

**RECOMMENDATIONS FOR THE REPORTING OF SURGICALLY RESECTED
SPECIMENS OF COLORECTAL CARCINOMA**

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Scope of guidelines

The reporting of colorectal cancer is facilitated by the provision of a checklist giving the features required for good patient care. However, the practicalities of applying such a checklist may not be straightforward. Familiar examples include finding the prescribed number of lymph nodes, distinguishing mesenteric tumor deposits from replaced lymph nodes, and deciding if a cluster of malignant cells in a lymph node sinus counts as a metastasis. Checklists have traditionally focused on prognostic factors and particularly tumor stage. It is becoming increasingly clear that additional factors, whether these are morphological or molecular, will be needed for future clinical management. It is also evident that prognosis is strongly influenced by surgical technique, most notably by the introduction of total mesorectal excision in the case of rectal cancer. Adjuvant therapy is playing an increasingly important role in the management of colorectal cancer and it is inevitable that both morphological and molecular markers will be used to predict responses to the expanding range of therapeutic modalities. Neo-adjuvant or pre-operative radiotherapy is being offered to patients with advanced rectal cancer and can greatly modify the pathological findings in the operative specimen. For all the preceding reasons, the work of the diagnostic pathologist has become increasingly complex and demanding. The 6th edition of the TNM classification fails to meet many of the challenges posed by the realities of modern cancer management. In fact, by changing the rules for staging without strong justification and introducing diagnostic criteria that are unhelpful and lacking a good evidence base, there is a real danger that the community of

pathologists will fail to engage with reporting recommendations in a standardized manner and that the quality of reporting will fall.

Quality reporting is facilitated by the development of checklists that are simple to use and encompass the most important pathological features. The checklist represents “what”, but will not be applied in a consistent and reproducible manner unless it is supported by “why” and also by “how”. At the same time the following guideline is not intended as a detailed treatise on dissection and histological examination. It merely serves to identify the more controversial and difficult components of reporting and to offer practical advice that will directly meet the needs of pathologists as well as benefiting other clinicians and ultimately the patient. In general we have followed and built upon the recommendations of AJCC 6th edition Cancer Staging Manual, the guidelines of the College of American Pathologists (CAP), and the TNM classification of intestinal tumors. We have varied from these recommendations only where we have identified elements that are clearly ambiguous and we have then reached consensus on alternatives that are more evidence-based and/or conform to a more practically-based approach. We cannot eliminate subjectivity and arbitrariness altogether (there are clear elements of both in ostensibly objective TNM staging) but trust that in difficult cases pathologists will be able to use their training, experience and commonsense to reach an informed decision.

Features the Association recommends for inclusion in the final report are selected on the basis that they are generally accepted as being of prognostic importance, required for therapy and/or traditionally expected.

A. Gross description

1. How the specimen was received: fresh, in formalin, opened, unopened, etc.

2. How the specimen was identified: labeled with (name, number) and designated as (e.g. right hemicolectomy).

3. Parts of intestine included: length of each segment, other structures included (e.g. terminal ileum, appendix, anal canal, attached/adherent organs, identified vessels).

4. Tumor description.
 - a. Site within colorectum. In the case of rectal cancer state the distance of the most distal point of the anterior peritoneal reflection from the distal margin and the length of the tumor above and below the reflection. State, if possible, the quadrant showing the site of deepest tumor invasion (anterior, right lateral, posterior and left lateral) and estimate the proportion of the circumference that is involved (multiples of 10%).

 - b. Distance (cm) to nearest margin (given as distal or proximal, if known). Distance from circumferential or radial margin is based on microscopic evaluation (see B.9 below)

 - c. Gross subtype (e.g. polypoid, ulcerating, structuring, annular, infiltrative, linitis plastica).

