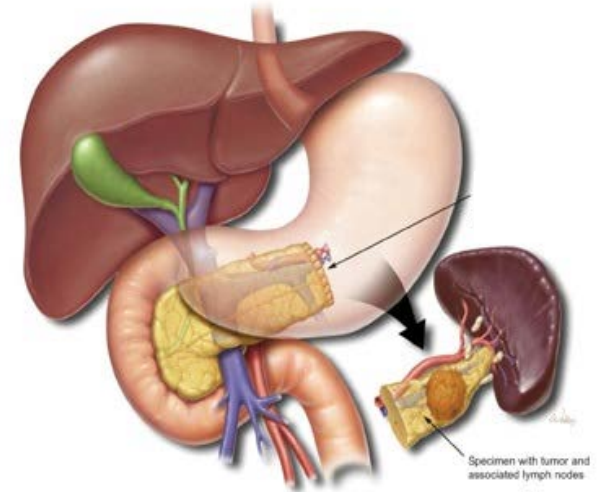
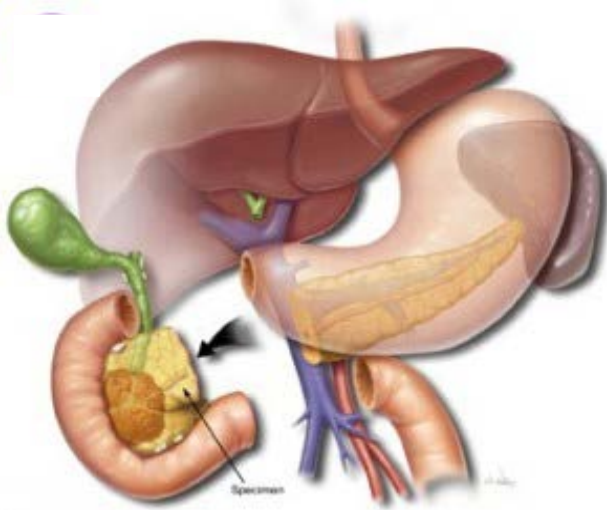


# Pancreas adenocarcinoma: *Evolving treatment strategies*



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SON Fall Update 2016, Oct 22 2016

# CONFLICT OF INTEREST DECLARATION

I, **Alice Wei** declare that in the past 3 years:

I have been a member of an Advisory Board or equivalent with the following companies\*: Ethicon, Histosonic, Celgene, Sanofi, Takeda, Bayer

I have been a member of the following speakers' bureau: None

I have done speaking engagements for the following companies\*: Sanofi, Celgene

I have received payment or funding from the following companies\*

(includes gifts, grants, honoraria, and 'in kind' compensation): None

I have done consulting work for the following companies\*: Cancer Care Ontario

I have held a patent for a product referred to in the program or that is marketed by a commercial organization: None

I or my family hold individual shares in the following companies\*: None

I have participated in a clinical trial for the following companies\*: None

## MANAGING POTENTIAL BIAS

no commercial uses will be discussed

*\*pharmaceutical, medical device, or communications companies*

# Learning Objectives

1. Understand the changing definitions of surgical resectability for pancreas adenocarcinoma
2. Learn about the evolving multi-modality strategies for the treatment of pancreas cancer

# Question 1: Survival for pancreatic adenocarcinoma

1. Survival remains dismal. Survival rates are unchanged over the past few decades
2. Giving chemotherapy +/- radiotherapy before surgery results in better survival than giving it after surgery
3. Borderline resectable tumours are determined by the relationship between the tumour and the vasculature
4. Outcomes following surgery depend on patient co-morbidities

# Estimated New Cases of Cancer in 2015



**Males**  
**100,500 New Cases**

Site	Percent	New Cases
Prostate	23.9%	24,000
Colorectal	13.9%	13,600
Lung	13.5%	14,000
Bladder	6.1%	6,200
Non-Hodgkin's lymphoma	4.5%	4,500
Kidney	3.9%	3,900
Melanoma	3.6%	3,700
Leukemia	3.5%	3,500
Oral	2.9%	2,900
<b>Pancreas</b>	<b>2.4%</b>	<b>2,400</b>



**Females**  
**96,400 New Cases**

Site	Percent	New Cases
Breast	25.9%	25,000
Lung	13.5%	13,000
Colorectal	11.5%	11,100
Body of uterus	6.5%	6,300
Thyroid	5.0%	4,800
Non-Hodgkin's lymphoma	3.8%	3,700
Melanoma	3.2%	3,100
Ovary	2.9%	2,800
Leukemia	2.8%	2,700
<b>Pancreas</b>	<b>2.5%</b>	<b>2,400</b>

The pancreas is the 10<sup>th</sup> most common site of new cancers in Canada (**4,800 new cases total**)

# Estimated Cancer Deaths in 2015



**Males**  
**41,000 Deaths**

Site	Percent	Deaths
Lung	26.60%	10,900
Colorectal	12.4%	5,100
Pancreas	4.6%	1,900
Bladder	4.0%	1,650
Esophagus	3.9%	1,600
Leukemia	3.8%	1,550
Non-Hodgkin's lymphoma	3.5%	1,450
Stomach	3.2%	1,300
Brain/CNS	3.0%	1,250



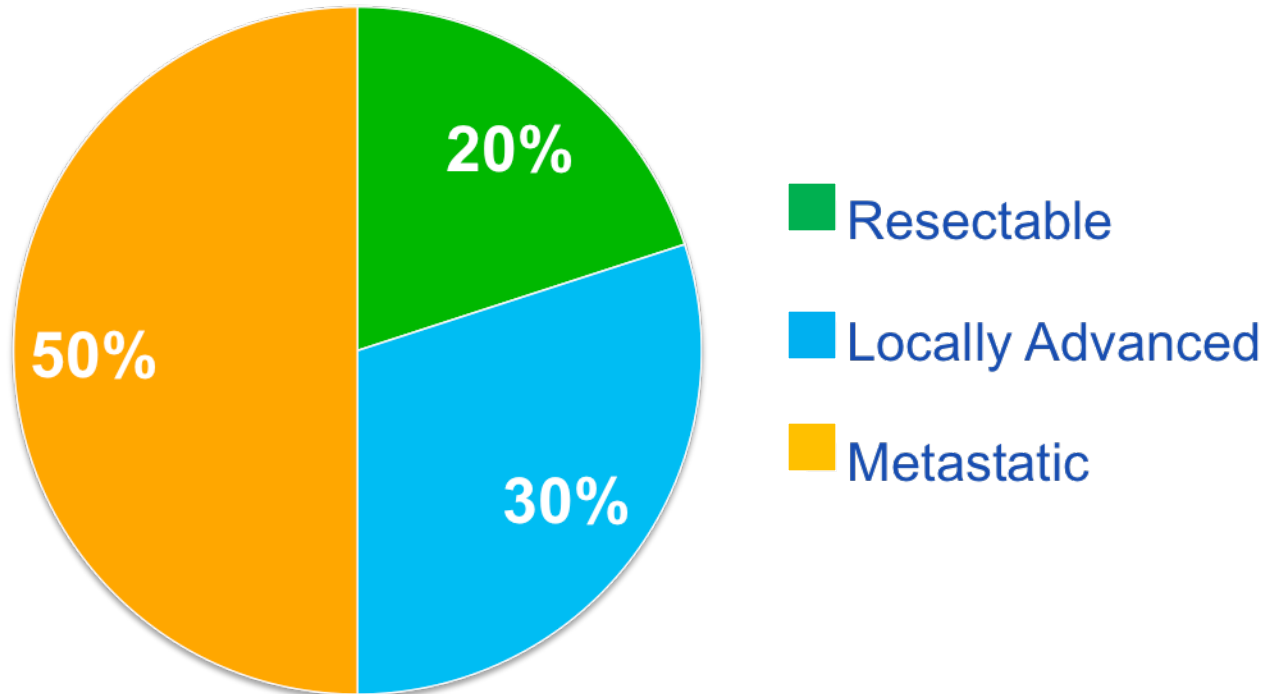
**Females**  
**37,000 Deaths**

Site	Percent	Deaths
Lung	27.0%	10,000
Breast	13.6%	5,000
Ovary	4.7%	1,750
Non-Hodgkin's lymphoma	3.3%	1,200
Leukemia	3.1%	1,150
Body of uterus	2.8%	1,050
Brain/CNS	2.3%	860
Stomach	2.1%	760

