What is the Role of Radiation Therapy for Pancreatic Cancer?

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Pancreatic Cancer: Radiation Therapy and Translational Paradigms

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Outline

- How Does Radiation Work?
- Pancreas anatomy review
- Pancreas Cancer Classification, Work-up, Management
- What are the types of radiation therapy?
- What is stereotactic radiation therapy?
- When should radiation be delivered?
- What are the side effects of radiation therapy?
- New Directions
Radiation Therapy: Basics

- External beam radiation is like an X-ray but has much more energy.
- Radiation travels through the skin, hits the tumor cells and damages the DNA of the cell.
- This results in death of the cancer cell.
- Radiation preferentially kills cells which are growing rapidly.
- Cancer cells have difficulty repairing the radiation damage.

Anatomy and Patterns of Spread

- Aorta
- Celiac plexus of nerves
- Portal vein
- Lymph nodes
- Duodenum
- Superior mesenteric blood vessels
- Liver
- Ligament of Treitz
- Jejunum

Image from sodahead.com
Pancreas Anatomy

Imaging on Presentation
Pancreatic Cancer: Multi-D Management

Biopsy-Proven or Suspected Pancreatic Cancer

Staging Work-up: H&P, Genetics, Family Hx, Functional Status
Imaging: CT scan, MRI, Functional Imaging (PET)
Labs: CBC, LFTs, Ca 19-9

Resectable
- No encasement of the SMA, celiac trunk
- No metastasis
- No obstruction of the portal vein/SMV confluence
- No encasement of the IVC, aorta

Borderline Resectable
- Severe unilateral SMV/portal vein impingement
- Tumor abuts SMA/IVC
- Gastro-duodenal artery encasement up to origin at hepatic artery
- Colon invasion

Unresectable
- Encasement of the SMA, celiac trunk
- Metastasis
- Obstruction of the portal vein/SMV confluence
- Encasement of the IVC, aorta
Timing of Radiation Therapy

- **Adjuvant** = Resected = Tumor Removed
  - Given to patients after the tumor has been removed
- **Neoadjuvant** = Preoperative = Before Surgery
  - Given to patients where the plan is that they will go to surgery
- **Definitive** = Locally advanced = Unresectable
  - Tumor is unlikely to be removed (10-20%)
- **Palliative**
  - Often given to patients with metastatic disease to help with pain

Radiation Oncology Terminology

- **Gy**: Is the term used for dose delivered in units of Joules/Kg of tissue
- **Fraction**: A treatment of radiation
  - Standard-Once a day, 5 days a week (QD)
  - Hyperfractionation-More than one treatment a day (twice daily)
  - Hypofractionation-Full dose delivered over shorter time period (one week vs. 5 weeks)
- **Simulation**: Obtain a CT scan of the patient in the position they will be treated
- **Treatment planning**: Develop plans which deliver dose to the tumor with attempts to limit the dose to the normal tissues
Types of Radiation Therapy

- **External Beam (X-ray) Radiation Therapy**
  - Palliative (2 fields)
  - Conformal Radiation (3-4 Fields)
  - Intensity Modulated Radiation Therapy (IMRT) (3-10 fields)
    - RT field is “modulated” by moving leafs during treatment
  - Stereotactic Body Radiation Therapy (SBRT) (5-100’s fields)
    - Many modulated fields focus on tumor, need image guidance

- **Intraoperative Radiation Therapy (IORT)**
  - Delivered with brachytherapy (catheters) or X-rays (electrons) at the time of surgery

Modern Treatment Devices

- CYBER-KNIFE
- TRILOGY
- SYNERGY
IMRT: Duodenal Sparing

SBRT: Duodenal Sparing
What is Stereotactic Radiation Therapy?

- Very focused radiation delivered with multiple beams
- High doses of radiation delivered daily (5-30 Gy) over a shorter period of time (1-5 days)
- Provides precise geometric targeting and dose delivery
- Allows potent potentially ablative doses while minimizing RT to adjacent normal tissues

Standard RT vs. Stereotactic RT

**Standard Radiation Therapy**
- Delivered over 5-6 weeks, Mon-Friday
- Low doses of RT/day (1.8 – 2 Gy)
- Large margins
- Less beams of radiation
- Usually combined with chemotherapy
- Normal tissue can repair
- Shorter treatment times per day (10-15 minutes)
- Acute > Chronic toxicity
- Less Convenient (worse quality of life)
- Good long term data

**Stereotactic Radiation Therapy**
- Delivered over one week
- High doses of RT/day (5-30 Gy)
- Small margins
- More difficult for normal tissues to repair the damage
- Treatment times sometimes >1 hour
- Chronic > Acute Toxicity
- Better quality of life
- Less data on this therapy
Unique Challenges of SBRT to Pancreatic Cancer