- d. Dimensions (state longitudinal and transverse dimensions, unless tumor is circumferential).
- e. Macroscopic depth of invasion (the final T stage requires histological confirmation).
- f. Appearance of serosa deep to tumor (e.g. retracted).
- g. Appearance of mesorectal excision in the case of rectal cancer (complete when invested by shiny fascia and with only minor breaches <5mm across, nearly complete but with breaches in fascia greater than 5mm, incomplete with breaches extending to the muscularis propria).¹

Note: Consideration should be given to transverse slicing of well-fixed but unopened rectal specimens for the assessment of mesorectal spread and clearance at the circumferential resection margin (painted with ink prior to fixation).² This procedure avoids distortion of the mesorectum that occurs when opening the specimen anteriorly (where the mesorectum is thinnest). Digital photographs of the bowel rings also provide a direct comparison with slices obtained by imaging modalities and are useful for surgical correlation. The various measurements of the tumor can be reconstructed from the rings. Routine blocks for histology can be taken from the rings following photography.

5. Presence of features of obstruction (proximal dilatation).

6. Presence of perforation.

7. Additional pathology (e.g. polyps, inflammatory bowel disease, diverticular disease).

8. Lymph nodes identified.

9. Tissue submitted for special investigation.

B. Diagnostic information

1. Site of tumor and part of bowel resected.

2. Histological type: the WHO/UICC classification of colorectal adenocarcinoma is recommended.³

- a. Adenocarcinoma, NOS.
- b. Mucinous carcinoma (>50% mucinous).
- c. Signet ring cell carcinoma (>50% signet ring cells).
- d. Squamous cell carcinoma.
- e. Adenosquamous carcinoma.
- f. Small cell undifferentiated carcinoma.
- g. Medullary carcinoma
- h. Undifferentiated carcinoma.
- i. Carcinoid, NOS.
- j. Other (specify).

Note: In mucinous carcinoma 50% of the area of the tumor should comprise epithelium that is differentiated towards mucin production as evidenced by the presence of mucin (identified H&E sections) that is intracellular and/or luminal and/or interstitial. This recommendation differs slightly from the WHO classification of mucinous carcinoma that stipulates that >50% of the tumor should be composed of mucin. It is more meaningful biologically to focus on differentiation by epithelium towards mucin production rather than the amount of mucin that happens to accumulate in distended glands or extracellular pools. Medullary carcinoma has a solid pattern overall, but cribriforming and/or areas of glandular differentiation may identify it as a variant of adenocarcinoma. These tumors show relatively little nuclear pleomorphism. Nuclei are often vesicular with a prominent nucleolus while cytoplasm is abundant and eosinophilic. The tumors are very well circumscribed and are associated with marked lymphocytic infiltration. Many show DNA microsatellite instability and the prognosis is relatively good despite the lack of glandular differentiation. We recommend that medullary carcinoma should not be graded (grade not applicable). While tumor typing does not have major prognostic significance, the fact that certain types (mucinous and signet ring as well as medullary) are associated with DNA microsatellite instability and Lynch syndrome (hereditary nonpolyposis colorectal cancer) provides a justification for reporting these variants.⁴

3. Histological grade: A modification of the WHO/UICC classification is recommended.³

- a. Well differentiated: Simple or complex tubules, easily discerned nuclear polarity, uniformity of nuclear size, close resemblance to benign precursor lesion.
- b. Moderately differentiated: Less regular glandular differentiation, nuclear polarity poorly discerned or lost.
- c. Poorly differentiated: Highly irregular glands or loss of glandular differentiation and loss of nuclear polarity.

Note: The terms well, moderate and poor differentiation are equivalent to Grades 1 – 3 in the UICC/TNM/AJCC systems. Grading is subjective, particularly for mucinous carcinoma, but the distinction between low-grade (well and moderate) versus high grade (poor) has been shown to be prognostically useful.⁵ Signet ring cell carcinoma should be Grade III or poorly differentiated. Grade IV applies to undifferentiated carcinoma and is grouped with high-grade. The use of a four grade (I – IV) or a two grade system (low versus high grade) is equally acceptable but we recommend that grading be based on the worst area even if this does not predominate.⁶ However, the worst area should be distinguished from the finding at the invasive margin of focal de-differentiation or tumor budding (see B.4 below). Undifferentiated carcinoma should be distinguished from the relatively undifferentiated medullary carcinoma that is not associated with a particularly adverse prognosis. We recommend that medullary carcinoma should not be graded.