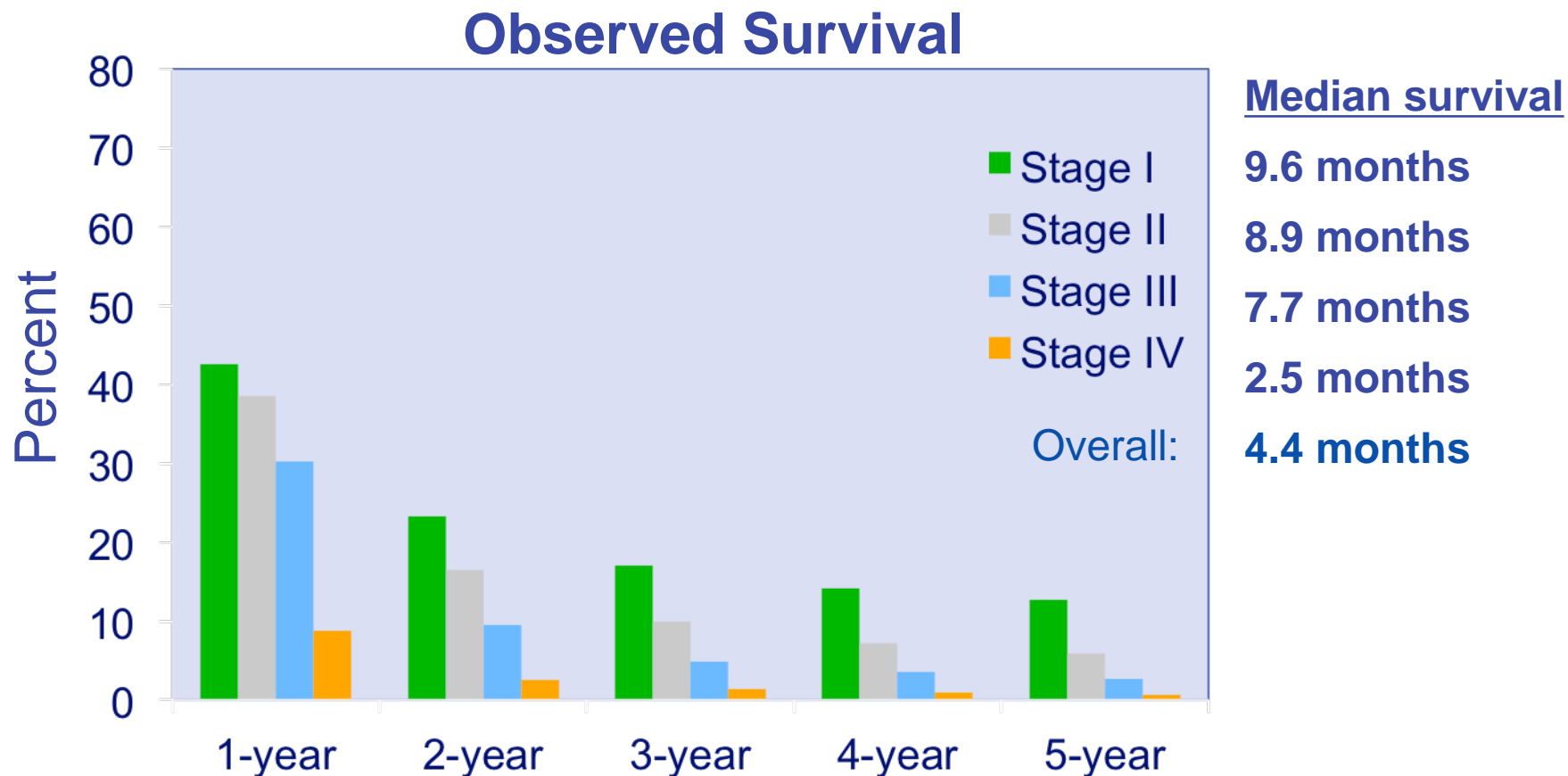
**Pancreatic cancer incidence  $\approx$  mortality rates**

**Pancreatic cancer is the 4<sup>th</sup> leading cause of cancer death among men and women in Canada (4,600 deaths total)**

