Pathologic evaluation is a critical component of the management of patients with colorectal cancer, from initial diagnosis through definitive treatment. Pathologic stage of the tumor following resection is the single most powerful prognostic indicator in colorectal cancer, and it typically determines the appropriateness of adjuvant treatment as well. Numerous additional pathologic factors are known to have prognostic significance that is independent of stage and may help to further substratify tumors. In this chapter, the pathologic features of colorectal cancers that predict outcome after surgical resection and have direct bearing on patient care are reviewed.

It should be noted that the pathologic evaluation of a colorectal cancer specimen may be more accurate and complete if the pathologist has knowledge of pertinent clinical and operative data. The principal responsibility for providing essential clinical information lies with the referring clinician(s). In addition, in some cases, orientation of the specimen or indication of anatomic areas of special concern may also be required of the referring clinician (surgeon). Requisition forms for pathology are designed to accommodate clinical information and may serve as the basic means of communication with the pathologist.

**DIAGNOSTIC BIOPSY IN COLORECTAL CANCER**

Masses or ulcers discovered by rectal examination, imaging, or endoscopic studies that are suspicious for colorectal carcinoma typically require biopsy confirmation as carcinomas before initiating treatment. A number of benign and malignant lesions may mimic colorectal carcinoma and require exclusion on biopsy. Other malignancies that may resemble colon cancer include colorectal lymphomas, carcinoid tumors, gastrointestinal stromal tumors (mural sarcomas), metastatic tumors that exhibit tropism for the gastrointestinal tract (eg, malignant melanoma), and malignancies of adjacent organs that directly invade the colorectum (eg, cancers of the ovary, endometrium, bladder, or prostate). Benign lesions that may mimic colorectal cancer include adenomas, hamartomas, solitary rectal ulcers, stercoral ulcers, endometriomas, and Crohn’s disease or diverticular disease with mural stricturing. Multiple biopsies taken from the edges and base of an ulcerating lesion or from the surface of a polypoid mass typically reveal the correct diagnosis. When an obstructing mass is present, however, it may be difficult to pass an endoscope to obtain diagnostic tissue and, in this situation, brush cytology may be useful to confirm the diagnosis. Even when direct access to the tumor is possible, biopsies may fail to reveal a definitive diagnosis if the lesion is extensively ulcerated or otherwise necrotic. In these cases, elevated serum carcinoembryonic antigen (CEA) levels and/or the presence of associated adenomatous epithelium from the edge of the mass increase the certainty that the tumor is a carcinoma.

The type and amount of information that can be derived from a diagnostic biopsy are limited. The presence of carcinoma can be unequivocally established with a successful biopsy, but the histologic type of tumor, the tumor grade, and the presence of invasion may be difficult or even impossible to determine. If the presence of tissue invasion can be identified with certainty, it is never possible to determine the depth of invasion from biopsy material.
PATHOLOGIC EVALUATION OF A MALIGNANT POLYPS

Diagnosis and treatment of colon cancers by endoscopic polypectomy has become commonplace. Most often, the cancer is unsuspected at endoscopy and revealed only on microscopic examination of the polypectomy specimen. Malignant polyps are defined as adenomas containing carcinoma that invades through the muscularis mucosae into the submucosa regardless of the overall proportion of the adenoma that is replaced by cancer (Figure 5–1). They encompass both polypoid carcinomas, in which the entire polyp head is replaced by carcinoma, and adenomas with focal malignancy. By definition, malignant polyps exclude adenomas containing intraepithelial carcinoma or intramucosal carcinoma because these polyps possess no biological potential for metastasis (see Definition of pTis below). Polyps containing invasive malignancy represent approximately 5 percent of all adenomas,\(^1\)\(^2\) and the chance that any given adenoma will contain an invasive malignancy increases with polyp size. The incidence of invasive carcinoma in adenomas of any histologic type that are greater than 2 cm in size ranges from 35 to 53 percent\(^3\) with villous adenomas having a higher incidence than tubular adenomas of equal size. Therefore, any polyp greater than 2 cm in diameter should be approached with the suspicion that it might harbor an invasive cancer. If technically possible, it is recommended that these polyps be removed in toto in one piece with as great a margin as possible at the base or stalk.

Malignant polyps constitute a form of early colorectal carcinoma that may be cured by endoscopic polypectomy alone.\(^4\)\(^–\)\(^6\) Following polypectomy alone, however, the incidence of an unfavorable outcome (i.e., lymph node metastasis or local recurrence from residual malignancy) for malignant polyps varies from about 10 to 20 percent.\(^7\)\(^8\) The histopathologic evaluation of malignant polyps removed endoscopically is critical to define polyps with an increased risk of residual or recurrent disease and directly affects the clinical management of the patient.\(^4\) The following histopathologic parameters have been shown to significantly increase the risk of adverse outcome:\(^9\)\(^–\)\(^18\)

- High tumor grade (poorly differentiated adenocarcinoma, signet-ring cell carcinoma, small-cell

\(\text{Figure 5–1. Malignant polyp. Low-grade (moderately differentiated) adenocarcinoma arising in a tubulovillous adenoma is seen infiltrating the submucosa of the polyp head where it is associated with a sclerotic stromal response. In the absence of lymphatic invasion, this low-grade cancer, located well above the resection margin of the polyp stalk, would be cured by polypectomy alone and require no further therapy.}\)
carcinoma, or undifferentiated carcinoma) (Figures 5–2, 5–3)
• Tumor at or less than 1 mm from the resection margin (Figure 5–4)
• Small (thin-walled) vessel (lymphatic or venular) involvement by tumor (Figure 5–5).

