Diagnostic Difficulties Encountered Among Colorectal Polyps

Rhonda K. Yantiss, M.D.
Professor of Pathology and Laboratory Medicine
Department of Pathology and Laboratory Medicine
Weill Cornell Medical College, New York, NY

Case 1

- Geneticist colleague
  - “I had my first colonoscopy yesterday upon turning 50 last week (I know I don’t look a day over 49)”
  - Three polyps removed
    - 0.7 cm polyp in rectosigmoid colon
    - 0.5 cm flat lesion in mid transverse colon
    - 0.5 cm flat lesion in descending colon
  - No family history of cancer
Polyps of Distal Colon

Descending colon
Rectosigmoid colon

Mid-Transverse Colon Polyp
Summary of Findings

- Two small (<1.0 cm) tubular adenomas of the distal colon
- One 5 mm non-dysplastic serrated polyp of the transverse colon
- Management dictated by tubular adenomas, so transverse colon polyp is mostly irrelevant....but what do we call the serrated polyp?

Classification of Serrated Polyps

Yes \[\text{Is Dysplasia Present?}\] No

| Serrated Adenoma | Sessile Serrated Polyp with Dysplasia | Hyperplastic Polyp | Sessile Serrated Polyp |

Complete removal, followed similar to tubular and villous adenomas
**Hyperplastic Polyps**

- Small
- More common in distal colon

**Sessile Serrated Polyp/Adenoma**

- More common among women
- More common among older patients
- Predilection for abdominal colon, proximal to splenic flexure
- May be large (>1 cm)
- Atypical features not seen in hyperplastic polyps
Sessile Serrated Polyp/Adenoma

Adherent mucus cap

Mostly flat or "thickened fold"

Sessile Serrated Polyp/Adenoma

Expanded mucosa reflects elongated crypts
Sessile Serrated Polyp/Adenoma

Dilated crypts flatten on muscularis mucosae and show lateral branching

Non-Dysplastic Serrated Polyps

Hyperplastic polyp

Sessile serrated polyp
Proliferation in Serrated Polyps

Symmetric proliferative zone

Asymmetric proliferative zone

Hyperplastic polyp

Sessile serrated polyp

Sessile Serrated Polyp/Adenoma

Prevalence

- 2% of colonoscopy patients in general population
- 8% of colonoscopy patients in general population when evaluated by experienced gastroenterologist
- 20% of non-dysplastic serrated polyps in pathology material

**Sessile Serrated Polyp with Dysplasia**

*Mixed Adenomatous/Hyperplastic Polyp*

- Non-dysplastic epithelium

**Non-Dysplastic Serrated Polyps**

**Cancer Risk**

<table>
<thead>
<tr>
<th>Number</th>
<th>Few</th>
<th>Many</th>
</tr>
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<tbody>
<tr>
<td>Size</td>
<td>Small</td>
<td>Large</td>
</tr>
<tr>
<td>Type</td>
<td>Hyperplastic polyp</td>
<td>Sessile serrated polyp</td>
</tr>
<tr>
<td>Location</td>
<td>Left</td>
<td>Right</td>
</tr>
</tbody>
</table>

Increasing cancer risk (7% at 5 years in serrated polyposis syndrome)

### Subclassifying Serrated Polyps

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Sessile Serrated Polyp</th>
<th>Microvesicular Hyperplastic Polyp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Proximal</td>
<td>Distal</td>
</tr>
<tr>
<td>Size</td>
<td>Large (≥1 cm)</td>
<td>Small (&lt;5 mm)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Molecular Features</th>
<th>Ki-67 distribution (proliferation)</th>
<th>MUC2 (colonic goblet cell mucin)</th>
<th>MUC5AC (gastric foveolar cell mucin)</th>
<th>MUC6 (pyloric gland mucin)</th>
<th>Annexin A10</th>
<th>KRAS mutation</th>
<th>BRAF mutation</th>
<th>CIMP high</th>
<th>Partial loss of MLH-1 staining</th>
<th>MSI-H</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Abnormal</td>
<td>Yes</td>
<td>Yes</td>
<td>Common (53-90%)</td>
<td>Common (100%)</td>
<td>Infrequent</td>
<td>Common (~80%)</td>
<td>Common (~75%)</td>
<td>Common (33-50%)</td>
<td>No</td>
</tr>
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**Serrated Lesions of the Colorectum: Review and Recommendations From an Expert Panel**

