

Updated AJCC Staging of Hepatobiliary Cancers

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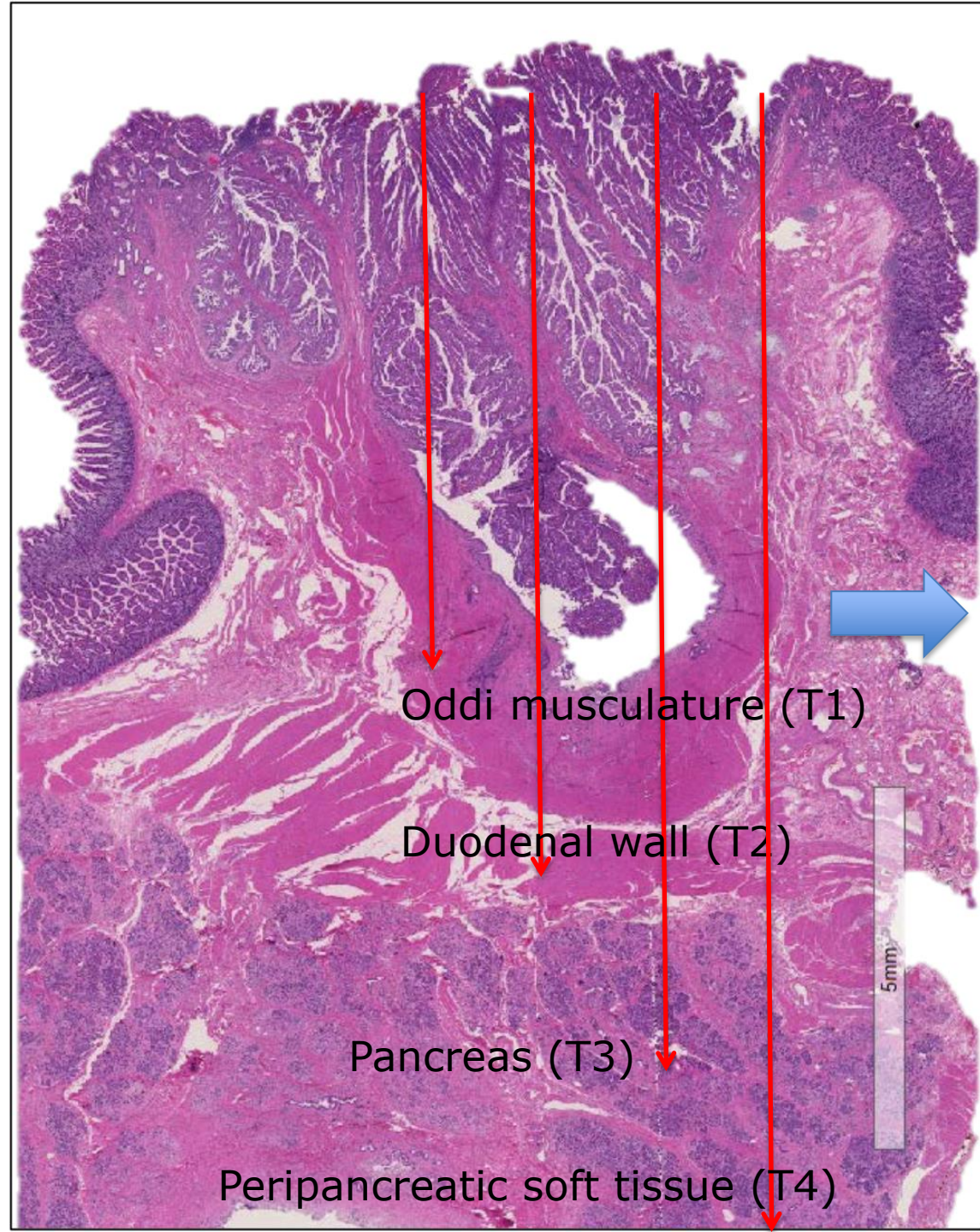
Outline

- **Ampulla**
- **Pancreas**
- **Gallbladder**
- **Distal extrahepatic bile ducts**
- **Perihilar bile ducts**
- **Intrahepatic bile ducts**
- **Liver**

Ampulla: Problems in staging in AJCC 7th edition

Over-simplification
of 3D structure
of ampulla

Lack of definition
of “peripancreatic
soft tissues” (T4)





Duodenum

This histological section shows the duodenum with its characteristic mucosal folds and underlying muscularis propria. A large, irregular mass of soft tissue is visible in the duodenal groove, extending through the muscularis propria and into the serosa. A black bracket on the right side of the image highlights this tumor mass. The pancreatic duct is visible on the left side of the image, surrounded by pancreatic tissue.

Duodenal muscularis propria (MP)

Pancreatic duct with
pancreatic tissue on
both sides

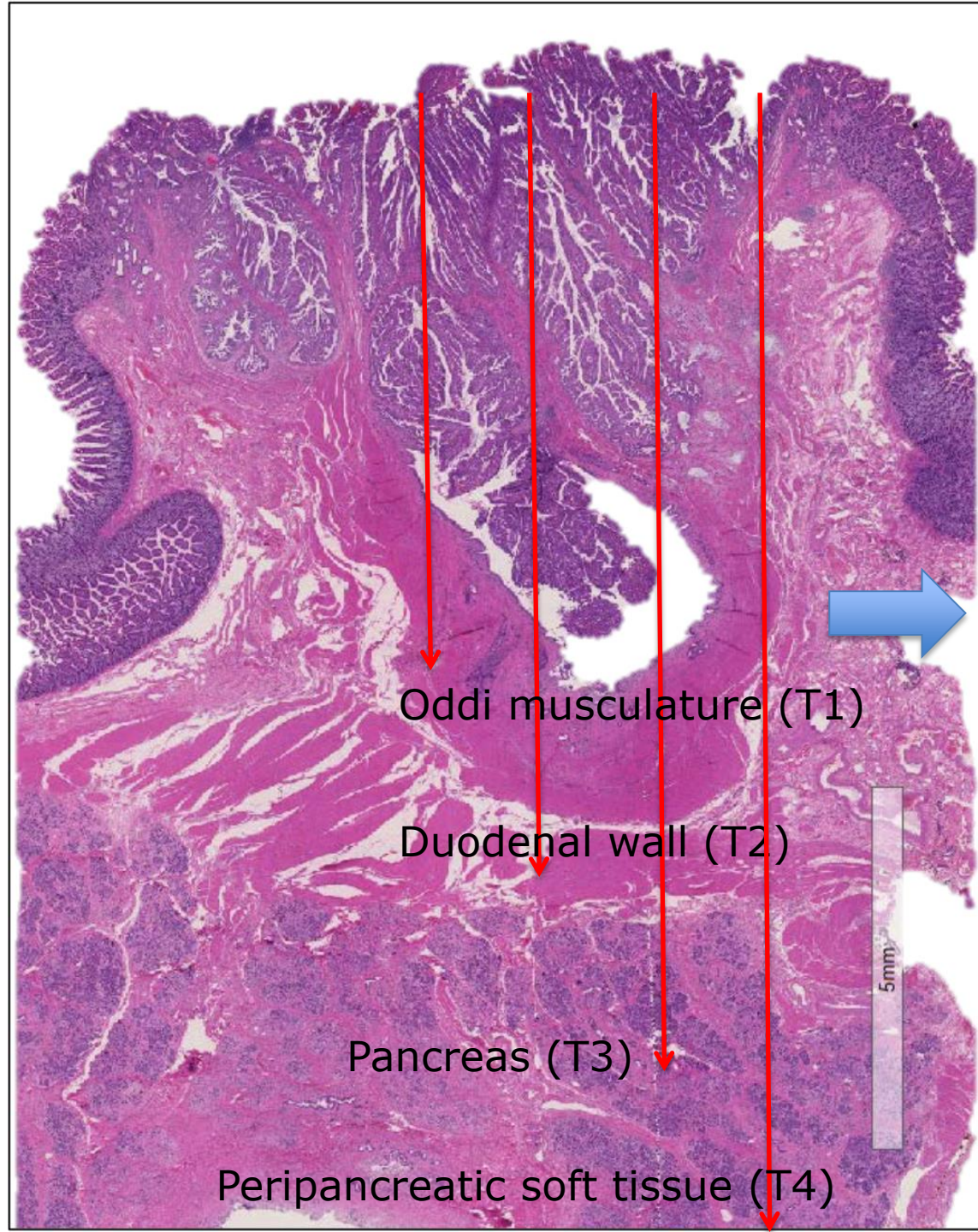
Ampullary tumor below MP of duodenum (in the duodenal groove) → Is the soft tissue in the groove area considered “peripancreatic soft tissue” (T4)? How about extension to the duodenal serosa (T4)?

Ampulla: Problems in staging in AJCC 7th edition

Lack of definition of "duodenal wall invasion" (T2)

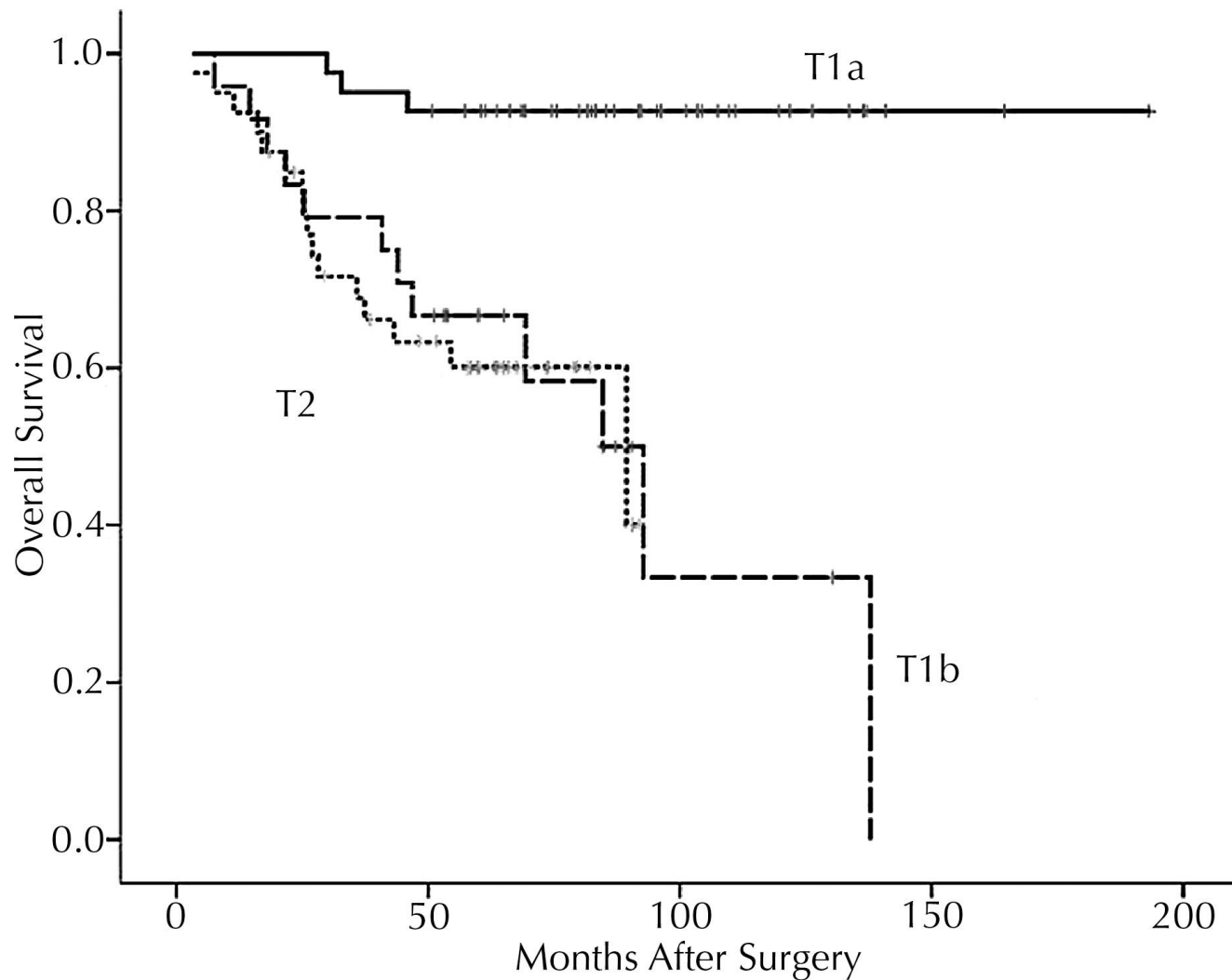
No outcome data regarding ampullary carcinoma with duodenal submucosa versus muscle wall invasion

