What Advanced Practitioners Need to Know About the Diagnosis and Treatment of Patients With Pancreatic Cancer

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2016 JADPRO Live APSHO

Learning Objectives

1. Summarize available treatments for patients beyond first-line chemotherapy agents for patients with relapsing or refractory pancreatic cancer
2. Describe the signs of serious toxicities associated with agents used to treat pancreatic cancer as they relate to mechanism of action and approaches to managing the toxicities
3. Identify candidates who are considered high-risk for pancreatic cancer and initial screening modalities
4. Discuss recent advances in the treatment of patients with pancreatic cancer that support an interdisciplinary approach to care

Financial Disclosures

- Dr. Herman has acted as a consultant for Oncosil and received royalties from Elekta.
- Ms. Hacker-Prietz has nothing to disclose.

Case

- A 87 y/o male presents with a 3-week history of obstructive jaundice, bilirubin is 9.6
- CT scan shows a pancreatic head mass compressing the bile duct, encases the SMA, tumor is FDG-avid
- He undergoes EUS and ERCP with successful placement of a metal bile duct stent and biopsy is positive for adenocarcinoma

CT Scan

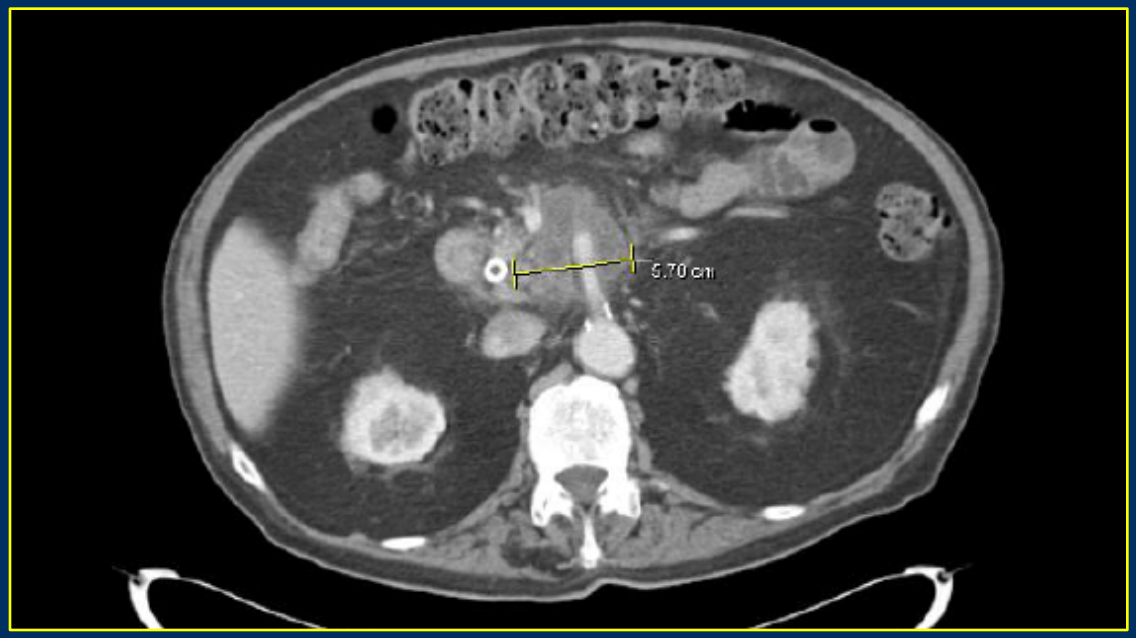


Image courtesy of Dr. Joseph Herman.

Case

Patient presents to our pancreas cancer multidisciplinary clinic to discuss treatment options for his locally advanced, unresectable disease.

Why does pancreas cancer have a poor prognosis?

- Anatomy: proximity to critical vessels
- Biology: early metastatic spread
- Physiology: exocrine insufficiency, cachexia
  - Poor tolerance to treatment
- Treatment resistance
- Delay in diagnosis/treatment (need biomarkers)
- Lack of adherence to evidence based approaches

Pancreatic Adenocarcinoma

- 15-20% have potentially resectable disease
- 49000 new cases and 41000 deaths in 2015
- Margin negative resection (R0) remains the only potential cure
  - Patients with complete, incomplete or margin positive resection (R0 or R1 residual microscopic / R2 residual macroscopic disease respectively) have progressively decreasing survival rates

Accurate staging is crucial to avoid non beneficial surgery. Margin + surgery is associated with similar Px as metastatic.

Khorana AA. JCO 2016
Conlon KC. Ann Surg 1996.

Multidisciplinary Care for Patients with Cancer

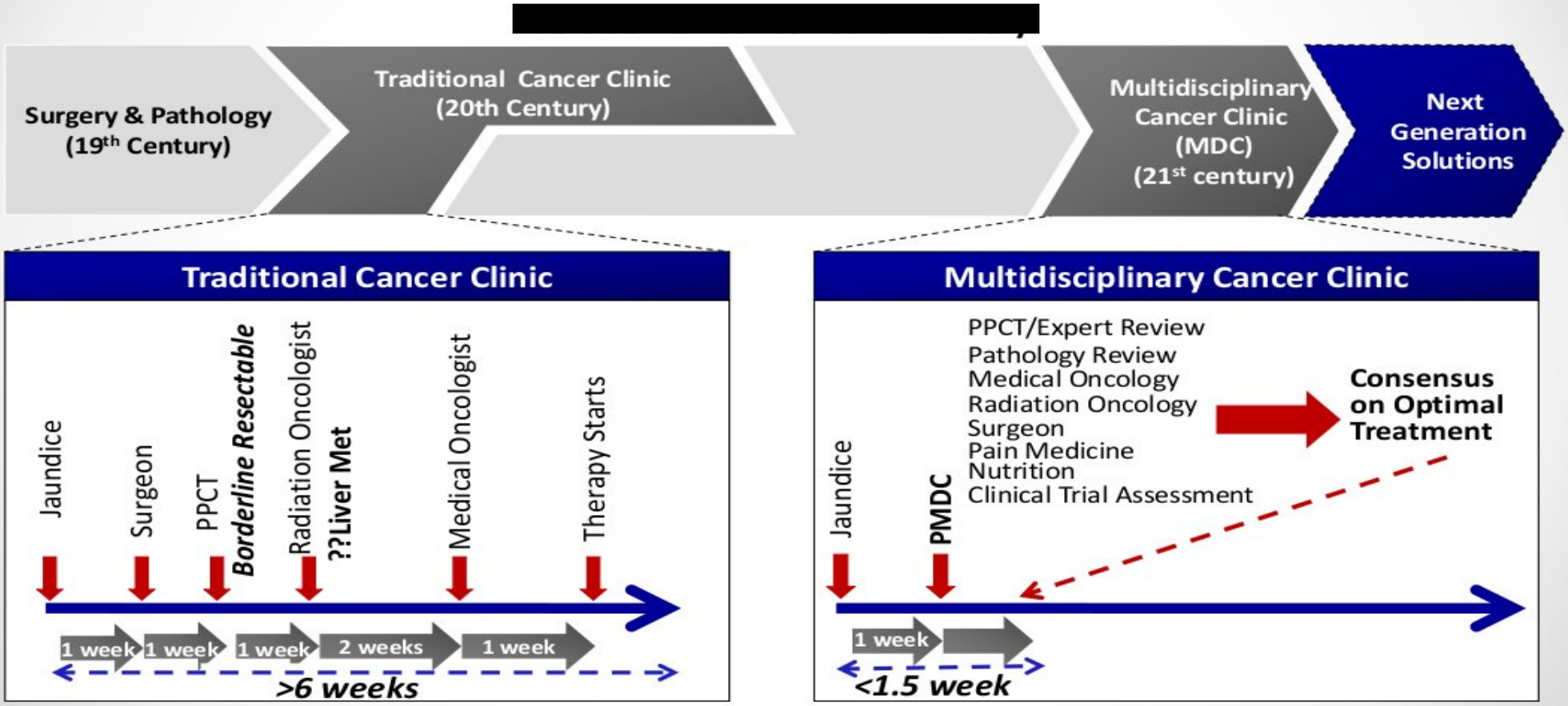
- Multidisciplinary cancer clinics are increasingly more prevalent in management of patients with malignancies

- Potential benefits of multidisciplinary clinics
  - Specialists to work together / consensus recommendations
  - Patient ease / reduction of patient anxiety
  - Increased patient exposure to support services
  - Augment clinical trial enrollment

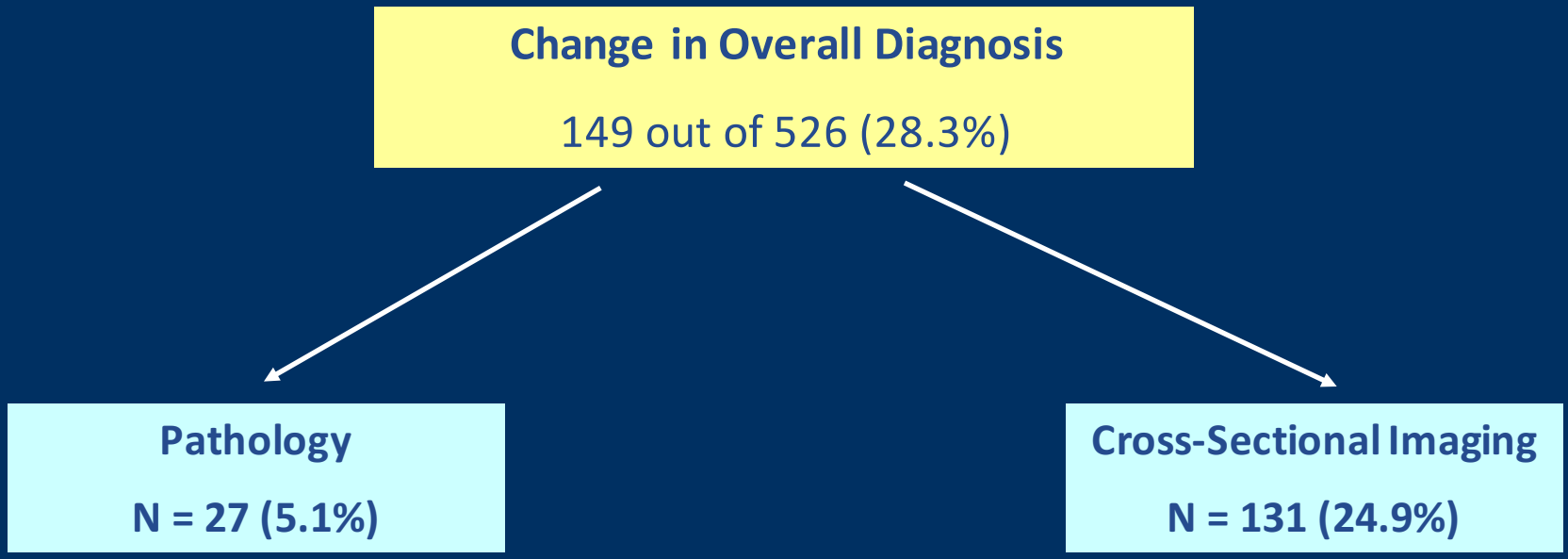
Pancreatic MDC: Case Review

- Present Cases using outline
- Review Pathology
- Review Images CT/PET/MRI/ EUS
- Discuss Case and reach consensus
- See patients and discuss options
- Enroll in trials/studies
- Dictate note and cc to referring physicians

Traditional Clinic vs. PMDC



MDC Impact: Change in Diagnosis

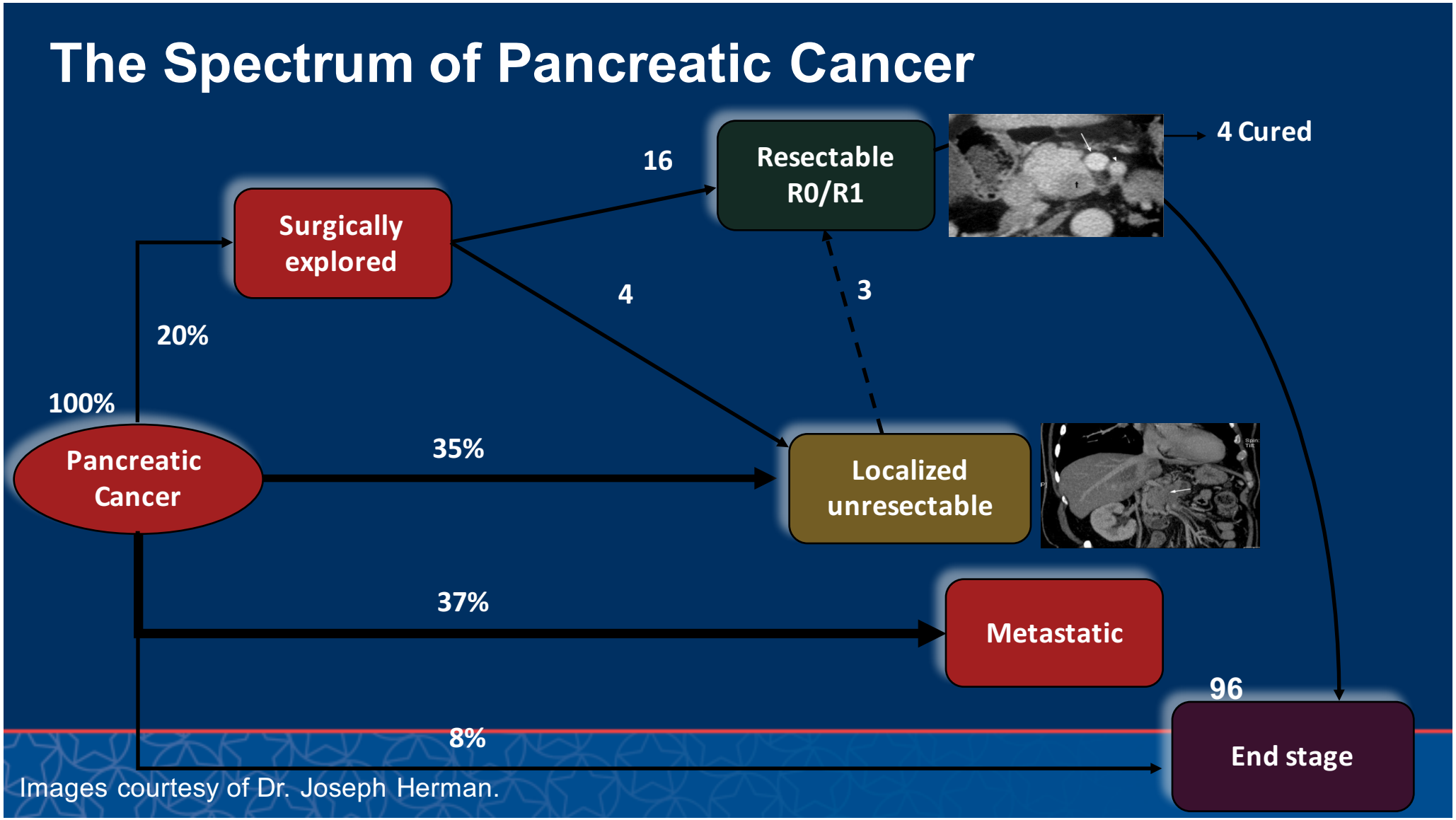


Pancreatic Imaging

- ✓ High quality imaging and accurate [template] reporting is crucial
  - ✓ EUS
    - ✓ More detailed evaluation but limited for determining metastases and full local extent of disease
    - ✓ Added advantage of biopsy and fiducial placement
  - ✓ CT
    - ✓ MDCT, thin slice, biphasic, 3-D (reconstructions), CT angiogram (CTA)
  - ✓ MRI
    - ✓ Used in cases where CT doesn't show a mass (problem solving)
    - ✓ Takes much longer (1 hr+ vs 10 minutes, more operator dependent, less accessible, higher cost)
    - ✓ MRCP—cholangiopancreatography

