Protocol for the Examination of Specimens from Patients with Primary Carcinomas of the Colon and Rectum

Well differentiated neuroendocrine neoplasms (carcinoid tumors) are not included.

Based on AJCC/UICC TNM, 6th edition
Protocol web posting date: July 2008
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Procedures
• Excisional Biopsy (Polypectomy)
• Local Excision (Transanal Disk Excision)
• Colectomy (Total, Partial, or Segmental Resection)
• Rectal Resection (Low Anterior Resection or Abdominoperineal Resection)

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Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: July 2008
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COLON AND RECTUM: Excisional Biopsy (Polypectomy)

Check 1 Response Unless Otherwise Indicated

Tumor Site (Note A)
___ Cecum
___ Right (ascending) colon
___ Hepatic flexure
___ Transverse colon
___ Splenic flexure
___ Left (descending) colon
___ Sigmoid colon
___ Rectum
___ Not specified

*Specimen Integrity
*___ Intact
*___ Fragmented

*Polyp Size
*Greatest dimension: ___ cm
*Additional dimensions: ___ x ___ cm
*___ Cannot be determined (see Comment)

*Polyp Configuration
*___ Pedunculated with stalk
*Stalk length: ___ cm
*___ Sessile

Size of Invasive Carcinoma
Greatest dimension: ___ cm
*Additional dimensions: ___ x ___ cm
___ Cannot be determined (see Comment)

* Data elements with asterisks are not required for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.
Histologic Type *(Note B)*
___ Adenocarcinoma
___ Mucinous adenocarcinoma
___ Signet-ring cell carcinoma
___ Small cell carcinoma
___ Squamous cell carcinoma
___ Adenosquamous carcinoma
___ Medullary carcinoma
___ Undifferentiated carcinoma
___ Other (specify): __________________________
___ Carcinoma, type cannot be determined

Histologic Grade *(Note C)*
___ Not applicable
___ Cannot be determined
___ Low-grade (well differentiated to moderately differentiated)
___ High-grade (poorly differentiated to undifferentiated)

Tumor Extension *(Note D)*
___ Cannot be determined
Invasion (deepest):
___ Lamina propria
___ Muscularis mucosae
___ Submucosa
___ Muscularis propria

Margins (check all that apply)

Deep Margin (Stalk Margin)
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
   Distance of invasive carcinoma from margin: ___ mm
___ Involved by invasive carcinoma

Mucosal/Lateral Margin
___ Not applicable
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma
___ Involved by adenoma

Venous (Large Vessel) Invasion (V) *(Note E)*
___ Not identified
___ Present
___ Indeterminate

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Lymphatic (Small Vessel) Invasion (L) (Note F)
___ Not identified
___ Present
___ Indeterminate

*Type of Polyp in Which Invasive Carcinoma Arose (Note G)
*___ Tubular adenoma
*___ Villous adenoma
*___ Tubulovillous adenoma
*___ Traditional serrated adenoma
*___ Sessile serrated adenoma
*___ Hamartomatous polyp
*___ Indeterminate

*Additional Pathologic Findings (check all that apply)
*___ None identified
*___ Inflammatory bowel disease
    *___ Active
    *___ Quiescent
*___ Other (specify): ________________________________

*Ancillary Studies
*Specify: ________________________________
___ Not performed

*Comment(s)
**Surgical Pathology Cancer Case Summary (Checklist)**

Protocol web posting date: July 2008  
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**COLON AND RECTUM: Resection, Including Transanal Disk Excision of Rectal Neoplasms**

Check 1 Response Unless Otherwise Indicated

**Specimen (check all that apply) (Note A)**  
___ Terminal ileum  
___ Cecum  
___ Appendix  
___ Ascending colon  
___ Transverse colon  
___ Descending colon  
___ Sigmoid colon  
___ Rectum  
___ Anus  
___ Other (specify): ____________________________  
___ Not specified

**Procedure**  
___ Right hemicolectomy  
___ Transverse colectomy  
___ Left hemicolectomy  
___ Sigmoidectomy  
___ Rectal/rectosigmoid colon (low anterior resection)  
___ Total abdominal colectomy  
___ Abdominoperineal resection  
___ Transanal disk excision (local excision)  
___ Other (specify): ____________________________  
___ Not specified

**Specimen Length (if applicable)**  
*Specify: ___ cm

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Tumor Site (check all that apply) *(Note A)*
___ Cecum
___ Right (ascending) colon
___ Hepatic flexure
___ Transverse colon
___ Splenic flexure
___ Left (descending) colon
___ Sigmoid colon
___ Rectosigmoid
___ Rectum
___ Colon, not otherwise specified
___ Cannot be determined (see Comment)

Tumor Size
Greatest dimension: ___ cm
*Additional dimensions: ___ x ___ cm
___ Cannot be determined (see Comment)

Macroscopic Tumor Perforation *(Note H)*
___ Present
___ Absent
___ Cannot be determined

*Macroscopic Intactness of Mesorectum *(Note I)*
*___ Not applicable
*___ Complete
*___ Near complete
*___ Incomplete
*___ Cannot be determined