In the presence of one or more of these features, the risk of an adverse outcome following polypectomy alone is estimated to be about 10 to 25 percent. Therefore, if one or more of these high-risk features are found on pathologic examination of a resected polyp, further therapy may be indi-
cated. Optimal management is decided on an individual case basis, but segmental resection of the involved colonic segment, local excision (e.g., transanal disk excision for a low rectal lesion), or radiation therapy may be considered. In the absence of high-risk features, the chance of adverse outcome is extremely small, and polypectomy alone is considered curative.

In the pathologic assessment of malignant polyps for high-risk features, interobserver variability is greatest in relation to small vessel invasion. This feature may be impossible to diagnose definitively in

![Image](image1.png)

**Figure 5-4.** Involvement of the cauterized resection of a malignant polyp by invasive carcinoma. Malignant glands are present less than 1 to 2 mm from the resection margin of the polyp base/stalk and are involved by electrocautery artifact (arrow). This close approach of tumor to the polyp resection margin is an adverse prognostic factor for a malignant polyp treated by polypectomy alone.

![Image](image2.png)

**Figure 5-5.** Lymphatic invasion by carcinoma within the submucosa of the head of a malignant polyp. A small cluster of carcinoma cells is seen within a thin-walled channel lined by endothelial cells.
some cases and ultimately may be judged as being indeterminate. An absolute diagnosis of vessel invasion is dependent upon finding carcinoma cells within an endothelial-lined space. Contraction artifact in the tissue, tumor-induced stromal sclerosis, or extracellular mucin pools produced by the cancer may all complicate the evaluation of vessel invasion. Examination of additional tissue levels of the specimen, review by a second observer, and/or immunohistochemical staining for endothelial markers (eg, factor VII or CD34) may or may not help to resolve the dilemma. In published cases in which the malignant polyps have lacked definitive evidence of high-risk features but the patients have gone on to die of their disease, lymphatic invasion had been judged (on blinded review) as indeterminate because of a lack of interobserver agreement. Thus, even the suspicion of small vessel invasion may be regarded as ominous.

**PATHOLOGIC EVALUATION AND STAGING OF SURGERICALLY RESECTED COLORECTAL CANCER**

The pathology report of a colorectal cancer resection specimen typically documents the anatomic site of the malignancy, the histologic type, the parameters that determine the local tumor stage, and the histopathologic confirmation of distant metastasis, if applicable. Other features that are reported include those that have additional prognostic or predictive value as well as those that may be important for clinicopathologic correlation or quality control (eg, actual tumor size versus size measurement by imaging techniques). The essential pathologic features of a colorectal cancer and the clinical significance of these findings are reviewed individually below.

**Anatomic Site of the Tumor**

Documentation of the exact anatomic location of a colorectal carcinoma is a fundamental part of the pathologic assessment. This is performed as part of the gross or macroscopic examination of the specimen. Orientation of the specimen may be difficult in some cases because of distortion of the anatomy by tumor and/or lack of anatomic landmarks that make it possible to differentiate the proximal from the distal end of the resected segment. In these cases, orientation of the specimen by the surgeon may be required.

Typically, the anatomic site of the tumor is documented by measurement from known landmarks according to general guidelines defining colonic topography. Clinical data may also be helpful in establishing the tumor site in many cases. In general, four major anatomic divisions of the colon are recognized: the right (ascending) colon, the middle (transverse) colon, the left (descending) colon, and the sigmoid colon. The right colon is subdivided into the cecum (peritoneally located and measuring about 6 × 9 cm) and the ascending colon (retroperitoneally located and measuring 15 to 20 cm long). The descending colon, also located retroperitoneally, is 10 to 15 cm in length. The descending colon becomes the sigmoid colon at the origin of the mesosigmoid, and the sigmoid colon becomes the rectum at the termination of the mesosigmoid. The upper third of the rectosigmoid segment is covered by peritoneum on the front and both sides. The middle third is covered by peritoneum only on the anterior surface. The lower third (also known as the rectum or rectal ampulla) has no peritoneal covering. 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. When measuring below with a rigid sigmoidoscope, it extends 16 cm from the anal verge. 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.

Additional guidelines for assigning a tumor site have been established by the American Joint Committee on Cancer (AJCC). Tumors located at the border between two subsites of the colon (eg, 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. Tumors may also be classified as overlapping when anatomic distinction between two subsites is precluded because of tumor distortion of the anatomy. For example, a tumor may be classified as rectosigmoid when differentiation between rectum and sigmoid according to the above guidelines is not possible.
Tumor Size

The tumor dimensions recorded by the pathologist on gross examination of the specimen are considered the definitive determination of tumor size. Although it is recorded as an element of tumor documentation and may be important for quality control purposes (eg, size determinations made via imaging modalities), tumor size is not related to outcome. Eight separate studies have shown that tumor size is of no prognostic significance in colorectal cancer.27–34

Tumor Configuration

Tumor configuration is usually recorded as exophytic (fungating), endophytic (ulcerative), diffusely infiltrative (linitis plastica), or annular (Figures 5–6 to 5–9). Exophytic growth may be further defined as pedunculated or sessile. Overlap among these types is common. The clinical significance of tumor configuration is moot. Most studies have failed to demonstrate an independent influence of gross tumor configuration on prognosis.32,35,36 In three studies, however, exophytic growth proved to be an adverse prognostic factor on multivariate analysis.37–39 The uncommon linitis plastica configuration (see Figure 5–8) appears to be consistently associated with an unfavorable prognosis,40 but the prognostic import may be related primarily to the histologic type (signet-ring cell carcinoma) and high grade of carcinomas (see Tumor Grade below) that typically exhibit this gross morphology.

Histologic Type

For consistency and uniformity in reporting, the internationally accepted histologic classification of colorectal carcinomas proposed by the World Health Organization (WHO) (Table 5–1 and Figures 5–12 to 5–17) is recommended by the College of American Pathologists and is usually used in pathology reports.41,42 It should be noted, however, that medullary carcinoma has been added to the revised WHO classification to be published in 2000. Medullary carcinoma is a distinctive type of nongland-forming carcinoma that previously would have been classified as an undifferentiated carcinoma. It is composed of uniform polygonal tumor cells that exhibit solid growth in nested, organoid, or trabecular...
lar patterns and are characteristically infiltrated by lymphocytes (tumor infiltrating lymphocytes) (Figures 5–10, 5–11). The importance of this unique type is its strong association with microsatellite instability and DNA repair gene dysfunction.

