Proton Therapy for Pancreatic Cancer

R. Charles Nichols Jr., M.D.

June 4, 2014
Disclosures

• None
Overview

• What is proton therapy?
• Pancreas cancer.
  – Nature of the disease
  – Role of radiotherapy
  – Limitations of x-ray based therapies
  – Why protons may change the management paradigm for this malignancy
How does Proton Therapy differ from conventional photon (x-ray) radiotherapy?

- Protons are charged particles.
- They deposit energy at a defined depth in tissue.
- The Bragg Peak.
Bragg Peak

- The depth where the proton deposits its energy depends on its energy as it enters the tissue.
- Higher energy – deeper penetration.
Clinical use of the Bragg Peak

- A “point dose” would be useless to treat most cancers.
- To make protons useful, we create a “Spread Out Bragg Peak” (SOBP)
Spread out Bragg Peak

By delivering an array of proton beam energies, a “Spread out Bragg Peak” (SOBP) is created.
Clinical Relevance of the SOBP

- The SOBP can be configured to deliver dose to the full depth of the tumor target.

- Entry Dose is Minimized
- Exit Dose is Eliminated
Photons (X-Rays)

Highest Dose is near the point of beam entry.

Tumor Dose is less than the entry dose.

Dose is also delivered beyond the tumor target.

Conventional Radiation Therapy Deposits most energy before target.
Protons

Entry dose is low.

Highest Dose is at the depth of the tumor target.

There is NO exit dose beyond the target.

TARGETED PROTON THERAPY: Deposits most energy on target
Proton Therapy

• A photon and a proton walk into a bar…
• Protons know when to stop.
Pancreas Cancer

The head of the pancreas is the most common site of origin.

Gastric outlet obstruction can occur when the pancreatic head mass occludes the duodenum.

Painless jaundice is the most common presenting symptom due to bile duct obstruction.

Because the pancreas abuts critical blood vessels, surgical cure is “difficult.”
The Whipple Procedure

Organs removed during a Whipple

Most common anatomy after Whipple
Pancreatic Cancer Facts

- 43,140 Annual Cases
- 36,800 Annual Deaths
  - *Why is this remotely interesting?*
Pancreatic Cancer Facts...

- 43,140 Annual Cases
  - 50% present with distant metastases
  - 50% are localized to the pancreas
    - 30% are locally advanced / unresectable
    - 20% are “resectable” (curable)
Localized Disease

- 21,500 Annual Cases
  - 13,000 unresectable
    - Current median survival is between 9 and 11 months.
  - 8,500 are “resectable” (curable)
    - Surgical “cure” rate is only 20%
Unresectable Cancer

- Blood vessel encasement is the most common reason for unresectability.
Treatment options - Unresectable

Radiotherapy (with chemotherapy)
Chemotherapy alone
Chemoradiation (or chemotherapy alone) with the goal of conversion to resectability.
Unresectable Pancreas
UFPTI - PC01 Protocol

59.40Gy (RBE) in 33 fractions
Oral Capecitabine (1000mg PO BID) on Tx Days.
11 patients enrolled.
Closed to accrual 2013
UFPTI - PC01 Protocol

Results

No grade 2 or higher GI toxicity
4 of 11 achieved a response to justify surgical exploration
3 patients resected
18.4 month median survival
69% freedom from local progression at 2 years.
UFPTI - PC01 Protocol

Results

1- and 2-year Local Control, 86% and 69%
1- and 2-year Overall Survival, 61% and 31%
What about the 20% of patients who present with “resectable” pancreatic cancer?
Resectable pancreas cancers:

(including “marginally resectable”)
8500 cases annually in NA
Standard therapy is surgery +/- “adjuvant therapy.”
5 year survival rate is 20%
Statement:

• Proton therapy has the potential to improve the therapeutic index over x-rays in the treatment of many malignancies.
Is proton therapy only...

- A more *elegant* form of radiotherapy?
- A more *sophisticated* form of radiotherapy?
Or...

• …does the improvement in the therapeutic index with protons offer the potential to change the management paradigm of a particular malignancy?
Or...

- ...does the improvement in the therapeutic index with protons offer the potential to change the management paradigm of a particular malignancy?
- **Resectable pancreatic cancer.**
Fact

• Local control is a necessary condition for cure of any solid malignancy.
More Facts

• Local control is a necessary condition for cure.

• Surgery is a necessary condition for local control.
More Facts

• Local control is a necessary condition for cure.
• Surgery is a necessary condition for local control*

* usually
More Facts

• Local control is a necessary condition for cure.
• Surgery is a necessary condition for local control*
• **Surgery is not a sufficient condition for local control.**

*usually
The problem with the Whipple...

