Radiation Therapy in Stage II and III Rectal Cancer

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Abstract Over the past 25 years, significant advances have been made in the management of patients with rectal cancer. Phase III studies have shown the efficacy of postoperative radiation therapy and chemotherapy in improving local control and survival of patients with resected stage II and III disease. Data from the randomized German CAO/ARO/AIO-94 trial of preoperative versus postoperative chemoradiation have provided a strong rationale and support for the use of preoperative chemoradiation in the treatment of patients with clinical stage II and III rectal cancer. Current phase III studies are evaluating novel combinations of chemotherapy and targeted agents with radiation therapy.

In 2007, 41,420 new cases of rectal cancer are expected to be diagnosed in the United States (1). The therapeutic mainstay of this malignancy is surgery. In patients with early-stage tumors (i.e., lesions confined to the rectal wall without lymph node metastasis), 5-year survival is excellent, with contemporary series reporting ≥80% cure rates. In contrast, local and systemic failure pose significant risks to patients undergoing resection of more advanced-stage tumors. Both preoperative and postoperative chemoradiation have been used to prevent local and systemic failure and improve survival for these patients.

The rationale of adjuvant radiation therapy stems from pattern of failure analyses of patients undergoing surgery only for advanced rectal cancer. The goal of using radiation therapy as an adjuvant treatment for rectal cancer is straightforward: to prevent local recurrence with its associated morbidity and mortality in patients with locally advanced tumors. Over the past 25 years, advances have been made in the multimodality management of patients with resectable rectal cancer. Improved local control and survival have been seen with the addition of chemotherapy to pelvic radiation therapy. Chemotherapeutic agents serve as radiosensitizers to enhance the therapeutic efficacy of radiation therapy and to target occult systemic micrometastasis.

This review discusses the current indications and controversies in the use of chemoradiation in the treatment of patients with rectal cancer.

Adjuvant Therapy

The observation of high local recurrence rates following "curative" resection has led to studies exploring the potential benefit of postoperative adjuvant therapy (2, 3). Advantages of postoperative therapy include the ability to selectively treat patients at high risk of local failure based on pathologic stage. Disadvantages include a potentially hypoxic postsurgical bed, making radiation therapy less effective, with potentially higher complication rates due to increased small bowel in the radiation field. Another disadvantage is larger radiation treatment volume, especially if the patient undergoes abdominoperineal resection and the perineal scar needs to be treated.

Several large trials have evaluated postoperative radiation therapy with or without chemotherapy (4–6). In general, surgery alone has resulted in a 25% local failure rate and 40% to 50% long-term survival for T_3/T_4 or node-positive patients, whereas adding radiation therapy with chemotherapy has yielded lower local failure rates of 10% to 15% and higher survival rates of 50% to 60%.

The National Surgical Adjuvant Breast and Bowel Project R-01 study randomized 555 patients with Dukes' B and C disease into three arms after surgery: observation, postoperative chemotherapy consisting of eight cycles of MOF [i.e., 1-(2-chloroethyl)-3-(traru-4-methylcyclohexyl)-1-nitrosourea (semustine), vincristine, and 5-fluorouracil (5-FU)], and postoperative radiation treatment only of 46 to 47 Gy (7). Postoperative chemotherapy improved disease-free and overall survival compared with observation and postoperative radiation treatment only; however, the benefit of improved overall survival with MOF was restricted to males in a subset analysis. Patients receiving postoperative radiation therapy showed a trend toward improved local control but not overall survival.

The National Surgical Adjuvant Breast and Bowel Project R-02 study enrolled 694 patients with Dukes' stage B and C disease and asked two questions. (*a*) Does the addition of radiation to chemotherapy improve outcome? (*b*) Is MOF superior to 5-FU and leucovorin (5-FU/LV) in males (8)? The study design consisted of four treatment arms for males and two treatment arms for females. In males, five cycles of MOF were compared with six cycles of 5-FU/LV, with or without radiation therapy. In females, 5-FU/LV only was compared with 5-FU/LV with radiation therapy. The radiation dose was 50.4 Gy. At 5 years, cumulative locoregional failure was 13% for the chemotherapy only arm compared with 8% with the addition of combined radiation therapy and chemotherapy.