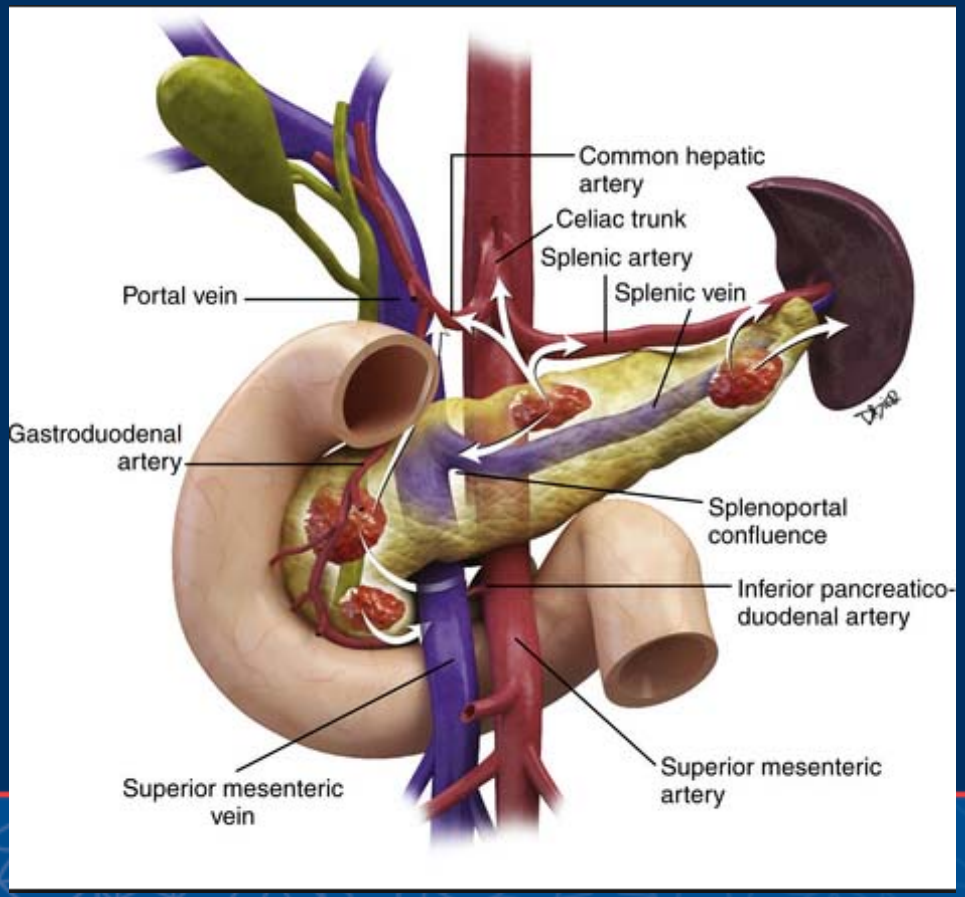
Al-Hawary MM. Radiology Jan 2014 AND Gastroenterology Jan 2014
NCCN 1.2016; www.asco.org/guidelines/PCPC JCO 2016

The Spectrum of Pancreatic Cancer



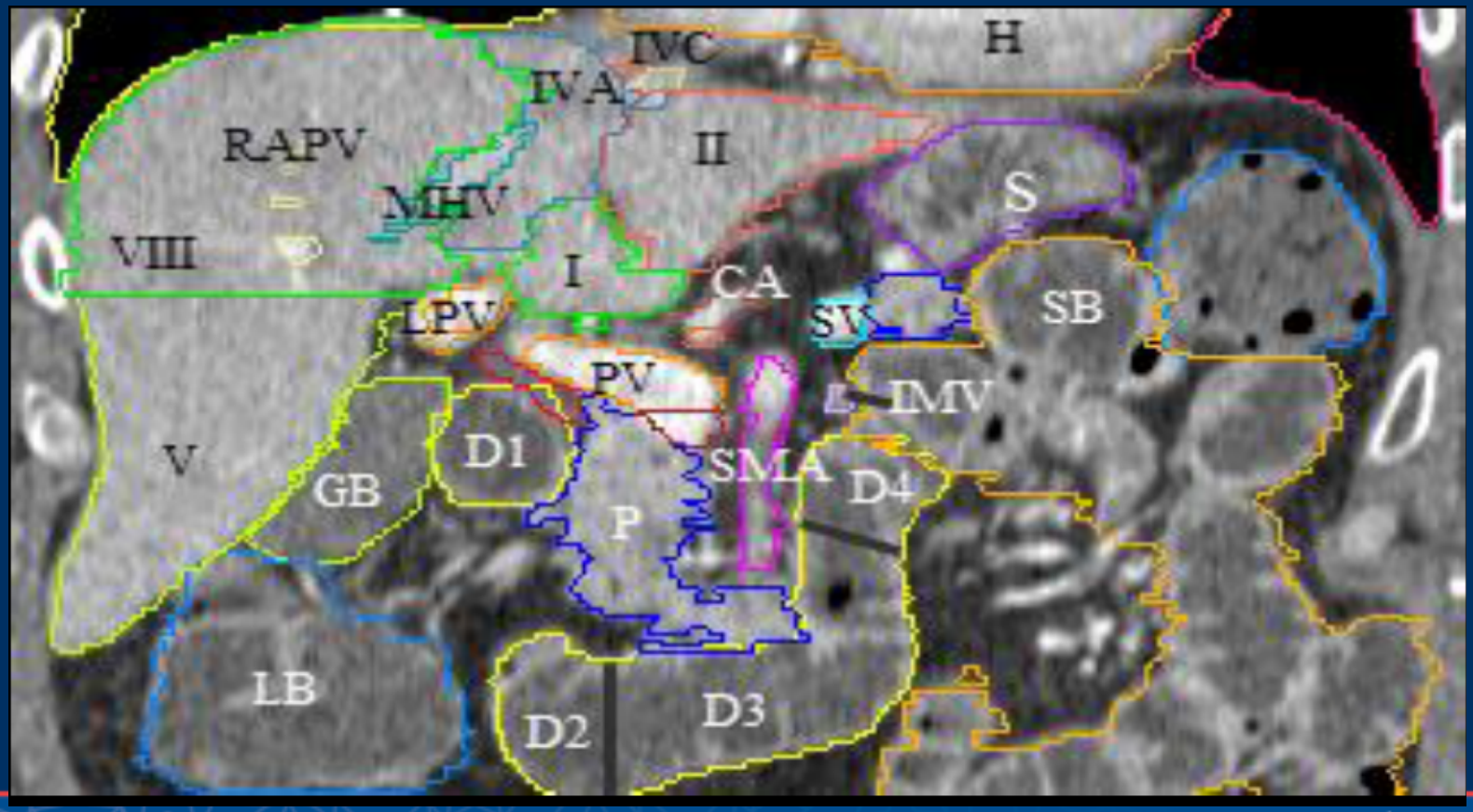
Images courtesy of Dr. Joseph Herman.

Anatomy



- Complex anatomy
- Head/uncinate, body, tail
- Intimate vascular anatomy

GI Atlas


IVC
H
IVA
RAPV
II
MHV
S
VIII
I
CA
SB
LPV
SV
PV
IMV
V
D1
SMA
D4
GB
P
LB
D2
D3

Anatomy (Axial)

- Tumor (T)
- Duodenum (D)
- Small bowel (SB)
- Stomach (S)
- Kidney (K)
- Liver (L)
- Cord (C)

3-D CT Reconstruction

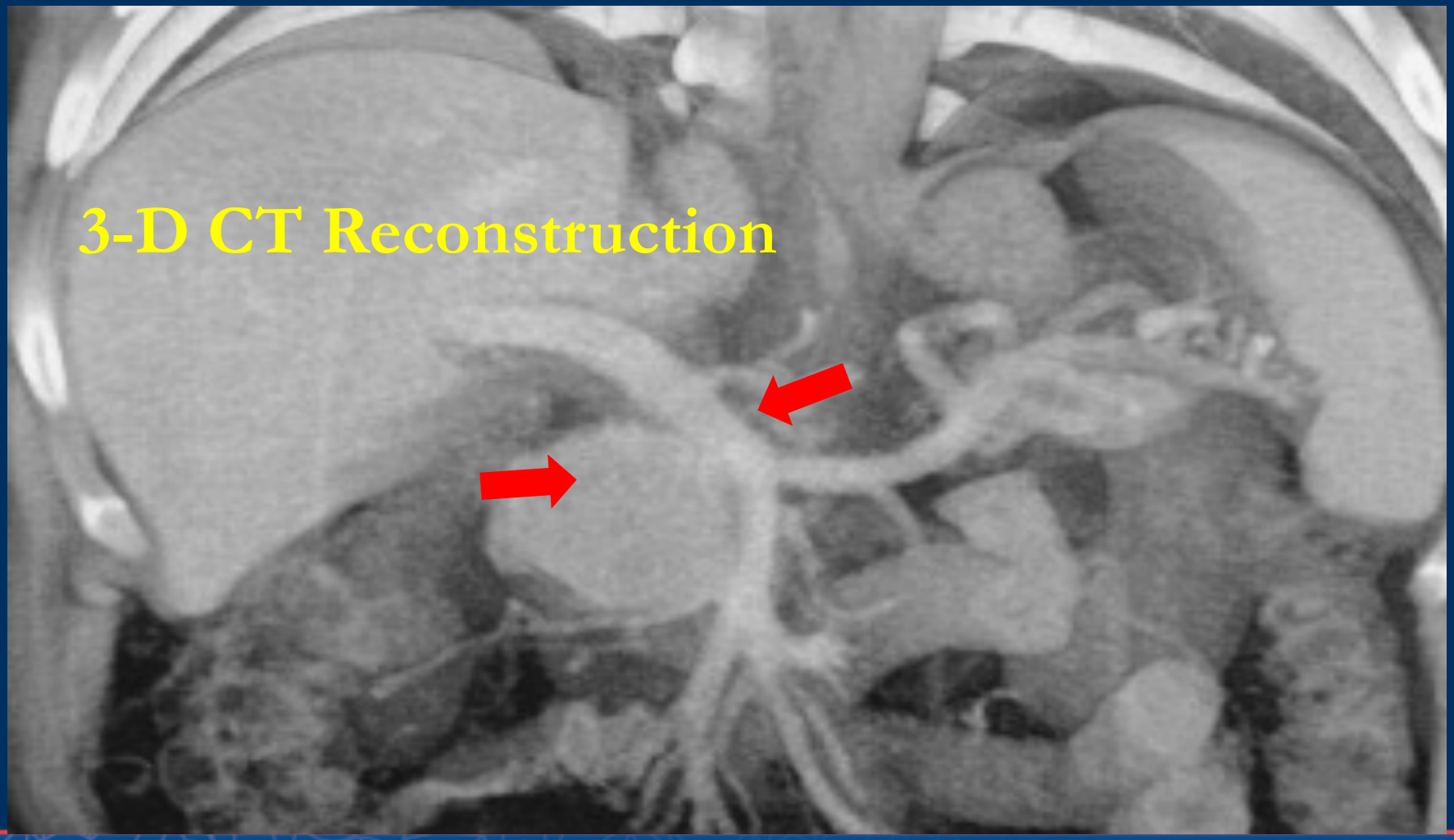


Image courtesy of Dr. Joseph Herman.

