

Review Article

Pathologic Assessment of Rectal Carcinoma after Neoadjuvant Radio(chemo)therapy: Prognostic Implications

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Neoadjuvant radio(chemo)therapy is increasingly used in rectal cancer and induces a number of morphologic changes that affect prognostication after curative surgery, thereby creating new challenges for surgical pathologists, particularly in evaluating morphologic changes and tumour response to preoperative treatment. Surgical pathologists play an important role in determining the many facets of rectal carcinoma patient care after neoadjuvant treatment. These range from proper handling of macroscopic specimens to accurate microscopic evaluation of pathological features associated with patients' prognosis. This review presents the well-established pathological prognostic indicators and discusses challenging features in order to provide both surgical pathologists and treating physicians with a checklist that is useful in a neoadjuvant setting.

1. Introduction

Preoperative radiotherapy with or without chemotherapy (RCT) followed by total mesorectal excision (TME) has become a standard treatment for locally advanced rectal cancers [1–4]. The increasing use of RCT in rectal cancer creates new challenges for surgical pathologists, particularly in evaluating morphologic changes and tumour response to preoperative treatment. Various systems have been suggested for grading tumour response to RCT [5–10]. However, the majority of these systems do not consistently correlate with prognosis [11–14], and their reproducibility is poor [11, 15–17]. Moreover, RCT alters the macroscopic and microscopic assessment and prognostic relevance of a few well-recognized pathological features (i.e., tumour and nodal stage, circumferential resection margin, and lymphovascular invasion) [18–20]. For example, difficulty exists when no remaining tumours can be identified on macroscopic examination. In this context, accurate pathological tumour stage (ypT)

depends on how assiduously the pathologists search for residual tumour, as well as on the number of blocks and slide sections processed. In addition, RCT may significantly decrease the number of retrieved lymph nodes [19]. This could cause underestimation of the nodal status in the absence of rigorous lymph node search. Controversy also persists concerning the optimal distal and circumferential margins [21–28]. Thus, surgical pathologists play an important role in determining the many facets of rectal carcinoma patient care after neoadjuvant treatment. These range from proper handling of macroscopic specimens to accurate microscopic evaluation of pathological features associated with patients' prognosis.

The aim of this review is to present the well-established pathological prognostic indicators and discuss challenging features, especially those with clinical impact, in order to provide a checklist that is useful in a neoadjuvant setting, for both surgical pathologists and treating physicians.

2. Macroscopic Assessment of TME Specimen

The TME technique is based on the sharp dissection of the avascular plane between autonomic nerve plexuses and the mesorectum. This operation results in the excision of the rectum enveloped by a mesorectal fat column of 2 to 3 cm. This part of the review presents the methods of assessment of mesorectum quality, circumferential resection margin (CRM), distal resection margin, and lymph nodes.

2.1. Evaluation of the Mesorectum. TME specimen handling begins with assessment of the quality of the mesorectum (Table 1) [29]. Inspection of the mesorectal surface gives the first indication of its quality. Full thickness slicing of the tumour and the mesorectum allows a good assessment of the adequacy of excision and the regularity of the CRM, which is the second indicator of the resection quality.

2.2. Specimen Processing. Quirke et al. [29] and Nagtegaal et al. [30] have developed an approach for the assessment and processing of the TME specimen. This assessment is performed by direct visual inspection of the fresh specimen; the anterior and posterior planes of the mesorectum are photographed to document their smoothness or irregularity. Then, the mesorectal fat is inked; care should be taken not to ink the peritonealized surfaces of the specimen, especially anteriorly, where the serosa extends lower down, as this may produce artifact and lead to difficulty in interpreting serosal involvement by upper rectal tumours that are either circumferential or anterior in their location [31]. Then, the specimen is measured and cut open along the anterior aspect from the top, leaving the bowel intact at a level just above the peritoneal reflection. After placing loose, formalin-soaked gauze wicks into the unopened segment of the rectum, the specimen should be pinned under tension on a corkboard to minimize shrinkage [32]. After an optimal fixation of at least 72 hours, the unopened segment is sliced transversely at 5 mm intervals in order to identify the area of deepest invasion, and the slices are photographed again to keep a record of the quality of the excised mesorectum, the tumour size, localization, and distance to all surgical margins. Concerning tumour sampling, the guideline of the Belgian Project on Cancer of the Rectum (PROCARE; <http://www.kankerregister.org/>), which was adapted from Quirke et al. [29] and Nagtegaal et al. [30], suggests that five initial blocks be taken from the site of the tumour or suspicious area. In cases with obvious macroscopic tumour remnant, in addition to taking the superficial and deepest part of the tumour, sections showing the closest relationship of tumour to CRM or to peritoneal surface as well as those containing the transition from suspicious mesorectal nodules to the CRM should be taken, as this allows proper evaluation of other pathological prognostic parameters [33]. When only mucin pools are found on gross examination, the entire suspicious zone must be sampled for accurate staging purpose, as residual viable tumour cells can be present upon microscopic examination in most cases [7]. Obviously, the pathologist should be informed about the precise location of the tumour before RCT in order to target tissue sampling effectively.

Recommended method for tumour sampling and examination in rectal carcinoma following radio(chemo)therapy and surgery is as follows.

Step 1. Take 5 blocks from the tumour or scarred area (assuming no obvious tumour was found grossly). These should include the superficial and deep part of the tumour as well as the relationship between the tumour and the CRM or peritoneal surface. If there are any mesorectal nodules, blocks containing their relation to the CRM should also be taken.

Step 2. If no viable microscopic tumour is identified within the initial 5 blocks, the entire scarred area should be sampled.

Step 3. If no residual tumour is found after examining sections from the additional blocks, three levels should be cut through each block. If no viable tumour cells are present even after rigorous examination of these sections, complete pathologic response or ypT0 can be reasonably and reliably reported.

2.3. Distal Margin. The distal margin, although less important than the CRM in terms of frequency of involvement and impact on recurrence, is still important to assess. There are two issues to keep in mind when considering the distal margin: the extent of intramural and extramural continuous tumour growth and the discontinuous distal mesorectal spread through lymphatics. In 20% of cases with positive nodes, there is lymphatic spread distal to the primary tumour. Furthermore, in many cases these positive distal nodes are located >2 cm away from the main tumour mass [34]. By contrast, intramural distal spread >2 cm is seen in only 3.6% of cases [35]. Zhao et al. [36] found that the rate of discontinuous tumour deposits within the distal mesorectum was 17.8% and that the extent of distal mesorectal spread was greater than the extent of intramural spread. From their data, they concluded that a 1.5 cm distal rectal wall margin and a 4 cm distal mesorectal margin are necessary to achieve adequate surgical clearance. Yet, in many cases, distal rectal wall margin of ≤ 1 cm also proved to be sufficient in preventing local recurrence, particularly in tumours limited to the rectal wall [37, 38].

One final issue to keep in mind, when measuring the distal margin, is shrinkage artifact. Goldstein et al. [39] have shown that a 5 cm length of colon and rectum in vivo is equivalent to 3 cm after resection and 2.2 cm after fixation. This highlights, once again, the importance of pinning the specimen on a corkboard to reduce the degree of shrinkage.

2.4. Lymph Node Retrieval. Lymph node status probably constitutes the single most important prognostic determinant in patients with rectal cancer whether treated preoperatively or not [40, 41]. International guidelines recommend that at least 12 lymph nodes are needed for adequate CRC staging [42, 43]. Nevertheless, there has been evidence suggesting that preoperative RCT for rectal cancer could reduce lymph node yield by roughly 33% [19, 44]. Despite this finding, a high motivation to retrieve as many nodes as possible must be maintained, since several studies support the concept that

TABLE 1: Assessment of the quality of mesorectal excision or completeness of resection*.

	Complete	Nearly complete	Incomplete
Mesorectum	Intact, smooth	Moderate bulk, irregular	Little bulk
Defects	Not deeper than 5 mm	Unexposed muscularis propria	Exposed muscularis propria
Coning	No coning	Moderate	Yes
CRM	Smooth, regular	Irregular	Irregular

CRM, circumferential resection margin.

