

Pre- and Postoperative Adjuvant Therapy for Locally Advanced Rectal Cancer

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Abstract

The conventional therapy for locally advanced rectal cancer involves surgery and adjuvant therapy. The standard adjuvant therapy is combined modality treatment, including 5-fluorouracil chemotherapy and radiation. The standard of care in terms of timing of adjuvant therapy, whether pre- or postoperative, continues to evolve, and potential advantages and disadvantages exist for both neoadjuvant and adjuvant combined modality therapy. Newer modalities of assessment, such as endoscopic ultrasound, have had an impact on more accurate staging of locally advanced rectal cancer, thus impacting the choice of therapy. Continued emphasis on improving survival, decreasing local recurrence, and minimizing treatment toxicity to improve quality of life are the goals of ongoing research in the field of rectal cancer.

Rectal cancer is a significant health issue in the United States. In 2004, it is estimated that 40,570 new cases of rectal cancer will be diagnosed, with a slight male predominance (23,220 cases in men and 17,350 cases in women).¹ Survival is directly related to the stage at the time of diagnosis, with 5-year survival rates approaching 90% for patients with stage I resected disease, 50–60% for patients with stage II disease and 30–40% for stage III disease (Table 1).² Potentially curative therapy is possible for patients with stage I, II, or III rectal cancer and for a few patients with stage IV disease. Unlike colon cancer, patients who have had surgical resection as primary therapy are at a significant risk for both local and systemic recurrence. Symptomatic local failure is a consequence of the anatomic constraints of the rectum and the difficulty in obtaining wide radial margins. Local recurrence of rectal cancer leads to significant morbidity and impact on quality of life.³ The goals of adjuvant treatment of rectal cancer are to decrease both the rates of local recurrence and of systemic disease and, ultimately, improve overall survival rates.

Combined modality therapy, with chemotherapy and radiation, is the standard of adjuvant care in North America. The timing, dose, and schedule of radiation, as well as the appropriate systemic chemotherapy, remain active areas of study. Randomized clinical trials have explored the impact of local therapy with radiation with or without chemotherapy on the rate of local and systemic recurrence. Local therapy given prior to surgical resection has the advantage of downstaging the tumor to allow for sphincter-sparing therapy and avoiding radiation to healthy small bowel, which tends to drop down into the pelvis after surgical resection. The disadvantage, however, is that accurate pathologic staging is sacrificed. This may lead to radiation being delivered to early-stage tumors in which benefit has not been demonstrated or understaging of lymph nodes that were involved prior to radiation. The efficacy of adjuvant therapy for rectal cancer should be judged on whether the therapy decreases local recurrence and improves disease-free and, ultimately, overall survival.³ This review will focus on the evolution, current state, and future direction of adjuvant therapy for locally advanced rectal cancer.

Surgery

Rectal cancer is defined as a tumor that arises below the peritoneal reflection, within 12 cm of the anal verge on endoscopy. Tumors in the upper and middle rectum can often be

Keywords

Adjuvant therapy, rectal cancer, combined modality therapy, endoscopic ultrasound

Table 1. American Joint Committee on Cancer TNM Staging System for Rectal Cancer

Primary Tumor (T)	
Tx -	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa or nonperitonealized perirectal tissue
T4	Tumor directly invades other organs or structures, and/or perforates visceral peritoneum
Lymph Nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	No regional lymph node metastasis
N2	Metastasis in 4 or more regional lymph nodes
Metastasis (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping			
Stage	T	N	M
0	Tis	N0	M0
I	T1-2	N0	M0
IIA	T3	N0	M0
IIB	T4	N0	M0
IIIA	T1-2	N1	M0
IIIB	T3-4	N1	M0
IIIC	Any T	N2	M0
IV	Any T	Any N	M1

approached with a low anterior resection (LAR), thus preserving the anal sphincter. Traditionally, distal rectal tumors, those considered to have an inferior edge up to 6 cm from the anal verge, require a more extensive surgical intervention to gain adequate negative distal margins. The abdominoperineal resection (APR) results in a permanent colostomy and a high incidence of sexual and genitourinary dysfunction. Retrospective data and a prospective randomized trial by the National Surgical Adjuvant Breast and Bowel Project (NSABP) have demonstrated that even a 2 cm distal margin is acceptable in terms of overall survival and local recurrence.^{4,5} One of the goals of neoadjuvant therapy is to decrease tumor size, making a sphincter-sparing surgery technically feasible.

