

Overview of Pancreatic Cancer

Randall Brand, MD

Professor of Medicine

Division of Gastroenterology, Hepatology and Nutrition

University of Pittsburgh Medical Center

Pancreatic Cancer: Overview of Talk

- Background
- Risk Factors
- Clinical Presentation
 - New Onset Diabetes
- Diagnostic modalities
- Staging
- Palliation

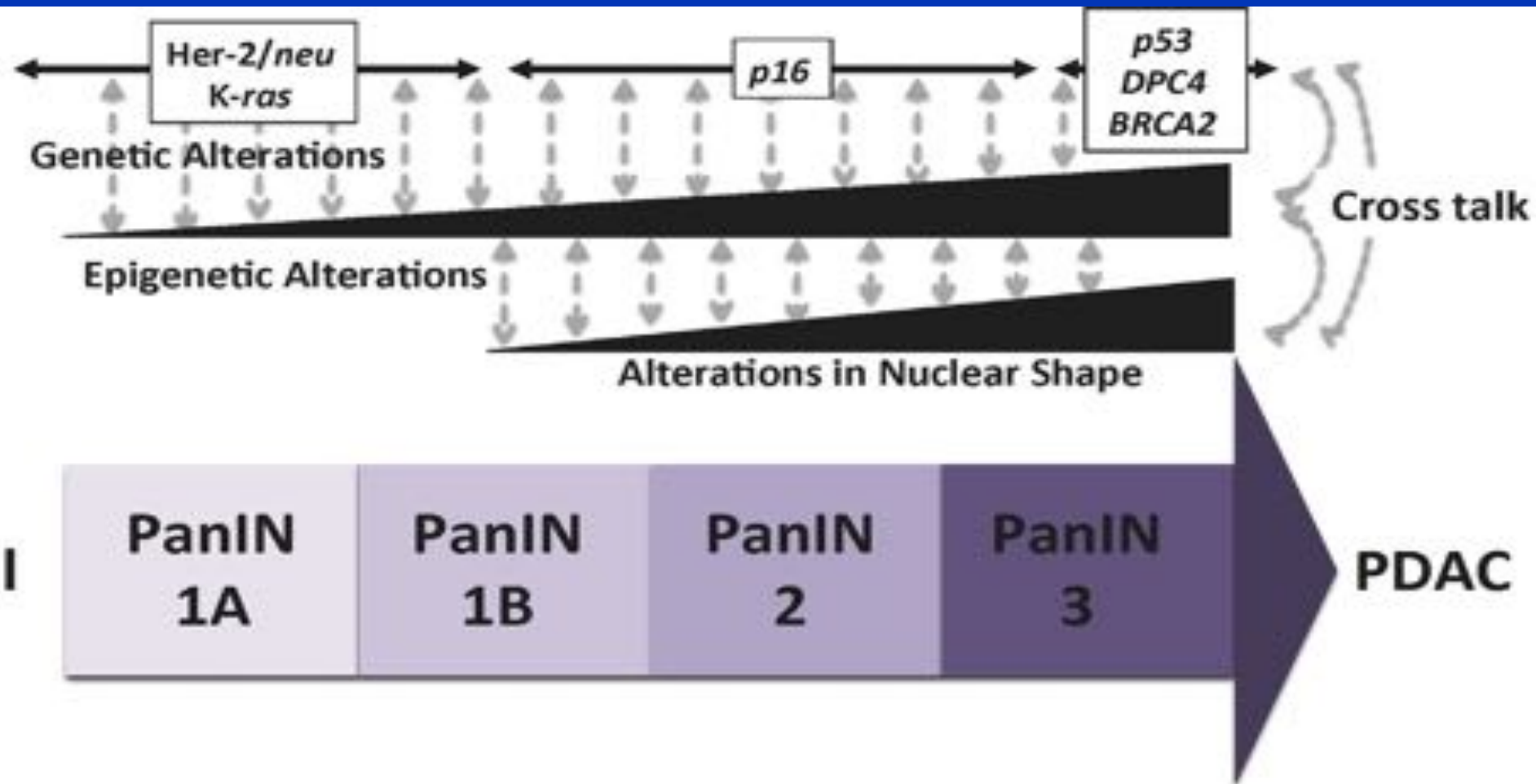
Pancreatic Cancer

- Incidence
 - In the US in 2018: 55,440 new diagnoses
44,330 deaths
 - ~1.6% life-time risk of developing
- Third leading cause of cancer related mortality in the US
 - Surpass colon cancer by as early as 2020
- Over 90% of tumors are adenocarcinomas
- Other tumors types include neuroendocrine, acinar and lymphomas