Serrated lesions of the colorectum are the precursors of perhaps one-third of colorectal cancers (CRCs). Cancers arising in serrated lesions are usually in the proximal colon, and account for a disproportionate fraction of cancer identified after colonoscopy. We sought to provide guidance for the clinical management of serrated colorectal lesions based on current evidence and expert opinion regarding definitions, classification, and significance of serrated lesions. A consensus conference was held over 2 days reviewing the topic of serrated lesions from the perspectives of histology, molecular biology, epidemiology, clinical aspects, and serrated polyposis. Serrated lesions should be classified pathologically according to the World Health Organization criteria as hyperplastic polyp, sessile serrated adenoma/polyp (SSA/P) with or without cytological dysplasia, or traditional serrated adenoma (TSA). SSA/P and TSA are premalignant lesions, but SSA/P is the principal serrated precursor of CRCs. Serrated lesions have a distinct endoscopic appearance, and several lines of evidence suggest that on average they are more difficult to detect than conventional adenomatous polyps. Effective colonoscopy requires an endoscopist trained in the endoscopic appearance of serrated lesions. We recommend that all serrated lesions proximal to the sigmoid colon and all serrated lesions in the rectosigmoid >5mm in size, be completely removed. Recommendations are made for post-polypectomy surveillance of serrated lesions and for surveillance of serrated polyposis patients and their relatives.
"We recommend that a single unequivocal architecturally distorted, dilated, and/or horizontally branched crypt, particularly if it is associated with inverted maturation, is sufficient for a diagnosis of SSA/P."

"Clinical recommendations made here are considered strong by the panel, but are supported by low quality or very low quality evidence, and are likely to change when higher quality evidence becomes available."


Sessile Serrated Polyp

**Goals of Detection**

- Identify a potential precursor to sporadic colon cancers with MSI-H
  - Usually proximal colon of older women
- How frequently do we see sporadic MSI-H cancers in rectum?
  - Uncommon (we have not had a case yet, despite universal MSI testing for several years)
- No prospective data suggesting a single abnormal crypt is important
**Take Home Points**

- Most non-dysplastic serrated polyps are easily classified
  - Polyps distal to splenic flexure are usually hyperplastic
  - Proximal colonic lesions are sessile serrated polyps
- Difficult polyps with a few dilated crypts
  - I don't make a diagnosis of sessile serrated polyp in the rectum, unless the findings are unequivocal
    - We aren't trying to prevent rectal cancer
  - "Hyperplastic polyp" with atypical features is difficult to defend in the ascending colon
  - Biologically important polyps are likely the minority (larger than 1 cm, proximal to splenic flexure)

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**Case 2**

- 50-year old man with family history of colon cancer
  - Mother had rectal cancer at age 60
- Endoscopy revealed two polyps in ascending colon
  - Small nodule that proved to be a prominent lymphoid aggregate
  - Large non-bleeding sessile polyp
- Received fragmented polypectomy specimen
Histologic Features
Histologic Features

Is that still in the mucosa?

Histologic Features

What about this?
Is the tumor in the muscularis mucosae, or through it?
Summary of Findings

- Epithelial neoplasm with high-grade dysplasia and infiltrating cancer cells
- Location of infiltrating component is not entirely clear (intramucosal carcinoma vs. invasive adenocarcinoma)
  - Infiltrating tumor cells have high-grade cytologic atypia
  - Signet rings cells are present

Diagnostic Considerations

- Invasive adenocarcinoma, high-grade, with signet ring cells
- Intramucosal adenocarcinoma with signet ring cells (pTis)
- Are these two situations equivalent (i.e. are signet ring cells bad, even if they are limited to the mucosa)?
15 patients
- 7 had no endoscopic recurrence or resection
- 7 underwent resection after polypectomy
  • 5 with no lymph node metastases or residual disease
  • 1 with a second carcinoma in resection specimen (intramucosal lesion, presumed metastasis)
  • 1 with perianal Paget disease

Polypectomy adequate therapy for lesions confined to muscularis mucosae


High-Grade “Intramucosal” Carcinoma
On High-Grade Intramucosal Carcinoma...

