Staging Updates in Colorectal Cancer

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March 05, 2017

Good checklists are precise, efficient, to the point, and easy to use. They do not try to spell out everything.

AJCC 8th edition/CAP protocol updates
Colorectal Cancer
- Definition of T4a
- Tumor deposits
- Tumor budding
Appendix

pT3 and pT4: AJCC 8th edition

<table>
<thead>
<tr>
<th>pT classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT3</td>
<td>Tumor invades through the muscularis propria into pericolorectal tissues</td>
</tr>
<tr>
<td>pT4a</td>
<td>Tumor invades through the visceral peritoneum</td>
</tr>
<tr>
<td>pT4b</td>
<td>Tumor directly invades or is adherent to other organs or structures</td>
</tr>
</tbody>
</table>

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

- Ulceration
- Hyperplasia
- Inflammation
- Fibrosis
- Vascular proliferation

Serosal reaction

Free floating cells on the peritoneal surface

Colonic adenocarcinoma with perforation

Tumor separated from the serosal surface through inflammatory reaction

T4a: challenges

- Tumor within 1 mm of serosal surface and serosal reaction
- Elastic stain

Tumor ≤1 mm with reaction

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panarelli, AJSP 2014</td>
<td>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</td>
</tr>
<tr>
<td>Shepherd, Gastroenterology 1997</td>
<td>Adverse outcome only with Direct invasion of serosal surface Free floating tumor cells-some studies</td>
</tr>
<tr>
<td>Lennon, AJCP 2003</td>
<td></td>
</tr>
<tr>
<td>Douard, AJCP 2004</td>
<td></td>
</tr>
</tbody>
</table>
pT4a: suspicious features

- Tumor close to serosal surface with serosal reaction
- Acellular mucin at or close to serosal surface
  Not considered as pT4a (AJCC 8th edition)
  Deeper levels, additional sections

T4a: challenges

- Tumor within 1 mm of serosal surface
- Elastic stain

Elastic stain

- Elastic lamina not continuous
- Routine use uncommon

pT4a: clinical significance

- Prognosis
- Peritoneal recurrence
- Choice of therapy
  - NCCN guidelines: High risk feature in stage II
  - Likely adjuvant chemotherapy
  - Possible HIPEC (Hyperthermic Intraperitoneal Chemotherapy)

ASCO GI meeting 2017

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

AJCC 8th edition/CAP protocol updates

Colorectal Cancer
- Definition of T4
- Tumor deposits
- Tumor budding
- Appendix

Baratti, Ann Surg Oncol 2016
Elias, J Clin Oncol 2009
## 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.”

## Challenges in Interpretation

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

## Challenges in Interpretation

<table>
<thead>
<tr>
<th>Distance from Invasive Front</th>
<th>Study</th>
<th>Size of Tumor Deposit</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2 mm</td>
<td>Ueno, Am J Surg 2014</td>
<td>&gt;2 mm</td>
</tr>
<tr>
<td>&gt;5 mm</td>
<td>Nagayoshi, Dis Colon Rectum 2014</td>
<td>&gt;5 mm</td>
</tr>
<tr>
<td>&gt;10 mm</td>
<td>Gopal, Mod Pathol 2014</td>
<td>&gt;10 mm</td>
</tr>
</tbody>
</table>

**AJCC definition**
- No minimum distance
- No minimum size

## 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

## Extramural Venous Invasion or Tumor Deposit

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Spread</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein (2000)</td>
<td>VI with extravascular spread</td>
<td>Tumor deposit</td>
</tr>
<tr>
<td>Lin (2015)</td>
<td>Tumor Deposit</td>
<td>Vascular invasion</td>
</tr>
<tr>
<td>Nagayoshi (2014)</td>
<td>Tumor Deposit</td>
<td>Vascular invasion</td>
</tr>
<tr>
<td>Ueno (2011)</td>
<td>Tumor Deposit</td>
<td>Vascular invasion</td>
</tr>
</tbody>
</table>

## Challenges in Interpretation

**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
- Elastic stain: increases detection rate

Recommendations:
- Record separately from small vessel invasion
- Consider elastic stain

Invasive adenocarcinoma T3, 20 negative lymph nodes

Pathologic Stage
- T3N0: stage II
- T3N0 with VI: Stage II

NCCN guidelines
- Vascular invasion is a high risk feature in stage II disease
Challenges in Interpretation

