

# Pancreatic resection for cancer: macroscopy, margins and reporting

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# The pancreateoduodenectomy

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- Complex anatomy
- Complex topography
  - Different organs
  - Margins vs surfaces
  - Tumor
  - Normal tissue
  - Vessels

Heterogeneous nomenclature:

Uncinate margin  
SMA-margin  
SMV-margin  
SMA/SMV-margin  
**Medial-margin (vascular groove)**  
Retroperitoneal margin  
Posterior margin  
...

# Most relevant prognostic factors are assessed during pathologic examination

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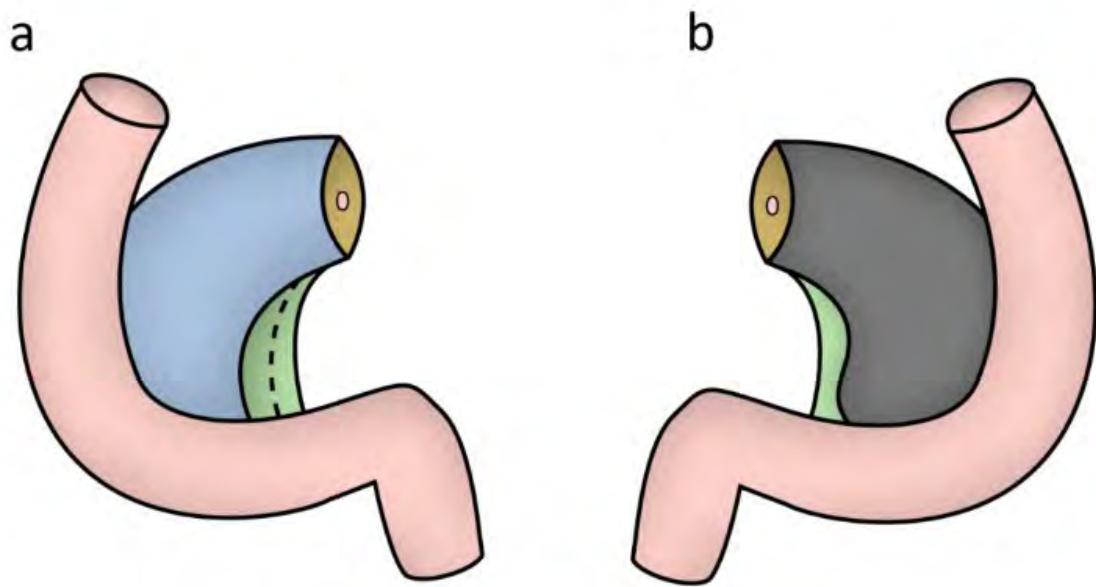
TABLE 2. Multivariate Survival Analysis of 538 Pancreatic Head Adenocarcinoma (Missing Values, N = 23)

Parameter	HR	95% CI	P
R0 vs R1 (direct)	0.73	0.54–0.98	0.0391
R1 ( $\leq$ 1 mm) vs R1 (direct)	0.71	0.54–0.95	0.0193
G3 vs G1/2	1.58	1.23–1.98	<0.0001
PLN $\geq$ 8 vs pN0	3.00	1.97–4.55	<0.0001
PLN 4–7 vs pN0	2.12	1.38–3.25	0.0006
PLN 1–3 vs pN0	1.66	1.11–2.49	0.0138
pT1/2 vs pT3/4	0.24	0.06–0.98	0.0472
CA 19–9 $<$ 37 vs $\geq$ 37 [U/mL]	0.73	0.56–0.96	0.0218

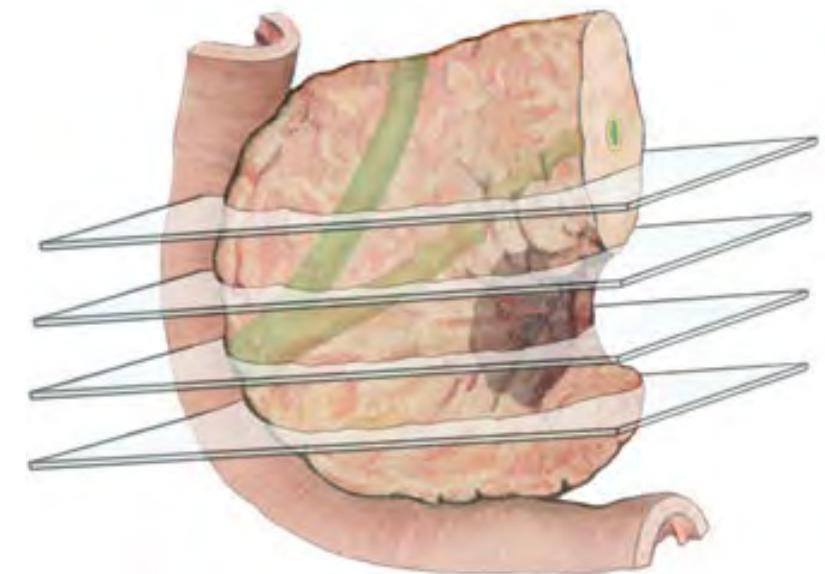
Strobel et al, Ann Surg 2017

# The axial slicing method

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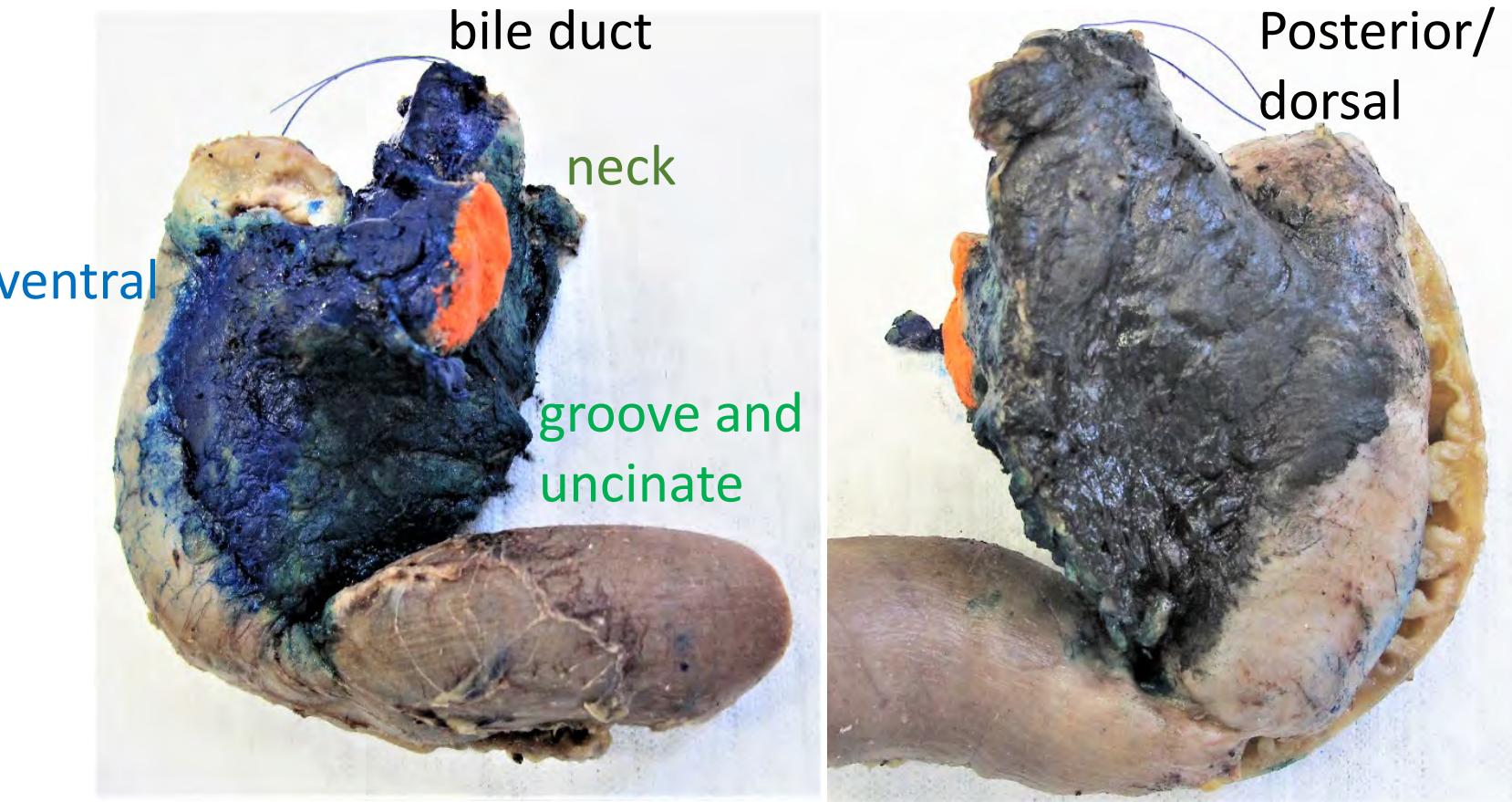
Standardized inking procedure



Axial slicing

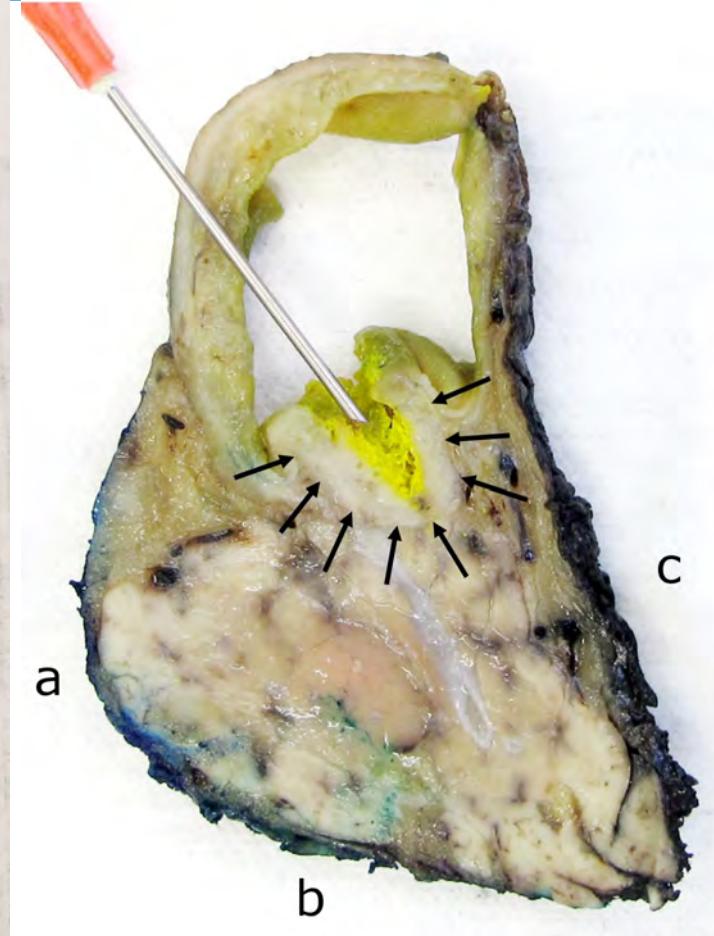
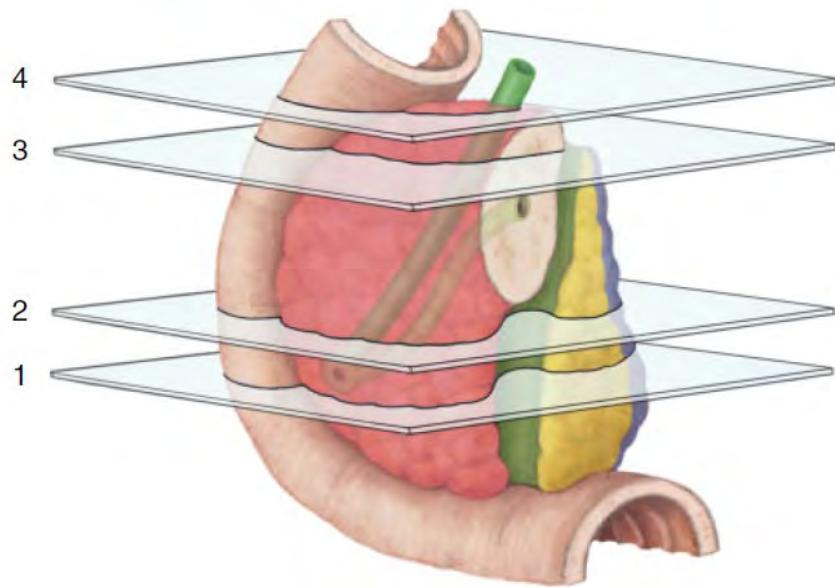
Esposito et al, Ann Surg Oncol 2008  
Schlitter & Esposito, Cancers 2010  
Esposito et al, World J Gastroenterol 2014  
Verbeke et al, Br J Surg 2006

# Standardized grossing



- Inking of relevant margin/surfaces according to a predefined color-code
- Axial slicing
- (Sub)total embedding of cystic lesions /tumor bed after NAT

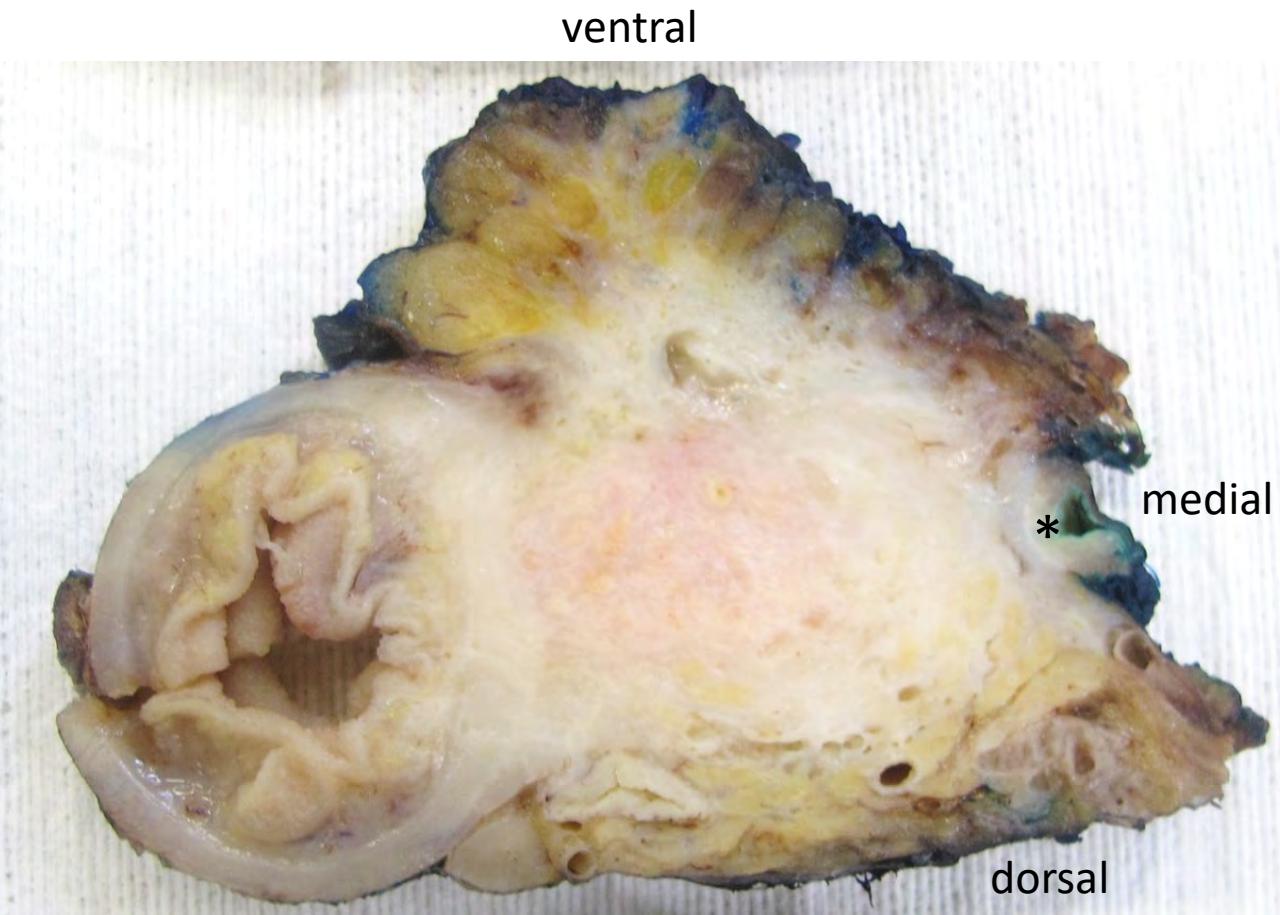
# Standardized grossing



Verbeke & Gladhaugh, Br J Surg 2012

Häberle & Esposito 2017, in: Pancreatic Cancer  
ISBN : 978-1-4939-6631-8

# PDAC: TNM



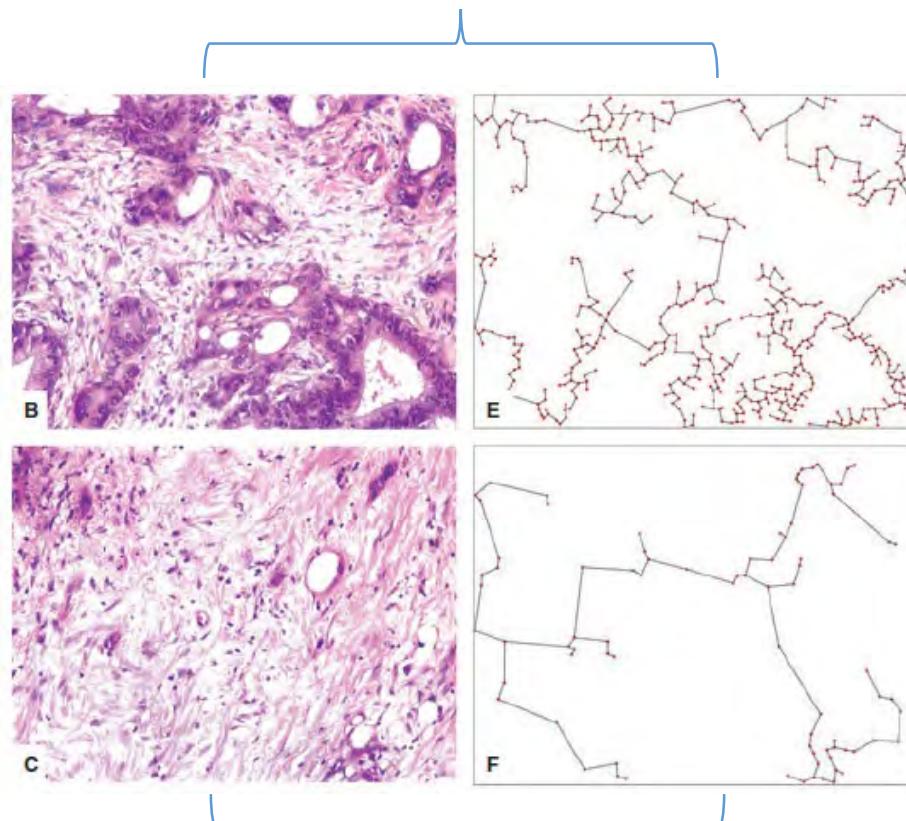
<b>T1</b>	Tumor 2 cm or less
<b>T1a</b>	$\leq 0,5$ cm
<b>T1b</b>	$> 0,5$ cm $< 1$ cm
<b>T1c</b>	$\geq 1$ cm $\leq 2$ cm
<b>T2</b>	$> 2-4$ cm
<b>T3</b>	$> 4$ cm
<b>T4</b>	Infiltration of coeliac artery and/or superior mesenteric or hepatic artery
<b>N1</b>	1-3 LN metastases
<b>N2</b>	$> 3$ LN metastases

