THE ROLE OF RADIATION THERAPY IN MANAGEMENT OF PANCREATIC ADENOCARCINOMA

TIMUR MITIN, MD, PhD
RESECTABLE DISEASE
Resection offers the only possibility of long term survival.

This possibility is not high:
- 5 yr survival after R0 resection is ~20%
- Median survival for resectable disease is ~20 months.
**A TALE OF TWO CONTINENTS**

**United States** (support for CRT)
- GITSG 91-73
- RTOG 97-04

**Europe (support for chemo alone)**
- EORTC 40891
- ESCPAC-1
- CONKO-1 (chemo alone study)
- ESPAC-3 (chemo alone study)
Failure to Adhere to Protocol Specified Radiation Therapy Guidelines Was Associated With Decreased Survival in RTOG 9704 - A Phase III Trial of Adjuvant Chemotherapy and Chemoradiotherapy for Patients with Resected Adenocarcinoma of the Pancreas

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RTOG 97-04
SECONDARY ANALYSIS
## Head of Pancreas Patients Only (n=359)

<table>
<thead>
<tr>
<th>Adjustment Variables</th>
<th>Comparison</th>
<th>Adjusted HR</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Gemcitabine vs. 5-FU</td>
<td>0.79 (0.62, 0.99)</td>
<td>0.043</td>
</tr>
<tr>
<td>Nodal Involvement</td>
<td>No vs. Yes</td>
<td>1.47 (1.13, 1.91)</td>
<td>0.0036</td>
</tr>
<tr>
<td>Tumor Diameter</td>
<td>&lt;3 vs. ≥ 3cm</td>
<td>1.25 (0.98, 1.59)</td>
<td>0.070</td>
</tr>
<tr>
<td>Surgical Margin Status</td>
<td>Negative</td>
<td>Ref level</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>1.07 (0.82, 1.40)</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>0.94 (0.69, 1.27)</td>
<td>0.68</td>
</tr>
<tr>
<td>RT QA Score</td>
<td>&lt; PP vs. PP</td>
<td>0.75 (0.60, 0.95)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Abbreviations: 5-FU, fluorouracil; HR, hazard ratio; C.I., confidence interval

Hazard Ratio (HR) > 1 indicates increased risk of death for the second variable. HR < 1 indicates decreased risk of death for the second variable

† p-value from Chi-square test using the Cox proportional hazards model.
RTOG 0848

**Data Stratification**

- **Nodal Status**:
  - 1: involved
  - 2: uninvolved

- **CA19-9 result**:
  - 1: $\leq 90$
  - 2: $> 90 - 180$

- **Surgical margins**:
  - 1: positive (R1)
  - 2: negative (R0)

- **Randomize**
  - If no progression, then:
    - Gemcitabine x 5 cycles

**Randomization Arms**

- **Arm 3**:
  - 1 cycle of chemotherapy

- **Arm 4**:
  - 1 cycle of chemotherapy followed by XRT with either capecitabine or 5-FU

Accrual: 347/950
SEER REGISTRY ANALYSIS

- National Propensity-Adjusted Analysis of Adjuvant RT
- McDade et al., Cancer 2010
  - 1988-2005, 5676 patients, 40% received adjuvant RT
  - Predictors of improved OS on MVA: white race, married status, earlier stage, tumors < 2 cm, well-differentiated path, LN-, recent diagnosis (within 6 years) and receipt of adjuvant RT.
  - RT: HR of 0.587 (0.545 – 0.631, p<0.0001)
  - Benefit remained significant after propensity adjustment for the likelihood of receiving RT (HR 0.774; 0.719-0.834).
  - Median survival: 10 months no RT vs 18 months with RT (p<0.0001)
- Sugawara et al., Journal of Surgical Oncology 2014
  - 2004 – 2009, 2532 patients, 40% received adjuvant RT
  - On MVA RT associated with improved cause-specific survival (HR 0.654) and OS (HR 0.647)
  - Median survival: 16 months no RT vs 20 months with RT (p<0.0001)
Most, but not all, pancreatic cancers are metastatic
  - 12% of patients with no metastatic disease at autopsy
  - 18% of patients with limited metastatic burden, not deemed directly contributing to their cause of death
- Genetic markers may help distinguish pancreatic cancer with predilection for local progression vs systemic spread
- SMAD4 (Dpc4) tumor suppressor gene
  - Lost in up to 80% of pancreatic cancers
  - Immunohistochemical assessment of SMAD4 protein is a reliable predictor of gene status
  - Loss in a surgically resectable carcinoma corresponds to a relative risk of 3.3 of development of widespread mets compared to those with intact Dpc4 labeling.

