Defining the Optimal Therapy for Rectal Cancer

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For physicians trained in the United States, postoperative combined modality therapy has become the accepted standard for patients with rectal cancer who are at high risk for locoregional and distant recurrence. In 1990, the results of two randomized trials demonstrating improved survival for postoperative chemotherapy with radiation therapy compared with either surgery alone or with postoperative radiation therapy alone led to an National Institutes of Health Consensus Conference recommendation that all patients with stage II or III rectal cancer should receive postoperative combined modality therapy. Two subsequent intergroup trials have retained control arms of postoperative radiation therapy with 5-fluorouracil-based chemotherapy, perpetuating the role of such treatment in clinical practice. However, there is not universal agreement that high-risk patients require all three modalities of therapy—surgery, radiation therapy, and chemotherapy—or even the proper order of such therapy. There is widespread use of preoperative radiation therapy given without chemotherapy in Europe. At least one clinical trial, designed by the European Organization for Research and Treatment of Cancer, is testing the benefit of both preoperative chemoradiation and postoperative chemotherapy when given concurrently or sequentially with radiotherapy, with preoperative radiation alone as the standard treatment arm. Independent of the timing of treatment, it has been a historical fact that most studies have typically asked whether chemotherapy adds to the benefit of adjuvant radiation therapy in high-risk rectal cancer patients.

The acceptance of radiation therapy as an additional local therapy after potentially curative surgery is primarily based on clinical observations of the risk of local recurrence and on the significant morbidity of locoregional failure. More than 50 years ago, second-look procedures were instituted in patients who were thought to be at high risk of recurrence after surgery for rectal cancer. Predating currently available radiographic techniques, these procedures allowed identification of local failures and regional lymph node metastases as common initial sites of recurrence (1). Although it was recognized that many patients with initial locoregional recurrence subsequently developed distant metastases as well, the rationale was established for additional local therapy in the form of either preoperative or postoperative radiation therapy. Save for a single randomized trial of preoperative radiation therapy, controlled trials have demonstrated either reduction in local recurrence with postoperative radiation therapy or tumor and lymph node downstaging with preoperative radiation therapy but no improvement in overall survival (2).

Although it is accepted that a beneficial outcome of adjuvant treatment of rectal cancer is prevention of clinically relevant local recurrences, most clinicians and patients would agree that overall survival and quality of life are more pertinent end points of treatment. Balancing the potential benefits in reduction of locoregional failure alone after combined modality therapy are the short- and long-term toxic effects of such treatment. Quality-of-life assessments have suggested that the increased complications of postoperative radiation therapy and chemotherapy may be offset by improved recurrence and survival rates when compared with postoperative radiation therapy alone (3). However, retrospective analyses of patients treated with postoperative chemotherapy and radiation therapy suggest that such treatment may also be associated with major long-term alterations in bowel function, an observation that can be supported by any clinician listening carefully to the symptoms of patients who have been treated with the current standard of care (4). It is possible that altering the sequence of treatment may reduce these late morbidities, although two attempts to directly compare preoperative with postoperative chemoradiation in the United States have failed, in large part because of patient or physician preferences and biases.

Since it is likely that most of the long-term morbidity of postoperative chemotherapy and radiation therapy is due to the late effects of the radiation therapy, it is reasonable to ask whether all patients should be exposed to this treatment and whether similar clinical outcomes could be achieved with improved surgical techniques or with systemic chemotherapy alone. The establishment of the efficacy of adjuvant chemotherapy for high-risk extrapelvic colon cancer has strengthened the desire to reverse the original combined modality question and to ask whether radiation therapy adds to the benefit from adjuvant chemotherapy.

