What is the Role of Radiation Therapy for Pancreatic Cancer?

Presented by
Pancreatic Cancer Action Network
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August 22, 2012

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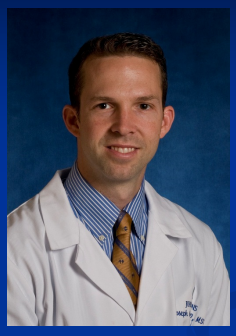

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August 22, 2012

Pancreatic Cancer: Radiation Therapy and Translational Paradigms

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Outline

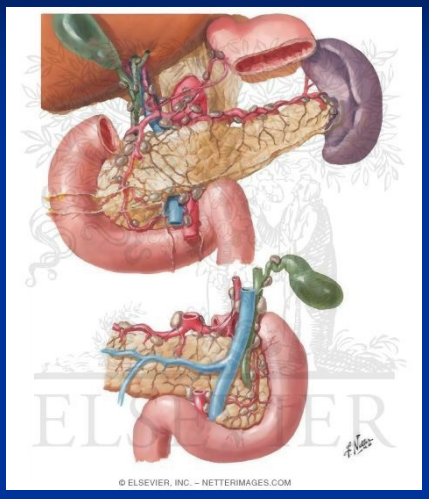
- How Does Radiation Work?
- Pancreas anatomy review
- Pancreas Cancer Classification, Work-up, Management
- What are the types of radiation therapy?
- What is stereotactic radiation therapy?
- When should radiation be delivered?
- What are the side effects of radiation therapy?
- New Directions