By convention, some histologic types are always assigned a specific histologic grade. For example, signet-ring cell carcinoma, small-cell carcinoma, and undifferentiated carcinoma (histologic type) are all defined as high grade.

Histologic type is always designated in the pathology report, but aside from a few notable exceptions, the histologic type has no prognostic significance. The exceptions include rare types such as signet-ring cell carcinoma and small-cell carcinoma, which are prognostically unfavorable, and medullary carcinoma, which is prognostically favorable. As mentioned above, the latter is a histologic type that was not formerly recognized in the WHO classification (and would have been classified as undifferentiated carcinoma by that system) but is now known to be associated with microsatellite instability and/or the hereditary nonpolyposis colon cancer (HNPCC) syndrome.

To date, no large studies on prognostic factors in colorectal cancer have considered the relationship between the genetic status of the tumor (ie, with or without microsatellite instability), histologic type, and outcome. This shortfall is particularly relevant to mucinous carcinoma, a histologic type representing a high proportion of microsatellite unstable colorectal cancers but, overall, occurring most frequently without microsatellite instability. Thus, it is not surprising that among all of the histologic types of colorectal cancer, the prognostic significance of mucinous carcinoma has been the most controversial. A few studies, largely limited to univariate analyses, have indicated that mucinous adenocarcinoma may be an adverse prognostic factor. More specifically, mucinous carcinoma has been linked with adverse outcome only if occurring in specific anatomic regions of the bowel (eg, the rectosigmoid) or in a specific subset of patients (ie, those less than 45 years of age). In yet other studies, an association with decreased survival has been demonstrated only when mucinous carcinoma and signet-ring cell carcinoma have been grouped together and compared to typical adenocarcinoma. However, data of this type may be merely a reflection of the aggressive biologic behavior of signet-ring cell tumors. Only one multivariate analysis has shown mucinous carcinoma to be a stage-independent predictor of adverse outcome, but the study was limited to tumors presenting with large bowel obstruction, which is itself an adverse prognostic factor.

The signet-ring cell type of adenocarcinoma and small-cell (oat-cell) carcinoma are the only histologic types of colonic carcinoma that consistently have been found to have a stage-independent adverse effect on prognosis. Small-cell carcinoma is a malignant neuroendocrine carcinoma that is similar histologically and biologically to small-cell (oat-cell) carcinoma of the lung. Less clear is the general prognostic significance of focal neuroendocrine differentiation that may occur as a vari-

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**Table 5–1. WORLD HEALTH ORGANIZATION CLASSIFICATION OF COLORECTAL CARCINOMA**

<table>
<thead>
<tr>
<th>Description</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>adenocarcinoma in situ/severe dysplasia</td>
<td>NOS</td>
</tr>
<tr>
<td>adenocarcinoma (Figure 5–12)</td>
<td>Adenocarcinoma (Figure 5–12)</td>
</tr>
<tr>
<td>mucinous (colloid) adenocarcinoma (&gt; 50% mucinous) (Figure 5–13)</td>
<td>Mucinous (colloid) adenocarcinoma (&gt;50% mucinous) (Figure 5–13)</td>
</tr>
<tr>
<td>signet-ring cell carcinoma (&gt; 50% signet-ring cells) (Figure 5–14)</td>
<td>Signet-ring cell carcinoma (&gt;50% signet-ring cells) (Figure 5–14)</td>
</tr>
<tr>
<td>squamous cell (epidermoid) carcinoma</td>
<td>Squamous cell (epidermoid) carcinoma</td>
</tr>
<tr>
<td>adenosquamous carcinoma</td>
<td>Adenosquamous carcinoma</td>
</tr>
<tr>
<td>small-cell (oat-cell) carcinoma (Figure 5–15)</td>
<td>Small-cell (oat-cell) carcinoma (Figure 5–15)</td>
</tr>
<tr>
<td>[medullary carcinoma] (see Figures 5–10, 5–11)</td>
<td>Medullary carcinoma (see Figures 5–10, 5–11)</td>
</tr>
<tr>
<td>undifferentiated carcinoma (Figure 5–16)</td>
<td>Undifferentiated carcinoma (Figure 5–16)</td>
</tr>
<tr>
<td>other (eg, papillary carcinoma) (Figure 5–17)</td>
<td>Other (eg, papillary carcinoma) (Figure 5–17)</td>
</tr>
</tbody>
</table>

*The term "carcinoma, NOS" (not otherwise specified) is not part of the WHO classification.
able feature in other histologic types of colorectal cancer. Two studies, the most recent of which included a multivariate analysis of 350 cases, have indicated that extensive neuroendocrine differentiation may adversely affect outcome. \(^6^2,\(^6^3\)

In summary, based on current evidence, it must be concluded that the only histologic types of colorectal cancer that are prognostically significant are signet ring cell and small-cell carcinomas (prognostically unfavorable) and medullary carcinoma (prognostically favorable). Mucinous carcinoma, when it is associated with microsatellite instability, is also prognostically favorable, but this association cannot be determined from histopathologic examination alone.

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**Figure 5–10.** Medullary carcinoma of the colon. This histologic type of colonic carcinoma is characterized at low magnification by solid growth, pushing tumor borders.

