TNM Staging System of Colorectal Carcinoma

A Critical Appraisal of Challenging Issues

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- Context.—Colorectal cancer is the leading cause of morbidity and death among gastrointestinal tumors and ranks fourth after lung, breast, and ovarian cancers. Despite a continuous refinement of the T (tumor), N (node), and M (metastasis) staging system to express disease extent and define prognosis, and eventually to guide treatment, the outcome of patients with colorectal cancer may vary considerably even within the same tumor stage. Therefore, the need for new factors, either morphologic or molecular, that could more precisely stratify patients into different risk categories is clearly warranted.

Objectives.—To present the state of the art with regard to the colorectal cancer staging system and to discuss confusing and/or challenging issues, including the assessment of peritoneal membrane involvement, vascular invasion, tumor deposits, and pathologic tumor response to neoadjuvant chemoradiotherapy.

Data Sources.—Literature review of relevant articles indexed in PubMed (US National Library of Medicine) and primary material from the authors’ institutions.

Conclusions.—Two emerging needs exist for the TNM system, namely, further stratification of patients with the same tumor stage and incorporation of nonanatomic factors, the latter including molecular and treatment factors. The identification and classification of morphologic features encountered in the pathologic examination of colorectal cancer specimens may be difficult and a source of subjective variability. Enhanced pathologic analysis, agreed-upon standard protocols, and standardization should improve the completeness and accuracy of pathology reports.

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THE CURRENT STAGING SYSTEM OF COLORECTAL CARCINOMA: GENERAL CONSIDERATIONS

Significant improvements have been made in the staging system of colorectal carcinoma (CRC) since the classical proposals by Dukes and Jass. The original 1932 Dukes classification,1 devised for rectal cancer, was based on the extent of disease, as evaluated by the degree of tumor infiltration through the bowel wall, and the presence or absence of lymph node involvement. This staging system underwent several subsequent modifications by Dukes himself and other investigators,2–4 but problems included the lack of consideration for the extent of lymph node involvement, the tumor grade, and other pathologic features of tumors. In 1987, Jeremy Jass addressed some of these issues by adding 2 biologically oriented tumor characteristics, that is, the nature of the advancing front of the tumor (pushing or infiltrating) and the presence or absence of lymphocytic infiltration at the advancing edge.5

A major criticism of this classification, however, concerns the weak interobserver reproducibility of these features.6

Although the current 6th edition of the TNM staging system for CRC, published by the International Union against Cancer (UICC),7 still relies predominantly on the assessment of the anatomic extent of disease at the time of diagnosis, it has several undoubted advantages over the previously reported staging systems. First, it includes a full stratification of the bowel wall involvement and the peritoneal serosa and takes into account the number of regional lymph node metastases. Secondly, it is multidisciplinary in design, incorporating both clinical (pretreatment classification: cTNM) and pathologic (postsurgical classification: pTNM; postsurgical and after preoperative chemoradiotherapy: ypTNM) staging approaches, thereby fitting with modern concepts of multimodality therapies. Thirdly, it is dynamic, since it has been subjected to a continuous updating through an ongoing expert review of existing data,8–9 resulting in several editions following one another over time. The major changes made in the last 3 editions7,10,11 are listed in the Table and will be considered in some detail in the next sections.

Although many factors have been proposed as useful independent prognosticators of recurrence and overall survival in CRC,12–14 tumor stage still continues to play a fundamental role in the management of patients as the most powerful and reliable predictor of prognosis.15 Moreover, it represents the operational basis for choosing the most appropriate therapy and for evaluating the efficacy of different therapeutic methods through the comparison of expected survival rates. In this scenario,
cancer staging is an essential component of patient care, cancer research, and control activities, even in light of the impressive progress that has been attained in the fields of clinical strategies and molecular medicine.

As the structure of TNM classification of CRC is basically quantitative (pT1 to pT4 according to the involved layers of the intestinal wall and pN1 or pN2 according to the number of metastatic lymph nodes), the insertion of qualitative features related to either the pT or pN category could alter the inherent essence of this classification approach. However, the inclusion of non-anatomic factors seems necessary to better estimate prognosis and plan treatment, avoiding the potential risk of considering TNM system insufficient for clinical use.

When pathologists examine a CRC specimen, they are taking a single snapshot of the tumor at a given time, thereby providing information on the extent of tumor diffusion. A quantitative assessment of tumor extension, however, is insufficient to provide additional diagnostic, prognostic, and possibly predictive information required to plan the best therapeutic strategy. In other words, it is also essential to make a qualitative evaluation of the tumor itself that documents its aggressiveness and provides information on how to prevent progression.

Usually, chemotherapy is administered if the tumor has involved regional lymph nodes or if adverse prognostic factors are present.

Tumor spread may proceed by the invasion of nerves, lymphatic vessels, and veins, with consequent lymph node and visceral metastases or by transperitoneal spread leading to carcinomatosis. However, it may be extremely difficult to recognize the association of the tumor with such exploited structures. This is the case with the destructive invasion of veins that may be hard to identify if residual remnants of vascular channels are not visible or when hidden colonization of the peritoneal layer remains out of sight.

TUMOR INFILTRATION THROUGH THE INTESTINAL WALL AND BEYOND (pT1–4: STAGES I–II)

Patients actually may be cured, particularly for low-stage tumors that are confined to the intestinal wall and with no regional lymph node metastases. Accordingly, no adjuvant therapy is planned for pT1-2pN0 tumors, independent of the morphologic characteristics. This is different for pT3pN0 tumors, stage IIA tumors according to the American Joint Committee on Cancer (AJCC) and UICC and B2 tumors according to the modified Astler and Coller classification. These tumors represent a wastebasket category including lesions with unpredictable behavior, for which there may be concern that the disease is really “early” and low risk. In this event, if adverse prognostic indicators are present, such as high-tumor grade, vascular invasion, and tumor budding, the neoplasm is at high risk for recurrence, providing indications for adjuvant therapy.