A total mesorectal excision (TME), as opposed to the previous practice of blunt dissection, has become the standard surgical procedure for the resection of rectal cancer whether an APR or LAR is required. With TME, the rectum and mesorectum are sharply dissected as an intact single unit with negative surgical margins, with the goal of improved local control. Local recurrence rates after blunt dissection are quite variable in the literature, ranging from 14–30%.⁶ Two large series examining local recurrence following TME have been reported. In one series of 115 consecutive patients, the local recurrence rate was 3.7% at 5 years. In a second series of 246 consecutive patients, the local recurrence rate was 7.3% at a median follow-up of 5 years.^{7,8} In the hands of an experienced surgeon, TME can significantly decrease the risk of local recurrence.

Staging

Accurate preoperative staging of rectal cancer is essential to determine the appropriate surgical procedure and adjuvant therapy. In the 6th edition of the American Joint Committee on Cancer (AJCC) Staging Manual, the TNM and group staging system has been revised for rectal cancer to better predict prognosis and aid in treatment decisions. The digital rectal exam (DRE), performed by the surgeon preoperatively, is the most accurate test to define the tumor in relation to the dentate line and, therefore, determine the type of surgical procedure which will be required and assess the degree of tumor fixation. Determination of accurate T, N, and M stage may require transrectal endoscopic ultrasound (EUS), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET).

Abdominal and pelvic CT scans are recommended by the National Comprehensive Cancer Network (NCCN) guidelines in the initial workup of a patient with a rectal lesion. CT scan will identify large rectal tumors, enlarged lymph nodes and distant metastases to the pelvis, peritoneum, or liver. CT cannot accurately determine depth of tumor invasion (T stage) between layers of the rectal wall or distinguish between enlarged lymph nodes as being reactive or malignant (N stage). MRI can offer a clearer visualization of perirectal tumor invasion but does have some limitation in accurately assessing wall invasion. MRI using an endorectal probe does allow accurate identification of the multiple rectal layers and an accurate T stage.⁹

Table 2. Randomized Trials of Postoperative Adjuvant Therapy

Study	Patients, N	Treatment	Local Recurrence	Overall Survival	Comment
GITSG, 1985 ^{14, 15}	227	Observation vs RT (40–48Gy) vs 5-FU/semustine vs RT+5-FU/semustine		54% combined therapy vs 27% surgery ($P=0.05$)	
NSABP R-01, 1988 ¹⁶	555	Observation vs RT (46–47 Gy) vs 5-FU/semustine/vincristine		Improved overall survival with chemotherapy vs surgery alone ($P=.05$)	
NCCTG, 1991 Krook et al ⁶	204	RT (45–54 Gy) vs RT+5-FU (preceded and followed by 5-FU/semustine)	13.5% vs 25% ($P=.036$)	29% reduction in death rate ($P=.043$)	
O'Connell et al, 1994 ¹⁸	660	Semustine/5-FU→RT (45 Gy) + 5-FU→5-FU vs semustine/5-FU→RT + CI 5-FU→ semustine/5-FU vs 5-FU→5-FU + RT→5-FU vs 5-FU→CI 5-FU + RT→5-FU	NS	60% with bolus vs 70% with CI ($P=.005$)	No survival advantage with addition of semustine
NSABP R-02, 2000 ¹⁷	694	RT (45 Gy) + semustine/vincristine/5-FU vs semustine/vincristine/5-FU vs 5-FU + LV vs 5-FU + LV + RT	13% C/RT vs 8% RT ($P=.02$)	NS	
Intergroup 0114, 2002 Tepper et al ¹⁹	1,695	5-FU→RT (45 Gy) + 5-FU→5-FU vs 5-FU/LV→RT + 5-FU/LV→5-FU/LV vs 5-FU/Lev→RT + 5FU/Lev→5-FU/Lev vs 5-FU/LV/Lev→RT + 5FU/LV/Lev→5-FU/LV/Lev	Low risk 9% vs 18% high risk ($P<.0001$)	Low risk 76% vs high risk 55% ($P=.0001$)	No OS/LR difference by treatment arm
Intergroup 0144, 2003 Smalley et al	1,917	Bolus 5-FU→RT + CI 5-FU→ bolus 5-FU vs CI 5-FU→CI 5-FU + RT→ CI 5-FU vs bolus 5-FU/LV/Lev→ RT + bolus 5-FU (wk 1,5)→ bolus 5-FU/LV/Lev	NS	NS	Increase in Grade 4 hematologic toxicity in bolus 5-FU arms

