CANCER EDUCATION DAY

The Landscape of Pancreatic Cancer: Hope and Optimism

Dr. Akmal Ghafoor

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Presenter Disclosure

- **Relationships with financial sponsors:**
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  - **Patents**: N/A
  - **Advisory Board:** Board for Janssen

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Knowledge Test

1. Pancreatic cancer is the 8th leading cause of cancer death in Canada.
   A. True
   B. False
2. Adjuvant chemo is recommended after resection of pancreatic cancer.
   A. True
   B. False
3. Folforinox chemo is the accepted first line option for newly diagnosed metastaic pancreatic adenocarcinoma with patients ECOG performance status of 0-1.
   A. True
   B. False

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Learning Objectives

- To learn about treatment options and progress made in a) resectable b) borderline/locally advanced and c)metastatic pancreatic cancer
- To touch upon novel precision medicine initiatives

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Brief Overview of Pancreatic Cancer

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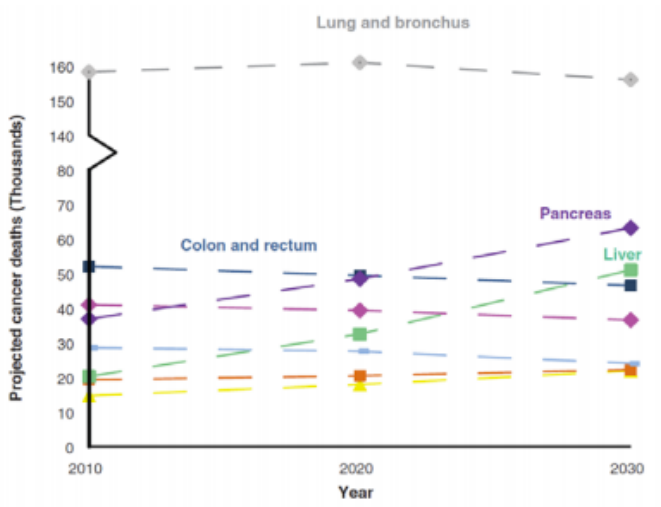
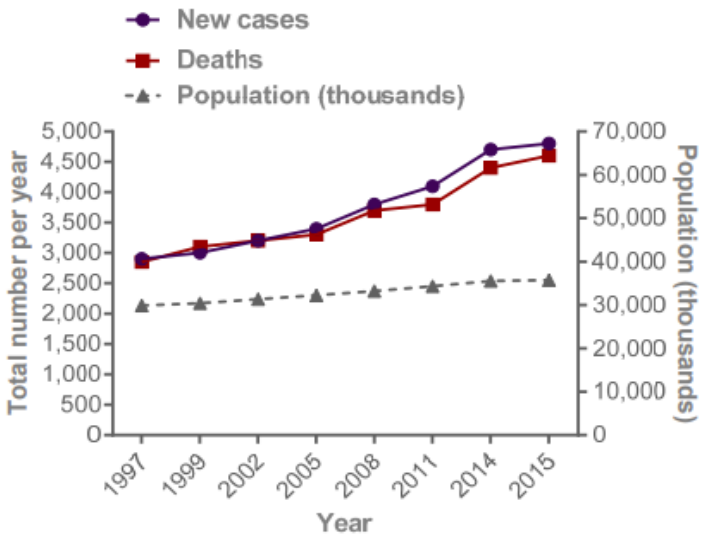
Overview

Pancreatic cancer will become 2nd most lethal cancer in the US by 2030



Pancreatic cancer rates will double in Canada by 2030



Stats Canada

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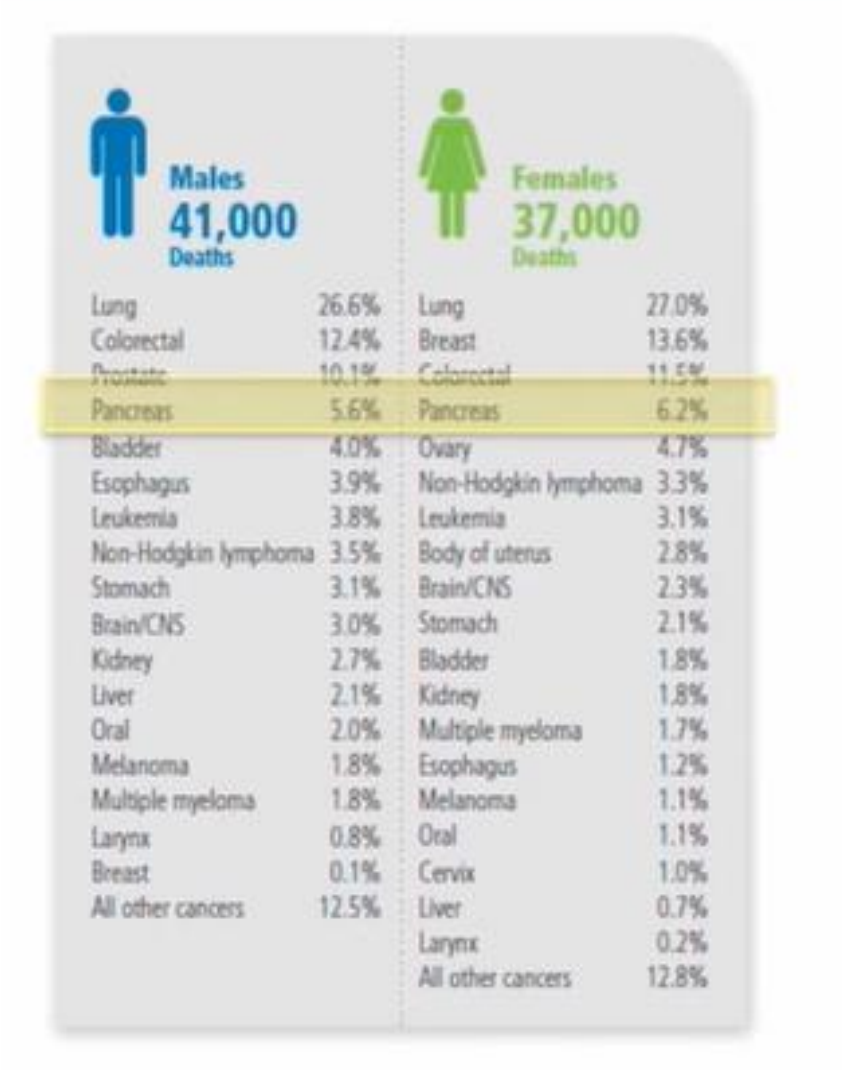
Overview

- Pancreatic cancer is the 4th most common cause of cancer-related deaths in Canada



Males 41,000 Deaths		Females 37,000 Deaths	
Lung	26.6%	Lung	27.0%
Colorectal	12.4%	Breast	13.6%
Prostate	10.1%	Colorectal	11.5%
Pancreas	5.6%	Pancreas	6.2%
Bladder	4.0%	Ovary	4.7%
Esophagus	3.9%	Non-Hodgkin lymphoma	3.3%
Leukemia	3.8%	Leukemia	3.1%
Non-Hodgkin lymphoma	3.5%	Body of uterus	2.8%
Stomach	3.1%	Brain/CNS	2.3%
Brain/CNS	3.0%	Stomach	2.1%
Kidney	2.7%	Bladder	1.8%
Liver	2.1%	Kidney	1.8%
Oral	2.0%	Multiple myeloma	1.7%
Melanoma	1.8%	Esophagus	1.2%
Multiple myeloma	1.8%	Melanoma	1.1%
Larynx	0.8%	Oral	1.1%
Breast	0.1%	Cervix	1.0%
All other cancers	12.5%	Liver	0.7%
		Larynx	0.2%
		All other cancers	12.8%

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Stats Canada

Pancreatic Risk Factors

Risk Factor	Risk Estimate (95% CI)
Current cigarette smoking	• OR = 2.20 (1.71–2.83)[1]
Past cigarette smoking: 1–10 years since quitting 15–20 years since quitting	 • OR = 1.64 (1.36–1.97)[1] • OR = 1.12 (0.86–1.44)[1]
Diabetes mellitus (> 10 years' duration)	• OR = 1.15 (1.16–1.96)[2]
BMI (> 35 kg/m^2)	• OR = 1.55 (1.16–2.07)[3]
Heavy alcohol (> 6 drinks/day)	• OR = 1.46 (1.16–1.83)[4]
Pancreatitis (> 2 years)	• OR = 2.71 (1.96–3.74)[5]

