

Staging updates in AJCC 8th ed Colorectal and selected GI sites

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Outline

- **Updates in Colorectal cancer**

 - Definition of T4a

 - Tumor deposits

 - Isolated tumor cells

 - Adenocarcinoma arising in a polyp

- **Selected other updates**

 - Liver, pancreas, gallbladder, ampulla

Definition of pT4

AJCC 8th edition

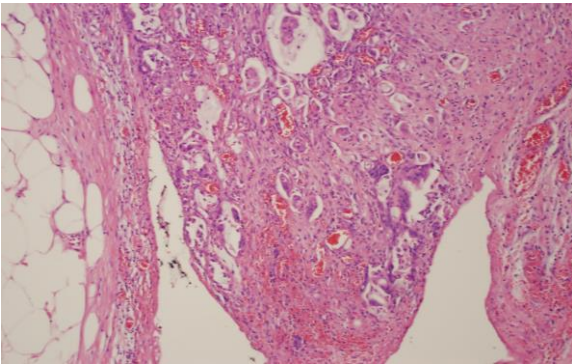
T category	Definition
pT4a	Tumor invades through the visceral peritoneum
pT4b	Tumor directly invades other organs or structures

Criteria for serosal involvement

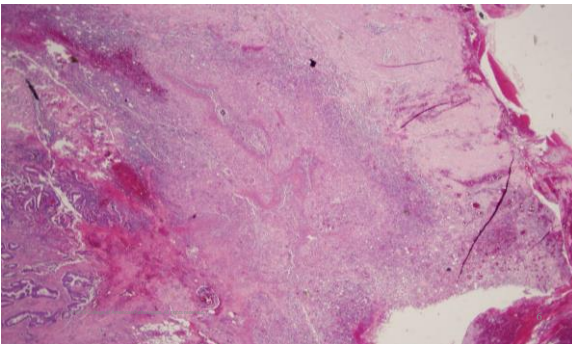
- Tumor directly extends to involve serosal surface
- Tumor continuous with serosal surface through perforation (inflammatory reaction)

Shepherd, Gastroentrol 1997
Peterson, Gut 2002
Ludeman, Histopathol 2005
Stewart, Histopathol 2006

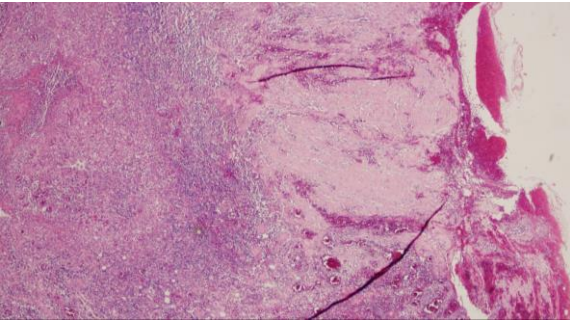
Tumor directly extends to serosal surface



Colonic adenocarcinoma with perforation



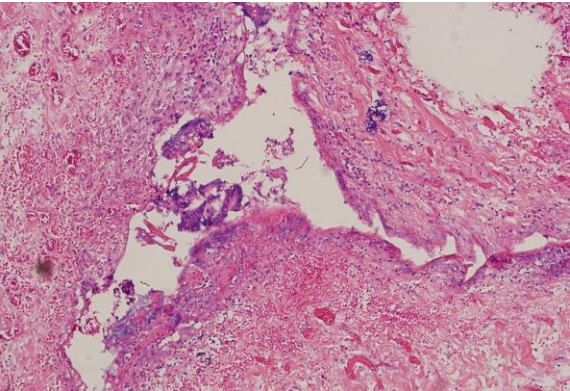
Perforation: tumor continuous with serosal surface through inflammatory reaction



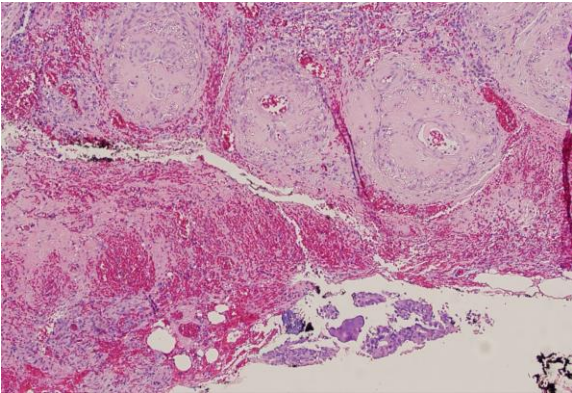
T4a: challenges

- Free floating tumor cells
- Tumor within 1 mm of serosal surface
- Acellular mucin on serosal surface
- Elastic stain

