



Pancreatic Cancer

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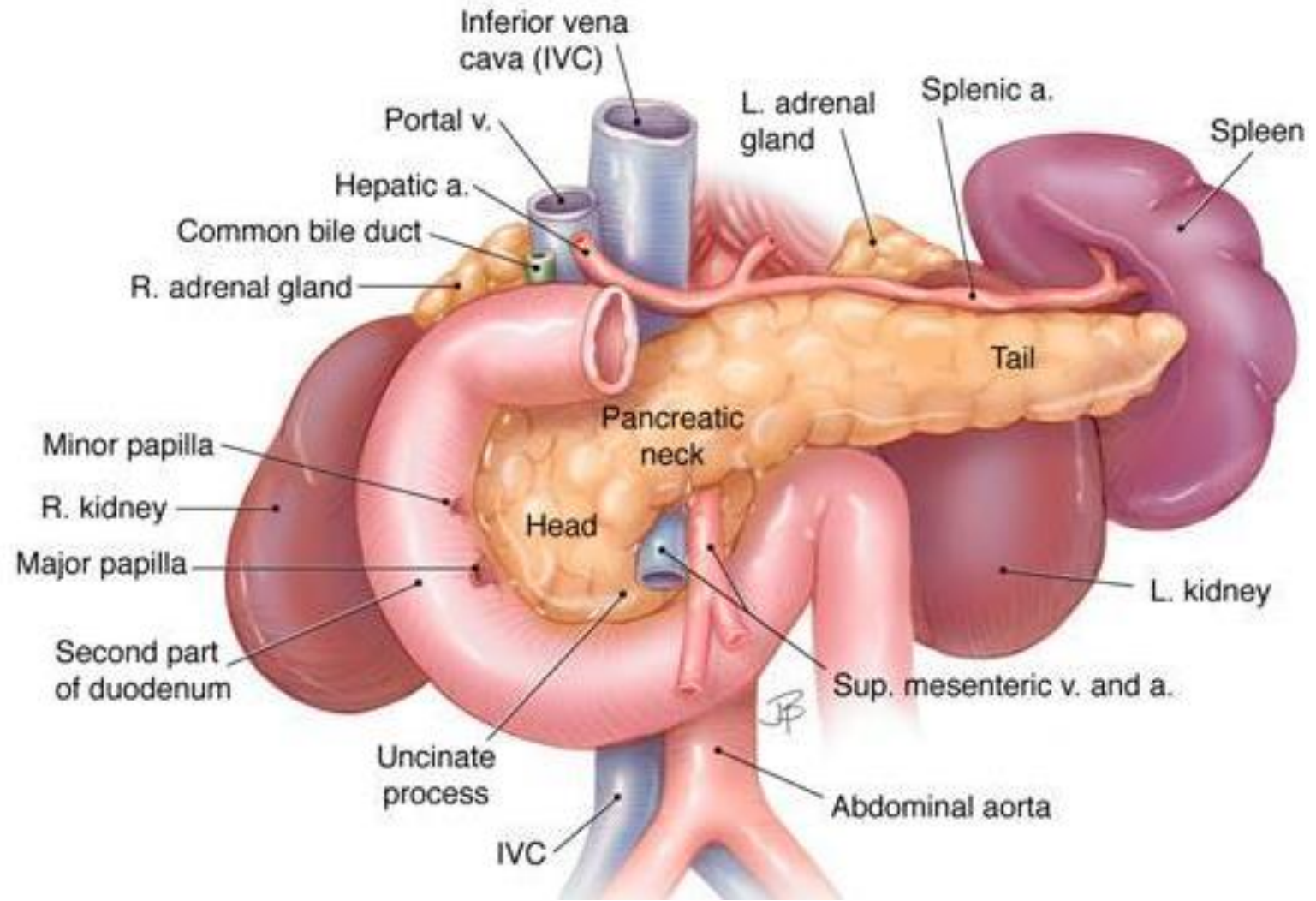
University of Texas MD Anderson Cancer Center

Banner MD Anderson, Gilbert, Az

Pancreatic Cancer Stats

- Third leading cause of cancer death in men and women in the United States^{1,2}
 - 53,070 patients will be diagnosed 41,780 will die in 2016
- Poor prognosis
 - 74% die in the first 12 mo, 5-year survival = 8%

