Pancreatic Cancer Updates in Management

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2017 Estimated Deaths from Cancer in the United States

Estimated Deaths

Males			Females		
Lung & bronchus	84,590	27%	Lung & bronchus	71,280	25%
Prostate	26,730	8%	Colon & rectum	23,110	8%
Pancreas	22,300	7%	Pancreas	20,790	7%
Liver & intrahepatic bile duct	19,610	6%	Ovary	14,080	5%
Leukemia	14,300	4%	Uterine corpus	10,920	4%
Esophagus	12,720	4%	Leukemia	10,200	4%
Urinary bladder	12,240	4%	Liver & intrahepatic bile duct	9,310	3%
Non-Hodgkin lymphoma	11,450	4%	Non-Hodgkin lymphoma	8,690	3%
Brain & other nervous system	9,620	3%	Brain & other nervous system	7,080	3%
All Sites	**318,420**	**100%**	**All Sites**	**282,500**	**100%**

2020 Pancreas cancer will be the 2nd leading cause of death in the US

Aims

- Discuss management and surveillance of premalignant lesions of the pancreas
- Work-up of newly diagnosed pancreas cancer
- Define resectable, borderline and locally advanced unresectable pancreas cancer
- Surgical updates and safety
- Outline neoadjuvant treatment options
- Clinical trials

Genetics

Syndrome	Estimated Cumulative Risk Pancreatic Cancer	Estimated Increased Risk Compared to General Population
Peutz-Jeghers syndrome (STK11)	11-36% by age 65-70 years	132 fold
Familial pancreatitis (PRSS1, SPINK, CFTR)	45-53% by age 70-75 years	26-87 fold
Melanoma Pancreatic Cancer Syndrome (CDKN2A)	14-17% by age 70-75 years	20-47 fold
Lynch Syndrome (MLH1, MSH2, MSH6)	4% by age 70 years	9-11 fold

Genetics

Syndrome	Estimated Cumulative Risk Pancreatic Cancer	Estimated Increased Risk Compared to General Population
Hereditary breast and ovarian syndrome (BRCA1, BRAC2)	1.4-1.5% (women), 2.1-4.1% (men) by age 70	2.4-6 fold
Familial pancreatic cancer	>3 first degree relatives, 7-16% by age 70 2 first degree relatives 3% by age 70	>3 first degree relatives - 32 fold >2 first degree relatives - 6.4 fold 1 first degree relative - 4.6 fold

Background-Premalignant lesions of pancreas

- Pancreatic cysts are identified in 2.4-19% of patients undergoing CT or MRI
- Most common
  - Intraductal papillary mucinous neoplasm (IPMN)
  - Mucinous cystic neoplasm (MCN)
  - Solid pseudopapillary neoplasm (SPN)
  - Serous cystadenoma (SCA)
  - Pseudocyst

Laffan et al. AJR Am J Roentgenol 2008;191:802-807
Lee et al. Am J Gastroenterol 2010;105:2079-2084

Premalignant lesions of pancreas

Impression

IMPRESSION:

1. Two fat-containing ventral hernias. The more superior hernia, which is an umbilical hernia, contains inflamed peritoneal fat but does not contain any bowel. The lower hernia contains fat and no bowel.

2. Small indeterminate low density pancreatic lesion in the uncinate process. Further evaluation with nonemergent abdominal MRI is recommended.

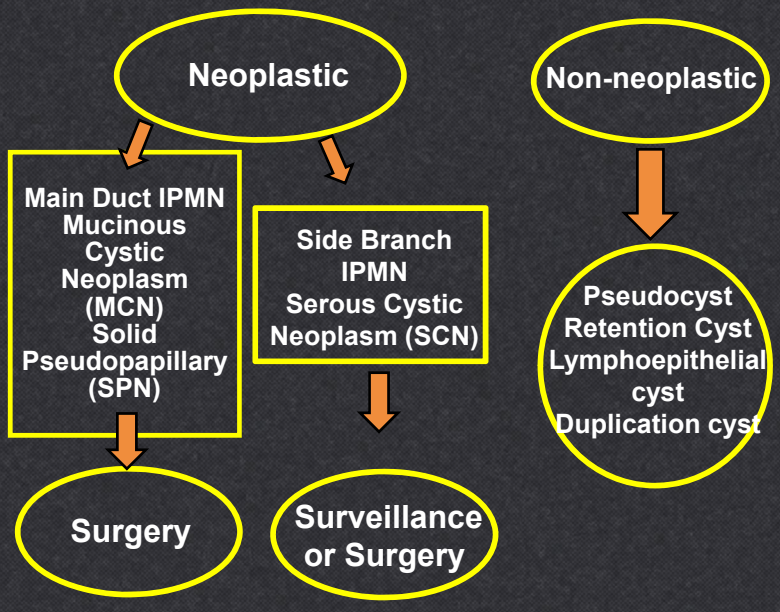
3. Postsurgical changes from cholecystectomy, hysterectomy, and probable tubal ligation.