# Clinical stage at diagnosis



# Prognosis and clinical stage

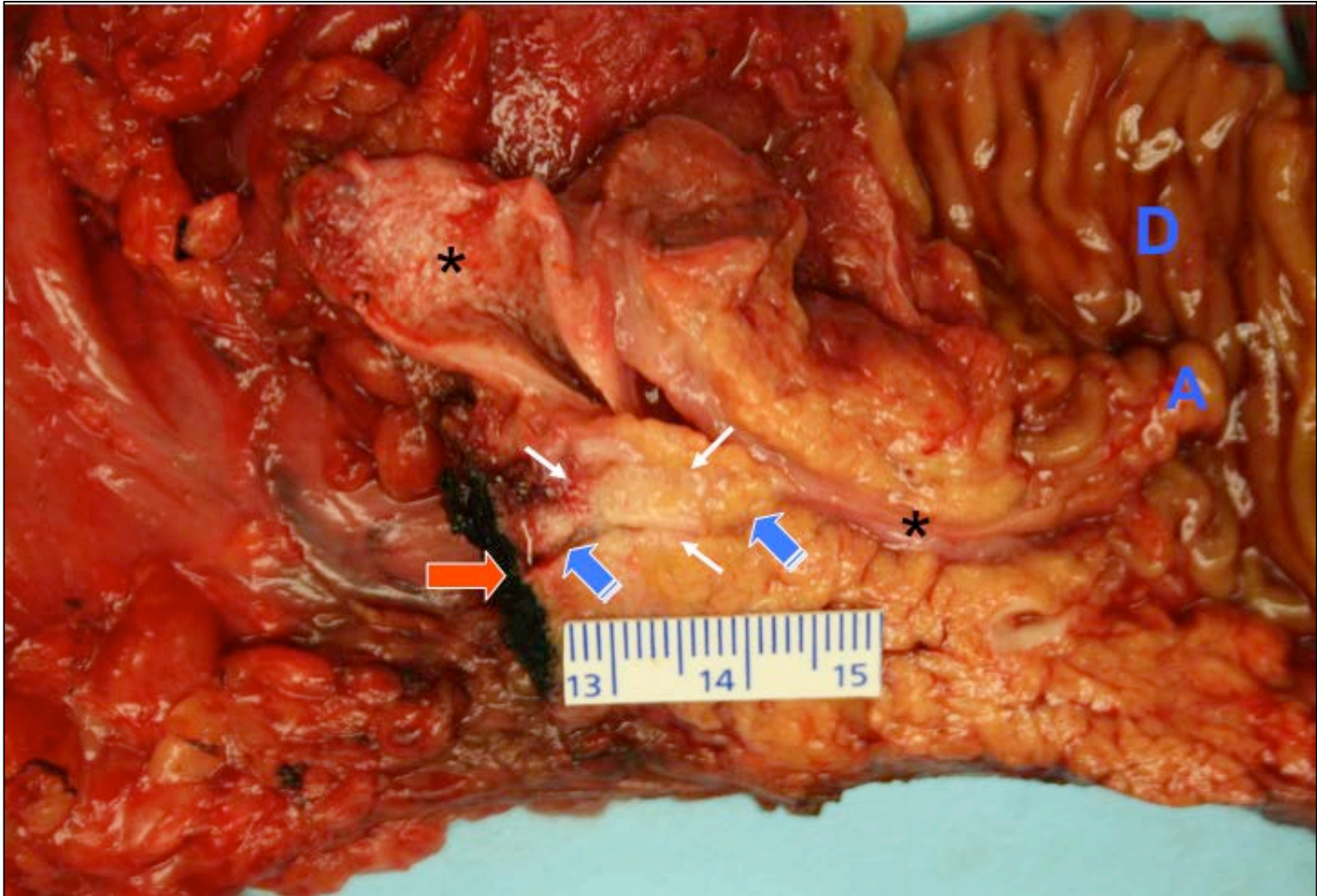




# Goals of Treatment

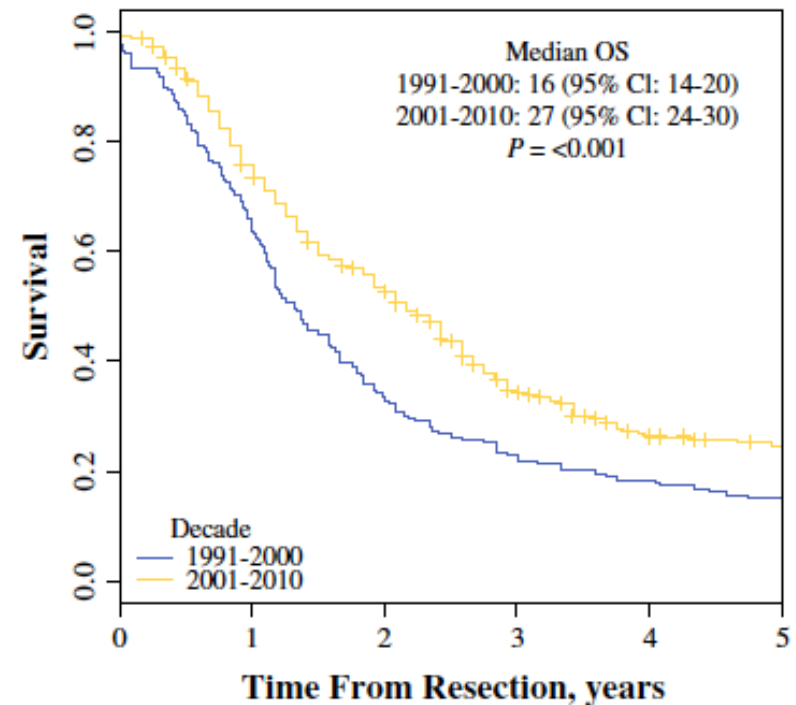
- Surgical resection is the only curative treatment for pancreatic cancer
- Primary goals of treatment for locally advanced disease:
  - Conversion therapy
    - Neoadjuvant therapy for initially unresectable disease with the goal of conversion to resectable status
  - Improved survival
    - Usually only beneficial to patients with adequate performance status (ECOG performance status 0 or 1, good pain management, patent biliary stent, and adequate nutritional intake)
  - Palliation and improved quality of life
    - Multidisciplinary management of symptoms due to biliary obstruction, gastric outlet obstruction, and cancer-related pain
    - Prevent and lessen/relieve suffering while ensuring optimal quality of life

# How do we get to this?



# Role of surgery for pancreatic adenocarcinoma

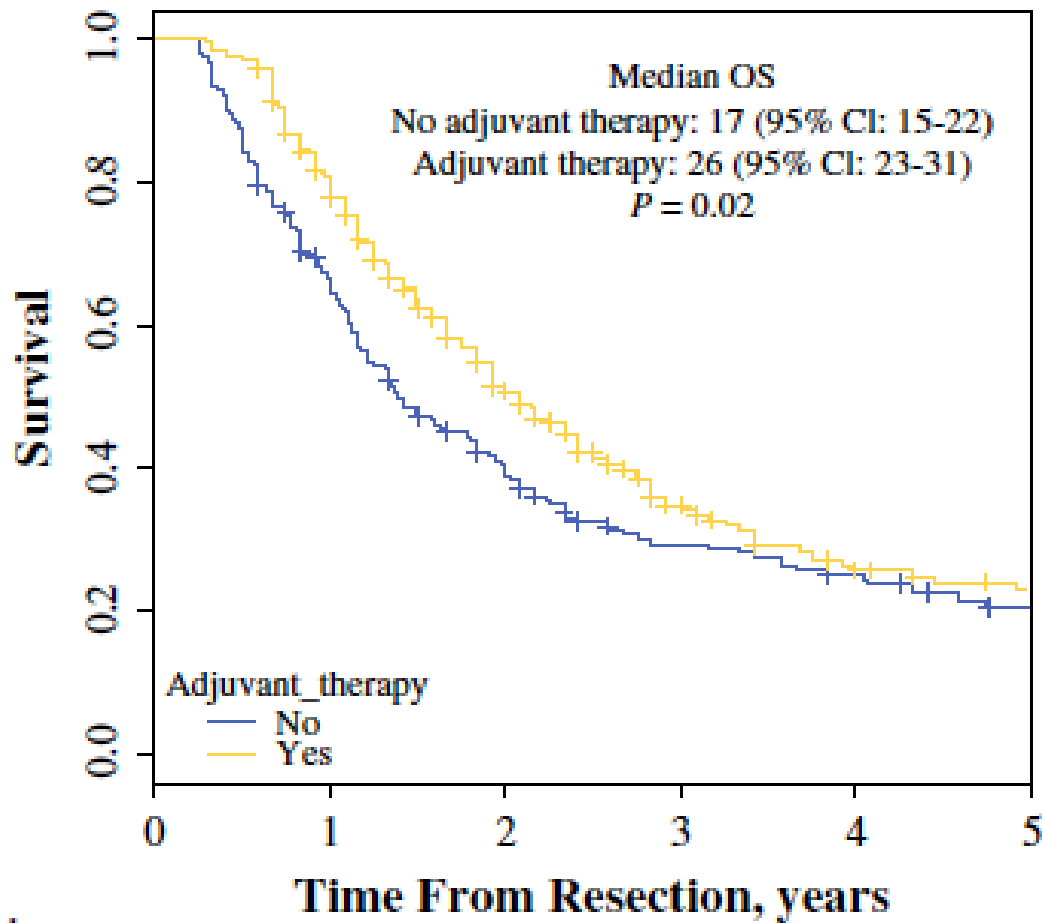
- best for long term survival
  - median OS 20-27 months<sup>1-4</sup>
- Goals of surgery
  - relief of symptoms
  - obtain R0 resection
- Multi-modality Rx optimal
- MCC discussion required for resectability<sup>5</sup>
  - important for LAPC



No. at risk	0	1	2	3	4	5
1991-2000	179	118	62	42	33	27
2001-2010	310	232	161	93	58	43

FIG. 1 Overall survival between time periods, including the entire cohort ( $n = 489$ ). *CI* confidence interval, *OS* overall survival

# Adjuvant therapy is important

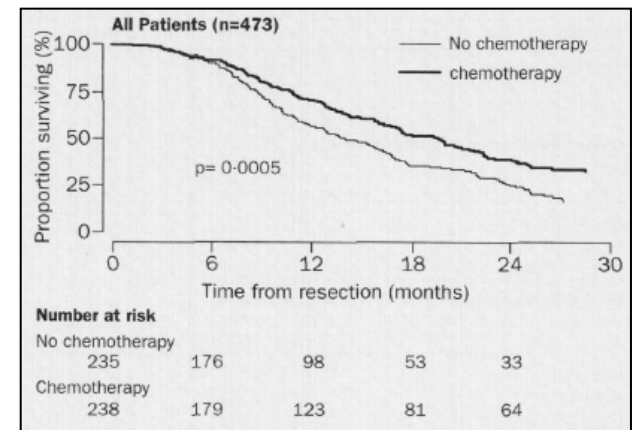


No. at risk						
No Adjuvant therapy	185	127	79	51	40	30
Adjuvant therapy	248	200	130	73	46	36