Anatomy



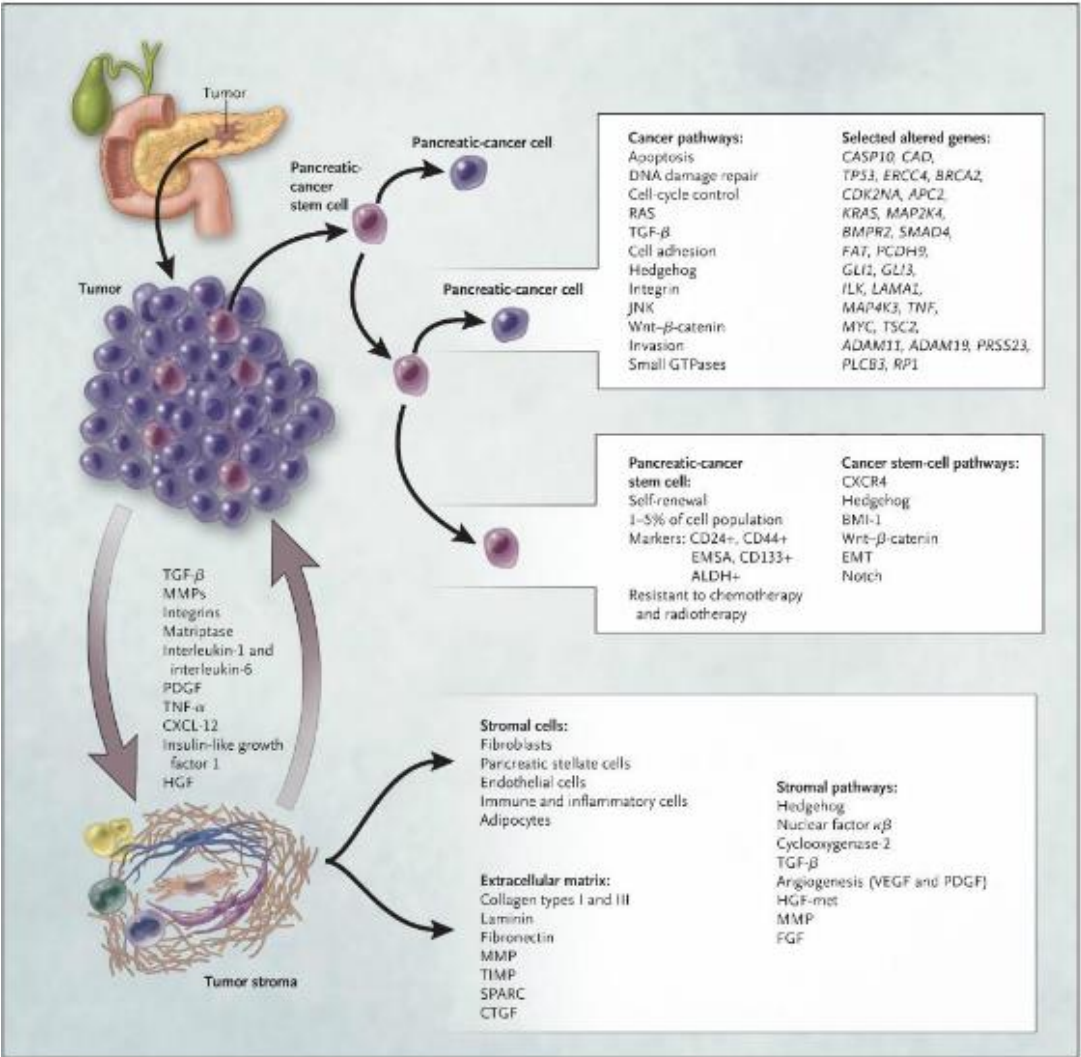
Risk Factors

- Smoking (~3X)
- Association (less conclusive evidence) with moderate alcohol intake, high fat diet, recent history of diabetes (type 2), hx of chronic pancreatitis.
- Familial history (5-10%)

Carcinogenesis and Molecular Events

- *PRECANCEROUS LESIONS: PANIN1-3, IPMN, MCN*
- Tumor suppressor genes: p16 (95%), *TP53* (75%), *DPC4* (*SMAD4*), *CDKN2* (95%)
- Oncogenes: *KRAS* (90%), *AKT2*,
- DNA mismatch repair genes

Pancreatic Cancer: Key Pathways



Familial Pancreatic Cancer

- Index case + at least 2 first degree relatives
- NFPTR (Johns Hopkins): 270 families with FPC
- Genetic Syndromes:
 - Familial Atypical MM (p16), 15-20 X
 - BRCA2 or PALB2, 10 X
 - HNPCC (Lynch Sy)
 - Hereditary pancreatitis (trypsinogen gene)
 - Peutz-Jeghers Sy (STK11)