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Clinical Presentation

- Clinical presentation depends on the stage of disease and the location of the primary tumour:
  - The pancreatic head, neck, or uncinate process (70%)
  - The body or tail (20%)
  - Multifocal disease (10%)

Clinical Presentation

- Most tumors arise in the pancreatic head; signs and symptoms may include:
  - Right-upper quadrant or epigastric pain (79%)
  - Jaundice (56%)
  - Nausea or vomiting secondary to obstruction of the gastric outlet (51%)
  - Diarrhea (43%)
  - Steatorrhea due to pancreatic insufficiency (25%)
  - New or worsening back pain (49%) could signal cancer in the pancreatic body or tail1
  - Systemic manifestations may include profound and rapid weight loss (85%), anorexia (83%), or thromboembolic disease (3%

Clinical Staging with Respect to TNM Classification

Stage	Tumour grade	Node status	Distant metastases
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1–3	N1	M0
III	T4	N0–1	M0
IV	T1–4	N0–1	M1

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Case, Jan 2012

- 61-year-old accountant
- Presents to the emergency department at a community hospital with obstructive jaundice and abdominal pain
- PMH; recent diagnosis of DM, H/o gout

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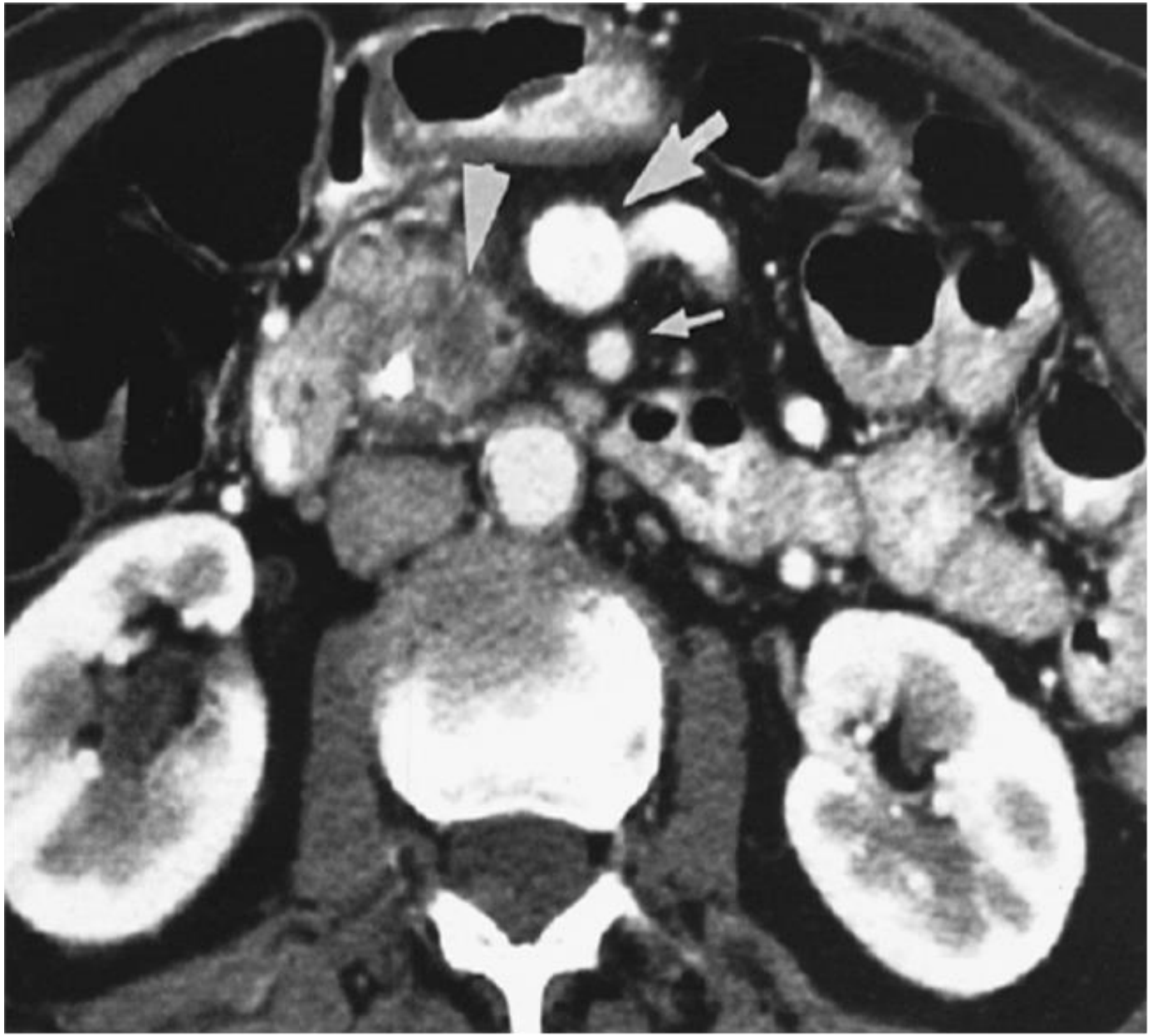
Evaluation in Emergency Department

- Laboratory tests:
  - CBC normal
  - Glucose 11.2 mmol/L
  - Creatinine and electrolytes normal
  - AST 250
  - Bilirubin 178
- CT abdomen and pelvis shows 2.0 cm mass in head of the pancreas
  - Marked dilatation of the biliary tree and gall bladder
  - Pancreatic duct dilated
  - Tumour abutting the superior mesenteric and portal veins
  - No arterial involvement
  - No evidence of disease elsewhere



CT Abdomen and Pelvis

Treatment Plan

- Patient underwent a pancreaticoduodenectomy (Whipple's resection)
- Pathology:
  - Moderately differentiated adenocarcinoma of the pancreas
  - 1/31 nodes positive
  - Margins clear
- Any further treatment needed? Yes!

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Options

- Charite Onkologie (CONKO)-001 Trial

Multicentre, open-label, phase III randomized trial (n = 368)

	Gemcitabine (n = 179)	Observation (n = 175)	*p* value
Median DFS	13.4 months	6.7 months	< 0.001
Median OS	22.8 months	20.2 months	0.01
5-year survival	20.7%	10.4%	
10-year survival	12.2%	7.7%	

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Options

- ESPAC 3 Trial

Randomized controlled phase III trial (n = 1,088)

	5-FU/Folinic Acid (n = 551)	Gemcitabine (n = 537)	*p* value
Median PFS	14.1 months	14.3 months	0.53
Median OS	23.0 months	23.6 months	0.39
2-year OS	48.1%	49.1%	—

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Adjuvant Chemotherapy

- Adjuvant chemotherapy is recommended for all patients, based on results from multiple randomized trials
- Treatment with adjuvant gemcitabine or 5-FU leads to a 10% improvement in the 5-year overall survival rate
- Gemcitabine may be the preferred agent, owing to its more favourable toxicity profile vs. 5-FU in the ESPAC 3 trial

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What's New in Adjuvant Therapy

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Updates in Adjuvant Therapy

PRODIGE 24/CCTG PA.6, an Unicancer GI trial: a multicenter international randomized phase III trial of adjuvant mFOLFIRINOX versus gemcitabine (gem) in patients with resected pancreatic ductal adenocarcinomas.