The involvement of peritoneal surface (pT4) and the acute presentation of intestinal wall perforation but still without lymph node involvement (AJCC/UICC stage IIB and B3 tumors of the modified Astler and Coller classification) also identifies high-risk disease requiring adjuvant therapy.

The strong prognostic impact of the T4 category and the chemotherapy effect may possibly explain the paradoxical difference on survival, which is worse with T4N0M0 (stage IIB) than with T1-2N1M0 (stage IIIA) disease, when applying the criteria of the TNM 6th edition.

Consequently, prognostic indicators have to be accurately documented in the pathologic report, particularly when the tumor has spread into perivisceral fat. The following paragraphs take into account a reasoned selection of the most important predictors of prognosis.

Tumor Grade

Although tumor grade is consistently recognized as an important prognostic parameter, there is at present no consensus on grading system, with different proposals based on 2-, 3-, or 4-tiered stratifications and significant degrees of interobserver variability (Figure 1).

Another source of variation derives from the differences in tumor grading between the superficial part of a tumor and the invasive front, where tumors are generally less differentiated. In practice, the method for assessing tumor grade varies greatly, since it can be based solely on percentage of gland formation or on the worst pattern,

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Abbreviations: ITC, isolated tumor cells; TDs, tumor deposits.

Figure 1. Difficulties in assessing tumor grade: the top right of the slide shows a high-grade lesion, whereas the lower left shows a low-grade lesion (hematoxylin-eosin, original magnification \( \times 20 \)).

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regardless of its relative amount. An interesting proposal has been made recently by Ueno et al^{23} that takes into account the extent of poorly differentiated component of CRC, defined as a tumor area with no glandular formation, irrespective of mucin-producing or invasive growth pattern. Grade 3 was applied to tumors for which the poorly differentiated component fully occupied the microscopic field of an ×40 objective lens. For tumors having a smaller component, cancer clusters composed of at least 5 cells, but not forming glands, were counted in the microscopic field of an ×4 objective lens where the clusters were the most common. Tumors with less than 10 clusters were classified as grade I and those with at least 10 clusters as grade II. Grade I tumors demonstrated 99.3% cancer-related 5-year survival rate; grade II, 86.0%; and grade III, 68.9%, independent of pT and pN stage.^{23}

### Tumor Budding

In the past few years, the difficulties encountered in grading CRC have been partially met by distinguishing tumor budding—that is, microscopic clusters of undifferentiated cancer cells at the invasive front of tumor—from tumor grade. The current recommendations are for scoring and reporting these 2 features separately.^{24} However, the reporting of tumor budding generated the same difficulties encountered with tumor grade: although several studies have shown that tumor budding is independently associated with lymph node and distant metastasis and shorter disease-free survival and overall survival, for stages I to III consensus criteria for assessment methods (Figure 2, A through D) and cutoff values have not been yet established.^{34}

### Invasive Growth Pattern and Lymphocytic Infiltration

Although both these features have been shown to have an independent prognostic role, their assessment still remains highly subjective, with significant interobserver variability, in particular when specific definitions or diagnostic criteria are not provided.^{35,36}

**pT3: Spreading Beyond the Bowel Wall**

When tumor extends to the perivisceral fat, this environment elicits important changes, such as epithelial and mesenchymal remodeling that include changes in the shape and motility properties of the neoplastic cells, stromatogenesis, and neoangiogenesis. Moreover, in the perivisceral fat, the tumor cells come into close proximity to anatomic structures that favor metastatic diffusion, that is, lymphatic vessels, neural bundles, and extramural veins.

The complexity in the evaluation of factors related to tumor aggressiveness increases significantly in this setting. The prognostic heterogeneity of pT3 CRC^{37,38} has been addressed by subdividing this category according to the depth of soft tissue invasion by using a 4-tiered (pT3a: $< 1$ mm, pT3b: 1–5 mm, pT3c: 5–15 mm, pT3d: $> 15$ mm)^{39} or 2-tiered stratification ($\leq 4$ mm/$> 4$ mm; $\leq 5$ mm/$> 5$ mm; $< 6$ mm/$\geq 6$ mm)^{38-41} because of existing data indicating that the deeper the tumor invades into the peri muscular tissues, the worse the prognosis.^{37,38,41-43}

However, this measurement is difficult at best, particularly in polyoid tumors (Figure 3) that deform the profile of the muscularis propria or in widely ulcerated tumors that destroy the muscular wall, thereby hampering a correct evaluation of tumor penetration (Figure 4).

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**The Challenge of Malignant Polyps**

Following the development of screening programs that have resulted in a successful reduction of CRC mortality rate, pathologists are frequently asked to exhaustively evaluate malignant polyps in which the malignant component has overtaken the muscularis mucosae and invaded the submucosal layer. Malignant polyps are an early form of invasive CRC but may be associated with metastasis,^{44} local recurrence,^{45} and increased mortality rate.^{46} On the contrary, the risk for distant spreading of intramucosal CRC (that shares with intraepithelial neoplasia the carcinoma in situ category) is very low to nonexistent because of the limited lymphatic drainage within the lamina propria.^{47}

In the current TNM system, malignant polyps are considered as a monolithic group (all staged pT1 tumors), but there is a growing body of literature supporting the need to distinguish them as low-risk lesions (that could lead to unnecessary resections if inappropriately recognized) or high-risk lesions (potentially life-threatening tumors requiring major surgical procedures). A significant fraction of malignant polyps is constituted of high-risk lesions in which local residual disease, in the form of either neoplastic remnants in the intestinal wall or regional lymph node metastases, may be found in 30% to 40% of patients undergoing radical surgery.^{48} Overall, the nodal frequency of involvement from malignant polyps is about 10%,^{49} but this involvement is less than 1% in low-risk lesions and about 40% in high-risk lesions.^{49,49}

The assessment of risk factors in malignant polyps has basically not changed in Western countries since 1993,^{45,50,51} with 3 features defining a malignant polyp as a high-risk lesion, namely, a high grade, lymphatic invasion (L factor), and positive resection margin (R classification). The latter is considered positive when the clearance is 1 mm or less or a high-magnification microscopic field or is included into the band of coagulation artifacts.^{52}

None of these factors, however, can affect TNM tumor staging, at least according to the current rules, although there has been a proposal to subdivide stage I according to the absence or presence of blood/lymphatic vessel invasion.^{16,53} Tumor budding (Figure 2, B and D) seems the best candidate for a refinement of our current classification, but its incorporation into routine surgical pathology reporting is still considered premature^{44} for the reasons previously detailed.