Lack of correlation of ampullary staging system with clinical outcome

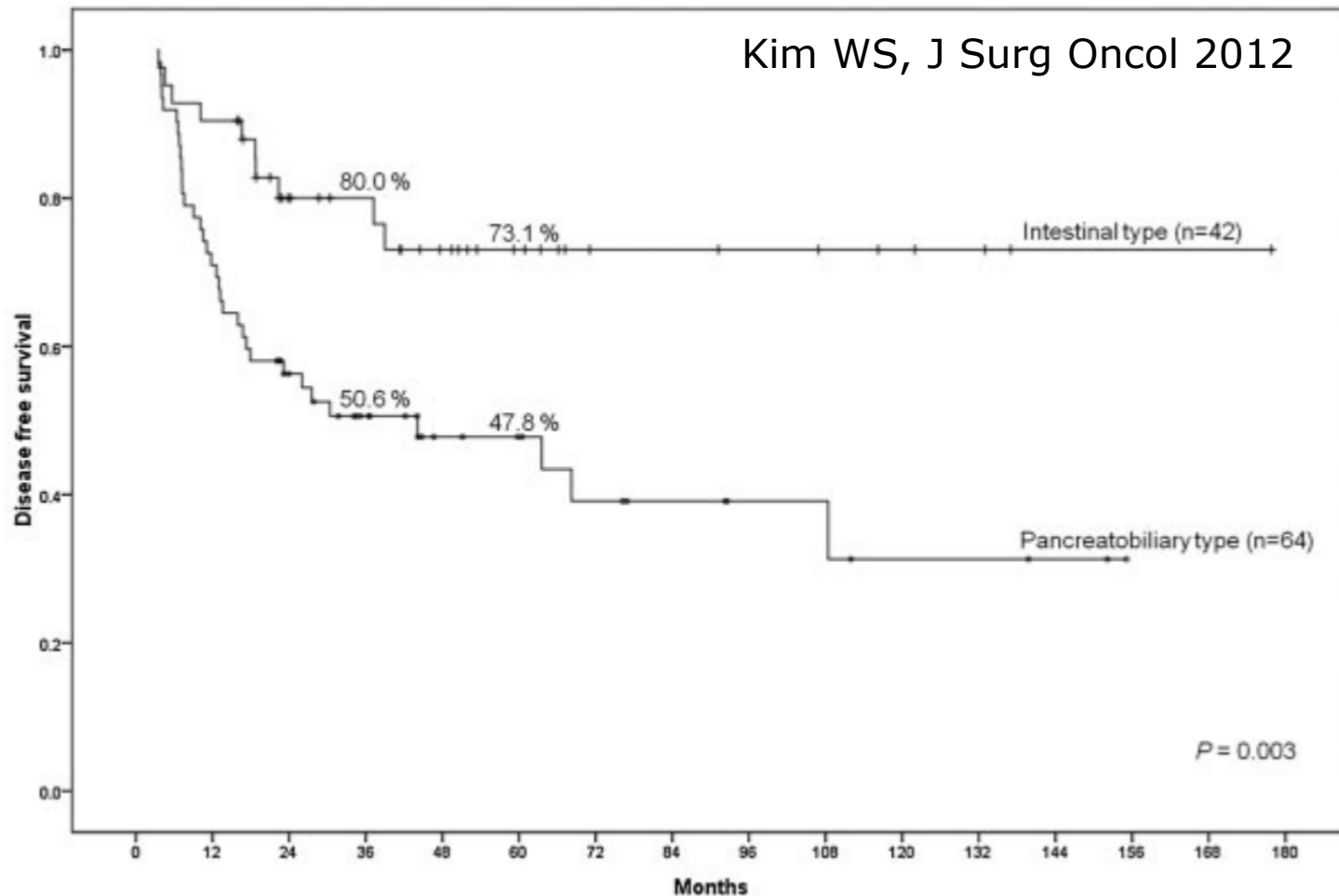


Ampulla: AJCC 8th edition

Change	Details
T1 subdivision	T1a: Limited to ampulla of Vater or sphincter of Oddi T1b: Invades beyond the sphincter of Oddi and/or into the duodenal submucosa
T2 redefined	Invasion into the muscularis propria of duodenum
T3 subdivision	T3a: Directly invades the pancreas (up to 0.5 cm) T3b: Extends > 0.5 cm into the pancreas or extends into peripancreatic or periduodenal tissue or duodenal serosa
T4 redefined	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, irrespective of size (consistent with pancreatic cancer staging)
N categories	N1: Up to 3 LNs N2: 4 or more LNs



The 5-year survival rates for patients with T1a, T1b, and T2 tumors were 98%, 72%, and 60%, respectively ($p < 0.0001$)

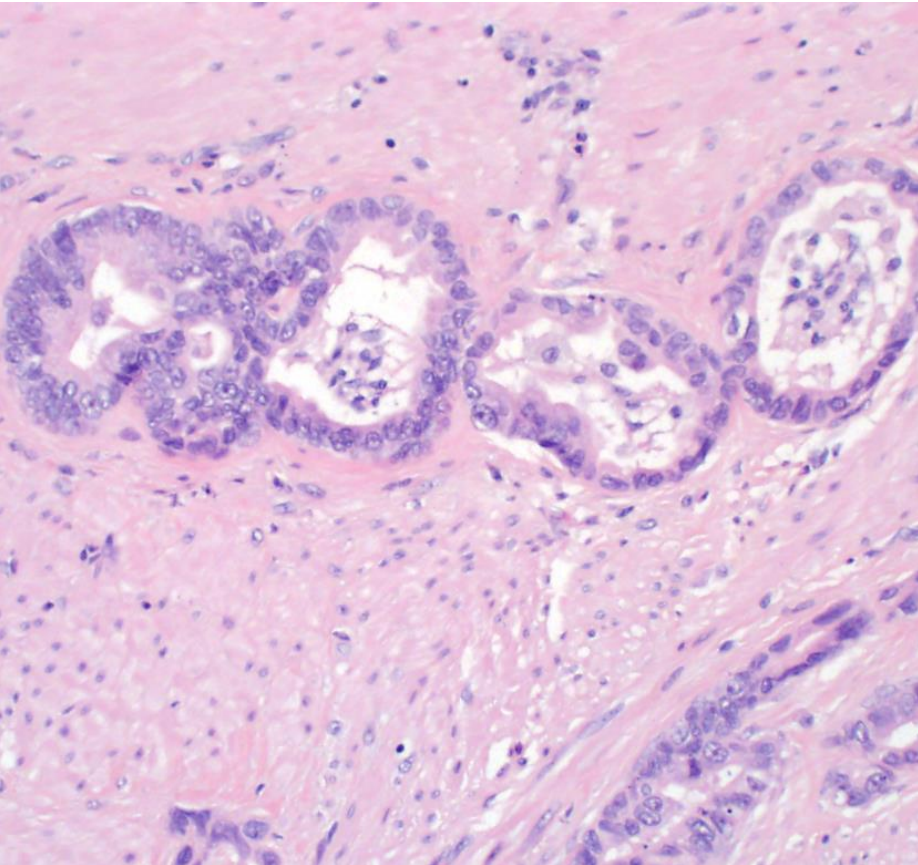


Histologic subtypes should be characterized for patient care, as it may help guide the use of adjuvant therapy:

Gemcitabine-based (pancreaticobiliary) vs. 5-fluorouracil (FU)-based (intestinal)

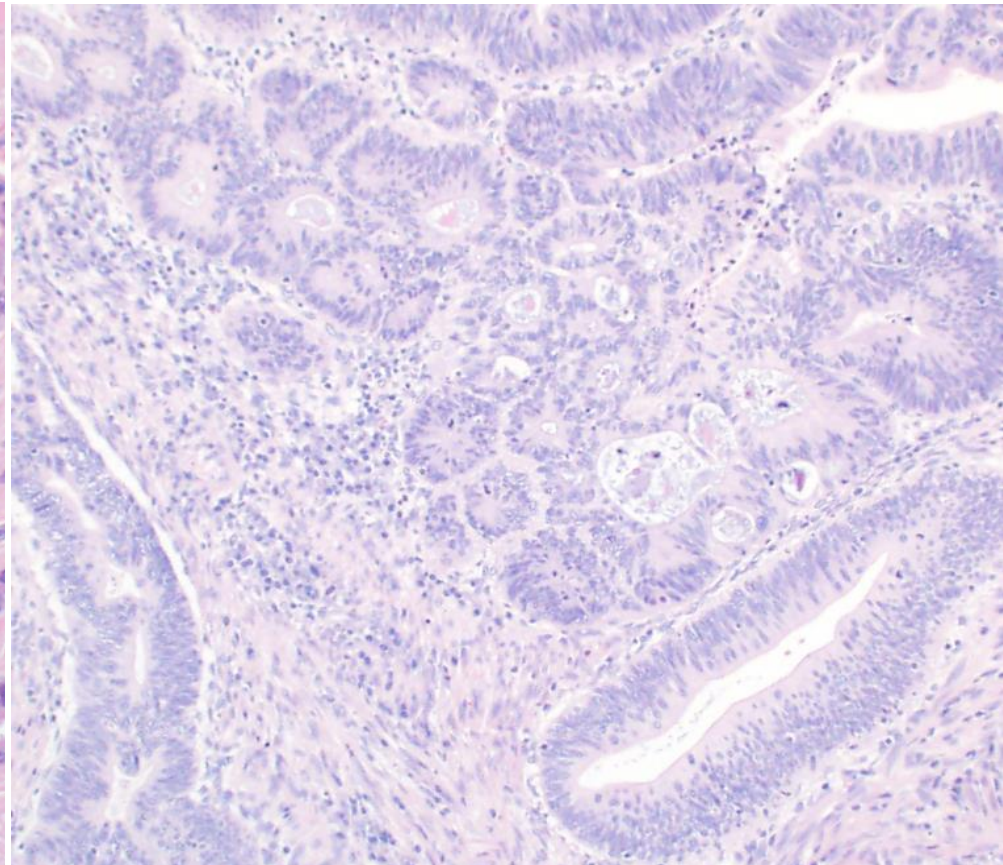
Pancreaticobiliary

- Resemble pancreatic cancer
- Simple or branching glands
- Rounded, cuboidal to low columnar, without pseudostratification
- Desmoplastic stroma



Intestinal

- Resemble colon cancer
- Complex cribriform architecture
- Tall, columnar, pseudostratified
- Dirty necrosis
- Extracellular mucin