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Additionally, treatment with 5-FU/LV improved relapse- and disease-free survival, but not overall survival, compared with treatment with MOF. Although postoperative radiation treatment did not seem to improve overall survival in this trial or National Surgical Adjuvant Breast and Bowel Project R-01, local control was improved.

Trials conducted by the Gastrointestinal Study Group and Mayo-North Central Cancer Treatment Group showed improvement in survival with the combination of adjuvant chemoradiation (4, 6). The Gastrointestinal Study Group study was a four-arm trial of 227 patients with stage B2 to C rectal cancer randomized to either surgery only, postoperative chemotherapy of 5-FU and semustine, postoperative radiation treatment only, or postoperative chemotherapy and radiation therapy of 40 to 44 Gy with concurrent 5-FU (4). The severe acute toxicity rate was 61% in the combined modality treatment arm compared with 31% with chemotherapy only and 18% with radiation only. In a 9-year update, postoperative chemotherapy with radiation therapy significantly improved overall survival to 54% versus 27% with surgery only. Local failure rate was decreased to 10% with combined modality therapy versus 25% with surgery only. In this trial, the overall survival advantage was significant (i.e., ~2-fold) in patients receiving combined modality treatment after surgical resection.

The Mayo-North Central Cancer Treatment Group study compared postoperative radiation therapy with postoperative radiation therapy and chemotherapy (6). The results showed improved local control and survival in patients who received combined modality treatment versus postoperative irradiation only.

Based on the results of the above-mentioned studies, the NIH Consensus Conference recommended that the combined use of radiation therapy and chemotherapy is more effective than postoperative radiation only, with a greater potential for improved survival (9). Several subsequent studies have attempted to delineate optimal chemotherapy agents and delivery options in the combined modality treatment.

The North Central Cancer Treatment Group 86-47-51 study compared chemotherapy regimens added to postoperative radiation therapy. Stage II to III rectal cancer patients (n = 660) were randomized to either 5-FU or 5-FU plus semustine followed by a second randomization to the method of delivery of 5-FU [bolus versus continuous venous infusion (CVI)] during radiation therapy (10). At median follow-up of 46 months, there was a 27% improvement in relapse-free survival of 63% versus 53% in favor of CVI 5-FU compared with bolus 5-FU. Four-year overall survival was 70% versus 60% in favor of CVI 5-FU. Time to relapse and rate of distant metastasis were also lower with CVI delivery. No difference in local recurrence was seen. Patients receiving bolus 5-FU had a higher rate of leucopenia, whereas patients treated with CVI had more acute severe diarrhea. Semustine was of no added benefit.

The Intergroup 0114 study compared different chemotherapy regimens with radiation treatment in 1,695 patients with stage II and III rectal cancer (11, 12). The four treatment arms were as follows: bolus 5-FU only, 5-FU/LV, 5-FU plus levamisole, and 5-FU/LV plus levamisole. Levamisole was not given during radiation treatment. Radiation treatment dose was 45 Gy, with a 5.4- to 9-Gy boost (to a total of 50.4-54 Gy). At median follow-up of 7.4 years, no difference in overall or disease-free survival was noted between the four groups. The three-drug regimen had greater toxicity, and levamisole and leucovorin did not seem to add any benefit to 5-FU.

Neoadjuvant Therapy

Preoperative radiation therapy. Considerable debate has evolved about the optimal approach to adjuvant therapy in rectal cancer. Although both preoperative and postoperative adjuvant therapy can be effective, interest has been intense in a neoadjuvant approach. The potential for improved tumor downstaging, resectability rates, and enhanced sphincter preservation probability in the distal rectum has stimulated the use of a neoadjuvant approach in the management of this malignancy. Historically, trials using modest doses of preoperative radiation therapy have been undertaken, with results consistently showing improvement in local control but minimal or no improvement in overall survival (13–16). More recent studies in Europe have shown that neoadjuvant radiation therapy results in improvement of both local control and survival, leading to a significant effect on the current management of this malignancy (17, 18).