CT Angiogram

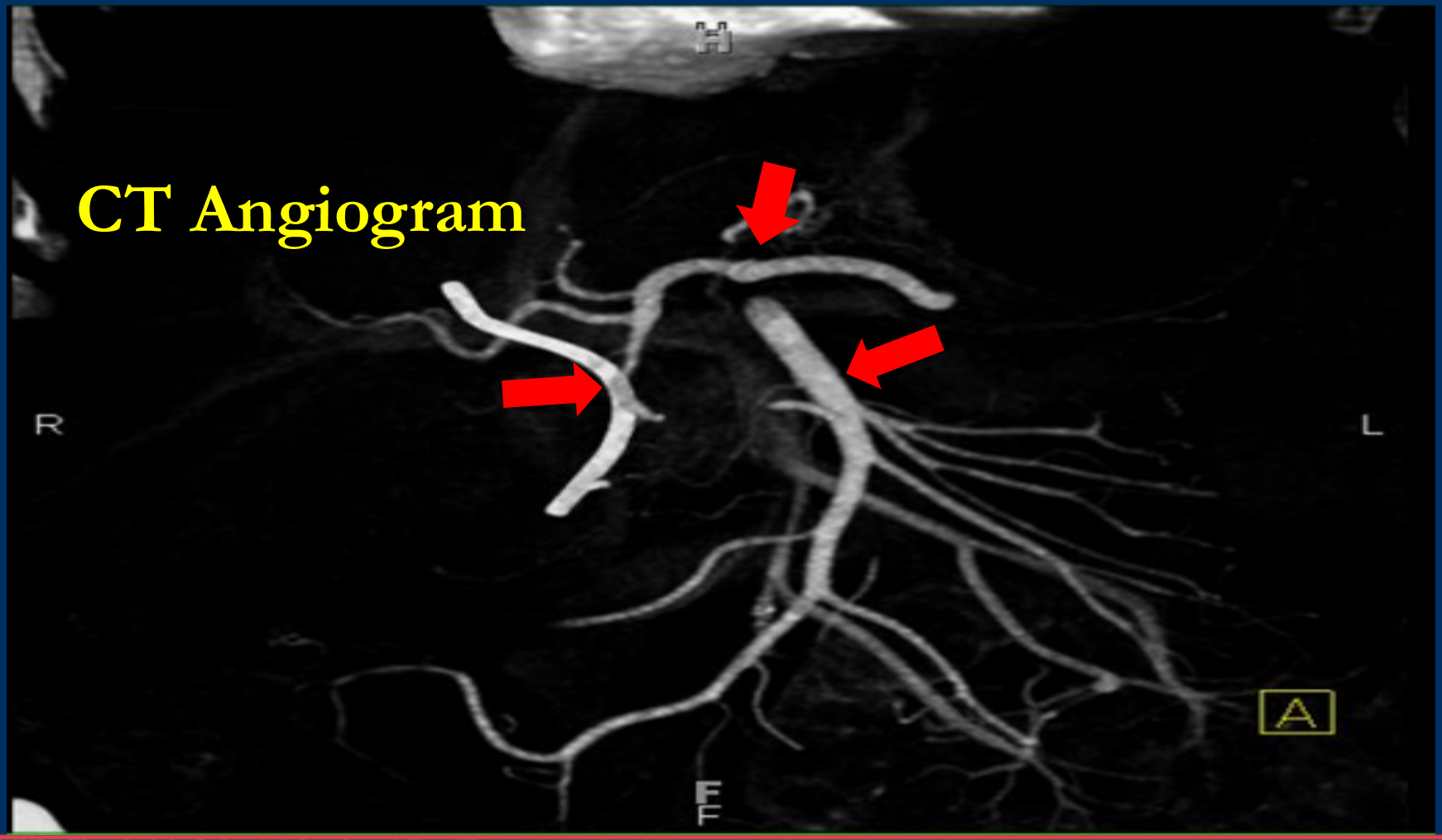
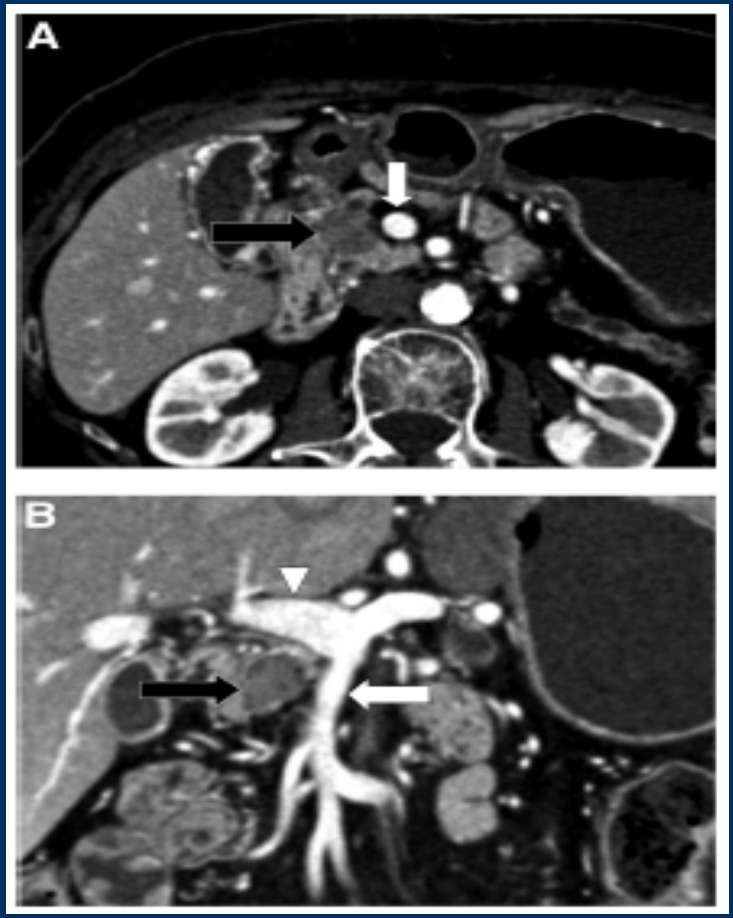
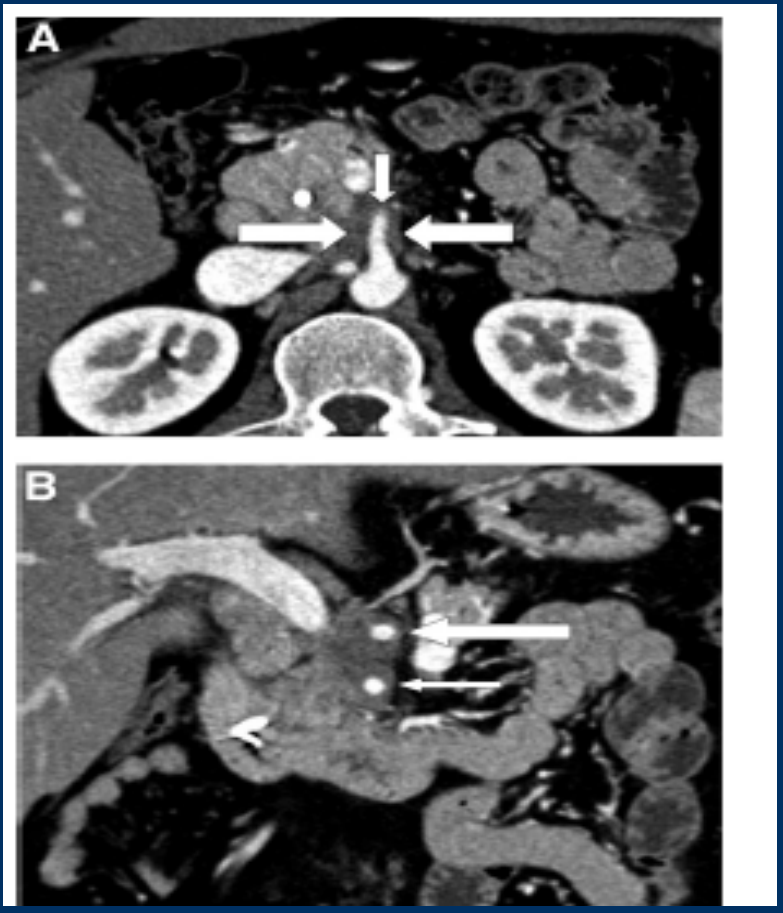


Image courtesy of Dr. Joseph Herman.

Resectable



Unresectable



Images courtesy of Dr. Joseph Herman.

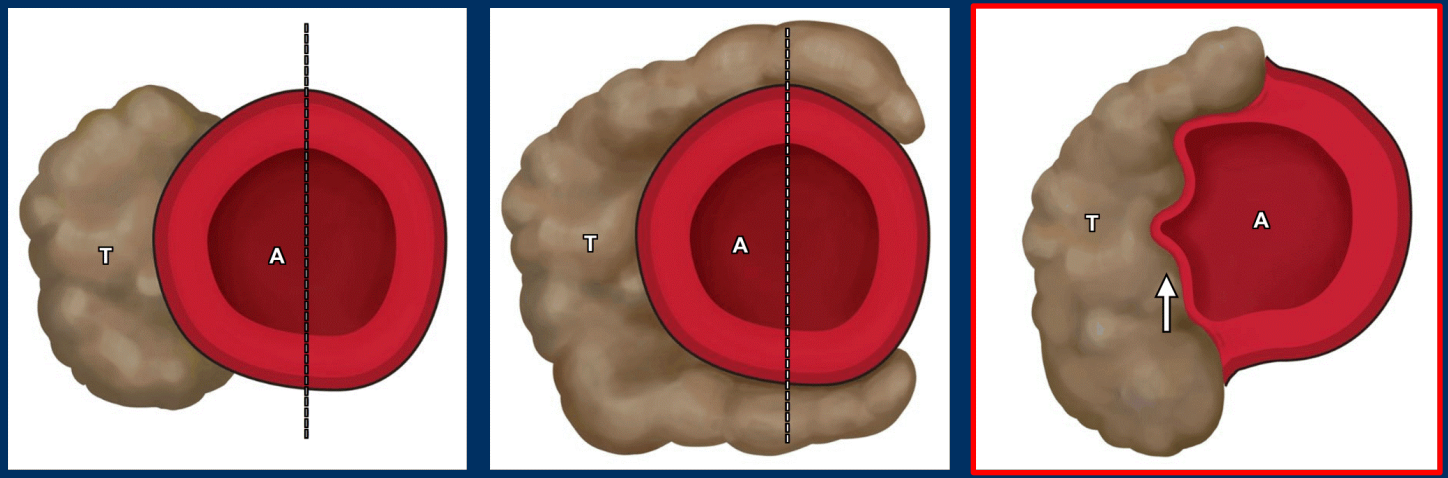
Borderline Resectable

Images courtesy of Dr. Joseph Herman.

Resectability: Arterial contact

Assessment based on:

- degree of tumor contact with the vessel circumference
- whether vessel caliber narrowing or contour deformity is present



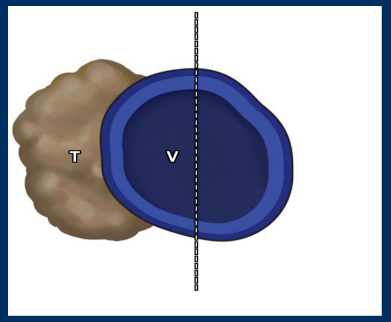
Less than 180

More than 180

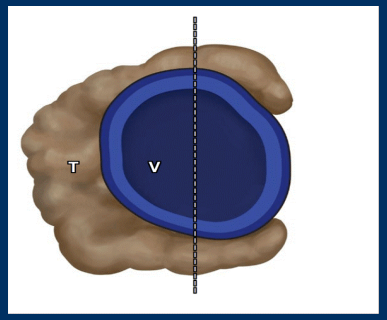
Deformity

Slide(s) courtesy of Dr. Mahmoud Al-Hawary

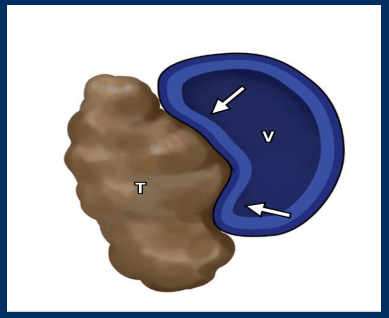
Resectability: Venous Contact



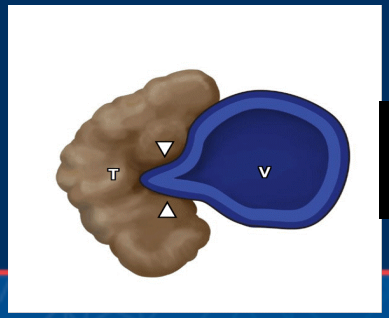
Less than 180



More than 180



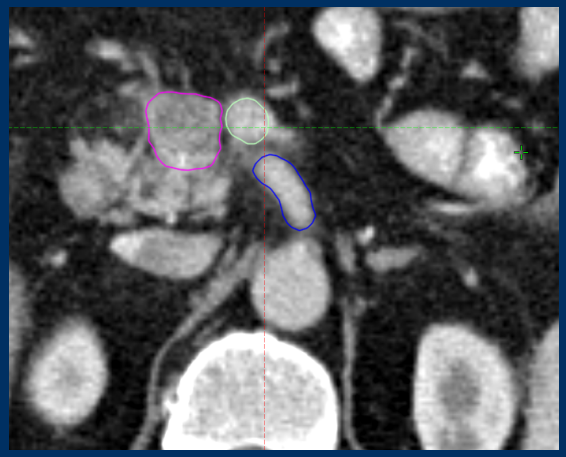
Deformity

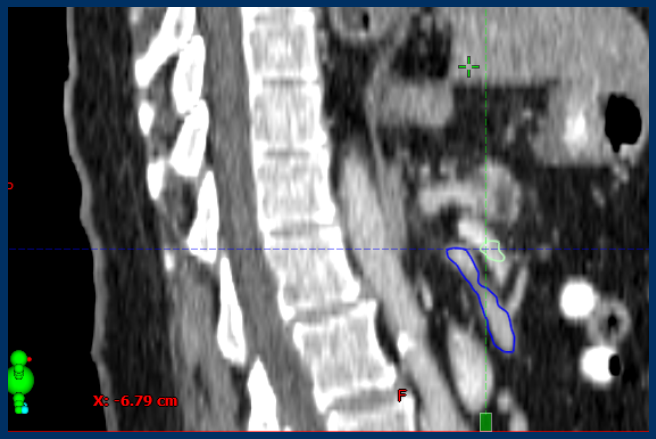


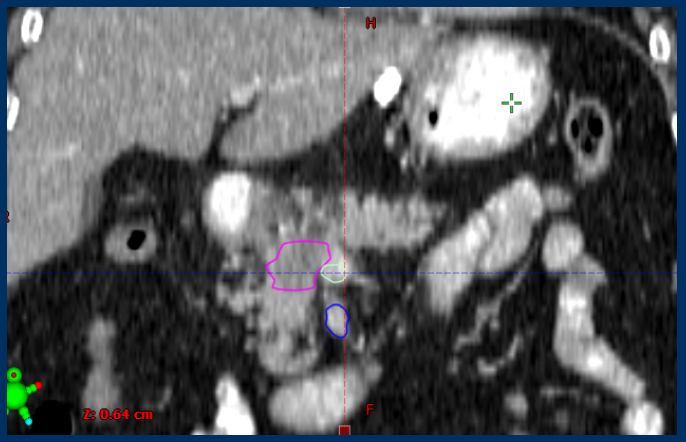
Tear drop Deformity

Slide(s) courtesy of Dr. Mahmoud Al-Hawary

Case with SMV solid contact < 180%







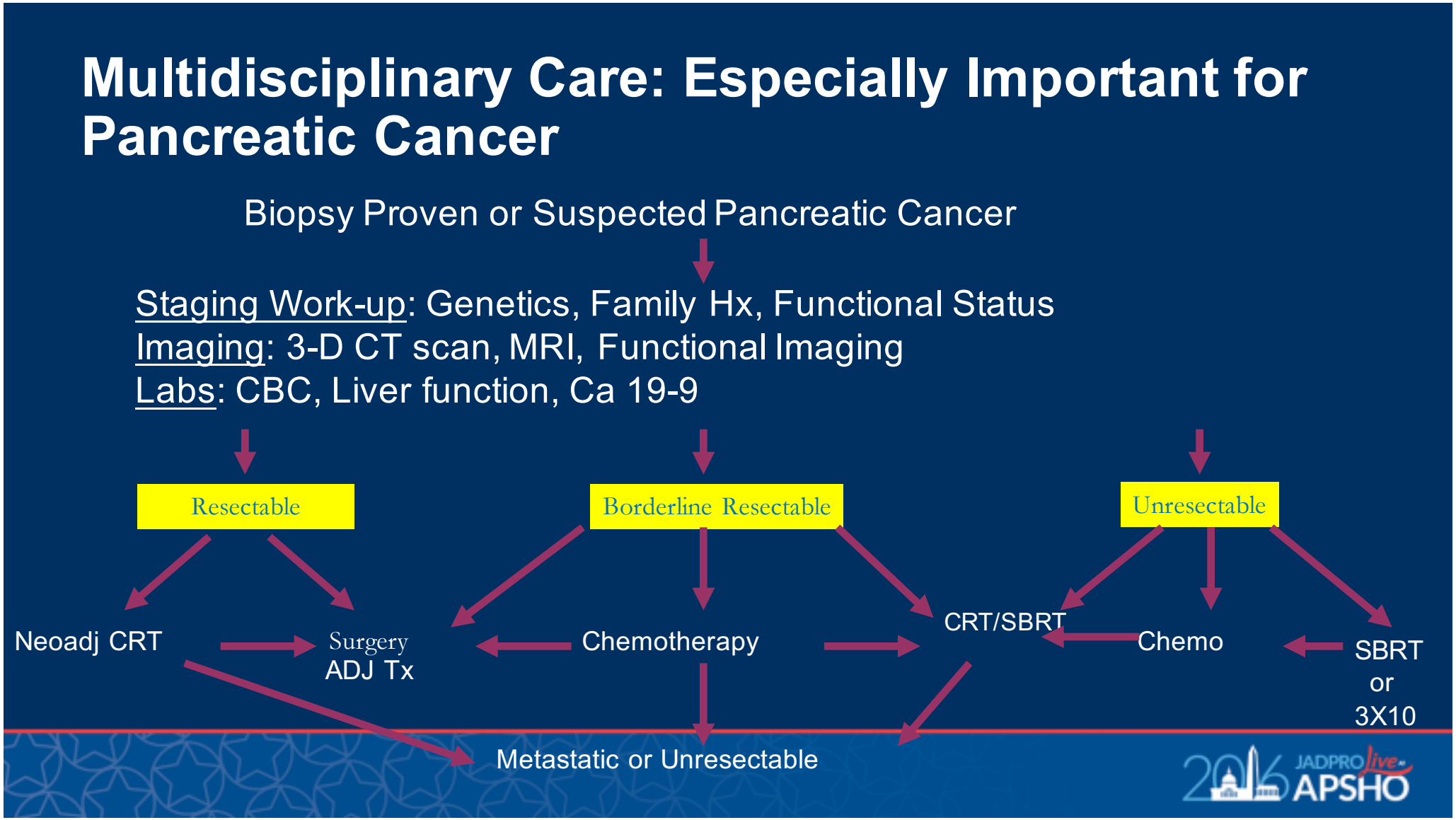
- Tumor
- SMV
- SMA

Images courtesy of Dr. Joseph Herman.

