Pathological assessment of the rectal cancer resection specimen

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Summary

As it greatly reduces local recurrences, total mesorectal excision (TME) became the standard surgical treatment for rectal cancer. Also, the multidisciplinary team approach contributed to an improved outcome of rectal cancer patients. The pathologist has a crucial role in this process as proper pathological assessment of the TME specimen provides important prognostic information for the oncologist and identifies patients that require further therapy. TME resection specimens require a specialized macroscopic handling and pathological work-up. The external surface of the TME resection specimen should be carefully inspected and the quality of the mesorectal excision should be assessed. Adequate evaluation of the mesorectal excision requires examination of both the specimen as a whole (fresh) and transverse slides (after fixation). In addition, careful macroscopic and microscopic evaluation of the completeness of tumor resection is required and the distance of the tumor to the circumferential resection margin (CRM) must be measured. Tumor involvement of the CRM (tumor <1 mm from the CRM) strongly correlates with local recurrence, distant metastasis, and poor survival. In patients with a negative CRM, incomplete mesorectal resection leads to a higher recurrence rate and lower survival. In addition, it is important that pathologists establish the number of tumor-positive lymph nodes with a yield as high as possible. Several studies support the concept that the more nodes are examined, the more accurate is the staging. For reporting rectum cancer resection specimens, the use of pathology report forms is recommended as this ensures the completeness and consistency of data reporting.

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Introduction

The best way to optimize rectal cancer patient care is by a multidisciplinary team approach, including a surgeon, a radiologist, a pathologist, a gastroenterologist, a radiotherapist, and a medical oncologist. This leads to significant improvements in the outcome of rectal cancer treatment.[1] However, it is a prerequisite that all members of the different medical disciplines of the team have sufficient background knowledge of imaging, pathology, treatment modalities, and prognostic factors of this disease. This review focuses on the gross pathology of rectal cancer, with description of the mesorectum, and includes some digital images of rectal cancer resection specimens. In addition, an overview is given of microscopic features that are important for determination of further management and prognosis of rectal cancer, and the benefit of pathological report forms e.g. as proposed by the Belgian *PROCARE* working group (multidisciplinary Belgian PROject on CAncer of the REctum) is emphasized.[2]

The mesorectum and total mesorectal excision (TME): role of the pathologist in judging the completeness and quality of mesorectal excision

