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The Staging of Colorectal Cancer: 2004 and Beyond

Carolyn C. Compton MD, PhD; Frederick L. Greene, MD

ABSTRACT Stage is the strongest predictor of survival for patients with colorectal cancer. Accurate staging also is critical for appropriate patient management and meaningful clinical research. Uniform staging criteria applied in a uniform manner are essential for accurate evaluation of therapies and outcomes. Historically, numerous different staging systems for colorectal cancer have been employed, but a single internationally recognized system is required to ensure a common language for cancer that is understood by clinicians in all specialties. For the tumor, node, metastasis system to remain relevant, it has to continuously undergo critical evaluation and change when clinically indicated. (*CA Cancer J Clin* 2004;54:295-308.) © American Cancer Society, Inc., 2004.

Dr. Compton is Chair, Pathology, and Pathologist-in-Chief, McGill University, Montreal, Canada.

Dr. Greene is Chair, Department of General Surgery, Carolinas Medical Center, Charlotte, NC.

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INTRODUCTION

The tumor, node, metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC)¹ and the International Union Against Cancer (UICC)² is now the standard for colorectal cancer staging recommended by the College of American Pathologists,³ the Royal College of Pathologists,⁴ the Commission on Cancer of the American College of Surgeons,⁵ and the National Cancer Institute (Common Data Elements).⁶ The TNM staging system is also widely used by national, regional, and local tumor registries in the United States and internationally. In short, it is the international language of colorectal cancer staging in all disciplines. The TNM system has three additional advantages over other staging systems. First, it is data-driven and has a process in place for continuous improvement based on ongoing expert review of existing data.⁷ Second, it has a comprehensive set of definitions and rules of application that ensure uniform use. Third, it is multidisciplinary in design and is pertinent to all modern techniques of stage evaluation.

For two decades, worldwide agreement on cancer staging between the AJCC and the UICC has created a staging vocabulary that has been used extensively in the United States to quantify tumor burden in patients with colorectal cancer.⁸ The current sixth edition of the *AJCC Cancer Staging Manual*¹ includes refinements of colorectal cancer staging that are based on large data sets from the National Cancer Data Base (NCDB), which was created through a partnership of the American College of Surgeons and the American Cancer Society.⁹

The prime motivation for having a unified and worldwide system of cancer staging is to assure a common language is used by all those caring for cancer patients and, in the case of TNM, to maintain a dialogue in solid tumor management that will be understood by clinicians in all specialties. Although the individual parameters of the TNM system are periodically updated to reflect the most current and robust data, the basic structure of the TNM system has been constant since its inception. The system incorporates both clinical and pathologic staging approaches and can encompass the newest and most technically advanced methodologies in either realm. Because the TNM system can be applied to the preoperative evaluation of patients, this system, more so than the pathologically based Dukes classification or its variations, is more meaningful and helpful to clinicians, especially in the setting of preoperative patient management.

The development of new staging strategies and the updating of the TNM system depend on outcome studies and the collection of outcome data as represented by the NCDB. To have meaningful large, national data sets, patients must be staged using similar systems, especially if outcomes are to be categorized and compared worldwide. Continued use of older and outdated staging systems such as Dukes for the categorization of colorectal cancer patients

compromises the goals of achieving a universal common language to describe cancer patients and of eliminating the data compromise that result from the use of multiple staging strategies for the same tumor.

DIFFERENCES BETWEEN 1997 AND 2002 VERSIONS

One of the important challenges facing the TNM system is the necessity to change staging classifications as newer information comes forward that more accurately defines prognosis within staging parameters. To maintain the relevance of the TNM system, outcomes research based on large data sets such as the NCDB is carried out on a regular basis. The current stage groupings for colorectal cancer^{1,2} were redefined based on a recent analysis of outcomes in patients with Stage III colon cancer (defined as the presence of any adenocarcinoma of the colon with metastatic tumor in regional lymph nodes). Through the first five editions of the *AJCC Cancer Staging Manual*, Stage III has been defined as a single group based on the tenet that the positive nodal involvement is a stronger adverse prognostic indicator than the depth of penetration (T category) of the primary tumor. The hypothesis that depth of penetration and the number of nodes involved in the mesentery may be important prognostic indices was tested in an analysis of NCDB data on more than 50,000 patients diagnosed with Stage III colon cancer from 1987 through 1993.¹⁰ The observed survival was calculated by actuarial life table methods for three new node-positive subgroups with different degrees of local extent of disease (Figure 1),¹⁰ and the Cox proportional hazards model was used to test the prognostic strength of selected covariates. By this analysis, three distinct subcategories within a traditional Stage III cohort of colon cancer were identified as follows: Stage IIIA (T1/2, N1), Stage IIIB (T3/4, N1), and Stage IIIC (any T, N2). The 5-year observed survival rates for these three subcategories were 59.8%, 42.0%, and 27.3%, respectively. Differences among subgroups were significant ($P < 0.0001$). Thus, it was determined that the existing staging system for node-positive colon cancer failed to appreciate the prognostic importance of

depth of penetration and the differences between having less than four nodes or four or more nodes positive, and the TNM groupings for Stage III were modified accordingly in the current iteration of the TNM system (Tables 1 and 2).^{1,2}