The Swedish rectal preoperative radiation trial included 1,168 patients with resectable Dukes' A to C rectal cancer from 1987 to 1990 (17). Patients were randomized to 25 Gy in 5-Gy fractions in 1 week followed by surgery 1 week later versus surgery only. The surgery was scored as curative if margins were negative. At median follow-up of 7 years, a significant reduction in local control was seen in all three Duke stages with preoperative radiation therapy versus surgery only. The 5-year local recurrence rate with preoperative radiation therapy and surgery was 11% compared with 27% for surgery only. This study showed a 10% absolute overall survival advantage at 5 years for preoperative radiation therapy compared with surgery alone (58% versus 48%, respectively; P = 0.004).

One caveat of the Swedish study was that the surgery only arm did not use total mesorectal excision (TME), which may have resulted in the unacceptably high local failure rate of 27%. Additionally, late effects analysis suggested more bowel movement frequency, incontinence, urgency, and soiling in the preoperative radiation treatment arm, although overall quality of life was rated as good (20). This trial set the standard of care in many European centers; however, the radiation schedule of 25 Gy in 5-Gy fractions may have induced significant acute and late toxicity, and the short interval between radiation and surgery may not have allowed sufficient time for tumor regression (downstaging) for enhanced rates of sphincter preservation.

Justification for a longer interval following preoperative radiation treatment before surgery was shown in a French trial, Lyon 90-01, which delivered 39 Gy in 3-Gy fractions without chemotherapy preoperatively (21). This trial randomized patients to surgery either 2 or 6 weeks after radiation therapy. Local control and overall survival after median follow-up of 33 months were the same in both arms of the study; however, pathologic complete response was 7% versus 14% (P = 0.17), and pathologic downstaging was 10% versus 26% (P = 0.007), in favor of the longer interval before surgery.

The experience of Heald et al. (22) suggests that treatment with TME only may be sufficient for achieving high local control rates. CKVO 95-04, a Dutch multicenter phase III study of 1,861 patients, was undertaken to evaluate the role of short-course preoperative radiation with TME. Patients were

randomized to TME only versus 25 Gy in 5-Gy fractions preoperatively followed by TME (18). Fixed tumors were excluded from the study, and >50% of the patients had T_1/T_2 disease. Overall survival was the same in both study arms (82% at 2 years); however, local recurrence at 2 years was 8.2% in the TME only arm compared with 2.4% in the preoperative arm, highlighting the value of radiation therapy even with TME. Sphincter preservation was the same in both arms, and there was no clear evidence of any downstaging effect. At 26%, the perineal complication rate was slightly higher in the preoperative radiation arm compared with 18% in the TME arm, whereas all other complications were equal. Follow-up analysis showed a higher incidence of sexual dysfunction and slower recovery of bowel function, more fecal incontinence, and generally poorer quality of life with short-course preoperative radiation therapy; however, local control benefit persisted.

Two meta-analyses of ~6,000 patients each were undertaken to explore the benefit of preoperative radiation treatment. One analysis, which included 14 randomized controlled trials, concluded that neoadjuvant radiation treatment was associated with significantly less local recurrence and a cause-specific and overall survival benefit (23). The second meta-analysis also reported the results of 14 randomized controlled trials of preoperative radiation therapy (5). In this analysis, a significant reduction in local recurrence and a disease-specific survival benefit were noted, although 5-year survival (at ~45%) was not significantly different.

Radiation *versus* Chemoradiation

The improvement in outcome with chemoradiation in postoperative trials has led to similar approaches being adopted in the neoadjuvant therapy of this malignancy. In the United States, this approach has become widely accepted. In Europe, however, several groups have undertaken studies to examine the potential benefit of neoadjuvant chemoradiation versus neoadjuvant radiation therapy only.

Preoperative radiation therapy was compared with combined preoperative chemotherapy and radiation therapy in the French FFCD 9203 study (14). Patients with resectable T_3 and T_4 tumors were randomized to 45 Gy of radiation only versus radiation with concurrent bolus 5-FU/LV. Four cycles of chemotherapy were administered after surgery. At median follow-up of 81 months, the abdominoperineal resection rate was 42% in both treatment arms. Combined treatment led to improved pathologic complete response of 11.4% versus 3.6% in the radiation only arm and improved 5-year local failure rates (8.1% versus 16.5%, respectively). Five-year survival was 67% in both treatment arms.