4. Tumor budding.

Note: Tumor budding refers to the de-differentiation or loss of cell cohesion at the invasive margin that gives rise to single tumor cells or small clusters of up to four cells. Tumor budding is associated with poor prognosis, an infiltrative invasive margin, vascular invasion, lymph node metastasis and distant metastasis.⁷⁻¹² Because of the adverse prognostic effect, the possibility of quantifying tumor budding,⁹ and the possible confusion of tumor budding with poor differentiation we recommend that this feature be distinguished from tumor grade and scored separately as present or absent.

5. Depth of invasion: This is based on the T component of the TNM classification.¹³

- a. Invasion of submucosa but not muscularis propria (T1).
- b. Invasion into but not through the muscularis propria (T2).
- c. Invasion through the muscularis propria into subserosal adipose tissue and/or mesenteric fat (T3).
- d. Invasion into adjacent organs (state which) (T4a).
- e. Invasion through serosa with tumor on free peritoneal surface (T4b). State if accompanied by perforation.

Note on spread beyond muscularis propria (T3): The outer edge of the muscularis propria was used initially in the Dukes classification as the line of demarcation for determining whether a tumor was within or beyond the bowel

wall. This practice was followed by the TNM system. T3 indicates spread in continuity beyond the bowel wall and does not apply to either lymphatic or venous invasion within the mesenteric layer. It should be noted that this long established TNM rule does not appear to apply to nodules of tumor in the mesenteric fat that lack the 'form and smooth contour' of a replaced lymph node. These are classified in the T category (i.e. T3) in the 6th editions of the TNM staging system and AJCC staging manual and the CAP guidelines and despite the fact that these examples of discontinuous extramural extension are considered as the likely sequelae of venous invasion.^{13,14} Since such metastatic deposits are usually associated with advanced disease (at least T3 on the basis of direct spread in continuity), most cases will not present a diagnostic dilemma. Occasionally, cancer may spread as far as the outer edge of the muscularis propria but not beyond. If no muscle separates the cancer from mesenteric tissue then the muscle coat should be interpreted as breached (T3). Studies have shown that the extent of spread beyond the bowel wall has prognostic significance in the case of rectal cancer.¹⁵ However, a large study of colorectal cancer showed that the extent of spread beyond the muscle coat had no impact upon prognosis provided that there was no transperitoneal spread (T4b) or involvement of the circumferential resection margin.¹⁶ We recommend giving a measurement of the extent of spread beyond the muscularis propria in mm but not the use of T3 substages. This measurement will necessarily be an approximation only when the muscularis propria has been destroyed by tumor.

Note on invasion through serosa: Although invasion into adjacent organs (T4a) and transperitoneal spread (T4b) are grouped together as pT4 for the purposes of deriving a final stage, there is evidence that invasion through the serosa predisposes to tumor spread within the peritoneal cavity and a particularly poor prognosis.^{17,18} Therefore the peritoneal surface deep to the tumor should be carefully sampled, especially in areas of retraction, and positive findings should be reported separately from invasion of adjacent organs. See also comments on staging below (C.1). The determination of transperitoneal spread is not straightforward. T4b should apply when tumor cells are observed on the free peritoneal surface even if admixed with fibrin. When tumor is within 1 mm of the free peritoneal surface this should be recorded as an indication of possible transperitoneal spread but staged as T3 on the basis that the peritoneum serves as an effective barrier to malignant spread. According to the TNM system, stage T4a applies to the finding of macroscopic adherence of the tumor to adjacent organs. If there is no microscopic evidence of invasion of adjacent organs then the pathological stage becomes pT3. We recommend that the pathological report should refer only to a single T stage that is based on microscopic findings.

Note on Tis: Although the TNM/AJCC classification includes a level Tis to represent either *in-situ* carcinoma or carcinoma showing invasion of lamina propria (intramucosal carcinoma), we note that this practice is based primarily on the aim of achieving a uniform staging system across all organ systems. Because colorectal neoplasia has not been shown to have metastasizing potential until it has

invaded the submucosa we prefer to avoid the term Tis and instead use the term high grade dysplasia (equivalent to high grade intra-epithelial neoplasia). We also note that it is frequently impossible to determine whether or not there is microscopic invasion of the lamina propria except in the rarely encountered situations of poorly differentiated or signet ring cell carcinoma. Adenomas with Tis should be regarded as adenomas and not as carcinomas for the purposes of diagnosis and cancer registration.

