SPECIAL ARTICLE

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

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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. In general, 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 Inc., Ethicon Endo Surgery Inc., and Ethicon Endo Surgery. The primary objective of this initiative is to help practicing surgeons improve their critical appraisal skills. In 2007, EBRS also included 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) website. 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 the EBRS-CRS website through the Canadian Association of General Surgeons website (www.cags-accg.ca), the American College of Surgeons website (www.facs.org/education/ebrs.html), the Canadian Society of Colon and Rectal Surgeons (CSRCS) website (www.cscrs.ca), and the American Society of Colon and Rectal Surgeons (ASCRS) website (www.fascrs.org), All journal articles and reviews are available electronically through the website. Surgeons who participate in the current (modules) packages can receive CME and/or Maintenance of Certification credits by completing an evaluation and a series of multiple choice questions. For further information about EBRS-CRS, readers are directed to the CAGS, ACS, CSCRS, and ASCRS websites 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 websites, a condensed version of the reviews will be published in the *Diseases of the Colon & Rectum*. We hope readers will find EBRS useful in improving their critical appraisal skills and also in keeping abreast of new developments in general surgery. Comments about EBRS may be directed to mmckenzie@mtsinai.on.ca.

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SELECTED ARTICLE

Neuman HB, Elkin EB, Guillem JG, et al. Treatment for patients with rectal cancer and a clinical complete response

to neoadjuvant therapy: a decision analysis. *Dis Colon Rectum*. 2009;52:863–871.

QUESTION: What are the benefits of surgery vs observation in patients with rectal cancer who have a clinical complete response (cCR) after neoadjuvant chemoradiation therapy (CRT)?

DESIGN: This study was designed based on a Markov state-transition model.

BASE CASE: The base case for this study was a 65-year-old man who was medically fit to undergo major surgery without distant metastases, who had, according to clinical evaluation, a complete response to neoadjuvant CRT.

TREATMENT ALTERNATIVES: Patients with cCR after preoperative CRT underwent surgery (sphincter-preserving surgery and abdominoperineal resection) or observation.

OUTCOMES CONSIDERED: Life expectancy and quality-adjusted life years were the outcomes considered.

SOURCES OF ESTIMATES FOR PROBABILITIES AND UTILITIES: Baseline probabilities were derived from a systematic search of the literature and expert consensus. Utilities (numeric estimates of preference for a given health state or outcome) were derived from published reports.

RESULTS: Surgery was the preferred option with an increased life expectancy of 0.54 years and 0.29 quality-adjusted life years.

SENSITIVITY ANALYSES: The analyses demonstrated that observation was preferred to surgery if the ability to correctly identify patients with true complete responses exceeded 58%, if quality-of-life after surgery was poor (utility <0.81), or if the relative reduction in recurrence with surgery was $<43\%$ compared with observation.

CONCLUSION: Surgical resection was the preferred management strategy, compared with observation alone for the average person with rectal cancer with a cCR after neoadjuvant therapy.

COMMENTARY: Neoadjuvant CRT is currently the accepted standard of care in North America for low T3/T4 and/or node-positive rectal cancer without evidence of distant metastases. The finding that some rectal cancer specimens in patients treated with CRT before surgery have no detectable cancer cells has led to clinicians questioning the need for surgery in patients with a cCR. The temptation to observe these patients to spare them the morbidity and functional consequences of a total mesorectal excision must be tempered by the risk of tumor relapse from clinically occult tumor deposits. Given that some patients with a cCR still have cancer cells in the bowel wall and/or in the mesorectal lymph nodes, and that clinical examination correlates poorly with the final pathology, most surgeons still recommend surgery for patients with rectal cancer treated with CRT independent of the clinical tumor response. However, this is one of the most controversial topics in the management of rectal cancer.

This decision analysis was performed to evaluate the relative benefits of surgery vs observation in patients with rectal cancer who have cCR after neoadjuvant CRT. The model simulated outcomes for patients with stage I to III rectal cancer by use of a base case of a 65-year-old man who was medically fit to undergo major surgery and was without distant metastases who had, according to clinical evaluation, a complete response to CRT. Two strategies, observation and radical resection, were compared to determine which was preferable in terms of life expectancy and quality-adjusted life years. Probabilities were generated by a systematic search of the literature and by expert opinion. Many of the studies used to generate probabilities were based on treatment of stage II and III rectal cancer and may not be applicable to patients with stage I disease. Some probabilities were derived from case series of patients, in some cases, from single institutions. The quality of evidence supporting the relevant probabilities differed significantly between the 2 strategies; probabilities used to evaluate the surgical resection strategy were supported by higher-quality evidence than those for observation strategy, where probabilities were largely derived from expert opinion. Utilities for surgical outcomes were obtained from previously published studies.

The authors found that surgery was the preferred strategy with an average gain in life of 6.5 months and quality-adjusted years of 3.5 months. The preferred strategy was sensitive to varying 3 parameters so that observation became the preferred option when 1) the ability to select patients with a pathological complete response was greater than 58%, 2) the utility associated with surgery was lower than 0.81, and 3) the relative risk reduction in recurrence with surgery vs observation decreased to 43% or less. Readers might question whether a difference in quality-adjusted life expectancy with surgery of only 0.29 Quality Adjusted Life Years (ie, 15 weeks) is significant. However, in general, a gain of 2 months is considered important and would not be considered a "toss-up" by the average patient.

