Protocol for the Examination of Excisional Biopsy or Polypectomy Specimens From Patients With Primary Carcinoma of the Colon and Rectum

Version: 4.3.0.0

Protocol Posting Date: December 2023

The use of this protocol is recommended for clinical care purposes but is not required for accreditation purposes.

This protocol may be used for the following procedures AND tumor types:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excisional biopsy</td>
<td>Excisional Biopsy (Polypectomy), Endoscopic Mucosal Resection, Endoscopic Mucosal Dissection, or Transanal Disk Excision</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma</td>
<td>Invasive carcinomas including small cell and large cell (poorly differentiated) neuroendocrine carcinoma</td>
</tr>
</tbody>
</table>

The following should NOT be reported using this protocol:

<table>
<thead>
<tr>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forceps biopsy</td>
</tr>
<tr>
<td>Resection (consider the Colon Resection protocol)</td>
</tr>
<tr>
<td>Cytologic specimens</td>
</tr>
</tbody>
</table>

The following tumor types should NOT be reported using this protocol:

<table>
<thead>
<tr>
<th>Tumor Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-differentiated neuroendocrine tumors (consider the Colorectal NET protocol)</td>
</tr>
<tr>
<td>Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocol)</td>
</tr>
<tr>
<td>Sarcoma (consider the Soft Tissue protocol)</td>
</tr>
</tbody>
</table>

Authors

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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.

* Denotes primary author.

Accreditation Requirements

The use of this case summary is recommended for clinical care purposes but is not required for accreditation purposes. The core and conditional data elements are routinely reported. Non-core data elements are indicated with a plus sign (+) to allow for reporting information that may be of clinical value.
Summary of Changes

v 4.3.0.0

- Added elements for Endoscopic Mucosal Resections and Transanal Disk Excision specimens
- Added a "Procedure" question
- Added "Depth of Submucosal Invasion" question
- LVI question update from "Lymphovascular Invasion" to "Lymphatic and/or Vascular Invasion"
- Added a "Perineural Invasion" question
- Update to "Margin" section
CASE SUMMARY: (COLON AND RECTUM: Excisional Biopsy (Polypectomy))

Standard(s): AJCC-UICC 8

This case summary is recommended for reporting biopsy specimens, but is not required for accreditation purposes.

SPECIMEN

Procedure
___ Excisional biopsy (polypectomy)
___ Endoscopic mucosal resection (EMR)
___ Endoscopic submucosal dissection (ESD)
___ Transanal disk excision
___ Other (specify): ____________________
___ Not specified

+Specimen Integrity
___ Intact
___ Fragmented

TUMOR

Tumor Site (Note A)
___ Cecum: _________________
___ Ileocecal valve: _________________
___ Ascending colon: _________________
___ Hepatic flexure: _________________
___ Transverse colon: _________________
___ Splenic flexure: _________________
___ Descending colon: _________________
___ Sigmoid colon: _________________
___ Rectosigmoid region: _________________
___ Rectum: _________________
___ Other (specify): _________________
___ Not specified

Histologic Type (Note B)
___ Adenocarcinoma
___ Mucinous adenocarcinoma
___ Signet-ring cell carcinoma (poorly cohesive carcinoma)
___ Medullary adenocarcinoma
___ Serrated adenocarcinoma
___ Micropapillary carcinoma
___ Adenoma-like adenocarcinoma
___ Adenosquamous carcinoma
___ Undifferentiated carcinoma
___ Carcinoma with sarcomatoid component
___ Large cell neuroendocrine carcinoma
___ Small cell neuroendocrine carcinoma
___ Mixed neuroendocrine-non-neuroendocrine neoplasm
___ Other histologic type not listed (specify): __________________
___ Carcinoma, type cannot be determined: __________________
+Histologic Type Comment: __________________

Histologic Grade (Note C)
___ G1, well differentiated
___ G2, moderately differentiated
___ G3, poorly differentiated
___ G4, undifferentiated
___ Other (specify): __________________
___ GX, cannot be assessed: __________________
___ Not applicable: __________________

+Size of Invasive Carcinoma
___ Greatest dimension in Centimeters (cm): _________________ cm
+Additional Dimension in Centimeters (cm): ____ x ____ cm
___ Cannot be determined (explain): _________________

