Preoperative Radiation Therapy for Pancreatic Cancer: When, Where, and How

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Piedmont Atlanta Hospital

Piedmont Healthcare Pancreas Cancer Conference
Georgia Tech Hotel and Conference Center
October 5, 2019
Disclosures:

I have no current relationships to disclose

An embedded video demonstrates RapidArc treatment delivery, a trademark of Varian Medical Systems (VMS)

The presenter has received honoraria from VMS >10y ago, none more recently than 10y ago.

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https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000267
Preoperative Radiation Therapy for Pancreatic Cancer: **When**, Where, and How

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<table>
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<th>RT (Y/N)</th>
<th>Dose</th>
<th>MS (m)</th>
<th>5-y OS</th>
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<tr>
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<td>Y</td>
<td>40</td>
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<td>N</td>
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<td>24</td>
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<td>NS</td>
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<tr>
<td></td>
<td>Gemcitabine + CRT</td>
<td>45</td>
<td>Y</td>
<td>50.4</td>
<td>24</td>
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<td>GERCOR</td>
<td>CRT + 5-FU</td>
<td>230</td>
<td>Y</td>
<td>50.4</td>
<td>17.1</td>
<td>18</td>
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<td>CRT + Gemcitabine</td>
<td>221</td>
<td>Y</td>
<td>50.4</td>
<td>20.5</td>
<td>22</td>
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<td>Observation</td>
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<td>N</td>
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<td>20.2</td>
<td>9</td>
<td>0.005</td>
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<td></td>
<td>Gemcitabine</td>
<td>133</td>
<td>N</td>
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<td>22.8</td>
<td>21</td>
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<td></td>
<td>5-FU</td>
<td>551</td>
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<td></td>
<td>Gemcitabine</td>
<td>537</td>
<td>N</td>
<td></td>
<td>23.6</td>
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</tbody>
</table>

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; GERCOR, Groupe Coordinateur Multidisciplinaire en Oncologie; GITSG, Gastrointestinal Tumor Study Group; MS, median survival; NS, not statistically significant; OS, overall survival; S, statistically significant; (s), split course.
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Preoperative Radiation Therapy for Pancreatic Cancer: When, Where, and How

- Operable Pancreatic Cancer
- As a Component of Neoadjuvant Therapy
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Preoperative Radiation Therapy for Pancreatic Cancer: When, Where, and How

- Operable Pancreatic Cancer
- As a Component of Neoadjuvant Therapy
A major challenge with pancreatic cancer management is in the discrimination of clearly resectable tumors from those that would likely be accompanied by a positive resection margin if upfront surgery was attempted. The standard of care for clearly resectable pancreatic cancer remains surgery followed by adjuvant therapy, but there is considerable controversy over whether such therapeutic adjuvant strategies should include radiotherapy. Furthermore, in a malignancy with such high rates of distant metastasis, investigators are now exploring the feasibility and outcomes of delivering therapy in the neoadjuvant setting, both for clearly resectable as well as borderline resectable tumors. In this review, we explore the current standard of care of upfront surgery for clearly resectable cancers followed by adjuvant therapy, focusing on the role of radiotherapy. We highlight the difficulties in interpreting a literature fraught with inconsistencies in how resectable vs borderline resectable cancers are defined and treated. Finally, we explore the role of neoadjuvant strategies in the modern era.
"For clearly resectable tumors, a neoadjuvant approach may be preferred."
Neoadjuvant vs Adjuvant Therapy for Resectable Pancreatic Cancer: The Evolving Role of Radiation

• Improve patient selection
  • Avoidance of surgery in progressors
Neoadjuvant vs Adjuvant Therapy for Resectable Pancreatic Cancer: The Evolving Role of Radiation

- Improve patient selection
  - Avoidance of surgery in progressors
- Improve surgical outcomes
  - Higher pathologic response rates
Neoadjuvant vs Adjuvant Therapy for Resectable Pancreatic Cancer: The Evolving Role of Radiation

- Improve patient selection
  - Avoidance of surgery in progressors
- Improve surgical outcomes
  - Higher pathologic response rates
- Cost Effective
Table 1 Comparison of Radiographic Definitions of Borderline Resectable Pancreatic Cancer

