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Management of Pancreatic Cancer: Perspectives from a Multidisciplinary Clinic

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Department of Medicine
Division of Oncology
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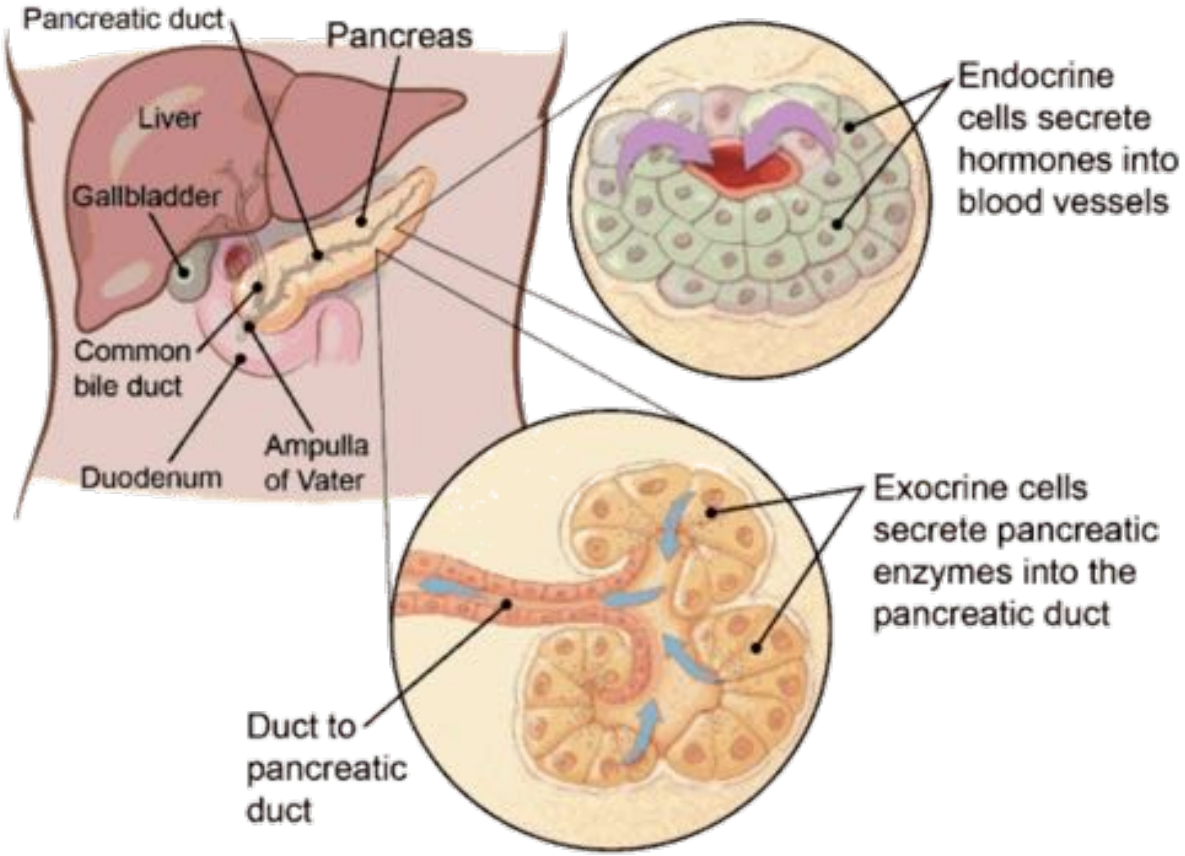
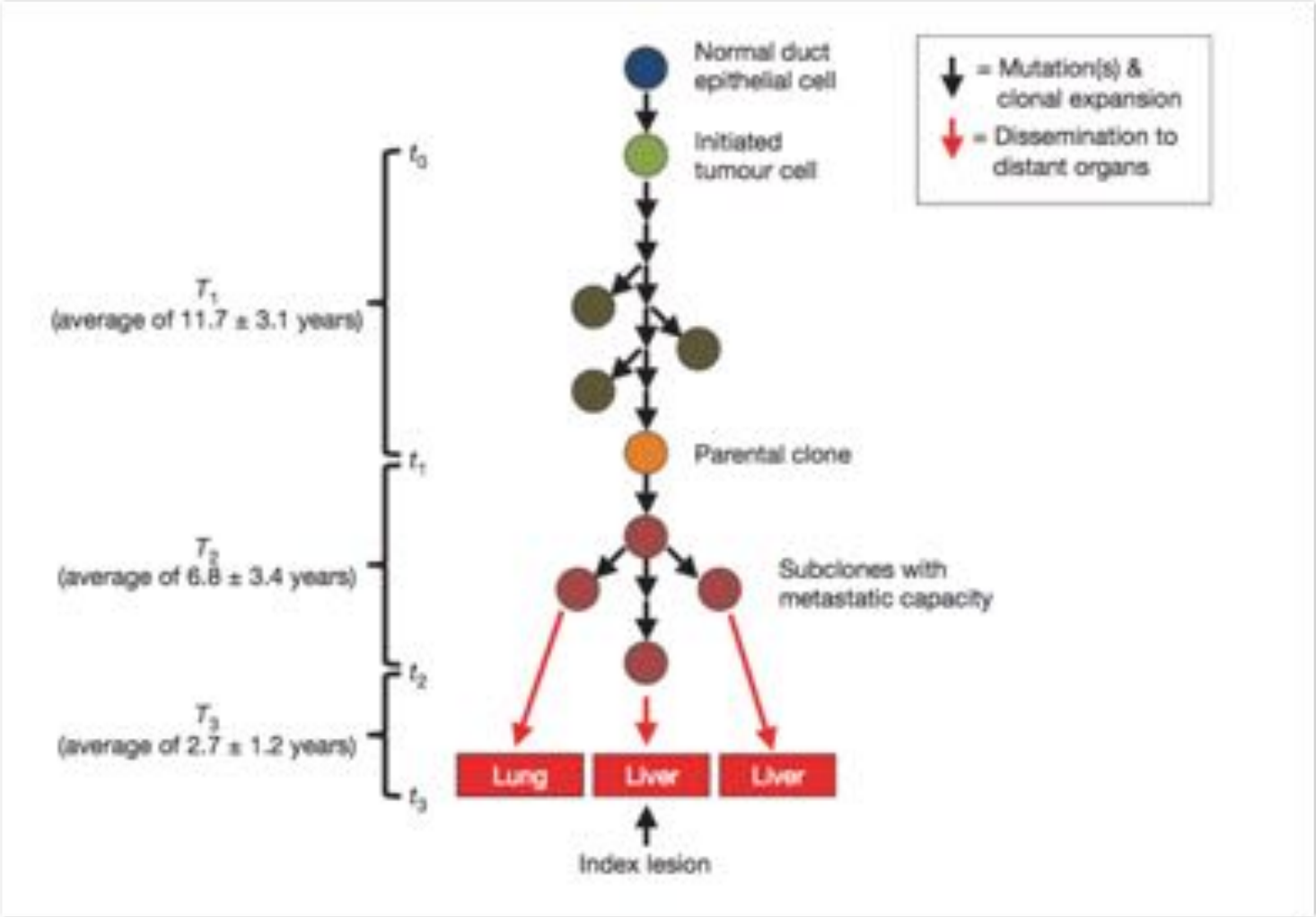
Pancreatic Ductal AdenoCarcinoma (PDAC)

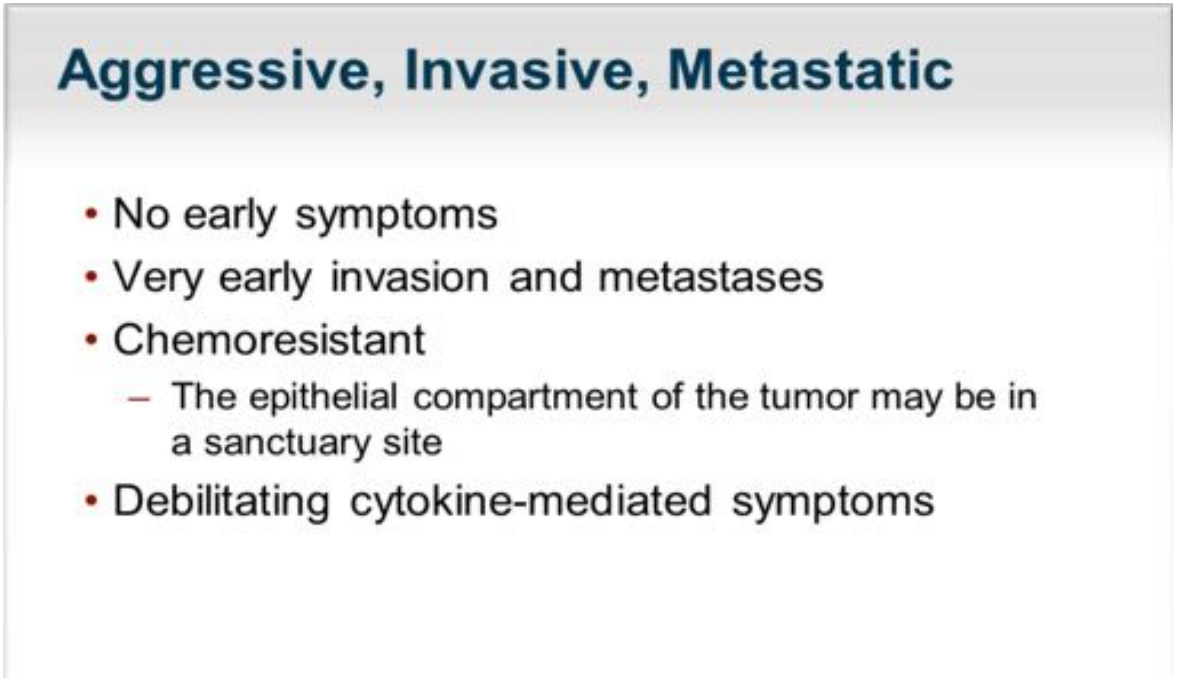


Is Pancreatic Adenocarcinoma a Systemic Disease?

