Pathology and prognostic determinants of colorectal cancer

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INTRODUCTION

Carcinoma of the colon or rectum (colorectal cancer [CRC]) is a common malignancy. Surgical resection is the primary treatment modality for early stage CRC (stage I through III) (table 1), and the most powerful tool for assessing prognosis following potentially curative surgery is pathologic analysis of the resected specimen. Although the parameters that determine pathologic stage are the strongest predictors of postoperative outcome, other clinical, molecular, and histologic features may influence prognosis independent of stage. Among patients with stage IV disease, prognosis is more closely tied to the location and extent of distant metastatic disease.

Here we will discuss the pathology of CRC and the major determinants of prognosis following surgical resection, with particular attention to the strength of the evidence supporting each factor. The molecular pathogenesis of CRC and the clinical presentation and staging evaluation for colon and rectum cancer are discussed elsewhere. (See "Molecular genetics of colorectal cancer" and "Clinical presentation, diagnosis, and staging of colorectal cancer" and "Pretreatment local staging evaluation for rectal cancer".)

PATHOLOGY

Gross appearance — Although all colorectal cancers (CRCs) originate from adenomas or flat dysplasia, they evolve into different morphologic patterns with invasion and expansion. Tumors in the proximal or right colon usually appear grossly as polypoid or fungating exophytic masses. Occult bleeding may result in the clinical presentation of an unexplained iron deficiency anemia.

By contrast, tumors involving the distal or left colon are more commonly annular or encircling lesions that produce an "apple-core" or "napkin-ring" appearance (image 1A-B). The bowel lumen becomes constricted and narrowed, producing symptoms of bowel dysfunction (eg, constipation, diarrhea, or bowel obstruction). The presence of clinical bowel obstruction or perforation of the bowel wall worsens the prognosis overall [1,2].

Despite differences in their gross appearance, right- and left-sided colon cancers are microscopically similar, and they seem to have a similar prognosis when they present with locoregional disease [3]. However, in the setting of metastatic disease, at least some data suggest a worse prognosis for those with a right-sided primary tumor [4,5].

Synchronous colon cancers, defined as two or more distinct primary tumors separated by normal bowel and not due to direct extension or metastasis, occur in 3 to 5 percent of patients with CRC [6,7]. The incidence is closer to 2.5 percent when patients with Lynch syndrome (hereditary nonpolyposis CRC [HNPCC]) are excluded [8]. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis".)

Synchronous primaries have the same prognosis as a solitary cancer when the highest stage of disease at presentation is compared [7].

Histology — The vast majority of malignant tumors of the colon and rectum are carcinomas. Other histologic types of tumors (neuroendocrine neoplasms, hamartomas, mesenchymal tumors, lymphomas) are relatively unusual. Of the carcinomas, more than 90 percent are adenocarcinomas. The most recent World Health Organization (WHO) classification of tumors of the colon and rectum is provided in the table (table 2).

Some of these morphologic variants carry prognostic significance. As an example, signet ring cell carcinomas are an aggressive adenocarcinoma subtype with a poor prognosis overall, while the medullary adenocarcinoma subtype, which is often associated with deficient mismatch repair (MMR) proteins, has a relatively favorable prognosis [9]. (See 'Mismatch repair deficiency' below.)

Histologic grade of differentiation takes into account the degree to which there are well-formed glands, an indication of the degree of cell-cell cooperation, maintenance of polarization, and coordinated secretion of cell product into a central lumen. The greater the presence of these

features, the higher the degree of differentiation and the lower the grade. The inclusion of cytologic or other features in the estimation of grade is variable. Gland formation is always present to greater or lesser degrees in well-differentiated and moderately differentiated tumors (low-grade tumors when using a two-tiered grading system), respectively. By contrast, poorly differentiated or undifferentiated adenocarcinomas (high-grade tumors) do not form well-defined glandular structures, consisting predominantly of solid sheets or cords of infiltrating cells, often with marked cellular atypia, pleomorphism, and a high mitotic rate. In the majority of studies, the prognostic significance of grade falls out on statistical analysis as a two-tiered stratification variable: low grade (well and moderately differentiated) versus high grade (poorly differentiated or undifferentiated).

The College of American Pathologists (CAP) and the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) both specify the use of a four-tiered grading system for CRC [10,11]. This is primarily to ensure correct mapping of cancer grade in United States cancer registries, which have long used three- or four-tiered systems. The CAP recommends grade assignment based solely on the degree of gland formation, as follows [11]:

- **Grade 1** – Well differentiated (>95 percent gland formation)
- **Grade 2** – Moderately differentiated (50 to 95 percent gland formation)
- **Grade 3** – Poorly differentiated (<50 percent gland formation)
- **Grade 4** – Undifferentiated (no gland or mucin formation; no squamous or neuroendocrine differentiation)

In contrast, in the most recent (fifth) edition of the WHO Classification of Digestive System Tumours, the WHO recommends use of a two-tiered system, collapsing well and moderately differentiated into low grade, and poorly differentiated into high grade [12]. This simplifies grading but preserves the prognostic power of grade as demonstrated in most publications on the topic, which typically collapsed three- and four-tiered data into a two-tiered grade classification for prognostication analysis.

Many tumors produce mucin, which may remain within the cells (eg, signet ring cells) or be secreted. Extracellular mucin not confined within tumor glands may facilitate the dissection and penetration of a tumor through the colonic wall [13]. Tumors producing copious amounts of extracellular mucin (ie, mucin comprising ≥50 percent of the tumor mass) are classified as mucinous carcinomas (table 3). This histologic type accounts for approximately 11 to 17 percent of all CRCs [13-16]. Mucinous carcinomas have a predilection for the right side of the colon [17,18], and they may have a poor responsiveness to upfront (neoadjuvant) chemoradiotherapy [19] and adjuvant chemotherapy [20], although this is a somewhat

controversial area, particularly with appendiceal mucinous neoplasms [21]. (See 'Histologic type, grade of differentiation, and presence of mucin' below.)

In some non-gland-forming carcinomas, intracellular mucin may be a dominant feature that displaces tumor cell nuclei to the side. When ≥50 percent of the tumor is made up of cells of this type, it is classified as a signet ring cell carcinoma (picture 1). It accounts for only 1 to 2 percent of all CRCs, but signet ring cell carcinoma is an aggressive variant with a propensity for extensive intramural spread and peritoneal carcinomatosis [13,22,23]. As an example, in one report of 1600 consecutive patients with CRC, 13 of the 14 patients with signet ring cell carcinomas had stage III or IV disease at diagnosis, and nine had peritoneal spread [23]. Signet ring cell carcinoma has a high incidence of microsatellite instability and a strong association with Lynch syndrome. (See 'Mismatch repair deficiency' below.)

Some cancers, particularly those arising in the distal colon, contain areas of squamous differentiation and are termed adenosquamous carcinomas [24]. These rare tumors account for between 0.05 and 0.2 percent of all colorectal malignancies and are associated with higher overall and colorectal-specific mortality as compared with adenocarcinoma [25,26].

Approximately 10 percent of CRCs, particularly poorly differentiated tumors, contain foci of neuroendocrine differentiation. Non-gland forming tumors with a predominance of neuroendocrine differentiation are classified as well-differentiated neuroendocrine (carcinoid) tumors, which have a more favorable prognosis than adenocarcinomas, and poorly differentiated neuroendocrine carcinomas, which have a poor prognosis overall. However, the prognostic importance of focal neuroendocrine differentiation within other histologic types such as an adenocarcinoma is unclear. Assessment of neuroendocrine differentiation should be made on routine hematoxylin and eosin (H&E) stained sections; the data are insufficient to recommend the use of special stains (ie, chromogranin, neuron-specific enolase, or synaptophysin). (See 'Focal neuroendocrine differentiation' below and "Pathology, classification, and grading of neuroendocrine neoplasms arising in the digestive system".)

The medullary carcinoma subtype (table 3) is a distinctive type of non-gland forming cancer composed of large eosinophilic, polygonal cells that grow in solid sheets and are heavily infiltrated by small lymphocytes (ie, tumor-infiltrating lymphocytes) [27]. The importance of recognizing this tumor type is its association with tumors that are deficient in one or more MMR proteins, including those that arise in the setting of Lynch syndrome [28]. These tumors characteristically have a high degree of microsatellite instability, frequently in combination with a *BRAF* mutation, and are associated with a good prognosis. Large bowel tumors with microsatellite instability are more common in the right colon; are more often of the mucinous, signet ring, or medullary histologic type; and have abundant tumor-infiltrating lymphocytes or

are rimmed by a Crohn-like, germinal center-producing lymphoid reaction. (See 'Mismatch repair deficiency' below.)

Appendix cancer — Cancer of the vermiform appendix is rare. Primary malignant tumors of the appendix are found in 0.1 percent of all appendectomy specimens; the majority are carcinoids, but approximately one-third are adenocarcinomas. Significantly, metachronous or synchronous primary neoplasms, particularly involving the gastrointestinal (GI) tract, are common in patients with appendiceal tumors. (See "Epithelial tumors of the appendix" and "Well-differentiated neuroendocrine tumors of the appendix".)

Appendiceal adenocarcinomas commonly spread intraperitoneally. When these carcinomas are mucin secreting and present with peritoneal dissemination, they produce the clinical picture of a pseudomyxoma peritonei. The histologic spectrum of tumors that are associated with this clinical pattern ranges from low-grade appendiceal mucinous neoplasms (LAMNs) to invasive high-grade signet ring cell adenocarcinomas. (See "Epithelial tumors of the appendix", section on 'Peritoneal disease spread and pseudomyxoma peritonei'.)

Primary mucinous epithelial ovarian carcinoma only rarely presents similarly, but may be considered in the differential diagnosis [29]. Immunohistochemistry (IHC) can help with the distinction. (See 'Immunohistochemistry' below and "Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Clinical features and diagnosis".)

The natural history and prognosis of appendiceal adenocarcinomas differ from that of adenocarcinomas arising in other large bowel sites [30]. As a result, the current AJCC Tumor, Node, Metastasis (TNM) cancer staging manual contains a separate staging classification for appendiceal cancers (table 4). (See "Epithelial tumors of the appendix".)

Immunohistochemistry — Cytokeratin 20 (CK20) and caudal-type homeobox 2 (CDX2) are two of the most sensitive and specific markers of intestinal differentiation and are extremely useful IHC markers in correctly identifying adenocarcinomas of colorectal origin [31-33]. IHC for CK20 and CK7 can be particularly helpful in the differential diagnosis of a primary appendiceal malignancy versus mucinous ovarian cancer (table 5) [34,35]. (See 'Appendix cancer' above.)

However, an important caveat is that unlike conventional colorectal adenocarcinomas, medullary carcinomas of the colon with high levels of microsatellite instability frequently lack CDX2 and CK20 expression, and instead, they may express markers not commonly associated with CRC, such as calretinin, CK7, SATB2, and CDH17 [36-39].

IHC is also helpful to identify deficient expression of DNA MMR. This is clinically useful in three ways:

- With sporadic somatic MMR gene mutation, tumor tissue will show loss of staining for one or more of the MMR proteins, but the surrounding normal mucosa will be positive, which also serves as an internal control for the stain. Tumors with deficient MMR proteins have a relatively favorable prognosis, and this may be used in the decision-making process for adjuvant chemotherapy, particularly for patients with stage II (node-negative) colon cancer. (See "Adjuvant therapy for resected stage II colon cancer", section on 'Molecular factors, including circulating tumor DNA'.)

- Germline mutations in the MMR genes that cause Lynch syndrome typically result in a truncated or lost MMR protein that can be detected as **loss of staining of the protein** on tumor IHC testing [40,41]. Typically testing is carried out for *MLH1*, *PMS2*, *MSH2* and *MSH6*. The likelihood of finding a germline mutation in one of the MMR genes based on IHC results varies depending on the protein that is absent (table 6) [42]. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Immunohistochemistry'.)

- Deficient MMR status may identify those patients who might benefit from immunotherapy targeting the immune checkpoint programmed cell death receptor 1 (PD-1).

PATTERNS OF SPREAD AND STAGING

Colorectal cancers (CRCs) can spread by lymphatic and hematogenous dissemination, as well as contiguous and transperitoneal spread. The most common metastatic sites are the regional lymph nodes, liver, and lungs. Because the venous drainage of the intestinal tract is via the portal system, the first site of hematogenous dissemination is usually liver, followed by lungs, bone, and many other sites, including (rarely) brain. However, tumors arising in the distal rectum may metastasize initially to the lungs because the inferior rectal vein drains into the inferior vena cava rather than into the portal venous system.

TNM staging — The Tumor, Node, Metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) is the preferred staging system for CRC [43]. The older Duke's classification, including the Astler-Coller modification, is no longer used.

As in all of the TNM staging classifications, radiographic, endoscopic (including biopsy), and intraoperative findings are used to assign a clinical stage (cT, cN, cM), while assessment of pathologic stage (pT, pN, pM) requires gross pathologic or histopathologic examination. (See "Clinical presentation, diagnosis, and staging of colorectal cancer", section on 'Staging' and

"Pretreatment local staging evaluation for rectal cancer", section on 'Principles of rectal cancer staging by imaging'.)

If distant metastases are confirmed by pathologic assessment, assignment of pM1 is appropriate. Otherwise, no pM category is assigned. The designation pM0 does not exist since it would denote pathologic confirmation of the absence of distant metastases anywhere in the body (a determination possible only at autopsy).

The most recent (eighth edition, 2017) revision of the TNM staging classification is outlined in the table (table 1) [44]. Compared with the earlier 2010 version, the M1c stage has been introduced to reflect peritoneal carcinomatosis as a poor prognostic factor, and nodal micrometastases (tumor clusters >0.2 mm in diameter) are now scored as positive given the results of a meta-analysis demonstrating a poor prognosis in these patients [45]. (See 'Nodal micrometastases' below.)

This version also acknowledges the following factors, which are important to consider when making decisions about treatment, given their prognostic and predictive impact, but are not yet incorporated into the formal staging criteria:

- Preoperative serum carcinoembryonic antigen (CEA) levels. (See "Clinical presentation, diagnosis, and staging of colorectal cancer", section on 'Tumor markers'.)
- Tumor regression score, which reflects the pathologic response to preoperative radiation therapy, chemoradiotherapy, or chemotherapy (table 7), and status of the circumferential resection margin for rectal cancers. (See 'Tumor regression after neoadjuvant therapy' below and 'Circumferential (radial) margin' below and "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Prognosis and extent of tumor regression'.)
- Lymphovascular and perineural invasion. (See 'Lymphovascular invasion' below and 'Perineural invasion' below.)
- Microsatellite instability, which reflects deficiency of mismatch repair enzymes and is both a prognostic factor and predictive of a lack of response to fluoropyrimidine therapy. (See 'Mismatch repair deficiency' below.)
- Mutation status of *KRAS*, *NRAS*, and *BRAF*, because mutations in these genes are associated with treatment resistance to agents targeting the epidermal growth factor receptor (EGFR). (See 'RAS and BRAF' below.)

Regional nodes — The regional lymph nodes for each segment of the large bowel are designated in the figure (figure 1) [44]. The prognostic impact of the total number of resected and involved nodes is discussed in detail below. (See 'Regional nodes' below.)