The mesorectum is defined as the visceral mesen-

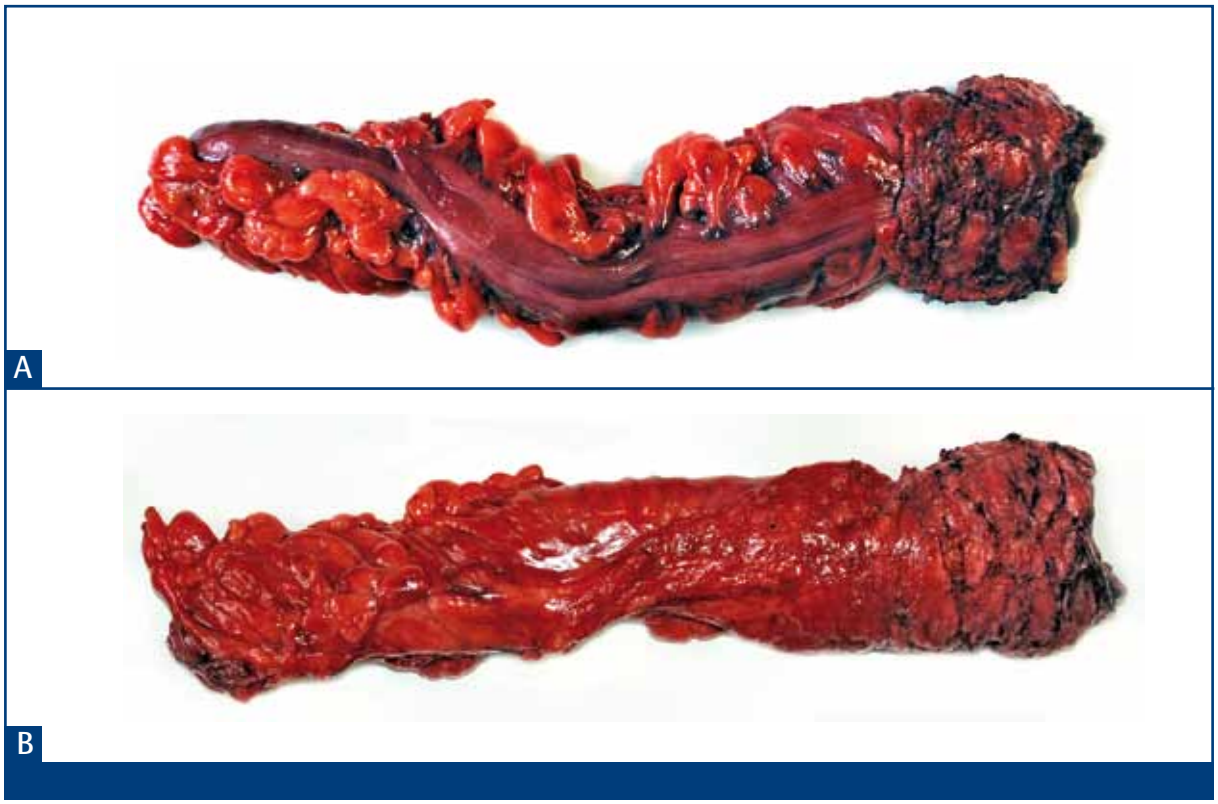

Figure 1. Anterior (A) and posterior (B) view of a TME resection specimen.

tery surrounding the rectum. It is a fatty connective tissue layer, enveloped by a thin fascia. It is the continuity of the mesosigmoid which progressively surrounds the whole rectum under the peritoneal reflection of the pouch of Douglas. It contains the blood vessels as well as the lymphatic ducts and lymph nodes of the rectum. In 1982, *Heald et al* introduced the concept of "Total Mesorectal Excision (TME)", leading to improved patient outcome, particularly with regard to local recurrence.[3] This concept includes 2 aspects: *firstly*, an anatomical sharp dissection under direct vision in the plane that separates the visceral mesorectal fascia from the parietal pelvic fascia ("the holy plane"), without any tearing or disruption of the mesorectal circumferential fascia and with preservation of the surrounding nerve plexuses; and *secondly*, the resection of the mesorectum down to the striated pelvic floor (the levator muscles), avoiding to leave in place its most distal part, potentially the site of foci of tumor cell deposits. This also facilitates low anastomosis and sphincter-preservation. For cancer of the upper third of the rectum a "Partial Mesorectal Excision (PME)" can be performed.[4] In this case the mesorectal dissection is conducted 5 cm distally to the lower edge of the tumor (measured *in situ*) in a plane at 90° to the rectal wall with sharp mesorectal dissection, differencing this procedure from the formerly performed conventional blunt digital dissection of anterior resection (AR).

A multidisciplinary team approach has led to significant improvements in outcome of rectal cancer treatment.[1] The pathologist has a crucial role in this process, not only by determining the pathological stage of rectal cancer, but also by the assessment of the completeness of tumor resection and assessment of the quality of the mesorectal excision.[5,6] Macroscopic as well as microscopic evaluation of the circumferential resection margin of the (TME) specimen by the pathologist has been shown to be of paramount importance.[5,6] The circumferential resection margin (CRM) is the surgically-created plane of dissection produced during the removal of the rectum from its surrounding tissue. It is the non-peritonealised bare area of the resection specimen. The largest area is located posteriorly, where it begins much higher than anteriorly, at the mesocolon of the sigmoid and extends downwards as an enlarging triangle.[7] Below the peritoneal reflection it becomes a circumferential margin and extends downwards to the bottom of the mesorectum and the distal excision margin or, in an APR, down to

Figure 2. Severely irregular mesorectum in an APR specimen: the muscle layer is visible about 1 cm below the peritoneal reflection. The description of the quality of the mesorectal surface in an APR specimen is limited to the description of the rectum above the sphincters.

the anal skin (*Figure 1*).[7] Tumor involvement of the CRM is the single most important factor for predicting the risk of local recurrence in rectal cancer patients.[6,8-10] It is also important in the prediction of distant metastasis and overall survival.[10] Tumors within 1 mm of the surgically created margin have a greatly increased risk of recurrence.[8,9] One study still showed a high incidence of recurrence at 2 mm, but this finding could not be confirmed in subsequent studies.[1,11,12]