T. Conroy, P. Hammel, M. Hebbar, M. Ben Abdelghani, A.C. Wei, J-L. Raoul, L. Choné, E. François, P. Artru, J. Biagi, T. Lecomte, E. Assenat, R. Faroux, M. Ychou, J. Volet, A. Sauvanet, C. Jouffroy, P. Rat, F. Castan, J-B. Bachet, for the CCTG and the UNICANCER-GI /PRODIGE Group

Institut de Cancérologie de Lorraine, Nancy; Hôpital Beaujon, Clichy; Hôpital Huriez, Lille; Centre Paul Strauss, Strasbourg; Princess Margaret Hospital, Toronto; Institut Paoli-Calmettes, Marseille; University hospital, Nancy; Centre Antoine-Lacassagne, Nice; Hôpital Jean-Mermoz, Lyon; Kingston General Hospital, Kingston; Hôpital Trousseau, Tours; University Hospital, Montpellier; CHD Vendée, La Roche-sur-Yon; Institut du Cancer de Montpellier, Montpellier; Centre Hospitalier Universitaire, Dijon; Hôpital Pitié-Salpétrière, Paris; Canadian Cancer Trials Group, Kingston, Canada; R&D UNICANCER, Paris; France

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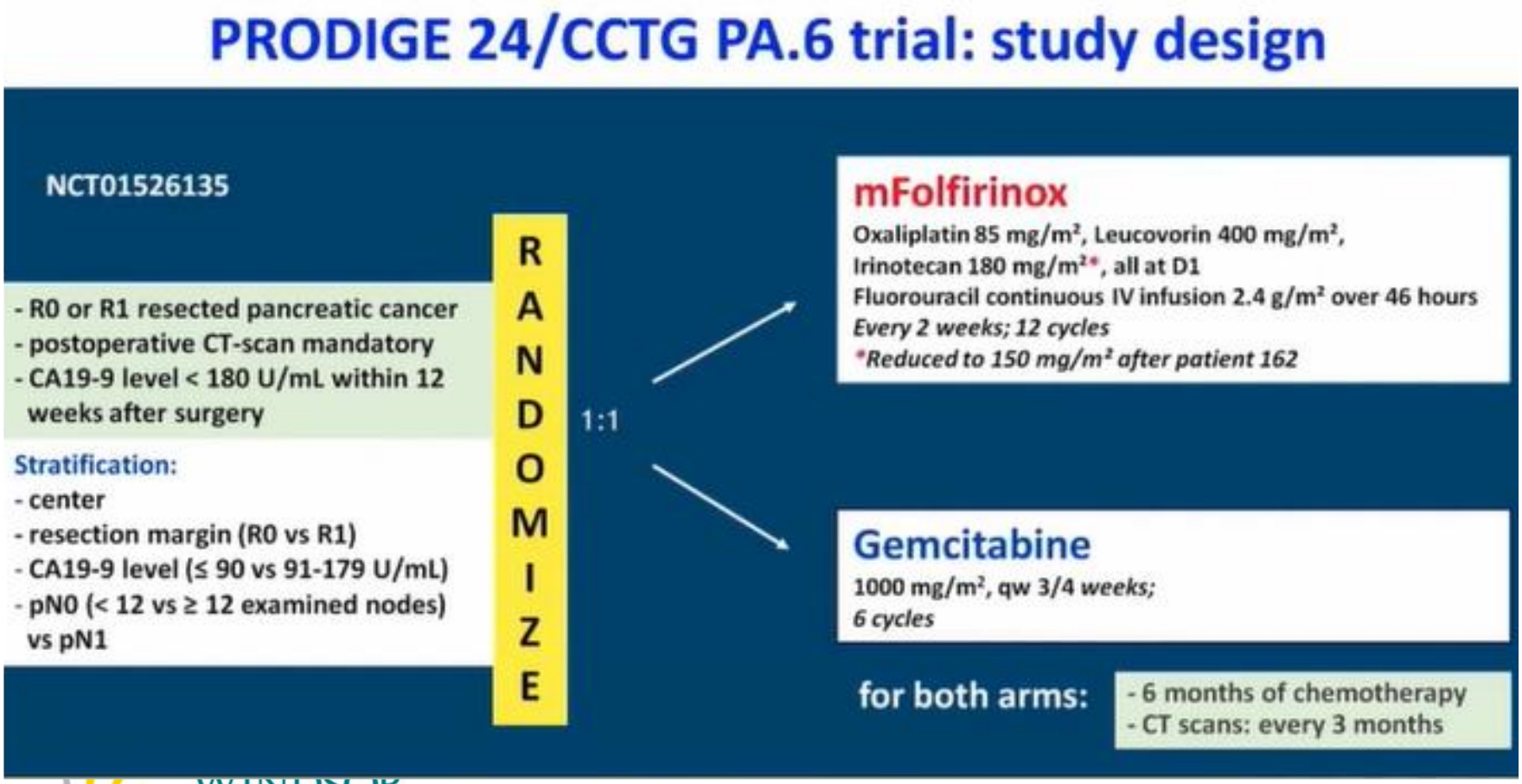
Updates in Adjuvant Therapy



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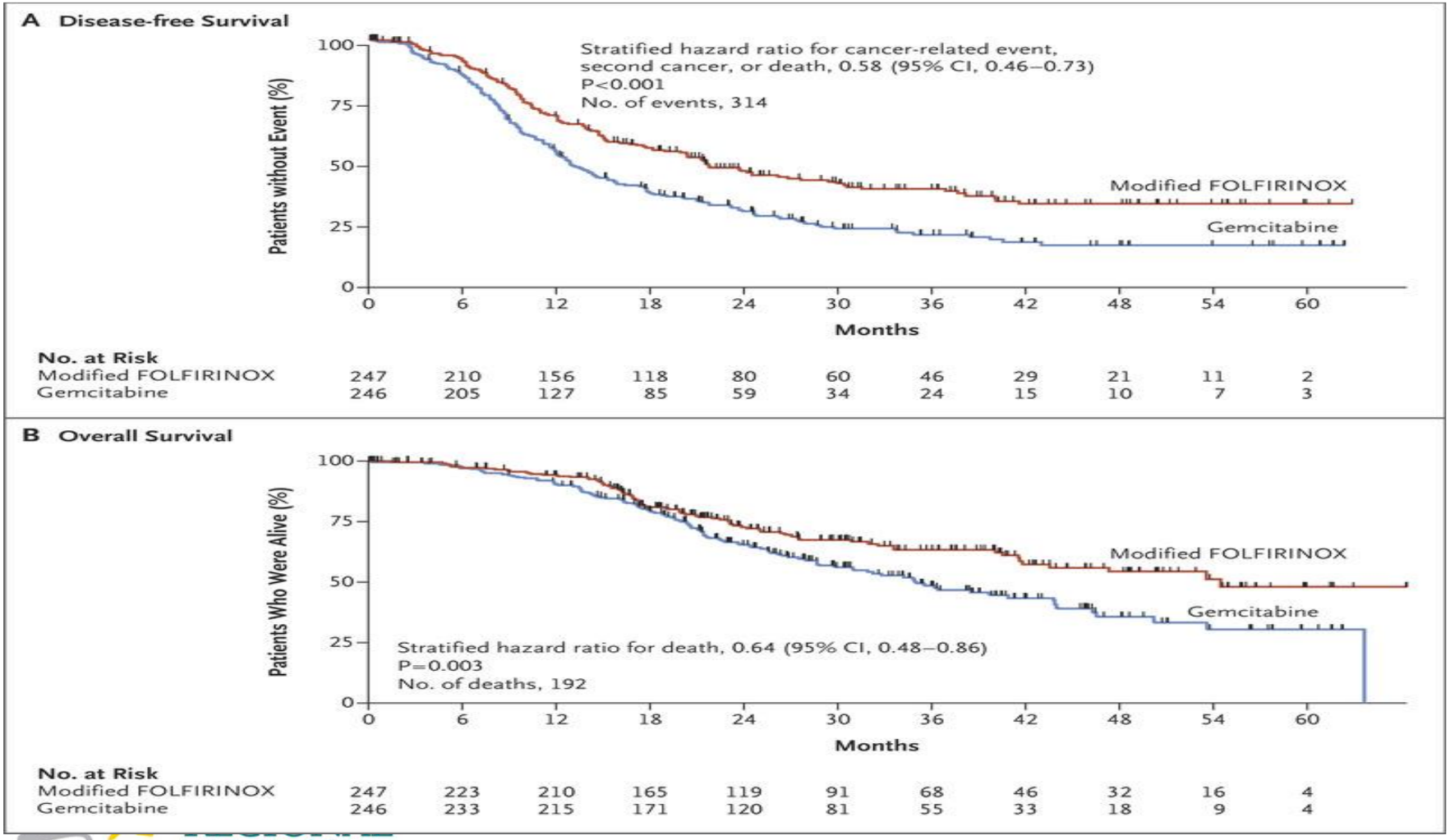
Updates in Adjuvant Therapy