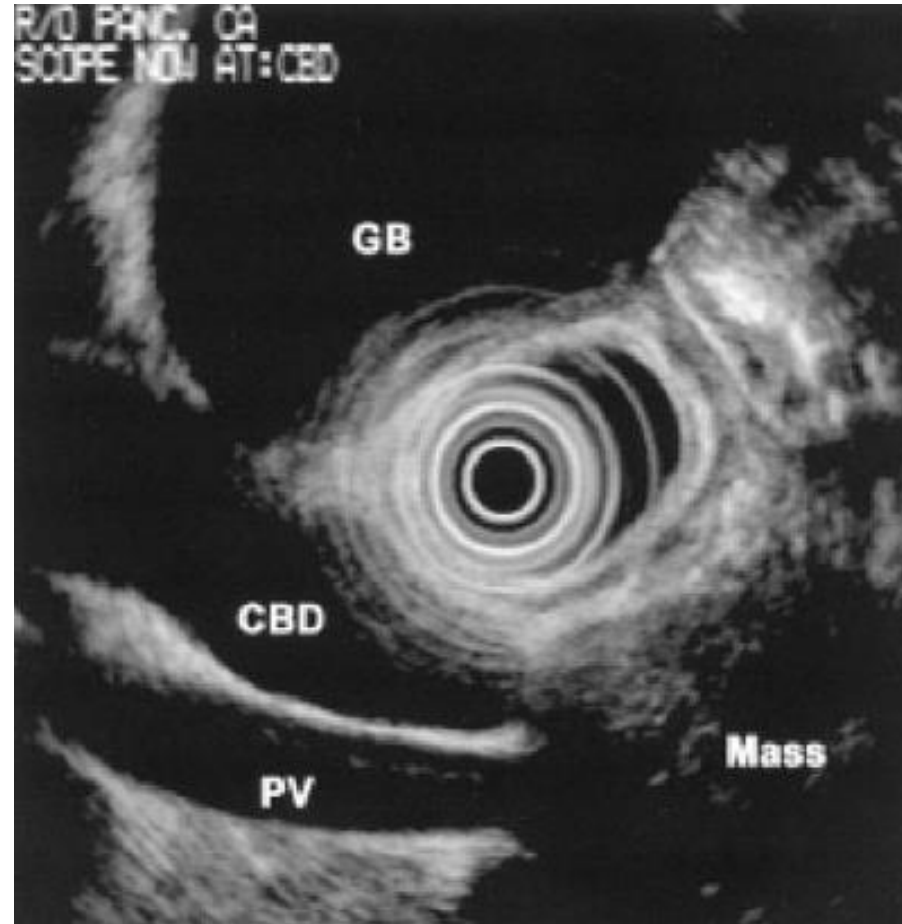
Symptoms in Pancreatic Cancer

Head of Pancreas		Body and Tail of Pancreas	
Symptoms	% Patients	Symptoms	% Patients
Weight Loss	92%	Weight Loss	100%
Jaundice	82%	Pain	87%
Pain	72%	Nausea	43%
Anorexia	64%	Weakness	42%
Nausea	45%	Vomiting	37%
Vomiting	37%	Anorexia	33%
Weakness	35%	Constipation	27%
Dark Urine	63%	Food Intolerance	7%
Light Stool	62%	Jaundice	7%

Diagnostic Tools

- Spiral computerized tomography
- Positron emission tomography
- Endoscopic ultrasound
- ERCP with brushings and lavage
- Laparoscopic staging
- Biomarker examination of serum CA 19-9