Tumor Extent (Note D)
___ Invades lamina propria
___ Invades muscularis mucosae
___ Invades submucosa
___ Invades muscularis propria
___ Cannot be determined: __________________

+Depth of Sub-mucosal Invasion (Note D)
___ Less than 1 mm
___ Greater than or equal to 1 mm and less than 2 mm
___ Greater than 2 mm
___ Exact depth in Millimeters (mm): _________________ mm
___ Cannot be determined (explain): _________________

Lymphatic and / or Vascular Invasion (Note E) (select all that apply)
___ Not identified
___ Small vessel
___ Large vessel (venous)
___ Present (not otherwise specified)
___ Cannot be determined: __________________

Perineural Invasion (Note E)
___ Not identified
___ Present
___ Cannot be determined: ____________________

**Tumor Budding Score (Note F)**

___ Low (0-4)
___ Intermediate (5-9)
___ High (10 or more)
___ Cannot be determined: ____________________

**+Number of Tumor Buds (Note F)**

___ Specify number in one 'hotspot' field (in an area = 0.785 mm2): __________________ per 'hotspot' field
___ Other (specify): __________________
___ Cannot be determined: ____________________

**+Type of Polyp in which Invasive Carcinoma Arose (Note G)**

___ Tubular adenoma
___ Villous adenoma
___ Tubulovillous adenoma
___ Traditional serrated adenoma
___ Sessile serrated adenoma / sessile serrated polyp / sessile serrated lesion
___ Hamartomatous polyp
___ Other (specify): __________________

**Polyp Size (required only for polypectomy specimens)**

___ Not applicable
___ Greatest polyp dimension in Centimeters (cm): _________________ cm

**+Additional Polyp Dimension in Centimeters (cm): _________________ cm**
___ Cannot be determined (explain): __________________

**Polyp Configuration (required only for polypectomy specimens)**

___ Not applicable
___ Pedunculated with stalk

**+Stalk Length**

___ Specify length in Centimeters (cm): _________________ cm
___ Other (specify): __________________
___ Cannot be determined: __________________
___ Sessile

**Tumor Dimension(s) (required only for intact endoscopic mucosal resections / transanal disk excision / endoscopic mucosal dissection)**

___ Not applicable
___ Greatest dimension in Centimeters (cm): _________________ cm

**+Additional Dimension in Centimeters (cm): ______ x ______ cm**
___ Cannot be determined (explain): __________________

**Margin Orientation Status (required only if applicable)**

___ Not applicable
__ Oriented
__ Unoriented

Number of Specimen Fragments (required only if specimen is fragmented)
__ Not applicable (specimen is intact)
__ Exact number (specify): _________________
__ Cannot be determined

+Dimension of Largest Fragment
__ Greatest dimension of the largest fragment in Centimeters (cm): _________________ cm
  +Additional Dimension of the Largest Fragment in Centimeters (cm): ____ x ____ cm
__ Cannot be determined (explain): _________________

+Tumor Comment: _________________

MARGINS

Margin Status for Invasive Carcinoma
__ All margins negative for invasive carcinoma

Distance from Invasive Carcinoma to Deep / Stalk Margin
Specify in Centimeters (cm)
__ Exact distance in cm: _________________ cm
__ Greater than 1 cm
Other
__ Other (specify): _________________
__ Cannot be determined: _________________
__ Not applicable: _________________

+Distance from Invasive Carcinoma to Peripheral / Lateral Mucosal Margin
Specify in Centimeters (cm)
__ Exact distance in cm: _________________ cm
__ Greater than 1 cm
Other
__ Other (specify): _________________
__ Cannot be determined: _________________
__ Not applicable: _________________
__ Invasive carcinoma present at margin

Margin(s) Involved by Invasive Carcinoma (select all that apply)
__ Deep (stalk): _________________
__ Peripheral / lateral mucosal
__ Other (specify): _________________
__ Cannot be determined (explain): _________________
__ Other (specify): _________________
__ Cannot be determined (explain): _________________
__ Not applicable

Margin Status for Non-Invasive Tumor (select all that apply)
__ All margins negative for adenoma
__ Adenoma present at mucosal margin: _________________
___ Other (specify): _________________
___ Cannot be determined (explain): _________________
___ Not applicable

+Margin Comment: _________________

ADDITIONAL FINDINGS

+Additional Findings (select all that apply)
___ None identified
___ Ulcerative colitis
___ Crohn disease
___ Other polyp(s) (specify type[s]): _________________
___ Other (specify): _________________

SPECIAL STUDIES (Note H)
For reporting molecular testing and immunohistochemistry for mismatch repair proteins, and for other cancer biomarker testing results, the CAP Colorectal Biomarker Template should be used. Pending biomarker studies should be listed in the Comments section of this report.

