Simulating Watch and Wait for Rectal Cancer

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For decades, it has been accepted that surgical resection is the cornerstone for the curative treatment of rectal cancer. Conventional treatment for patients with locally advanced stages II and III rectal cancers has included preoperative radiation with concurrent chemotherapy, before radical resection, to improve local control. Unfortunately, surgery is not without its risk for serious complications, which can include anastomotic leak, perineal wound dehiscence, and even mortality. Moreover, surgery for rectal cancer may necessitate a permanent colostomy or have significant impact on subsequent bowel function and quality of life. Historically, surgery has been deferred in patients who have been too ill or have refused surgery.1 However, building on the pioneering work of Habr-Gama et al,2 several units have reported their preliminary experiences with a watch-and-wait strategy among patients with rectal cancer that responds well to preoperative chemoradiation.

The rationale for a watch-and-wait strategy is appealing. After contemporary neoadjuvant chemoradiotherapy, approximately 50% of patients will experience a significant clinical response, and 10% to 20% of patients will have a pathologic complete response (pCR), with no evidence of residual tumor.3,4 Thus, clinicians and patients infrequently engage in the sometimes unsettling discussion of the good news of a pCR, but with the reality that the rectum had to be removed and a permanent ostomy was required or that lifelong bowel dysfunction could be anticipated. Although there is increasing interest in such a strategy, questions remain regarding the oncologic safety, particularly when compared with the excellent outcomes that can be achieved with surgical resection. In the article that accompanies this editorial,5 the authors have used a decision-analytic approach to tackle this question.

Decision analysis can be a particularly useful approach for comparing the effectiveness of alternative approaches with treatment where the benefits and harms must be balanced for individual patients or patient cohorts. Ultimately, inferences regarding the choice of treatment will depend on the probability of the potential outcomes and the patient’s value of the outcomes; thus, the approach inherently involves a trade-off. The result of decision analysis is particularly robust when there is strong evidence regarding the input data or assumptions regarding the likelihood for each of the base-case conditions or intermediate outcomes of interest (eg, detection of pCR, rate of relapse, or potential for salvage) and the utilities of the given health states (ie, the quantitative measure of the value that a patient places on a given outcome state relative to perfect health). Consistent with its roots in comparative effective research, the primary outcome of interest is, thus, typically overall or absolute survival that can be measured in quality-adjusted life expectancy. However, as is not uncommon in situations where decision-analytic methods are used to address clinical questions for which high-quality randomized data is lacking, investigators must often rely on lower-quality data or expert opinion to fill in the gaps.

In their analysis, Smith et al6 specifically evaluated the impact of age on the treatment decisions by modeling both fit and comorbidity-affected hypothetical 60- and 80-year-old patients separately and concluded that survival was not compromised by a watch-and-wait strategy in any patient group and that, in fact, it was associated with significantly improved absolute but not disease-free survival in both the hypothetical fit and comorbid 80-year-old cohorts. Their findings are in contrast to a previous analysis in Diseases of the Colon & Rectum, which used almost the same evidence base but concluded that, in the base case, surgery is beneficial for the average patient with rectal cancer and clinical complete response after neoadjuvant therapy.6

These simulations highlight many of the issues concerning watch and wait after neoadjuvant treatment for rectal cancer. These important issues include the ability to clinically identify patients with a pCR and the assumption that, among complete responders, long-term oncologic outcomes are equal to those after surgical resection. In addition, important model parameters, such as baseline estimates of surgical mortality, risks for relapse after surgery vs observation, outcomes after salvage resection for local relapse after observation, and utilities associated with the outcome states, have critical impacts on

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the results of the simulation experiments. In the current analysis, the authors have relied heavily on data from one prospective cohort report and expert opinion to define key base-case assumptions. Compared with the previous analysis, the current model assumes a higher rate of correctly identifying patients with pCR, a higher rate of local relapse for both groups, a higher rate of surgical salvage if relapse recurs after observation, and a significantly higher rate of surgical mortality based on data from the United Kingdom.

Although decision analysis can be a powerful tool to compare treatment options, interpretation of the results should consider the robustness of the data used to develop the underlying assumptions and the extent to which they can be generalized or are dependent on expert opinion. In the analysis by Smith et al, although many of the base-case estimates for watch and wait come from highly selected patients in units with long-standing interests in the watch-and-wait strategy, the mortality estimates for surgery come from the United Kingdom National Health Service. The combination of these disparate base-case cohorts raises the question of the generalizability of the findings. In fact, among the 80-year-old cohorts, the model is primarily influenced by early postoperative mortality, that is, 11.8% and 16.4% among the fit and comorbid groups. As the sensitivity analysis shows, the model was most sensitive to perioperative mortality and the probability of correctly identifying complete response.

Although one can argue about the validity of the base-case estimates, there is good evidence now regarding the favorable prognosis of patients with tumor response to neoadjuvant chemoradiotherapy. In fact, patients with pCR after total mesorectal excision have a negligible risk for local failure, and risk for distant relapse may be <10%. It is likely that good results can also be anticipated among patients with a pCR without surgery. What is still lacking is an easily applied, reliable way of identifying patients who have a pCR. Proposed approaches have included close serial endoscopic examinations, posttreatment high-resolution MRI to assess tumor regression, and metabolic imaging. Although the standard for evaluating the watch-and-wait strategy may be a randomized noninferiority trial among eligible patients, few would argue that such a study will be feasible today.

Rectal cancer management is becoming increasingly complex, and there is likely to be a subset of patients who may be able to avoid surgery. Smith et al are commended for tackling this difficult issue in the face of limited data and helping to highlight the important priorities for continued investigation.

REFERENCES