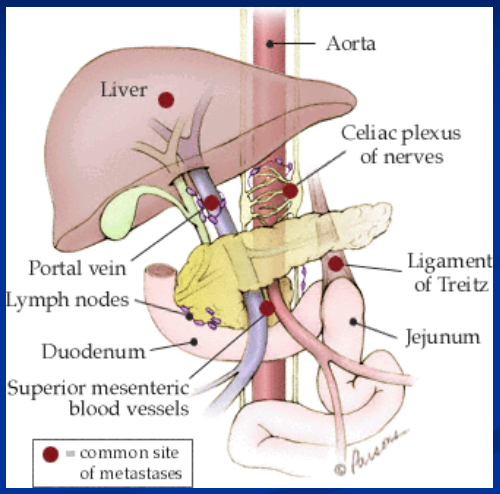
Radiation Therapy: Basics

- 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

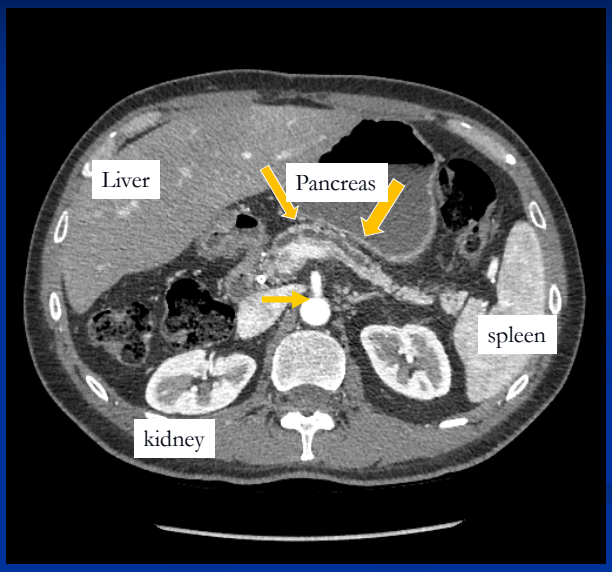
Image from sodahead.com

Anatomy and Patterns of Spread

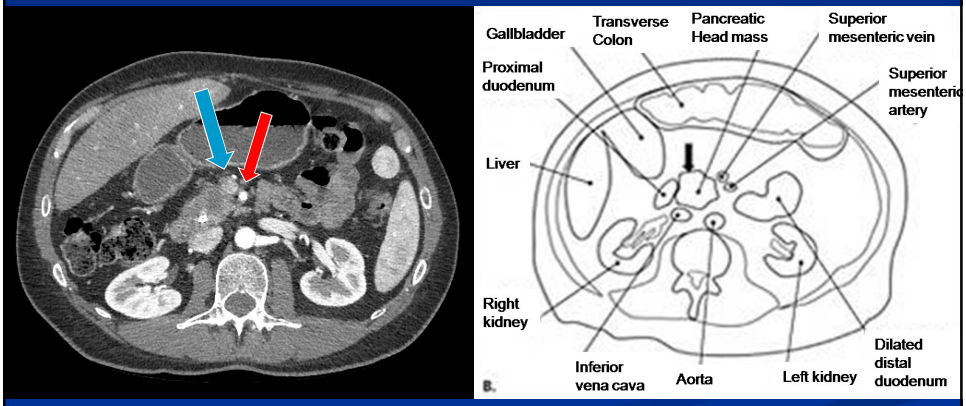




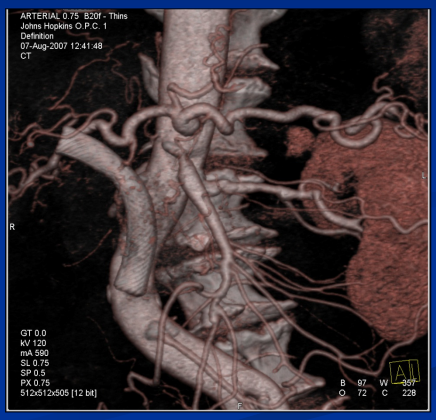
Pancreas Anatomy



Imaging on Presentation



3-D CT Scan



Compliments of Elliott Fishman, MD

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	Borderline Resectable	Unresectable
– No encasement of the SMA, celiac trunk – No metastasis – No obstruction of the portal vein/SMV confluence – No encasement of the IVC, aorta	– Severe unilateral SMV/portal–vein impingement – Tumor abuts SMA/IVC – Gastroduodenal artery encasement up to origin at hepatic artery – Colon invasion	– Encasement of the SMA, celiac trunk – Metastasis – Obstruction of the portal vein/SMV confluence – Encasement of the IVC, aorta

Timing of RadiationTherapy

- 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)
  - Hypfractionation-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