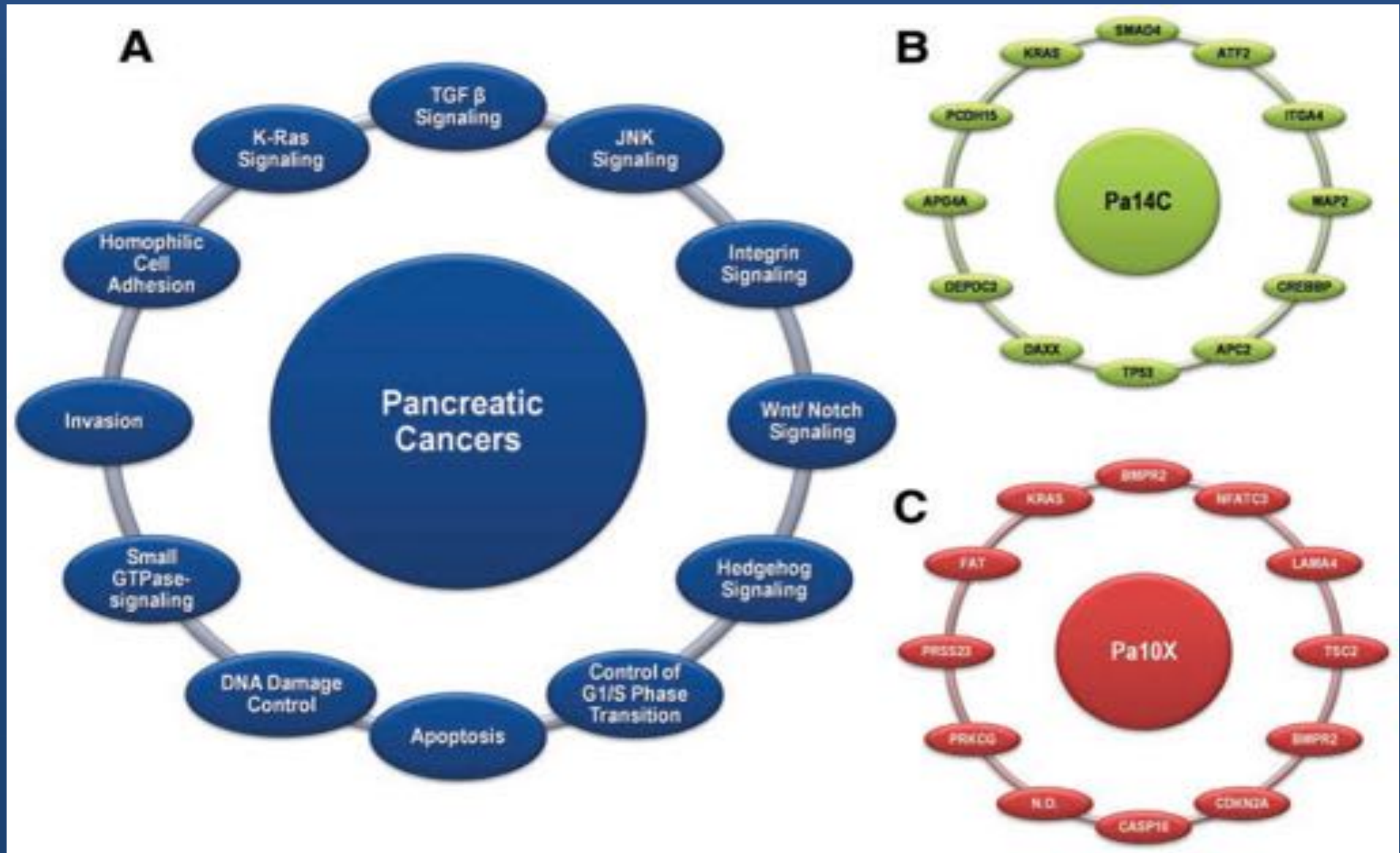
Pancreatic Adenocarcinoma: Precursor lesions

- Pancreatic Intraepithelial Neoplasias (PanINs)
- Mucinous cystic neoplasms
- Intraductal Papillary Mucinous Neoplasms (IPMNs)

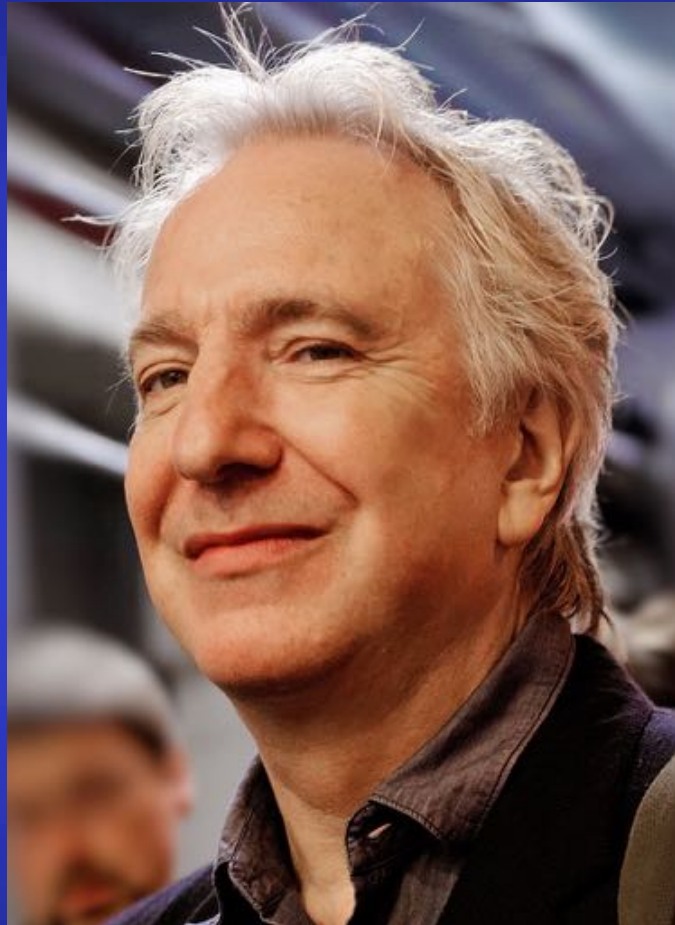
Cross talk between genetics, epigenetics, and nuclear structure in a revised comprehensive progression model for pancreatic cancer (Lomberk and Urrutia Surg Clin N Am 2015)