Subgroup	Modified FOLFIRINOX (N=247)	Gemcitabine (N=246)	Unstratified Hazard Ratio (95% CI)	P Value
	no. of events/total no. of patients			
Sex				0.42
Male	78/142	96/135	0.68 (0.50–0.92)	
Female	56/105	84/111	0.56 (0.40–0.78)	
Age				0.88
<65 yr	83/152	103/140	0.61 (0.46–0.82)	
≥65 yr	51/95	77/106	0.63 (0.44–0.90)	
WHO performance-status score				0.10
0	61/122	96/127	0.51 (0.37–0.71)	
1	73/123	80/115	0.77 (0.56–1.06)	
Diabetes				0.59
No	100/183	123/177	0.66 (0.50–0.86)	
Yes	33/62	52/64	0.55 (0.35–0.85)	
Tumor location				0.89
Head	105/193	129/175	0.62 (0.48–0.80)	
Other	28/53	47/67	0.62 (0.39–0.98)	
Tumor grade				0.69
Well differentiated	32/70	58/79	0.52 (0.34–0.81)	
Moderately differentiated	75/124	91/125	0.69 (0.51–0.93)	
Poorly differentiated or undifferentiated	21/35	23/29	0.62 (0.34–1.13)	
Primary tumor status				0.82
pT1 or pT2	16/31	16/25	0.67 (0.34–1.34)	
pT3 or pT4	118/216	164/221	0.62 (0.49–0.79)	
Nodal status				0.10
pN0	25/55	33/61	0.89 (0.53–1.49)	
pN1	109/192	147/185	0.54 (0.42–0.69)	
Tumor stage				0.31
IA or IB	3/12	8/14	0.36 (0.10–1.38)	
IIA or IIB	127/226	167/226	0.64 (0.50–0.80)	
III or IV	4/9	5/6	0.07 (0.01–0.61)	
Status of surgical margins				0.15
R0	73/148	88/134	0.72 (0.53–0.98)	
R1	61/99	92/112	0.52 (0.37–0.72)	
Superior-mesenteric-vein resection				0.29
No	122/228	161/221	0.61 (0.48–0.77)	
Yes	12/19	19/25	0.92 (0.44–1.91)	
Portal-vein resection				0.86
No	112/215	145/204	0.62 (0.49–0.80)	
Yes	22/32	35/42	0.64 (0.37–1.11)	
Postoperative CA 19-9 level				0.85
≤90 U/ml	123/231	166/226	0.61 (0.48–0.77)	
>90 U/ml	11/16	14/20	0.74 (0.33–1.64)	
Early stopping of treatment				0.49
No	83/158	137/192	0.56 (0.42–0.73)	
Yes	51/80	42/51	0.53 (0.35–0.81)	
Overall	134/247	180/246	0.62 (0.49–0.77)	

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What's New in Neoadjuvant Therapy

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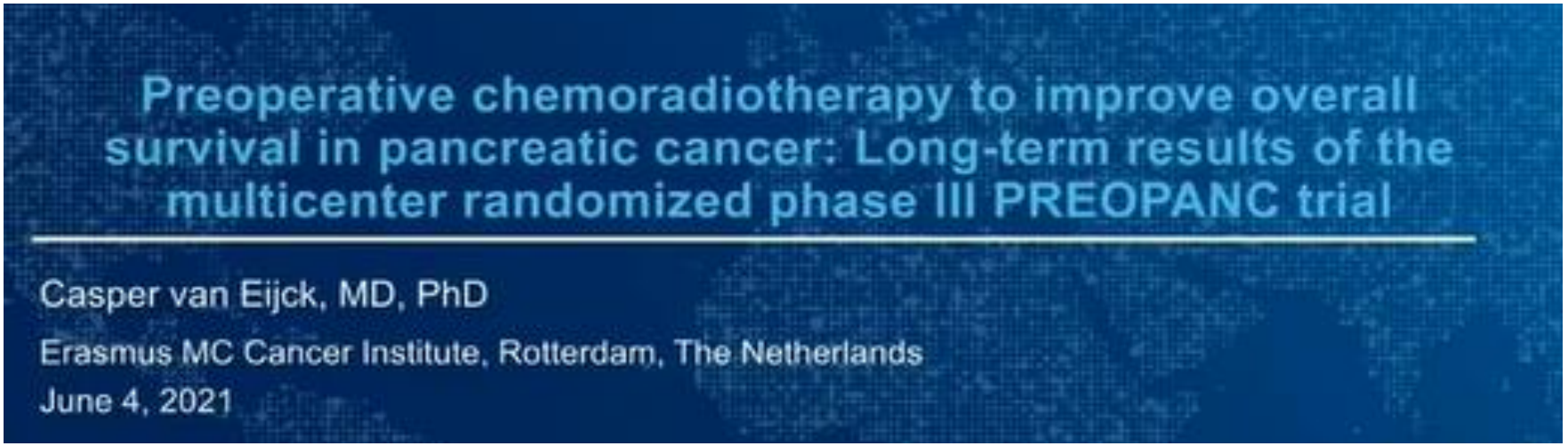
Updates in Neoadjuvant Therapy



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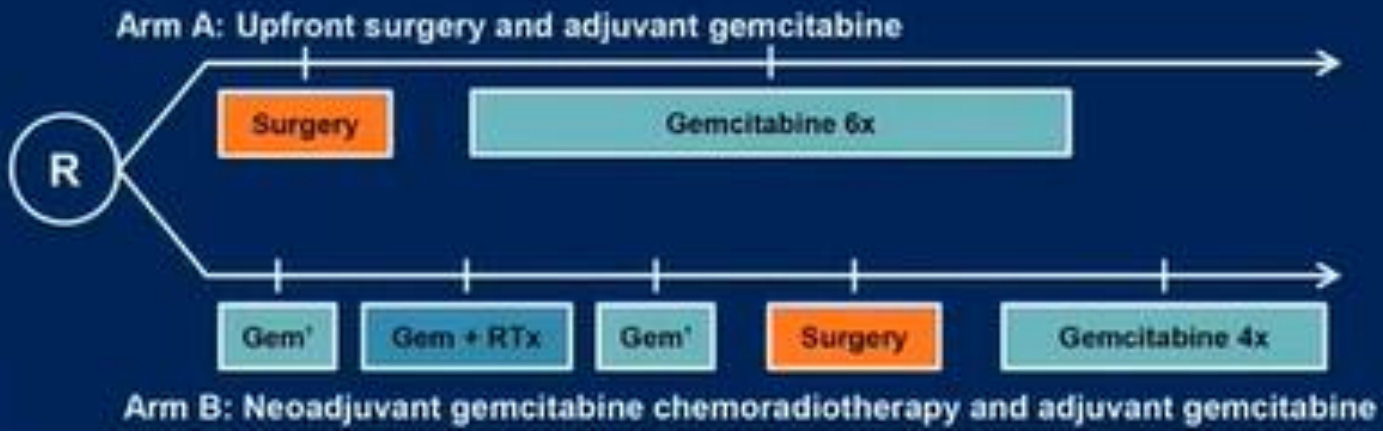
Updates in Neoadjuvant Therapy

Trial design

- Nationwide, multicenter, randomized controlled trial
- 16 centers in the Netherlands, N=246
- Primary end point: overall survival by intention-to-treat
- Secondary end points: resection rate, R0 resection rate, toxicity



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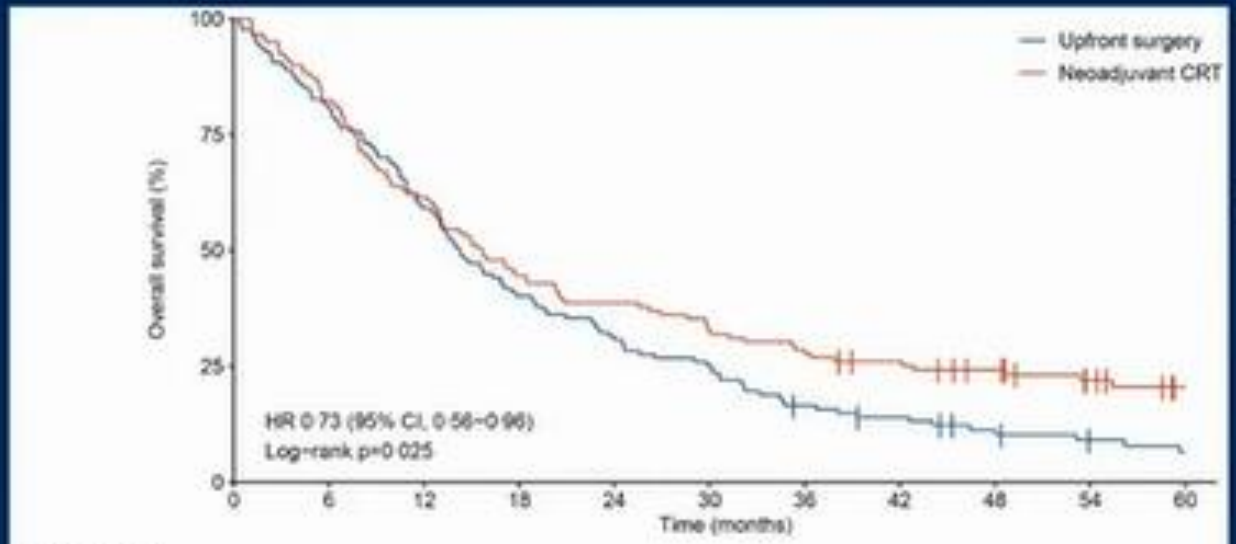
Updates in Neoadjuvant Therapy