4. Fatty liver.

5. Sigmoid diverticulosis without evidence of acute diverticulitis.

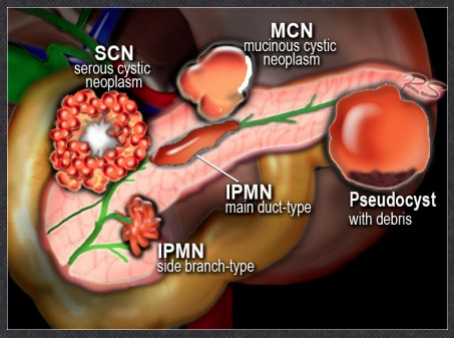
I personally viewed and interpreted these images and I have reviewed and approved this report.

Pancreatic Cystic Lesions



IPMN

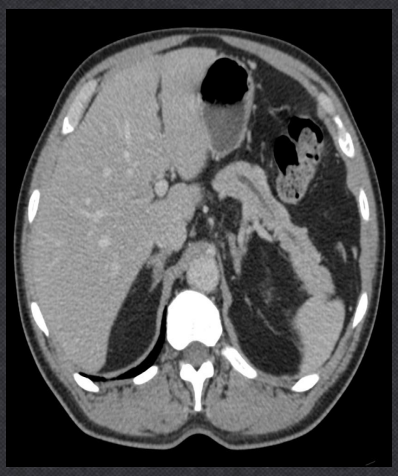
- Main Duct IPMN
- Branch Duct IPMN
- Mixed type IPMN



Main duct IPMN

Branch duct IPMN

Mixed type IPMN



IPMN-Incidence of malignancy

	All (Mean)	Main Duct (Mean)	Branch Duct (Mean)	Mixed Type (Mean)
Malignant	8.2-66.7% (40.4)	35.7-100% (62.2)	6.3-51% (24.4)	34.6-78.9% (57.6)
Invasive	1.2-49.6% (30.8)	11.1-80.8% (43.6)	1.4-30% (16.6)	19.2-64.9% (45.3)

Tanaka et al. Pancreatology 2012

IPMN

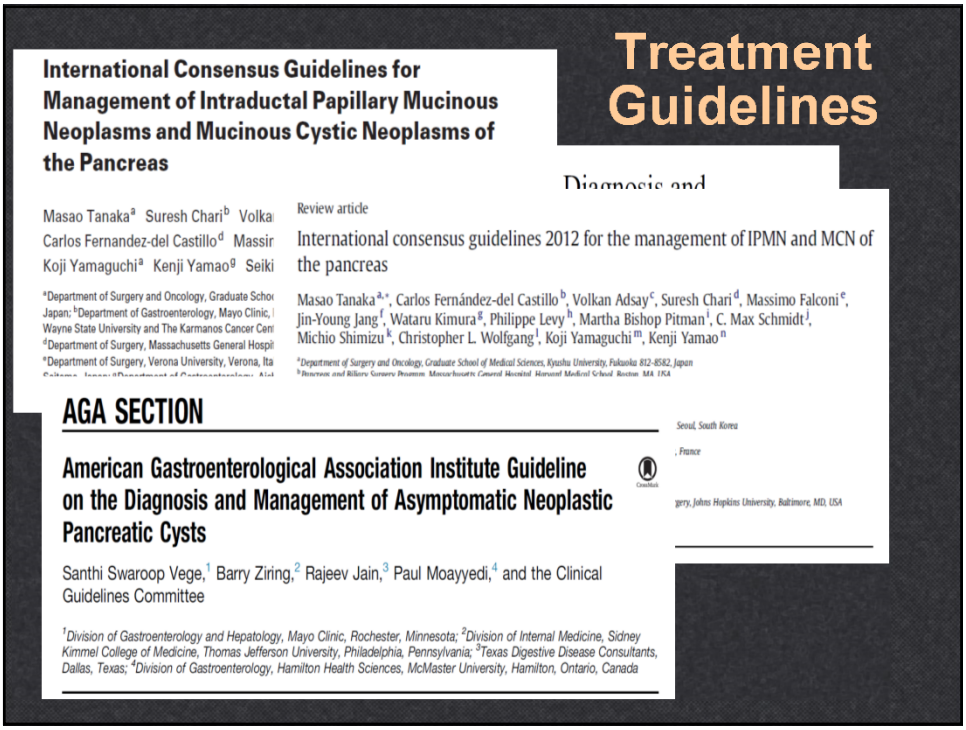
- Symptoms
  - Most are asymptomatic
  - Vague abdominal pain
  - Nausea/vomiting
  - Pancreatitis
  - Jaundice
  - Weight loss
  - Diabetes

- Most common in males in their 50's

Diagnosis and Work-up

- Referral to pancreatic expert
- History of pancreatitis?
  - YES-Pseudocyst likely
- Symptoms?
- Imaging
  - Detect cystic lesions
  - Determine main vs. branch duct
  - Determine risk of malignancy and ability to resect
- EUS
  - Cyst fluid analysis
  - FNA
  - Presence of mural nodule or other high risk features

Treatment Guidelines



International Consensus Guidelines for Management of Intraductal Papillary Mucinous Neoplasms and Mucinous Cystic Neoplasms of the Pancreas

Masao Tanaka[a] Suresh Chari[b] Volka
Carlos Fernandez-del Castillo[d] Massir
Koji Yamaguchi[a] Kenji Yamao[g] Seiki

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Wayne State University and The Karmanos Cancer Cen
[d]Department of Surgery, Massachusetts General Hospi
[e]Department of Surgery, Verona University, Verona, Ita

