Abdominal Radiology (2019) 44:3751–3754
https://doi.org/10.1007/s00261-019-02134-9

SPECIAL SECTION: RECTAL CANCER

Pathologist's perspective on primary rectal cancer

Kenneth Friedman[1]

Published online: 20 July 2019

Abstract
Evaluation of primary rectal cancer specimens places the pathologist in a unique position relative to peers, as it is one of the few specimens where the report influences not just patient outcomes but also the quality of the surgical technique itself. With ever-increasing data indicating that the completeness of the mesorectal excision and adequate resection margins are critical for reduced local recurrence rates and improved clinical outcome, the pathologist is faced with the challenge of implementing methods to optimize the evaluation of primary rectal cancers.

Keywords Rectal neoplasms/pathology · Rectum/pathology · Colorectal neoplasms/pathology · Neoplasm staging

Introduction

Proper pathologic assessment of the total mesorectal excision, or TME, has important implications for both the patient and the surgeon. A complete, high-quality TME reduces local recurrence rates from 20–30% to 8–10% and increases 5-year survival from 48 to 68% [1, 2]. With the addition of preoperative radiotherapy, local recurrence rates can be further reduced from 8 to 2.6% [2]. The quality of the TME also provides surgeons with feedback as to their technique and has been shown to be superior to other indirect measures of surgical quality [3]. The College of American Pathologists (CAP) has standardized a grading system for assessing the quality of the TME [4]. The mesorectum can be graded "complete" when the surface is smooth with no defects greater than 5 mm in depth, "near complete" when the mesorectum is slightly less bulky or there are surface defects greater than 5 mm, and "incomplete" if surface defects expose the muscular wall (muscularis propria). Despite a relatively subjective set of criteria, the interrater agreement rate is high among pathologists and surgeons [5], and reporting of the completeness of the TME is now a required portion of the pathology report.

Other aspects of pathological evaluation of primary rectal cancers are just as important. For example, it has been suggested that tumor involvement of the circumferential (radial) resection margin (CRM) is the most critical factor in predicting local recurrence [6]. A positive CRM increases the risk of local recurrence by 3.5-fold and doubles the risk of death from disease. The CAP guidelines consider a positive CRM as tumor present 1 mm or less from the inked non-peritonealized surface and a negative CRM as tumor present greater than 1 mm from this surface. Evaluation of the distal margin becomes critical with low anterior resections, where 2 cm is generally considered an adequate clearance. The status of regional lymph nodes remains an important prognostic factor in colorectal cancer, and procurement of at least 12 lymph nodes is still a key quality measure for colon cancer care in the United States [7]. Data have shown that an adequate lymph node harvest is more difficult in obese patients [8] and in those who have received neoadjuvant therapy [9]. In addition, it has been shown that many nodal metastases occur in lymph nodes smaller than 5 mm in diameter [10].

Clearly, a thorough and meticulous pathologic evaluation of the macroscopic and microscopic features of rectal cancer specimens is crucial. Ironically, there is little standardization among pathologists and no formal recommendation as to the macroscopic handling of rectal cancer specimens. In fact, there is little standardization for the macroscopic handling of many specimens. Yet, if one thinks of the gross examination of a specimen as akin to the physical examination of a patient, there is little wonder as to why. Nonetheless, there are protocols that have been developed to overcome

✉ Kenneth Friedman
Kenneth.Friedman@uhhospitals.org

[1] Department of Pathology, University Hospitals Cleveland Medical Center, 11100 Euclid Ave., Cleveland, OH 44106, USA

subjectivity and improve consistency in the evaluation of these specimens. Both Quirke and Nagtegaal have done much to improve awareness of the importance of an adequate TME, and Quirke's approach to macroscopic handling was followed in the Dutch TME trial [11, 12]. We have found this approach to be of great value in capturing the necessary required pathologic reporting elements as well as allowing for excellent correlation with radiologic images.