Iacobuzio-Donahue et al., JCO 2009
### Table 3. Relationship of Genetic Features to Patterns of Failure in Advanced Stage Pancreatic Cancer

<table>
<thead>
<tr>
<th>Metastatic Burden by Gene for Primary Carcinoma</th>
<th>Locally Destructive</th>
<th>Locally Confined</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>KRAS2 (n = 59)</td>
<td></td>
<td></td>
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<tr>
<td>No.</td>
<td>6/7</td>
<td>86</td>
<td>11/11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17/18</td>
</tr>
<tr>
<td>TP53 (n = 58)</td>
<td></td>
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</tr>
<tr>
<td>No.</td>
<td>6/6</td>
<td>100</td>
<td>6/11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12/17</td>
</tr>
<tr>
<td>DPC4 (n = 65)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>2/8</td>
<td>22</td>
<td>5/11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7/20</td>
</tr>
</tbody>
</table>

Iacobuzio-Donahue et al., JCO 2009
Boone et al., J of Surg Onc, 2014. Univ of Pittsburgh
- Retrospective review of 117 patients undergoing resection
- SMAD4 loss in 70%
- Metastatic disease:
  - 13.3% vs 51.4% at 1 year
  - 36.8% vs 78.5% at 2 years
- On logistic regression analysis:
  - SMAD4 loss was associated with 6 times odds ratio of developing metastatic disease
  - Neoadjuvant treatment did not affect the predictive value of preoperative SMAD4
THE ROLE OF SBRT IN ADJUVANT SETTING

- 2006 – 2010, 24 patients at Univ of Pittsburgh
  - 8 patients with close margins of 1 – 2.5 mm
  - 16 patients with positive margins
- Single fraction SBRT 20-24 Gy
- Median target volume 11 cc (4.5 – 30 cc)

**Results:**
- Median follow up 12.5 months
- Median OS 26.7 months
- OS1: 80%, OS2: 57%
- Freedom from Local Progression:
  - at 6 mos: 95%, at 1 year 66%, at 2 years 44%
  - 19/24 patients resumed or started a 6-month course of gemcitabine at a median interval of 18 days (range, 9-31 days) post-SBRT

**Toxicity:**
- No grade 3 - 5 toxicity
- 3 patients (12.5%) grade 1-2 acute GI toxicity
- 2 patients (8.3%) grade 1-2 late toxicities

Rwigema, et al., Am J Clin Oncol 2011
BIDMC, Boston

8 patients with pT3N0-1, positive margins
- 7 head and 1 tail lesions
- 10 Gy SBRT boost to positive margins, followed by 45-50.4 Gy of fractionated RT to pancreatic bed with concurrent capecitabine
- With a median followup of 8.8 months:
  - PFS 75% (2 patients progressed systemically and died)
  - Remaining 6 patients were free of disease
  - 100% local control at death or last follow-up.

ASTRO 2007 abstract, IJROBP 2007; 69:S307
LOCALLY ADVANCED DISEASE
LOCALLY ADVANCED

- Median survival 7-12 months
- Ideally enroll on protocol
Rationale: Management of locally advanced disease was controversial.

Retrospective analysis of 181 pts from 4 prospective Phase II and III GERCOR studies

Compared chemotherapy to chemoradiation (decision was investigator’s choice)

- Gem based chemo x 3 months → Chemo
- Gem based x 3 months → chemoradiation (55 Gy + 10 Gy boost + 5-FU)
- 30% developed metastatic disease within 3 months of chemo
- 70% (128) eligible
## Conclusions:

- **Chemotherapy should be first line treatment for LAPC.**
- **If no progression of disease after three months, CRT could increase survival.**

### Table: Comparing Chemo and CRT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chemo</th>
<th>CRT</th>
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<tbody>
<tr>
<td>PFS</td>
<td>7.4 mon</td>
<td>10.8 mon</td>
</tr>
<tr>
<td>OS</td>
<td>11.7 mon</td>
<td>15 mon</td>
</tr>
<tr>
<td>1 yr survival</td>
<td>47.5%</td>
<td>65.3%</td>
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</tbody>
</table>
Median survival 7-12 months
Ideally enroll on protocol
Otherwise, FOLFIRINOX based chemo x 2-4 months → 5FU based chemoradiation

Begin chemoradiation if:
- Radiographic local progression
- CA 19-9 increase
- Symptoms
- Chemo poorly tolerated
RTOG 1201

- Gem/abraxane x 3
- Gem/abraxane x 1 + IMRT 63 Gy
- Gem/abraxane x 1 + RT 50.4 Gy