IHC Subtyping of Ampullary Adenocarcinoma

Study	Definition of subtype
<p>Ang DC, AJSP 2014</p> <p>Panel of CK20, CDX2, MUC1, and MUC2</p> <p>>25% staining considered +</p>	<p><u>Intestinal type:</u></p> <ul style="list-style-type: none">• CK20+ <u>or</u> CDX2+ <u>or</u> MUC2+ and MUC1 negative, or• CK20+, CDX2+ <u>and</u> MUC2+, Irrespective of MUC1 <p><u>Pancreaticobiliary type:</u></p> <ul style="list-style-type: none">• MUC1+, but CDX2- <u>and</u> MUC2-, Irrespective of CK20

By combining this schema with H&E evaluation, 92% of cases could be classified, including 75% of poorly differentiated and 69% of mixed types

Two-Stain Approach

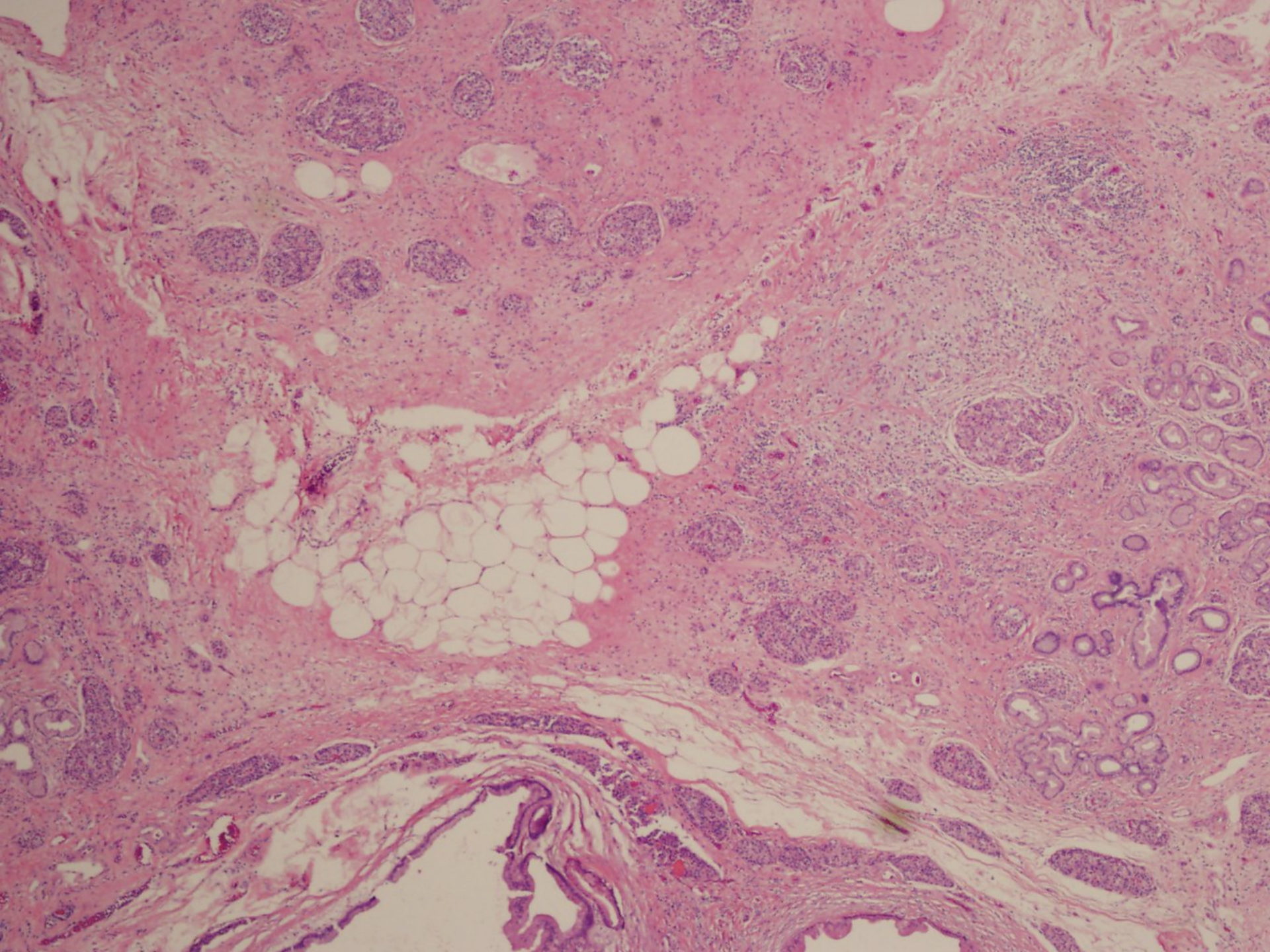
Studies	Definition of subtype
Scheuneman A, Br J Cancer 2015; Chang DK, J Clin Onc 2013 MUC1: any + CDX2: H-score >35%	<u>Pancreaticobiliary:</u> Histology, MUC1+, CDX2- <u>Intestinal type:</u> All others

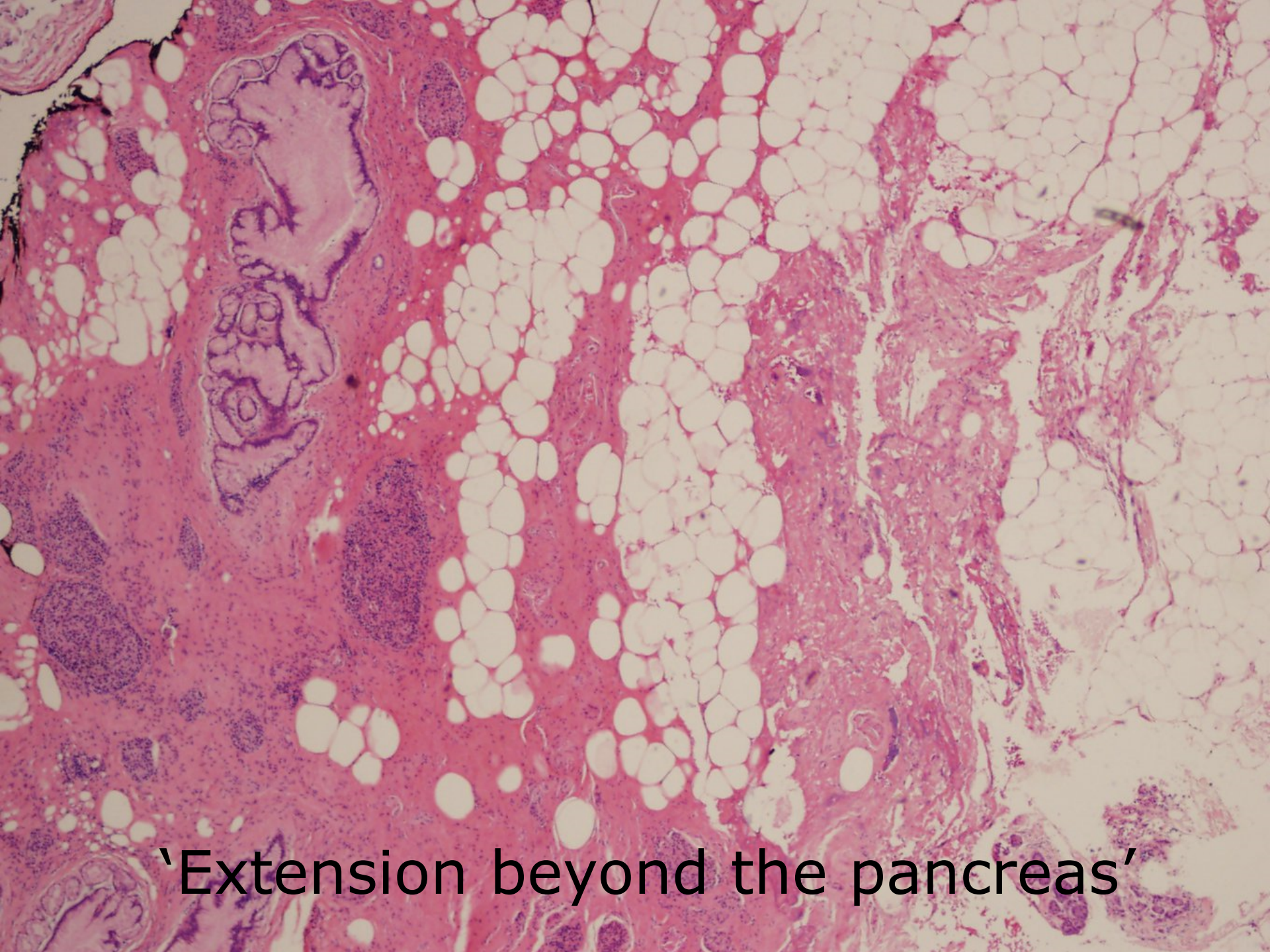
- Regardless of approach, 10-20% ambiguous
- Up to 40% of cases are mixed type, thus biopsies may not be representative

Ang DC, AJSP 2014; Scheuneman I, Br J Cancer 2015; Reid MD, Mod Pathol 2016; Perysinakis I, Int J Surg Pathol 2017

Pancreas: Problems in staging in AJCC 7th edition

T stage	Problems
T3 criteria	<ul style="list-style-type: none">- 'Extension beyond the pancreas' (peripancreatic tissue) not well defined- Approximately 95% of the cases, leaving only a handful of cases classifiable as T1/2, which makes this category invalid for practical purposes.
T1, T2, T3	<ul style="list-style-type: none">- Lack of correlation with outcome