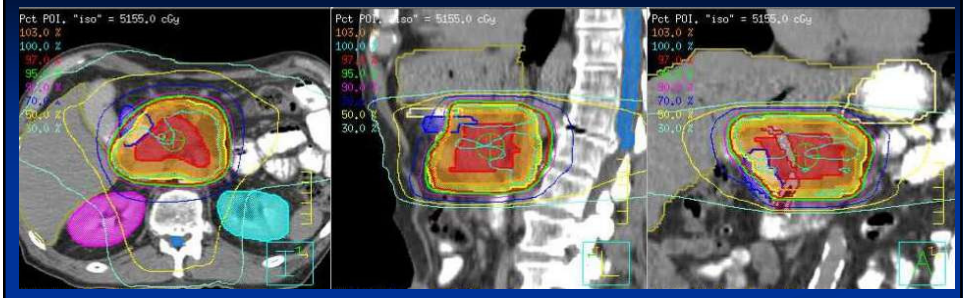
Modern Treatment Devices

CYBER-KNIFE

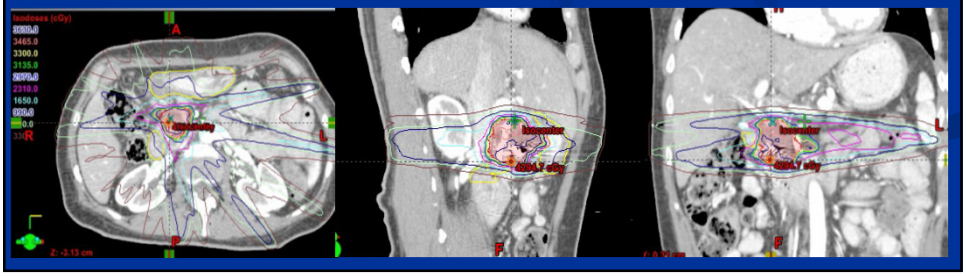
TRILOGY

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

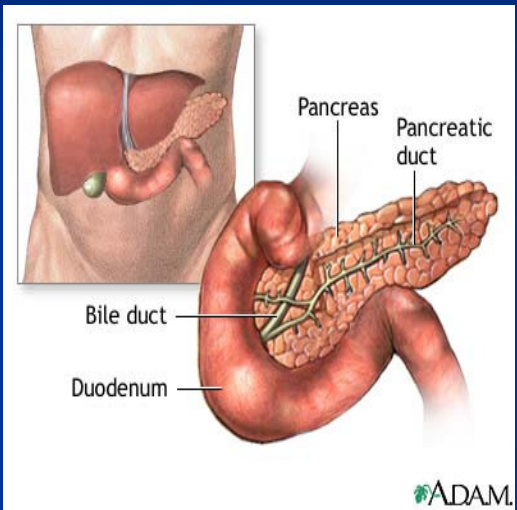
Standard Radiation Therapy

- 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

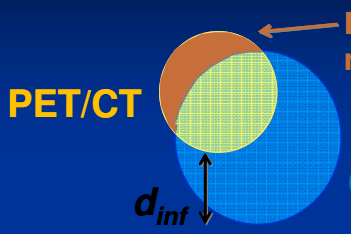


- Proximity of Pancreas to small bowel:
  - Delivery of even moderate doses of RT to small bowel is assoc. with high risk of late stenosis, ulceration, bleeding, perforation
  - Risk of late bowel complications heightened by use of large doses of RT

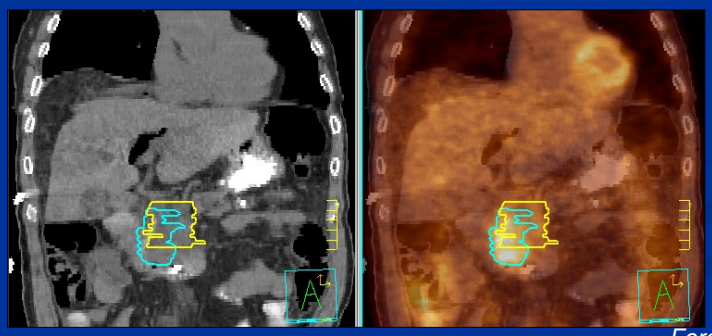
Technical Advances in SBRT

- 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)
- Advances in Tumor Motion Compensation (Lax et al 1994, Onimaru et al 2003, Underberg et al 2005, Wilson 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



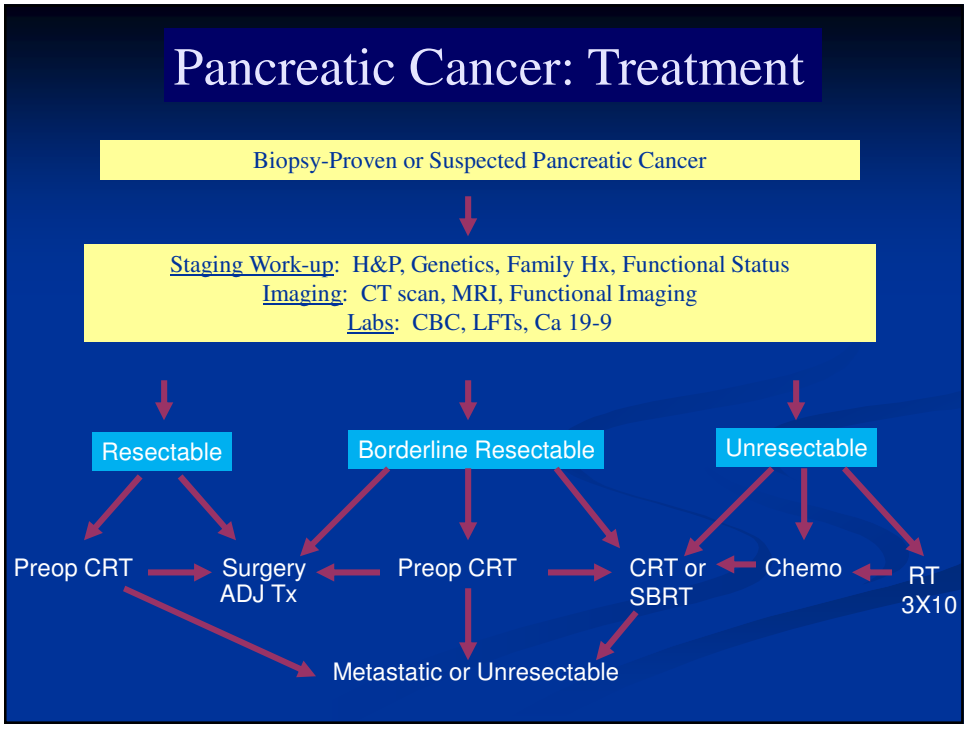
Mean TumorVolume
CT=90 cm
PET/CT =56 cm
N=20, P>0.5