Review article

International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas

Masao Tanaka[a,*], Carlos Fernández-del Castillo[b], Volkan Adsay[c], Suresh Chari[d], Massimo Falconi[e], Jin-Young Jang[f], Wataru Kimura[g], Philippe Levy[h], Martha Bishop Pitman[i], C. Max Schmidt[j], Michio Shimizu[k], Christopher L. Wolfgang[l], Koji Yamaguchi[m], Kenji Yamao[n]

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Seoul, South Korea

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gery, Johns Hopkins University, Baltimore, MD, USA

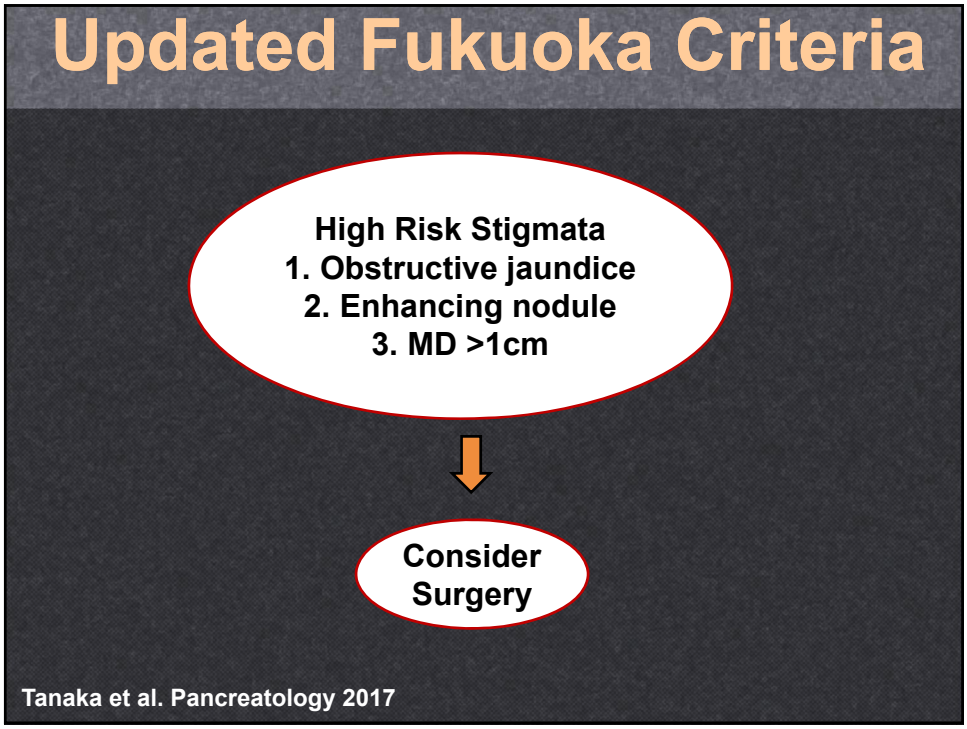
AGA SECTION

American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts

Santhi Swaroop Vege,[1] Barry Ziring,[2] Rajeev Jain,[3] Paul Moayyedi,[4] and the Clinical Guidelines Committee

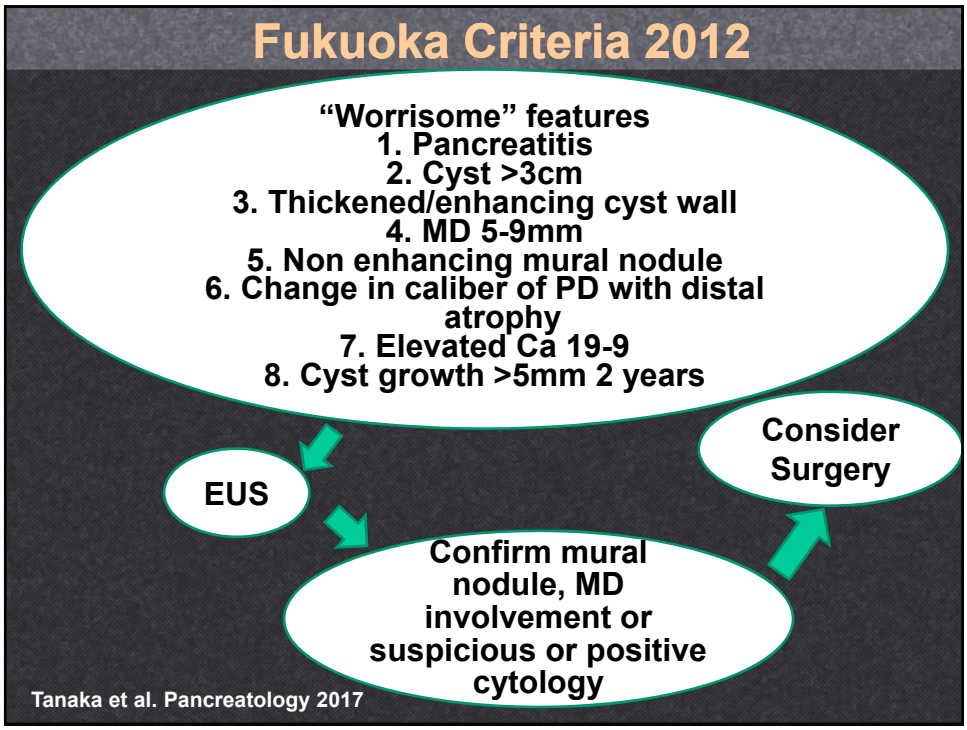
[1]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; [2]Division of Internal Medicine, Sidney Kimmel College of Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania; [3]Texas Digestive Disease Consultants, Dallas, Texas; [4]Division of Gastroenterology, Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada

Updated Fukuoka Criteria



Tanaka et al. Pancreatology 2017

Fukuoka Criteria 2012



Tanaka et al. Pancreatology 2017

Updated Fukuoka Criteria

How big is it?