The 12 pathways and processes whose component genes were genetically altered in most pancreatic cancers Jones et al. Science 2008



Who is this?



By Marie-Lan Nguyen - [1], CC BY 2.0,
<https://commons.wikimedia.org/w/index.php?curid=46478797>

Pancreatic Cancer Risk Factors

Adapted from Brand et al. GUT 2007

- Male
- Black
- Ashkenazi Jewish decent
- Obesity
- Smoking
- Diabetes mellitus
- H. pylori infection
- History of any cancer in a first-degree relative
- Non-O blood type
- Cystic Fibrosis
- Chronic pancreatitis

Hereditary Disorders associated with PC

Recognized genetic syndromes with a known germline mutation associated PC development

2 or more cases of PC (with at least a pair of FDR)

Known as “Familial Pancreatic Cancer”

Syndromes Associated with Pancreatic Adenocarcinoma

Syndrome	Relative Risk of PC	Gene
Familial Atypical Multiple Mole Melanoma (FAMMM)	13 to 39-fold	p16
Familial Breast and Ovarian	2-fold and 3 to 9-fold	BRCA1 and 2
Fanconi Anemia, Breast CA	Unknown	PALB2
FAP	5-fold	APC
Lynch Syndrome	9 to 11-fold	MLH1, MSH6 MSH2, PMS2
Peutz-Jeghers Syndrome	132-fold	STK11/LKB1
Hereditary Pancreatitis	53-fold	PRSS1
Li-Fraumeni syndrome	7-fold	p53
Ataxia -telangiectasia	~3-fold	ATM

Role of Smoking in Pancreatic Cancer Development

- Cigarette smoking is the most significant and reproducible environmental risk factor
- Most epidemiology studies report a 2 to 3-fold increased risk for PC in smokers
- Estimated that ~25% of PC cases strongly associated with smoking

Pancreatic Adenocarcinoma



Adenocarcinoma: Signs and Symptoms

- Usually presents late
- Early, no characteristic signs or symptoms
 - Vague, dull midepigastria discomfort
 - Weight loss
 - Anorexia
 - Diarrhea
 - Weakness
 - Depression

Adenocarcinoma: Signs and Symptoms

- Additional signs and symptoms
 - Jaundice
 - **Diabetes**
 - Thrombophlebitis
 - Acute pancreatitis

Diabetes and Pancreatic Cancer

Historical Prespective

- Bright (*Med Chir Trans*) 1833: described DM occurring 6 months prior to PC
- Bell (*AJP*) 1957, diabetics had excess cases of PC
- Green (*Diabetes*) in 1958: half of cases had DM or glycosuria at time of PC diagnosis
- Clark and Mitchell (*BMJ*) 1961
 - Two types of association:
 - (a) cancer of the pancreas developing in patients who have suffered from diabetes for some years
 - (b) cancer of the pancreas accompanied by new onset DM in ~15% of cases