In situ cancer — Traditionally, the term "carcinoma in situ" refers to cytologically malignant epithelial cells that do not penetrate the basement membrane or invade the underlying stroma. However, in the staging of CRC, the pTis category includes stromal invasion of malignant cells through the lamina propria into but not through the muscularis mucosa. This is unique to the large bowel and justified because the colorectal mucosa, unlike the mucosa elsewhere in the gastrointestinal (GI) tract and in other organs, lacks stromal lymphatics. As a result, tumors invading up to the muscularis mucosa lack access to the regional lymphatic vasculature and cannot metastasize via this route. It has been recommended that the terms "intraepithelial carcinoma" (without stromal invasion) and "intramucosal carcinoma" (with mucosal stromal invasion) be used to differentiate the two lesions included in the pTis category [46], but this distinction has not been made in either the current 2010 or newest 2017 TNM classifications [43,44].

Posttherapy staging for rectal cancer — The TNM staging system was initially devised for tumors that had not been previously treated. Preoperative or neoadjuvant therapy is increasingly employed for rectal tumors. Compared with initial surgery followed by adjuvant therapy, neoadjuvant therapy is associated with less long-term treatment-related toxicity, and in some cases, preservation of sphincter function. (See "Neoadjuvant therapy for rectal adenocarcinoma".)

For rectal cancers, the pathologic TNM stage of disease in the resected specimen following neoadjuvant treatment is classified differently (the ypTNM classification) (table 1) as compared with tumors that have not received neoadjuvant treatment [43]. The prognostic implication of the posttreatment pathologic stage is discussed below. (See 'Tumor regression after neoadjuvant therapy' below and "Neoadjuvant therapy for rectal adenocarcinoma".)

PROGNOSTIC DETERMINANTS

The most important indicator of outcome after resection of colorectal cancer (CRC) is the pathologic stage at presentation [47]. Five-year survival stratified by tumor stage at diagnosis for rectal cancer using the 2010 American Joint Committee on Cancer (AJCC; seventh edition of the AJCC Cancer Staging Manual) staging criteria is illustrated in the figure (figure 2) [43]. Five-year survival stratified by tumor stage at diagnosis for colon cancer using the 2010 staging criteria is illustrated in the figure (figure 3) [43]. (See 'TNM staging' above.)

Among patients receiving neoadjuvant (presurgical) treatment for rectal cancer, the posttreatment stage (given a yp designation in the AJCC staging system, see above) is a more accurate predictor of outcome than the pretreatment clinical stage. Five-year survival according to pathologic stage after chemoradiotherapy for rectal cancer is outlined in the table (table 8). (See 'Posttherapy staging for rectal cancer' above and 'Tumor regression after neoadjuvant therapy' below.)

Beyond pathologic stage at presentation, the most important prognostic determinants for CRC are the presence of extramural tumor deposits, lymphovascular and perineural invasion, histologic grade of differentiation, the preoperative level of serum carcinoembryonic antigen (CEA), microsatellite instability (MSI), and *RAS* and *BRAF* mutations.

The below sections will summarize the most recent information on prognostic determinants for CRC, according to the most recent (2017) Tumor, Node, Metastasis (TNM) staging classification from the AJCC [44].

Pathologic features

Local tumor extent — The local extent of disease (ie, depth of tumor penetration) independently influences survival [48-51]. However, evaluation and reporting of features that determine the T category is variable, particularly the presence or absence of serosal involvement. (See 'Histology' above.)

There exists significant confusion as to the definition of serosal "involvement." Histologic determination of serosal penetration is difficult, and conservative interpretation may lead to understaging of disease. As an example, cytologic examination of serosal scrapings reveals malignant cells in up to 26 percent of histologically defined pT3 specimens [51,52]. However, when there is uncertainty as to the greatest degree of tumor extension, assignment of the lesser value is justified by the general rules of AJCC staging. The AJCC Cancer Staging Manual suggests multiple-level sectioning and/or submission of additional blocks of tissue to assess serosal involvement by direct extension of tumor or through inflammation, either of which are categorized as T4a [44]. The prognostic significance of tumor that closely (<1 mm) approaches the serosal surface but does not penetrate the serosa is unclear but has been suggested to portend a higher risk of peritoneal relapse [53].

The histopathologic findings associated with peritoneal tumor involvement are heterogeneous, and standard guidelines for their diagnostic interpretation are lacking. Local peritoneal involvement may be reflected by any of the following [51]:

- A mesothelial inflammatory and/or hyperplastic reaction with tumor close to the serosal surface
- Tumor present at the serosal surface with an inflammatory reaction, mesothelial hyperplasia, and/or erosion or ulceration
- Free tumor cells on the serosal surface within the peritoneum with underlying ulceration of the visceral peritoneum

All three types of local peritoneal involvement can be used to define serosal involvement (ie, T4a tumors [43]), and all adversely impact prognosis [28,51]. The presence of free cells on the serosal surface is more likely than the other two forms of peritoneal involvement to predict intraperitoneal recurrence and/or persistence [51]. In cases in which peritoneal involvement is uncertain, the lesser category (ie, T3) should be assigned [54,55]. (See 'TNM staging' above.)

For portions of the colorectum that are not peritonealized (eg, posterior aspects of the ascending and descending colon, lower portion of the rectum), the T4a category is not applicable (figure 4).

Among the factors that have been studied and determined not to exert a significant impact on prognosis are tumor size [49,56,57] and gross tumor configuration [56,58]. However, newer data suggest that tumor size may be an adverse prognostic factor for colon but not rectal cancer [59]. Overall size >4.5 cm was an independent predictor of poor outcome, but the optimal cut-point for size indicative of an adverse prognosis varied with anatomic location in the colon, decreasing from right to left.

Residual tumor — Residual tumor after definitive therapy is an adverse prognostic factor [28,46,60,61]. As an example, in a report of 152 patients with T4 colon cancers (table 1), 10-year recurrence-free survival was significantly less for the 42 patients with incompletely resected cancers compared with those with fully resected T4N0 or T4 node-positive disease (19 versus 88 and 58 percent, respectively) [60].

The completeness of resection is largely dependent on the status of the circumferential (radial) resection margin, although the designation is global, and includes the transverse margins and other disease observed but not removed at surgery [43]. (See 'Circumferential (radial) margin' below.)

The R designation indicates local residual disease after therapy is complete and is appropriate only in the setting of M0 disease. The residual disease codes in the TNM staging system (R0, R1, and R2) are defined as follows [62]:

- **R0** – Indicates complete tumor resection with all margins histologically uninvolved
- **R1** – Incomplete tumor resection with microscopic surgical resection margin involvement (margins grossly uninvolved)
- **R2** – Incomplete tumor resection with gross residual tumor that was not resected (primary tumor, regional nodes, or macroscopic margin involvement)

An expanded R classification has been proposed that takes into account the minimal distance between tumor and resection margin [63]. However, these modifications to the R classification have not yet been adopted by the AJCC, and they are not a part of either the 2010 or the 2017 edition of the TNM staging manual [43,44].

Circumferential (radial) margin — The circumferential resection margin (CRM) corresponds to the surgically dissected nonperitonealized surface of the specimen. This term applies to any aspect of the colorectum that is not covered (or partially covered, as with the ascending and descending colon and rectosigmoid) by a serosal layer of mesothelial cells and that must be dissected from the retroperitoneum (or subperitoneum in order to remove the viscus). For mid and distal rectal cancers that are entirely subperitoneal in location, the entire external surface of the specimen is considered a CRM. (See "Radical resection of rectal cancer", section on 'Radial margins'.)

By contrast, for colonic segments that are completely encased by a peritonealized (serosal) surface (eg, cecum, transverse, and sigmoid colon), the only surgical margin that is surgically dissected is the mesenteric margin, unless the cancer is adherent to or invading an adjacent organ or structure. In such cases, the CRM is a relevant radial margin only when the point of deepest tumor penetration is on the mesenteric aspect of the bowel and extends to the surface of this margin with or without serosal penetration. These concepts are illustrated in the figure (figure 5). (See "Surgical resection of primary colon cancer", section on 'Resection margins'.)

For rectal cancer, the quality of the surgical technique and the status of the CRM is one of most important predictive factors for both local and distant recurrence as well as survival [64-69]. Total mesorectal excision (TME) with adequate surgical clearance around the penetrating edge of the tumor decreases the rate of local relapse. With this approach, all mesorectal soft tissues encasing the rectum (which includes the mesentery and all regional nodes) are removed intact, and the circumferential surface is the mesorectal fascia. Guidelines for grading the quality and completeness of the mesorectum in a TME are outlined in the table (table 9) [70]. (See "Radical resection of rectal cancer", section on 'Total mesorectal excision'.)

In the analysis of the surgical specimen, the distance between the closest leading edge of the tumor and the CRM should be measured and recorded, in mm. Whether or not the CRM is designated as "positive" [71,72], there is level 1 evidence that the risk of local recurrence and death is increased if the distance between the deepest point of penetration by the tumor and the CRM is ≤1 mm [64,73-76]. In the rectum, a positive CRM denotes T3 disease with an R1 or R2 resection (ie, microscopic or macroscopic involvement of the margin by tumor) and not T4a disease (figure 4). Therefore, the College of American Pathologists (CAP) recommends recording a CRM as positive if tumor is identified 1 mm or less from the nonperitonealized surface of a resection specimen [11].

Although studies defining the relationship between CRM status and outcome are lacking for colonic cancers, it is reasonable to expect a greater risk for local tumor recurrence in any nonperitonealized segment, as with rectal cancer. For patients who have not received radiation therapy preoperatively, CRM positivity represents an indication for postoperative radiation therapy, regardless of the local tumor extent, particularly for rectal cancers. (See "Adjuvant therapy for resected rectal adenocarcinoma in patients not receiving neoadjuvant therapy", section on 'Indications and rationale for adjuvant therapy'.)

Regional nodes — Regional lymph node involvement is one of the strongest predictors of outcome following surgical resection of CRC, second only to the presence of distant metastasis. Nodal spread is an indication for adjuvant therapy for both colon cancer and rectal cancer to reduce the risk of lethal cancer metastases recurring in distant organs. (See "Adjuvant therapy for resected stage III (node-positive) colon cancer" and "Adjuvant therapy for resected rectal adenocarcinoma in patients not receiving neoadjuvant therapy".)

Whether fatal distant metastases are seeded by lymph node metastases or whether regional lymph nodes act as a barrier for trapping primary CRC cells that have intrinsic potential for metastatic competence is debated. Distant metastatic spread typically follows venous and not lymphatic drainage, and at least some data suggest that lymphatic and distant metastases arise from independent tumor subclones in a substantial number of cases [77,78]. These findings support the view that lymph node involvement reflects intrinsic metastatic potential.

For both colon and rectal cancers, the incidence of regional node involvement is related both to the depth of transmural invasion of the primary tumor and to histologic grade. The number of involved lymph nodes is a strong predictor of outcome [43,79-82]. As a result, the TNM classification stratifies nodal involvement according to the number of involved lymph nodes (table 1). The number of involved nodes influences outcome in both the N1 and N2 categories, regardless of the T category, both for rectal and colon cancer. In addition to the number of involved nodes, the total number of lymph nodes in the surgical specimen directly

influences prognosis for both stage II (node-negative) and stage III (node-positive) disease [83-88]. These relationships are depicted in the figures (figure 6A-B) [44].

The use of a lymph node ratio (LNR; the ratio of metastatic to examined lymph nodes) has been suggested as a means of incorporating both the number of involved nodes and the total number examined into prognostic stratification [89-91]. As an example, five-year survival rates according to LNR from the INT-0089 trial are illustrated in the table (table 10) [89].

A systematic review of 16 studies including 33,984 patients with stage III colon or rectal cancer concluded that the LNR was an independent predictor of overall, disease-free, and cancer-specific survival, and that the prognostic separation obtained by the LNR was superior to that of the number of positive nodes (ie, the N stage) [91]. However, there is no consensus as to the optimal cutoff values defining the LNR category with the best outcomes. There are no prospective trials addressing this issue, and the values used in the available retrospective analyses vary widely [91].

The reason for the relationship between total number of nodes in the specimen and outcomes is unclear. The most obvious explanation is that removal of more nodes increases the accuracy of staging. However, the strong association between total lymph node count and survival is not entirely explained by improvements in staging [88,92,93]. The larger number of nodes may reflect the quality of the surgery and a more complete resection of the mesenteric pedicle. Alternatively, the differences between individual patients with colon cancer in terms of the number of lymph nodes present may reflect underlying biologic variability. As an example, tumor factors may stimulate lymph nodes to enlarge, reflecting immune system recognition of the tumor and more favorable survival outcomes with a higher number of lymph nodes that is independent of the number of metastatic lymph nodes. Such biological differences could contribute to the lack of association between average node counts, the frequency of nodal positivity, and survival in several hospital-based series [94-97] and in population-based analyses from the Surveillance, Epidemiology, and End Results (SEER) database [88,93].

Despite the disparate findings, guidelines from expert groups recommend at least 12 nodes be examined histologically to accurately determine nodal status; however, this number was derived empirically based on older observational data that was not adjusted for variables such as T-stage and tumor grade and the use of preoperative chemoradiotherapy for rectal cancer [28,83,84,98,99]. (See 'Tumor regression after neoadjuvant therapy' below.)

At least in the United States, this "benchmark" is not being met in a sizable minority of patients who undergo initial surgery, particularly those treated in community hospitals [100,101]. Rates of inadequate node retrieval seem to be improving over time in academic institutions (dropping

from 38 to 5 percent between 1998 and 2005 in National Comprehensive Cancer Network [NCCN] member institutions in one report [102]).

It has long been recognized that the frequency of detecting nodal disease is influenced by the methodology of node handling and assessment, which is quite variable [103]. Surgical technique may contribute to variation in the number of nodes contained in a resection specimen [104], while diligence in the search for nodes, the use of fat clearing or other techniques to increase macroscopic visualization of nodes, and the pathologist's threshold for an acceptable number of evaluated nodes are variables in pathologic technique. If fewer than 12 nodes are present in the surgical specimen, additional techniques such as fat clearing should be used to try to increase the nodal yield [28,105].

The relevance of the 12-node threshold has been questioned for patients with rectal cancer who have received neoadjuvant therapy prior to resection. Removal of 12 or more nodes is often not achievable after neoadjuvant therapy, and lower nodal counts in this setting have not been associated with understaging or inferior survival [106]. (See "Neoadjuvant therapy for rectal adenocarcinoma".)

Extranodal extension of tumor is associated with an increased risk of recurrent disease and mortality [107]; it should be noted in the pathologic assessment of resection specimens [54,55].

Nodal micrometastases — Controversy exists as to the prognostic significance of isolated tumor cells (ITCs) or micrometastases in regional nodes.

The influence of ITCs and nodal micrometastases has been brought to the forefront by the development of sentinel node mapping and techniques such as immunohistochemistry (IHC) and reverse-transcriptase polymerase chain reaction (RT-PCR) to detect tumor-specific RNA, which detect small clusters or single tumor cells in lymph nodes [108,109]. The use of these supplemental assays may result in upstaging of up to 50 percent of patients with CRC who have histologically negative nodes, depending on the pT category [110-113]. (See "Surgical resection of primary colon cancer", section on 'Role of sentinel node mapping'.)