The inherent value of any cancer staging system is its reproducibility and applicability to current methods of pathologic assessment. Because the Stage III group is defined by the identification and quantification of involved mesenteric lymph nodes, accuracy of staging is directly proportional to the aggressiveness of surgical resection and nodal identification in this group of patients. The AJCC and the College of American Pathologists have recommended examination of at least 12 lymph nodes to assume identification of Stage III patients.^{1,3} Goldstein et al.¹² have shown that nodal metastases in patients with T3 tumors were present in 22% of specimens with fewer than 15 identified nodes compared with 85% in specimens with 15 or greater recovered nodes. Patients without nodal metastases also show a survival advantage when a greater number of nodes are identified, indicating the positive effect of the greater magnitude of mesenteric resection.¹²⁻¹⁹ Other studies have suggested additional benchmarks for nodal excision. Although some have supported the concept of “upstaging” patients with Stage I or II colorectal cancer using immunohistochemical identification of nodal involvement with or without sentinel node assessment,^{20,21} there is no clear evidence to support the suggestion that treatment decisions should be based on “micrometastatic” nodal involvement. The AJCC and UICC continue to recommend that nodal assessment for colorectal cancer should depend on traditional hematoxylin and eosin techniques. To be relevant, however, the current TNM system must be dynamic enough to incorporate future changes in molecular or genetic identification if supported by outcomes analysis. Recommendations for subclassifying traditional Stage III patients into three new prognostic groups reflect this approach and are included in the sixth edition of the *AJCC Cancer Staging Manual*.¹

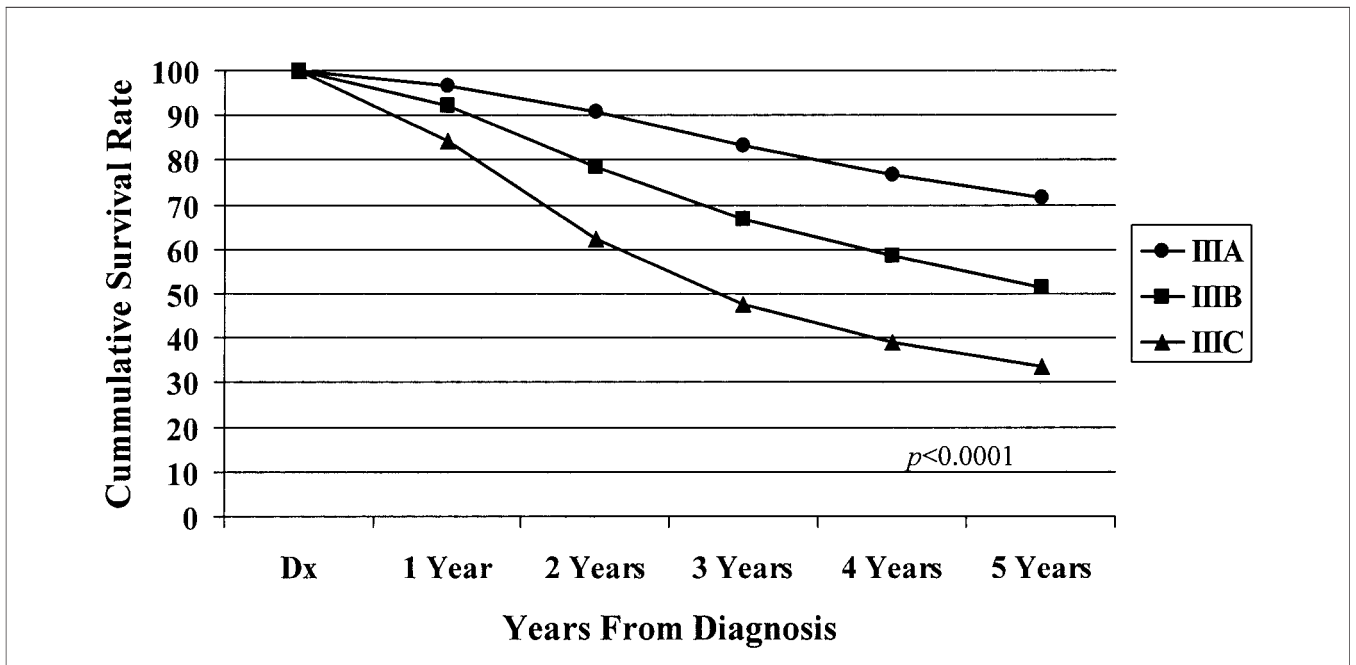


FIGURE 1 Outcomes Stratified by Subclassification of Stage III Colorectal Cancer.

Based on data from patients registered in the National Cancer Data Base from 1987 to 1993 (Adapted from Greene FL, Stewart AK, Norton HJ¹⁰ with permission from Lippincott Williams & Wilkins).

GENERAL RULES OF APPLICATION

In the TNM system, pathologic staging information derived from surgical resection specimens is considered the most accurate determination of local extent of disease. Typically, it also determines the appropriateness of postoperative adjuvant treatment. Additional pathologic factors and prognostic features may help to sub-stratify tumors of like stage into different risk categories. In rectal cancer, in particular, the macroscopic features of the resection specimen and the microscopic status of the circumferential resection margin are powerful predictors of risk of both local recurrence and overall survival. Accurate pathologic staging in colorectal cancer also is fundamental to understanding the spectrum of disease presentation, results of treatment interventions, and outcomes in clinical trials.