<table>
<thead>
<tr>
<th>AHPBA-SSAT-SSO</th>
<th>MD Anderson</th>
<th>NCCN</th>
<th>Intergroup (Alliance A021101)</th>
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</thead>
<tbody>
<tr>
<td>SMV-PV</td>
<td>Abutment,</td>
<td>Abutment with impingement or narrowing</td>
<td>Interface between tumor and vessel measuring 180° or greater of the circumference of the vessel wall or reconstructable occlusion or both</td>
</tr>
<tr>
<td></td>
<td>encasement, or occlusion</td>
<td>narrowing</td>
<td></td>
</tr>
<tr>
<td>SMA</td>
<td>Abutment</td>
<td>Abutment</td>
<td>Interface between tumor and vessel measuring less than 180° of the circumference of the vessel wall</td>
</tr>
<tr>
<td>CHA</td>
<td>Abutment or short-segment encasement</td>
<td>Abutment or short-segment encasement</td>
<td>Reconstructable, short-segment interface between tumor and vessel of any degree</td>
</tr>
<tr>
<td>Celiac trunk</td>
<td>No abutment or encasement</td>
<td>Abutment</td>
<td>Interface between tumor and vessel measuring less than 180° of the circumference of the vessel wall</td>
</tr>
</tbody>
</table>

Abbreviations: AHPBA, Americas Hepatopancreatobiliary Association; CHA, common hepatic artery; SSAT, Society for Surgery of the Alimentary Tract; SSO, Society of Surgical Oncology.
Preoperative Radiation Therapy for Pancreatic Cancer: When, Where, and How

Preoperative Modified FOLFIRINOX Treatment Followed by Capecitabine-Based Chemoradiation for Borderline Resectable Pancreatic Cancer: Alliance for Clinical Trials in Oncology Trial A021101.


Abstract

IMPORTANCE: Although consensus statements support the preoperative treatment of borderline resectable pancreatic cancer, no prospective, quality-controlled, multicenter studies of this strategy have been conducted. Existing studies are retrospective and confounded by heterogeneity in patients studied, therapeutic algorithms used, and outcomes reported.

OBJECTIVE: To determine the feasibility of conducting studies of multimodality therapy for borderline resectable pancreatic cancer in the cooperative group setting.

DESIGN, SETTING, AND PARTICIPANTS: A prospective, multicenter, single-arm trial of a multimodality treatment regimen administered within a study framework using centralized quality control with the cooperation of 14 member institutions of the National Clinical Trials Network. Twenty-nine patients with biopsy-confirmed pancreatic cancer preregistered, and 23 patients with tumors who met centrally reviewed radiographic criteria registered. Twenty-two patients initiated therapy (median age, 64 years [range, 50-76 years]; 55% female). Patients registered between May 29, 2013, and February 7, 2014.

INTERVENTIONS: Patients received modified FOLFIRINOX treatment (85 mg/m2 of oxaliplatin, 180 mg/m2 of irinotecan hydrochloride, 400 mg/m2 of leucovorin calcium, and then 2400 mg/m2 of 5-fluorouracil for 4 cycles) followed by 5.5 weeks of external-beam radiation (50.4 Gy delivered in 28 daily fractions) with capecitabine (825 mg/m2 orally twice daily) prior to pancreatectomy.

MAIN OUTCOMES AND MEASURES: Feasibility, defined by the accrual rate, the safety of the preoperative regimen, and the pancreatectomy rate.

RESULTS: The accrual rate of 2.6 patients per month was superior to the anticipated rate. Although 14 of the 22 patients (64% [95% CI, 41%-83%]) had grade 3 or higher adverse events, 15 of the 22 patients (68% [95% CI, 49%-88%]) underwent pancreatectomy. Of these 15 patients, 12 (80%) required vascular resection, 14 (93%) had microscopically negative margins, 5 (33%) had specimens that had less than 5% residual cancer cells, and 2 (13%) had specimens that had pathologic complete responses. The median overall survival of all patients was 21.7 months (95% CI, 15.7 to not reached) from registration.

CONCLUSIONS AND RELEVANCE: The successful completion of this collaborative study demonstrates the feasibility of conducting quality-controlled trials for this disease stage in the multi-institutional setting. The data generated by this study and the logistical elements that facilitated the trial's completion are currently being used to develop cooperative group trials with the goal of improving outcomes for this subset of patients.
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The recent international consensus on definition and criteria of BRPC has defined patients according to three distinct dimensions:

ANATOMICAL
• Tumor that is at high risk for margin-positive resection R1/R2

BIOLOGICAL
• Findings that raise the possibility … of extrapancreatic metastatic disease
  - high serum Ca 19-9 levels (>500 IU/mL)
  - radiologically suspected but unproven metastases

CONDITIONAL
• The conditional definition of BRPC includes patients at high risk for morbidity or mortality after surgery because of performance status and comorbidities.
Chemoradiation Strategies

• Chemoradiation appears to increase the expected R0 resection rate for patients with BRPC.
  • Patients with arterial involvement at diagnosis would all be expected to have positive margins, whereas in the experience from MD Anderson Cancer Center, nearly all patients who have completed chemoradiation with or without initial chemotherapy were able to undergo R0 resection even though the radiographic stage rarely changed.
Chemoradiation Strategies

