**Optimal Pathologic Staging: Defining Stage II Disease**

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**Abstract**

Tumor stage remains the most important determinant of prognosis in colorectal cancer and is the basis of all authoritative patient management guidelines. The pathologic assessment of stage II disease is especially critical because it may help to identify patients at additional risk for whom surgery alone may not be curative. Accurate analysis of regional lymph nodes, extent of tumor penetration, and circumferential resection margins constitute the most crucial issues. For assignment of pN0, adequacy of the surgical resection and thoroughness of the lymph node harvest from the resection specimen are both essential. The minimum number of lymph nodes has been variably determined to be between 12 and 18 for assignment of pN0, but the confidence level increases with increasing numbers of nodes examined. The ability of exhaustive analysis of sentinel lymph nodes using special techniques to substitute for an exhaustive lymph node harvest and standard node examination has not been definitively shown. Although special techniques may facilitate the identification of minute amounts of tumor (i.e., isolated tumor cells) in regional lymph nodes, the prognostic significance of such findings remains unclear. Additional stage-independent pathologic features that have been validated as adverse prognostic factors include involvement by tumor of mural lymphovascular channels, venous vessels, or the surgical resection margin of the operative specimen and high tumor grade. The presence of these features may help to identify patients for whom surgery alone will not be curative and adjuvant therapies may be appropriate.

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Despite an increasing focus on molecular prognostic and predictive factors, the anatomic extent of disease at presentation (stage) continues to be the strongest predictor of survival in patients with colorectal cancer and the basis of appropriate patient management. Uniform staging criteria applied in a uniform manner are also essential for valid clinical research and accurate evaluation of therapies and outcome. The tumor-node-metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC; ref. 1) and the International Union Against Cancer (UICC; ref. 2) is now considered the international standard for colorectal cancer staging. TNM staging is recommended by the College of American Pathologists (CAP; ref. 3), Royal College of Pathologists (4), Commission on Cancer of the American College of Surgeons (5), and the National Cancer Institute (Common Data Elements; ref. 6) and widely used by tumor registries in the United States and internationally. TNM staging that provides broadly applicable prognostic information for cancer patients is also used to assist in patient management decisions, determine eligibility for clinical trials, evaluate the effects of treatment, and facilitate information exchange between institutions and care providers. TNM staging has added advantage over other staging systems because it is data driven and continuously updated based on ongoing expert review of existing data (7). The system is multidisciplinary in design, allows for the incorporation of all technological approaches to staging, and has a comprehensive set of definitions and rules of application that ensure uniform use. In addition, the predictive accuracy of TNM staging can be increased through incorporation of validated adverse or favorable prognostic features into the overall assessment process.

As defined by the current (6th) edition of the AJCC Cancer Staging Manual (1), stage II colorectal cancer is defined primarily by clinical evidence that distant metastasis is absent (cM0) and pathologic confirmation that the primary tumor penetrates through the muscularis propria (pT3 or pT4) and that mesenteric nodes within the lymphatic drainage area of the tumor are free of metastatic disease (pN0). This anatomic extent of disease corresponds to the watershed between tumor that is most likely curable through surgical excision and tumor that is unlikely to be cured by resection alone. Although complete surgical resection without adjuvant treatment is the standard of care currently recommended for stage II colorectal cancer and is curative in the majority of cases, death from disease still occurs in 20% of patients (8–10).

Accurate determination of stage II disease (i.e., transmural, localized tumor without regional nodal metastasis) is critical because it largely determines whether adjuvant therapy should be administered. Pathologic assessment of the surgical resection specimen for anatomic extent of disease is considered the definitive step in assigning stage II disease, as both transmural extension of the tumor and disease-free status of the regional lymph nodes are confirmed by microscopic examination. Although seemingly straightforward, pathologic examination
peritoneal involvement by tumor demands meticulous pathologic analysis and may require extensive sampling and/or serial sectioning; thus, such involvement can be missed on routine histopathologic examination. In fact, cytologic examination of serosal scrapings has been shown to reveal malignant cells in as many as 26% of tumor specimens categorized as pT3 by histologic examination alone (18, 20).