6. Lymph node metastases – stated as number of involved nodes and total number of nodes. Using the TNM system, N0 indicates no nodes with metastases, N1 indicates 1-3 nodes with metastases and N2 indicates 4 or more nodes with metastases. This applies only to the regional lymph nodes that directly drain the tumor. Involvement of the nodes obtained from the lateral pelvic wall (e.g. common or external iliac lymph nodes) indicates distant disease and is staged as M1 in the TNM system.¹³ Direct invasion of a regional lymph node should be regarded as a metastasis.

Note on lymph node numbers: All macroscopically evident (palpable and/or visible) lymph nodes in a well-fixed specimen should be dissected and examined histologically.¹⁹⁻²¹ Many factors influence lymph node numbers apart from the care taken in the dissection^{22,23} and the range for node numbers can be from 0 – 100 or more. There is ***no unacceptably low number of lymph nodes*** for an individual dissection but the ***mean number of nodes*** in a series of dissections gives an indication of good practice and should be approximately 12-15. In the

case of rectal cancer and the increasing use of neo-adjuvant (pre-operative) radiotherapy, the mean number may fall below 12 despite an intense search. The decision to return to the specimen when low numbers of lymph nodes are found will depend on whether the person who performed the initial dissection has a proven track-record for finding lymph nodes. The surgeon-pleasing practice of boosting lymph node numbers by submitting extra blocks of mesenteric fat (following an adequate initial dissection) that may contain minute lymphoid aggregates has not been shown to increase the proportion of lymph node metastasis-positive cases or to improve the survival of lymph node negative cases. The reduced survival in stage II cases with few lymph nodes may be due to factors other than under-staging such as depressed tumor immunity.^{21,24,25} In lymph node positive cases it is usual to find one or more of the positive nodes in the mesenteric tissues deep to the tumor (the likely location for sentinel nodes). Therefore it is prudent to be particularly careful in examining extramural tissues deep to the tumor. These sub-tumoral nodes may be included within tumor slices if encased by tumor or dissected out if free.

Note on lymph node sampling for metastases: Multiple slicing of lymph nodes, step-sectioning, immunostaining, and molecular technology will increase the metastasis-positive rate and lead to ‘upstaging’.²⁶⁻²⁸ However, such occult metastatic disease will usually take the form of minute tumor deposits down to cell clusters or even single cells floating in a sinus. The effort of detecting such occult disease is considerable but could be lessened by being combined with *ex*

vivo sentinel lymph node mapping.²⁹⁻³¹ Nevertheless, sentinel node sampling has a false negative rate for lymph node positivity of around 5-10%.²¹ Additionally, there is no consensus that occult metastatic disease detected by immunohistochemistry or other methods discriminates between high- and low-risk groups of patients.³² The 6th edition of the TNM classification has finessed the situation by stating that intra-nodal tumor cell clusters measuring less than 0.2 mm do not constitute metastases and do not affect the N stage.¹⁴ This advice is arbitrary though does make biologic sense and fits with the lack of clinical significance of occult nodal metastases according to the majority of observational data.³² However, we would prefer to base the diagnostic decision not on an imposed size rule but on evidence of establishment of the metastasis. Single cells or small clusters in a sinus should not be equated with lymph node metastasis but should be recorded if seen. Tumor foci that show evidence of growth (e.g. glandular differentiation, distension of sinus, or stromal reaction) should be diagnosed as a lymph node metastasis irrespective of size.