• Standard approach is to use standard doses of RT (50.4 Gy in 28 fractions) with concurrent chemotherapy (gemcitabine or capecitabine).
• The primary tumor, SMA, and celiac axis should always be contoured and included within the margin.
• Some customization of the nodal coverage is appropriate depending on the likelihood of the patient proceeding to surgery.
• MDACC recommends including the porta hepatis only in those patients who are most likely to undergo resection because of the fact that usually more gastroduodenal mucosa has to be included, which increases the risk of toxicity.
RESULTS: The accrual rate of 2.6 patients per month was superior to the anticipated rate. Although 14 of the 22 patients (64% [95% CI, 41%-83%]) had grade 3 or higher adverse events, 15 of the 22 patients (68% [95% CI, 49%-88%]) underwent pancreatectomy. Of these 15 patients, 12 (80%) required vascular resection, 14 (93%) had microscopically negative margins, 5 (33%) had specimens that had less than 5% residual cancer cells, and 2 (13%) had specimens that had pathologic complete responses. The median overall survival of all patients was 21.7 months (95% CI, 15.7 to not reached) from registration.

CONCLUSIONS AND RELEVANCE: The successful completion of this collaborative study demonstrates the feasibility of conducting quality-controlled trials for this disease stage in the multi-institutional setting. The data generated by this study and the logistical elements that facilitated the trial's completion are currently being used to develop cooperative group trials with the goal of improving outcomes for this subset of patients.

- 22 patient, single-arm study
- 15 underwent pancreatectomy
  - 12 required vascular resection
  - 14 had R0 resection
  - 5 pts (33%) had <5% residual CA cells
  - 2 pts (13%) had pCR
FIGURE 2. Overall survival among patients with locally advanced pancreatic cancer according to treatment group. CR indicates chemoradiotherapy; CCR, induction chemotherapy followed by chemoradiotherapy.

FIGURE 3. Progression-free survival among patients with locally advanced pancreatic cancer according to treatment group. CR indicates chemoradiotherapy; CCR, induction chemotherapy followed by chemoradiotherapy.
Figure 1 Initial staging pancreatic protocol CT showing pancreatic head adenocarcinoma that is borderline resectable by virtue of venous abutment next to the superior mesenteric vein (SMV).
Figure 2: Same patient after neoadjuvant therapy, restaging pancreatic protocol CT before surgery shows improvement.
Management of Borderline Resectable Pancreatic Cancer

Matthew H.G. Katz, MD,* Christopher H. Crane, MD,† and Gauri Varadhachary, MD‡
### Preoperative Radiation Therapy for Pancreatic Cancer: *When*, *Where*, and *How*

Table 2: Selected Preoperative Trials in Borderline Resectable Pancreatic Cancer

<table>
<thead>
<tr>
<th>References</th>
<th>No. of Patients With BRPC Only (NCCN Criteria in Majority)</th>
<th>Preoperative Regimen</th>
<th>Resection</th>
<th>R0 Resection in Patients With BRPC</th>
<th>OS in All Patients (May Include Resectable and Unresectable)</th>
<th>OS in Patients With Resected BRPC</th>
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<tr>
<td><em>Retrospective data</em></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Katz (2008)</td>
<td>84</td>
<td>Gem or C + RT (in some, pre-RT or adjuvant systemic chemotherapy)</td>
<td>32 (38%)</td>
<td>31 (97%)</td>
<td>21 mo</td>
<td>40 mo</td>
</tr>
<tr>
<td>Stokes (2011)</td>
<td>40</td>
<td>C + RT adjuvant Gem</td>
<td>16 (46%)</td>
<td>12 (75%)</td>
<td>12 mo</td>
<td>23 mo</td>
</tr>
<tr>
<td>Takahashi et al</td>
<td>80</td>
<td>Gem + RT</td>
<td>43 (54%)</td>
<td>54%</td>
<td>NA</td>
<td>25 mo*</td>
</tr>
<tr>
<td>Chuong et al</td>
<td>57</td>
<td>GTX followed by SBRT median 25-35 Gy in 5 fx</td>
<td>32 (56%)</td>
<td>31 (97%)</td>
<td>16.4 mo</td>
<td>19.3 mo</td>
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<tr>
<td><em>Prospective data</em></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Kim et al</td>
<td>39</td>
<td>GEMOX (2 cycles) + RT (adjuvant GEMOX × 2 cycles)</td>
<td>24 (62%)</td>
<td>84%†</td>
<td>18 mo</td>
<td>25 mo</td>
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<tr>
<td>Motoi et al</td>
<td>16</td>
<td>Gem + S1 × 2 cycles</td>
<td>NA§</td>
<td>87%†</td>
<td>18 mo</td>
<td>NA∥</td>
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<tr>
<td>Lee et al</td>
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<td>Gem + C × 3-6 cycles</td>
<td>11 (61%)</td>
<td>82%</td>
<td>16 mo</td>
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</table>

Abbreviations: C, capecitabine; Gem, gemcitabine; GEMOX, gemcitabine and oxaliplatin; GTX, gemcitabine, docetaxel, and capecitabine; NA, not available.