Viewed under the microscope, peritoneal involvement by tumor may be associated with a spectrum of pathologic features. Three types of local peritoneal involvement have been defined: (a) a mesothelial inflammatory and/or hyperplastic reaction with tumor close to (but not at) the serosal surface; (b) tumor present at the serosal surface with inflammatory reaction, mesothelial hyperplasia, and/or erosion/ulceration; and (c) free tumor cells on the serosal surface (in the peritoneum) with underlying ulceration of the visceral peritoneum (18). All three (and especially the latter two) types of local peritoneal involvement are associated with decreased survival. In contrast, tumor well clear of the serosa has no independent adverse effect on prognosis (18). Therefore, it has been recommended that the definition of T4 be modified to encompass the last two reactions outlined above (3). A tumor may be classified as pT4 based on positive cytologic specimens obtained by scraping the serosa overlaying the primary tumor (20, 21).

Involvement of the serosa may occur in the presence or absence of involvement of adjacent organs. Conversely, involvement of adjacent organs may occur in the presence or absence of serosal involvement, depending on the anatomic location of the involved structure. Direct invasion of adjacent organs or structures or other segments of the colorectum by way of the serosa or mesocolon (e.g., invasion of the sigmoid colon by carcinoma of the cecum) should be classified as pT4. In contrast, intramural extension of tumor from one subsite (segment) of the large intestine into an adjacent subsite or the ileum or anal canal does not affect pT classification.

**N category issues**

*What counts as a regional lymph node?* Regional lymph node groups corresponding to anatomic subsites of the colorectum are shown in Table 1. In colorectal cancers that involve more than one site or subsite by continuous longitudinal extension, regional lymph nodes are defined as those in all involved sites and subsites. In rare cases, regional nodes of the primary tumor site are free of malignancy, but nodes in the drainage area of an organ directly invaded by a T4 tumor contain metastasis. In this circumstance, the lymph nodes of the invaded site are considered as those of the primary site and classified in the N category.

*How many lymph nodes are necessary?* The accuracy and predictive value of stage II assignment are directly proportional to the thoroughness of the surgical technique in removing all regional nodes and the pathologic examination of the resection specimen in identifying and harvesting all regional lymph nodes for microscopic assessment. AJCC and CAP have recommended examination of at least 12 lymph nodes to assign stage II disease (1, 3). It has been shown that a minimum of 12 to 18 lymph nodes must be examined to accurately predict regional node negativity in colorectal cancer (22–31). Thus, it has been suggested that 12 lymph nodes be considered the minimal acceptable harvest from a careful specimen.
of increased numbers of lymph nodes is itself associated with studies have shown that conventional pathologic examination linked to lymph node harvest in stage II disease. Numerous number of nodes accurately or reliably stages all patients. recovered lymph nodes increased, suggesting that no minimum node increased in a continuous manner as the number of predictive probability of identifying a single positive 45 years, Goldstein et al. (32) showed by mathematical analysis with pT3 colorectal cancer resected at a single institution over z 15 nodes were recovered (22). In a study of >2,400 patients f metastasis was found in c pM1. tasis in the external iliac or common iliac nodes is classified as (hemorrhoidal), and inferior rectal (hemorrhoidal) nodes. Metastasis in the external iliac or common iliac nodes is classified as pM1.