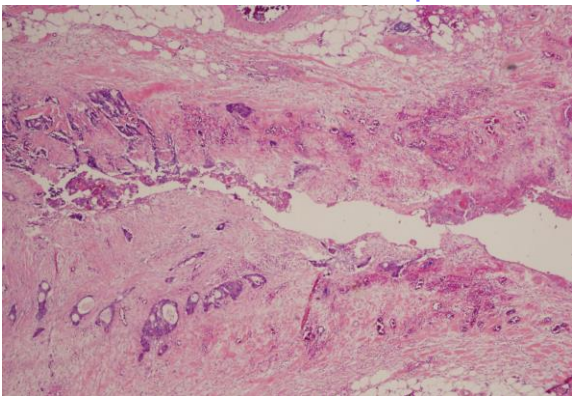
Free floating tumor cells in clefts and mesothelial 'ulceration'



Disrupted serosal surface with free floating tumor cells



Additional sections: obvious pT4a



Tumor ≤ 1 mm with reaction

Study	Results
Panarelli, AJSP 2014	Positive cytology from serosal surface of specimens: 46% pT3 ≤ 1 mm from serosal surface 55% of pT4a Peritoneal recurrence: 11% in pT3 ≤ 1 mm 18% in pT4a
-Shepherd, Gastroenterology 1997 -Lennon, AJCP 2003 -Douard, AJCP 2004	Peritoneal/pelvic recurrence only with Direct invasion of serosal surface Free floating tumor cells

Not T4a (AJCC 8th)

- Tumor close to serosal surface with serosal reaction
- Acellular mucin

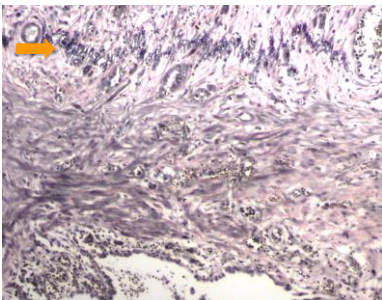
Deeper levels, additional sections

Elastic stain

- Submesothelial elastic lamina
- Involvement associated with poor prognosis in some studies

Shinto, Dis Col Rectum 2004
Kojima, AJSP 2010
Grin, Hum Pathol 2013

Elastic stain



- Difficult to interpret
- Elastic lamina discontinuous
 - Retracted by desmoplasia
 - Variable distance from mesothelium

pT4a: clinical significance

- Prognosis
- Peritoneal recurrence
- Choice of therapy

NCCN guidelines: High risk feature in stage II
Likely adjuvant chemotherapy
Possible local radiation or intra-peritoneal chemo in the future

ASCO GI meeting 2017

Home • Meeting Library • Virtual Meeting • 2017 Gastrointestinal Cancers Symposium
Breakout Session: Pro/Con-Hyperthermic Intraperitoneal Chemotherapy for Metastatic Colorectal Cancer

General Session
Cancers of the Colon, Rectum, and Anus Track
2017 Gastrointestinal Cancers Symposium



Pro
Hans J. Schil, MD
Speaker

Watch Video



Con
David P. Ryan, MD
Speaker

Watch Video

- Some but not all studies: advocated HIPEC
- No clear guidelines

Baratti, Ann Surg Oncol 2016
Elias, J Clin Oncol 2009

Outline

- Updates in Colorectal cancer

Definition of T4a
Tumor deposits
Isolated tumor cells

Tumor deposits: AJCC 7th Edition

- Discrete foci of tumor in pericolic fat
- No evidence of residual lymph node tissue
- N1c in the absence of nodal involvement

Tumor Deposits Reasons for discrepancy

- Minimum distance from invasive front
- Minimum size
- Venous invasion/perineural invasion or tumor deposit
- Tumor deposit after neoadjuvant therapy

Challenges in Interpretation

Distance from Invasive Front	Study	Study	Size of Tumor Deposit
>2 mm	Ueno, Am J Surg 2014	Nagtegaal, J Clin Oncol 2011	<3 mm
>5 mm	Nagayoshi, Dis Colon Rectum 2014	Nagayoshi, Dis Col Rectum 2014	Only if grossly identified
>10 mm	Gopal, Mod Pathol 2014	Lin, Oncol Targets 2015	
		Other studies	Criteria not specified