EUS



Histology and Imaging

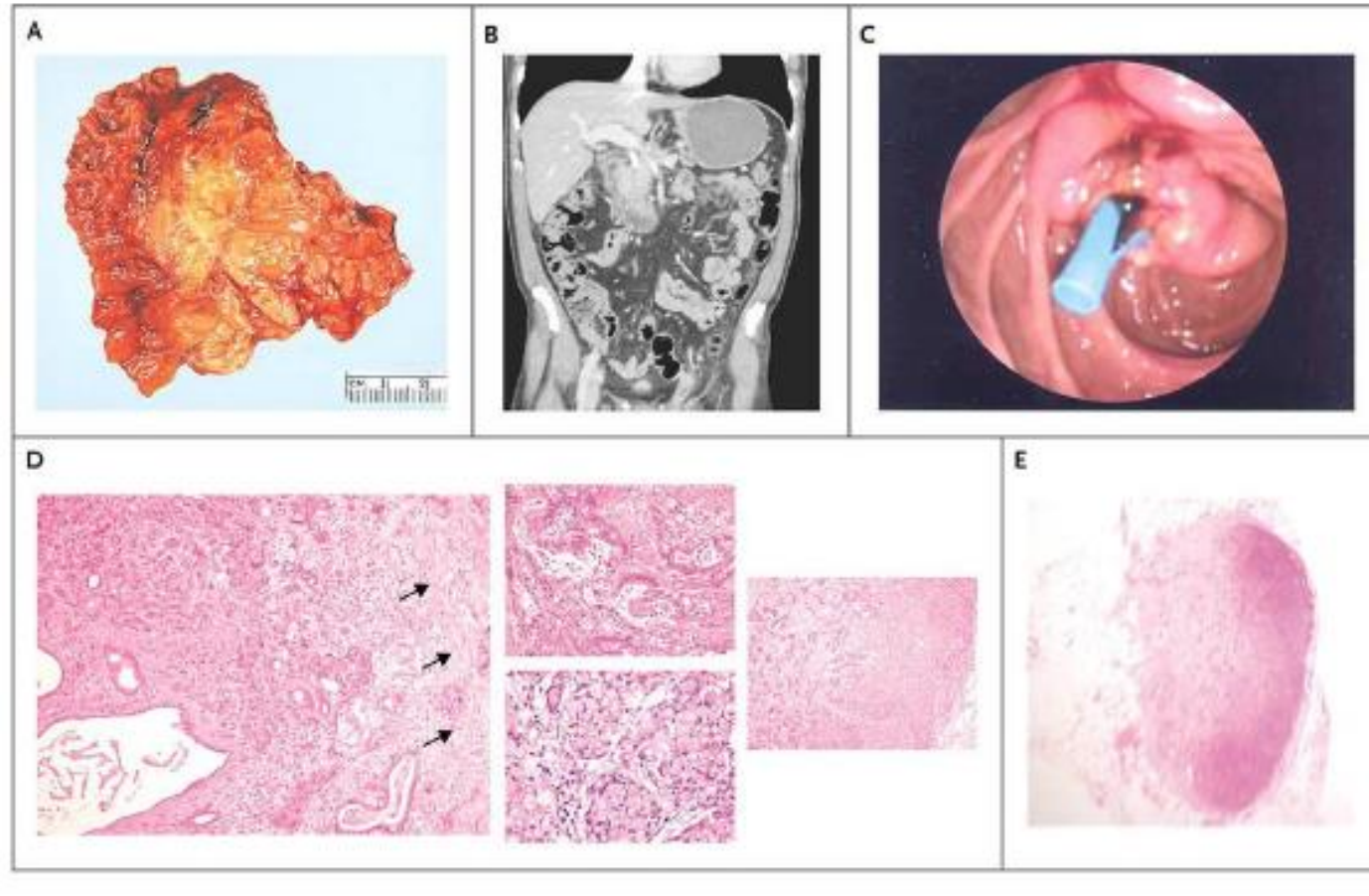


Table 1. Staging of Pancreatic Cancer.*

Stage	Tumor Grade	Nodal Status	Distant Metastases	Median Survival† mo	Characteristics
IA	T1	N0	M0	24.1	Tumor limited to the pancreas, ≤2 cm in longest dimension
IB	T2	N0	M0	20.6	Tumor limited to the pancreas, >2 cm in longest dimension
IIA	T3	N0	M0	15.4	Tumor extends beyond the pancreas but does not involve the celiac axis or superior mesenteric artery
IIB	T1, T2, or T3	N1	M0	12.7	Regional lymph-node metastasis
III	T4	N0 or N1	M0	10.6	Tumor involves the celiac axis or the superior mesenteric artery (unresectable disease)
IV	T1, T2, T3, or T4	N0 or N1	M1	4.5	Distant metastasis

* N denotes regional lymph nodes, M distant metastases, and T primary tumor.

† Data are from Bilimoria et al.⁴⁵

Treatment Options by Stage

- Stage I (localized)
 - Radical pancreatic resection
 - Adjuvant chemotherapy (5-FU) and irradiation
- Stage II and III (regional, locally advanced)
 - Resection ± adjuvant chemoradiation with 5-FU when possible
 - Chemotherapy (5-FU) and irradiation for unresectable disease
 - Systemic chemotherapy (5-FU) or Gemcitabine based
- Stage IV (metastatic)
 - First-line gemcitabine monotherapy (approved) or 5-FU
 - Gemcitabine after 5-FU failure (approved)
 - Pain relieving procedures: celiac axis nerve or intrapleural block
 - Palliative surgery (as above)

Surgical Therapy

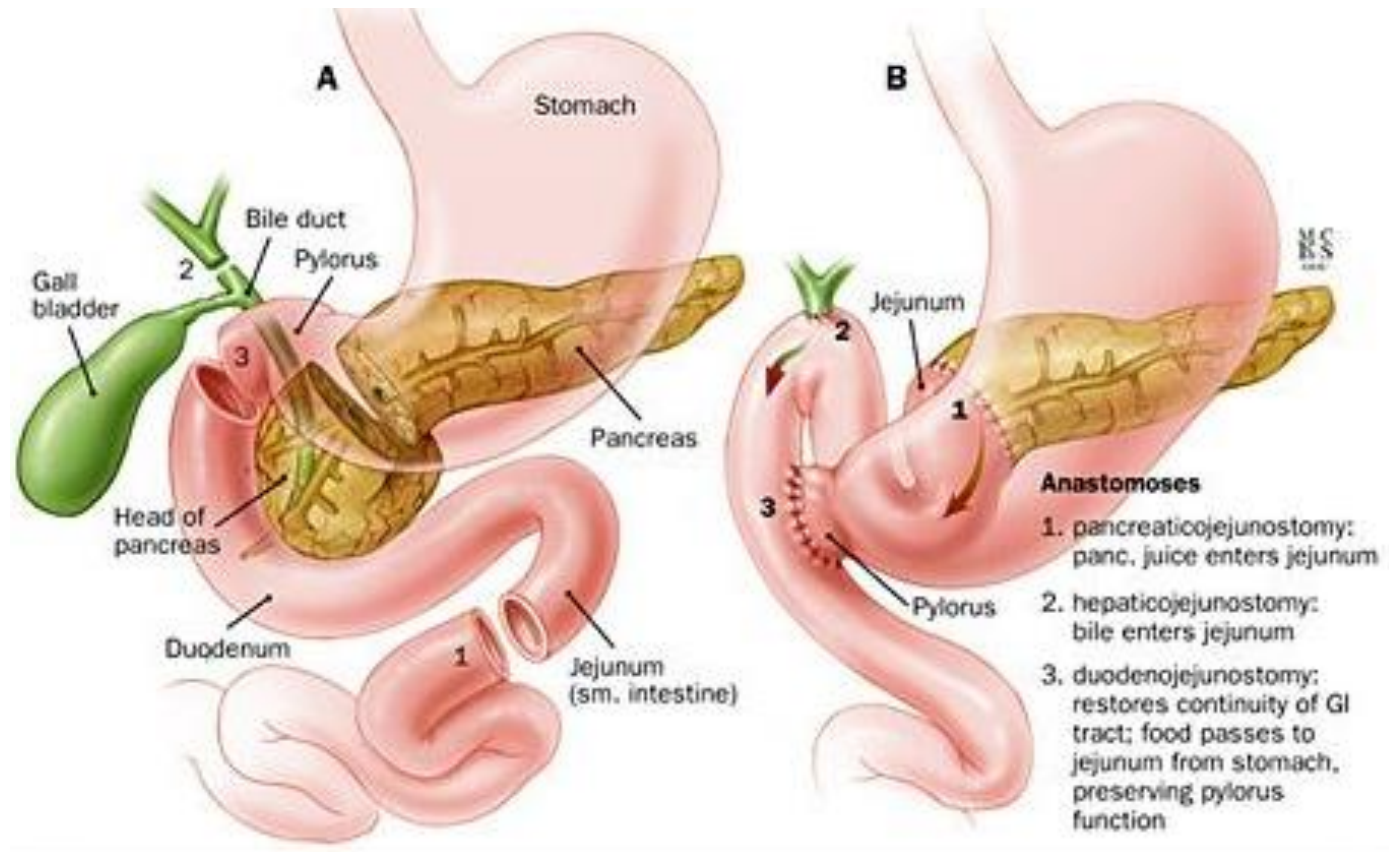
- Of those undergoing exploration, only 20-25% have truly resectable disease
- Pancreatico-duodenectomy (The “Whipple procedure”), mortality 5-15%; 5-year survival for T1-T2 lesions 15-20%
- Distal pancreatectomy (for body and tail lesions)