**Table 1.** Regional lymph node groups in anatomic subsites of the colorectum

<table>
<thead>
<tr>
<th>Anatomic subsite</th>
<th>Regional lymph node group</th>
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<tbody>
<tr>
<td>Cecum</td>
<td>Anterior cecal</td>
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<tr>
<td></td>
<td>Posterior cecal</td>
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<tr>
<td></td>
<td>Ileocolic</td>
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<tr>
<td></td>
<td>Right colic</td>
</tr>
<tr>
<td>Ascending colon</td>
<td>Ileocolic</td>
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<tr>
<td></td>
<td>Right colic</td>
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<tr>
<td></td>
<td>Middle colic</td>
</tr>
<tr>
<td>Hepatic flexure</td>
<td>Middle colic</td>
</tr>
<tr>
<td></td>
<td>Right colic</td>
</tr>
<tr>
<td>Transverse flexure</td>
<td>Middle colic</td>
</tr>
<tr>
<td>Splenic flexure</td>
<td>Middle colic</td>
</tr>
<tr>
<td>Descending colon</td>
<td>Left colic</td>
</tr>
<tr>
<td></td>
<td>Inferior mesenteric</td>
</tr>
<tr>
<td>Sigmoid colon</td>
<td>Left colic</td>
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<tr>
<td></td>
<td>Inferior mesenteric</td>
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<tr>
<td></td>
<td>Sigmoid</td>
</tr>
<tr>
<td></td>
<td>Superior rectal sigmoidal</td>
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<tr>
<td></td>
<td>Sigmoid mesenteric*</td>
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<tr>
<td>Rectosigmoid colon</td>
<td>Perirectal 1</td>
</tr>
<tr>
<td></td>
<td>Left colic</td>
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<tr>
<td></td>
<td>Sigmoid mesenteric</td>
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<tr>
<td></td>
<td>Sigmoidal</td>
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<tr>
<td></td>
<td>Inferior mesenteric</td>
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<tr>
<td></td>
<td>Superior rectal</td>
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<td></td>
<td>Middle rectal</td>
</tr>
<tr>
<td>Rectum</td>
<td>Perirectal 1</td>
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<tr>
<td></td>
<td>Sigmoid mesenteric</td>
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<tr>
<td></td>
<td>Inferior mesenteric</td>
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<tr>
<td></td>
<td>Lateral sacral</td>
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<tr>
<td></td>
<td>Presacral</td>
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<tr>
<td></td>
<td>Internal iliac</td>
</tr>
<tr>
<td></td>
<td>Sacral promontory</td>
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<tr>
<td></td>
<td>Superior rectal</td>
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<tr>
<td></td>
<td>Middle rectal</td>
</tr>
<tr>
<td></td>
<td>Inferior rectal</td>
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</table>

*Lymph nodes along the sigmoid arteries are considered pericolic nodes, and their involvement is classified as pN1 or pN2 according to the number involved.

*Perirectal lymph nodes include the mesorectal (paraproctal), lateral sacral, presacral, sacral promontory (Gerota), middle rectal (hemorrhoidal), and inferior rectal (hemorrhoidal) nodes. Metastasis in the external iliac or common iliac nodes is classified as pM1.

dissection. Increasingly, however, evidence indicates that this bar should be raised, as the greater the number of nodes examined, the greater the likelihood that metastasis will be found. In one study of T3 tumors, for example, nodal metastasis was found in ~22% of cases if <15 lymph nodes were harvested from the specimen compared with 85% of cases if ≥15 nodes were recovered (22). In a study of >2,400 patients with pT3 colorectal cancer resected at a single institution over 45 years, Goldstein et al. (32) showed by mathematical analysis that the predictive probability of identifying a single positive node increased in a continuous manner as the number of recovered lymph nodes increased, suggesting that no minimum number of nodes accurately or reliably stages all patients.

More importantly, it has been shown that clinical outcome is linked to lymph node harvest in stage II disease. Numerous studies have shown that conventional pathologic examination of increased numbers of lymph nodes is itself associated with an increased survival advantage in stage II disease (22–29, 33), indicating a positive effect of optimal mesenteric resection by the surgeon, optimal lymph node harvest from the resection specimen by the pathologist, or both. Similarly, a large study based on Intergroup Trial INT-0089, which included 3,759 patients with stage III or high-risk stage II disease, showed that both overall and cause-specific survival increased as more lymph nodes were examined, suggesting that the number of lymph nodes analyzed is itself an independent prognostic variable in colorectal cancer (23). In contrast, survival is significantly worse in patients with stage II colon cancer (i.e., roughly equivalent to stage III disease) in cases in which less than seven to nine lymph nodes are harvested from the resection specimen (34–36).