7. Presence of mesenteric tumor deposits.

Note: Histological examination of dissected nodal structures may disclose the presence of nodules of tumor that are not contained within recognizable lymph nodes. These may be either small lymph nodes or lymphoid aggregates that have been totally replaced by tumor or discontinuous foci of tumor within a perineural, perivascular or intravascular location.³³ The 5th edition of the TNM classification

states that such nodules should be counted as lymph nodes if they are greater than 3mm in diameter.³⁴ The 6th edition of the TNM classification recognizes the heterogeneity of these lesions and suggests that they be classified as positive lymph nodes if they occur in the connective tissue of a lymph drainage area and have the ‘form and smooth contour of a lymph node’ (size not stipulated).^{13,14} If they have an irregular contour then they should be classified under T as discontinuous extramural extension (i.e. T3) (see note on T3 stage under B.5 above). The 6th editions of both TNM and AJCC indicate that nodules with an irregular contour may also be coded as venous invasion. Since careful histologic examination of the non-lymph node-like group of metastatic nodules indicates that some cancer foci occur in perineural or perivascular spaces,³³ it is unclear why they should all be classed as intra-vascular invasion. It is probable that many represent metastasis within a minute lymphoid aggregate. The preceding points appear to relate to nodules that were identified macroscopically during dissection and are therefore likely to be larger than 3mm. Metastatic or discontinuous tumor foci that are identified only *microscopically* pose further difficulty. The 6th edition of AJCC cancer staging manual indicates that the presence of multiple *microscopic* metastatic foci in pericolic fat (it is unclear if this is meant to exclude perirectal fat) should be equated with lymph node involvement for the purposes of nodal staging.¹³ The 6th edition of TNM classification of malignant tumors does not discuss the significance of multiple microscopic metastatic foci in pericolic fat.¹⁴ Taken to its logical conclusion, the preceding advice can result in lesions with identical microscopic appearances being diagnosed as either lymph nodes or

vascular invasion merely on the basis of size, number, and anatomical location. It is necessary to disentangle the preceding incompatible suggestions in a way that recognizes the adverse significance of mesenteric tumor nodules but avoids subjective assessments and the use of arbitrary advice relating to either the size or number of lesions. The use of the subjective descriptor ‘form and smooth contour of a lymph node’ may lead to inappropriate upstaging.³⁵ In the light of this finding, the Royal College of Pathologists (United Kingdom) (www.rcpath.org/resources/pdf/UpdatedStatementonTNM61edited.pdf) has elected to recommend that its members follow the guidelines of the 5th and not the 6th TNM classification. The current dilemma can be traced to two facts: (1) the historical precedent of placing too much reliance on an unnecessarily limited set of prognostic variables (such as lymph node status) for the purposes of stratifying patients and making therapeutic decisions, and (2) the impossibility of determining the actual nature of a high proportion of mesenteric deposits. It is recommended that in the situation where small mesenteric tumor deposits cannot be diagnosed as replaced lymph nodes, the total number and the size of the largest deposit should be recorded and the clinician should be made aware that these lesions are likely to be associated with an adverse prognosis.³³ Fortunately, small metastatic deposits in the mesentery tend to be associated with unequivocal nodal involvement so that final N stage is not often determined on the basis of an isolated mesenteric deposit.

8. Other sites biopsied for metastatic disease (e.g. peritoneum, adjacent organs, liver, ovary). Discontinuous peritoneal deposits that are not included in sections of the tumor bed should be counted as distant disease or M1 in the TNM system.

9. Adequacy of local excision: circumferential (deep, lateral or radial), proximal and distal. Assessment of the proximal and distal resection margins is performed routinely in surgical specimens of colorectal cancer, as it is in other organs, but these margins are rarely involved unless close (less than 2 cm) or the tumor is poorly differentiated. In the case of the rectum, the mesorectum below the peritoneal reflection should be inked and following adequate fixation the tumor should be sliced transversely at 2-3mm intervals.³⁶ Alternatively the unopened rectal resection can be sliced into 2-3mm rings (see A.4 above). Tumor slices should be selected for histology on the basis of close proximity of the advancing tumor edge to the inked circumferential margin and the presence in the mesorectum of lymph nodes or veins containing suspected tumor. In the TNM system R0 indicates no margin involvement (or residual disease), R1 indicates microscopic involvement (excision complete grossly), and R2 indicates gross residual disease that was not resected. We do not use R for coding purposes and regard its use as optional. The distance from the advancing edge of the tumor to the closest resection margin should be given in mm. A tumor margin should be regarded as involved microscopically if there is tumor within 1 mm from a resection margin.² This advice is based on a majority of studies though an increased incidence of local recurrence was described in one study when tumor was within 2mm of the circumferential resection margin.³⁷ Similar consideration should be given to the deep or non-peritonealized resection margin in other

parts of the colon (e.g. cecum, ascending colon, and descending colon) and when tumor is growing beyond a section of bowel wall that is retroperitoneal.