For very low primary rectal tumors an abdominoperineal resection (APR) is required. Mesorectal excision in this case will remove lymphatic, vascular, and neural pathways of metastasis, but there will often be involvement of the surgical resection margin at the level of the sphincters.[13,14] The tapering of the mesorectum towards the levators emphasizes that there is less tissue for the carcinoma to transverse before involving the surgical plane of resection in the low mesorectum and anal canal. In addition, good visualization and access are limited with the classical approach of APR and it was shown that the plane of resection lies within the sphincter muscle, the submucosa, or lumen in more than one third of the APR cases. In the remainder, the plane of resection lies on the sphincteric muscles.[14] This predisposes to circumferential resection margin (CRM) involvement, except in the very early stages. In addition, a high intra-operative perforation rate was observed.[14] Neoadjuvant therapy has an important place here in downsizing the tumor, enabling complete resection. Moreover, a more radical operation with a predominantly perineal surgical approach, creating a CRM outside the levators and giving wider clearance is being considered for low rectal tumors.[13,14]

Gross external appearance of the surgically resected specimen: macroscopic inspection

The first task of the pathologist when receiving the surgical excision specimen following TME is the visual inspection of the completeness of resection of the mesorectum.[5-8,15] Preferentially, the resection specimen should be examined in the fresh, unfixed state. More importantly however, is that it should be delivered unopened to the pathologist. The external surface of the TME should be carefully inspected and the quality of the mesorectal excision should be assessed and can be graded (complete, nearly complete, incomplete).[5,6] The mesorectal surface of a good resection should be smooth with a good bulk of mesorectum. There should be no coning near the distal margin. Defects at the surface should be less than 5 mm deep. In case of perforation of the resection specimen or in case the muscular layer is visible exteriorly, the resection is classified as incomplete (*Figure 2*). In the *PROCARE* protocol the following terminology is used: smooth and regular, mildly irregular or severely irregular (*Table 1*).[2] This slightly adapted terminology was introduced to avoid misinterpretation of the notion of "incomplete" resection, as in case of advanced tumor growth it is not always possible to avoid margin involvement. A Dutch study demonstrated that despite extensive surgical training only 57% of operations were judged to be complete excisions and nearly one quarter (24%) were classified as incomplete excisions.[5] In resection specimens reported to be incomplete, there was a significantly higher rate of circumferential margin involvement and a higher rate of overall recurrence and local tumor recurrence.[5] In patients with a positive CRM,

Table 1. Grading of the quality of mesorectal excision in TME specimens as proposed in the PROCARE guidelines. Both the specimen as a whole (fresh) and transverse slices (after fixation) should be examined in order to allow adequate evaluation of the mesorectal excision.		
Smooth, regular	-	intact mesorectum with only minor irregularities of a smooth mesorectal surface - no defect deeper than 5 mm - no coning toward the distal margin of the specimen* - a smooth circumferential resection margin on slicing
Mildly irregular	-	moderate bulk to the mesorectum, but irregularity of the mesorectal surface - moderate coning of the specimen allowed* - the muscularis propria invisible at every site, with the exception of the insertion of the levator muscles
Severely irregular	-	little bulk to the mesorectum with defects down onto the muscularis propria and/or very irregular circumferential resection margin on slicing
** Coning refers to the tendency for the surgeon to cut towards the rectum wall during distal dissection, rather than staying outside of the visceral mesorectal fascia; this gives a conical appearance to the surgical resection specimen.*		

assessment of the quality of surgery added nothing to the prediction of local recurrence above CRM involvement alone. However, in patients with a negative CRM and incomplete resection, the overall recurrence rate was doubled from 15 to 29% and survival decreased from 91 to 77%.[5] No prognostic difference was observed between patients with a complete mesorectum compared to those with a nearly complete mesorectum.[5]

It is important to realize that there is less mesorectal tissue anteriorly and laterally than posteriorly.[7] In addition the size of the mesorectum varies widely between individuals and is related to several factors such as to body mass, gender, and degree of cachexia.[16]

In an APR specimen, the description of the quality of the mesorectal surface is limited to the description of the rectum above the sphincter.