T1= mostly in case of IPMN/MCN

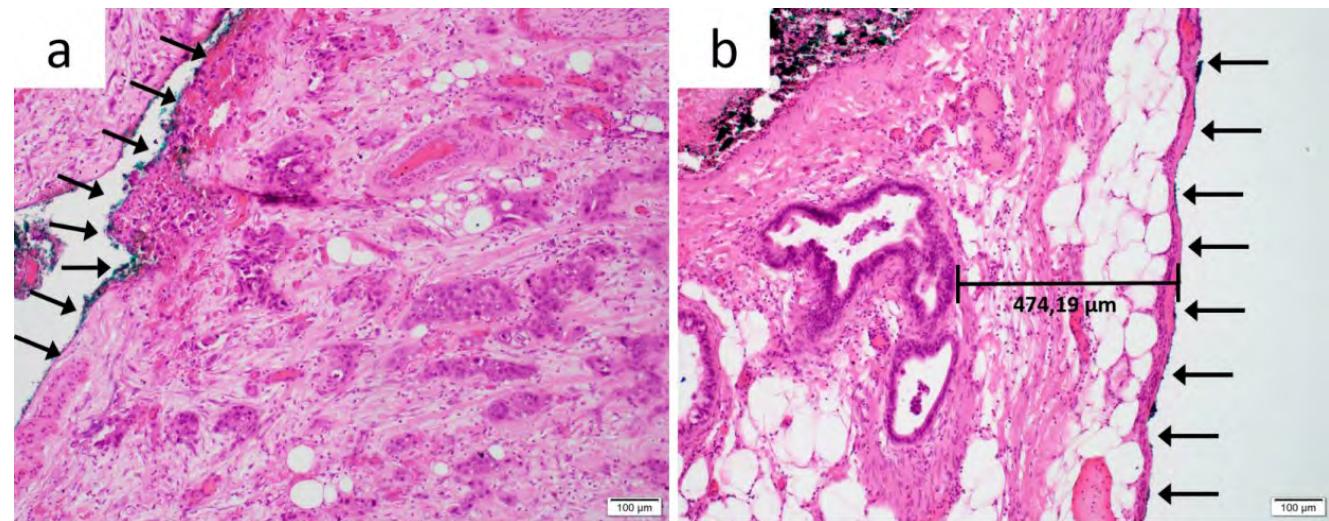
T4= mostly non-resectable

# PDAC: Resection margin status

center



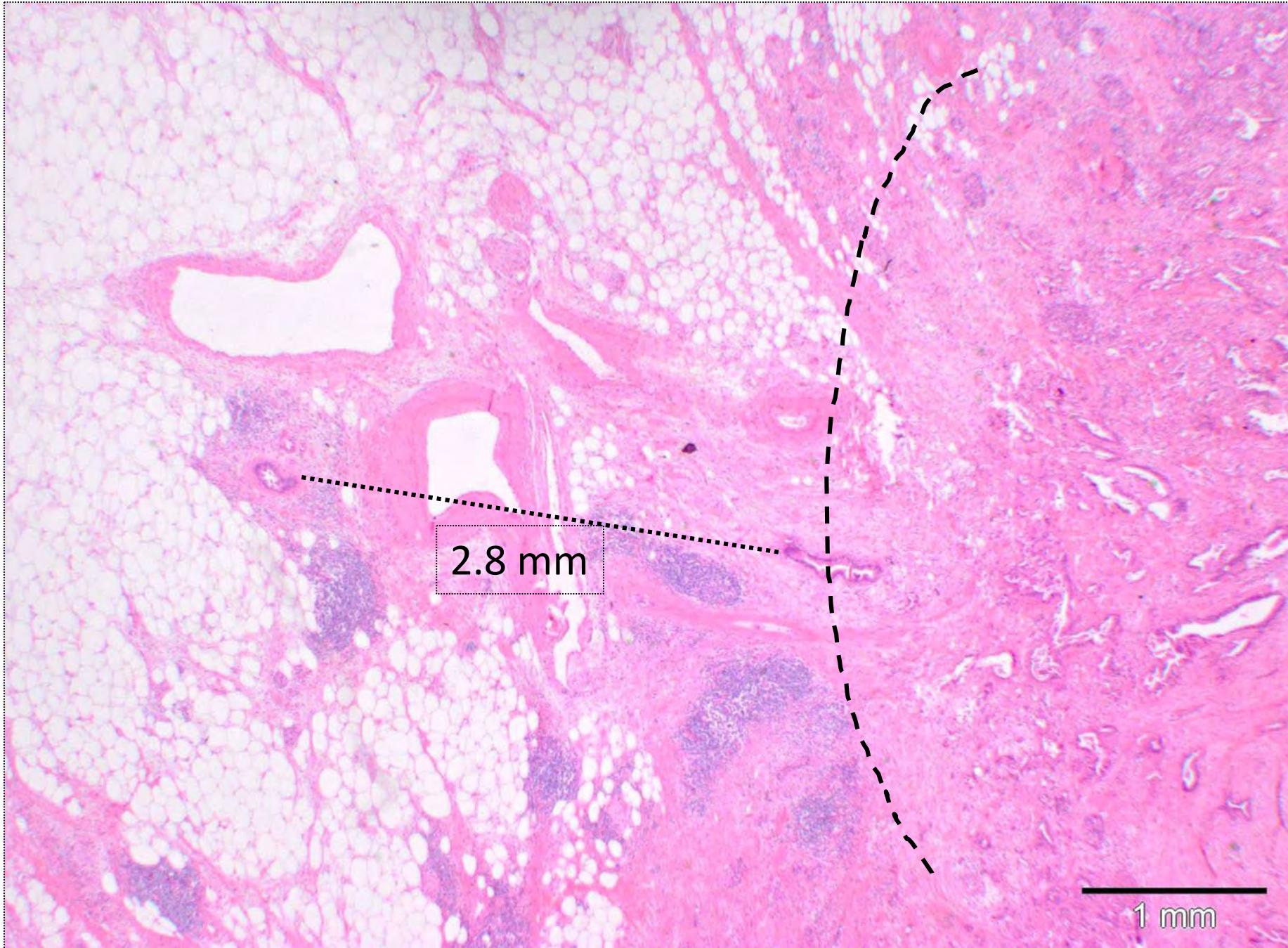
The 1-mm rule



Both R1!

Relevant margins: neck, bile duct, medial, dorsal

periphery



# How high is the R1-rate in pancreatic cancer?

Author	N. of patients	R1/R2	Study period
Willett et al. 1993	72	51%	1978-1991
Yeo et al. 1997	282	29%	1990-1996
Richter et al. 2003	194	35%	1972-1998
Wagner et al. 2004	211	24%	1993-2001
Cameron et al. 2006	405	36%	1969-2003
Kuhlmann et al. 2006	160	<b>50% (R1)</b>	1992-2001
Verbeke et al. 2006	26	<b>85% (R1)</b>	1995-2003
Winter et al. 2006	1175	42%	1970-2006
Raut et al. 2007	360	<b>17% (R1)</b>	1990-2004
Esposito et al. 2008	111	<b>76% (R1)</b>	2005-2006
Hernandez et al. 2009	202	<b>22% (R1)</b>	1995-2008
Campbell et al. 2009	163	<b>79% (R1)</b>	1997-2007
Jamieson et al. 2010	148	<b>74% (R1)</b>	1996-2007

17-85%



Schlitter & Esposito, Cancers 2010

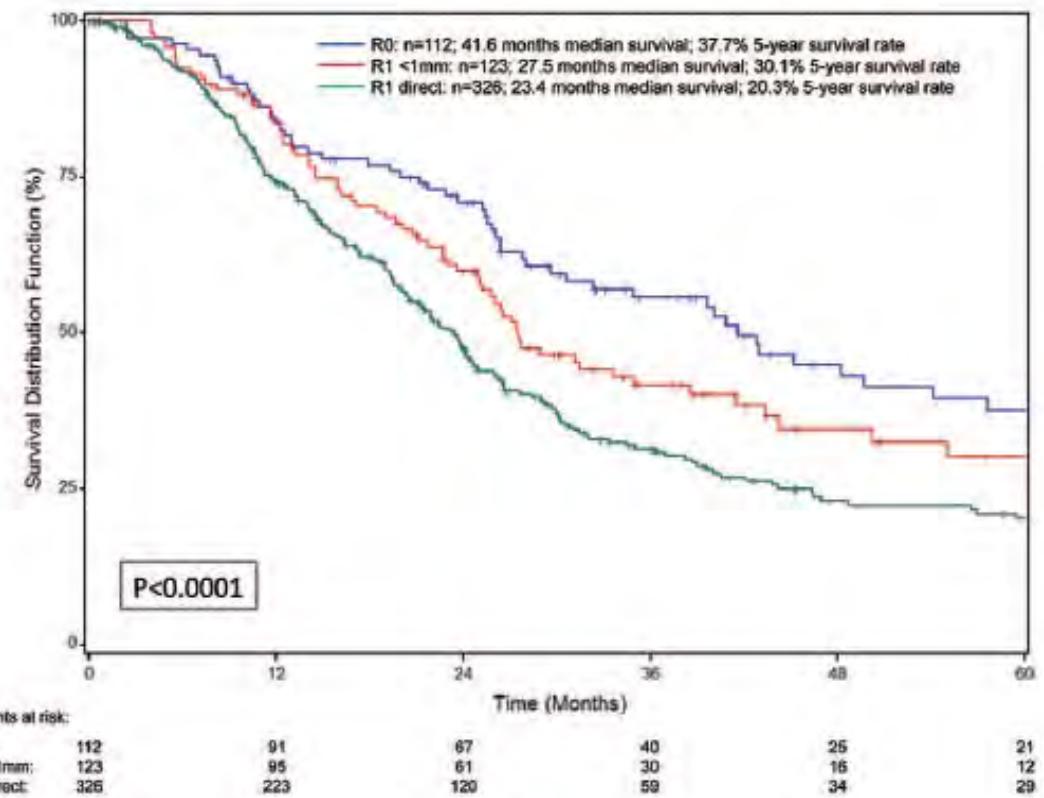
# The method is important!

Table 1

Comparison of the rate of microscopic margin involvement (R1) and median survival after surgical resection of ductal adenocarcinoma of the pancreas between studies using the axial slicing technique or another grossing technique

Reference (Year)	Number of Patients	R1 Rate (%)	Median Survival R0	Median Survival R1
<b>Axial Slicing Technique</b>				
Verbeke et al, <sup>1</sup> 2006	54	85	37	11
Esposito et al, <sup>16</sup> 2008	111	76	—	—
Menon et al, <sup>17</sup> 2009	27	82	>55	14
Campbell et al, <sup>18</sup> 2009	163	79	25	15
Jamieson et al, <sup>19</sup> 2010	1848	74	26	15
<b>Other Technique</b>				
Willet et al, <sup>20</sup> 1993	72	51	20	12
Millikan et al, <sup>21</sup> 1999	84	29	17	8
Benassai et al, <sup>22</sup> 2000	75	20	17	9
Sohn et al, <sup>6</sup> 2000	616	30	12	19
Neoptolemos et al, <sup>12</sup> 2001	111	19	17	11
Raut et al, <sup>15</sup> 2007	360	17	28	22
Westgaard et al, <sup>23</sup> 2008	40	45	16	11
Hsu et al, <sup>24</sup> 2010	509	44	19	11
Gnerlich et al, <sup>25</sup> 2012	285	34	22	16

# The „new“ R-status is relevant for the prognosis



N= 561

R0: 20%

R1: 80%

R0: median survival 41.6 Mo.

R1 (<1mm): median survival 27.5 Mo.

R1 (classical definition): median survival 23.4 Mo.

# Towards an international standardization

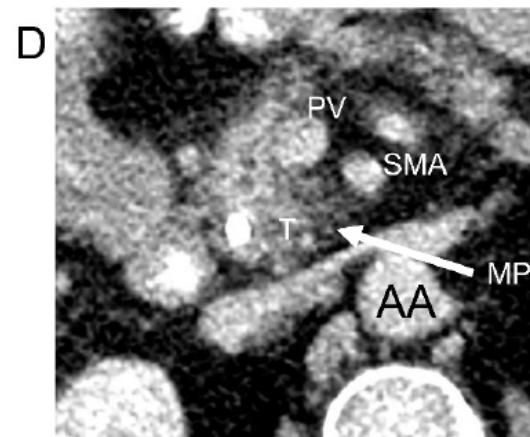
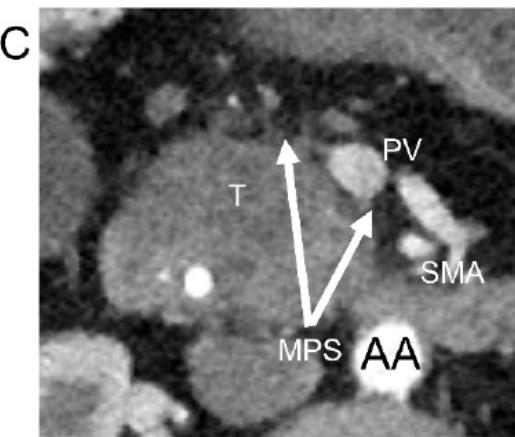
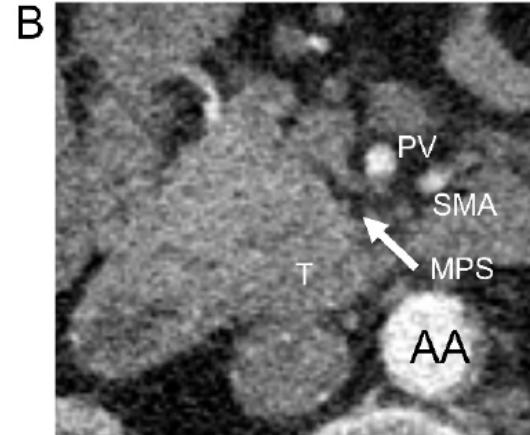
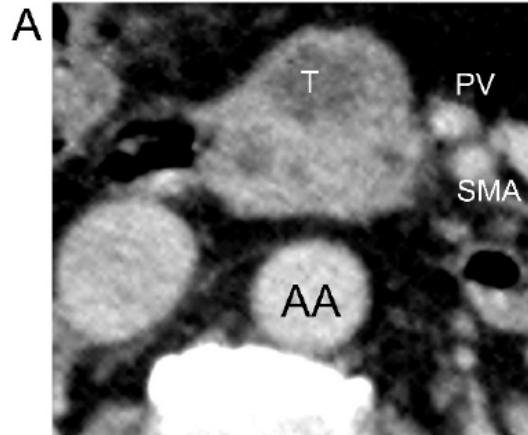
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- 1-mm rule FINALLY applied in CAP and AJCC guidelines (2017)
- Attempts at standardization

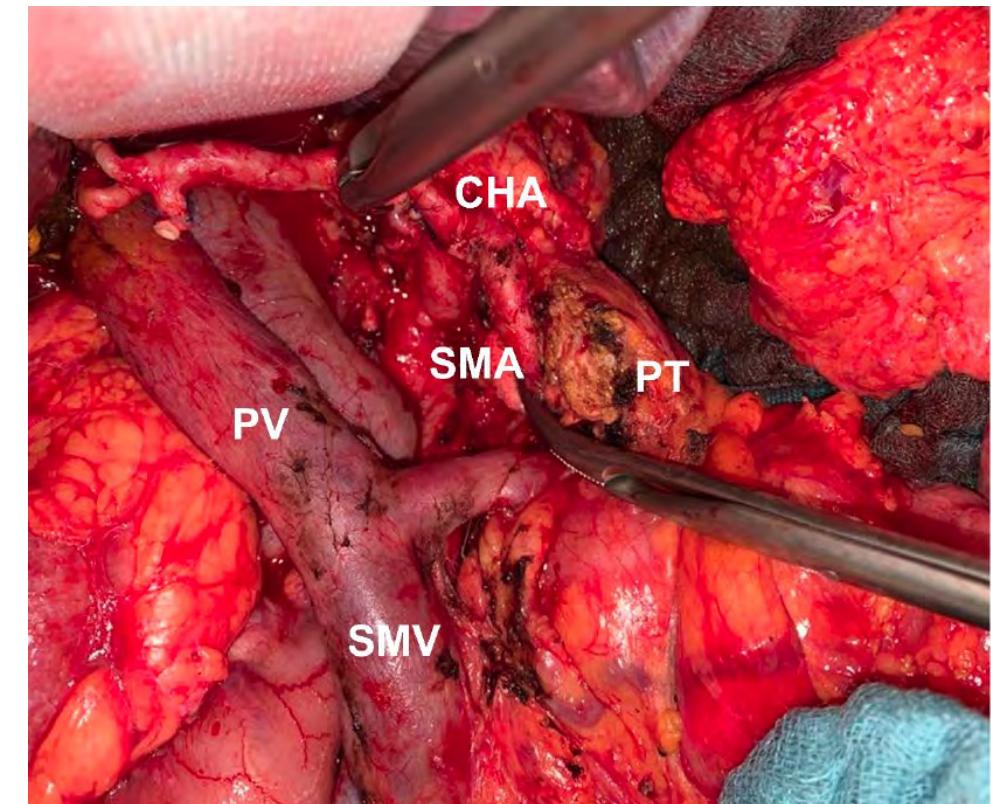
Towards a More Standardized Approach to Pathologic Reporting of Pancreatoduodenectomy Specimens for Pancreatic Ductal Adenocarcinoma

*Cross-continental and Cross-specialty Survey From the Pancreatobiliary Pathology Society Grossing Working Group*

# Impact on therapy: Mesopancreatic fat resection



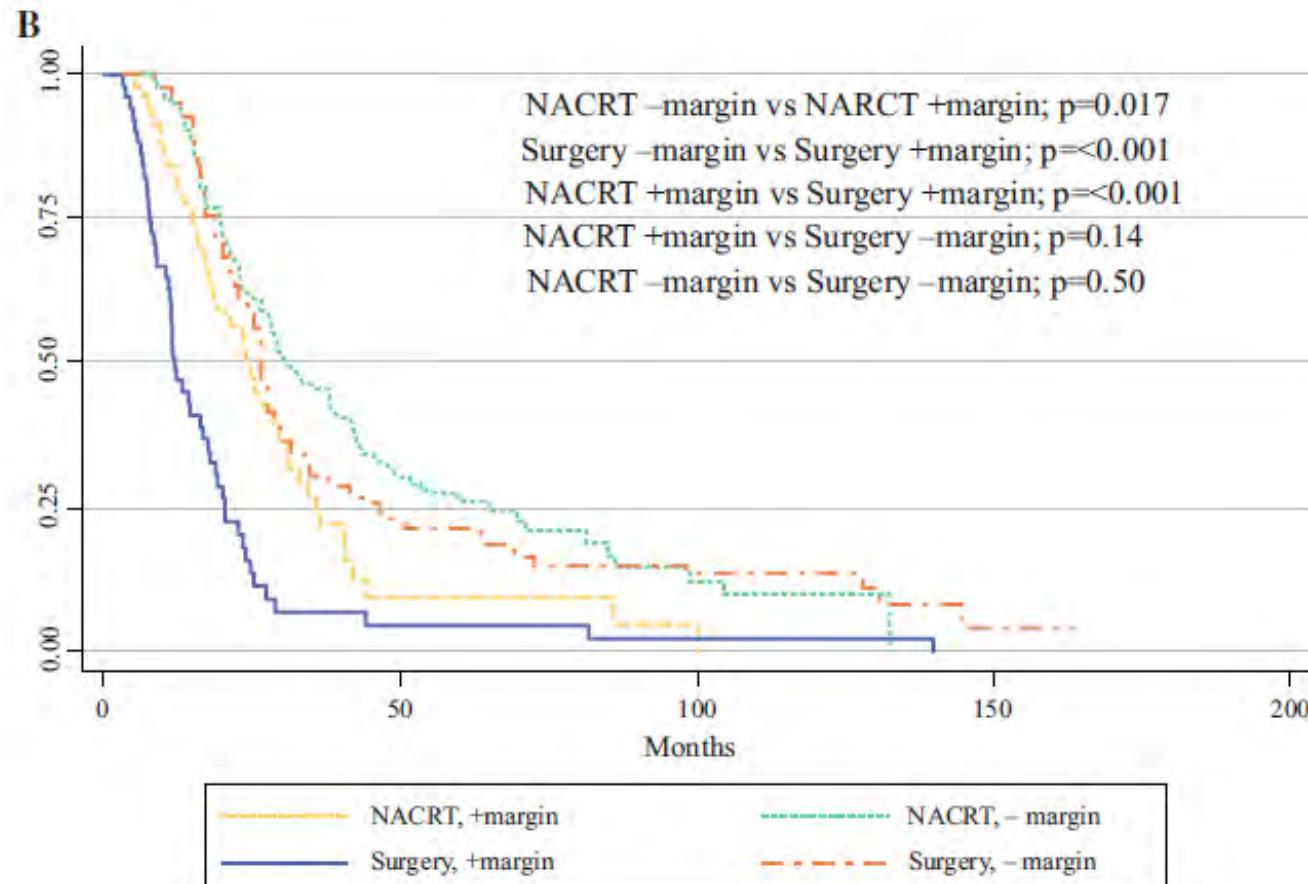
Multidetector-CT



Safi et al, Cancers 2021

Safi et al, Pancreatology 2021

# Impact on therapy: Role for neoadjuvant therapy?



# Relevance of standardized reporting

Verbeke C, Brosens L, Campbell F, Del Chiaro M, Esposito I, Feakins RM, Fukushima N, Gill A, Kakar S, Kench J, Krasinskas AM, Van Laethem JL, Schaeffer DF, Washington MK (2020). *Carcinoma of the Exocrine Pancreas Histopathology Reporting Guide*. International Collaboration on Cancer Reporting; Sydney, Australia. ISBN: 978-1-922324-03-0.

