ethernet x2
- Serial I/O
- ABC module
- Dummy mouse & keyboard
- Patient breathing apparatus
- Patient view screen
- CAT5 ethernet
- PS/2
Patient breathing apparatus

digital flow-meter

balloon valve

connect to compressor/vacuum

millipore filter
ABC procedures: oral prompting into breath hold for RT session

beam on

Press spacebar to terminate breath-hold.

Transducer Size

Medium

Trigger Mode

Inhale

Breath-Hold [sec]

25

Breath-Hold

Status

16
Methods

- Implement on a PC at the console.
Methods

- Implement on a PC at the console.
- Online access to conebeam CT, kV projection, and MV projection imaging.
Liver SBRT – Clinical Patient #1

Treat

[Image of a computer interface with a screenshot of a medical scan and a diagram indicating treatment]

☑ Treat
Liver SBRT – Clinical Patient #1

Treat

✅
Free Breathing CBCT Alignment to Bone
Final Setup with kV orthogonal pair @ breath hold (quasi-orthogonal in this case)

G = 262° (kV = 352°)

G = 0° (kV = 90°)
Additional kV images from each beam angle during treatment
Tumor Response: PET/CT and PERCIST
- Patient underwent a Whipple.
- No residual tumor
- Node and margin negative

SBRT Pre/Post Treatment
Tumor Response: PET/CT and PERCIST

PANCREATIC: PERCIST Analysis: PERCIST Assessment

<table>
<thead>
<tr>
<th>Study Week &amp; Description</th>
<th>Liver (3cm VOL LBM)</th>
<th>PERCIST</th>
<th>Disease (LBM)</th>
<th>% Difference (Peak)</th>
<th>PERCIST Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>sd</td>
<td>%RSD</td>
<td>Val (Alg)</td>
<td>Mean</td>
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<td>BASELINE PET WB AC 3D</td>
<td>1.42</td>
<td>0.11</td>
<td>8.1%</td>
<td>2.36 (B)</td>
<td>3.60</td>
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<tr>
<td>Week 11 PET WB AC 3D</td>
<td>1.37</td>
<td>0.12</td>
<td>8.7%</td>
<td>1.60 (F)</td>
<td>1.72</td>
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<tr>
<td>Week 44 PET WB AC 3D</td>
<td>1.37</td>
<td>0.11</td>
<td>8.3%</td>
<td>1.60 (F)</td>
<td>6.10</td>
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</tbody>
</table>

Assessment Criteria: PMR|CMR, Follow-up Peak = PERCIST Threshold; PMR: %Diff < -30%, Δ > 0.8 SUL; PMD: %Diff > -30%, Δ > 0.8 SUL; SMD: -30% < %Difference < -30%

Flags: "U<" = Uptake is <50 minutes, "U>" = Uptake is >70 minutes; "L(b)" = Liver mean is 20% and/or 0.3 SUL units different from baseline; "L(p)" Liver mean differs from prior

Notes: 1) %RSD is the Relative Standard Deviation of the measurement statistic, expressed as a percentage
2) PERCIST Threshold calculated using either Baseline algorithm (B) 1.5*(liver mean) + 2*(liver sd) or Follow-up algorithm (F) 1.0*(liver mean) + 2*(liver sd)
3) For graphing purposes, when no disease was detected at a particular timepoint, the PERCIST threshold for that timepoint was used as a data point

Friday, November 18, 2011
Analysis performed by the IRAT Laboratory of The Johns Hopkins University
CA 19-9 Response after SBRT

PET SUV MAX=3.8

PET SUV MAX=2.6

PET SUV MAX=1.8

PET SUV MAX=2.9
### Patient Characteristics

<table>
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<th>Characteristic</th>
<th>No.</th>
<th>total</th>
<th>%</th>
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<tr>
<td>Age, years</td>
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<tr>
<td>Mean</td>
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<td>SD</td>
<td>9.8</td>
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<tr>
<td>Median</td>
<td>68.5</td>
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<td>Other</td>
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<td>Histologic Grading</td>
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<td>Poorly differentiated</td>
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<td>9.4</td>
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<tr>
<td>Gemcitabine</td>
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<td>Mean doses pre-SBRT</td>
<td>2.2</td>
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<tr>
<td>SD</td>
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<tr>
<td>Mean doses post-SBRT</td>
<td>8.3</td>
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<td></td>
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<tr>
<td>SD</td>
<td>5.6</td>
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<tr>
<td>CA 19-9</td>
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<tr>
<td>Mean, pre-SBRT (SD)</td>
<td>425.4</td>
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<td>750.7</td>
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<tr>
<td>Mean, post-SBRT (SD)</td>
<td>260.3</td>
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<td>616.9</td>
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<tr>
<td>Mean, last (SD)</td>
<td>894.3</td>
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<td>2586.1</td>
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<tr>
<td>Median, pre-SBRT (range)</td>
<td>143</td>
<td>(0 – 3191)</td>
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<td>Median, post-SBRT (range)</td>
<td>43.9</td>
<td>(0 – 3191)</td>
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<td>Median, last (range)</td>
<td>83.8</td>
<td>(0 – 13773)</td>
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<tr>
<td>&gt;=90 at baseline</td>
<td>19</td>
<td></td>
<td>59.4</td>
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<tr>
<td>&lt;90 at baseline</td>
<td>13</td>
<td></td>
<td>40.6</td>
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</tbody>
</table>
Median survival: 15.9 months (95% CI, 9.14 – upper limit not yet reached)
Median follow-up: 12.0 months (range, 2.1-22.6)
Hazard ratio for CA19-9 $\geq$ 90 U/mL at diagnosis: 6.18 ($p=0.021$)