*Estimated from graphs.
†R0 resection rate is for the whole group (resectable + BRPC).
‡Two years survival probability at 31.5%.
§NA for BRPC alone, 85% for BRPC + resectable cancer.
Benefits of Neoadjuvant Chemoradiotherapy in BRPC

- Maximize potential for R0 resection
- Maximize early exposure of micrometastatic disease to systemic therapy
- Gauge cancer behavior and select for surgery those most likely to benefit
- Reduce anastomotic fistula rates b/w pancreas and jejunum
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<thead>
<tr>
<th>Group</th>
<th>Morbidity</th>
<th>Mortality</th>
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<tr>
<td>All patients</td>
<td>34.2%</td>
<td>5.3%</td>
</tr>
<tr>
<td></td>
<td>[28.3%–40.4%]</td>
<td>[4.1%–6.8%]</td>
</tr>
<tr>
<td></td>
<td>$I^2 = 75.8%$</td>
<td>$I^2 = 29.2%$</td>
</tr>
<tr>
<td></td>
<td>[68.2%–81.5%]</td>
<td>[7%–46.1%]</td>
</tr>
<tr>
<td></td>
<td>($n = 50$)</td>
<td>($n = 85$)</td>
</tr>
<tr>
<td>Tumor resectable before treatment (group 1)</td>
<td>26.7%</td>
<td>3.9%</td>
</tr>
<tr>
<td></td>
<td>[20.7%–33.3%]</td>
<td>[2.2%–6.0%]</td>
</tr>
<tr>
<td></td>
<td>$I^2 = 67.2%$</td>
<td>$I^2 = 51.9%$</td>
</tr>
<tr>
<td></td>
<td>[48.8%–79%]</td>
<td>[26.9%–68.3%]</td>
</tr>
<tr>
<td></td>
<td>($n = 22$)</td>
<td>($n = 30$)</td>
</tr>
<tr>
<td>Tumor non-resectable before treatment (group 2)</td>
<td>39.1%</td>
<td>7.1%</td>
</tr>
<tr>
<td></td>
<td>[29.5%–49.1%]</td>
<td>[5.1%–9.5%]</td>
</tr>
<tr>
<td></td>
<td>$I^2 = 67.5%$</td>
<td>$I^2 = 0%$</td>
</tr>
<tr>
<td></td>
<td>[49.8%–78.9%]</td>
<td>[0%–23.4%]</td>
</tr>
<tr>
<td></td>
<td>($n = 23$)</td>
<td>($n = 43$)</td>
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<table>
<thead>
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<th>Group</th>
<th>Estimated Median Survival ($m_p$)</th>
<th>Estimated Survival Probability (Resected)</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Resected (Range)</td>
<td>Not Resected (Range)</td>
</tr>
<tr>
<td>All patients</td>
<td>22.4 (9–62)</td>
<td>9.5 (6–21)</td>
</tr>
<tr>
<td></td>
<td>(n = 70)</td>
<td>(n = 51)</td>
</tr>
<tr>
<td>Tumor resectable before treatment (group 1)</td>
<td>23.3 (12–54)</td>
<td>8.4 (6–14)</td>
</tr>
<tr>
<td></td>
<td>(n = 27)</td>
<td>(n = 19)</td>
</tr>
<tr>
<td>Tumor non-resectable before treatment (group 2)</td>
<td>20.5 (9–62)</td>
<td>10.2 (6–21)</td>
</tr>
<tr>
<td></td>
<td>(n = 29)</td>
<td>(n = 25)</td>
</tr>
</tbody>
</table>

$n$, number of assessable studies for each group.

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<table>
<thead>
<tr>
<th>Potential Explanation Factor Variable</th>
<th>Resection Rate</th>
<th>Exploration Rate</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Toxicity</th>
<th>Morbidity</th>
<th>Mortality</th>
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</thead>
<tbody>
<tr>
<td>Institution</td>
<td>16.7% (17.4%)</td>
<td>13.3% (15.0%)</td>
<td>30.2% (31.9%)</td>
<td>20.9% (16.7%)</td>
<td>27.2% (10.7%)</td>
<td>12.8% (24.9%)</td>
<td>34.8% (35.2%)</td>
<td>20.8% (14.3%)</td>
<td>22.5% (19.6%)</td>
</tr>
<tr>
<td>Study design</td>
<td>1.2% (2.9%)</td>
<td>0.6% (1.6%)</td>
<td>3.1% (1.0%)</td>
<td>10.7% (4.0%)</td>
<td>4.1% (1.8%)</td>
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<td>8.7% (2.0%)</td>
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The fraction of explained variance is given in %. Values in parentheses represent the fraction of explained variance in % from univariable analysis.