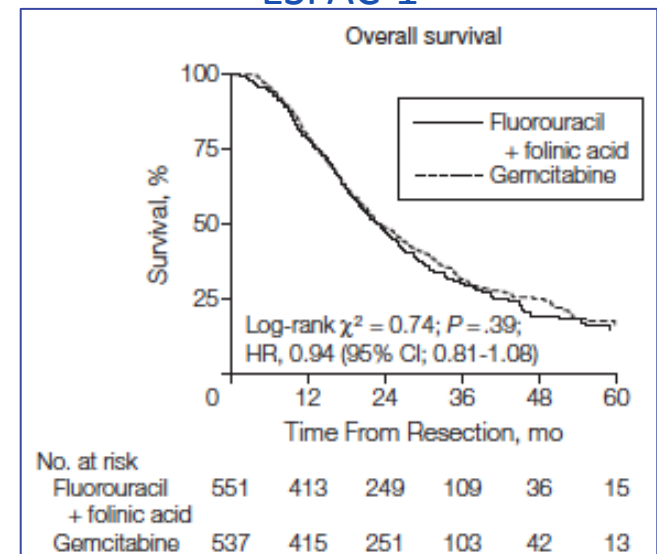


# New adjuvant regimens on the horizon?

- 5 FU and gemcitabine<sup>1,2</sup>
  - OS ~ 20-23 months
  - Gemcitabine → ↓ side effects
  
- ESPAC-4 → Gem/capecitabine vs. Gem<sup>3</sup>
  - 730 pts analyzed
  - OS GEM/CAP = 28.0 months (95% CI: 23.5 – 31.5) vs GEM = 25.5 months (22.7 – 27.9)
  
- Trial results pending
  - Folfirinox vs. Gem (PA.6)
  - Gem/Abraxane vs. Gem
    - accrual complete



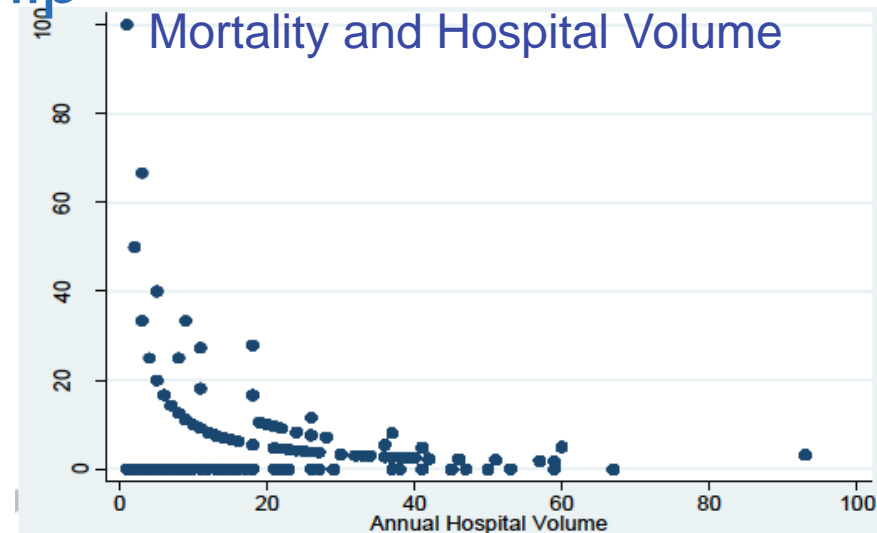
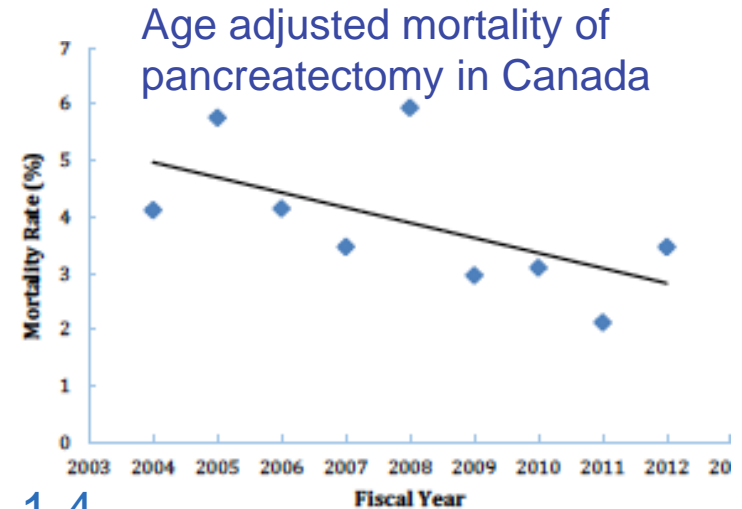
ESPAC-1



ESPAC-3

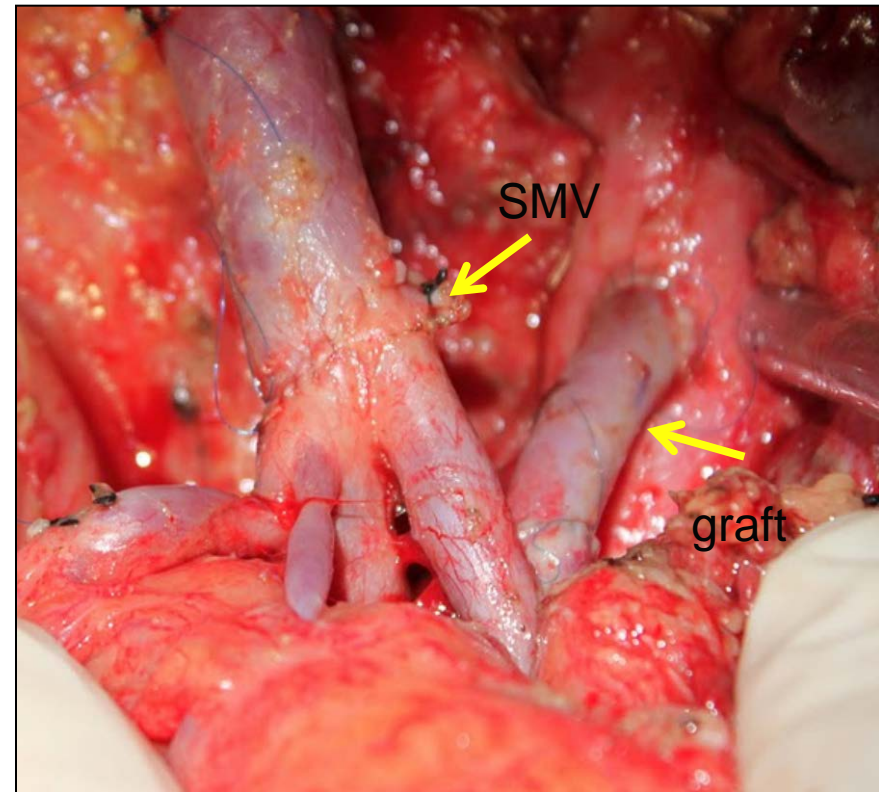
# Pancreatectomy has evolved

- Patient selection is better
  - staging is more sensitive
  - CT/ EUS/ MRI
- Pancreatectomy is safer
- Volume-outcome relationship<sup>1-4</sup>
  - ↑ volumes =
  - ↓ peri-operative mortality
  - ↓ cancer related mortality



# Technical advances allow bigger resections

- Vascular resections
  - PV resection routine
  - arterial resections
    - increasing experience
- Minimally invasive surgery
  - staging laparoscopy
  - laparoscopic/ robotic pancreatectomies
- More complex resections
  - obtain negative margin
- Better perioperative care



**SMV and SMA resection with SFV graft**

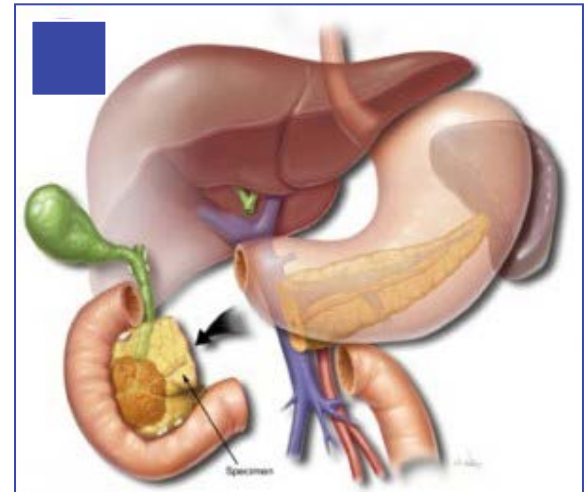
# Key principles of resectability

- Localized disease
  - no evidence of metastatic disease
- Resectable with R0 intent
  - recognition of need for vascular resection/reconstruction
  - judicious use of arterial resection in selected populations may have a role
- Adequate performance status

