SPECIAL ARTICLE

Canadian Association of General Surgeons, the American College of Surgeons, the Canadian Society of Colon and Rectal Surgeons, and the American Society of Colon and Rectal Surgeons: Evidence Based Reviews in Surgery – Colorectal Surgery

Arden M. Morris, M.D. • Erin D. Kennedy, M.D. • D. Blair Macdonald, M.D.
Heidi Nelson, M.D. for the members of the Evidence Based Reviews in Surgery Group

The term "evidence-based medicine" was first coined by Sackett and colleagues as "the conscientious, explicit and judicious use of the current best evidence in making decisions about the care of individual patients."[1] The key to practicing evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding, and reading all of the medical literature is impossible for an individual clinician. For clinicians to practice evidence-based medicine, they must have the skills to read and interpret the medical literature so they can determine the validity, reliability, credibility, and utility of individual articles, ie, critical appraisal skills. Generally, critical appraisal requires that the clinician have some knowledge of biostatistics, clinical epidemiology, decision analysis, and economics as well as clinical knowledge.

The Canadian Association of General Surgeons and the American College of Surgeons jointly sponsor a program entitled "Evidence Based Reviews in Surgery" (EBRS), supported by an educational grant from Ethicon Endo Surgery Inc and Ethicon Endo Surgery Canada. The primary objective of this initiative is to help practicing surgeons improve their critical appraisal skills. EBRS has a module covering topics in colorectal surgery. Each academic year, 6 clinical articles are chosen for review and discussion. The articles are selected not only for their clinical relevance to colorectal surgery, but also to cover a spectrum of methodological issues important to surgeons; for example, causation or risk factors for disease, natural history or prognosis of disease, quantifying disease (measurement issues), diagnostic tests and the diagnosis of disease, and the effectiveness of treatment. Both methodological and clinical reviews of the article are performed by experts in the relevant areas and posted on the Evidence Based Reviews in Surgery-Colorectal Surgery (EBRS-CRS) Web site. In addition, a listserv discussion is held where participants can discuss the monthly article. Members of the Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS) can access EBRS-CRS through the Canadian Association of General Surgeons Web site (www.cags-accg.ca), the American College of Surgeons Web site (www.facs.org/education/ebrs.html), the Canadian Society of Colon and Rectal Surgeons (CSRCS) Web site (www.cscrs.ca), and the American Society of Colon and Rectal Surgeons (ASCRS) Web site (www.fascrs.org). All journal articles and reviews are available electronically through the Web site. Surgeons who participate in the monthly packages can receive 6 CME and/or Maintenance of Certification credits by completing an evaluation and a series of multiple-choice questions each month. For further information about EBRS-CRS, readers are directed to the CAGS, ACS, CSCRS, and ASCRS Web sites or should email the administrative coordinator, Marg McKenzie at mmckenzie@mtsinai.on.ca

In addition to making the reviews available through the CAGS and the ACS Web sites, a condensed version of the reviews will be published in the *Diseases of the Colon & Rectum*. EBRS is useful in improving your critical appraisal skills, keeping abreast of new developments in colorectal surgery, and, most importantly, you are able to obtain 6 CME credits each month from anywhere that you have access to a computer. Comments about EBRS may be directed to mmckenzie@mtsinai.on.ca

SELECTED ARTICLE

Taylor FG, Quirke P, Heald RJ, et al. Preoperative high-resolution magnetic resonance imaging can identify good prognosis stage I, II, and III rectal cancer best managed by