AJCC definition

- No minimum distance
- No minimum size

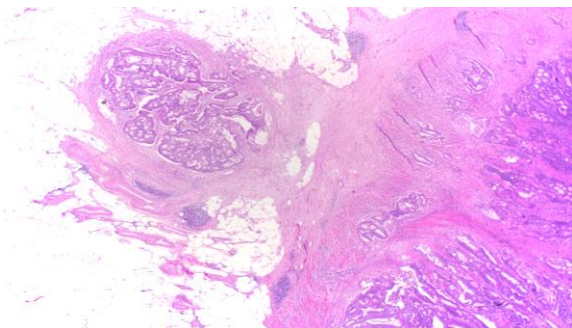
Venous invasion or tumor deposit

	VI with extravascular spread	VI confined to vessel wall
Goldstein (2000)	Tumor deposit	
Lin (2015) Nagoyoshi (2014) Ueno (2011)	Tumor Deposit	Vascular invasion

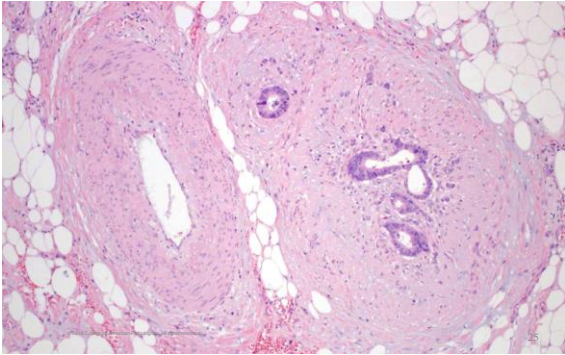
Tumor deposits: AJCC 8th Edition

- Tumor focus in the pericolic/perirectal fat or in adjacent mesentery within the lymph drainage area of the primary tumor, but without identifiable lymph node or vascular structure
- Vessel wall or its remnant (H&E, elastic, or any other stain): vascular (venous) invasion
- Tumor focus in or around a large nerve: PNI

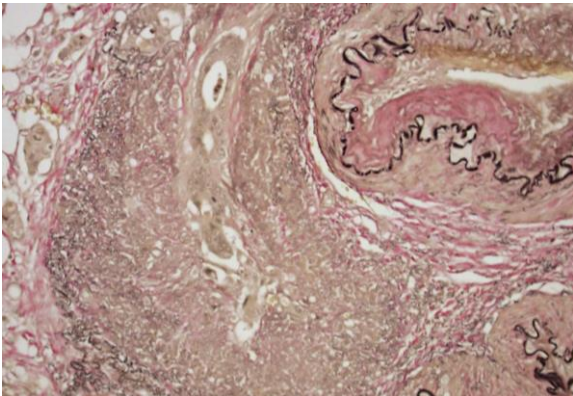
'Protruding Tongue' sign



'Orphan Artery' sign

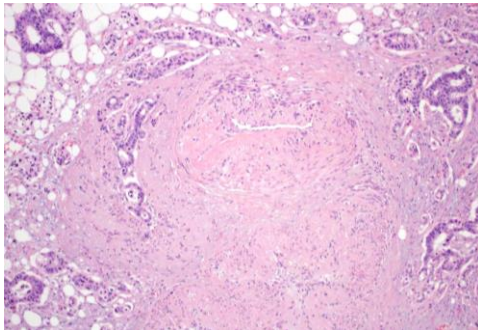


Elastic stain: venous invasion



T3 tumor, negative lymph nodes

T3N1c: stage III or T3N0 with V1: Stage II



CRC: Extramural venous invasion

- Independent predictor of poor outcome
- NCCN: High risk feature in stage II disease
- Likely to receive chemotherapy

Recommendations:

- Record separately from small vessel invasion
- Consider elastic stain

Messenger, J Clin Pathol 2011
Kirsch, Human Pathol 2012

Challenges in Interpretation

- Minimum distance from invasive front
- Minimum size
- Replaced lymph node or tumor deposit
- Venous invasion/perineural invasion or tumor deposit
- Tumor deposit after neoadjuvant therapy

Tumor deposit after therapy

- Residual primary tumor can be mistakenly classified as N1c
- Proximity to areas of fibrosis or acellular mucin favors residual primary tumor
- Elastic stain: venous invasion

Nagtegaal, J Clin Oncol 2011

N1c in practice

Lymph node	Thick capsule Subcapsular sinus Rim of lymphocytes
Venous invasion	Accompanying artery Elastic stain
Perineural invasion	Large nerves
Tumor deposit	No remnant lymph node, large nerve or vein

