Combined-Modality Therapy of Rectal Cancer With Irinotecan-Based Regimens

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By Bruce D. Minsky, MD [2]

There are two conventional treatments for clinically resectable rectal cancer. The first is surgery followed by postoperative combined-modality therapy if the tumor is T3 and/or N1/2. The second, if the tumor is ultrasound T3 or clinical T4, is preoperative combined-modality therapy followed by surgery and postoperative chemotherapy. There are a number of new chemotherapeutic agents that have been developed for the treatment of colorectal cancer. Phase I/II trials are examining the use of new chemotherapeutic agents in combination with pelvic radiation therapy, most commonly in the preoperative setting. There is considerable interest in integrating irinotecan (Camptosar) into preoperative combined-modality therapy regimens for rectal cancer. Based on these trials, the recommended regimen for patients who receive irinotecan-based combined-modality therapy is continuous infusion fluorouracil (5-FU), irinotecan, and pelvic radiation. New trials examining preoperative combined-modality therapy regimens substituting capecitabine (Xeloda) for continuous infusion 5-FU are in progress.

There are two conventional treatments for clinically resectable rectal cancer. The first is surgery followed by postoperative combined-modality therapy if the tumor is T3 and/or N1/2.[1] The second, if the tumor is ultrasound T3 or clinical T4, is preoperative combined-modality therapy followed by surgery and postoperative chemotherapy.[2] Postoperative Therapy Rationale and Results

The National Cancer Institute Consensus Conference concluded that combined-modality therapy was the standard postoperative adjuvant treatment for patients with T3 and/or N1/2 disease.[1] Pelvic radiation therapy decreases local recurrence but does not improve survival. As would be predicted, randomized data do not reveal a survival advantage of pelvic radiation plus elective para-aortic and liver radiation vs pelvic radiation alone.[3] The standard design is to deliver six cycles of chemotherapy with concurrent radiation during cycles 3 and 4. A randomized trial by Lee et al suggests that radiation should start with cycle 1 rather than cycle 3.[4] However, since a number of patients did not receive the treatment arm to which they were randomized, further data are needed before recommending a change in sequence. For patients treated with postoperative combined-modality therapy who received fluorouracil (5-FU) as a single agent, there was a 10% survival advantage with continuous infusion (CI) 5-FU vs bolus 5-FU.[5] The INT 0144 postoperative adjuvant rectal trial reported results at the American Society of Clinical Oncology (ASCO) 2003 annual meeting.[6] Patients were randomized to three arms: (1) bolus 5-FU → CI 5-FU/radiation therapy (RT) → bolus 5-FU; (2) CI 5-FU → CI 5-FU/RT → CI 5-FU; (3) bolus 5-FU/leucovorin/levamisole (Ergamisol) → bolus 5-FU/leucovorin/levamisole/RT → bolus 5-FU/leucovorin/levamisole. There was a significant decrease in grade 3+ hematologic toxicity in arm 2; however, there was no significant difference in 3-year survival. Local control data were not reported. Given these results, CI 5-FU with radiation is recommended, and either arm 1 or 2 is a reasonable choice. If arm 1 is chosen, the bolus chemotherapy segment should be the Roswell Park regimen (weekly) rather than the Mayo Clinic regimen (monthly). The INT 0114 trial revealed that with longer follow-up the results are not as favorable.[7] With a median follow-up of 7.4 years, the 7-year local failure rate was 17% and the survival rate was 56%. Patients with high-risk (T3, N+ or T4) disease have lower survival rates than those with lower-risk (T1/2, N- or T3, N0) disease (45% vs 70%). There is an increase in acute toxicity associated with this improvement in local control and survival with postoperative combined-modality therapy. For example, the incidence of grade 3+ toxicity in the combined-modality arms of the Gastrointestinal Tumor Study Group and Mayo/North Central Cancer Treatment Group (NCCTG) 79-47-51 trials was 25% to 50%. Furthermore, the percentages of patients finishing the prescribed six cycles of chemotherapy in those trials were only 65% and 50%, respectively. Retrospective data suggest that the acute toxicity with preoperative combined-modality therapy may be less than in the postoperative setting.[8] The randomized German trial of preoperative vs postoperative combined-modality therapy trial has confirmed these data.[9,10] Do All Patients Require Postoperative Adjuvant Therapy?
There are retrospective data that suggest there may be a subset of patients with T3, N0 disease who may not require adjuvant therapy, as well as patients with stage I disease who should be considered for adjuvant therapy. Retrospective trials examining patients at both Massachusetts General Hospital[11] and Memorial Sloan-Kettering Cancer Center[12] have identified favorable subsets of patients with T3, N0 disease who, following surgery alone, had a 10-year actuarial local recurrence rate of < 10%. In addition to such other modifications as smooth nodules in the fat being staged as node positive and irregular nodules as vascular invasion (VI is microscopic and VI2 is macroscopic), the 6th edition of the American Joint Committee on Cancer staging system subdivides stage III into IIIA (T1/2, N1), IIIB (T3/4, N1), and IIIC (any T, N2).[13] The prognostic validity of this change was supported by both the pooled analysis of Intergroup and National Surgical Adjuvant Breast and Bowel Project (NSABP) postoperative trials[14] and the retrospective analysis of the American College of Surgeons National Cancer database.[15] The 5-year survival of stages IIIA, IIIB, and IIIC in the pooled analysis was 81%, 57%, and 49%, respectively, and in the National Cancer database it was 55%, 35%, and 25%, respectively. Based on 5-year survival data, radiation does not improve the results of chemotherapy alone in stages T3, N0 and T1/2, N1 disease. However, local control data are needed before recommending chemotherapy alone for this subset of patients. Preoperative Therapy Rationale