Handling the TME specimen

The relation of the tumor to the serosal surface should be determined, i.e. above, at, or below the peritoneal reflection. After examination of the external surface, the resection margin should be painted with india ink. The resection specimen is opened anteriorly above the peritoneal reflection starting at its proximal end without extension into the tumor. This allows effective evaluation of the anterior CRM that would otherwise be destroyed by the opening process. Ideally, the resection specimen should be pinned out on a corkboard to avoid shrinkage and left floating with the cork upwards in formalin fixative for at least 48 hours.[18] Placement of gauze or paper tissue wick soaked in formalin within the lumen of the intact bowel segment is necessary to enhance fixation. After fixation, the resection specimen should be sectioned in parallel cuts of 3-4 mm intervals, perpendicularly to the length of the bowel. The long fixation time is required to make the tissue firmer and facilitates serial cross-sectional slicing of the specimen. This allows the assessment of the deepest point of tumor invasion and to measure the distance to the place where the tumor is closest to the CRM. The number of tissue blocks to be taken from the tumor is 3 at minimum.[2] At least one tissue block should include the transition from the surrounding normal mucosa to the tumor and at least one tissue block should be taken of the deepest point of invasion.[2,19] The latter permits microscopic confirmation and refinement of gross observations at the area of greatest macroscopic concern. It is known that, in particular after radiotherapy, the presence of fibrosis may make macroscopic assessment of the tumor inaccurate. It is often impossible to distinguish therapy-induced fibrosis from tumor invasion.[20] In this case, sufficient tissue blocks should be taken from all macroscopically suspected areas in order not to miss the deepest point of invasion. No distinction should be made between various modes of involvement of the CRM, continuous spread, discontinuous tumor deposits, or involved lymph nodes. The orientation of grossly suspicious nodes that are closely related to the CRM should thus be preserved in sections. Tissue slices can be embedded as large-area (giant) blocks or as conventional small blocks. Formalin fixation will allow additional molecular pathological examination.

Figure 3. Cross-sections of the TME resection specimen shown in Figure 1 (upper left is proximal, lower right is distal); quality of mesorectal excision: smooth, regular.

Important to note is that both the specimen as a whole (fresh) and the transverse slides (after fixation) should be examined in order to allow adequate evaluation of the mesorectal excision (*Figure 3*). Digital imaging of the exterior surface prior to cutting and of whole transverse slides can be performed to document the findings.

If the tumor is located close to the distal or proximal section margins, it is advisable to demonstrate the relationship of the tumor to the margin by taking sections perpendicular to the margin.

Node-positive patients may benefit from chemotherapy. It is important to establish the number of tumor-positive lymph nodes with a yield as high as possible.[6] All lymph nodes should be submitted for microscopic examination. At least 12 lymph nodes should be found and embedded according to the current TNM guidelines.[21-23] It may, however, be difficult to find enough lymph nodes in rectal cancer specimens, especially after preoperative radiochemotherapy.[24,25] However, a high motivation to find as many nodes as possible must be maintained, since several studies support the concept that the more nodes are examined, the more accurate is the staging.[6] When less than 7 lymph nodes have been analysed, the proportion of cancers with lymph node involvement is underestimated.[26] Determination of the lymph node ratio in node-positive colon cancer may be an alternative.[27] There is insufficient scientific evidence to recommend micro-dissection techniques or fat clearance to increase the number of harvested lymph nodes. [21] Furthermore, associated lesions such as polyps and IBD also need to be sampled.[21]

Histological examination

The histological type of the tumor according to the WHO classification is reported and the tumor is graded.[28] Different grading systems are used in the literature.[28] Either a 4 or a 2-tiered descriptive system can be used. The 4-tiered system divides the tumors into well, moderate, or poorly differentiated and undifferentiated tumors. The 2-tiered descriptive system reports tumors as either high grade (poorly and undifferentiated tumors) or low grade (well and moderately differentiated tumors). In the 2-tiered descriptive system, the high grade corresponds to less than 50% of glandular structures of the surface analysed. Signetring cell colorectal carcinomas (composed for more than 50% of signetring cells) and mucinous colorectal adenocarcinomas (more than 50% of the lesion composed of pools of extracellular mucin-containing malignant epithelium as acinar structures, strips of cells, or single cells) are by definition poorly differentiated, while medullary carcinoma of the colon by convention is considered as undifferentiated carcinoma.[28] For accurate grading of colorectal adenocarcinomas superficial and deep parts of the tumor must be included.[19]

The depth of tumor invasion, the number of lymph nodes involved and metastatic disease must be reported.[21] It is recommended to include the pTNM classification system, which is used in many international trials (*Table 2*). The depth of invasion is described in relation to the anatomical structures, i.e. mucosa, submucosa, muscularis propria, mesorectal tissue, and serosa. The number of positive lymph nodes as well as the total number of exam-