However, the biological significance of these micrometastases is unclear; their detection has been shown to alter prognosis in some [114] but not all studies. One reason is that some authors define ITCs as not only single-tumor cells in the subcapsular or marginal sinus, but also clumps of up to 20 tumor cells or small clusters of tumor cells measuring ≤0.2 mm in greatest dimension [115]. Micrometastases, on the other hand, are defined as clusters of tumor cells measuring ≥0.2 mm in greatest dimension. A meta-analysis demonstrated a poor prognosis for patients with tumor clusters ≥0.2 mm in diameter, but not for ITCs [45].

In the current 2010 TNM staging classification, ITCs and micrometastases do not count as positive nodal disease, although the presence of ITCs, whether detected by standard histologic techniques or IHC, are coded as pN0 (i+), and a tumor that is detected only by special molecular techniques such as RT-PCR is coded as pN0 (mol+) [43]. (See 'TNM staging' above.)

However, largely based on the meta-analysis, in the most recent (2017) eighth edition revision, which is scheduled to take effect in the United States on January 1, 2018, nodal micrometastases (tumor clusters >0.2 mm in diameter) are specifically designated as positive, while isolated tumor cells are not scored at all (table 1). Outside of the United States, the Union for International Cancer Control (UICC) has implemented the eighth edition changes as of January 1, 2017.

Extramural non-nodal tumor deposits — The seventh edition AJCC Cancer Staging Manual classification was the first to use the term "tumor deposits" to designate discrete nodules of tumor of any size or shape within the pericolic or perirectal fat or in adjacent mesentery in the lymphatic drainage area of the tumor that are not associated with identifiable lymph node or vascular structures [43]. In the eighth edition, tumor deposits are defined as "discrete tumor nodules within the lymph drainage area of the primary carcinoma without identifiable lymph node tissue or identifiable vascular or neural structure" and are codified as N1c [10]. They are considered the equivalent of nodal metastases (a lymph node replaced by tumor), even if they lack residual nodal architecture, and even in the absence of metastases in any of the identified regional lymph nodes elevate the cancer to stage III. Each tumor deposit should be counted separately, and the number recorded in the pathology report. However, the number of tumor deposits is **not** added to the number of positive nodes in the N category if one or more of the identified regional nodes contains metastatic tumor (see 'TNM staging' above). The most recent 2017 revision further clarifies the definition of tumor deposits (table 1) [44].

The presence of these tumor deposits is a strong adverse prognostic feature [116-122]. The adverse influence on prognosis is seen in patients both with [117,121] and without [116,118] nodal metastases. The presence of extramural extranodal tumor deposits is strongly linked to the presence of extramural venous invasion [116,120].

Tumor regression after neoadjuvant therapy — In appropriately selected patients with rectal cancer, neoadjuvant chemoradiotherapy is associated with significant tumor response and downstaging [123]. For these patients, prognosis is best determined by the posttreatment pathologic stage (ie, the ycTNM or ypTNM classification). (See 'TNM staging' above.)

Among patients receiving initial chemoradiotherapy for rectal cancer, tumor eradication, as detected by pathologic examination of the resected specimen, is associated with a significantly

better prognosis as compared with patients with residual tumor, particularly residual nodal disease [124]. Similarly, minimal residual disease is associated with a better prognosis than is gross residual disease [125]. Outcomes stratified by posttreatment pathologic stage after chemoradiotherapy for rectal cancer are depicted in the table (table 8). Although several grading systems for tumor response have been advocated (table 11), a four-point tumor regression score is recommended by the AJCC (table 7) [43,44]. (See "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Prognosis and extent of tumor regression'.)

Lymphovascular invasion — Tumor invasion into veins or small nonmuscularized vessels that may represent either postcapillary lymphatics or venules is an important prognostic determinant [58,126-129]. Both venous invasion, particularly of extramural veins, and lymphatic invasion represent independent adverse prognostic factors [28,57,126,130-134].

Venous and angiolymphatic invasion should be reported as present or absent in all tumors, including malignant polyps, and the anatomic location specified as intramural or extramural. The diagnosis of lymphovascular invasion (LVI) requires identification of tumor cells either within an endothelial-lined channel or surrounded by an elastic lamina. Small vessels not definitively interpreted as lymphatics or venules should be identified as angiolymphatic vessels.

Given its prognostic importance, LVI is one of the clinicopathologic factors that is included in the definition of "high-risk" stage II colon cancer from the American Society of Clinical Oncology (ASCO) [135], National Comprehensive Cancer Network (NCCN) [136], and European Society for Medical Oncology (ESMO) (table 12) [137]. The presence of these high-risk features might influence the use of adjuvant chemotherapy in this setting. (See "Adjuvant therapy for resected stage II colon cancer", section on 'Clinicopathologic features'.)

Perineural invasion — There is level 1 evidence that perineural invasion (PNI) is associated with a poor prognosis in multivariate analysis [128,138-144]. Given its prognostic importance, PNI is another of the clinicopathologic factors included in the definition of "high-risk" stage II colon cancer from ASCO [135], the NCCN [136], and ESMO (table 12) [137] that might influence the use of adjuvant chemotherapy in this setting. The finding of PNI should be recorded in the pathology report and designated on the TNM staging form even though it does not influence stage. (See "Adjuvant therapy for resected stage II colon cancer", section on 'Clinicopathologic features'.)

Histologic type, grade of differentiation, and presence of mucin — As a general rule, histologic type has not proven to be an independent prognostic factor for colorectal adenocarcinomas with the exception of a few high-grade subtypes (eg, signet ring, poorly differentiated, or undifferentiated tumors) [14,56,58,145-148].

Histologic grade reflects the degree of tumor differentiation and is a feature that has consistently been demonstrated to be a stage-independent prognostic factor [48,49,56,149-152]. However, histologic grading is subjective, with significant interobserver variability and no single widely accepted, uniformly used system [153,154]. The interpretation of grade can be based on the entire tumor or by one single worst area, by the amount of gland formation alone, or by a combination of glandular formation and other structural or cytologic features. This issue is discussed in detail above. (See 'Histology' above.)

Many tumors produce mucin, which may remain within the cells (signet ring cells) or be secreted. Extracellular mucin dissects through the colonic wall, aiding the local extension of the tumor [13]. Tumors producing copious amounts of extracellular mucin (ie, mucin comprising ≥50 percent of the tumor mass) are classified as mucinous carcinomas. (See 'Histology' above.)

While signet ring cancers are clearly associated with an inferior prognosis, the influence of an extracellular mucinous component on prognosis is unclear; the available data are conflicting [148]. Tumor site, mismatch repair (MMR) status, and the effect of preoperative treatment (for rectal cancer) may influence the prognostic impact of mucinous histology:

- At least some data suggest that the presence of mucin is independently associated with worse outcomes in rectal but not colonic tumors [148], but there are conflicting data about the independent prognostic impact of mucinous subtype in rectal cancer [155]. Others report that modern treatment using preoperative short-course radiation therapy or long-course chemoradiotherapy for rectal cancer may have improved outcomes, narrowing the gap between common adenocarcinomas and mucinous cancers [156].

- Furthermore, tumors, particularly right-sided tumors, are associated with MMR deficiency (dMMR; the biologic footprint of which is the presence of high levels of MSI [MSI-H]), which have a relatively more favorable prognosis. This was shown in a series of 394 consecutive patients with stage III CRC who received adjuvant chemotherapy; three-year survival was significantly better for those with nonmucinous histology (79 versus 57 percent) [157]. Although the numbers were small, for the 26 patients with tumors that were deficient in one or more MMR proteins, there was no difference in outcomes for mucinous versus nonmucinous tumors. Similarly, among the 123 patients with proximal (right-sided) tumors, mucinous histology was not associated with a significantly worse outcome. (See 'Mismatch repair deficiency' below.)

Tumor border and tumor budding — The configuration of the tumor at the advancing edge (ie, the tumor border) has prognostic significance that is independent of stage. Specifically, an irregular, infiltrating pattern of growth as opposed to a smooth pushing (expansile) border has

been demonstrated to be an independent adverse prognostic factor by several multivariate analyses [146,158,159]. The following characteristics are indicative of an infiltrating border [146]:

- Inability to define the limits of tumor invasion and/or distinguish host tissue from malignant tissue by naked eye examination of a microscopic slide of the border
- On microscopic examination of the tumor border, dissection of tumor through the full thickness of the muscularis propria without a stromal response and/or dissection of mesenteric adipose tissue by small glands or irregular clusters or cords of cells and/or perineural invasion

Tumor "budding" is another specific tumor border feature that is defined as microscopic clusters of undifferentiated cancer cells just ahead of the invasive front of the tumor [160]; this has also been referred to as "focal dedifferentiation" [154,161]. It is hypothesized that tumor budding reflects a detachment of cells and invasion of stroma at the invasive front of a carcinoma, and it is presumed to be an early step in the metastatic process. Some data suggest that tumor budding, especially when it is extensive, may be of greater prognostic value than grade and that its prognostic value is independent of the overall tumor border configuration [154,160,162]. A three-tiered grading system for tumor budding (BD1 through 3) was endorsed by the International Tumor Budding Consensus Conference [163,164], with specimens having BD3 budding (≥ 10 buds) being associated with a greater risk of recurrence in stage II colorectal cancer. A systematic review concluded that resected colorectal cancers with high levels of tumor budding are more likely to develop disease recurrence (odds ratio 5.50, 95% CI 3.64-8.29) and a cancer-related death at five years (odds ratio 4.51, 95% CI 2.55-7.99) than those without high levels of tumor budding.

High levels of tumor budding are included as one of the clinicopathologic features of high-risk stage II colon cancer that are used in the decision-making process for adjuvant chemotherapy, and according to an updated ASCO guideline on treatment of stage II cancer, patients whose tumors display this feature may be offered systemic therapy [135]. (See "Adjuvant therapy for resected stage II colon cancer".)

Host immune response — As in many other types of cancer, the presence of tumor-infiltrating lymphocytes is a favorable prognostic factor in most studies [165-174]. In particular, a high density of CD8+ T cells and CD45RO+ cells (both CD4+ and CD8+ lymphocytes that have been exposed to antigen, ie memory, cells) within these lymphoid populations has been associated with the absence of pathologic evidence of early metastatic invasion, earlier stage, and improved patient survival [166,168,169,171,173]. These data have led some to suggest that this

response indicates that defensive host mechanisms were operative [166]. However, there are no direct data to support such a hypothesis.

More recently, a high density of a different type of T cell, regulatory T cells (which are characterized by the CD4+CD25+ phenotype and thought to modulate the antitumor immune response [175]), was found to have a stronger prognostic significance in CRC than either infiltrating CD8+ or CD45RO+ cells [176]. (See "Normal B and T lymphocyte development", section on 'Regulatory T cells (Tregs)'.)

Further, a Crohn disease-like lymphoid reaction characterized by peritumoral lymphoid aggregates is a common feature of MSI-H tumors [177,178] and has also been associated with an improved prognosis [174,179-181].

Several large studies of CRC have shown that tumor lymphocytic reaction and T-cell subpopulations are significant prognostic biomarkers, even after adjusting for stage, lymph node count, and well-established prognostic biomarkers, including *BRAF* mutation [179,182]. Lymphoid infiltration may represent a favorable prognostic marker because of its association with deficiency of MMR, the biologic footprint of which is MSI. Tumors containing numerous lymphoid cells frequently have mutations in DNA MMR genes and high levels of MSI-H [183-186]. Medullary carcinoma, a unique histologic type of CRC that is almost always MSI-H and has a strong association with Lynch syndrome, is characterized by intratumoral lymphocytic infiltrates. However, in at least one report, MSI-H and intratumoral lymphocytic infiltration were each independent prognostic factors [187]. (See 'Mismatch repair deficiency' below.)

The contribution of tumor infiltrating lymphocytes to the favorable prognosis of MSI-H tumors is further supported by studies showing that subpopulations of these cells are associated with a distinct molecular phenotype [188] and that the good prognosis of molecularly defined subgroups of CRC that are enriched for MSI-H tumors is characterized by overexpression of genes specific to cytotoxic lymphocytes. (See 'Molecular classification' below.)

Despite these convincing data, at present, the host immune response is not yet considered to represent a standard prognostic indicator for clinical use. Nevertheless, multinational efforts are underway combining tumor and immune factors to develop and validate an "immunoscore" to quantify the in situ immune infiltrate as a novel instrument for classification and prognostication of CRC [189-192].

Peritumoral fibrosis — A desmoplastic stromal response is common in invasive CRCs and is responsible for their typical hard consistency. In some [51,146,193,194], but not all, studies [195-197], fibrosis is an independent adverse prognostic factor.

Microvessel density — Intratumoral microvessel density (MVD) is a reflection of tumor-induced angiogenesis. MVD has been independently associated with shorter survival in some but not all studies. A meta-analysis of all studies relating MVD expression to prognosis concluded that at least some of the variability could be explained by the different methods of MVD assessment [198]. There was a significant inverse correlation between IHC expression and survival when MVD was assessed using antibodies against CD31 or CD34, but not factor VIII.

There is a need for validation of MVD in large studies of prognostic factors using multivariate analysis; however, standard guidelines for staining, evaluation, and interpretation of MVD are lacking [28].

Focal neuroendocrine differentiation — Although extensive neuroendocrine differentiation is an adverse prognostic factor in CRC, the significance of scattered or focal neuroendocrine differentiation is unclear; the available data are conflicting [199-204]. (See 'Histology' above.)

Tumor location — In many (but not all [205]) studies, primary tumor location is a prognostic factor in CRC [206-211]. In a meta-analysis of 66 studies including 1,427,846 patients with all stages of disease, left-sided primary tumor location (tumor location at or beyond the splenic flexure) was associated with a significantly reduced risk of death (hazard ratio [HR] 0.82, 95% CI 0.79-0.84), and this was independent of stage (although the effect size was greater for metastatic disease), race, use of adjuvant chemotherapy, year of study, and quality of the included studies [208].

Tumor location might simply be a proxy for molecular biology. As an example, in one study, mutations in *BRAF* or *KRAS* (which are associated with an inferior prognosis) were more common in proximal (right-sided) cancers, while distal (left-sided) tumors were more likely to be nonmutated [212]. Data from The Cancer Genome Atlas have demonstrated a difference in the distribution of the consensus molecular subtypes between right- and left-sided tumors [213]. (See 'Molecular classification' below.)

However, the data are inconsistent:

- A better prognosis for left-sided as compared with right-sided tumors has been shown in populations with *RAS* wild-type tumors [210,214]. (See 'RAS and BRAF' below.)
- Others have shown a better outcome for right-sided tumors that are *RAS* but not *BRAF* mutated [214].
- Hypermutated tumors (ie, those with higher mutation burdens, often described as >10 mutations per megabase [215,216]) that are MSI-H (and are associated with a better

outcome) are much more likely to be right sided.

Accumulating data suggest that tumor sidedness might also be a predictive factor for response to therapies that target the epidermal growth factor receptor (EGFR) in patients with *RAS* wild-type metastatic CRC. This subject is discussed in detail elsewhere. (See "Systemic therapy for nonoperable metastatic colorectal cancer: Selecting the initial therapeutic approach", section on 'EGFR inhibitors versus bevacizumab and the influence of tumor sidedness'.)