In the TNM system, the designation “T” refers to the local extent of the untreated primary tumor at the time of diagnosis and initial workup. The designation “N” refers to the status of the regional lymph nodes, and “M” refers to distant metastatic disease at this time. The symbol “p” used as a prescript refers to the pathologic determination of the TNM (eg,

pT1), as contrasted with the clinical determination (designated by the prescript “c”). Pathologic classification is based on gross and microscopic examination of the resection specimen of a previously untreated primary tumor. Assignment of pT requires a resection of the primary tumor or biopsy adequate to evaluate the highest pT category. pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is based on evidence acquired through a variety of techniques that include but are not limited to physical examination, radiologic imaging, endoscopy, biopsy, and surgical exploration. Clinical staging is carried out during initial evaluation of the patient before any cancer-directed therapy is initiated, and once assigned, it is not changed on the basis of subsequent information. When pathologic staging information becomes available, it is added to but does not replace the clinically derived staging parameters, even though the pathologically derived parameters are considered more accurate (and therefore definitive) by convention. Clinical staging ends at the time of diagnostic

TABLE 1 AJCC/UICC TNM, Definitions*

	Category	Definition
Primary tumor (T)	TX	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	Tis	Carcinoma in situ (intraepithelial or intramucosal carcinoma)
	T1	Tumor invades the submucosa
	T2	Tumor invades the muscularis propria
	T3	Tumor invades through the muscularis propria into the subserosa or into the nonperitonealized pericolic or perirectal tissues
		Optional expansions of T3:† pT3a-minimal invasion: <1 mm beyond the border of the muscularis propria pT3b-slight invasion: 1–5 mm beyond the border of the muscularis propria pT3c-moderate invasion: >5–15 mm beyond the border of the muscularis propria pT3d-extensive invasion: >15 mm beyond the border of the muscularis propria
Regional lymph nodes (N)	T4	Tumor directly invades other organs or structures (T4a) or perforates the visceral peritoneum (T4b)
	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph nodes metastasis
	N1	Metastasis in one to three lymph nodes
Distant metastasis (M)	N2	Metastasis in four or more lymph nodes
	MX	Presence of distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis

*Adapted from Greene FL, Page DL, Fleming ID, et al. (eds)¹ with permission from Springer-Verlag.

†Wittekind C, Greene FL, Hensen DE (eds).¹¹

workup if a decision is made not to treat the patient.¹ It is considered the definitive stage if pathologic classification is not possible.

It is the grouping of a T, an N, and an M parameter that determines the stage of a tumor and relates to its prognosis. The clinical staging parameters evaluated before treatment are reported separately and remain unchanged in the patient's medical record as documentation of the basis for treatment planning. They may be revised only if more accurate clinical staging information becomes available (eg, higher resolution imaging studies) before initiation of treatment or before making the decision not to treat the patient. In such cases, the revised classification is considered the definitive clinical stage. For the final stage grouping, TNM parameters representing a combination of clinically and pathologically derived data (eg, pT1, pN0, cM0) are used when only partial pathologic data are available. This is often the case because distant metastatic status is commonly unconfirmed pathologically (pMX), and a clinically determined M category is assigned in the final stage grouping. The definitions of the individual TNM categories and stage groupings for colorectal carcinoma are shown in Tables 1

and 2.^{1,2,11} TNM stage-related survival is shown in Figure 2 (A. Stewart, personal communication, 2003).

The first general rule of TNM staging is that all cancer cases should be confirmed microscopically.¹¹ Masses or ulcers discovered by rectal examination, imaging, or endoscopic studies that are suspicious for colorectal carcinoma typically require biopsy confirmation as carcinomas before initiating treatment. However, according to UICC rules of staging, microscopically unconfirmed cases can be staged clinically but should be analyzed and reported separately. This rule would apply, for example, to cases in which neither biopsy confirmation nor surgical resection is possible. Although clinical diagnosis of established colorectal carcinoma is usually accurate, a number of benign and malignant conditions that may mimic colorectal carcinoma grossly require exclusion on biopsy. For example, other tumors that may resemble colorectal carcinoma include colorectal lymphomas, carcinoid tumors, gastrointestinal stromal tumors (mural sarcomas), metastatic tumors that exhibit tropism for the gastrointestinal tract (eg, malignant melanoma), malignancies of adjacent organs that directly invade the

TABLE 2 AJCC/UICC Stage Groupings

	TNM			Modified Astler- Coller	Dukes
	T	N	M		
Stage 0	Tis	N0	M0	N/A	N/A
Stage I	T1	N0	M0	Stage A	A
	T2	N0	M0	Stage B1	A
Stage IIA	T3	N0	M0	Stage B2	B
Stage IIB	T4	N0	M0	Stage B3	B
Stage IIIA	T1,T2	N1	M0	Stage C1	C
Stage IIIB	T3,T4	N1	M0	Stage C2,C3	C
Stage IIIC	Any T	N2	M0	Stage C1,C2,C3	C
Stage IV	Any T	Any N	M1	Stage D	N/A

colorectum (eg, cancers of the ovary, endometrium, bladder, or prostate), or appendiceal tumors that extend into the cecum. Because TNM staging for the colorectum is applicable only to primary carcinomas of the colon and rectum, these tumors would all be excluded from classification by the colorectal TNM system. Benign lesions that may mimic colorectal cancer include adenomas, hamartomas, colitis cystica profunda, solitary rectal ulcers, stercoral ulcers, endometriomas, and Crohn disease or diverticular disease producing mural strictures.