Results – Overall survival by intention-to-treat

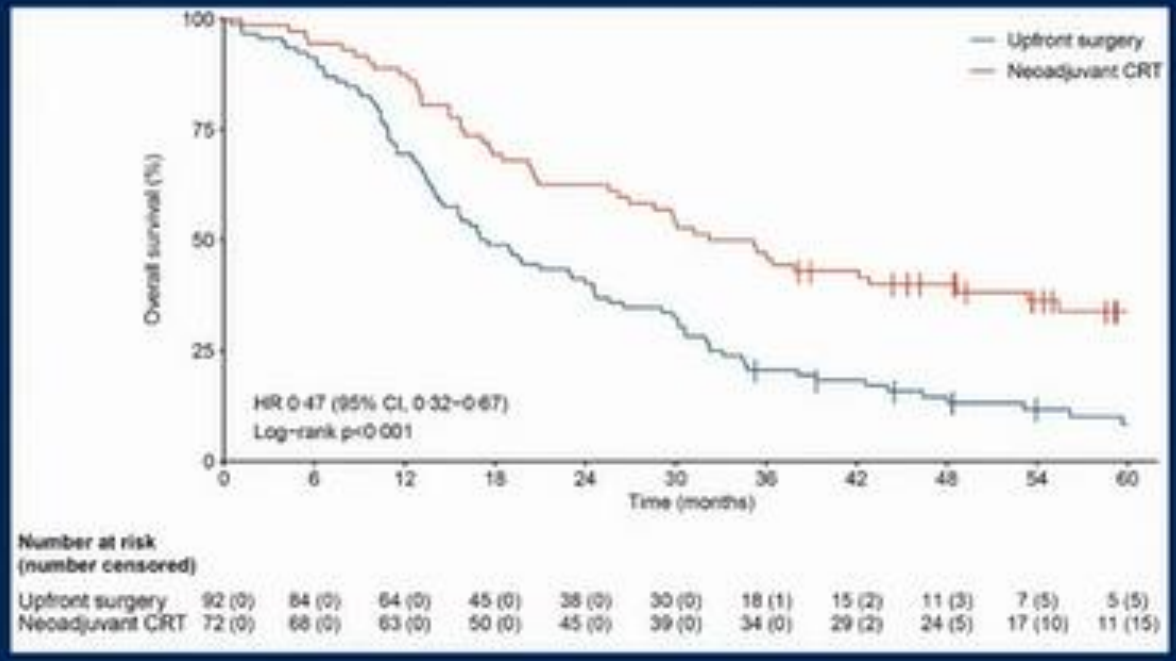


Median overall survival:
Upfront surgery: 14.3 mo
Neoadjuvant CRT: 15.7 mo

5-year survival:
Upfront surgery: 6.5%
Neoadjuvant CRT: 20.5%

Updates in Neoadjuvant Therapy

Results – Patients that underwent resection



Median overall survival:
Upfront surgery: 17.3 mo
Neoadjuvant CRT: 33.7 mo

5-year survival:
Upfront surgery: 8.4%
Neoadjuvant CRT: 33.9%

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Updates in Neoadjuvant Therapy

Conclusion

-Preoperative gemcitabine-based CRT for resectable or borderline resectable pancreatic cancer improves long term overall survival compared to immediate surgery with adjuvant gemcitabine.

-Further data needed for role of RT in this setting
- -Control arm of Gem alone
- -Included resectable and borderline resctable disease
- -Negative A021501 trial

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What About Metastatic Disease?

Median survival of metastatic pancreatic cancer is 3-6 mo.

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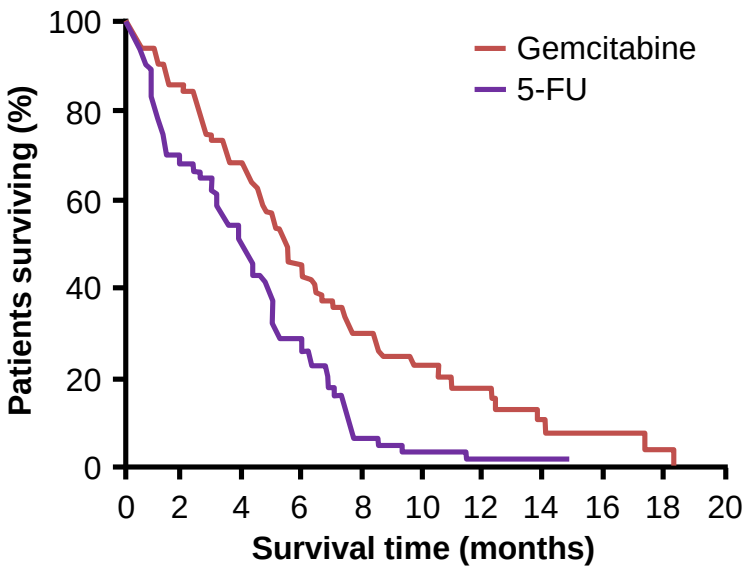
Metastatic Pancreatic Cancer: the Basis for Gemcitabine as the Mainstay of Treatment

- Pivotal study defining role for gemcitabine as first-line treatment for patients with advanced pancreatic cancer
  - Median survival (vs. bolus 5-FU): 5.65 vs. 4.41 months (p = 0.0025)
  - 1-year survival: 18% vs. 2%
  - Clinical benefit*: 23.8% vs. 4.8% (p = 0.0022)
  - Response rate: 5.4% vs. 0% (p = NS)



*A composite of measurements of pain (analgesic consumption and pain intensity), Karnofsky performance status, and weight. Clinical benefit required a sustained (≥ 4 weeks) improvement in at least 1 parameter without worsening in any others

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Case, Nov 2014

- 54 yr old with H/o abdominal pain, CT scan revealed mass in pancreas with liver mets.
- Ca 19-9, 576
- Biopsy liver mets, adenoca
- Surgical Eval in London, not a surgical candidate
- Folforinox chemo started in Nov 2014