- <1cm Imaging 2-3 years
- 1-2cm Imaging yearly x 2 years then lenghten
- 2-3cm EUS in 3-6 months alternating with MRI Consider surgery in young patients
- >3cm Close surveillance, MRI and EUS every 3-6 months Strongly consider surgery

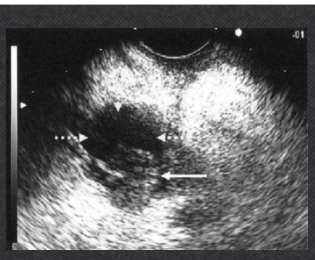
Tanaka et al. Pancreatology 2017

Interpreting Cyst Fluid

Diagnosis of Pancreatic Cystic Neoplasms: A Report of the Cooperative Pancreatic Cyst Study

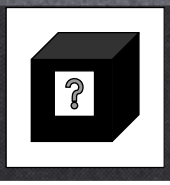
WILLIAM R. BRUGGE,* KENT LEWANDROWSKI,† ELIZABETH LEE–LEWANDROWSKI,† BARBARA A. CENTENO,§ TARA SZYDLO,* SUSAN REGAN,‖ CARLOS FERNANDEZ DEL CASTILLO,¶ ANDREW L. WARSHAW,¶ and THE INVESTIGATORS OF THE CPC STUDY

*Gastrointestinal Unit, ¶Department of Surgery, †Department of Pathology, ‖Department of Internal Medicine-Clinical Epidemiology Unit, Massachusetts General Hospital, Boston, Massachusetts; and §Departments of Interdisciplinary Oncology and Pathology, H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, Tampa, Florida

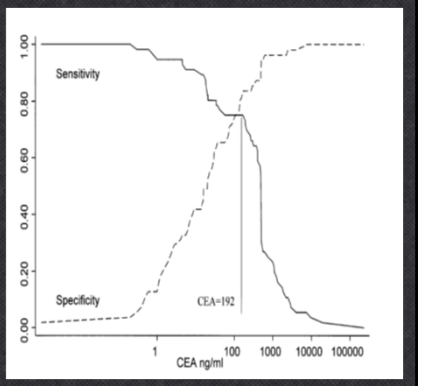


Brugge WR et al. Gastroenterology 2004;126:1330-6

Interpreting Cyst Fluid



- CEA
  - Distinguish mucinous from non-mucinous lesions
- >192
  - Sensitivity 73%
  - Specificity 84%

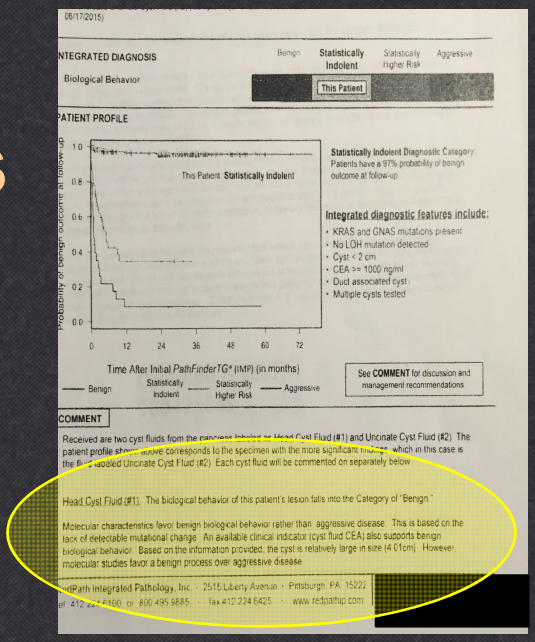


Brugge WR et al. Gastroenterology 2004;126:1330-6.

Molecular Analysis of Cyst Fluid

- Interpace Diagnostics
  - Formerly RedPath
- Provide mutational analysis
  - Proprietary test which they do not reveal
  - Mutational Profile
    - LOH markers
    - Oncogenes
    - DNA quantity and quality
    - Clinical information

Fluid Analysis



06/17/2016)

INTEGRATED DIAGNOSIS

Biological Behavior

Benign | Statistically Indolent | Statistically Higher Risk | Aggressive

This Patient

PATIENT PROFILE

Probability of benign outcome at follow-up

This Patient: Statistically Indolent

Time After Initial PathFinderTG® (IMP) (in months)

Benign | Statistically Indolent | Statistically Higher Risk | Aggressive

Statistically Indolent Diagnostic Category:
Patients have a 97% probability of benign outcome at follow-up

Integrated diagnostic features include:
- KRAS and GNAS mutations present
- No LOH mutation detected
- Cyst < 2 cm
- CEA >= 1000 ng/ml
- Duct associated cyst
- Multiple cysts tested

See COMMENT for discussion and management recommendations

COMMENT

Received are two cyst fluids from the pancreas labeled as Head Cyst Fluid (#1) and Uncinate Cyst Fluid (#2). The patient profile shown above corresponds to the specimen with the more significant findings, which in this case is the fluid labelled Uncinate Cyst Fluid (#2). Each cyst fluid will be commented on separately below.