Clinical features — Certain clinical features are associated with prognosis, including high preoperative levels of the serum tumor marker carcinoembryonic antigen (CEA) and the presence of obstruction or perforation.

Preoperative serum CEA — In most (but not all [217]) studies, high levels of preoperative serum of the tumor marker CEA are of prognostic significance, although the optimal cutoff value is debated:

- In several studies, CEA levels ≥5.0 ng/mL have an adverse impact on survival that is independent of tumor stage [48,128,218-225]. As an example, in a series of 17,910 patients diagnosed with colon cancer of any stage and reported to the SEER database in 2004, at a short median follow-up (27 months), an elevated preoperative CEA level was associated with a significantly increased risk of overall mortality (HR for death 1.60, 95% CI 1.46-1.76) [224]. Elevated CEA was an independent prognostic factor across all stages, and within each stage grouping, the prognosis of the subset of patients with elevated CEA was similar to or worse than a subset of patients identified as having a normal preoperative CEA level and who belonged to a higher AJCC stage grouping. An intriguing finding was that patients with node-negative disease and an elevated preoperative CEA level had a worse prognosis (HR for death 1.75, 95% CI 1.48-2.09) than did those with node-positive disease and a normal preoperative CEA level (HR for death 1.58, 95% CI 1.30-1.91).

- Others suggest that a cutoff level of 3.0 ng/mL yields maximal sensitivity and specificity for recurrence [226].

Regardless of the cutoff value used, these data have led some to recommend that preoperative CEA elevation be incorporated into the conventional TNM staging system for colon cancer [28]. The current 2017 revision (table 1) does not include serum CEA in stage assignment, but recommends that the information be collected for prognostic value (and for postoperative monitoring for recurrence) [43,44]. However, while patients with node-negative cancer and a high preoperative CEA could be considered at higher than average risk for recurrence after surgery alone, and this might influence the decision to administer adjuvant chemotherapy, particularly if other risk factors (eg, obstruction, perforation) are present, there are no data that

directly support benefit for adjuvant chemotherapy in this particular setting. Furthermore, at least one report refutes the association of high preoperative serum CEA levels with poor prognosis, as long as levels normalize following resection [217].

Elevated preoperative CEA levels are not considered one of the clinicopathologic factors that define "high-risk" stage II colon cancer by ASCO [135], or the NCCN [136], but they are considered a minor factor in the ESMO guidelines (table 12) [137]. (See "Adjuvant therapy for resected stage II colon cancer", section on 'Higher-risk stage II disease'.)

Bowel obstruction and/or perforation — Many (but not all [128,227,228]) series report an adverse prognostic impact of clinical obstruction at the time of diagnosis for colon and rectal cancers [229-236]. Similarly, gross perforation is also noted to be an adverse prognostic feature in most [230,234-240] but not all [128,228,241] reports. Although many of these reports indicate that obstruction and/or perforation were independently predictive of poorer survival on multivariate analysis, some have concluded that CRCs that need emergency surgery because of issues like obstruction or perforation generally show a more aggressive histopathologic profile (more advanced stage, unfavorable histologic features) than do elective cases [242].

Both obstruction and perforation are considered to represent clinicopathologic factors that define "high-risk" stage II colon cancer from the NCCN [136], ESMO [137], and ASCO [135] (table 12). The presence of these high-risk features might influence the use of adjuvant chemotherapy in this setting. (See "Adjuvant therapy for resected stage II colon cancer", section on 'Clinicopathologic features'.)

Molecular factors — The prognostic value of a wide variety of promising and potentially clinically applicable molecular markers has been studied in CRC. To date, the only factor that is routinely used for decision-making in clinical care is MMR deficiency. Another marker is used for its predictive capacity (*RAS* mutations predict a lack of efficacy for agents targeting the EGFR), and a third marker (*BRAF* mutations) has potential utility as a prognostic and predictive factor. An updated guideline on molecular biomarkers for the evaluation of CRC from the combined American Society for Clinical Pathology (ASCP)/CAP/Association for Molecular Pathology (AMP)/ASCO recommends the following [11,243]:

- Clinicians should order MMR status testing in patients with CRC for prognostic stratification and/or for the identification of patients at high risk for Lynch syndrome. (See 'Mismatch repair deficiency' below.)

- Colorectal carcinoma patients being considered for anti-EGFR therapy must receive *RAS* mutational testing, including *KRAS* and *NRAS* codons 12 and 13 of exon 2; 59 and 61 of exon

3; and 117 and 146 of exon 4 (expanded or extended *RAS* testing). (See 'RAS and BRAF' below.)

- *BRAF* V600 mutational analysis should be performed in dMMR tumors with loss of MLH1 to evaluate for Lynch syndrome risk. The presence of a *BRAF* mutation strongly favors a sporadic tumor, but the absence of a *BRAF* mutation does not exclude the risk of Lynch syndrome. (See 'RAS and BRAF' below.)

  There is insufficient evidence to recommend use of *BRAF* c.1799 p.V600 mutational status as a predictive molecular biomarker for response to anti-EGFR inhibitors. In support of the lack of a recommendation, the committee cited conflicting results from two meta-analyses addressing the benefit of anti-EGFR therapy in patients with *RAS* wild-type but *BRAF*-mutant CRC [244,245].

  However, this is a controversial area. The most recent TNM staging classification (eighth edition, 2017) considers *BRAF* mutations to have both prognostic (level 1 evidence) and predictive (level 1 evidence) significance [44]. (See 'TNM staging' above.)

This subject is discussed in detail elsewhere. (See "Systemic therapy for nonoperable metastatic colorectal cancer: Approach to later lines of systemic therapy", section on 'RAS wild-type, BRAF mutated tumors'.)

Mismatch repair deficiency — Mutations in one of several DNA MMR genes are found in Lynch syndrome (hereditary nonpolyposis CRC [HNPCC]) and in 15 to 20 percent of sporadic colon cancers [246]. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis".)

The characteristic genetic signature of dMMR tumors is a high number of DNA replication errors (RER+) and high levels of DNA MSI, defined as instability in ≥30 percent of microsatellite loci [247,248]. The term MSI refers to the expansion or contraction of short repeated DNA sequences that are caused by the insertion or deletion of repeated units.

Among patients with localized CRCs, tumors that are dMMR (MSI-H) are associated with longer survival than proficient MMR (pMMR) tumors that either have low microsatellite instability (MSI-L; ie, showing instability in <30 to 40 percent of microsatellite loci) or are microsatellite stable (MSS), both in Lynch-related and sporadic cases, despite often being poorly differentiated [187,247-256]. (See "Molecular genetics of colorectal cancer", section on 'Microsatellite instability high versus low'.)

The biologic basis for this finding is unknown. MSI is one of the clinically significant prognostic factors that are recommended for collection in both the current 2010 and the newest 2017 TNM staging criteria for CRC [43,44]. (See 'TNM staging' above.)

The better prognosis of dMMR tumors in early stage disease may be limited to individuals who lack a *BRAF* V600E mutation [257].

The prognostic influence of MSI is less clear in patients with metastatic CRC, a population in which the prevalence of MSI-H disease is low (approximately 3.5 percent) [258]. At least one report suggests an adverse influence of MSI on prognosis in this setting, a finding attributed, at least in part, to the higher frequency of *BRAF* mutations in this population [259,260].

In addition to the better prognosis afforded by the presence of MMR deficiency in an individual tumor, the bulk of available data support that adjuvant fluorouracil-based chemotherapy is less beneficial for patients with MSI-H (dMMR) tumors. This topic is discussed in detail elsewhere. (See "Adjuvant therapy for resected stage II colon cancer", section on 'Patients with deficient MMR'.)

MMR deficiency also identifies patients who might benefit from immunotherapy using immune checkpoint inhibitors in the setting of advanced disease.

As noted above, MMR deficiency is found in tumors from patients with Lynch syndrome (HNPCC, which accounts for one-third of all dMMR CRCs) as well as in 15 to 20 percent of sporadic colon cancers (which account for two-thirds of all dMMR CRCs). Emerging data suggest that there might be differences in the biologic behavior of these two groups. In one study, Lynch-associated dMMR patients presented with more somatic mutations and neoantigens compared with sporadic dMMR tumors, which may be associated with a stronger immune reaction and better survival overall [261]. Whether this heterogeneity will translate into a better response to immune checkpoint inhibitors in patients with advanced disease is not established. Furthermore, whether the utility of dMMR status as a predictive factor for adjuvant fluoropyrimidine therapy in earlier stage disease might differ according to the molecular mechanism underlying the loss of MMR awaits further study [262].

Methods for testing for dMMR/MSI are discussed in detail elsewhere. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Identification of individuals at risk for Lynch syndrome'.)

RAS and BRAF — The pathogenesis of CRC involves the accumulation of genetic and epigenetic modifications within pathways that regulate proliferation, apoptosis, and angiogenesis. (See "Molecular genetics of colorectal cancer".)

RAS and *BRAF* mutations are of prognostic and predictive value in metastatic CRC:

- *KRAS* mutations involving either codon 12 or 13 can be identified in 12 to 75 percent of tumors; they have been independently associated with a worse prognosis in most [263-269] (albeit not all [270-272]) studies. One potential explanation is that different mutations within the gene may exert disparate prognostic influences. As an example, the multicenter RASCAL study evaluated the prognostic significance of mutations in codon 12 or 13 in 2721 patients from 13 countries [264]. In multivariate analysis, only codon 12 mutations were independently associated with an increased risk of recurrence and death. However, in a later analysis that was expanded to include 4268 patients and 12 possible mutations within codons 12 and 13, only one specific mutation on codon 12, found in 9 percent of the cohort, was significantly associated with an adverse outcome and only in patients with node-positive disease [273].

  Although less information is available, *NRAS* mutations are also associated with an inferior prognosis [274].

  The activation of the EGFR signaling cascade is a well-described pathway leading to colon tumorigenesis. Mutations within the *RAS* and *BRAF* oncogenes located downstream of EGFR within this pathway lead to its constitutive activation, even if the EGFR is blocked. Consequently, tumors with mutated *KRAS* and *NRAS* are unresponsive to anti-EGFR therapy. (See "Systemic therapy for metastatic colorectal cancer: General principles", section on 'RAS'.)

- *BRAF* activating mutations, most of which occur in codon 600 (V600E), occur in less than 10 percent of sporadic CRCs (but are especially associated with cigarette smoking) and are a strong negative prognostic marker for both early stage and advanced/recurrent tumors in non-MSI-H tumors [255,260,267,268,275-279]. For MSI-H tumors, in which most of the *BRAF* mutations occur, the presence of a mutation does not have the same adverse prognostic significance [269,280].

  The available data also support the view that *BRAF* V600E mutations confer resistance to anti-EGFR therapy. (See "Molecular genetics of colorectal cancer", section on 'Hypermethylation phenotype (CIMP+) pathway'.)

  Less is known about *BRAF* mutations that occur outside of codon 600. In one report in which 9643 patients with metastatic CRC underwent next-generation sequencing, there were 208 with non-V600 *BRAF* mutations (2.2 percent of the total and accounting for 22 percent [one-fifth] of all of the *BRAF* mutations) [281]. Compared with *BRAF* V600E mutations, the cancers that harbored a non-V600 *BRAF* mutation arose in younger

individuals (58 versus 68 years), were less often found in women (46 versus 65 percent), and were less often high grade (13 versus 64 percent) or right sided (36 versus 81 percent). Furthermore, patients whose tumors had a non-V600 *BRAF* mutation also had significantly better median overall survival as compared with both *BRAF* V600E mutations and wild-type *BRAF* metastatic CRC (61 versus 11 versus 43 months, respectively). There are no data addressing the predictive value of non-V600 *BRAF* mutations for response to anti-EGFR agents.

In view of these data, the most recent TNM staging classification considers *RAS* and *BRAF* V600E mutations to have both prognostic (level 1 evidence) and predictive (level 1 evidence) significance. Therefore, testing for *RAS* and *BRAF* mutational status has become part of routine pathological evaluation for CRC greater than stage I. (See "Systemic therapy for metastatic colorectal cancer: General principles", section on 'BRAF mutations' and "Systemic therapy for metastatic colorectal cancer: General principles", section on 'RAS'.)

All other molecular markers — The prognostic value of a wide variety of promising and potentially clinically applicable molecular markers has been studied in CRC, including:

- DNA content (aneuploidy)
- Tumor suppressor genes (LOH 1p, LOH 8p; LOH 5q; *SMAD4*, *TP53* gene)
- Oncogenes other than *RAS* and *BRAF* (eg, *c-myc*)
- Apoptosis/cell suicide-related genes (*Bcl-2*; *BAX*; Apoptosis protease activating factor-1 [*APAF1*])
- DNA synthesis-related genes (thymidylate synthetase; thymidine phosphorylase)
- Growth factors and growth factor receptor genes (transforming growth factors a and b, human epidermal growth factor receptor-2 [*HER2*])
- Cyclins and cyclin dependent kinase inhibitor genes (p27; p21)
- Angiogenesis-related genes (vascular endothelial growth factor [VEGF])
- Adhesion molecule and glycoprotein genes (CD44; E-cadherin [*CDH1*]; sialo-Tn antigen)
- Matrix metalloproteinases and their inhibitors (MMPs; urokinase-type plasminogen activator)
- Metastasis suppressor genes (eg, *NM23H1B*)
- Overexpression of, and high circulating levels of microRNA
- Epigenetic aberrations such as methylation levels
- Peroxisome proliferator-activated receptor-gamma (*PPARG*)
- Circulating tumor DNA
- Soluble type IV collagen
- Deletions in 18q

The independent influence of these markers on prognosis remains unproven. Variability in assay methodology, conflicting results from various studies examining the same factor, and the prevalence of multiple small studies that lack statistically robust, multivariate analyses all contribute to the lack of conclusive data.

As an example, *TP53*, which probably represents the most widely studied gene in CRC, has been analyzed according to loss of heterozygosity, p53 protein overexpression by IHC, and detection of mutations by either direct sequencing or single strand polymorphism analysis. Despite a large number of publications and a systematic review, the impact of *TP53* abnormalities on prognosis in CRC remains uncertain [282]. Even among reports that use a single-assay system, the reagents used vary considerably, confounding interpretation of the results.

Before any of these markers can be incorporated into clinically meaningful prognostic stratification systems, more studies are required using multivariate analysis, well-characterized patient populations, reproducible and current methodology, and standardized reagents. Guidelines to standardize reporting of tumor marker studies have been proposed by an international group [283].

Prognostic molecular profiles — Gene expression profiling has identified molecular signatures, such as the 12-gene recurrence score (Oncotype DX Colon Cancer Assay), that may augment conventional prognostic indicators in their ability to predict colon cancer outcomes among patients with node-negative (stage II) and node-positive (stage III) disease [284]. However, before these tools can be adopted for widespread clinical use, external validation in prospective clinical trials is needed to assess their reliability [285] and prognostic and predictive utility (ie, their ability to predict which patients would be predicted to benefit from specific chemotherapy approaches) [286].