23% of GTV not included PET volume

Ford et al. ASTRO 2008

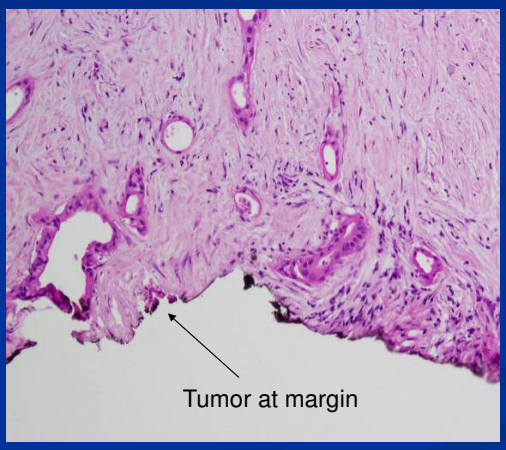
Pancreas Cancer Treatment Options



Adjuvant Therapy (after surgery)

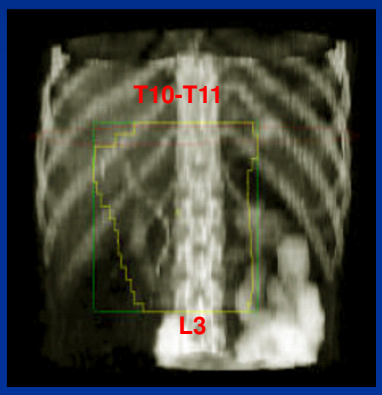
- High likelihood that there are cancer cells in the blood stream, lymph system, and tumor bed
- The cancer can return locally in the tumor bed and/or distantly (mostly liver)
- Need chemotherapy or targeted therapy through the IV or oral pills to treat cancer cells
- Radiation therapy kills cells in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

R1 Positive Margin



2010 Gatrointestinal Cancers Symposium

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)

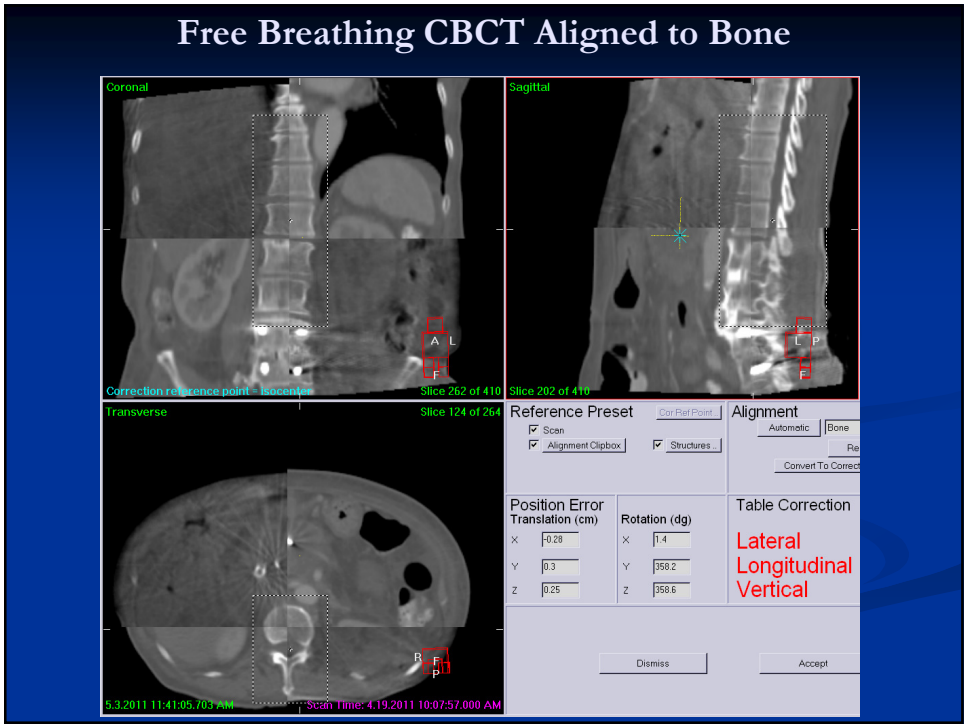
- Targets tumor only (not regional LN's) with very sharp dose fall-off around the target
- Can be used in adjuvant/neoadjuvant/unresectable setting
- Organ motion must be accounted for
- Image guidance and fiducial marker placement also required
- High local control rates (70 – 90^{+}%)
- Care must be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