In Asia, a refined microstaging system has been developed that includes histologic features (tumor grade, cribriform pattern, and tumor budding), incorporates different classifications for assessing the extent of invasion specifically conceived for pedunculated (Haggitt classification)^{30} and sessile lesions (Kikuchi classification),^{55} and measures width and depth of submucosal invasion.^{49} Microstaging of malignant polyps should also include the ratio between adenoma and adenocarcinoma components, a criterion based on the assumption that the lower the cancer volume, the lower the metastatic potential. It is difficult, however, to precisely quantify the relative predictive value of these parameters, probably because most studies are retrospective and monoinstitutional, include a relatively small number of malignant polyps, and deal with a multitude of inhomogeneous parameters.^{48,49,52,56}

Large, prospective, multi-institutional, and multiparametric studies dealing with an extensive evaluation of
malignant polyps are clearly warranted—by using adequate step sectioning of polyps to avoid losing significant information—in keeping with the experience of sentinel lymph node examination in breast cancer.57

**Lymphatic and Venous Invasion**

Colorectal carcinoma exploits the lymphatic and venous drainage of the intestinal wall for dissemination to regional lymph nodes and distant organs. Vascular invasion is also an adverse prognostic factor in CRC, since it has been demonstrated repeatedly to be an independent prognostic factor.34,58,59

The detection of small-vessel invasion in malignant polyps serves as an indicator for possible lymph node involvement and, hence, for radical surgery,24,49,60 whereas the diagnosis of vascular invasion in stage II CRC identifies high-risk patients for whom an adjuvant therapy may be administered.17–19 The current TNM classification states that vascular invasion has to be considered among pT-related qualitative features, which predict poor prognosis, but do not affect tumor staging.6,62 Some proposals have already been put forward to include venous invasion among stage-influencing factors in CRC, similarly to renal, hepatic, and testicular tumors.7 However, the reported detection of vascular invasion in CRC ranges from 10% to 89%,58 most likely because of the different criteria used for its identification or because of patient selection. Suffice it to say that in some studies, for instance, no distinction was made between venous and lymphatic vessels,8,12 intramural and extramural venous invasion, or colonic and rectal localization of the primary tumors.66 In this regard, extramural vascular invasion was found to be most predictive of survival.67,68

The diagnosis of vascular invasion in CRC specimens may be exceedingly difficult with conventional hematoxylin-eosin staining alone.69 The use of ancillary techniques such as elastic stain and immunohistochemical markers of endothelial cells facilitates the detection of vascular invasion considerably.58,69–73 Immunohistochemistry to identify vascular endothelium seems more helpful in identifying lymphatic and small–blood vessel invasion,69,74 whereas this does not hold true for identifying venous invasion because the endothelium of many involved veins is destroyed.73 Accordingly, several authors have endorsed elastic tissue stains (Figure 5, A and B) for the detection of venous invasion.76–73

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Figure 2. A, Malignant polyp. B, The arrows indicate budding clusters. C, Lymphatic capillary invasion. D, Cytokeratin AE1–3 immunostaining highlights tumor budding more than hematoxylin-eosin (B). The areas in the boxes in A and D are shown at higher-power magnification in B and C, respectively (hematoxylin-eosin, original magnifications ×40 [A] and ×100 [B]; cytokeratin AE1–3, original magnifications ×400 [C] and ×100 [D]).
Figure 3. Difficulties in measuring the depth of soft tissue invasion for a polypoid lesion. The arrow indicates the muscularis propria bended by the tumor.

Figure 4. Difficulties in measuring the depth of soft tissue invasion for an ulcerated lesion (hematoxylin-eosin, original magnification ×3).

Figure 5. Elastic-hematoxylin-eosin stain (Shikata) highlights vessel wall. A, Suspected peritumoral venous invasion (black arrows) (hematoxylin-eosin, original magnification ×40). B, Elastic-hematoxylin-eosin stain shows intramural vessel invasion, both venous (empty arrows) and arterial (empty arrowhead). Black arrows indicate the sites of suspected venous invasion: there is no vein wall (elastic-hematoxylin-eosin, original magnifications ×40).

Figure 6. Tumor deposits confined to a vascular space (“vascular invasion type”) (hematoxylin-eosin, original magnification ×400).

Figure 7. Tumor deposits other than vascular-invasion type: there is no associated structure and the shape is irregularly round, thus making their classification as vascular invasion or nodal metastasis difficult (hematoxylin-eosin, original magnification ×100).
A different approach for increasing the detection of venous invasion is to examine a larger number of veins by increasing the number of tissue blocks submitted and the number of slides examined,68,71,75 or by submitting tangential blocks in addition to perpendicular blocks.62,71

**Tumor Deposits**

Tumor deposits (TDs) are discrete nodules of adenocarcinoma deposited in pericolonic and perirectal fat. Their prevalence ranges from 6% to 64% in the mesorectum77 and from 17% to 55% along the length of the colon.78,79 Tumor deposits are histologically heterogeneous and may be associated with several types of recognizable anatomic structures such as veins, lymphatic vessels, and nerves, whereas in other cases, tumor cells are seen scattered in small aggregates in the perivisceral adipose tissue. This may account for the different classifications that TDs have undergone over time. For example, Ueno and Mochizuki80 considered as TD all cancer cell aggregations detectable in the pericolonic and perirectal fat and not associated with lymph node metastases, thereby including vessel invasion, perineural invasion, “nodular” pattern, and “scattering” pattern.