Do not add tumor deposits and lymph nodes for

- N category
- Assessing adequacy of LN dissection

Rock, Arch Path Lab Med, 2014
Liu/Kakar, USCAP 2016

Isolated tumor cells

Size of nodal metastasis	AJCC 7 th edition
0.2 to 2 mm	Micrometastasis pN1mi
Less than 0.2 mm	Isolated tumor cells (ITC) pN0 (i+) pN0 (mol+)

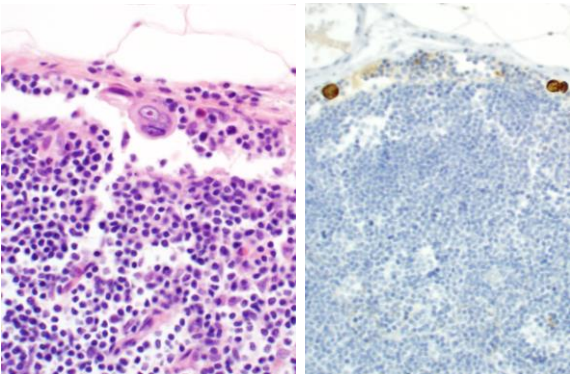
Isolated tumor cells, micrometastasis

Study	Design	Conclusion
Sloothak, Eur J Surg Oncol 2014	Meta-analysis 5 studies	-Increased recurrence with micrometastasis -No increased risk with ITC
Rahbari, JCO 2012	Meta-analysis 39 studies	-Increased recurrence with micrometastasis -Insufficient data for ITC
Mescoli, JCO 2012	Keratin in N0, n=312	-Higher relapse with ITC (14% vs. 5%)
Protic, J Am Coll Surg 2015	Keratin in N0, n=312 Prospective	-Higher relapse with ITC (17% vs. 3%) -T3 and T4 (not T1 and T2)
Greenon, Cancer 1994	Keratin in N0, n=50	-Higher relapse with ITC (43% vs. 3%)

AJCC 8th edition

Size of nodal metastasis	AJCC 8 th edition
0.2 to 2 mm	Use pN1 pN1mi not necessary
Less than 0.2 mm	Use N0 No definite recommendation for using N0(i+)

Isolated tumor cells



Adenocarcinoma in polyp

AJCC 8th edition: definitions clarified

- Intramucosal adenocarcinoma (Tis)
Not beyond muscularis mucosa
- Invasive adenocarcinoma (T1 or beyond)
Submucosa or beyond

Tis and T1 in practice

- Clarify in report

Intramucosal adenocarcinoma is Tis and has virtually no propensity for LN mets

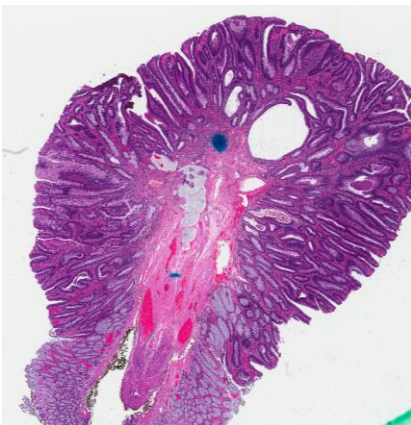
- T1 adenocarcinoma in polyp

Include prognostic factors to enable decision about resection

Invasive adenocarcinoma (T1) in polyp

Indications for colectomy

Prognostic features
Grade: poor differentiation
Lymphovascular: present
Margin: ≤ 1 mm
Depth of submucosal invasion
Tumor budding



Pedunculated polyp: Haggitt levels

Level 1: Head

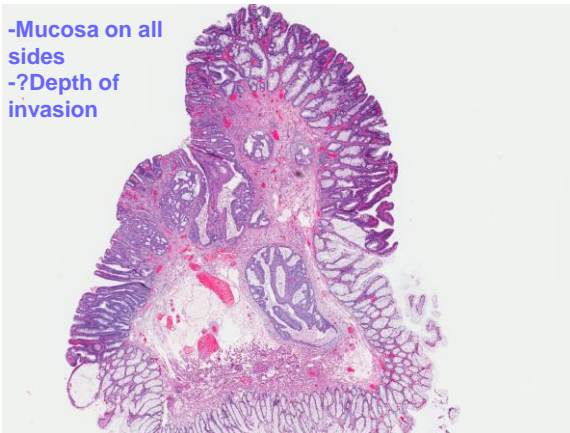
Level 2: Neck

Level 3: Stalk

Level 4: Beyond stalk

Kikuchi levels SM1, SM2 and SM3

- Difficult to judge depth in absence of muscularis propria
- Measure depth from base of muscularis mucosa: >1 mm is a high risk feature