Preoperative therapy (most commonly combined-modality therapy) has gained acceptance as a standard adjuvant therapy. The potential advantages of the preoperative approach include decreased tumor seeding, less acute toxicity, increased radiosensitivity due to more oxygenated cells, and enhanced sphincter preservation.[2] The primary disadvantage of preoperative radiation therapy is possibly overtreating patients with either early-stage (T1/2, N0) or undetected metastatic disease. However, the imaging techniques discussed above allow more accurate selection, thereby decreasing the number of patients who are overtreated. Retrospective data suggest that preoperative combined-modality therapy increases pathologic downstaging compared with preoperative radiation without chemotherapy[16] and is associated with a lower incidence of acute toxicity compared with postoperative combined-modality therapy.[8] In general, the incidence of grade 3+ acute toxicity during the combined-modality segment is 15% to 25%, the complete response rates are 10% to 30% pathologic and 10% to 20% clinical, and the incidence of local recurrence is 0% to 10%. The recently completed randomized European Organization for Research and Treatment of Cancer (EORTC) trial 22921 is addressing whether preoperative combined-modality therapy is more effective than preoperative radiation therapy, and if the postoperative chemotherapy component is necessary. The preliminary results reveal an increase in the pathologic complete response (pCR) rate in those patients receiving chemotherapy concurrent with radiation.[16a] The local control and survival rates are pending. There are 12 modern randomized trials of preoperative radiation therapy (without chemotherapy) for clinically resectable rectal cancer.[2] All use low to moderate doses of radiation. Overall, most of the trials showed a decrease in local recurrence, and in five trials this difference reached statistical significance. Although in some trials a subset analysis has revealed a significant improvement in survival, the Swedish Rectal Cancer Trial is the only one that reported a survival advantage for the total treatment group. Two meta-analyses report conflicting results. While both reveal a decrease in local recurrence, the analysis by Camma et al[17] reported a survival advantage whereas the analysis by the Colorectal Cancer Collaborative Group[18] did not. Intensive Short-Course Preoperative Radiation