Histologic Type *(Note B)*
___ Adenocarcinoma
___ Mucinous adenocarcinoma
___ Signet-ring cell carcinoma
___ Small cell carcinoma
___ Squamous cell carcinoma
___ Adenosquamous carcinoma
___ Medullary carcinoma
___ Undifferentiated carcinoma
___ Other (specify): __________________________
___ Carcinoma, type cannot be determined

Histologic Grade *(Note C)*
___ Not applicable
___ Cannot be assessed
___ Low-grade (well differentiated to moderately differentiated)
___ High-grade (poorly differentiated to undifferentiated)
___ Other (specify): __________________________

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**Histologic Features Suggestive of Microsatellite Instability (Note J)**

*Intratumoral Lymphocytic Response (tumor-infiltrating lymphocytes)*

* ___ None
* ___ Mild to moderate (0 to 2 per high-power [X400] field)
* ___ Marked (3 or more per high-power field)

*Peritumor Lymphocytic Response (Crohn-like response)*

* ___ None
* ___ Mild to moderate
* ___ Marked

*Tumor Subtype and Differentiation (check all that apply)*

* ___ Mucinous tumor component (specify percentage: ____%)
* ___ Medullary tumor component
* ___ High histologic grade (poorly differentiated)

**Microscopic Tumor Extension**

___ Cannot be assessed
___ No evidence of primary tumor
___ Intramucosal carcinoma, invasion of lamina propria
___ Tumor invades submucosa
___ Tumor invades muscularis propria
___ Tumor invades through the muscularis propria into the subserosal adipose tissue or the nonperitonealized pericolic or perirectal soft tissues but does not extend to the serosal surface

**Maximal Extension (check all that apply)**

___ Tumor directly invades adjacent structures (specify): ______________________
___ Tumor microscopically involves the serosal surface (visceral peritoneum)

**Margins (check all that apply) (Note K)**

**Proximal Margin**

___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma
___ Intramucosal carcinoma/adenoma absent at proximal margin
___ Intramucosal carcinoma/adenoma present at proximal margin

**Distal Margin**

___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma
___ Intramucosal carcinoma/adenoma absent at distal margin
___ Intramucosal carcinoma/adenoma present at distal margin

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**Circumferential (Radial) or Mesenteric Margin**

- Not applicable
- Cannot be assessed
- Uninvolved by invasive carcinoma
- Involved by invasive carcinoma (tumor present 0-1 mm from margin)

If all margins uninvolved by invasive carcinoma:

Distance of invasive carcinoma from closest margin: ___ mm \( OR \) ___ cm

Specify margin: __________________________

**Lateral Margin (for noncircumferential transanal disk excision)**

- Cannot be assessed
- Uninvolved by invasive carcinoma
  
  Distance of invasive carcinoma from closest lateral margin: ___ mm
  
  *Specify location (eg, o’clock position), if possible:
  __________________________

- Involved by invasive carcinoma
  
  *Specify location (eg, o’clock position), if possible:
  __________________________

- Uninvolved by adenoma
- Involved by adenoma

**Treatment Effect (applicable to carcinomas treated with neoadjuvant therapy)** *(Note L)*

- No prior treatment
- Present
  
  *No residual tumor (complete response, grade 0)
  *Marked response (grade 1, minimal residual cancer)
  *Moderate response (grade 2)
- No definite response identified (grade 3, poor or no response)
- Not known

**Vascular (Large Vessel) Invasion (V) (Note E)**

- Not identified
- Present
- Indeterminate

**Lymphatic (Small Vessel) Invasion (L) (Note F)**

- Not identified
- Present
- Indeterminate

*Discontinuous Extramural Extension (irregular tumor nodules in pericolorectal adipose tissue without histologic evidence of residual lymph node) *(Note M)*

* Not identified
* Present
* Cannot be determined

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Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.
*Perineural Invasion (Note F)
  * ___ Not identified
  * ___ Present

*Type of Pre-existing Polyp in Which Invasive Carcinoma Arose (Note G)
  * ___ None identified
  * ___ Tubular adenoma
  * ___ Villous adenoma
  * ___ Tubulovillous adenoma
  * ___ Traditional serrated adenoma
  * ___ Sessile serrated adenoma
  * ___ Hamartomatous polyp
  * ___ Indeterminate

Pathologic Staging (pTNM) (Note N)

TNM Descriptors
  ___ None
  ___ m (multiple primary tumors)
  ___ r (recurrent)
  ___ y (post-treatment)

Primary Tumor (pT)
  ___ pTX: Cannot be assessed
  ___ pT0: No evidence of primary tumor
  ___ pTis: Carcinoma in situ, intraepithelial (no invasion)
  ___ pTis: Carcinoma in situ, invasion of lamina propria
  ___ pT1: Tumor invades submucosa
  ___ pT2: Tumor invades muscularis propria
  ___ pT3: Tumor invades through the muscularis propria into the subserosa or the nonperitonealized pericolic or perirectal soft tissues
  ___ pT4a: Tumor penetrates the visceral peritoneum
  ___ pT4b: Tumor directly invades other organs or structures

