An Embarrassment of Riches: Neoadjuvant Therapy of Rectal Cancer

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Two decades ago, therapy for locally advanced rectal cancer included surgery followed by additional radiation therapy or fluorouracil (FU) chemotherapy. The principles of surgery for rectal cancer included the freeing of the rectum from the surrounding mesorectal tissues via blunt dissection with a low anterior, sphincter-sparing resection whenever possible. Sphincter preservation was rarely accomplished for tumors within reach of the examining finger on rectal examination. With the exception of the introduction of mechanical stapling devices permitting low anterior resections for low-lying lesions, surgical techniques remained static for decades. Single-agent FU was delivered in a bolus technique, as it had been since the 1960s, and radiation therapy, although technically improved, was similar to that used in the 1950s. Adjuvant therapy was embraced by many in the 1980s; in the early 1990s the results of randomized trials led a National Cancer Institute Consensus Conference to endorse the use of postoperative radiation therapy and chemotherapy for patients with T3 or node-positive disease.

Until recently, gastrointestinal oncologists had only one drug in their armamentarium, so they spent the 1960s through 1990s testing minor variations of agents and modulations of timing while staying with the same basic approaches. What did we learn from the investigations of that era? First, continuous infusion FU as an adjuvant with radiation is superior to bolus FU in reducing both local and distant recurrences, but it does not appear that additional intensification of continuous-infusion FU is of much benefit. Second, TME improves outcomes compared with conventional blunt dissections, but the application of this technique by US surgeons is uneven. The expertise of the surgeon as an important prognostic factor in determining outcome has been well documented. Third, although TME is superior to conventional or inadequate surgery, it does not produce a high enough level of local tumor control to be adequate sole local therapy for many patients, and adjuvant radiation therapy and chemotherapy further reduces local recurrence rates. Fourth, recent data from Sauer et al show that preoperative radiochemotherapy is superior to postoperative therapy, when appropriate high-risk patients can be defined. Fifth, the results obtained in adjuvant treatment of cancer of the colon cannot easily be extrapolated to treatment of rectal cancer.

With respect to chemotherapy and biologic agents to combine with radiation therapy, we have gone from one choice to a plethora of options. The challenge to the academic gastrointestinal oncology community is to find ways to rapidly test in definitive clinical trials the most promising new treatment approaches from a wide variety of...
opportunities. For example, there were 22 abstracts presented at the 2004 American Society of Clinical Oncology Annual Meeting reporting the outcomes from small phase I and II trials of neoadjuvant radiation plus various chemotherapy or biologic agents for patients with rectal cancer.

Which of the newer agents or approaches should we emphasize in current and future clinical studies of adjuvant therapy for rectal cancer? Multiple trials in metastatic colon and rectal cancer supply clues, but the results are often contradictory. In metastatic colorectal cancer, oxaliplatin and irinotecan combined with infused or oral FU have each produced similar improvements in time to progression or survival compared with single-agent FU. Cetuximab and bevacizumab also have benefits when added to standard cytotoxic therapy. Virtually all of these newer agents have substantial radiation-sensitizing properties in model systems, suggesting potential benefit in the neoadjuvant setting. Capecitabine; UFT; and other oral agents have shown promise in obviating the need for an indwelling intravenous line, but their equivalence to standard methods of FU administration or incremental benefits, if any, are unclear. The number of possible permutations and combinations of all these agents (not even considering new agents in the drug development pipeline) with surgery and radiation well exceeds the ability of the oncology community to test them effectively.

The well-done study by Hofheinz in this issue of the Journal of Clinical Oncology is in the vanguard of reports using new agents or combinations of agents as radiation sensitizing treatment. As such, it illustrates some problems, and raises more questions than answers. The authors used a standard phase I design, with escalation of the capecitabine dose while holding constant the irinotecan and radiation therapy dose. The authors were attentive to the details of radiation and surgery. The maximum-tolerated dose resulted in a lower dose of capecitabine than that used without irinotecan. The pathologic complete response rate, although promising (21%), is similar to that reported in many other recent reports with a variety of combinations. Given that irinotecan has never been shown to be an effective adjuvant treatment in rectal cancer, in contradistinction to continuous infusion FU, the question can be raised whether the trade-off of a higher dose of irinotecan with a lower dose of the fluorinated pyrimidine is wise, particularly in patients being treated for cure.