**Figure 5–11.** Medullary carcinoma of the colon. At high magnification, the characteristic polygonal cells, nested to an organoid growth pattern, and large numbers of tumor infiltrating lymphocytes of this tumor type are seen.
Tumor Grade

In general practice, the histologic grading of colorectal cancer, to a large degree, is evaluated subjectively. Although a number of grading systems have been suggested in the literature, a single widely accepted and uniformly employed standard for grading is lacking. Among the suggested grading schemes, the number of grades as well as the criteria for distinguishing among different grades vary markedly. In some systems, grades are defined on the basis of a single microscopic feature, such as the degree of gland formation, and in other systems a large number of features are included in the evalua-

Figure 5–12. Adenocarcinoma of the colon. This histologic type of carcinoma is the most common variety of colon cancer and is characterized by well-formed glands, varying in size and mucin content.

Figure 5–13. Mucinous (colloid) carcinoma of the colon. This histologic type is characterized by the production of large amounts of extracellular mucin. Although any colonic adenocarcinoma may contain foci of mucinous tumor, classification as a mucinous carcinoma requires that more than half of the mass of the neoplasm must be comprised of tumor with mucinous differentiation.
Irrespective of the complexity of the criteria, however, most systems stratify tumors into three or four grades as follows:

- **Grade 1**—Well differentiated
- **Grade 2**—Moderately differentiated
- **Grade 3**—Poorly differentiated
- **(Grade 4—Undifferentiated)**

Variation in the appearance of individual histologic features may vary widely enough to make implementation of even the simplest grading systems problematic, however, and, ultimately, subjective. Thus, a significant degree of interobserver variability in the grading of colorectal cancer exists. Nevertheless, despite this variability, histologic grade has repeatedly been shown by multivariate

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**Figure 5–14.** Signet-ring cell carcinoma of the colon. This histologic type is characterized by dysmorphic cells that contain single, large mucin vacuoles in their cytoplasm. Although any colonic adenocarcinoma may contain foci of signet-ring cell formation, classification as a signet-ring cell carcinoma requires that more than half of the mass of the neoplasm be comprised of signet-ring-type cells.

**Figure 5–15.** Small-cell carcinoma of the colon. This type of tumor is characterized histologically by cells with scanty cytoplasm, a high mitotic rate, and an ovoid to angulated shape. They closely resemble small carcinoma of the lung and, like their pulmonary counterparts, have ultrastructural and immunohistochemical features of neuroendocrine differentiation.
analysis to be a stage-independent prognostic factor.\textsuperscript{27,28,30–32,36,37,45,48,65–71} Specifically, it has been demonstrated that high tumor grade is an adverse prognostic factor. It is noteworthy that in the vast majority of studies documenting the prognostic power of tumor grade, the subclassifications have been collapsed to produce a two-tiered stratification for data analysis as follows:

- **Low Grade:** Well differentiated and moderately differentiated (Figure 5–18)
- **High Grade:** Poorly differentiated and undifferentiated (Figure 5–19).

In general practice, a two-tiered grading system based solely on the proportion of gland formation by the tumor (greater or less than 50 percent gland

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**Figure 5–16.** Undifferentiated carcinoma of the colon. As its name implies, this histologic type of carcinoma shows little evidence of cellular differentiation. This example shows highly pleomorphic dysplastic cells with no evidence of gland formation or mucin production.

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**Figure 5–17.** Papillary carcinoma of the colon. Carcinomas that form papillations with fibrovascular cores and epithelial tufts (micropapillations) may sometimes occur in the colon and may be classified as papillary carcinomas (histologic type).
formation) would also be expected to greatly reduce interobserver variability since the widest variations in grading concern the stratification of low-grade tumors into well or moderately differentiated categories. Pathologic identification of poorly differentiated or undifferentiated tumors is more consistent, and interobserver variability in diagnosing high-grade carcinoma is relatively small. Therefore, in light of its proven prognostic value, relative simplicity, and reproducibility, the use of a two-tiered grading system for colorectal carcinoma (i.e., low grade and high grade) would be
advisable. Such a system has been recommended by the colorectal working group of a 1999 Consensus Conference sponsored by the College of American Pathologists.72

Pathologic Stage

The best estimation of prognosis in colorectal cancer is related to the anatomic extent of disease determined on pathologic examination of the resection specimen.40 Although a large number of staging systems have been developed for colorectal cancer over the years, use of the TNM (Tumor, Nodes, Metastasis) Staging System of the AJCC and the International Union Against Cancer (UICC) is recommended by the College of American Pathologists.24,41 The TNM system is widely used by national, regional, and local tumor registries in the United States, and it is internationally accepted.

In the TNM system, the designation “T” refers to the local extent of the primary tumor at the time of diagnosis, “N” refers to the status of the regional lymph nodes, and “M” refers to distant metastatic disease. The symbol “p” used as a prescript refers to the pathologic determination of the TNM (eg, pT1), as opposed to the clinical determination (designated by the prescript “c”). Pathologic classification is based on gross and microscopic examination of the resection specimen of a previously untreated primary tumor. Assignment of pT requires 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 (cTMN) is usually determined by imaging techniques carried out before treatment during initial evaluation of the patient or when pathologic classification is not possible.24 It is the grouping of T, N, and M parameters that determines the stage of the tumor and relates to prognosis. Thus, it is inappropriate to use the term “stage” in reference to an individual TNM category (eg, “T stage”). A TNM stage grouping can be constructed using a combination of clinically derived and pathologically derived data (eg, pT1, cN0, cM0). However, when pathologic data become available, they typically replace the corresponding clinically determined parameter. This convention is based on the assumption that pathologically derived data are more accurate.

The definitions of the individual TNM categories and the TNM stage groupings for colorectal carcinoma are shown in Tables 5–2 and 5–3 and Figures 5–20 to 5–23. The corresponding 5-year survival rates for the TNM stages are shown in Table 5–4.73,74 It is considered the responsibility of the pathologist to assign a pTNM stage grouping when reporting on a colorectal cancer resection specimen. Thus, the pathologically determined T and N categories of the tumor should be explicitly assigned and included in the pathology report. However, the pathologist often lacks knowledge of the status of distant metastatic disease, and assignment of pMX is appropriate in this circumstance. It also may be appropriate to use other staging systems (eg, Dukes’ or Modified Astler-Coller classifications) in pathology reporting.