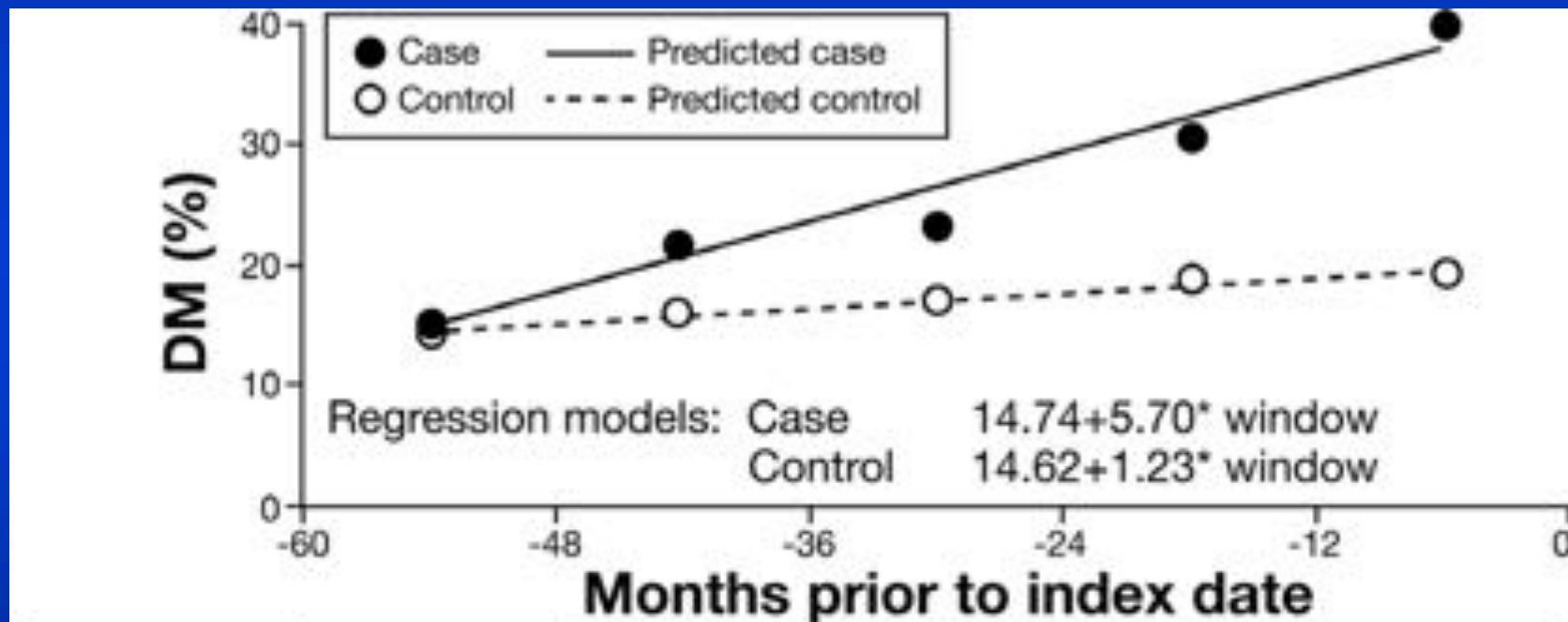
Summary Relative Risks for the Association between DM and PC according to DM duration from two large meta-analysis studies

1. Ben et al. European J of Cancer 2011: 35 studies from 1966-2010
2. Huxley et al. Br J of Cancer 2005: 36 studies from 1966 to 2005

DM Duration (years)	Ben et al. RR (95% CI)	Huxley et al. RR (95% CI)
<1	5.38 (3.49-8.30)	
1-4	1.95 (1.65-2.31)	2.05 (1.87-2.25)
5-9	1.49 (1.05-2.12)	1.54 (1.31-1.81)
>10	1.47 (0.94-2.31)	1.51 (1.16-1.96)

Observed and predicted prevalence of DM at 12-month intervals before the index date (Chari et al Gastro 2008)

- 736 PC cases, 1875 matched controls
- 40% DM vs. 19% controls DM (FBS>126 over 5-yrs)



Time	-48 to -60	-36 to -48	-24 to -36	-12 to -24	+1 to -12
Window	0	1	2	3	4
Cases (no.)	157	160	165	168	685
Controls (no.)	891	1,027	1,071	1,172	1,162
P	.76	.06	.04	.001	<.0001

Comparison of Performance Characteristics of Different Classifier Models for Pancreatic Cancer in New-Onset Diabetes

Model	Sensitivity	Specificity	Pancreatic cancer prevalence	Sensitivity with > 12 –month lead time	Proportion in low risk group
Glycemically-defined New-onset Diabetes			0.9%		
A: + weight loss >2.5kg	44%	84%	1.9%	47%	0
B: + Δ BG + Δ weight loss	78%	75%	2.1%	71%	35%
C: + Δ BG categories + Δ weight loss	78%	80%	4.5%	71%	48%

Who is this?



https://commons.wikimedia.org/wiki/File:Michael_Landon_1990.jpg#/media/File:Michael_Landon_1990.jpg

Current Imaging Tools

- Radiographic Imaging
 - Transabdominal Ultrasound
 - Computed Tomography (CT)
 - Magnetic Resonance (MRI)
 - Positron Emission Tomography (PET)
- Endoscopic Imaging
 - Endoscopic Ultrasound (EUS)
 - Endoscopic Retrograde Cholangiopancreatography (ERCP)
 - Cholangiopancreatography



CT



EUS

EUS for the Pancreas

- EUS superior for tumor detection (<2cm) and staging compared to MDCT
- Advantage: ability to biopsy pancreatic masses and lymph nodes
- Limitations: cost, availability, skilled endosonographers



Current Status of PC Biomarkers: CA 19-9

- Most widely studied
- Sialyated Lewis^a antigen associated with circulating mucins
- Commercially available
- Detected in serum and juice

CA 19-9: Effects of Selecting Different Cutoff Points

(Neiderau et al. Pancreas 1992)

CA 19-9	Sens(%)	Spec(%)
15	92	60
37	85	81
75	80	90
250	70	95
500	60	98
1,000	40	99

Who is this?



https://commons.wikimedia.org/wiki/File:Sally_Ride_in_1984.jpg#/media/File:Sally_Ride_in_1984.jpg

