2017 GIPS Companion Meeting

Staging of Colorectal Cancer and selected GI sites

AJCC 8th edition and CAP protocol updates

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Outline

- Updates in CRC
  - Definition of T4
  - Tumor deposits
  - Isolated tumor cells
  - Tumor budding
- Selected other updates
  - Pancreas, gallbladder, ampulla

CRC: AJCC 8th edition and CAP protocol updates

Category	Update/clarification
T category	Intramucosal adenocarcinoma Definition of T4a
N category	Definition of tumor deposit Isolated tumor cells
M category	Definition of M1a, M1b, M1c

Prognostic factors	Update/clarification
Tumor budding	Reporting guidelines
Venous invasion	Separate from small vessel LVI

pT3 and pT4
AJCC 8th edition

pT classification	Definition
pT3	Tumor invades through the muscularis propria into pericolorectal tissues
pT4a	Tumor invades through the visceral peritoneum
pT4b	Tumor directly invades other organs or structures

Criteria for serosal involvement (T4a)

- Tumor at serosal surface
  - Reaction: mesothelial hyperplasia, vascular proliferation, inflammation, erosion/ulceration
- Free tumor cells on serosal surface with serosal reaction
- Tumor continuous with serosal surface through perforation (inflammatory reaction)

T4a: pitfalls and challenges

- Tumor within 1 mm of serosal surface
- Peritonealized vs. non-peritonealized regions

Tumor ≤1mm with reaction

- 13 (46%) pT3 ≤1 mm from serosal surface had +ve cytology
- All had serosal reaction
- Peritoneal recurrence same as conventional pT4a tumors

Panarelli, AJSP 2013

pT4a: AJCC 8th edition

- Tumor <1 mm with reaction
- Acellular mucin at or <1 mm from surface
- Deeper levels, additional sections

Not considered as pT4a

pT4 and radial margin

Site	pT classification
Peritonealized sites	pT4a: serosal surface Radial margin: not on specimen surface but same as mesenteric margin
Retroperitoneal sites	pT4a: not applicable Radial margin: involved ≤1mm

Anatomic subsite	Relation to peritoneum
Cecum	Peritoneal
Transverse colon	Peritoneal
Sigmoid colon	Peritoneal
Ascending colon	Anterior, lateral: peritoneal Posterior: retroperitoneal
Descending colon	Anterior, lateral: peritoneal Posterior: retroperitoneal
Rectum, upper 1/3	Anterior, lateral: peritoneal Posterior: retroperitoneal
Rectum, middle 1/3	Anterior: peritoneal Posterior, lateral: retroperitoneal
Rectum, lower 1/3	Retroperitoneal

pT4a: significance

- **Adverse prognosis**
- **Peritoneal recurrence**
- **High risk feature as per NCCN guidelines for stage II disease: may lead to chemotherapy**

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)
Greenson, Cancer 1994	Keratin in N0, n=50	-Higher relapse with ITC (43% vs. 3%)

AJCC 8th edition

Size of nodal metastasis	AJCC 7th edition	AJCC 8th edition
0.2 to 2 mm	Micrometastasis pN1mi	Use pN1 pN1mi not necessary
Less than 0.2 mm	Isolated tumor cells pN0 (i+) pN0 (mol+)	Use N0 No definite recommendation for using N0(i+)

Tumor deposits: AJCC 7th Edition

"Discrete foci of tumor found in the pericolic or perirectal fat or in adjacent mesentery away from the leading edge of tumor, showing no evidence of residual lymph node tissue but within the lymph drainage area of the primary carcinoma."

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

AJCC definition does not mention

- Any minimum distance
- Any minimum size

Tumor deposit or LVI

- Small vessel lymphovascular invasion
  - Thin vascular channels lined by endothelium
  - No smooth muscle or elastic layer
- Venous invasion
  - Vessels with smooth muscle or elastic layer
  - Tumor nodules surrounded by elastic lamina

Intramural: submucosa or muscularis propria

Extramural: beyond muscularis propria

CRC: Extramural venous invasion

- Independent predictor of poor outcome
- UK Royal College: 25% rate for audit

Recommendations

- Record separately from small vessel invasion
- 4-5 sections of tumor
- Elastic stain: routinely/suspicious areas

Messenger, J Clin Pathol 2011
Kirsch, Human Pathol 2012

CRC: Extramural venous invasion

Review H&E for venous invasion

- 'Protruding tongue' sign
- 'Orphan artery' sign

Consider elastic stain

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
- If vessel wall or its remnant is identified (H&E, elastic, or any other stain), it should be classified as vascular (venous) invasion
- Tumor focus in or around a large nerve should be classified as PNI

Tumor deposit vs. venous invasion

- Both associated with adverse outcome
- Record extramural VI separately
- Consider elastic stain

AJCC 8th edition definition

Influences stage II vs. stage III

Example: T3 tumor with no LN mets
VI with extravascular extension

- If regarded as tumor deposit
  T3N0 with VI (stage II)
- If not regarded as tumor deposit
  T3N1c (stage III)

Tumor deposits in practice

Histologic features	
Venous invasion	Accompanying artery Elastic stain
Perineural invasion	Large nerves
Tumor deposit	No remnant lymph node, large nerve or vein
Tumor deposit or residual tumor after neoadjuvant	H&E, use judgment Elastic stain for venous invasion