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

doi:10.1371/journal.pmed.1000267.t007


https://doi.org/10.1371/journal.pmed.1000267
https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000267
## Potential Explanation Factor Variable

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<th>PD</th>
<th>Toxicity</th>
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doi:10.1371/journal.pmed.1000267.t007
Benefits of Neoadjuvant CTX-XRT

- Reassessment may identify those patients presenting with rapid progressive or disseminated disease at restaging who therefore have a very poor prognosis and for whom surgery is unlikely to provide any benefit.


https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000267
“On the other hand, there is the potential risk for tumor progression during neoadjuvant therapy, i.e. patients with initially resectable tumors might present with local or distant tumor progression at restaging, which might not have occurred in the setting of an initial tumor resection. In addition, neoadjuvant treatment protocols usually require histological confirmation before initiation of therapy, resulting in additional invasive diagnostic measures.”

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- Potential for tumor progression during Neoadj CTX-XRT
  - Pts who would have been resectable at dx, could progress and become incurable during neoadj CTX-XRT
- Histologic confirmation requires additional dx procedures (eg EUS) with occasional complications/morbidity or delay.
Clearly, only randomized controlled trials can clarify which of the hypothetical advantages/disadvantages are real and which ones are not.
Oncological Benefits of Neoadjuvant Chemoradiation With Gemcitabine Versus Upfront Surgery in Patients With Borderline Resectable Pancreatic Cancer: A Prospective, Randomized, Open-label, Multicenter Phase 2/3 Trial.
OBJECTIVE:
This study was performed to determine whether neoadjuvant treatment increases survival in patients with BRPC.
SUMMARY BACKGROUND DATA:
Despite many promising retrospective data on the effect of neoadjuvant treatment for borderline resectable pancreatic cancer (BRPC), no high-level evidence exists to support the role of such treatment.
METHODS:

- Phase II/III multicenter RCT
- 110 patients with BRPC who were randomly assigned to:
  - gemcitabine-based neoadjuvant chemoradiation treatment (54 Gy external beam radiation) followed by surgery or
  - upfront surgery followed by chemoradiation treatment from four large-volume centers in Korea.
- The primary endpoint was the 2-year survival rate
- Interim analysis was planned at the time of 50% case enrollment.
RESULTS:

- 8 pts withdrew consent
- 27 pts allocated to neoadj tx
- 23 pts to upfront surgery
- On intention-to-treat analysis,
  - Neoadj CTX-XRT yielded 40.7% 2yOS, 21 mo med OS
  - Adj CTX-XRT yielded 26.0% 2yOS, 16 mo med OS (p=0.028)

- R0 resection rate
  - Neoadj CTX-XRT yielded 51.8% R0 resection
  - Adj CTX-XRT yielded 26.1% R0 resection (p=0.004)

- The safety monitoring committee decided on early termination of the study on the basis of the statistical significance of neoadjuvant treatment efficacy.
CONCLUSION:
This is the first prospective randomized controlled trial on the oncological benefits of neoadjuvant treatment in BRPC. Compared to upfront surgery, neoadjuvant chemoradiation provides oncological benefits in patients with BRPC.
Benefits of Neoadjuvant Chemoradiotherapy in BRPC

• Maximize potential for R0 resection
Benefits of Neoadjuvant Chemoradiotherapy in BRPC

• Maximize potential for R0 resection
• Maximize early exposure of micrometastatic disease to systemic therapy
Benefits of Neoadjuvant Chemoradiotherapy in BRPC

- Maximize potential for R0 resection
- Maximize early exposure of micrometastatic disease to systemic therapy
- Gauge cancer behavior and select for surgery those most likely to benefit
Benefits of Neoadjuvant Chemoradiotherapy in BRPC

• Maximize potential for R0 resection
• Maximize early exposure of micrometastatic disease to systemic therapy
• Gauge cancer behavior and select for surgery those most likely to benefit
• Reduce anastamotic fistula rates b/w pancreas and jejunum
Preoperative Radiation Therapy for Pancreatic Cancer: When, Where, and How
PRINCIPLES OF RADIATION THERAPY RECOMMENDATIONS BASED ON TREATMENT SETTING

• RT Dosing:
  ‣ For chemoradiation, the following RT doses have been reported: 36 Gy in 2.4 Gy fractions to 45–54 Gy in 1.8–2.0 Gy fractions (doses higher than 54 Gy may be considered on a clinical trial).
  ‣ For resectable cases, it may be reasonable to resect within a few weeks of RT. However, with borderline resectable cases, it may be optimal to resect 4–8 weeks after RT to allow for downstaging and sterilization of the margin. Surgical resection can be performed >8 weeks following RT; however, radiation-induced fibrosis may potentially increase the difficulty of the resection.