Pancreatic Cancer Stages

- Stage 0: Tis, N0, M0
 - Stage IA: T1, N0, M0
 - Stage IB: T2, N0, M0
 - Stage IIA: T3, N0, M0
 - Stage IIB: T1-3, N1, M0
 - Stage III: T1-3 and N2 or
T4 any N, M0
 - Stage IV: Tany, Nany, M1
- Tis: confined to top layers of pancreatic duct cells
- T1: Cancer less than 2 cm
- T2: Cancer is 2 to 4 cm in size
- T3: Cancer bigger than 4 cm
- T4: Cancer growing outside the pancreas into major blood vessels
- N0: Not spread to lymph nodes (LN)
- N1: Spread to no more than 3 nearby LN
- N2: Spread to 4 or more nearby LN
- M0: Not spread to distant sites
- M1: Cancer spread to distant sites

Stage Distribution and 5-year Relative Survival by Stage at Diagnosis for 2001-2007, All Races, Both Sexes

Stage at Diagnosis	Stage Distribution (%)	5-year Relative Survival (%)
Localized	8	21.5
Regional	27	8.6
Distant	53	1.8
Unknown (unstaged)	13	4.2

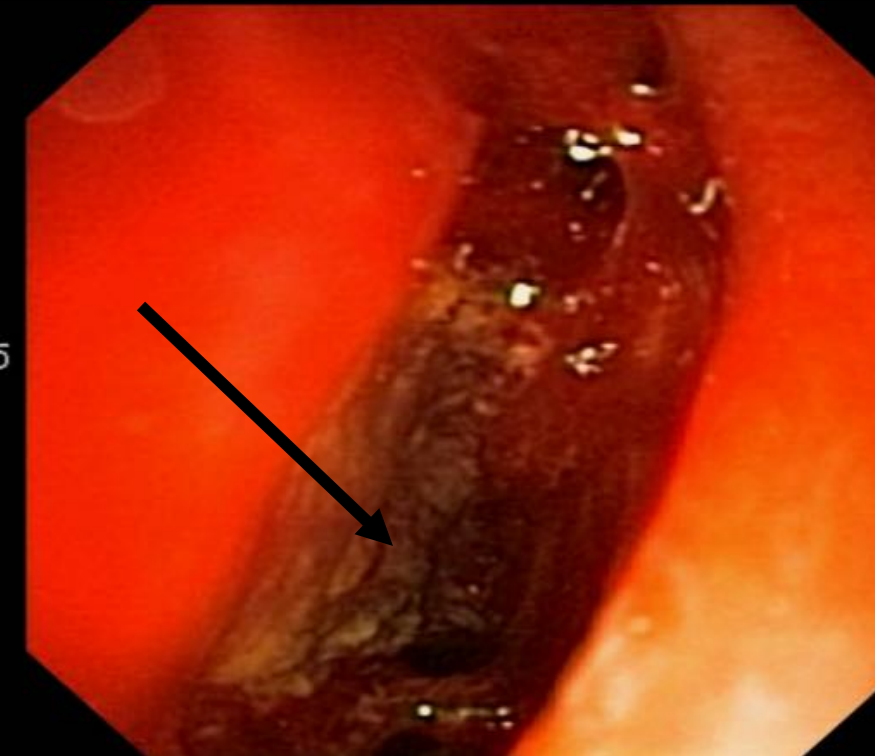
Adapted from NCI's SEER Cancer Statistics Review

Pancreatic Adenocarcinoma: Staging

- CT scan of abdomen/pelvis
- Endoscopic Ultrasound may be useful
- Possible Laparoscopy
- Unclear if PET scans are helpful