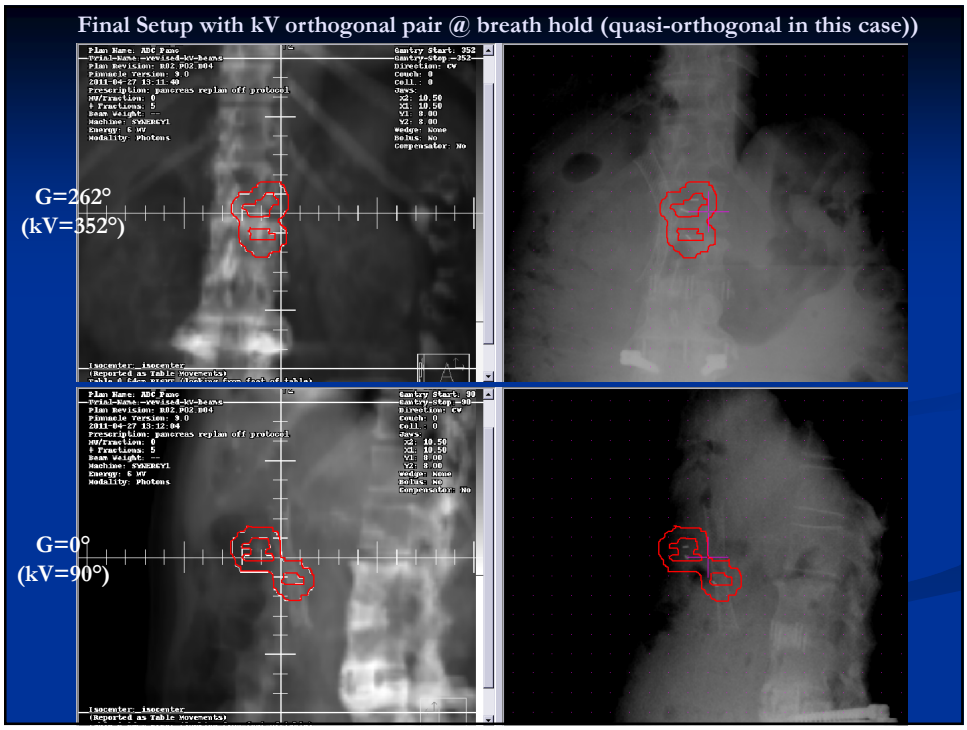
J1003: Phase II Multi-Institutional Study of SBRT for Unresectable Pancreas Cancer

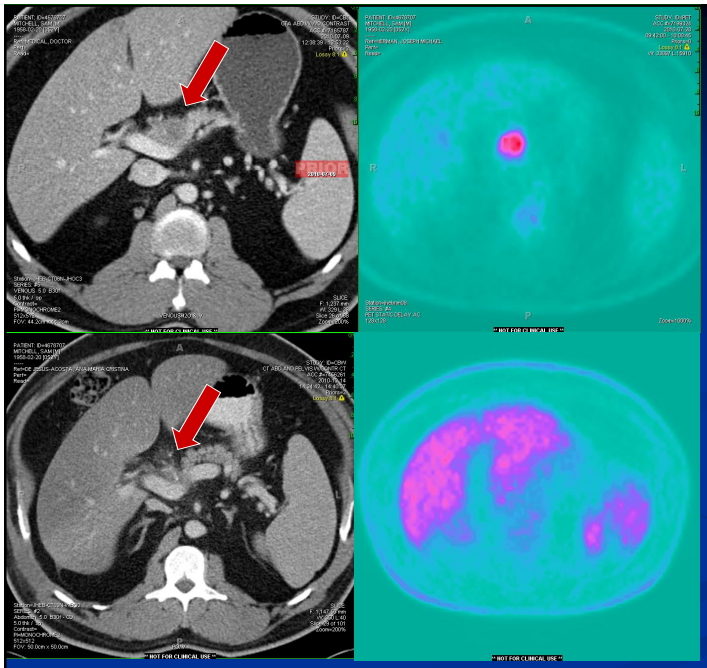
Locally Advanced Pancreatic Cancer (Gemcitabine, up to 1 Cycle allowed)* → 2 week break → SBRT 6.6 Gy x 5 Mon-Fri → >2 week break → Gemcitabine Chemotherapy (3 wks on, 1 wk off) Until toxicity or progression

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.