The Swedish Rectal Cancer Trial is the only randomized trial of preoperative radiation therapy to report a significant improvement in survival. Patients with clinically resectable (T1-3) rectal cancer were randomized to receive 25 Gy in 1 week followed by surgery 1 week later vs surgery alone.[19] Those who received preoperative radiation had a significant decrease in local recurrence (12% vs 27%) and a corresponding improvement in 5-year survival (58% vs 48%). It is important to analyze these positive results in the context of the rest of the literature. First, given that the other 11 randomized trials of preoperative radiation therapy do not report a survival benefit, these data clearly need to be confirmed by additional studies. The most recent trial to report results was the Dutch CKVO 95-04 trial, which randomized 1,805 patients with clinically resectable (T1-3) disease to surgery alone (with a total mesorectal excision [TME]) or intensive short-course preoperative radiation followed by TME.[20] Although radiation significantly decreased local recurrence (8% vs 2%), there was no difference in 2-year survival (82%). With longer follow-up, 5-year local failure was higher with TME (12%); however, it was still significantly decreased (to 6%) with preoperative radiation.[21] Second, even if future trials confirm a survival benefit, there are other equally important end points in rectal cancer that need to be addressed. These include acute toxicity, sphincter preservation and function, and quality of life. For example, acute toxicity in the Dutch
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CKVO 95-04 trial included 10% neurotoxicity, 29% perineal wound complications, and 12% postoperative leaks.[22] In the patients who developed postoperative leaks, 80% required surgery resulting in 11% mortality. The presence of a positive circumferential margin is an important sign of negative prognosis. In the Dutch CKVO trial, 17% of patients had positive circumferential margins; they received 50 Gy postoperatively. Postoperative radiation did not compensate for positive margins.[23] Unfortunately, few centers in the United States perform the necessary pathologic examination to detect positive circumferential margins. Data from Beets-Tan et al.[24] suggest that preoperative magnetic resonance imaging can identify patients who will have positive margins and can be used to better select patients for preoperative therapy. It is not possible to compare accurately the local control and survival results of intensive short-course radiation with conventional preoperative combined-modality therapy. This is because of selection bias in favor of the series using intensive short-course radiation. The conventional preoperative combined-modality therapy regimens are limited to patients with clinical T3 disease, whereas most trials that use intensive short-course preoperative radiation include patients with clinical T1-3 disease. Sphincter Preservation With Preoperative Radiation

A major goal of preoperative therapy is sphincter preservation. From this viewpoint, the advantage of preoperative therapy is to decrease the volume of the primary tumor. When the tumor is located in close proximity to the dentate line, this decrease in tumor volume may allow the surgeon to perform a sphincter-conserving procedure that would not otherwise be possible. However, if the tumor directly invades the anal sphincter, sphincter preservation is unlikely even when a complete response is achieved. One of the most important controversies with preoperative therapy is whether the degree of downstaging is adequate to enhance sphincter preservation. Furthermore, if preoperative radiation therapy is effective, what regimen (intensive short course vs conventional course) is preferred? An analysis of 1,316 patients treated on two previously published Scandinavian trials of intensive shortcourse radiation revealed that downstaging was most pronounced when the interval between the completion of radiation and surgery was at least 10 days.[25] In the Dutch CKVO 95-04 trial, where the interval was 1 week, there was no downstaging.[26] None of the other randomized trials of intensive short-course preoperative radiation address the issue of sphincter preservation, and it is not an end point of the trials. When the goal of preoperative therapy is sphincter preservation, conventional doses and radiation techniques are recommended. These include multiple-field techniques to a total dose of 45 to 50.4 Gy at 1.8 Gy/fraction. Surgery should be performed 4 to 7 weeks following completion of radiation. Unlike the intensive short-course radiation regimen, this conventional design allows for two important events to occur: first is the recovery from the acute side effects of radiation, second is adequate time for tumor downstaging. Data from the Lyon R90-01 trial of preoperative radiation suggest that an interval > 2 weeks following completion of radiation increases the chance of downstaging.[27] It is not known whether increasing the interval between the end of intensive shortcourse radiation and surgery to ≥ 4 weeks will increase downstaging. This question is being addressed in an ongoing randomized trial from Sweden (Stockholm III trial). Preoperative Prospective Clinical Assessment

The most accurate method with which to determine if preoperative therapy increases sphincter preservation is to perform a prospective clinical assessment. In this setting, the operating surgeon examines the patient prior to the start of preoperative therapy and declares the type of operation required. It should be noted that this assessment is based on an office examination and may not accurately reflect the assessment when the patient is relaxed under general anesthesia. The only way to account for this potential bias is to perform a randomized trial of preoperative vs postoperative therapy. The results of the German CAO/ARO/AIO 94 randomized trial of preoperative vs postoperative combined-modality therapy suggest that this assessment is accurate in 80% of cases.[9,28] Clinical Experience With Sphincter Preservation