In brief, upon receipt of the specimen, the external surface of the mesorectum is evaluated and graded per CAP guidelines as "complete," "nearly complete," or "incomplete." Overall measurements of the specimen are taken, and the TME is artificially divided into four quadrants comprising anterior/posterior, and left/right planes by the application of tissue ink. The lumen is opened until gross tumor is palpated, at which point no further opening occurs. If no gross tumor can be palpated, as is oftentimes the case in patients who have received preoperative neoadjuvant therapy, the lumen is opened completely from proximal to distal. Specimens fix overnight in 10% buffered formalin. After fixation, the specimen is serially sectioned, or "bread loafed," every 3 mm from distal to proximal and the slices positioned on the table oriented relative to the patient's anatomic position (Fig. 1). This allows for correlation with preoperative MRI findings. Visual inspection of each cross-sectional slice allows for documentation of the extent of tumor invasion, distance to the closest CRM, and involvement of any lymph nodes. Routine sections of the specimen are then taken for microscopy and always include proximal and distal margins, tumor or entire tumor bed if treated, and lymph nodes. Our institution performs whole mount tissue processing on tumor sections, which generates large glass slides (e.g., 4 × 3 inches) as opposed to the standard size of a glass slide (1 × 3 inches). This allows for an entire cross section to be analyzed under the microscope at once.

Rectal cancer slides are then subject to microscopic examination and interpretation by a pathologist who has received subspecialty training in Gastrointestinal Pathology so that several important staging and outcome parameters can be assessed. Assessment of the distance to the closest CRM is of utmost importance and requires diligence on the part of the pathologist to examine the entire inked outer surface for the closest viable tumor approach (Figs. 2, 3). Tumor response to preoperative therapy is another critical parameter, whereby eradication of tumor or even minimal residual disease are associated with improved prognoses [13]. Pathologists must be aware of the various histopathologic changes that occur following neoadjuvant treatment. These include changes to the tumor itself, such as a reduction in tumor diameter, development of single cells or small tumor nests, and changes to the surrounding tissue, including fibrosis, acellular mucin deposits, and a peri-tumoral lymphocytic response. While several tumor regression grading systems exist, we have found the modified Ryan scheme, based on the volume of residual primary tumor cells, to be the most robust method in minimizing interobserver variability [14]. Acellular mucin pools in treated patients are considered to represent completely eradicated tumor and are not used in assigning a pT or pN category. Lymphovascular invasion is assessed by examining small vessels

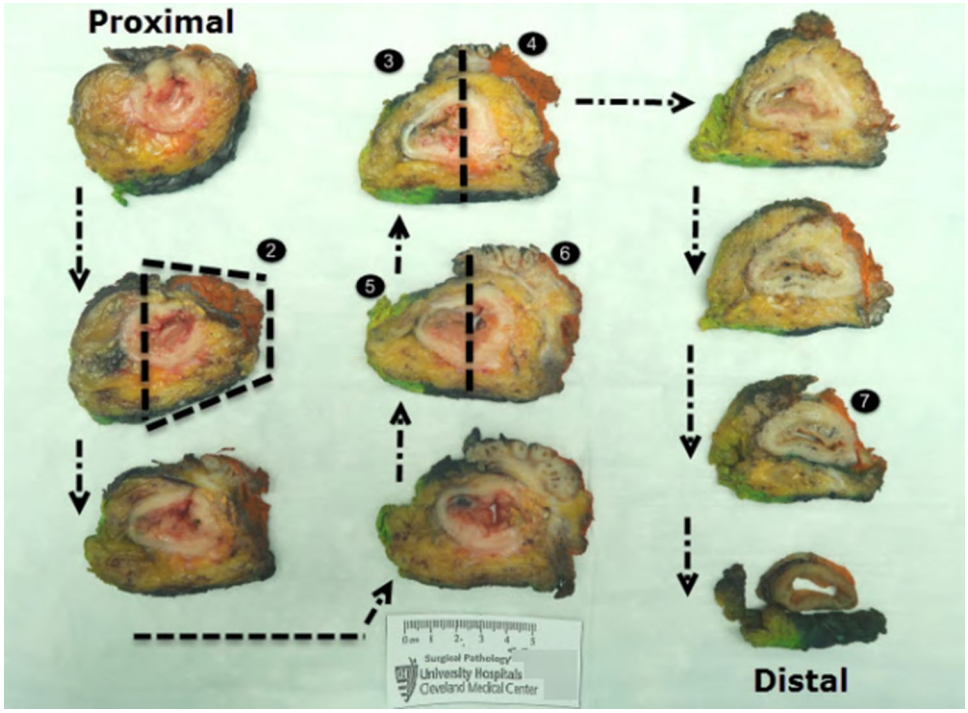

Fig. 1 Modified Quirke method for rectal cancer grossing. Serial cross sections every 3 mm allow adequate inspection of the extent of the cancer, and its relation to adjacent structures and the circumferential resection margin. The dotted lines correspond to the sections taken for microscopy, and the adjacent numbers refer to the corresponding number on the glass slide