RT=radiation therapy; NS=not significant; 5-FU=5-fluorouracil; LV=leucovorin; Lev=levamisole; OS=overall survival; LR=local response; GITSG=Gastrointestinal Tumor Study Group; NSABP=National Surgical Adjuvant Breast and Bowel Project; NCCTG=North Central Cancer Treatment Group; CI=continuous infusion; C/RT=chemo/radiotherapy; CI=continuous infusion.

EUS can identify the separate layers of the rectal wall—the mucosa, the submucosa, the muscularis propria, and the interface between the muscularis and the perirectal fat.⁹ In addition, EUS can distinguish by echogenic characteristics lymph nodes involved with tumor as opposed to reactive. Thus, an accurate T stage and N stage can be determined with EUS. The accuracy of EUS in T staging of rectal tumors

ranges from 80% to 95%, as compared to 65–75% for CT.¹⁰ A small study of 10 patients compared the effectiveness of endorectal MRI in preoperative staging, addressing the question of tumor depth of invasion only, to the results obtained with endorectal ultrasound. The accuracy for both methods was 70–80%, and the difference between the 2 modalities was not statistically significant.¹¹ The accuracy of lymph

Table 3. Randomized Trials of Preoperative Radiation in Rectal Cancer

Study	Patients, N	Treatment	Local Recurrence	Overall Survival
Swedish Rectal Cancer Trial, 1997 ²⁸	1,168	25 Gy/5 fractions + surgery vs surgery	11% vs 27% ($P<.001$)	5-yr OS improved 58% vs 48% ($P=.004$)
Dutch Colorectal Cancer Group, 2001 ²⁹	1,861	25 Gy/5 fractions + TME vs TME	2.4% vs 8.2% ($P=.001$)	NS

OS=overall survival; TME=total mesorectal excision; NS=not significant.

node staging by EUS has been widely studied, and results range from 70% to 85%.¹²

The improved accuracy of staging with EUS can have a significant clinical impact, as demonstrated in a prospective evaluation of 80 patients with newly diagnosed rectal cancer.¹³ Preoperative CT scans and EUS were performed, and initially only the CT scan results were revealed to the colorectal surgeon, who created a management plan in conjunction with his/her physical exam. The EUS results were then provided to the surgeon, and the plan was reevaluated. The addition of the EUS T stage results led to a change in management in 31% (25 of 80) of patients, with all the patients being upstaged by EUS T stage. The management plan for these patients was changed to include neoadjuvant therapy, compared with the initial plan of proceeding directly to surgery based on CT staging results. Overstaging patients is also a concern when evaluating optimal staging modalities, as neoadjuvant therapy administered to patients with early stage disease (T1/2, N0) can result in unnecessary toxicities and surgical delay. The positive predictive value for EUS in this prospective evaluation was 100%; no early stage patients were exposed to unnecessary neoadjuvant therapy.¹³

Postoperative Adjuvant Therapy

In 1990 the National Institutes of Health (NIH) convened a consensus conference to review the studies of adjuvant therapy for colorectal cancer and recommended combined modality adjuvant therapy for stage II and III rectal cancer based on the preliminary efficacy and safety results of multiple studies.³ The Gastrointestinal Tumor Study Group (GITSG) randomized 227 patients with resected rectal cancer with tumor extension into the perirectal fat and/or involvement of the mesorectal or pelvic lymph nodes (T3, T4N0, or TanyN1–2) to observation with no further cancer therapy, postoperative radiation 40–48 Gy, postoperative chemotherapy with bolus 5-fluorouracil (5-FU)/semustine or a combination of chemotherapy and radiation. This study, which had planned to accrue more than 500 patients, was terminated early when it became clear that postoperative therapy had a significant impact on disease recurrence.¹⁴ The greatest difference in outcomes was noted between the combined therapy group and the surgery only group, with an improvement in survival (54% compared with 27%, $P=.05$, respectively).¹⁵ Acute toxicity was significant in the combined therapy group, consisting of thrombocytopenia, diarrhea, and leukopenia.