POLYPECTOMIZED COLORECTAL CANCERS

The diagnosis and treatment of colorectal cancers by endoscopic polypectomy have become commonplace. The cancer may be unsuspected at endoscopy and revealed only on microscopic examination of the polypectomy specimen. Malignant polyps are adenomas that contain any amount of invasive carcinoma, which is defined as tumor that penetrates through the muscularis mucosae into the submucosa. They

TABLE 3 The Prognostic Significance of Serosal Involvement by Tumor in Colorectal Carcinoma*

	Five-year Survival Rate (%)	Median Survival Time (mo.)
pT4a,M0	49	58.2
pT4b,M0	43	46.2
pT4a,M1	12	22.7
pT4b,M1	0	15.5

*Adapted from Wittekind C, Greene FL, Hensen DE, et al. (eds).¹¹ with permission from John Wiley & Sons.

also encompass polypoid carcinomas, in which the entire polyp head is replaced by carcinoma. By definition, malignant polyps exclude adenomas containing intraepithelial carcinoma or intramucosal carcinoma because these polyps possess no biological potential for metastasis (see "Definition of pTis" below). Polyps containing invasive carcinoma represent about 5% of all adenomas.^{22,23} Malignant polyps constitute a form of early carcinoma (pT1) that may often be cured by endoscopic polypectomy alone.²⁴⁻²⁶ However, the incidence of an unfavorable outcome (ie, lymph node metastasis or local recurrence from residual malignancy) for malignant polyps treated by polypectomy alone varies from about 10% to 20%.^{27,28} Pathologic evaluation is critical in defining malignant polyps with an increased risk of residual or recurrent disease, and the subsequent clinical management of the patient may be based, in part, on the findings.²⁴ The histopathologic parameters that are known to be associated with a significantly increased risk of adverse outcome are: (1) high tumor grade (or histologic type that is, by convention, always considered high grade, such as poorly differentiated adenocarcinoma, signet-ring cell carcinoma, small cell carcinoma, or undifferentiated carcinoma); (2) tumor at or less than 1 mm from the resection margin; and (3) small (thin-walled) vessel (presumed lymphatic) involvement by tumor (classified as L1 in the L classification of the AJCC/UICC).²⁹⁻³⁸

If one or more of these high-risk features are found on pathologic examination, the risk of an adverse outcome (regional nodal metastasis or local recurrence) following polypectomy is estimated to be about 10% to 25%,^{30,39-41} and further therapy may be indicated.

PATHOLOGIC DETAILS OF TNM ASSESSMENT

T Category Issues

Accurate assignment of pathologic T and N categories is usually possible for cancer-directed surgical resection specimens. If there is doubt concerning the correct T, N, or M parameter that should be applied, the lower (ie, less advanced) category should be assigned and also applied to the stage grouping.¹¹

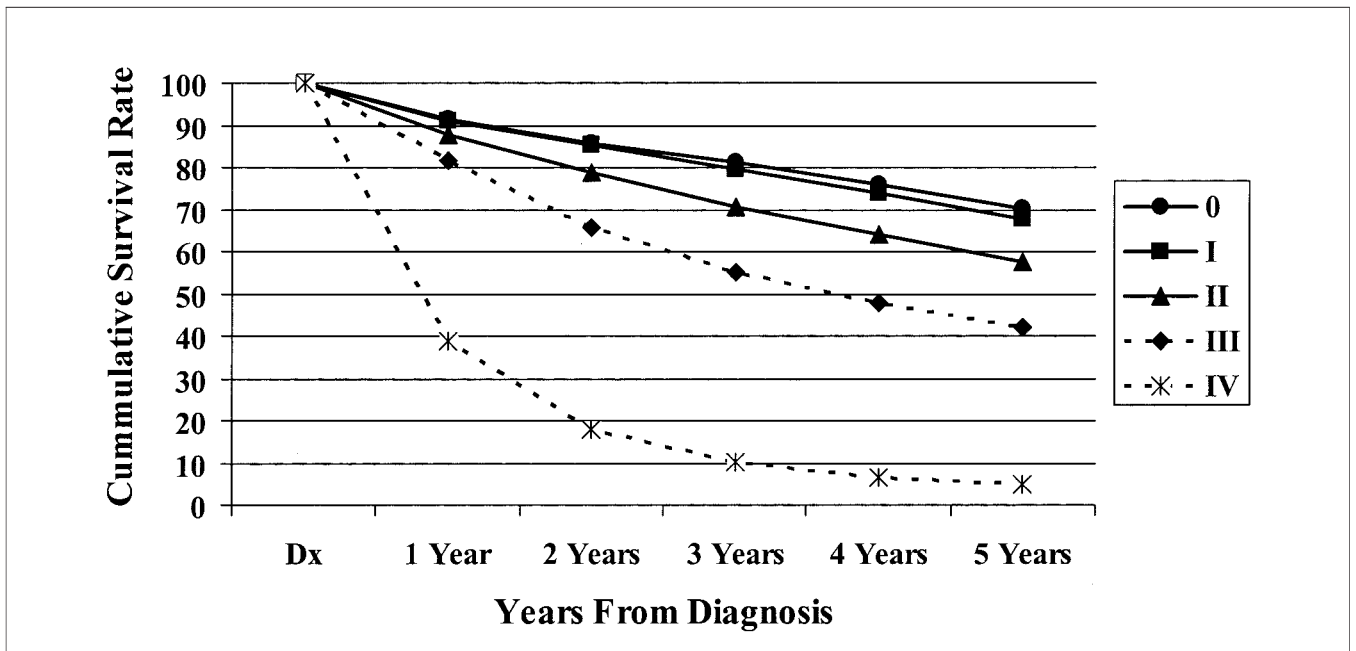


FIGURE 2 Relationship Between TNM Stage and Survival in Colorectal Carcinoma. Data from Andrew Stewart, National Cancer Data Base of the Commission on Cancer, personal communication, 2003.