Head Cyst Fluid (#1): The biological behavior of this patient's lesion falls into the Category of "Benign."

Molecular characteristics favor benign biological behavior rather than aggressive disease. This is based on the lack of detectable mutational change. An available clinical indicator (cyst fluid CEA) also supports benign biological behavior. Based on the information provided, the cyst is relatively large in size (4.01cm). However, molecular studies favor a benign process over aggressive disease.

RedPath Integrated Pathology, Inc. · 2515 Liberty Avenue · Pittsburgh, PA 15222
tel 412-[illegible]100 or 800.495.9885 · fax 412.224.6425 · www.redpathip.com

IPMN

Pathology: BD-IPMN with high grade dysplasia

Surveillance

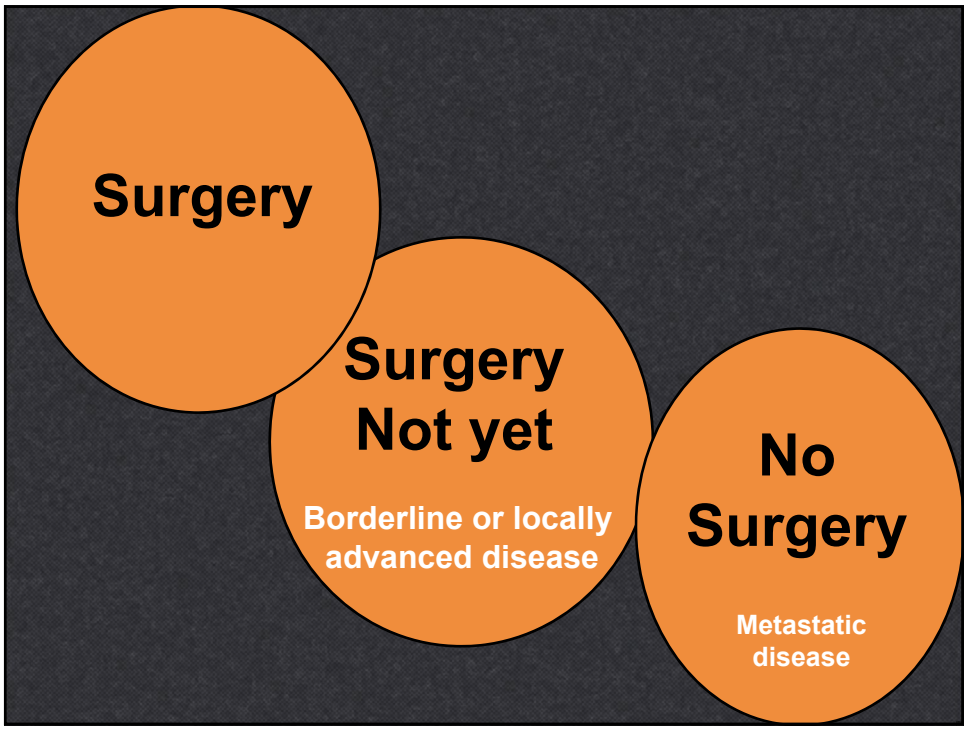
- No high quality data to base recommendations
- Great variation in literature
- MCN's are almost always solitary and require no surveillance imaging

Basic algorithm for all cancers

- NAME IT
- STAGE IT
- TREAT IT
- Presentation: Painless jaundice, weight loss, abdominal pain, diabetes
- Work-up: Cross sectional imaging, labs, EUS/ERCP as necessary
- Preoperative assessment: medical clearance, assess resectability, need for neoadjuvant therapy
- Proceed to OR or chemotherapy
- Patients with distant metastatic disease chemotherapy is the mainstay of treatment

Defining Resectability

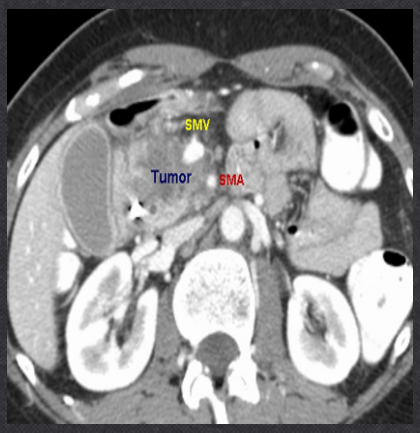
Resectability Status	Arterial	Venous
Resectable	No arterial contact (celiac, SMA, CHA)	<180 degrees without vein contour irregularity
Borderline	Tumor contact with CHA, <180 degrees SMA	>180 degrees SMV/PV, reconstruction possible, contact with IVC
Locally Advanced-Unresectable	Tumor >180 degrees SMA, celiac, first jejunal SMA branch	Unreconstructible SMV/PV,