**Carcinoma of the Exocrine Pancreas  
Histopathology Reporting Guide** 

Family/Last name \_\_\_\_\_ Given name(s) \_\_\_\_\_ Date of birth DD - MM - YYYY

Patient identifiers \_\_\_\_\_ Date of request DD - MM - YYYY Accession/Laboratory number \_\_\_\_\_

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.  
 indicates multi-select values  indicates single select values

**NEOADJUVANT THERAPY (Note 1)**

Information not provided  
 Not administered  
 Administered (select all that apply)  
 Chemotherapy  
 Radiotherapy  
 Other, specify

**TUMOUR SITE (select all that apply) (Note 4)**

No macroscopically visible tumour  
 Pancreatic head  
 Pancreatic body  
 Pancreatic tail  
 Other, specify

**OPERATIVE PROCEDURE (select all that apply) (Note 2)**

Whipple pancreatectoduodenectomy  
 Pylorus-preserving pancreatectoduodenectomy  
 Distal pancreatectomy  
 Total pancreatectomy  
 Subtotal pancreatectomy  
 Pancreatic resection (pick one of the options above) extended with one or more of the following additionally resected organs/structures:  
 Vein  
 Superior mesenteric vein  
 Portal vein  
 Artery  
 Superior mesenteric artery  
 Common hepatic artery  
 Celiac trunk  
 Other, specify

**TUMOUR DIMENSIONS (Note 5)**

Maximum tumour dimension (largest tumour)  
 mm

Additional dimensions (largest tumour)  
 mm x  mm

Dimensions of additional smaller tumour foci  
 mm x  mm x  mm  
 mm x  mm x  mm

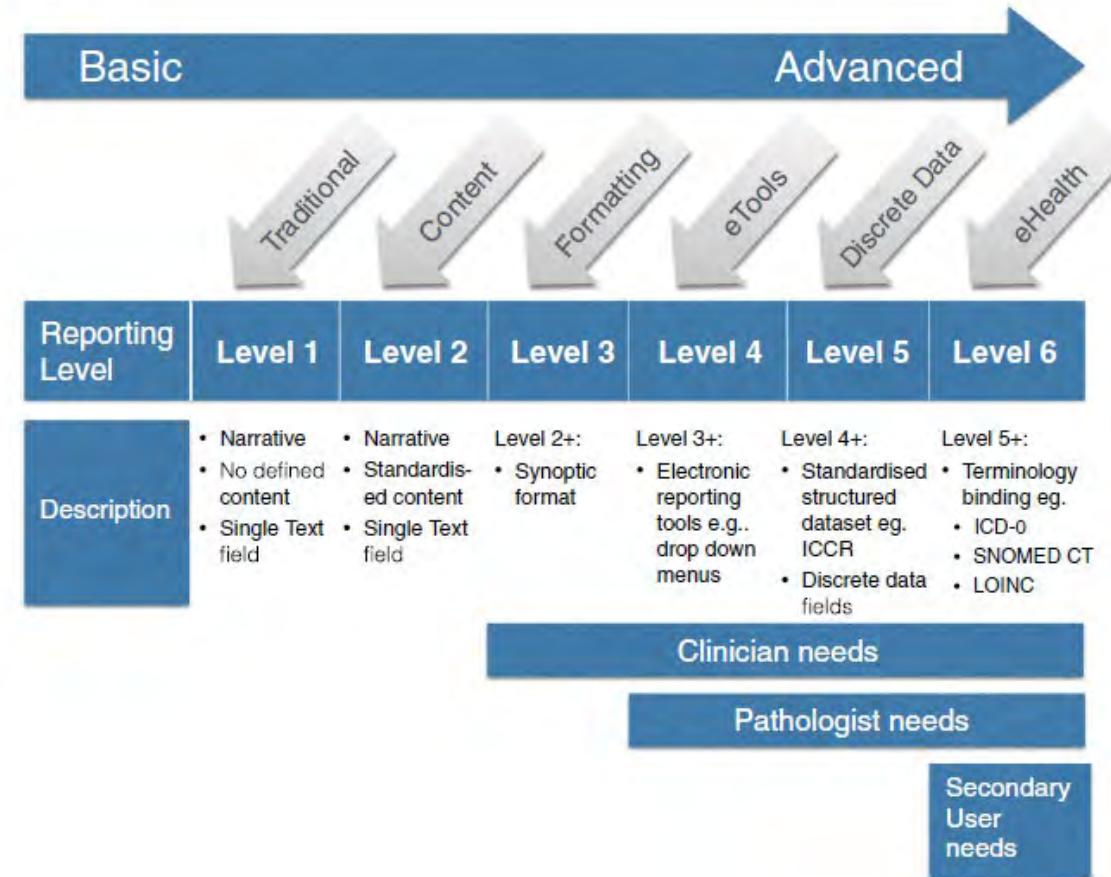
Method of measurement (in case of neoadjuvant treatment)\*  
 Approach 1 (largest overall dimensions)  
 Approach 2 (summation of dimensions of each tumour focus)

\* See Note for an explanation of the approaches to the method of measurement following neoadjuvant treatment.

Version 1.0 Published April 2020 ISBN: 978-1-922324-03-0  
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# Levels of standardized reporting



# Pancreatic ductal adenocarcinoma: morphological patterns, histological subtypes and grading.

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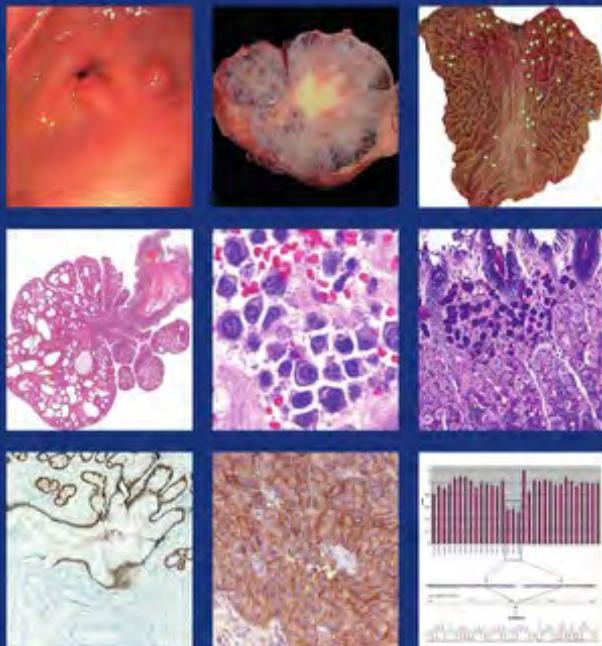
# WHO 2019

## WHO classification of tumours of the pancreas

WHO Classification of Tumours • 5th Edition

### Digestive System Tumours

Edited by the WHO Classification of Tumours Editorial Board



#### Benign epithelial tumours and precursors

- 8441/0 Serous cystadenoma NOS  
Macrocytic (oligocystic) serous cystadenoma  
Solid serous adenoma  
Von Hippel-Lindau syndrome-associated serous cystic neoplasm  
Mixed serous-neuroendocrine neoplasm  
8441/3 Serous cystadenocarcinoma NOS  
8148/0 Glandular intraepithelial neoplasia, low grade  
8148/2 Glandular intraepithelial neoplasia, high grade  
8453/0 Intraductal papillary mucinous neoplasm with low-grade dysplasia  
8453/2 Intraductal papillary mucinous neoplasm with high-grade dysplasia  
8453/3 Intraductal papillary mucinous neoplasm with associated invasive carcinoma  
8455/2\* Intraductal oncocytic papillary neoplasm NOS  
8455/3\* Intraductal oncocytic papillary neoplasm with associated invasive carcinoma  
8503/2 Intraductal tubulopapillary neoplasm  
8503/3 Intraductal papillary neoplasm with associated invasive carcinoma  
8470/0 Mucinous cystic neoplasm with low-grade dysplasia  
8470/2 Mucinous cystic neoplasm with high-grade dysplasia  
8470/3 Mucinous cystic neoplasm with associated invasive carcinoma

#### Malignant epithelial tumours

- 8500/3 Duct adenocarcinoma NOS  
8480/3 Colloid carcinoma  
8490/3 Poorly cohesive carcinoma  
8490/3 Signet-ring cell carcinoma  
8510/3 Medullary carcinoma NOS  
8560/3 Adenosquamous carcinoma  
8576/3 Hepatoid carcinoma  
8014/3 Large cell carcinoma with rhabdoid phenotype  
8020/3 Carcinoma, undifferentiated, NOS  
8035/3 Undifferentiated carcinoma with osteoclast-like giant cells  
8550/3 Acinar cell carcinoma  
8551/3 Acinar cell cystadenocarcinoma  
8154/3 Mixed acinar-neuroendocrine carcinoma  
8154/3 Mixed acinar-endocrine-ductal carcinoma  
8552/3 Mixed acinar-ductal carcinoma  
8971/3 Pancreatoblastoma  
8452/3 Solid pseudopapillary neoplasm of the pancreas  
Solid pseudopapillary neoplasm with high-grade carcinoma

#### Pancreatic neuroendocrine neoplasms

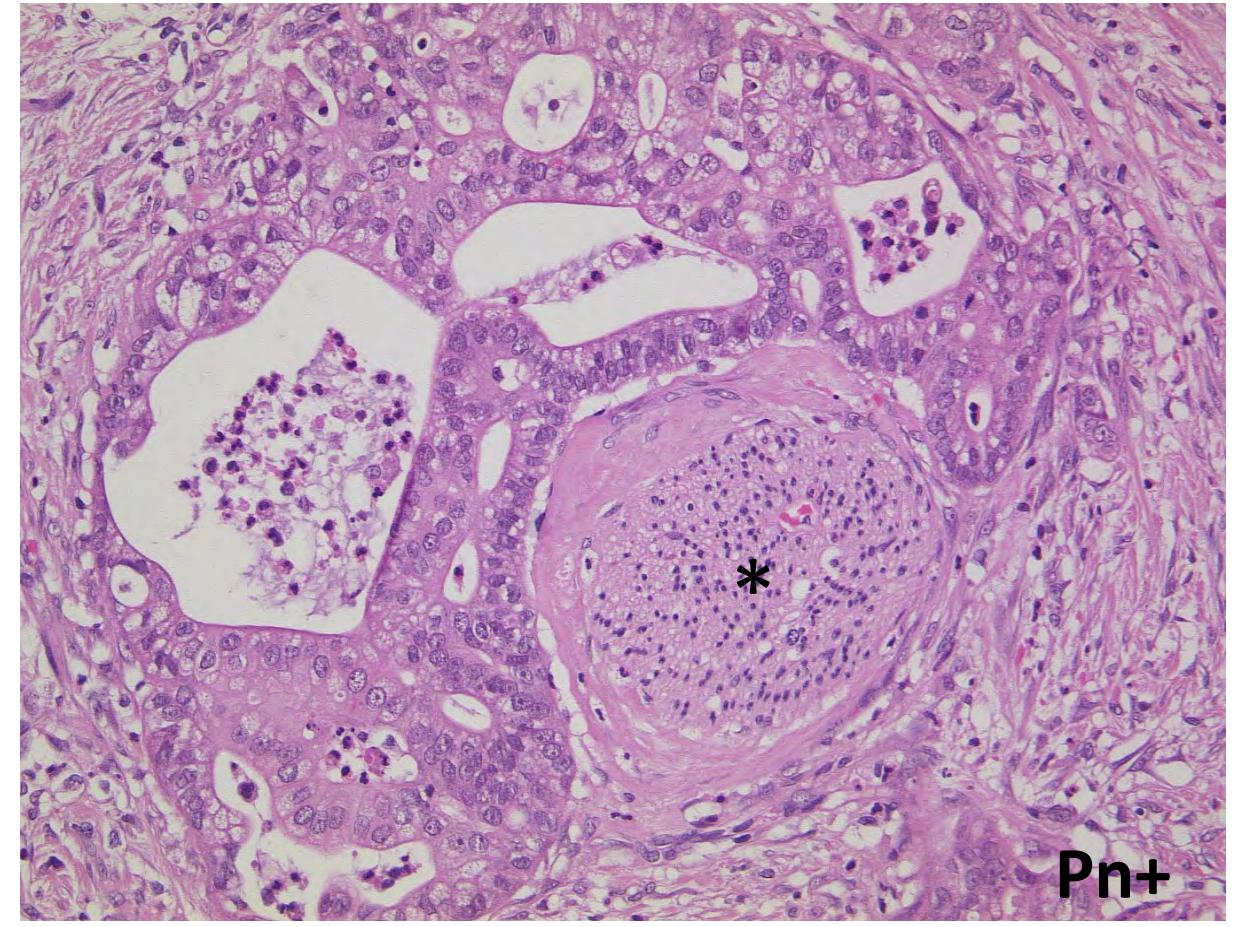
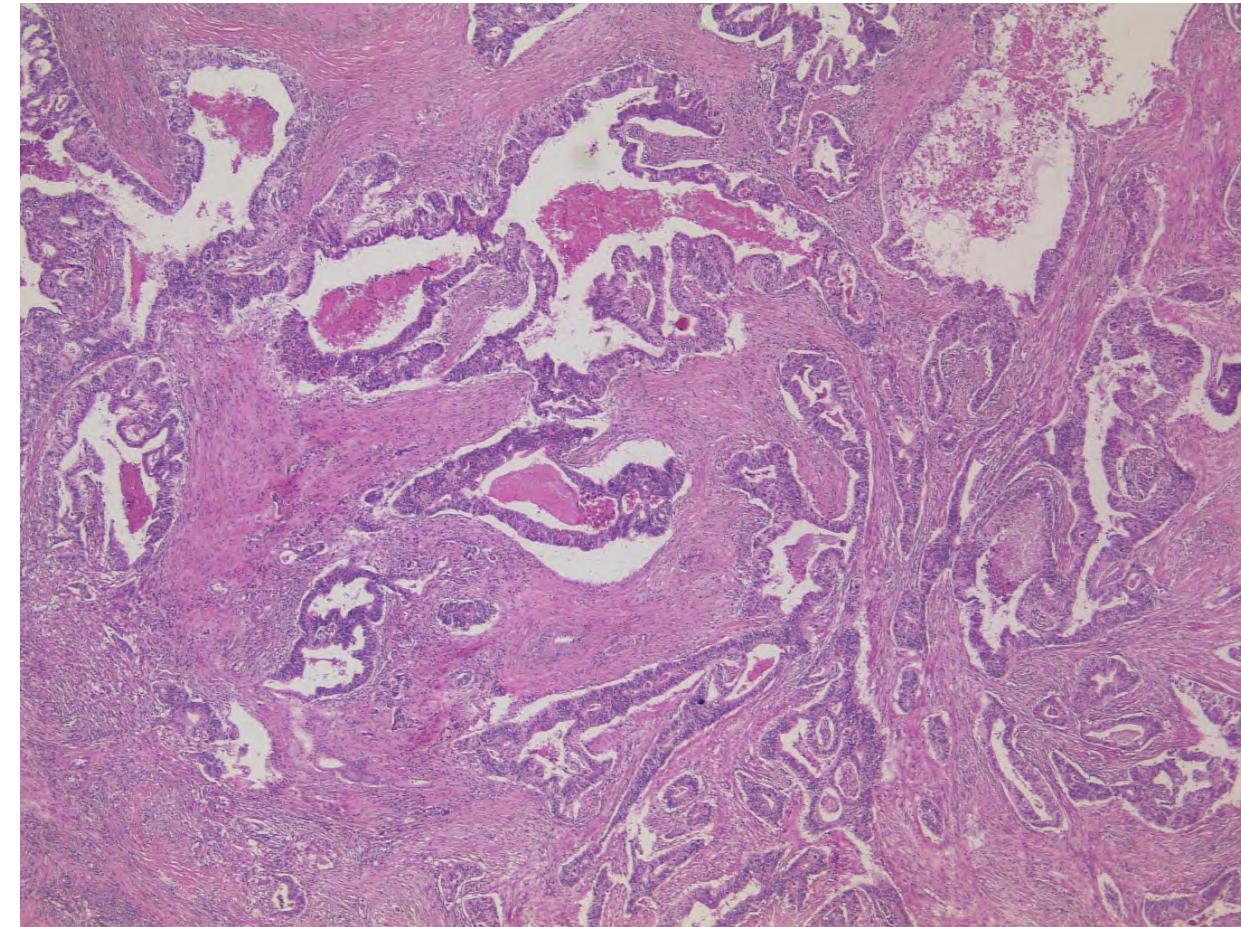
- 8150/0 Pancreatic neuroendocrine microadenoma  
8240/3 Neuroendocrine tumour NOS  
8240/3 Neuroendocrine tumour, grade 1  
8249/3 Neuroendocrine tumour, grade 2  
8249/3 Neuroendocrine tumour, grade 3  
8150/3 Pancreatic neuroendocrine tumour, non-functioning  
Oncocytic neuroendocrine tumour, non-functioning pancreatic  
Pleomorphic neuroendocrine tumour, non-functioning pancreatic  
Clear cell neuroendocrine tumour, non-functioning pancreatic  
Cystic neuroendocrine tumour, non-functioning pancreatic

#### Functioning pancreatic neuroendocrine tumours

- 8151/3\* Insulinoma  
8153/3\* Gastrinoma  
8155/3\* VIPoma  
8152/3\* Glucagonoma  
8156/3\* Somatostatinoma  
8158/3 ACTH-producing tumour  
8241/3 Enterochromaffin-cell carcinoid  
8241/3 Serotonin-producing tumour  
8246/3 Neuroendocrine carcinoma NOS  
8013/3 Large cell neuroendocrine carcinoma  
8041/3 Small cell neuroendocrine carcinoma  
8154/3 Mixed neuroendocrine-non-neuroendocrine neoplasm (MINEN)  
8154/3 Mixed acinar-endocrine carcinoma  
8154/3 Mixed acinar-neuroendocrine carcinoma  
8154/3 Mixed acinar-endocrine-ductal carcinoma

# Ductal adenocarcinoma, NOS

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# Ductal adenocarcinoma: Grading

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## The Klöppel's system

**TABLE 1.** The Current WHO Grading Scheme\* for Pancreatic Ductal Adenocarcinoma

Tumor Grade (Score Range)	Glandular Differentiation (Score)	Mucin Production (Score)	Mitoses per 10 HPF (Score)	Nuclear Features (Score)
1 (1–1.6)	Well differentiated (1)	Intensive (1)	≤5 (1)	Little polymorphism (1)
2 (1.7–2.3)	Moderately differentiated duct-like structures tubular glands (2)	Irregular (2)	6–10 (2)	Moderate polymorphism (2)
3 (2.3–3.0)	Poorly differentiated glands, mucoepidermoid and pleomorphic structures (3)	Abortive (3)	>10 (3)	Marked polymorphism and increased size (3)

\*Based on Klöppel et al.<sup>23,26</sup>

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- Focus on poorly differentiated areas
- Sum of the points/4
- **Relevant prognostic factor!**