Despite the strength of the data showing the critical nature of adequate lymph node assessment in colorectal cancer, significant variation in lymph node recovery from resection specimens exists within and among medical centers (37–40). In addition, the average number of lymph nodes examined per specimen is often found to be lower than the minimal recommended number, suggesting that a large number of patients with colorectal cancer are staged inadequately (41, 42). The number of lymph nodes recovered from resection specimens is dependent on several factors. Surgical technique, surgery volume, and patient factors (e.g., age and anatomic variation) alter the actual number of nodes in a resection specimen (37, 39, 40), but the diligence and skill of the pathologist in identifying and harvesting lymph nodes in the specimen also are major factors (40). Because it has been shown that nodal metastasis in colorectal cancer is often found in small lymph nodes (<5 mm in diameter; refs. 30, 43), diligent search for lymph nodes is required on gross examination of resection specimens. Of note, many pathologists are uninformed about the necessity of examining a critical number of lymph nodes to accurately stage colorectal cancers. One Canadian study showed that only 58% of pathologists were aware of guidelines for lymph node retrieval in colorectal cancer at all and that as few as 25% knew that a minimum of 12 nodes is necessary for accurate designation of node negativity (44). In cases where pathologists and surgeons are educated about the quantitative aspect of lymph node retrieval and assessment, however, a durable improvement in clinical practice can be achieved that more than doubles the average number of nodes reported in stage II disease (45).

If <12 nodes are found after careful gross examination, additional techniques (i.e., visual enhancement techniques, such as fat clearing) should be considered despite the lack of formal standards for this practice (46). All grossly negative or equivocal lymph nodes should be submitted entirely for microscopic examination (46). Currently, histologic examination of one tissue level is the minimum requirement, and additional tissue levels are optional; however, thorough examination of large nodes may include serial sectioning on gross examination and submission of all slices for standard microscopic assessment.

**What counts as metastasis?** On microscopic examination, tumor in a regional lymph node, whether arriving via afferent lymphatics or direct invasion through the capsule, is regarded as metastatic disease. If tumor arrives via afferent lymphatic vessels, it must already have entered the subcapsular sinus and the parenchyma to qualify in the N category as metastasis. If
tumor is seen only within lymphatic vessels, the finding is categorized as lymphatic involvement and annotated as L1, but the tumor is classified as pN0.

Another important convention in the pathologic analysis of resection specimens is the counting of discrete rounded nodules of tumor of any size seen in the extramural fat discontinuous from the leading edge of the tumor as replaced lymph nodes (1, 2, 14). For the purpose of pN assignment, each nodule is counted separately as a positive node. This rule, brought forth in the 6th editions of AJCC and UICC staging manuals, is based on evidence showing that pericolonic tumor deposits of any size correlate with shorter survival, independent of otherwise observable lymph node metastasis (31, 47). The evidence also indicates that the number of pericolonic tumors correlates inversely with disease-free survival (31). In contrast, extramural tumor nodules with irregular contours are not categorized as replaced lymph nodes, but rather as discontinuous extramural extension of tumor, probably via thin-walled veins. Therefore, cases with findings of this type and negative regional lymph nodes are classified as pN0, but increased risk may be implied.

Definitive data are lacking on the biological significance and clinical effect on outcome of very small amounts of tumor in regional nodes. Although some studies have supported the concept of “upstaging” patients with stage II colon cancer using immunohistochemical identification of tumor cells in regional nodes with or without sentinel node assessment (48, 49), the overall evidence is not definitive (50, 51). Currently, stage-related outcome statistics from large databases, such as the National Cancer Data Base of the Commission on Cancer, are derived entirely from studies in which the pathologic evaluation of regional lymph nodes has been done by conventional histologic staining of macroscopically identified lymph nodes. Therefore, at present, the AJCC, UICC, and CAP continue to recommend standard H&E techniques for the nodal assessment of colon cancer. Changes in these recommendations are under consideration but will ultimately be based on the validation of other approaches, including immunohistochemical or molecular analysis by outcome analysis.

