Staging of Colorectal Cancer and selected GI sites
AJCC 8th edition and CAP protocol updates

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University of California San Francisco

2017 GIPS Companion Meeting

Outline
• Updates in Colorectal cancer
  Definition of T4a
  Tumor deposits
  Isolated tumor cells
  Tumor budding
• Selected other updates
  Pancreas, gallbladder, ampulla

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 pericoloecal tissues</td>
</tr>
<tr>
<td>pT4a</td>
<td>Tumor invades through the visceral peritoneum</td>
</tr>
<tr>
<td>pT4b</td>
<td>Tumor directly invades 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)

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

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Tumor directly extends to serosal surface
Free floating cells on the peritoneal surface

Colonic adenocarcinoma with perforation

Tumor separated from the serosal surface through inflammatory reaction

Tumor ≤1 mm with reaction

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panarelli, AJSP 2014</td>
<td>Peritoneal recurrence: 11% in pT3 ≤1 mm</td>
</tr>
<tr>
<td>-Shepherd, Gastroenterology 1997</td>
<td>18% in pT4a</td>
</tr>
<tr>
<td>-Lennon, AJCP 2003</td>
<td>Adverse outcome only with Direct invasion of serosal surface</td>
</tr>
<tr>
<td>-Douard, AJCP 2004</td>
<td>Free floating tumor cells</td>
</tr>
</tbody>
</table>

Not T4a (AJCC 8th)

- Tumor close to serosal surface with serosal reaction
- Deeper levels, additional sections

Outline

- Updates in Colorectal cancer
  - Definition of T4a
  - Tumor deposits
  - Isolated tumor cells
  - Tumor budding
**Tumor deposits: AJCC 7th Edition**

- Discrete foci of tumor in pericolic fat
- No evidence of residual lymph node tissue

**Variability 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>&lt;3 mm</td>
</tr>
<tr>
<td>&gt;5 mm</td>
<td>Nagoyoshi, Dis Colon Rectum 2014</td>
<td>Only if grossly identified</td>
</tr>
<tr>
<td>&gt;10 mm</td>
<td>Gopal, Mod Pathol 2014</td>
<td>Criteria not specified</td>
</tr>
</tbody>
</table>

AJCC definition
- No minimum distance
- No minimum size

**Venous invasion or tumor deposit**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein (2000)</td>
<td>Tumor deposit</td>
</tr>
<tr>
<td>Lin (2015)</td>
<td>Tumor Deposit</td>
</tr>
<tr>
<td>Nagoyoshi (2014)</td>
<td>Vascular invasion</td>
</tr>
<tr>
<td>Ueno (2011)</td>
<td></td>
</tr>
</tbody>
</table>

**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
Tumor deposit

- Lymph node, vessel, nerve
- Consider elastic stain

Isolated tumor cells

<table>
<thead>
<tr>
<th>Size of nodal metastasis</th>
<th>AJCC 7th edition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2 to 2 mm</td>
<td>Micrometastasis pN1mi</td>
</tr>
<tr>
<td>Less than 0.2 mm</td>
<td>Isolated tumor cells (ITC) pN0 (+)</td>
</tr>
</tbody>
</table>

Outline

- Updates in Colorectal cancer
  - Definition of T4a
  - Tumor deposits
  - Isolated tumor cells
  - Tumor budding

Isolated tumor cells, micrometastasis

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sloothak, Eur J Surg Oncol 2014</td>
<td>Meta-analysis 5 studies</td>
<td>Increased recurrence with micrometastasis - No increased risk with ITC</td>
</tr>
<tr>
<td>Rahbari, JCO 2012</td>
<td>Meta-analysis 39 studies</td>
<td>Increased recurrence with micrometastasis - Insufficient data for ITC</td>
</tr>
<tr>
<td>Mescoli, JCO 2012</td>
<td>Keratin in N0, n=312</td>
<td>Higher relapse with ITC (14% vs. 5%)</td>
</tr>
<tr>
<td>Prodic, J Am Coll Surg 2015</td>
<td>Keratin in N0, n=312 Prospective</td>
<td>Higher relapse with ITC (17% vs. 3%) - T3 and T4 (not T1 and T2)</td>
</tr>
<tr>
<td>Grenson, Cancer 1994</td>
<td>Keratin in N0, n=50</td>
<td>Higher relapse with ITC (43% vs. 3%)</td>
</tr>
</tbody>
</table>
**AJCC 8th edition**

<table>
<thead>
<tr>
<th>Size of nodal metastasis</th>
<th>AJCC 8th edition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2 to 2 mm</td>
<td>Use pN1</td>
</tr>
<tr>
<td></td>
<td>pN1mi not necessary</td>
</tr>
<tr>
<td>Less than 0.2 mm</td>
<td>Use N0</td>
</tr>
<tr>
<td></td>
<td>No definite recommendation for using N0(i+)</td>
</tr>
</tbody>
</table>

**Outline**

- Updates in Colorectal cancer
  - Definition of T4a
  - Tumor deposits
  - Isolated tumor cells
  - Tumor budding

**Tumor budding**

- Individual or small discrete cell clusters (<5 cells) at the invasive edge

**Tumor budding**

- Independent adverse prognostic factor
  - Colectomy for malignant polyps
  - Adjuvant therapy in stage II

- Recommended:
  - Not mentioned: AJCC 8th edition, NCCN
  - UICC, ADASP, UK Royal College

**Limitations**

- No standard way of counting tumor buds
- H&E or cytokeratin stain

**Consensus statements**

- Counting tumor buds

**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 mm²)
  - 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

<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>0.949</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

Three-tier system for reporting

<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>&lt;5</td>
<td>5-9</td>
<td>≥10</td>
</tr>
</tbody>
</table>