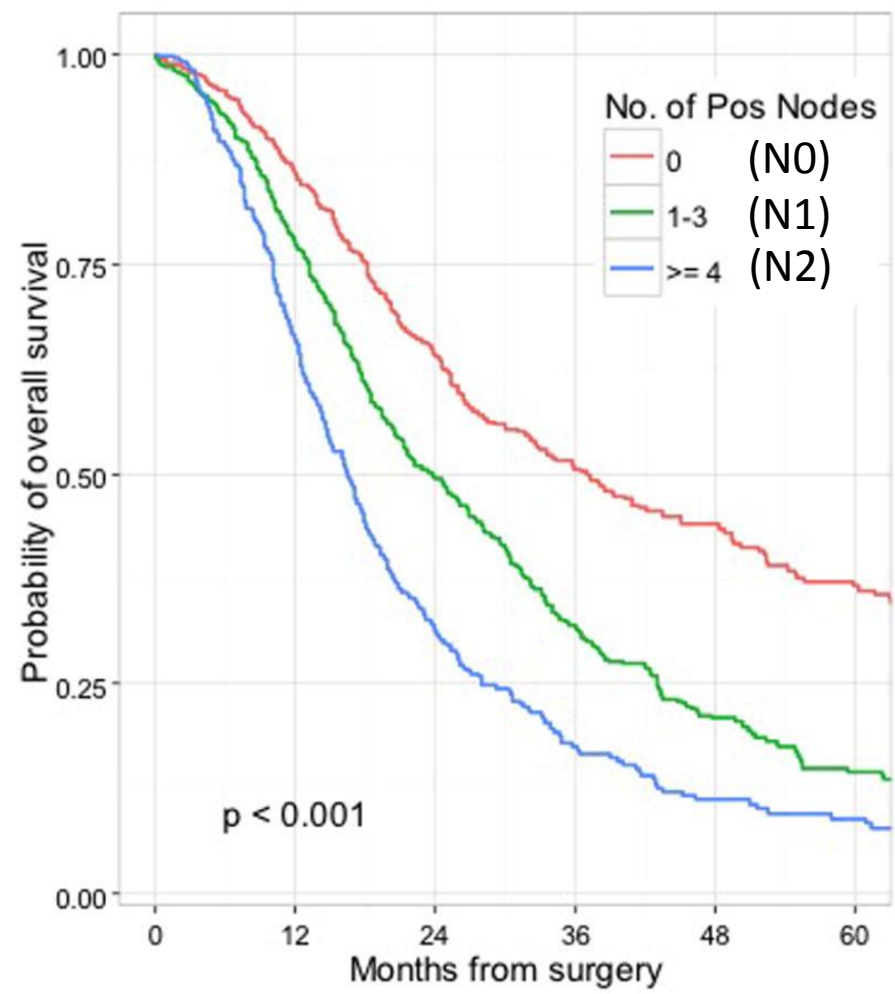
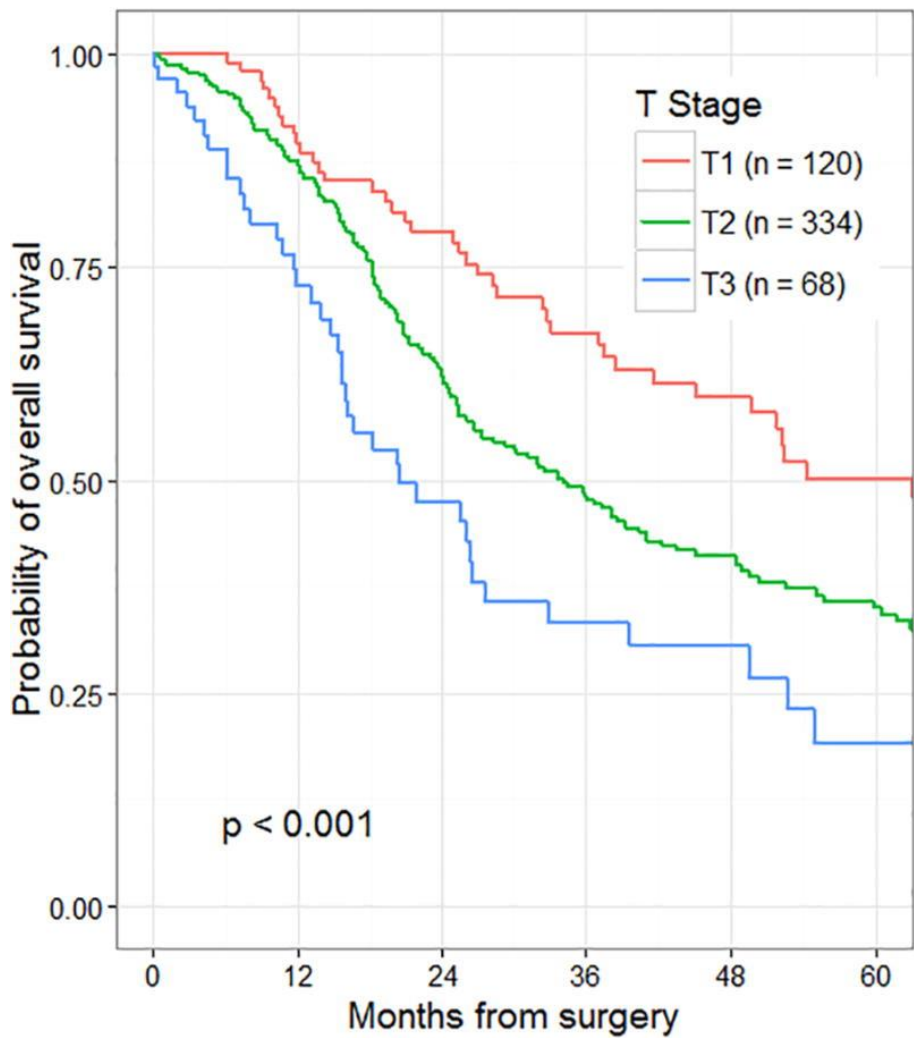
'Extension beyond the pancreas'

Pancreas: Problems in staging in AJCC 7th edition

T stage	Problems
T3 criteria	<ul style="list-style-type: none">- 'Extension beyond the pancreas' (peripancreatic tissue) not well defined- Approximately 95% of the cases, leaving only a handful of cases classifiable as T1/2, which makes this category invalid for practical purposes.
T1, T2, T3	<ul style="list-style-type: none">- Due to uneven staging groups, lack of correlation with outcome

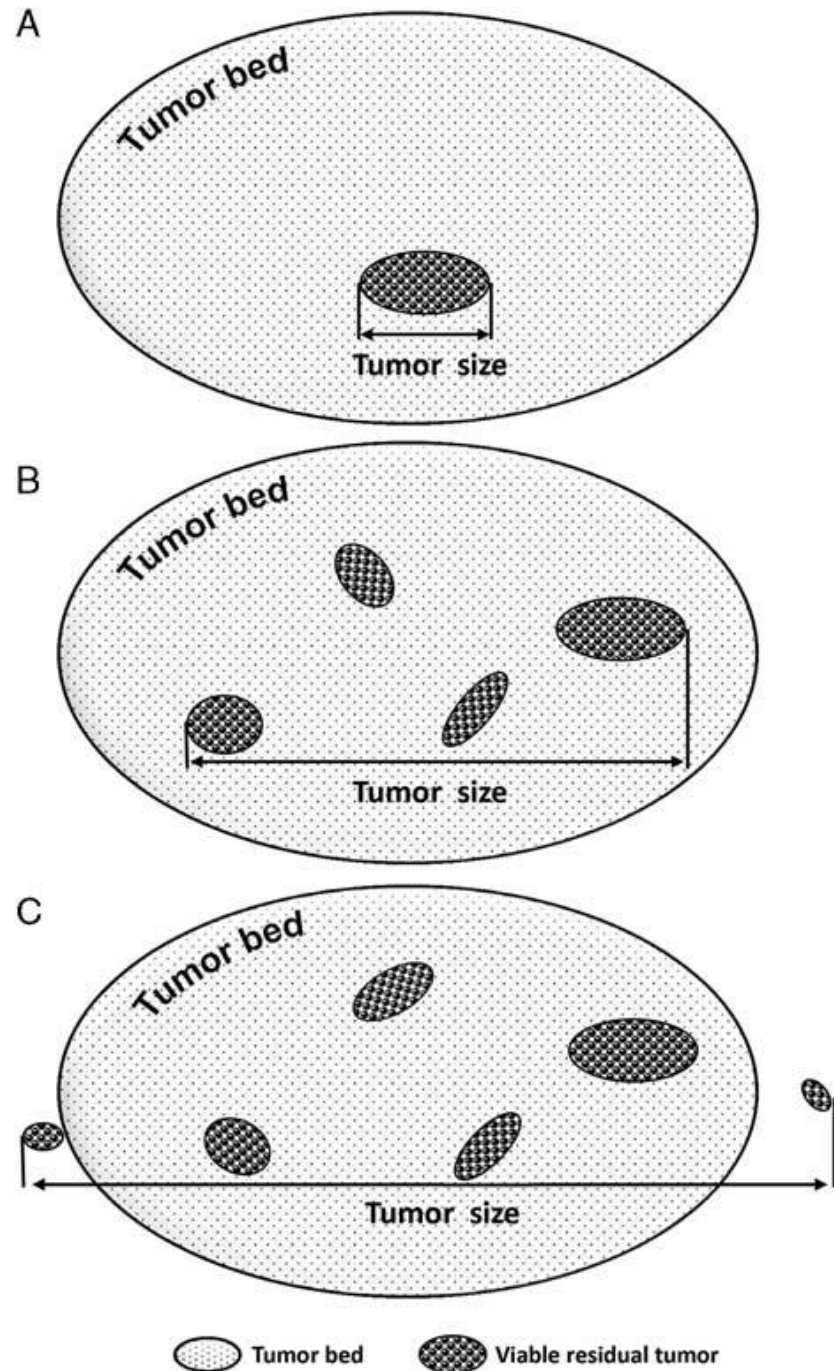
Pancreas: AJCC 8th edition

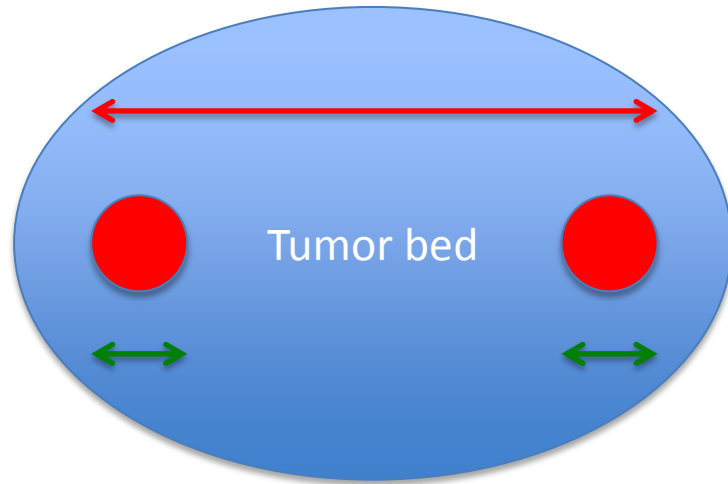
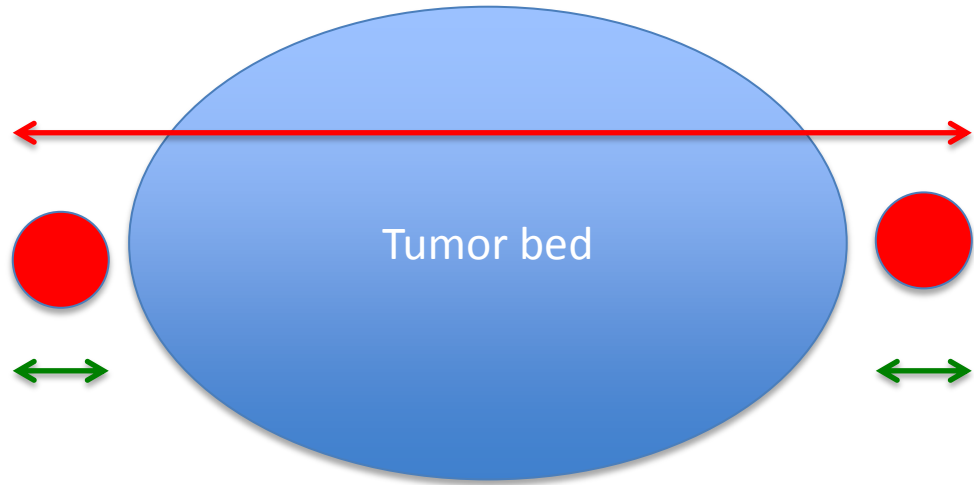
Change	Details
T1 subdivision	T1: Up to 2 cm - T1a: ≤ 0.5 cm - T1b: > 0.5 cm and < 1 cm - T1c: 1–2 cm
T2 and T3 based on size	T2: > 2 cm and ≤ 4 cm T3: > 4 cm Extrapancreatic extension is no longer part of the T-classification
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery (considered unresectable)
N categories	N1: Up to 3 LNs N2: 4 or more LNs