Until the clinical effect of minute amounts of tumor in either regional lymph nodes or distant metastatic sites has been defined, collecting data in a uniform manner using standardized diagnostic and reporting criteria, such as those defined by AJCC and UICC, is imperative. Isolated tumor cells (ITC) have been defined as small numbers of tumor cells detected only by special techniques or seen histologically but measuring ≤0.2 mm. According to current recommendations, ITCs are classified as N0 or M0, as appropriate (1, 14, 52). Because it has not yet been proven that ITCs (as either a single focus in a single node, multiple foci within a single node, or micrometastatic involvement of multiple nodes) have an adverse effect on outcome, N0 is considered justified. In contrast, small amounts of metastatic tumor that measure >0.2 mm, but <2.0 mm, are defined as “micrometastasis” and classified as N1 or M1. Conventions for reporting ITCs and micrometastasis are shown in Table 2. The number of lymph nodes involved by micrometastasis or ITCs should be clearly stated in the pathology report. Currently, the data are considered insufficient to recommend either the routine examination of multiple tissue levels of paraffin blocks or the use of special/ancillary techniques, such as immunohistochemistry for epithelial and/or tumor-associated antigens (e.g., cytokeratin and carcinoembryonic antigen) or PCR, to identify tumor RNA/DNA. Furthermore, these techniques increase the cost of pathologic analysis and currently lack quality control standards. Pending definitive data, it is recommended that any pathologist-reported ITC be accompanied by a note stating that the biological significance of this finding is currently unknown. To date, data on the prognostic effect of ITCs in colorectal cancer are conflicting (53–56).

### Additional Pathologic Issues: Features That Modify Risk in Stage II Colorectal Cancer

**Status of surgical resection margin in cancer-directed surgery**

Optimal outcome in stage II disease is predicated on complete removal of all detectable tumor on surgical resection. This is the goal of all cancer-directed surgery, and the status of resection margins of the resultant excision specimen constitutes an important measure of successful attainment of the goal.

Pertinent margins of a colorectal cancer resection specimen include the proximal and distal transverse margins, mesenteric pedicle margin, and, where applicable, circumferential (radial) margin. CRM represents the retroperitoneal or perineal adventitial soft tissue margin of the resected portion of bowel. In all segments of the large intestine that are either incompletely encased (ascending colon, descending colon, and upper rectum) or not encased (lower rectum) by peritoneum, CRM is created at operation by dissection of the retroperitoneal or subperitoneal aspect away from the sidewall of the abdomen or perineum, respectively.

Transverse margins are typically the least problematic for the pathologist and surgeon alike. If the distance between tumor and the nearest transverse margin is ≥5 cm, anastomotic recurrence is very rare. Thus, it can be argued that histologic examination of the proximal and/or distal margin is necessary if these margins are ≥5 cm from the tumor (57). In fact, guidelines of the Royal College of Pathologists in the United Kingdom suggest that donuts from stapling devices, which are the true margins of resection, need not be examined histologically if the tumor is >3 cm from the cut end of the main specimen (4). In low anterior rectal resection specimens of

### Table 2. Annotation for ITCs and micrometastasis

<table>
<thead>
<tr>
<th>Annotation</th>
<th>ITCs</th>
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<tbody>
<tr>
<td>pN0(i-)</td>
<td>No ITC detected morphologically</td>
</tr>
<tr>
<td>pN0(i+)</td>
<td>Positive morphologic (H&amp;E or immunohistochemical) findings for ITC</td>
</tr>
<tr>
<td>pN0(mol-)</td>
<td>No regional lymph node metastasis histologically, negative nonmorphologic (molecular) findings for ITC</td>
</tr>
<tr>
<td>pN0(mol+)</td>
<td>No regional lymph node metastasis histologically, positive nonmorphologic (molecular) findings for ITC</td>
</tr>
<tr>
<td>pM1(mol)</td>
<td>Micrometastasis</td>
</tr>
<tr>
<td>pM1(mi)</td>
<td>Metastatic tumor in regional node, no larger than 2.0 mm, but &gt;0.2 mm in dimension</td>
</tr>
<tr>
<td>pM1(mi)</td>
<td>Metastatic tumor in distant site, no larger than 2.0 mm, but &gt;0.2 mm in dimension</td>
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</table>
rectal cancers, however, wide distal cuffs of normal mucosa may be difficult or impossible to achieve due to anatomic constraints. In this circumstance, a margin of 2 cm is accepted as adequate for tumors with transmural penetration. As standard practice, the distance of the tumor from the transverse margins should be measured on gross pathologic examination, but microscopic examination may be considered optional if the closest distance is >5 cm.