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>TO</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ (intraepithelial or intramucosal carcinoma) (Figure 5–20)</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades the submucosa (Figure 5–21)</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades the muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades through the muscularis propria into the subserosa (Figure 5–22) or into the nonperitonealized pericolic or perirectal tissues</td>
</tr>
<tr>
<td></td>
<td>pT3a – minimal invasion: &lt; 1 mm beyond the border of the muscularis propria</td>
</tr>
<tr>
<td></td>
<td>pT3b – slight invasion: 1 to 5 mm beyond the border of the muscularis propria</td>
</tr>
<tr>
<td></td>
<td>pT3c – moderate invasion: &gt; 5 to 15 mm beyond the border of the muscularis propria</td>
</tr>
<tr>
<td></td>
<td>pT3d – extensive invasion: &gt; 15 mm beyond the border of the muscularis propria (see Figure 5–22)</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor directly invades other organs or structures (T4a) or perforates the visceral peritoneum (T4b) (Figure 5–23)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional Lymph Nodes (N)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>NO</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in 1 to 3 lymph nodes</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in 4 or more lymph nodes</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant Metastasis (M)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Presence of distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>
depending upon institutional tradition, but it is suggested that these are to be used in addition to (not in place of) the TNM stage grouping.

Specific issues related to the assignment of pathologic TNM are discussed in detail below.

**Definition of pTis**

For colorectal carcinomas, the staging category pTis (carcinoma in situ) includes both malignant cells that are confined within the glandular basement membrane (intraepithelial carcinoma) and those that are invasive into the mucosal lamina propria (intramucosal carcinoma) (Figure 5–20). Carcinoma that extends into but not through the muscularis mucosae also is included in the pTis category. Penetration of the muscularis mucosae and invasion of the submucosa are classified as pT1. High-grade (severe) dysplasia and intraepithelial carcinoma sometimes may be used synonymously, especially in cases of inflammatory bowel disease.75

It is noteworthy that for all organ systems other than the large intestine, carcinoma in situ refers exclusively to malignancy that has not yet penetrated the basement membrane of the epithelium from which it arose, and invasive carcinoma encompasses all tumors that penetrate the underlying stroma. Stromal invasion of any degree is a feature of extreme importance in all non-colorectal sites because of the possible access of tumor cells to stromal lymphatics or blood vessels and the consequent risk of metastasis. In colorectal cancer, however, the designation pTis (ie, carcinoma in situ) is used to refer both to intraepithelial malignancies and to cancers that have invaded the mucosal stroma (intramucosal carcinomas) because the colonic mucosa is biologically unique. In contrast to the mucosa elsewhere in the gastrointestinal tract (or, indeed, in the entire body), tumor invasion of the lamina propria has no associated risk of regional nodal metastasis. Therefore, for the colon and rectum, inclusion of intramucosal carcinoma in the pTis category is justified. Neverthe-

<table>
<thead>
<tr>
<th>Stage</th>
<th>Modified Astler-Coller Stages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis N0 M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1 N0 M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2 N0 M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>N0 M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T N1 M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T N2 M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T Any N M1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0, I (Tis, T1; N0; M0)</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>Stage I (T2; N0; M0)</td>
<td>80–85%</td>
</tr>
<tr>
<td>Stage II (T3, T4; N0; M0)</td>
<td>70–75%</td>
</tr>
<tr>
<td>Stage III (T2; N1-3; M0)</td>
<td>70–75%</td>
</tr>
<tr>
<td>Stage III (T3; N1-3; M0)</td>
<td>50–65%</td>
</tr>
<tr>
<td>Stage III (T4; N1-3; M0)</td>
<td>25–45%</td>
</tr>
<tr>
<td>Stage IV (M1)</td>
<td>&lt; 3%</td>
</tr>
</tbody>
</table>

Figure 5–20. Intramucosal carcinoma (pTis). A focus of carcinoma that invades the lamina propria (arrow) of the adenoma in which it is arising is classified as carcinoma in situ (pTis) in the TNM staging system.
less, the term carcinoma in situ in reference to colorectal cancer can be confusing, depending upon whether it is used to refer to the T category of the TNM staging system or to intraepithelial tumor only, as it does in all other epithelial systems. Therefore, the terms intraepithelial carcinoma and intramucosal carcinoma are preferred descriptive terms for colorectal tumors in the pTis category.72,76

Optional Expansion of pT3

The extent of perimuscular invasion has been reported to influence prognosis, whether or not regional lymph node metastasis is present. Thus, optional expansion pT3 has been proposed and is shown in Table 5–2.26 However, since extramural extension of > 5 mm is the critical subdivision that

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Figure 5–21. Adenocarcinoma invading the submucosa (pT1). Adenocarcinoma is seen invading the submucosa of the head of an adenomatous polyp in which it is arising.

Figure 5–22. Colonic carcinoma with transmural invasion and deep penetration of the subserosal fat (pT3d). This macroscopic view of a transverse section through the tumor at the point of deepest penetration shows extramural extension of more than 15 cm (arrow).
has been demonstrated to have an adverse effect on prognosis in most studies, a simpler subdivision of pT3a/b and pT3c/d may be justified.\textsuperscript{26} Extramural extension of the tumor within lymphatics or veins does not count as local spread of tumor as defined by pT3 (Figures 5–24, 5–25).\textsuperscript{26}

**Subclassification of pT4**

The highest category of local extent of colorectal tumor, pT4 includes both extension into adjacent organs or structures and penetration of the parietal peritoneum with or without involvement of an adjacent structure (see Figure 5–23). Serosal penetration is a particularly ominous feature. A number of large studies have evaluated serosal penetration as a separate pathologic variable and have demonstrated by multivariate analysis that this feature has independent adverse prognostic significance.\textsuperscript{27,32,77,78} The median survival time following surgical resection for cure has been shown to be significantly shorter with pT4 tumors that penetrate the visceral peri-

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**Figure 5–23.** Colonic carcinoma with transmural invasion and penetration of the serosal surface (pT4b). A microscopic nodule of tumor is seen penetrating the peritonealized surface of the colon (arrow).