Herman et al. ASCO 2012
SBRT Trial: Safety and QOL

- **Toxicity:**
  - Acute Grade 2: anorexia (37%), fatigue (28%), nausea (22%), abd pain (19%), weight loss (9%), diarrhea (3%);
  - Acute Grade 3/4: nausea (15%)
  - Late Grade ≥3 GI toxicity (9%). (1 GI Bleed)
  - Mean QOL score 4 wks post-SBRT was similar to baseline (p=0.38). At 6 mos there was a trend towards improved QOL (p=0.07).
**Recent Series of SBRT/SABR in Locally Advanced Pancreatic Cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th># Patients</th>
<th>Dose</th>
<th>Tox</th>
<th>LC</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schellenberger et al</td>
<td>20</td>
<td>25 Gy x 1</td>
<td>15% G2, 5% G4</td>
<td>94%</td>
<td>11.8 mo</td>
</tr>
<tr>
<td>Mahadevan et al</td>
<td>36</td>
<td>8-12 Gy x3</td>
<td>25% G2, 14% G3</td>
<td>78%</td>
<td>14.3 mo</td>
</tr>
<tr>
<td>Polistina et al</td>
<td>23</td>
<td>10 Gy x 3</td>
<td>No G2 or higher</td>
<td>70% PR or better</td>
<td>10.6 mo</td>
</tr>
<tr>
<td>Herman et al.</td>
<td>32</td>
<td>6.6 Gy x 5</td>
<td>9% G3-4</td>
<td>87%</td>
<td>14.9 mo</td>
</tr>
</tbody>
</table>
First Case: 87 y/o (6.6 Gy x 5)

Pre SBRT

Post SBRT (24 months)
Volumetric Modulated Arc Therapy (VMAT)
VMAT: SBRT and IMRT
VMAT: SBRT and IMRT

Figure 1. Averaged cumulative dose-volume histograms for (A) PTV, (B) duodenum, (C) right kidney, (D) left kidney, (E) spinal cord, (F) stomach, and (G) liver for NS VMAT (black solid line), DS VMAT (black dashed line), NS IMRT (gray solid line), and DS IMRT (gray dashed line). NS, non-duodenal sparing; DS, duodenal sparing; VMAT, volumetric modulated arc therapy; IMRT, intensity modulated radiation therapy; PTV, planning target volume.
Figure 3. Representative axial slices showing contoured regions of interest and isodose distributions for (A) NS VMAT, (B) DS VMAT, (C) NS IMRT, and (D) DS IMRT plans. As delineated by the legend in the top left corner of each image, isodose lines are shown every 500 cGy from 500-2500 cGy. NS, non-duodenal sparing; DS, duodenal sparing; VMAT, volumetric modulated arc therapy; IMRT, intensity modulated radiation therapy; PTV, planning target volume.
Patient Selection
Oncospace: SBRT Trial

- Providing a common web-based repository for collecting and analyzing SBRT trial data
- Multi-institutional access
  - Johns Hopkins
  - Memorial Sloan Kettering
  - Stanford
- Store treatment response, toxicities, quality of life and radiation dosimetry of patients on the trial
- Data is transferred electronically from Mosaiq and Pinnacle for Hopkins patients, entered by others
Clinical Data Collection

- Diagnosis
- On Tx Visit
- Follow Up
- Medications
- Outcomes
- Protocol
Dose Volume Histograms
Future Directions

- Can we develop “patient specific” treatments based on genetic data and/or tumor response?
- Can we add specific agents to enhance tumor response and prevent metastatic spread?
Can pancreas tumor biopsy (EUS) be used to guide treatment?

Autopsy Study

- DPC4 immunolabeling:
  - DPC4 loss (mutated) = metastatic spread
  - DPC4 Intact = locally destructive tumors \((p=0.007)\).

- DPC4 status at diagnosis – potential for stratifying patients into treatment regimens emphasizing local versus systemic therapy.

Iacobuzio et al.
DPC4 Status and Patterns of Failure
RTOG 1201: Study Using DPC4 status to Guide the Selection of Upfront Chemotherapy and RT in Patients with Unresectable Pancreatic Cancer

Eligibility: Locally Advanced Unresectable
No prior Chemotherapy or RT

1st Endpoint: Median OS
2nd Endpoints: Safety; DFS/OS (subcohort); Local Progression Free Surv; DM rates; Retrospective biomarkers: TBD
Early Stopping Rules: Based on toxicity, OS, PFS
Conclusions

- Fractionated SBRT (6.6 Gy x 5) appears safe with less acute toxicity than conventional RT and less late toxicity compared to a single fraction (25 Gy x 1) with promising preliminary results.
- Need to combine aggressive chemo in patients with ca 19-9>90.
- Oncospace can allow us to evaluate clinical trial data in “real time.”
- Pre-clinical biopsies may be used to guide treatment decisions in the future:
  - Sequence of treatment
  - Responsiveness to RT (Conventional vs. SBRT)
  - Optimal combination(s) of targeted agents and or chemotherapy with RT.
Standard Management

- **Multi-D evaluation:**
  - Pain/Protonix/Pancreatic enzymes/Protocol (4 P’s)

- **Borderline resectable and Unresectable: (Good PFS):** 2-6 mos of chemo then 50-54 (2 Gy) IMRT with Capecitabine. Reassess q 2 mos with 3-D CT scan.

- **Unresectable (Poor PFS):** 2-6 mos of Gem then 5 Gy x 5 or 50-54 Gy (2 Gy) with Capecitabine.

- Avoid SBRT if invasion through bowel or stomach on endoscopy
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