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

Invasive adenocarcinoma in polyp

Indications for colectomy

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

*Required as per CAP protocol

AJCC: T definition

pT	Definition
Tis	Carcinoma in situ, invasion of lamina propria/ muscularis mucosa (Intramucosal adenocarcinoma) Virtually no chance of lymph node metastasis
T1	Tumor invades submucosa (Invasive adenocarcinoma) Stromal desmoplasia

Tumor budding

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

Limitations

- **No standard way of counting tumor buds**
- **Inter-observer variability**
- **Routine use of cytokeratin stain unclear**

International Tumor Budding Consensus Conference, Bern 2016

Consensus Statements

- **Tumor budding is defined as a single tumor cell or a cell cluster consisting of 4 tumor cells or less**

Consensus statements
Counting tumor buds

- **Tumor budding is counted on H&E**

Use of cytokeratin

-Not recommended, most data is based on H&E
-Can use it in challenging cases (obscuring inflammation) but count should be done on H&E

Consensus statements
Counting tumor buds

- **The hot spot method (single field at the invasive front, size 0.785 mm^2)**

-Scan the entire invasive front in all tumor sections
-Choose a 'hotspot'
-Count in 20x field
-Apply appropriate correction factor based on microscope

Conversion table

	Objective Magnification: 20x			
Eyepiece FN Diameter	Eyepiece FN Radius	Specimen FN radius	Specimen Area	Normalization Factor
(mm)	(mm)	(mm)	($mm^{2)}$	
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

Three-tier system for reporting

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

Consensus statements
Counting tumor buds

- **Tumor budding is an independent predictor of lymph node metastasis in pT1 CRC**
- **Tumor budding is an independent predictor of survival in stage II CRC**
- **Tumor budding should be taken into account along with other clinicopathologic features in a multidisciplinary setting**

CAP synoptic: tumor budding

Recommended, not mandatory element

- Total number of tumor buds in 0.785 mm^2 ('hotspot method'): ___
- Tumor budding score:
  - __ Low (<5)
  - __ Intermediate (5-9)
  - __ High (≥10)

Challenging situations

- Glandular fragmentation
  - Prominent inflammation
  - Perforation
  - Necrosis
- Histologic subtypes
  - Not applicable

Other changes: CAP protocol

Microsatellite instability

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

Pancreas

Change	Details
T1 subcategories	T1a, T1b, and T1c based on size
T2 and T3 based on size	T2: 2-4 cm T3: >4 cm Extrapancreatic extension is no longer part of the definition.
N categories	N1: Up to 3 lymph nodes N2: 4 or more lymph nodes

Gallbladder

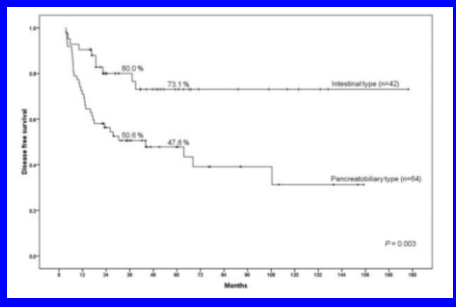
Change	Details
Subdivision of T2	T2a: Tumors on the peritoneal side T2b: Tumors on the hepatic side
N categories	7th edition: N1 and N2 defined by location 8th edition: Number-based N1: 1-3 positive nodes N2: 4 or more positive nodes.
Minimum no. of LN	Recommendation: evaluation of six or more nodes

Ampulla

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

Ampullary adenocarcinoma

Pancreaticobiliary subtype more aggressive than intestinal



Kim, J Surg Oncol 2012

AJCC 8th edition: Ampulla

- **"Validation of histologic subtypes as an independent prognostic variable has not been firmly established"**

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)

Ampullary adenocarcinoma

Histologic subtypes

Pancreaticobiliary	Intestinal
-Cuboidal to low columnar epithelium -No nuclear pseudostratification -Rounded but with marked variation in size and shape -Desmoplastic stroma	-Resemble colon cancer -Cribriform architecture -Tall, often pseudostratified columnar epithelium -Oval nuclei in basal aspect -'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

- 92% were classified
- 75% poorly differentiated, 69% mixed

Ampullary adenocarcinoma

Immunohistochemistry

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

Ampullary adenocarcinoma

Immunohistochemistry: Problems

- **15-20% ambiguous**
- **Biopsies not representative**
- **Noninvasive tumors included in some studies**
- **Not independent predictor of outcome**

Reid, Mod Pathol 2016

AJCC staging and CAP checklists

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
BRAF mutation	*Wnt* activation	*KRAS* mutation	*TGFβ* activation
	Myc activation		EMT genes
Immune infiltration		Metabolic dysregulation	Angiogenesis Prominent stroma
Worse outcome after relapse			Worse outcome

Guinney, Nat Genetics, 2015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JOURNAL OF CLINICAL ONCOLOGY | E D I T O R I A L S

TNM Staging in Colorectal Cancer: T Is for T Cell and M Is for Memory

Elizabeth K. Broussard and Mary L. Disis, *Tumor Vaccine Group, Center for Translational Medicine in Women's Health, University of Washington, Seattle, WA*

- **Host immune response better prognostic indicator than TNM**
- **'Immunoscore': Quantify the immune infiltrate**

Galon, J Pathol 2014

TNM-I staging

Immunoscore

- **CD3 and CD8**
- **Numbers in center and invasive front**
- **5 categories: I-0 to I-4**

Galon, J Transl Med 2012