COLLEGE of AMERICAN PATHOLOGISTS

Staging Challenges in Lower GI Cancers

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CAP

AJCC 8th edition and CAP protocol updates

Category	Update/clarification
T category	Intramucosal adenocarcinoma Definition of T4a
N category	Definition of tumor deposit
M category	Definition of M1a, M1b, M1c
Prognostic factors	**Update/clarification**
Tumor budding	Reporting guidelines
Venous invasion	Separate from small vessel LVI
M category	Definition of M1a, M1b, M1c

CAP

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, inflammation, erosion/ulceration**
- **Free tumor cells on serosal surface with serosal reaction**
- **Tumor continuous with serosal surface through perforation (inflammatory reaction)**

T4a: 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

  Fibroinflammatory: 12

  Vascular: 8, abscess:1

  Rx mesothelial:6

  Hemorrhage/fibrin on serosa: 11

pT4a: suspicious features

- Tumor close to serosal surface with reaction
- Acellular mucin at or <1 mm from surface

Not considered as pT4a

Deeper levels, additional sections

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

pT3 or pT4a: significance

- **Prognosis**
- **Peritoneal recurrence**
- **Choice of therapy**
  - **Chemotherapy in stage II**

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

Pathology report

- Intramucosal adenocarcinoma (pTis)
  - No desmoplasia
    - Single cell infiltration in lamina propria
- Tis, not at risk for LN metastasis
- No invasive adenocarcinoma (pT1)

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**

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, no LN mets**
- **VI with extravascular extension**

Pathologic staging

- **T3N0 with VI (stage II)**
- **T3N1c (stage III)**

Tumor deposit 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 (T1) in polyp

Indications for colectomy

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

*Required as per CAP protocol

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 guidelines

Tumor budding in CRC

- Independent prognostic factor
  - High risk feature in stage II disease
- Adenocarcinoma arising in polyps
  - Strongly correlates with lymph node mets

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**
- **Tumor budding and tumor grade are not the same**

Consensus statements

Counting tumor buds

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

Use of cytokeratin

-Not recommended, most data is based on H&E stain
-Can increase tumor bud counts 3x
-Increased reproducibility in some studies
-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 (mm)	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

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	**<5**
Intermediate	**5-9**
High	**≥10**

Consensus statements

- **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 clinicopathological features in a multidisciplinary setting**

CAP synoptic: tumor budding

- **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**
  - **Tumor cells in mucin: not tumor budding**
  - **Signet ring: likely high, by definition**

Other changes

Microsatellite instability

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

Other changes

Isolated tumor cells/micrometastasis

- **Tumor focus <0.2 mm: N0**
- **Tumor focus <0.2-2.0 mm: N1 (or higher)**
- **N0 (ITC+) and N1 (mic) not necessary**

Appendix

Category	Change/update
T category	-LAMN: No T1 or T2 -LAMN invasive into muscularis propria considered Tis
T category	-LAMN: Acellular mucin on serosal surface considered T4a -'Right lower quadrant' removed from definition of T4a
M category	Acellular mucin in peritoneum included in M1a
Grade of peritoneal disease	-Three-tier scheme recommended: well (G1), moderately (G2), poorly differentiated (G3) Based on criteria proposed by Davison et al* -Stage IVA and IVB distinguished based on grade

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