The present article is a useful addition to the discourse, in that it brings many of the salient variables to be considered in making this important decision to the attention of both patients and clinicians. A growing list of modest case series examines the role of observation vs resection, often with a palpable bias in one direction or the other. By contrast, the methodology of this decision analysis was rigorous and used the best available evidence from multiple sources included in the model to assist in decision making. The conclusion that surgery is beneficial for the average patient who has a cCR would be in keeping with the cautious approach favored by most North American colorectal cancer surgeons.

However, there are some serious limitations to this decision analysis. The main limitations are the assumptions made in constructing the model, such as the fitness of

the patient to undergo surgery, and the lack of strong evidence relating to some of the critical parameters such as the rate of pathologic complete response (pCR) in those having a cCR, and the risk of recurrence in patients with a pCR who are treated with observation alone. These variables can at present only be roughly estimated based on inadequate data.

One key prerequisite to treating patients nonoperatively is the ability to define and determine cCR. Of the many series reporting pCR following neoadjuvant CRT, only a small number report cCR rates, and an even smaller proportion disclose the criteria used to determine cCR. Timing is an important variable because response clearly evolves beyond 2 weeks and even beyond 8 weeks. Habr Gama et al[2] routinely evaluate clinical response at 10 weeks. Furthermore, conventional imaging studies performed during and immediately after CRT have not been very useful for predicting which patients thought to have a cCR will have a pCR. New strategies including the use of conventional imaging at different time intervals, the use of new imaging technology such as molecular imaging, or the search for tumor DNA in the tumor bed or in the peripheral blood may help to increase the accuracy of identifying pCR. The threshold value in this model was 58%. Although this falls within the plausible range (19%–90%), only if one can consistently predict pCR in more than half of patients does observation become a credible option.

Second, there is a paucity of prospectively collected data on outcomes of unresected patients following cCR. Furthermore, there is no agreement about what constitutes a cCR and what criteria should be used to define it. In addition, there has not yet been enough collective experience with observation in patients who had a cCR to know with certainty whether individual pathological variables such as lymphovascular invasion, poor differentiated histology, or systemic immunosuppression affect prognosis, and what the extent of that impact would be. It will require considerably greater experience with observation to ascertain this.

Third, the long-term outcome of patients who have achieved pCR (determined by local excision) is not yet known with certainty. Whereas recurrence rates in this group appear favorable at 5 years, leading the authors to assume a base case relapse rate of 6%, it is possible that local and distant relapses will manifest themselves in the longer term, as has been generally noted following local excision of early stage cancers without CRT. Similarly, the long-term impact of local failure after observation in patients with a cCR is not known. Habr-Gama and colleagues suggest that surgical salvage is technically feasible in the majority of such cases, and the risk of early relapse is uncommon, but the follow-up of these patients is short. In general, there is a lack of prospectively collected data on outcomes of unresected patients following cCR.

Finally, the generalizability of the results of this decision analysis may be limited when one recalls that the patient on whom the model is constructed is a 65-year-old otherwise healthy man. The median age of patients presenting with colorectal cancer is 70, and the majority of patients have at least one salient comorbidity. Age will presumably impact both operative mortality and morbidity, the utility of surgery after radiation, and the ability to affect surgical salvage several years down the line, as will the age-related increase in comorbidities. Other variables such as BMI may also affect the ability to effect a durable surgical salvage. Many of the probabilities were derived from T2 tumors, which are less likely to be associated with nodal disease and more likely to undergo cCR and pCR than T3 and T4 tumors.

Despite serious uncertainties as to the oncologic outcomes associated with observation only following cCR, practice has previously changed in many centers, in particular, in Brazil and the United Kingdom. The easy availability of the Habr-Gama publications to patients and the favorable short-term outcomes have created patient demand for a "wait and see" approach, sometimes without appropriate selection criteria. Clinicians who choose to apply a "wait and see" policy to individual patients in their practice (or whose patients choose to adopt this strategy) should record the objective results on which their cCR designation is based, and should then monitor these individuals assiduously according to a predefined schedule. At a minimum, this would permit a degree of self-assessment, at least for a busy colorectal cancer surgeon who manages an adequate volume of potentially curable patients. Ideally, a well-annotated collective experience could then be generated to guide future decision making for a wide spectrum of patients presenting with primary rectal cancer.

The model presented in this article is helpful in pointing out some of the important considerations, but is to a significant extent based on premature assumptions and limited evidence. It does help us to identify areas where evidence is currently lacking such as salvage surgery for local recurrence after observation, and areas on which to focus our research efforts, such as interventions to increase the likelihood of a pCR and diagnostic modalities that increase the identification of patients who have a pCR. Ultimately, this debate will only be solved by a well-designed clinical trial. Currently, although the note of caution sounded by the authors in their conclusion is appropriate, we should continue to view resection as the standard.

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