Yachida, S., Jones, S., Bozic, I., Antal, T., Leary, R., Fu, B., Kamiyama, M., et al. (2010). Distant metastasis occurs late during the genetic evolution of pancreatic cancer. *Nature*, *467*(7319)



What makes this disease so difficult to treat



No screening paradigm has shown efficacy in improving overall survival of pancreatic cancer

- **CA19-9 not of sufficient predictive value**
- **EUS/CT impractical and also not predictive**

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That most difficult Pest

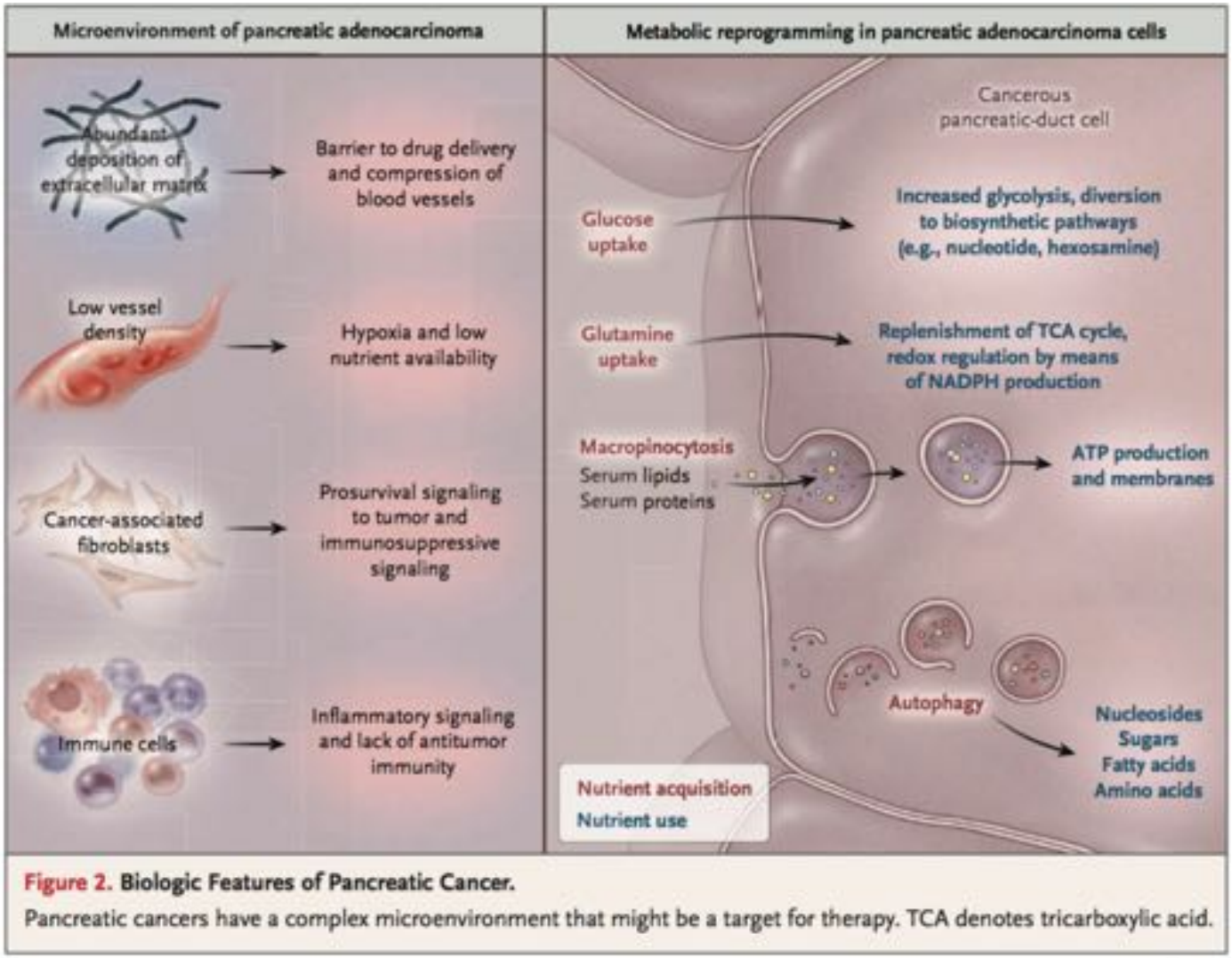

Figure 2. Biologic Features of Pancreatic Cancer.

Pancreatic cancers have a complex microenvironment that might be a target for therapy. TCA denotes tricarboxylic acid.

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Classic Presentation

Mid-50's – 80 year old

- Unintentional Weight loss
- Loss of Appetite
- Early satiety
- Fatigue
- Worsening or new onset diabetes
- Abdominal or back pain
- Obstruction
  - Jaundice

Classic Evaluation

- If jaundiced: rapid evaluation
  - CT, EUS
  - ERCP (sometimes PTC via Interventional Radiology)

- Usual: weeks-months
  - Multiple visits to PCP,
  - ER
  - Blood tests
    - Occasionally these lead to liver evaluation

- Eventually:
  - Cross sectional imaging
  - Biopsy
  - CA19-9
    - Caveat: 10% of White and up to 30% of AA do not have an elevated CA19-9

MDC components

- GI: diagnosis and bridging to treatment (biliary stenting)
  - Screening
  - EUS, Resectable vs local vs metastatic
  - ERCP
  - Intestinal stents in case of Gastric or other tumor obstruction
- Radiology
  - Resectable vs local vs metastatic
  - Blood vessel / tumor interface
  - Screening
  - Interventional Radiology : PTC if internal stenting problematic
- Pathology: Screening and Genomics
  - Identification: Adenocarcinoma vs Neuroendocrine vs Acinar
  - Atypical (adenosquamous, Colloid)
  - Genomic sequencing for targeted therapy
- Surgical Oncology: Screening and resection
  - Resectable vs local vs metastatic
  - Only known curative treatment
- Medical Oncology
  - Chemotherapy can be used before, or after surgery, local or met disease
- Radiation Oncology
  - Treatment vs palliation
- Dietary
  - PDAC is a systemic inflammatory disease, with appetite and lean muscle loss
- Palliative Care
  - Pain, nausea, constipation, diarrhea, weight loss
- Behavioral Health
  - Anxiety, depression, and Family issues
- Genetics
  - Patient specific and family screening and counseling