- Be careful
  - Cancer in the mucosa does not elicit desmoplasia, even if it is present in the submucosa or deeper wall
  - I generally don't make a diagnosis of intramucosal carcinoma unless I have the entire lesion (i.e. polypectomy)
- If everyone is confident that disease is confined to mucosa, additional surgery (colectomy) may not be necessary

Diagnosis

- Invasive adenocarcinoma, arising in a tubulovillous adenoma
- Superficial fragments of adenocarcinoma associated with an adenoma probably ok as alternate diagnosis
- Once we’ve decided the patient has cancer, are we done?
### Histologic Risk Factors in Malignant Polyps

<table>
<thead>
<tr>
<th>Feature</th>
<th>Residual Disease</th>
<th>Recurrent Disease</th>
<th>Lymph Node Metastases</th>
<th>Hematogenous Metastases</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection Margin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>30%</td>
<td>17%</td>
<td>7%</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Negative</td>
<td>3%</td>
<td>1%</td>
<td>9%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Odds Ratio</td>
<td>15</td>
<td>17.9</td>
<td>0.8</td>
<td>8.2</td>
<td>6.2</td>
</tr>
<tr>
<td>Poor Differentiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>18%</td>
<td>0%</td>
<td>23%</td>
<td>20%</td>
<td>15%</td>
</tr>
<tr>
<td>Absent</td>
<td>9%</td>
<td>0%</td>
<td>7%</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>Odds Ratio</td>
<td>2.2</td>
<td>0.0</td>
<td>3.9</td>
<td>3.9</td>
<td>9.2</td>
</tr>
<tr>
<td>Vascular Invasion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>18%</td>
<td>0%</td>
<td>35%</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Negative</td>
<td>15%</td>
<td>0%</td>
<td>7%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Odds Ratio</td>
<td>1.2</td>
<td>7.0</td>
<td>1.8</td>
<td>1.8</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Diagnosis

- Invasive adenocarcinoma, high-grade with signet ring cells, arising in a tubulovillous adenoma

Note: The lesion is not adequately excised. No vascular invasion identified.

- So the patient will get a colectomy
- Now, are we done?

Histologic Features

- Signet ring cells
- Tumor infiltrating lymphocytes
Follow-Up

- **Germline evaluation**
  - *MLH1* exon 7-8 deletion
  - Patient had Lynch syndrome
- **Colonic resection**
  - Invasive adenocarcinoma extending into muscularis propria
  - Eighteen negative regional lymph nodes
Take Home Points

- Be careful when thinking about “high-grade dysplasia” and “intramucosal adenocarcinoma” (pTis) in polypectomy and biopsy specimens
  - Invasive carcinoma in the mucosa generally lacks a desmoplastic stromal reaction
  - Colonized mucosa can look “adenomatous”
- Report on tumor grade, vascular invasion, and margin status when cancers come in “polyps”
- Tumor (or adenoma) infiltrating lymphocytes and heterogeneous patterns should prompt consideration of MSI-H
  - Recognition important if Lynch syndrome is a consideration

Case 3

- 78-year old male with rectal bleeding and elevated serum CEA
- Underwent colonoscopy
Histologic Features

High-grade dysplasia

Histologic Features

Submucosal epithelium

Extruded mucin pools
Histologic Features

High-grade cytologic and architectural atypia

Diagnostic Considerations

- Invasive adenocarcinoma
- Adenoma with misplaced epithelium and high-grade dysplasia/intramucosal adenocarcinoma
Histologic Features

So we are really only worried about this

This is in the mucosa

Histologic Features

Lobular arrangement of glands
Histologic Features

Lamina propria

Histologic Features
Histologic Features

- Hemosiderin deposits

Diagnosis

- Adenoma with high-grade dysplasia and misplaced epithelium
Adenoma with Misplaced Epithelium

Classic Features

- Pedunculated polyps of sigmoid colon (85% of cases)
  - Presumably subjected to luminal trauma
- Lobular aggregates of mucosal elements in submucosa
- Inflammatory-type changes
  - Fibrosis and splayed smooth muscle cells
  - Hemosiderin and blood
  - Extruded mucin pools, dilated crypts