...is that even with negative nodes and negative surgical margins, 50% to 80% of patients will suffer a local failure if they do not receive postoperative radiotherapy.
The problem with the Whipple...

...is that even with negative nodes and negative surgical margins, **50% to 80% of patients will suffer a local failure** if they do not receive postoperative radiotherapy.
...is that so surprising?

Close retroperitoneal / vascular margins
…is that so surprising?

Half of the involved organ is left behind!

Organs removed during a Whipple

Most common anatomy after Whipple
Are you ready for the bad news?

- Hopkins data:
  - Pawlik TM, Surgery, 2007
    - 905 Whipples from 1995 to 2005
      - Node positivity was…
        » 79.3%
      - Margin positivity was …
        » 41.1%
Are you ready for more bad news?

- MSKCC Data:
  - 625 resections from 2000 to 2009
    - Margin positivity…**16%**
    - Node positivity…**70%**
In other words...

- Margin negative, node negative Whipples are uncommon.
Or, less diplomatically...

- While the Whipple procedure is an operation performed on cancer patients...
- ... it is not a cancer operation.
So what can be done to improve local and regional control?
Postoperative X-Rays?
Problems with postoperative radiotherapy…
Problems with postoperative radiotherapy…

1.) Long delay between surgery and radiotherapy.
Problems with postoperative radiotherapy…

1.) Long delay between surgery and radiotherapy.
2.) Bowel toxicity limits x-ray dose to +/- 50Gy.
Problems with postoperative radiotherapy...

1.) Long delay between surgery and radiotherapy.
2.) Bowel toxicity limits x-ray dose to +/- 50Gy.
Problems with postoperative radiotherapy…

MGH data shows a **36% local/regional failure rate** at 3 years after postoperative chemoradiation.

RTOG 97-04 shows a **23% to 28% local failure rate**.
Summarizing...
Summarizing…

1.) Surgery is necessary (but not sufficient) for cure.
Summarizing…

1.) Surgery is necessary (but not sufficient) for cure.

2.) Postoperative radiotherapy may not be effective.
Too Late…
Too Little…
Any suggestions?
Preoperative radiotherapy!
…not so fast
...not so fast

...50% of attendees surveyed at the 2012 international GI meeting in San Francisco would not recommend preoperative radiotherapy for a marginally resectable patient even after a non-response to first line chemotherapy.
The bottom line...

Pancreas surgeons, with few exceptions, do not like operating on previously irradiated patients.
Why?
Why?

- Billiaryjejunal Anastomosis
- Postoperative Nutrition
- Gastrojejunal Anastomosis
- Pancreaticojejunal Anastomosis

Most common anatomy after Whipple
Are we at an impasse?
Maybe not...

What if we could convince surgeons that preoperative radiotherapy could be delivered without the gastrointestinal toxicity of x-ray based therapy?
Does dosimetry suggest that protons improve the therapeutic index for pancreatic cancer?
Clinical Investigation

Protons Offer Reduced Normal-Tissue Exposure for Patients Receiving Postoperative Radiotherapy for Resected Pancreatic Head Cancer

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Protons versus IMRT

– 8 consecutive patients planned for IMRT and treated at the University of Maryland in 2008 (50.40Gy/28fx to PTV)
– Corresponding proton plans generated at UFPTI

• Small Bowel V20 (15.4% vs. 47.0% p=0.03)
• Gastric V20 (2.3% vs. 20.0% p=0.03)
• Right Kidney V18 (27.3% vs. 50.5% p=0.02)
Protons versus IMRT

Bowel Sparing
Protons versus IMRT

Gastric Sparing
Protons versus IMRT

Bowel Sparing
Does dosimetry suggest that protons improve the therapeutic index for pancreatic cancer?
Does dosimetry suggest that protons improve the therapeutic index for pancreatic cancer?