**Figure 5–24.** Whole mount microscopic section of colonic carcinoma showing transmural intravascular extension. The arrows point to a focus of transmural extension of a carcinoma within a muscular vein. By direct extension, the tumor only shallowly penetrates the inner layer of the muscularis propria and would be classified as pT2 in the TNM classification.
toneum compared with pT4 tumors without serosal involvement, with or without distant metastasis (Table 5–5). A free perforation of a colorectal carcinoma into the peritoneal cavity is also classified as T4b. A more recent study on the importance of local peritoneal involvement in curative resections by Shepherd and colleagues has suggested that the prognostic power of this feature may supersede that of either local extent of tumor (T category) or regional lymph node status (N category).

Although it is undisputedly important, serosal penetration is often difficult to assess histopathologically and may be underdiagnosed for several reasons. Documentation of peritoneal involvement by tumor demands meticulous pathologic analysis and may require extensive sampling and/or serial sectioning. Thus, it can be missed on routine histopathologic examination, a fact that has been emphasized in the literature. It has been shown that cytologic examination of serosal scrapings reveals malignant cells in as many as 26 percent of tumor specimens categorized as pT3 by histologic examination alone. In addition, the histopathologic findings associated with peritoneal penetration are heterogeneous, and standard guidelines for their diagnostic interpretation are lacking. Therefore, interobserver variability in the diagnosis of peritoneal penetration may be substantial, and since most pathologists tend to err on the side of conservative interpretation, underdiagnosis is common.

In the study by Shepherd and colleagues, the spectrum of microscopic features that may be seen with local peritoneal involvement by tumor was recognized and specifically addressed. Three types of local peritoneal involvement were defined and analyzed separately: (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; and (3) free tumor cells on the serosal surface (in the

| Table 5–5. MEDIAN SURVIVAL TIME FOLLOWING SURGICAL RESECTION FOR CURE |
|---------------------------------|----------------|----------------|
|                                | 5-Year Survival Rate | Median Survival Time (mo) |
| pT4a,M0                        | 49%              | 58.2           |
| pT4b,M0                        | 43%              | 46.2           |
| pT4a,M1                        | 12%              | 22.7           |
| pT4b,M1                        | 0%               | 15.5           |
peritoneum) with underlying ulceration of the visceral peritoneum. All three types of local peritoneal involvement were associated with decreased survival, whereas tumor well clear of the serosal had no independent adverse effect on prognosis. Thus, it has been recommended that, in the definition of T4b, the phrase “involves the visceral peritoneum” be used instead of “penetrates the visceral peritoneum” and that the definition of “involvement” encompass the three types outlined above.

It should be noted that direct invasion of other organs or structures includes invasion of other segments of the colorectum by way of the serosa or mesocolon (eg, invasion of the sigmoid colon by carcinoma of the cecum). In contrast, intramural extension of tumor from one 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.

**Evaluation of Regional Lymph Nodes**

All TNM stage-related outcome data are derived from studies in which the pathologic evaluation of the regional lymph nodes has been performed by conventional histologic staining of macroscopically identified lymph nodes. It has been shown that many, if not most, nodal metastases in colorectal cancer are found in small lymph nodes (less than 5 mm in diameter), the criteria for radiologic assessment of lymph node metastasis based on large size notwithstanding. Therefore, aggressive search for all lymph nodes, both small and large, is essential.

There are few universally accepted pathology practice standards for lymph node dissection and examination in colorectal cancer specimens, but typically, all lymph nodes found are submitted for microscopic examination. It has been shown that 12 to 15 negative lymph nodes predict for regional node negativity. Therefore, 12 regional lymph nodes are regarded as the minimum number to be accepted from a careful lymph node dissection and, if fewer than 12 nodes are found, it has been suggested that additional techniques (ie, visual enhancement techniques such as fat clearing) be considered. However, the actual number of lymph nodes present in any given resection specimen may be limited by anatomic variation, surgical technique, or both. It is recommended that all grossly negative or equivocal lymph nodes be submitted entirely for microscopic examination. For grossly positive lymph nodes, microscopic examination of a representative sample may be adequate for confirmation.

Regional lymph nodes must be examined separately from lymph nodes outside of the anatomic site of the tumor because metastases in any lymph node in the regional nodal group are classified as pN disease whereas all other nodal metastases are classified as pM1. The regional lymph node groups of the anatomic subsites of the colorectum are:

- **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 Colon**—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

On microscopic examination, tumor in a regional lymph node, whether arriving there via afferent lymphatics or direct invasion through the capsule (Figure 5–26), is regarded as metastatic disease. Microscopic examination of the extramural adipose tissue may reveal discrete nodules of tumor that may represent metastases in the external iliac or common iliac nodes is classified as pM1.
lymph nodes that have been replaced by metastatic tumor but cannot be identified as such with certainty. In order to eliminate arbitrary decisions by different pathologists as to whether or not such nodules are to be interpreted as nodal metastasis, the AJCC/UICC have established the following guidelines. Any extramural tumor nodule within the regional lymph node distribution of the tumor that measures > 3 mm in diameter but lacks histologic evidence of residual lymph node tissue is classified as pN disease. However, tumor nodules measuring ≤ 3 mm in diameter are classified in the pT3 category as discontinuous extramural extension of tumor. Multiple nodules > 3 mm in size should be considered as metastasis in a single lymph node for classification.