Adenoma with Misplaced Epithelium
Differential Diagnosis

Invasive Adenocarcinoma

Adenoma with Misplaced Epithelium

Differential Diagnosis

Invasive Adenocarcinoma

Adenoma with Misplaced Epithelium
Adenoma with Misplaced Epithelium

Background of benign mucosal elements

Immunohistochemistry

P53 in Cancer

P53 in Adenoma

Take Home Points

- Think about submucosal epithelial misplacement
  - Lobular arrangement of submucosal epithelium
  - Associated lamina propria or non-neoplastic epithelium
  - Inflammatory changes
    - A few paucicellular mucin pools in submucosa
    - Hemorrhage or hemosiderin
    - Circumferential arrangement of fibrosis and smooth muscle around submucosal epithelium

- Think about carcinoma
  - More than mild cytologic atypia
  - Infiltrative appearance
  - Numerous, irregular mucin pools, especially if there is a lot of associated epithelium

Case 4

- 75-year old man underwent colonoscopy for clinical history of polyps
- Found to have a 3 cm sessile polyp in the right colon
- Mostly (70%) resected to reveal tubulovillous adenoma with low-grade dysplasia
- Patient underwent surgical resection 35 days after initial colonoscopy and biopsy
  - 14 negative lymph nodes
  - Margins free of adenoma
Histologic Features

Histologic Features
Diagnostic Considerations

- Invasive adenocarcinoma with mucinous areas
- Not cancer
  - Adenoma with misplaced epithelium (weird for a sessile polyp in the right colon)
  - Adenoma with misplaced epithelium for other reasons (i.e. endoscopic manipulation)

Histologic Features

Rounded contour, communication with luminal surface
Histologic Features

Associated lamina propria

Histologic Features

Associated with edge of benign gland and lamina propria
Histologic Features

Disrupted, benign-appearing glands
Histologic Features

Not overtly malignant, no stromal reaction

Ki-67 Immunohistochemistry
P53 Immunohistochemistry

Diagnosis

Epithelial displacement (misplacement) in an adenoma secondary to endoscopic manipulation
Biopsy Related Changes in Adenomas

- Similar histologic features compared to adenomas with misplaced epithelium, although more closely mimic carcinoma
- Features typical of polyps that are not completely resected at first procedure
  - Usually in right colon (polyps with misplaced epithelium occur in sigmoid colon)
  - Often sessile
  - Frequently large

Another Case

Layered fibrin and granulation tissue with entrapped epithelium
Another Case

Epithelium and granulation tissue

Mimics of Submucosal Invasion

Biopsy-Related Changes
Mimics of Submucosal Invasion

Biopsy-Related Changes

Mucin pools in adenoma with low-grade dysplasia

Erosion or disruption of crypt with granulation tissue
Mimics of Submucosal Invasion

Biopsy-Related Changes

Single cells associated with disrupted, regenerative crypts

Pathologic Features of Sampled Adenomas

<table>
<thead>
<tr>
<th>Histologic feature</th>
<th>Adenomas with Biopsy-Related Displaced Epithelium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytologic Features</td>
<td></td>
</tr>
<tr>
<td>Overlying surface adenoma</td>
<td></td>
</tr>
<tr>
<td>Low-grade dysplasia</td>
<td>15/16 (94%)</td>
</tr>
<tr>
<td>High-grade dysplasia</td>
<td>1/16 (6%)</td>
</tr>
<tr>
<td>Submucosal epithelium</td>
<td></td>
</tr>
<tr>
<td>Low-grade dysplasia</td>
<td>15/16 (94%)</td>
</tr>
<tr>
<td>High-grade dysplasia</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other Features</td>
<td></td>
</tr>
<tr>
<td>Single cells/clusters</td>
<td>6/16 (38%)</td>
</tr>
<tr>
<td>Lamina propria</td>
<td>14/16 (88%)</td>
</tr>
<tr>
<td>Extruded mucin</td>
<td>12/16 (75%)</td>
</tr>
<tr>
<td>Granulation tissue</td>
<td>3/16 (19%)</td>
</tr>
<tr>
<td>Fibrosis with fibroblastic proliferation</td>
<td>4/16 (25%)</td>
</tr>
<tr>
<td>Hemorrhage/hemosiderin</td>
<td>7/16 (44%)</td>
</tr>
<tr>
<td>Erosions or ulcers</td>
<td>7/16 (44%)</td>
</tr>
<tr>
<td>Disrupted benign glands</td>
<td>3/16 (19%)</td>
</tr>
</tbody>
</table>