Regional Lymph Nodes (pN)
  ___ pNX: Cannot be assessed
  ___ pN0: No regional lymph node metastasis
  ___ pN1: Metastasis in 1 to 3 regional lymph nodes
  ___ pN2: Metastasis in 4 or more regional lymph nodes

Specify: Number examined: ___
  Number involved: ___

Distant Metastasis (pM)
  ___ Cannot be assessed (pMX)
  ___ pM1: Distant metastasis
    *Specify site(s): ______________________________

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*Additional Pathologic Findings (check all that apply)*
*___ None identified
*___ Adenoma(s)
*___ Chronic ulcerative proctocolitis
*___ Crohn disease
*___ Dysplasia arising in inflammatory bowel disease
*___ Other polyps (type[s]): ___________________________
*___ Other (specify): ___________________________

*Ancillary Studies *(Note O)*
*Specify: ___________________________________________
*___ Not performed

**Comment(s)**
Explanatory Notes

A. Anatomic Sites
The protocol applies to all carcinomas arising in the colon and rectum. It excludes carcinomas of the vermiform appendix.

The colon is divided as shown in Figure 1. The right colon is subdivided into the cecum and the ascending colon. The left colon is subdivided into the descending colon and sigmoid colon (see Table).

Anatomic Subsites of the Colon and Rectum

<table>
<thead>
<tr>
<th>Site</th>
<th>Relationship to Peritoneum (see Note K)</th>
<th>Dimensions (approximate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cecum</td>
<td>Entirely covered by peritoneum</td>
<td>6 x 9 cm</td>
</tr>
<tr>
<td>Ascending colon</td>
<td>Retroperitoneal; posterior surface lacks peritoneal covering; lateral and anterior surfaces covered by visceral peritoneum (serosa)</td>
<td>15-20 cm long</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>Intraperitoneal; has mesentery</td>
<td>Variable</td>
</tr>
<tr>
<td>Descending colon</td>
<td>Retroperitoneal; posterior surface lacks peritoneal covering; lateral and anterior surfaces covered by visceral peritoneum (serosa)</td>
<td>10-15 cm long</td>
</tr>
<tr>
<td>Sigmoid colon</td>
<td>Intraperitoneal; has mesentery</td>
<td>Variable</td>
</tr>
<tr>
<td>Rectum</td>
<td>Upper third covered by peritoneum on anterior and lateral surfaces; middle third covered by peritoneum only on anterior surface; lower third has no peritoneal covering</td>
<td>12 cm long</td>
</tr>
</tbody>
</table>

The transition from sigmoid to rectum is marked by the fusion of the tenia coli of the sigmoid to form the circumferential longitudinal muscle of the rectal wall approximately 12 to 15 cm from the dentate line. The rectum is defined clinically as the distal large intestine commencing opposite the sacral promontory and ending at the upper border of the anal canal (Figure 2). When measuring below with a rigid sigmoidoscope, it extends 16 cm from the anal verge.

Tumors located at the border between 2 subsites of the colon (e.g., cecum and ascending colon) are registered as tumors of the subsite that is more involved. If 2 subsites are involved to the same extent, the tumor is classified as an "overlapping" lesion.

A tumor is classified as rectal if its inferior margin lies less than 16 cm from the anal verge or if any part of the tumor is located at least partly within the supply of the superior
rectal artery. A tumor is classified as rectosigmoid when differentiation between rectum and sigmoid according to the previous guidelines is not possible.

B. Histologic Types
For consistency in reporting, the histologic classification proposed by the World Health Organization (WHO) is recommended and is shown in the following.

WHO Classification of Colorectal Carcinoma
Adenocarcinoma
Mucinous (colloid) adenocarcinoma (greater than 50% mucinous)
Signet-ring cell carcinoma (greater than 50% signet-ring cells)
Squamous cell carcinoma
Adenosquamous carcinoma
Medullary carcinoma
Small cell carcinoma (high-grade neuroendocrine carcinoma)
Undifferentiated carcinoma
Other (specify)

# By convention, signet-ring cell carcinomas, small cell carcinomas, and undifferentiated carcinomas are high grade (see Note C). The only histologic types of colorectal carcinoma that have been shown to have adverse prognostic significance independent of stage are signet-ring cell carcinoma and small cell carcinoma (high-grade neuroendocrine carcinoma).

## Medullary carcinoma is a distinctive histologic type strongly associated with high levels of microsatellite instability (MSI-H), indicative of defects in normal DNA repair gene function. Medullary carcinoma may occur either sporadically or in association with hereditary nonpolyposis colon cancer (HNPCC). This tumor type is characterized by solid growth in nested, organoid, or trabecular patterns, with no immunohistochemical evidence of neuroendocrine differentiation. Medullary carcinomas are also characterized by numerous tumor infiltrating lymphocytes (see Note J).

### The term "carcinoma, NOS" (not otherwise specified) is not part of the WHO classification.

C. Histologic Grade
A number of grading systems for colorectal cancer have been suggested, but a single widely accepted and uniformly used standard for grading is lacking. Most systems stratify tumors into 3 or 4 grades as follows.