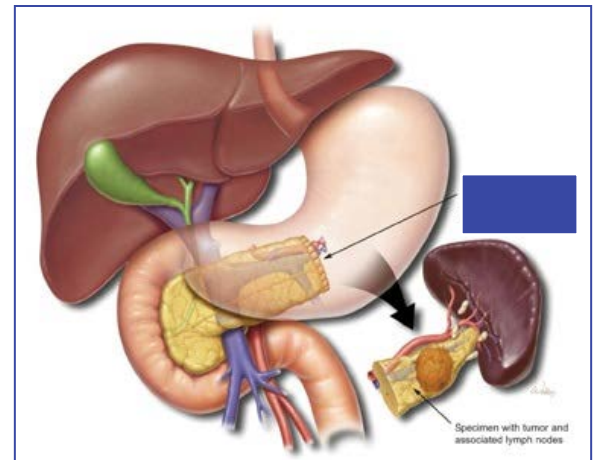


# Important Surgical Outcomes

- Negative margins
  - rates of positive margins
    - < 1mm or tumour at margin?
  - difficulty in assessing margins
    - most margins are R1<sup>1,2</sup>
  - 5 mm margin optimal
- Adequate lymph nodes retrieval
  - $\geq 12$  lymph nodes<sup>3</sup>
  - LN Ratio < 0.2 better if N1<sup>4</sup>
- Complications
  - anastomotic leaks
  - delayed gastric emptying
  - bleeding
  - endocrine/exocrine insufficiency



pancreaticoduodenectomy



distal pancreatectomy

# Complications after pancreaticoduodenectomy<sup>1</sup>

Characteristic	<i>n</i> = 635	
	No. of Patients	%
Overall complications	323	51
Gastrointestinal bleed	14	2.2
Intra-abdominal bleed	32	5
Urinary tract infection	18	3
Wound infection	76	12
Major complications	132	21
Delayed gastric emptying	72	11
Pancreatic leak	73	12
Grade A	17	3
Grade B*	45	7
Grade C	12	2
Intra-abdominal abscess	133	21
Clavien Grade IIIa	104	16
Clavien Grade IIIb	34	5
Perioperative mortality	9	1.4

# Assessing resectability

- dedicated pancreatic imaging

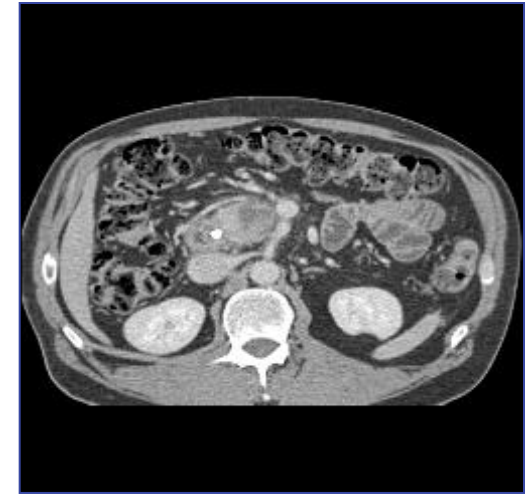
- CT preferred → MRI for problem solving
- What is the relationship to vessels?
- Are metastases present?

- Tissue diagnosis

- mandatory for neoadjuvant therapy
- use EUS unless never-resectable

- Laparoscopy/ PET

- limited role



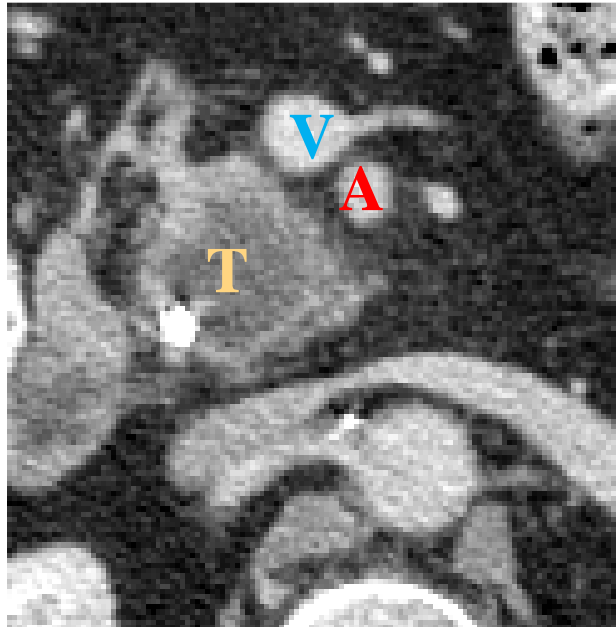
tumor clear of major vessels



tumor with PV involvement

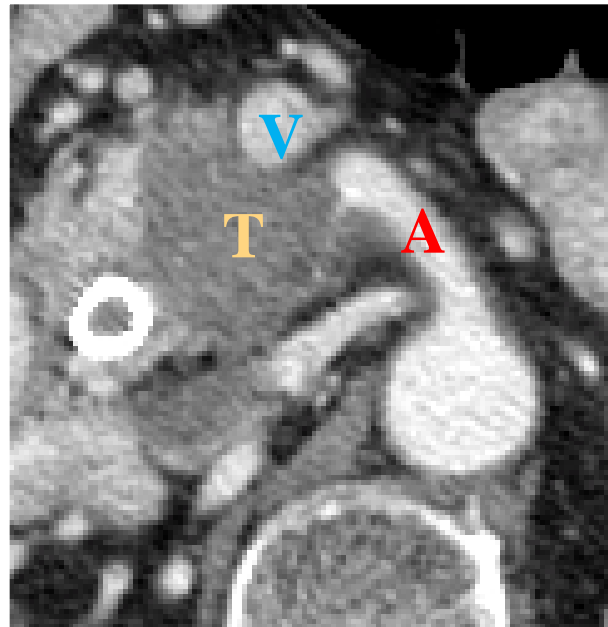
# Clinical spectrum of resectability

**Resectable**



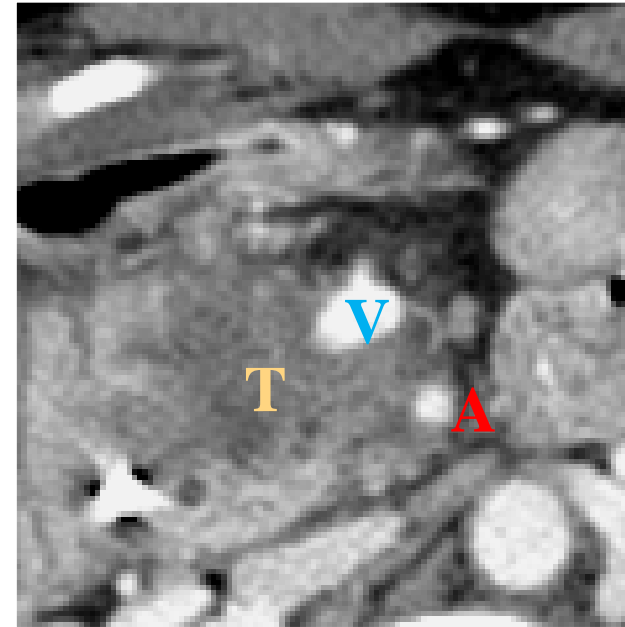
R0 likely

**Borderline Resectable**



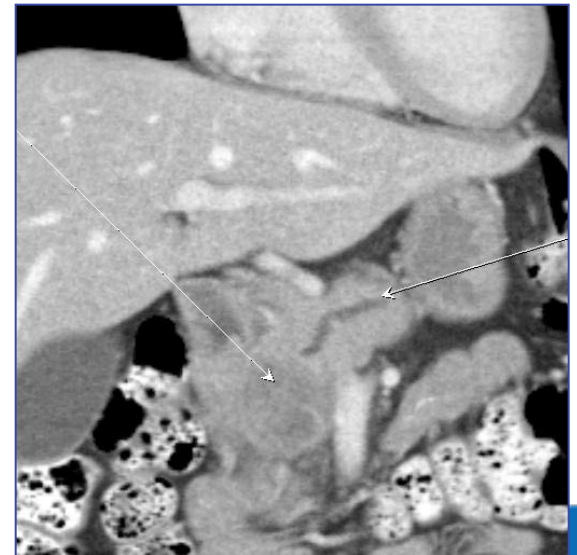
R1 likely  
Surgery possible but  
results suboptimal