The diagnosis of regional lymph node metastasis is limited to the use of conventional pathologic techniques (either gross or histologic). The biologic significance of minute amounts of metastatic tumor, known as micrometastases (tumor measuring ≤ 2.0 mm: Figure 5–27), is controversial. Currently, the data are insufficient to recommend either the routine examination of multiple tissue levels of paraffin blocks or the use of special/ancillary techniques such as immunohistochemistry for epithelial and/or tumor-associated antigens (eg, cytokeratin, carcinoembryonic antigen, etc.) or polymerase chain reaction (PCR) techniques to identify tumor RNA/DNA. All of these methods are costly and some can be difficult to quality control. More importantly, however, the significance of the findings generated from such analyses has yet to be proven.

In one recent study of stage 2 colorectal cancers (N = 26), more than 50 percent of cases showed evidence of micrometastatic disease in “negative” regional lymph nodes analyzed by RT-PCR for CEA. The 5-year survival rate was 50 percent for patients with micrometastatic disease and 91 percent for patients without micrometastasis. However, in a larger study (N = 77) using immunohistochemistry to identify micrometastasis (found in 25% of cases), no difference in the 10-year survival was observed among patients with and without micrometastasis. Clearly, larger statistically robust studies with careful quality control of methodology are required to further define the biologic significance of minute amounts of metastatic tumor in regional nodes and its impact on outcome. Pending definitive studies, it is recommended that any histologically identified focus of tumor that is ≤ 2.0 mm but > 0.2 mm be classified as N1 by the pathologist but be accompanied by a note stating that the biologic significance is unknown. Isolated tumor cells, cell clusters that measure ≤ 0.2 mm on H&E stains, or micrometastasis detected only
by special studies (immunohistochemical or molecular) should be reported but classified as N0.

**Definition of Distant Metastasis**

As stated above, metastasis to any nonregional lymph node or metastasis to any distant organ or tissue is categorized as M1 disease. Peritoneal seeding of abdominal organs is also considered M1 disease, as is positive peritoneal fluid cytology. Isolated tumor cells found in the bone marrow are classified as distant micrometastasis, but, like nodal micrometastasis (see above), their significance is as yet unproven. Multiple tumor foci in the mucosa or submucosa of adjacent bowel (satellite lesions or skip metastasis) are not classified as distant metastasis. Satellite lesions must, however, be distinguished from additional primary tumors in which there is obvious evidence of origin from an overlying adenoma.

**Pathologic Staging of Residual Colorectal Carcinoma**

By definition, the TNM categories describe the anatomic extent of malignant tumors that have not been previously treated, and the predictive value of the corresponding TNM stage groupings is based solely on data derived from outcome studies of such tumors following complete surgical resection. Tumor that remains in a resection specimen after previous (neoadjuvant) treatment of any type (radiation therapy alone, chemotherapy therapy alone, or any combined modality treatment) is codified by the TNM using a prescript y to indicate the post-treatment status of the tumor. For many therapies, the classification of residual disease has been shown to be a strong predictor of post-treatment outcome. In addition, the ypTNM classification provides a standardized framework for the collection of data needed to accurately evaluate new therapies.

In contrast, a tumor remaining in the patient after primary surgical resection (eg, corresponding to a proximal, distal, or radial resection margin [see below] that is shown to be involved by tumor on pathologic examination) is categorized by a system known as R classification (Table 5–6).

**Pathologic Staging of Recurrent Colorectal Carcinoma**

In contrast to residual disease, tumor that is locally recurrent after a documented disease-free interval
Pathology and Staging

following surgical resection should be classified according the TNM categories and modified with the prefix r (eg, rpT1). By convention, the recurrent tumor is topographically assigned to the proximal segment of the anastomosis unless the proximal segment is small bowel.24,26

Status of Surgical Resection Margins (Proximal, Distal, Radial, and Mesenteric)

The pertinent margins of a colorectal cancer resection specimen include the proximal, distal, and mesenteric margins, and, when appropriate, the radial margin. The radial margin represents the retroperitoneal or perineal adventitial soft tissue margin closest to the deepest penetration of tumor. For all segments of the large intestine that are either incompletely encased (ascending colon, descending colon, upper rectum) or not encased (lower rectum) by peritoneum, the radial margin is created by blunt dissection of the retroperitoneal or subperitoneal aspect, respectively, at operation.

Multivariate analysis has suggested that tumor involvement of the radial margin (Figure 5–28) is the most critical factor in predicting local recurrence in rectal cancer.85–88 For this reason, routine assessment of the radial margin is recommended in all applicable colorectal cancers, and measurement of the distance from the tumor to the radial margin, representing the surgical clearance around the tumor, is also suggested.41,86 It is recommended that the radial resection margin be considered involved if tumor is present ≤ 1 mm from the nonperitonealized surface of the resection specimen. For segments of the colon that are completely encased by a peritonealized (serosal) surface (eg, transverse and sigmoid colon), the mesenteric resection margin may be relevant since tumors may extend to this margin with (pT4) or without (pT3) penetrating the serosal surface. It should be examined when the point of deepest penetration of the tumor is on the mesenteric aspect of the colon. For those tumors limited to an

<table>
<thead>
<tr>
<th>R Classification System</th>
<th>Description</th>
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<tbody>
<tr>
<td>RX</td>
<td>Presence of residual tumor cannot be assessed</td>
</tr>
<tr>
<td>R0</td>
<td>No residual tumor</td>
</tr>
<tr>
<td>R1</td>
<td>Microscopic residual tumor</td>
</tr>
<tr>
<td>R2</td>
<td>Macroscopic residual tumor</td>
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Figure 5–28. Radial margin (nonperitonealized surface) of a rectosigmoid resection specimen involved by tumor. Tumor glands are seen infiltrating the circumferential soft tissue resection margin of the nonperitonealized surface of the resection specimen (arrows), a finding that is associated with a significantly increased risk of local recurrence of tumor.
antimesenteric peritonealized aspect of the bowel, the mesenteric margin is not relevant.