Familial Pancreatic Cancer Genes

Individual	Increased Risk	Age 50	Age 70
No History	1	0.05%	0.5%
Hereditary Non-polyposis Colorectal Cancer	8	1%	3.7%
BRCA2 **(Breast-Ovarian)**	3.5-10	0.5-2%	5%
Familial Atypical Multiple Mole Melanoma (p16)	20-34	1%	10-17%
Familial **Pancreatitis (*PRSS1*)**	50-80	2.5%	25-40%
Peutz-Jeghers (*STK11/LKB1*)	132	6.6%	30-60%

Multidisciplinary Care: Especially Important for Pancreatic Cancer



Timing of 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

Current Approach

What Is the Optimal Chemotherapy Regimen for Pancreatic Cancer?

Chemotherapy:
FOLFIRINOX VS. GEMCITABINE/ NAB-PACLITAXEL
Phase III Trials

	FOLFIRINOX	Gemcitabine/nab-paclitaxel
Sample size	342	861
Locations	France	N America, Eastern + Western Europe, Australia
Eligibility criteria, PS	ECOG 0-1	KPS 70-100
% head / non-head	39% / 61%	43% / 57%
Survival, median (mo)	11.1	8.5
Survival, % at one year	48	35
Toxicity (grade ¾)	Fatigue 23.6% Neutropenia 45.7%	Fatigue 17% Neutropenia 38%
QoL data?	Yes	No

Conroy et al. NEJM 2011

Von Hoff et al. NEJM 2013

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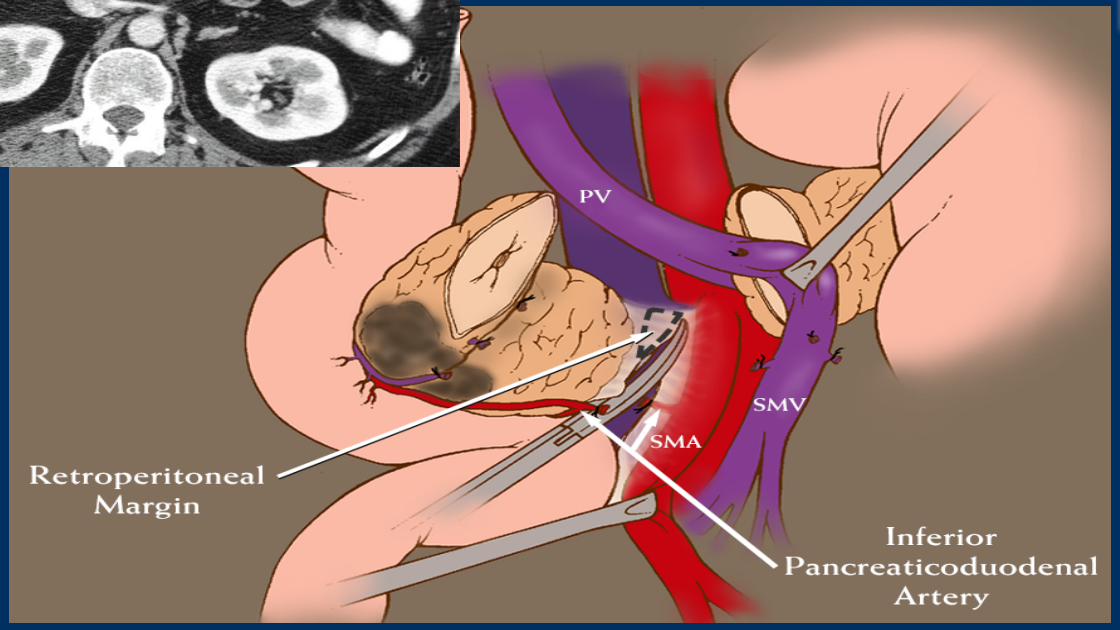
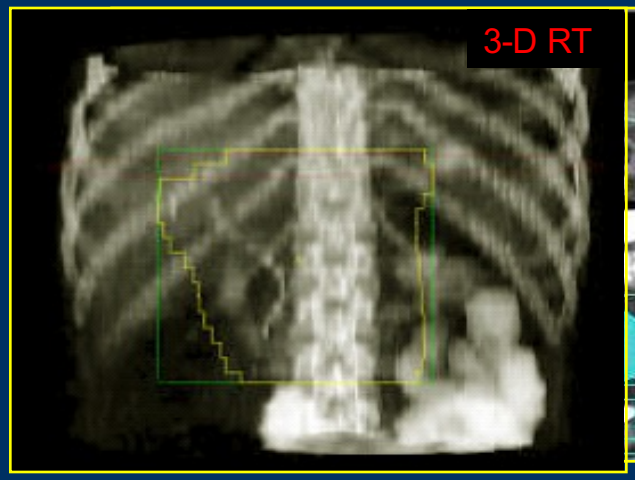
Unique Challenges of Radiation for Pancreatic Cancer

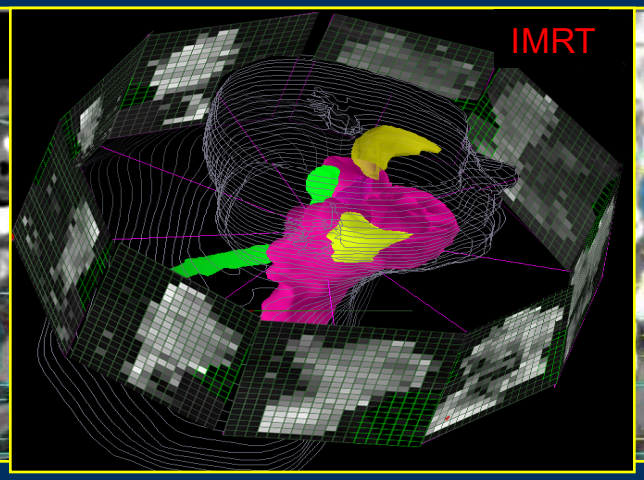


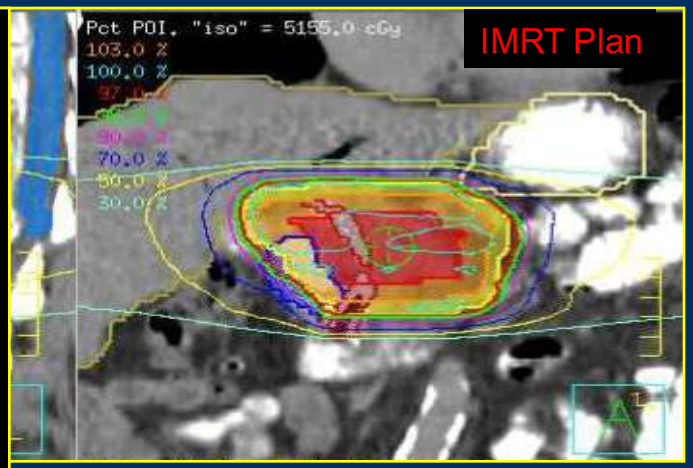
- Proximity of Pancreas to small bowel:
  - RT to bowel can cause ulceration, bleeding, and perforation
  - Risk of late bowel complications increases with higher doses of RT

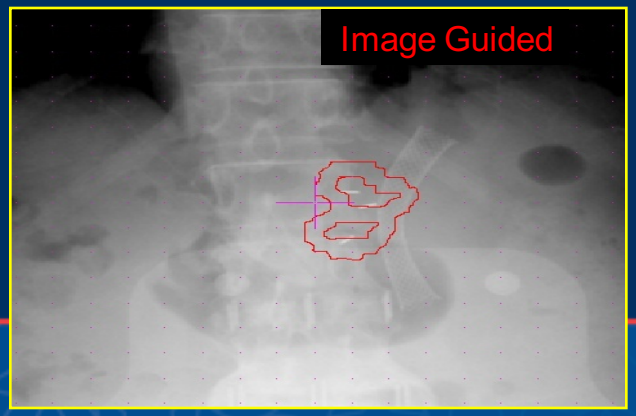
Courtesy N. Merchant

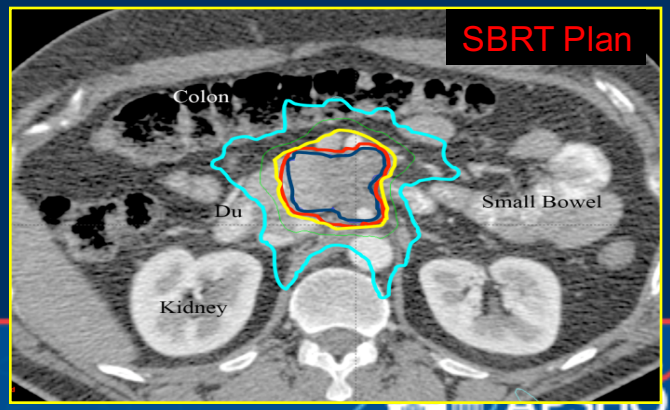
Evolution of Radiation Therapy Delivery



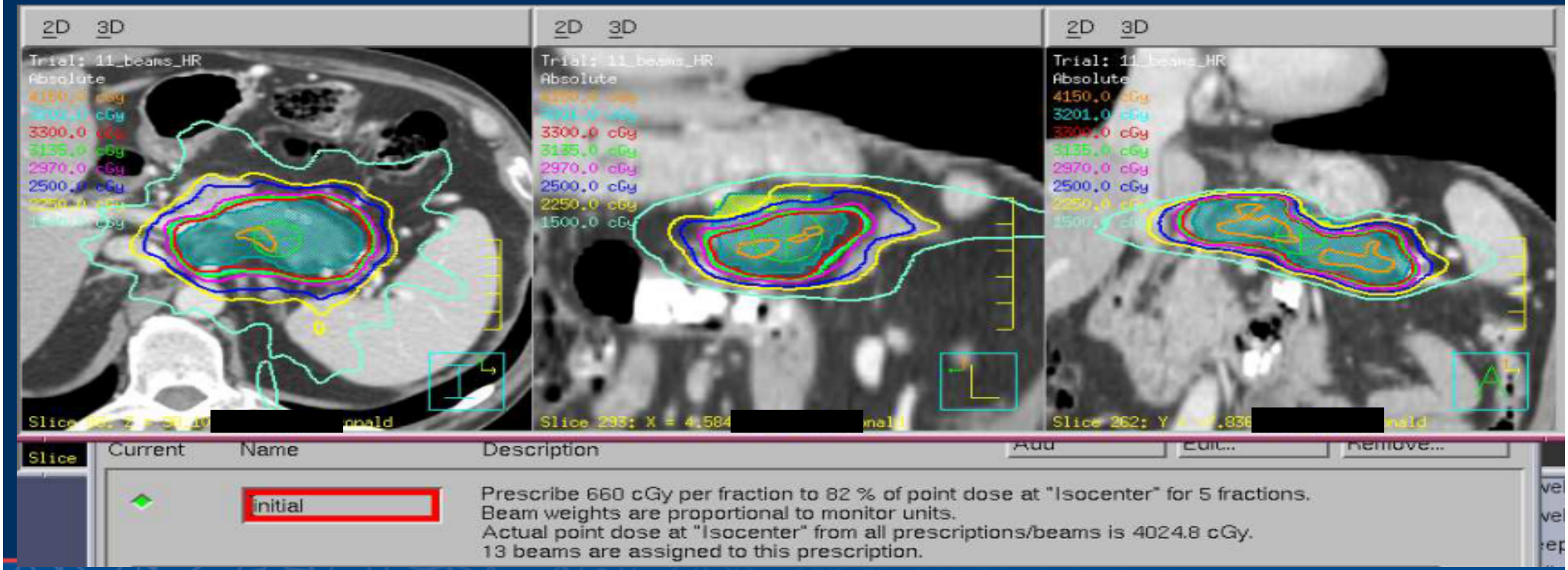








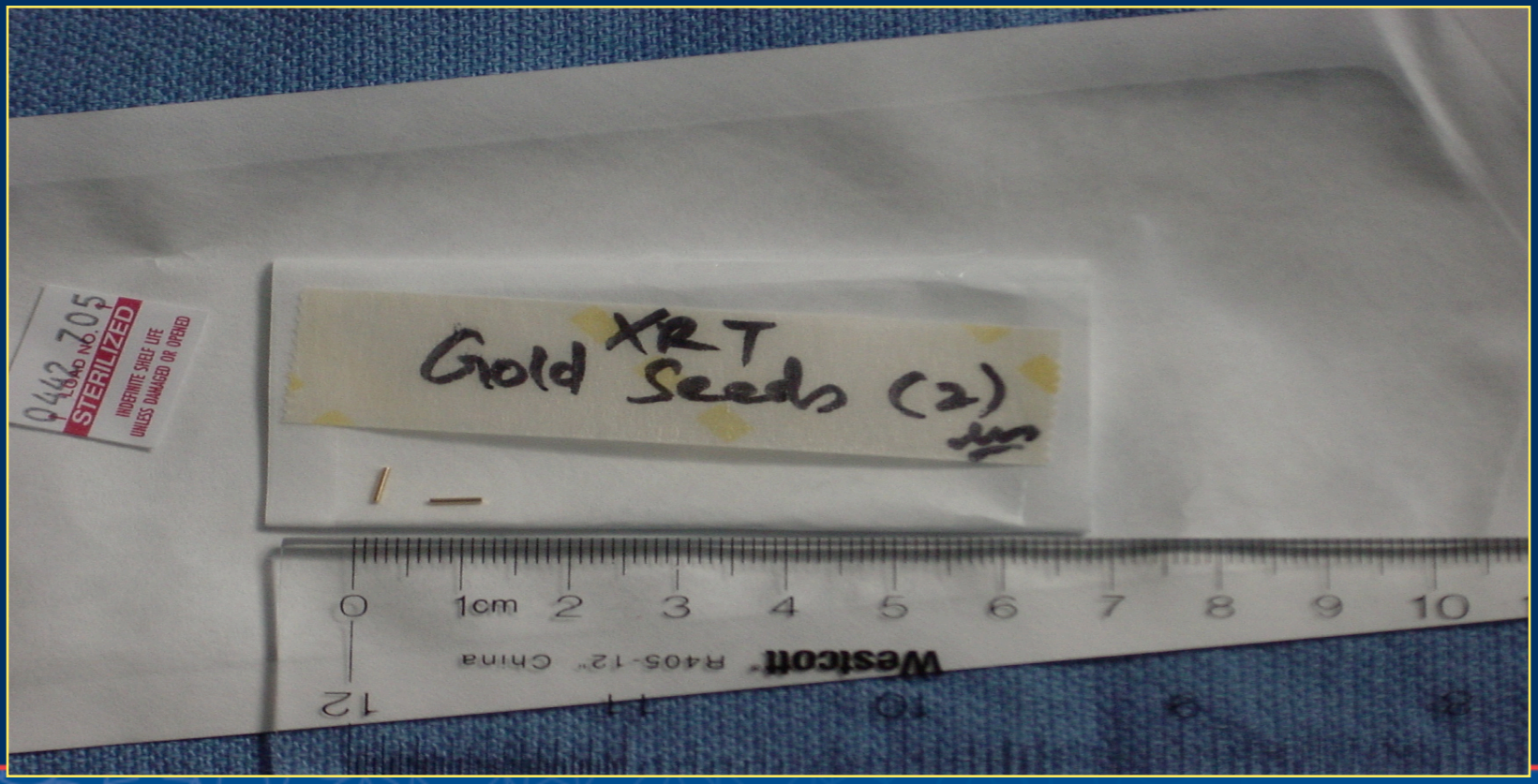
Pancreas Stereotactic Body Radiation Therapy (SBRT)