**Unresectable**



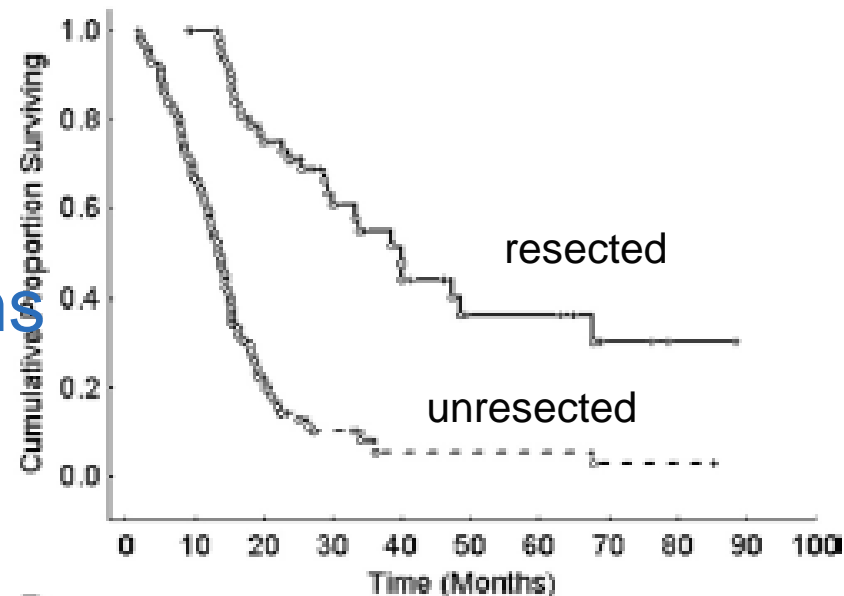
# Resectable pancreatic cancer

- No metastases
- Venous involvement absent or minimal (<180° no deformity)
- Normal arterial tissue planes
- Rx:
  - Upfront resection standard
  - Neoadjuvant therapy only
    - High risk patients
    - Clinical trial



# Borderline resectable disease

- Technically resectable but high risk for margin-positive resection
- Subset of locally advanced disease
- Various classification systems
  - NCCN Guidelines <sup>1</sup>
  - MD Anderson Cancer Center<sup>2</sup>
- Neoadjuvant treatment common



OS borderline resectable pancreas cancer resected vs. unresected patients <sup>3</sup>

# NCCN (2016) Criteria for resectability<sup>1</sup>

Resectability Status	Arterial	Venous
Resectable	No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or $\leq 180^\circ$ contact without vein contour irregularity.
Borderline Resectable <sup>2</sup>	<p><u>Pancreatic head /uncinate process:</u></p> <ul style="list-style-type: none"> <li>• Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction.</li> <li>• Solid tumor contact with the SMA of <math>\leq 180^\circ</math></li> <li>• Presence of variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present as it may affect surgical planning.</li> </ul> <p><u>Pancreatic body/tail:</u></p> <ul style="list-style-type: none"> <li>• Solid tumor contact with the CA of <math>\leq 180^\circ</math></li> <li>• Solid tumor contact with the CA of <math>&gt;180^\circ</math> without involvement of the aorta and with intact and uninvolved gastroduodenal artery [some members prefer this criteria to be in the unresectable category]</li> </ul>	<ul style="list-style-type: none"> <li>• Solid tumor contact with the SMV or PV of <math>&gt;180^\circ</math>, contact of <math>\leq 180^\circ</math> with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction.</li> <li>• Solid tumor contact with the inferior vena cava (IVC).</li> </ul>
Unresectable <sup>2</sup>	<p>• Distant metastasis (including non-regional lymph node metastasis)</p> <p><u>Head/uncinate process:</u></p> <ul style="list-style-type: none"> <li>• Solid tumor contact with SMA <math>&gt;180^\circ</math></li> <li>• Solid tumor contact with the CA <math>&gt;180^\circ</math></li> <li>• Solid tumor contact with the first jejunal SMA branch</li> </ul> <p><u>Body and tail</u></p> <ul style="list-style-type: none"> <li>• Solid tumor contact of <math>&gt;180^\circ</math> with the SMA or CA</li> <li>• Solid tumor contact with the CA and aortic involvement</li> </ul>	<p><u>Head/uncinate process</u></p> <ul style="list-style-type: none"> <li>• Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)</li> <li>• Contact with most proximal draining jejunal branch into SMV</li> </ul> <p><u>Body and tail</u></p> <ul style="list-style-type: none"> <li>• Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)</li> </ul>

# Arterial involvement

- Solid c
- Solid c
- Solid c  
aorta/

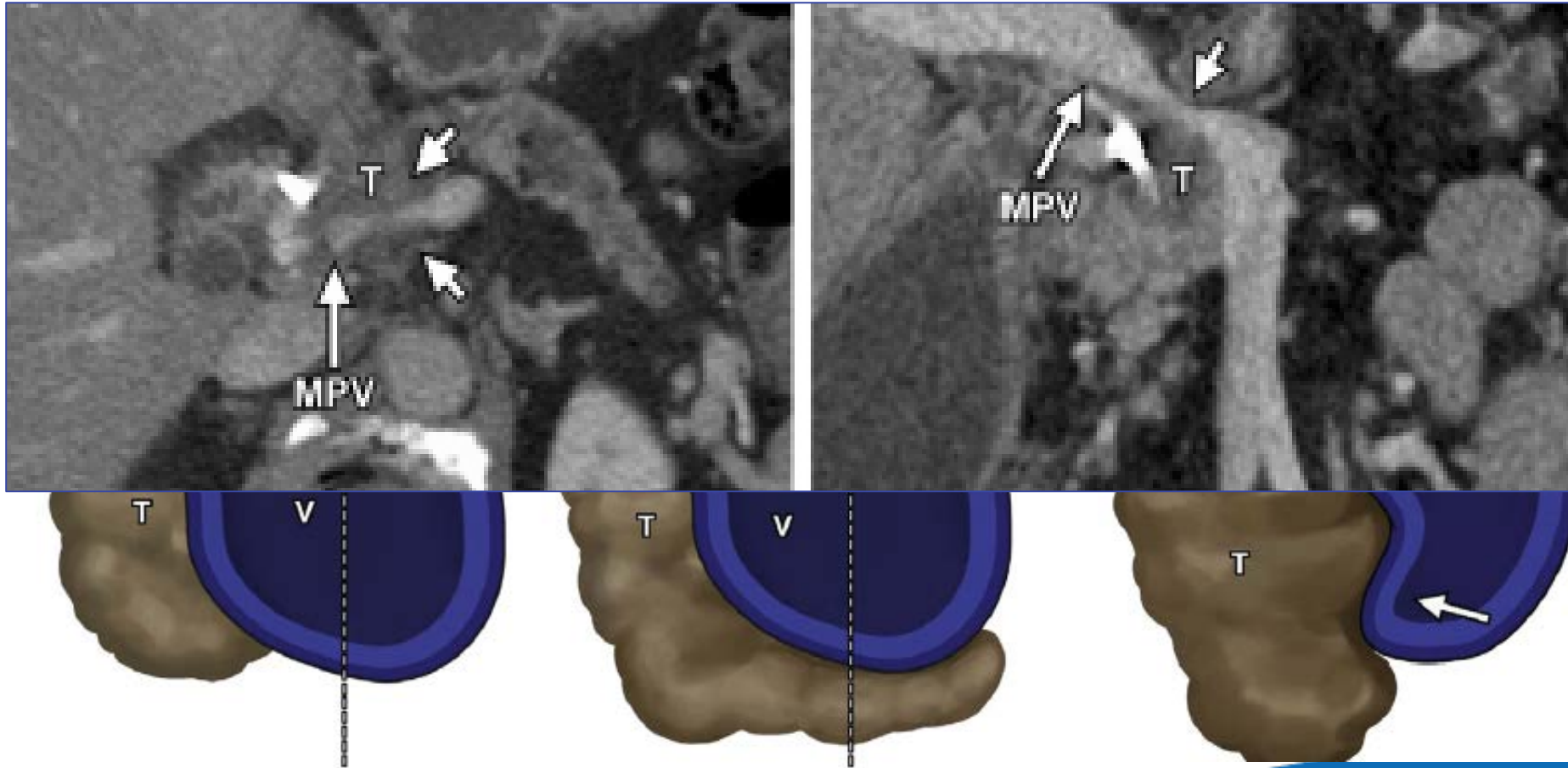


when



# Venous involvement

- *Solid* tumour contact  $\geq 180$  or  $< 180$  with deformity or thrombus, that is suitable for reconstruction