* Both the whole fresh specimen and formalin-fixed slices are examined to achieve optimal assessment.

the more the nodes that are examined, the more accurate the staging. Moreover, the ratio of positive to total nodes retrieved, the so-called metastatic lymph node ratio, has been shown to be even more significantly associated with local recurrence and survival [45–47]. A number of adjunctive methods including alcohol treatment, xylene clearance, and ether-based methods have been developed in order to address the challenge of lymph node yield, but most of them require special equipment or the use of noxious volatile compounds [48–50]. Therefore, in many pathology laboratories, routine visual inspection, palpation, and dissection are still the standard of practice for lymph node retrieval, and meticulous examination, as well as the enthusiasm of the examiner, is one of the most important factors in determining the number of lymph nodes retrieved.

Once again, it is important to stress that the lateral mesorectal surface closest to the suspect nodes should be sampled together with the nodes to allow accurate evaluation of the CRM [33]. Thus, the orientation of suspicious perirectal nodules that are closely related to the CRM should be well preserved during the cut-up process, while the normally looking lymph nodes can be harvested in the usual manner, taking care not to overcount nodes that appear in more than one slice due to serial transverse slicing.

3. Microscopic Assessment

3.1. Tumour Histological Type. In the pathological reporting of colorectal cancer (CRC), the internationally accepted histological classification of colorectal carcinomas proposed by the World Health Organization [51] (WHO) is recommended by the College of American Pathologists (CAP) [52]. Based on this classification, the majority of rectal cancers are adenocarcinomas of no special type. Besides a few exceptions, histological type has no stage-independent prognostic significance [52]. The exceptions include the non-gland-forming tumours such as signet-ring cell carcinoma, small-cell carcinoma, and undifferentiated carcinoma, which are prognostically unfavorable [53–55], and medullary carcinoma, which is prognostically favorable [56]. In contrast to the findings in a few studies, mainly limited to univariate analyses, suggesting that mucinous adenocarcinoma may be an adverse prognostic factor [57–60], larger studies did not confirm mucinous histology to be a stage-independent predictor of poor outcome [61–66]. On the other hand, mucinous carcinoma tends to be prognostically favorable when associated with microsatellite instability (MSI) [67–69].

In summary, based on current evidence, it can be concluded that the only histological types of CRC that are prognostically significant are signet-ring cell and small-cell carcinoma (poor prognosis) and medullary and MSI-related mucinous carcinoma (favorable prognosis).

3.2. Tumour Differentiation Grade. In the WHO classification [70], grading of colorectal adenocarcinoma is based on the extent of gland formation. Therefore, the non-gland-forming histological types (e.g., signet-ring, small-cell, and undifferentiated carcinoma) are always regarded as high-grade or poorly differentiated tumours. In most cases, however, the estimation of the degree of glandular formation is subjective, resulting in interobserver variation, mainly in grading well and moderately differentiated tumours. The lack of uniformity in histopathological grading is further complicated by a number of different grading systems without consensus among pathologists [52, 71–73]. At present, the available data are insufficient to support one approach over the other, and the issue remains problematic. Irrespective of the complexity of the criteria, most systems stratify adenocarcinomas into four grades:

- (i) Grade 1: well differentiated (>95% glandular formation),
- (ii) Grade 2: moderately differentiated (50%–95% glandular formation),
- (iii) Grade 3: poorly differentiated (5%–50% glandular formation),
- (iv) Grade 4: undifferentiated (<5% glandular formation).

Nevertheless, the most recent World Health Organization series on tumours of the digestive system recommends using the two-tier grading system (low versus high grade) in grading colorectal cancer [74]. Despite interobserver variation in assessment and the lack of standardization, histological grade has been repeatedly shown by multivariate analyses to be a stage-independent prognostic factor in a nonneoadjuvant setting [75–77]. After RCT, however, its impact on patient survival remains debatable [5, 11, 13, 78–80].

3.3. Lymphovascular and Perineural Invasion. The prognostic significance of lymphovascular (LVI) and perineural (PNI) invasion has been suggested and largely confirmed in a nonneoadjuvant setting [76, 77, 81–84]. Venous invasion has been demonstrated by numerous multivariate analyses to be

an independent adverse prognostic factor in CRC [76, 77, 81, 82, 85–87]. In series of studies identifying the exact location of the involved vessels (i.e., extramural as opposed to intramural location), it was found that the extramural type was most predictive of survival [87–89]. In some studies, LVI, without distinction between venous and lymphatic vessels, has been found to be prognostically significant [81, 90]. More discordant results have been reported for lymphatic vessel invasion alone [91, 92]. It is likely that the disparities among existing studies on vascular invasion are related to inherent problems in the pathological identification of this feature. Definitive diagnosis of vascular invasion requires the identification of tumour within an endothelial-lined channel. However, this may be difficult when tumour induced vascular fibrosis or endothelial destruction is present. In addition, fixation artifact in the tumour may mimic small vessel involvement. For these reasons, interobserver variation may be substantial in the interpretation or recognition of vascular invasion. Additional limitations in the detection of vessel invasion are related to specimen sampling. For example, it has been shown that the reproducibility of detection of extramural venous invasion increases proportionally from 59% with examination of 2 blocks of tissue at the tumour periphery to 96% with examination of 5 blocks [89, 93, 94]. Other studies have suggested that taking various types of tissue blocks such as tangential ones in addition to perpendicular blocks raises the chances of detecting extramural venous invasion [94, 95].

Following preoperative RCT, the prognostic significance of LVI and PNI has been demonstrated in several studies, mostly by univariate analysis [96–98]. A study by Du et al. [97] showed that the disease progression of patients with LVI in irradiated tumours was significantly delayed as compared with that with LVI-positive tumours in nonirradiated tumours. They suggested that the aggressiveness of those tumour cells in the blood or lymphatic vessels may have been significantly weakened by radiotherapy, though they were not completely eliminated. In this respect, the stage-independent prognostic impact of LVI and PNI after RCT needs to be confirmed in larger studies with multivariate analysis.

3.4. Tumour Deposits (TDs). Tumour deposits (TDs) are discrete adenocarcinoma nodules encountered in the pericolic and perirectal fat during routine histopathological examination of advanced CRC specimens. Their prevalence in the mesorectum ranges from 6% to 64% [99–101]. TDs 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 carcinoma cells are seen scattered in small aggregates in the perirectal adipose tissue. This may account for the different classifications that TDs have undergone over time [102–104], particularly in the TNM classification series. Table 2 summarizes the major changes in the last four editions of TNM classification for colorectal cancer.

The TNM5 introduced the 3 mm rule, resulting in a classification based exclusively on size, independent of histological features. Accordingly, discontinuous mesorectal tumour cell

aggregates were considered as being primary tumour extensions (pT category) if measured ≤ 3 mm or as lymph node metastasis (pN category) if > 3 mm [105].

The TNM6 replaced the size criterion with the shape criterion. Based on this classification, discontinuous mesorectal tumour nodules were considered as venous invasion if they have an irregular contour and as regional lymph node metastasis if they have the shape and smooth contour of a lymph node [106].

These two classifications have limited value since the TD classifications are based on a single morphologic criterion (i.e., size or shape). Moreover, the 3 mm rule was based on unpublished data, which were subsequently not confirmed [102, 107], and the shape criterion is insufficient to consistently distinguish different types of tumour involvement of the perivisceral fat [108], being the source of interobserver variation [107]. In 2009, Puppa et al. [103] proposed a new categorization of TDs:

- (i) vascular-invasion type (extramural venous or lymphatic invasion): pT category,
- (ii) non-vascular-invasion type (smooth contour, surrounded by lymphocytes, not associated with veins or nerves): pN category,
- (iii) aggressive TDs (scattering pattern, not surrounded by lymphocytes, having close association with large vessels or neural invasion): pM1a (in-transit metastasis).

The TNM7 again introduced changes regarding the definition and classification of TDs. In the last edition, discrete foci of tumour found in the perivisceral fat or in adjacent mesentery away from the leading edge of the tumour and showing no evidence of residual lymph node tissue are considered to be TDs. If TDs are observed in lesions that would otherwise be classified as T1 or T2, then the primary tumour classification is not changed, but the nodule is classified in N1c category [109].