WHO 2000

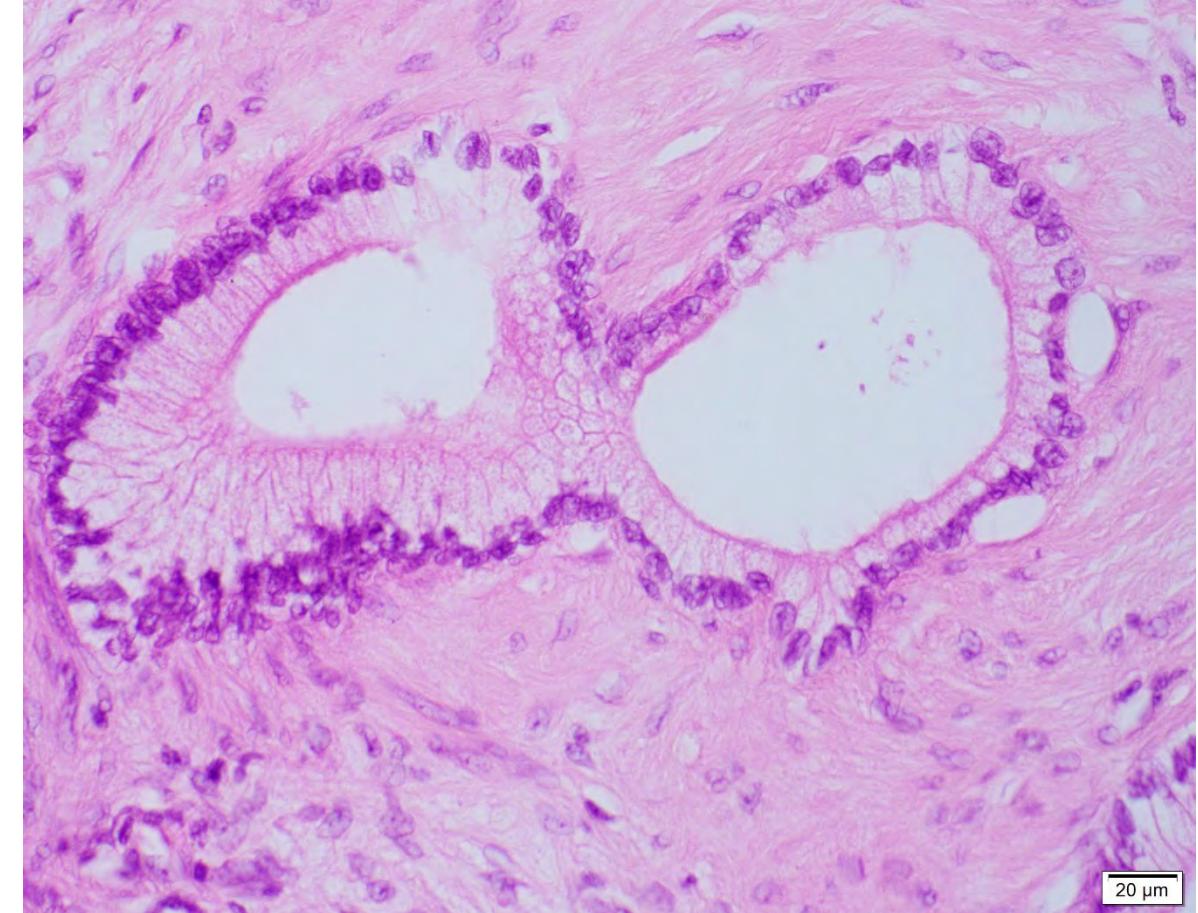
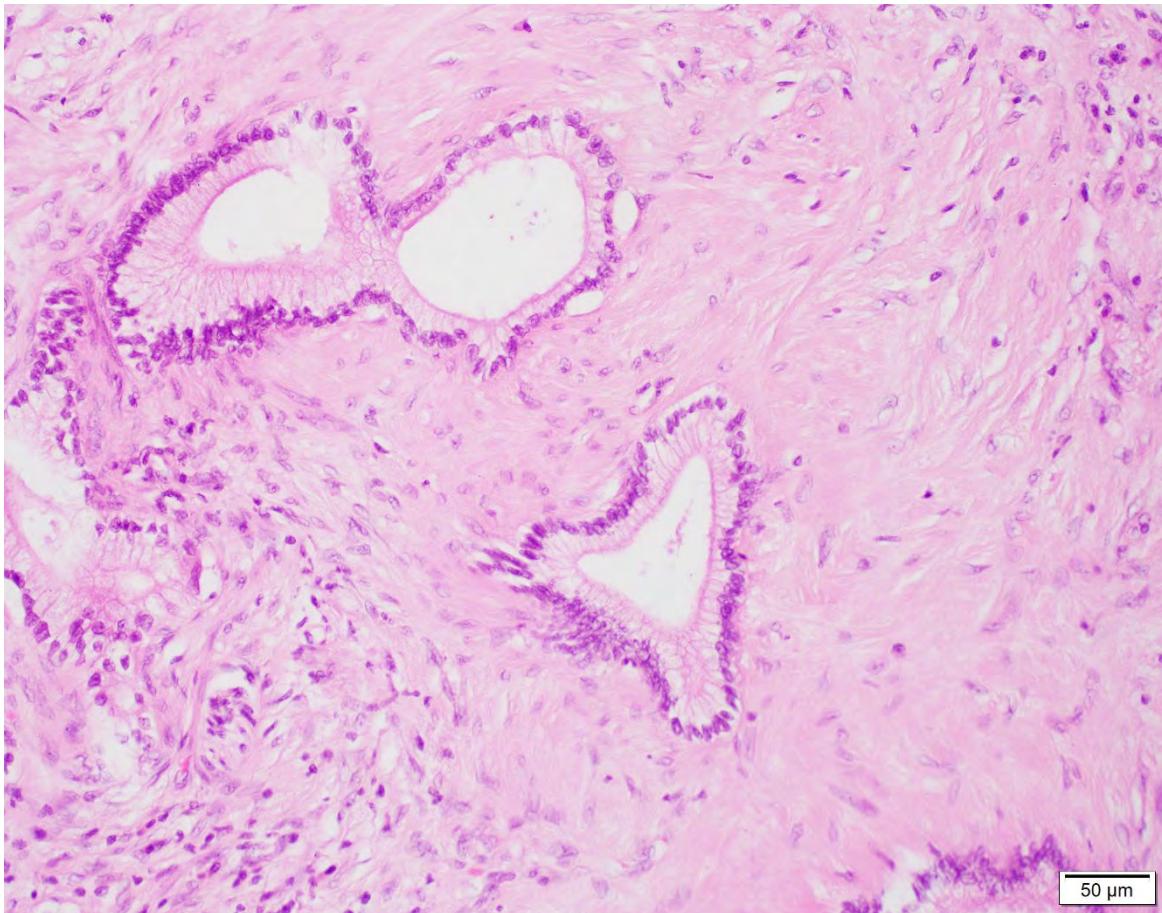
**G1**

Well-formed tubules and glands

Low nuclear polymorphism

Mucin production

Few mitoses ( $\leq 5/10$  HPF)



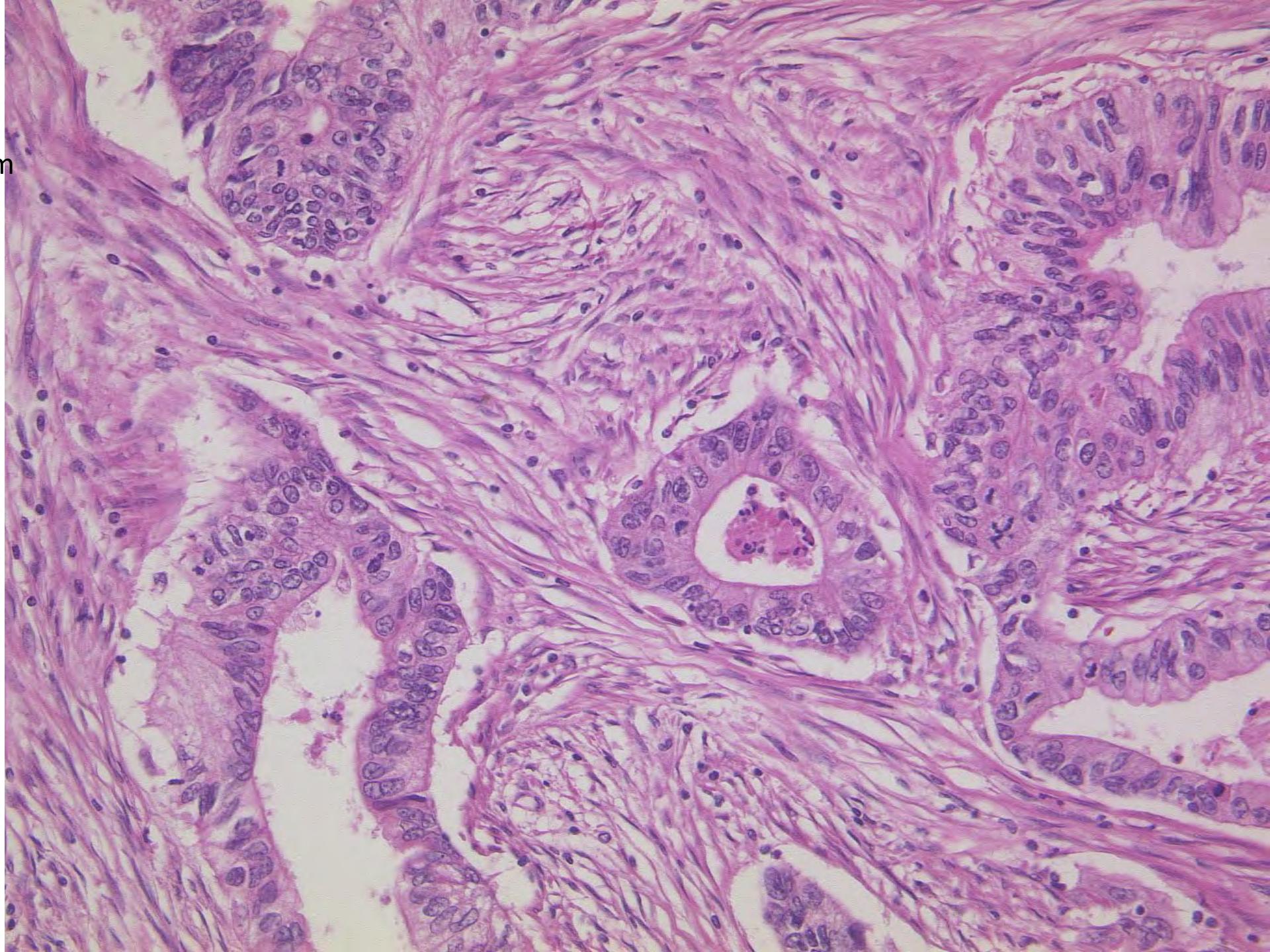
**G2**

Cribiform structures

Moderate nuclear polymorphism

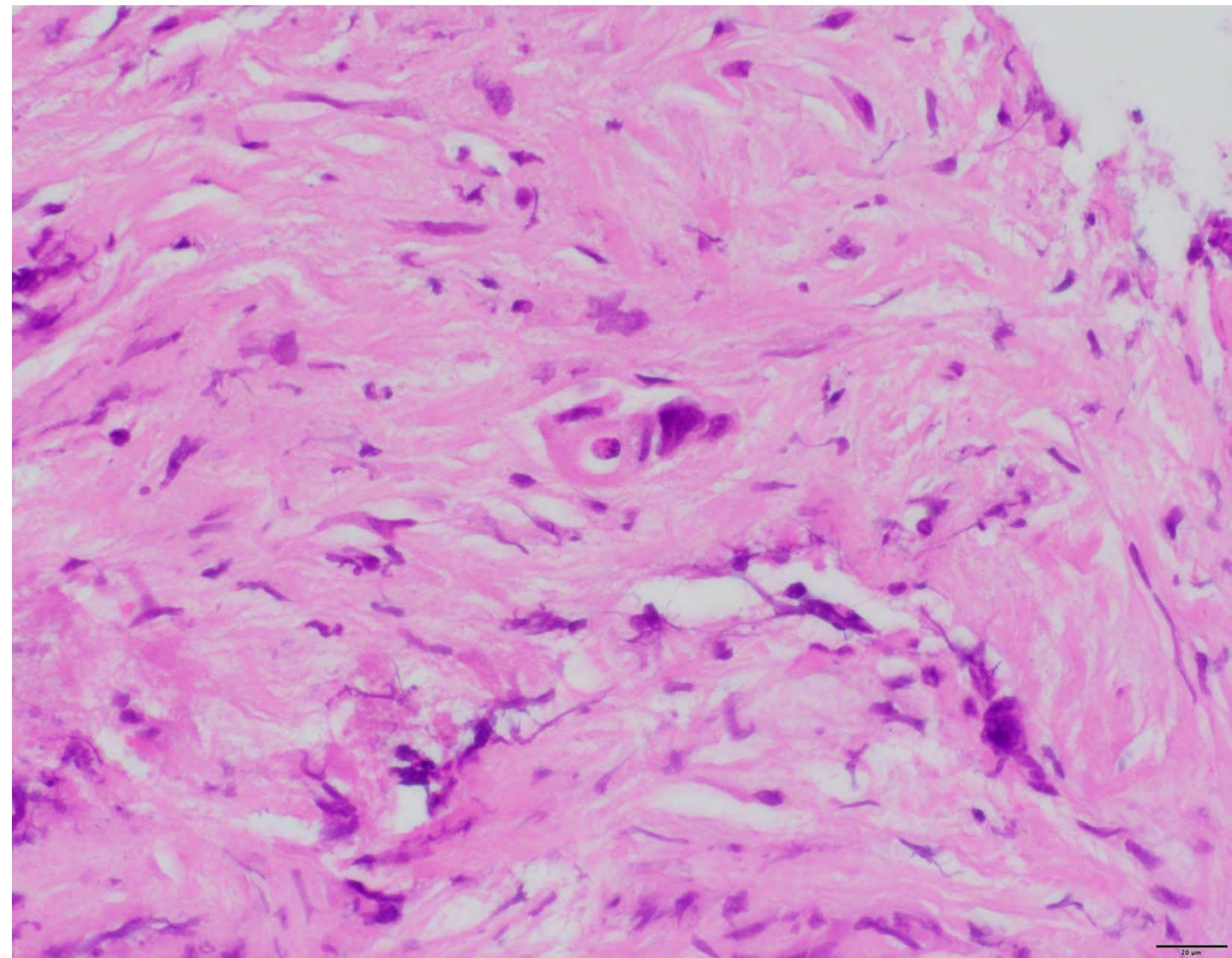
Reduced mucin production

Mitoses: 6-10/10 HPF



**G3**

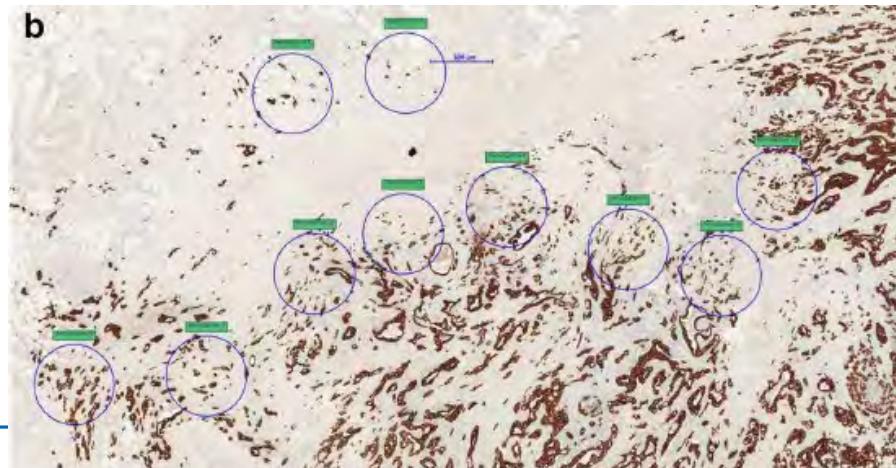
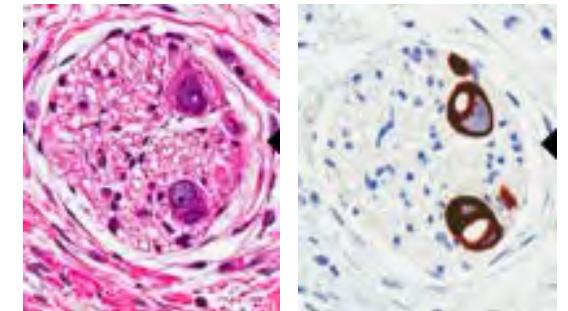
Poorly formed glands, solid growth  
High nuclear polymorphism  
No mucin  
Mitoses: >10/10 HPF



# Role of tumor budding?

## Tumor budding

- is a strong prognosticator in PDAC
- is associated with EMT
- is associated with high levels of anti-tumor immunity
- A moderately reproducible method of assessment (pan-CK in 10 HPF) has shown a moderate reproducibility among pathologists



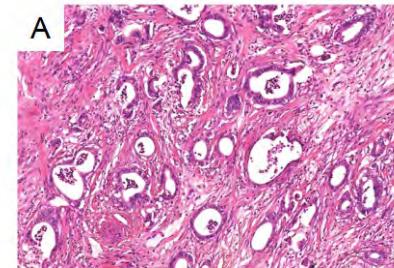
Karamitopoulou et al, Virchows Archiv 2021  
Sadozai et al, Cancers 2021  
Petrova et al, Virchows Archiv 2020  
Lawlor et al, Cancers 2019  
Lohneis et al, Br J Surg 2018

# Morphological heterogeneity

PDAC NOS 92,1%

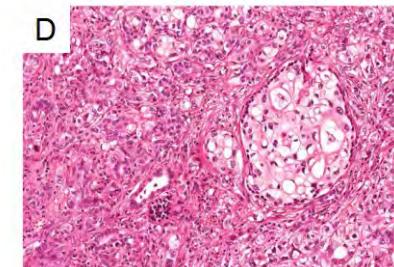
„Pure“ PDAC, NOS

51.1%

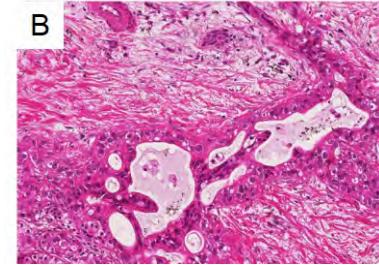


Classical ductal

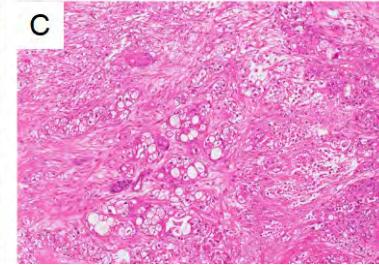
PDAC, NOS,  
With additional  
components 41%



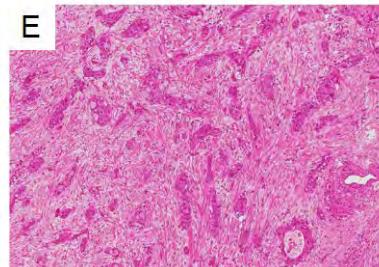
complex



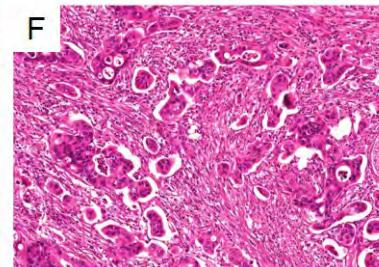
cribriform



clear cell

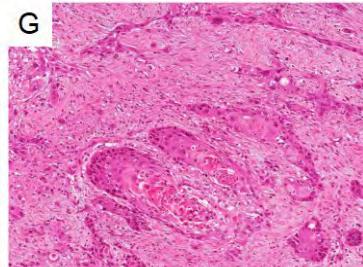


gyriform

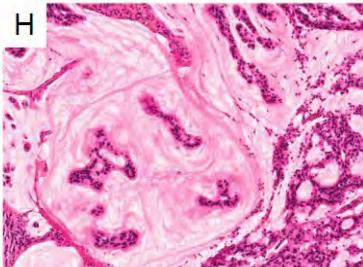


micropapillary

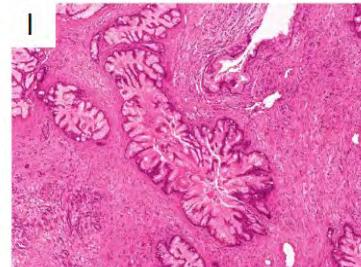
Homogeneous Variants 7.9%



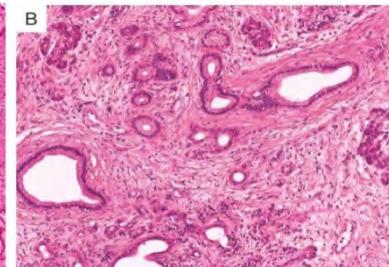
Adenosquamous carcinoma



Colloid carcinoma



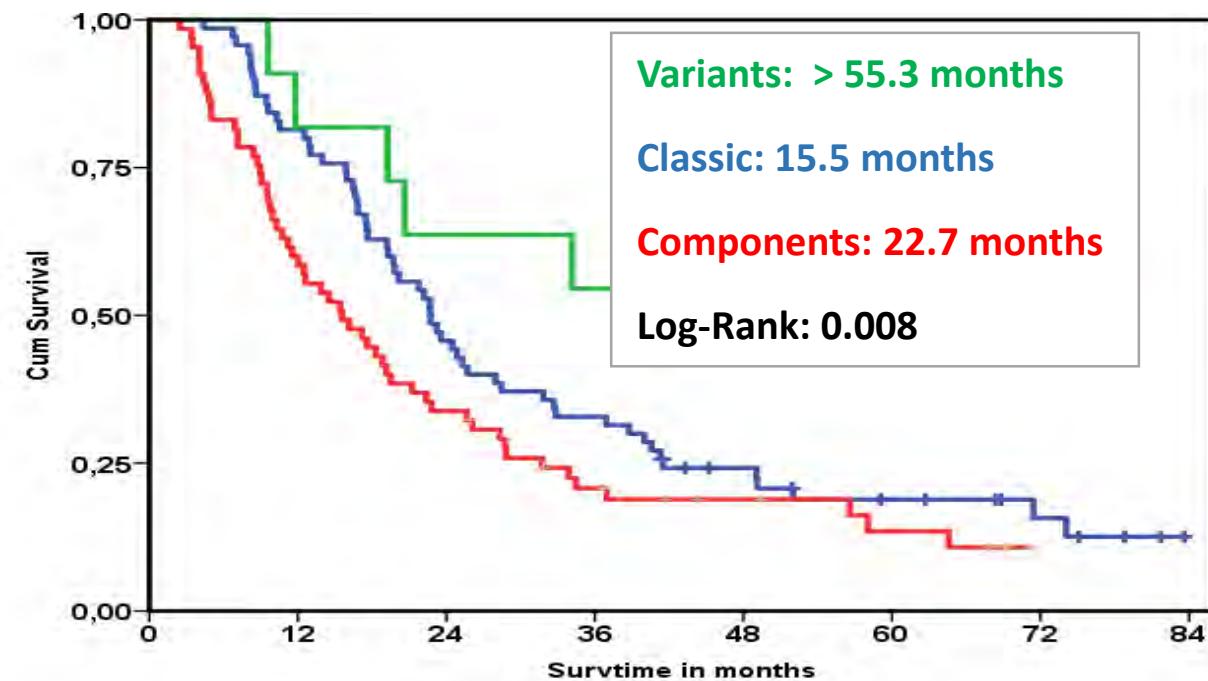
Papillary carcinoma



Tubular carcinoma

# Correlation between morphology and outcome

## Overview



## Details

Morphology	Survival (months)
pure classical PDAC	22.7
with cribriform component	28.7
with clear cell component	17.6
with papillary component	13.9
with gyriform component	12.5
with complex component	10.0
colloid variant	still alive with > 53.5
medullary variant	still alive with > 75.1
adenosquamous variant	4.1 and 10.0 months
tubular variant	>68.8, >55.3 and 19.3 months