Because of its association with local recurrence, involvement of the radial or the mesenteric margin has implications for adjuvant therapy. Whether the primary tumor is classified as pT3 (without serosal penetration) or pT4b (with serosal penetration), resection is considered complete only if all surgical margins are negative, including the radial margin. That is, whether or not the tumor penetrates a serosal surface, resection is considered complete if the resection margins are free of tumor. If a radial or mesenteric margin is involved by tumor, however, adjuvant therapy (eg, local radiation) may be appropriate irrespective of the T category of the tumor.

Venous, Lymphatic, or Perineural Invasion by Tumor

In at least 10 different studies, venous invasion by tumor has been demonstrated by multivariate analysis to have an independent adverse impact on outcome and by univariate analysis in several additional studies. Some studies identifying venous invasion as an adverse prognostic factor on univariate analysis have failed, however, to confirm its independent impact on prognosis on multivariate analysis. Similarly disparate results have also been reported for lymphatic invasion (Figure 5–29). In several studies, vascular invasion as a general feature was found to be prognostically significant by multivariate analysis, but no distinction between lymphatic and venous vessels was made. In other studies, the location of the vascular involvement (eg, invasion of extramural veins: Figure 5–30) has been a strong determinant of prognostic significance. Overall, therefore, data from existing studies are difficult to amalgamate. Nevertheless, the importance of venous and lymphatic invasion by tumor is strongly suggested and largely confirmed by the literature.

It is likely that the disparities among existing studies on vessel invasion are directly related to inherent problems related to the pathologic analysis of this feature. Definitive diagnosis of vessel invasion requires the identification of tumor within an endothelial-lined channel. However, assessment of vessel invasion may be difficult and may be complicated by tumor-induced fibrosis and fixation artifact. Interobserver variability may be substantial in the interpretation of small vessel (ie, lymphatic or post-capillary venule) invasion, and large vessel (ie, muscular vein) invasion

Figure 5–29. Extramural small vessel (lymphatic) invasion by tumor. Small clusters of tumor cells are seen within thin-walled, endothelial-lined channels in the subserosa.
with tumor infiltration of the vessel wall and destruction of the vascular architecture may also be difficult to recognize. Special techniques, such as immunohistochemical staining of endothelium or elastic tissue stains of venous walls (Figure 5–31), may increase the ease and accuracy of evaluation. Because these techniques are labor intensive, time consuming, and expensive, however, they are not routinely performed. Additional limitations in the detection of vessel invasion are related to specimen sampling. For example, it has been shown that the reproducibility of detection of extramural venous invasion increases proportion-
ally from 59 percent with examination of two blocks of tissue at the tumor periphery to 96 percent with examination of five blocks. At present, however, no widely accepted standards or guidelines for the pathology evaluation of vessel invasion exist, and pathology sampling practices may vary widely on both individual and institutional levels. Complicating this issue is the impact of cost containment on surgical pathology practice, which, in general, has tended to reduce overall sampling of resection specimens. The College of American Pathologists is recommending that at least three blocks (optimally five blocks) of tumor at its point of deepest extent be submitted for microscopic examination.

Figure 5–32. Tumor border configuration of the infiltrating type. The jagged leading edge of this carcinoma shows long tongues and irregular buds of tumor that penetrate the extramural soft tissue.

Figure 5–33. Tumor border configuration of the pushing type. The smooth leading edge of this carcinoma bluntly interfaces with the surrounding tissue.
Tumor Border Configuration and Perineural Invasion

For colorectal cancer, the growth pattern of the tumor at the advancing edge (tumor border) has been shown to have prognostic significance that is independent of stage and may predict liver metastasis. Specifically, an irregular, infiltrating pattern of growth (Figure 5–32), as opposed to a pushing border (Figure 5–33), has been demonstrated to be an independent adverse prognostic factor by several univariate \(^43,56,96,97\) and multivariate analyses.\(^33,46,47,59,77,98,99\) Defined as microscopic clusters of undifferentiated cancer cells just ahead of the invasive front of the tumor, irregular growth at the tumor periphery has also been referred to as focal dedifferentiation.\(^95\) and tumor budding.\(^98\) It is recommended that pathologic assessment of tumor border configuration be routinely reported in transmurally invasive colorectal tumors.

Jass and colleagues\(^46\) assessed interobserver variability among pathologists evaluating tumor border configuration in general practice (no specific definition provided) and found only a 70 percent (fair) agreement in diagnosis of infiltrating growth pattern. However, concordance was found to improve to 90 percent when diagnostic criteria for defining infiltrating growth were employed (Table 5–7 and Figures 5–34 and 5–35).\(^46\)

Host Lymphoid Response to Tumor

Lymphocytic infiltration of tumor or peritumoral tissue is indicative of a host immunologic response to the invasive malignancy and has been shown by multivariate analysis in several studies to be a favorable prognostic factor.\(^36,46,56,59\) In contrast, other studies have either failed to confirm the prognostic significance of a peritumoral lymphoid reaction\(^33,100\) or demonstrated its significance only by univariate analysis.\(^43,100–103\) The results of these studies are difficult to compare since the histologic criteria for qualitative and quantitative evaluation differ from study to study. Some of the specific features that have been studied include perivascular lymphocytic cuffing in the muscularis propria, perivascular lymphocytic cuffing in the pericolonic fat or subserosa, lymphocytic infiltration at the tumor edge, and a transmural Crohn’s-like lymphoid reaction (Figure 5–36). In some reports, however, little if any explanation of the criteria used for evaluation of this parameter has been offered. Therefore, although this feature appears promising as a favorable prognostic factor, further studies using comparable criteria are needed for confirmation.
REFERENCES