Grade 1 Well differentiated
Grade 2 Moderately differentiated
Grade 3 Poorly differentiated
Grade 4 Undifferentiated

Despite a significant degree of interobserver variability, histologic grade has repeatedly been shown by multivariate analysis to be a stage-independent prognostic factor. Specifically, it has been demonstrated that high tumor grade is an adverse prognostic factor. It is noteworthy that in the majority of studies documenting the prognostic power of tumor grade, the number of grades has been collapsed to produce a 2-tiered stratification for data analysis as follows.
Low-grade: Well differentiated and moderately differentiated  
High-grade: Poorly differentiated and undifferentiated  

The widest variations in grading concern the stratification of low-grade tumors into well- or moderately-differentiated categories, whereas interobserver variability in diagnosing high-grade carcinoma is relatively small. Therefore, in light of its proven prognostic value, relative simplicity, and reproducibility, a 2-tiered grading system for colorectal carcinoma (ie, low grade and high grade) is recommended. The following criteria for grading based on gland formation alone are suggested.  

<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade</td>
<td>Greater than or equal to 50% gland formation</td>
</tr>
<tr>
<td>High grade</td>
<td>Less than 50% gland formation</td>
</tr>
</tbody>
</table>

D. Carcinoma in an Adenomatous Polyp  
Colorectal adenomas containing invasive adenocarcinoma that extends through the muscularis mucosae into the submucosa have been defined as "malignant polyps." This term encompasses cases in which the entire polyp head is replaced by carcinoma and adenomas with focal malignancy, but the definition excludes adenomas with high-grade dysplasia (intraepithelial carcinoma) or intramucosal carcinoma (invasive carcinoma limited to the lamina propria or invading no deeper than the muscularis mucosae), because these polyps possess negligible biological potential for metastasis (see Tis in Note N).  

Malignant polyps removed by endoscopic polypectomy require evaluation of histologic factors related to the risk of adverse outcome (ie, lymph node metastasis or local recurrence from residual malignancy) following polypectomy. Factors shown to have independent prognostic significance and are important in determining the need for further surgical treatment include the following:  

- Histologic grade  
- Extent (level) of invasion  
- Status of the resection margin  
- Lymphatic/venous vessel involvement  

An increased risk of adverse outcome has been shown to be associated with the following:  

- High-grade carcinoma  
- Tumor at or less than 1 mm from the resection margin  
- Lymphatic/venous vessel involvement  

E. Venous (Large Vessel) Invasion  
Venous invasion has been demonstrated by multivariate analysis to be an independent adverse prognostic factor. Invasion of extramural veins, in particular, has been shown to be an independent indicator of unfavorable outcome and increased risk of occurrence of hepatic metastasis.  

The significance of intramural venous invasion is less clear, because data specific to this issue are lacking. Nevertheless, it is recommended that the presence or absence of venous invasion and its anatomic location should be reported in all cases.  

Venous invasion is coded as follows in the AJCC staging system.
Venous Invasion (V)
- VX: Venous invasion cannot be assessed
- V0: No venous invasion
- V1: Microscopic venous invasion
- V2: Macroscopic venous invasion

F. Lymphatic (Small Vessel) and Perineural Invasion
In several studies, both lymphatic invasion\(^{20}\) and perineural invasion\(^{21}\) have been shown by multivariate analysis to be independent indicators of poor prognosis. The prognostic significance, if any, of the anatomic location of these structures is not defined. Furthermore, it is not always possible to distinguish lymphatic vessels from postcapillary venules, because both are small, thin-walled structures. Thus, the presence or absence of tumor invasion of small, thin-walled vessels should be reported in all cases, and its anatomic location within the colonic wall noted.\(^{14}\)

Lymphatic invasion is coded as follows in the AJCC staging system.

Lymphatic Vessel Invasion (L)
- LX: Lymphatic vessel invasion cannot be assessed
- L0: No lymphatic vessel invasion
- L1: Lymphatic vessel invasion

G. Polyps
Distinction should be made between traditional serrated adenomas, which exhibit cytologic features of adenomas, and the newly described sessile serrated adenomas.\(^{22}\) The sessile serrated adenoma may be the precursor lesion for colorectal carcinomas with high levels of microsatellite instability; they are more commonly found in the right colon and are characterized by serrated architecture with bulbous dilatation of deep crypts and lack of overt nuclear atypia, in most cases.

H. Perforation
Tumor perforation is an uncommon complication of colorectal cancer, but one that is associated with a poor outcome, including high in-hospital mortality and morbidity.\(^{23}\) Perforation of the uninvolved colon proximal to an obstructing tumor is also associated with high mortality because of generalized peritonitis and sepsis. Reported perforation rates range from 2.6% to 9%. Perforation is more likely to occur in older patients.