• Treatment Planning:
  ‣ Elective nodal irradiation (ENI) is controversial for resectable/borderline resectable/locally advanced disease. If ENI is performed, patients should receive concurrent fluoropyrimidine-based chemotherapy or dose-reduced gemcitabine when using conventional fractionation regimens. (See Principles of Chemotherapy, PANC-F)
Chemoradiation Strategies

• Standard approach is to use standard doses of RT (50.4 Gy in 28 fractions) with concurrent chemotherapy (gemcitabine or capecitabine).
• The primary tumor, SMA, and celiac axis should always be contoured and included within the margin.
• Some customization of the nodal coverage is appropriate depending on the likelihood of the patient proceeding to surgery.
• MDACC recommends including the porta hepatis only in those patients who are most likely to undergo resection because of the fact that usually more gastroduodenal mucosa has to be included, which increases the risk of toxicity.
# PRINCIPLES OF RADIATION THERAPY

## Table 1: Normal Tissue Dose Volume Recommendations for Chemoradiation Utilizing Conventional Fractionation

<table>
<thead>
<tr>
<th>Organ at Risk (OAR)</th>
<th>Neoadjuvant/Definitive/Palliative and Recurrent Recommendations</th>
<th>Adjuvant Recommendations&lt;sup&gt;f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney (right and left)</td>
<td>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 &gt;18 Gy.</td>
<td>For 3D conformal plans in patients with two normally functioning kidneys, at least 50% of the right kidney and at least 65% of the left kidney must receive &lt;18 Gy. For IMRT planning, mean dose to bilateral kidneys must be &lt;18 Gy. If only one kidney is present, not more than 15% of the volume of that kidney can receive ≥18 Gy and not more than 30% can receive ≥14 Gy.</td>
</tr>
<tr>
<td>Stomach, duodenum, jejunum</td>
<td>Max dose 55 Gy.</td>
<td>Max dose ≤54 Gy; &lt;10% of each organ volume can receive between 50 and 53.99 Gy; &lt;15% of the volume of each organ can receive between 45 and 49.99 Gy.</td>
</tr>
<tr>
<td>Liver</td>
<td>Mean dose cannot exceed 30 Gy.</td>
<td>Mean liver dose must be ≤25 Gy.</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Max dose to a volume of at least 0.03 cc must be ≤45 Gy.</td>
<td>Max dose ≤45 Gy.</td>
</tr>
</tbody>
</table>
Preoperative Radiation Therapy for Pancreatic Cancer: When, Where, and How
Radiobiology 101

- All tissues are made up of molecules with atoms as their building blocks. In the center of every atom is the nucleus. Orbiting the nucleus of the atom are negatively charged electrons.
Radiobiology 101

- When X-rays pass through cellular tissues, dose is delivered. Dose is a measure of ionization events in the tissues being irradiated.
- The end result of ionization events is damage to molecules within the cells, especially the DNA in the nucleus of the cell.
- Dose was formerly measured in RAD (Radiation Absorbed Dose); now measured in the SI unit of Gray (Gy).
- 100 rad = 100 cGy = 1Gy.
Radiobiology 101

- The *lethal event* ionizing radiation causes is the double-strand-break; damage to both strands of the DNA double helix in close proximity.
- Damaging the DNA destroys the ability to divide or proliferate and leads to cell death.
Radiobiology 101

- Rapidly dividing cells like cancer cells sustain more permanent damage and subsequent cell death than occurs in the relatively senescent normal cell population.

- This permits selective destruction of cancer cells growing among normal cells.