A similar study, European Organization for Research and Treatment of Cancer 22921, randomized patients to four arms: 45 Gy only versus 45 Gy plus 5-FU/LV followed by surgery, with patients further randomized to adjuvant therapy with 5-FU/LV (24). This study showed that patients undergoing chemoradiation versus radiation only had increased tumor downstaging (14% versus 5.3%, respectively; $P = 0.0001$) but no difference in resectability (99.5% versus 94.3%, respectively), 5-year survival (65% in both arms), or progression-free survival (56% versus 54%, respectively). After further follow-up, the addition of chemotherapy to preoperative radiation was shown to further enhance sphincter preservation (55.3% versus 52.8%, respectively; $P = 0.05$) as well as local control (92.3% versus 82.9%, respectively; $P = 0.0016$; ref. 25). No survival benefit was seen in patients receiving adjuvant chemotherapy after surgery.

Another randomized phase III French trial, GRECCAR, compared sphincter preservation in patients with T_3 or N_1 distal rectal cancer undergoing preoperative radiation therapy with and without chemotherapy (26). Two hundred seven patients were randomized to radiation therapy (45 Gy) with CVI 5-FU versus radiation only (45 Gy plus 18-Gy boost). No difference in sphincter preservation was observed between the two randomized arms.

A study was undertaken by the Polish Rectal Cancer Group to determine whether short-course radiation (25 Gy in 5-Gy fractions) as neoadjuvant therapy versus protracted chemoradiation (50.4 Gy using 1.8- to 2-Gy fractions with concomitant bolus 5-FU/LV given during weeks 1 and 5) leads to improved outcome (27). Preliminary analysis showed a higher pathologic complete response (16% versus 1%), fewer positive radial margins (4% versus 13%), and reduced primary tumor size in patients undergoing chemoradiation. There was no difference between the two treatment arms in sphincter preservation. More recently, these investigators reported long-term survival and local recurrence results (28). Actuarial 4-year overall survival was 67.2% in the short-course group and 66.2% in the chemoradiation group ($P = 0.96$); crude incidence of local recurrence was 9.0% and 14.2%, respectively ($P = 0.17$). Based on these data, the investigators concluded that neoadjuvant chemoradiation did not increase survival, local control, sphincter preservation, or late toxicity compared with short-course radiation therapy.

In contrast to the above-mentioned studies, institutional experience from the United States has shown significantly higher rates of downstaging and enhanced sphincter preservation with the use of preoperative chemoradiation. In addition, several institutional studies suggest an improvement in overall survival. Thus, notwithstanding the results of randomized studies, most investigators in the United States currently use a combined modality approach in the treatment of this malignancy.

Preoperative versus postoperative chemoradiation therapy. Three phase III trials have compared preoperative versus postoperative chemoradiation treatment. The first trial, Radiation Therapy Oncology Group 94-01/Intergroup 0417, accrued 53 patients but closed early due to poor accrual. No results were presented. The National Surgical Adjuvant Breast and Bowel Project R-03 was scheduled to accrue 900 patients but closed after accruing 267 patients (29). In this trial, patients with operable rectal cancer were randomized (and stratified by age and sex) to one of two treatment arms: surgery followed by one cycle of 5-FU/LV and then concurrent bolus 5-FU/LV (weeks 1 and 5) with radiation treatment or one cycle of 5-FU/LV and then concurrent chemotherapy and radiation treatment followed by surgery. All patients received adjuvant 5-FU/LV for four cycles. Although underpowered, the results showed that patients in the preoperative arm had a 10% sphincter preservation advantage (44% versus 34%), with slightly higher grade 4 and 5 toxicity (34% versus 23%) and diarrhea (24% versus 12%). Clinical complete response was 23%, and pathologic complete response was 10% in the preoperative arm. Disease-free survival at 1 year was 83% versus

78% in the preoperative and postoperative arms, respectively (P = not significant).