Yes.
Does this elegant dosimetry translate into reduced radiotherapy toxicity?
Proton therapy with concomitant capecitabine for pancreatic and ampullary cancers is associated with a low incidence of gastrointestinal toxicity

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Abstract
Background. To review treatment toxicity for patients with pancreatic and ampullary cancer treated with proton therapy at our institution. Material and methods. From March 2009 through April 2012, 22 patients were treated with proton therapy and concomitant capecitabine (1000 mg PO twice daily) for resected (n = 5); marginally resectable (n = 7); and unresectable/inoperable (n = 12) biopsy-proven pancreatic and ampullary adenocarcinoma. Two patients with unresectable disease were excluded from the analysis for reasons unrelated to treatment. Proton doses ranged from 50.40 cobalt gray equivalent (CGE) to 59.40 CGE. Results. Median follow-up for all patients was 11 (range 5-36) months. No patient demonstrated any grade 3 toxicity during treatment or during the follow-up period. Grade 2 gastrointestinal toxicities occurred in three patients, consisting of vomiting (n = 3), and diarrhea (n = 2). Median weight loss during treatment was 1.3 kg (1.17% of body weight). Chemotherapy was well-tolerated with a median 99% of the prescribed doses delivered. Percentage weight loss was reduced (p = 0.0596) and grade 2 gastrointestinal toxicity was eliminated (p = 0.0000) in patients treated with plans that avoided anterior and left lateral fields which were associated with reduced small bowel and gastric exposure. Discussion. Proton therapy may allow for significant sparing of the small bowel and stomach and is associated with a low rate of gastrointestinal toxicity. Although long-term follow-up will be needed to assess efficacy, we believe that the favorable toxicity profile associated with proton therapy may allow for radiotherapy dose escalation, chemotherapy intensification, and possibly increased acceptance of preoperative radiotherapy for patients with resectable or marginally resectable disease.
UF Experience: 3/09 to 4/12

• 20 evaluable patients
  • Unresectable / Inoperable disease … 10
  • Marginally resectable disease … 5
  • Resected (postop RT) … 5
Proton Dose

• 20 patients
  – Unresectable / Inoperable … 59.40CGE
  – Marginally resectable … 50.40CGE
  – Resected (postop) … 54.00CGE
    • All patients received Capecitabine at 1000mg PO BID during RT.
    • 90% to 100% of prescribed doses taken
      – Median 99%
Grade 3 acute toxicity

- None
Grade 3 *late* toxicity

• None
Grade 2 GI toxicity

- 3 (out of 20) patients
  - Vomiting … 3
  - Diarrhea … 2
Field design (early)
Field design (current)
Grade 2 GI toxicity (current field arrangement)

- None
Weight loss (17 patients - current field design)

- Median 1.1 lbs
- Range +10.4 to -14.1 lbs
Does this elegant dosimetry translate into reduced radiotherapy toxicity?
Does this elegant dosimetry translate into reduced radiotherapy toxicity?

Yes.
Dosimetry suggests the potential for meaningful improvements in the therapeutic ratio when protons are used in the setting of resected pancreatic cancer.
Summary #2

- Our early experience suggests a low rate of toxicity in pancreatic cancer patients receiving proton therapy with concomitant chemotherapy.
Summary #3

• The lack of toxicity associated with proton radiotherapy may improve the willingness of surgeons to accept neoadjuvant (proton) radiotherapy for patients with operable disease.
Summary #4

• If this happens, proton therapy will change the management paradigm for patients with resectable pancreatic cancer.
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• Improve local/regional control rates.
Summary #4

• If this happens, proton therapy will change the management paradigm for patients with resectable pancreatic cancer.
• Improve local/regional control rates.
• ...and perhaps improve the cure rate for this lethal malignancy.
UFPTI protocols:

- PC01 ... Unresectable disease ... 59.40CGE with concomitant Capecitabine (closed)
- PC02 ... Resectable and marginally resectable disease ... 50.40CGE with concomitant Capecitabine.
- PC03 ... Postoperative adjuvant with weekly Gemcitabine
  - 50.40CGE for R0 resections
  - 54.00CGE for R1 resections
  - 59.40CGE for R2 resections
The next step with neoadjuvant proton therapy...

- What about those nodes???
Nodal Coverage?

• Many (most) neoadjuvant protocols treat only the gross disease (PC02).

• Would covering the regional nodes increase the toxicity of neoadjuvant proton therapy?

» Richard Lee MD PGY-4 Roswell Park CC – 2012
Dosimetric Comparison

• 12 consecutive patients with non-metastatic pancreatic head cancers underwent simulation for neoadjuvant proton radiotherapy.
Simulation…

- Small bowel and IV contrast.
- 4D scans to account for target movement.
- 5mm PTV expansions on all (internal) CTV targets.
PTVs

- PTV1…gross disease only
- PTV2… gross disease plus nodal expansions using the RTOG (postop) contouring atlas.
Case 1: ROI’s

[Images of contrast-enhanced CT scans showing various structures with color coding]

Structures:
- PV
- PI
- AORTA
- SMA
- CA
- Tumor Bed

PTVs
- PTV1: gross disease only
- PTV2: gross disease plus nodal expansions using the RTOG (postop) contouring atlas.
PTVs
• PTV1… gross disease only
• PTV2… gross disease plus nodal expansions using the RTOG (postop) contouring atlas.
Case 1: Coronal/Sagittal Views
Optimized plans generated...