However, there was not a notable increase in late toxicity and therefore the combined therapy was felt to be tolerable for the beneficial outcome.

The NSABP subsequently reported results of the R-01 trial, in which patients had been randomized to surgery alone or postoperative radiation or chemotherapy with 5-FU, semustine, and vincristine.¹⁶ A significant improvement in disease-free survival ($P=.006$) and overall survival ($P=.05$) at 5 years was seen in the chemotherapy group when compared to surgery alone. There was also a trend toward decrease in local recurrence with postoperative radiation (25% compared with 16%) but this difference just failed to reach statistical significance ($P=.06$).

A North Central Cancer Treatment Group (NCCTG) trial randomized 204 patients to postoperative radiation therapy or postoperative radiation therapy with bolus 5-FU/semustine.⁶ Patients randomized to radiation received 45 Gy over a 5-week period. Patients randomized to chemoradiation received 2 cycles of chemotherapy consisting of bolus 5-FU/semustine, followed by 45 Gy radiation over 5 weeks with bolus 5-FU weeks 1 and 5 of radiation. After completion of radiation, patients in the chemoradiation group received 2 additional cycles of 5-FU/semustine. With the addition of chemotherapy, local recurrence was reduced by 46% (25% for radiation alone compared to 13.5% with chemoradiation, $P=.036$), and there was a 37% reduction in distant metastatic disease in the group treated with combined modality therapy (46% compared to 28.8% in chemoradiation, $P=.011$). An important outcome of this study was the improvement in overall survival in the combined therapy group, with a reduction in cancer-related deaths by 29% at a median of 7 years of follow-up ($P=.043$).

The NSABP R-02 trial offered further support for the use of combined modality postoperative therapy.¹⁷ Six hundred ninety-four patients with stage II or III rectal cancer were randomized to receive postoperative 5-FU-based chemotherapy, consisting of weekly bolus 5-FU/leucovorin for 6 weeks, with a 2-week break, for 6 cycles, with or without radiation. A 13% local recurrence rate was identified for patients treated with chemotherapy alone and the rate decreased to 8% for patients randomized to receive the combined therapy. The addition of radiation did not improve overall survival or disease free survival when compared to chemotherapy alone.

Subsequent studies evaluated the role of continuous infusion 5-FU with concurrent radiation. A significant advantage was demonstrated for infusional 5-FU with radiation as compared to bolus 5-FU with radiation in terms of rate of tumor relapse (47% with bolus 5-FU compared to 37% with continuous infusion, $P=.01$) and distant metastases (40% compared to 31%, $P=.03$).¹⁸ Importantly, the use of continuous infusion 5-FU led to a statistically significant 10% increase in overall survival, as compared to the group treated with the bolus administration (which had previously been the standard). The toxicity profile differed with the method of 5-FU administration, with severe diarrhea occurring more often in the group treated with continuous infusion 5-FU but more myelosuppression in the group receiving bolus 5-FU therapy.

In the midst of this emerging knowledge of the superiority of combined modality therapy, the United States Gastrointestinal Intergroup designed a study to define the optimal postoperative chemotherapy regimen.¹⁹ Intergroup study 0114 randomized 1,695 patients with stage II or III rectal cancer (T3 or T4, N+) who underwent curative resection to 1 of 4 different 5-FU-based chemotherapy arms. The tested regimens consisted of bolus 5-FU alone, 5-FU with leucovorin, 5-FU with levamisole, and 5-FU with leucovorin and levamisole. Following surgical resection, patients received 2 cycles of chemotherapy followed by concurrent chemoradiation and then 2 additional cycles of chemotherapy, depending on which arm they had been randomized to. At a median follow-up of 7.4 years, there was no difference in overall survival or disease-free survival between the comparison chemotherapy regimens. Local recurrence did not differ by treatment type but there was a difference by disease stage, with identifiable low- and high-risk groups. Patients with low-risk disease, defined as T1-2N+ or T3N0, had a local recurrence rate of 9% as compared to 18% in the high-risk group ($P<.0001$) which included those patients with T3N+ or T4N(any) tumors. Overall survival also differed in the low-risk versus high-risk group, with a 5-year survival of 76% compared to 55%, and a 7-year survival of 55% compared to 45%, respectively ($P<.0001$).

