Diseases of the Colon & Rectum

Letters to the Editor

Treatment of Rectal Cancer Without Radiotherapy?

To the Editor—I read with interest the article by Law *et al.*[1] addressing oncologic outcome after anterior resection for Stage II rectal adenocarcinoma. Unfortunately, the data provided in the article do not support the authors' arguments regarding the lack of benefit of neoadjuvant radiotherapy for patients with rectal cancer.

The exclusion of patients undergoing neoadjuvant therapy, those undergoing abdominoperineal resection (APR), those undergoing noncurative resection, and most importantly, those ultimately proven to have Stage III disease, makes any conclusion the authors make regarding lack of benefit of neoadjuvant radiotherapy suspect. Given the imprecision of our current pretreatment staging methods, a surgeon cannot accurately predict which patients will be ultimately proven to have "optimal" Stage II tumors on final histology. Retrospectively selecting these "optimal" patients for analysis, while excluding those with unfavorable features, introduces selection bias.

Given the accumulating data that postoperative radiotherapy has less oncologic benefit and greater toxicity than preoperative radiotherapy,[2] it is difficult to accept the authors' premise that neoadjuvant radiotherapy is unnecessary. If one chooses not to use neoadjuvant radiotherapy, and the patient has a positive resection margin or Stage III disease, the optimal treatment window for radiotherapy has most likely passed.

In addition, the finding that their selected, optimal patients (Stage II, negative resection margins, nonfixed, non-APR) had a local pelvic recurrence rate of 6 percent could be interpreted to be an argument *for* neoadjuvant radiotherapy. The local recurrence rate after neoadjuvant radiotherapy plus proctectomy in series of unselected patients with pretreatment Stages II and III disease (including patients undergoing APR and patients with fixed tumors) is only 6 percent.[3] Additionally, univariate analysis in the Dutch rectal cancer trial revealed that neoadjuvant radiotherapy reduced local recurrence in Stage II patients compared with surgery alone.[4]

Decisions regarding the use of neoadjuvant radiotherapy for patients with rectal cancer should be based on data from studies that include all patients who undergo treatment with curative intent, rather than on data regarding highly selected patients identified by retrospective subgrouping.

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The Authors Reply

To the Editor—We appreciate Dr. Read's comments about our study on the oncologic outcome of patients with Stage II cancer without radiation.[1] It was not our intention to assess the value of adjuvant radiation in rectal cancer in this retrospective

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study, and we did not claim that adjuvant therapy is of no benefit to the management of the rectal cancer. The suggestion to include all patients with analysis according to the intention-to-treat principle is certainly the preferred method of analysis in randomized, controlled trials. However, in our treatment protocol, radiation was not routine for patients with Stage II and Stage III rectal cancer. Instead adjuvant chemoradiation was given to the high-risk groups, which we have identified in our previous publications.[2,3] There has previously been a selection bias in the group of patients with adjuvant radiation therapy. In the current study, our objective was to evaluate a group of patients with a relatively low risk of disease recurrence and attempt to find the risk factors associated with poor disease outcome.

The view on adjuvant radiation for rectal cancer is still evolving. Despite the recommendation of postoperative chemoradiation for patients with Stage II and Stage III rectal cancer by the National Institutes of Health in 1990,[4] there is still no consensus regarding both the use of adjuvant radiation and the timing and regimen of radiation therapy. This is because there has been significant improvement in the surgical technique in the past two decades, and low local recurrence and favorable survival can be achieved in patients with surgery alone.[5,6] We agree with Dr. Read that there is increasing evidence that preoperative chemoradiation is associated with better oncologic outcome and less toxicity than postoperative chemoradiation. This has been demonstrated in the recently published German trial, which compared preoperative chemoradiation with postoperative chemoradiation.[7] Actually, we are currently offering preoperative chemoradiation to high-risk patients.

Opinions are still divided regarding the adoption of neoadjuvant therapy to all patients or to selected patients in the presence of optimal surgical treatment. Although the Dutch trial[8] attempted to answer this question, the inclusion of all patients for neoadjuvant therapy and the radiation therapy regimen used in the Dutch trial is not the usual practice in North America or many other parts of the world. Results of rectal cancer surgery showed wide variation among surgeons and institutions. Our study attempted to evaluate the outcome of patients with a relatively low risk of recurrent disease and who received optimal surgery. We also tried to evaluate the role of adjuvant chemotherapy in this group of patients.