GI Platform session: Mon AM

[T73] Tumor Budding Assessed by the International Tumor Budding Consensus Conference (ITBCC): Recommendations is a Strong Predictor of Disease-Free Survival in Stage II Colon Cancer

Outline

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  - Tumor budding
- Selected other updates
  - Pancreas, gallbladder, ampulla

Pancreas

<table>
<thead>
<tr>
<th>Change</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 subcategories</td>
<td>T1a: ≤0.5 cm, T1b: &gt;0.5 cm, T1c: 1-2 cm</td>
</tr>
<tr>
<td>T2 and T3 based on size</td>
<td>T2: &gt;2 cm, T3: &gt;4 cm Extrapancreatic extension is no longer part of the definition.</td>
</tr>
<tr>
<td>N categories</td>
<td>N1: Up to 3 lymph nodes, N2: 4 or more lymph nodes</td>
</tr>
</tbody>
</table>
### Gallbladder

<table>
<thead>
<tr>
<th>Change</th>
<th>Details</th>
</tr>
</thead>
</table>
| Subdivision of T2 | T2a: Tumors on the peritoneal side  
T2b: Tumors on the hepatic side |

Shindoh, Ann Surg 2015

### Ampulla

<table>
<thead>
<tr>
<th>Change</th>
<th>Details</th>
</tr>
</thead>
</table>
| 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 |

### Pancreaticobiliary vs Intestinal

<table>
<thead>
<tr>
<th>Pancreaticobiliary</th>
<th>Intestinal</th>
</tr>
</thead>
</table>
| -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

**Pancreaticobiliary vs intestinal**

**Immunohistochemistry**

Study Definition of subtype

<table>
<thead>
<tr>
<th>Study</th>
<th>Definition of subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>INT:</td>
<td></td>
</tr>
</tbody>
</table>
CK20+, CDX2+, MUC2+, MUC1+  
>25% staining considered +ve |
| PB:  |  
MUC1+, CDX2-, MUC2-  
Irrespective of CK20 |

- 92% were classified  
- 75% poorly differentiated, 69% mixed
Ampullary adenocarcinoma
Histologic typing: Problems

- 15-20% ambiguous
- Not independent predictor of outcome
- Biopsies may not be representative
- Survival data based on histology not strong as noninvasive tumors included in some studies

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

AJCC staging and CAP checklists
The Future

Consensus Molecular Subtypes (CMS)
6 gene expression studies

<table>
<thead>
<tr>
<th>CMS1</th>
<th>CMS2</th>
<th>CMS3</th>
<th>CMS4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSI/Immune</td>
<td>Canonical</td>
<td>Metabolic</td>
<td>Mesenchymal</td>
</tr>
<tr>
<td>14%</td>
<td>37%</td>
<td>13%</td>
<td>23%</td>
</tr>
<tr>
<td>MSI-high</td>
<td>High copy number alteration</td>
<td>Low copy number alteration</td>
<td>High copy number alteration</td>
</tr>
<tr>
<td>CIMP-high</td>
<td>Right</td>
<td>High stage</td>
<td></td>
</tr>
<tr>
<td>BRAF mutation</td>
<td>Wnt activation</td>
<td>KRAS mutation</td>
<td>TGFβ activation</td>
</tr>
<tr>
<td>Immune infiltration</td>
<td>Metabolic dysregulation</td>
<td>Angiogenesis</td>
<td>Prominent stroma</td>
</tr>
<tr>
<td>Worse outcome after relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Guinney, Nat Genetics, 2015

Ampullary adenocarcinoma
Immunohistochemistry

<table>
<thead>
<tr>
<th>Study</th>
<th>Definition of subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheuneman, Br J Cancer 2015</td>
<td>PB: PB histology, MUC1+, CDX2-</td>
</tr>
<tr>
<td></td>
<td>INT: all others</td>
</tr>
</tbody>
</table>

MUC1: any CDX2: score >35

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

- 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

---

**Pathology report**

AJCC: T3 N1c M1
- V1 P0 N1 R1 Bd3
- MSI-H
- PDL-1 positive
- Immunoscore I-4
- KRAS, NRAS, BRAF, PIK3CA, PTEN, p53
- CMS, type 1 (molecular subtype)
- Whole exome, RNA seq……..

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**Perysinakis, Int J Surg path 2017**

Eighteen carcinomas were classified as intestinal type and 29 carcinomas as pancreatobiliary type.

Univariate analysis revealed that CK20 and CDX2 expression correlates with intestinal type, whereas MUC1 positivity indicates pancreatobiliary type. A marginally significant trend was shown for intestinal-type tumors toward larger size and more frequent MUC2 expression.

Using multivariate analysis CK20 (P = .003) and MUC1 (P = .004) were identified as independent predictors of the intestinal and pancreatobiliary types, respectively.

On univariate survival analysis, overall survival was adversely influenced by the number of infiltrated lymph nodes, elevated CA19-9 serum levels, jaundice, poor differentiation, T4 stage, N1 stage, TNM stage III, and CDX2 immunonegativity.

Multivariate analysis identified TNM stage as the only independent prognostic factor in ampullary adenocarcinoma (P = .048).

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**CAP synoptic: tumor budding**

Recommended, not mandatory element

- Total number of tumor buds in 0.785 mm² (‘hotspot method’): ___
- Tumor budding score:
  - Low (<5)
  - Intermediate (5-9)
  - High (>10)

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**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

NCCN guidelines
EGAPP guidelines, Nat Genetics, 2009

**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

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

**T4a: challenges**

- Tumor within 1 mm of serosal surface
- Use of elastic stain

**T4a: challenges**

- Tumor within 1 mm of serosal surface
- Elastic stain

**Elastic stain**

- Elastic lamina discontinuous
- Routine use uncommon
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**Isolated tumor cells**