A retrospective study sought to identify prognostic factors in stage T3N0 rectal cancer and to identify patients with T3 disease who benefit from therapy.²⁰ Pathologic characteristics, local recurrence rates, and survival were evaluated for patients with T3N0 disease who had undergone surgery with curative intent, between 1968 and 1985. This was prior to the widespread use of TME as well as standard adjuvant therapy. Consequently, none of the patients reviewed received adjuvant chemotherapy or radiation. A subset of patients was identified who had excellent long-term rates of local control and recurrence-free survival after surgery alone, based on independent risk factors of depth of invasion, vessel involvement, and tumor grade. For patients with less than 2 mm of perirectal fat invasion, no vessel involvement and well-differentiated tumors, 10-year rates of local control and recurrence-free survival were 95% and 87%, respectively. In contrast, patients without these favorable factors had much

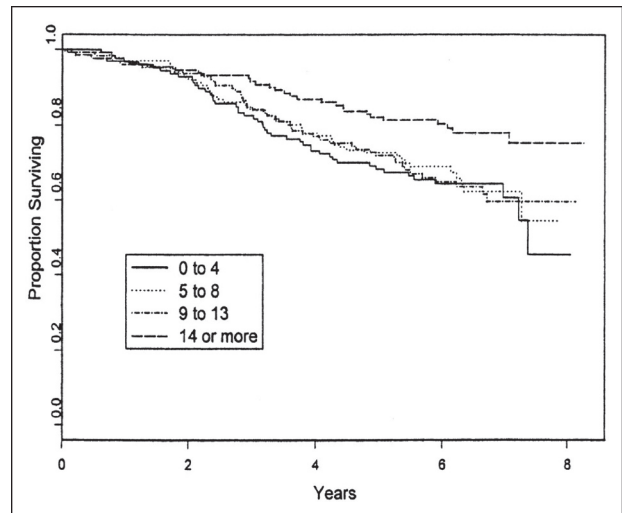


Figure 1. Survival for N0 patients by nodes-examined quartiles.

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lower rates of local control and recurrence-free survival, at 71% and 55%, respectively. Thus, there is evidence that not all patients with resected rectal cancer, nor all patients with T3 lesions, are at the same risk of recurrence. With standardized TME, a group of patients may be identified that do not benefit from combined modality adjuvant therapy. A retrospective analysis of survival outcomes for 5,987 patients with stage III disease supported the substratification of node-positive patients that appeared in the 6th edition of the AJCC staging manual.²¹ Stage IIIA patients had a 5-year overall survival of 55.1%, which decreased to 35.3% for stage IIIB and to only 24.5% for stage IIIC patients, with all of these differences reaching statistical significance. The finding of a survival difference does not at this point impact treatment decisions, as patients in all subsets of stage III disease benefited from adjuvant therapy. Patients treated with surgery alone compared to those treated with adjuvant combined modality therapy had a significant disadvantage in 5-year overall survival, an outcome observed in all stage III subsets. Further subset stratification on pooled data from a number of the major adjuvant studies identified intermediate-risk, moderately high-risk and high-risk patients, with different survival and relapse rates. Prospective validation of these risk categories is the subject of future trials.²²

The most important prognostic indicator for potentially curative rectal cancer remains lymph node involvement. Intergroup study 0114 evaluated the impact of lymph node sampling differences. Interestingly, even among node-negative patients, the absolute number of lymph nodes assessed by the pathologist had an impact on outcome.²³ The 5-year survival rate was 68% if between 0 and 5 lymph nodes were examined and found to be negative for tumor, as compared to 82% if greater than 14 lymph nodes were examined. A statistically significant difference in overall survival and relapse rate was seen between all groups of node-negative patients

who had less than 14 lymph nodes examined and those that had 14 or more nodes examined (Figure 1). The survival advantage is felt to be attributable to more accurate staging based on increased lymph node sampling.