COMMENTS

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 and well-differentiated neuroendocrine tumors. 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 1).

![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.](image)

<table>
<thead>
<tr>
<th>Site</th>
<th>Relationship to Peritoneum</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 anorectal ring, which corresponds to the proximal border of the puborectalis muscle palpable on digital rectal examination (Figure 2).\textsuperscript{1} When measuring below with a rigid sigmoidoscope, it extends 16 cm from the anal verge.

![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.](image)

Tumors located at the border between two subsites of the colon (e.g., cecum and ascending colon) are registered as tumors of the subsite that is more involved. If two 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.\textsuperscript{3} The rectum commences at the sacral promontory, and the junction of sigmoid colon and rectum is anatomically marked by fusion of tenia coli to form the circumferential longitudinal muscle of the rectal wall. Intraoperatively, the rectosigmoid junction corresponds to the sacral promontory. A tumor is classified as rectosigmoid when differentiation between rectum and sigmoid according to the previously mentioned guidelines is not possible.\textsuperscript{4}

References

B. Histologic Types

For consistency in reporting, the histologic classification proposed by the World Health Organization (WHO) is recommended.¹

The histologic types of colorectal carcinoma that have been shown to have adverse prognostic significance independent of stage are signet-ring cell carcinoma² and poorly differentiated neuroendocrine carcinoma, such as small cell carcinoma (poorly differentiated neuroendocrine carcinoma).³

Medullary carcinoma is a distinctive histologic type strongly associated with high levels of microsatellite instability (MSI-H), indicative of defects in DNA repair gene function. Medullary carcinoma may occur either sporadically or in association with Lynch syndrome.⁴⁵⁶ 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 and a better prognosis.

Micropapillary carcinoma is characterized by small, tight clusters of tumor cells in cleft-like spaces, and is often present in association with conventional adenocarcinoma. This variant is strongly associated with lymphovascular invasion and lymph node metastasis.⁷

Serrated adenocarcinomas are characterized by neoplastic glands showing prominent serrations, tumor cells with basal nuclei and eosinophilic cytoplasm, and no or minimal luminal necrosis. These tumors are thought to be related to traditional serrated adenomas and may have a more aggressive course than conventional adenocarcinoma.⁸

References


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:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Well differentiated (&gt;95% gland formation)</td>
</tr>
<tr>
<td>2</td>
<td>Moderately differentiated (50-95% gland formation)</td>
</tr>
<tr>
<td>3</td>
<td>Poorly differentiated (&lt;50% gland formation)</td>
</tr>
<tr>
<td>4</td>
<td>Undifferentiated (no gland formation or mucin; no squamous or neuroendocrine differentiation)</td>
</tr>
</tbody>
</table>

Despite a significant degree of interobserver variability, histologic grade has been shown to be an important prognostic factor in many studies, with strong correlation between poor differentiation and adverse outcome. While some studies have stratified grade into a two-tiered low- and high-grade system, a three- or four-tier system is more commonly used for gastrointestinal carcinomas. The AJCC has specified use of a four-tiered grading system for colorectal cancer for the 8th edition of the TNM manual. Pathologists should use the four-tier histologic grading scheme as specified above to prevent errors in data recording. As per WHO, the grading scheme applies to adenocarcinoma, not otherwise specified, and not to histologic variants. For example, medullary carcinomas behave as low grade tumors even though they may appear poorly differentiated. This grading scheme is also not applicable to poorly differentiated neuroendocrine carcinomas.