I. Mesorectal Envelope
The quality of the surgical technique is a key factor in the success of surgical treatment for rectal cancer, both in the prevention of local recurrence and in long-term survival. Numerous studies have demonstrated that total mesorectal excision (TME) improves local recurrence rates and the corresponding survival by as much as 20%. This surgical technique entails precise sharp dissection within the areolar plane outside (lateral to) the visceral mesorectal fascia in order to remove the rectum. This plane encases the rectum, its mesentery, and all regional nodes and constitutes Waldeyer fascia. High-quality TME surgery reduces local recurrence from 20% to 30% to 8% to 10% or less and increases 5-year survival from 48% to 68%.\(^{24,25}\) Adjuvant therapy in the presence of a high-quality TME may further reduce local recurrence (from 8% to 2.6%).\(^{25}\)
Pathologic evaluation of the resection specimen has been shown to be a sensitive means of assessing the quality of rectal surgery. It is superior to indirect measures of surgical quality assessment, such as perioperative mortality, rates of complication, number of local recurrences, and 5-year survival. It has been shown that macroscopic pathologic assessment of the completeness of the mesorectum of the specimen, scored as complete, partially complete, or incomplete, accurately predicts both local recurrence and distant metastasis. Microscopic parameters, such as the status of the circumferential resection margin, the distance between the tumor and nearest circumferential margin (ie, “surgical clearance”), and the distance between the tumor and the closest distal margin, are all important predictors of local recurrence and may be affected by surgical technique. There is strong evidence that the status of the circumferential resection margin is a powerful predictor of local recurrence but is inconsistently evaluated and underreported.

The nonperitonealized surface of the fresh specimen is examined circumferentially, and the completeness of the mesorectum is scored as described in the following. The entire specimen is scored according to the worst area.

Incomplete
- Little bulk to the mesorectum
- Defects in the mesorectum down to the muscularis propria
- After transverse sectioning the circumferential margin appears very irregular

Nearly Complete
- Moderate bulk to the mesorectum
- Irregularity of the mesorectal surface with defects greater than 5 mm, but none extending to the muscularis propria
- No areas of visibility of the muscularis propria except at the insertion site of the levator ani muscles

Complete
- Intact bulky mesorectum with a smooth surface
- Only minor irregularities of the mesorectal surface
- No surface defects greater than 5 mm in depth
- No coning towards the distal margin of the specimen
- After transverse sectioning the circumferential margin appears smooth

J. Histopathologic Features Suggestive of Microsatellite Instability
Identification of MSI-H colorectal tumors is important, as mismatch repair deficiency may serve as a prognostic marker of patient outcome, a predictive marker of response to chemotherapy, and as a screening tool for HNPCC (Lynch syndrome). Revised Bethesda guidelines for HNPCC detection recommend testing colorectal tumors for microsatellite instability under the following circumstances:

1. Colorectal cancer diagnosed in a patient who is younger than 50 years
2. Presence of synchronous, metachronous, or other HNPCC-associated tumors (endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, small bowel, and brain tumors and sebaceous adenomas and keratoacanthomas), regardless of age
3. Colorectal cancer with MSI-H histology in a patient who is younger than 60 years
4. Colorectal cancer in 1 or more first-degree relatives with an HNPCC-related tumor, with 1 of the cancers being diagnosed at younger than 50 years.
5. Colorectal cancer diagnosed in 2 or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.

# MSI-H histologic features are defined as presence of tumor-infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring cell differentiation, or medullary growth pattern.26

Tumor-infiltrating lymphocytes are closely associated with microsatellite instability and medullary architecture (see previous) and should be distinguished from Crohn-like peritumoral infiltrates (lymphoid aggregated or follicles are the tumor edge, not associated with pre-existing lymph node).27 Although absolute cut-off values have not been established, only moderate- and high-density intratumoral lymphocytes (approximately 3 or more per high-power field using hematoxylin-eosin [H&E]-stained sections) should be considered significant.28

Other pathologic features associated with MSI-H status in colorectal carcinomas include right-sided location, high-grade histology, and lack of dirty necrosis.28

K. Margins
It may be helpful to mark the margin(s) closest to the tumor with ink following close examination of the serosal surface for puckering and other signs of tumor involvement. Margins marked by ink should be designated in the macroscopic description of the surgical pathology report. The serosal surface (visceral peritoneum) does not constitute a surgical margin.

In addition to addressing the proximal and distal margins, the circumferential (radial) margin (Figure 3, A through C) must be assessed for any segment either unencased (Figure 3, C) or incompletely encased by peritoneum (Figure 3, B) (see Note A). The circumferential margin represents the adventitial soft tissue margin closest to the deepest penetration of tumor (Figure 4) and is created surgically by blunt or sharp dissection of the retroperitoneal or subperitoneal aspect respectively. Multivariate analysis has suggested that tumor involvement of the circumferential margin is the most critical factor in predicting local recurrence in rectal cancer.29 A positive circumferential margin in rectal cancer increases the risk of recurrence by 3.5-fold and doubles the risk of death from disease. For this reason, the circumferential margin should be assessed in all rectal carcinomas as well as colonic segments with nonperitonealized surfaces. The distance between the tumor and radial margin should be reported (see Note I). The circumferential margin is considered negative if the tumor is more than 1 mm from the inked nonperitonealized surface but should be recorded as positive if tumor is located 1 mm or less from the nonperitonealized surface because local recurrence rates are similar with clearances of 0 to 1 mm. This includes tumor within a lymph node as well as direct tumor extension, but if circumferential margin positivity is based solely on intranodal tumor, this should be so stated.