For colorectal carcinomas, the staging category pTis (carcinoma in situ) includes both malignant cells that are confined by the glandular basement membrane (intraepithelial carcinoma) and those that have invaded into the mucosal lamina propria (intramucosal carcinoma). Intramucosal carcinoma that extends into but not through the muscularis mucosae also is included in the pTis category. Penetration of the muscularis mucosae and invasion of the submucosa is classified as pT1. High-grade (severe) dysplasia and intraepithelial carcinoma sometimes may be used synonymously, especially in cases of inflammatory bowel disease.²

It is noteworthy that for all organ systems other than the large intestine, carcinoma in situ refers exclusively to malignancy that has not yet penetrated the basement membrane of the epithelium from which it arose, and invasive carcinoma encompasses all tumors that penetrate the underlying stroma. Stromal invasion of any degree is a feature of extreme importance in all noncolorectal sites because of the possible access of tumor cells to stromal lymphatics or blood vessels and the consequent risk of metastasis. In colorectal cancer, however, the designation pTis (ie, carcinoma in situ) is used to

refer both to intraepithelial malignancies and to cancers that have invaded the mucosal stroma (intramucosal carcinomas) because the colorectal mucosa is biologically unique. In contrast to the mucosa elsewhere in the gastrointestinal tract (or, indeed, in the rest of the human body), tumor invasion of the lamina propria has no associated risk of regional nodal metastasis. Therefore, for the colon and rectum, inclusion of intramucosal carcinoma in the pTis category is justified. Nevertheless, the term carcinoma in situ in reference to colorectal cancer can be confusing, depending on whether it is used to refer to the T category of the TNM staging system or to intraepithelial tumor only, as it does in all other epithelial systems. Therefore, the terms intraepithelial carcinoma and intramucosal carcinoma may be the preferred descriptive terms for colorectal tumors in the pTis category.^{42,43}

Colorectal cancer that has penetrated into but not completely through the muscularis propria is classified as T2. The T3 category refers to all transmurally invasive tumors that are confined to the perimuscular soft tissue (ie, that have neither violated the serosal surface nor infiltrated an adjacent structure). The min-

imal criterion for assignment of pT3 is the absence of any mural muscle between the leading edge of the tumor and the extramural soft tissue. Although it is not required as a mandatory part of pT3 assessment, measurement of the depth of extramural soft tissue invasion may be justified, because data indicate that the deeper a tumor invades into the perimuscular tissues, the worse the prognosis.¹¹ Extramural extension exceeding 5 mm appears to be the critical cut point linked to adverse outcome in most studies.¹¹ This adverse prognostic association is observed whether or not regional lymph node metastasis is present. Extramural extension of the tumor within lymphatics or veins does not count as local spread of tumor as defined by T3, but extramural tumor nodules discontinuous from the primary tumor mass that are irregular in shape are included in the T category as pT3.¹¹ If such nodules have smooth contours, they are classified by convention as replaced lymph nodes.

The highest category of local extent is pT4, which includes both extension into adjacent organs or structures (pT4a) and penetration of the parietal peritoneum with or without involvement of an adjacent structure (pT4b).¹¹ A free perforation of a colorectal carcinoma into the peritoneal cavity is also classified as T4b.¹¹ Among the features that define T4 tumors, serosal penetration is the most dire. A number of large studies have evaluated serosal penetration as a separate pathologic variable and have demonstrated by multivariate analysis that it has independent adverse prognostic significance.⁴³⁻⁴⁶ The median survival time following surgical resection for cure is significantly shorter for pT4 tumors that penetrate the visceral peritoneum compared with pT4 tumors without serosal involvement, with or without distant metastasis (Table 3).¹¹ A careful pathologic study of local peritoneal involvement by Shepherd et al.⁴⁶ has suggested that the prognostic power of this feature may supersede that of regional lymph node metastasis (N category).

Despite its biologic importance, serosal involvement is often underdiagnosed by pathologists. Documentation of peritoneal involvement by tumor demands meticulous pathologic analysis and may require extensive sampling and/or serial sectioning. Thus, it can be missed on routine

histopathologic examination. In fact, it has been shown that cytologic examination of serosal scrapings reveals malignant cells in as many as 26% of tumor specimens categorized as pT3 by histologic examination alone.^{46,47}

Viewed under the microscope, peritoneal involvement by tumor may be associated with a spectrum of features. Three types of local peritoneal involvement have been defined: (1) a mesothelial inflammatory and/or hyperplastic reaction with tumor close to, but not at, the serosal surface; (2) tumor present at the serosal surface with inflammatory reaction, mesothelial hyperplasia, and/or erosion/ulceration; and (3) free tumor cells on the serosal surface (in the peritoneum) with underlying ulceration of the visceral peritoneum.⁴⁶ All three types of local peritoneal involvement were associated with decreased survival, especially the latter two. In contrast, tumor well clear of the serosa had no independent adverse effect on prognosis.⁴⁶ Therefore, it has been recommended that the definition of T4b be modified to encompass reactions 2 and 3 outlined above.³ It is also possible to classify a tumor as pT4b based on positive cytologic specimens obtained by intraoperatively scraping the serosa overlying the primary tumor.¹¹

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 (eg, invasion of the sigmoid colon by carcinoma of the cecum) all should be classified as pT4. In contrast, intramural (longitudinal) extension of tumor from one subsite (segment) of the large intestine into an adjacent subsite or into the ileum (eg, for a cecal carcinoma) or anal canal (eg, for a rectal carcinoma) does not affect the pT classification.¹¹