Dis Colon Rectum 2013; 56: 798–802
DOI: 10.1097/DCR.0b013e3182905b57

surgery alone: a prospective, multicenter, European study. *Ann Surg.* 2011;253:711–719.
QUESTION: Can MRI-predicted good prognosis rectal cancers be safely treated with surgery alone?
DESIGN: This is a subgroup analysis of a prospective cohort study.
SETTING: This study was conducted at academic and community general hospitals in the United Kingdom, Sweden, Norway, and Germany.
PATIENTS: All patients included in the MERCURY study who were staged as MRI-defined "good" prognosis tumors were included in this study. "Good" prognosis included MRI-predicted safe circumferential resection margins, with MRI-predicted T1T2/T3a/T3b (less than 5 mm spread from muscularis propria), any N-category (N0–N2), and extramural venous invasion regardless of MRI N-stage. Based on these criteria, good prognosis patients proceeded directly to surgery and did not receive preoperative or postoperative radiotherapy.
ASSESSMENT OF PROGNOSTIC FACTORS: The primary prognostic factors were overall survival, disease-free survival, and local recurrence.
RESULTS: Four patients (3.3%) had positive circumferential resection margins (CRMs). None of these patients developed local recurrences. The overall local recurrence rate was 3%. Overall and disease-free survival for all patients with MRI "good prognosis" at 5 years was 68% and 85%.
CONCLUSION: The preoperative identification of good prognosis tumors with the use of MRI allows stratification of patients and better targeting of preoperative therapy. This study suggests that MRI can be used to select patients who are likely to have a good outcome with primary surgery alone, but further studies are required before this approach is adopted into practice.
COMMENTARY: The National Institutes of Health Consensus Statement of 1990[2,3] recommended that all patients with stage II and III rectal cancer should receive radiation therapy. However, although preoperative chemoradiotherapy can improve outcomes, we also know it comes with lasting and significant disabilities, and it can prolong the care of the typical patient by nearly 10 months, as well. A Cochrane review[4] of 19 trials in 2008 reported that preoperative radiation therapy increases perineal and pelvic infections, increases the risk of late rectal and sexual dysfunction, but only marginally improves (an absolute difference of 2% if the expected survival is 60%) overall mortality. Furthermore, they noted that preoperative radiation improved local recurrence rates, but they stated that the magnitude of benefit was heterogeneous. So, in summary, we are overtreating the majority of patients with rectal cancer for the benefit of the minority.

The MERCURY study was designed to determine the diagnostic accuracy of MRI in assessing the depth of extramural spread and thus in predicting a safe surgical resection margin by using a histopathologic reference as the standard. The hypothesis was that optimal preoperative MRI staging could select patients with rectal cancer amenable to cure by surgery alone. Patients were recruited from 11 different hospitals that ranged from busy general hospitals to specialized university teaching hospitals. There was standardization of total mesorectal excision (TME) technique and pro forma data collection, and pathology and radiology workshops were held to ensure high quality throughout the trial.[5] Based on the MRI criteria shown in Table 1, patients with "good prognosis" tumors underwent immediate surgery with TME and those with "poor prognosis" tumors received preoperative chemoradiotherapy (CRT) followed by TME. The evidence for the MRI criteria used to classify "good" and "poor" prognosis tumors is primarily based on the work of Merkel et al and previous work by the MERCURY group led by Dr Gina Brown.[6]

TABLE 1. MRI classification used by the MERCURY Group

MRI criteria	*Good prognosis*	*Poor prognosis*
CRM	>1 mm (clear)	<1 mm (involved)
T-category	T1, T2, T3a, or T3b	T3c, T3d, or T4
EMVI	Negative	Positive
N-category	Any	Any

CRM = circumferential resection margin; EMVI = extramural vascular invasion.

Of 374 patients included in the MERCURY study, 141 were considered to have a good prognosis. Nineteen of these had preoperative radiation for unspecified reasons. Thus, Taylor and colleagues present the local recurrence and overall and disease-free survival data after 5 years of follow-up of the subcohort of 122 patients who were considered to have a good prognosis and did not have preoperative radiation.

Sixty-five of the 122 patients with the following MRI-predicted stage (24 T3aN0, 19 T3bN0, 7 T2N1, 6 T3aN1, 7 T3aN1, and 2 T3bN2) avoided the combined-modality preoperative CRT that is still the accepted standard treatment in North America and recommended by the National Comprehensive Cancer Network guidelines.[7] They also avoided the associated morbidity and costs of this treatment. Final pathology revealed node-positive disease in 44 patients (N1–N2), and all of these patients received adjuvant single-agent systemic chemotherapy as per protocol. They were not given postoperative CRT, which is common practice at many North American centers when positive nodes are detected after primary surgical management. Four patients had positive CRMs, but none of these patients developed local recurrences.

Overall, there were 4 (3.3%) local recurrences in 122 patients with "good prognosis" MRI-predicted T2 or T3 tumors. The authors explicitly state that only 1 MRI-predicted T3 tumor recurred locally, so the other 3 recurrences must have been from MRI-predicted T2 tumors (1 pT2,

TABLE 2. Results

Outcome	*Result, %*	*95% CI, %*
Local recurrence		
MRI-predicted T2	4.7	1.2–14.0
MRI-predicted T3	1.7	0.3–9.1
Disease-free survival		
Stage II	76.0	56.7–87.6
Stage III	95.0	69.5–99.3
Overall survival		
Stage II	65.7	48.7–78.5
Stage III	81.0	74.0–88.0

1 pT3, and 1 pT4). Therefore, local recurrences included 3/64 (4.7%) in the 64 MRI-predicted T2 disease and 1/58 (1.7%) in the MRI-predicted T3 disease group. The results are as follows (Table 2).