# Morphological heterogeneity

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## Conventional PDAC (51-**78%**) (other components <30%)

### **Morphological patterns** (11-41%)

- Clear cell/foamy glands
- Cystic-papillary
- Large-duct
- *Complex\**

### **Variants** (8-11%)

- Colloid
- Adenosquamous
- Undifferentiated
  - With rhabdoid features
  - With osteoclastic-like giant cells
- Medullary
- Micropapillary
- Hepatoid
- Signet ring
- *Tubular\**

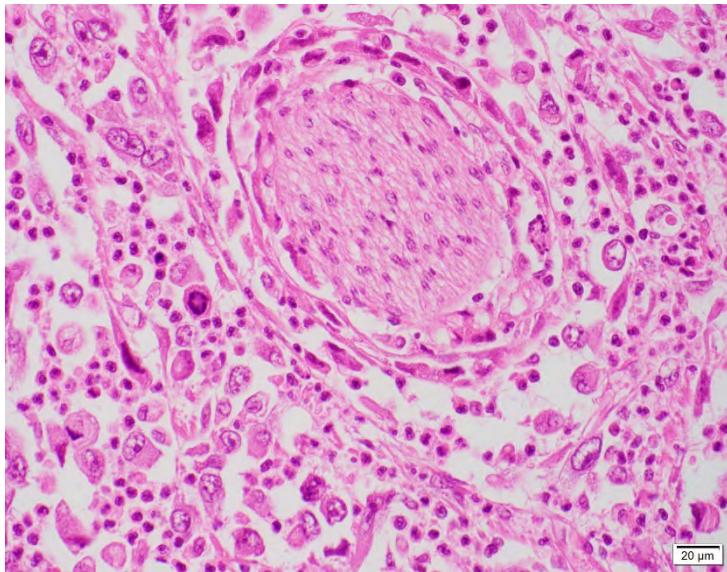
WHO 2019

\*Schlitter et al, Sci Rep 2017

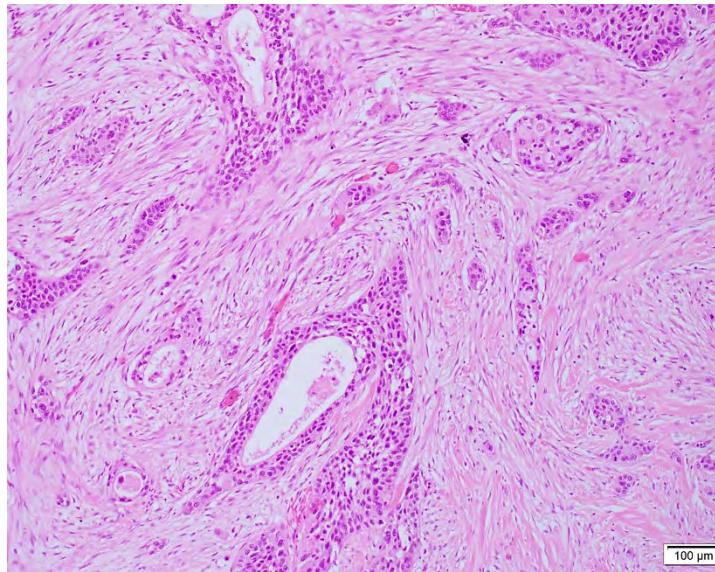
Düsseldorf series

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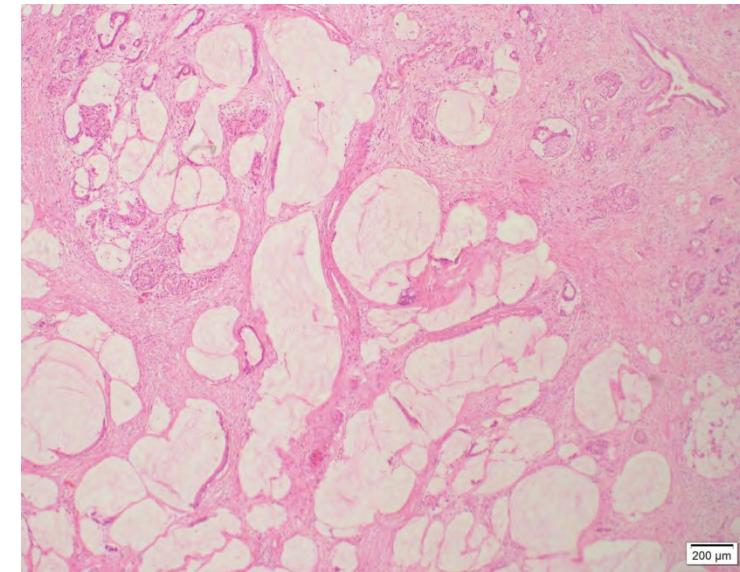
# Patterns and variants



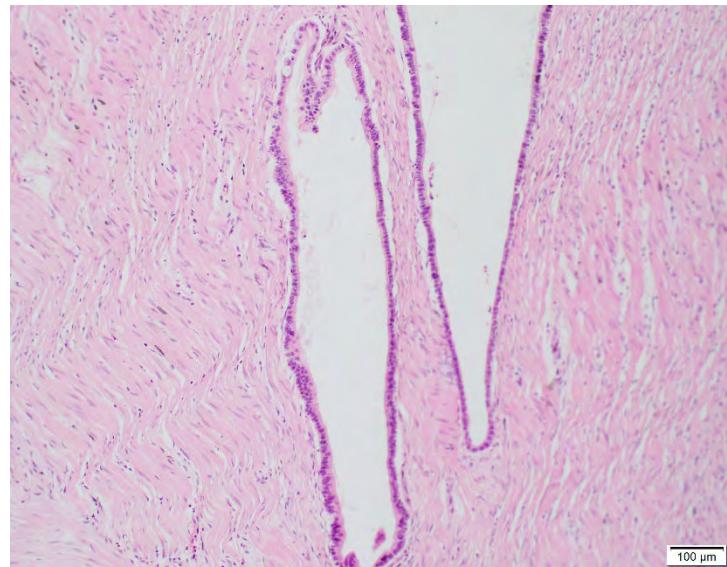
undifferentiated



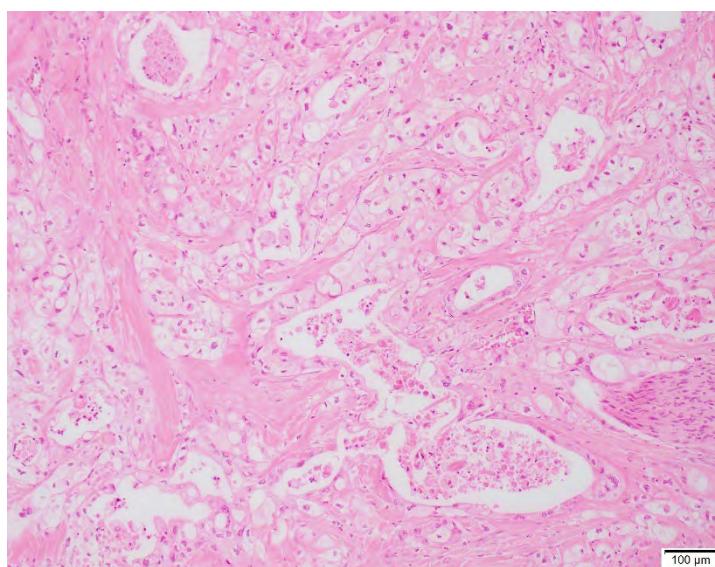
adenosquamous



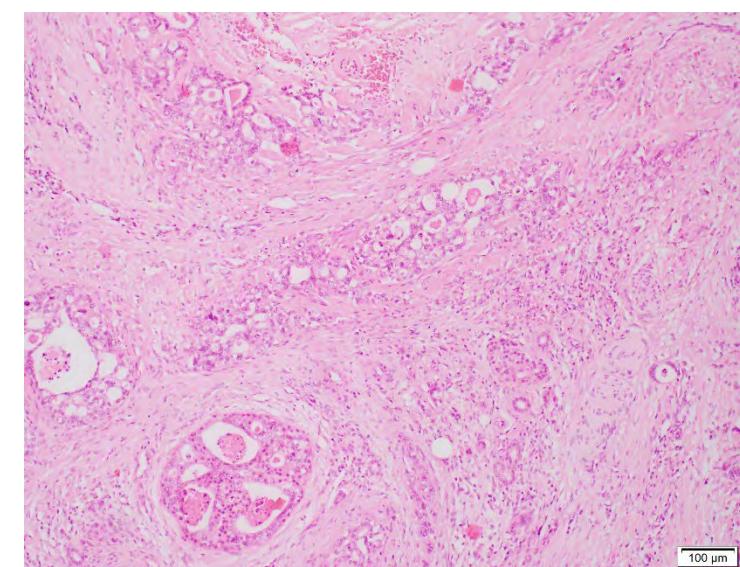
colloid



large duct



clear cell



complex

# Variants

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(about 10% of all PDAC)

## With better prognosis

than PDAC NOS

- **Mucinous („colloid“) (GNAS Mut.)**
- **Undifferentiated with osteoclastic-like giant cells**
- Medullary (MSI-high, KRAS wt)

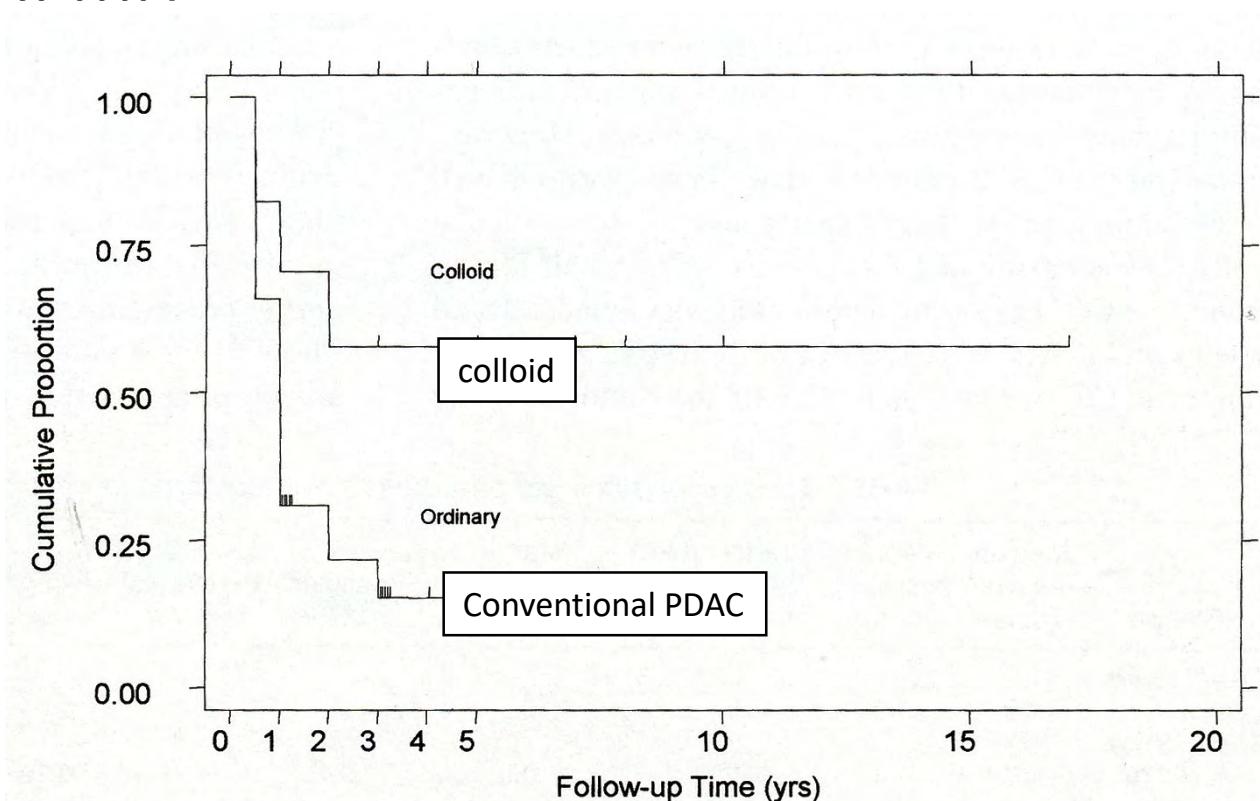
## With worse prognosis

than PDAC NOS

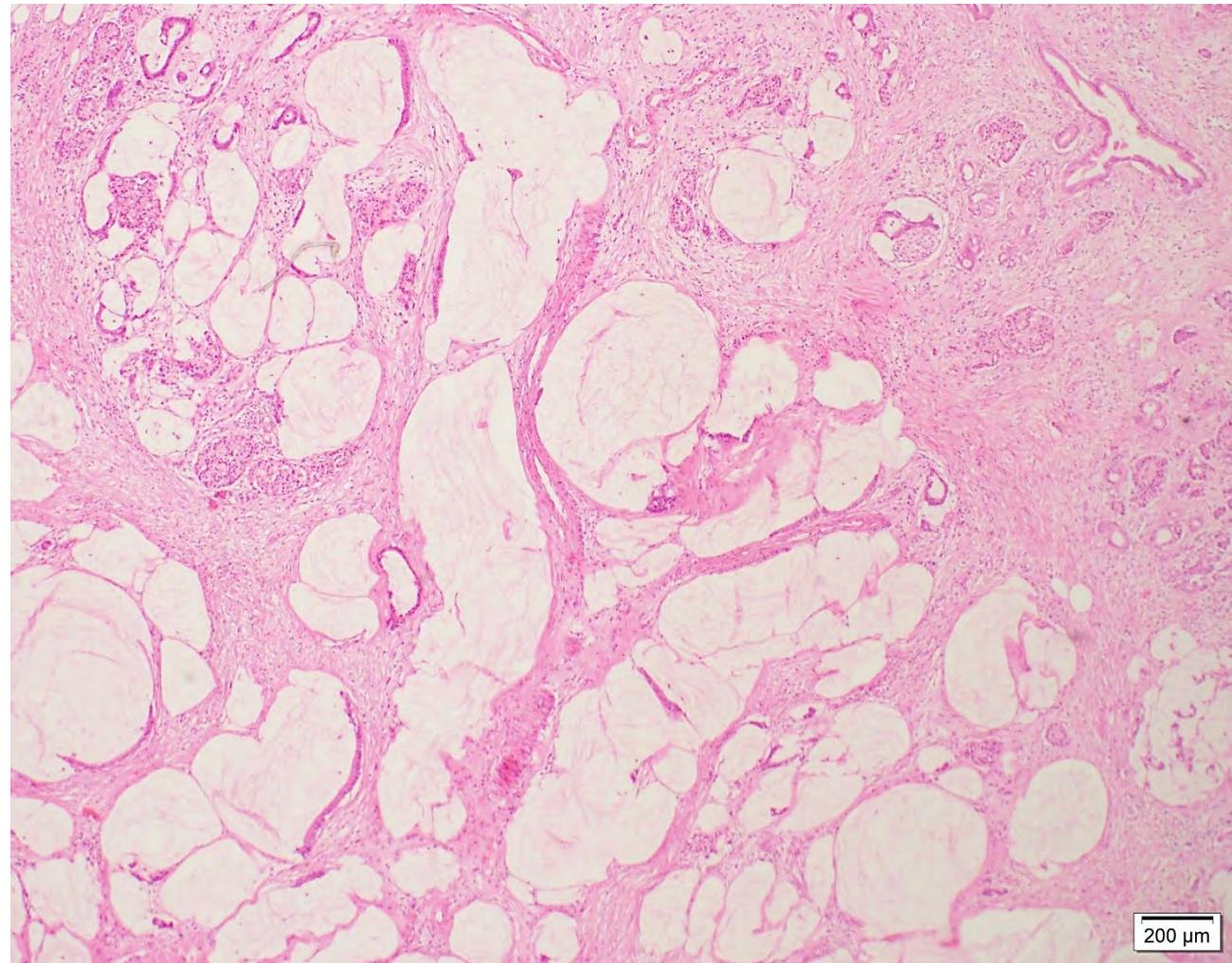
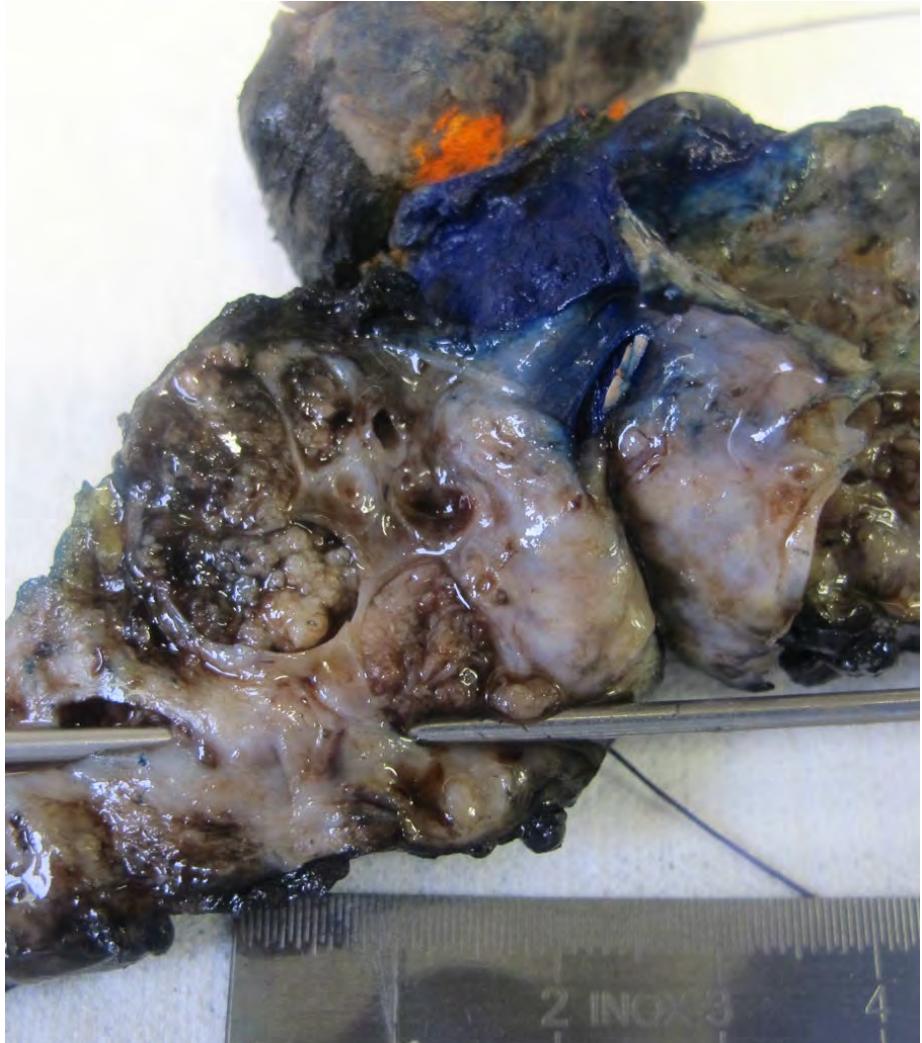
- **Adenosquamous (TP53 Mut., 3p Loss)**
- **Undifferentiated (↑ KRASmut copy number)**
- Micropapillary
- (Hepatoid) (*Fign* Insertionen)
- (signet ring)