Table 2. Pathological TNM classification according to the 5th edition of TNM – pTNM5.	
T	**Primary tumor**
TX	primary tumor cannot be assessed
T0	no evidence of primary tumor
Tis	carcinoma *in situ*: intraepithelial or invasion of lamina propria
T1	tumor invades submucosa
T2	tumor invades muscularis propria
T3	tumor invades through muscularis propria into subserosa or into non-peritonealized periodic or rectal tissue
T4	tumor directly invades other organs or structures and/or perforates visceral peritoneum
N	**Regional lymph nodes**
NX	regional lymph nodes cannot be assessed
N0	no regional lymph node metastasis
N1	metastasis in 1 to 3 regional lymph nodes
N2	metastasis in 4 or more regional lymph nodes
M	**Distant metastases**
MX	distant metastasis cannot be assessed
M0	no distant metastasis
M1	distant metastasis

ined lymph nodes must be included. Data are insufficient to recommend the routine use of tissue levels or special/ancillary techniques.[21] Important to know is that many involved lymph nodes are small, sometimes only a few millimeters in size.[29] This can explain the poor correlation with prediction of involved lymph nodes preoperatively by MRI.[30] If the pathologists are using the 6th edition of TNM, his correlation may even be worse, owing to the classification of all round extramural tumor deposits as completely involved lymph nodes without residual lymphoid tissue.[23] Extramural tumor deposits with an irregular contour are considered as vascular invasion. In the 5th edition of TNM, extramural deposits that are not obviously within lymph nodes are regarded as discontinuous extensions of the main tumor if they measure <3 mm, but as lymph node involvement if they measure >3 mm in diameter.[22] Whilst the evidence for this definition is weak, it does at least have the advantage of being quantitative and, therefore, reproducible and it may increase pathologist/radiologist agreement.[30] The UK and much of Scandinavia refused to move to TNM6 as the evidence base is inadequate for the classification of lymph node and venous invasion, and in addition, the interobserver variability is poor.[30] It has also been advocated by the *PROCARE* working group to stick to the 3 mm rule of the TNM5 classification.[2]

The distance to the circumferential regression margin (CRM) must be measured. A positive CRM is defined as tumor extension (either continuous or discontinuous) or the presence of a positive lymph node <1 mm from the radial, non-peritonealised soft tissue edge.[8-10] With regard to the interpretation of studies about treatment outcome, it should be emphasized that a positive and negative CRM according to this definition cannot be compared with the UICC residual tumor (R) classification.[22,23] A positive CRM corresponds in part to R1 (if tumor is found directly at the CRM), and in part to R0 (if the CRM is tumor-free, but the tumor is located less than 1 mm from the CRM). It is recommended to measure and mention on the report the exact margin distance (*Figure 4*).[11] Also the distance to the longitudinal resection margins should be recorded. Peritoneal involvement and vascular invasion must also be reported as they identify patients with poorer prognosis that may need further treatment.[31] An adequate distinction between involvement of CRM and peritoneal involvement is very important. If the tumor is present in the mesorectal tissue at a distance <1 mm of the CRM, it is a T3 tumor with positive margins. If the tumor is located at or above the peritoneal reflection and penetrates the visceral peritoneum, but is located >1 mm from the CRM, it is a T4 tumor with negative margins. Vascular invasion into extramural veins should be described. Presence of perineural and/or lymphatic invasion may be mentioned. The V and L substaging can be

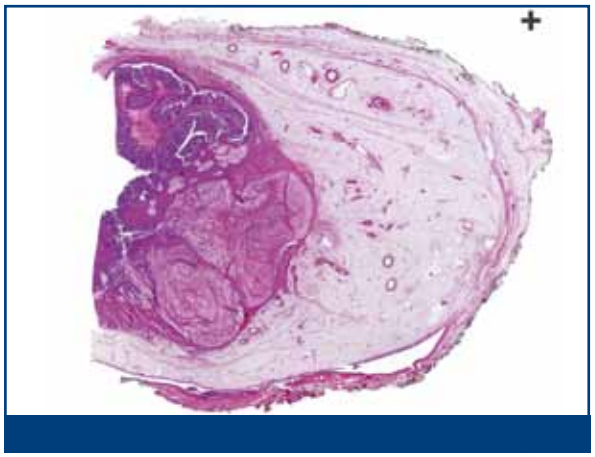

Figure 4. Slide of a large-area (giant) block, allowing to measure the distance of the tumor to the CRM (the resection margin is painted with india ink).