- This differential effect is maximized by fractionation; spreading dose out over many treatments.
Radiobiology 101

- Makes use of the unique sensitivities of rapidly dividing cancer cells to reduce and potentially eliminate the population of cancer cells.
- Can sterilize a tissue or organ of viable cancer cells, while leaving normal tissues functionally intact.
Treatment Technique Evolution

Figure 1 | Wilhelm Conrad Röntgen (1845–1923). He received the Nobel Prize in Physics in 1901 for the discovery of X-rays. For further information on Wilhelm Conrad Röntgen, see REF 2. © Photo courtesy of Science Photo Library.
Hairstyle Evolution
What Goes Around…
Linear Accelerator for EBRT Delivery

- Electrons are accelerated to near the speed of light
- Electrons slam into a metal target, generating X-rays as they decelerate
- These X-rays are directed at the target and surrounding tissues, treating the cancer
Volumetric Arc Radiotherapy Delivery
Table 3. Incidence of acute Grade 3–4 gastrointestinal toxicity among patients treated with IMRT versus 3-D conformal treatment plans

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>3-D conformal</th>
<th>IMRT</th>
<th>$p$</th>
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<tr>
<td></td>
<td>$n$ (%)</td>
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<tr>
<td>Nausea/vomiting</td>
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</tr>
<tr>
<td>Grade 0–2</td>
<td>402 (89)</td>
<td>46 (100)</td>
<td>0.016</td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>49 (11)</td>
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<tr>
<td>Diarrhea</td>
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Abbreviations: IMRT = intensity-modulated radiation therapy; 3-D = three dimensional.
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Preoperative Radiation Therapy for Pancreatic Cancer: When, Where, and How

NCCN Guidelines Version 3.2019
Pancreatic Adenocarcinoma
NCCN Evidence Blocks™

PRINCIPLES OF RADIATION THERAPY
TREATMENT PLANNING: RADIATION DELIVERY

Simulation:

- For localized, intact pancreatic cancer (resectable, borderline, and locally advanced), placement of 1–5 (preferably ≥3) gold fiducial markers may be useful for targeting purposes. Placement of fiducial markers directly into the tumor and/or periphery under EUS is preferred. Stents can assist with targeting; however, they can shift and are therefore less reliable than fiducials.

- Position patient supine with arms up in an Alpha Cradle or equivalent immobilization device that will be custom-made for each patient. The simulation scan range should include approximately T4/T5 to L5/S1 (upper abdomen).

- CT simulation (2 to 3 mm slices) should be performed with IV (assuming adequate kidney function) and oral contrast. Multiphase IV contrast delivery may facilitate disease delineation. Patients with a contrast allergy may premedicate with steroids and antihistamines. If premedication is contraindicated, use an MRI (ideally in a similar treatment position) or a recent diagnostic scan for treatment planning, if available.

- If the patient receives oral contrast, consider giving the same volume of water prior to treatment each day to mimic simulation anatomy. Some radiation oncologists may prefer to not use oral contrast at simulation and treat with an empty stomach.

Motion Management:³

- Respiratory motion should be accounted for determining the internal target volume (ITV). This may be accomplished utilizing a 4D-CT scan.

- Motion management using respiratory gating or breath-hold, respiratory tracking, or abdominal compression may be used to reduce cranio-caudal tumor/fiducial marker motion, typically reducing from an 11 to 22 mm peak to ≤5 mm.

- Use of respiratory gating, ABC, or respiratory tracking requires real-time cone-beam CT, fluoroscopy, or kV imaging for setup and to confirm fiducial location during treatment.

- 3-D conformal RT (3D-CRT), intensity-modulated RT (IMRT), and SBRT with breathhold/gating techniques can result in improved planning target volume (PTV) coverage with decreased dose to OARs.⁴,⁵

Dose and Fractionation:

- It is imperative to evaluate the dose-volume histogram (DVH) of the PTV and the critical OARs such as the duodenum, stomach, liver, kidneys, spinal cord, and bowel. See Table 1. Normal Tissue Dose Volume Recommendations (PANC-G, 5 of 7). No definitive dose constraints for SBRT currently exist but are emerging.

- While these examples of limits are empirical they differ based on dose per fraction, total dose delivered, and disease status (adjuvant vs. unresectable). Studies have shown that the tolerability of radiation is largely dependent on PTV size/elective nodal irradiation (ENI), types of concurrent systemic/targeted therapy, and whether conformal (3-D, IMRT, SBRT) vs. conventional radiation is used.

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Preoperative Radiation Therapy for Pancreatic Cancer: When, Where, and How

NCCN Guidelines Version 3.2019
Pancreatic Adenocarcinoma
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Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References

PANC-G
2 OF 7
Preoperative Radiation Therapy for Pancreatic Cancer: When, Where, and How

NCCN Guidelines Version 3.2019
Pancreatic Adenocarcinoma
NCCN Evidence Blocks™

PRINCIPLES OF RADIATION THERAPY
TREATMENT PLANNING: RADIATION DELIVERY

Simulation:
• For localized, intact pancreatic cancer (resectable, borderline, and locally advanced), placement of 1–5 (preferably ≥3) gold fiducial markers may be useful for targeting purposes. Placement of fiducial markers directly into the tumor and/or periphery under EUS is preferred. Stents can assist with targeting; however, they can shift and are therefore less reliable than fiducials.
• Position patient supine with arms up in an Alpha Cradle or equivalent immobilization device that will be custom-made for each patient. The simulation scan range should include approximately T4/T5 to L5/S1 (upper abdomen).
• CT simulation (2 to 3 mm slices) should be performed with IV (assuming adequate kidney function) and oral contrast. Multiphase IV contrast delivery may facilitate disease delineation. Patients with a contrast allergy may premedicate with steroids and antihistamines. If premedication is contraindicated, use an MRI (ideally in a similar treatment position) or a recent diagnostic scan for treatment planning, if available.