Size of tumor after neoadjuvant therapy

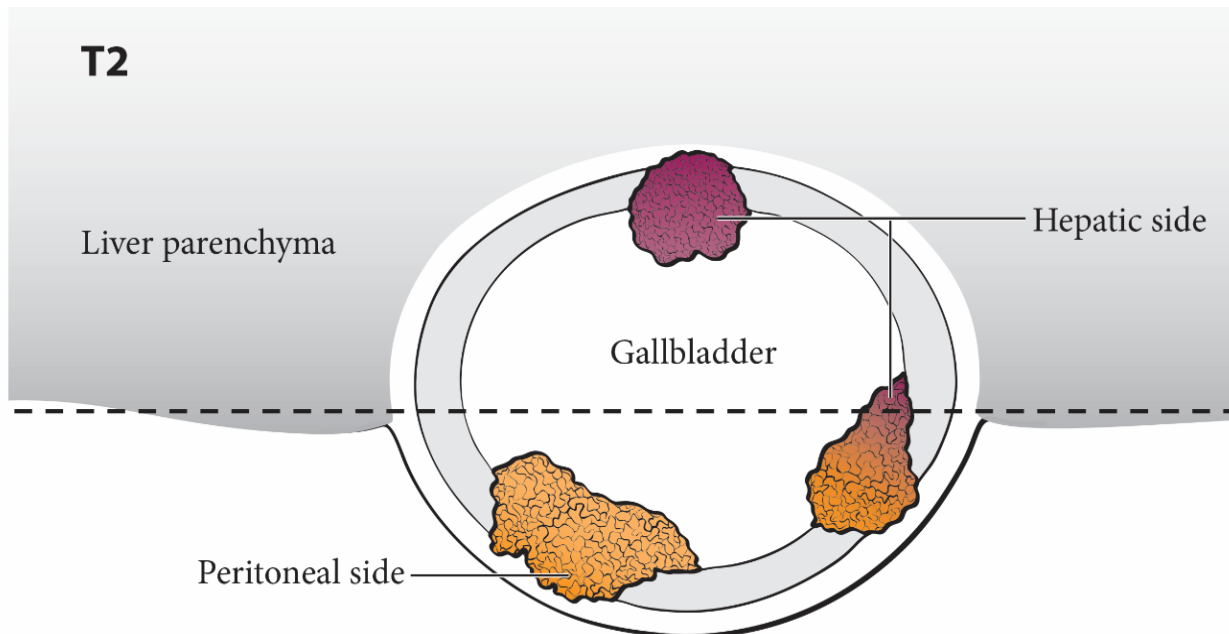
- Submit the entire tumor bed
- Measure viable tumor foci and add them, or
- Measure the largest dimension of the entire area involved by viable residual tumor, including intervening non-tumor areas



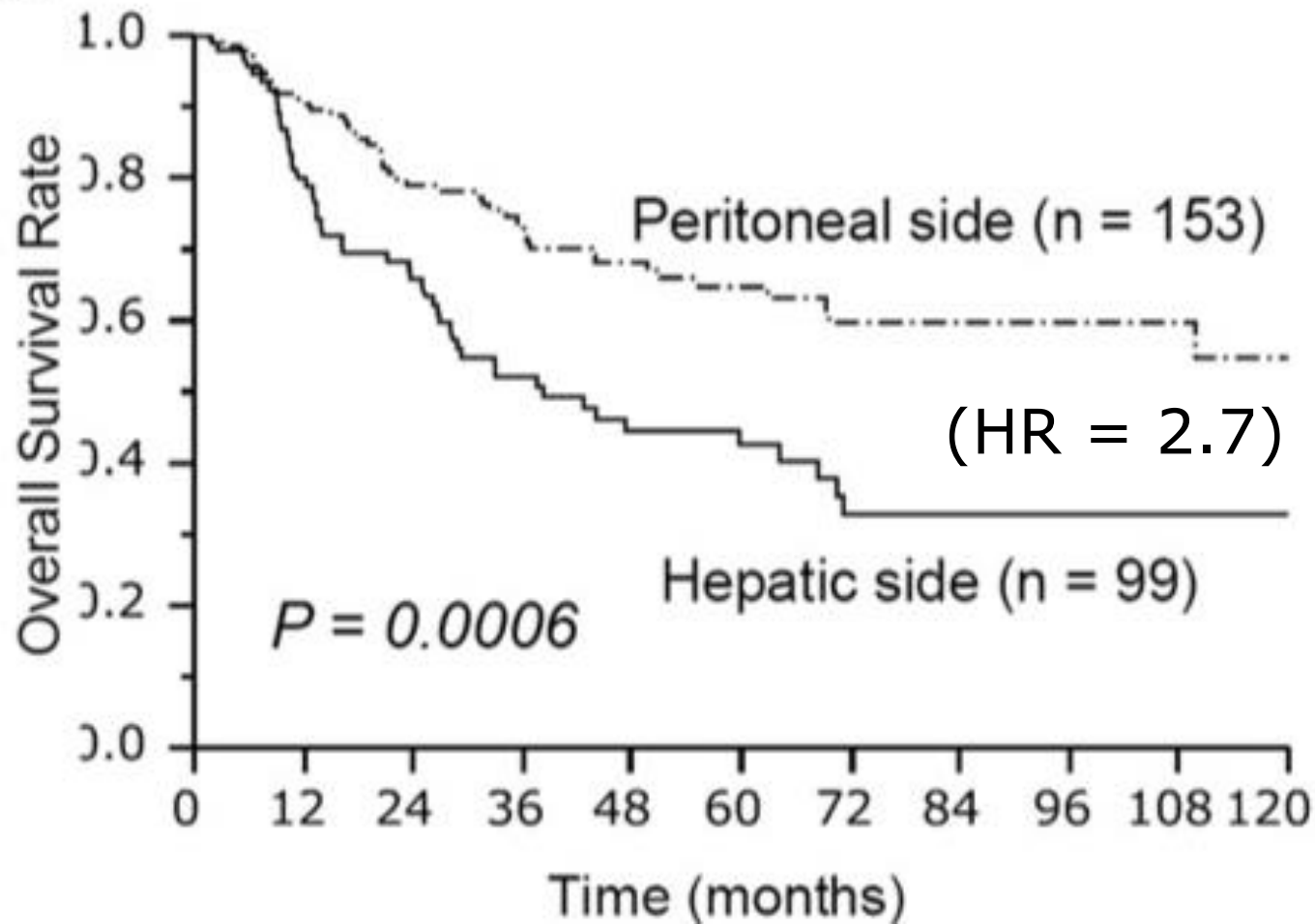


Gallbladder: AJCC 8th edition

Change	Details
Subdivision of T2	Tumor invading perimuscular connective tissue <ul style="list-style-type: none">- T2a: On the peritoneal side, without involvement of the serosa- T2b: On the hepatic side or both sides, with no extension into the liver
N categories	N1: Up to 3 LNs N2: 4 or more LNs



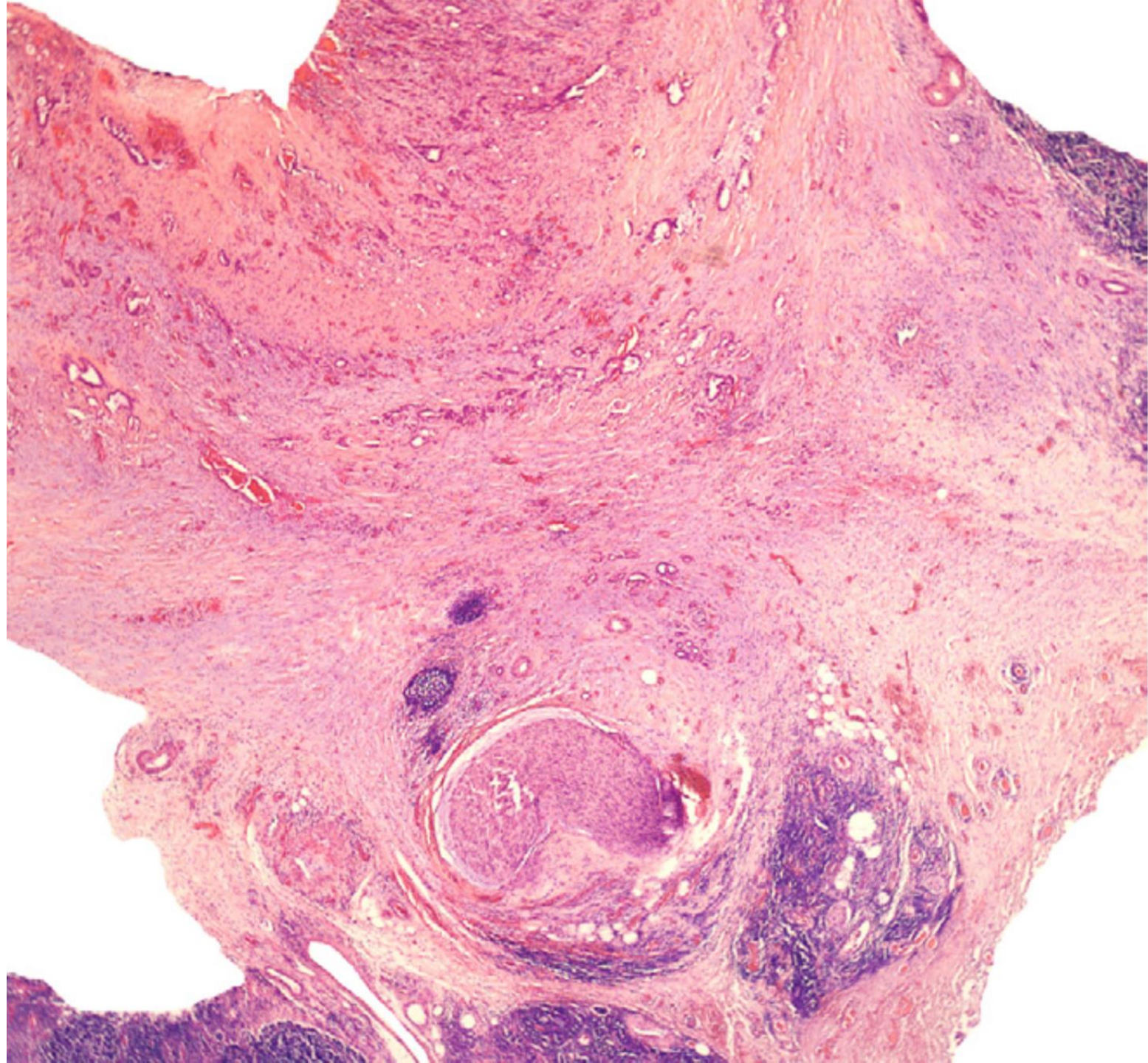
T2



The 5-year survival rate for T2 tumors on the hepatic side was worse (43%) than that on the peritoneal side (65%)