used to indicate the presence of vascular or lymphatic invasion.[22]

Distant metastasis is reported as M1 if confirmed at histological examination. Non-regional lymph nodes are classified as metastases and should be described separately. A positive cytological peritoneal fluid is also classified as M1.[22]

Neoadjuvant radiochemotherapy changes

The pathologist should be informed about preoperative treatment, as in case of neoadjuvant radiochemotherapy (ypTNM) it is advised to estimate tumor regression by means of a semiquantitative grading system, e.g. the Dworak regression grade (*Table 3*), where regression of the primary tumor is semiquantitatively determined by the amount of viable tumor versus the amount of fibrosis, ranging from no evidence of any treatment effect to a complete response with no viable tumor identified.[20] Regression grading is important for prognosis with a complete response having a better outcome than microscopic disease and the latter doing better than moderate, mild, or no regression.[20,30,32,33] Before concluding that there is complete response with no viable tumor identified, embedding of the whole suspicious area and the application of step sectioning is suggested.[20] To combine rigorous dissection with practicality, it is recommended that 5 initial blocks are taken from the site of the tumor. If no tumor is present, the complete suspicious area should be embedded. If there is still no tumor, then 3 levels should be cut through each block. If finally there is still no tumor found, then the patient is reported as having a complete response.[34]

Pathological reporting of rectal cancer resection specimens

Use of pathology report forms ensures the completeness and consistency of data reporting. This is not only important for determination of individual patient prognosis and further treatment, but also for assessment of quality of rectal surgery, and the overall management of the disease. Two pathological report forms are proposed by the Belgian *PROCARE* working group, one for PME, TME, or APR, and a second form for local (transanal) resection. The last updated version of the checklists can be downloaded from *www.kankerregister.be* (menu: procare/working) or *www.registreducancer.be* (menu: procare/working). The protocol for local resection specimens includes the pathological subclassification into 3 levels of the depth of invasion in superficial (mucosal or submucosal) cancer (*Table 4*).

Conclusions

Total mesorectal excision (TME) became the standard surgical treatment for rectal cancer, as it greatly reduces local recurrences.[1,3] TME and a multidisciplinary oncologic team approach have led to significant improvements in outcome of rectal cancer treatment.[1] Pathologists play a key role in this process. Proper pathological assessment of the TME specimen provides important prognostic information for the oncologist and identifies patients that require further therapy.[6,15]

TME resection specimens require a special pathological work-up, as pathologists not only have to determine the pathological stage of rectal cancer, but in addition they have to assess the completeness of tumor resection and the quality of the mesorectal excision.[5,6] For this purpose it is important that the resection specimen is delivered unopened to the pathologist.[5,6,8] Assessment of the quality of mesorectal excision must be based on a macroscopic observation of the external surface as well as evaluation of cross-sectional slides.[5,6] Careful macroscopic as well as microscopic assessment of the distance of the tumor to the circumferential resection margin (CRM) is of high importance, as this is the most significant predictor of local recurrence.[6,8-10] In patients with a negative CRM, incomplete mesorectal resection leads to a higher recurrence rate and lower survival.[5] For an adequate benefit of a multidisciplinary oncologic team approach, it is necessary that all members of the different medical disciplines of the team have sufficient background knowledge of imaging,

Table 3. Dworak regression grade.[20]	
Grade 0	no regression
Grade 1	dominant tumor mass with obvious fibrosis and/or vasculopathy
Grade 2	dominantly fibrotic changes with few tumor cells or groups (easy to find)
Grade 3	very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucous substance
Grade 4	no tumor cells, only fibrotic mass (total regression or response)

Table 4. Pathological subclassification of the extent of invasion in superficial cancer.	
pTis – Primary tumor: invasion of lamina propria	
m1	superficial third of the mucosa
m2	middle third of the mucosa
m3	deepest third of the mucosa
pT1 – Primary tumor: invasion of submucosa	
sm1	superficial third of the submucosa or invasion depth of less than 0.5 mm
sm2	middle third of the submucosa or invasion depth of between 0.5 and 1 mm
sm3	deepest third of the submucosa or invasion depth of more than 1 mm

pathology, treatment modalities, and prognostic factors of this disease. In this context, visiting the pathologist in the cut-up room, assisting in the evaluation of the circumferential resection margin, and studying pathological cross-sections can be useful, especially for both the training surgeon and the radiologist. Also digital imaging of the exterior surface prior to cutting and of whole transverse slides will provide feedback to other medical disciplines of the team.

