Preoperative Chemoradiation for Rectal Cancer: “Apples & Pears, Tables and Chairs...”

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In the previous issue of the *Annals of Surgical Oncology*, Dr. Bozzetti and colleagues from the National Cancer Institute, in Milan, Italy presented a modest 32 patient retrospective study of the efficacy of combined radiation and chemotherapy delivered preoperatively for what is described as stage II and III (York Mason) rectal cancer.1 The primary end point of the study was the response of the primary lesion to the preoperative therapy.

It is important to begin by noting that virtually every aspect of adjuvant therapy for rectal cancer, preoperative versus postoperative therapy, the efficacy of chemotherapy, and the efficacy and timing of radiotherapy, is now controversial. With this in mind, it seems reasonable to ask the following two questions of any study that purports to address the clinical care of rectal cancer:

1. What new information on the care of rectal cancer does the study provide?
2. Will the study influence our approach to patients with this potentially lethal disease?

The current climate of controversy and uncertainty regarding optimal adjuvant therapy for rectal cancer was not always the case. For several years in the early 1990s we enjoyed a brief period of resolute clarity on the issue. At that time the results of two independent, multi-institution, prospective randomized trials, Gastrointestinal Tumor Study Group (GITSG) 7175 and the North Central Cancer Treatment Group 79-47-51 trial, demonstrated statistically significant improvement in local control and overall survival for combined radiation and chemotherapy arms delivered after surgical resection of stage II and III (or Dukes’ stage equivalent) rectal cancer.2,3 These results prompted the National Institutes of Health (NIH) to publish a Consensus Conference Clinical Annoucement on adjuvant therapy for rectal cancer in 1991.4 The statement read in part "combined postoperative chemotherapy and radiation therapy improves local control and survival in stage II and III patients [with rectal cancer] and is recommended."4 Unfortunately, this golden age of evidence-based clinical consensus was short lived. Increasing interest in preoperative combined modality approaches and confounding clinical trial results increasingly challenged the NIH consensus statement.

Publication in 1997 of the Swedish Rectal Cancer Trial provided a full plate of food for thought on both sides of the Atlantic.5 Dr. Pahlman's team at the University of Uppsala prospectively randomized 1168 patients with resectable rectal cancer to one of two simple treatment arms: (1) surgery alone; or (2) 25 Gy of radiation delivered in 5 Gy fractions over 5 days followed by surgical resection 1 week later. Following a minimum of 5-years follow-up, the rate of local recurrence was 11% in the group that received radiotherapy before surgery and 27% in the group treated with surgery alone (P < .001). Overall 5-year survival was 58% in the radiotherapy-plus-surgery group and 48% in the surgery alone group (P = .0004). It is important to note that these results were obtained using less than half of the standard North American radiotherapy dose, followed by surgery at 1 week as opposed to the 5 to 6 weeks employed in North American preoperative regimens. The Swedish results were also obtained without one drop of chemotherapy.

Meanwhile, North American attempts to complete a phase III prospective randomized controlled trial comparing preoperative chemoradiation with postoperative chemoradiation for rectal cancer failed. Both the Inter-group 0147 and the National Surgical Adjuvant Breast and Bowel Project R0-3 trials closed prematurely having...
acrued a fraction of their intended targets. Passionate views in both the preoperative and postoperative therapy camps prevented many surgeons from submitting their patients to randomization. Hence a range of crucial questions, including the impact of tumor downsizing on rates of sphincter preservation and subsequent recurrence and survival are unlikely to be addressed in this country in a randomized prospective fashion in the foreseeable future.

A further significant challenge to the 1991 consensus statement arose in 2000 with the publication of the National Surgical Adjuvant Breast and Bowel Project R-02 prospective randomized trial of postoperative chemotherapy with or without radiotherapy for stage II and III carcinoma of the rectum. The authors of the trial described R-02’s “principal goal” as clarifying whether “the addition of radiotherapy would enhance the benefits obtained with chemotherapy alone.” Note the assumption, in light of the Swedish trial results, that chemotherapy provides a clear benefit. At 5-year follow-up the R0-2 study concluded “postoperative radiotherapy resulted in no beneficial effect on disease free survival (p=.90) or overall survival (P=.89)...although it reduced the cumulative incidence of locoregional relapse from 13% to 8% (p=.02).”6 The reasons for this confounding result are not clear. Some have suggested that the delay in delivery of radiotherapy in R-02, which extended up to 21 weeks after surgery, was too great and contrasted significantly with the 60-day delay employed in the GITSG 7175 design. Whatever the explanation, 10 years and 6 months after publication of the original NIH statement “consensus” is not the word that comes to mind to describe current thinking regarding adjuvant therapy for rectal cancer.

With this brief historical review in mind we may now return to the Bozzetti study. The first sentence of the study abstract sets the stage by acknowledging the current lack of consensus. The question is whether this study provides the tools we need to rebuild a consensus? The study is compromised by a variety of treatment variations and outcome comparisons that are considerably less than ideal. For example, with regard to the therapy described, the chemotherapeutic regimen for the first 23 patients (“doxifluridine 500 mg/m²/day per os, plus leucovorin 30 mg per os”) differs from that received by the next nine patients (“5-fluorouracil 225 mg/m²/day”). This difference is neither compared nor analyzed.

The results reported include a reduction in mean tumor size and length of 58%. The fact that rectal adenocarcinomas respond, some dramatically, to neoadjuvant chemoradiation is not a novel observation. The constructive question, given the state of the literature described above, is: “What is the impact of this therapeutic approach on the surgery required, rates of sphincter preservation, local recurrence, and disease-free and overall survival?” The authors report they were able to perform sphincter saving operations “on most” of the patients (81.2%) in the study. This observation, as presented, is of very limited value. In contrast to similar studies referenced in the report there are no data on the percentage of subjects thought to be eligible for sphincter preserving surgery before their preoperative therapy. No direct comparison is possible within the study as described in the Methods section. The authors do compare their 81% with a sphincter preservation rate of 26.5% performed during an apparently separate study by their group, on an unspecified number of middle-low rectal cancer patients not described in the Methods section, none of whom received preoperative chemotherapy or radiotherapy. No survival data are reported for either, precluding the one comparison that matters most.

The authors apply the term “downstaging” to describe reductions in T stage based on pre- and postchemoradiation endorectal ultrasound evaluations. The notion that downsizing facilitates increased rates of sphincter preserving surgery without compromising rates of local recurrence or long-term survival is less than certain and remains unproven. In my view it remains vitally important to recognize that downsizing is not synonymous with downstaging. The data presented illustrate this nicely. Referring to “tumor regression grade” the authors report that two thirds of their subjects demonstrated a significant pathologic regression. The authors compare this result with yet another retrospective study of 59 rectal cancer patients treated with radiation only before resection and report a statistically significant improvement in “tumor regression grade” for the combined radiation and chemotherapy group. This is the third separate group of subjects introduced into the study results, and, as with the second group described above, it is not detailed in the Methods section. This study design is clearly less than optimal. The fact is 88% of the patients studied in this series had viable residual cancer cells in their resected specimens. These data clearly suggest that modified, less radical procedures, performed on down-sized rectal tumors may be at increased risk of local recurrence because of residual microscopic disease. This problem is significantly compounded by the fact that postchemoradiation clinical evaluation of response is notoriously unreliable as a predictor of pathologic response. The authors readily concede this point, noting postchemoradiation endorectal ultrasound “did not prove to be very accurate in assessing the pathologic T stage.” This renders patient selection for sphincter preservation secondary to downsizing, based on clinical evaluation,