It seems that the different editions of TNM replace one subjective definition with another. Moreover, they do not appear to have prospectively tested this new TD classification and evaluated its reproducibility, since TNM7 states that a perivisceral nodule should be recorded as a positive lymph node if the nodule is considered by the pathologist to be a totally replaced lymph node (generally having a smooth contour) [109].

In summary, although the existing classifications of TDs need further improvement in terms of reproducibility and prognostic stratification, results from most studies on patients not receiving preoperative RCT indicated a worse prognosis for patients with TDs: increased local recurrence rates, increased development of distant metastases, and decreased survival [107]. In studies by Ratto et al. [99, 110] who looked at the incidence and prognostic impact of TDs in rectal cancer specimen after RCT, TDs occurred in up to 15.40% of cases and their presence was associated with reduced disease-free and overall survival. In contrast, Nagtegaal and Quirke [107] and Quirke et al. [111] considered the presence of TDs as a sign of good response to RCT.

TABLE 2: Major changes in the last 4 editions of TNM classification for colorectal cancer.

Edition (year)	T category	N category	M category	Stage grouping
4th (1987)	—	Introducing N3 category	—	—
5th (1997)	—	Removing N3 category	—	—
	TDs: introducing the 3 mm rule			—
	TDs: replacing the 3 mm rule with the contour rule			Subdividing stage III into IIIA, IIIB, and IIIC
6th (2002)	T4 split into T4a and T4b	ITC considered as N0	—	
	Changes in TD classification			
7th (2009)	—	Subdividing N1 into N1a, N1b, and N1c and N2 into N2a and N2b	M1 split into M1a and M1b	Subdividing stage IV into IVA and IVB

ITC, isolated tumour cells.

Whether or not the presence of TDs after RCT is a stage-independent predictor of poor outcome remains questionable. In daily practice, the presence of TDs must be included in the pathology report, specifying their total number, size, and growth patterns, in order to create more homogeneous groups of patients for enrolment in clinical trials [112].

3.5. Pathological Stage. Pathological staging following complete resection has long been considered the most powerful prognostic indicator in CRC [113]. The same holds true in rectal carcinoma after preoperative RCT [114–116]. Although a large number of staging systems have been developed for CRC over the years, the tumour node metastasis (TNM) staging system of the American Joint Cancer Committee (AJCC) and International Union Against Cancer (UICC) is by far the most widely recommended. Table 2 lists the major changes made in the last four editions [109, 113, 117]. TNM 7th edition received a number of criticisms primarily for the new classification of TDs which lacks both scientific evidence and reproducibility [118, 119]. In reporting CRC, some centers prefer the 5th edition of the TNM classification to the other editions, mainly because of the reproducibility in TD classification [118, 120]. For future evaluation of the prognostic relevance of the changes in TNM classification, however, the 7th edition should be used, yet the conflicting feature, that is, TDs, should be reported in detail with description of their number, size, and growth pattern.

For accurate staging of treated rectal carcinoma, it is important to keep in mind that when microscopic remnants of tumour are not found, the scarred area must be entirely sampled [73, 120]. Moreover, if viable tumour is not present even after examining sections from the whole scarred area, three levels should be cut through each block to exclude residual tumour foci, as suggested in the CORE phase II study [121].

3.6. Acellular Mucin (aMUC). In routine microscopic examination of neoadjuvantly treated rectal carcinoma specimens, mucus pools can be encountered in up to one-third of cases [122, 123]. With regard to this, a few recent studies have demonstrated that the presence of acellular mucin (aMUC) in

rectal carcinoma after neoadjuvant RCT did not have significant impact on patient outcome [122, 124, 125]. de Campos-Lobato et al. looked at the prognostic value of aMUC in rectal cancer patients achieving ypT0 after preoperative RCT and concluded that aMUC did not affect local recurrence but may suggest a more aggressive tumour biology [125]. These findings are in support of the current CAP consensus statement that acellular mucin pools are not to be regarded as residual tumour and that their presence is to be recorded separately from the ypT category [122].

3.7. Local Inflammatory Response. The tumour associated inflammatory infiltrate has long been considered a type of host response and an important prognostic factor in rectal cancer [126, 127]. After preoperative RCT, rectal cancer could undergo tumour regression by eradication of carcinoma cells and replacement by fibrous or fibroinflammatory tissues [123, 128, 129]. Nagtegaal et al. [130] and Shia et al. [123] found that patients with an extensive fibroinflammatory infiltrate around the tumour had lower recurrence rates. Two recent studies by Debucquoy et al. [128, 129] showed a better disease-free survival in rectal cancer patients whose TME specimens contained fibroinflammatory changes after RCT (Figure 1). Overall, a marked inflammatory cell component is not commonly seen in posttreatment rectal tumours [123, 128, 129]. Shia et al. [123] reported that, in 60% of cases, the inflammatory infiltration was only minimal. These findings imply an impaired or inhibited immune function in patients treated with RCT. Accordingly, it can be suggested that patients who maintain a more extensive inflammatory response at the tumour bed after RCT have a better outcome, and this factor is relevant in assessing the prognosis of these patients [123, 128, 129].

3.8. Therapy Response Assessment. Response to RCT ranges from minimal treatment effects to complete eradication of the primary tumour. Some authors used cellular-response grading which is based on the amount of residual viable tumour in relation to stromal fibrosis [5–8, 16, 131], whereas others looked at stage shift in the treated specimens, including tumour and nodal downstaging, when assessing response

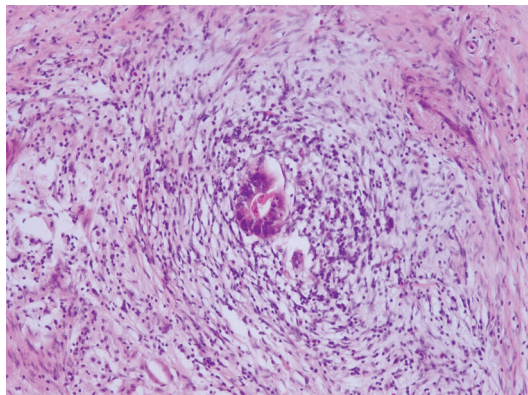


FIGURE 1: Pronounced fibroinflammatory changes after neoadjuvant RCT.

[11, 132, 133]. To date, none of the cellular-response grading systems has gained universal acceptance [11, 134], not only because the majority of them could not consistently predict patient outcome [11–14] but also because their reproducibility is poor, particularly for categories defining moderate to minimal regressive changes [11, 15–17]. On the other hand, evaluation of downstaging is objective and reproducible. Moreover, downstaging has been consistently demonstrated to correlate significantly with improved survival [11, 128, 129, 135]. Nevertheless, no study has investigated the prognostic impact of both cellular-response grading and downstaging in the same study cohort. Some studies [14, 136–138] specifically examined the prognostic impact of pathological complete response (pCR), defined by the complete absence of viable tumour cells in the primary tumour site (ypT0). The precise classification of pCR or ypT0 can be an effort- and time-consuming task provided that residual viable tumour cells could be identified in many cases upon rigorous microscopic examination (i.e., multilevel sectioning of the blocks containing the scarred area) [7, 121]. In this regard, the varying proportion of pCR observed in previous studies might have been due to the difference in dissection and examination methods used in each laboratory. In spite of this variation, the pCR status has been shown, in a few randomised trials and other studies, to significantly correlate with decreased local recurrence rate and improved survival [137–143].

3.9. Circumferential Resection Margin (CRM). On microscopic examination, the distance of the tumour to the CRM may be the single most critical factor in predicting local recurrence (LR) after RCT and surgery [13, 29, 37]. The CRM involvement by tumour also has been shown to predict distant recurrence and overall survival (OS) in some studies [27, 144]. Although the definition of positive CRM varies among studies [27, 28], the majority of them involving several thousands of patients support the use of 1 mm as cut-off value for involved CRM [27]. The methods on which CRM measurement is based have been discussed in a study by Nagtegaal et al. [30] who looked at the difference in LR rates among cases with positive CRM as measured from the deepest point of invasion of the primary tumour and

those with positive CRM as measured from invaded lymph nodes in the perirectal fat. They showed that patients with a positive CRM due to direct tumour extension developed local recurrence more frequently than those with a positive CRM due to positive nodes (22.1% versus 12.4%, $p = 0.06$). However, in the same study, there was no difference in the rate of local recurrence between patients with a positive CRM due to positive nodes compared to those with a negative CRM. As previously described, TDs are a frequent phenomenon in the mesorectum. Nevertheless, to date, no study has examined the prognostic relevance of CRM measurement based on the distance from lateral resection margin to TDs. Therefore, to allow further investigations on the prognostic significance of these two new CRM measurement methods (i.e., based on distance from positive nodes or TDs), it is recommended that, in cases with positive lymph nodes or TDs, practicing pathologists keep a record of the distance from the lateral resection margin to these perirectal tumour nodules in addition to reporting the classic CRM.