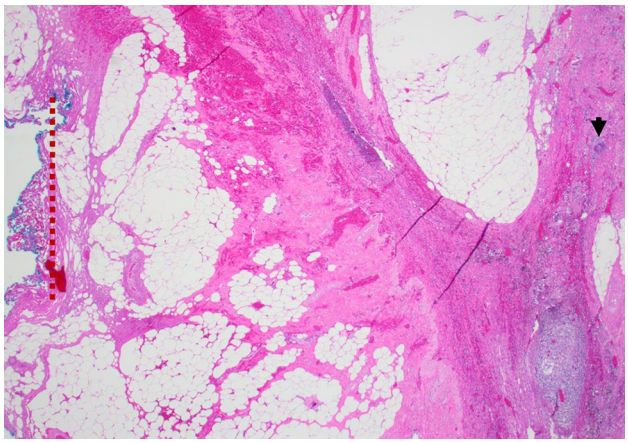

Fig. 2 A negative CRM, showing a malignant gland (right, short arrow) located 6.0 mm from the closest cauterized radial margin (left, red dotted line). Hematoxylin and eosin, ×2 magnification

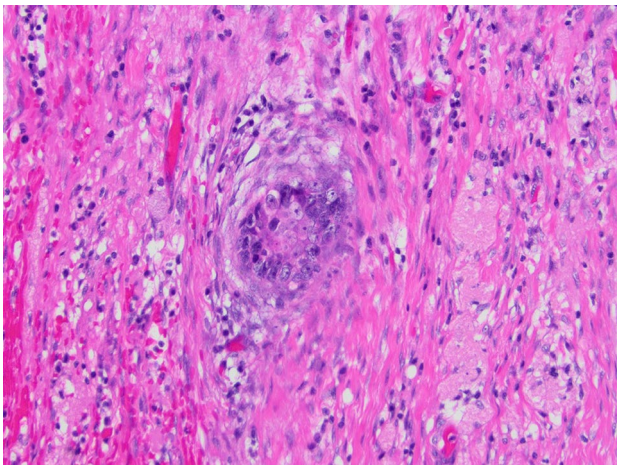

Fig. 3 Malignant gland embedded in smooth muscle, corresponding to the closest CRM as seen in Fig. 2. Hematoxylin and eosin, ×20

(lymphatics, capillaries, post-capillary venules) and large vessels (venous), the difference being that large vessels contain an endothelial-lined space with either an identifiable smooth muscle layer or elastic lamina. While routine hematoxylin- and eosin (H&E)- stained slides can give a clue as to whether large venous invasion is present, the use of an elastic stain can lead to a 2- to 3-fold increase in venous invasion and is highly encouraged in our department. This is especially important when we are considering extramural (beyond the muscularis propria) venous/large vessel invasion, given its significant adverse impact on prognosis and risk of liver metastasis [15]. Perineural invasion is also a negative prognostic factor, usually identifiable on routine H&E-stained slides, and is always reported when present, no matter the size or location of the nerve involved. Sterilization of tumor at the primary site, however, does not ensure the absence of lymph node metastasis, thus requiring meticulous lymph node sampling. Occasionally, pathologists are faced with the dilemma of whether a well-circumscribed nodule in the adjacent mesentery or peri-rectal fat represents a lymph node involved by tumor or a tumor deposit. The definition of a tumor deposit is relatively strict in that they must represent a discrete tumor nodule without identifiable lymph node tissue or vascular or neural structure. Sometimes, this requires the use of multiple step sections or an elastic stain to rule out vascular or neural involvement. In cases without positive lymph nodes but with a proven tumor deposit, the pN status changes to pN1c as opposed to pN0 and represents an adverse prognostic factor. Other potential prognostic criteria, such as assessment of the peritumoral lymphocytic response, are not routinely performed due to limitations in standardized criteria for measuring the inflammatory reaction and currently conflicting data with regard to its impact on overall survival.

It has become clear that a thorough macroscopic assessment, e.g., the modified Quirke method described above, and microscopic assessment, e.g., the use of whole mount slides, may not be practical for all pathology institutions, yet the need for an accurate and standardized assessment of rectal cancer specimens is becoming increasingly important. A multidisciplinary approach that incorporates such an assessment of rectal cancers is a goal of the Commission on Cancer's recently established National Accreditation Program for Rectal Cancer (NAPRC). The NAPRC standards for accreditation require a Pathologist with training and expertise in rectal pathology to be present as gross photography images of TME specimens and microscopic pathology are discussed in a multidisciplinary setting with radiologists, surgeons, and oncologists. Research initiatives involving collaboration between radiologists and pathologists are underway correlating findings on posttreatment preoperative MRI studies with histopathologic findings during gross and microscopic examinations. By doing so, this "RadPath" initiative hopes to be able to predict patients that have had a complete pathologic response to neoadjuvant therapy, in order to avoid the morbidity associated with surgery [16].