Invasive adenocarcinoma (T1) in polyp Indications for colectomy

Prognostic features
Grade: poor differentiation
Lymphovascular: present
Margin: ≤ 1 mm
Depth of submucosal invasion
Tumor budding

Tumor budding

- Individual or small discrete cell clusters (<5 cells) at the invasive edge
- Independent adverse prognostic factor
 - Adjuvant therapy in stage II
 - Colectomy for malignant polyps
- Recommended:
 - UICC, ADASP, CAP, UK Royal College
 - Not included in NCCN

Steering Committee

- Prof. Gian Carlo Ghossein, MD, Professor of Pathology, Carcinoma/Medical Center, Switzerland
- Dr. Heather Dawson, MD, Professor of Pathology, University of Bern, Switzerland
- Prof. Richard Kirsch, MD, Department of Laboratory Medicine and Pathology, Mount Sinai Hospital, University of Toronto, Canada
- Prof. Alessandro Lugli, MD, Professor of Pathology, University of Bern, Switzerland
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- Prof. Ino Zivcec, PhD, Professor of Pathology, University of Bern, Switzerland

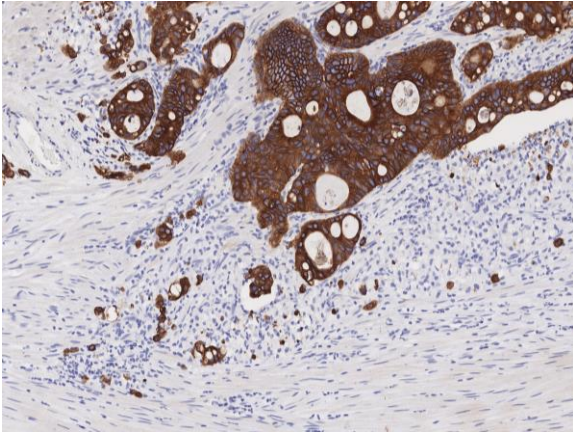
Participants

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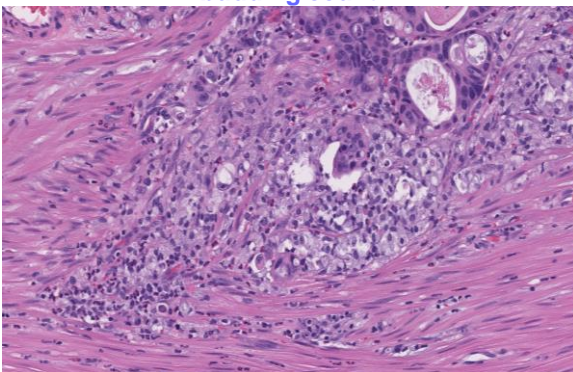
Consensus statements

Counting tumor buds

- Tumor budding is counted on H&E
- Use of cytokeratin**
- Most of the data is based on H&E stain
 - Can increase tumor bud counts 3x
 - Can use it in challenging cases (obscuring inflammation), but final count should be done on H&E



Go back to H&E stain for budding count



Consensus statements
Counting tumor buds

- **The hot spot method (single field at the invasive front, size 0.785 mm²) is recommended**
 - Choose a 'hotspot'
 - Count in 20x field
 - Apply appropriate correction factor for your microscope

Conversion table

Eyepiece FN Diameter (mm)	Objective Magnification: 20x			
	Eyepiece FN Radius (mm)	Specimen FN radius (mm)	Specimen Area (mm ²)	Normalization Factor
18	9.0	0.450	0.636	0.810
19	9.5	0.475	0.709	0.903
20	10.0	0.500	0.785	1.000
21	10.5	0.525	0.866	1.103
22	11.0	0.550	0.950	1.210
23	11.5	0.575	1.039	1.323
24	12.0	0.600	1.131	1.440
25	12.5	0.625	1.227	1.563
26	13.0	0.650	1.327	1.690

Consensus statements

Counting tumor buds

- A three-tier system should be used along with the budding count in order to facilitate risk stratification in CRC

Tumor budding score (0.785 mm ²)	
Low	0-4
Intermediate	5-9
High	≥10

Other changes: CAP protocol

Microsatellite instability

- Morphologic features omitted
- Universal testing recommended
- MMR immunohistochemistry or PCR