Panarelli, et al. Mod Pathol 2015; 28(Suppl 2): 183A
Take Home Points

Think about prior manipulation of polyp
- Atypical epithelium associated with clearly benign epithelium and lamina propria in submucosa
- Gland disruption
- Apparently infiltrative cells embedded in granulation tissue or fibrin
- Myofibroblastic stromal response, not clearly desmoplasia
- Tattoo pigment or other evidence of procedure

Clinical history of prior biopsy is not always provided

Thank You
Difficulties in Staging Colorectal Cancers

Rhonda K. Yantiss, MD
Professor Department of Pathology and Laboratory Medicine
Department of Pathology and Laboratory Medicine
Weill Medical College of Cornell University

Colorectal Carcinoma
Pathologic Assessment of Specimens

- Gold standard for evaluating extent of disease
- Identify histologic prognostic factors
- Measure efficacy of neoadjuvant therapy
- Facilitate ancillary (molecular) studies
- Provide quality assessment (surgery, radiology, pathology)
- Guide treatment decisions (adjuvant therapy and clinical trials)
**Treatment Implications of Stage**

- **Stage I (T1-T2, N0, M0):** Surgical resection
- **Stage II (T3-T4, N0, M0):** Surgical resection, potential adjuvant chemotherapy in high-risk cases
- **Stage III (any T, N1 or N2, M0):** Surgical resection and adjuvant/neoadjuvant chemotherapy + radiation
- **Stage IV (any T, any N, M1):** Chemotherapy with potential surgery

**Colorectal Cancer Reporting in 2015**

*Selected Problematic Issues*

- Subjective interpretative issues
  - How do I recognize a T4 tumor?
- Microscopic disease in lymph nodes
  - Can I ignore isolated tumor cells?
- Tumor deposits and lymph nodes
Recognition of pT4

TNM Staging AJCC 7th Edition  
*Tumor (T)*

- pTis: Tumor limited to muscularis mucosae
- pT1: Tumor limited to submucosa
- pT2: Tumor limited to muscularis propria
- pT3: Tumor extends into pericolic tissue
- pT4: Tumor penetrates serosa (pT4a) or invades adjacent organs (pT4b)*

*AJCC 6th edition:
  pT4a=invasion of adjacent organs
  pT4b=serosal penetration*
Changing Definitions of pT4a and pT4b

- Overestimated bad prognosis of serosal penetration (6th edition)
  - Inability to recognize subtle (most) cases
  - Data skewed in direction of patients with extensive serosal involvement (and a bad prognosis)
- Makes sense
  - Tumor that invades another organ should do worse than one that is less extensive

CAP Cancer Staging Protocol/AJCC Staging

- Tumor present at peritoneal surface
- Tumor cells on peritoneal surface
The Importance of Gross Examination

Fat is not circumferential on the abdominal colon
Recognizing Serosal Penetration *Gross Examination*

Recognizing Serosal Penetration *Gross Examination*
Recognizing Serosal Penetration *Gross Examination*

Recognizing Serosal Penetration *Gross Examination*
Recognizing Serosal Penetration *Gross Examination*

Features of Serosal Penetration (Localized Peritoneal Involvement)
CAP Cancer Staging Protocol/AJCC Staging

Tumor present at peritoneal surface

Tumor cells on peritoneal surface

Present in nearly one-third of surgically resected colonic carcinomas

**Serosal Penetration**

- Relationship between serosa and tumor classified as "local peritoneal involvement"
  - Free tumor cells on serosal surface (LP4)
  - Tumor present at surface in association with serosal reaction (LP3)
  - Tumor within 1 mm of serosa associated with a serosal reaction (LP2)
    - Mesothelial hyperplasia
    - Fibroinflammatory response
    - Fibrin on serosa
  - Tumor clear of serosa without any reaction (LP1)

Serosal Penetration

Tumor <1 mm from the peritoneal surface with a reaction

Recognizing Serosal Penetration

Tumor <1 mm from Serosal Reaction (LP2)

Fibrin on serosa (erosion/ulcer)
Survival of Patients with Peritoneal Involvement