The mesenteric resection margin is the only relevant circumferential margin in segments completely encased by peritoneum (eg, transverse colon) (Figure 3, A). Involvement of this margin should be reported even if tumor does not penetrate the serosal surface.
Sections to evaluate the proximal and distal resection margins can be obtained either by longitudinal sections perpendicular to the margin or by en face sections parallel to the margin. The distance from the tumor edge to the closest resection margin(s) may also be important, particularly for low anterior resections. For these cases, a distal resection margin of 2 cm is considered adequate; for T1 and T2 tumors, 1 cm may be sufficient distal clearance. Anastomotic recurrences are rare when the distance to the closest transverse margin is 5 cm or greater.

In cases of carcinoma arising in a background of inflammatory bowel disease, proximal and distal resection margins should be evaluated for dysplasia and active inflammation.

In the AJCC system, tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown in the following.

RX Presence of residual tumor cannot be assessed
R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

L. Treatment Effect

Neoadjuvant chemoradiation therapy in rectal cancer is associated with significant tumor response and downstaging. Because eradication of the tumor, as detected by pathologic examination of the resected specimen, is associated with a significantly better prognosis, specimens from patients receiving neoadjuvant chemoradiation should be thoroughly sectioned, with careful examination of the tumor site. Minimal residual disease has been shown to have a better prognosis than gross residual disease. While several grading systems for tumor response have been advocated, a 3-point tumor regression grade has been shown to provide good interobserver reproducibility compared to 5-grade schemas and to provide similar prognostic significance.

Tumor regression should be assessed only in the primary tumor; lymph node metastases should not be included in the assessment.

Acellular pools of mucin in specimens from patients receiving neoadjuvant therapy are considered to represent completely eradicated tumor and are not used to assign pT stage or counted as positive lymph nodes.

M. Discontinuous Extramural Extension

Irregular tumor deposits in pericolic or perirectal fat are considered discontinuous extramural extension and are not counted as lymph nodes replaced by tumor. Most examples are due to lymphovascular or, more rarely, perineural invasion.
N. TNM and Stage Groupings
Surgical resection remains the most effective therapy for colorectal carcinoma, and the best estimation of prognosis is derived from the pathologic findings on the resection specimen. The anatomic extent of disease is by far the most important prognostic factor in colorectal cancer.

The protocol recommends the TNM staging system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) but does not preclude the use of other staging systems.

By AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

TNM Descriptors
For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y” and “r” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor prior to multimodality therapy (ie, before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval and is identified by the “r” prefix: rTNM.

T Category Considerations
pTis. For colorectal carcinomas, "carcinoma in situ" (pTis) as a staging term includes cancer cells confined within the glandular basement membrane (intraepithelial carcinoma, synonymous with high-grade dysplasia) or invasive into the mucosal lamina propria, up to but not through the muscularis mucosae (intramucosal carcinoma). Tumor extension through the muscularis mucosae into the submucosa is classified as T1 (Figure 5).

pT4. Direct invasion of other organs or structures includes invasion of other segments of colorectum by way of the serosa or mesocolon, for example, invasion of the sigmoid colon by carcinoma of the cecum, is classified as pT4 (Figure 6, A through D). In such a case, both an adjacent organ and the visceral peritoneum are penetrated by tumor. Intramural extension of tumor from 1 subsite (segment) of the large intestine into an
adjacent subsite or into the ileum (eg, for a cecal carcinoma) or anal canal (eg, for a rectal carcinoma) does not affect the pT classification.\(^4\)

Tumor that is adherent to other organs or structures macroscopically is classified as T4. However, if no tumor is found within the adhesion microscopically, the tumor should be assigned T3.\(^1\)

For rectal tumors, invasion of the external sphincter is classified as T3, whereas invasion of the levator ani muscle(s) is classified as T4.

Tumor in veins or lymphatics does not affect the pT classification.

**Subdivision of T4 into T4a and T4b.** Serosal involvement by tumor cells (pT4a) has been demonstrated by multivariate analysis to have a negative impact on prognosis,\(^3^4\) as does direct invasion of adjacent organs (pT4b). Visceral peritoneal involvement can be missed without thorough sampling and/or sectioning, and malignant cells have been identified in serosal scrapings in as many as 26% of specimens categorized as pT3 by histologic examination alone.\(^3^4\) The absence of standard guidelines for assessing peritoneal involvement may contribute to underdiagnosis.

Shepherd and colleagues\(^3^4\) defined the spectrum of microscopic patterns of peritoneal involvement as follows.

1. A mesothelial inflammatory and/or hyperplastic reaction with tumor close to, but not at, the serosal surface
2. Tumor present at the serosal surface with inflammatory reaction, mesothelial hyperplasia, and/or erosion/ulceration
3. Free tumor cells on the serosal surface (in the peritoneum) with underlying ulceration of the visceral peritoneum

All the previously listed types of peritoneal involvement were associated with decreased survival, especially types 2 and 3. In contrast, tumor well clear of the serosa had no independent adverse effect on prognosis. Therefore, it is recommended that the T4a category encompass types 2 and 3 of serosal involvement, detailed previously. Free perforation into the peritoneal cavity is always classified as pT4.