There are eight phase I/II trials that have reported results in patients with clinically resectable rectal cancer who underwent a prospective clinical assessment by their surgeon prior to the start of preoperative therapy and were declared to need an abdominoperineal resection. All use conventional doses and radiation therapy techniques. Three use radiation therapy alone[27,29,30] and four use combined-modality therapy.[31-35] The incidence of sphincter preservation is only 23% in the NSABP series[31] and 44% in the Lyon series.[27] In the remaining five series it is approximately 70%. A valid concern of surgeons is that in order to perform sphincter preservation in those patients who would otherwise require abdominoperineal resection, the distal resection margin may be suboptimal (≤ 1 cm). Can preoperative therapy compensate for this? Retrospective data from Moore et al reveal that with preoperative combined modality therapy, the 3-year local control rates were similar regardless of whether the margins were > 2 cm, < 2 cm, > 1 cm, or < 1 cm,
provided they were negative.[36] Sphincter preservation without good function is of questionable benefit. In a series of 73 patients who underwent surgery, Grumann and associates reported that the 23 patients who underwent an abdominoperineal resection had a more favorable quality of life compared with the 50 who underwent a low anterior resection.[37] Although preoperative combined-modality therapy may adversely affect sphincter function, the impact is most likely less than postoperative combined-modality therapy.[38] In the four of eight preoperative series discussed above that report functional outcome, the majority (approximately 75%) have good to excellent sphincter outcome. Functional results continue to improve up to 1 year after surgery. Three randomized trials of preoperative vs postoperative combined-modality therapy for clinically resectable T3 rectal cancer have been performed. Two are from the United States (INT 0147, NSABP R0-3) and one is from Germany (CAO/ARO/ AIO 94). All three use conventional doses and radiation therapy techniques and concurrent 5-FU-based chemotherapy, and all require a preoperative clinical assessment declaring the type of operation required. Unfortunately, low accrual has resulted in early closure of both the NSABP R-03 and INT 0147 trials. A preliminary report of the NSABP R-03 trial (with a median follow-up of 3 years) revealed that patients who received preoperative therapy had a lower local failure rate (5% vs 9%) and higher survival (85% vs 78%); however, neither reached statistical significance.[10] The German trial completed the planned accrual of over 800 patients and randomized patients with T3/4 and/or N+ rectal cancers ≤16 cm from the anal verge to preoperative combined-modality therapy (with CI 5-FU) vs postoperative combined-modality therapy.[9] In order to help remove surgical bias, patients were stratified by surgeon. Compared with postoperative combined-modality therapy, patients who receive preoperative therapy had a significant decrease in local failure (6% vs 12%, P = .006), acute toxicity (28% vs 40%, P = .005), chronic toxicity (10% vs 23%, P = .04), and in those 194 patients judged by the surgeon to require and APR, a significant increase in sphincter preservation (39% vs 20%, P = .004). With a median follow-up of 40 months there was no difference in 5-year survival (74%). Given the improved local control, acute and long-term toxicity profile, and sphincter preservation reported in the German trial, patients with T3 rectal cancer who require combined-modality therapy should receive it preoperatively. Predicting the Response of the Primary Tumor

Although some series show no correlation,[39,40] most suggest that there is improved outcome with increasing pathologic response to preoperative therapy.[41-47] Analyses of biopsies examining selected molecular markers such as c-K-ras,[48] thymidylate synthase,[49] p27kip1,[50] p53,[51-54] apoptosis,[55,56] deleted in colorectal cancer gene,[54] epidermal growth factor receptor,[57] TP53,[52] and Ki-67[58] have had varying success in helping to select patients who may best respond to preoperative therapy. Since all of the studies are limited retrospective trials and most do not examine multiple markers, the need for adjuvant therapy should still be based solely on T and N stage at this time. Fortunately the new Intergroup rectal trials will prospectively collect tissues for these and other markers. Novel Combined-Modality Regimens

Introduction

There are a number of new chemotherapeutic agents that have been developed for the treatment of colorectal cancer. Phase I/II trials are examining the use of new chemotherapeutic agents in combination with pelvic radiation therapy, most commonly in the preoperative setting. Selected agents include UFT (uracil and tegafur),[59] raltitrexed (Tomudex),[60] oxaliplatin (Eloxatin),[61-65] irinotecan (Camptosar),[66] gefitinib (Iressa),[67] and capecitabine (Xeloda)[68] with pelvic radiation therapy. Combinations of new agents such as C225 with irinotecan in patients in advanced colorectal cancer are under development.[69] This and other new chemotherapeutic agents will likely be combined with pelvic radiation in the future. Phase III trials are needed to determine if these regimens offer an advantage over those with 5-FU-based combined-modality therapy. Irinotecan-Based Regimens