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

N1c in practice

<table>
<thead>
<tr>
<th>Lymph node</th>
<th>Thick capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subcapsular sinus</td>
</tr>
<tr>
<td></td>
<td>Rim of lymphocytes</td>
</tr>
<tr>
<td>Venous invasion</td>
<td>Accompanying artery</td>
</tr>
<tr>
<td>Perineural invasion</td>
<td>Large nerves</td>
</tr>
<tr>
<td>Tumor deposit</td>
<td>Round outline, no remnant lymph node, large nerve or vein</td>
</tr>
</tbody>
</table>

Do not add tumor deposits and lymph nodes for
- N category
- Assessing adequacy of LN dissection

AJCC 8th edition/CAP protocol updates

Colorectal Cancer
- Definition of T4
- Tumor deposits
- Tumor budding

Appendix

Tumor budding in CRC

- Independent prognostic factor
  - High risk feature in stage II disease
- Adenocarcinoma arising in polyps
  - Strongly correlates with lymph node metastasis
- Guidelines:
  - Not included in AJCC 8th edition, NCCN guidelines
  - Recommended: UICC, ADASP, UK and Australia Royal College
  - CAP checklist: optional element

Mitrovic, Mod Pathol 2012
Koehler, Hum Pathol 2016

Limitations

- No standard way of counting tumor buds
- Inter-observer variability
- Different studies: H&E, cytokeratin
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 (obscurings inflammation), but final 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 mm²) is recommended
  - Choose a 'hotspot'
  - Count in 20x field
  - Apply appropriate correction factor for your microscope
### Conversion table

<table>
<thead>
<tr>
<th>Eyepiece FN Diameter (mm)</th>
<th>Eyepiece FN Radius (mm)</th>
<th>Specimen FN radius (mm)</th>
<th>Specimen Area (mm²)</th>
<th>Normalization Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>9.0</td>
<td>0.450</td>
<td>0.636</td>
<td>0.810</td>
</tr>
<tr>
<td>19</td>
<td>9.5</td>
<td>0.475</td>
<td>0.709</td>
<td>0.903</td>
</tr>
<tr>
<td>20</td>
<td>10.0</td>
<td>0.500</td>
<td>0.785</td>
<td>1.000</td>
</tr>
<tr>
<td>21</td>
<td>10.5</td>
<td>0.525</td>
<td>0.866</td>
<td>1.103</td>
</tr>
<tr>
<td>22</td>
<td>11.0</td>
<td>0.550</td>
<td>0.950</td>
<td>1.210</td>
</tr>
<tr>
<td>23</td>
<td>11.5</td>
<td>0.575</td>
<td>1.039</td>
<td>1.323</td>
</tr>
<tr>
<td>24</td>
<td>12.0</td>
<td>0.600</td>
<td>1.131</td>
<td>1.440</td>
</tr>
<tr>
<td>25</td>
<td>12.5</td>
<td>0.625</td>
<td>1.227</td>
<td>1.563</td>
</tr>
<tr>
<td>26</td>
<td>13.0</td>
<td>0.650</td>
<td>1.327</td>
<td>1.690</td>
</tr>
</tbody>
</table>

### 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

<table>
<thead>
<tr>
<th>Tumor budding score (0.785 mm²)</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-4</td>
<td>5-9</td>
<td>≥10</td>
</tr>
</tbody>
</table>

### Other changes

**Microsatellite instability in CRC**

- Universal testing recommended
- Morphologic features omitted from new protocol
- Screening: MSI by PCR or MMR immunohistochemistry
- Colorectal Cancer Biomarkers Checklist

### Appendix: staging updates

**Low grade appendiceal mucinous neoplasm (LAMN)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Change/update</th>
</tr>
</thead>
<tbody>
<tr>
<td>T category</td>
<td>-LAMN invasive into muscularis propria considered Tis</td>
</tr>
<tr>
<td></td>
<td>-T1 and T2 not applicable to LAMN</td>
</tr>
<tr>
<td>T category</td>
<td>-LAMN: Acellular mucin on serosal surface considered T4a</td>
</tr>
<tr>
<td></td>
<td>-‘Right lower quadrant’ removed from definition of T4a</td>
</tr>
</tbody>
</table>