The TNM 5th edition introduced the 3-mm rule, providing a classification based exclusively on the size, independent of histologic features. Accordingly, all discrete tumor cell collections in the perivisceral fat were considered as being primary tumor extensions if they were 3 mm or less in diameter (pT category) or as lymph node metastases if larger than 3 mm (pN category).

In the TNM 6th edition,7 the size criterion was abandoned and replaced with shape, thus enabling a tumor nodule in the pericolic/perirectal adipose tissue to be considered venous invasion if the nodule has an irregular contour and as regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node.

The above classifications are limited, since in both TNM editions a single morphologic criterion was indicated. Moreover, the 3-mm rule was based on unpublished data that were subsequently not confirmed,79,80 and the form and contour (shape) criterion, which has become a unique diagnostic clue, is not sufficient to consistently distinguish different types of tumor involvement of the perivisceral fat,79 as it is a source of interobserver variation.79 In the classification by Ueno and Mochizuki,80 on the other hand, lesions of different origin were grouped together, with a consequent overlap in patterns in a certain number of patients.

The same uncertainty encountered in the classification of TDs is clearly reflected in the assessment of their prognostic relevance, inasmuch as these lesions have often been mixed with other types of venous77,80,82,83 or lymphatic invasion,77,81 lymph node metastasis,77 nerve infiltration,77,80–84 or otherwise nonspecified infiltration of the perivisceral fat,80,82,83 thus making it difficult to compare data from different studies. Accordingly, although the results of a recent meta-analysis, based on survival involving 3714 patients, confirmed the consistent adverse prognostic value of TDs, they illustrated differences in the hazard ratios between the different studies.79

Therefore, the prognostic value of these heterogeneous lesions is attenuated by lumping them together. Studies that considered as TDs all those metastatic occurrences not associated with lymph node involvement showed that these lesions, when grouped as a whole, have a prognosis similar to that of stage III disease,82,85 thereby failing to provide evidence to substantiate the inclusion of TDs in the TNM system.79

Recently, in 2 independent studies,78,86 a new approach was proposed for the classification of TDs, which was based on a combination of different pathologic features including shape; morphologic appearance78,86; the presence of lymphoid tissue not organized in the residual lymph node structures78; and the degree of preexistent anatomic structures, including lymphatic vessels, veins, and nerves.78,86

Thus, 3 types of TDs can be identified on the foregoing basis.78,86

1. Tumor deposits confined to a vascular (lymphatic or venous vessel) space: “vascular invasion type”86 (Figure 6). In this event, Cox proportional regression analysis has shown a hazard ratio of 2.5 with prognostic information being greatest when treated as a T factor.86 This categorization is in accord with the current TNM staging system in which V and L are descriptors of the T category.7

2. Tumor deposits other than the vascular invasion type,86 that is, with no evident association with veins and nerves (Figure 7). These lesions are the most intriguing, since their nature is uncertain and they may represent the end product of a variety of processes.79 To avoid a wastebasket category, however, we believe that an enhanced pathologic analysis in these selected cases is necessary, since the examination of multiple levels can assess the actual nature of TDs in many cases,81,84 and using special stains may be helpful (Figure 8, A through C).

Accordingly, when a TD is near the intestinal wall, the review of multiple sections may even exclude the presence of a TD and suggest a continuous growth instead,79 thereby resulting in the assignment of the T category. In other cases, the remnants of preexisting structures may be detected, allowing a correct classification. However, when the nature of such a TD remains uncertain, despite all efforts, or the additional workload is not possible, the most suitable category is the N factor, as demonstrated by Ueno et al.86 Accordingly, such lesions (“extranodal cancer deposits nonvascular invasion-type”)86 showed a hazard ratio of 4.7 that was nearer to nodal involvement than to “aggressive extranodal cancer deposits” (hazard ratio of 8)79 (see below for details).

Some of these TDs are not associated with veins and nerves but are surrounded by lymphatic tissue instead (Figures 8 and 9). The presence of such lymphoid tissue featuring “pericolonic tumor deposits with lymphocytes” correlates with lymphatic invasion and with the occurrence and the extent of lymph node metastases.78 These particular lesions exhibit a less adverse impact on survival in comparison with TDs involving venous vessels or nerves that instead closely correlated with distant metastases.78 Therefore, pericolonic tumor deposits with lymphocytes most likely represent a peculiar pattern of lymphatic invasion.

3. Tumor deposits, extramural venous and perineural type of invasion (Figure 10, A and B). These lesions, like the ones originally described by Goldstein and Turner,81 present an irregular shape and infiltrative appearance,78,81 are not surrounded by lymphocytes (“tumor deposits without lymphocytes”),78 and typically are in close association with large vessels and/or
nerves,76,81,86 thus their strikingly ominous appearance (aggressive extranodal cancer deposits).86

These lesions have been associated with very poor clinical outcome,76,86 independently of tumor stage,76 that is worse by far than lymph node metastases and any other type of vascular invasion.76,86 The other features of these TDs that mirror tumor aggressiveness were their size76,86 and their absolute number.76,81 Therefore, assigning these lesions to the pM category as in-transit metastases of CRC was recently proposed.75 In particular, a suggestion has been made to classify those TDs without lymphocytes that

Figure 8. Enhanced pathologic analysis for a tumor deposit: 3 sections at different levels (A, B, and C). The middle section (B), stained with elastic–hematoxylin-eosin stain (Shikata), shows that the vein is not involved; rather, this is an invasion of lymphatic tissue (hematoxylin-eosin, original magnifications ×200 [A and C]; Shikata, original magnification ×200 [B]).

Figure 9. Tumor deposits surrounded by lymphatic tissue as a result of lymphatic invasion (hematoxylin-eosin, original magnification ×200).