4. Summary and Conclusion

Preoperative RCT induces changes in both gross appearance of the surgical specimen and its pathological features, which could have impact on patient management and outcome. First of all, the assessment of the mesorectum is necessary as it is an important indicator of the resection quality. Then, the resected specimen should be sampled and examined properly, as summarized in Steps 1, 2, and 3, warranting not leaving out any prognostically relevant samples, particularly those containing the relationship of the lateral margins with the primary tumour and mesorectal nodules. Standardized protocols for the grossing of TME specimens should be available in order for pathologists, pathology residents, and pathologists' assistants to handle these specimens in a uniform and effective manner. Pathological features that have been consistently reported to significantly influence patient outcome after RCT include posttreatment pathological stage (ypTNM), microscopic status of the CRM, and local fibroinflammatory response, whereas the stage-independent prognostic value of histologic grade, LVI, PNI, and TDs requires further investigation in neoadjuvant setting. Concerning therapy response assessment, downstaging appears to be better than cellular-response grading in terms of both reproducibility and clinical outcome prediction.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

- [1] Colorectal Cancer Collaborative Group, "Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials," *The Lancet*, vol. 358, no. 9290, pp. 1291–1304, 2001.
- [2] C. Cammà, M. Giunta, F. Fiorica, L. Pagliaro, A. Craxì, and M. Cottone, "Preoperative radiotherapy for resectable rectal

- cancer: a meta-analysis," *Journal of the American Medical Association*, vol. 284, no. 8, pp. 1008–1015, 2000.
- [3] "Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial," *The New England Journal of Medicine*, vol. 336, no. 14, pp. 980–987, 1997.
 - [4] E. Kapiteijn, C. A. M. Marijnen, I. D. Nagtegaal et al., "Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer," *The New England Journal of Medicine*, vol. 345, no. 9, pp. 638–646, 2001.
 - [5] C. Rödel, P. Martus, T. Papadopoulos et al., "Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer," *Journal of Clinical Oncology*, vol. 23, no. 34, pp. 8688–8696, 2005.
 - [6] H. Bouzourene, F. T. Bosman, W. Seelentag, M. Matter, and P. Coucke, "Importance of tumor regression assessment in predicting the outcome in patients with locally advanced rectal carcinoma who are treated with preoperative radiotherapy," *Cancer*, vol. 94, no. 4, pp. 1121–1130, 2002.
 - [7] O. Dworak, L. Keilholz, and A. Hoffmann, "Pathological features of rectal cancer after preoperative radiochemotherapy," *International Journal of Colorectal Disease*, vol. 12, no. 1, pp. 19–23, 1997.
 - [8] A.-M. Mandard, F. Dalibard, J.-C. Mandard et al., "Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations," *Cancer*, vol. 73, no. 11, pp. 2680–2686, 1994.
 - [9] R. Ryan, D. Gibbons, J. M. P. Hyland et al., "Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer," *Histopathology*, vol. 47, no. 2, pp. 141–146, 2005.
 - [10] F. M. Vecchio, V. Valentini, B. D. Minsky et al., "The relationship of pathologic tumor regression grade (TRG) and outcomes after preoperative therapy in rectal cancer," *International Journal of Radiation Oncology Biology Physics*, vol. 62, no. 3, pp. 752–760, 2005.
 - [11] A. Rullier, C. Laurent, M. Capdepon, V. Vendrely, P. Bioulac-Sage, and E. Rullier, "Impact of tumor response on survival after radiochemotherapy in locally advanced rectal carcinoma," *The American Journal of Surgical Pathology*, vol. 34, no. 4, pp. 562–568, 2010.
 - [12] C. Jakob, T. Liersch, W. Meyer et al., "Prognostic value of histologic tumor regression, thymidylate synthase, thymidine phosphorylase, and dihydropyrimidine dehydrogenase in rectal cancer UICC stage II/III after neoadjuvant chemoradiotherapy," *The American Journal of Surgical Pathology*, vol. 30, no. 9, pp. 1169–1174, 2006.
 - [13] M. J. E. M. Gosens, R. A. Klaassen, I. Tan-Go et al., "Circumferential margin involvement is the crucial prognostic factor after multimodality treatment in patients with locally advanced rectal carcinoma," *Clinical Cancer Research*, vol. 13, no. 22, pp. 6617–6623, 2007.
 - [14] S. Pucciarelli, P. Toppan, M. L. Friso et al., "Complete pathologic response following preoperative chemoradiation therapy for middle to lower rectal cancer is not a prognostic factor for a better outcome," *Diseases of the Colon and Rectum*, vol. 47, no. 11, pp. 1798–1807, 2004.
 - [15] M. Gosens, J. van Krieken, H. J. Rutten et al., "A critical appraisal of therapy induced tumor regression in rectal carcinoma," *Annals of Oncology*, vol. 17, supplement 1, article I31, 2006.
 - [16] R. Glynne-Jones and N. Anyemene, "Histologic response grading after chemoradiation in locally advanced rectal cancer: a proposal for standardized reporting," *International Journal of Radiation Oncology Biology Physics*, vol. 73, no. 4, pp. 971–973, 2009.
 - [17] A. C. Bateman, E. Jaynes, and A. R. Bateman, "Rectal cancer staging post neoadjuvant therapy—how should the changes be assessed?" *Histopathology*, vol. 54, no. 6, pp. 713–721, 2009.
 - [18] O. Zmora, G. M. Dasilva, B. Gurland et al., "Does rectal wall tumor eradication with preoperative chemoradiation permit a change in the operative strategy?" *Diseases of the Colon & Rectum*, vol. 47, no. 10, pp. 1607–1612, 2004.
 - [19] Y. H. Ha, S.-Y. Jeong, S.-B. Lim et al., "Influence of preoperative chemoradiotherapy on the number of lymph nodes retrieved in rectal cancer," *Annals of Surgery*, vol. 252, no. 2, pp. 336–340, 2010.
 - [20] A. Rullier, C. Laurent, M. Capdepon et al., "Lymph nodes after preoperative chemoradiotherapy for rectal carcinoma: number, status, and impact on survival," *The American Journal of Surgical Pathology*, vol. 32, no. 1, pp. 45–50, 2008.
 - [21] E. Van Cutsem, M. Dicato, K. Haustermans et al., "The diagnosis and management of rectal cancer: expert discussion and recommendations derived from the 9th world congress on gastrointestinal cancer, Barcelona, 2007," *Annals of Oncology*, vol. 19, supplement 6, pp. vi1–vi8, 2008.
 - [22] H. G. Moore, E. Riedel, B. D. Minsky et al., "Adequacy of 1-cm distal margin after restorative rectal cancer resection with sharp mesorectal excision and preoperative combined-modality therapy," *Annals of Surgical Oncology*, vol. 10, no. 1, pp. 80–85, 2003.
 - [23] J. J. Mezhir, K. D. Smith, A. Fichera, J. Hart, M. C. Posner, and R. D. Hurst, "Presence of distal intramural spread after preoperative combined-modality therapy for adenocarcinoma of the rectum: what is now the appropriate distal resection margin?" *Surgery*, vol. 138, no. 4, pp. 658–664, 2005.
 - [24] B. Kuvshinov, I. Maghfoor, B. Miedema et al., "Distal margin requirements after preoperative chemoradiotherapy for distal rectal carcinomas: are < or = 1 cm distal margins sufficient?" *Annals of Surgical Oncology*, vol. 8, pp. 163–169, 2001.
 - [25] A. Rutkowski, M. P. Nowacki, M. Chwalinski et al., "Acceptance of a 5-mm distal bowel resection margin for rectal cancer: is it safe?" *Colorectal Disease*, vol. 14, no. 1, pp. 71–78, 2012.
 - [26] H. M. Khani, K. Smedh, and W. Kraaz, "Is the circumferential resection margin a predictor of local recurrence after preoperative radiotherapy and optimal surgery for rectal carcinoma?" *Colorectal Disease*, vol. 9, no. 8, pp. 706–712, 2007.
 - [27] R. Glynne-Jones, S. Mawdsley, and J. R. Novell, "The clinical significance of the circumferential resection margin following preoperative pelvic chemo-radiotherapy in rectal cancer: why we need a common language," *Colorectal Disease*, vol. 8, no. 9, pp. 800–807, 2006.
 - [28] I. D. Nagtegaal, C. A. M. Marijnen, E. K. Kranenbarg, C. J. H. van de Velde, and J. H. J. M. Van Krieken, "Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit," *American Journal of Surgical Pathology*, vol. 26, no. 3, pp. 350–357, 2002.
 - [29] P. Quirke, P. Durdey, M. F. Dixon, and N. S. Williams, "Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision," *The Lancet*, vol. 2, no. 8514, pp. 996–999, 1986.
 - [30] I. D. Nagtegaal, C. J. H. van de Velde, E. van der Worp, E. Kapiteijn, P. Quirke, and J. H. J. M. van Krieken, "Macroscopic

- evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control," *Journal of Clinical Oncology*, vol. 20, no. 7, pp. 1729–1734, 2002.
- [31] L. Ludeman and N. A. Shepherd, "Serosal involvement in gastrointestinal cancer: its assessment and significance," *Histopathology*, vol. 47, no. 2, pp. 123–131, 2005.
 - [32] N. S. Williams, M. F. Dixon, and D. Johnston, "Reappraisal of the 5 centimetre rule of distal excision for carcinoma of the rectum: a study of distal intramural spread and of patients' survival," *British Journal of Surgery*, vol. 70, no. 3, pp. 150–154, 1983.
 - [33] T. B. Halvorsen, "Tissue sampling and histological grading in colorectal cancer. Are routine sections representative?" *APMIS*, vol. 97, no. 3, pp. 261–266, 1989.
 - [34] E. Morikawa, M. Yasutomi, K. Shindou et al., "Distribution of metastatic lymph nodes in colorectal cancer by the modified clearing method," *Diseases of the Colon and Rectum*, vol. 37, no. 3, pp. 219–223, 1994.
 - [35] K. Shirouzu, H. Isomoto, and T. Kakegawa, "Distal spread of rectal cancer and optimal distal margin of resection for sphincter-preserving surgery," *Cancer*, vol. 76, no. 3, pp. 388–392, 1995.
 - [36] G.-P. Zhao, Z.-G. Zhou, W.-Z. Lei et al., "Pathological study of distal mesorectal cancer spread to determine a proper distal resection margin," *World Journal of Gastroenterology*, vol. 11, no. 3, pp. 319–322, 2005.
 - [37] P. Quirke, "Limitations of existing systems of staging for rectal cancer: the forgotten margin," in *Rectal Cancer Research*, N. Rajagopalan, Ed., pp. 63–81, Springer, New York, NY, USA, 2001.
 - [38] L. Stocchi, H. Nelson, D. J. Sargent et al., "Impact of surgical and pathologic variables in rectal cancer: a United States community and cooperative group report," *Journal of Clinical Oncology*, vol. 19, no. 18, pp. 3895–3902, 2001.
 - [39] N. S. Goldstein, A. Soman, and J. Sacksner, "Disparate surgical margin lengths of colorectal resection specimens between in vivo and in vitro measurements: the effects of surgical resection and formalin fixation on organ shrinkage," *American Journal of Clinical Pathology*, vol. 111, no. 3, pp. 349–351, 1999.
 - [40] S.-C. Chuang, Y.-C. Su, C.-Y. Lu et al., "Risk factors for the development of metachronous liver metastasis in colorectal cancer patients after curative resection," *World Journal of Surgery*, vol. 35, no. 2, pp. 424–429, 2011.
 - [41] S.-G. Yeo, D. Y. Kim, T. H. Kim et al., "Pathologic complete response of primary tumor following preoperative chemoradiotherapy for locally advanced rectal cancer: long-term outcomes and prognostic significance of pathologic nodal status (KROG 09-01)," *Annals of Surgery*, vol. 252, no. 6, pp. 998–1004, 2010.
 - [42] H. Nelson, N. Petrelli, A. Carlin et al., "Guidelines 2000 for colon and rectal cancer surgery," *Journal of the National Cancer Institute*, vol. 93, no. 8, pp. 583–596, 2001.
 - [43] L. P. Fielding, P. A. Arsenault, P. H. Chapuis et al., "Clinicopathological staging for colorectal cancer: an international documentation system (IDS) and an international comprehensive anatomical terminology (ICAT)," *Journal of Gastroenterology and Hepatology*, vol. 6, no. 4, pp. 325–344, 1991.
 - [44] B. Morcos, B. Baker, M. Al Masri, H. Haddad, and S. Hashem, "Lymph node yield in rectal cancer surgery: effect of preoperative chemoradiotherapy," *European Journal of Surgical Oncology*, vol. 36, no. 4, pp. 345–349, 2010.
 - [45] J. W. T. Dekker, K. C. Peeters, H. Putter, A. L. Vahrmeijer, and C. J. H. van de Velde, "Metastatic lymph node ratio in stage III rectal cancer; prognostic significance in addition to the 7th edition of the TNM classification," *European Journal of Surgical Oncology*, vol. 36, no. 12, pp. 1180–1186, 2010.
 - [46] C. L. Klos, L. G. Bordeianou, P. Sylla, Y. Chang, and D. L. Berger, "The prognostic value of lymph node ratio after neoadjuvant chemoradiation and rectal cancer surgery," *Diseases of the Colon and Rectum*, vol. 54, no. 2, pp. 171–175, 2011.
 - [47] W. Ceelen, Y. van Nieuwenhove, and P. Pattyn, "Prognostic value of the lymph node ratio in stage III colorectal cancer: a systematic review," *Annals of Surgical Oncology*, vol. 17, no. 11, pp. 2847–2855, 2010.
 - [48] S. J. Cawthorn, N. M. Gibbs, and C. G. Marks, "Clearance technique for the detection of lymph nodes in colorectal cancer," *British Journal of Surgery*, vol. 73, no. 1, pp. 58–60, 1986.
 - [49] J. W. Hyder, T. M. Talbott, and T. C. Maycroft, "A critical review of chemical lymph node clearance and staging of colon and rectal cancer at Ferguson Hospital, 1977 to 1982," *Diseases of the Colon & Rectum*, vol. 33, no. 11, pp. 923–925, 1990.
 - [50] N. Y. Haboubi, P. Clark, S. M. Kaftan, and P. F. Schofield, "The importance of combining xylene clearance and immunohistochemistry in the accurate staging of colorectal carcinoma," *Journal of the Royal Society of Medicine*, vol. 85, no. 7, pp. 386–388, 1992.
 - [51] J. R. Jass and L. H. Sobin, *Histological Typing of Intestinal Tumours: World Health Organization*, Springer, New York, NY, USA, 2nd edition, 1989.
 - [52] C. C. Compton, "Updated protocol for the examination of specimens from patients with carcinomas of the colon and rectum, excluding carcinoid tumors, lymphomas, sarcomas, and tumors of the vermiform appendix: a basis for checklists. Cancer Committee," *Archives of Pathology and Laboratory Medicine*, vol. 124, no. 7, pp. 1016–1025, 2000.
 - [53] J. B. Green, A. E. Timmcke, W. T. Mitchell, T. C. Hicks, J. B. Gathright Jr., and J. E. Ray, "Mucinous carcinoma—just another colon cancer?" *Diseases of the Colon and Rectum*, vol. 36, no. 1, pp. 49–54, 1993.
 - [54] G. B. Secco, R. Fardelli, E. Campora et al., "Primary mucinous adenocarcinomas and signet-ring cell carcinomas of colon and rectum," *Oncology*, vol. 51, no. 1, pp. 30–34, 1994.
 - [55] B. Brenner, L. H. Tang, D. S. Klimstra, and D. P. Kelsen, "Small-cell carcinomas of the gastrointestinal tract: a review," *Journal of Clinical Oncology*, vol. 22, no. 13, pp. 2730–2739, 2004.
 - [56] G. Lanza, R. Gafà, M. Matteuzzi, and A. Santini, "Medullary-type poorly differentiated adenocarcinoma of the large bowel: a distinct clinicopathologic entity characterized by microsatellite instability and improved survival," *Journal of Clinical Oncology*, vol. 17, no. 8, pp. 2429–2438, 1999.
 - [57] H. C. Umpleby and R. C. N. Williamson, "Carcinoma of the large bowel in the first four decades," *British Journal of Surgery*, vol. 71, no. 4, pp. 272–277, 1984.
 - [58] B. D. Minsky, C. Mies, T. A. Rich, A. Recht, and J. T. Chaffey, "Colloid carcinoma of the colon and rectum," *Cancer*, vol. 60, no. 12, pp. 3103–3112, 1987.
 - [59] D. A. Symonds and A. L. Vickery, "Mucinous carcinoma of the colon and rectum," *Cancer*, vol. 37, no. 4, pp. 1891–1900, 1976.
 - [60] Y. Kanemitsu, T. Kato, T. Hirai et al., "Survival after curative resection for mucinous adenocarcinoma of the colorectum," *Diseases of the Colon and Rectum*, vol. 46, no. 2, pp. 160–167, 2003.
 - [61] B. D. Minsky, "Clinicopathologic impact of colloid in colorectal carcinoma," *Diseases of the Colon & Rectum*, vol. 33, no. 8, pp. 714–719, 1990.