SBRT Consultation and Patient Selection

- Multidisciplinary review: (3 P's)
  - PPI (for 6 months after SBRT)
  - Pancreatic Enzymes
  - Pain Control
- Avoid SBRT if:
  - *Direct invasion* of duodenum or stomach by EUS
  - Tumor size >8 cm
  - Non-regional LNs
- EUS-fiducials (research biopsy), FNA/Stent

Fiducials


Gold XRT Seeds (2)
STERILIZED
0 1cm 2 3 4 5 6 7 8 9 10
Westcott R405-12" China

4D Simulation

Simulation/Motion Management

Immobilization

Alpha-Cradle and wing board

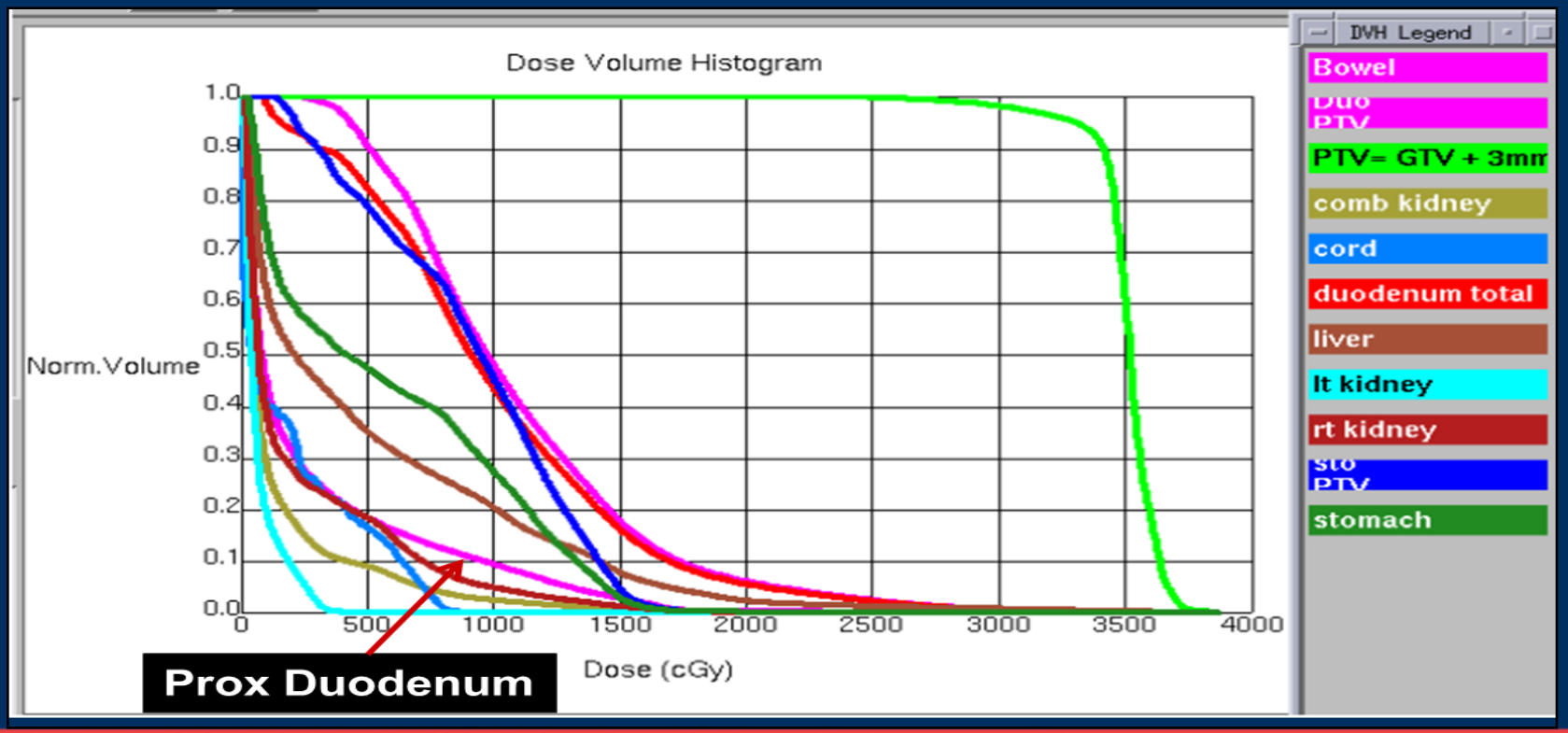
Image courtesy of Dr. Joseph Herman.

Simulation

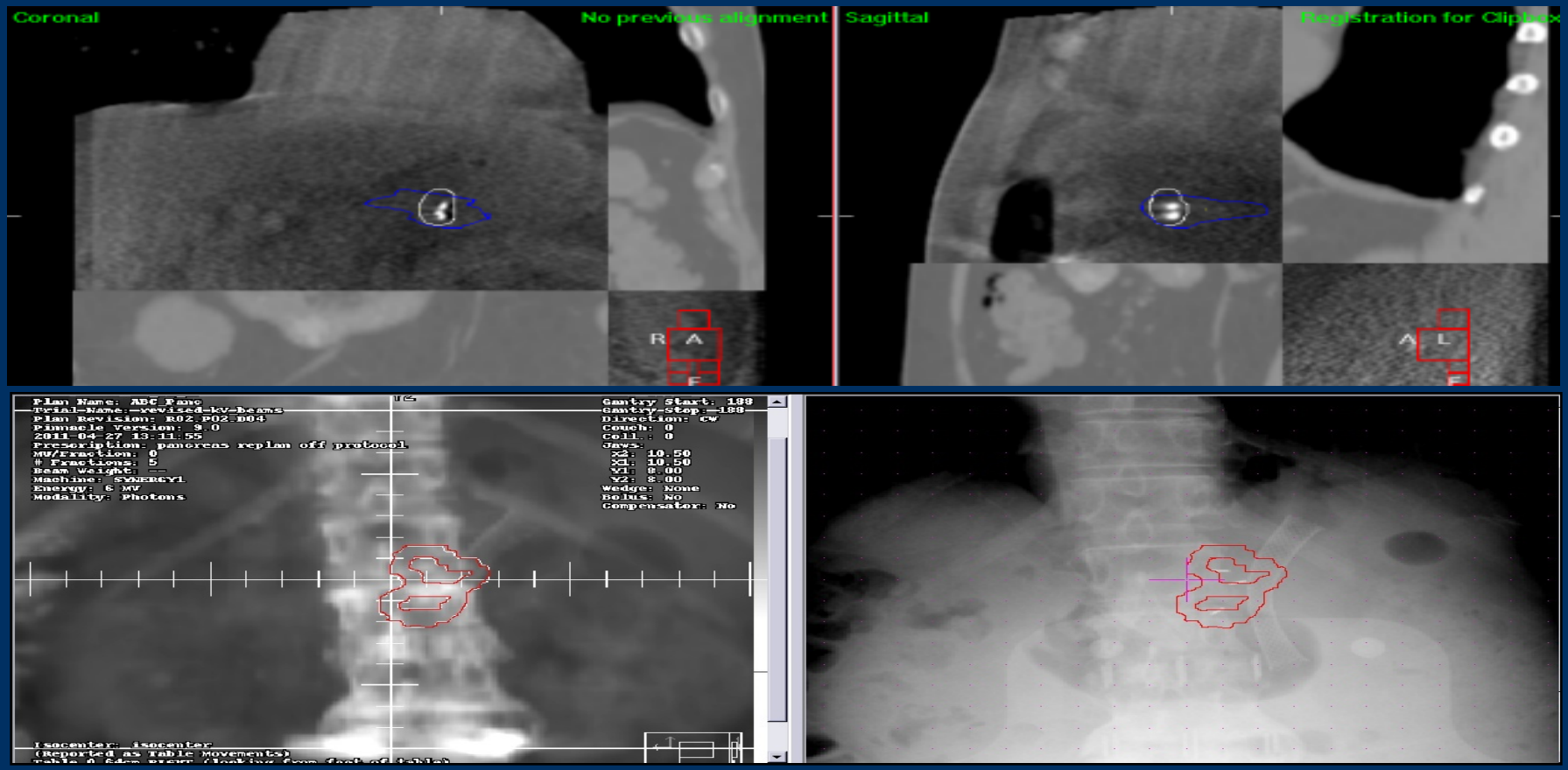
- 2 mm cuts
- IV contrast
- NPO 2 hr prior
- 240 cc oral contrast

- 4-D CT: ABC or gating if >3 mm motion (fiducial or stent)
  - No abdominal compression

SBRT Dose-Volume Histogram



ABC: Breath Hold ABC and KV Images for Fiducial Alignment

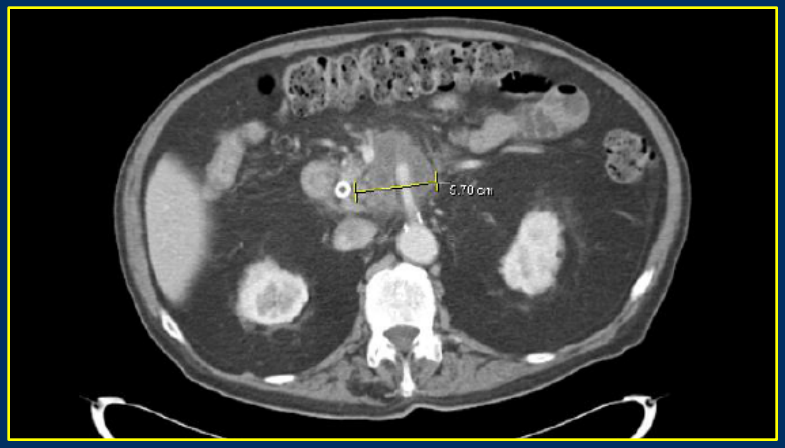


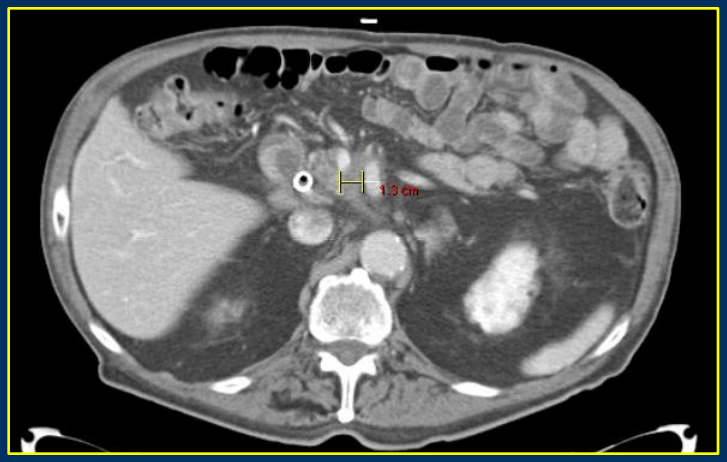
DRR KV

Images courtesy of Dr. Joseph Herman.

Case (cont)

- After gem (1 cycle) and SBRT he continued maintenance gem
- 3 months: PET/CT shows stable disease, but no PET avidity
- 6 months: CT shows 30% response, CA 19-9=36
  - He elects to discontinue gem
- 30 months: CT scan (below)





Pre SBRT

Post SBRT (30 months)

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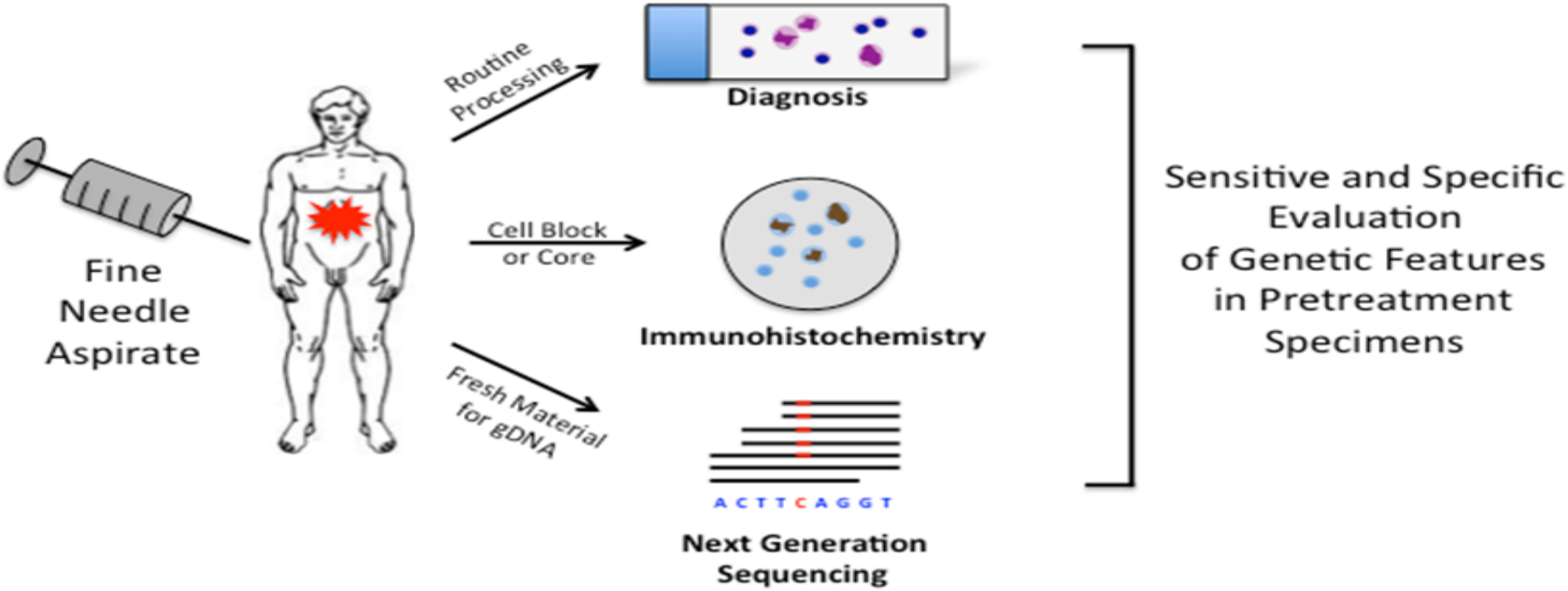
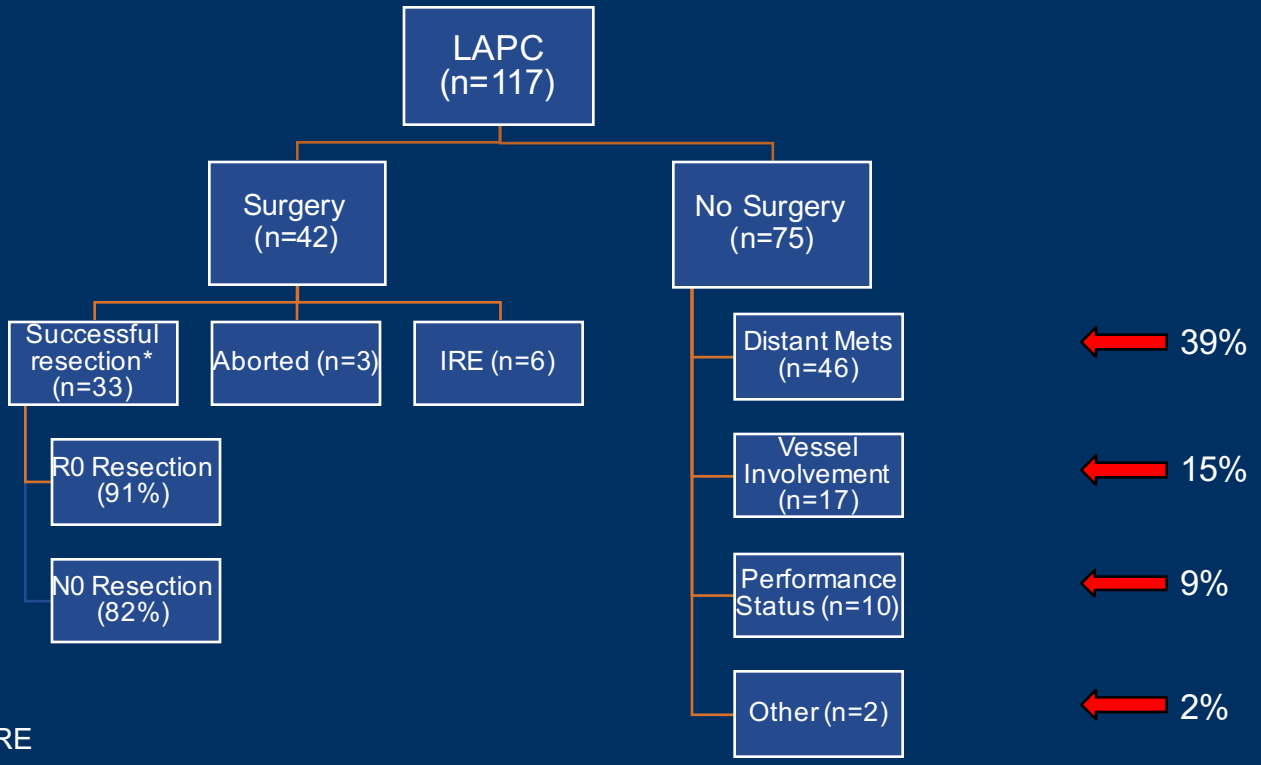
Patient Selection