Molecular classification — Efforts are underway to develop gene expression-based classifications of CRC. There appear to be at least three molecular pathways leading to colorectal tumorigenesis (table 13): the chromosomal instability (CIN) pathway, which is typified by the inherited condition familial adenomatous polyposis (FAP); the mutator-phenotype/DNA mismatch repair pathway, which is implicated in the inherited condition Lynch syndrome as well as in a proportion of sporadic CRCs in which there is loss of DNA MMR function; and the hypermethylation phenotype hyperplastic/serrated polyp pathway, which is characterized by a high frequency of methylation of some CpG islands (CpG island hypermethylation phenotype [CIMP]-positive) [287]. (See "Molecular genetics of colorectal cancer", section on 'Molecular pathways to colorectal tumorigenesis'.)

Several independent groups have proposed CRC subtypes based on distinct global gene expression profiles [288-291]. One proposed molecular classification system suggests the presence of four unique clinically relevant molecular subtypes with distinguishing features [288]:

- **CMS1 (MSI-like)** – Contains most MSI-H tumors with mutations in genes encoding DNA MMR proteins, resulting in high mutational burden. The MSI-like subtype is also enriched for tumors with a CIMP and mutations in the *BRAF* oncogene.
- **CMS2 (canonical)** – Subtype with high CIN as well as activation of the Wnt and MYC pathways. (See "Molecular genetics of colorectal cancer", section on 'APC gene'.)
- **CMS3 (metabolic)** – Enriched in tumors with *KRAS* mutations and shows disruption of metabolic pathways.
- **CMS4 (mesenchymal)** – Mesenchymal phenotype and frequently, CIMP phenotype.

Increasingly, molecular classification schemes such as these have been associated with prognosis and response to therapy both in the adjuvant and metastatic disease settings [286,288,292,293]. The CMS1 tumors have a good prognosis, the CMS4 tumors have a poor prognosis, and the CMS2 and CMS3 types have an intermediate prognosis.

Furthermore, in keeping with the prognostic importance of peritumoral inflammatory response, fibrosis, and microvessel density, the available evidence suggests that these molecular subtypes are correlated with microenvironmental (ie, immune, fibroblastic, and angiogenic) signatures [294-296]:

- The good-prognosis MSI-enriched subgroup (CMS1) is characterized by overexpression of genes specific to cytotoxic lymphocytes [294]. (See 'Host immune response' above.)
- The poor prognosis mesenchymal subgroup expresses markers of lymphocytes and of cells of monocytic origin, and they display an angiogenic, inflammatory, and immunosuppressive signature that is also found in other tumors, including breast and kidney cancers. This initially led to speculation that epithelial-to-mesenchymal transition of the tumor cells might be responsible for the tumor aggressiveness [289-291].

  However, pathologically, these tumors have a high density of fibroblasts [294], and they share a gene program induced by transforming growth factor-beta (TGF-b) in tumor stromal cells [295], suggesting that the elevated expression of mesenchymal genes is mainly contributed by tumor-associated stromal cells and not epithelial tumor cells [295]. In fact, transcriptional signatures built to specifically report the abundance of cancer-

associated fibroblasts, leucocytes, or endothelial cells all have significantly higher expression in samples of the mesenchymal subtype. Stromal cells in these tumors likely produce the chemokines and cytokines that favor tumor-associated inflammation and support angiogenesis, resulting in a poor prognosis. (See 'Peritumoral fibrosis' above.)

- By contrast, the canonical and metabolic subtypes with intermediate prognosis exhibit low immune and inflammatory signatures.

While these results are intriguing and may pave the way for future molecularly based prognostic stratification systems that aid in the selection of specific therapy [297-299], molecular classification is not yet ready for incorporation into available staging systems or prognostic models, and it is difficult to reproduce at point of care since it requires analysis of a large number of genes.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Colorectal cancer".)

SUMMARY

- **Histology and immunohistochemistry**
  - The vast majority of tumors of the colon and rectum are carcinomas. Other histologic types (neuroendocrine neoplasms, hamartomas, mesenchymal tumors, lymphomas) are relatively unusual. Of the carcinomas, more than 90 percent are adenocarcinomas. (See 'Histology' above.)
  - Cytokeratin (CK) 20 and caudal-type homeobox 2 (CDX2) are two of the most sensitive and specific markers of intestinal differentiation and are extremely useful immunohistochemistry (IHC) markers in correctly identifying adenocarcinomas of colorectal origin. IHC for CK20 and CK7 can be particularly helpful in distinguishing a primary appendiceal malignancy versus mucinous ovarian cancer (table 5). (See 'Immunohistochemistry' above.)
- **Prognostic determinants**
  - **Tumor stage**

- The most powerful tool for assessing prognosis following potentially curative surgery for colorectal cancer (CRC) is pathologic analysis of the resected specimen. The most important pathologic characteristics are the presence of distant metastases, local tumor extent, nodal positivity (particularly the number of involved lymph nodes), residual disease, extramural tumor deposits, lymphovascular and perineural invasion, histologic grade of differentiation, and for patients treated with neoadjuvant therapy prior to resection of a rectal cancer, the tumor regression grade. (See 'Pathologic features' above.)

- The depth of tumor invasion, the status of the regional nodes, and the presence or absence of metastases are used to define the tumor stage, which is then used to derive the prognostic stage groupings. Five-year survival stratified by tumor stage at diagnosis for colon cancer using the American Joint Committee on Cancer (AJCC) 2010 staging criteria is illustrated in the figure (figure 3). Five-year survival stratified by tumor stage at diagnosis for rectal cancer using the 2010 staging criteria is illustrated in the figure (figure 2). (See 'TNM staging' above.)

  Among patients receiving neoadjuvant (presurgical) treatment for rectal cancer, the posttreatment stage (given a yp designation in the AJCC staging system) is a more accurate predictor of outcome than the pretreatment clinical stage. Five-year survival according to pathologic stage after chemoradiotherapy for rectal cancer is outlined in the table (table 8). (See 'Posttherapy staging for rectal cancer' above and 'Tumor regression after neoadjuvant therapy' above.)

- **Other clinicopathologic features** – Further stratification of outcomes can be achieved by the identification of patients with a high preoperative serum level of the tumor marker carcinoembryonic antigen (CEA), clinical obstruction at the time of diagnosis, and macroscopic perforation of the tumor. (See 'Clinical features' above.)

- **Molecular factors**

  - Molecular features may also influence outcome, independent of stage at presentation. However, the only factors that are used for clinical decision making at present are the status of the DNA mismatch repair (MMR) proteins (the biologic footprint of deficient MMR [dMMR] status is microsatellite instability), and *BRAF* and *RAS* mutations. These factors are prognostic, but dMMR status is also predictive of efficacy of fluoropyrimidine-based chemotherapy. (See 'Mismatch repair deficiency' above and 'RAS and BRAF' above.)

- Until large, statistically robust studies are completed with multivariate analysis of an array of potential prognostic factors and their interaction with each other, no other molecular or genetic markers should be used routinely to develop treatment recommendations or to estimate prognosis in patients with resected CRC. (See 'All other molecular markers' above.)

- Gene expression-based tumor classification may help clarify the importance of the tumor microenvironment to biologic behavior, and molecularly based prognostic stratification systems may someday be used to select specific therapy. However, molecular classification is not yet ready for incorporation into available staging systems or other prognostic models. (See 'Molecular classification' above.)

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Topic 2484 Version 103.0

GRAPHICS

Colorectal cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4	Tumor invades* the visceral peritoneum or invades or adheres¶ to adjacent organ or structure
T4a	Tumor invades* through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades* or adheres¶ to adjacent organs or structures
* Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (ie, respectively, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina). ¶ Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classification should be used to identify the presence or absence of vascular or lymphatic invasion whereas the PN prognostic factor should be used for perineural invasion.	
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis

N1	One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the: ▪ Subserosa ▪ Mesentery ▪ Nonperitonealized pericolic, or perirectal/mesorectal tissues
N2	Four or more regional nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive

Distant metastasis (M)

M category	M criteria
M0	No distant metastasis by imaging, etc; no evidence of tumor in distant sites or organs. (This category is not assigned by pathologists.)
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a	Metastasis to one site or organ is identified without peritoneal metastasis
M1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

Prognostic stage groups

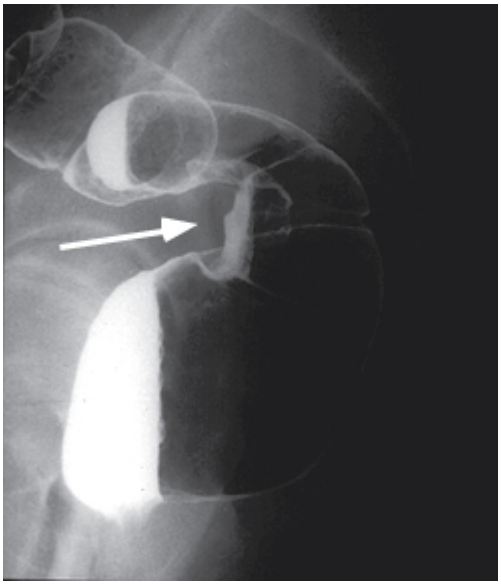
When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1, T2	N0	M0	I
T3	N0	M0	IIA
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T1-T2	N1/N1c	M0	IIIA
T1	N2a	M0	IIIA
T3-T4a	N1/N1c	M0	IIIB

T2-T3	N2a	M0	IIIB
T1-T2	N2b	M0	IIIB
T4a	N2a	M0	IIIC
T3-T4a	N2b	M0	IIIC
T4b	N1-N2	M0	IIIC
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB
Any T	Any N	M1c	IVC

TNM: Tumor, Node, Metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 111438 Version 10.0

Rectal cancer as seen on barium enema

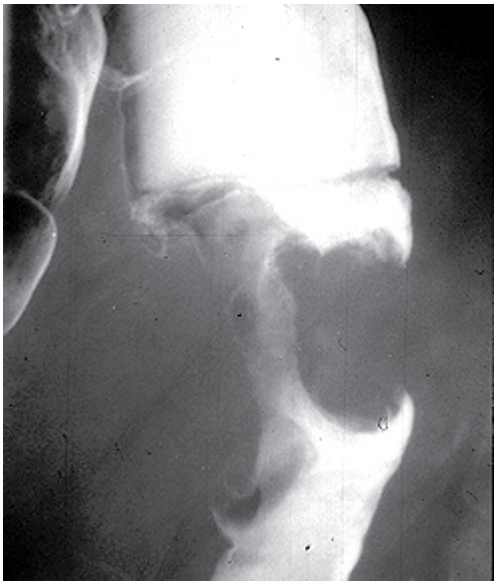


Double-contrast barium enema shows an eccentric mass arising from the anterior wall of the rectum (arrow).

Courtesy of Jonathan Kruskal, MD, PhD.

Graphic 82202 Version 3.0

Cancer of the colon as seen on barium enema



Double contrast barium enema shows an apple-core lesion surrounding the lumen of the descending colon.

Courtesy of Jonathan Kruskal, MD.

Graphic 75818 Version 3.0

World Health Organization (WHO) classification of tumors of the colon and rectum

Benign epithelial tumors and precursors
Serrated dysplasia, low grade
Serrated dysplasia, high grade
Hyperplastic polyp, microvesicular type
Hyperplastic polyp, goblet cell
Adenomatous polyp, low-grade dysplasia
Adenomatous polyp, high-grade dysplasia
Tubular adenoma, low grade
Tubular adenoma, high grade
Villous adenoma, low grade
Villous adenoma, high grade
Tubulovillous adenoma, low grade
Tubulovillous adenoma, high grade
Advanced adenoma
Glandular intraepithelial neoplasia, low grade
Glandular intraepithelial neoplasia, high grade
Malignant epithelial tumors
Adenocarcinoma NOS
Serrated adenocarcinoma
Adenoma-like adenocarcinoma
Micropapillary adenocarcinoma
Mucinous adenocarcinoma
Poorly cohesive carcinoma
Signet ring cell carcinoma
Medullary adenocarcinoma
Adenosquamous carcinoma
Carcinoma, undifferentiated, NOS
Carcinoma with sarcomatoid component
Neuroendocrine tumor NOS

Neuroendocrine tumor, grade 1
Neuroendocrine tumor, grade 2
Neuroendocrine tumor, grade 3
L cell tumor
Glucagon-like peptide-producing tumor
PP/PYY-producing tumor
Enterochromaffin cell carcinoid
Serotonin-producing tumor
Neuroendocrine carcinoma NOS
Large cell neuroendocrine carcinoma
Small cell neuroendocrine carcinoma
Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)

NOS: not otherwise specified; PP: pancreatic polypeptide; PYY: peptide YY.

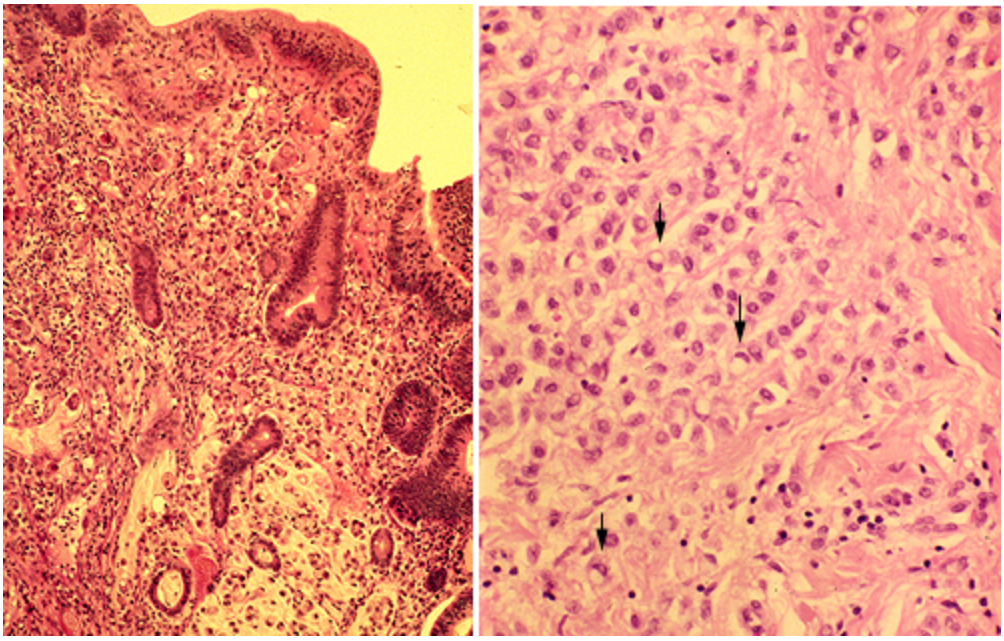
Graphic 122435 Version 1.0

World Health Organization classification of carcinomas of the colon and rectum

Adenocarcinoma
Cribriform comedo-type adenocarcinoma
Medullary carcinoma
Micropapillary carcinoma
Mucinous (colloid) adenocarcinoma (>50% mucinous)
Serrated adenocarcinoma
Signet-ring cell carcinoma (>50% signet-ring cells)
Adenosquamous carcinoma
Spindle cell carcinoma
Squamous cell (epidermoid) carcinoma
Undifferentiated carcinoma

Graphic 68703 Version 3.0

Histologic appearance of a signet ring colon carcinoma



Focus of signet ring carcinoma arising within an adenomatous polyp. Left panel: low power view; right panel, higher power view demonstrating typical signet ring cells, which are identified by black arrows.