- [62] M. Okuno, T. Ikehara, M. Nagayama, Y. Kato, S. Yui, and K. Umeyama, "Mucinous colorectal carcinoma: clinical pathology and prognosis," *The American Surgeon*, vol. 54, no. 11, pp. 681–685, 1988.
- [63] L. Xie, P. J. Villeneuve, and A. Shaw, "Survival of patients diagnosed with either colorectal mucinous or non-mucinous adenocarcinoma: a population-based study in Canada," *International Journal of Oncology*, vol. 34, no. 4, pp. 1109–1115, 2009.
- [64] O. Sasaki, W. S. Atkin, and J. R. Jass, "Mucinous carcinoma of the rectum," *Histopathology*, vol. 11, no. 3, pp. 259–272, 1987.
- [65] C. A. Purdie and J. Piris, "Histopathological grade, mucinous differentiation and DNA ploidy in relation to prognosis in colorectal carcinoma," *Histopathology*, vol. 36, no. 2, pp. 121–126, 2000.
- [66] T. B. Halvorsen and E. Seim, "Influence of mucinous components on survival in colorectal adenocarcinomas: a multivariate analysis," *Journal of Clinical Pathology*, vol. 41, no. 10, pp. 1068–1072, 1988.
- [67] L. Messerini, M. Ciantelli, S. Baglioni, A. Palomba, G. Zampi, and L. Papi, "Prognostic significance of microsatellite instability in sporadic mucinous colorectal cancers," *Human Pathology*, vol. 30, no. 6, pp. 629–634, 1999.
- [68] S. Popat, R. Hubner, and R. S. Houlston, "Systematic review of microsatellite instability and colorectal cancer prognosis," *Journal of Clinical Oncology*, vol. 23, no. 3, pp. 609–618, 2005.
- [69] R. Gryfe, H. Kim, E. T. K. Hsieh et al., "Tumor microsatellite instability and clinical outcome in young patients with colorectal cancer," *The New England Journal of Medicine*, vol. 342, no. 2, pp. 69–77, 2000.
- [70] S. Hamilton, B. Vogelstein, and S. Kudo, "Carcinoma of the colon and rectum," in *World Health Organization Classification of Tumors-Pathology and Genetics of Tumors of the Digestive System*, S. Hamilton and L. Aaltonen, Eds., pp. 105–119, IARC Press, Lyon, France, 2000.
- [71] J. R. Jass, "The grading of rectal cancer: historical perspectives and a multivariate analysis of 447 cases. J. R. Jass, W. S. Atkin, J. Cuzick, H. J. R. Bussey, B. C. Morson, J. M. A. Northover, I. P. Todd. *Histopathology* 1986; 10: 437–459," *Histopathology*, vol. 41, no. 3A, pp. 56–58, 2002.
- [72] R. S. Grinnell, "The grading and prognosis of carcinoma of the colon and rectum," *Annals of Surgery*, vol. 109, no. 4, pp. 500–533, 1939.
- [73] J. R. Jass, J. O'Brien, R. H. Riddell, and D. C. Snover, "Pathology AoDoAaS. Recommendations for the reporting of surgically resected specimens of colorectal carcinoma: Association of Directors of Anatomic and Surgical Pathology," *American Journal of Clinical Pathology*, vol. 129, pp. 13–23, 2008.
- [74] F. T. Bosman, F. Carneiro, and R. H. Hruban, *WHO Classification of Tumours of the Digestive System*, International Agency for Research on Cancer, 4th edition, 2010.
- [75] R. C. Newland, O. F. Dent, M. N. B. Lyttle, P. H. Chapuis, and E. L. Bokey, "Pathologic determinants of survival associated with colorectal cancer with lymph node metastases: a multivariate analysis of 579 patients," *Cancer*, vol. 73, no. 8, pp. 2076–2082, 1994.
- [76] P. H. Chapuis, O. F. Dent, R. Fisher et al., "A multivariate analysis of clinical and pathological variables in prognosis after resection of large bowel cancer," *British Journal of Surgery*, vol. 72, no. 9, pp. 698–702, 1985.
- [77] L. S. Freedman, P. Macaskill, and A. N. Smith, "Multivariate analysis of prognostic factors for operable rectal cancer," *The Lancet*, vol. 2, no. 8405, pp. 733–736, 1984.
- [78] T. Sprenger, H. Rothe, K. Jung et al., "Stage II/III rectal cancer with intermediate response to preoperative radiochemotherapy: do we have indications for individual risk stratification?" *World Journal of Surgical Oncology*, vol. 8, article 27, 2010.
- [79] D. Edler, M. Hallström, P. G. Johnston, I. Magnusson, P. Ragnhammar, and H. Blomgren, "Thymidylate synthase expression: an independent prognostic factor for local recurrence, distant metastasis, disease-free and overall survival in rectal cancer," *Clinical Cancer Research*, vol. 6, no. 4, pp. 1378–1384, 2000.
- [80] N. K. Kim, S. H. Baik, J. S. Seong et al., "Oncologic outcomes after neoadjuvant chemoradiation followed by curative resection with tumor-specific mesorectal excision for fixed locally advanced rectal cancer: impact of postirradiated pathologic downstaging on local recurrence and survival," *Annals of Surgery*, vol. 244, no. 6, pp. 1024–1030, 2006.
- [81] F. Michelassi, G. E. Block, L. Vannucci, A. Montag, and R. Chappell, "A 5- to 21-year follow-up and analysis of 250 patients with rectal adenocarcinoma," *Annals of Surgery*, vol. 208, no. 3, pp. 379–389, 1988.
- [82] A. Horn, O. Dahl, and I. Morild, "The role of venous and neural invasion on survival in rectal adenocarcinoma," *Diseases of the Colon and Rectum*, vol. 33, no. 7, pp. 598–601, 1990.
- [83] J. B. Knudsen, T. Nilsson, M. Sprechler, Å. Johansen, and N. Christensen, "Venous and nerve invasion as prognostic factors in postoperative survival of patients with resectable cancer of the rectum," *Diseases of the Colon & Rectum*, vol. 26, no. 9, pp. 613–617, 1983.
- [84] J. Peng, W. Sheng, D. Huang et al., "Perineural invasion in pT3N0 rectal cancer: the incidence and its prognostic effect," *Cancer*, vol. 117, no. 7, pp. 1415–1421, 2011.
- [85] C. E. Dukes and H. J. Bussey, "Venous spread in rectal cancer: (section of proctology)," *Proceedings of the Royal Society of Medicine*, vol. 34, pp. 571–573, 1941.
- [86] I. C. Talbot, S. Ritchie, M. H. Leighton, A. O. Hughes, H. J. Bussey, and B. C. Morson, "The clinical significance of invasion of veins by rectal cancer," *British Journal of Surgery*, vol. 67, no. 6, pp. 439–442, 1980.
- [87] A. Sternberg, M. Amar, R. Alfici, and G. Groisman, "Conclusions from a study of venous invasion in stage IV colorectal adenocarcinoma," *Journal of Clinical Pathology*, vol. 55, no. 1, pp. 17–21, 2002.
- [88] B. Minsky and C. Mies, "The clinical significance of vascular invasion in colorectal cancer," *Diseases of the Colon & Rectum*, vol. 32, no. 9, pp. 794–803, 1989.
- [89] I. C. Talbot, S. Ritchie, M. Leighton, A. O. Hughes, H. J. Bussey, and B. C. Morson, "Invasion of veins by carcinoma of rectum: method of detection, histological features and significance," *Histopathology*, vol. 5, no. 2, pp. 141–163, 1981.
- [90] J. W. Huh, H. R. Kim, and Y. J. Kim, "Lymphovascular or perineural invasion may predict lymph node metastasis in patients with T1 and T2 colorectal cancer," *Journal of Gastrointestinal Surgery*, vol. 14, no. 7, pp. 1074–1080, 2010.
- [91] F. Crucitti, L. Sofo, G. B. Doglietto et al., "Prognostic factors in colorectal cancer: current status and new trends," *Journal of Surgical Oncology. Supplement*, vol. 48, no. 2, pp. 76–82, 1991.
- [92] B. D. Minsky, C. Mies, T. A. Rich, and A. Recht, "Lymphatic vessel invasion is an independent prognostic factor for survival in colorectal cancer," *International Journal of Radiation Oncology, Biology, Physics*, vol. 17, no. 2, pp. 311–318, 1989.
- [93] W. K. Blenkinsopp, S. Stewart-Brown, L. Blesovsky, G. Kearney, and L. P. Fielding, "Histopathology reporting in large bowel