Figure 10. A, Tumor deposit associated with a vein. B, Tumor deposit associated with veins and nerves (arrow) (hematoxylin-eosin, original magnifications ×100 [A] and ×20 [B]).
are associated with veins and/or nerves (aggressive extranodal cancer deposits) as pM1a category, while cases with distant (visceral) metastases would be designated as M1b category, just as with malignant melanoma. Actu-
ally, these TDs resemble metastatic in-transit melanoma, and interestingly, can be encountered in other types of adenocarcinoma; they thus reflect a more generalized and life-threatening mechanism of tumor invasion through preexisting anatomic structures.

Peritoneal Involvement (pT4)

In 2000, the pT4 category, which indicates the greatest local extent of CRC, was split into T4a and T4b subcategories and was incorporated into the TNM Supplement for the TNM 6th edition and into the CAP-approved protocol for the examination of specimens from patients with primary CRC. pT4a indicated tumors invading adjacent structures or organs, and pT4b indicated tumors involving visceral peritoneum, reflecting the fact that several studies demonstrated the adverse effect on outcome of the serosal invasion by tumor. In particular, 2 studies were taken into consideration. The first one showed the adverse prognostic inference for local peritoneal involvement in curative resection of colon cancer according to different patterns of tumor/mesothelium interface. The second study showed that the frequency of distant metastasis is higher in cases with perforation of the visceral peritoneum than in cases with direct invasion of adjacent organs or structures, and that the median survival time after curative surgery is shorter for patients with pT4b tumors than for those with pT4a tumors. Additional studies confirmed the strong negative impact on prognosis of free serosal involvement in colon and rectal cancer.

Such different behavior between pT4a and pT4b tumors is most likely due to the fact that tumor cells present on the free surface of the peritoneum would have a greater opportunity to seed into the peritoneal cavity, whereas tumor cells invading through a serosal surface that had previously become tightly adherent to adjacent structures (or organs) because of florid inflammation and fibrosis (Figure 12, A and B, and Figure 13, A and B) would remain confined. In the latter case, the involved visceral peritoneum would remain covered by the adhesion to adjacent structures or organs, entrapping tumor cells and

Figure 11. Free serosal invasion (T4b). Every macroscopic suspect for serosal involvement (A, box; C, arrows) should be sampled. The confirmation of peritoneal involvement at histologic analysis may be easy in some cases, such as B, in which 1 detaching large tumor island (magnified in the inset) can be seen, or it may require the interpretation of multiple sections, especially in proximity of deep peritoneal clefts (D). The transperitoneal invasion is magnified in the inset in D (hematoxylin-eosin, original magnifications ×20 [B], ×3 [D], and ×400 [insets B and D]).
making seeding into the peritoneal cavity more difficult; in these cases, en bloc resections may be performed safely and are effectively curative.\textsuperscript{91,92}

In the latest protocol for the examination of specimens from patients with primary CRC, however, the definitions of pT4a and pT4b have been inverted with no clear explanation for this change. pT4a now applies when tumor penetrates the visceral peritoneum and pT4b when the tumor directly invades other organs or structures.\textsuperscript{93,94}

Whichever is the more ominous category, peritoneal involvement develops more frequently not where the mesothelial cell-lined surface is flat, but where the peritoneal surface suddenly changes direction, often at an acute angle, within and/or at the end of deep peritoneal crevices adjacent to subserosal lobules of fat (Figure 11, A, C, and D). These clefts are the most common site of peritoneal involvement in CRC,\textsuperscript{95} making it particularly difficult to assess serosal involvement (Figure 11, D) which always requires extensive sampling and/or serial sectioning.\textsuperscript{43}

Besides these considerations, it should be kept in mind that there is heterogeneity in the definition of peritoneal landmark and of peritoneal invasion among different authors.\textsuperscript{96} This heterogeneity is associated with several problems: (1) the very definition of mesothelial surface, which has been intended as either the sole layer of mesothelial cells or in combination with the underlying collagenous basement membrane; (2) the very definition of peritoneal invasion, which may encompass only free-lying tumor cells (possibly the most significant); tumor invasion of the peritoneal/mesothelial surface; or tumor close to, but not involving, the surface. When the peritoneum is denuded or mesothelial cells are only focally recognizable, assessment of the interface between tumor and peritoneal surface is extremely difficult or even

Figure 12. A, Adenocarcinoma in the sigmoid colon with adhesion to the adnexum (top right, salpinx; lower right, inclusion cyst). The peritoneum is replaced by a fibroinflammatory reaction including giant multinucleated cells. In the adhesion site, there is no cancer; the lesion is still T3. B, Magnification of the area in the box in A (hematoxylin-eosin, original magnifications ×3 [A] and ×400 [B]).

Figure 13. A, Adenocarcinoma in the ascending colon (cecum) (the black arrow indicates the ileum) with adhesion to the sigmoid colon (white arrow). B, In the adhesion site, invasion of the muscular wall (empty black arrow) is observed and the tumor becomes a T4a lesion (hematoxylin-eosin, original magnification ×3).
impossible to make; in these cases, some authors used elastin stains to highlight the submesothelial elastic layer as a surrogate hallmark for peritoneal surface.96

THE ISSUE OF STAGE III

In the current7 and previous10 TNM editions, the only feature that has been taken into account for nodal staging has been the number of metastatic regional lymph nodes. Furthermore, the prognostic heterogeneity of stage III CRC95 has been addressed by stratifying the tumors into 3 substages (IIIA: pT1-2pN1; IIIB: pT3-4pN1; and IIIC: pT1-4pN2) and adopting criteria based on the depth of the intestinal wall involvement and the number of metastatic lymph nodes (with a cutoff of 3 positive lymph nodes for pN1 or pN2 categories).98 Missing additional features, however, such as the total number of lymph nodes examined, their size, their position in relation to the primary tumor, and the presence of extracapsular tumor spreading, may account for the remarkable differences in prognosis of patients belonging to the same risk category. In this regard, the prognostic significance of the volume and extent of lymph node metastatic involvement remains unsettled.99,100

With regard to extracapsular tumor spread, this feature has been reported as a negative prognostic factor in several gastrointestinal malignancies,101,102 including CRC.78,103 Considering the topography of metastatic lymph nodes, the precise prognostic value of the N3 category (tumor along a named artery, Figure 14), which was introduced in the 4th edition11 and removed in the 5th,10 remains undefined.