Resectable Pancreas Cancer

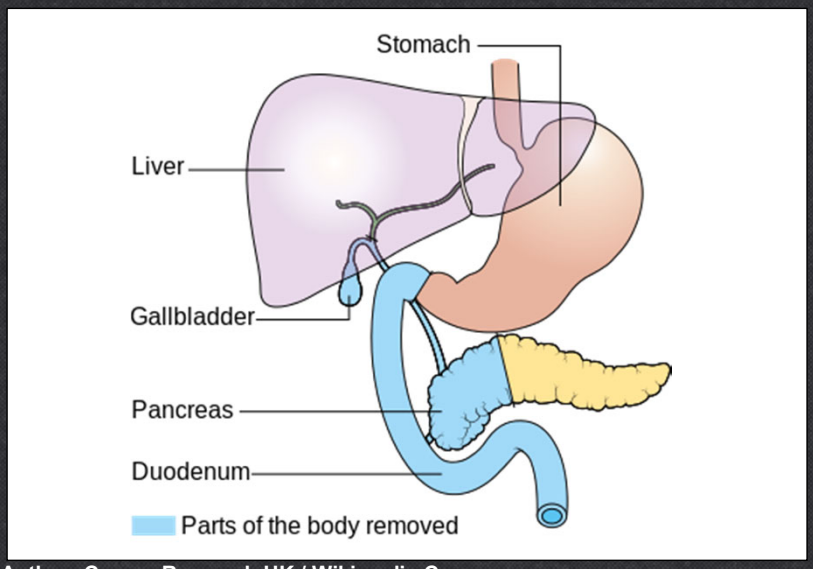
Borderline Resectable and Locally Advanced Unresectable Pancreas Cancer

Borderline resectable:
Abutment SMA



Locally advanced:
Encasement SMA

Pancreaticoduodenectomy (Whipple)



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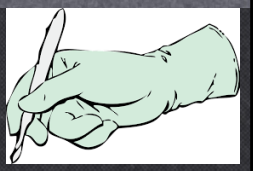
Improving surgical outcomes



- Perioperative mortality 2%
- Complication rates remain high 40-50%
- Average length of stay 8 days
- Pancreatic fistula 20%
- Diabetes 20%
- Adoption of minimally invasive and robotic surgery may further reduce length of stay

Surgeon volume and outcomes Quantity matters!

- High volume improves perioperative and long-term outcomes
- Included 14 different procedure types
- Pancreas surgery
- HV >5 vs. LV <5
- In hospital mortality 2.4 vs. 6.4%
- 51% reduction in hospital mortality

Birkmeyer et al : N Engl J Med. 2002 Apr 11;346(15):1128-37
Birkmeyer et al : N Engl J Med 2003; 349:2117-2127

Pasireotide for postoperative pancreatic fistulas

- Pasireotide
  - Somatostatin analogue with longer half life than octreotide and broader binding profile to octreotide receptors
  - Decreases pancreatic exocrine secretions
- Single center randomized trial
  - 152 subcutaneous pasireotide
    - 14 doses, first dose pre-surgery
  - 148 patients placebo
- Results
  - Pancreatic fistula 9% vs. 21% p = 0.006
  - Consistent for both whipple and distal pancreatectomy

Allen et al. NEJM 2014

Whipple with or without drains

- Multicenter randomized controlled trial
  - 68 drains
  - 69 no-drain
- Increase in complications in no-drain group
  - 52% vs. 68% p = 0.047
  - Higher average complication severity
  - Higher gastroparesis, intra-abdominal fluid collection, intra-abdominal abscess (10% vs. 25%), severe diarrhea, need for postoperative percutaneous drain, prolonged length of stay
- Data safety monitoring board stopped the study early because of an increase in mortality from 3% to 12% in patients undergoing whipple without drain

Van Buren et. al Ann Surg 2014

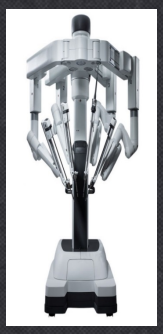
Distal pancreatectomy with and without drains

- Multicenter randomized controlled trial
  - Closed suction drain vs. no drain distal pancreatectomy
- Baylor
- Ohio State
- Indiana University

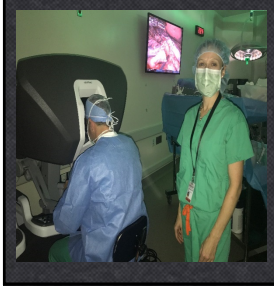
- No difference in complications or fistula rate