Despite falling short of defining a new practice paradigm, the study does support the application of MRI-predicted tumor extent as the most important and accurate tool to direct decision making. Magnetic resonance imaging is the best modality for evaluating the involvement of the potential CRM. The MERCURY study group demonstrated that MRI is highly specific for predicting a clear margin at surgery: 92% (327/354 cases).[5] Magnetic resonance imaging is also very good at determining the depth of the extension of tumor into the mesorectal fat (T3a/b vs T3c disease). The MERCURY study group demonstrated the equivalence of MRI and histopathology for determining maximal extramural depth of spread ±0.5 mm.[8] In comparison, MRI is only moderately accurate for differentiating between T2 versus T3 tumors. A recent meta-analysis of MRI to discriminate between early (T1/T2) versus advanced (T3/T4) tumors indicated a pooled sensitivity of 87% and a specificity of 75%.[9] Therefore, if extramural depth of invasion >5 mm (T3c) is accepted as the threshold for neoadjuvant treatment in North America, this will increase the utility of MRI by taking advantage of its greater accuracy in this regard. Greater accuracy will reduce MRI understaging events and lessen the need for postoperative CRT, thereby reducing costs and morbidity.

Lymph node status was not included in the MRI classification proposed by MERCURY, because lymph node evaluation on MRI as well as other imaging modalities is relatively poor.[9] Interestingly, the results of this study showed that lymph node involvement was not an independent predictor of local recurrence or survival and contradicts previous randomized controlled trial (RCT) data. Although the small proportion of node-positive cases in this study likely does not provide adequate power to strongly support this conclusion, this finding has significant implications on current guidelines for the selection of patients with rectal cancer for preoperative CRT. Characterizing mesorectal nodes remains a major limitation of all imaging modalities including MRI. Aside from the absence of visible nodes or, conversely, the presence of very large nodes, size criteria have been proven inaccurate and inferior to morphologic criteria. To achieve good sensitivity and specificity, the radiologist must analyze nodes for heterogeneous signal and border characteristics. Even so, a recent meta-analysis of MRI accuracy indicated a pooled sensitivity of 77% and a specificity of 71% for identifying lymph node metastases.[9] That level of node discrimination will lead to false positives or false negatives. For example, in this cohort of 122, only 22 patients were classified as node positive on preoperative MRI, whereas 44 were node positive at histopathology. A better imaging option for small nodes is not readily available; PET/CT has also been shown to be of no significant help for nodes less than 1 cm, and MR lymphographic contrast medium (ultrasmall super paramagnetic iron oxide) that has been reported to improve specificity is not approved for clinical use in the North America. Therefore, an accurate test for preoperative node characterization seems unlikely in the near future. If an accurate preoperative test is not available, a clear strategy for missed nodal disease will be needed. The centers in this study consistently used postoperative single-agent chemotherapy.

This study is important because the results suggest that, with better preoperative staging, a more selective approach to the use of preoperative CRT can be used and may result in similar, if not better, long-term outcomes than those achieved in previous RCTs. It is important to note that preoperative staging in all previous RCTs was based primarily on clinical examination, which has been shown to be highly inaccurate even in expert hands,[10] and overstaging was reported in 20% of patients in the German trial undergoing preoperative staging with transrectal ultrasound.[11] Therefore, the use of MRI criteria to select patients for preoperative CRT likely better reflects current clinical practice, and it may be that, with more appropriate preoperative staging (with MRI), lymph node involvement may not be as important a predictor of local recurrence as previous RCTs have shown. A more selective approach to the use of preoperative CRT is appealing, because functional outcomes are better with surgery alone, and better functional outcomes have been shown to be highly valued by patients in this setting.[12–15]

To understand how these new results "fit" with existing knowledge, we must understand the basis for the heterogeneity reported in the Cochrane review. The heterogeneity probably comes from both the imprecision of how we define and measure "risk" and from the confounding influences on "risk" from an ever-changing practice. Take, for example, how much more we know about how depth of invasion into the mesorectum influences the risk of recurrence. Tumors with minimal penetration of the muscularis behave remarkably differently from those that deeply penetrate the mesorectum, especially those

that breach the mesorectal fascia, leaving a positive CRM. Pathologic staging was not as refined at the time of the early rectal cancer adjuvant studies; ie, the Astler Coller staging was far more rudimentary as a prognostic tool than the current seventh edition of the American Joint Commission on Cancer staging manual.[16] Preoperative imaging was limited to CT, a poor predictor of depth of invasion. Over the same time, colon and rectal cancer screening became a routine part of practice, leading to earlier detection and earlier-stage tumors, and the rising awareness of the contribution of quality surgery to improved outcomes from surgery alone in centers that practiced optimal techniques. And so it is entirely believable that this constellation of practice changes and staging/imaging refinements could bring us back to the practice of surgery alone for some patients with stage II and III rectal cancer. Indeed, a recent report from a single-institution series shows local recurrence rates of 4.3% for surgery alone in this same population.[17]