Courtesy of Carolyn C Compton, MD, PhD.

Graphic 67584 Version 2.0

Appendix carcinoma TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* (intramucosal carcinoma; invasion of the lamina propria or extension into but not through the muscularis mucosae)
Tis(LAMN)	Low-grade appendiceal mucinous neoplasm confined by the muscularis propria. Acellular mucin or mucinous epithelium may invade into the muscularis propria. T1 and T2 are not applicable to LAMN. Acellular mucin or mucinous epithelium that extends into the subserosa or serosa should be classified as T3 or T4a, respectively.
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)

T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa or the mesoappendix
T4	Tumor invades the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or mesoappendix, and/or directly invades adjacent organs or structures
T4a	Tumor invades through the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or serosa of the mesoappendix
T4b	Tumor directly invades or adheres to adjacent organs or structures

Regional lymph nodes (N)

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph node measuring ≥0.2 mm) or any number of tumor deposits is present, and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the subserosa or mesentery
N2	Four or more regional lymph nodes are positive

Distant metastasis (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Intraperitoneal acellular mucin, without identifiable tumor cells in the disseminated peritoneal mucinous deposits
M1b	Intraperitoneal metastasis only, including peritoneal mucinous deposits containing tumor cells
M1c	Metastasis to sites other than peritoneum

NOTE: For specimens containing acellular mucin without identifiable tumor cells, efforts should be made to obtain additional tissue for thorough histologic examination to evaluate for cellularity.

Histologic grade (G)

G	G definition

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

Prognostic stage groups

When T is…	And N is…	And M is…	And grade is…	Then the stage group is…
Tis	N0	M0	–	0
Tis(LAMN)	N0	M0	–	0
T1	N0	M0	–	I
T2	N0	M0	–	I
T3	N0	M0	–	IIA
T4a	N0	M0	–	IIB
T4b	N0	M0	–	IIC
T1	N1	M0	–	IIIA
T2	N1	M0	–	IIIA
T3	N1	M0	–	IIIB
T4	N1	M0	–	IIIB
Any T	N2	M0	–	IIIC
Any T	Any N	M1a	–	IVA
Any T	Any N	M1b	G1	IVA
Any T	Any N	M1b	G2, G3, or GX	IVB
Any T	Any N	M1c	Any G	IVC

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

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Graphic 111127 Version 8.0

Differential diagnosis of unknown primary cancers based upon immunostaining for cytokeratin (CK) 7 and 20

CK7+ CK20+	CK7+ CK20-	CK7- CK20+	CK7- CK20-
Urothelial tumors	Non-small cell lung cancer	Colorectal cancer	Hepatocellular cancer
Mucinous ovarian cancer	Small cell lung cancer	Merkel cell cancer	Renal cell cancer
Pancreatic or biliary cancer	Breast cancer		Prostate cancer
	Endometrial cancer		Squamous cell lung cancer
	Nonmucinous ovarian cancer		Head and neck cancer
	Mesothelioma		
	Squamous cancer of cervix		
	Pancreatic or biliary cancer		

CK: cytokeratin; +: positive; -: negative.

Modified from: Dabbs D. Diagnostic Immunohistochemistry, 2nd ed, Churchill Livingstone, Philadelphia, PA 2006.

Graphic 58475 Version 4.0

Interpretation of immunohistochemistry results for mismatch repair genes

Result	Possible interpretation	Explanation/comments	Next steps to consider
Loss of MLH1 only (rare)	1. *MLH1* germline mutation. 2. *MLH1* promoter hypermethylation. 3. Bi-allelic (double) somatic *MLH1* or *PMS2* inactivation.	▪ Epigenetic silencing of the *MLH1* gene can occur through *MLH1* promoter hypermethylation. ▪ Bi-allelic (double) inactivation of *MLH1* can rarely cause isolated MLH1 loss.	1. *BRAF* V600E mutation testing (if negative, proceed to #2). 2. Tumor testing for *MLH1* promoter hypermethylation testing.¶ 3. Germline panel testing for at least the MMR genes if family history is suggestive of Lynch syndrome.* 4. Tumor sequencing to evaluate for bi-allelic (double) somatic *MLH1* inactivation due to mutation and/or LOH.
Loss of MLH1 and PMS2 (common)	1. *MLH1* germline mutation. 2. *PMS2* germline mutation. 3. *MLH1* promoter hypermethylation. 4. Bi-allelic (double) somatic *MLH1* inactivation through mutation and/or LOH. 5. Bi-allelic (double) somatic *PMS2* inactivation through mutation and/or LOH.	▪ Because the MLH1 and PMS2 proteins form a heterodimer, altered expression of either the MLH1 or PMS2 protein due to germline mutations frequently leads to loss of both MLH1 and PMS2 expression. ▪ Altered expression of either *MLH1* or *PMS2* due to bi-allelic (double) somatic mutation or LOH of the *MLH1* or *PMS2* gene can also lead to this pattern.	1. *BRAF* V600E mutation testing (if negative, proceed to #2). 2. Tumor testing for *MLH1* promoter hypermethylation.¶ 3. Tumor testing for bi-allelic (double) somatic *MLH1* or *PMS2* inactivation due to mutation and/or LOH. 4. Germline panel testing for at least the MMR genes if family history is

			suggestive of Lynch syndrome.*
Loss of PMS2 only (less common)	1. *PMS2* germline mutation. 2. Bi-allelic (double) somatic PMS2 inactivation through mutation and/or LOH. 3. *MLH1* germline mutation. 4. Bi-allelic (double) somatic *MLH1* inactivation through mutation and/or LOH.	▪ Because the MLH1 protein has heterodimer partner proteins other than the PMS2 protein, germline *PMS2* mutations may not cause loss of *MLH1* expression by IHC. ▪ PMS2 protein expression by IHC can be interpreted as equivocal—not clearly positive or negative. ▪ *MLH1* germline mutations have rarely been identified when tumors show loss of staining of PMS2 only; bi-allelic double somatic *MLH1* mutation or LOH could also mimic this.	1. Germline MMR panel testing.* 2. If panel testing is negative consider tumor testing for the MMR genes to identify bi-allelic (double) somatic *PMS2* or *MLH1* inactivation due to mutation and/or LOH. 3. If PMS2 expression by IHC is equivocal consider secondary MSI testing to confirm or rule out presence of dMMR.
Loss of MSH2 only (rare)	1. *MSH2* germline mutation. 2. *EPCAM* germline mutation. 3. Bi-allelic (double) somatic inactivation of *MSH2* through mutation and/or LOH.	▪ Strong likelihood of germline *MSH2* or *EPCAM.* ▪ Bi-allelic (double) somatic inactivation of *MSH2* is rare but has been reported.	1. Germline MMR panel testing.* 2. If panel testing is negative consider tumor testing for the MMR genes to identify bi-allelic (double) somatic *MSH2* inactivation due to mutation and/or LOH.
Loss of MSH2 and MSH6 (common)	1. *MSH6* germline mutation. 2. *MSH2* germline mutation. 3. *EPCAM* germline mutation. 4. Bi-allelic (double) somatic inactivation of *MSH2* through	▪ Because the MSH2 and MSH6 proteins form a heterodimer, alterations of expression of either the MSH2 or MSH6 protein due to germline or bi-allelic (double) somatic mutations in either the *MSH2* or *MSH6*	1. Germline MMR panel testing.* 2. If panel testing is negative consider tumor testing for the MMR genes to identify bi-allelic (double) somatic *MSH2* or *MSH6* inactivation due to

	mutation and/or LOH. 5. Bi-allelic (double) somatic inactivation of *MSH6* through mutation and/or LOH.	genes could cause this pattern on IHC.	mutation and/or LOH.
Loss of MSH6 (common)	1. *MSH6* germline mutation. 2. Bi-allelic (double) somatic inactivation of *MSH6* through mutation and/or LOH. 3. *MSH2* germline mutation. 4. Bi-allelic (double) somatic inactivation of *MSH2* through mutation and/or LOH.	▪ Because MSH2 has heterodimer partners other than MSH6, germline *MSH6* mutations may not cause loss of MSH2 expression by IHC and frequently cause loss of staining of MSH6 only; similar reasoning holds for bi-allelic (double) somatic *MSH6* inactivation through mutation and/or LOH.	1. Germline MMR panel testing.* 2. If panel testing is negative consider tumor testing for the MMR genes to identify bi-allelic (double) somatic *MSH6* inactivation due to mutation and/or LOH.
Loss of all 4 MMR proteins	1. Likely an artifact of tissue fixation and IHC staining procedures. 2. Germline mutation in any one of the Lynch syndrome genes		1. Consider MSI testing to confirm or rule out dMMR. 2. Germline MMR panel testing if family history warrants testing.*
All proteins expressed	1. Likely not Lynch syndrome if MSS. 2. If MSI-H, rare missense germline mutations in *MLH1, MSH2, MSH6,* and *PMS2* can demonstrate normal IHC. 3. If MSI-H, rare patients with bi-allelic (double) somatic alterations	Normal IHC is only approximately 85% sensitive for Lynch syndrome.	1. Consider MSI testing to confirm or rule out dMMR. 2. If MSI-H, germline MMR panel testing if family history warrants testing.* 3. If MSI-H and germline panel testing are negative consider tumor testing for the MMR genes to identify bi-allelic (double)

	due to mutation and/or LOH.		somatic inactivation due to mutation and/or LOH.

LOH: loss of heterozygosity; MMR: mismatch repair; dMMR: deficient mismatch repair; IHC: immunohistochemistry; MSI: microsatellite instability; MSI-H: high microsatellite instability.

* A multi-syndrome gene panel is an option if there is a personal or family history of other cancers (not associated with Lynch syndrome).

¶ Rarely, MLH1 methylated or BRAF V600E+ tumors can harbor germline MLH1 mutations. MLH1 methylation may also rarely be caused by constitutional MLH1 epimutation

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Adapted from: Weissman SM, Bellcross C, Bittner CC, et al. Genetic counseling considerations in the evaluation of families for lynch syndrome-a review. J Genet Couns 2011; 20:5.

Graphic 63906 Version 12.0

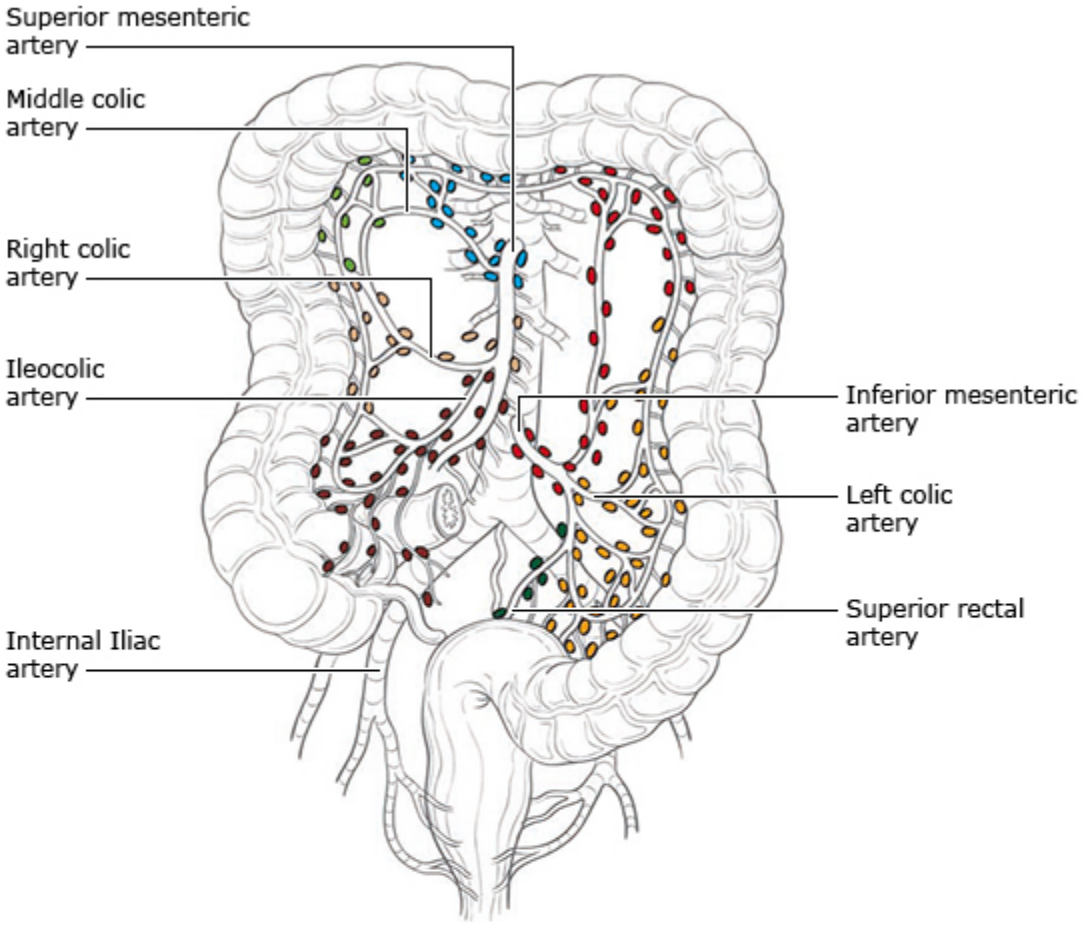
Modified Ryan scheme for tumor regression scoring in rectal cancer treated preoperatively

Description	Tumor regression score
No viable cancer cells (complete response)	0
Single cells or rare small groups of cancer cells (near-complete response)	1
Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response)	2
Extensive residual cancer with no evident tumor regression (poor or no response)	3

Modified from: Ryan R, Gibbons D, Hyland JM, et al. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Histopathology 2005; 47:141. http://onlinelibrary.wiley.com/wol1/doi/10.1111/j.1365-2559.2005.02176.x/abstract. Copyright © 2005. Reproduced with permission of John Wiley & Sons Inc. This image has been provided by or is owned by Wiley. Further permission is needed before it can be downloaded to PowerPoint, printed, shared or emailed. Please contact Wiley's permissions department either via email: permissions@wiley.com or use the RightsLink service by clicking on the 'Request Permission' link accompanying this article on Wiley Online Library (http://onlinelibrary.wiley.com).