CAO/ARO/AIO-94 was a definitive phase III study in favor of preoperative radiation therapy (30). Patients with clinically staged T_3 and T_4 or node-positive rectal cancer (n = 823) were randomized to either preoperative chemotherapy and radiation therapy followed by TME 6 weeks later or TME followed by postoperative chemotherapy and radiation therapy. Radiation therapy used was 50.4 Gy in 28-Gy fractions, with an additional 5.4 Gy delivered as a small volume boost in the postoperative arm; chemotherapy used was 5-FU, administered as 1 g/m^2/d as a 120-h CVI during the 1st and 5th week of radiotherapy. Patients in both treatment arms received four additional cycles of 5-FU at 500 mg/m^2/d for 5 days every 4 weeks. All surgeons were trained in the use of TME and asked before treatment to evaluate the possibility of sphincter preservation. The 5-year results revealed a pelvic recurrence of 6% versus 13% (P = 0.02) in favor of the preoperative arm. Distant recurrence was 36% versus 38% (P = not statistically significant), disease-free survival was 68% versus 65% (P = not significant), and overall survival was 76% versus 74% (P = not significant) in the preoperative versus postoperative arms, respectively. Significant tumor downstaging was seen after preoperative combined modality treatment, with an 8% pathologic complete response rate. Nodal positivity was 25% in the preoperative arm versus 40% in the postoperative arm. In 188 patients with low-lying tumors (declared by the surgeon before randomization to require abdominoperineal resection), a sphincter-preserving low anterior resection was done in 39% versus 19% of patients in the preoperative and postoperative arms, respectively (P = 0.004). Significantly fewer acute (27% versus 40%) and late toxicities (14% versus 24%) occurred in the preoperative than postoperative group, respectively. Thus, preoperative combined chemotherapy and radiation resulted in significantly fewer local failures in the pelvis (i.e., by half) and also doubled the sphincter preservation rate. Importantly, no difference in overall or disease-free survival was found between the two arms.

Preliminary results of the Medical Research Council CR07 trial were presented at the 2006 American Society of Clinical Oncology annual meeting (31). In this phase III study, 1,350 patients with clinically resectable rectal cancer were randomized to short-course preoperative radiation therapy (25 Gy in 5-Gy fractions) and TME versus TME followed by selective postoperative chemoradiation (45 Gy in 25-Gy fractions with 5-FU) in patients with tumor involvement of the circumferential resection margin. In addition, patients with stage III disease received postoperative adjuvant chemotherapy. In patients undergoing preoperative radiation therapy, compared with selective postoperative chemoradiation, local recurrence was significantly reduced (4.7% versus 11.1%, respectively). Furthermore, 3-year disease-free survival was significantly improved in patients undergoing preoperative radiation versus selective postoperative chemoradiation (79.5% and 74.9%, respectively). These results suggest that, even with TME and adjuvant chemotherapy, preoperative radiation improves outcome over adjuvant postoperative chemoradiation in patients with high-risk disease. In agreement with the results of CAO/ARO/AIO-94, this study further strengthens the role of preoperative therapy.

Concurrent chemotherapy options with radiation therapy. The delivery of chemotherapy has differed significantly in completed and ongoing clinical trials. 5-FU has been used concurrently with radiation therapy because of its well-established radiosensitizing effect; however, some studies have used bolus 5-FU, whereas others have used leucovorin-modulated 5-FU during radiation therapy. The results of the Intergroup study showing superiority of CVI 5-FU in the adjuvant setting have been extrapolated to preoperative strategies and seem to be the preferred treatment approach (10). Newer drugs, including oxaliplatin, irinotecan, and oral fluoropyrimidines, have recently been shown to be effective in the treatment of metastatic colorectal cancer and are now being incorporated into the testing of new strategies with neoadjuvant therapy (19). Capecitabine is an oral fluoropyrimidine prodrug that is readily absorbed in the gastrointestinal tract and mimics the efficacy of CVI 5-FU while avoiding the risk of side effects and complications due to a central line for CVI 5-FU (32). Other options being evaluated for neoadjuvant therapy include the addition of oxaliplatin or irinotecan to 5-FU and radiation therapy (33–36). Early data from phase I to II trials suggest that an oxaliplatin dose of 60 mg/m^2 can be combined safely with 5-FU–based chemotherapy and radiation therapy approaches with acceptable grade 3 toxicity; additionally, promising rates of clinical and pathologic downstaging have been reported. The reported toxicity of concurrent irinotecan (50 mg/m^2 once weekly) with CVI 5-FU and radiation therapy is higher, but tolerable, and yields pathologic complete responses of 25% to 30% (37). The National Surgical Adjuvant Breast and Bowel Project R04 study is a phase III trial comparing preoperative radiation therapy and capecitabine with or without oxaliplatin versus preoperative radiation therapy and CVI of 5-FU with or without oxaliplatin in the treatment of patients with operable carcinoma of the rectum.