Local Disease Staging

Intergroup radiographic criteria

	Potentially Resectable	Borderline Resectable	Locally Unresectable
SMV-PV	T-V-I < 180°	T-V-I ≥ 180° and/or reconstructable occlusion	Unreconstructable Occlusion
SMA	No T-V-I	T-V-I < 180°	T-V-I ≥ 180
CHA	No T-V-I	Reconstructable short-segment T-V-I of any degree	Unreconstructable
Celiac Trunk	No T-V-I	T-V-I < 180	T-V-I ≥ 180

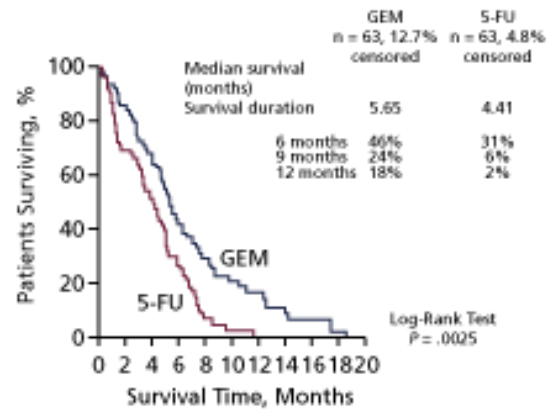
Whipple



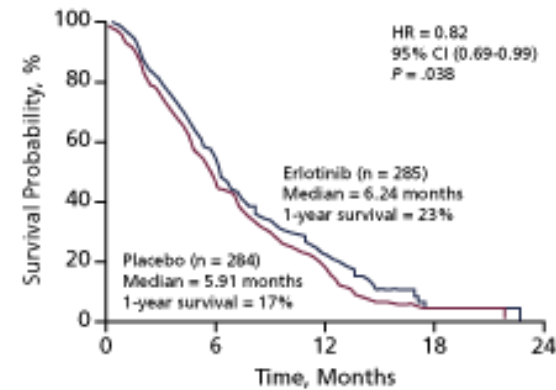
Systemic Therapy for Pan Ca

- Objective tumor response difficult to determine due to severe desmoplastic reaction
- Deterioration even in the absence of bulky disease (pain, asthenia, cachexia)