# Mucinous „colloid“ carcinoma

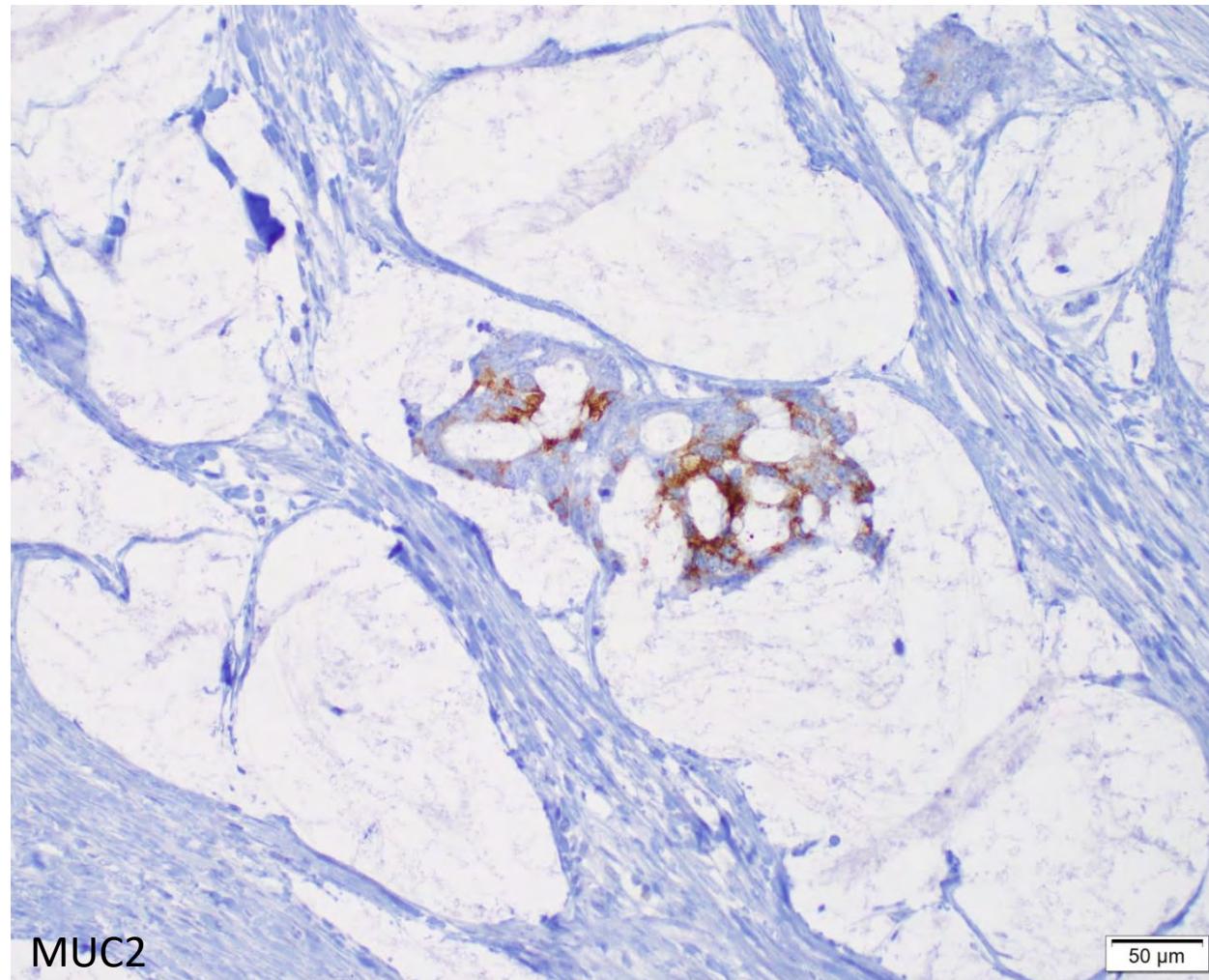
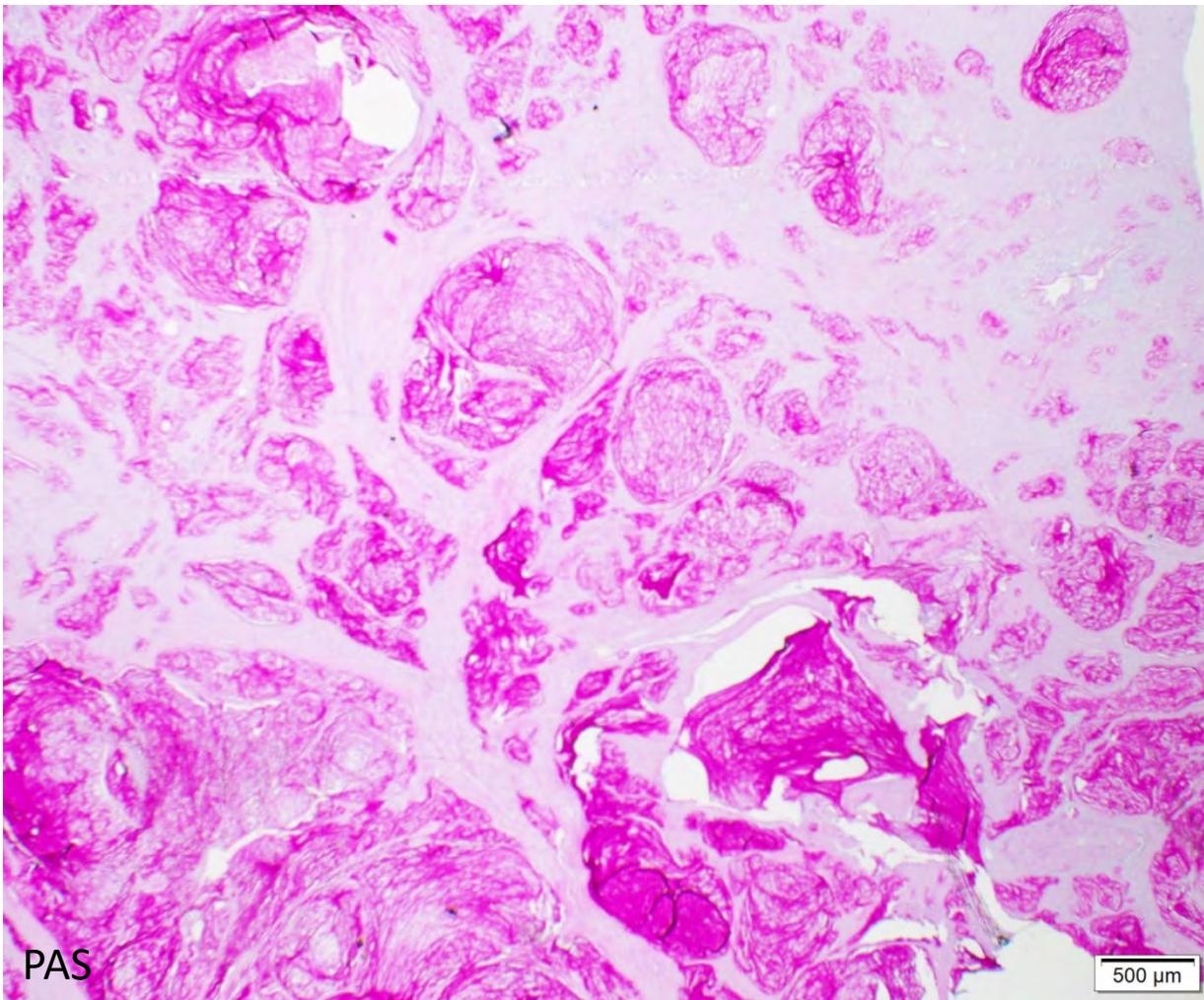
- 80% extracellular mucin
- Usually associated with intestinal IPMN
- Better prognosis than PDAC!



# Mucinous „colloid“ carcinoma



# Mucinous „colloid“ carcinoma



# Undifferentiated carcinoma with osteoclastic-like giant cells

N=38 (vs 725 PDAC NOS)

< 2% of PDAC

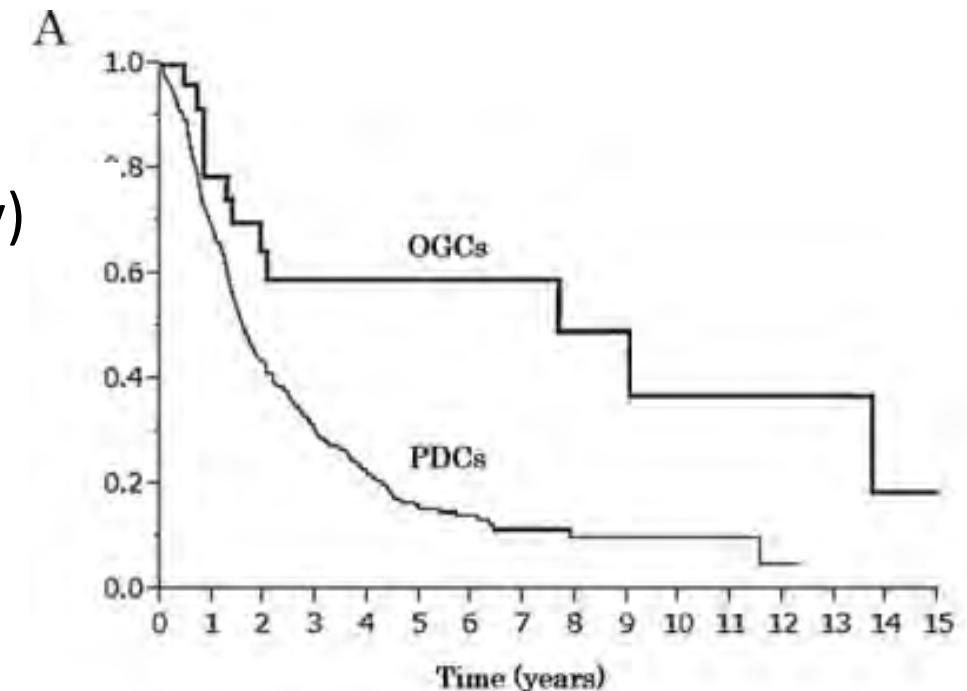
Pat. are younger than PDAC patients (about 10 y)

F:M=2:1

Usually larger than PDAC NOS (5.3 vs 3.2 cm)

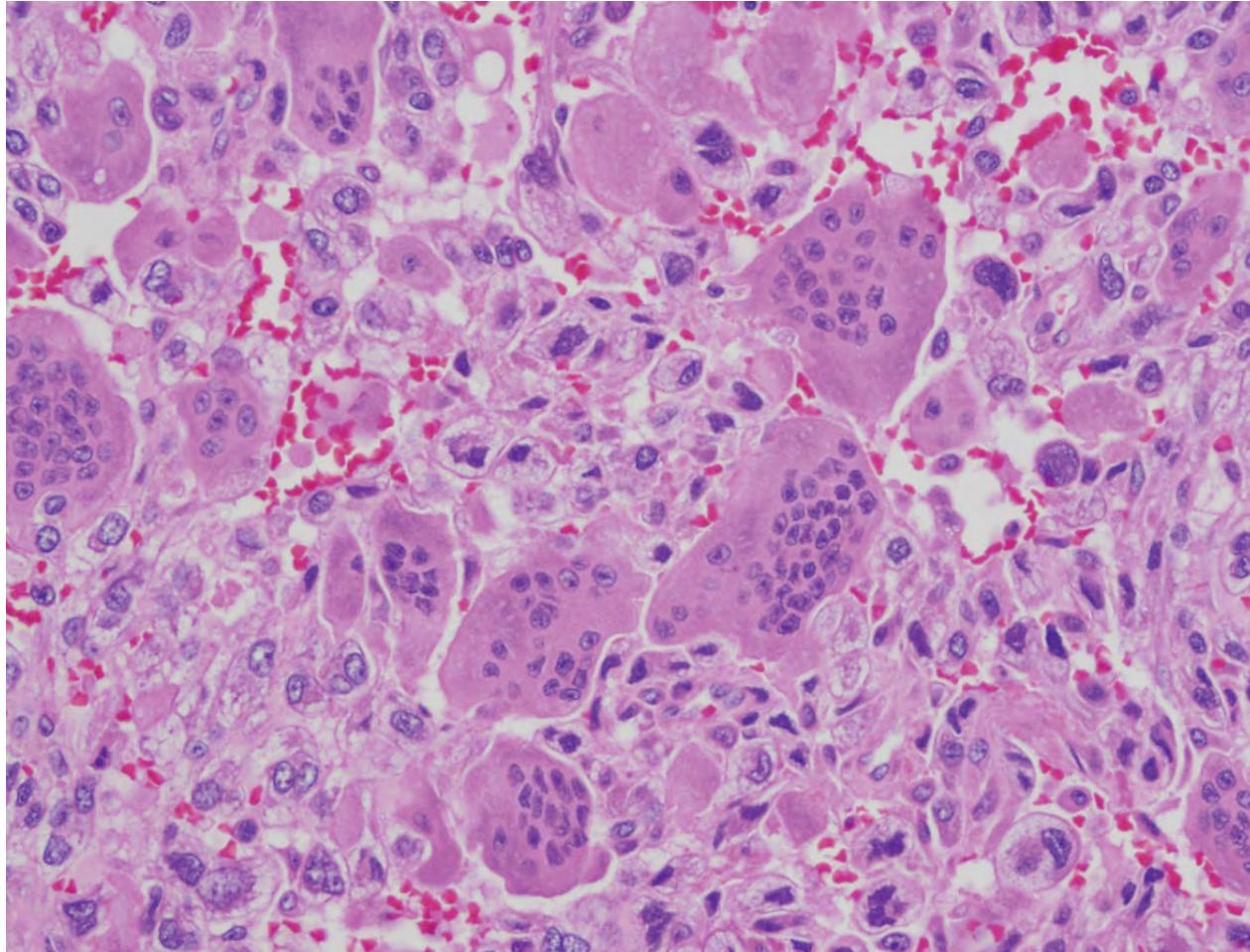
5y survival: 59.1%

Median survival: 7.67 years



# Undifferentiated carcinoma with osteoclastic-like giant cells

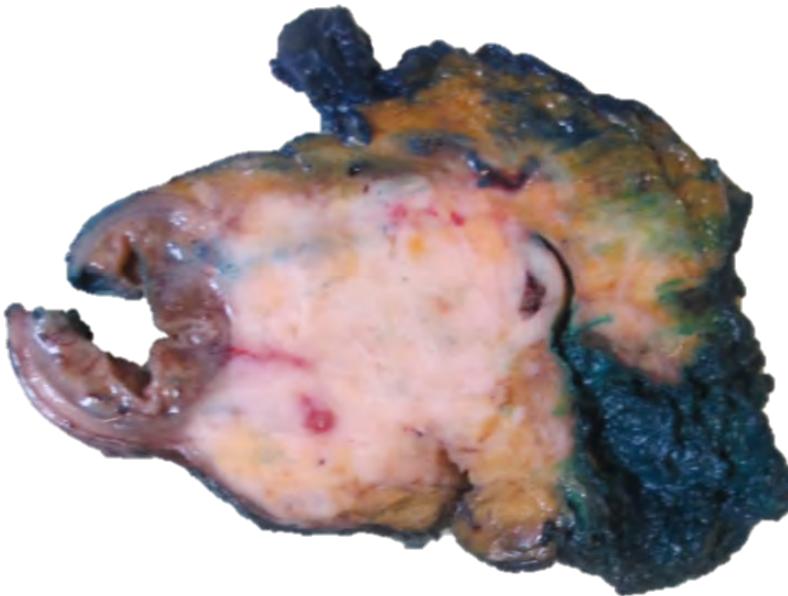
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CD68+  
CK-

# Undifferentiated (anaplastic) carcinoma

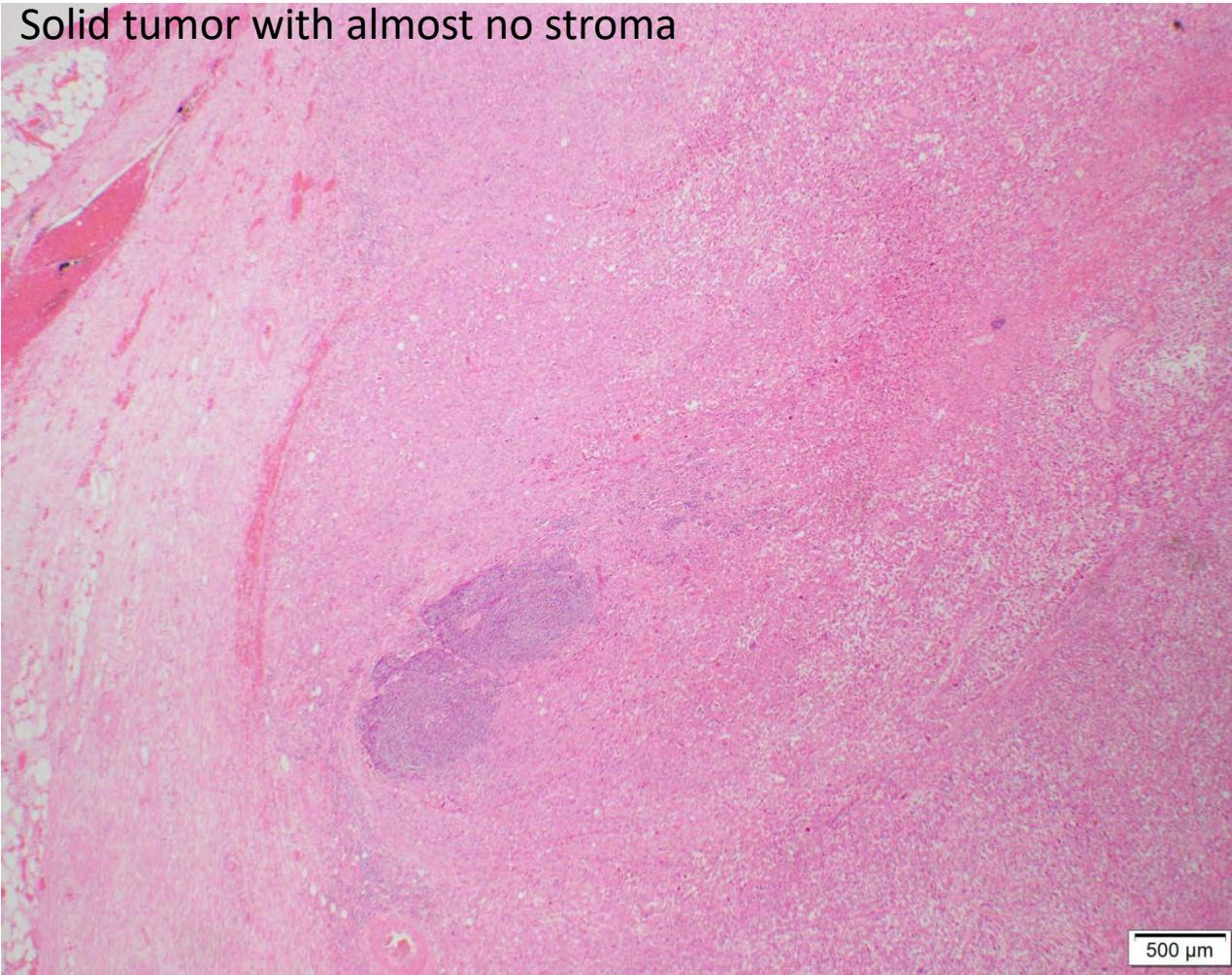
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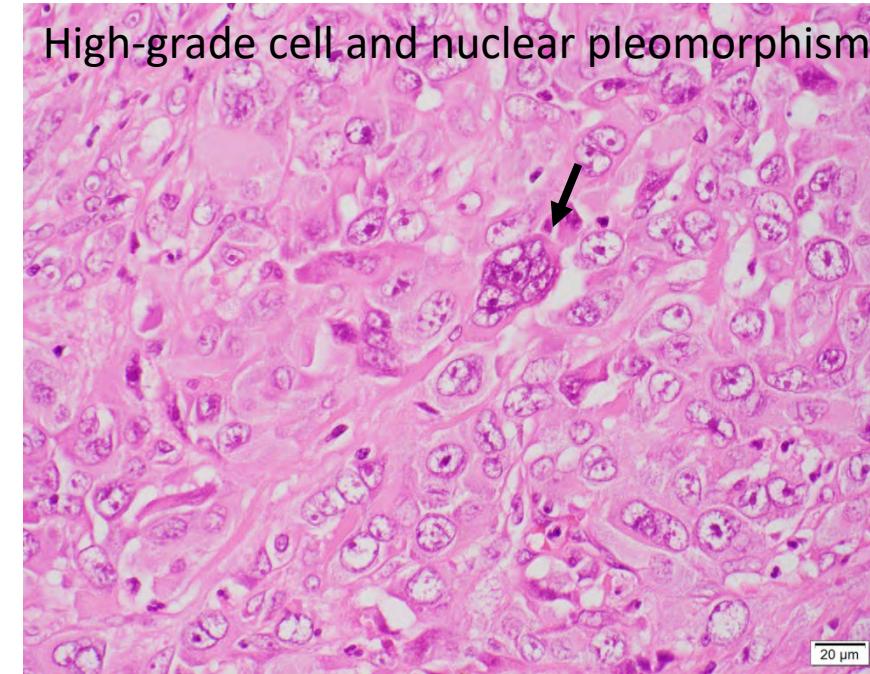
- Rare PDAC variant (<1%) with aggressive course
- Numerous growth types and denominations (anaplastic, pleomorphic, spindle cell carcinoma, sarcomatoid carcinoma, carcinosarcoma...)
- KRAS mutations are frequent, a „*mutant allele-specific imbalance*“ is reported
- Rhabdoid variant shows SMARCB1-loss and wt-KRAS