Although Dukes himself modified his staging system by dividing stage C into C1 (with involvement of local lymph nodes) and C2 (with involvement of lymph nodes at the point of ligature),4 the precise prognostic implications of lymph node metastasis location remain currently controversial because such a distant colonization has been supported as an adverse prognosticator in a certain number of studies,104–108 but not confirmed in others.109,110 In addition, these differences may be due to different definitions of lymph nodal stations and/or different surgical approaches.

In this regard, major differences in the extent of lymph node dissection may be related to changes over time in surgical techniques; variability among surgeons in types of resection performed, considering, in particular, high versus low ligation of the inferior mesenteric artery; total mesorectal excision; and extended (lateral) lymphadenectomy for rectal cancer.111–114 The ambiguous definitions of inferior mesenteric lymph nodes are another source of variability.108,114 This lack of standardized methods for lymph node salvage can thus account for differences in tumor staging, making comparison between different institutions unreliable.112 In the Japanese staging system, for example, pN-stage assignment is decided exclusively on the basis of the lymph node metastasis location.115 The most important aspect pertaining to the lymph node issue in CRC staging in Western countries, however, remains the number of excised lymph nodes. There are 2 strictly correlated issues to take into account: the number of

Figure 14. Left hemicolectomy: involvement of apical lymph nodes (the arrow indicates a metastatic lymph node) by a sigmoidorectal cancer (lower third).

Figure 15. Left hemicolectomy: the circumferential (radial) margin (lower third) and the retroperitoneal sigmoidal margin up to the ligature. White arrow, inferior mesenteric artery; black arrow, inferior mesenteric vein.

Figure 16. Macroscopic view of the circumferential radial margin in rectal resection specimens. Positive lymph node close to the inked margin (lower left).
positive lymph nodes, which directly affects nodal staging (pN1, if 3 or less lymph nodes; pN2, if more than 3 lymph nodes), and the total number of lymph nodes excised at the time of surgery, which always should be accurately documented in the pathology report. 43 For the former issue, it is generally accepted that the subdivision into pN1 and pN2 allows nodal stratification of metastatic lymph nodes for stage grouping when matched with pT category. 4,106,116

It is obvious that the detection of metastatic deposits in lymph nodes can be increased by examining multiple sections, 117,118 although the occurrence of small tumor cell deposits (micrometastasis or isolated tumor cells) does not seem to bear independent prognostic implications. 117 It is different for the total number of excised lymph nodes for which 2 main statements have been made: (1) There is a minimum number of lymph nodes required for adequate nodal staging; 119,120 (2) There is no minimum number of examined lymph nodes for accurately staging patients with CRC. 121,122 For practical purposes, it has been suggested that 12 lymph nodes should be considered as the minimum acceptable harvest from a careful specimen dissection. 43 This requirement was incorporated by the National Quality Forum 113 as a quality surveillance indicator.

There is indeed a growing body of literature indicating that a high nodal harvest is related to improved survival in both stages II 120,124,125 and III 126,127 disease. The number of nodes recovered at sampling depends on multiple factors, including patient factors (age, sex, and body mass index), tumor characteristics (size, grade, and stage), 128 antitumor immune response, 129 and disease management (surgical techniques, surgeon and hospital volumes, diligence and experience of pathologist during gross examination, and neoadjuvant therapy). 128–131 Accordingly, the introduction of quality control and training programs in referring hospitals has been shown to increase lymph node examination rates. 128,132

An accurate manual gross dissection of lymph nodes along with dehydration in organic solvents 123 or arterial methylene blue injection 134 has been proposed to improve the node harvest in CRC specimens. A reasonable solution to express the number of metastatic lymph nodes over the total number of harvested nodes with 1 single indicator is to use the ratio between them, which has also been indicated as a strong prognosticator in CRC. 135–139

Another aspect that is not addressed by the current TNM staging system is the different potential for aggressiveness of lymph node metastases, whose appraisal could enable a more accurate prognostic stratification of patients. Along these lines, we have recently demonstrated that expression of fascin, a marker of epithelial cell motility, was detectable in about 60% of stage III colorectal primary tumors and metastases, and that patients with lymph node metastases immunoreactive for fascin experienced a more aggressive clinical course than patients with negative lymph node metastases; this distinction allows an independent stratification into different risk categories for relapse and progression. 140 In other words, we believe that this marker might mirror the different aggressiveness potential of tumor cells not clearly forecasted by simple stage grouping.

METASTATIC DISEASE (pM, STAGE IV)

Stage IV is the most advanced stage of the TNM system. It is no longer considered a monolithic entity, 141 and several proposals have been advanced for stratifying it. 142,143

Specifically, the current staging system does not take into account the improvements that have been made in surgical techniques for resectable metastases and the impact of modern chemotherapy on rendering initially unresectable CRC liver metastases operable, while at the same time distinguishing between patients with a chance of cure at presentation and those for whom only palliative treatment is possible. 143

Furthermore, it has been shown that R1 liver resection is not an independent predictor of poor overall survival in patents treated with chemotherapy and repeated surgery, and the survival is similar to that of R0 resection (despite a higher recurrence rate); the contraindication of R1 resection should be revisited in the current era of effective chemotheraphy 144 and of expanded criteria for resectability of hepatic colorectal metastases.

ASSESSING THE REGRESSION OF TREATED RECTAL CARCINOMAS (yTNM): AN OPEN ISSUE FOR THE PATHOLOGIST

Difficulties encountered in assigning pT and pN categories have been exacerbated when staging rectal carcinomas resected after neoadjuvant therapy.

yT Category

A few critical issues should be pointed out.