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Surgical Resectability

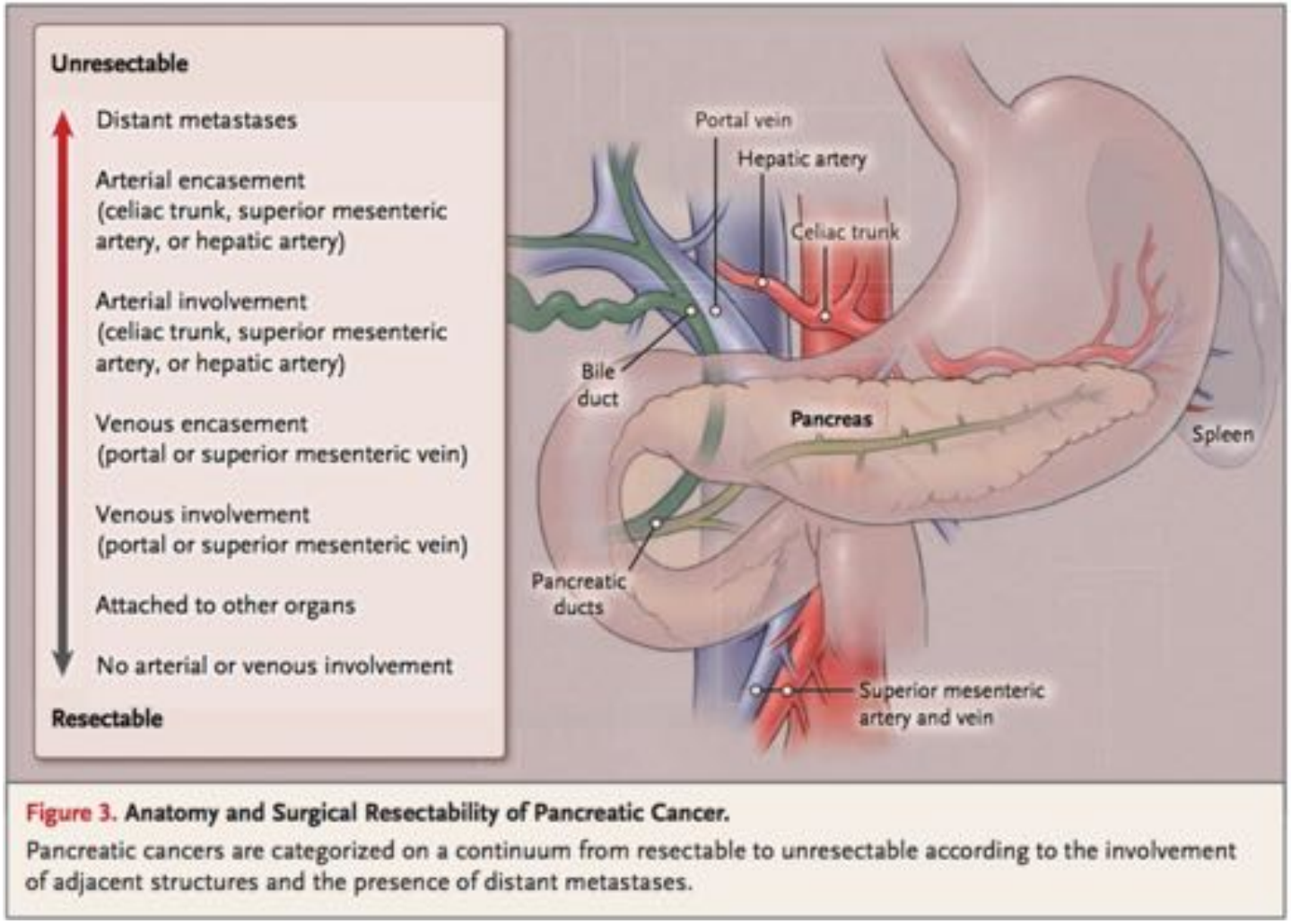
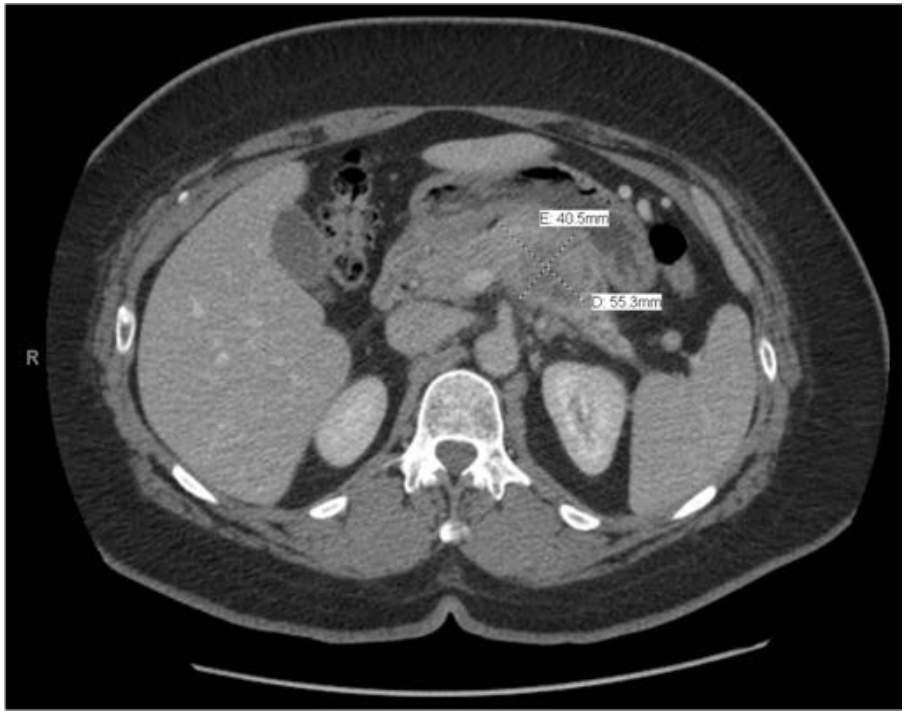


Figure 3. Anatomy and Surgical Resectability of Pancreatic Cancer.

Pancreatic cancers are categorized on a continuum from resectable to unresectable according to the involvement of adjacent structures and the presence of distant metastases.

Pancreatic Adenocarcinoma as seen in the MDC



- **Possibilities**
  - Resection alone
  - Upfront Resection f/b chemotherapy +/- radiation
  - Chemotherapy upfront then surgery +/- radiation +/- more chemotherapy

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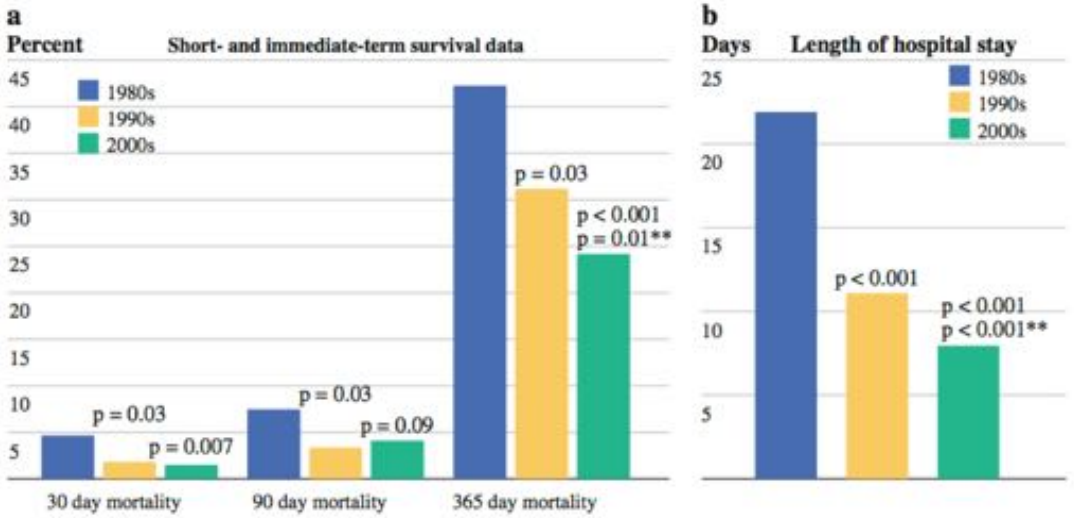
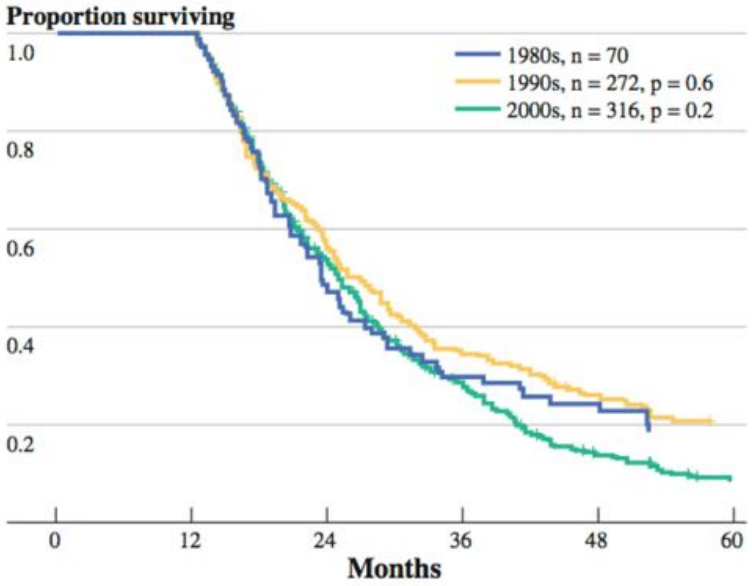
Pancreatic Adenocarcinoma

3 Decades of "Progress"

Winter, J. M. et al. (2012). Survival after Resection of Pancreatic Adenocarcinoma: Results from a Single Institution over Three Decades. *Annals of surgical oncology 19*(1), 169–175





Adjuvant Trials thorugh the ages: Highlights

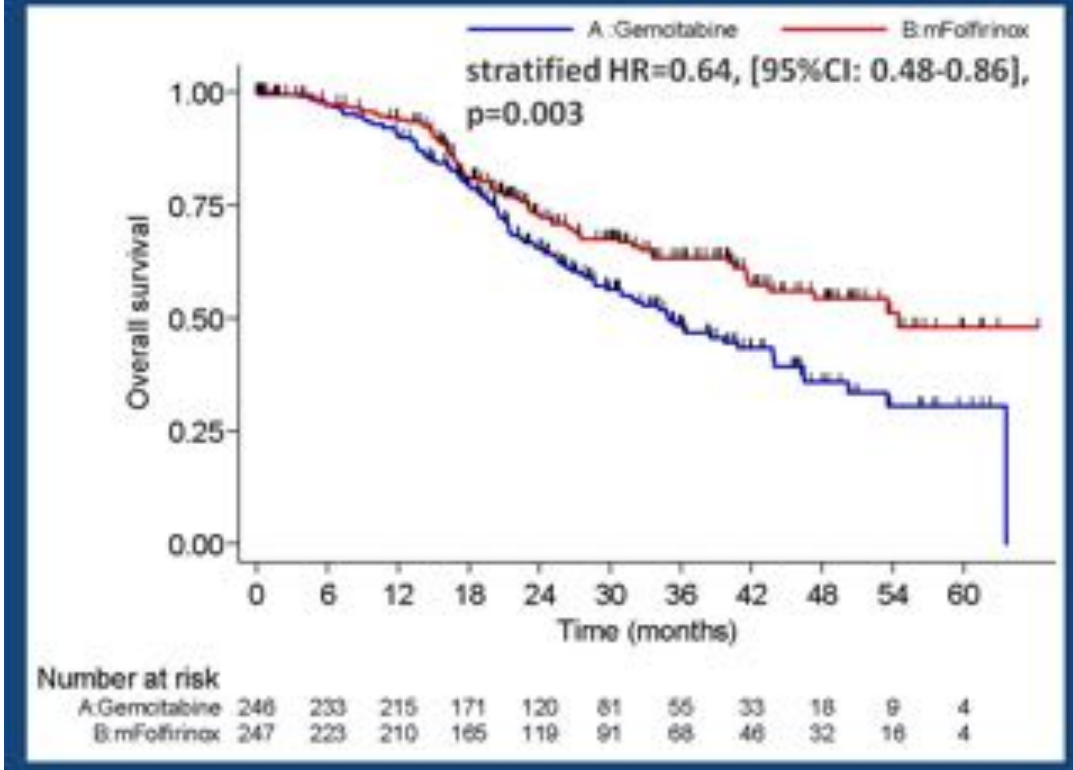
ESPAC Trials: 5 Year Overall Survival

Trial	Treatment	No. of pts (N=2092)	5-Year OS (95% CI)	Stratified Log-Rank X^2	p-value
ESPAC-1	5FU/FA	149	21 (14.6 – 28.5) %		
	No chemotherapy	143	8.0 (3.8 – 14.1) %	7.03	0.030*
	Chemoradiotherapy (5FU/Rad)	145	10.8 (6.1 – 17.0) %		
ESPAC-3	GEM	539	17.5 (14.0 – 21.2) %	0.74	0.390*
	5FU/FA	551	15.9 (12.7 – 19.4) %		
ESPAC-4	GEM	366	16.3 (10.2 – 23.7) %	4.61	0.032†
	GEMCAP	364	28.8 (22.9 – 35.2) %		