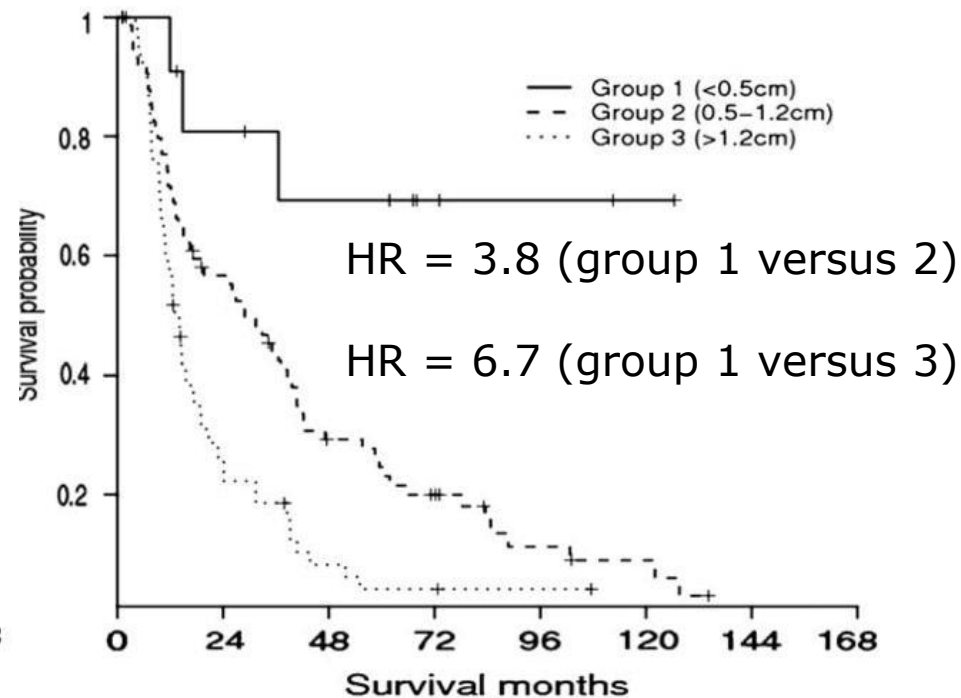
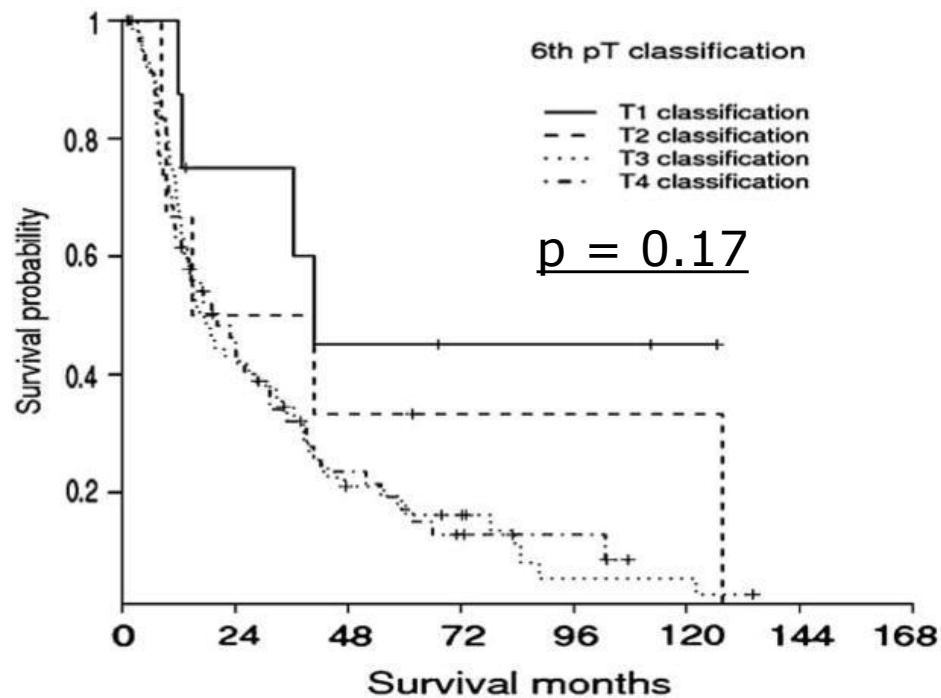
Distal Extrahepatic Bile Duct: Problems in staging in AJCC 7th edition

T stage	Problems
T1, T2	<ul style="list-style-type: none">- 'Extension beyond the wall of the bile duct' (T2) difficult to define- In the intrapancreatic distal bile duct cancers, the distinction between bile duct wall and pancreas may not be obvious- Lack of correlation with outcome

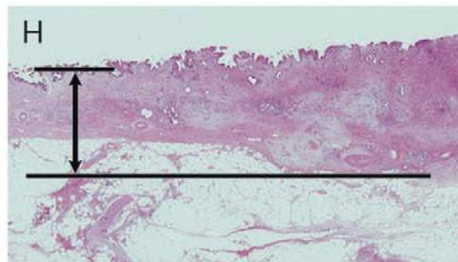
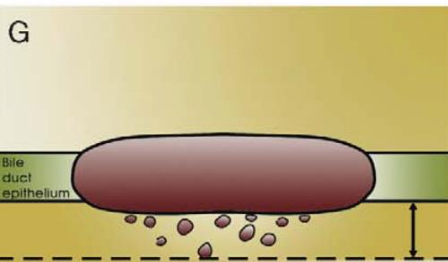
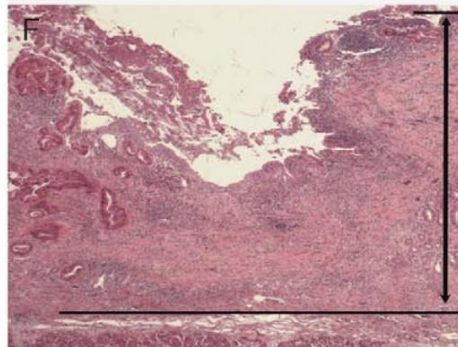
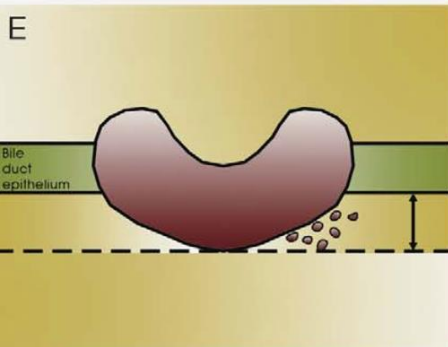
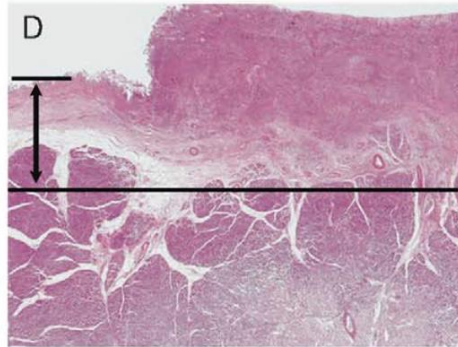
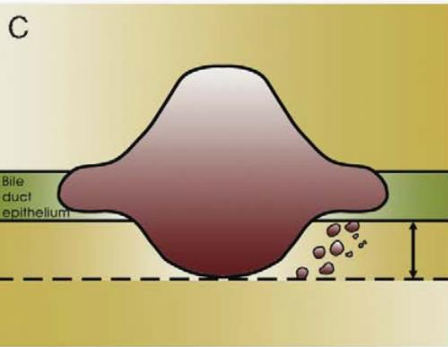
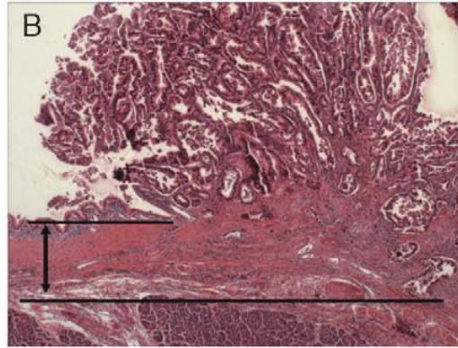
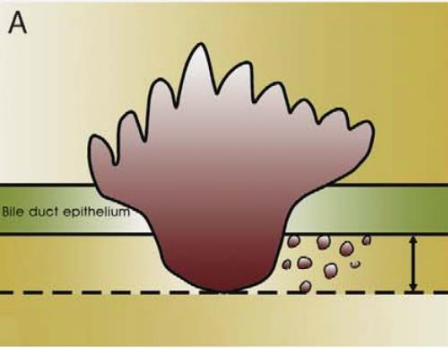


Distal Extrahepatic Bile Ducts: AJCC 8th edition

Change	Details
T1, T2, T3 based on measurement of tumor depth	T1: Tumor invades the bile duct wall with a depth <0.5 cm T2: 0.5-1.2 cm T3: >1.2 cm
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery
N categories	N1: Up to 3 LNs N2: 4 or more LNs



The 5-year survival rates of patients with T1, T2, and T3 were 69%, 22%, and 4%, respectively ($p < 0.0001$)



Depth of invasion is measured from the basal lamina of the adjacent normal bile duct epithelium to the deepest invasive tumor cells.

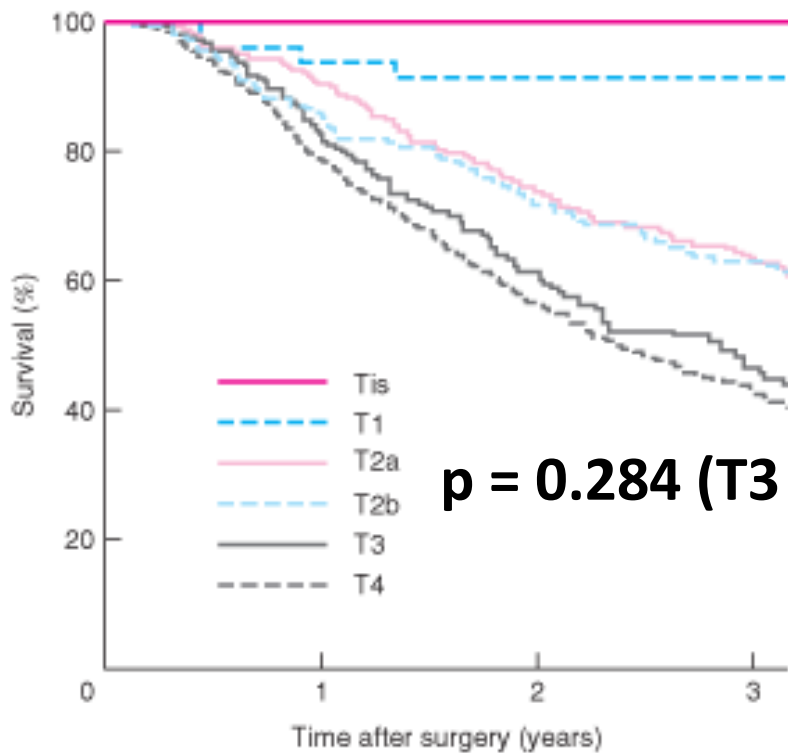
If the depth is difficult to determine, a best estimate is used.