VanBuren Ann Surg 2017

Robotic Whipple

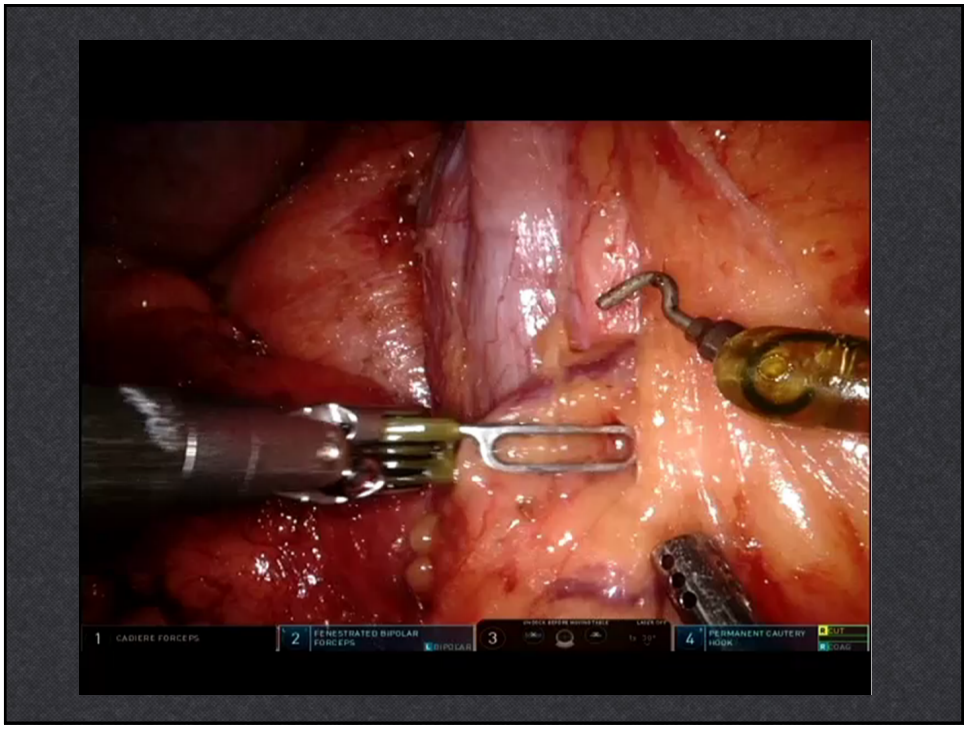


- Surgeon sits in room controlling robotic arms to perform surgery through small incisions
- Decrease length of stay, less post operative pain, quicker recovery



Open Whipple

Robotic Whipple



The role of Neoadjuvant Chemotherapy

Preoperative/Neoadjuvant therapy in pancreatic cancer: Meta-analysis

Group	Estimated Median Survival (m_e)		Estimated Survival Probability (Resected)	
	Resected (Range)	Not Resected (Range)	1 Year (Range)	2 Year (Range)
All patients	22.4 (9–62) (n = 70)	9.5 (6–21) (n = 51)	78.9% (0%–100%) I^2 = 48.1% [28.7%–62.3%] (n = 54)	49.2% (0%–82%) I^2 = 85.2% [80.5%–88.7%] (n = 37)
Tumor resectable before treatment (group 1)	23.3 (12–54) (n = 27)	8.4 (6–14) (n = 19)	77.9% (48%–100%) I^2 = 70.7% [52.6%–81.8%] (n = 18)	47.4% (25%–70%) I^2 = 69.1% [42.2%–83.4%] (n = 11)
Tumor non-resectable before treatment (group 2)	20.5 (9–62) (n = 29)	10.2 (6–21) (n = 25)	79.8% (0%–100%) I^2 = 92.1% [89.8%–93.9%] (n = 29)	50.1% (0%–82%) I^2 = 88.6% [84%–91.9%] (n = 21)

n, number of assessable studies for each group.
doi:10.1371/journal.pmed.1000267.t006

Gillen et al. PLoS Med 7(4): e100267 2010

Neoadjuvant therapy- The Ohio State Experience

- Borderline resectable (BRPC) and locally advanced unresectable (LAPC)
- 43 patients
  - 18 BRPC
  - 25 LAPC
- Modified FOLFIRINOX
  - No bolus 5-FU, no LV, decreased irinotecan
- Radiation based on response and intended surgery

Blazer Ann Surg Onc 2015 Apr; 22(4):1153-9

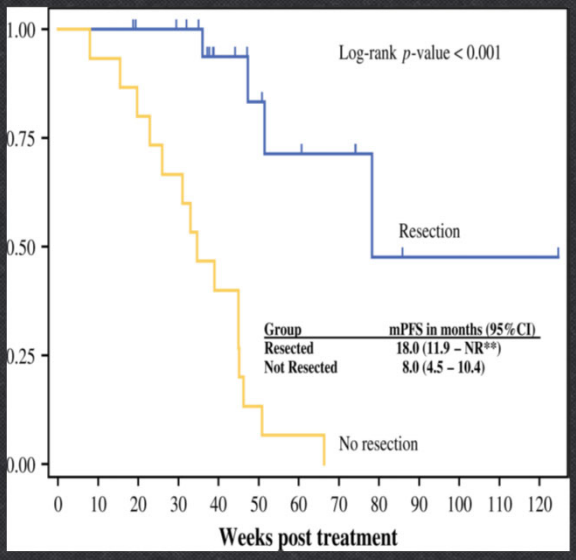
Results

Summary of patient characteristics and responses to therapy

Characteristic	Total (n = 43) n (%)	LA (n = 25) n (%)	BR (n = 18) n (%)
Mean age (years)	62.4 ± 9.4	62.6 ± 10.0	62.2 ± 8.7
Performance status (ECOG) 0–1	43 (100)	25 (100)	18 (100)
Male	23 (53.5)	12 (48)	11 (61)
Tumor location			
Head	25 (58)	9 (36)	16 (89)
Body/tail	18 (42)	16 (64)	2 (11)
Vascular involvement			
Arterial	15 (35)	13 (52)	2 (11)
Venous	11 (25.5)	2 (8)	9 (50)
Both	17 (39.5)	10 (40)	7 (39)
Mean mFOLFIRINOX cycles: n (range)	4.9 (1–14)	5.3 (1–14)	4.4 (1–8)
Chemoradiation	23 (54)	15 (60)	8 (44)
Median baseline CA19-9: n (range)	335.97 (<15.00– 10,943.97)	184.80 (<15.00– 1,355.05)	650.88 (<15.00– 10,943.97)
CA19-9 reduction[a]	26/37 (70)	13/20 (65)	13/17 (76)
Radiographic response (CR + PR)[b]	9/40 (23)	2/23 (9)	7/17 (41)
Surgical exploration	31 (72)	16 (64)	15 (83)
Resected	22 (51)	11 (44)	11 (61)
Vascular resection	4/22 (18)	3/11 (27)	1/11 (9)
Negative margins	19/22 (86)	10/11 (91)	9/11 (82)