N Category Issues

Stage-related outcome data are derived from studies in which the pathologic evaluation of

the regional lymph nodes has been performed by conventional histologic staining of macroscopically identified lymph nodes. Because it has been shown that many nodal metastases in colorectal cancer are found in small lymph nodes (less than 5 mm in diameter),^{48,49} a diligent search for lymph nodes in resection specimens is essential. The number of lymph nodes recovered from resection specimens varies widely and is dependent on several factors. Patient factors such as age and anatomic variation, surgical technique, and diligence of the pathologist in harvesting all existing nodes are significant factors. 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.^{12-19,49,50} For this reason, it has been suggested that 12 lymph nodes be considered the minimum acceptable harvest from a careful specimen dissection. If fewer than 12 nodes are found after careful gross examination, additional techniques (ie, visual enhancement techniques such as fat clearing) may be considered.⁴² It has been further recommended that all grossly negative or equivocal lymph nodes be submitted entirely for microscopic examination⁴² and that involvement of grossly positive lymph nodes be confirmed by either complete or partial microscopic examination. At present, routine assessment of regional lymph node metastasis is limited to the use of conventional pathologic techniques (gross assessment and histologic examination of one tissue level).

Regional lymph nodes must be examined separately from lymph nodes outside of the anatomic site of the tumor because metastasis in any lymph node in the regional nodal group is classified as pN disease, whereas all other nodal metastases are classified as pM1. On microscopic examination, tumor in a regional lymph node, whether arriving there via afferent lymphatics or direct invasion through the capsule, is regarded as metastatic disease. In addition, microscopic examination of the extramural adipose tissue may reveal discrete nodules of tumor that may represent lymph nodes that have been replaced by metastatic tumor but cannot be identified as such with certainty. By AJCC/UICC convention, extramural tumor nodules of any size with smooth contours are

counted as replaced regional lymph nodes.^{1,2,11} For purposes of pN assignment, each nodule is counted separately as a positive node. This rule, brought forward in the sixth editions of the AJCC and UICC staging manuals, is based on evidence suggesting that pericolonic tumor deposits of any size correlate with shorter survival and do so independently of otherwise observable lymph node metastasis.⁵⁰ The evidence also indicates that the number of pericolonic tumor deposits correlates inversely with disease-free survival.⁵⁰

The regional lymph node groups corresponding to the anatomic subsites of the colorectum are listed on Table 4. Occasionally, however, a colorectal cancer may involve more than one site or subsite by continuous longitudinal extension. For example, a cecal carcinoma may extend across the ileocecal valve into the ileum. In these cases, the regional lymph nodes are defined as those of all involved sites and subsites. In rare cases, the regional nodes of the primary tumor site are free of malignancy, but the nodes in the drainage area of

TABLE 4 Definitions of Regional Lymph Node Groups in Anatomic Subsides of the Colorectum

Colorectum Subsite	Definition
Cecum	Anterior cecal, posterior cecal, ileocolic, right colic
Ascending colon	Ileocolic, right colic, middle colic
Hepatic flexure	Middle colic, right colic
Transverse colon	Middle colic
Splenic flexure	Middle colic, left colic, inferior mesenteric
Descending colon	Left colic, inferior mesenteric, sigmoid
Sigmoid colon	Inferior mesenteric, superior rectal sigmoidal, sigmoid mesenteric*
Rectosigmoid colon	Perirectal, † left colic, sigmoid mesenteric, sigmoidal, inferior mesenteric, superior rectal, middle rectal
Rectum	Perirectal, † sigmoid mesenteric, inferior mesenteric, lateral sacral, presacral, internal iliac, sacral promontory, superior rectal, middle rectal, inferior rectal

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

†Perirectal lymph nodes include the mesorectal (para-proctal), 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.

an organ directly invaded by the primary tumor contain metastases. In this circumstance, the lymph nodes of the invaded site are considered as those of the primary site and are classified in the N category.¹¹

Increasingly, attention is being focused on alternative methods of detecting very small amounts of metastatic tumor. To assess the biologic significance and clinical impact of minute amounts of tumor detected in metastatic sites, it is imperative to collect data using uniform diagnostic and reporting criteria such as those defined by the AJCC and UICC. 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, ITC are classified as N0 or M0, as appropriate.^{1,11,51} Because the biologic significance of ITC (either a single focus in a single node, multiple foci within a single node, or micrometastatic involvement of multiple nodes) is as of yet unproved, classification as N0 is considered justified. In contrast, small amounts of metastatic tumor that measure greater than 0.2 mm but less than 2.0 mm are defined as micrometastases and classified as N1 or M1. The conventions for reporting of ITC and micrometastases are shown in detail in Table 5. The number of lymph nodes involved by micrometastases or ITC should be clearly stated in the pathology report. Currently, however, the data are insufficient to recommend either the routine examination of multiple tissue levels of paraffin blocks or the use of special/ancillary techniques such as immunohistochemistry for epithelial and/or tumor-associated antigens (eg, cytokeratin, carcinoembryonic antigen) or polymerase chain reac-

tion techniques to identify tumor RNA/DNA. Furthermore, all of these approaches are costly, and some can be difficult to quality control. Pending definitive data, it is recommended that any ITC reported by the pathologist be accompanied by a note stating that the biologic significance is unknown.⁴³

M Category Issues

In colorectal cancer, pM1 disease encompasses pathologically documented metastasis to any nonregional lymph node, the parenchyma of any distant organ or tissue, and/or the peritoneum of any abdominal structure. Positive peritoneal fluid cytology and tumor present (only) in lymphatic vessels of a distant site are also considered pM1 disease.