An obvious problem of using irinotecan in this setting is that three agents (radiotherapy, FU, and irinotecan) with significant overlapping gastrointestinal toxicity are being used concurrently. It is striking that the number of complications related to surgery seems especially high for a single-institution trial. This may be a consequence of a small sample size, or perhaps more experience and refinement of the approach is necessary before introduction of this regimen into a phase III study is considered. Oxaliplatin combined with FU has efficacy in metastatic disease and also acts as a potent radiation sensitizer. It is unknown if the results with oxaliplatin, irinotecan, FU, or some combination of these agents would be improved when combined with a biologic agent. Although laboratory-based studies of combinations could provide clues to help direct the clinical research community on how to make choices from among the panoply of regimens available, it is clear that not every approach could, or should, be tested in a phase III setting.

The combination of drugs with radiation is an important area for clinical development. However, there are many difficult issues in the optimization of combined-modality treatment. Timing of radiation with the chemotherapeutic or biologic agent will often be critical to outcome, and this is likely also to be true of timing of various drug combinations, especially when interactions are likely. The authors of this study paid careful attention to the timing of the delivery of radiation and irinotecan to maximize the interaction. They did not do as well with capecitabine. Although capecitabine comes much closer than bolus FU to having a uniform distribution over time, there are still substantial peaks and valleys in the serum concentration. Given known radiobiological data, this will almost certainly have significant effects on radiation sensitization. At our institution, when the combination of radiation and capecitabine is used, we deliver the drug approximately 1 hour before the radiation to maximize tumor sensitization. Timing is likely also to be important with other agents. For example, oxaliplatin, based on work by Blackstock et al (submitted for publication), should likely be given a number of hours before radiation to maximize benefit. Little information exists on the optimal timing for most of the biologics when combined with radiation.

At present, despite the lack of good laboratory data, there are a few specific directions for clinical research that may be most productive. First, ensure that adequate studies have been done of timing of agents as well as pharmacokinetics and dynamics to maximize the likelihood of exploiting either drug plus radiation or drug plus drug interactions. This is especially important with the biologic agents. Second, studies of FU analogs are unlikely to produce substantially improved results, so these studies should not be emphasized. Third, there is little reason, at present, to prefer studies of bevacizumab or cetuximab, one over the other. Fourth, the preliminary results with oxaliplatin and irinotecan seem similar in terms of efficacy, so the preference for one over the other will only come from direct comparative clinical trials; the choice of one over the other may be based more on toxicity profiles than efficacy, and the gastrointestinal toxicity of irinotecan may be a negative. Newly developed trials within the GI Intergroup will, in fact, be addressing many of these issues.

There is enough information for all of these agents to understand that none of them is likely to be “home runs,” and that they may provide small, but clinically relevant
incremental improvements in survival, in local control, sphincter preservation, and in reduction of systemic metastases. We must use our clinical research resources wisely in designing therapies most likely to produce benefits. The greatest benefits will almost certainly come from combinations that are initially chosen for evaluation in patients based on evidence from laboratory models. In rectal cancer, we have a major advantage in that there is the potential to acquire tissue for analysis of molecular characteristics before and after neoadjuvant therapy. For example, small single-institutional studies should be able to define whether we are affecting the molecular targets of interest with a new biologic agent, and then returning with these data to the laboratory may allow us to define alternate pathways that are impeding tumor control. These studies also may offer the opportunity of defining patient subsets that are more or less likely to respond to a given therapy. This information can be correlated with short-term outcomes such as pathologic complete response rate and more traditional long-term outcomes such as local recurrence rate and survival. Overall the data appear to suggest that pathologic complete response to chemoradiotherapy therapy is a good (although imperfect) surrogate marker for long-term outcome. The report by Hofheinz et al7 is an excellent example of what will certainly be many forthcoming reports on iterations of drugs used to enhance radiation in rectal cancer. As a carefully done and meticulously reported study, it is a model of a well-done clinical trial. Future studies with molecular correlates present an enormous opportunity for the clinical oncology community to focus our clinical efforts.

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