Conclusion

Pathologists face a unique challenge when evaluating primary rectal cancer specimens. A thorough macroscopic and microscopic approach to the specimen is needed, as reporting criteria have a significant effect on patient outcomes and the quality of surgery. Now more than ever, the pathologist's involvement as part of a multidisciplinary approach with radiology, oncology, and surgical colleagues is proving necessary for optimal quality of care.

References

1. Arbman G, Nilsson E, Hallböök O, Sjödahl R. Local recurrence following total mesorectal excision for rectal cancer. *Br J Surg*. 1996;83(3):375-379.
2. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med*. 2001;345(9):638-646. https://doi.org/10.1056/nejmoa010580
3. García-Granero E, Faiz O, Muñoz E, et al. Macroscopic assessment of mesorectal excision in rectal cancer: a useful tool for improving quality control in a multidisciplinary team. *Cancer*. 2009;115(15):3400-3411. https://doi.org/10.1002/cncr.24387
4. cp-gilower-colonrectum-17protocol-4010.pdf. https://documents.cap.org/protocols/cp-gilower-colonrectum-17protocol-4010.pdf. Accessed May 5, 2019.
5. Goebel EA, Stegmaier M, Gorassini DR, Kubica M, Parfitt JR, Driman DK. Grading of Total Mesorectal Excision Specimens: Assessment of Interrater Agreement. *Dis Colon Rectum*. 2018;61(6):686. https://doi.org/10.1097/dcr.0000000000000994
6. Birbeck KF, Macklin CP, Tiffin NJ, et al. Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. *Ann Surg*. 2002;235(4):449-457.
7. November 30 R, 2018. CoC Quality of Care Measures. American College of Surgeons. https://www.facs.org/quality-programs/cancer/ncdb/qualitymeasures. Accessed May 5, 2019.
8. Görög D, Nagy P, Péter A, Perner F. Influence of obesity on lymph node recovery from rectal resection specimens. *Pathol Oncol Res POR*. 2003;9(3):180-183.
9. Wijesuriya RE, Deen KI, Hewavisenthi J, Balawardana J, Perera M. Neoadjuvant therapy for rectal cancer down-stages the tumor but reduces lymph node harvest significantly. *Surg Today*. 2005;35(6):442-445. https://doi.org/10.1007/s00595-004-2956-5
10. Märkl B, Rößle J, Arnholdt HM, et al. The clinical significance of lymph node size in colon cancer. *Mod Pathol Off J U S Can Acad Pathol Inc*. 2012;25(10):1413-1422. https://doi.org/10.1038/modpathol.2012.92
11. Maughan NJ, Quirke P. Modern Management of Colorectal Cancer — A Pathologist's View. *Scand J Surg*. 2003;92(1):11-19. https://doi.org/10.1177/145749690309200103
12. Quirke P, Morris E. Reporting colorectal cancer. *Histopathology*. 2007;50(1):103-112. https://doi.org/10.1111/j.1365-2559.2006.02543.x
13. Gavioli M, Luppi G, Losi L, et al. Incidence and clinical impact of sterilized disease and minimal residual disease after preoperative radiochemotherapy for rectal cancer. *Dis Colon Rectum*. 2005;48(10):1851-1857. https://doi.org/10.1007/s10350-005-0133-6
14. Ryan R, Gibbons D, Hyland JM, Treanor D, White A, Mulcahy HE, et al. Pathological response following long- course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Histopathology*. 2005;47:141–6. https://doi.org/10.1111/j.1365-2559.2005.02176.x
15. Betge J, Pollheimer MJ, Lindtner RA, et al. Intramural and extramural vascular invasion in colorectal cancer: prognostic significance and quality of pathology reporting. *Cancer*. 2012;118(3):628-638. https://doi.org/10.1002/cncr.26310
16. Allen SD, Padhani AR, Dzik-Jurasz AS, Glynne-Jones R. Rectal Carcinoma: MRI with Histologic Correlation Before and After Chemoradiation Therapy. *Am J Roentgenol*. 2007;188(2):442-451. https://doi.org/10.2214/ajr.05.1967