Based on the significant survival advantage of irinotecan/5-FU/leucovorin vs 5-FU/leucovorin or irinotecan alone in patients with metastatic colorectal cancer,[70] there is considerable interest in integrating irinotecan into preoperative combined-modality therapy regimens for rectal cancer. There are a number of phase I/II trials combining irinotecan with radiation therapy. They use irinotecan either as monotherapy with once-a-day radiation[71] or hyperfractionated radiation,[72,73] or more commonly in combination with bolus or CI 5-FU.[35,66,74-77] A phase I trial of escalating doses of weekly irinotecan (8 to 13 mg/m² daily) weeks 1, 2, 4, and 5 plus concurrent 50.4 Gy in 28 patients with T3/4 rectal cancer was reported by Minsky et al.[71] Of the 16 patients treated at the recommended dose level of 10 mg/m², the pathologic complete response rate was 5% and the grade 3+ acute toxicity rate was 29%. Since these results were inferior to prior regimens tested at Memorial Sloan-Kettering, this irinotecan-alone regimen was not brought into phase II study. The other trial using irinotecan alone with preoperative radiation was reported by Volter and colleagues.
from Lausanne.[72,73] Twenty patients with T3/4 rectal cancer were entered in this phase I trial. Irinotecan was escalated from 30 to 105 mg/m² weekly * 3 and hyperfractionated radiation (1.6 Gy bid to 41.6 Gy) began on week 2. The high incidence of anastomotic leak and/or abscess (30%) may have been related, in part, to the hyperfractionated radiation. The recommended dose level of irinotecan was 90 mg/m². The remaining trials added CI 5-FU to the preoperative radiation/irinotecan combination. Klaute and associates from the University of Rostock performed a phase II trial in 26 patients with a variety of stages of rectal cancer.[75] Doses were fixed: irinotecan (40 mg/m² weekly), CI 5-FU (250 mg/m²/d), and radiation therapy (50.4 Gy). The incidence of grade 3+ toxicity was 15% hematologic and 35% diarrhea. In the 15 patients who underwent surgery, the response rates were 26% pathologic and 26% clinical. Even higher complete response rates were reported in a phase II trial from Mehta et al from Stanford.[35] A total of 32 patients with T3 disease were treated with irinotecan (50 mg/m² weekly * 4), CI 5-FU (200 mg/m²/d), and 50.4 Gy. The grade 3+ acute toxicity was 28% diarrhea and 21% mucositis. The pathologic complete response rate was 37%. The largest experience has been reported by Mitchell and colleagues from Thomas Jefferson University.[76] Forty-six patients with T3/4 rectal cancer were entered on a phase I trial of irinotecan (30 to 60 mg/m² weekly * 4), CI 5-FU (225 to 300 mg/m²/d), and radiation therapy (45 to 54 Gy). This complicated phase I trial had both escalation and attenuation of the irinotecan, 5-FU, and radiation doses. Overall, there was a 24% pathologic complete response and a 15% clinical complete response rate. In an updated report of 67 patients, the pathologic complete response rate was 25%.[77] Patients whose tumors have microsatellite instability had a higher complete response rate than those without microsatellite instability. The recommended dose level was irinotecan at 50 mg/m² weekly * 4, CI 5-FU at 225 mg/m²/d, and radiation therapy at 54 Gy. This regimen is being compared to a regimen of preoperative CI 5-FU plus twice-a-day radiation in the randomized phase II Radiation Therapy Oncology Group protocol R-0012. Levine and colleagues developed a similar regimen.[66] Based on their phase I trial in 12 patients, the recommended schedule was irinotecan at 60 mg/m² weekly * 4, CI 5-FU at 200 mg/m²/d, and radiation therapy at 45 Gy. The replacement to RTOG R-0012 is RTOG 0247, which is a phase II randomized comparison of preoperative combined-modality therapy with irinotecan plus capecitabine and 50.4 Gy vs oxaliplatin plus capecitabine and 50.4 Gy. Conclusions: The ideal irinotecan-based preoperative combined-modality regimen has not been determined. The phase I/II trials suggest that preoperative irinotecan plus radiation therapy is most effective when combined with 5-FU. The preliminary data reveal encouraging high complete response rates following preoperative therapy. However, it should be emphasized that the higher complete response rates need to be confirmed in randomized trials. Given the advantage of CI vs bolus 5-FU in the Mayo/NCCCTG 86-47-51 postoperative rectal adjuvant trial[78] as well as the more favorable toxicity profile of irinotecan when combined with CI 5-FU compared with bolus 5-FU,[79] the recommended regimen for patients who receive irinotecan-based combined-modality therapy is CI 5-FU, irinotecan, and pelvic radiation. New trials examining preoperative combined-modality therapy regimens substituting capecitabine for CI 5-FU are in progress.

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Dr. Minsky has received research funding from, acted as a consultant for, and served on the speaker’s bureau for Pfizer, Roche, Sanofi, Genentech, and Bristol-Myers Squibb.

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