1. Although ypT can be used as a measurement for tumor downstaging, by following the same rules as untreated cancers, tumor remnants might be left behind in surrounding tissue, resulting in inadequate determination of T stage. 145

2. Finding or excluding the presence of tumor remnants after an adequate surgical specimen sampling requires that at least 5 blocks be taken from the center of the lesion or the entire area if no macroscopic tumor is visible. 24,146 If no tumor is found after routine microscopic examination, multiple step sectioning should be considered, 24 or at least 3 cut levels through each block, as suggested in the capecitabine, oxaliplatin, radiotherapy, and excision (CORE) phase II study, 146,147 to assure reliable staging. 24

Obviously, the pathologist should be informed about the precise location of the tumor before radiochemotherapy in order to target tissue sampling effectively. 24

The current TNM 6th edition states in its supplement booklet 24 that only viable tumor cells should be taken into account for staging purposes and not signs of regressed tumor tissue such as scars, fibrotic areas, fibrotic nodules, granulation tissue, and mucin lakes in either intestinal wall, perivisceral fat, or regional lymph nodes. This is in stark contradiction to what was previously stated in the 2nd edition of the TNM Supplement, 46 which reports that ‘ypTNM should consider not only viable tumour cells but also signs of regressed tumour tissue such as scars, fibrotic areas, fibrotic nodules, granulation tissue, mucin lakes, etc.’ An important consequence of this statement is that tumors with the same histologic characteristics could undergo different staging or inappropriate adjuvant treatments if pathologists are not aware of these practical implications.

3. Having to choose among several proposed regression indexes that have been advanced to quantify pathologic responses, together with the variation in the definitions used in different studies, is associated with poor reproducibility. 145,146

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Although several studies showed a correlation between tumor regression and disease-free survival (DFS)\textsuperscript{151-155} and overall survival\textsuperscript{156}—and it has been argued that the regression index may predict DFS more reliably than downstaging\textsuperscript{152}—some studies failed to confirm the independent impact of tumor regression on overall survival\textsuperscript{157} and DFS in multivariate analysis.\textsuperscript{158} Other studies actually concluded that pathologic stage is more accurate in predicting DFS than tumor response,\textsuperscript{158} while some indicated no correlation with overall survival and DFS.\textsuperscript{159,160}

\textbf{yN Category}

As chemoradiotherapy induces significant nodal downstaging with fewer positive lymph nodes, with a median of only 2 involved nodes,\textsuperscript{159} and because proximal lymph node involvement (along the trunk of inferior mesenteric artery) seems to be an important prognostic factor,\textsuperscript{160} the utility of ypN category has been seriously challenged, and a new classification incorporating lymph node location has been advocated.\textsuperscript{161}

Moreover, since preoperative radiochemotherapy for advanced rectal carcinoma also may result in a significant decrease of lymph nodes retrieved, besides the fewer lymph node metastases,\textsuperscript{159} it is not clear if the minimum acceptable harvest of 12 lymph nodes still applies to these cases, since the use of the ‘‘x’’ suffix is discouraged when few lymph nodes have been assessed.\textsuperscript{160}

Another feature to consider is that neoadjuvant therapy may render negative an unknown number of initially positive nodes, making ypN0 a heterogeneous group of tumors for patients who had initially node-negative disease and for patients whose metastatic tumors responded well to treatment.\textsuperscript{145}

\textbf{yM Category}

The assessment of pathologic response of colorectal liver metastases after preoperative chemotherapy was evaluated recently in 2 large studies. One study (n = 112 patients) used a semiquantitative analysis of the proportion of viable cells remaining, with a scale of 1 to 5.\textsuperscript{161} In the second (n = 305 patients), a semiquantitative analysis of the proportion of residual cancer cells in relation to the total tumor area was performed.\textsuperscript{162} In both studies, the pathologic response predicted postoperative survival,\textsuperscript{161,162} suggesting a new outcome end point after hepatic resection of colorectal metastases\textsuperscript{162} (and thus a further task for pathologists).

\textbf{Additional Descriptors and Auxiliary Classifications}

The primary role of every staging system is to stratify patients into prognostically and therapeutically homogeneous groups.\textsuperscript{18} In the previous sections, we showed that this role is not completely fulfilled by the current TNM system, as demonstrated by the prognostic heterogeneity of diverse tumors stages, including early CRC (malignant polyps). We also discussed the nonanatomic factors that enable high-risk tumors to be identified within each stage. Since all these factors are ineffective for changing category and stage, despite their established importance, they were inserted as prefixes and suffixes, as optional (“L,” “V,” and “C”) or additional (“m,” “y,” “r,” and “a”) descriptors— their presence indicating cases needing separate analysis\textsuperscript{15}—or as (“X”), cases in which there was lack of information or uncertainty in assigning a given category.\textsuperscript{160}

Moreover, since the TNM parameters do not encompass a descriptor of “tumor remaining in the patient” after primary surgical resection,\textsuperscript{43} the TNM system embraced an auxiliary classification, the “R” classification (RX, R0, R1, R2), which denotes the absence or presence of residual tumor after treatment. It describes the amount of residual tumor as macroscopic or microscopic,\textsuperscript{161} reflects the effect of treatment, influences further therapeutic procedures, and is a strong predictor of prognosis.\textsuperscript{39,163}

The relevance of such R classification for the pathologist is primarily related to resection margin evaluation. Tumor present microscopically or macroscopically at a resection margin corresponds to R1 or R2, respectively.\textsuperscript{43}

Since proximal and distal resection margins that are usually provided separately by the surgeon are very rarely involved unless close to tumor (<2 cm),\textsuperscript{2} their histologic examination may be neglected when adequately distant from the tumor (3 or 5 cm according to different authors).\textsuperscript{8} On the contrary, it is mandatory for the pathologist to assess the status of the circumferential (radial) resection margin, which represents the retroperitoneal or perineal adventitial soft tissue margin closest to the deepest penetration of tumor. This margin is created by blunt dissection of the retroperitoneal or subperitoneal aspect, respectively, when excising large bowel segments, which are either incompletely encased (ascending and descending colon, upper rectum) or not encased (lower rectum) by peritoneum (Figures 15 and 16).\textsuperscript{43,94}