**N Category Considerations**

The regional lymph nodes for the anatomical subsites of the large intestine (Figure 7) are as follows.

- **Cecum:** anterior cecal, posterior cecal, ileocolic, right colic
- **Ascending colon:** ileocolic, right colic, middle colic
- **Hepatic flexure:** middle colic, right colic
- **Transverse colon:** middle colic
- **Splenic flexure:** middle colic, left colic, inferior mesenteric
- **Descending colon:** left colic, inferior mesenteric, sigmoid
- **Sigmoid colon:** inferior mesenteric, superior rectal sigmoidal, sigmoid mesenteric
- **Rectosigmoid:** perirectal, left colic, sigmoid mesenteric, sigmoidal, inferior mesenteric, superior rectal, middle rectal
- **Rectum:** perirectal, sigmoid mesenteric, inferior mesenteric, lateral sacral, presacral, internal iliac, sacral promontory, superior rectal, middle rectal, inferior rectal
Nodes along the sigmoid arteries are considered pericolic nodes, and their involvement is classified as N1 or N2 according to the number involved.

Perirectal lymph nodes include the mesorectal (paraproctal), lateral sacral, presacral, sacral promontory (Gerota), middle rectal (hemorrhoidal), and inferior rectal (hemorrhoidal) nodes. Metastasis in the external iliac or common iliac nodes is classified as distant metastasis.4

Submission of lymph nodes for microscopic examination. All grossly negative or equivocal lymph nodes are to be submitted entirely.14 Grossly positive lymph nodes may be partially submitted for microscopic confirmation of metastasis.

Variables affecting number of lymph nodes found in colorectal resection specimens include thoroughness of pathologic examination, surgical procedure performed, variations in immune response,35 and individual patient anatomy. Lymph nodes may be more difficult to identify in specimens from patients who are obese36 or elderly, or after neoadjuvant therapy.37

There is no universal agreement upon the minimum number of lymph nodes that predict for regional node negativity,38-40 although 12 to 15 lymph nodes has been advocated.14 Removal and pathologic examination of at least 12 lymph nodes from resected colon cancer cases has been proposed by the Commission on Cancer and endorsed by the National Quality Forum as a quality improvement measure; such quality improvement measures are intended to be used for internal monitoring of performance within an organization or group so that analyses and subsequent remedial actions can be taken, as appropriate (see http://www.facs.org/cancer/qualitymeasures.html). If fewer nodes are found, re-examining the specimen for additional lymph nodes, with or without visual enhancement techniques, should be considered.14 The pathology report should clearly state the total number of lymph nodes examined and the total number involved by metastases. Data are insufficient to recommend routine use of tissue levels or special/ancillary techniques.14

Nonregional lymph nodes. For microscopic examination of lymph nodes in large resection specimens, lymph nodes must be designated as regional versus nonregional, according to the anatomic location of the tumor. Metastasis to nonregional lymph nodes is classified as distant metastasis and designated as M1.

Lymph nodes replaced by tumor. A tumor nodule in the pericolonic/perirectal fat without histologic evidence of residual lymph node tissue is classified in the N category as regional nodal metastasis (lymph node replacement by tumor) if the nodule has the form and smooth contour of a lymph node. If the nodule has an irregular contour, it is recommended that the nodule be classified in the pT category as discontinuous extramural extension.1,4 Extramural smooth-contour tumor nodules are counted individually as replaced lymph nodes when assigning the pN category.

Micrometastasis and isolated tumor cells. A micrometastasis is defined as tumor measuring greater than 0.2 mm but less than or equal to 2.0 mm in greatest dimension. Micrometastases are classified as N1(mic) or M1(mic) in lymph nodes or at distant sites, respectively. Isolated tumor cells (ITCs) are defined as single tumor cells or small clusters of tumor cells measuring 0.2 mm or less, usually found by special techniques such as immunohistochemical staining, and are classified as N0.4 Because the biologic
significance of ITCs (either a single focus in a single node, multiple foci within a single node, or micrometastatic involvement of multiple nodes) remains unproven, N0 is considered justified. The number of lymph nodes involved by micrometastases or ITCs should be clearly stated.

Routine assessment of regional lymph nodes is limited to conventional pathologic techniques (gross assessment and histologic examination) and data are currently insufficient to recommend special measures to detect micrometastasis or ITCs. Thus, neither multiple levels of paraffin blocks nor the use of special/ancillary techniques such as immunohistochemistry are recommended for routine examination of regional lymph nodes. Specific denotation of the assigned N category is suggested as follows for cases in which ITCs are the only evidence of possible metastatic disease.