References


D. High-Risk Features of Carcinoma in an Adenomatous Polyp and Local Excisions

Polypectomy and local excisions for early CRC may suffice as the definitive treatment of early colorectal carcinoma (pT1 tumors) and hence proper assessment of the specimens is needed to assess the risk of residual carcinoma and adverse outcomes (nodal or distant metastasis). The risk assessment based on various histological features forms the basis of subsequent management of the patient, especially oncologic surgical resection.
Adenomatous polyps, either sessile or pedunculated, containing invasive adenocarcinoma that extends through the muscularis mucosa into the submucosa have been defined as **malignant polyps**. The carcinoma in such cases can be focal or extensive. The definition excludes adenomas with high-grade dysplasia or intramucosal carcinoma (invasive carcinoma limited to the lamina propria or invading no deeper than the muscularis mucosa), because these polyps possess negligible biological potential for metastasis.

Malignant polyps can be removed by endoscopic polypectomy or local excision (submucosal excision/dissection, or transanal disc excision). Such specimens require evaluation of a variety of histologic features that can predict the risk of any adverse outcome (i.e., lymph node metastasis or local recurrence from residual malignancy) following polypectomy and help decide further management. Histologic features shown to have prognostic significance and helpful in determining the need for further surgical treatment include:

- Histologic type and grade
- Status of the resection margin
- Lymphatic/venous vessel involvement
- Tumor budding
- Depth of invasion

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

- High-grade carcinoma
- Tumor at or less than 1 mm from the resection margin
- Lymphatic/venous involvement (see note E)
- High-grade tumor budding (see note F)
- Deep submucosal invasion

Histologic grade and type should be reported as noted earlier (Notes B and C). Certain histologic types are by definition considered high grade (e.g., micropapillary-type, signet-ring cell-type, etc.). The evaluation of margin, especially the cauterized stalk margin for pedunculated polyps and deep resection margin for local excisions is considered important. Lymphatic and vascular involvement also needs to be evaluated and is often aided by special stains. Tumor budding that was earlier recognized as a “poor differentiation at the advancing edge of the tumor” remains one of most important independent histologic features for adverse outcomes in this setting (see note F). Assessment of the depth of submucosal invasion in early colon carcinoma has also been shown to be important in predicting adverse outcomes, but the methodology has varied and evolved with time. In pedunculated polyps the depth of invasion was evaluated as four levels (head, neck, stalk, and beyond stalk) called Haggitt levels. However, this is difficult to apply in sessile polyps and poorly oriented or fragmented specimens. Submucosal involvement has also been divided into superficial, mid, and deep levels (Kikuchi levels sm1, sm2 and sm3), but require presence of the entire submucosa in the specimen and hence cannot be applied to pedunculated polyps and sessile polyps that typically contain only a part of the submucosa. Other systems use actual measurement of depth of invasion and show the risk of nodal metastasis is none to minimal when the depth of invasion is < 1mm and becomes significant with invasion of ≥2mm. However, it can be difficult to accurately assess the depth or extent of submucosal involvement due to improper orientation and when the muscularis mucosae is completely destroyed due to tumor invasion and extensive desmoplasia. In such a setting, it has been suggested to draw a line joining preserved muscularis mucosae at the edges of the tumor to indicate the likely level of muscularis mucosae or when that is not possible,
measure the depth of invasion from the surface of the tumor. Each method for evaluating submucosal involvement has certain limitations, and while one is not clearly superior to the other, the Haggitt levels and Kikuchi levels can only be applied to a small subset of malignant polyps and hence the actual measurement of the depth appears most practical for the sake of consistency and the recommended method for malignant polyps.

References

E. Lymphatic, Vascular, and Perineural Invasion
It is recommended that small vessel vascular invasion should be reported separately from venous (large vessel) invasion. Small vessel invasion indicates tumor involvement of thin-walled structures lined by endothelium, without an identifiable smooth muscle layer or elastic lamina. Small vessels include lymphatics, capillaries, and postcapillary venules. Differentiation of lymphatics from other vascular channels requires application of lymphatic specific endothelial markers like D2-40. Small vessel invasion is associated with lymph node metastasis and has been shown to be an independent indicator of adverse outcome in several studies. The higher prognostic significance of extramural small vessel invasion has been suggested, but the importance of anatomic location in small vessel invasion (extramural or intramural) is not well defined.

Tumor involving endothelium-lined spaces with an identifiable smooth muscle layer or elastic lamina is considered venous (large vessel) invasion. Circumscribed tumor nodules surrounded by an elastic lamina
on hematoxylin-eosin (H&E) or elastic stain are also considered venous invasion. Venous invasion can be extramural (beyond muscularis propria) or intramural (submucosa or muscularis propria). Extramural venous invasion has been demonstrated by multivariate analysis to be an independent adverse prognostic factor in multiple studies and is a risk factor for liver metastasis.\textsuperscript{4} The significance of intramural venous invasion is less clear.