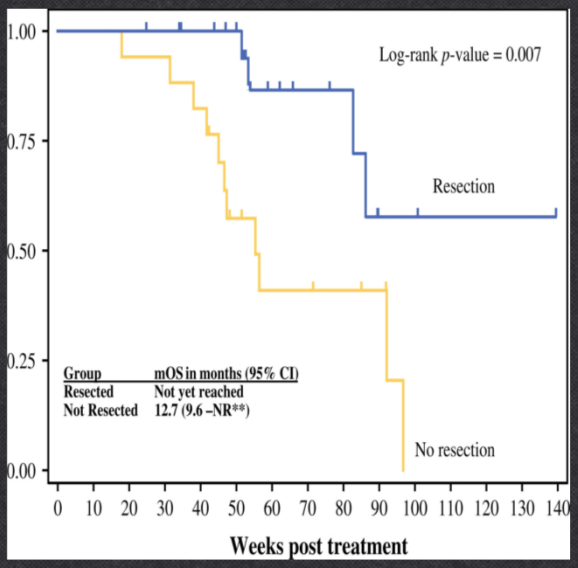
Blazer Ann Surg Onc 2015 Apr; 22(4):1153-9

Results



Blazer Ann Surg Onc 2015 Apr; 22(4):1153-9

Results



Blazer Ann Surg Onc 2015 Apr; 22(4):1153-9

Blazer Ann Surg Onc 2015 Apr; 22(4):1153-9

Neoadjuvant therapy for patients with resectable disease

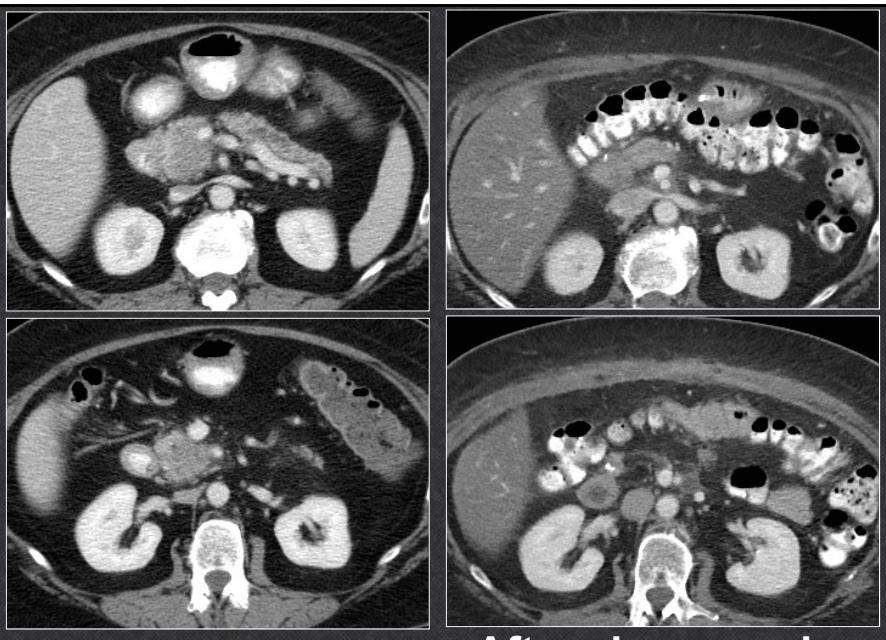
- Common in some major cancer centers
- NCCN guidelines now acceptable to offer neoadjuvant therapy
- NEOPAC Trial
  - Accruing in Europe
  - Resectable pancreas cancer
  - Randomized to Surgery vs. preoperative gemcitabine and oxaliplatin followed by surgery
  - All patients adjuvant gemcitabine

ESPAC-4

- Multi-center randomized controlled trial
- 732 patients gemcitabine alone vs. gemcitabine and Capecitabine
- Median OS 28 months vs. 25.5 months (HR 0.82)
- 29% 5 year survival vs.16%
- No increased toxicity compared with gemcitabine alone
- 60% R1 resection

Making the unresectable, resectable

- Locally advanced and borderline resectable
  - Considered as “potentially” or “never” resectable
- mFOLFIRINOX x 2 months then reassess
- Gemcitabine + radiation (36Gy or 50Gy) if stable or progressive disease
- Surgery after maximum response with planned vascular resection



Pre-treatment

After chemo and chemo/XRT

Conclusions

- Premalignant lesions are common and diagnosis and management best by multidisciplinary teams
- Modest improvement in pancreatic cancer survival with newer chemotherapy options
- Surgery for pancreatic cancer is safe
  - Hospital volume and surgeon volume are important for outcomes
- Management by multidisciplinary teams and enrollment in clinical trials is most important for improving outcomes in the future