In contrast, the issues and challenges about CRM are significant for both pathologist and surgeon. In rectal cancer in particular, CRM is the factor of greatest importance in predicting risk of local recurrence, which is itself a strong predictor of survival in this disease (12, 13, 58–61). Emerging data on CRM involvement in the colon suggest a similar relationship to risk of local recurrence (60, 62). Therefore, routine assessment of CRM is recommended in all applicable colorectal cancers, and measurement of the distance from the tumor to the nearest CRM, corresponding to the “surgical clearance” around the tumor, is suggested (13, 31). Based on published data from clinical trials, risk of local recurrence is strongly increased if tumor is ≤1 mm from the nonperitonealized surface of the specimen (61). In contrast, risk of recurrence is very low with clearance >2 mm and can be considered “negative.” Because more recent data have shown that risk of local recurrence also is significantly increased with clearances between 1 and 2 mm, the current recommendation is that clearance of ≤2 mm should be considered a “positive” CRM (63). In any case, reporting of the actual clearance measurement (rather than assignment of positive or negative status alone) is recommended.

In segments of the colon that are completely encased by a peritonealized (serosal) surface (e.g., transverse and sigmoid colon), the resection margin of the mesenteric pedicle also may be a relevant “radial margin,” as tumors may extend to this margin with (pT4) or without (pT3) penetrating the serosal surface. Examination is essential if the point of deepest tumor penetration is on the mesenteric aspect of the colon, especially if the mesentery has been trimmed close to the colonic wall. In tumors limited to an antimesenteric peritonealized aspect of the bowel, the mesenteric margin usually is not relevant.

Because CRM involvement is associated with increased risk of local recurrence, patient management is directly affected, and such involvement is typically an indication for adjuvant radiation directed at the anatomic site corresponding to the positive CRM. Therefore, it is extremely important that the pathologist carefully differentiate peritonealized from non-peritonealized surfaces of the resection specimen and examine them separately. For example, if tumor is present on a peritonealized surface, it is categorized as pT4 but may not require adjuvant radiation if the resection margins (including the CRM) are free of tumor; however, if tumor is present on a nonperitonealized surface (i.e., the CRM), adjuvant radiation may be appropriate irrespective of the T category of the tumor. Nevertheless, it should be recognized that radiation therapy does not always compensate for a positive CRM, underscoring the importance of optimal surgical technique in achieving adequate clearance (64).

**Lymphatic and venous involvement by tumor**

Venous invasion by tumor has been shown repeatedly to be a stage-independent adverse prognostic factor by multivariate (16, 65–73) and univariate analysis (74–77); however, some studies identifying venous invasion as an adverse factor by univariate analysis have failed to confirm its independent effect on prognosis by multivariate breakdown (76, 77). Similarly, disparate results have also been reported for lymphatic invasion (67, 68, 72, 75, 77–81). In other reports, “vascular” invasion as a general feature is prognostically significant, but no distinction was made between lymphatic and venous vessels. In a few studies, location and type of vessel involved (e.g., extramural veins) were both considered strong determinates of prognostic effect (31, 70). Overall, therefore, data from existing studies are difficult to amalgamate. Nevertheless, the importance of venous and lymphatic invasion by tumor is strongly suggested and largely confirmed in the literature.

In part, disparities among existing studies on vessel invasion may be related to inherent problems in definitive diagnosis of vessel invasion, which typically requires the identification of tumor cells (single or groups) within an endothelial-lined channel; however, histologic artifacts that mimic vessel invasion and pathologic changes that obscure it (e.g., vascular destruction by tumor) are both common. Thus, interobserver variation may be substantial. Special techniques, such as immunohistochemical stains to identify endothelium or special stains to identify the elastic tissue remains of venous walls, may or may not increase the ease or accuracy of evaluation. Because these techniques are also labor intensive, time consuming, and expensive, they are not done routinely. Detection of vessel invasion in any given case is also affected by specimen sampling. Reproducibility of extramural venous invasion detection has been shown to increase proportionally with the number of tissue blocks taken (i.e., from 59% with two blocks to 96% with five blocks; ref. 82). At present, no widely accepted standards or guidelines for the pathologic evaluation of vessel invasion exist, and pathology sampling practices vary widely on both individual and institutional levels. Sampling practices are further influenced by cost containment issues, which in general have encouraged reduced sampling of resection specimens. CAP has suggested that at least three blocks (and optimally five blocks) of tumor at its point of deepest extent be submitted for microscopic examination (3, 46).