- cancer," *Journal of Clinical Pathology*, vol. 34, no. 5, pp. 509–513, 1981.
- [94] A. Sternberg, A. Mizrahi, M. Amar, and G. Groisman, "Detection of venous invasion in surgical specimens of colorectal carcinoma: the efficacy of various types of tissue blocks," *Journal of Clinical Pathology*, vol. 59, no. 2, pp. 207–210, 2006.
- [95] K. Dirschmid, A. Lang, G. Mathis, A. Haid, and M. Hansen, "Incidence of extramural venous invasion in colorectal carcinoma: findings with a new technique," *Human Pathology*, vol. 27, no. 11, pp. 1227–1230, 1996.
- [96] P. Das, J. M. Skibber, M. A. Rodriguez-Bigas et al., "Clinical and pathologic predictors of locoregional recurrence, distant metastasis, and overall survival in patients treated with chemoradiation and mesorectal excision for rectal cancer," *The American Journal of Clinical Oncology*, vol. 29, no. 3, pp. 219–224, 2006.
- [97] C.-Z. Du, W.-C. Xue, Y. Cai, M. Li, and J. Gu, "Lymphovascular invasion in rectal cancer following neoadjuvant radiotherapy: a retrospective cohort study," *World Journal of Gastroenterology*, vol. 15, no. 30, pp. 3793–3798, 2009.
- [98] J. G. Guillem, D. B. Chessin, A. M. Cohen et al., "Long-term oncologic outcome following preoperative combined modality therapy and total mesorectal excision of locally advanced rectal cancer," *Annals of Surgery*, vol. 241, no. 5, pp. 829–838, 2005.
- [99] C. Ratto, R. Ricci, C. Rossi, U. Morelli, F. M. Vecchio, and G. B. Doglietto, "Mesorectal microfoci adversely affect the prognosis of patients with rectal cancer," *Diseases of the Colon and Rectum*, vol. 45, no. 6, pp. 733–742, 2002.
- [100] C. Ono, K. Yoshinaga, M. Enomoto, and K. Sugihara, "Discontinuous rectal cancer spread in the mesorectum and the optimal distal clearance margin in situ," *Diseases of the Colon and Rectum*, vol. 45, no. 6, pp. 742–749, 2002.
- [101] Y. Shimada and Y. Takii, "Clinical impact of mesorectal extranodal cancer tissue in rectal cancer: detailed pathological assessment using whole-mount sections," *Diseases of the Colon and Rectum*, vol. 53, no. 5, pp. 771–778, 2010.
- [102] N. S. Goldstein and J. R. Turner, "Pericolonic tumor deposits in patients with T3N+M0 colon adenocarcinomas: markers of reduced disease free survival and intra-abdominal metastases and their implications for TNM classification," *Cancer*, vol. 88, no. 10, pp. 2228–2238, 2000.
- [103] G. Puppa, H. Ueno, M. Kayahara et al., "Tumor deposits are encountered in advanced colorectal cancer and other adenocarcinomas: an expanded classification with implications for colorectal cancer staging system including a unifying concept of in-transit metastases," *Modern Pathology*, vol. 22, no. 3, pp. 410–415, 2009.
- [104] H. Ueno, H. Mochizuki, Y. Hashiguchi et al., "Extramural cancer deposits without nodal structure in colorectal cancer: optimal categorization for prognostic staging," *American Journal of Clinical Pathology*, vol. 127, no. 2, pp. 287–294, 2007.
- [105] L. H. Sobin and I. D. Fleming, "TNM classification of malignant tumors, fifth edition (1997). Union Internationale Contre le Cancer and the American Joint Committee on Cancer," *Cancer*, vol. 80, no. 9, pp. 1803–1804, 1997.
- [106] L. Sobin and C. Wittekind, *TNM Classification of Malignant Tumors*, Wiley-Liss, New York, NY, USA, 6th edition, 2002.
- [107] I. D. Nagtegaal and P. Quirke, "Colorectal tumour deposits in the mesorectum and pericolon; a critical review," *Histopathology*, vol. 51, no. 2, pp. 141–149, 2007.
- [108] G. Puppa, P. Maisonneuve, A. Sonzogni et al., "Pathological assessment of pericolonic tumor deposits in advanced colonic carcinoma: relevance to prognosis and tumor staging," *Modern Pathology*, vol. 20, no. 8, pp. 843–855, 2007.
- [109] L. Sobin, M. Gospodarowicz, and C. Wittekind, *TNM Classification of Malignant Tumors*, Wiley-Blackwell, New York, NY, USA, 7th edition, 2009.
- [110] C. Ratto, R. Ricci, V. Valentini et al., "Neoplastic mesorectal microfoci (MMF) following neoadjuvant chemoradiotherapy: clinical and prognostic implications," *Annals of Surgical Oncology*, vol. 14, no. 2, pp. 853–861, 2007.
- [111] P. Quirke, G. T. Williams, N. Ectors, A. Ensari, F. Piard, and I. Nagtegaal, "The future of the TNM staging system in colorectal cancer: time for a debate?" *Lancet Oncology*, vol. 8, no. 7, pp. 651–657, 2007.
- [112] P. Greco and G. Magro, "Staging in colorectal cancer: problems for pathologists," *Histopathology*, vol. 51, no. 4, pp. 553–555, 2007.
- [113] C. C. Compton, L. P. Fielding, L. J. Burgart et al., "Prognostic factors in colorectal cancer—college of American Pathologists Consensus Statement 1999," *Archives of Pathology & Laboratory Medicine*, vol. 124, no. 7, pp. 979–994, 2000.
- [114] H.-M. Quah, J. F. Chou, M. Gonen et al., "Pathologic stage is most prognostic of disease-free survival in locally advanced rectal cancer patients after preoperative chemoradiation," *Cancer*, vol. 113, no. 1, pp. 57–64, 2008.
- [115] L.-J. Kuo, M.-C. Liu, J. J.-M. Jian et al., "Is final TNM staging a predictor for survival in locally advanced rectal cancer after preoperative chemoradiation therapy?" *Annals of Surgical Oncology*, vol. 14, no. 10, pp. 2766–2772, 2007.
- [116] A. K. P. Chan, A. Wong, D. Jenken, J. Heine, D. Buie, and D. Johnson, "Posttreatment TNM staging is a prognostic indicator of survival and recurrence in tethered or fixed rectal carcinoma after preoperative chemotherapy and radiotherapy," *International Journal of Radiation Oncology, Biology, Physics*, vol. 61, no. 3, pp. 665–677, 2005.
- [117] F. Greene, D. Page, and I. Fleming, *AJCC Cancer Staging Manual*, Wiley-Liss, New York, NY, USA, 2002.
- [118] A. Gurrera, P. Amico, and P. Greco, "Tumour deposits classification in colorectal cancer: is TNM5 better than TNM7?" *Journal of Pathology*, vol. 222, no. 3, pp. 320–321, 2010.
- [119] P. Quirke, C. Cuvelier, A. Ensari et al., "Evidence-based medicine: the time has come to set standards for staging," *Journal of Pathology*, vol. 221, no. 4, pp. 357–360, 2010.
- [120] P. Quirke and E. Morris, "Reporting colorectal cancer," *Histopathology*, vol. 50, no. 1, pp. 103–112, 2007.
- [121] H. Rutten, D. Sebag-Montefiori, and R. Glynne-Jones, "Capecitabine, oxaliplatin, radiotherapy and excision (CORE) in patients with MRI-defined locally advanced rectal adenocarcinoma: results of an international multicenter phase II study," *Journal of Clinical Oncology*, vol. 24, article 153, 2006.
- [122] J. Shia, M. McManus, J. G. Guillem et al., "Significance of acellular mucin pools in rectal carcinoma after neoadjuvant chemoradiotherapy," *The American Journal of Surgical Pathology*, vol. 35, no. 1, pp. 127–134, 2011.
- [123] J. Shia, J. G. Guillem, H. G. Moore et al., "Patterns of morphologic alteration in residual rectal carcinoma following preoperative chemoradiation and their association with long-term outcome," *American Journal of Surgical Pathology*, vol. 28, no. 2, pp. 215–223, 2004.
- [124] K. D. Smith, D. Tan, P. Das et al., "Clinical significance of acellular mucin in rectal adenocarcinoma patients with a