NCCN guidelines
EGAPP guidelines, Nat Genetics, 2009

Outline

- Updates in Colorectal cancer

 - Definition of T4a

 - Tumor deposits

 - Isolated tumor cells

- Selected other updates

 - Pancreas, gallbladder, ampulla

Ampulla: staging challenges

Location

- Intra-ampullary

- Peri-ampullary

Histologic subtype

- Pancreaticobiliary

- Intestinal

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 more than 0.5 cm into the pancreas or extends into peripancreatic or periduodenal tissue or duodenal serosa

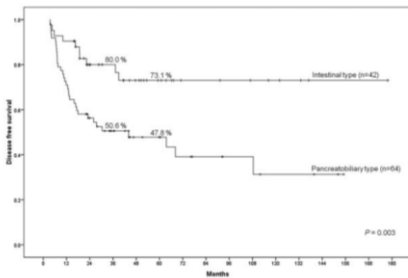
Adsay, Semin Diagn Pathol 2012

Ampulla

Change	Details
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, irrespective of size

Adsay, Semin Diagn Pathol 2012

Ampullary adenocarcinoma Pancreaticobiliary vs intestinal

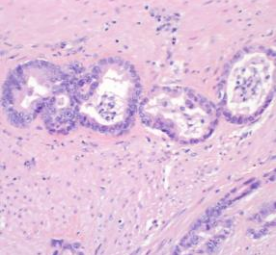
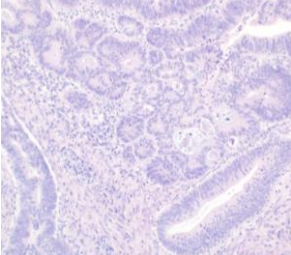


Kim, J Surg Oncol 2012

AJCC 8th edition: Ampulla

Recommendation

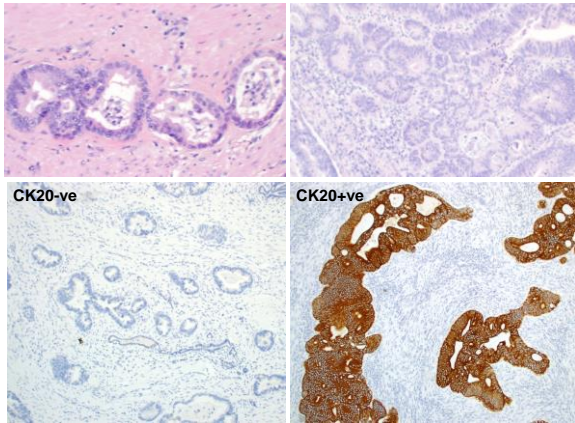
- Histologic subtypes should be characterized for patient care
- May help guide the use of adjuvant therapy
Gemcitabine-based (pancreaticobiliary) vs.
5-FU based (gastrointestinal)

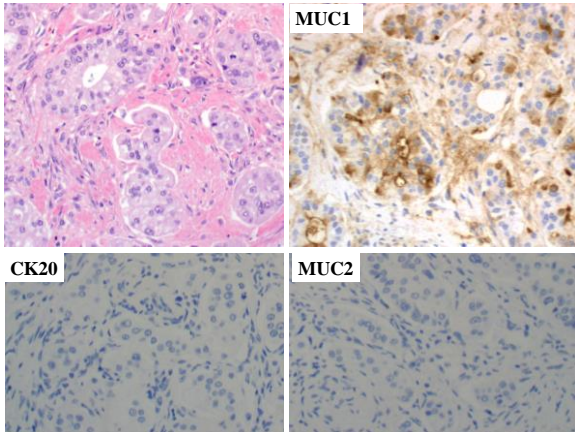
Pancreaticobiliary	Intestinal
-Rounded, cuboidal to low columnar -No pseudostratification -Marked variation in size shape -Desmoplastic stroma	-Resemble colon cancer -Cribriform architecture -Tall, pseudostratified columnar - 'Dirty necrosis' - Extracellular mucin
	

Ampullary adenocarcinoma

Immunohistochemistry

Study	Definition of subtype
Ang, AJSP 2014 CK20, CDX2, MUC1, MUC2 >25% staining considered +ve	INT: • CK20+ or CDX2+ or MUC2+ and MUC1 negative, or • CK20+ CDX2+ and MUC2+ Irrespective of MUC1 PB: MUC1+, CDX2- MUC2- Irrespective of CK20





Ampullary adenocarcinoma

Immunohistochemistry

Study	Definition of subtype
Scheuneman, Br J Cancer 2015	PB: PB histology, MUC1+, CDX2-
MUC1: any CDX2: score >35	INT: all others