Perineural invasion has been shown to be an independent indicator of poor prognosis.\textsuperscript{5,6,7} While some series did not find perineural invasion to be a significant predictive factor in stage II disease,\textsuperscript{8,9} many studies have confirmed its adverse effect on survival in stage II disease.\textsuperscript{3,10} Extramural perineural invasion may have a greater adverse prognostic effect,\textsuperscript{6} but the distinction between intramural and extramural perineural invasion has not been well studied.

References


F. Tumor Budding

The presence of single cells or small clusters of less than five cells at the advancing front of the tumor is considered as peritumoral tumor budding. Numerous studies have shown that high tumor budding in adenocarcinoma arising in polyp is a significant risk factor for nodal involvement,\textsuperscript{1,2,3,4,6,6} with tumor budding being the most significant factor in some studies.\textsuperscript{3} Different criteria for evaluating and reporting tumor budding have been followed in literature. An international tumor budding consensus conference (ITBCC) in 2016 recommended the following criteria for evaluating tumor budding:\textsuperscript{2}
(1) Tumor budding counts should be done on H&E sections. In cases of obscuring factors like inflammation, immunohistochemistry for keratin can be obtained to assess the advancing edge for tumor buds, but the scoring should be done on H&E sections.

(2) Tumor budding should be reported by selecting a “hotspot” chosen after review of all available slides with invasive tumor. The total number of buds should be reported in an area measuring 0.785 mm², which corresponds to 20x field in some microscopes (use appropriate conversion for other microscopes, see table below).

(3) Both total number of buds and a three-tier score (based on 0.785 mm² field area) should be reported: low (0-4 buds), intermediate (5-9 buds), and high (10 or more buds).

This is not a required element, but it is recommended that this feature be reported for cancers arising in polyps (see note D) as well as for stage I and II cases.

<table>
<thead>
<tr>
<th>Objective Magnification:</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyepiece FN Diameter</td>
<td>Specimen FN Radius</td>
</tr>
<tr>
<td>(mm)</td>
<td>(mm)</td>
</tr>
<tr>
<td>18</td>
<td>9.0</td>
</tr>
<tr>
<td>19</td>
<td>9.5</td>
</tr>
<tr>
<td>20</td>
<td>10.0</td>
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<tr>
<td>25</td>
<td>12.5</td>
</tr>
<tr>
<td>26</td>
<td>13.0</td>
</tr>
</tbody>
</table>

Table. ITBCC Normalization Table for Reporting Tumor Budding According to Microscope.
To obtain tumor bud count for your field of view, divide by the normalization number.

References


G. Polyps
The adenocarcinoma can arise in adenomatous (tubular, tubulovillous, or villous) or serrated (sessile serrated adenoma/polyp or traditional serrated adenoma) polyp. Sessile serrated adenoma often develops cytologic dysplasia resembling tubular adenoma during neoplastic progression. These are presumed to be the precursors of right-sided adenocarcinomas with high levels of microsatellite instability (MSI-H).1

References

H. Ancillary Studies
Universal testing for microsatellite instability and/or status of DNA mismatch repair enzymes by immunohistochemistry is recommended by the EGAPP guidelines.1,2 MSI-high cancers are associated with right-sided location, tumor infiltrating lymphocytes, Crohn-like infiltrate, pushing borders, mucinous/signet ring/medullary subtypes, intratumoral heterogeneity (mixed conventional, mucinous, and poorly differentiated carcinoma), high-grade histology, and lack of dirty necrosis.3,4 In view of recommendations for universal testing and chance of missing cases of Lynch syndrome with testing based on Bethesda guidelines and implications for treatment with immune check-point inhibitors,4 evaluation of histologic features associated with MSI is redundant and is no longer included in the synoptic comment.

Further details about mismatch repair enzyme immunohistochemistry and PCR for MSI testing, as well as other ancillary molecular testing in colorectal cancer (such as KRAS, BRAF, Her2, etc.) can be found in the CAP Colon and Rectum Biomarkers protocol.

References