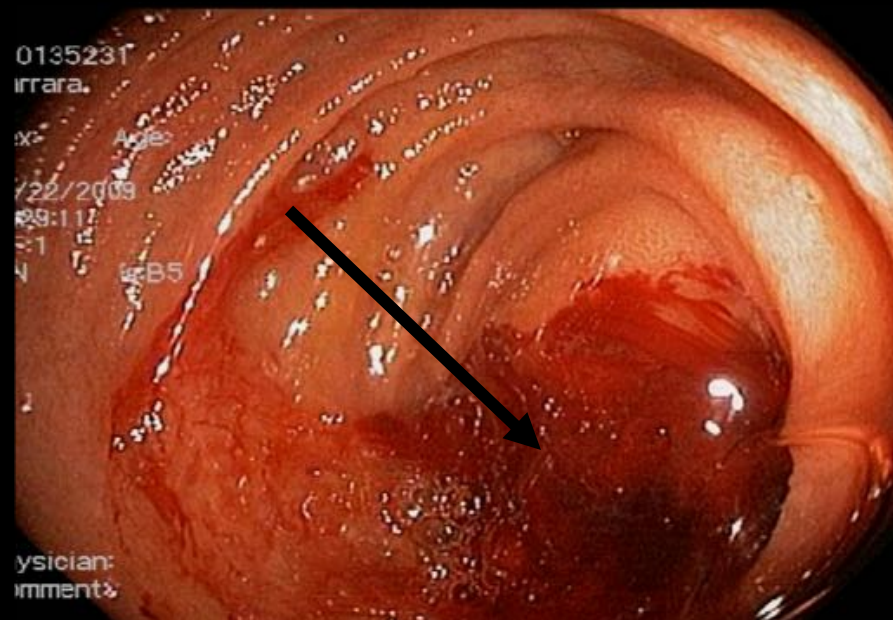
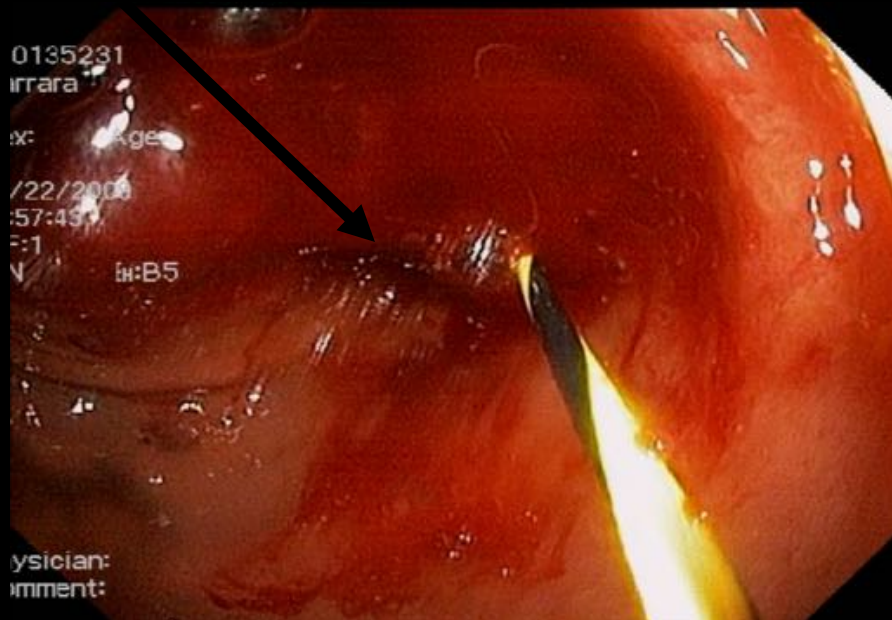
Pancreatic Carcinoma: Palliation

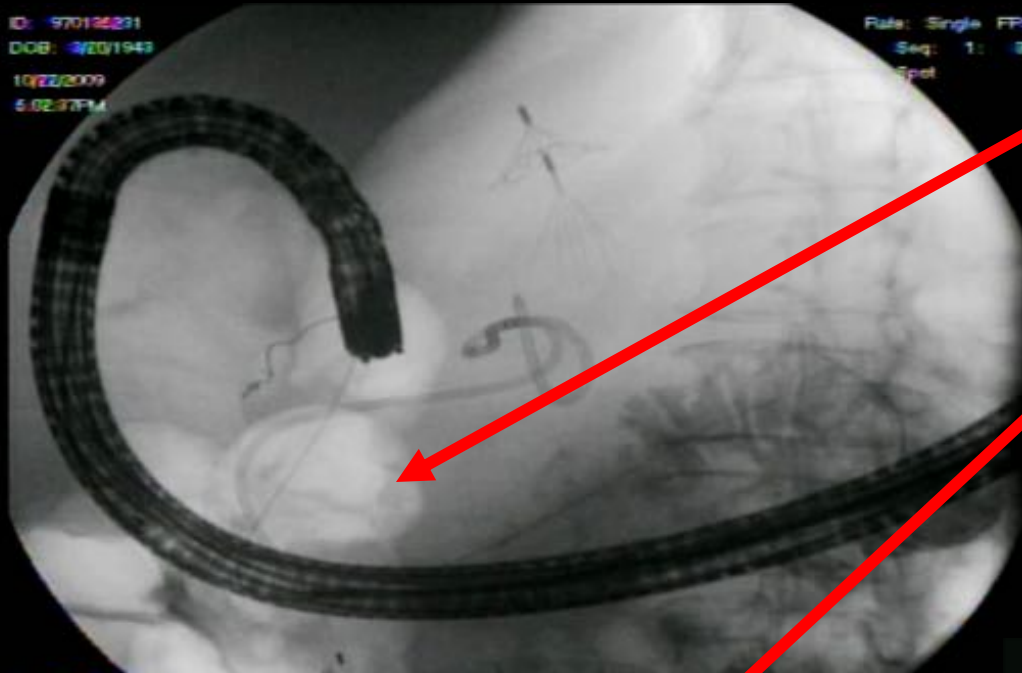
- Biliary obstruction
 - ERCP
 - Percutaneous transhepatic cholangiography
 - Surgical bypass
- Duodenal obstruction
 - Endoscopic stent placement
 - Surgical bypass
- Pain control
 - Narcotics
 - Celiac Neurolysis



Duodenal Obstruction from
Extrinsic compression
(pancreatic head cancer)