Motion Management:
• Respiratory motion should be accounted for determining the internal target volume (ITV). This may be accomplished utilizing a 4D-CT scan.
• Motion management using respiratory gating or breath-hold, respiratory tracking, or abdominal compression may be used to reduce cranio-caudal tumor/fiducial marker motion, typically reducing from an 11 to 22 mm peak to ≤5 mm.
• Use of respiratory gating, ABC, or respiratory tracking requires real-time cone-beam CT, fluoroscopy, or kV imaging for setup and to confirm fiducial location during treatment.
• 3-D conformal RT (3D-CRT), intensity-modulated RT (IMRT), and SBRT with breathhold/gating techniques can result in improved planning target volume (PTV) coverage with decreased dose to OARs.4,5

Dose and Fractionation:

kidneys, spinal cord, and bowel. See Table 1. Normal Tissue Dose Volume Recommendations (PANC-G, 5 of 7). No definitive dose constraints for SBRT currently exist but are emerging.
• While these examples of limits are empirical they differ based on dose per fraction, total dose delivered, and disease status (adjuvant vs. unresectable). Studies have shown that the tolerability of radiation is largely dependent on PTV size/elective nodal irradiation (ENI), types of concurrent systemic/targeted therapy, and whether conformal (3-D, IMRT, SBRT) vs. conventional radiation is used.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Fiducial Markers under End-Expiration Breath Hold Respiratory Gating
Simulation:

- For localized, intact pancreatic cancer (resectable, borderline, and locally advanced), placement of 1–5 (preferably ≥3) gold fiducial markers may be useful for targeting purposes. Placement of fiducial markers directly into the tumor and/or periphery under EUS is preferred. Stents can assist with targeting; however, they can shift and are therefore less reliable than fiducials.

- Position patient supine with arms up in an Alpha Cradle or equivalent immobilization device that will be custom-made for each patient. The simulation scan range should include approximately T4/T5 to L5/S1 (upper abdomen).

- CT simulation (2 to 3 mm slices) should be performed with IV (assuming adequate kidney function) and oral contrast. Multiphase IV contrast delivery may facilitate disease delineation. Patients with a contrast allergy may premedicate with steroids and antihistamines. If premedication is contraindicated, use an MRI (ideally in a similar treatment position) or a recent diagnostic scan for treatment planning, if available.

- If the patient receives oral contrast, consider giving the same volume of water prior to treatment each day to mimic simulation anatomy. Some radiation oncologists may prefer to not use oral contrast at simulation and treat with an empty stomach.

Motion Management:

- Respiratory motion should be accounted for determining the internal target volume (ITV). This may be accomplished utilizing a 4D-CT scan.

- Motion management using respiratory gating or breath-hold, respiratory tracking, or abdominal compression may be used to reduce cranio-caudal tumor/fiducial marker motion, typically reducing from an 11 to 22 mm peak to ≤5 mm.

- Use of respiratory gating, ABC, or respiratory tracking requires real-time cone-beam CT, fluoroscopy, or kV imaging for setup and to confirm fiducial location during treatment.

Dose and Fractionation:

- It is imperative to evaluate the dose-volume histogram (DVH) of the PTV and the critical OARs such as the duodenum, stomach, liver, kidneys, spinal cord, and bowel. See Table 1. Normal Tissue Dose Volume Recommendations (PANC-G, 5 of 7). No definitive dose constraints for SBRT currently exist but are emerging.

- While these examples of limits are empirical they differ based on dose per fraction, total dose delivered, and disease status (adjuvant vs. unresectable). Studies have shown that the tolerability of radiation is largely dependent on PTV size/elective nodal irradiation (ENI), types of concurrent systemic/targeted therapy, and whether conformal (3-D, IMRT, SBRT) vs. conventional radiation is used.
Fig. 1. Representative dose–volume histogram comparing three dimensional conformal and intensity-modulated radiation therapy plans.
Fig. 2. Axial comparison of typical intensity-modulated radiation therapy (left) and three-dimensional (right) treatment plans.
"We just made a big cancer breakthrough. Have a cigar."