# MD Anderson Classification<sup>1</sup>

- Type A: vascular involvement

- Type B: potential metastases

- Type C: poor performance status

**Table 1.** Clinical and Demographic Characteristics of 160 Patients with Borderline Resectable Pancreatic Cancer

Characteristic	All patients	Borderline resectable type			p Value*
		A	B	C	
Total patients, n	160	84	44	32	
Age, y					
Median (mean)	63 (63)	60 (61)	61 (61)	73 (71)	0.001
Range	36-90	37-81	36-77	50-90	
Gender, n (%)					NS
Male	84 (52)	37 (44)	26 (59)	21 (66)	
Female	76 (48)	47 (56)	18 (41)	11 (34)	
Tumor location in pancreas, n (%)					NS
Head/uncinate	142 (89)	73 (87)	40 (91)	29 (91)	
Body/tail	18 (11)	11 (13)	4 (9)	3 (9)	
Prereferral laparotomy, n (%)	38 (24)	16 (19)	19 (43)	3 (9)	0.001
Bypass	31 (19)	12 (14)	16 (36)	3 (9)	0.003
Exploration only	7 (4)	4 (5)	3 (7)	0 (0)	NS
Prereferral therapy	12 (8)	7 (8)	5 (11)	0 (0)	NS
Systemic chemotherapy	6 (4)	3 (4)	3 (7)	0 (0)	NS
External-beam radiation	7 (4)	5 (6)	2 (5)	0 (0)	NS
Pretreatment CA19-9, U/mL					
All patients					
Median (mean)	212 (838)	190 (803)	269 (954)	324 (767)	NS
Range	2.3-11,482	2.3-11,482	9.1-7,194	13-3,787	
Patients who underwent pancreatectomy, n (%)					
Median (mean)	218 (961)	154 (1,138)	211 (773)	324 (831)	NS
Range	9-11,482	19-11,482	9-7,194	32-2,797	
Patients who did not undergo pancreatectomy					
Median (mean)	203 (746)	190 (582)	578 (1,159)	268 (730)	NS
Range	2-6,725	2-6,725	23-3,996	13-3,787	
Pancreatectomy performed, n (%)					
Yes	66 (41)	32 (38)	22 (50)	12 (38)	NS
No	94 (59)	52 (62)	22 (50)	20 (62)	

\*p value for comparison between borderline resectable types.

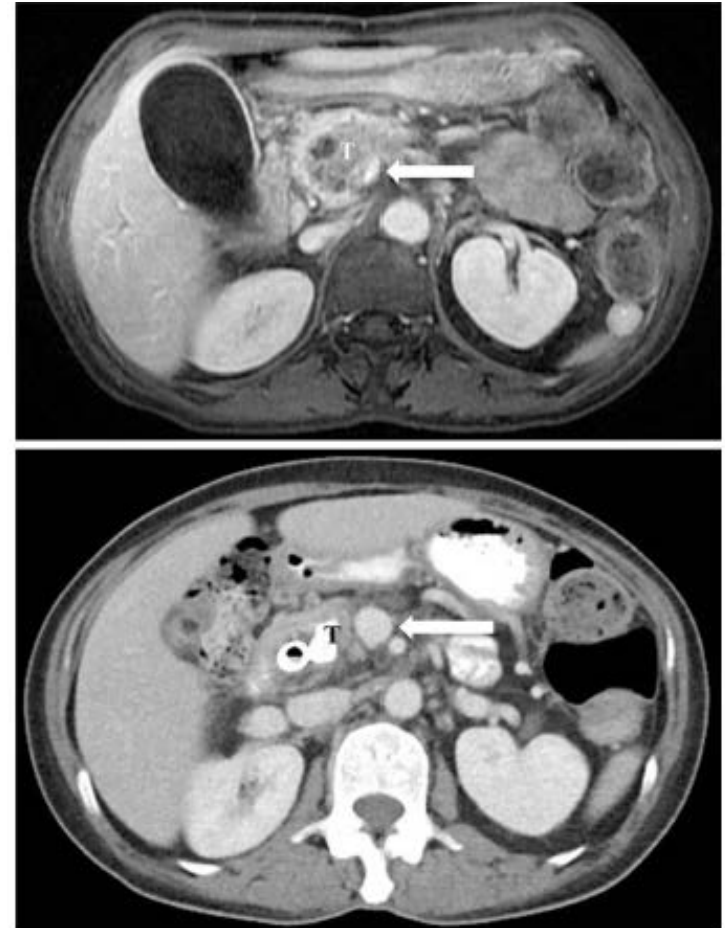
**Table 3.** Rates of Resection, Pathologic Response, and Survival for 160 Patients with Borderline Resectable Pancreatic Cancer

MD Anderson borderline type	Patients					Median survival, mo			p Value*	
	Total		Resected		Treatment effect IIb, III or IV*	All patients	Resected patients	Patients who did not undergo resection		
	n	%	n	%	n	%				
A	84	52	32	38	19	59	21	40	15	0.001
B	44	28	22	50	13	59	16	29	12	0.001
C	32	20	12	38	5	42	15	39	13	0.009
Total	160		66	41	37	56	18	40	13	0.001

\*Percent of patients with that type of disease who underwent resection; treatment effect not reported in 3 of 66 patients who underwent pancreatectomy.  
 †p value for comparison of median survival times of resected and nonresected patients.

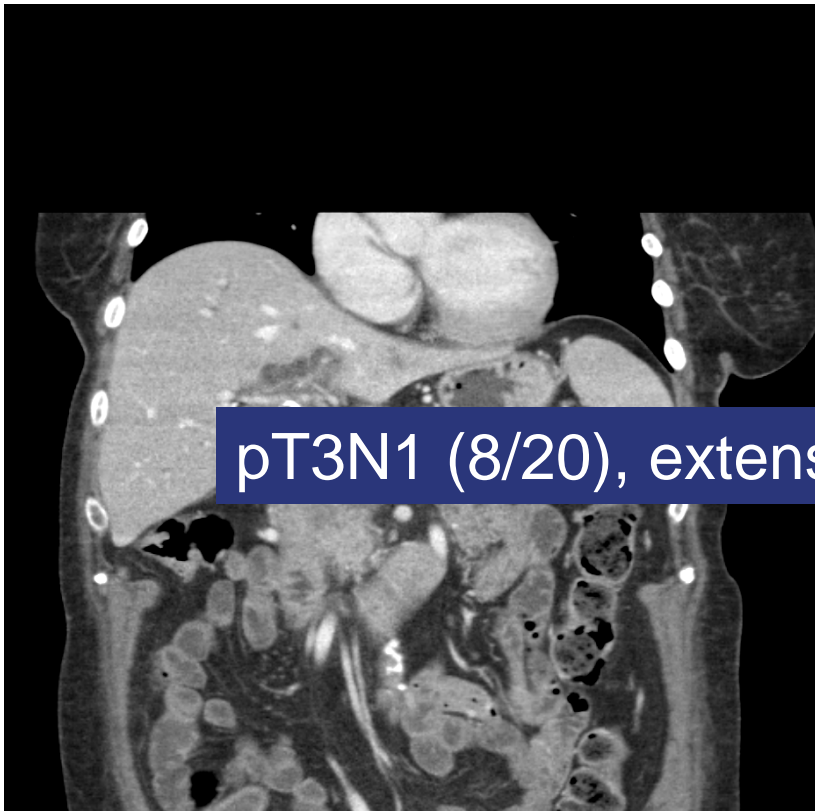
# Conversion therapy → downstaging?