Courtesy of Dr. Andres Gelrud

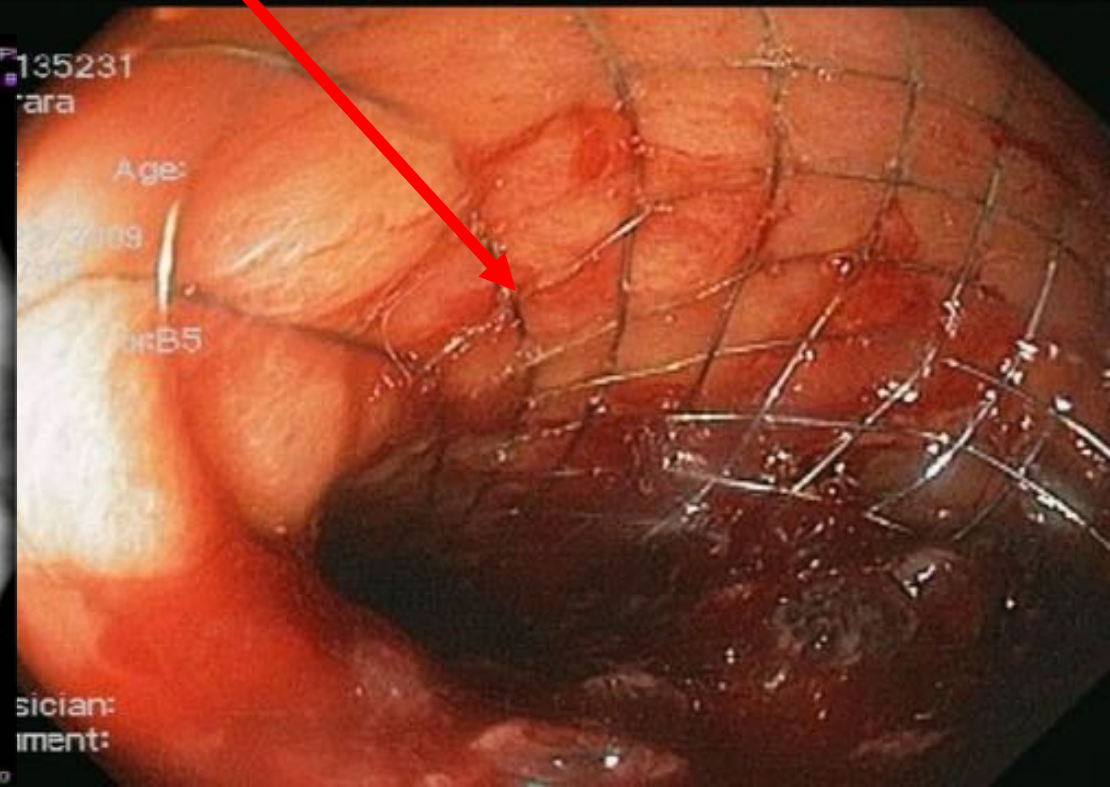
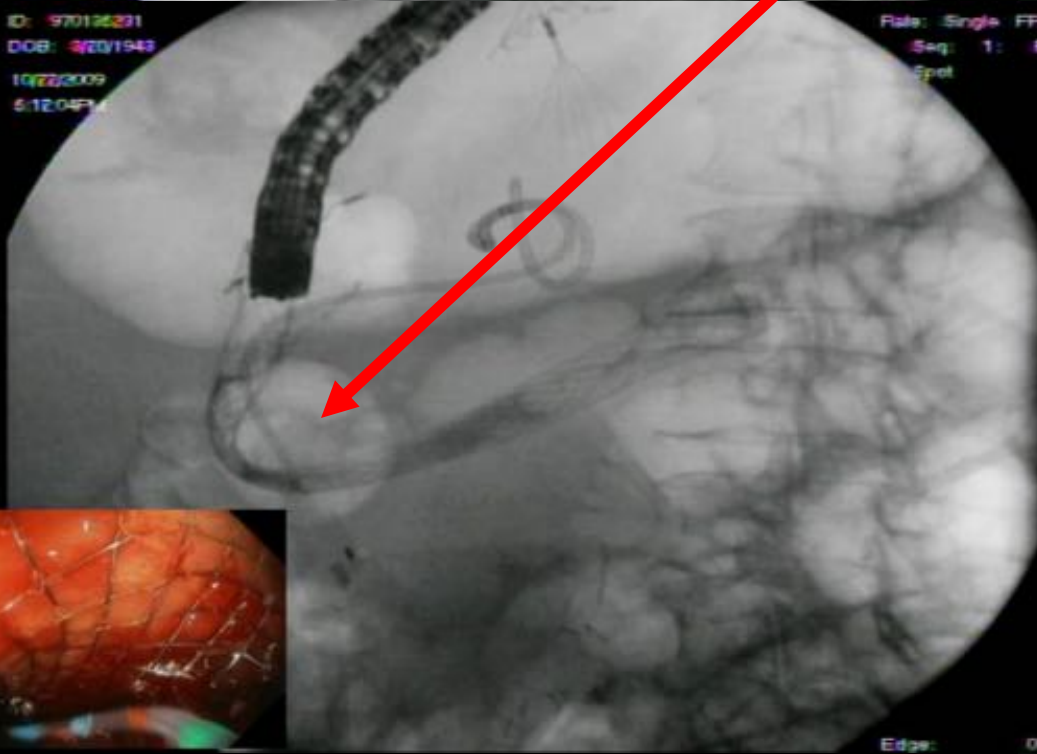