*Stratification factor: resection margin status; †stratification factors: resection margin status and country

PRODIGE (3 drugs 5FU, Irinotecan Oxaliplatin FOLFRINOX vs Gem)

Overall Survival



Median overall survival:

- **54.4 months** [95%CI: 41.8-NR] **with mFolfirinox**
- **35.0 months** [95%CI: 28.7-43.9] **with Gemcitabine**

3-year overall survival:

No OS events=192

- **63.4% (mFolfirinox) vs 48.6 % (Gem)**

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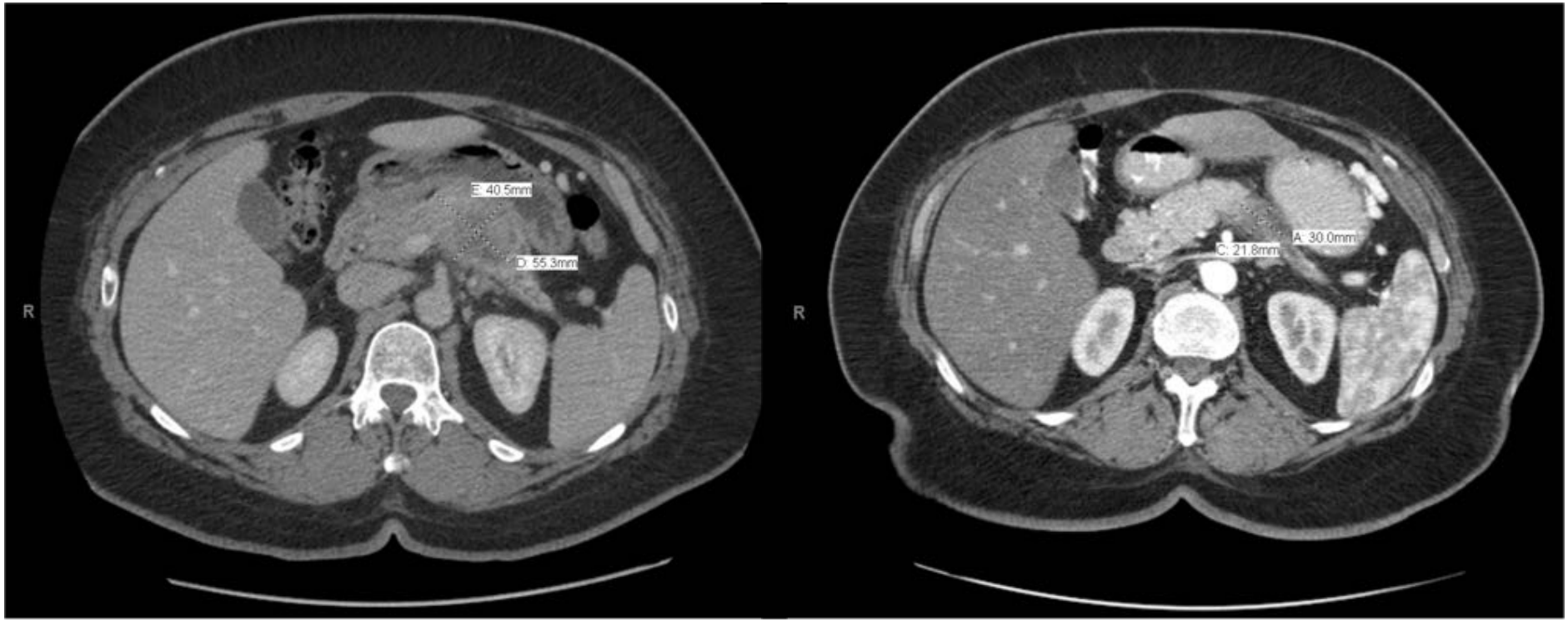
Neoadjuvant Therapy

- Potential benefits
  - Occult micrometastatic disease may become visible, can save resection morbidity
  - Potential to decrease rate of positive margins
  - Deliver chemotherapy and/or radiation without delay 40% adjuvant delayed > 8 weeks)
  - Can be delivered without affecting perioperative mortality / morbidity
  - In vivo drug sensitivity

- No level 1 evidence whether this approach is better than resection and adjuvant treatment

Case Summary MB



8/2011 6 cycles FOLFIRINOX 12/2011

CA19-9: 648 to < 37

6 cycles adjuvant FOLFIRINOX

May 2018: NED

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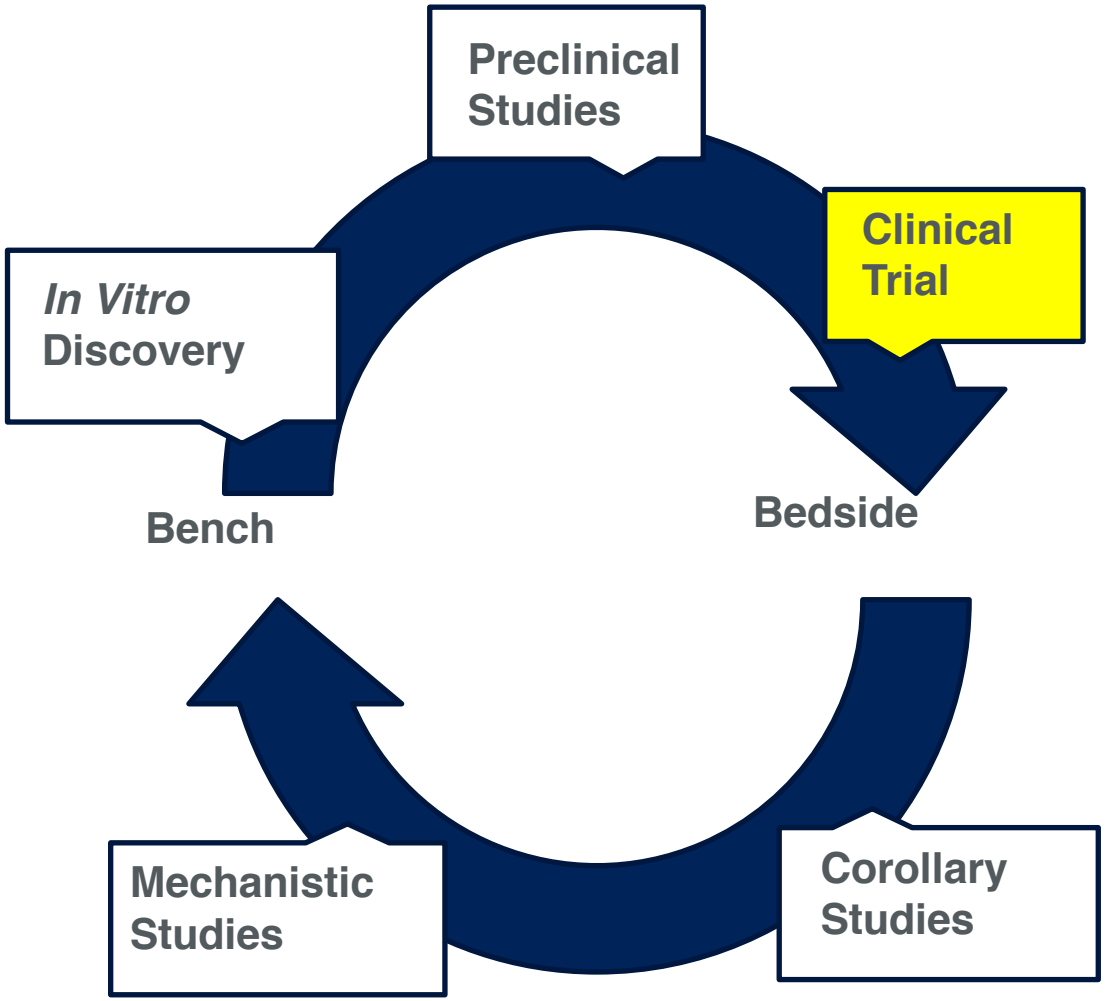
Paradigm