Stratify by:
Ca19-9 < 90
SMAD4 status
Representative pancreatic SBRT plan:
(A) axial view showing pancreatic tumor (GTV: green), a typical PTV (red), and the duodenum (magenta);
(B) coronal view demonstrating tumor relationship with the duodenum;
(C) dose distribution for a plan treating to 33 Gy in 5 fractions. Isodose lines: green = 45 Gy; magenta = 40 Gy; cyan = 33 Gy; blue = 30 Gy; light green = 20 Gy; and brown = 10 Gy.
<table>
<thead>
<tr>
<th>References</th>
<th>Patients</th>
<th>Dose</th>
<th>Local Control (1 y Unless Specified)</th>
<th>Median Survival (mo)</th>
<th>Toxicity</th>
<th>Chemo</th>
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<tbody>
<tr>
<td>Koong et al(^{26})</td>
<td>15</td>
<td>15-25 Gy × 1</td>
<td>100%</td>
<td>11</td>
<td>33% Grades 1 and 2 0% ≥ Grade 3</td>
<td>None</td>
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<tr>
<td></td>
<td></td>
<td>LA or LR</td>
<td></td>
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<tr>
<td>Koong et al(^{27})</td>
<td>16</td>
<td>25 Gy × 1 (boost)</td>
<td>94%</td>
<td>8.3</td>
<td>69% Grades 1 and 12.5% ≥ Grade 3</td>
<td>5-FU with EBRT prior to boost</td>
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<td></td>
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<td>LA</td>
<td></td>
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<tr>
<td>Hoyer et al(^{34})</td>
<td>22</td>
<td>15 Gy × 3</td>
<td>57%</td>
<td>5.4</td>
<td>79% ≥ Grade 2 4.5% Grade 4</td>
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<tr>
<td>Schellenberg et al(^{28})</td>
<td>16</td>
<td>25 Gy × 1</td>
<td>100%</td>
<td>11.4</td>
<td>19% Acute 47% Late</td>
<td>1 Cycle induction GEM + post-SBRT GEM</td>
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<tr>
<td>Didolkar et al(^{35})</td>
<td>85</td>
<td>5-10 Gy × 3</td>
<td>92%</td>
<td>18.6</td>
<td>22.3% ≥ Grade 3</td>
<td>Post-SBRT GEM</td>
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<td></td>
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<tr>
<td>Mahadevan et al(^{36})</td>
<td>36</td>
<td>8-12 Gy × 3</td>
<td>78%</td>
<td>14.3</td>
<td>33% Grades 1 and 2 8% Grade 3</td>
<td>Post-SBRT GEM</td>
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<td>LA</td>
<td></td>
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<tr>
<td>Polistina, et al(^{32})</td>
<td>23</td>
<td>10 Gy × 3</td>
<td>82% 6 mo</td>
<td>10.6</td>
<td>20% Grade 1 0% ≥ Grade 2</td>
<td>6 wk induction GEM</td>
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<td>LA</td>
<td>50% 1 y</td>
<td></td>
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<tr>
<td>Mahadevan et al(^{31})</td>
<td>39</td>
<td>8-12 Gy × 3</td>
<td>85%</td>
<td>20</td>
<td>41% Grades 1 and 2 0% ≥ Grade 3 (acute) 9% Grade 3 (late)</td>
<td>2 Cycles induction GEM</td>
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<td>LA</td>
<td></td>
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<tr>
<td>Rwigema et al(^{38})</td>
<td>71</td>
<td>24 Gy (med) × 1 (94%)</td>
<td>71.7% 6 mo</td>
<td>10.3</td>
<td>39.5% Grades 1 and 2 4.2% Grade 3</td>
<td>90% Received chemo (various regimens)</td>
</tr>
<tr>
<td>LA, LR, RPM, and MD</td>
<td></td>
<td>8-10 Gy × 2-3 (6%)</td>
<td>48.5% 1 y</td>
<td></td>
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<tr>
<td>Schellenberg et al(^{29})</td>
<td>20</td>
<td>25 Gy × 1</td>
<td>94%</td>
<td>11.8</td>
<td>15% Grades 1 and 2 5% ≥ Grade 3</td>
<td>1 Cycle induction GEM + post-SBRT GEM</td>
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<td>LA</td>
<td></td>
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<tr>
<td>Goyal et al(^{37})</td>
<td>19</td>
<td>20-25 Gy × 1</td>
<td>81%</td>
<td>14.4</td>
<td>11% Grades 1 and 2 16% Grade 3</td>
<td>68% Received chemo (5-FU or GEM based)</td>
</tr>
<tr>
<td>LA or LR</td>
<td></td>
<td>8-10 Gy × 3</td>
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<tr>
<td>Lominska et al(^{40})</td>
<td>28</td>
<td>4-8 Gy × 3-5</td>
<td>86%</td>
<td>5.9</td>
<td>7% Grade 3 (late)</td>
<td>5-FU or GEM prior to SBRT</td>
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<tr>
<td>Gurka et al(^{33})</td>
<td>10</td>
<td>5 Gy × 5</td>
<td>40%</td>
<td>12.2</td>
<td>0% ≥ Grade 3</td>
<td>1 cycle GEM prior, 6 cycles GEM total</td>
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<td>LA</td>
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<tr>
<td>Chuong et al(^{28})</td>
<td>73</td>
<td>5-10 Gy × 5</td>
<td>81%</td>
<td>16.4 BR</td>
<td>5% Grade 3 (late)</td>
<td>3 cycles GTX</td>
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<td>BR or LA</td>
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<td></td>
<td></td>
<td>15 LA</td>
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</tbody>
</table>
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THANK YOU!