10. Pre-operative radiotherapy and tumor regression. Changes secondary to pre-operative radiotherapy include ulceration, fibrosis of submucosa, tumor regression, mucin lakes, calcification, shrinkage of lymph nodes, and down-staging.³⁸⁻⁴⁰ Pathological staging following therapy (designated ypTNM) is based on the finding of viable tumor cells and not on the inferred site of involvement. Therefore mucin pools with no viable tumor should not be used to infer a stage with the ypTNM system. However, it is reasonable to suggest a pre-treatment stage on the basis of the presence of mucin lakes in the bowel wall or lymph nodes. Tumor regression should be scored as: (1) complete or marked, (2) moderate, (3) little or none.⁴⁰ It may be necessary to sample tissues widely to demonstrate complete regression, though the prognosis is unlikely to be affected by the persistence of small tumor foci.⁴⁰ At least five blocks should be taken from the center of the lesion. If no tumor is found then the entire area should be blocked and consideration given to step-sectioning to deem that a tumor has regressed completely. The pathologist should be told the location of the tumor prior to radiotherapy so that sampling of tissues can be targeted efficiently. Given the tendency of radiotherapy to cause lymph node atrophy all deposits of tumor in the mesentery should be equated with lymph node metastasis.

11. Inflammatory infiltrate. A peritumoral inflammatory reaction that includes lymphocytes has been associated with a favorable prognosis but the assessment of this feature is subjective.⁶ Tumor infiltrating (intra-epithelial) lymphocytes and a Crohn-like

reaction are also associated with a favorable prognosis and with the presence of DNA microsatellite instability (occurring in both Lynch syndrome and sporadically).⁴¹⁻⁴⁶ Relatively low numbers of tumor infiltrating lymphocytes have been shown to be both sensitive and specific for the presence of DNA microsatellite instability.^{43,44} We recommend that ten X40 high-power fields be assessed and that tumor infiltrating lymphocytes are scored as present if at least one field shows 5 intra-epithelial lymphocytes. A Crohn-like reaction may be scored as present if at least four transmural lymphoid aggregates are counted in an X4 field.

12. Venous invasion. We advocate the recording of invasion of extramural veins^{47,48} but regard the use of a V code as optional.

13. Other significant disease (e.g. polyps, inflammatory bowel disease, diverticular disease).

14. If it is not possible to provide prognostically important information then this should be stated in the report.

C. Features considered optional in the final report

The following features are considered optional because they represent specific institutional preferences (e.g. the use of staging that requires the specific marking of lymph nodes), there is no widespread consensus with respect to their prognostic

significance, or their assessment is subjective and has been associated with inter-observer variation.

1. Stage: The repeated modifications of the TNM system are not only difficult to keep up with by all those involved with patient care but continue to have shortcomings with respect to the prognostic grouping that are generated. The over-dependence on a static staging system and failure to heed the independent effects of other adverse prognostic features (e.g. incomplete resection, transperitoneal spread, perforation, venous invasion, absence of lymphocytic infiltration, tumor grade and budding, and mesenteric deposits) cannot lead to the best possible prognostic grouping. We regard the conversion of T and N findings into a final stage (I to IV) as optional since critically important information regarding distant disease (M) is rarely known to the pathologist. The TNM Supplement states that the final TNM classification rests with a designated individual who has access to the most complete data.⁴⁹ We also find the proliferation of letters for coding purposes, the changing rules with each TNM edition, and the inevitable differences from organ to organ a source of confusion and irritation. The use of 'p' for pathological staging is very useful in clinicopathological correlation but is redundant in pathology reports. The pathologist is encouraged to place greater emphasis on the accurate identification of prognostic information and including this in the report by means of simple and unambiguous language.