Careful analysis of the rectal cancer resection specimen with grading and staging of the tumor need to be performed.[21] In particular, a high motivation to find as many lymph nodes as possible must be maintained, as node-positive patients may benefit from chemotherapy. Also, several studies support the concept that the more nodes are examined, the more accurate is the staging.[6] It is also advised to report the degree of tumor regression after neo-adjuvant radiochemotherapy.[20,30,32,33] For regression grading to mean anything, it is however necessary to standardize the assessment. Before concluding that there is complete response with no viable tumor identified, embedding of the whole suspicious area and cutting of 3 levels through each tissue block is suggested.[20,34]

Use of pathology report forms for reporting rectum cancer resection specimens is highly recommended, as it ensures the completeness and consistency of data reporting.

The next challenge now is the search for immunohistochemical or molecular markers, that will identify patients who respond favourably to preoperative treatment to shrink or destroy the tumor preoperatively and further increase the percentage of curative surgery.

References

1. Quirke P. Training and quality assurance for rectal cancer: 20 years of data is enough. Lancet 2003;4:695-701.

2. PROCARE: multidisciplinary Belgian PROject on CAncer of the Rectum. Multidisciplinary guidelines for the treatment of rectal cancer can be downloaded from www.kankerregister.be (menu: procare) or www.registreducancer.be (menu: procare).

3. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery-the clue to pelvic recurrence? Br J Surg 1982;69:613-6.

4. Law WL, Chu KW. Anterior resection for rectal cancer with mesorectal excision. A prospective evaluation of 622 patients. Ann Surg 2004;240:260-8.

5. Nagtegaal ID, Van de Velde CJ, Van der Worp E, Kapiteijn E, Quirke P, Van Krieken JH, et al. Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. J Clin Oncol 2002;20:1729-34.

6. Maugham NJ, Quirke P. Modern management of colorectal cancer - a pathologist's view. Scand J Surg 2003;92:11-9.

7. Parfitt JR, Driman DK. The total mesrorectal excision specimen for rectal cancer. A review of its pathological assessment. J Clin Pathol 2007;60:849-55.

Key messages for clinical practice

1. A multidisciplinary team approach significantly improves the outcome of rectal cancer patients. The pathologist has a crucial role in this process, by assessment of the quality of the mesorectal excision and the completeness of tumor resection.

2. The proximity of the tumor to the circumferential resection margin (CRM) is the most important factor for predicting the risk of local recurrence in rectal cancer patients. Tumor involvement of the CRM strongly correlates with local recurrence, distant metastasis and poor survival.

3. Macroscopic evaluation of the completeness of mesorectal excision has additional value in patients without CRM involvement. Incomplete mesorectal resection in patients with a negative CRM leads to a higher recurrence rate and lower survival.

4. The number of tumor-positive lymph nodes should be established with a yield as high as possible. Several studies support the concept that the more nodes are examined, the more accurate is the staging.

5. Assessment of tumor regression post neoadjuvant treatment needs standardization. Before concluding that there is complete response with no viable tumor identified, embedding of the whole suspicious area and cutting of 3 levels through each tissue block is suggested.

8. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumor spread and surgical excision. Lancet 1986;2:996-9.

9. Adam IJ, Mohamdee MO, Martin IG, Scott N, Finan PJ, Johnston D, et al. Role of circumferential margin involvement in the local recurrence of rectal cancer. Lancet 1994;344:707-11.

10. Wibe A, Rendedal PR, Svensson E, Norstein J, Eide TJ, Myrvold HE, et al. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. Br J Surg 2002;89:327-34.

11. Nagtegaal ID, Marijnen CA, Kranenbarg EK, Van de Velde CJ, Van Krieken JH, for the pathology review committee and the cooperative clinical investigators. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimetre but two millimetres is the limit. Am J Surg Pathol 2002;26:350-7.

12. Birbeck KF, Macklin CP, Tiffin NJ, Parsons W, Dixon MF, Mapstone NP, et al. Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. Ann Surg 2002;235:449-57.