In this issue of the Journal, the National Surgical Adjuvant Breast and Bowel Project (NSABP) reports the mature results of the R-02 trial, which compared postoperative chemotherapy alone with postoperative chemoradiotherapy (5). This study design was derived from the first NSABP rectal adjuvant trial, which compared surgery alone with postoperative chemotherapy or with postoperative pelvic radiation therapy (6). That trial engendered much discussion, as much for the primary results of the trial as for the exploratory analyses of the effect of treatment based on sex and age. The primary end point for survival showed a marginally significant improvement in overall survival ($P = .05$) for chemotherapy alone compared with surgery. Although radiation therapy was associated with a reduction in locoregional recurrence (25% for surgery alone versus 16% for postoperative radiation therapy; $P = .06$), there was no significant benefit in disease-free or overall survival. Subset analysis of these data suggested that younger males were the primary beneficiaries of the effects of adjuvant chemotherapy with 5-fluorouracil, vincristine, and semustine.

These results led to the study design of R-02, in which sex-
specific chemotherapy was mandated. When the chemotherapy arms were combined and compared with the combined modality treatment arm, the addition of radiation therapy was not found to have a significant effect on relapse-free survival or overall survival. Cumulative locoregional failure was not common in either arm compared with earlier trials, but there was a significant reduction in this end point, from 13% for chemotherapy alone to 8% for combined modality therapy. However, it is difficult to assess this end point in most adjuvant trials, including this one, because specific modes and schedules of radiographic assessment were not mandated and investigators were obviously not blinded to the assigned treatment, which could bias ascertainment of local failure. These results, nonetheless, are believable, on the basis of earlier trials and on biologic and clinical plausibility. The trial did not include quality-of-life end points that could have substantiated the conclusion that reduction in the incidence of locoregional recurrence alone is a worthy outcome. Although clinicians who treat patients with pelvic recurrences may believe that such failures are almost always worth preventing, even in the presence of systemic metastases, the lack of data from this trial and others on the long-term morbidity of postoperative radiation therapy prevents a quantitative analysis of this conclusion.

The results of this trial are likely to spur brisk discussion in the oncology community concerning the role of adjuvant radiation therapy in the treatment of patients with high-risk rectal cancer after surgical resection. Proponents of total mesenteric excision as primary surgery, reported to be associated with extraordinarily low local failure rates, would say that the issue of postoperative radiation therapy is a bit of a tempest in a teapot. However, in typical surgical practice in the United States, where such procedures are not standard, locoregional recurrence remains a clinically relevant problem to be prevented by whatever modalities are most effective with the least toxicity. Wholesale elimination of postoperative radiation therapy certainly seems premature, but extending the conclusions of this trial is of primary importance in the development of clinical trials.

Our current monolithic approach to the high-risk patient needs to be altered. If radiation therapy reduces local recurrence, then perhaps its use should be limited to those patients with particularly high-risk anatomic or biologic determinants for this pattern of failure. Retrospective analyses have suggested that tumors with greater local extension (macroscopic T3 or T4) or multiple lymph node involvement are at highest risk for local recurrence; perhaps the use of radiation therapy should be restricted to these situations. Conversely, the patient with lymph node-negative, stage II disease with minimal wall invasion, although technically now eligible for most postoperative treatment protocols, might better be treated with systemic chemotherapy alone. Only prospective clinical trials can definitively determine the best treatment in these settings. However, the evidence presented in NSABP permits consideration of deletion of radiation therapy in clinical practice, particularly in patients considered to be at low risk for local recurrence or when the morbidity of postoperative radiation therapy is considered to be high. Future trials in rectal cancer should also address issues that are being investigated in extrapelvic colon cancer. For example, combination chemotherapy in advanced colorectal cancer, typically combining 5-fluorouracil with either irinotecan or oxaliplatin, appears to result in significant improvement in response rate compared with 5-fluorouracil alone. Combination chemotherapy, given alone or concurrently and sequentially with radiation therapy, should be compared with the current standard of postoperative radiation therapy and 5-fluorouracil. In addition to the usual anatomic staging for prognosis and selection of treatment, newer determinants of tumor biology, such as thymidylate synthase expression and chromosome 18 allelic loss, and host factors, such as age and sex, should be prospectively evaluated in the next generation of rectal adjuvant studies. The status quo established by the National Institutes of Health Consensus Conference a decade ago has been challenged by the results of NSABP R-02, but any discomfiture resulting from uncertainties introduced by this trial should prompt the evolution of innovative clinical trials to establish optimal therapies for patients with curatively resected rectal cancer.

References