Perihilar Bile Duct: Problems in staging in AJCC 7th edition

T stage	Problems
T1, T2	'Extension beyond the wall of the bile duct' difficult to define (T2)
T3, T4	Branches of portal vein or hepatic artery as well as primary and secondary biliary radicals are not definable by histologic or even gross examination

Perihilar Bile Ducts: AJCC 8th edition

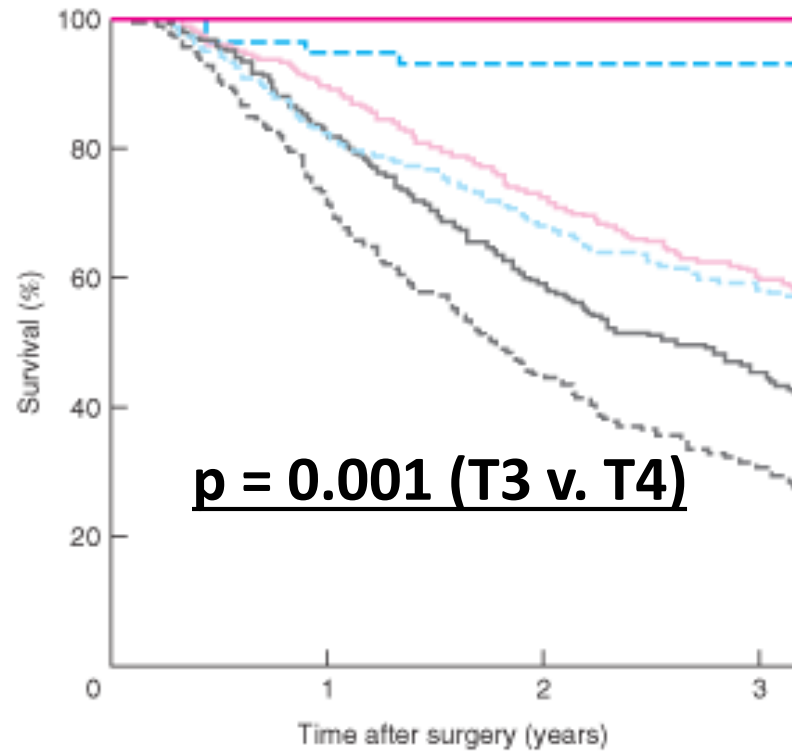
Change	Details
T4 redefined	Tumor invades the main portal vein or its branches bilaterally, or the common hepatic artery; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement Bilateral second-order biliary radical invasion has been removed
N categories	N1: Up to 3 LNs N2: 4 or more LNs



p = 0.284 (T3 v. T4)

No. at risk				
	0	1	2	3
Tis	6	5	4	3
T1	48	41	34	28
T2a	305	257	172	119
T2b	195	150	117	85
T3	214	157	96	54
T4	584	427	251	155

a UICC T classification



p = 0.001 (T3 v. T4)

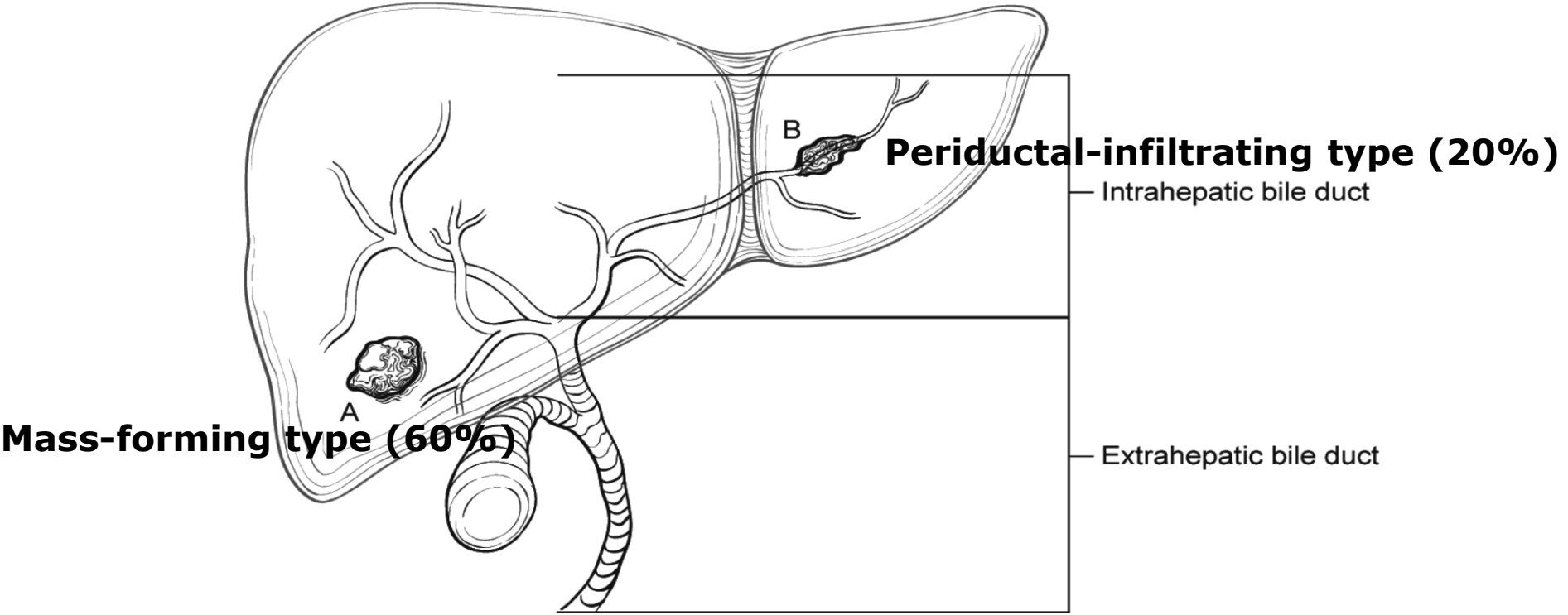
No. at risk				
	0	1	2	3
Tis	8	6	5	4
T1	58	51	41	34
T2a	425	354	237	159
T2b	318	239	170	119
T3	329	248	143	86
T4	214	139	78	42

b Proposed T classification

Removal of bilateral second-order biliary radical invasion from the T4 determinants enhances the prognostic ability of the staging system

Intrahepatic Bile Ducts: AJCC 8th edition

Change	Details
T1 subdivision based on size	T1a: Solitary tumor ≤ 5 cm without vascular invasion T1b: >5 cm without vascular invasion
T2 redefined	Solitary tumor with intrahepatic vascular invasion, or multiple tumors, with or without vascular invasion
T3 redefined	Tumor perforating the visceral peritoneum
T4 redefined	Tumor involving local extrahepatic structures (such as colon, duodenum, stomach, common bile duct, retrohepatic vena cava, hepatoduodenal ligament, abdominal wall, and diaphragm) by direct invasion Due to its unclear association with outcome, periductal growth pattern is no longer part of the T classification.

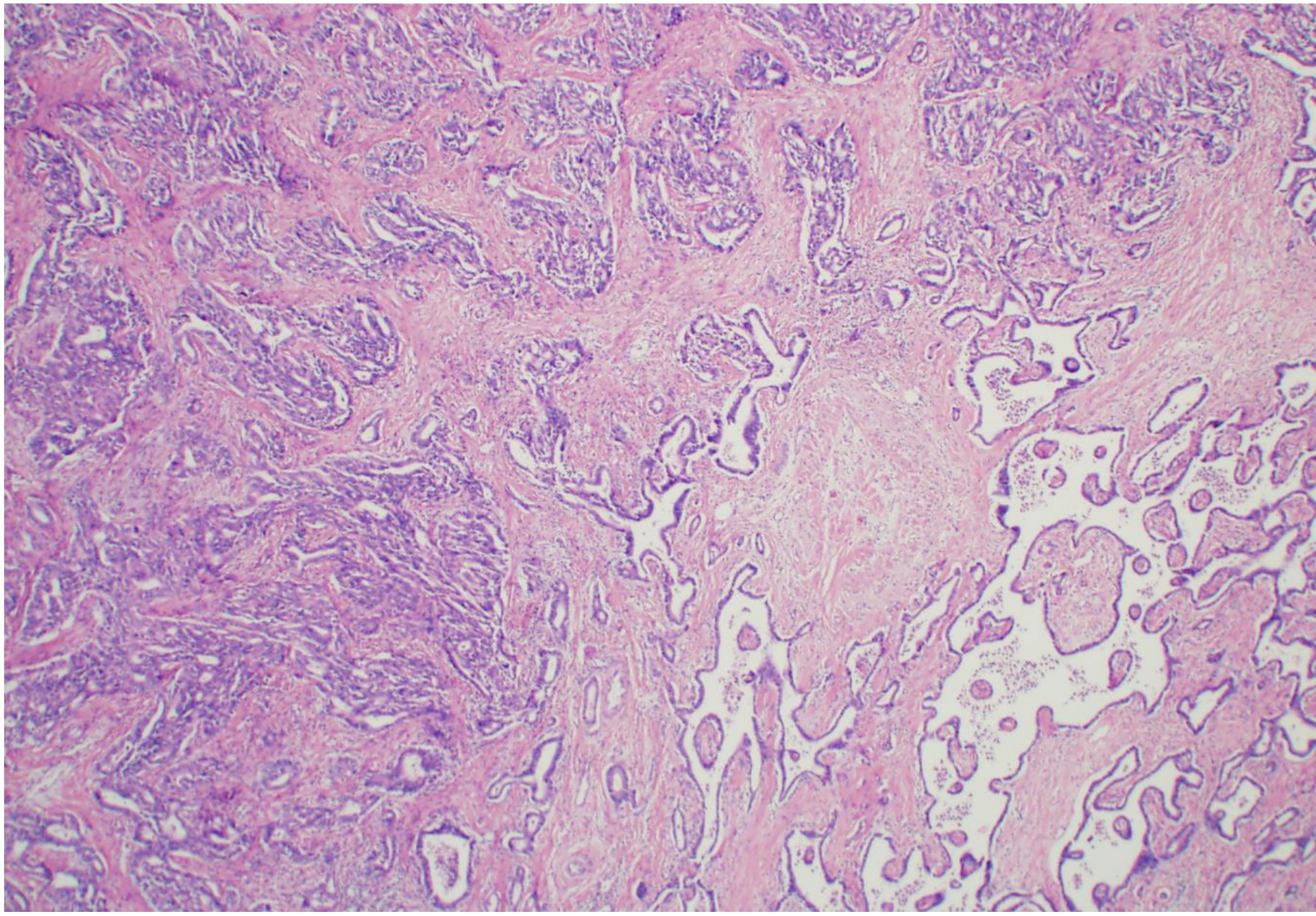


Earlier studies suggested a poor outcome for periductal infiltrating (PI) type, while some recent studies have suggested a relatively favorable prognosis compared to the mass-forming type (MF).