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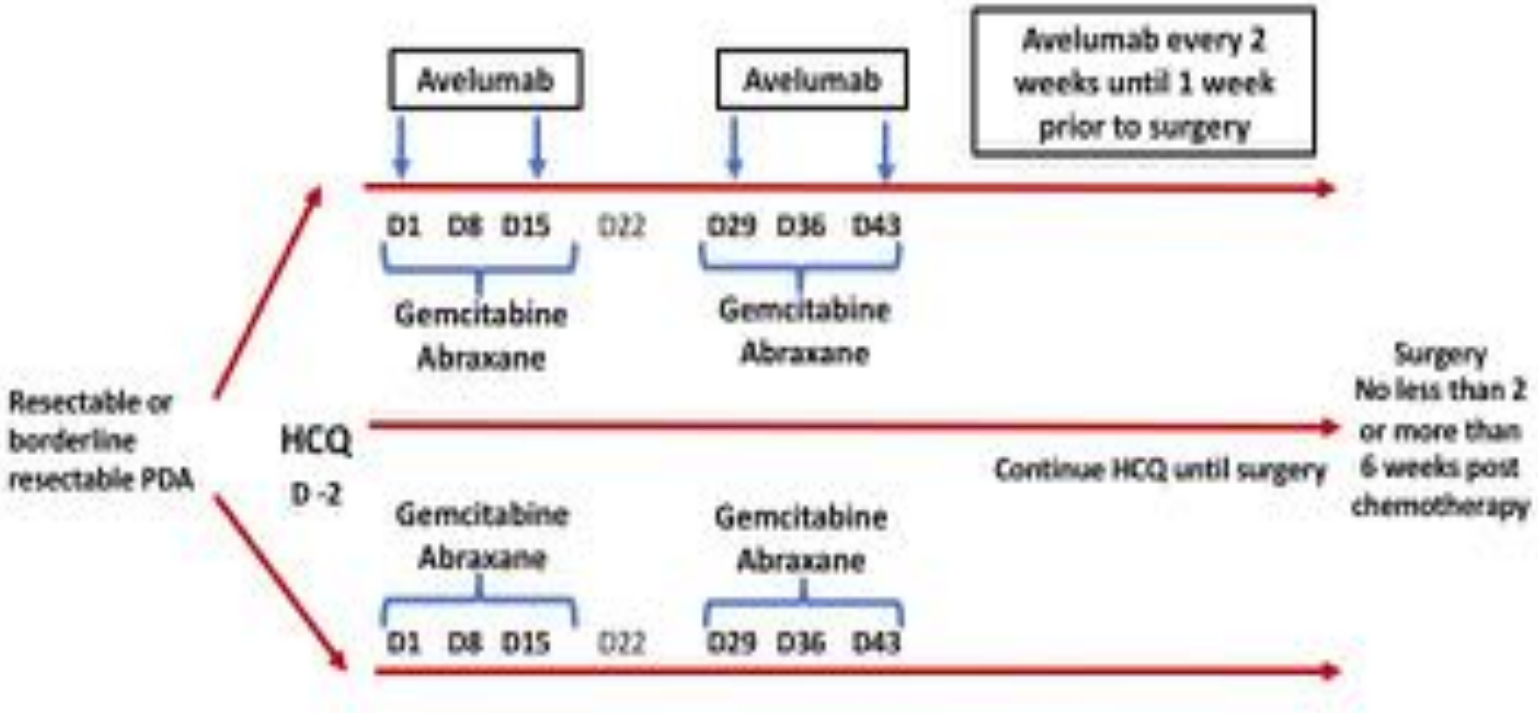
Trial



- Phase II
- Response adaptive randomization
- Primary endpoint: Histopathologic response
- Secondary endpoints: Ca 19-9, Correlative studies

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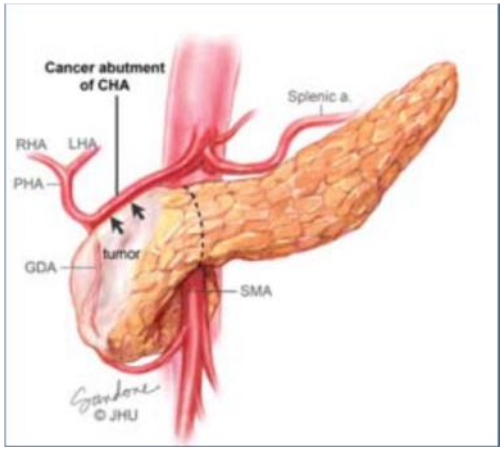
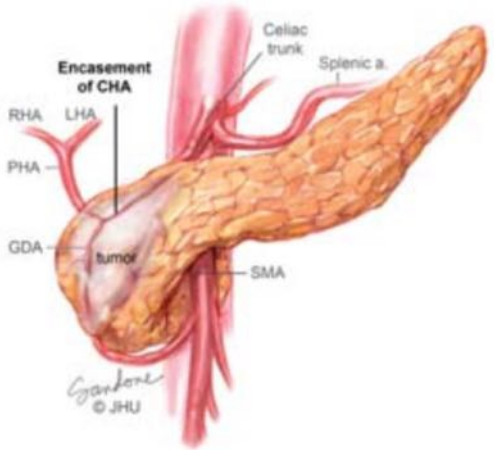
Locally Advanced Disease

- Borderline:
  - Tumors which involve the mesenteric vessel to a limited extent
    - patients with focal tumor abutment of the superior mesenteric artery, encasement of the gastroduodenal artery up to the hepatic artery, or involvement of the superior mesenteric vein/portal vein that is potentially resectable and reconstructable could all fall into this category.
    - While these patients are potentially resectable, the high likelihood of an incomplete resection has prompted interest in strategies to "downstage" the tumor prior to surgical exploration using chemotherapy with and without RT (neoadjuvant therapy).



- Locally Advanced Unresectable:
  - Tumors that heavily involve the
  - mesenteric and organ vasculature
    - Encasement of vasculature
    - No metastatic disease



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Locally Advanced Disease

Borderline

Katz, M. H. G., et al. (2012). Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators. *Cancer*.

- 122 patients who had their disease restaged after receiving preoperative therapy,
  - 84 patients (69%) had stable disease
  - 15 patients (12%) had a partial response to therapy
  - 23 patients (19%) had progressive disease.
  - 1 patient (0.8%) had their disease downstaged to resectable status after receiving neoadjuvant therapy,

- 85 patients (66%) underwent pancreatectomy.
  - mOS was 22 months (14-30 months).
  - mOS after pancreatectomy was 33 months (25-41 months)
  - not associated with RECIST response (P >.78)

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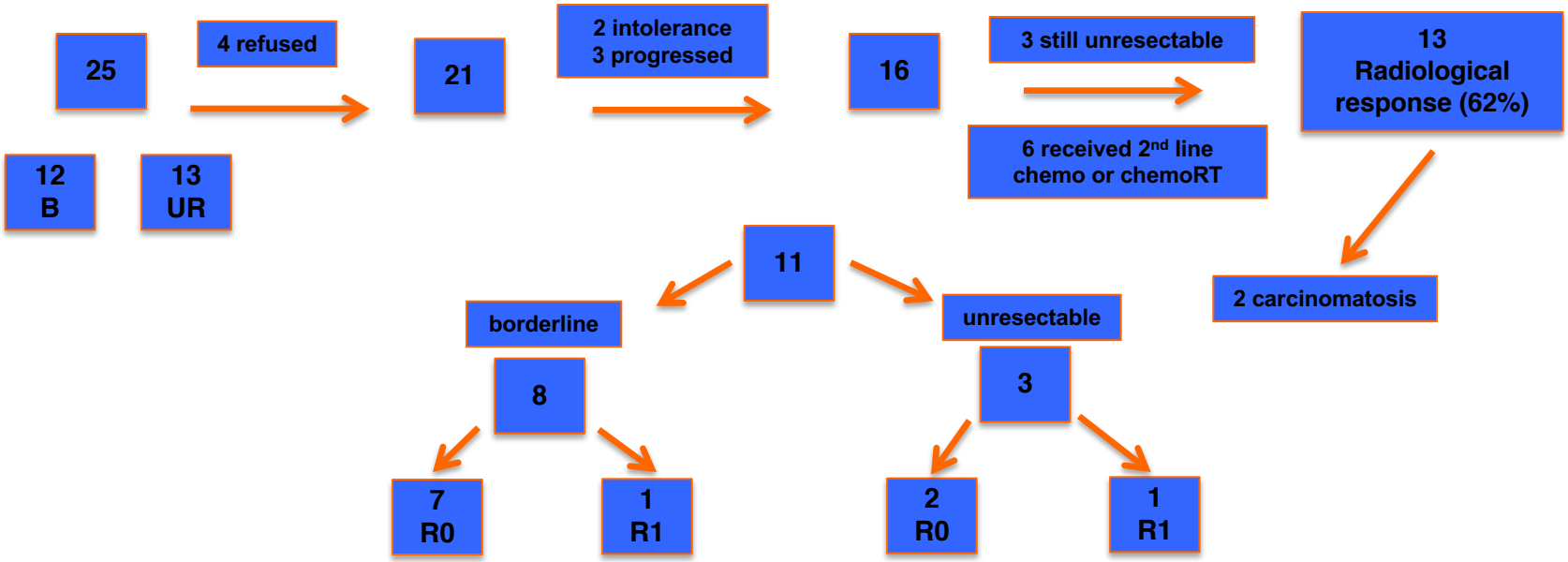
Locally Advanced Disease - UPMC experience FOLFIRINOX, Gem/Abraxane and SBRT



A rational balance:

- **Surgical input re: resectability at each treatment node**
- **Chemotherapy based on FOLFIRINOX vs Abraxane/Gem if good PS**

1. 3-6 months of systemic chemo
2. if no evidence of metastatic disease, then evaluation for resection
3. if unresectable switch to alternative chemotherapy
4. Consider chemoradiation for patients who appear unresectable and reevaluate for resectability