- a. Tis and T0: We advocate the term high grade dysplasia instead of Tis (see B.5 above). When no tumor is found in a surgical resection specimen following

excision of a malignant adenoma, we advocate giving a ‘global’ T1 stage rather than a T0 stage in the situation where both polyp and surgical specimen are available and the findings can be integrated. Stage T0 may be used when it is not possible to review the initial lesion. The prefix yp serves as a useful indication that pathological staging has followed neo-adjuvant therapy. For example, ypT0 serves to indicate histologically proven complete tumor regression following neo-adjuvant radiotherapy.

b. New staging in 6th edition of TNM and AJCC^{13,14}:

Stage II has been stratified as IIA (T3 N0 M0) and IIB (T4 N0 M0).

Stage III has been stratified as IIIA (T1-T2 N1 M0), IIIB (T3-T4 N1 M0), and IIIC (any T N2 M0). The good prognosis of lymph node positive cancers that are limited to the bowel wall has been known for some time.⁵⁰ This IIIA category was included previously as Astler-Coller stage C1. An evaluation of this re-invented stage has shown that the prognosis is better than for stage IIB disease.⁵¹ Whether this is due to the fact that stage III patients are more likely to receive adjuvant chemotherapy or because stage IIB disease includes patients with transperitoneal spread who at high risk of intra-abdominal recurrence is unknown.^{17,18} This illustrates the importance of recording all the discrete elements that are collapsed and lost within the final TNM stage.

c. Perforation and transperitoneal spread: The 6th edition of the TNM system still fails to incorporate the adverse feature of perforation⁵² in TNM staging. Additionally, by failing to separate transperitoneal spread (T4b) and involvement

of adjacent organs (T4a) (both grouped as T4) it will be difficult to determine the basis for the poor outcome of stage IIB disease.⁵¹

2. Results of ancillary tests and special investigations (e.g. (1) diagnostic markers such as differentiation antigens and loss of expression of DNA mismatch repair proteins, (2) prognostic markers such as alterations of TP53 and KRAS, loss of heterozygosity at 18q, DNA microsatellite status, gene expression profiling, (3) adjuncts to staging such as sentinel node sampling, and (4) predictive markers such as thymidylate synthase and EGFR).

3. Specific named lymph nodes. This has disappeared from the 6th edition of the TNM system as has N3 stage. Surgeons may now identify one or more sentinel nodes as part of lymphatic mapping or may sample the apical node. Prognosis worsens progressively with increasing numbers of involved nodes and additional N categories have been suggested on the basis of node numbers.⁵¹

4. Nature of invasive tumor margin as expanding or infiltrating. All cancers infiltrate normal tissues. The term ‘infiltrating’ applies to the subset with extensive and diffuse dissection of normal tissues by tumor regardless of the grade of differentiation and has been linked with a poor prognosis.^{53,54}

5. Peritumoral inflammatory reaction. An inflammatory reaction at the invasive margin that includes a population of lymphocytes has been associated with a good prognosis.

Since the assessment is subjective and more objective aspects of lymphocytic infiltration have been recommended for inclusion in the report, this feature is left as optional (see B.11).

6. Lymph vessel invasion. Invasion of small vessels is particularly important in locally excised colorectal cancer where it serves as an indication for additional possible lymph node involvement and hence for radical surgery.⁵⁵ While identified as a prognostic factor, small vessel involvement is a somewhat subjective feature. The use of an L code is optional.

7. Residual adenoma at the edge of the carcinoma. While unlikely to be of prognostic importance it is logical to note this observation along with the presence of discrete polyps. In addition, serrated polyps have been linked with subtypes of colorectal cancer showing DNA microsatellite instability and/or DNA methylation.⁵⁶

8. Presence of one or more histological features linked with DNA microsatellite instability (mucinous, signet ring cell or medullary type, tumor infiltrating lymphocytes, Crohn-like reaction). The revised Bethesda guidelines recommend testing for DNA microsatellite status if one or more of these features is present and the patient is <60 years of age.⁴

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