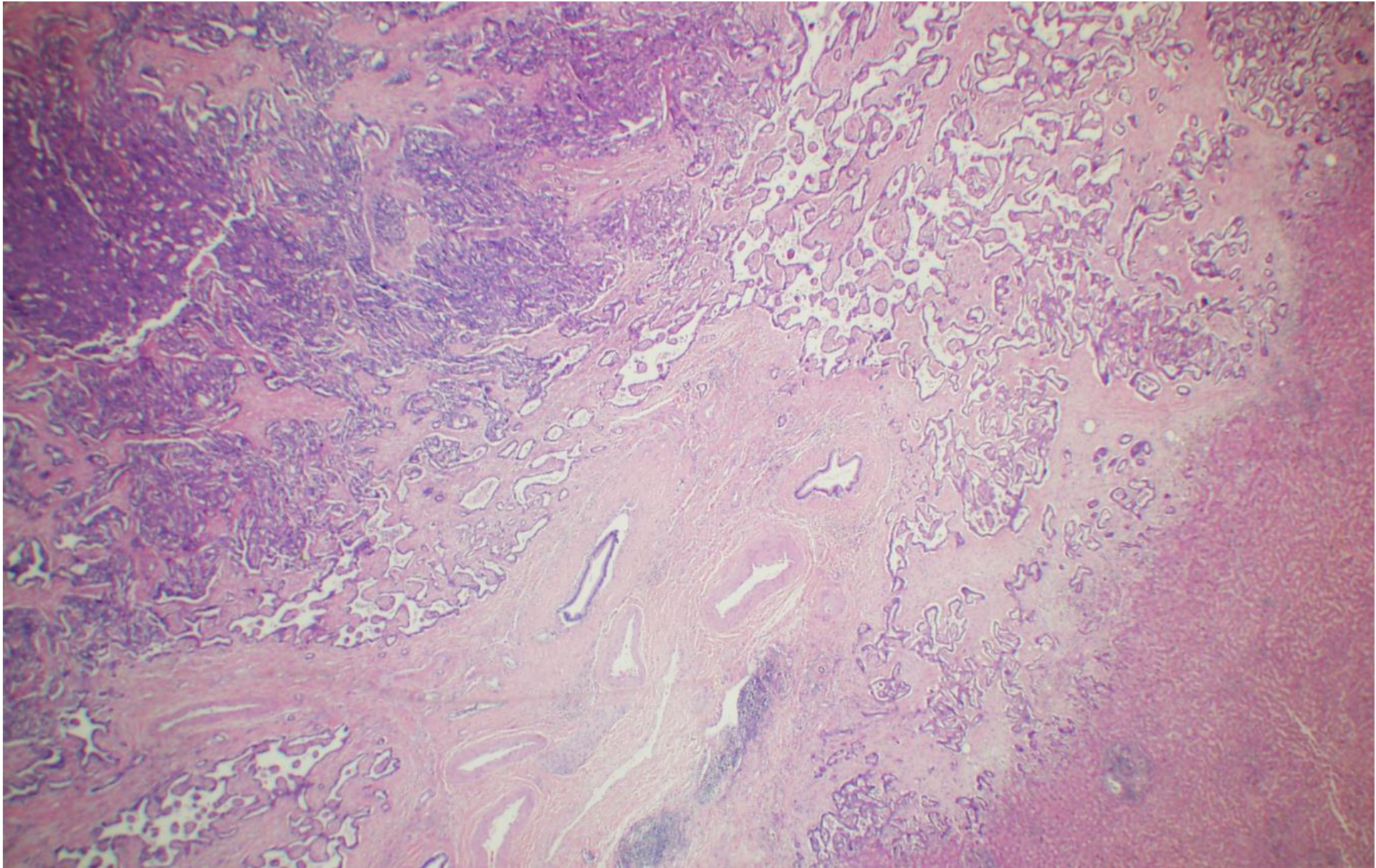
In one study, the 5-year survival rates after surgery for the patients with the PI type and the MF type without hilar invasion were 85.7% and 41.2%, respectively ($p = 0.032$).

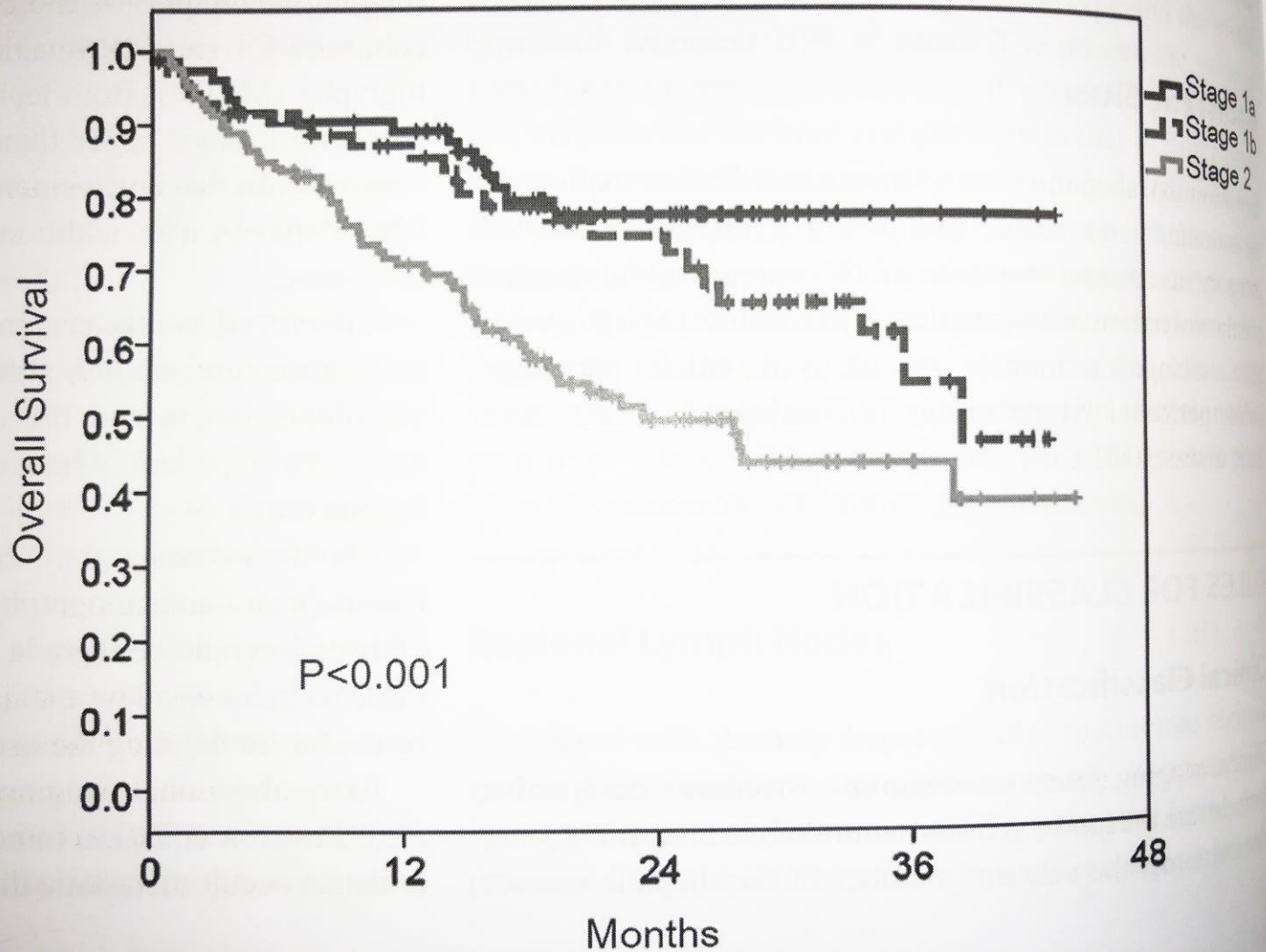
Uno M, Surg Today 2012 and Imai K, Hepatogastroenterology 2010

Cholangiocarcinoma, 3 cm, no VI → T1a



Periductal growth pattern is no longer part of the T-classification





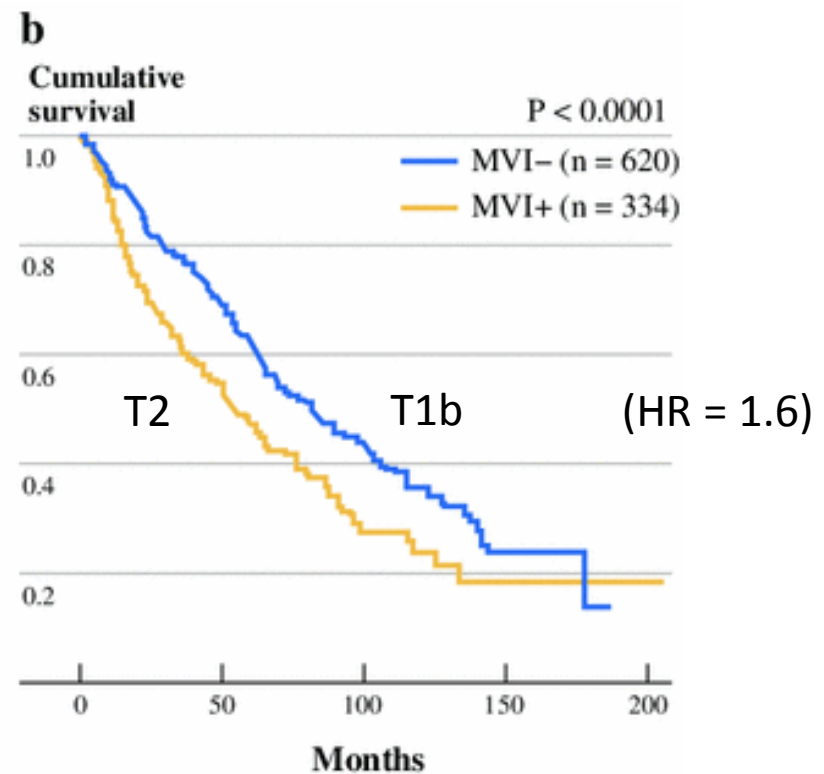
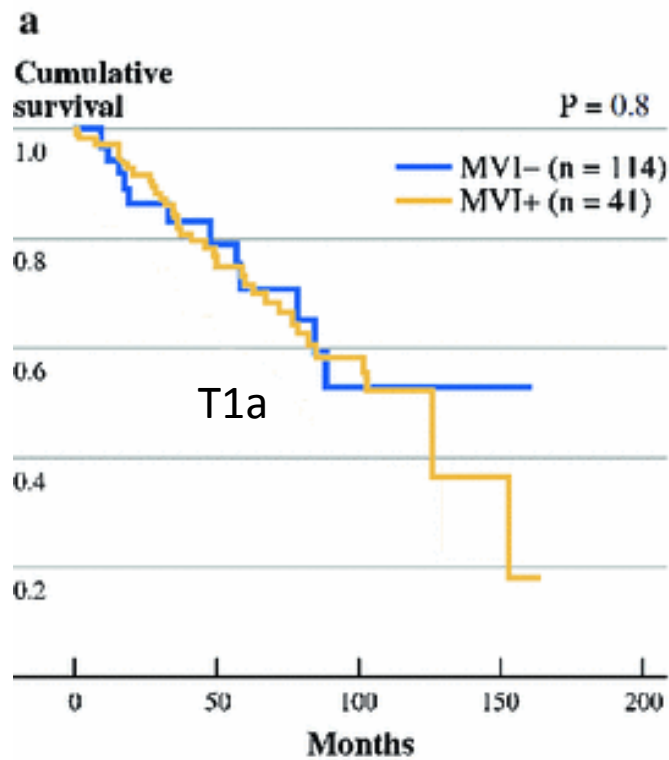
There are significant prognostic differences among T1a, T1b, and T2 ($p < 0.001$) based on National Cancer Database registry data

Important Considerations

- Satellite nodules and intrahepatic metastases are considered to be multiple tumors (at least T2).
- For combined HCC-cholangiocarcinoma, the size of the entire tumor is used for staging.

Liver: AJCC 8th edition

Change	Details
T1 subdivision	T1a: Solitary tumor ≤ 2 cm, regardless of vascular invasion T1b: Solitary tumor > 2 cm without vascular invasion
T2 redefined	Solitary tumor > 2 cm with vascular invasion , or multiple tumors, none > 5 cm
T3 redefined	Multiple tumors, at least one of which is > 5 cm
T4 redefined	Single tumor or multiple tumors of any size involving a major branch of the portal vein (right or left), hepatic vein (right, middle, or left), or hepatic artery (right or left), or tumor(s) with direct invasion of adjacent organs other than the gallbladder (including diaphragm) or with perforation of visceral peritoneum



(a) Tumor size 0–2 cm.

(b) Tumor size >2 cm

In patients with HCC up to 2 cm (T1), long-term survival was not influenced by the presence of MVI ($p = 0.8$). However, in patients with HCC larger than 2 cm (T2), patients with MVI had significantly worse survival ($p < 0.0001$)

Important Considerations

- Satellite nodules and intrahepatic metastases are considered to be multiple tumors (at least T2).
- For treated tumors, especially for tumors up to 2 cm, the entire tumor should be examined microscopically.
- For larger tumors, an additional section for each 1 cm is recommended, with additional sampling as necessary from the periphery of the tumor or areas that appear viable.
- Only size of viable tumor should be used for staging.

Thank you!

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