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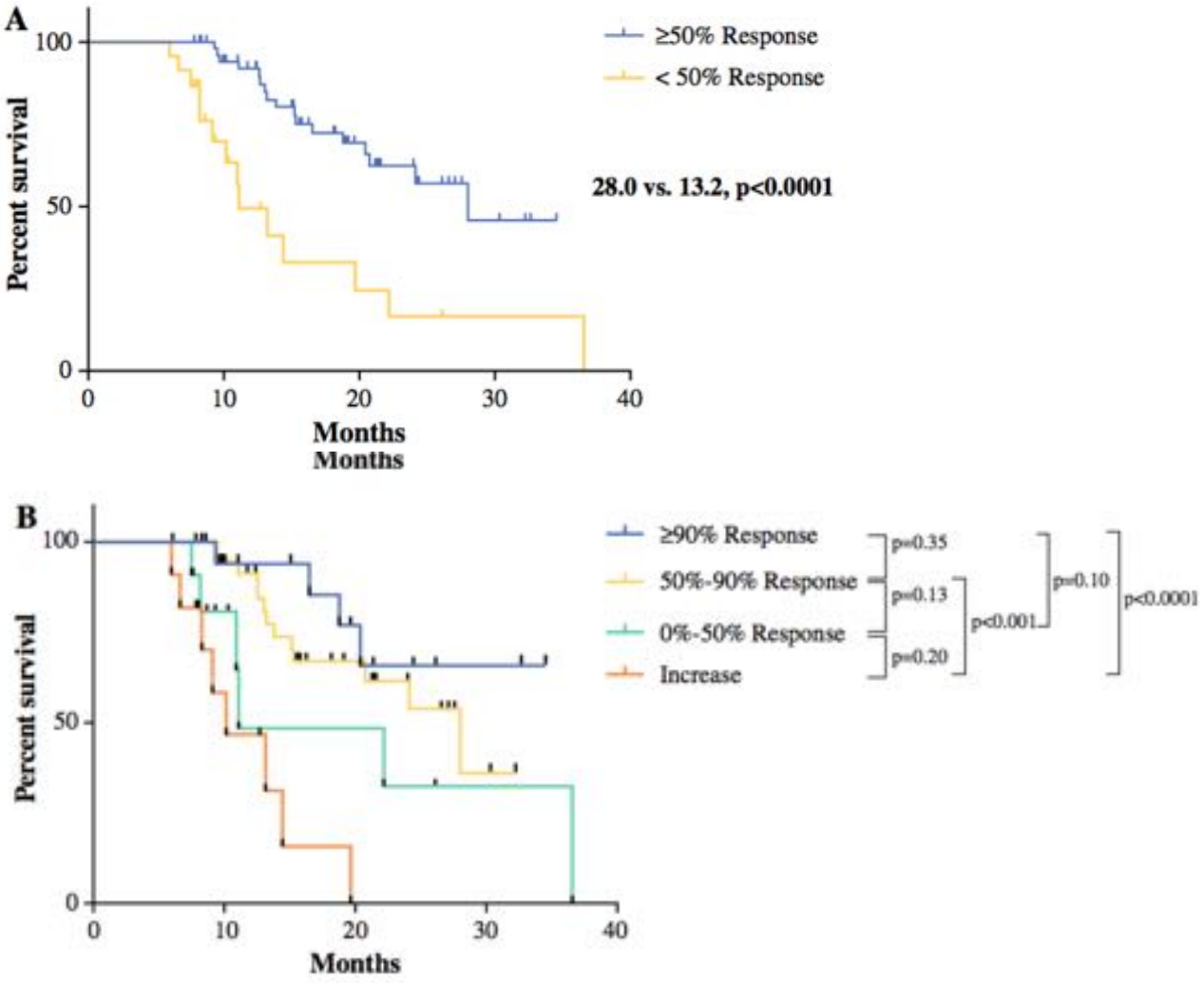
CA19-9 response to neoadjuvant therapy predicts OS

Boone BA, Steve J, Zenati MS, et al. Serum CA 19-9 Response to Neoadjuvant Therapy is Associated with Outcome in Pancreatic Adenocarcinoma. Ann Surg Oncol 2014;



Metastatic Disease Summary

- **Gemcitabine alone improves survival and QoL**
- **FOLFIRINOX broke the "Gem + something" mold**
  - Caveats are toxicity, but QOL improved in those who could receive it
  - All drugs off patent, further large trials difficult
  - mOS=11.1 v 6.8 mos, RR 32% DCR 70%
- **Abraxane/Gemcitabine**
  - Approved by FDA 9/2013
  - No inter-trial comparisons to FOLFIRINOX.
  - 40% patients had a KPS =70 (PS=2)
  - mOS= 8.7 v 6.7 mo, RR 23%, DCR=50%
- **Sequencing for Good PS patients?**
- **5FU with liposomal irinotecan, FOLFOX/OFF or 5FU alone in poor PS all options n the second line**

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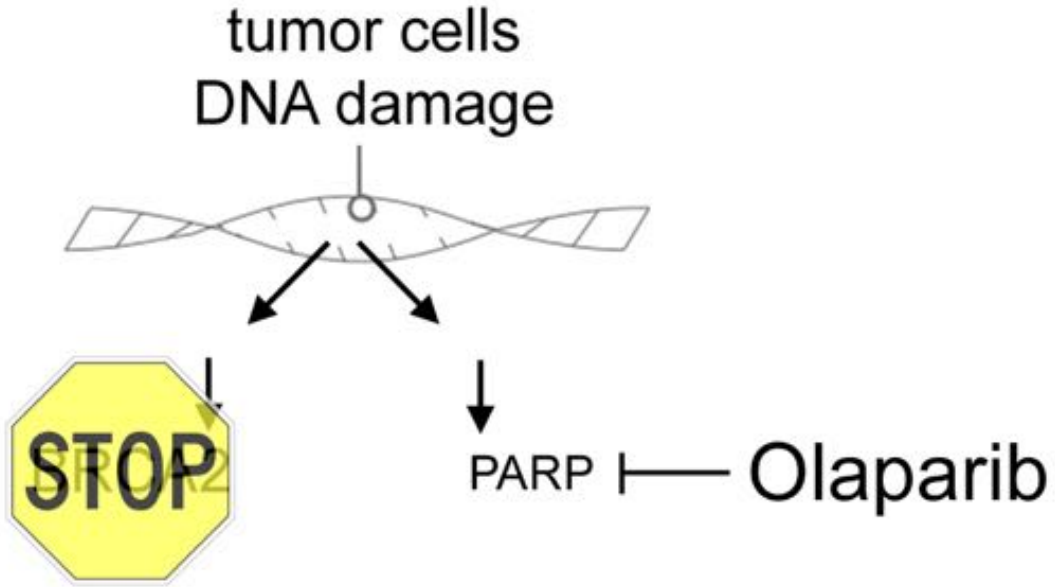
Pancreatic Adenocarcinoma

Hereditary Genetics and Pathology for Genome sequencing

- BRCA1 /2 and PALB2 (Partner and Localizer of BRCA2)
  - BRCA2 is the most common hereditary cause based on its prevalence
- HNPCC
  - Lifetime risk of 3-4%
- FAP
  - RR of 3-4X
- Familial atypical multiple mole melanoma (FAMMM)
  - *P16/CDKN2A*
  - 20-40 fold increase in RR
  - -estimated 20% lifetime risk by age 75 for the p16-Leiden (exon 2 deletion)
- Hereditary pancreatitis
  - Cationic trypsinogen gene (*PRSS1*)
  - 50% risk by age 75, 75% when paternally inherited
- Peutz-Jeghers Syndrome
  - *STK11/LKB1*
  - >100 fold increased risk
  - 50% risk by age 40
- ATM

Targeted Therapy: DNA Damage Repair

- **BRCA2**
  - **Penetrance varies on pedigree**
  - **3-5 X increased RR**
  - **Because of prevalence of BRCA2, most common cause of hereditary PC**
- **BRCA1**
- **PALP/B**



DEATH

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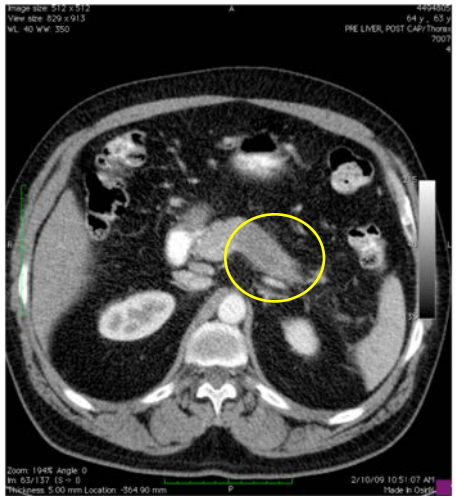
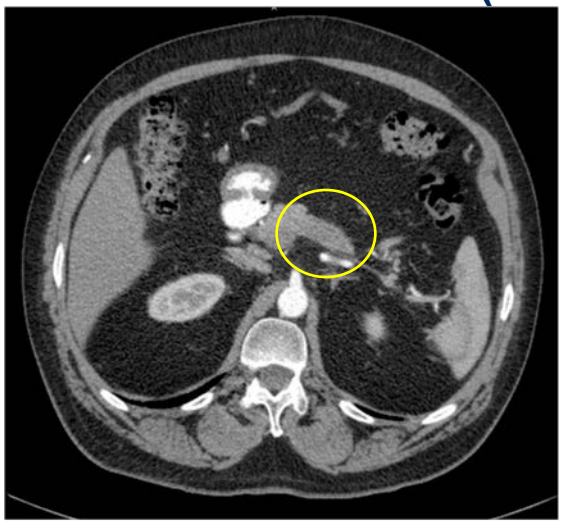
Combined Platinum and PARP inhibition BRCA2 carrier