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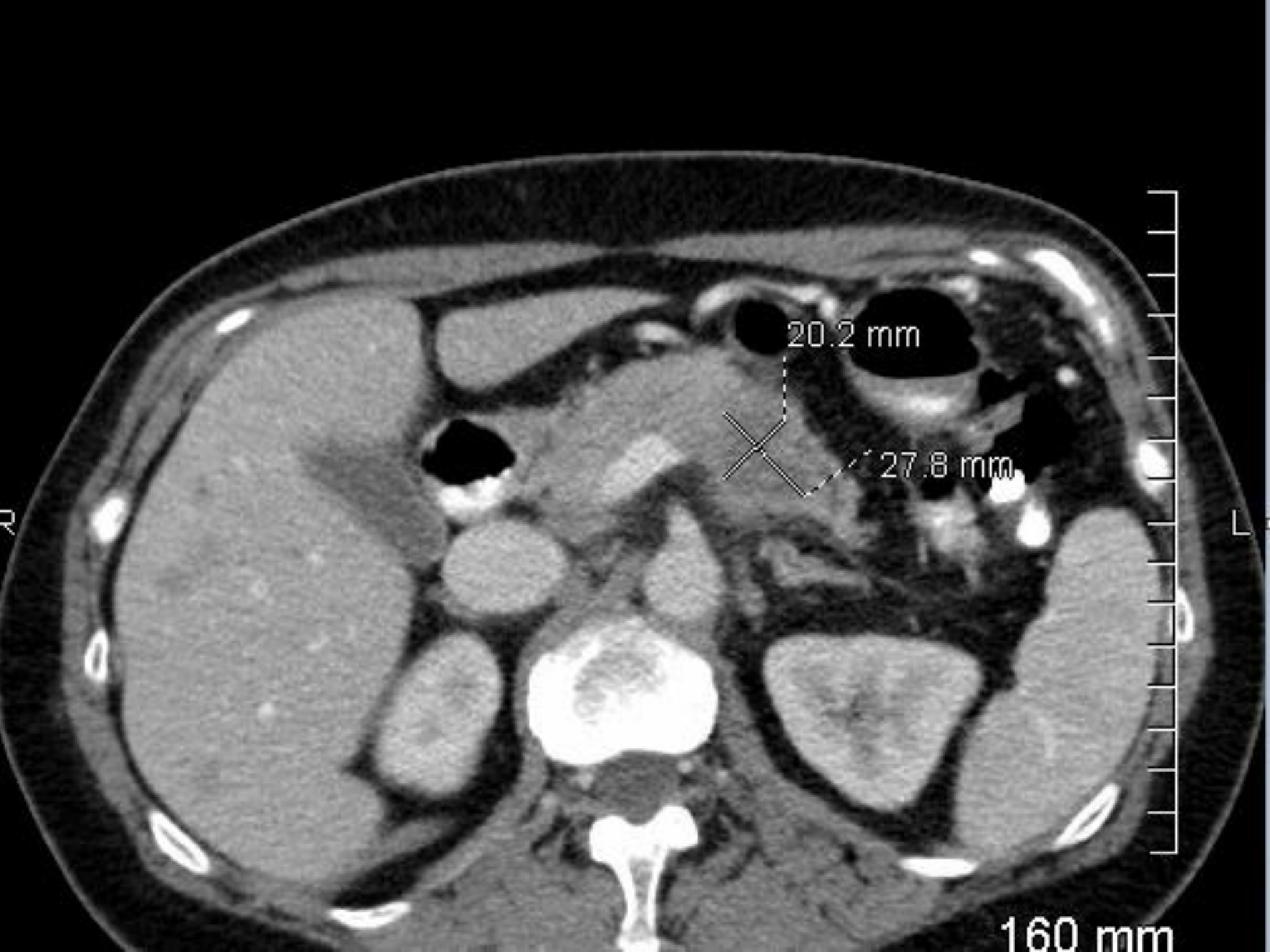
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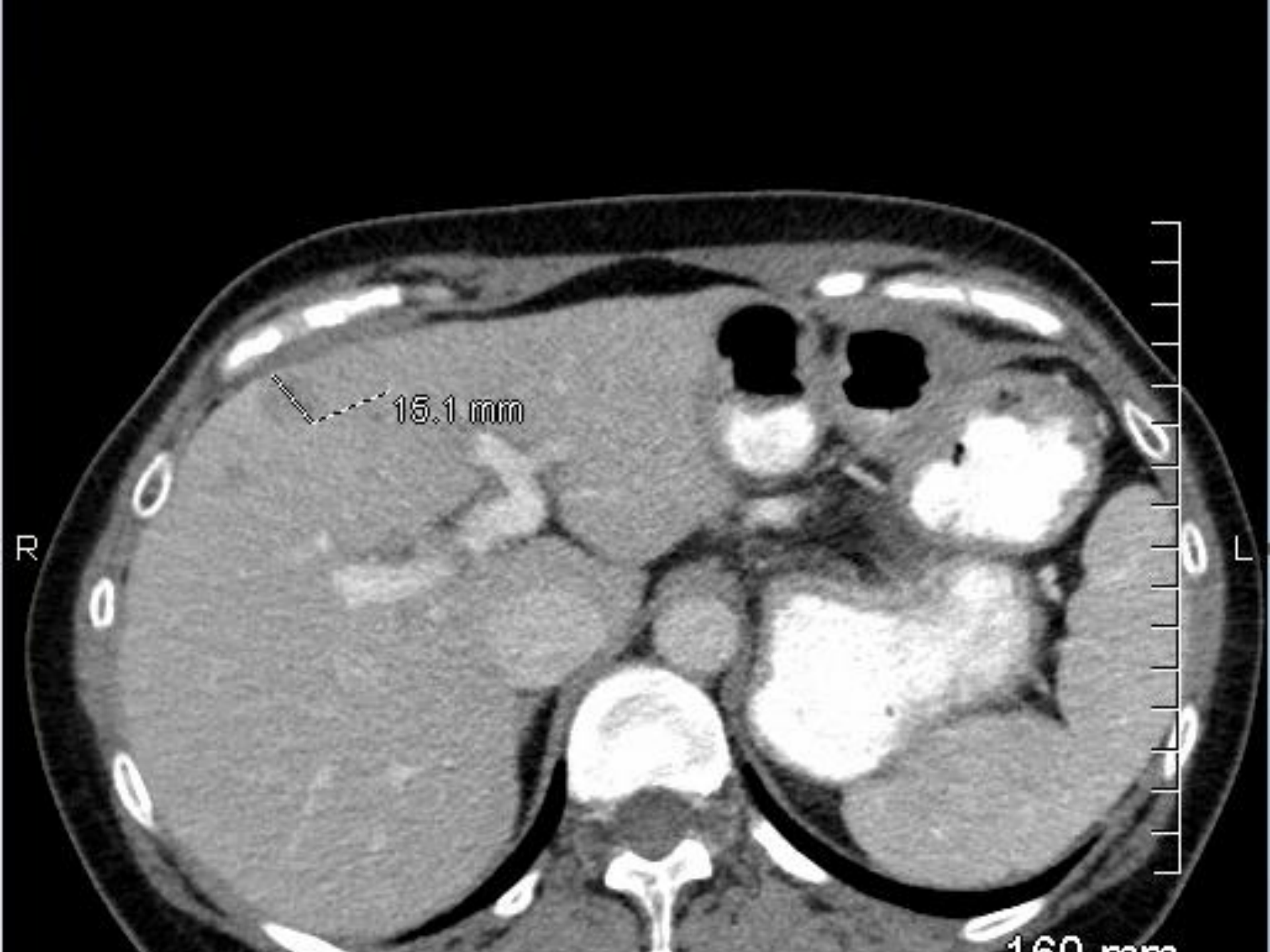
27.8 mm
160 mm


15.1 mm
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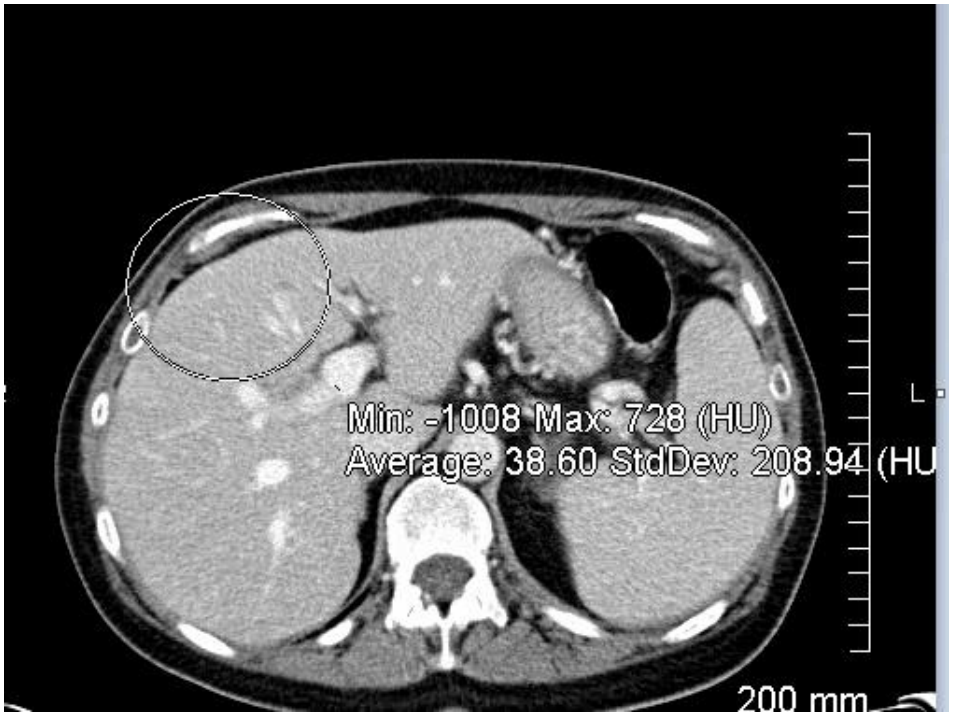
Case

- Patient has first restaging evaluation in march 2015
- CT Scan excellent response, CA19-9 decreases to 176
- Chemo course complicated by PE, started on blood thinners