Excluded from pM1 designation are ITC found in the bone marrow (like nodal ITC, distant ITC are not classified as metastasis or assigned pM1 because their significance is as yet unproved)⁵² and tumor foci in the mucosa or submucosa of adjacent bowel, also known as satellite lesions or skip metastasis (however, these must be distinguished from synchronous primary tumors).

Pathologic Staging of Multiple Carcinomas

For purposes of classification of multiple simultaneous tumors, the colon and the rectum are defined as one organ. The convention for codification of multiple simultaneous tumors requires that the cancer with the highest T category be staged and classified as the relevant or dominant tumor and the total number of tumors or the symbol "m" (for multiple) indicated in parenthe-

TABLE 5 Annotation for Isolated Tumor Cells and Micrometastases

	Annotation	Definition
Isolated tumor cells	pN0(i-)	No ITC* detected morphologically
	pN0(i+)	Positive morphological (H&E† or immunohistochemical) findings for ITC
	pN0(mol-)	No regional lymph node metastasis histologically, negative nonmorphological (molecular) findings for ITC
	pN0(mol+)	No regional lymph node metastasis histologically, positive nonmorphological (molecular) findings for ITC
Micrometastasis	pN1 (mi)	Metastatic tumor in regional node, no larger than 2.0 mm but >0.2 mm in dimension
	pM1(mi)	Metastatic tumor in distant site, no larger than 2.0 mm but >0.2 mm in dimension

*ITC = isolated tumor cells.

†H&E = hematoxylin and eosin stain.

ses after the pT category of the dominant tumor (eg, pT3(2) or pT3(m)). Simultaneous tumors may include multiple noninvasive cancers, multiple invasive cancers, or a combination of both noninvasive and invasive cancers. If a new primary cancer is diagnosed within two months, the new cancer is considered synchronous based on criteria used by the Surveillance, Epidemiology and End Results Program of the National Cancer Institute.⁵³

Pathologic Staging of Residual Carcinoma

Residual Tumor in the Resection Specimen After Neoadjuvant Therapy

By definition, the TNM categories describe the anatomic extent of malignant tumors that have not been previously treated, and the predictive value of TNM stage groupings is based solely on data derived from outcome studies of such tumors. For tumors treated before staging, the prognostic correlates related to stage are altered compared with tumors staged before treatment. However, the rules of application of TNM allow for documentation of the extent of posttreatment disease. The same TNM parameters are used but are codified by the prescript “y” to indicate the posttreatment status of the tumor.^{1,11} For the pathologist, this is relevant to tumor remaining in a resection specimen after previous (neoadjuvant) treatment of any type (radiation therapy alone, chemotherapy alone, or any combined modality treatment). For many therapies, the classification of residual disease also has been shown to be a strong predictor of posttreatment outcome. In addition, the ypTNM classification provides a standardized framework for the collection of data needed to accurately evaluate new therapies.

Residual Tumor in the Patient Following Resection for Cure (Cancer-directed Surgery)

In contrast to tumor remaining in a resection specimen after neoadjuvant therapy, tumor remaining in the patient after primary surgical resection is not evaluated or annotated using TNM parameters. It is categorized by a system known as the R classification, shown below.⁵⁴

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

The R classification was originally developed for clinical use to document the efficacy of the patient’s treatment. Not surprisingly, the R classification has stage-independent prognostic significance in that R1 and R2 are adverse prognostic factors compared with R0 status at any stage of disease. The relevance of the R classification to the pathologist is primarily related to resection margin evaluation. Tumor present microscopically or macroscopically at a resection margin corresponds to R1 or R2, respectively. This is based on the widely accepted convention that tumor present at a resection margin is likely to correspond to the presence of tumor on the opposite side of that margin (ie, within the tissue at the corresponding resection site in the patient). However, R0 status cannot necessarily be assigned by the pathologist to a case with negative resection margins because R0 status refers to absence of residual tumor anywhere in the patient, including distant metastatic sites, and must therefore be based on clinical information.^{11,54}

Surgical Resection Margin Status in Cancer-directed Surgery

The prognostic value of TNM stage in disease with no (or limited hepatic) distant metastasis at presentation is predicated on complete eradication of all detectable tumor on completion of therapy. Because surgery is the primary mode of therapy for the vast majority of colorectal cancer, optimal treatment is linked to complete excision of all detectable tumor. This is the goal of all cancer-directed surgery, and the status of the resection margins of the resultant excision specimen constitutes one measure of successful attainment of that goal.

The pertinent margins of a colorectal cancer resection specimen include the proximal and distal transverse margins, the mesenteric margin, and, when appropriate, the circumferential (radial) margin. The circumferential resection margin (CRM) represents the retroperitoneal

or peritoneal adventitial soft-tissue margin closest to the deepest penetration of tumor. For all segments of the large intestine that are either incompletely encased (ascending colon, descending colon, upper rectum) or not encased (lower rectum) by peritoneum, the CRM is created by blunt dissection of the retroperitoneal or subperitoneal aspect, respectively, at the time of the operation.

When the distance between the tumor and the nearest transverse margin is 5 cm or more, anastomotic recurrences are very rare. Therefore, it can be argued that histologic examination of the proximal and/or distal margin is unnecessary if these margins are 5 cm or more from the tumor.⁵⁵ In fact, guidelines from 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 greater than 3 cm from the cut end of the main specimen.⁴ In low anterior rectal resection specimens of rectal cancers, however, wide distal cuffs of normal mucosa may be hard to achieve due to anatomic constraints. In this circumstance, a margin of 2 cm is accepted as adequate, and in many cases, distal margins of 1 cm or less also prove sufficient, especially for T1 and T2 tumors. Thus, on pathologic examination, the distance of the tumor from the transverse margins is always recorded, but microscopic examination may be considered optional if the closest distance is greater than 5 cm.