Ampullary adenocarcinoma

Histologic typing: Problems

- 15-20% ambiguous even after immunohistochemistry
- Not independent predictor of outcome in some studies
- Biopsies may not be representative

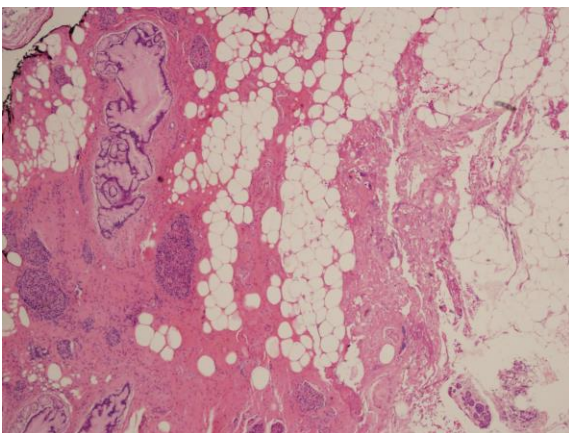
Reid, Mod Pathol 2016
Perysinakis, Int J Surg Pathol 2017

Pancreas: staging updates

- Changes in T category
- Changes in N category
- Definition of positive uncinete margin

Pancreas: Problems in staging in AJCC 7th edition

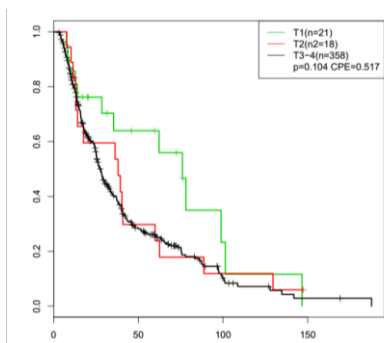
T stage	Problem
T1 T2 T3	-Uneven stage groupings -Lack of correlation with outcome
T3 criteria	-Extrapancreatic involvement



T1 vs. T2 vs. T3 uneven stage groupings

Study	T grouping
Ferrone, Surgery 2012 (n=499)	T1: 9% T2: 15% T3: 76%
Saka/Adsay, USCAP 2014 (n=250)	T1: 2% T2: 2% T3: 95%
Basturk/Allen/Klimstra, MSKCC, unpublished (n=397)	T1: 5% T2: 5% T3: 90%

Allen, Ann Surg 2017

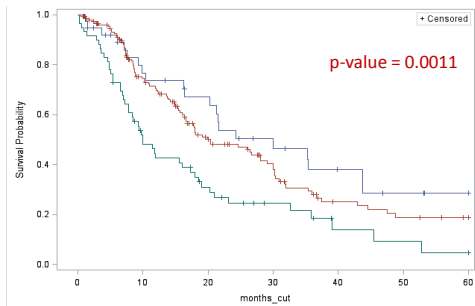


Pancreas staging: 8th edition

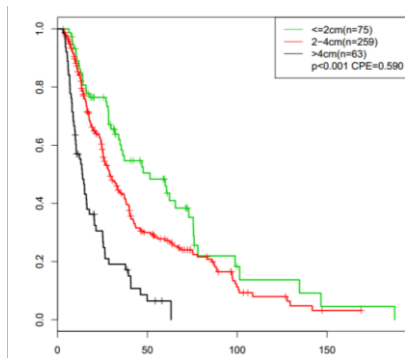
Change	Details
T1 subcategories	T1: Up to 2 cm T1a ≤ 0.5 cm T1b $>0.5 < 1$ cm T1c 1-2 cm
T2 and T3 based on size	T2: >2 and <4 cm T3: >4 cm Extrapancreatic extension is no longer part of the definition

Saka, Ann Surg Oncol 2016
Allen, Ann Surg 2017

Saka, Ann Surg Oncol 2016



Allen, Ann Surg 2017

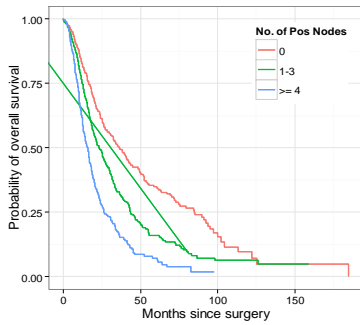


Pancreas staging: 8th edition

Change	Details
N categories	N1: Up to 3 lymph nodes N2: 4 or more lymph nodes

Saka, Ann Surg Oncol 2016
Allen, Ann Surg 2017

Allen, Ann Surg Oncol 2017



Definition of positive uncinete margin

Reference	Outcome
Campbell, Histopathol, 2009 (n=163)	Survival in tumor at margin same as tumor <1 mm
Chang, J Clin Pathol, 2009	Survival in tumor at margin same as tumor <1.5 mm
Van Den Broek, Eur J Oncol, 2009 (n=145)	Tumor <1 mm adverse prognostic factor