Graphic 111439 Version 1.0

Regional lymph nodes of the colon and rectum



Segment	Regional lymph nodes
Cecum	Pericolic, ileocolic, right colic
Ascending colon	Pericolic, ileocolic, right colic, right branch of the middle colic
Hepatic flexure	Pericolic, ileocolic, right colic, middle colic
Transverse colon	Pericolic, middle colic
Splenic flexure	Pericolic, middle colic, left colic
Descending colon	Pericolic, left colic, sigmoid, inferior mesenteric
Sigmoid colon	Pericolic, sigmoid, superior rectal (hemorrhoidal), inferior mesenteric
Rectosigmoid	Pericolic, sigmoid, superior rectal (hemorrhoidal), inferior mesenteric
Rectum	Mesorectal, superior rectal (hemorrhoidal), inferior mesenteric, internal iliac, inferior rectal (hemorrhoidal)

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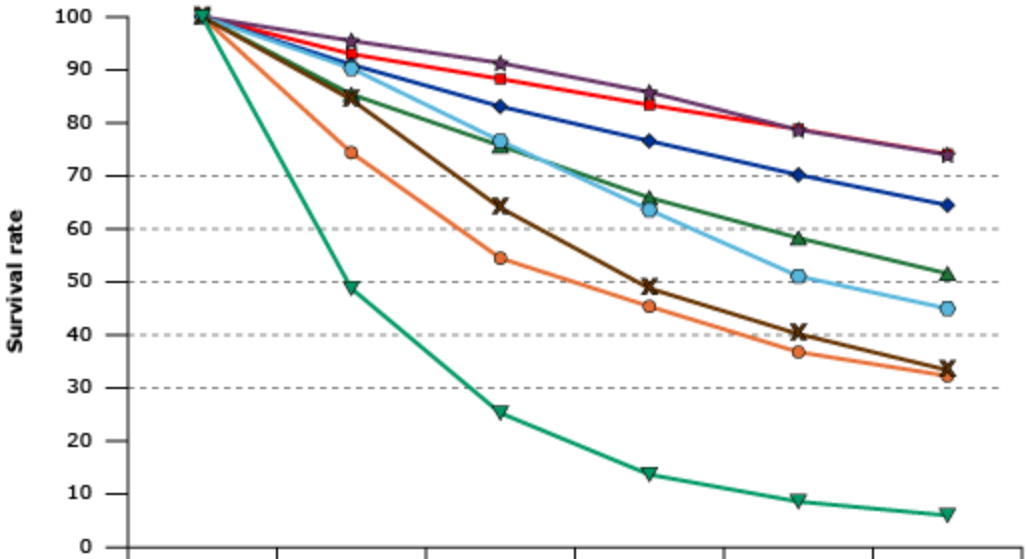
Graphic 111545 Version 6.0

Observed survival rates for 9,860 cases with adenocarcinoma of the rectum



	0	1	2	3	4	5
I	100.0	93.0	88.3	83.4	78.8	74.1
IIA	100.0	91.0	83.1	76.6	70.2	64.5
IIB	100.0	85.4	75.7	65.9	58.3	51.6
IIC	100.0	74.4	54.5	45.4	36.8	32.3
IIIA	100.0	95.5	91.3	85.8	78.7	74.0
IIIB	100.0	90.3	76.6	63.6	51.1	45.0
IIIC	100.0	84.4	64.0	48.8	40.2	33.4
IV	100.0	48.8	25.3	13.7	8.6	6.0

Years from diagnosis

Data from the SEER 1973-2005 Public Use File diagnosed in years 1998-2000. Stage I includes 3470; Stage IIA, 2752; Stage IIB, 165; Stage IIC, 268; Stage IIIA, 595; Stage IIIB, 615; Stage IIIC, 761; and Stage IV, 1234.

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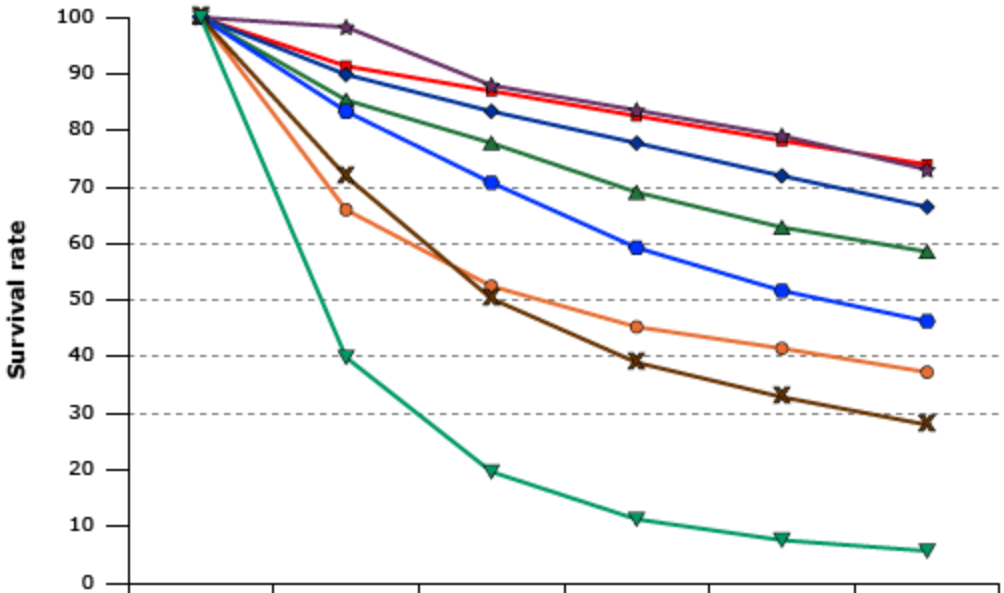
Graphic 60598 Version 12.0

Observed survival rates for 28,491 cases with adenocarcinoma of the colon



	0	1	2	3	4	5
I	100.0	91.4	87.0	82.6	78.2	74.0
IIA	100.0	89.9	83.4	77.8	72.0	66.5
IIB	100.0	85.4	77.8	69.1	62.9	58.6
IIC	100.0	66.0	52.5	45.3	41.5	37.3
IIIA	100.0	98.3	88.0	83.6	79.1	73.1
IIIB	100.0	83.4	70.8	59.3	51.7	46.3
IIIC	100.0	71.9	50.3	39.0	32.9	28.0
IV	100.0	39.9	19.7	11.3	7.6	5.7

Years from diagnosis

Data from the SEER 1973 to 2005 Public Use File diagnosed in years 1998 to 2000. Stage I includes 7417; Stage IIA, 9956; Stage IIB, 997; Stage IIC, 725; Stage IIIA, 868; Stage IIIB, 1492; Stage IIIC, 2000; and Stage IV, 5036.

SEER: Surveillance, Epidemiology, and End Results.

Graphic 81414 Version 14.0

5- and 10-year disease-free survival (DFS) according to posttreatment pathologic (yp) stage and tumor regression grade (TRG) at resection after neoadjuvant chemoradiotherapy in the German Rectal Cancer Study Group (CAO/ARO/AIO-94) trial

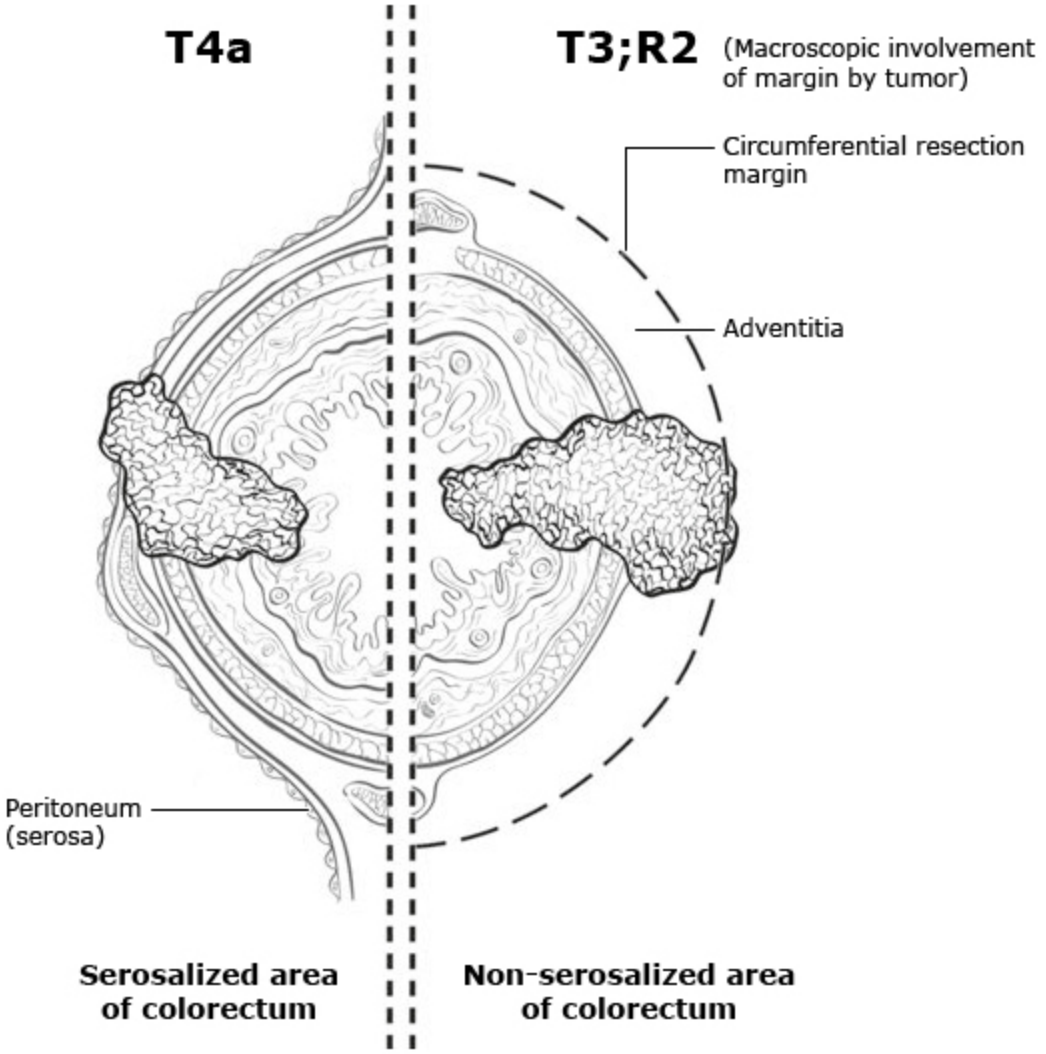
yp category	5-year DFS (%)	10-year DFS (%)
ypT		
T0	86	90
T1	95	95
T2	81	78
T3	65	66
T4	42	40
ypN		
N0	85	84
N1	65	59
N2	18	28
TRG	**5-year DFS (%)**	**10-year DFS (%)**
4	86	90
2-3	75	74
0-1	63	63

Five-tier system for TRG. Complete regression = TRG 4; intermediate regression = TRG 2-3; poor or no regression = TRG 0-1.

Data from: Rödel C, Martus P, Papadoupolos T, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol 2005; 23:8688 and Fokas E, Liersch T, Fietkau R, et al. Tumor regression grading after preoperative chemoradiotherapy for locally advanced rectal carcinoma revisited: updated results of the CAO/ARO/AIO-94 trial. J Clin Oncol 2014; 32:1554.

Graphic 111443 Version 2.0

Depiction of T4a lesions and the importance of the circumferential margin*

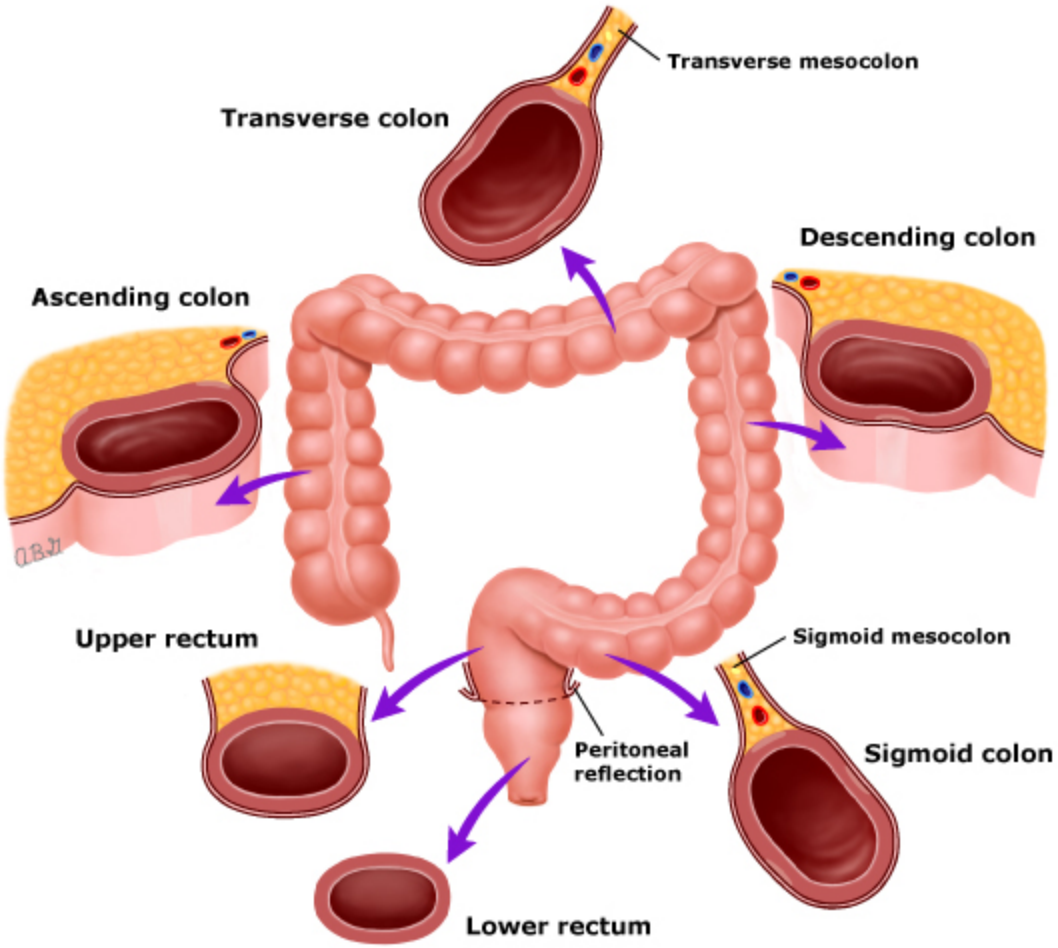


* In portions of the colorectum that are not peritonealized (eg, posterior aspects of the ascending and descending colon, lower portion of the rectum), the pT4a category is not applicable.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

Graphic 111550 Version 6.0

Idealized representation of the peritoneal and mesenteric relationships at various levels of the colon and rectum



Both the transverse and sigmoid colon are located intraperitoneally; at these levels, the visceral peritoneum forms a complete covering over the exterior of the bowel (the serosa), which is continuous with the mesentery (transverse and sigmoid mesocolon). In contrast, the ascending and descending colon lie within the lateral peritoneal cavity with their posterior and lateral surfaces in the retroperitoneum. At these levels, the visceral peritoneum is only present anteriorly and medially; there is no true mesentery, since the developing mesentery has fused to the posterior parietal peritoneum. The upper portion of the rectum lies above the peritoneal reflection. The anterior surface is covered by peritoneum (which forms the rectovesical pouch in men and the rectouterine pouch in women); there is no serosa over its posterior surface. The lower rectum lies beneath the peritoneum and has no serosal layer.

