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.
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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 random- ized 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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rates were similar regardless of whether the margins were > 2 cm, < 2 cm, > 1 cm, or < 1 cm, from Moore et al reveal that with preoperative combined modality therapy, the 3-year local control may be suboptimal (≤ 1 cm). Can preoperative therapy compensate for this? Retrospective data those patients who would otherwise require abdominoperineal resection, the distal resection margin approximately 70%. A valid concern of surgeons is that in order to perform sphincter preservation in cases.[9,28]

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 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,
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Introduction

Response of the Primary Tumor

Predicting the Pathologic Complete Response

Novel Combined-Modality Regimens

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 or 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 con current 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/NCCTG 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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