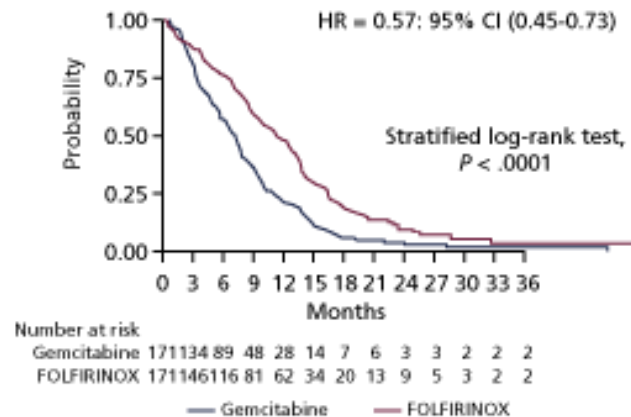
Incremental Benefits With New Agents¹⁻⁴



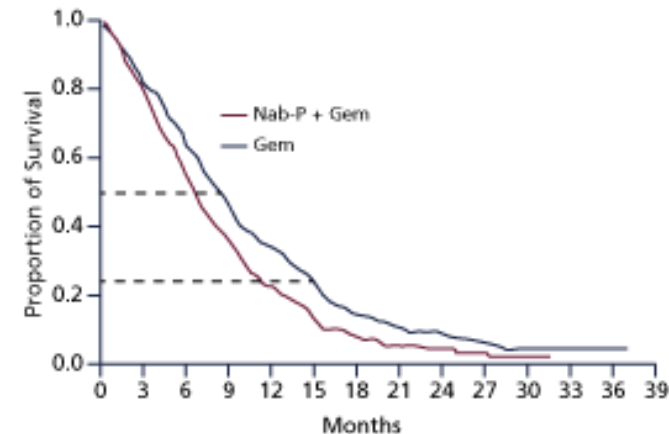
1995
Gemcitabine



2007
Gemcitabine/Erlotinib



2010
FOLFIRINOX

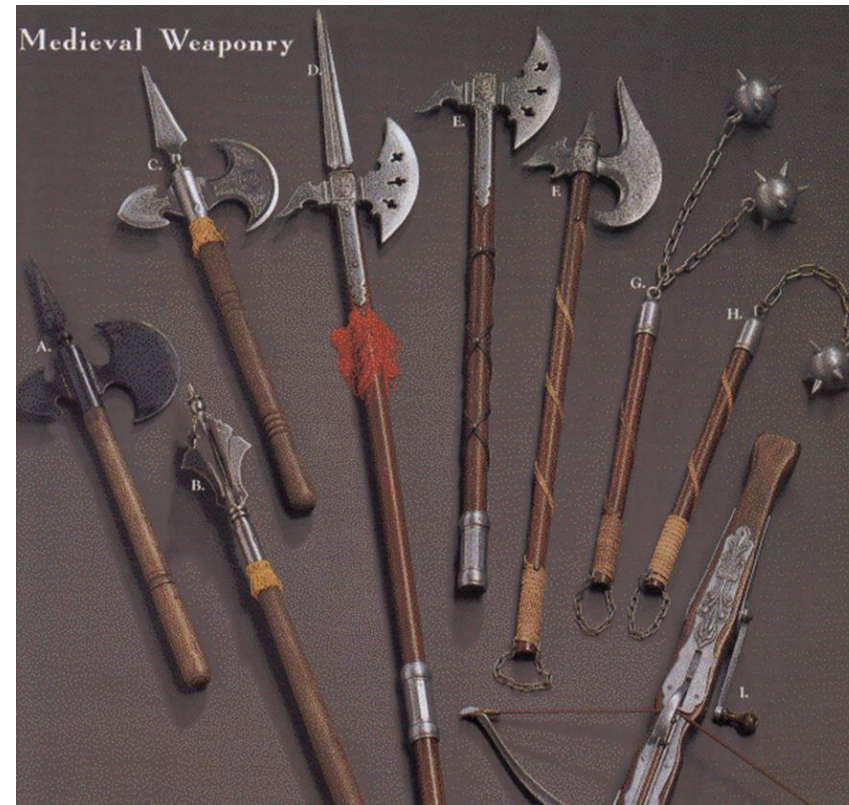


2013
Gemcitabine/Nab-Paclitaxel

1. Burris HA et al. *J Clin Oncol*. 1997;15:2403-2413. 2. Moore MJ et al. *J Clin Oncol*. 2007;25:1960-1966. 3. Conroy T et al. *N Engl J Med*. 2011;364:1817-1825 4. Von Hoff DD et al. *N Engl J Med*. 2013;369:1691-1703.

Systemic therapy choices: pick your best weapon!

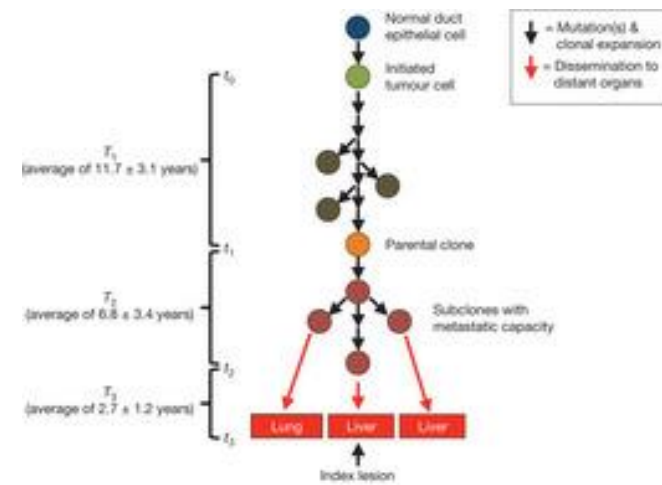
- Gemcitabine
- Fluorouracil
- EGFR TKI (Tarceva, erlotinib)
- Gemcitabine + nab-paclitaxel
- FOLFIRINOX (fluorouracil, leucovorin, irinotecan, oxaliplatin)