Gaps Between Recommendations and Clinical Practice

- 102 pathologists polled in North America and United Kingdom
  - 45 teaching hospitals and 57 community practices
  - 49 “GI” and 53 “general” pathologists
- To which of the following scenarios would you assign a stage of pT4a?
  - 92%: Tumor at or on the serosal surface or free within peritoneal cavity (LP3 and LP4)
  - 49%: Tumor <1mm from the serosal surface with a fibroinflammatory and serosal reaction (LP2)
  - 7%: Tumor <1 mm from the serosal surface without any fibroinflammatory serosal reaction (LP1)
- Cancer present <1 mm from the serosal surface with a fibroinflammatory peritoneal reaction is best staged as:
  - pT4a (45%) [For GI pathologists: Canada 32%, USA 87%, UK 50%]
  - pT3 without a comment (7%)
  - pT3 with a comment to suggest that there could be a breach of the peritoneum, and the tumor may behave like a pT4a tumor (48%)

• 120 colon cancers staged according to AJCC 7th ed.
• Serosal cytology smears
  - Positive cytology in 55% of tumors at serosal surface (pT4a)
  - 46% of tumors ≤1 mm from serosa that showed a tissue reaction (pT3 by strict criteria)

Recognizing Serosal Penetration

Entrapped Mesothelium Near Serosa

Clefts between Fat Lobules
Recognizing Serosal Penetration
*Clefts between Fat Lobules*

1. Recognizing Serosal Penetration
   *Entrapped Mesothelium*
Gross Perforation Through Tumor is at Least pT4a, Regardless of Histologic Findings

Recognizing Tumoral Perforation

Gross Examination
Recognizing Tumoral Perforation
Microscopic Examination

Recognizing Tumoral Perforation
Microscopic Examination
Recognizing Tumoral Perforation

Microscopic Examination

- Perpendicular arrays of capillaries
- Fibrin on serosa

Recognizing Tumoral Perforation

- ?Mesothelium
- Fibrin
- Cancer
Ancillary Techniques

**Assessment for Serosal Penetration**

*Elastin Stains*

- Subserosal elastic lamina
  - Directly subjacent to visceral peritoneum
- Destruction by invasive carcinoma
  - Detected with elastin stains
  - Surrogate marker of serosal penetration by tumor
Assessment for Serosal Penetration

**Elastin Stains**

- Tumor confined to muscularis propria
Assessment for Serosal Penetration

Elastin Stains

Problematic Issues

Elastin Stains

- Elastic lamina may not be present in all cases, especially tumors of right colon
- Elastic lamina may be retracted or incomplete at advancing front of cancer due to fibrosis
- Elastic fibrils may be present at advancing front of tumors that are not close to the peritoneal surface
  - Disruption of these fibrils does not necessarily imply serosal penetration
Lymph Nodes and Tumor Deposits

High-Risk Stage II Cancers
NCCN Guidelines

- Clinical features
  - Colonic obstruction by tumor
  - Colonic perforation
- Pathologic features
  - Tumor penetration of serosa (pT4a)
  - Close, indeterminate, or positive margins
  - Inadequate lymph node sampling (<12 negative nodes)
  - High-grade (G3-G4) features in a microsatellite stable (MSS) tumor
  - Lymphovascular or venous invasion
  - Perineural invasion
**TNM Staging**

**Regional Lymph Nodes (N)**

- All grossly negative nodes entirely submitted
- Minimum required number: 12-15
  - Clarifying solutions, additional sections
- No definite minimum after neoadjuvant treatment of rectal cancer
  - Fewer identified lymph nodes may be a marker of better response to therapy
- Lymph node detection
  - Patient factors (sex, obesity)
  - Length of resected colon
  - Surgeon and pathologist skill and experience
- Ratio (number positive/number collected) may be better prognostic indicator than number positive


**Small Lymph Node Deposits**

- Micrometastases (0.2-2 mm)
  - Classified as positive node
  - Categorized as pN1 (mic)
- Isolated tumor cells (single clusters <0.2 mm)
  - Classified as negative node
  - If only “positive” node has a tiny cluster (<0.2 mm), then categorized as pNO (i+)
    - Denotes “isolated tumor cells”, not “immunopositive”
**AJCC and CAP Guidelines**

**Regional Lymph Nodes (N)**

- **pN1 (mic)** for deposits 0.2-2 mm

- Isolated tumor cells (single clusters): **pN0 (i+)**

*Courtesy of Dr. Alexandros Polydorides, Mount Sinai Medical School, NY, NY*
Isolated Tumor Cells (i+)