Definition of positive uncinete margin

Reference	Outcome: R0 and R1
Royal College UK	Negative: Tumor \geq 1 mm from margin Positive: Tumor at or <1 mm from margin
CAP protocol	Adopted the same definition

Intrahepatic cholangiocarcinoma AJCC 7th edition

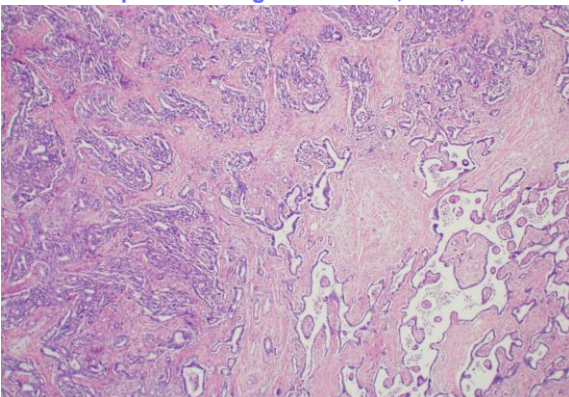
T category	Definition
T1	Solitary tumor without vascular invasion
T2	T2a: Solitary with vascular invasion T2b: Multiple tumors
T3	Involving visceral peritoneum or direct invasion into extrahepatic structures
T4	Tumor with periductal invasion

Periductal invasion

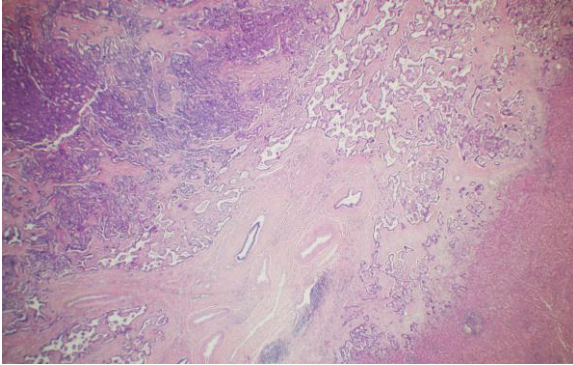
- Intrahepatic CC, macroscopic types
 Mass forming, periductal, intraductal, mixed
- Periductal: worse prognosis
 Extensive intraductal growth: T4
- Problems
 How extensive is 'extensive'
 Recent studies do not confirm worse outcome

Hirohashi, Hepatogastroenterol 2002
Uno, Surg Today, 2012

Intrahepatic cholangiocarcinoma, 3 cm, no VI



T1 or T4



Intrahepatic cholangiocarcinoma AJCC 8th edition

T category	Definition
T1	T1a: Solitary tumor ≤5 cm without vascular invasion T1b: Solitary tumor >5 cm without vascular invasion
T2	Solitary with intrahepatic vascular invasion or multiple tumors
T3	Involving visceral peritoneum
T4	Direct invasion into extrahepatic structures

Distal bile duct adenocarcinoma AJCC 8th edition

T category	Definition
T1	Tumor invades the bile duct wall with a depth of less than 5 mm
T2	Tumor invades the bile duct wall with a depth of 5-12 mm
T3	Tumor invades the bile duct wall with a depth more than 12 mm
T4	Tumor involves celiac axis, superior mesenteric artery, and/or common hepatic artery

Depth is measured from the basement membrane of adjacent normal or dysplastic epithelium to the point of deepest tumor invasion

**Perihilar bile duct adenocarcinoma
AJCC 8th edition**

T category	Definition
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2	T2a: Tumor invades beyond the wall of the bile duct to surrounding adipose tissue T2b: Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades 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

AJCC staging

The Future

**Consensus Molecular Subtypes (CMS)
6 gene expression studies**

CMS1 MSI/Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI-high CIMP-high	High copy number alteration	Low copy number alteration	High copy number alteration
Right	Left		High stage
<i>BRAF</i> mutation	<i>Wnt</i> activation <i>Myc</i> activation	<i>KRAS</i> mutation	<i>TGFβ</i> activation EMT genes
Immune infiltration		Metabolic dysregulation	Angiogenesis Prominent stroma
Worse outcome after relapse			Worse outcome

Guinney, Nat Genetics, 2015