# Undifferentiated (anaplastic) carcinoma

Solid tumor with almost no stroma

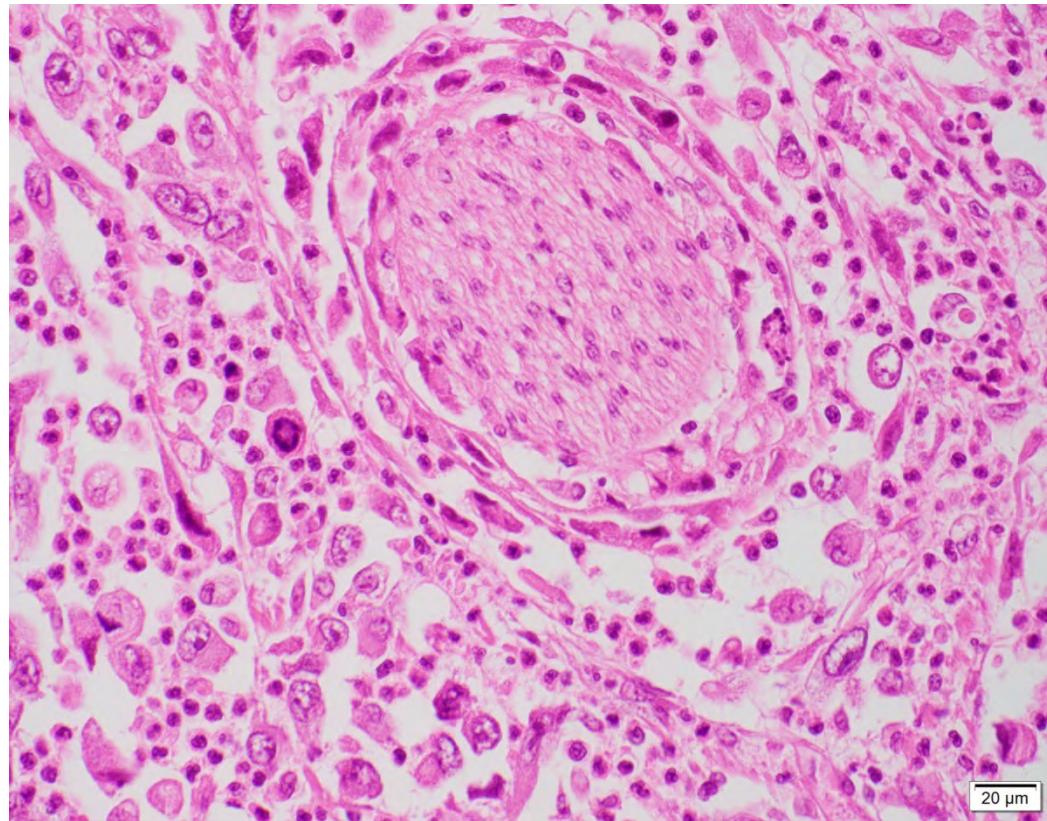


High-grade cell and nuclear pleomorphism

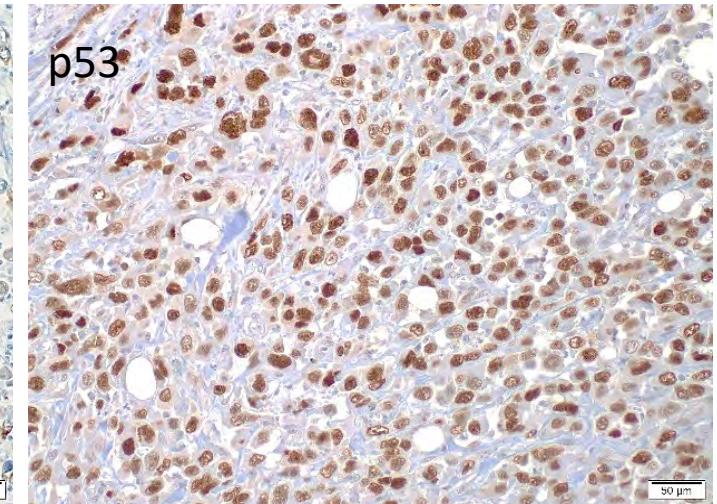
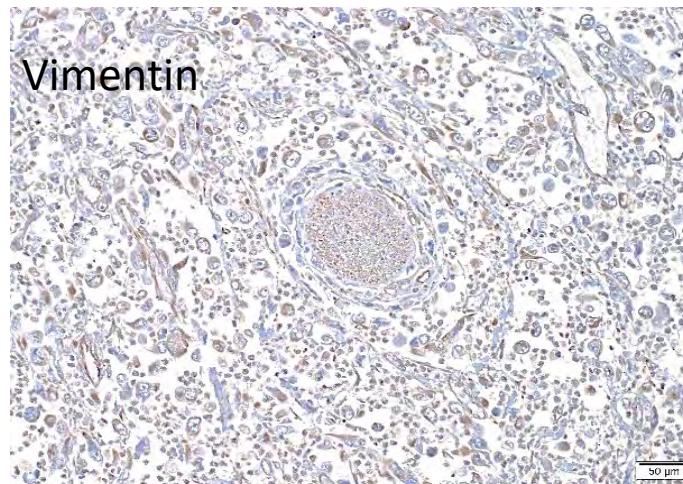
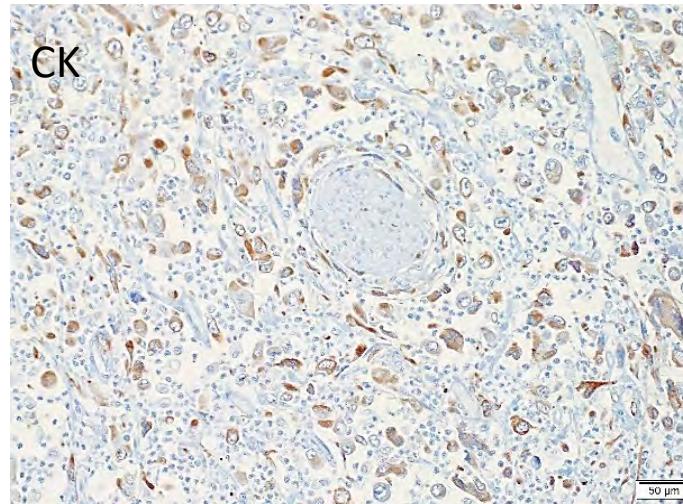


Tumor giant cells (CK +!)

# Undifferentiated (anaplastic) carcinoma

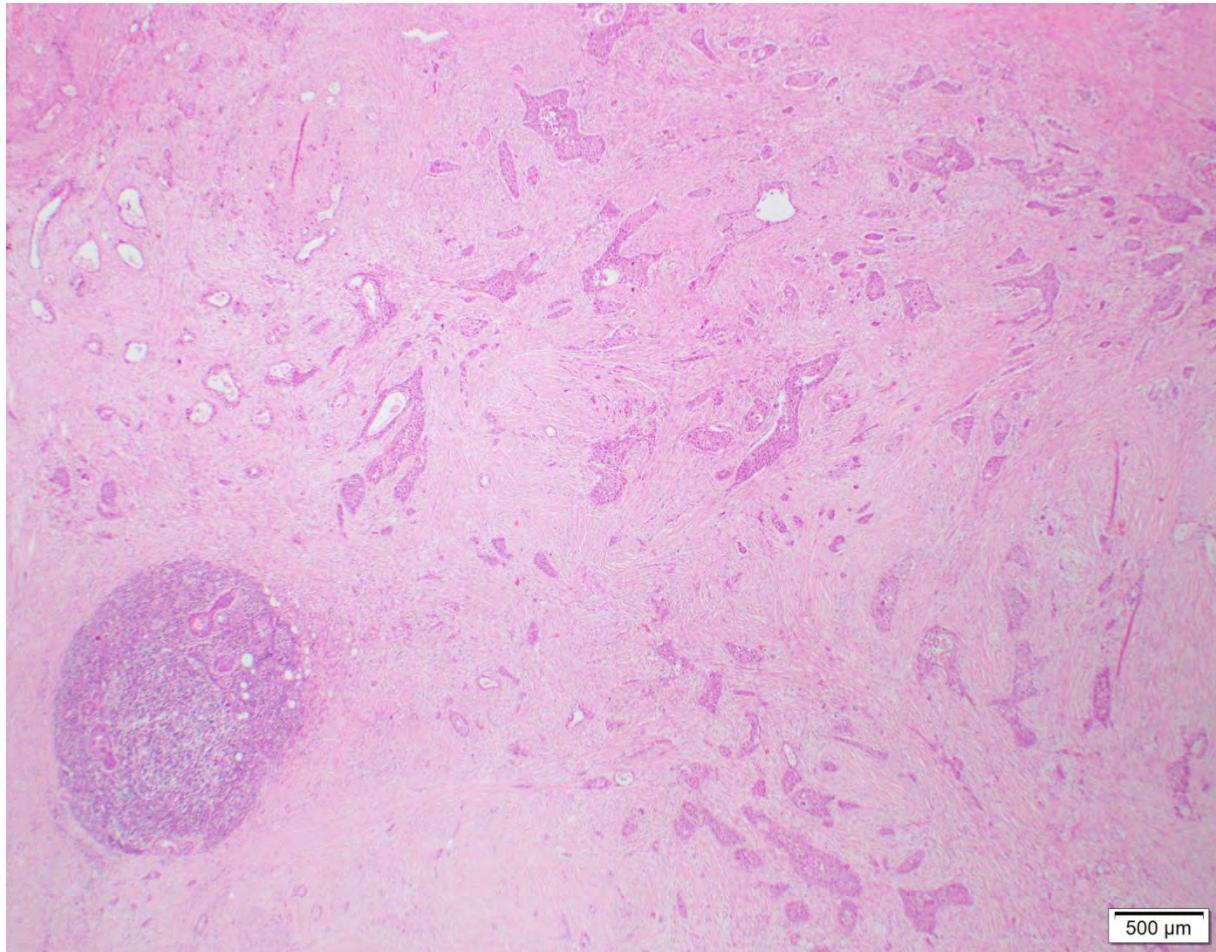


Dissociate growth

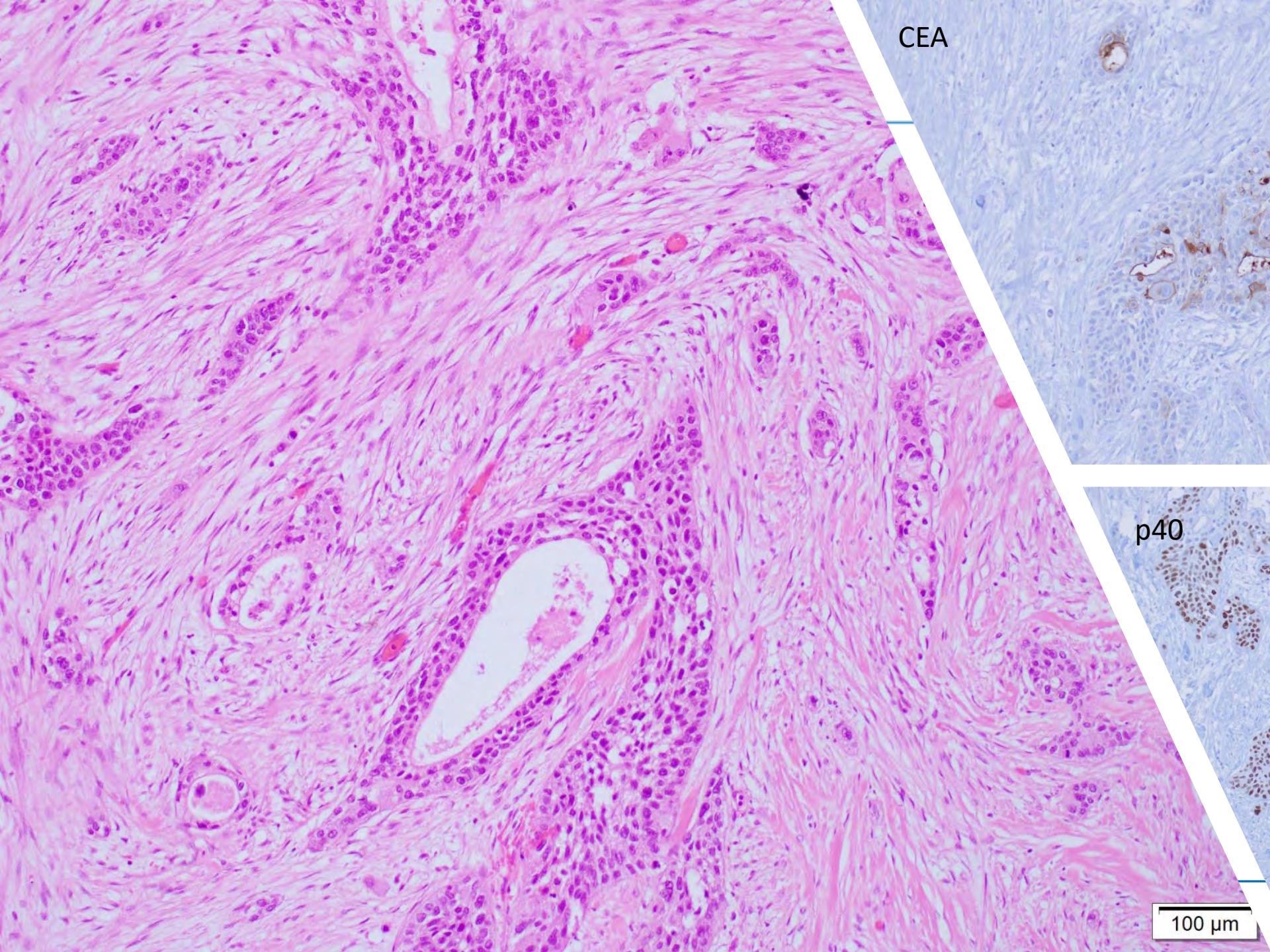


# Adenosquamous carcinoma

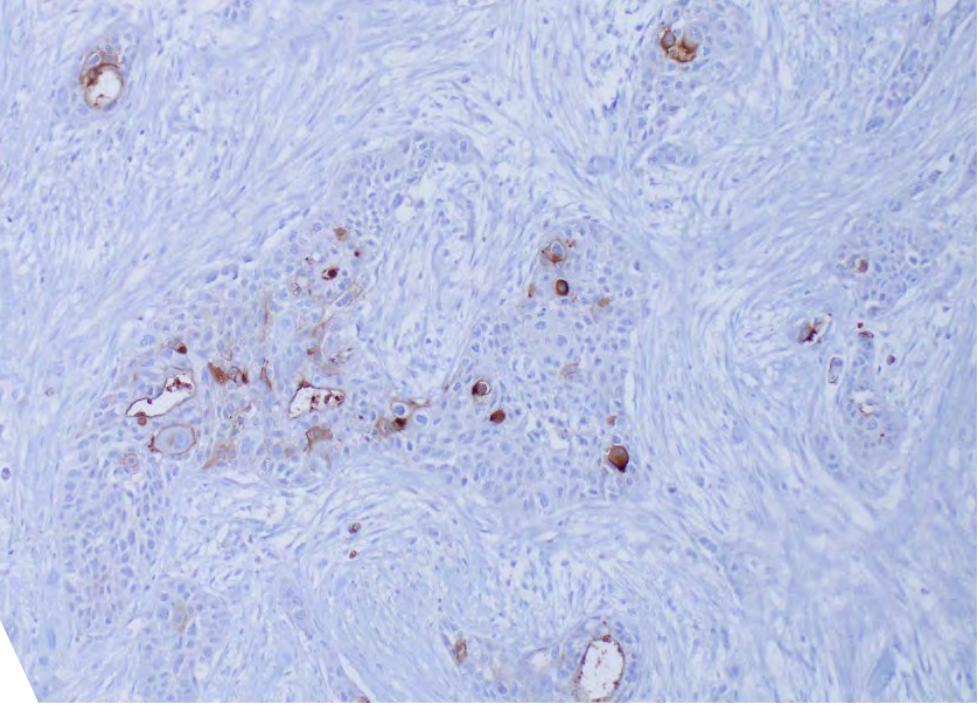
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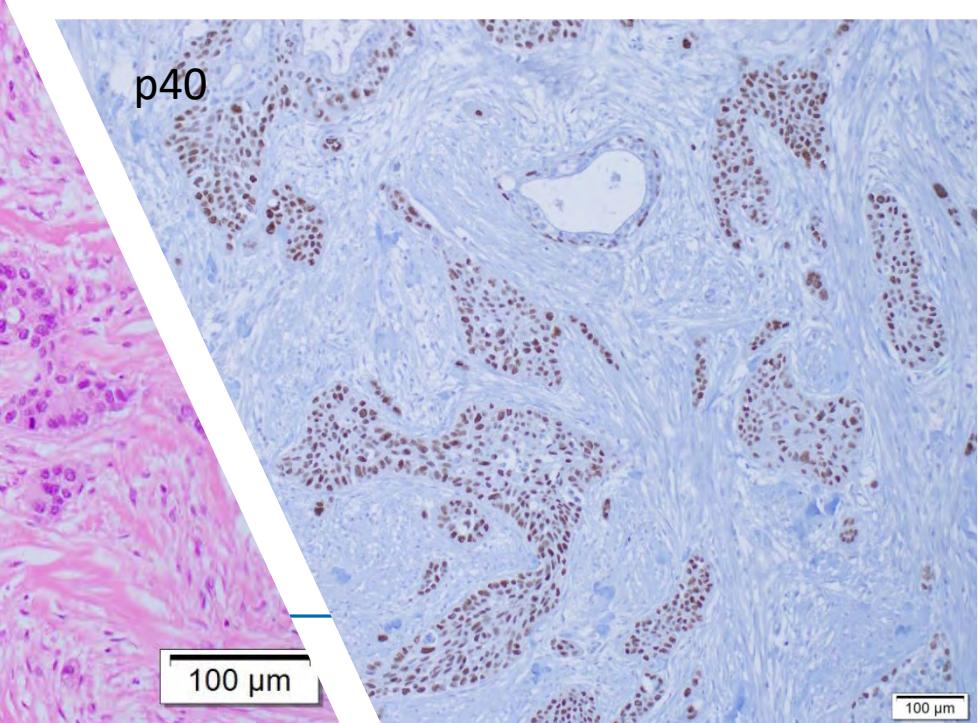
- Relatively rare variant (1%-10%) with aggressive course (median survival about 4 months)
- At least 30% squamous component (WHO)
- Pure squamous carcinomas are usually metastases (uterine cervix, lung)
- TMB similar to PDAC NOS
- *Enrichment for TP53 mutations and 3p losses*



CEA



p40



100 µm

100 µm

# Molecular heterogeneity

# Correlation between morphology and molecular subtyping

Collison et al.  
(Nat Med 2011)

Bailey et al.  
(Nature 2016)

Moffitt et al.  
(Nat Genet 2015)