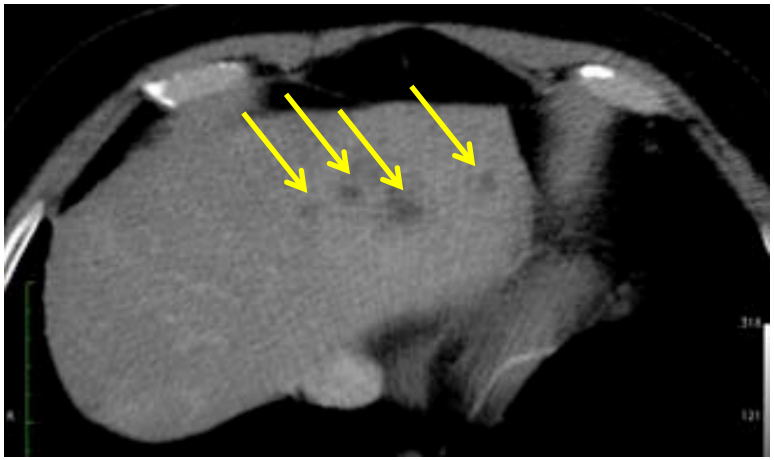
Hereditary Genetics and Pathology for Genome sequencing

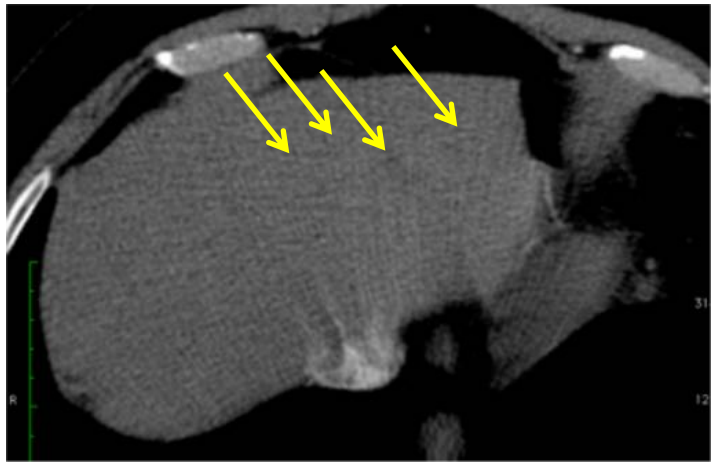
presentation



post treatment AZD2281 (olaparib)







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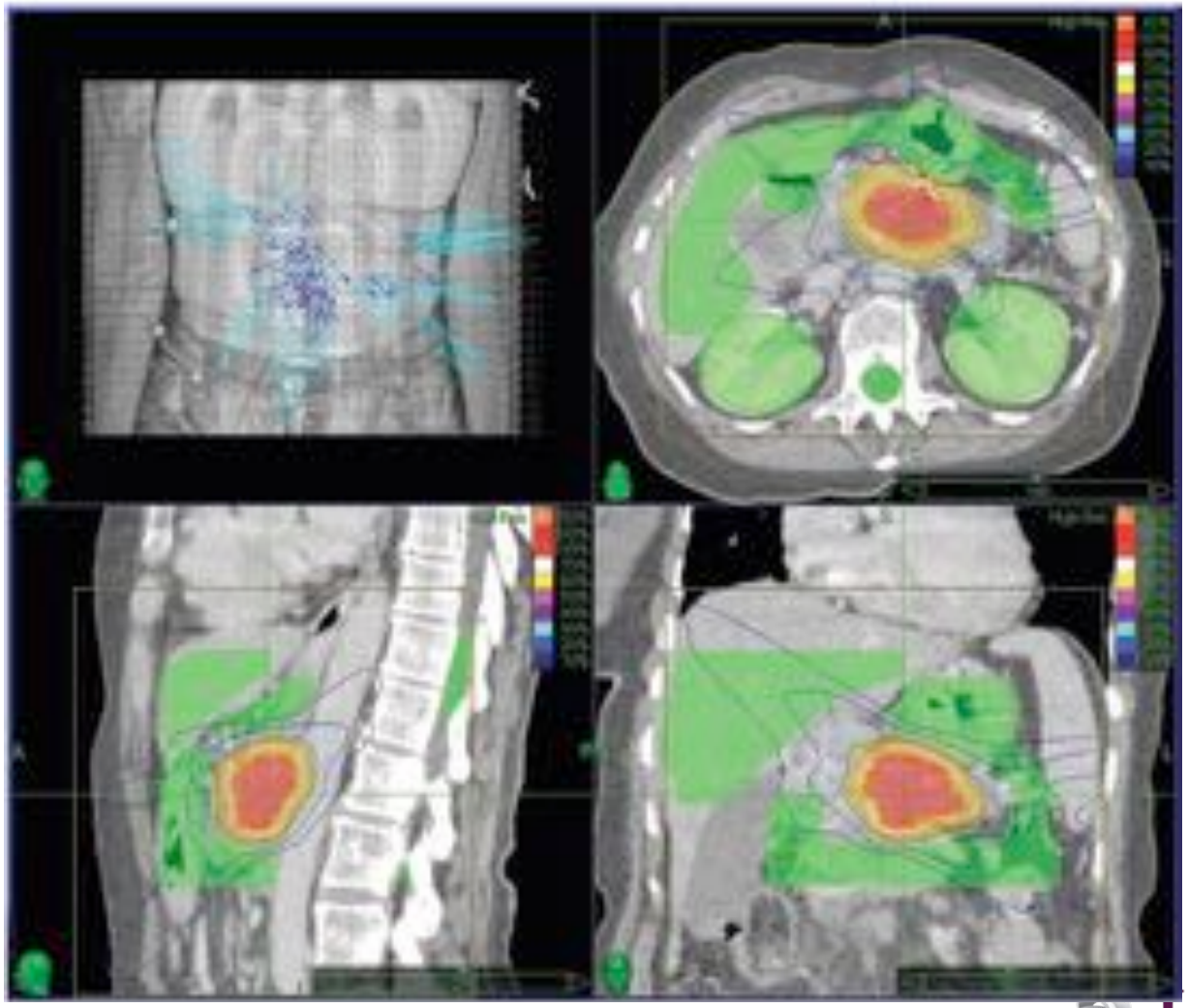
Radiation Oncology: EBRT and SBRT Treatment

SBRT plans



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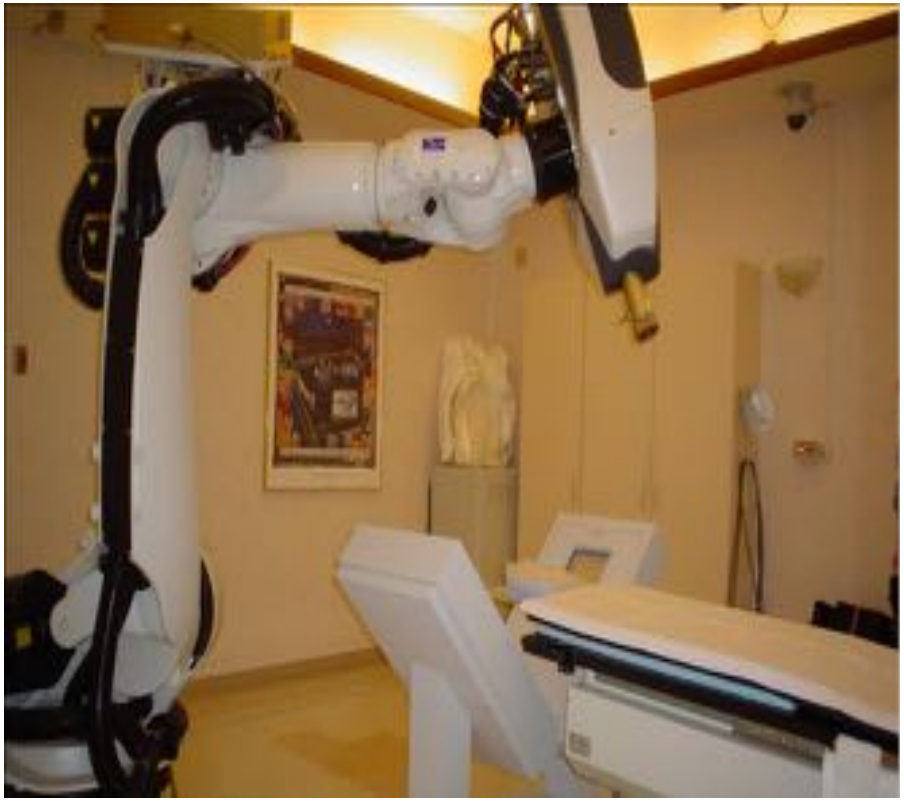

Case

- 68 yo (in 2014) gentleman who January 2014 c/o abdominal pain, weigh loss, cramping/ diarrhea.
  - EGD AND colonoscopy that were both unremarkable,
  - abdominal pain managed with Protonix, oral antibiotics without resolution.
- April 2014: Having lost 22 lbs (~10% body weight) with worsening post prandial pain.
  - Outside CT obtained, ? Uncinate pancreatic mass
  - EUS by his local physician, biopsy was inconclusive.
  - Repeat EUS locally, biopsy again inconclusive
- Referred to UPMC GI
  - 5/9/2014: EUS with 3 cm uncinate mass
    - cytology Atypical cells
- 5/29/14: Repeat EUS
  - mass identified 41 mm by 28 mm in maximal cross-sectional diameter. The endosonographic borders were poorly-defined. There was sonographic evidence suggesting invasion into the superior mesenteric vein (manifested by interface loss)
    - Cytology: Adenocarcinoma, SMAD4 loss

Case

- MDC clinic:
  - c/o early satiety, weight loss (5 more lbs past month), mid epigastric pain radiating to back under the ribs, constant. Post prandial nausea, bloating, pain and diarrhea about 2 hours after eating. Fasting glucose 147, HgA1C=7.4

  – Radiology/SurgOnc:
    - CT scan showed definitive ~ to just >180 involvement of the IVC and SMA, including the first jejunal branch. Felt to represent locally advanced disease.