Targeted agents with chemoradiation. The biological agent bevacizumab, which targets vascular endothelial growth factor, has been efficacious in the treatment of patients with metastatic colon and rectal cancer. Bevacizumab has been administered to patients with locally advanced rectal cancer before and in combination with 5-FU and radiation therapy. Phase I study results have shown that this agent is tolerable with chemoradiation and has profound antivascular effects and encouraging tumor downstaging rates (38). The Gastrointestinal Intergroup is currently conducting a phase III trial (Eastern Cooperative Oncology Group E5204) of adjuvant FOLFOX (i.e., 5-FU/LV/oxaliplatin) with or without bevacizumab after preoperative chemoradiation.

Radiation therapy techniques. Radiation oncologists have two primary goals in generating a radiation therapy plan: (*a*) appropriate coverage of the tumor (target) volume and (*b*) minimizing dose to the normal tissues adjacent to the target (avoidance structures; ref. 39). Conventional two-dimensional and three-dimensional radiotherapy planning makes use of multiple static fields. With these techniques, it is difficult to conform radiation dose coverage to targets, such as the primary tumor and at-risk lymphatic basins that may be irregularly shaped. Intensity-modulated radiation therapy makes use of multiple "fields within fields" that more accurately conform radiation dose to the target while sparing avoidance (normal) structures. To accomplish this, the treating physician uses the findings of physical exam, endoscopy, computed tomography, positron emission tomography-computed tomography, and/or magnetic resonance imaging to define the primary/gross disease (gross target volume), tissues at risk for subclinical tumoral

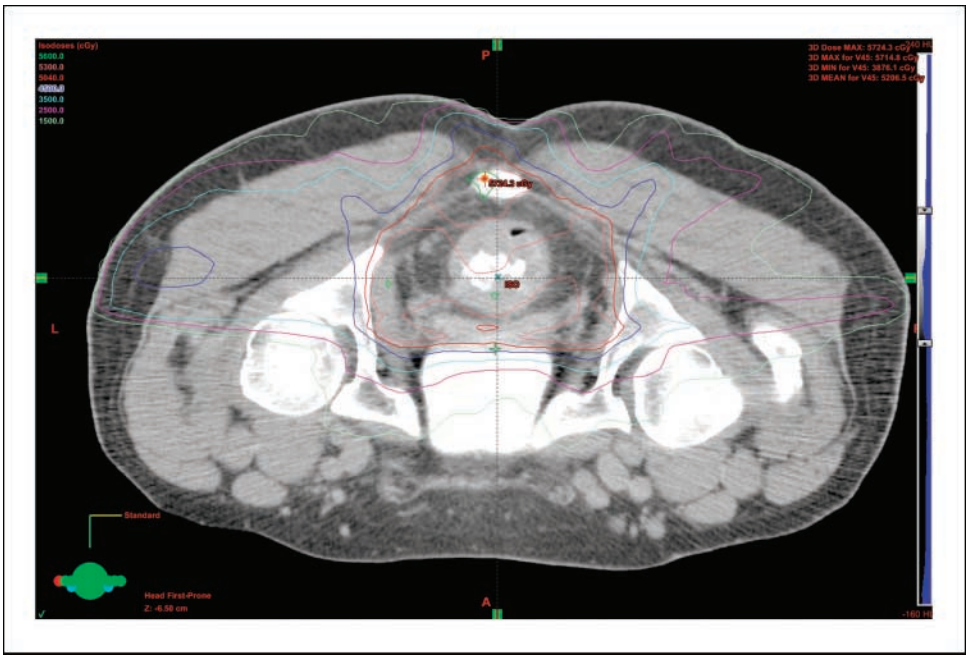

Fig. 1. Axial view of an intensity-modulated radiation therapy – treated 38-year-old male with clinical T_3N_1 rectal cancer receiving preoperative radiotherapy. Again, note relative sparing of normal structures relative to the thickened rectal tumor.