Free Breathing CBCT Aligned to Bone
Coronal
Sagittal
Correction reference point - isocenter
Slice 262 of 410
Slice 202 of 410
Transverse
Slice 124 of 264
5.3.2011 11:41:05.703 AM
Scan Time: 4.19.2011 10:07:57.000 AM
Reference Preset
Scan
Alignment Clipbox
Structures...
Alignment
Automatic
Bone
Position Error
Translation (cm)
Rotation (dg)
Table Correction
Lateral
Longitudinal
Vertical
Dismiss
Accept


Final Setup with kV orthogonal pair @ breath hold (quasi-orthogonal in this case))
G=262°
(kV=352°)
G=0°
(kV=90°)



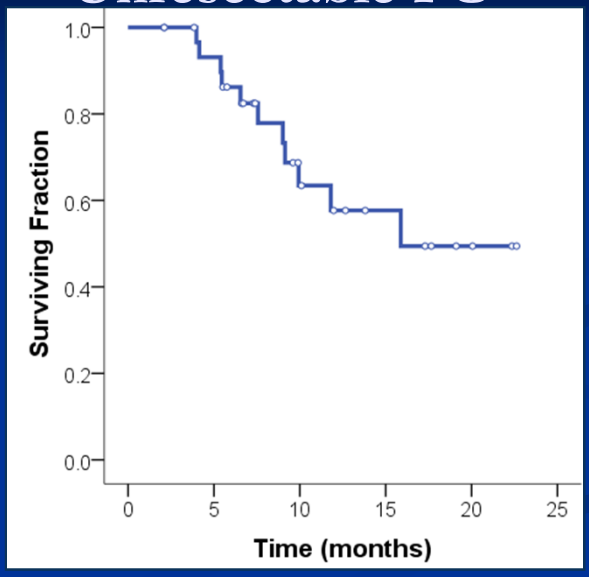
-Patient underwent a Whipple.
-No residual tumor
-Node and margin negative

SBRT Pre/Post Treatment

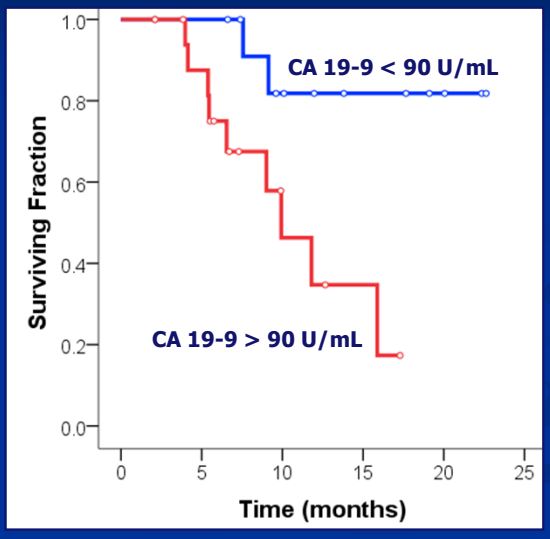
Patient Characteristics

Characteristic	total	
	No.	%
No. of patients	32	
Age, years		
Mean	69.9	
SD	9.8	
Median	68.5	
Range	53 – 88	
Sex		
Male	20	62.5
Female	12	37.5
Race		
Caucasian	28	87.6
African American	1	3.1
Asian	2	6.3
Other	1	3.1
Histologic Grading		
Adenocarcinoma NOS	21	65.6
Well differentiated	4	12.5
Moderately differentiated	4	12.5
Poorly differentiated	3	9.4
Gemcitabine		
Mean doses pre-SBRT	2.2	
SD	1.0	
Mean doses post-SBRT	8.3	
SD	5.6	
CA 19-9		
Mean, pre-SBRT (SD)	425.4	(750.7)
Mean, post-SBRT (SD)	260.3	(616.9)
Mean, last (SD)	894.3	(2586.1)
Median, pre-SBRT (range)	143	(0 – 3191)
Median, post-SBRT (range)	43.9	(0 – 3191)
Median, last (range)	83.8	(0 – 13773)
>=90 at baseline	19	59.4
<90 at baseline	13	40.6