Results: Surgical Implications

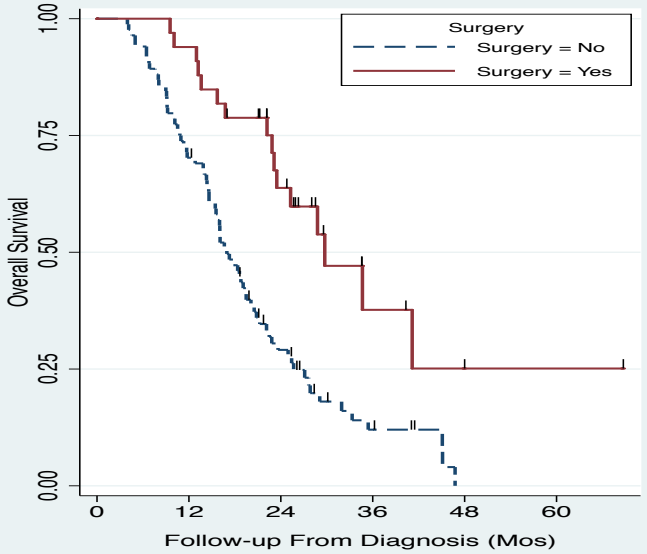


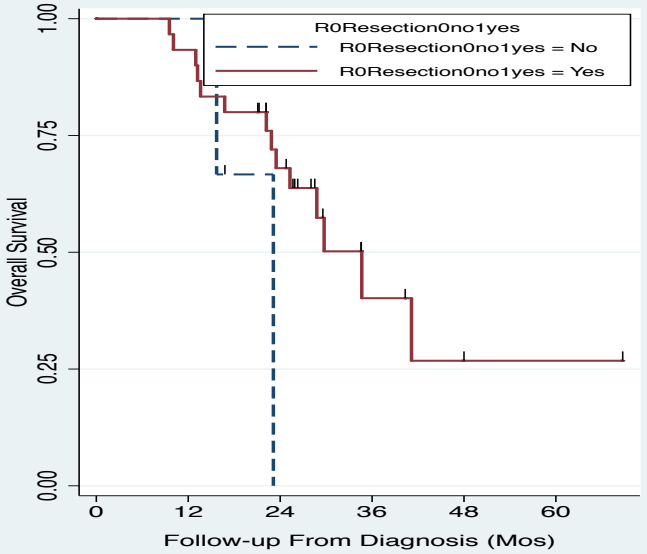
*Three patients went to surgery + IRE

Results: Surgical Implications

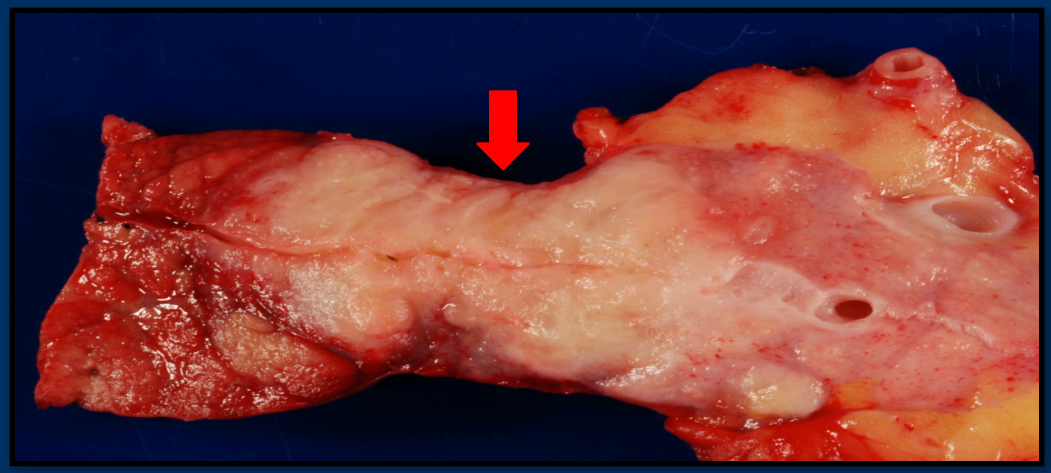
	Surgery	No Surgery	P-value
Age ≥65, % (years)	30%	58%	**0.006**
Male gender, %	55%	51%	0.74
Caucasian race, %	88%	82%	0.45
ECOG ≥2	0%	6%	0.23
Head lesion	49%	62%	0.19
Induction chemo	100%	90%	**0.05**
Multi-agent chemo	85%	66%	**0.04**
FOLFIRINOX-based chemo	64%	30%	**0.001**
Chemo ≥4 months	58%	30%	**<0.0001**
33 Gy SBRT dose	94%	76%	**0.03**

Results: Surgical Resection and Overall Survival



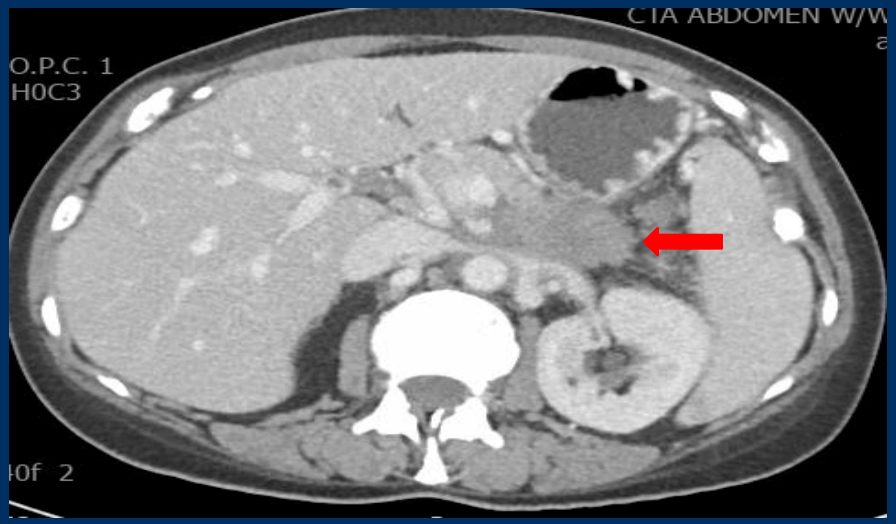


	Median OS (mos)	P-value
Surgery vs. no surgery	29.7 vs. 17.0	**0.0001**
R0 resection vs. R1/R2 resection	34.7 vs. 23.1	0.170



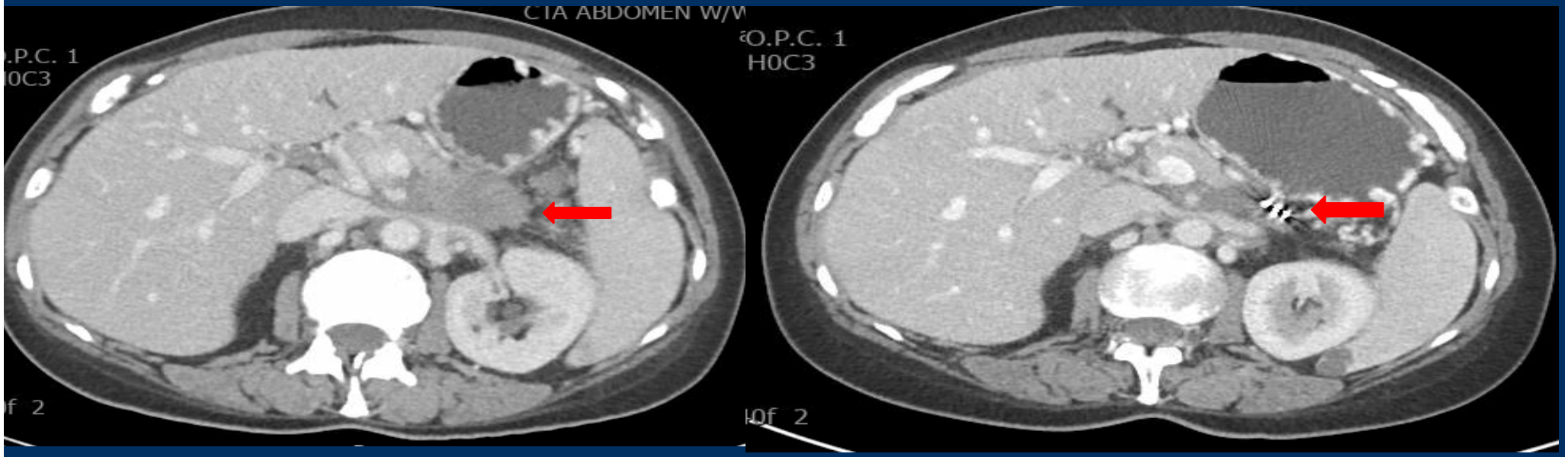
What are the pathologic outcomes when patients receive **multi-agent chemotherapy** +/- Radiation in patients with BRPC or LAPC?

Chemo → SBRT → Surgery



Images courtesy of Dr. Joseph Herman.

Chemo → ? → Surgery



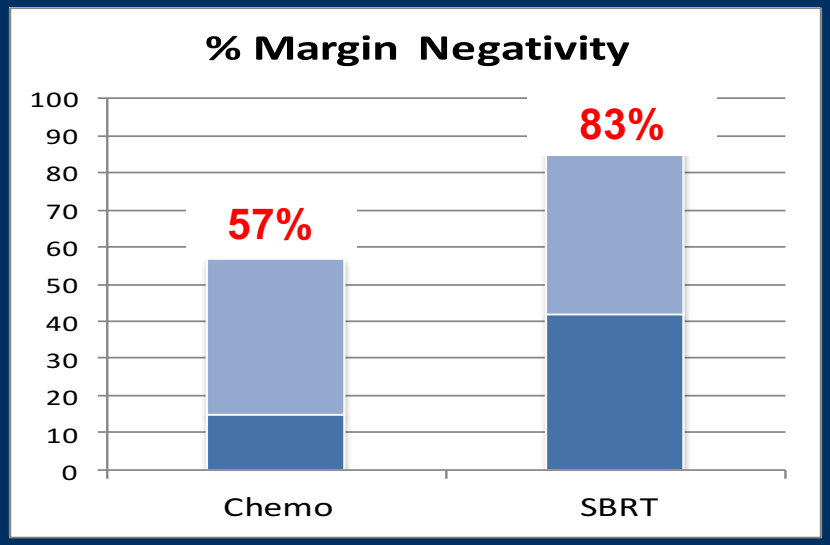
Images courtesy of Dr. Joseph Herman.

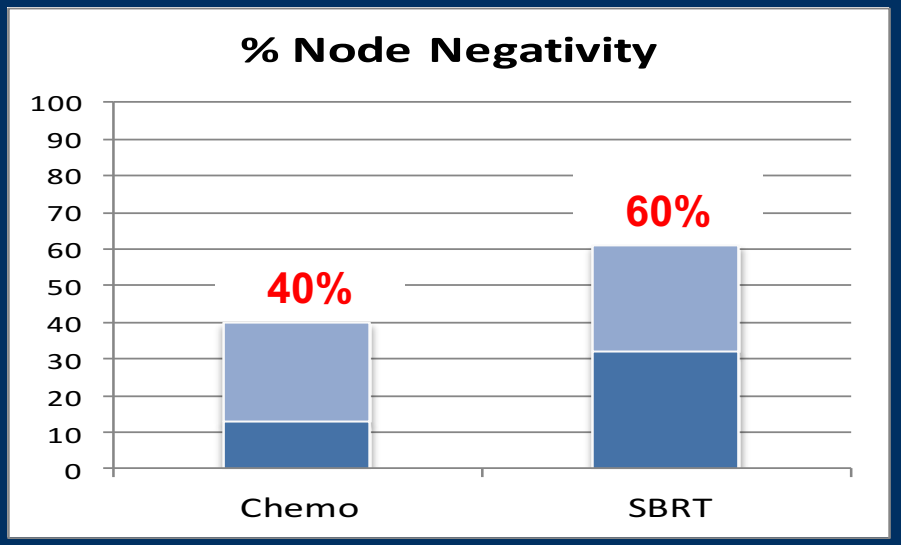
Hopkins: Neoadjuvant Chemo vs. Chemo + SBRT (N = 177)

- 2008 – 2016: Median follow-up 17.0 mo

Characteristic	Chemo group, n (%)	Chemo/SBRT group, n (%)
No. patients	67	110
Age ≥65	29 (43%)	45 (41%)
Male gender	39 (58%)	56 (51%)
Caucasian race	60 (90%)	98 (89%)
Head of pancreas lesion	50 (75%)	77 (70%)
Locally advanced disease	16 (24%)	56 (51%)
FOLFIRINOX-based chemotherapy	34 (51%)	79 (72%)
Chemotherapy duration ≥4 months	20 (30%)	63 (57%)

Hopkins: Neoadjuvant Chemo vs. Chemo + SBRT (N=177)





	Borderline		*Locally Advanced*	
	Chemo	**SBRT**	**Chemo**	**SBRT**
R0	62%	81%	63%	84%

	Borderline		*Locally advanced*	
	Chemo	**SBRT**	**Chemo**	**SBRT**
N0	42%	52%	50%	68%