- pathologic complete response to preoperative chemoradiation," *Annals of Surgery*, vol. 251, no. 2, pp. 261–264, 2010.
- [125] L. F. de Campos-Lobato, D. W. Dietz, L. Stocchi et al., "Clinical implications of acellular mucin pools in resected rectal cancer with pathologic complete response to neoadjuvant chemoradiation," *Colorectal Disease*, vol. 14, no. 1, pp. 62–67, 2010.
- [126] J. R. Jass, S. B. Love, and J. M. A. Northover, "A new prognostic classification of rectal cancer," *The Lancet*, vol. 1, no. 8545, pp. 1303–1306, 1987.
- [127] K. Klintrup, J. M. Mäkinen, S. Kauppila et al., "Inflammation and prognosis in colorectal cancer," *European Journal of Cancer*, vol. 41, no. 17, pp. 2645–2654, 2005.
- [128] A. Debucquoy, L. Goethals, L. Libbrecht et al., "Molecular and clinico-pathological markers in rectal cancer: a tissue micro-array study," *International Journal of Colorectal Disease*, vol. 24, no. 2, pp. 129–138, 2009.
- [129] A. Debucquoy, L. Libbrecht, V. Roobrouck, L. Goethals, W. McBride, and K. Haustermans, "Morphological features and molecular markers in rectal cancer from 95 patients included in the European Organisation for Research and Treatment of Cancer 22921 trial: prognostic value and effects of preoperative radio (chemo) therapy," *European Journal of Cancer*, vol. 44, no. 6, pp. 791–797, 2008.
- [130] I. D. Nagtegaal, C. A. Marijnen, E. K. Kranenbarg et al., "Local and distant recurrences in rectal cancer patients are predicted by the nonspecific immune response; specific immune response has only a systemic effect—a histopathological and immunohistochemical study," *BMC Cancer*, vol. 1, article 7, 2001.
- [131] J. M. D. Wheeler, E. Dodds, B. F. Warren et al., "Preoperative chemoradiotherapy and total mesorectal excision surgery for locally advanced rectal cancer: correlation with rectal cancer regression grade," *Diseases of the Colon & Rectum*, vol. 47, no. 12, pp. 2025–2031, 2004.
- [132] L. Moureau-Zabotto, B. Farnault, C. de Chaisemartin et al., "Predictive factors of tumor response after neoadjuvant chemoradiation for locally advanced rectal cancer," *International Journal of Radiation Oncology, Biology, Physics*, vol. 80, no. 2, pp. 483–491, 2011.
- [133] V. Valentini, C. Coco, A. Picciocchi et al., "Does downstaging predict improved outcome after preoperative chemoradiation for extraperitoneal locally advanced rectal cancer? A long-term analysis of 165 patients," *International Journal of Radiation Oncology Biology Physics*, vol. 53, no. 3, pp. 664–674, 2002.
- [134] J.-P. Machiels, S. Aydin, M.-A. Bonny, F. Hammouch, and C. Sempoux, "What is the best way to predict disease-free survival after preoperative radiochemotherapy for rectal cancer patients: tumor regression grading, nodal status, or circumferential resection margin invasion?" *Journal of Clinical Oncology*, vol. 24, no. 8, article 1319, 2006.
- [135] N. K. Kim, S. H. Baik, B. S. Min et al., "A comparative study of volumetric analysis, histopathologic downstaging, and tumor regression grade in evaluating tumor response in locally advanced rectal cancer following preoperative chemoradiation," *International Journal of Radiation Oncology Biology Physics*, vol. 67, no. 1, pp. 204–210, 2007.
- [136] E. D. Mignanelli, L. F. de Campos-Lobato, L. Stocchi, I. C. Lavery, and D. W. Dietz, "Downstaging after chemoradiotherapy for locally advanced rectal cancer: is there more (tumor) than meets the eye?" *Diseases of the Colon & Rectum*, vol. 53, pp. 251–256, 2010.
- [137] G. Theodoropoulos, W. E. Wise, A. Padmanabhan et al., "T-level downstaging and complete pathologic response after preoperative chemoradiation for advanced rectal cancer result in decreased recurrence and improved disease-free survival," *Diseases of the Colon & Rectum*, vol. 45, no. 7, pp. 895–903, 2002.
- [138] C. Capirci, V. Valentini, L. Cionini et al., "Prognostic value of pathologic complete response after neoadjuvant therapy in locally advanced rectal cancer: long-term analysis of 566 ypCR patients," *International Journal of Radiation Oncology Biology Physics*, vol. 72, no. 1, pp. 99–107, 2008.
- [139] L. F. de Campos-Lobato, L. Stocchi, A. da Luz Moreira et al., "Pathologic complete response after neoadjuvant treatment for rectal cancer decreases distant recurrence and could eradicate local recurrence," *Annals of Surgical Oncology*, vol. 18, no. 6, pp. 1590–1598, 2011.
- [140] J. F. Bosset, G. Calais, L. Mineur et al., "Preoperative radiation (Preop RT) in rectal cancer: effect and timing of additional chemotherapy (CT) 5-year results of the EORTC 22921 trial," *Journal of Clinical Oncology*, vol. 23, p. 247S, 2005.
- [141] T. Conroy, F. Bonnetain, O. Chapet et al., "Preoperative (preop) radiotherapy (RT)+5FU/folinic acid (FA) in T3,4 rectal cancers: preliminary results of the FFCD 9203 randomized trial," *Journal of Clinical Oncology*, vol. 22, article 3626, 2004.
- [142] M. S. Roh, L. Colangelo, S. Wieand et al., "Response to preoperative multimodality therapy predicts survival in patients with carcinoma of the rectum," *Journal of Clinical Oncology*, vol. 22, no. 14, article 3505, 2004.
- [143] M. Maas, P. J. Nelemans, V. Valentini et al., "Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data," *The Lancet Oncology*, vol. 11, no. 9, pp. 835–844, 2010.
- [144] S. B. Kelly, S. J. Mills, D. M. Bradburn, A. A. Ratcliffe, and D. W. Borowski, "Effect of the circumferential resection margin on survival following rectal cancer surgery," *British Journal of Surgery*, vol. 98, no. 4, pp. 573–581, 2011.