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Minimal Access Colorectal Surgery: Is It Truly Minimally Invasive?

To the Editor—Major laparoscopic surgery has taken huge strides since the recognition that big operations could be performed through small incisions by using specialized equipment. Initially the focus was on surgical procedures that were relatively simple but

had required large incisions for access, such as cholecystectomy and Nissen fundoplication. Gradually the indications were broadened to embrace all facets of general surgery, including esophageal, pancreatic, and colonic resection.[1–3] These procedures are challenging and have difficult learning curves.

Laparoscopic colonic surgery now has an established role in the management of both benign and malignant conditions.[3] In abdominal surgery, minimal access is the term used to describe the use of small incisions for gaining access to the abdominal cavity. All laparoscopic surgeons go to great lengths to point out that the route of access does not change the operation actually performed. It does not require enormous imagination to understand that there must be cosmetic and pain benefits for minimal access surgery. The more important question is the one that this article addresses. Does minimal access surgery equate to minimal invasion?

The answer is an unequivocal yes when one considers those procedures in which the incision is the predominant metabolic insult to the patient. Into this category go the original operations, which were developed in the early 1990s. Thus, an open cholecystectomy is only a major procedure when it requires a large incision to perform the procedure. Whether the procedure is performed laparoscopically or *via* a small incision the outcome is the same as shown in early trials.[4]

Is the same true when the major metabolic insult to the patient comes from the intra-abdominal dissection?

It is now generally accepted that proinflammatory mediators, including cytokines, are to a great extent responsible for the metabolic changes associated with injury and surgery. To a lesser extent, these metabolic changes are related to postoperative recovery.[5,6]

In a randomized, prospective study Wu *et al.*[7] demonstrated that although early serum cytokine responses to laparoscopic surgery for colonic cancer were decreased, the same concentrations of proinflammatory cytokines were found in the drainage fluid from the operative site compared with open surgery. The drainage fluid cytokine concentrations were far in excess of the concentrations found in the serum. Thus, it would seem reasonable to conclude that laparoscopic surgery results in a decreased serum cytokine response but does not, as would be expected, change the local production of cytokines from the operative site. Because cytokine production from the operative site was far in excess of that in the serum, it would seem, in major colonic surgery, that the skin wound probably has a minimal role compared with the peritoneal wound in metabolic responses after colorectal surgery.

Similar findings were shown in a study from Japan in patients undergoing major thoracoabdominal surgery.[8] In this study, the concentration of interleukin (IL)-6 in the drain fluid was several hundred times that seen in the serum after surgery. A similar study from Finland showed similar results for IL-1, IL-6, IL-8, transforming growth factor β, and IL-10 in patients undergoing colorectal surgery.[9]

Interestingly the production of cytokines after injury also seems to occur remotely from the wound. We have shown that IL-8 is found in the cerebrospinal fluid of patients who have a neck or femur fracture, and it has been shown that the skin produces cytokines after injury or hemorrhage remote from the site of injury.[10,11] Thus the cytokines measured in the serum are only a small part of the overall picture.

Do these data translate into clinical practice? Many of the benefits of laparoscopic surgery seem to be related to the way in which patients are treated after a laparoscopic operation.[12] Kehlet's group have shown that the benefits in postoperative recovery normally associated with laparoscopic colorectal surgery can be extended to open colorectal surgery by fast-track protocols. In a recent article, it was shown that postoperative fatigue and its recovery was similar for both laparoscopic and open colorectal resections when both groups of patients were treated in the same way.[13]

This would support the hypothesis that the skin wound, although a source of some morbidity, is not the major issue in colorectal surgery. The lesson learned from laparoscopic colorectal surgery is that one should ignore the external wound when patients are recovering from surgery. The wound is critical when the operation involves only minor peritoneal disruption but, when large peritoneal defects are created, then the skin wound becomes irrelevant to recovery. Thus, there should be major advantages to performing a cholecystectomy or a fundoplication through small incisions and little metabolic benefit when performing a major colorectal resection through minimal access surgery. When looked at critically, this indeed does seem to be the case.

Thus, minimal access does not necessarily equate to minimal invasion, and the terms should not be used interchangeably in the context of laparoscopic

colorectal surgery. Major laparoscopic procedures are here to stay, but future studies must include outcome measures of relevance to patient recovery and patient care must be optimized in hospital before improvements in outcome can be fully attributed to the size of the skin wound used to access the peritoneal cavity.

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