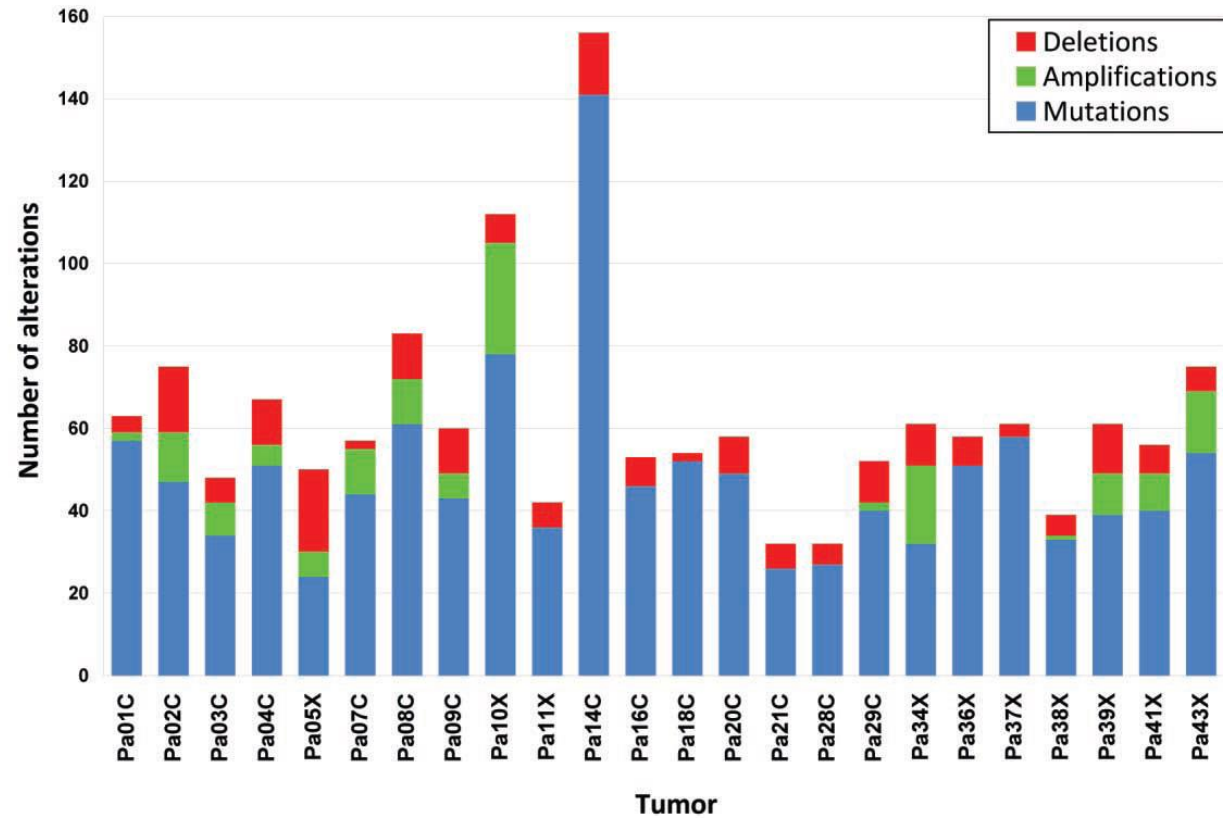
Why has it been so hard to improve outcomes of therapy in pancreatic cancer?

Eighty percent of pancreatic cancers are unresectable at diagnosis

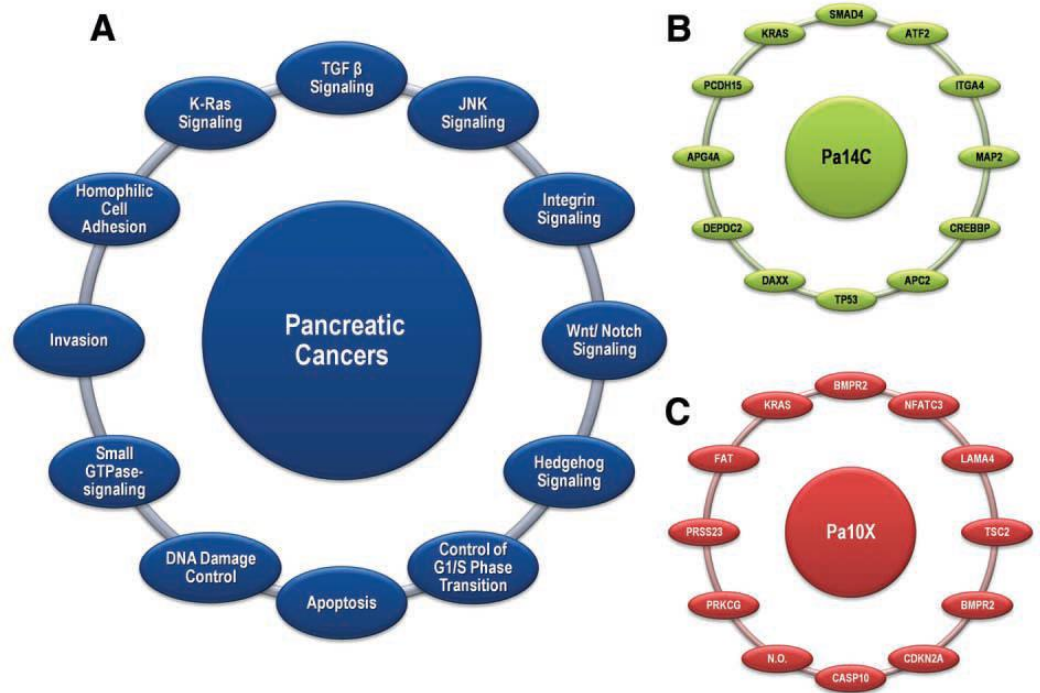
- Pancreatic cancer contains a mix of metastatic clones
- The average time from initial malignant transformation until metastatic transformation is 21.2 years
- Average patient age at tumor initiation is 39 years.



Pancreatic Cancer is Genetically Complex



Number of genetic alterations detected through sequencing and copy number analyses in each of the sequenced 24 cancers.



(A) The 12 pathways and processes whose component genes were genetically altered in most pancreatic cancers. (B and C) Two pancreatic cancers (Pa14C and Pa10X) and the specific genes that are mutated in them. The positions around the circles in (B) and (C) correspond to the pathways and processes in (A). Several pathway components overlapped, as illustrated by the BMPR2 mutation that presumably disrupted both the SMAD4 and Hedgehog signaling pathways in Pa10X. Additionally, not all 12 processes and pathways were altered in every pancreatic cancer, as exemplified by the fact that no mutations known to affect DNA damage control were observed in Pa10X.