- shrink locally advanced to potentially resectable?
- previous era
  - very little downstaging
  - very little pathologic response
- new regimens
  - Folfirnox
  - Gemcitabine-abraxane
- Radiologic response ≠ tumour response

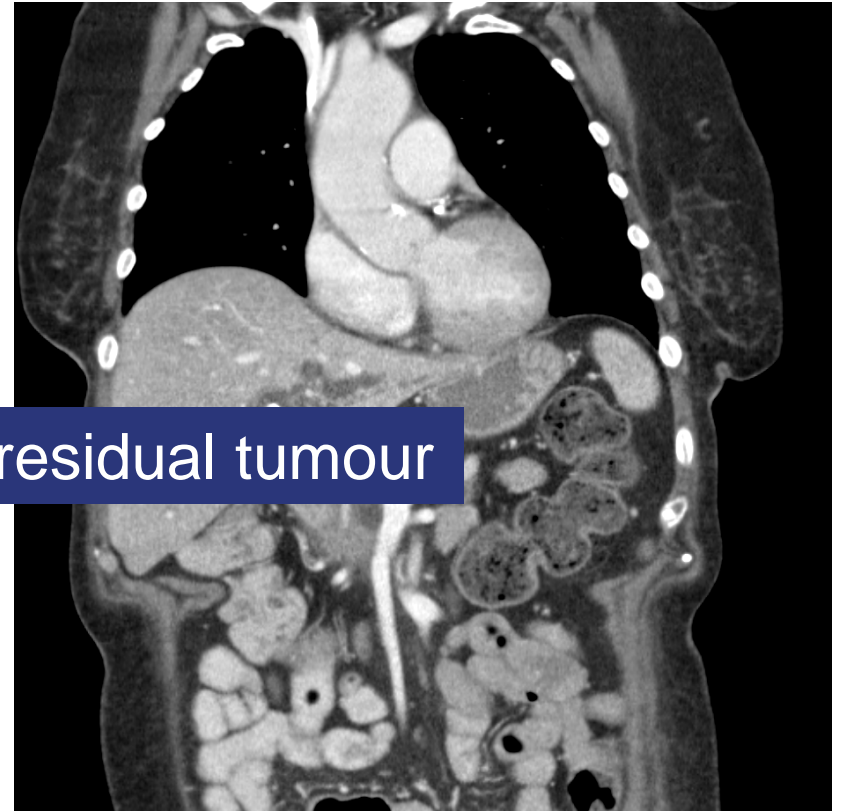


**FIG. 3** Radiographic response to mFOLFIRINOX. Magnetic resonance imaging (MRI) (*top panel*) before therapy and computed tomography (CT) (*bottom panel*) after 2 months of mFOLFIRINOX show reopening of the nearly occluded superior mesenteric vein (SMV) (*arrow*), with complete resolution of tumor (T) with residual calcification

# Case 1



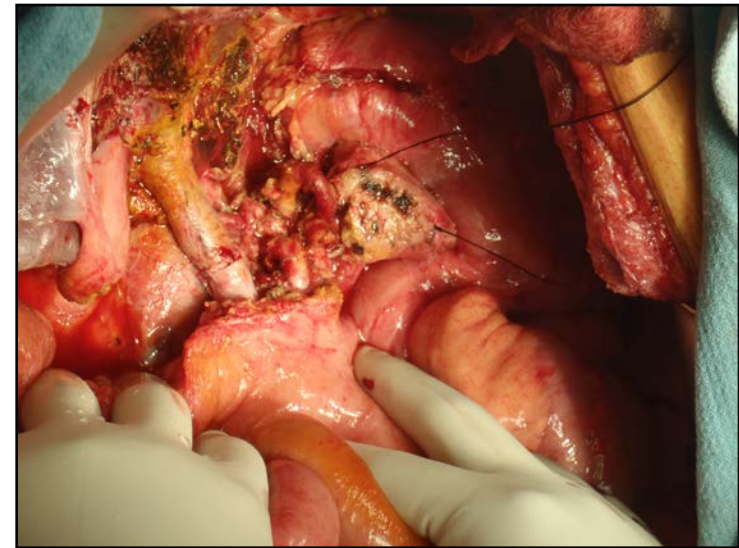
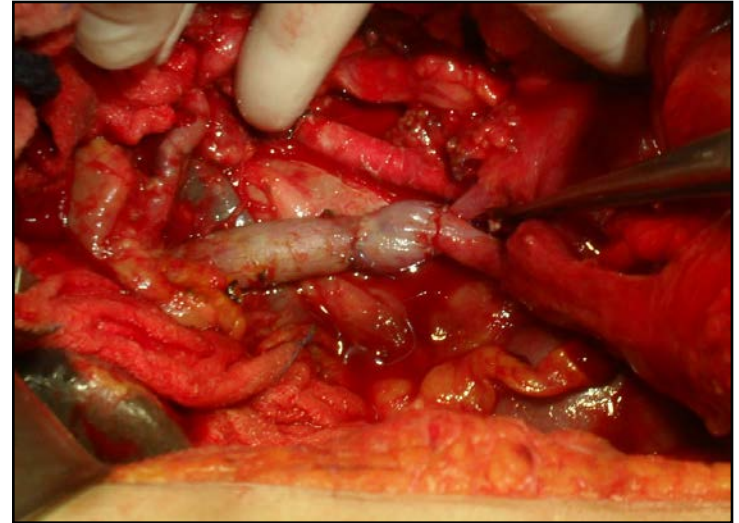
pT3N1 (8/20), extensive residual tumour

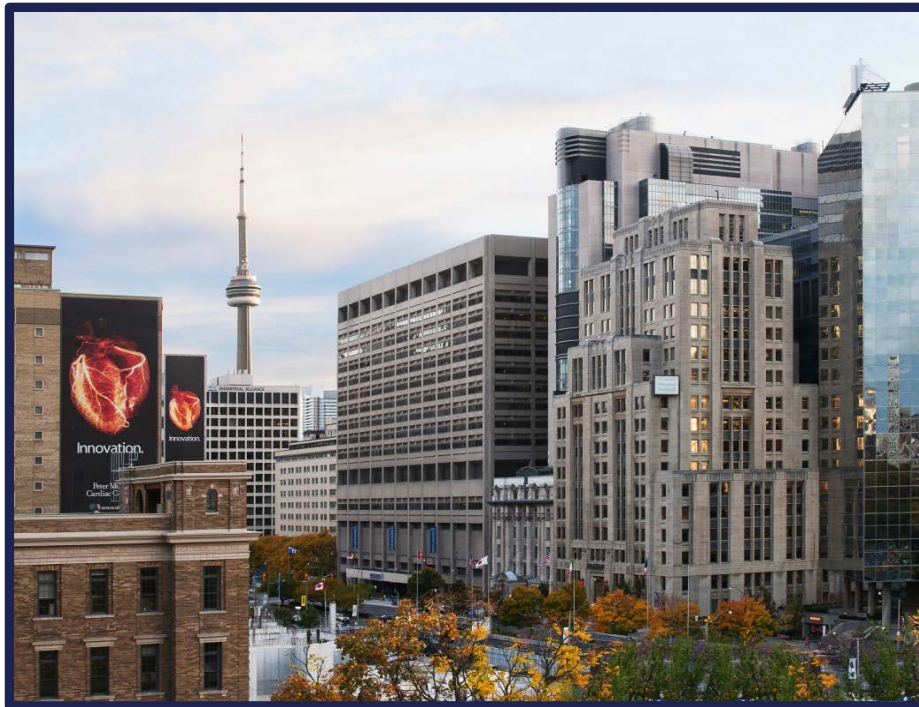


6 cycles Gem-Abiraxane

# Conclusions

- Resectability depends on
  - anatomic features of tumor
  - cancer biology
  - patient physiology
- Borderline resectable/Locally advanced cancers
  - resectability is surgeon dependent
  - multimodality approach
  - vascular reconstruction often required





Princess Margaret Hospital



Toronto General Hospital