- Biologic significance not entirely clear
- Limited data, mostly in breast cancer
- Guanylyl cyclase 2C (GUCY2C)
  - Colonic epithelium and adenocarcinoma
- Stage II colon cancer at risk for recurrence

**Tumor Deposits**

- Peritumoral nodule of cancer without residual nodal structure
  - Within regional lymph drainage of tumor
- Possible explanations
  - Lymph node metastasis with complete effacement of residual lymph node
  - Lymphovascular, venous, or perineural invasion with extravascular/extraneural extension
- Biologic importance
  - Poor prognostic factor, independent of T and N


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**TNM Staging Revisions Over Time**

*Tumor Deposits*

<table>
<thead>
<tr>
<th>TNM Staging System</th>
<th>Major Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>AJCC 6th edition (2002)</td>
<td>Tumor deposit 3 mm rule</td>
</tr>
<tr>
<td>AJCC 7th edition (2009)</td>
<td>3 mm rule replaced by contour rule</td>
</tr>
<tr>
<td></td>
<td>Isolated tumor cells considered negative</td>
</tr>
<tr>
<td></td>
<td>Subclassification of N1 (N1a and N1b) and N2 (N2a and N2b)</td>
</tr>
<tr>
<td></td>
<td>Peritumoral deposits classified as N1c, if no other regional lymph node metastases</td>
</tr>
</tbody>
</table>
**TNM Staging AJCC 5th Edition**

*“3 mm Rule” for Classifying Deposits*

- <3 mm considered extension of tumor
  - Staged in T category (pT3)
- >3 mm considered replaced lymph node
  - Staged in N category
- Reproducible, but clinically irrelevant

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**TNM Staging AJCC 6th Edition**

*“Contour Rule” for Classifying Deposits*

- Round nodule considered lymph node
  - Staged in N category
- Irregular nodule considered perineural or vascular invasion
  - Staged in T category (problematic if tumor T1 or T2)
TNM Staging AJCC 7th Edition

pN1c Classification of Deposits

- Intended to identify patients with stage I or II disease “at risk” for recurrence
- Classified in the “N” category to upstage patients for potential adjuvant therapy
- “N1c” chosen to denote these individuals for long term follow up in large, multi-institutional studies
  - Intended to be used with T1-T2 tumors
  - Now applied to T3 and T4 as well

Effects of Survival

Number and Type of Tumor Deposits

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Reporting of Peritumoral Deposits

If subjective impression is that a tumor nodule represents a replaced lymph node, it is staged as N1a, N1b, N2a, or N2b.

Tumor deposits are prognostically important and counted.
Staged as N1c if all nodes negative.

Helpful Diagnostic Features

- **Effaced lymph node**
  - Round shape
  - Peripheral rim of lymphocytes
  - Capsule
  - Peripheral lymphoid follicles
  - Subcapsular sinus

- **Tumor deposits**
  - Irregular contour
  - No organized lymphoid tissue
  - Not surrounded by capsule (parallel collagen fibrils)
  - Sometimes near arteries (reflecting effaced veins)

Lymph Node or Tumor Deposit?


Tumor Deposits vs. Lymph Node Metastases
Mountains out of Molehills
Mimics of Tumor Deposits

Venous Invasion

Clear cut venous invasion is not a tumor deposit

Mimics of Tumor Deposits

Peritoneal Seeding (M1)

Tumor spread along peritoneal surface is not a tumor deposit
Reporting Tumor Deposits and N1c

- Tumor nodule in regional lymph drainage
  - No residual lymph node architecture
- Tumor deposit may be considered if a nodule cannot be classified as
  - Lymph node
  - Lymphatic vessel invasion
  - Venous invasion
  - Perineural invasion

Tumor deposits do not affect T stage
Do not add tumor deposits to total positive lymph node count
  - Separately documented (and counted)
Do not use N1c if any lymph nodes contain metastases
N1c does not imply more advanced stage than N1a or N1b
Colorectal Cancer Staging

Take Home Points

• Tumor staging
  - Serosal penetration is underdiagnosed and likely single most important feature to identify
    • Can affect management (chemotherapy for Stage II)

• Lymph node issues
  - Inadequate harvest can affect management
  - Isolated tumor cells (<0.2 mm) are not currently classified as positive lymph nodes

• Documenting tumor deposits
  - Do not add to lymph node count or tumor stage
  - N1c limited to cases that are otherwise node-negative
  - Distinction from effaced nodes largely academic