<table>
<thead>
<tr>
<th>pN0</th>
<th>No regional lymph node metastasis histologically, no examination for isolated tumor cells (ITCs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN0(i-)</td>
<td>No regional lymph node metastasis histologically, negative morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs</td>
</tr>
<tr>
<td>pN0(i+)</td>
<td>No regional lymph node metastasis histologically, positive morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs</td>
</tr>
<tr>
<td>pN0(mol-)</td>
<td>No regional lymph node metastasis histologically, negative nonmorphologic (molecular) findings for ITCs</td>
</tr>
<tr>
<td>pN0(mol+)</td>
<td>No regional lymph node metastasis histologically, positive nonmorphologic (molecular) findings for ITCs</td>
</tr>
</tbody>
</table>

**TNM Stage Groupings**
Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically unfeasible), and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

<table>
<thead>
<tr>
<th>Stage 0</th>
<th>Tis</th>
<th>N0</th>
<th>M0*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1,T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T3,T4</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>Any T</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

* M0 is defined as no distant metastasis.

**O. Ancillary Studies**
Detection of defects in mismatch repair in colorectal carcinomas is important for detection of Lynch syndrome (a subset of HNPCC syndrome accounting for
approximately 2% of all colorectal carcinomas), and examination of the tissue for defective DNA mismatch repair is recommended if any of the criteria in the revised Bethesda guidelines (Note J)\textsuperscript{26} are met. In addition, emerging data suggest that high levels of microsatellite instability in sporadic colon cancers (approximately 15% of all sporadic cases) are associated with better outcome and may serve as a predictor of response to 5-FU-based chemotherapy, although these latter indications for testing are not clearly established and have not been accepted as standard of care.

Detection of high levels of microsatellite alterations (MSI) by polymerase chain reaction assay is definitional for defective DNA mismatch repair. This testing is performed on paraffin-embedded tissue and compares results of tumor DNA to that of non-neoplastic tissues from the same patient.

Testing for defective DNA mismatch repair may also be performed using immunohistochemistry. The most commonly used methods are immunohistochemistry for MLH1, MSH2, MSH6, and PMS2; antibodies are commercially available. Any positive reaction in the nuclei of tumor cells is considered as intact expression (normal), and it is common for intact staining to be somewhat patchy. An interpretation of expression loss should be made only if positive reaction is seen in internal control cells, such as the nuclei of stromal, inflammatory, or benign epithelial cells. Intact expression of all 4 stains indicates that mismatch repair enzymes tested are intact but does not entirely exclude Lynch syndrome, as approximately 5% of families may have a missense mutation (especially MLH1) that can lead to a nonfunctional protein with retained antigenicity. Defects in lesser-known mismatch repair enzymes may also lead to a similar result, but this situation is rare. Negative results in MLH1 may be due to Lynch Syndrome or methylation of the promoter region (as occurs in sporadic MSI colorectal carcinoma). Genetic testing is ultimately required for this distinction, although a specific \textit{b-raf} mutation is present in many sporadic cases, but not familial cancers. Loss of MSH2 expression essentially always implies Lynch syndrome. PMS2 loss is often associated with loss of MLH1 and is only independently meaningful if MLH1 is intact. MSH6 is similarly related to MSH2.

References


Colon and Rectum Protocol Figures

Figure 1. Anatomic subsites of the colon. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Ill. The original source for this material is the AJCC Cancer Staging Atlas (2006) edited by Greene et al. and published by Springer Science and Business Media, LLC, www.springerlink.com.

Figure 2. Anatomic subsites of the rectum. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Ill. The original source for this material is the AJCC Cancer Staging Atlas (2006) edited by Greene et al. and published by Springer Science and Business Media, LLC, www.springerlink.com.
**Figure 3.** A. Mesenteric margin in portion of colon completely encased by peritoneum (dotted line). B. Circumferential margin (dotted line) in portion of colon incompletely encased by peritoneum. C. Circumferential margin (dotted line) in rectum, completely unencased by peritoneum.

**Figure 4.** T4 (left side) with involvement of serosa (visceral peritoneum) by tumor cells in a segment of colorectum with a serosal covering. In contrast, the right side of the diagram shows T3 with macroscopically positive circumferential margin (designated R2 in AJCC staging system), corresponding to gross disease remaining after surgical excision. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Ill. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) edited by Greene et al² and published by Springer Science and Business Media, LLC, www.springerlink.com.
**Figure 5.** T1 tumor invades submucosa; T2 tumor invades muscularis propria; T3 tumor invades through the muscularis propria into the subserosa or into nonperitonealized pericolic, or perirectal tissues (adventitia). Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Ill. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) edited by Greene et al. and published by Springer Science and Business Media, LLC, www.springerlink.com.
Figure 6. A. T4b tumor showing direct invasion of coccyx. B. T4 tumor directly invading adjacent loop of small bowel. C. T4 tumor showing gross perforation of bowel through tumor (left). The right hand panel shows T4 tumor directly invading adjacent bowel. D. T4a tumor with involvement of serosa (visceral peritoneum) by tumor cells. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Ill. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) edited by Greene et al² and published by Springer Science and Business Media, LLC, www.springerlink.com.
Figure 7. The regional lymph nodes of the colon and rectum. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Ill. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) edited by Greene et al\textsuperscript{2} and published by Springer Science and Business Media, LLC, www.springerlink.com.