### WHO 2010

**Appendiceal adenoma: intact muscularis mucosa**

LAMN: Low grade carcinoma, rests on fibrous stroma, obliteration of MM
LAMN: Acellular mucin on serosal surface

Appendix

<table>
<thead>
<tr>
<th>Category</th>
<th>Change/update</th>
</tr>
</thead>
<tbody>
<tr>
<td>M category</td>
<td>Acellular mucin in peritoneum categorized M1a</td>
</tr>
</tbody>
</table>
| Grade of peritoneal disease | Three-tier scheme recommended*:  
  - Well differentiated (G1)  
  - Moderately differentiated (G2)  
  - Poorly differentiated (G3) |

*Based on criteria proposed by Davison et al*

Stage IVA and IVB distinguished based on grade

Appendiceal goblet cell carcinoid: use adenocarcinoma staging scheme

Acknowledgements

- Carolyn Compton, MD, PhD
- Kay Washington, MD

Lower GI Protocol Review Panel

- Kay Washington
- Chanjuan Shi
- Patrick Fitzgibbons
- Wendy Frankol
- Alyssa Krasinskas
- David Driman
- Marian Berho
- Gregory Lauwers
- Kalisha Hill
- John Jessup
- Michael Overman (appendix)
- Joseph Misdraji (appendix)
- Reetesh Pai (appendix)

Prophylactic HIPEC in CRC?

**Concept:**

Some CRC have a high risk of developing peritoneal carcinomatosis.  

- 5-year incidence of developing PC: 6% vs. 43% (p<0.004)  
- 5-year overall survival: 81% vs. 70% (p=0.047)

Extramural Venous Invasion

Intravascular Invasion  Extravascular Invasion

Perineural Invasion, Replaced Lymph node

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

CAP colorectal cancer checklist

- 14 required elements
- 4 optional elements

Pathology report
AJCC: T3N1c V1 R1 B1 P1
Molecular:
- KRAS exon 13 mutation
- NRAS, BRAF, PIK3CA: wild type
- PTEN absent
- TP53 mutation present
- Microsatellite stable
- Consensus molecular subtype 4 (CMS4)
- Next generation sequencing

Better outcome with neoadjuvant chemotherapy

Inclusion of one or a subgroup of 3 studies with appropriate data

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<table>
<thead>
<tr>
<th>Element</th>
<th>Key changes/updates</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4a definition</td>
<td>Clarification of definition</td>
</tr>
<tr>
<td></td>
<td>- Tumors &lt;1 mm from serosal surface: not T4a</td>
</tr>
<tr>
<td></td>
<td>- Tumors connected to surface through perforation: T4a</td>
</tr>
<tr>
<td>Tumor deposits</td>
<td>Exclude venous invasion, LN mets, PNI</td>
</tr>
<tr>
<td></td>
<td>Consider elastic stain for VI</td>
</tr>
<tr>
<td>Tumor deposits</td>
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<td>Tumor deposits</td>
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<tr>
<td>Tumor deposits</td>
<td></td>
</tr>
<tr>
<td>Invasive adenocarcinoma in polyp</td>
<td>Exclude venous invasion, LN mets, PNI</td>
</tr>
<tr>
<td></td>
<td>Consider elastic stain for VI</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive adenocarcinoma in polyp</td>
<td>Include prognostic variables: margin, differentiation, vascular invasion</td>
</tr>
<tr>
<td></td>
<td>Tumor budding, depth of invasion</td>
</tr>
<tr>
<td>Invasive adenocarcinoma in polyp</td>
<td></td>
</tr>
<tr>
<td>Invasive adenocarcinoma in polyp</td>
<td></td>
</tr>
<tr>
<td>Invasive adenocarcinoma in polyp</td>
<td></td>
</tr>
<tr>
<td>Isolated tumor cells and micrometastasis</td>
<td>Clarification of definition</td>
</tr>
<tr>
<td></td>
<td>- Nodes with ITC (&lt;0.2 mm) classified as N0</td>
</tr>
<tr>
<td></td>
<td>- Nodes with micromets (0.2-2 mm) as N1</td>
</tr>
<tr>
<td></td>
<td>- Designations like N0 (+) for ITC and N1(mic) for micromets not necessary</td>
</tr>
<tr>
<td>M1c category</td>
<td>Peritoneal carcinomatosis</td>
</tr>
</tbody>
</table>