Palliative Procedures

- Biliary and gastro-duodenal bypass
- Endoscopic biliary and duodenal stenting
- Celiac nerve blocks
- Palliative radiation therapy
- Portable paracentesis drains

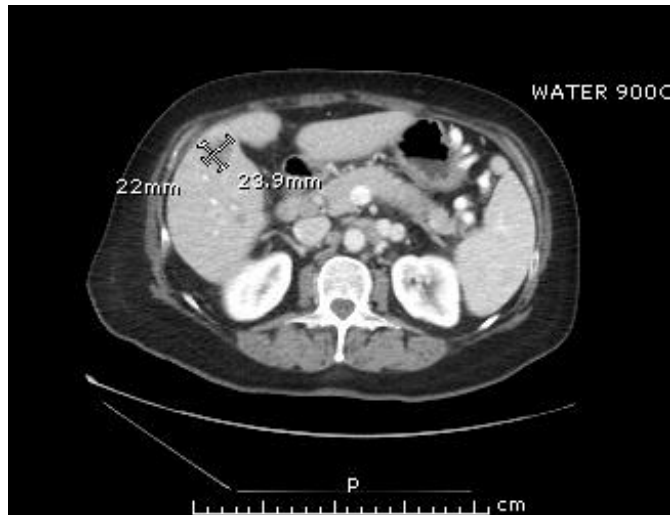
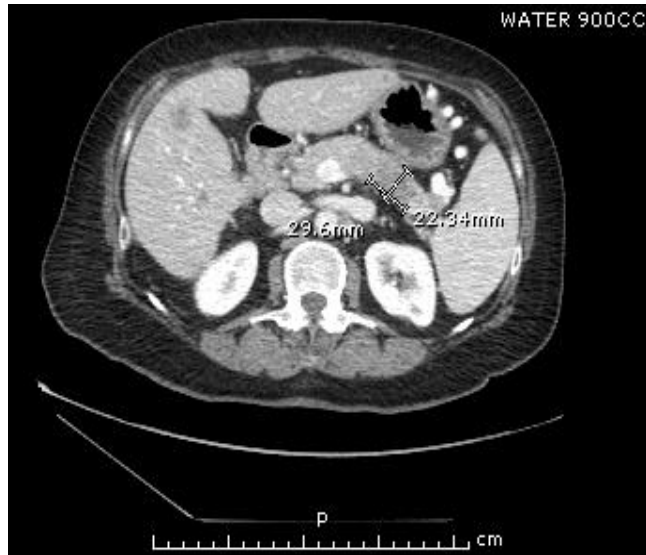
CASE

The events, characters and entities depicted
in this motion picture are fictional.
Any resemblance or similarity to any actual events,
entities or persons, whether living or dead,
is entirely coincidental.

Initial History

- 63-year-old ♀ with acute abdominal pain (7/10) and a history of 24-lb weight loss over last 4 months.
- Initial evaluation: Afebrile, abdomen diffusely tender, LABS: elevated transaminases and lipase (slightly); CT Scan from ER: mass in the tail of pancreas.
- EGD/ EUS: Mass in the tail biopsied; liver lesions and PA lymph nodes.

Staging



- Panc biopsy: adenocarcinoma
- ECOG PS 1
- PP CT scan shows tail mass 2X3 cm and also liver lesions, lymphadenopathy
- CA 19-9 is 1254

- PMH:
 - diabetes type 2 (2 yrs)
 - hypertension, hypothyroidism, HTN
 - ovarian mass removed the age 42
- Family History:
 - mother-breast ca at age 65
 - brother-prostate ca at age 55

Which of the following you would not do?

- A. Refer to hepatobiliary surgeon for pancreatectomy and resection of liver metastases
- B. Refer for celiac plexus block for pain control
- C. Start Gemcitabine + nab-Paclitaxel
- D. Start FOLFIRINOX with GCSF support

The Course and Treatment

- Patient underwent celiac plexus block and started on FOLFIRINOX plus GCSF.
- Negative for BRCA mutation.
- CA 19-9 response and radiologically stable disease/MR after 3 months on therapy
- At month 4 oxaliplatin omitted because of persisting thrombocytopenia and grade 2 neuropathy
- Month 6 CT scan:
 - worsening pain
 - PS is now ECOG 2



Targeting Individually: BRCA 2 mutation in Pancreatic Cancer

Images showing response of pancreatic cancer mass with BRCA 2 tailored chemotherapy



Chalasani P, Kurtin S, Dragovich T. JOP, 9 (3): 2008

New Offerings...



- BRCA 2 targeting therapy POLO trial (olaparib)
- Target stroma (hyaluronidase, PEG HP20)
- Delivery (nanoliposomal CPT-11, MM398)
 - NAPOLI-1 trial: MM398 + LVFU (*ESMO 2014*)
- Radioimmunotherapy (HPAM4-based ^{90}Y Tetraxetan-clivatuzumab)
 - Phase IB with low dose gemcitabine as a 2nd or 3d line (*Picozzi et al, EJC 2015*);

Thank You