- Proximity of Pancreas to small bowel:
  - Delivery of even moderate doses of RT to small bowel is assoc. with high risk of late stenosis, ulceration, bleeding, perforation
  - Risk of late bowel complications heightened by use of large doses of RT

Technical Advances in SBRT

- Advances in Immobilization/Set-Up Error
  - Custom body frames with CT/MRI compatible radio-opaque markers (Lax et al 1994)
  - Cone beam CT (Letourneau et al 2005)

  - 4-D CT scans (simulation)
  - Airway-Breathing-Control (ABC)
  - Respiratory gating (skin or tissue fiducials)
  - Abdominal compression devices
PET imaging for Pancreatic Tumor Delineation

Mean Tumor Volume
CT = 90 cm
PET/CT = 56 cm
N = 20, P > 0.5

23% of GTV not included PET volume

Pancreas Cancer Treatment Options
**Pancreatic Cancer: Treatment**

**Biopsy-Proven or Suspected Pancreatic Cancer**

**Staging Work-up:** H&P, Genetics, Family Hx, Functional Status

**Imaging:** CT scan, MRI, Functional Imaging

**Labs:** CBC, LFTs, Ca 19-9

- **Resectable**
  - Preop CRT
  - Surgery
  - ADJ Tx

- **Borderline Resectable**
  - Preop CRT
  - CRT or SBRT

- **Unresectable**
  - CRT or SBRT
  - Chemo
  - RT 3X10

**Adjuvant Therapy**
*(after surgery)*

- High likelihood that there are cancer cells in the blood stream, lymph system, and tumor bed
- The cancer can return locally in the tumor bed and/or distantly (mostly liver)
- Need chemotherapy or targeted therapy through the IV or oral pills to treat cancer cells
- Radiation therapy kills cells in the tumor bed and surrounding lymph regions
R1 Positive Margin

Pancreas: Standard Adjuvant Radiation Field vs. Preoperative/Neoadjuvant Radiation Field

Koong et al. Stanford; IJROBP 2004
Neoadjuvant Therapy

- If patients with a resectable tumor go directly to surgery, they will not have any chemotherapy or radiation until 4-8 weeks after surgery.
- If chemotherapy and/or Radiation are given before surgery it may improve the likelihood of removing all of the tumor (margins) and decrease the chance of spread after surgery (metastatic disease).
- Neoadjuvant therapy may prevent surgery if cancer spreads during treatment (metastatic disease).

Therapy for Borderline Resectable Cancer

- Pancreatic tumors that can be removed, but are more likely to have positive margins.
- Patients should receive chemotherapy plus radiation therapy over 2-4 months, then have repeat imaging.
- If the tumor is stable or decreased in size then patients should undergo surgery.
- If the tumor grows or spreads to other areas in their body (metastasis) then surgery should not be done and patients should be offered other therapy or supportive care.
Challenges to Neoadjuvant Therapy

- Lack of phase III data; no direct randomized controlled trial of neoadjuvant treatment.
- Optimal chemotherapy regimen, +/- targeted therapies, has yet to be determined.
- Some institutions recommend neoadjuvant therapy for all patients with resectable tumors.

Locally Advanced/Unresectable Pancreatic Cancer Treatment

- Tumor cannot be removed by surgery
- Goal is to try to shrink the tumor or keep it from growing
- Treatment options
  - Chemotherapy alone
  - Chemotherapy and Radiation (IMRT)
  - Stereotactic Radiation Therapy
  (Can also give chemotherapy followed by RT)
**SBRT (stereotactic body RT)**

- Targets tumor only (not regional LN’s) with very sharp dose fall-off around the target
- Can be used in adjuvant/neoadjuvant/unresectable setting
- Organ motion must be accounted for
- Image guidance and fiducial marker placement also required
- High local control rates (70 – 90%) +
- Care must be taken to spare small bowel, especially duodenum

**J1003: Phase II Multi-Institutional Study of SBRT for Unresectable Pancreas Cancer**

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

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-bx biopsy QOL, tumor markers.