13. Marr R, Birbeck K, Garvican J, Macklin CP, Tiffin NJ, Parsons WJ, et al. The modern abdominoperineal excision. The next challenge after total mesorectal excision. Ann Surg 2005;242:74-82.

14. Nagtegaal ID, Van de Velde CJ, Marijnen CA, Van Krieken JH, Quirke P. Low rectal cancer: a call for a change of approach in abdominoperineal resection. J Clin Oncol 2005;23:9257-64.

15. Nagtegaal ID, Van Krieken JH. The role of pathologists in the quality control of diagnosis and treatment of rectal cancer-an overview. Eur J Cancer 2002;38:964-72.

16. Torkzad MR, Blomqvist L. The mesorectum: morphometric assessment with magnetic resonance imaging. Eur Radiol 2005;15:1184-91.

17. Quirke P, Dixon MF. The prediction of local recurrence in rectal adenocarcinoma by histopathological examination. Int J Colorect Dis 1988;3:127-31.

18. Williams N, Dixon M, Johnston D. Reappraisal of the 5 centimeter rule of distal excision for carcinoma of the rectum: a study of distal intramural spread and patient' survival. Br J Surg 1983;70:150-4.

19. Halvorsen TB. Tissue sampling and histological grading in colorectal cancer. Are routine sections representative? APMIS 1989;97:261-6.

20. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Colorect Dis 1997;12:19-23.

21. Compton CC; 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. Arch Pathol Lab Med 2000;124:1016-25.

22. TNM classification of malignant tumors. 5th ed. New York: Wiley; 1997.

23. TNM classification of malignant tumors. 6th ed. New York: Wiley; 2002.

24. Marijnen CA, Nagtegaal ID, Kranenbarg EK, Hermans J, Van de Velde CJ, Leer JW, et al. No downstaging after short-term preoperative radiotherapy in rectal cancer patients. J Clin Oncol 2001;19:1976-84.

25. Rullier A, Laurent C, Capdepont M, Vendrely V, Bellean-

née G, Bioulac-Sage P, et al. Lymph nodes after preoperative chemoradiotherapy for rectal carcinoma: number, status, and impact on survival. Am J Surg Pathol 2008;32:45-50.
26. Caplin S, Cerottini J-P, Bosman FT, Constanda MT, Givel J-C. For patients with Dukes'B (TNM stage II) colorectal carcinoma, examination of six or fewer lymph nodes is related to poor prognosis. Cancer 1998;83:666-72.
27. De Ridder M, Vinh-Hung V, Van Nieuwenhove Y, Hoorens A, Sermeus A, Storme G. Prognostic value of the lymph node ration in node positive colon cancer. Gut 2006;55:1681.
28. Hamilton SR, Vogelstein B, Kudo S, Riboli E, Nakamura S, Hainaut P, et al. WHO histological classification of tumors of the colon and rectum. Pathology and genetics of tumors of the digestive system. Edited Hamilton SR, Aaltonen LA. Lyon: IARC-Press; 2000.
29. Wang C, Zhou Z-G, Wang Z, Li L, Zheng Y-C, Zhao G-P, et al. Mesorectal spread and micrometastases of rectal cancer studied with large slice technique and tissue microarray. J Surg Oncol 2005;91:167-72.
30. Quirke P. Pathology for the radiologist. Pathological insights into colorectal cancer. In: Contemporary issues in cancer imaging. Colorectal cancer. Edited by Brown G. Cambridge (UK): Cambridge University Press; 2007.
31. Shepherd NA, Baxter KJ, Love SB. Influence of local peritoneal involvement on pelvic recurrence and prognosis in rectal cancer. J Clin Pathol 1995;48:849-55.
32. Bouzourene H, Bosman FT, Seelentag W, Matter M, Coucke P. Importance of tumor regression assessment in predicting the outcome in patients with locally advanced rectal carcinoma who are treated with preoperative radiotherapy. Cancer 2002;94:1121-30.
33. Rödel C, Martus P, Papadoupolos T, Füzesi L, Klimpfinger M, Fietkau R, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol 2005;23:8688-96.
34. Quirke P, Morris E. Reporting colorectal cancer. Histopathology 2007;50:103-12.

Related BJMO articles

- Roels S, Mertens I, Haustermans K. Neoadjuvant treatment in resectable rectal cancer. BJMO 2008;2:9-15.
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