- Target dose 50.40CGE
- Point spinal cord maximum dose 45CGE
- Most plans 3:1 weighted PAO:RLO.
- Normal tissue exposures recorded.
PTV volumes…

- **PTV1** Median Volume...270.66cc
  - Range (133.33 to 495.61cc)
- **PTV2** Median Volume...541.75cc
  - Range (399.44 to 691.14cc)
Gross Tumor Only

A. Axial

B. Coronal

C. Sagital

Elective Nodes Included

A. Axial

B. Coronal

C. Sagital
Normal Tissue Exposures...
# Normal Tissue Exposures...

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<tr>
<th>V10</th>
<th>V30</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3%</td>
<td>8.3</td>
</tr>
<tr>
<td>(0-17%)</td>
<td>(3-22%)</td>
</tr>
</tbody>
</table>
Normal Tissue Exposures...

<table>
<thead>
<tr>
<th></th>
<th>Right Kidney</th>
<th>Left Kidney</th>
<th>Stomach</th>
<th>V30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>V18</td>
<td>V18</td>
<td>V20</td>
<td>V45</td>
</tr>
<tr>
<td>Gross tumor only</td>
<td>22.7% (0-68%)</td>
<td>3.9% (0-28%)</td>
<td>5.0% (0-33%)</td>
<td>1.1% (0-25%)</td>
</tr>
<tr>
<td>Elective Nodes included</td>
<td>34.6% (13-86%)</td>
<td>11.4% (1-31%)</td>
<td>7.5% (0-40%)</td>
<td>2.4% (0-24%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bowel Space</th>
<th>V20</th>
<th>V45</th>
<th>V50</th>
<th>V54</th>
<th>V30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12.7% (4-26%)</td>
<td>4.7% (1-16%)</td>
<td>2.3% (0-12%)</td>
<td>0% (0-0.1%)</td>
<td>4.3% (1-14%)</td>
</tr>
<tr>
<td></td>
<td>17.5% (7-38%)</td>
<td>10% (3-24%)</td>
<td>7.2% (1-20%)</td>
<td>0.3% (0-17%)</td>
<td>8.3 (3-22%)</td>
</tr>
</tbody>
</table>
Conclusion #1…

- The limited toxicity of proton therapy may allow for increased utilization of preoperative radiotherapy in patients with resectable and curable cancers.
Conclusion #2…

• The limited increase in normal tissue exposure when proton therapy is used to cover regional nodes may allow for safe coverage of high risk nodes in the neoadjuvant setting.
Aaron, so do you think that protons change the management paradigm for the treatment of resectable pancreatic cancer?
The theory and preliminary results are impressive but I would really like to learn more about the technical details.
Technical Issues

• Field Design and Weighting
• Target Motion
• Duodenal Exposure
Technical Issues

• Field Design and Weighting
• Target Motion
• Duodenal Exposure
Field Design and Weighting

The gastrointestinal toxicity of proton therapy for upper abdominal treatment comes from the anterior and left lateral fields. They also are associated with greater SOBP uncertainty since they pass through air filled spaces.
Field Design and Weighting

The PA or PAO field is the workhorse: 1.) Minimal uncertainty WRT distal SOBP; 2.) Minimal dose to small bowel.

The Lateral or Lateral Oblique Field delivers the “top off” dose. Because of uncertainty, use a wider SOBP for this field. This does not increase toxicity since given dose is relatively low.
Technical Issues

- Field Design and Weighting
- **Target Motion**
- Duodenal Exposure
Target Motion...

- 4D Scan with oral and IV contrast on the free breathing scan.
- The ITV is used as the CTV
- PTV expansion is protocol specific – generally 5 to 10mm
Technical Issues

- Field Design and Weighting
- Target Motion
- Duodenal Exposure
Duodenal Exposure

• With a 5mm PTV expansion, all segments of the duodenum get the full prescription dose.

• MDACC data suggests that we should be seeing a higher incidence of small bowel toxicity based in xray data which suggests limiting duodenal dose to 55Gy.
UFPTI GI Team

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- Soon Huh PhD
- Meng Wei Ho PhD
- Sang Lee PhD