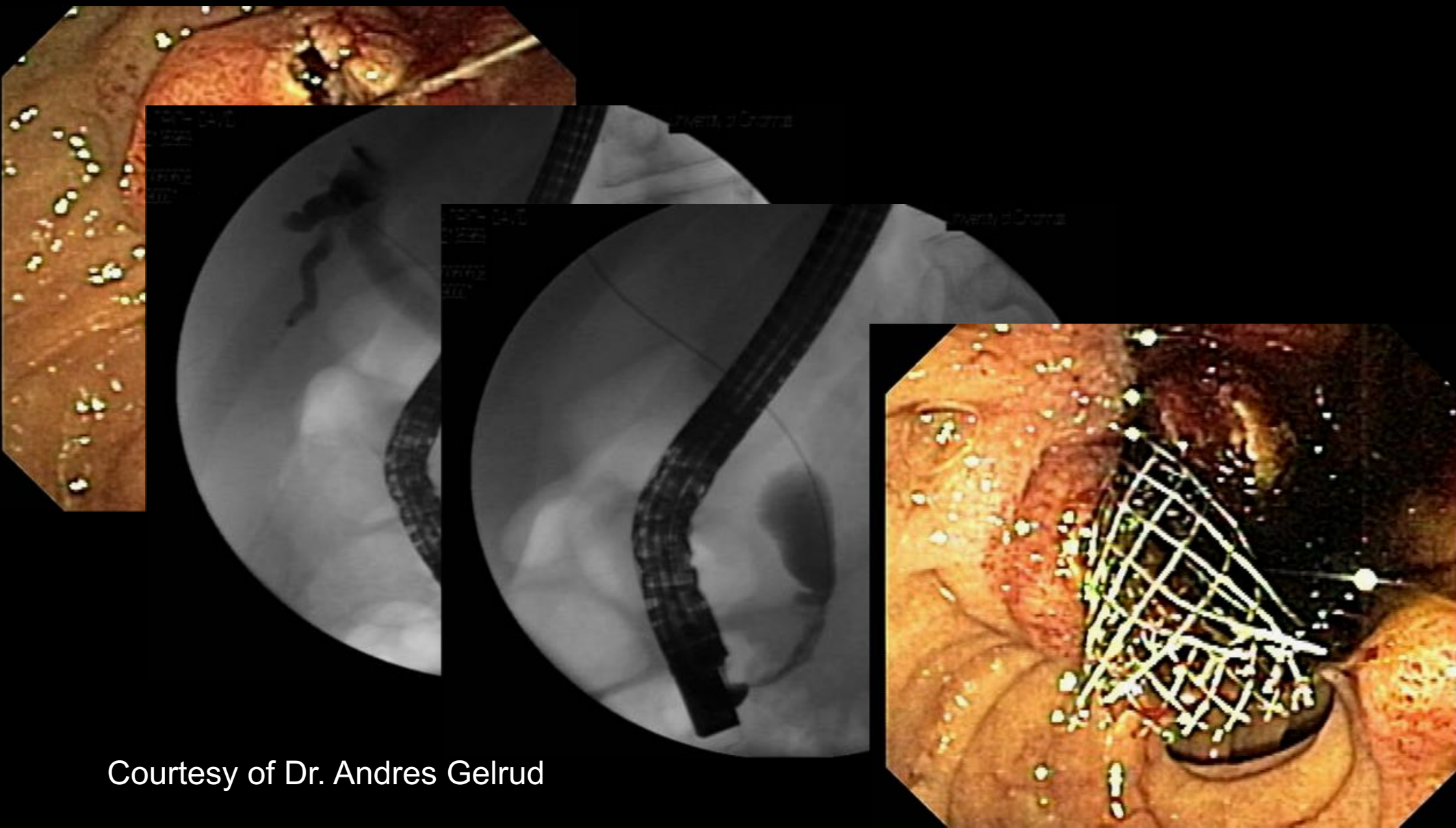
Duodenal Obstruction from
Extrinsic compression

s/p placement of duodenal stent

Courtesy of Dr. Andres Gelrud



Pancreatic head cancer with biliary obstruction



Courtesy of Dr. Andres Gelrud

What Do We Need to Improve Survival for Pancreatic Cancer

- Better defining who should be screened.
 - Expand beyond high risk individuals
 - New-onset diabetes (CPDPC consortium)
- Defining target for early detection
 - PanIN 3 or Stage 0 or 1A PC (Tis or T1)
 - IPMN with high-grade dysplasia or early invasive cancer (Tis or T1)
- Develop strategies for early detection (PCDC consortium and EDRN)
 - Risk stratifying current high risk populations undergoing PC surveillance
 - Detecting resectable PC patients
- Treatment
 - Personalized approach
 - Immune-based therapies

Who is this?



https://commons.wikimedia.org/wiki/File:RandyPausch_Wiki_2.jpg#/media/File:RandyPausch_Wiki_2.jpg

In September 2007, Carnegie Mellon professor Randy Pausch, who was dying of pancreatic cancer, delivered a one-of-a-kind last lecture that made the world stop and pay attention.

https://www.ted.com/talks/randy_pausch_really_achieving_your_childhood_dreams

THANK YOU FOR YOUR ATTENTION!!!