By AJCC/UICC convention, tumor cells within the lymphatics or veins of the primary tumor site do not affect pT classification. Intravascular spread via lymphatic or venous vessels is recorded separately and classified as L1 and V1, respectively. Conversely, LO and V0 indicate the absence of lymphovascular invasion, respectively, and should always be recorded explicitly in the pathology report to document that vascular invasion was sought and not found. In the absence of explicit reporting, the absence of vessel invasion cannot be assumed. All lymphatic vessels are relevant, including those within and peripheral to the primary tumor.

Tumor contained solely within the afferent lymphatic vessels of regional lymph nodes is classified as L1 but N0. Tumor cells must extend into the node proper to qualify as N1. In contrast, tumor within the lymphatics of a distant organ is classified as pM1. UICC recommends that extramural tumor nodules with irregular contours (i.e., not smooth and round) be regarded as discontinuous transmural extension and classified as pT3. Based on the belief that discontinuous transmural extension often occurs as a result of i.v. extension of tumor through the wall followed by centripetal penetration of the vessel into the perivascular soft tissues, it is also recommended...
that V1 be assigned to irregularly shaped (often stellate) extramural tumor nodules (14).

**Histologic type**

In the pathologic reporting of colorectal cancer, the internationally accepted histologic classification of colorectal carcinomas proposed by the WHO (Table 3) is recommended by CAP. According to this classification, most colorectal cancers are adenocarcinomas of no special type. Aside from a few notable exceptions, histologic type has no stage-independent prognostic significance (17, 67, 68, 73, 78, 83–90). Exceptions include the nongland-forming tumor types, such as signet-ring cell carcinoma, small cell carcinoma, and undifferentiated carcinoma, which are prognostically unfavorable (46, 91–93), and medullary carcinoma, which is prognostically favorable (94). Of note, all histopathologic types that are by convention always considered to be of high tumor grade are associated with adverse outcome (see “Tumor grade” section below). Thus, grade (rather than histologic type) is likely to be the dominant prognostic factor. The single exception is medullary carcinoma, a distinctive type of nongland-forming carcinoma composed of large polygonal tumor cells and abundant tumor-infiltrating lymphocytes, which was added to the revised WHO classification in 2000 (95). Previously, this tumor type would have been classified as an undifferentiated carcinoma in the WHO system. The importance of this unique histologic type is its strong association with defective DNA replication fidelity and high microsatellite instability, molecular features that are, in turn, associated with a more favorable stage distribution and prognosis than are microsatellite stable tumors (96–100). Most tumors of this type occur in the proximal colon in association with hereditary nonpolyposis colon cancer syndrome.

**Tumor grade**

In general, the grading of colorectal carcinoma is based on architectural features as well as cytologic features (e.g., pleomorphism and hyperchromatism); however, degree of gland formation is widely regarded as the most important feature in grading. Therefore, the nongland-forming histologic types of colorectal cancer (e.g., signet-ring cell carcinoma, small cell carcinoma, and undifferentiated carcinoma) are always assigned a high tumor grade. In adenocarcinoma, however, estimation of the degree of gland formation and assignment of grade are largely subjective. Lack of uniformity in histopathologic grading is further complicated by the existence in the literature of several different grading schemas without widespread acceptance and uniform use of any single system by practicing pathologists. Furthermore, the published systems vary markedly with regard to number, type, and relative importance of the specific features used to distinguish different grades. In some systems, grade is based on a single architectural feature, such as degree of gland formation, and in others, a large number of features are included in the evaluation. In rare cases, a suggested grading system has been based solely on cytologic criteria. Irrespective of the type or complexity of the criteria, however, most systems stratify tumors as well differentiated (grade 1), moderately differentiated (grade 2), poorly differentiated (grade 3), and, sometimes, undifferentiated (grade 4).

In routine practice, the pathologic diagnosis of grades 3 and 4 is relatively consistent, but differentiation between grades 1 and 2 is associated with a more significant degree of interobserver variability (82, 86, 101). Even in assignment of grade 3 (and grade 4), however, some variation in approach exists. Pathologists may base overall tumor grade on a qualitative impression of the sum of global histologic features or on the highest grade features seen anywhere in the neoplasm (whatever their extent; ref. 102), relative proportion of undifferentiated tumor (103, 104), or degree of differentiation along the advancing edge of the tumor (105).