OS Results of SBRT for Unresectable PC



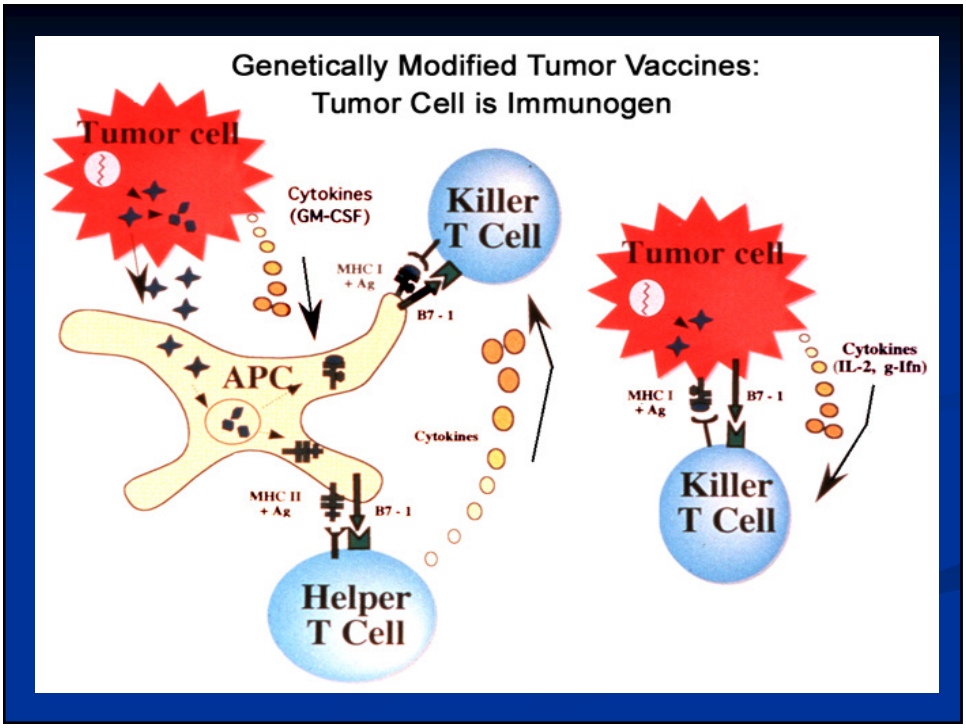
OS Stratified by Baseline CA 19-9 (</> 90)



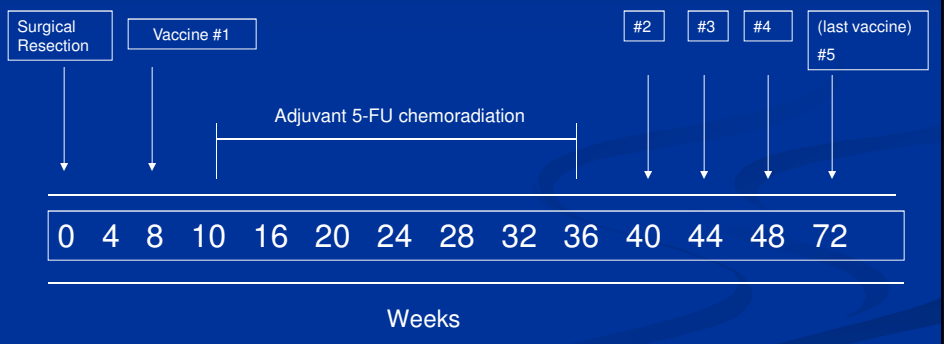
Resected Pancreas Cancer

JHU GM-CSF Pancreatic Vaccine

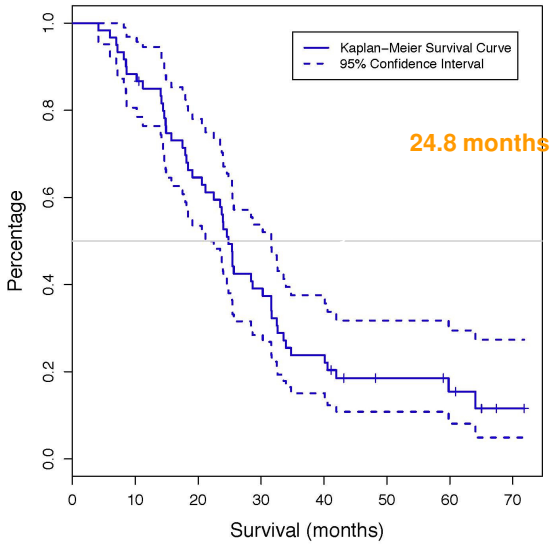
- Two pancreas cell lines have been developed from surgical specimens of subjects undergoing resection at JHH.
- These lines secrete GM-CSF which attract antigen presenting cells (APCs) to the vaccine site which subsequently present antigens to T-cells.
- These lines have undergone extensive regulatory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