Unfortunately, this study is limited by its nonrandomized design and small sample size. In particular, 47% (57/122) of the patients in this study had stage I tumors and 53% (65/122) had stage II and stage III tumors. And, because the patients with stage I tumors would not routinely be considered for preoperative CRT (in North America), when these patients are excluded from the analysis, the positive margin rate increases to 6.2% (4/65) and the local recurrence rate increases to 4.6% (3/65). Recently, a similar study was published with the use of MRI criteria of CRM <1 mm to select patients for preoperative CRT. This study reported a positive CRM rate of 1.5% (2/134), but it has not yet reported long-term outcomes.[18]

Therefore, the results of this study will need to be reproduced with larger sample sizes in multiple centers to establish the external validity and generalizability of this approach. A RCT comparing treatment based on the National Comprehensive Cancer Network clinical practice guidelines vs MRI-directed selective avoidance of neoadjuvant therapy in "good prognosis" tumors would provide a stronger basis to determine the best treatment and to change practice.

Additionally, we still lack widespread agreement on the MRI criteria. Although the MERCURY group defines a threatened CRM as <1 mm to the mesorectal fascia, many other groups consider a threatened CRM as <5 mm because a 1-mm margin leaves very little room for error, especially in a narrow, male pelvis and/or anterior tumor. Beets-Tan et al[19] used individual patient measurements (ie, not a cutoff) to predict the pathologic CRM based on the MRI-predicted CRM in 35 patients with T3 tumors. This study showed that an MRI-predicted CRM of 5 mm corresponded to a pathologic CRM of 1 mm in more than 95% of the cases. This has led to some controversy as to whether a threatened CRM should be defined as <1 mm or <5 mm to the mesorectal fascia on MRI. It is noteworthy that the MERCURY group has reported better interobserver agreement on CRM margin status at the 1-mm cutoff level ($k = 0.51$; 95% CI, 0.31–0.72) than at the 5-mm cutoff level (0.37; 95% CI, 0.17–0.57).[20] The relevance of a 1-mm cutoff has also been questioned given the relatively low percentage of tumors with a CRM <1 mm on MRI. In addition, the acceptance that lymph node status may not be a critical element for preoperative staging requires a considerable "leap of faith" based on the evidence provided in this study and shown in previous RCT data.

Last, high-quality MRI imaging and reporting must be achieved to accurately apply this MRI classification. Although the MERCURY group included 18 radiologists from 14 centers with 5 to 20 years of experience, this represents an expert group of highly motivated radiologists dedicated to the study and working at centers of excellence for rectal cancer. Therefore, although this group has reported relatively good interrater reliability for each of the MRI criteria, this must be evaluated in other centers to ensure that these results are reproducible.

ACKNOWLEDGMENTS

Members of the Evidence Based Reviews in Surgery Steering Committee: Nancy N. Baxter, M.D., Toronto, Ontario, Canada; Karen J. Brasel, M.D., Milwaukee, Wisconsin; Carl J. Brown, M.D., Vancouver, British Columbia, Canada; Prosanto K. Chaudhury, M.D., Montreal, Quebec, Canada; Celia M. Divino, M.D., New York, New York; Elijah Dixon, M.D., Calgary, Alberta, Canada; G. William N. Fitzgerald, M.D., St. Anthony, Newfoundland, Canada; S. Morad Hameed, M.D., Vancouver, British Columbia, Canada; Harry J. Henteleff, M.D., Halifax, Nova Scotia, Canada; Tyler G. Hughes, M.D., McPherson, Kansas; Lillian S. Kao, M.D., Houston, Texas; Andrew W. Kirkpatrick, M.D., Calgary, Alberta, Canada; Steven Latosinsky, M.D., London, Ontario, Canada; Tara M. Mastracci, M.D., Cleveland, Ohio; Robin S. McLeod, M.D., Toronto, Ontario, Canada; Arden M. Morris, M.D., Ann Arbor, Michigan; Timothy M. Pawlik, M.D., Baltimore, Maryland; Larissa K. Temple, M.D., New York, New York; Marg McKenzie, R.N., Toronto, Ontario, Canada.