Despite the lack of standardization and the existent interobserver variation in assessment, histologic grade has been shown repeatedly by multivariate analysis to be a stage-independent prognostic factor (16, 17, 65, 66, 71, 106–114). More specifically, high tumor grade is an adverse prognostic factor. In almost all studies documenting the prognostic power of tumor grade, three- or four-tiered grading schemas have been collapsed for data analysis as follows: low grade (grades 1 and 2) and high grade (grades 3 and 4). Based on these data, a two-tiered grading system (i.e., low and high) for colorectal carcinoma has been recommended by a multidisciplinary colorectal cancer working group of a consensus conference sponsored by CAP (46). Use of such a system would be expected to maintain the prognostic value of grade in colorectal cancer while increasing simplicity and reproducibility of assessment; however, consensus is needed as to whether undifferentiated tumor at the advancing edge of the cancer should be evaluated and reported separately or incorporated into the overall tumor grade. At present, available data are insufficient to support one approach over the other.

**Table 3. WHO classification of colorectal carcinoma**

<table>
<thead>
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<th>Classification</th>
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<tbody>
<tr>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Mucinous (colloid) adenocarcinoma (&gt;50% mucinous)</td>
</tr>
<tr>
<td>Signet-ring cell carcinoma (&gt;50% signet-ring cells)</td>
</tr>
<tr>
<td>Squamous cell (epidermoid) carcinoma</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
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<tr>
<td>Small cell (oat cell) carcinoma</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
</tr>
<tr>
<td>Other (e.g., papillary carcinoma)</td>
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</tbody>
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NOTE: The term “carcinoma, NOS” (not otherwise specified) is not part of the WHO classification.

**Conclusions**

In colorectal carcinoma, stage remains the strongest prognostic indicator and primary determinant in patient management. Stage II disease is defined by the presence of transmural tumor penetration in the absence of metastasis to either regional lymph nodes or distant sites. Transmural tumor penetration represents a critical point in tumor progression because the tumor has progressed locally, but metastasis has not yet occurred; additionally, ~80% of patients can be cured by complete surgical excision of the tumor. Yet, defining stage II colorectal carcinoma with confidence requires particular attention to several standard gross and microscopic pathologic issues. The most critical issues include status of the regional lymph nodes, extent of deepest tumor penetration,
and circumferential margin status. The diagnosis of serosal involvement by tumor is especially important and may be a more adverse prognostic feature than lymph node metastasis in colorectal carcinoma.

For assignment of pN0, the minimum number of lymph nodes has been variably determined to be between 12 and 18, but the confidence level increases with increasing numbers of nodes examined. The ability of exhaustive analysis of sentinel lymph nodes using special techniques to substitute for an exhaustive lymph node harvest and standard node examination has not been definitively shown. Although special techniques may facilitate the identification of minute amounts of tumor (i.e., ITCs) in regional lymph nodes, the prognostic significance of such a finding is unclear. Additional stage-independent pathologic features that have been validated as adverse prognostic factors include involvement by tumor of mural lymphovascular channels, venous vessels, or the surgical resection margin of the operative specimen and high tumor grade. The presence of these features may help to identify patients for whom surgery alone will not be curative and adjuvant therapies may be appropriate.

Improving the care of cancer patients is the overarching goal of the TNM process, including the continual effort to refine the staging systems themselves according to new data and to standardize and optimize their routine application. Ironically, however, changes made to the TNM staging system or its application, even if they are inarguably for the better, create additional challenges of their own. For example, resulting from clinical trials can be complicated or compromised by the use of various versions of the TNM staging system or changes in approaches to derivation of TNM variables over time. Taken to the extreme, the maturation of clinical trial data may be precluded and changes in treatment guidelines may be made without adequate evidence. This issue will assume a new level of complexity as molecular prognostic and predictive factors are incorporated into stage-based algorithms for patient management. As the rate of medical progress continues to accelerate, the dynamic tension between change and stability in the basic elements of patient management, such as TNM staging, may become more acute. Nevertheless, in realizing the best outcomes for cancer patients at any given point in time, it is essential to do well what is already known to be important.

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Optimal Pathologic Staging: Defining Stage II Disease
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