In rectal carcinoma, the CRM has been demonstrated to be the margin of greatest importance in predicting risk of local recurrence, which is itself a strong predictor of survival.⁵⁶⁻⁵⁹ In fact, multivariate analyses have suggested that tumor involvement of the CRM is the most critical factor in predicting local recurrence in rectal cancer.^{60,61} Emerging data on CRM involvement in the colon suggest a similar relationship to risk of local recurrence.⁶⁰ Therefore, routine assessment of the CRM is recommended in all applicable colorectal cancers, and measurement of the distance from the tumor to the nearest CRM, representing the surgical clearance around the tumor, is suggested.^{50,59} Based on published data from clinical trials, the risk of local recurrence is

strongly increased if tumor is present 1 mm or less from the nonperitonealized surface of the specimen.⁶¹ More recent data have suggested that the risk of local recurrence also is significantly increased with clearances of 2 mm or less (CJH Van de Velde, personal communication, January 2004). Thus, the current recommendation is that clearance of 2 mm or less should be considered a positive CRM.⁶² In contrast, the risk of recurrence is very low with clearance of more than 2 mm and can be considered negative or R0. In any case, reporting of the actual clearance measurement is recommended rather than assignment of positive or negative status alone.

For segments of the colon that are completely encased by a peritonealized (serosal) surface (eg, transverse and sigmoid colon), the mesenteric resection margin may be a relevant radial margin because tumors may extend to this margin with (pT4) or without (pT3) penetrating the serosal surface. It should be examined when the point of deepest penetration of the tumor is on the mesenteric aspect of the colon, especially when the mesentery has been trimmed close to the colonic wall. For those tumors limited to an antimesenteric peritonealized aspect of the bowel, the mesenteric margin usually is not relevant.

Because involvement of the CRM or the mesenteric margin is associated with an increased risk of local recurrence, it has implications for adjuvant therapy. Thus, it is extremely important that the pathologist carefully differentiate the peritonealized from the nonperitonealized surfaces of the resection specimen and examine them separately. For example, if a 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 (R0). However, if a tumor is present on a nonperitonealized surface (ie, the CRM), adjuvant radiation may be appropriate irrespective of the T category of the tumor.

Pathologic Staging of Recurrent Colorectal Carcinoma

Tumor that recurs after a documented disease-free interval following therapy is classified accord-

ing to TNM parameters but modified with the prefix “r” (eg, rT1). By convention, locally recurrent tumor is assigned topographically to the proximal segment of the anastomosis unless the proximal segment is the small intestine.^{1,11}

Lymphatic and Venous Involvement by Tumor of Any Stage: The L and V Classification Systems of the AJCC/UICC

Venous invasion by tumor has been demonstrated repeatedly to be a stage-independent adverse prognostic factor by multivariate^{44,45,62–69} and univariate analyses.^{70–73} However, some studies identifying venous invasion as an adverse factor on univariate analysis have failed to confirm its independent impact on prognosis on multivariate breakdown.^{73,74} Similar disparate results have also been reported for lymphatic invasion.^{64,65,69,72,74–78} In other reports, vascular invasion as a general feature was prognostically significant, but no distinction between lymphatic and venous vessels was made. In a few studies, the location as well as the type of the involved vessels (eg, extramural veins) were both considered strong determinates of prognostic impact.^{49,67} Therefore, data from existing studies are difficult to amalgamate. Nevertheless, the importance of venous and lymphatic invasion by tumor is strongly suggested and largely confirmed by the literature.

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 (eg, vascular destruction by tumor) are both common, and 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 performed routinely. Detection of vessel invasion in any given case is also affected by specimen sam-

pling. It has been shown that the reproducibility of extramural venous invasion detection increases proportionally with the number of tissue blocks taken, from 59% with two blocks to 96% with five blocks.⁴⁹ 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 impacted by cost containment issues, which in general have encouraged reduced sampling of resection specimens. The College of American Pathologists has suggested that at least three blocks (optimally five blocks) of tumor at its point of deepest extent be submitted for microscopic examination.^{3,42}

By AJCC/UICC convention, the presence of tumor cells within the lymphatics or veins of the primary tumor site does not affect the pT classification. Intravascular spread via lymphatic or venous vessels is recorded separately and classified as L1 and V1, respectively. Conversely, L0 and V0 indicate the absence of lymphovascular and venous invasion, respectively, and always should 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 the primary tumor and peripheral to the primary tumor.

Tumor contained solely within the afferent lymphatic vessels of regional lymph nodes is classified as L1 but N0. To qualify as N1, tumor cells must extend into the node proper (eg, into the subcapsular sinus). In contrast, tumor within the lymphatics of a distant organ is classified as pM1. The UICC recommends that extramural tumor nodules with irregular contours (ie, 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 intravenous 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.¹¹

CONCLUSIONS

The above discussion of the current TNM staging strategies must constantly be tested and perfected to avoid the fate of becoming irrelevant. As newer anatomic and molecular markers are uncovered, these must be applied to the

TNM staging of colorectal cancer and woven into our staging taxonomy. In addition, the future of our management of this large and important group of patients mandates not only a worldwide system of staging, but a commitment to utilize the system in our approach to patient management, clinical trials, registry reporting, and the dissemination of new knowledge through the development of scholarly manuscripts and presentations relating to this disease.

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