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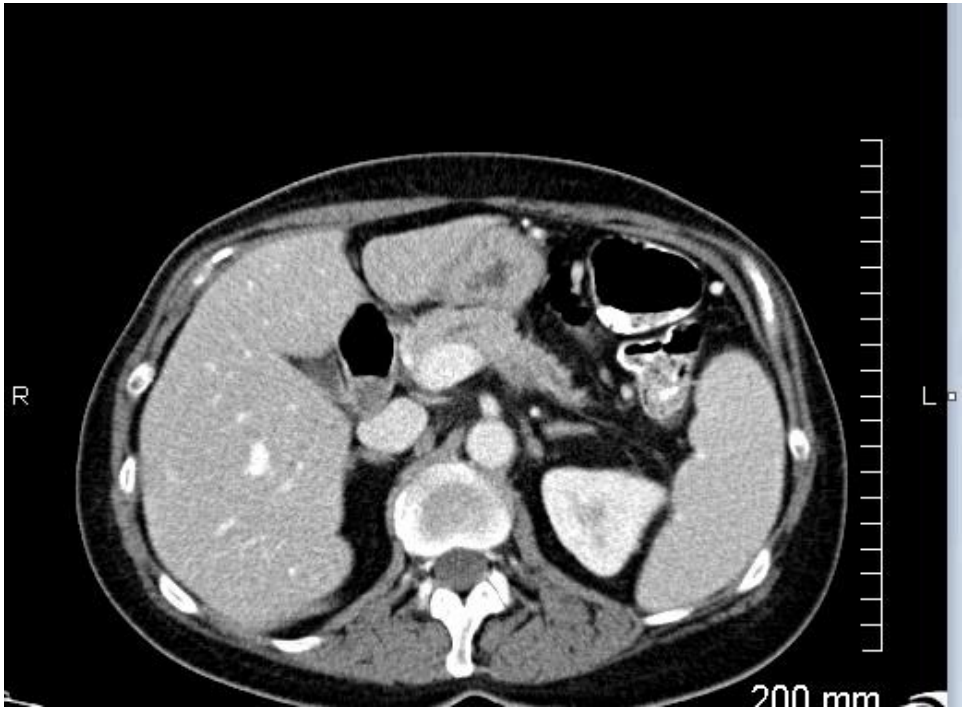
Case

- Pt con't on chemo, gets 30 cycles of folforinox chemo, pt clinically stable, given a break from Feb 2017
- Last CT scan Nov 2020, CT stable,NED
- Ca19-9 normal
- Patient discharged from the clinic after 5 years and remains in remission



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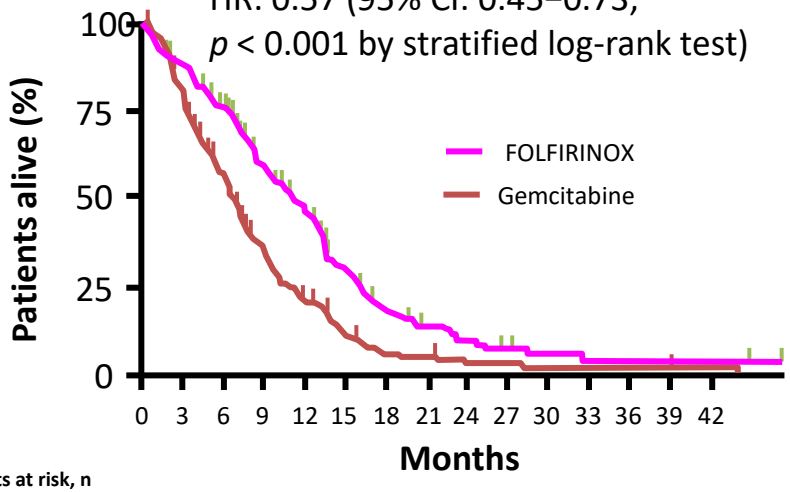
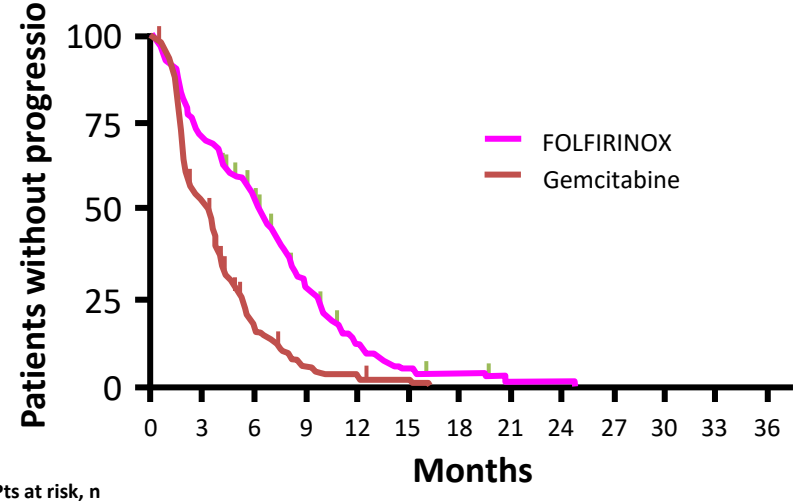
FOLFIRINOX vs. Gemcitabine: OS and PFS

OS



Pts at risk, n														
Gemcitabine	171	134	89	48	28	14	7	6	3	3	2	2	2	2	1
FOLFIRINOX	171	146	116	81	62	34	20	13	9	5	3	2	2	2	2

PFS



Pts at risk, n													
Gemcitabine	171	88	26	8	5	2	0	0	0	0	0	0	0
FOLFIRINOX	171	121	85	42	17	7	4	1	1	0	0	0	0

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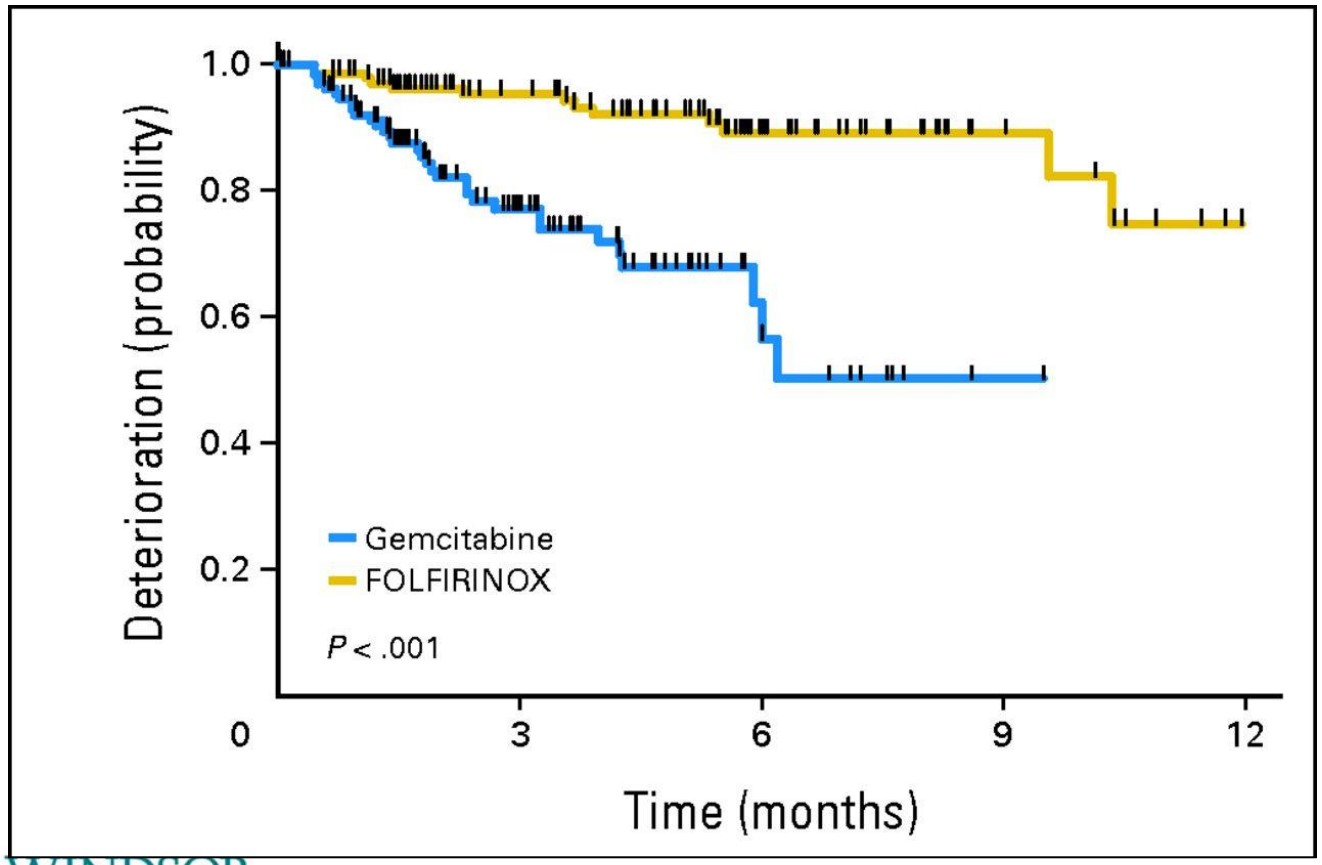
FOLFIRINOX vs. Gemcitabine: Quality of Life