In rectal cancer, this margin has been indicated as the most important.\textsuperscript{43} Its involvement (expressed by a distance equal to 0 mm, at most 1 mm, or at most 2 mm according to different definitions)\textsuperscript{164,165} is independently associated with shorter overall and disease-free survival,\textsuperscript{164,166,167} either when no preoperative therapy has been given or after neoadjuvant therapy (both radiotherapy and radiochemotherapy).\textsuperscript{157,165} Therefore, a meticulous pathologic analysis, both macroscopic and microscopic, is needed to assess the status of circumferential resection margin and to report the distance from the tumor and the mode of its involvement (Figure 16).\textsuperscript{164,166,168,169}

Similar accuracy is deserved for the evaluation of the deep or nonperitonealized resection margin of the other large bowel segments, for example, cecum and ascending/descending colon (Figure 15).\textsuperscript{24,170,171}

The use of enhanced pathology in the evaluation of CRC specimens for assessing various prognostic factors (with multiple blocks, multiple sectioning, and special staining techniques) or for documenting therapy effects merits the regular use of these auxiliary descriptors.

One of the strengths of the current TNM staging procedure is that the system “has a comprehensive set of definitions and rules of application that ensure uniform use,”\textsuperscript{8} but it may become limiting if many exceptions occur to rules (eg, cases needing separate analyses), with the risk that expansion with optional or additional terms will prevent uniform use.

Currently, the most important challenge for the pathologists and clinicians is how to integrate the anatomic factors with the increasing amount of nonanatomic descriptors,\textsuperscript{15} either molecular or morphologic. Considering the impressive progress in molecular medicine, the question of a molecularly oriented staging system is particularly current.
Toward a Molecular Staging of CRC

None of the various molecular factors thus far described in CRC\(^\text{13,172}\) has unequivocally entered clinical practice, with the remarkable exception of KRAS gene mutation testing, which is thought to be highly predictive of efficacy for anti-epidermal growth factor receptor therapy in metastatic CRC.\(^\text{172}\) Another promising factor is microsatellite instability, which has shown prognostic\(^\text{172,174–176}\) or predictive value.\(^\text{177,178}\)

As the search for a single molecular marker has been somewhat discouraged, given the genetic and biologic tumor heterogeneity of CRC,\(^\text{177}\) a different approach, based on the identification of clustered genetic alterations and multimarker phenotypes, is gaining wider acceptance. Recent studies have investigated the prognostic and staging potentialities of several molecular techniques, such as microarray gene expression profiling,\(^\text{180,181}\) membrane arrays,\(^\text{182}\) polymerase chain reaction sequencing,\(^\text{183}\) and immunohistochemistry.\(^\text{184–186}\) The resulting molecular characterization has allowed CRC to be grouped into diverse, discrete subtypes, each evolving through independent evolutionary pathways,\(^\text{179}\) in which different genetic alterations (mutations of APC, Braf, KRAS, and TP53; microsatellite instability; and DNA promoter hypermethylation)\(^\text{187}\) have been integrated with patient (gender) and tumor characteristics (location, histotype, grade, budding, inflammatory infiltrate, and serrated architecture).

An independent prognostic advantage of this multiple marker approach has been advocated over the well-established prognostic factors,\(^\text{181,184,185,188}\) thus paving the way toward a molecularly oriented staging system of CRC.

CONCLUSION

The optimal staging system of CRC should encompass both anatomic and nonanatomic factors, the latter including molecular and treatment factors. In addition to strictly tumor-related descriptors that have been advanced in the staging system, such as advancing margin, lymphocytic infiltration,\(^\text{3}\) venous invasion,\(^\text{63–65}\) tumor deposits,\(^\text{76}\) budding,\(^\text{27}\) circumferential margin status,\(^\text{145}\) distribution of lymph node metastases in rectal cancer,\(^\text{150}\) and feasibility of visceral metastases resection,\(^\text{143}\) there are also genetic characteristics (gene expression profiling patterns, clustering of genetic alterations, and multimarker phenotypes) that represent potential complementary adjuncts to tumor classification. These tests could become an integral part of a future staging system, in association with more traditional morphologic features, able of enhancing the prediction of patient outcome and ultimately allowing tailored therapy and improved patient care.\(^\text{15}\)

TAKE HOME MESSAGES

- The current CRC staging system is essentially based on anatomic descriptors referring to intestinal wall and peritoneal (pT1–pT4) infiltration, the number of involved regional lymph nodes (pN0–pN2), and occurrence of distant metastasis (pM). However, the role of nonanatomic factors, both morphologic and molecular, is becoming more relevant to prediction.
- However, it is difficult to calibrate the relative importance of these nonanatomic factors and provide a unitary proposal on the minimal panel of markers to be used for every case of CRC.
- There is an emerging need to further stratify patients with the same tumor stage or to improve tumor staging for planning most appropriate treatments. This consideration holds true especially for earlier-stage disease (stages I and II), for which the main question still remains as to whether further surgical procedures (for stage I) or adjuvant therapy (for stage II) are indicated according to the individual risk attribution.
- In a time of effective multimodality treatments, there is a need for the incorporation of treatment-related factors, such as circumferential margin assessment, in rectal cancer.
- There are open questions regarding (1) the precise classification of tumor deposits, (2) the subdivision of pT3 and pT4 categories, (3) the lack of consideration for nodal staging of the recovered lymph nodes (number and location), and (4) the best evaluation of tumor regression after neoadjuvant therapies.
- Enhanced pathologic analysis facilitates the detection and assessment of morphologic factors and allows assessment of the nature of most of them. The pathologist should be given sufficient time and resources to achieve and maintain the ability to perform this enhanced analysis.
- Agreed-upon standard protocols and standardization should be used for compiling pathology reports of CRC and malignant polyps, focusing particularly on factors that are underreported or that showed poor reproducibility among pathologists.
- Although phenogenotyping of CRC has not been incorporated into a definite staging algorithm thus far, the ultimate goal is the integration of morphologic and functional (biologic) information to create a more effective prognostic and predictive model.

References