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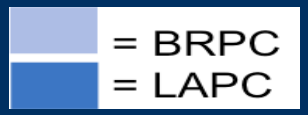
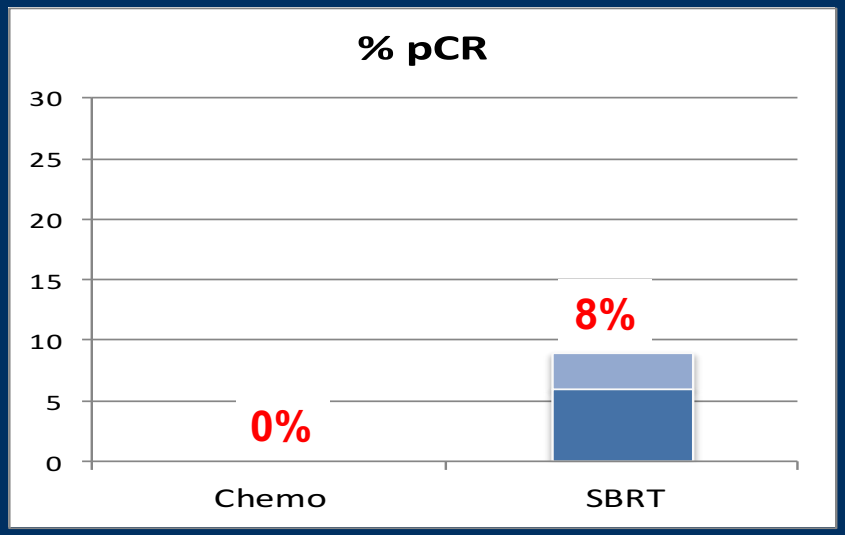
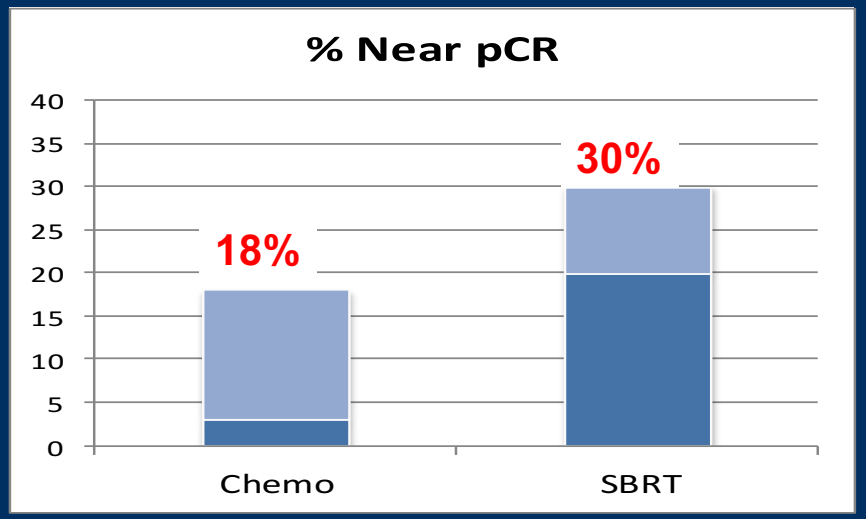
Pathologic Complete Response or Near Pathologic Complete Response

- Pathologic complete response (pCR)
  - No residual tumor can be identified or measured
- Near pCR
  - Scattered microscopic foci of single cells or groups of single cells
  - Typically within a dense area of fibrosis
  - Demonstrating marked treatment effect

Hopkins: Neoadjuvant Chemo vs. Chemo + SBRT (N=177)



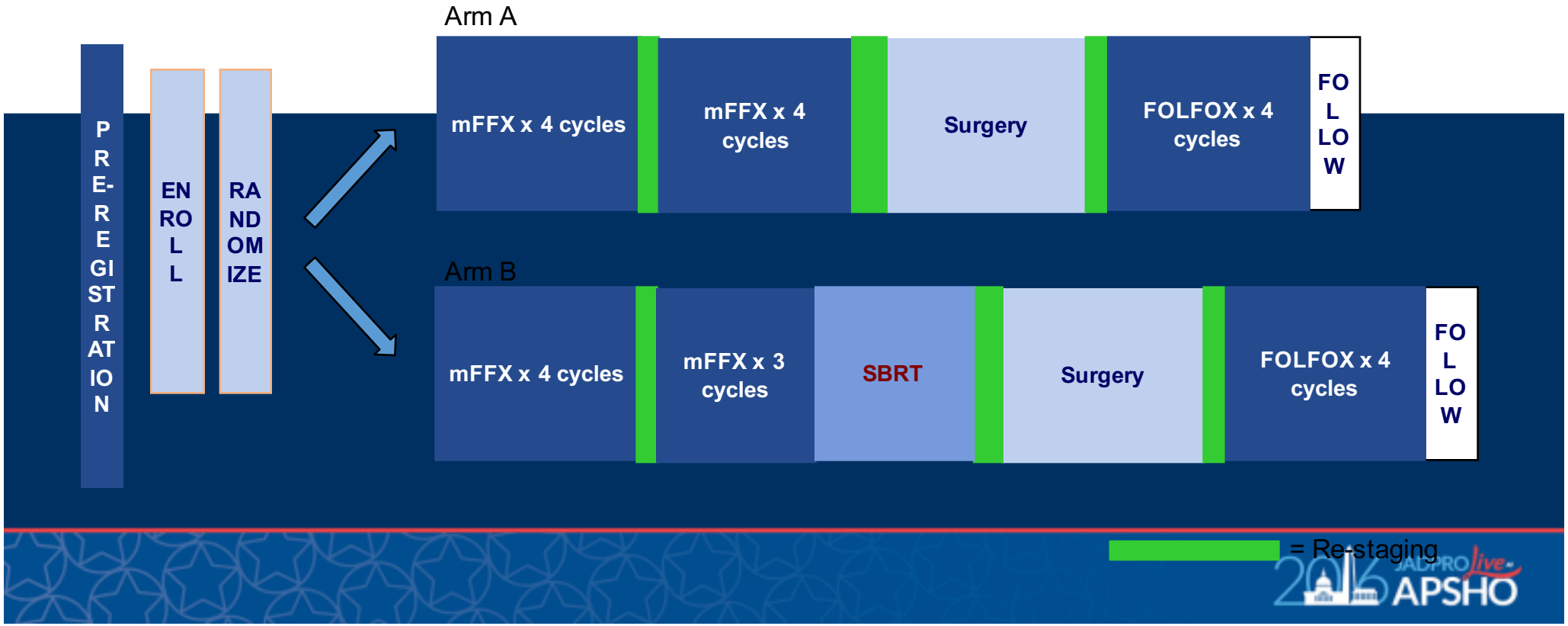




	Borderline		Locally Advanced	
	Chemo	SBRT	Chemo	SBRT
pCR	0%	6%	0%	12%

	Borderline		Locally Advanced	
	Chemo	SBRT	Chemo	SBRT
npCR	21%	20%	13%	39%

Proposed Alliance A021501: Preoperative Extended Chemotherapy vs. Chemotherapy Plus Hypofractionated Radiation Therapy for BRPC of the Head of the Pancreas



Conclusion

- Pancreas cancer has a poor survival and is the 3rd leading cause of cancer death
- CT staging is important to determine resectability
- Multiagent chemotherapy improves survival
- SBRT improves surgical outcomes, Alliance trial will formally test role

2015 Census

- 333,000
  - Advanced practitioners
- 2.3%
  - Oncology
- 1189
  - Physician assistants in oncology
- 217
  - Physician assistants in radiation oncology

NCCPA, 2015; AANP, 2015.

Need for Advanced Practitioners (APs)

- Increasing patient population in oncology and advancing technologies in radiation oncology and systemic treatment
  - Acute symptom management
  - Perform procedures
  - Reimbursable, 85-100%
  - Independent
  - Prescriptive authority
- 1997 ASTRO Joint Committee on Advanced Practice Nursing Roles
  - Educational information on implementing APs

J Oncol Pract; 2005 Sep; 1(3): 93–94; Int J Radiat Oncol Biol Phys. 1999 Sep 1;45(2):255-63.

Job Description

-History, physical exams, assessment/plans of new patient consults and follow ups, coordination of care, clinical documentation;

-Independent follow-up clinic

-consults by direct referral/non-urgent inpt consults-split w/resident

-Review of radiology imaging, labs, and other diagnostic procedures;

-Consenting patients for treatments;

-Signing of EPIC orders/medications

-coordinating SBRT patient setup & orders

-Attendance/H&Ps/presentation/coordination of care of PMDC patients

-Assisting with OTVs and acute clinic issues;

-Assisting with IORT cases-assessment & setup of equipment, documentation; consent

-Assisting with brachytherapy, including simulation, planning and setup of devices/equipment, plans, and patient setup, also includes resident teaching; skin, endorectal, IORT, bile duct brachy

-Managing protocol patients, pre/during/post therapy, maintaining clinic notes per protocol, data collection, attribution of toxicities, resident teaching, collecting/processing specimens;

-Protocol AE log updates/attributes

-Preceptor to PA students, medical students, and resident teaching

-Clinical research, including abstract submission, poster/oral presentations, conference attendance

-Tumor board attendance and discussion of patient cases;

-Initiates or modifies routine, complex, and emergent medication regimens and therapies.

- EPIC clinic note documentation & POE documentation,

-simulation setup notes,

-billing of encounters within mosaiq & MDC/EPIC

-Obtains treatment and diagnostic approvals including peer to peer review discussions and submission of letters of medical necessity, prior authorizations.

-EPIC efficient with documentation, orders, Meaningful Use criteria, and in-basket.

-Coordinates care in a multi-disciplinary setting to include appointments with other specialties, procedures, diagnostic studies, labs.

-Communicates with outside providers/discussion of results & care plan

-Y90-consults & consents

Role in GI Services

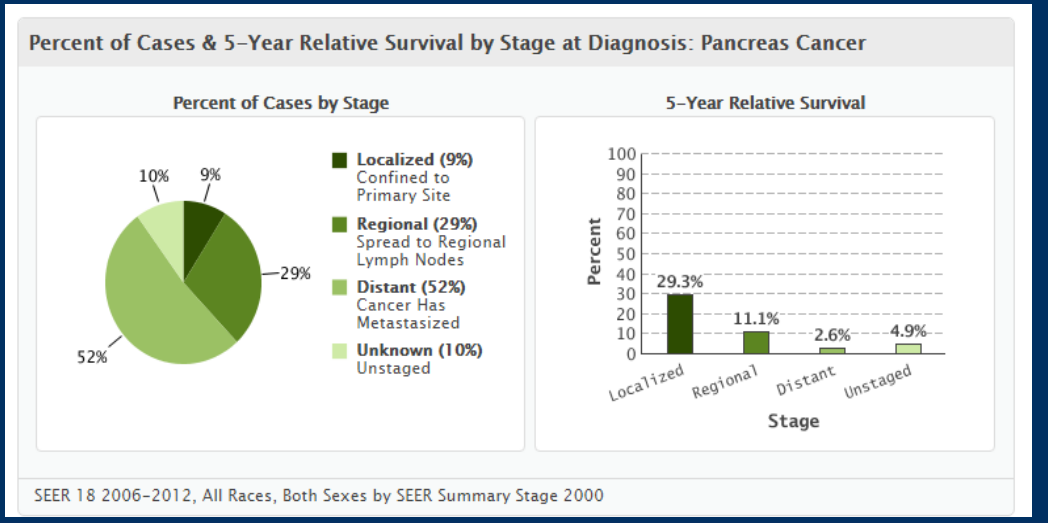
- Consultations/Follow-ups/MDC
- Symptom management/acute care
- Treatment Consent
- Clinical Trials
  - Enrollment/Consent Process, Protocol requirements/Documentation,
  - Appropriate timing/schema of events, protocol toxicity assessments/Data Collection
- Ordering/Review of Diagnostics studies
- Resident training
- Tumor board discussion

Team Effort

- JHU GI Rad/onc model
  - Attending physician, physician assistant, nurse, resident, clinical coordinator, admin assistant, & research staff
- Continuity of care
  - Residents change
  - Need for direct patient care
  - Physicians have numerous responsibilities

Pancreas Cancer Patients

- 7.7% 5 yr OS
- Most have active disease/treatments
- Symptom management
  - Disease related
  - Treatment related



SEER 18 2006-2012

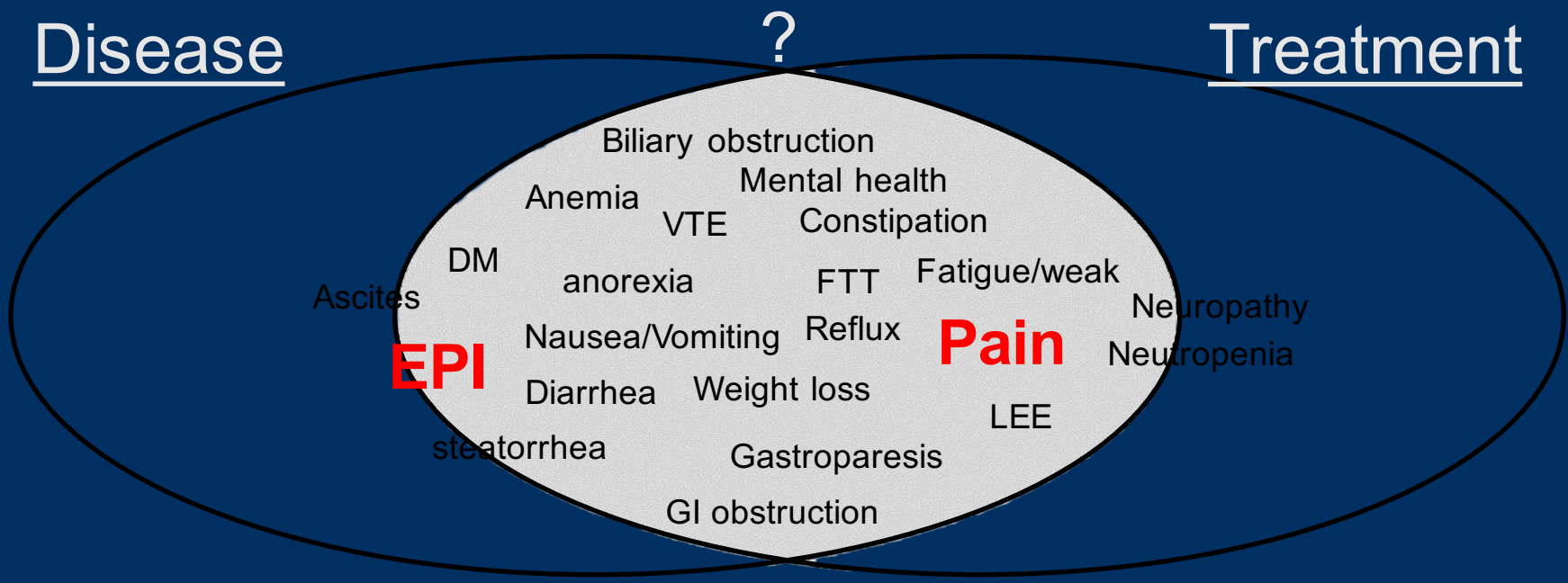
Pancreas Cancer Patients Things to Consider

- Goals
- Where they live
- Support system
- Family planning/fertility
- Symptom management
- Physical Therapy
- Work/Hobbies

Patient Education

- Symptom management
- On call numbers
- Expectations
- Treatment flow
- Facility services
  - Social work, nutrition, PT, pain, palliative care, housing, financial, support groups

Pancreas Cancer Symptoms



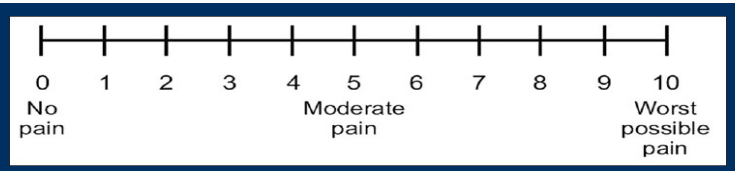
Pain

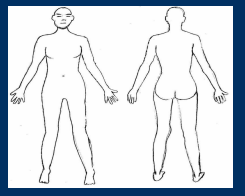
- Affects >70% of cancer patients
  - 75-80% initial presentation
- 40% survivors have chronic pain
- 75% multiple sites
- 75% require opioids
- 33% have functional deficits
- 60% QoL deficits