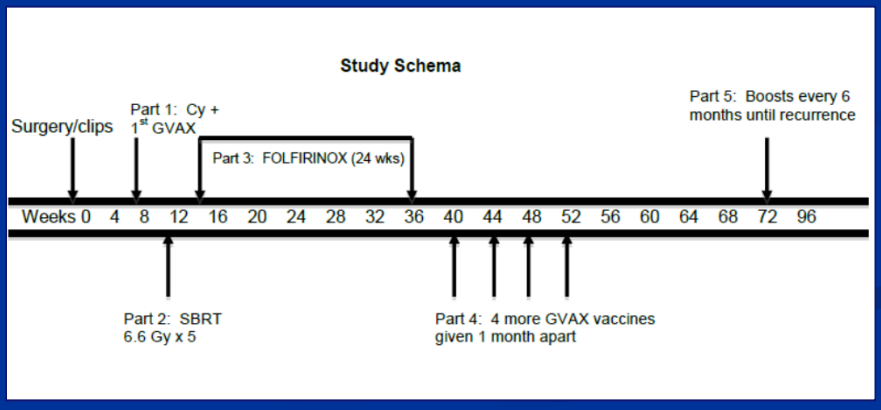
Design of Vaccine Adjuvant Phase II Study



Kaplan-Meier for OS: GVAX Patients



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

• 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

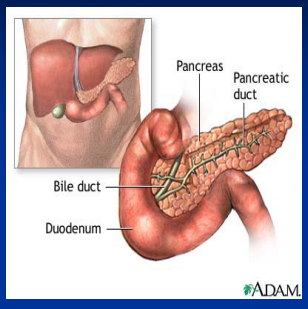
- Phase I/II trial of SBRT in patients with pancreatic cancer recurrence following definitive therapy
- Patients with recurrence after any combination of definitive treatment (chemotherapy +/- surgery, +/- RT) are eligible
- Cohort I (Previous RT): 5Gy x 5
- Cohort II (No previous RT): 6.6Gy x 5

Summary Treatment Options

- Unresectable (locally advanced)
  - Chemotherapy alone
  - Chemotherapy and Radiation Therapy
  - Stereotactic Body Radiation Therapy (SBRT)
- Resectable/borderline (neaodj/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

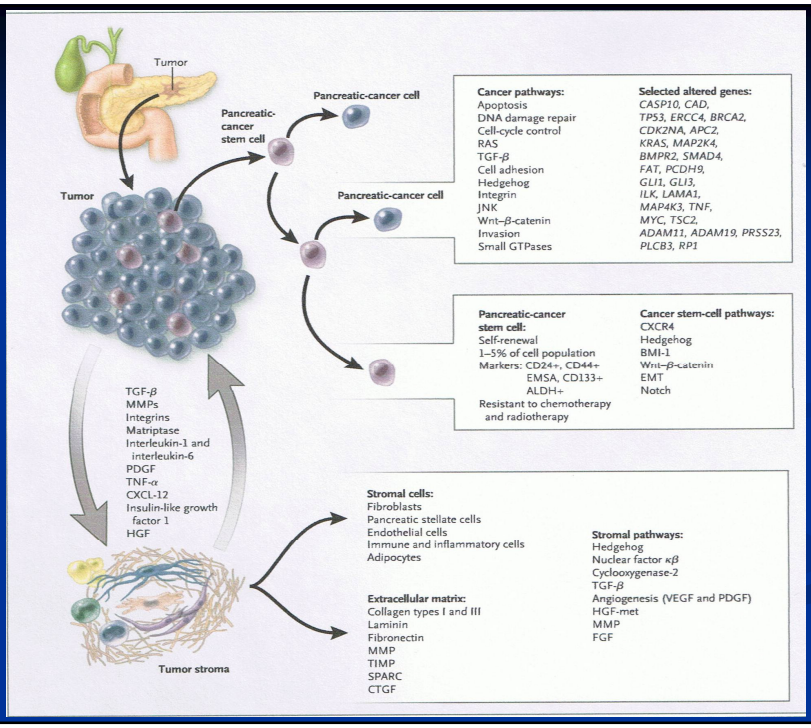
- The tumor suppressor gene SMAD4 (DPC4) encodes for the common intracellular mediator of the TGF-β superfamily pathway which regulates cell proliferation, differentiation, apoptosis, and migration
- In an **autopsy** series of advanced pancreatic cancer, *DPC4* gene status was highly correlated with 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

DPC4 Status and Patterns of Failure

- 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.



JOHNS HOPKINS MEDICINE
THE JOHNS HOPKINS HOSPITAL

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Thank you for your participation

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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.

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