involvement, including draining nodal basins (clinical target volume), as well as a third volume encompassing the gross and clinical target volumes, allowing additional "margin" to account for organ motion and daily positional differences (planning target volume). This is done using computer-based planning programs. Additionally, nearby normal structures at risk are defined. Dose constraints are then assigned to these organs along with a desired (prescription) dose to the gross, clinical, and planning target volumes. Intensity-modulated radiation therapy planning software can then be used to do "inverse planning," whereby computer search algorithms establish optimal (and sometimes unconventional) beam/field design, including varying dose "intensities" within an individual field, with the ultimate goal of meeting the prescribed target dose and normal tissue dose constraints. The result is a series of radiation doses that closely conform to the target volumes while minimizing dose to normal tissues (Figs. 1 and 2). In select situations, these techniques allow for safe tumoral

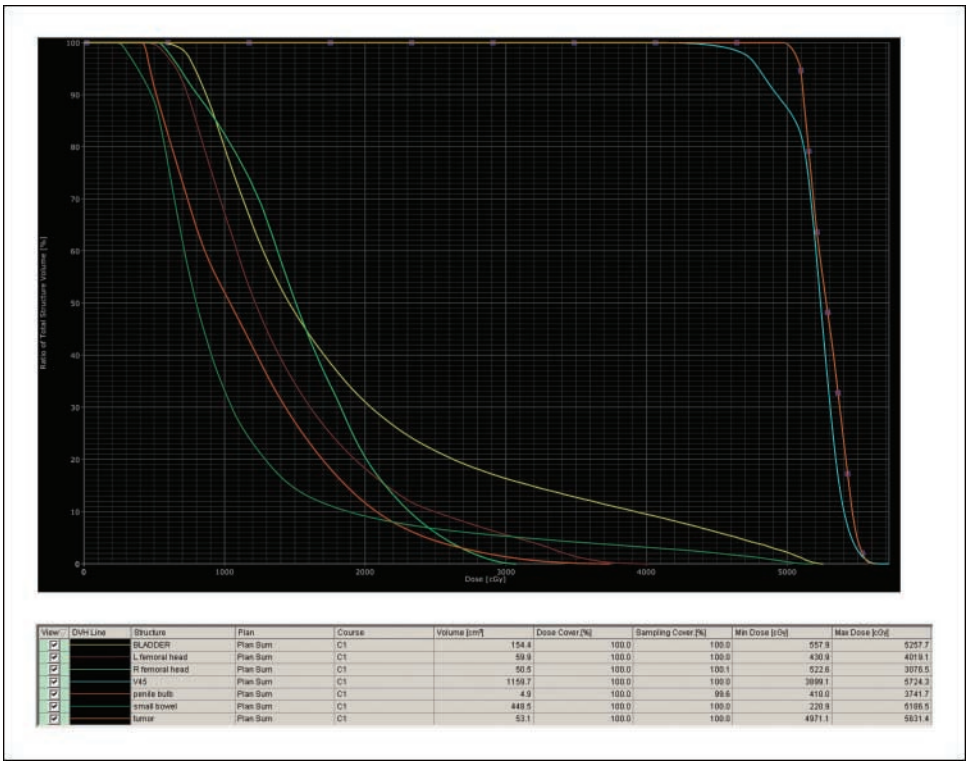

Fig. 2. Dose volume histogram for patient in Fig. 1. Note relative sparing of all normal structures compared with target volume.

dose escalation with improved avoidance of normal tissues, theoretically leading to improved tumor control.

Summary. For patients with clinical stage II and III rectal cancer, neoadjuvant treatment with radiation therapy and 5-FU–based chemotherapy is recommended. In the United States, radiation therapy treatment approaches usually use three-dimensional conformal radiation therapy techniques delivering 45 Gy to the tumor and pelvic lymphatics followed by additional irradiation to gross tumor to 50.4 to 54 Gy in 28 to 30 fractions over 5.5 to 6 weeks. 5-FU is usually administered as a continuous peripheral venous infusion during the entire course of radiation therapy. The use of capecitabine, oxaliplatin, and targeted agents such as bevacizumab and cetuximab during radiation therapy are under active investigation in clinical trials. Following completion of neoadjuvant therapy and surgical resection, patients who initially presented with T_3 and/or node-positive disease are generally treated with adjuvant chemotherapy.

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