Grossman and Nesbit, Cancer Related Pain; M. Abeloff; Palace et al. JCO 2016, V34 epub;

Defining Pain

- Good H&P
  - Define pain experience
- Review data
- Pain log
- Special populations
  - Elderly, comorbidities, hepatic/renal dysfxn, OSA, CAD, past abuse





Wong's Essentials of Pediatric Nursing, ©2001; Pain: Clinical Manual, ©1999; McGill Pain Questionnaire ©1975; Herr & Mobily, 1993

Pancreas Cancer Pain

- Generalized abdominal pain
- Epigastric pain
- Post prandial pain
- Back pain
- RUQ pain
- Peripheral pain

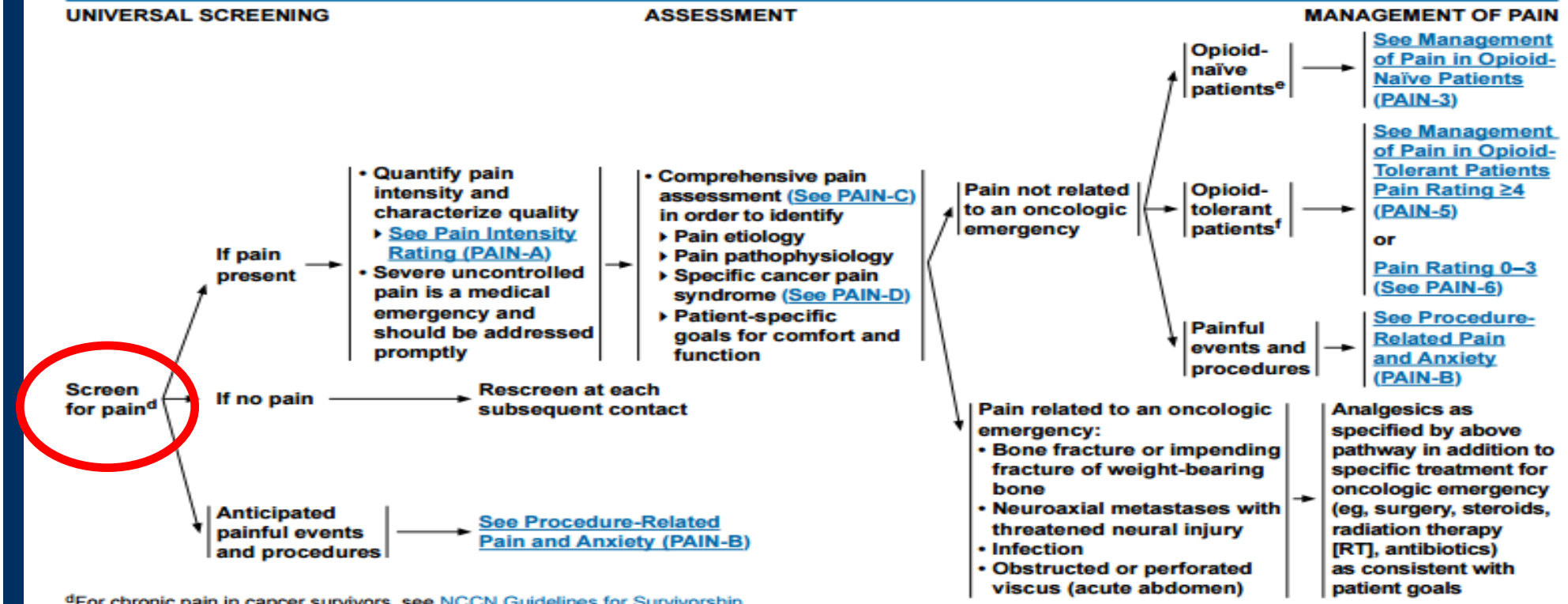
Pain Treatment

- Opioid vs non-opioid
- Interventional procedures
  - RT
  - Vertebroplasty
  - Pain blocks
  - Drains
- Non-pharmacologic therapies
  - Exercise, PT/OT
  - Acupuncture, massage, meditation
- Psychosocial

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Adult Cancer Pain

NCCN Guidelines Index
Adult Cancer Pain TOC
Discussion



[d]For chronic pain in cancer survivors, see NCCN Guidelines for Survivorship.

[e]Opioid naïve includes patients who are not chronically receiving opioid analgesic on a daily basis and therefore have not developed significant tolerance. The FDA identifies tolerance as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

[f]Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis. The FDA identifies tolerance as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

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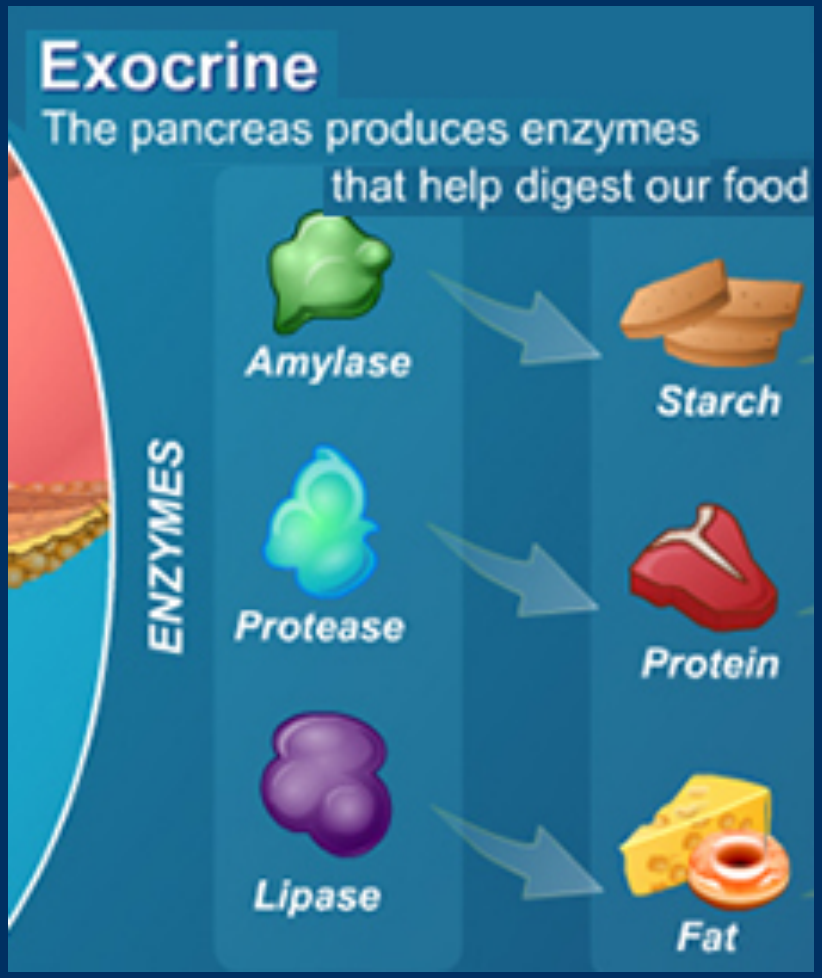
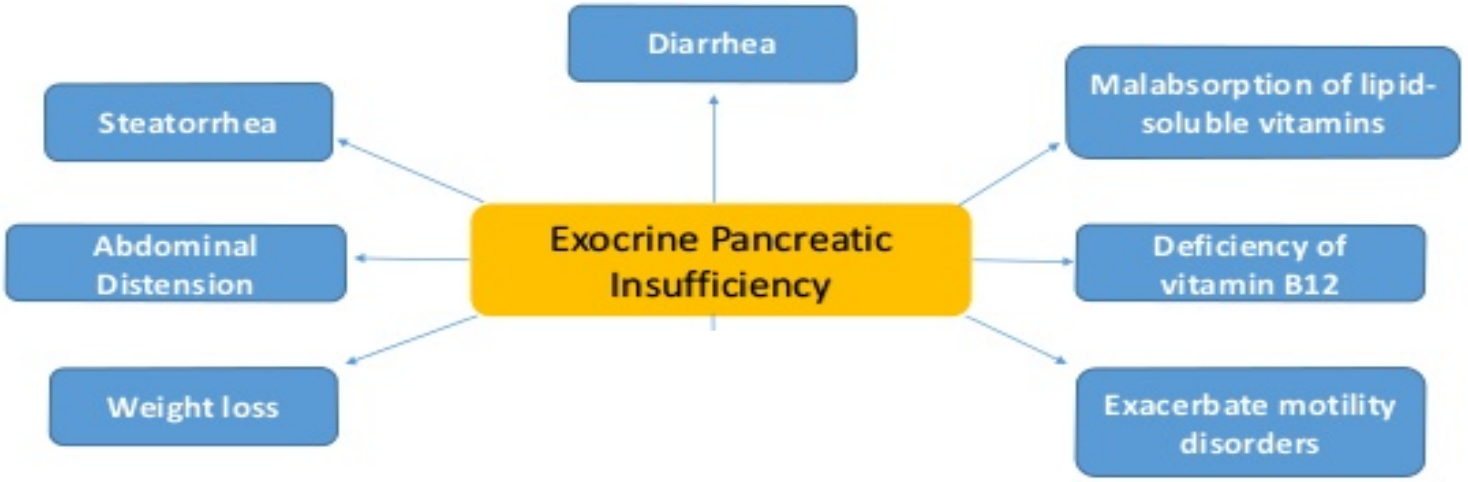
Exocrine Pancreatic Insufficiency (EPI)

- Loss of parenchyma
  - Pancreatitis, treatments
- Obstruction of the duct
  - Tumor location, fibrosis
- Surgery-injury/removal
  - Pancreatectomy, small bowel, bypass



National Pancreas Foundation, 2014

Overview of Exocrine Pancreatic Insufficiency Symptoms



Sajaratul Ibrahim, 2015

Enzyme Replacement Therapy

- Ask questions
- Intervene early
- Use appropriate dosing
- Easy to try
- Keep in mind cost/programs

Per-meal Lipase Unit Range

Minimum	Maximum
34,000	170,000

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JHU Pancreas Multidisciplinary Clinic

- Surgery, Medical Oncology, Radiation Oncology, GI/Endo, Pathology, Radiology, Pain & Palliative Care, Clinical trials/Research
  - Physicians, advanced practitioners, fellows, residents, students, coordinators
- Started in 2008 with 4-6 patients, currently up to 14 patients
- 1-2 day process
- Comprehensive review of case, images, pathology

Advanced Practitioner Role
JHU PMDC

- H&P
- Review imaging, pathology, treatments
- MDC conference presentation
- Discussion of recommendations/results
  - Patient, family, outside providers
- Clinical trial discussions
- Coordination of care w/outside providers
- Follow-up

Disciplines

- Surgery
  - Pancreaticoduodenectomy, distal, bypass
- Medical Oncology
  - Standard therapy, protocols
- Radiation Oncology
  - Neoadjuvant, adjuvant, palliative
- GI
  - EUS/FNA, ERCP/stent, blocks

Disciplines (cont)

- Pathology/Genetics
- Radiology
- Pain & Palliative Care
  - Medications, interventional procedures
- Research
  - Not just therapeutic agents/tx, QoL

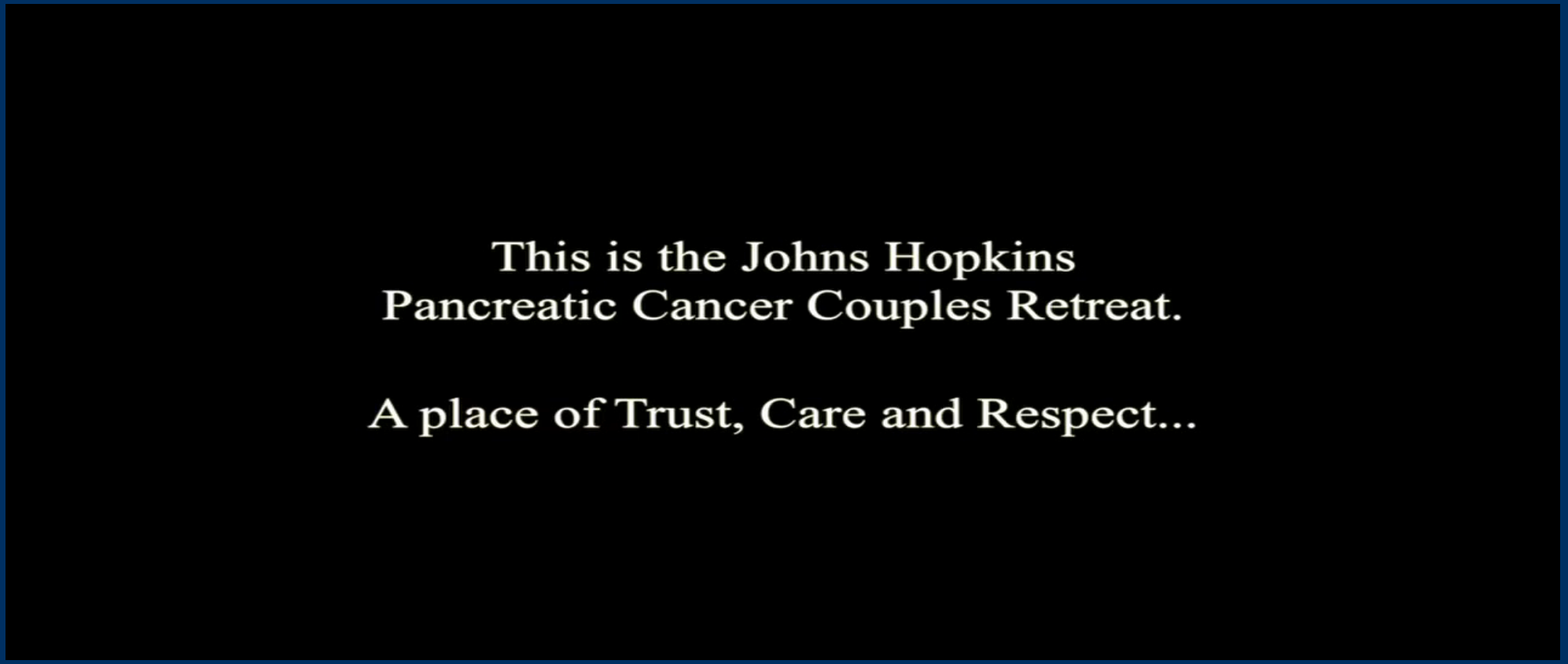
Other Disciplines to Consider

- Interventional Radiology
  - Tubes, drains, biopsies, pleurex
- Integrative Medicine
  - Acupuncture, meditation, PT
- US
  - Centesis, lines
- Psych
- Nutrition
- Survivorship
- Social Work

What Else Can APs Do?

- Community engagement
  - Couples retreats
- Clinical trials
  - Create, support
- Research
  - Publications, national & international meetings
- Education/Mentorship
  - Other APs, residents, students

The Sidney Kimmel Comprehensive Cancer Center, 2012



Conclusions

- Pancreas cancer patients
  - Sick/symptoms are multifactorial
  - Time/direct patient care
- Emergent role of APs have been increasing in awareness and utilization in specialty clinics-oncology
- Can assist in improving patient treatment flow, provider workflow, and overall patient care and patient experience
- Can be cost effective and time efficient in symptom management
- Can help fill the deficit of increasing demand
- Academic setting-teaching, publication, clinical trials

Special Thanks to…

- Dr. Joe Herman
- JHU Team GI
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  - Lauren Rosati
  - Carol Gergis
  - Waldo
- JHU Radiation Oncology
- JHU GI Oncology services
- PMDC
  - Mary H
  - Lindsay P
- JHU Couples Retreat Committee
- JADPRO

SMARTIE

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