REFERENCES

1. Evidence Based Medicine Working Group. Evidence-based medicine: a new approach to teaching the practice of medicine. *JAMA* 1992;268:2420–2425.
2. Nelson H, Sargent DJ. Refining multimodal therapy for rectal cancer. *N Engl J Med.* 2001;345:690–692.
3. NIH consensus conference: adjuvant therapy for patients with colon and rectal cancer. *JAMA* 1990;264:1444–1450.

4. Wong RK, Tandan V, De Silva S, Figueredo A. Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma. *Cochrane Database Syst Rev.* 2007;(2):CD002102.
5. MERCURY Study Group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. *BMJ.* 2006;333:779.
6. Merkel S, Mansmann U, Siassi M, Papadopoulos T, Hohenberger W, Hermanek P. The prognostic inhomogeneity in pT3 rectal carcinomas. *Int J Colorectal Dis.* 2001;16:298–304.
7. Engstrom PF, Arnoletti JP, Benson AB 3rd, et al. NCCN clinical practice guidelines in oncology: rectal cancer. *J Natl Compr Canc Netw.* 2009;7:838–881.
8. MERCURY Study Group. Extramural depth of tumor invasion at thin-section MR in patients with rectal cancer: results of the MERCURY study. *Radiology* 2007;243:132–139.
9. Al-Sukhni E, Milot L, Fruitman M, et al. Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. *Ann Surg Oncol.* 2012;19:2212–2223.
10. Brown G, Davies S, Williams GT, et al. Effectiveness of preoperative staging in rectal cancer: digital rectal examination, endoluminal ultrasound or magnetic resonance imaging? *Br J Cancer.* 2004;91:23–29.
11. Sauer R, Becker H, Hohenberger W, et al; German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med.* 2004;351:1731–1740.
12. Marijnen CA, van de Velde CJ, Putter H, et al. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. *J Clin Oncol.* 2005;23:1847–1858.
13. Peeters KC, van de Velde CJ, Leer JW, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients: a Dutch colorectal cancer group study. *J Clin Oncol.* 2005;23:6199–6206.
14. Kennedy ED, Schmocker S, Victor C, et al. Do patients consider preoperative chemoradiation for primary rectal cancer worthwhile? *Cancer.* 2011;117:2853–2862.
15. Kornmann M, Henne-Bruns D, Porzsolt F. Neoadjuvant treatment of rectal carcinoma: assessment of health care services by physicians and lay persons. *J Clin Oncol.* 2008;26:4866–4868.
16. Edge SE, Byrd DR, Compton CC, et al. *AJCC Cancer Staging Manual.* 7th ed. New York, NY: Springer; 2009.
17. Mathis KL, Larson DW, Dozois EJ, et al. Outcomes following surgery without radiotherapy for rectal cancer. *Br J Surg.* 2012;99:137–143.
18. Strassburg J, Ruppert R, Ptok H, et al. MRI-based indications for neoadjuvant radiochemotherapy in rectal carcinoma: interim results of a prospective multicenter observational study. *Ann Surg Oncol.* 2011;18:2790–2799.
19. Beets-Tan RG, Beets GL, Vliegen RF, et al. Accuracy of magnetic resonance imaging in prediction of tumour-free resection margin in rectal cancer surgery. *Lancet.* 2001;357:497–504.
20. Pedersen BG, Moran B, Brown G, Blomqvist L, Fenger-Grøn M, Laurberg S. Reproducibility of depth of extramural tumor spread and distance to circumferential resection margin at rectal MRI: enhancement of clinical guidelines for neoadjuvant therapy. *AJR Am J Roentgenol.* 2011;197:1360–1366.

RETRACTION

Perianal Versus Endoanal Application of Glyceryl Trinitrate 0.4% Ointment in the Treatment of Chronic Anal Fissure: Results of a Randomized Controlled Trial. Is This the Solution to the Headaches?: Retraction

Statistical errors have been detected in the article entitled "Perianal Versus Endoanal Application of Glyceryl Trinitrate 0.4% Ointment in the Treatment of Chronic Anal Fissure: Results of a Randomized Controlled Trial: Is This the Solution to the Headaches?" by Pérez-Legaz et al., published in the August 2012 issue of *Diseases of the Colon & Rectum*. The primary data has been lost and a re-analysis cannot be performed. This article has been retracted in full.

Robert D. Madoff, M.D.
Editor-in-Chief

REFERENCE

1. Pérez-Legaz J, Arroyo A, Moya P, et al. Perianal versus endoanal application of glyceryl trinitrate 0.4% ointment in the treatment of chronic anal fissure: results of a randomized controlled trial. Is this the solution to the headaches? *Dis Colon Rectum.* 2012;55:893–899.