Graphic 81248 Version 3.0

Grading of quality and completeness of the mesorectum in a total mesorectal excision (TME)

	Mesorectum	Defects	Coning	CRM
Complete	Intact, smooth	Not deeper than 5 mm	None	Smooth, regular
Nearly complete	Moderate bulk, irregular	No visible muscularis propria	Moderate	Irregular
Incomplete	Little bulk	Down to muscularis propria	Moderate/marked	Irregular

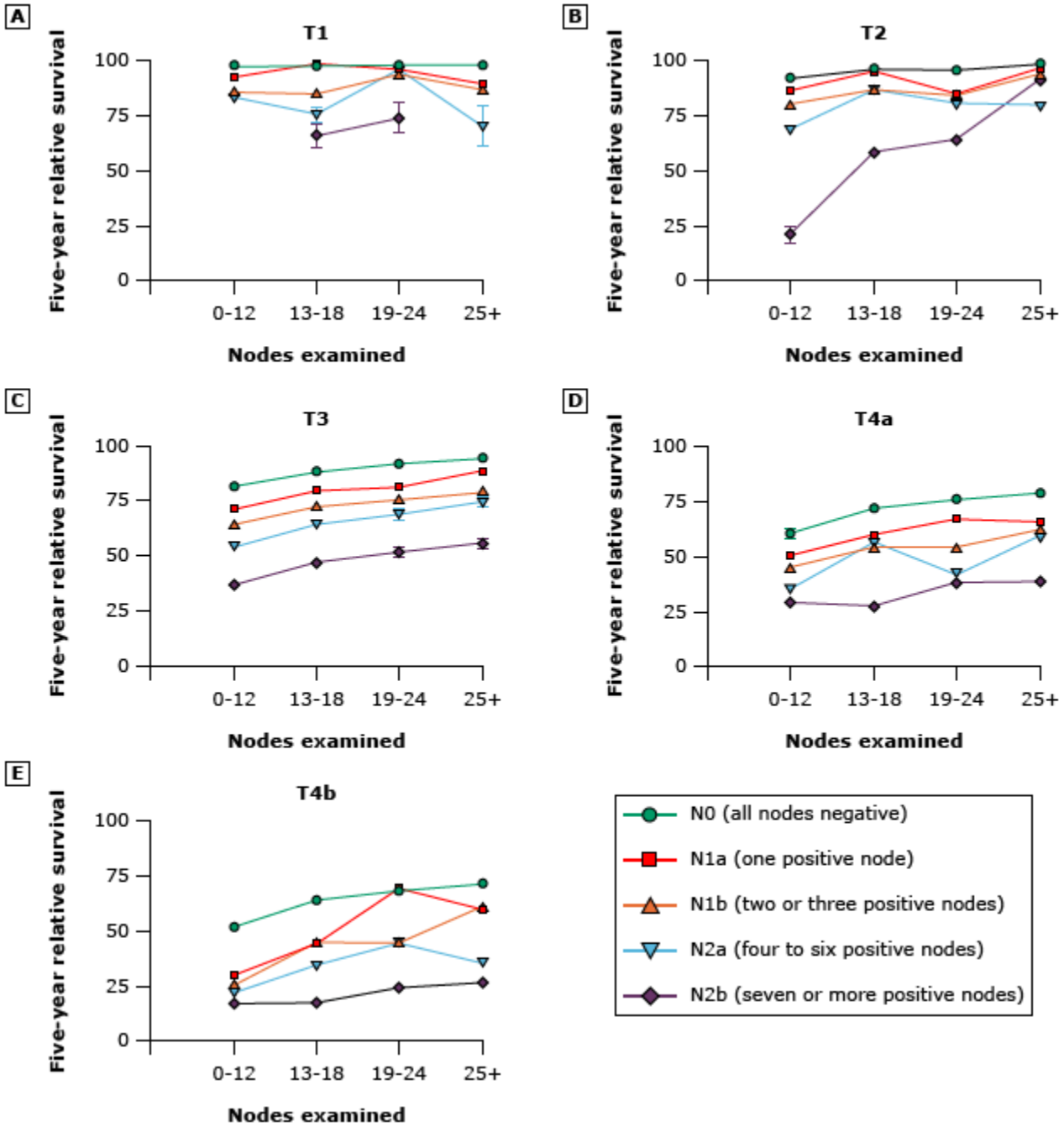
Both the specimen as a whole (fresh) and cross-sectional slices (fixed) are examined to make an adequate interpretation.

CRM: circumferential resection margin.

From: Parfitt JR, Driman DK. The total mesorectal excision specimen for rectal cancer: a review of its pathological assessment. J Clin Pathol 2007; 60:849. Reproduced with permission from BMJ Publishing Group Ltd. Copyright © 2007.

Graphic 111551 Version 1.0

Prognostic impact of the number of positive nodes, total number of nodes examined, and depth of the primary tumor for patients in a population-based cohort of 144,744 patients with colon cancer



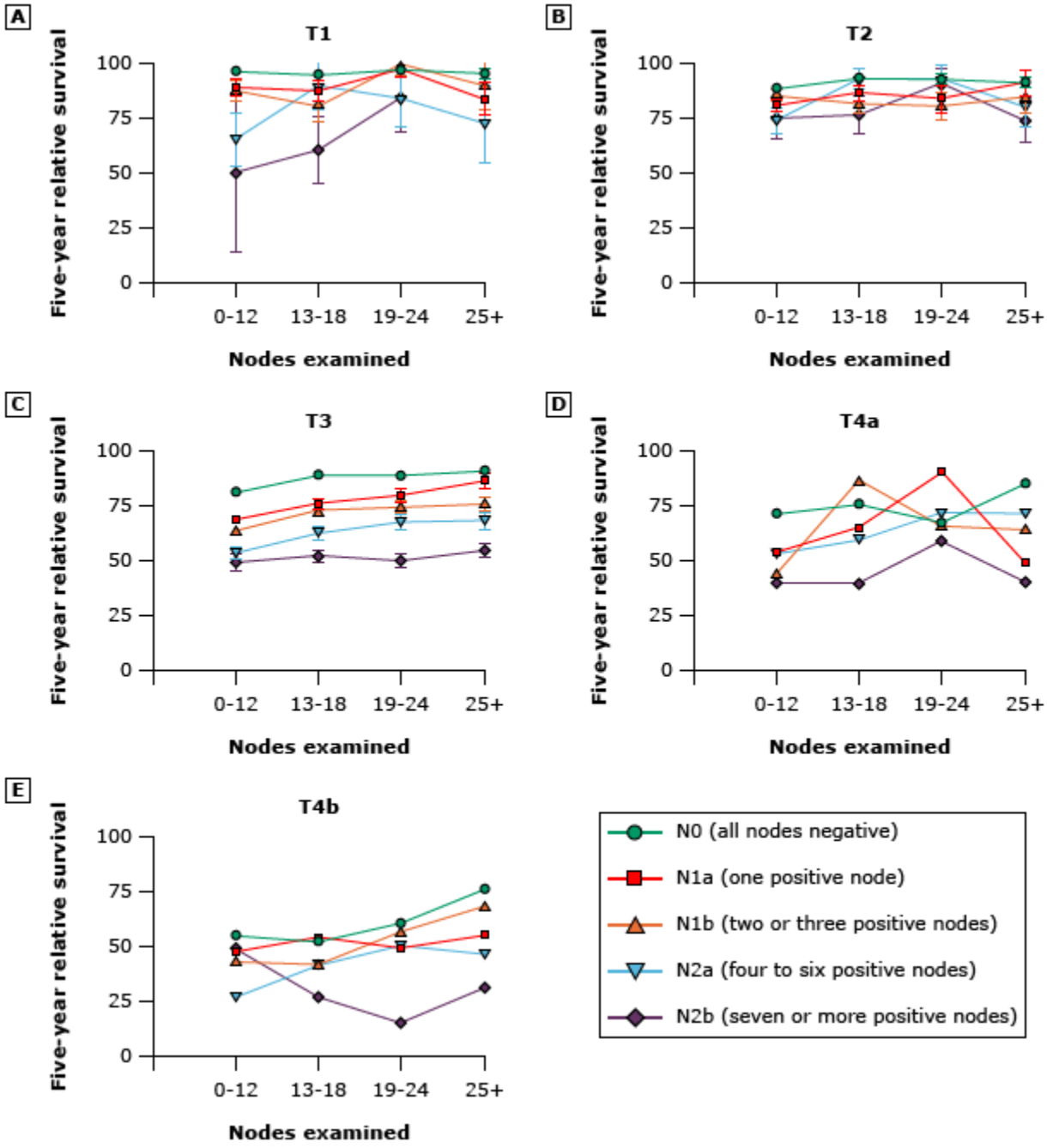
Impact of positive nodes, the total number of nodes examined, and the depth of primary tumor invasion in a population-based cohort of colon carcinoma. Data from 144,744 patients diagnosed with colon carcinoma between 2004 and 2011 and included in the population-based SEER database were analyzed for five-year relative survival. Each T category is presented separately. The N categories are color-coded as follows: green, N0 (all nodes negative); red, N1a (one positive node); orange, N1b (two or three positive nodes); light blue, N2a (four to six positive nodes); and purple, N2b (seven or more positive nodes). N1c category is not represented because there is not

yet a mature cohort in SEER with five-year relative survival. The lines for N category levels spread across the numbers of nodes examined. All patients were free of clinical metastases by surgical and clinical staging; that is, they were in stage groups I to III. Results are mean±SEM of five-year relative survival. Results suggest that the examination of more nodes for a given N category is associated with increasing survival. N0(i+) and N0mi are not included because they were not recorded previously for colorectal carcinoma.

SEER: Surveilance, Epidemiology, and End Results; SEM: standard error of the mean.

Graphic 111547 Version 6.0

Prognostic impact of the number of positive nodes, total number of nodes examined, and depth of the primary tumor for patients in a population-based cohort of 30,202 patients with rectal cancer



Impact of positive nodes, the total number of nodes examined, and the depth of primary tumor invasion in a population-based cohort of rectal carcinoma. Data from 30,202 patients diagnosed with rectal carcinoma between 2004 and 2010 and included in the population-based SEER database were analyzed for five-year relative survival. Each T category is presented separately. The N categories are color-coded as follows: green, N0 (all nodes negative); red, N1a (one positive node); orange, N1b (two or three positive nodes); light blue, N2a (four to six positive nodes); and purple, N2b (seven or more positive nodes). The N1c category is not

represented because there is not yet a mature cohort in SEER with five-year relative survival. The lines for N category levels spread across the numbers of nodes examined. All patients were free of clinical metastases by surgical and clinical staging; that is, they were in stage groups I to III. Results are mean±SEM of five-year relative survival except for T4a and T4b, for which the number of patients is small and the error is large. The results suggest that the examination of more nodes for a given N category is associated with increasing survival. N0(i+) and N0mi are not included because they were not recorded previously for colorectal carcinoma.

SEER: Surveillance, Epidemiology, and End Results; SEM: standard error of the mean.

Graphic 111546 Version 6.0

Five-year survival rates for resected colon cancer according to lymph node ratio in INT-0089

Endpoint	Lymph node ratio (total positive/total examined)			
	<0.05	0.05-0.19	0.2-0.39	0.4-1.0
Overall survival, %	79	73	63	52
Cause-specific survival, %	84	79	69	57
Disease-free survival, %	77	70	62	50

Data from Berger AC et al. J Clin Oncol 2005; 23:8706.

Graphic 68863 Version 3.0

Overview of the most commonly used systems for assessing tumor regression grade (TRG) following neoadjuvant therapy

Grade	Mandard	AJCC 2010	Rödel	MSKCC
TRG 0	–	No residual tumor cells	No regression	–
TRG 1	Absence of residual cancer, with fibrosis extending through the various layers of the oesophageal wall (complete regression)	Single cells or small groups	Fibrosis <25% of tumor mass	100% response
TRG 2	Rare residual cancer cells scattered through the fibrosis	Residual cancer with desmoplastic response	Fibrosis 25 to 50% of tumor mass	86 to 99% response
TRG 3	An increase in the number of residual cancer cells, but fibrosis still predominates	Minimal evidence of tumor response	Fibrosis >50% of tumor mass	<86% response
TRG 4	Residual cancer outgrowing fibrosis	–	Complete regression	–
TRG 5	Absence of regressive changes	–	–	–

AJCC: American Joint Committee on Cancer; MSKCC: Memorial Sloan Kettering Cancer Center.

Graphic 122436 Version 1.0

Definitions of "high risk" stage II colon cancer from expert groups

	ASCO (2022)	NCCN (2022)	ESMO (2020)
T4 primary tumor	+	+	+ (major)
Inadequately sampled nodes	+ (<12)	+ (<12)	+ (major) (<12)
Poorly differentiated or undifferentiated tumor*	+	+	+ (minor)
Perforation	+	+ (localized)	+ (major)
Clinical obstruction	+	+	+ (minor)
LVI	+	+	+ (minor)
PNI	+	+	+ (minor)
Close/indeterminate or positive margins		+	
High preoperative levels of serum CEA			+ (minor)
High tumor budding score (BD3, ≥10 buds)	+		

ASCO: American Society of Clinical Oncology; NCCN: National Comprehensive Cancer Network; ESMO: European Society for Medical Oncology; LVI: lymphovascular invasion; PNI: perineural invasion; CEA: carcinoembryonic antigen.

* Poorly differentiated or undifferentiated histology (only a high risk feature for tumors with proficient mismatch repair/no microsatellite instability).

Graphic 90035 Version 8.0

Molecular classification of colorectal carcinoma

Heredity	Chromosomal instability pathway	Mismatch repair pathway	Serrated/CIMP pathway		Hybrid pathway
	Hereditary and sporadic	Hereditary	Hereditary and sporadic		Sporadic
CIMP status	Negative	Negative	High	High	Low
MSI status	MSS	MSI-H	MSI-H	MSI-L	MSI-L or MSS
Chromosomal instability	Present	Absent	Absent	Absent	Present
KRAS mutation	+++	+/-	---	---	+++
BRAF mutation	---	---	+++	+++	---
MLH1 status	Normal	Mutation	Methylated	Partial methylation	Normal
MGMT methylation	---	---	+/-	+++	+++

CIMP: CpG island methylator phenotype; MSS: microsatellite stability; MSI: microsatellite instability; MSI-H: high-level microsatellite instability; MSI-L: low-level microsatellite instability; MGMT: O-6-methlyguanine DNA methyltransferase; +++: present; +/-: might or might not be present; ---: absent.

Noffsinger AE. Serrated polyps and colorectal cancer: New pathway to malignancy. Annu Rev Pathol 2009; 4:343. Reprinted, with permission, from the Annual Review of Pathology. Copyright © 2009 Volume 4, 2009 by Annual Reviews. www.annualreviews.org.

Graphic 72239 Version 2.0

Contributor Disclosures

Carolyn C Compton, MD, PhD No relevant financial relationship(s) with ineligible companies to disclose. **Kenneth K Tanabe, MD** Patent Holder: EGF SNP to determine risk for HCC [Cirrhosis, hepatocellular carcinoma]; Use of EGFR inhibitors to prevent HCC [Cirrhosis, hepatocellular carcinoma]. Consultant/Advisory Boards: Cancer Expert Now [GI cancers, melanoma]; GSK [GI Cancers]; Imvax [GI cancers]; Leidos [Melanoma, GI cancers]; Teledoc [GI cancers, melanoma]. Other Financial Interest: American Cancer Society [Honoraria as editor of Cancer]. All of the relevant financial relationships listed have been mitigated. **Sonali M Shah, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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