  – SurgOnc and MedOnc:
    - Neoadjuvant Chemotherapy
    - FOLFIRINOX (began July 2014)

  – RadOnc:
    - Would be a SBRT candidate before surgery if needed

  – Palliative Care:
    - Creon for malabsorption
    - Oxycodone 5 mg q 4 hours prn pain
    - Zofran 4 mg every 6 hours nausea
    - Referral to behavioral health for anxiety

  – Dietary:
    - Low carb diet for DM
    - Protein supplements

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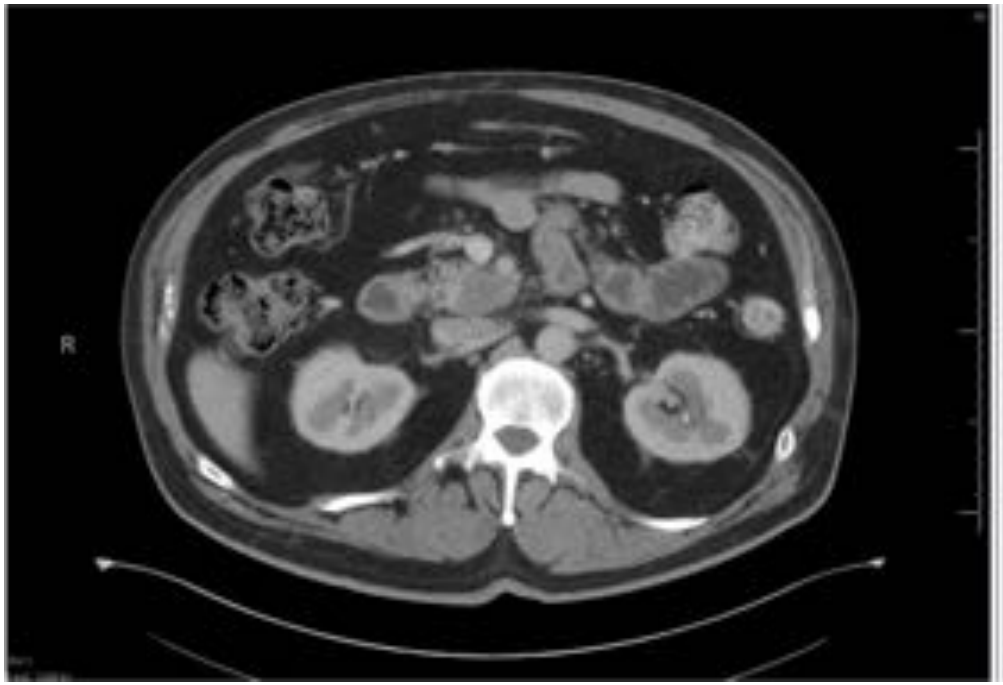
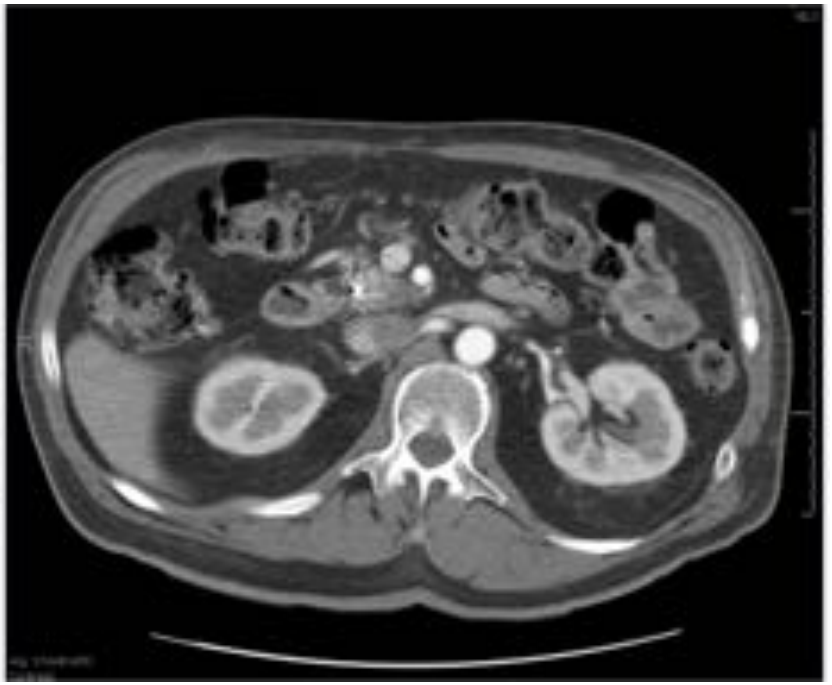
CTs

6/6/2014



4/1/2015



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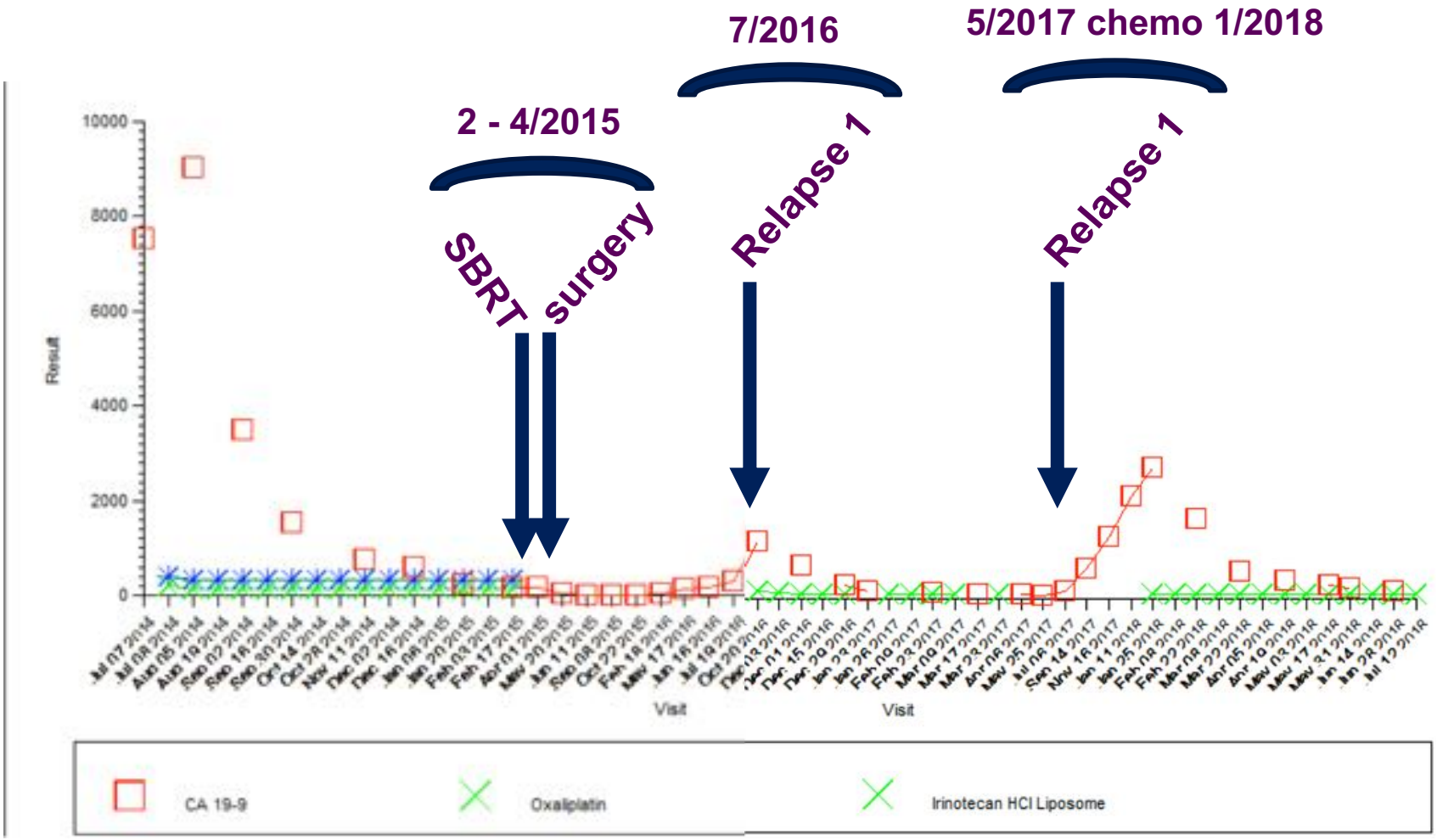
Case


7/2016
5/2017 chemo 1/2018
2 - 4/2015
SBRT
surgery
Relapse 1
Relapse 1
Result
10000
8000
6000
4000
2000
0
Visit
Visit
CA 19-9
Oxaliplatin
Irinotecan HCl Liposome

Supportive Care

- Primary Effects of Disease
  - anorexia
  - weight loss
  - wasting
  - pain
  - dysmotility/malabsorption
  - fatigue
- Primary Effects of Therapy
  - nausea
  - appetite
  - fatigue
  - neuropathy
  - diarrhea
- Interplay
  - Mind/body
  - Behavioral Health

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Questions?

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