Exocrine-like

Aberrantly  
differentiated  
endocrine exocrine  
(ADEX)

Quasi-  
mesenchymal

Squamous

Basal-like

Classical

Pancreatic  
progenitor

Classical

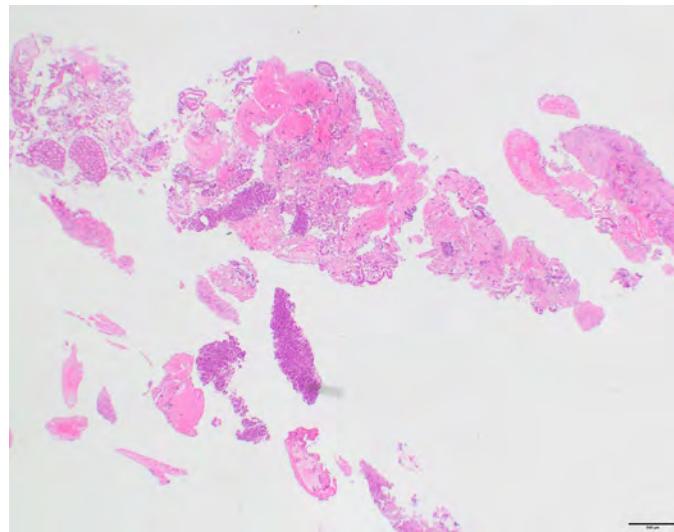
Immunogenic

- Poor prognosis, chemoresistance
- Poor response to FOLFIRINOX
- PD-1 and Pdl-1 positive
- T-cell inflamed signature

# Correlation between morphology and molecular subtyping

molecular

by immunoprofile



Collison et al. (Nat Med 2011)	Bailey et al. (Nature 2016)	Moffitt et al. (Nat Genet 2015)
Exocrine-like	Aberrantly differentiated endocrine exocrine (ADEX)	
Quasi-mesenchymal	Squamous	Basal-like
Classical	Pancreatic progenitor	Classical
	Immunogenic	

Muckenthaler et al. (Clin Cancer Res 2017)
KRT81-/HNF1A+ ≈ non-QM/squamous/basal-like
KRT81+/HNF1A- ≈ QM/squamous/basal-like

**Prognosis  
Therapy prediction**

KRT81 + / HNF1alpha - („squamous“)	78/214 (36.4%)
HNF1alpha + / KRT81 - („non-squamous“)	38/214 (17.8%)
Double positive (unclassifiable)	46/214 (21.5%)
Double negative	52/214 (24.3%)



**No correlation between KRT81/HNF1alpha expression and classical prognostic markers such as grading (Chi squared, two-tailed) nor with histomorphology (adenosquamous, p40)**

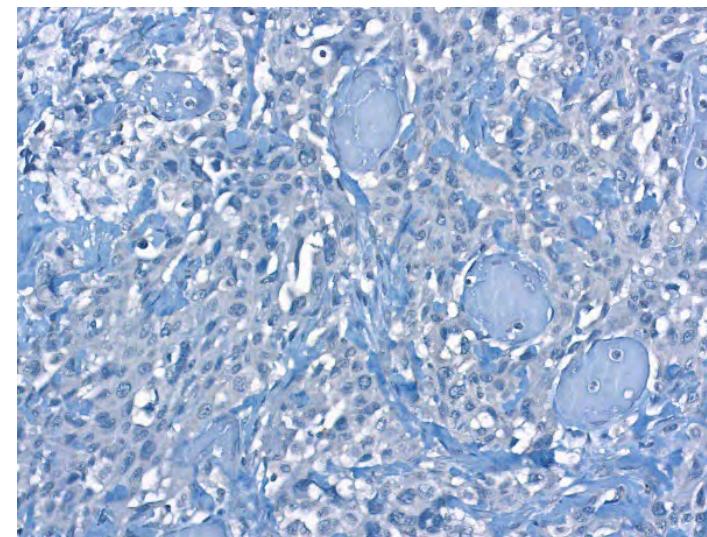
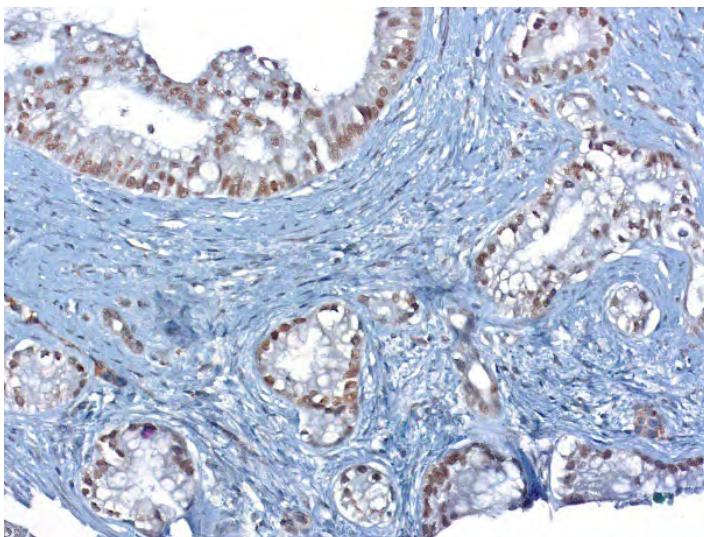
Häberle et al, unpublished

# GATA6

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GATA6: transcription factor related to pancreas development

**„Classical“ PDAC:** moderate to strong GATA6 expression, CK5-negative  
**Basal-like PDAC:** weak to no GATA6 expression, CK5-positive



# Smad4

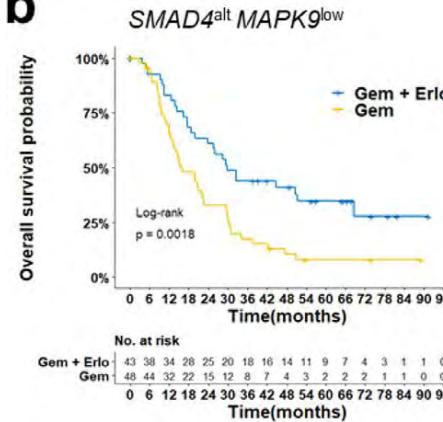
ORIGINAL ARTICLE

## Smad4 Loss Correlates With Higher Rates of Local and Distant Failure in Pancreatic Adenocarcinoma Patients Receiving Adjuvant Chemoradiation

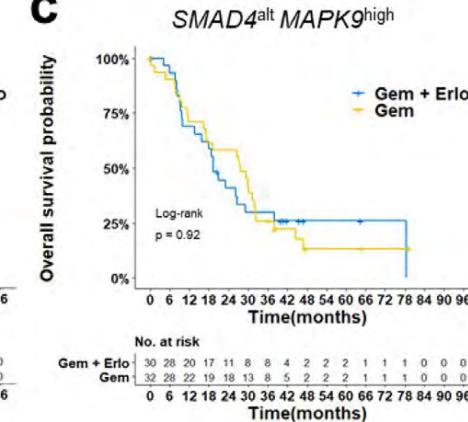
Herman et al, Pancreas 2018

Smad4 alteration + MAPK9-low associated with response to Gemcitabine + Erlotinib

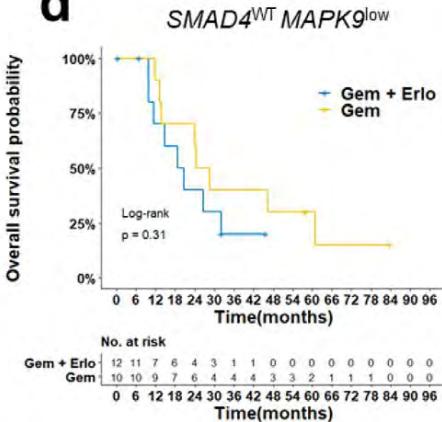
b



c



d



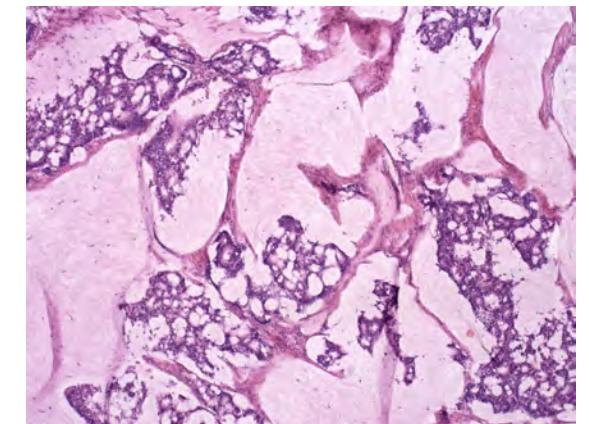
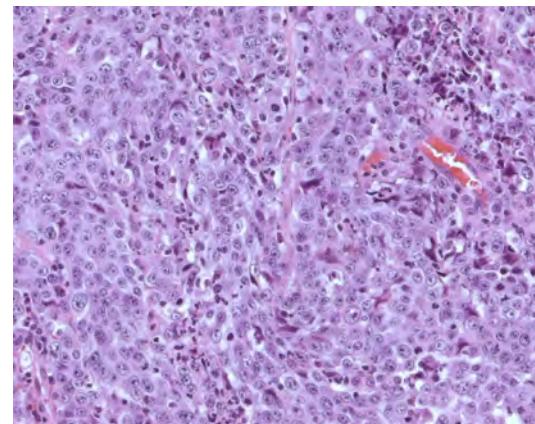
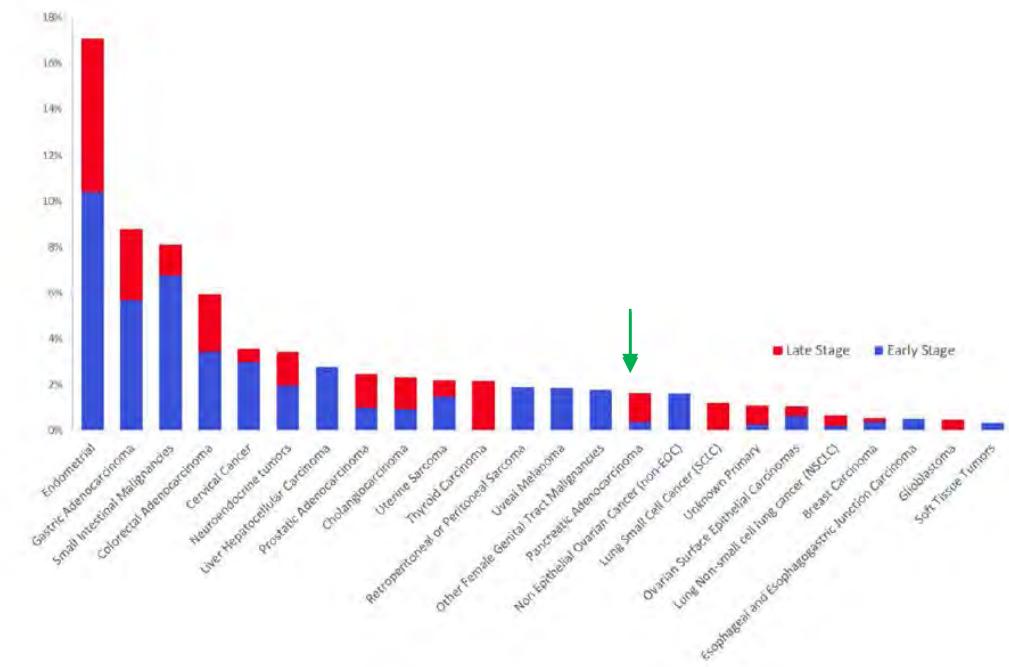
Mutation + CNV analysis, no IH!

Jacobuzio-Donahue et al, J Clin Oncol 2009

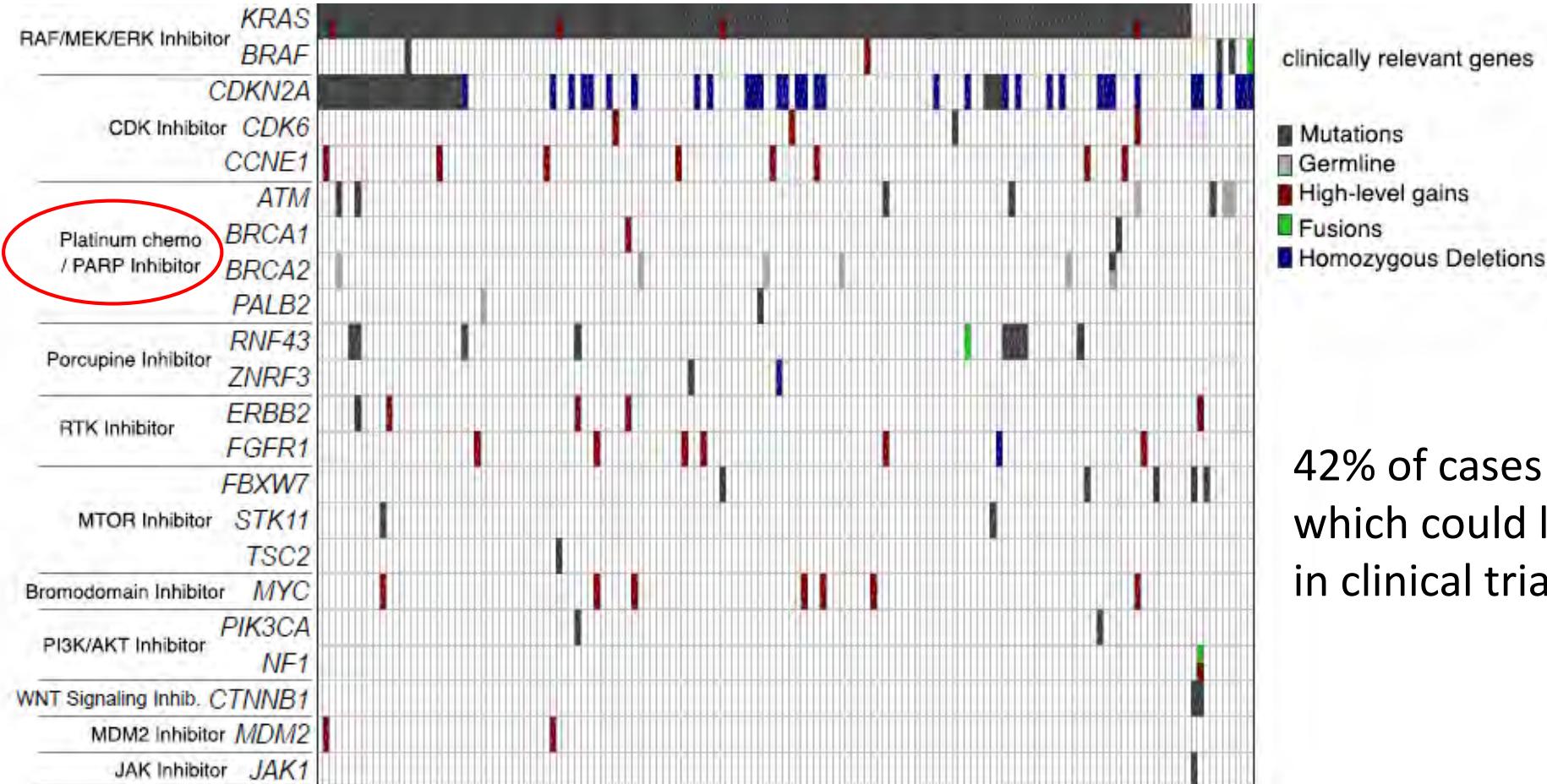
Hoyer et al, EBioMedicine 2021

# Microsatellites

- 1-2% of PDAC are MSI *high/dMMR*
- medullary and mucinous histology
- *KRAS* and *TP53* wt, high TMB, *JAK* and *KMT* mut.
- Association with Lynch possible
- No definite data on survival

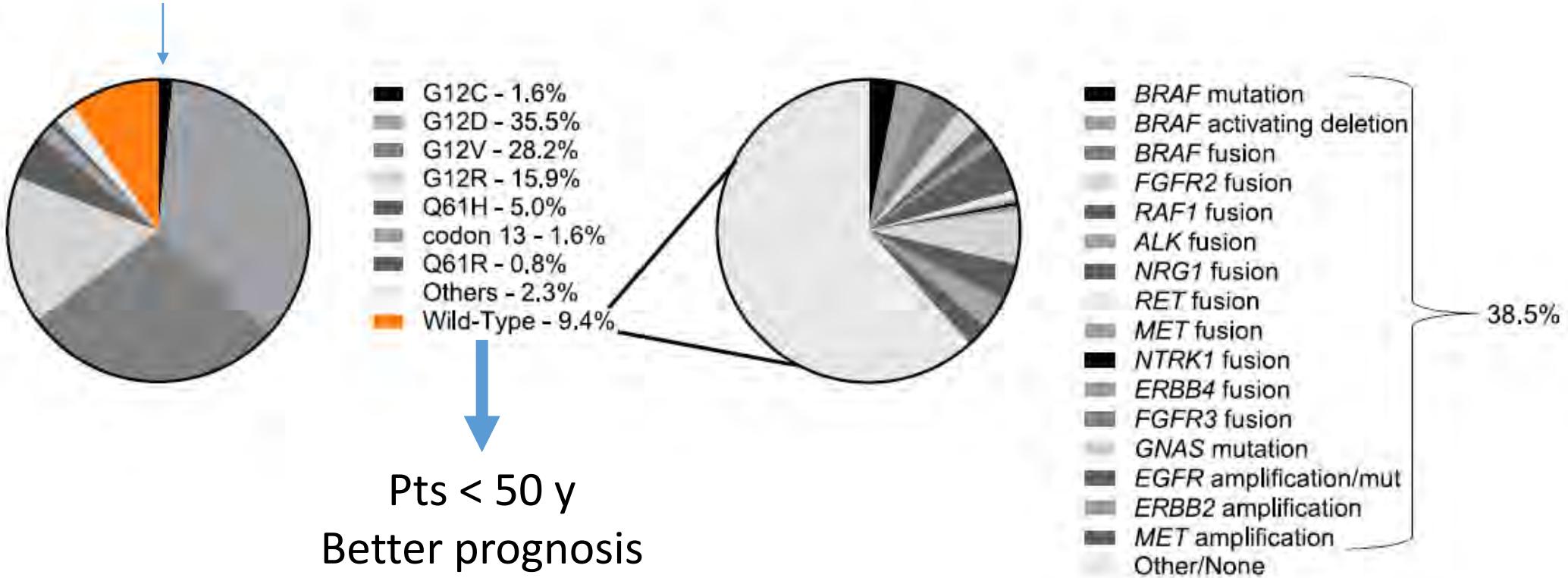


# Clinically relevant genetic changes



42% of cases with genetic changes,  
which could lead to enrollment  
in clinical trials

# KRAS and therapy

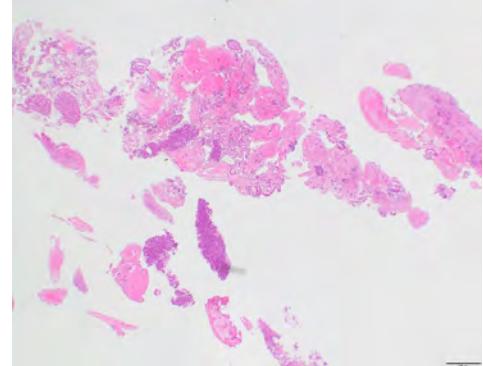


Lee & Pant, ASCO Educational Book 2021

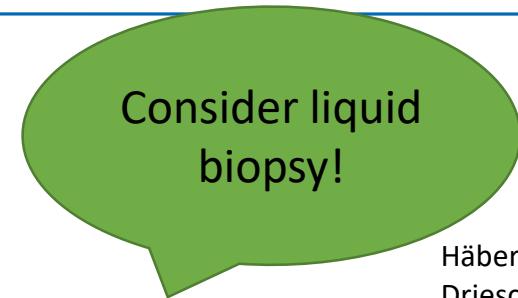
Singhi et al, Gastroenterology 2019

Schlitter...Esposito, Sci Rep 2017

# To conclude...



histology: PDAC, homog. variants  
grading (budding)  
Small IHC panel: p53, p40, (Smad4, GATA6)  
(MSI-IHC)  
(NGS)



Häberle et al, Sci Rep 2021  
Driescher et al, Cancers 2020



Neoad. Therapy?  
Adjuvant Therapy?  
Clinical trial?



TNM, resection margin status  
histology: PDAC, homog. Variants  
precursor lesion (IPMN/IOPN/ITPN/MCN?)  
grading, budding  
Large IH panel (MSI-IHC, immune profiling)  
MSI PCR  
NGS



@IEspositoPATH

Thank you!



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