Time Until Definitive Deterioration



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Summary of FOLFIRINOX in Advanced Pancreatic Cancer

- In the phase II/III FOLFIRINOX study, FOLFIRINOX demonstrated a significant improvement in OS, PFS, and ORR vs. gemcitabine
- Median OS: 11.1 vs. 6.8 months, HR 0.57, $p < 0.001$
- Median PFS: 6.4 vs. 3.3, HR 0.47, $p < 0.001$
- ORR 31.6% vs. 9.4%, $p < 0.001$

- FOLFIRINOX is an option for the treatment of patients with metastatic pancreatic cancer with good performance status

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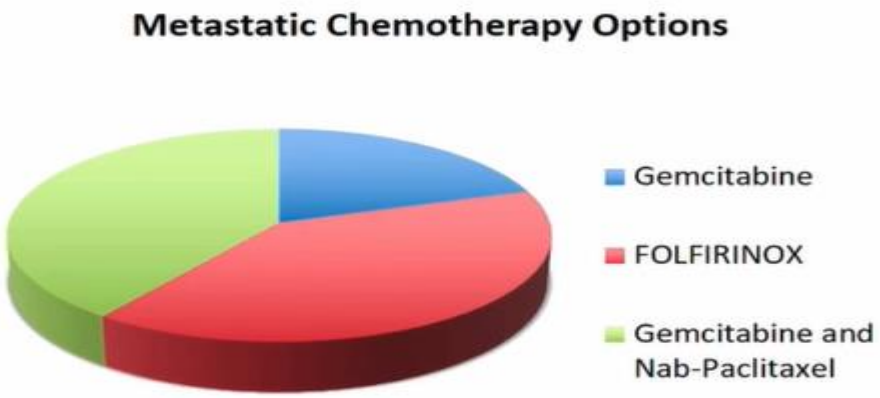
Metastatic PDAC: Where are We Now?



Treatment decision often made on basis of PS, age, comorbidities

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Personalized and Targeted Treatment Strategies

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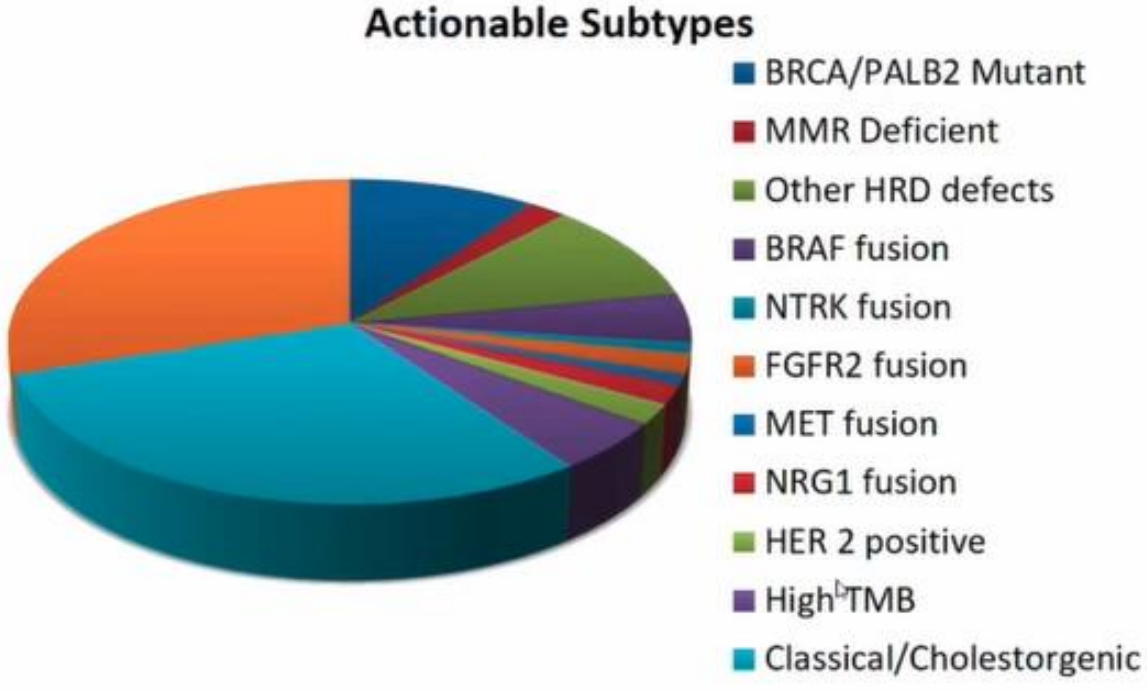
Clinical Implications for PDAC:

WGS/WTS data becoming increasingly important for therapeutic decision making



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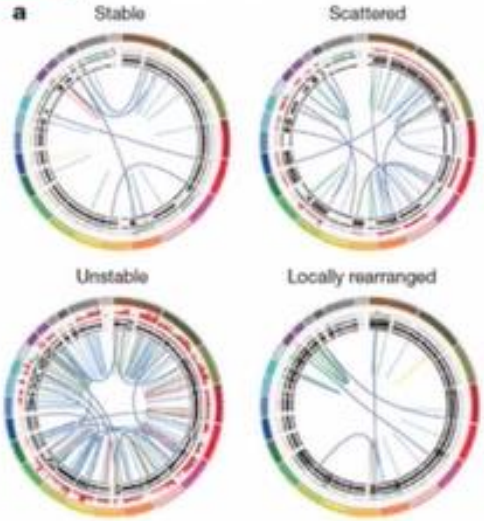
Predictive Value of BRCA/PALB2

Somatic BRCA mutation with 'unstable' chromosomal rearrangement subtype predicts response to adjuvant platinum-based therapy in resectable pancreatic cancer

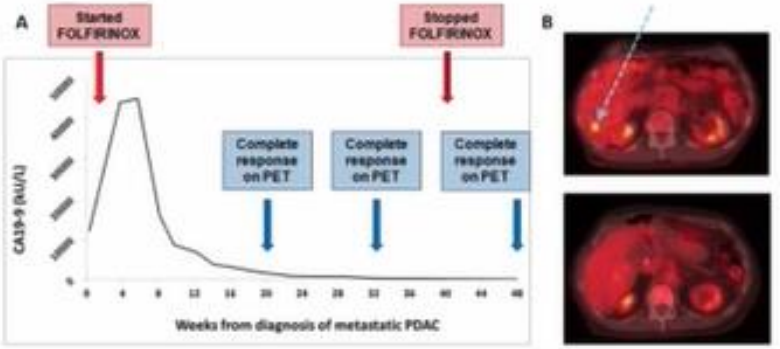


Waddell et al. *Nature*, 518:495 (2015)

- 20% of resected pancreatic tumours have germline or somatic BRCA mutations

Is BRCA mutation a predictive marker for platinum therapy in metastatic PDAC?

POG357: FOLFIRINOX response
Stable subtype
germline *BRCA1* with low HRd signature



Wong et al., Submitted

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Metastatic Pancreatic Cancer Options

- **Genomic profiling:**
  - BRACA/PALB2 +,mutant tumor benefit from platinum based chemo (Folforinox/folfox)
  - Parp inhibitors (Olaparib)maintenance role is still investigational
  - BRACA non mutant tumors, if positive for deficient MMR/MSI High tumors might benefit from checkpoint inhibitor therapy
- **Palliative care:**
  - Early integration very important for quality of life

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Hope and Optimism

- We have made strides in the management of pancreatic cancer and quality of life and longevity of pancreatic cancer patients has significantly improved.
- Need to collaborate closely with the healthcare team (surgeons/palliative care/family docs/genetic councillors and ancillary staff) to have more impact on the course of the disease.

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Thank You for Your Time

Any questions?