N=60

Trial open at Stanford, Johns Hopkins., Memorial Sloan Kettering.
Free Breathing CBCT Aligned to Bone

Final Setup with kV orthogonal pair @ breath hold (quasi-orthogonal in this case)

G=262° (kV=352°)

G=0° (kV=90°)
Patient underwent a Whipple.
- No residual tumor
- Node and margin negative

SBRT Pre/Post Treatment

Patient Characteristics

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OS Results of SBRT for Unresectable PC

OS Stratified by Baseline CA 19-9 (<>/90)
Resected Pancreas Cancer

JHU GM-CSF Pancreatic Vaccine

- Two pancreas cell lines have been developed from surgical specimens of subjects undergoing resection at JHH.
- These lines secrete GM-CSF which attract antigen presenting cells (APCs) to the vaccine site which subsequently present antigens to T-cells.
- These lines have undergone extensive regulatory testing
Design of Vaccine Adjuvant Phase II Study

Surgical Resection

Vaccine #1

Adjuvant 5-FU chemotherapy

0  4  8  10  16  20  24  28  32  36  40  44  48  72

Weeks
Pancreatic Tumor Cell Vaccine, Low Dose Cyclophosphamide, Fractionated SBRT, and FOLFIRINOX Chemotherapy in Patients with Resected Pancreatic Adenocarcinoma
Borderline Resectable Pancreas Cancer

- Up to 25% of pancreas cancer patients
- No defined standard of care
- No level I data to support current consensus recommendations of considering preoperative chemotherapy or chemoradiation

Alliance trial (Phase I/II)

Objectives: define a standard of care for borderline resectable disease, assess feasibility of multi-institutional study (QA, path review, etc), establish infrastructure for future trials

Dx/staging BLR PC  Re-stage  Re-stage
FFX 3 cycles XRT/5-FU 6 weeks Surgery Gem

- Second phase of the trial will randomize patients to FFX vs. gemcitabine for induction chemotherapy segment of treatment
Locally Progressive or Recurrent Pancreas Cancer

Recurrent Pancreas Cancer

- Phase I/II trial of SBRT in patients with pancreatic cancer recurrence following definitive therapy
- Patients with recurrence after any combination of definitive treatment (chemotherapy +/- surgery, +/- RT) are eligible
- Cohort I (Previous RT): 5Gy x 5
- Cohort II (No previous RT): 6.6Gy x 5
Summary Treatment Options

- Unresectable (locally advanced):
  - Chemotherapy alone
  - Chemotherapy and Radiation Therapy
  - Stereotactic Body Radiation Therapy (SBRT)

- Resectable/borderline (neoadj/preoperative):
  - Chemotherapy
  - Chemotherapy and Radiation

- Adjuvant (Resected):
  - Chemotherapy alone for 6 months
  - Chemotherapy plus Radiation (before or after Chemotherapy)
  - Observation (favorable pathology)

Encourage clinical trial enrollment
Decision based on imaging, performance status, patient preference

Common Side Effects of RT

- General
  - Symptoms usually from chemotherapy and RT
  - Anti-nausea meds help

- Acute
  - Usually occurs during treatment or shortly after
  - Nausea, Vomiting, Diarrhea, Fevers, Chills, Weight Loss
  - Less common with RT alone

- Chronic
  - Usually happens 3 months or greater after radiation therapy completed
  - Damage to bowel, kidneys, pancreas, liver, bile duct, spinal cord
  - Unlikely skin will be damaged
  - More focused radiation and lower dose per treatment decreases risk
Translational Questions

- Can we add novel chemotherapeutic and/or targeted agents to enhance pancreatic tumor response to radiation?
- Can we develop “patient specific” treatments based on genetic data and/or tumor response?
- Can we use a preclinical animal radiation platform to test novel combinations?

Background

- The tumor suppressor gene SMAD4 (DPC4) encodes for the common intracellular mediator of the TGF-β superfamily pathway which regulates cell proliferation, differentiation, apoptosis, and migration.
- In an autopsy series of advanced pancreatic cancer, DPC4 gene status was highly correlated with patterns of recurrence.
- Patients with DPC4 mutant (MT) gene status more often died of widely disseminated metastasis.
- Patients with DPC4 intact (WT) gene status more often died of localized disease.

Iacobuzio-Donahue et al. J Clin Oncol 27:1806-1813
Iacobuzio-Donahue et al. performed rapid autopsies on 76 patients with pancreatic cancer. Histologic features of end stage disease were assessed for correlation to:

- Stage at initial presentation
- Patterns of failure (locally destructive vs. metastatic)
- Status of the KRAS2, TP53, and DPC4 genes.

30% of patients died with locally destructive pancreatic cancer, and 70% died with widespread metastatic disease.
Team Members

- Surgery
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  - Mike Choti
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  - Cathy Stanford
- Social Work
  - Nancy Robinson
- Nutrition
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Thank you for your participation

Pancreatic Cancer Action Network
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If you have any questions about our Patient and Liaison Services (PALS) program, please contact (877) 272-6226 or e-mail pals@pancan.org.