Preliminary data from the most recently completed Inter-group rectal postoperative trial have been presented in abstract form. Trial 0144 was a 3-arm study randomizing patients to either bolus 5-FU before and after radiation therapy, with continuous-infusion 5-FU during radiation or to continuous-infusion 5-FU before and after radiation (46 days and 56 days, respectively) as well as during radiation, or to bolus 5-FU, leucovorin, and levamisole before and after radiation with 5-FU and leucovorin weeks 1 and 5 during radiation. There was an increase in grade 4 hematologic toxicity in the bolus 5-FU treatment arms but no significant difference in overall and recurrence-free survival between the groups.²⁴

Preoperative Therapy

The preoperative approach to adjuvant therapy has been favored in Europe for some time.²⁵ The potential advantages of neoadjuvant therapy are tumor regression and possible downstaging, with the goal of converting a planned APR into an LAR with concomitant sphincter preservation. In addition, preoperative therapy may decrease tumor seeding during surgery as well as decrease acute and late toxicity, as the irradiated bowel will be removed during surgical resection.²⁶ Radiation delivered postoperatively has the potential to cause increased toxicity as there may be increased small bowel adhesions from surgery and more small bowel filling the empty pelvis, therefore making it difficult to avoid unwanted radiation to this organ.²⁷

The Swedish Rectal Cancer Trial group conducted a study of 1,168 patients with resectable rectal cancer, randomizing them to either an intensive short course of preoperative radiation involving 5 fractions of 5 Gy over 5 days or to surgery alone. The 5×5 Gy preoperative radiation with immediate surgery is often favored in Europe for its efficacy in reducing local recurrence and its limited toxicity.²⁸ A significant reduction was seen in local recurrence rates in the group randomized to radiation, with a local failure rate of 11% at 5 years of follow-up, compared with 27% in the surgery alone group ($P<.001$).²⁹ The reduction in local failure rates was found in patients across all stages of disease, not just in more advanced stage disease as may have been expected. In addition to control of local disease, preoperative radiation improved the 5-year overall survival rate from 48% to 58%. It is important to note that the patients in this study did not undergo TME, which is a more complete resection of the mesorectum and theoretically reduces the incidence of residual tumor cells.

In the era of standardized surgery with TME, the impact of local therapy to decrease recurrence is unknown. The Dutch Colorectal Cancer Group randomized 1,805 patients with clinically resectable disease, stage I–IV, to surgery alone with TME or a short preoperative course of radiation consisting of 5 Gy over 5 days.³⁰ The median time from randomization to surgery for those assigned to radiation was 14 days. The

results supported the role of preoperative radiation to reduce local recurrence rates, with a significant reduction from 8.2% to 2.4% at 2 years ($P<.001$), though no difference in overall survival at 2 years was seen. While there was no difference in overall postoperative mortality, there was a statistically significant increase in perineal wound complications in the radiated group for those patients requiring an APR.³¹

The benefits of preoperative radiation have been explored in 2 meta-analyses. The Colorectal Cancer Collaborative Group analyzed 14 randomized trials comparing preoperative radiation to surgery alone and included a total of 6,350 patients.²⁶ Patients in the preoperative radiation group were found to be less likely to have positive nodes at the time of surgery (32% compared to 38%, $P<.0001$). Preoperative radiation was also associated with a reduction in both risk of any recurrence at 5 years (45.9% compared to 52.9%, $P<.00001$) and risk of isolated local recurrence (12.5% compared to 22%, $P<.00001$). While there was an increase in the rate of early deaths within 1 year after therapy in the neoadjuvant radiation group (8% compared with 4%, $P<.0001$), there was no difference in 5-year overall survival. The second meta-analysis collected data from 14 randomized trials on a total of 6,426 patients.³² This study found a similar significant reduction in local recurrence, but reported a 5-year overall survival advantage in the preoperative radiation group compared to surgery alone (odds ratio 0.84, $P=.03$). Patients had not been treated with chemotherapy in any of the analyzed trials.

It has been demonstrated that radiosensitizing chemotherapy enhances the effects of radiation in the postoperative setting. It is expected that the same should be seen in the preoperative setting. The European Organization for Research and Treatment of Cancer (EORTC) trial 22921 randomized 1,011 patients with T3 and T4 tumors considered resectable by DRE, CT scan, and optional EUS.³³ Patients were randomized to 4 treatment arms: preoperative radiation of 45 Gy over 5 weeks, preoperative radiation with concurrent 5-FU/leucovorin days 1–5 during weeks 1 and 5 of radiation, preoperative radiation and postoperative 5-FU/leucovorin, or preoperative radiation with concurrent 5-FU/leucovorin and postoperative 5-FU/leucovorin. A pooled analysis of the radiation and chemoradiation treatment arms reveal an increase incidence of grade 2 or higher toxicities in the patients randomized to chemoradiation as compared to preoperative radiation alone (54% compared to 37%, $P<.005$). This difference was accounted for primarily by increased rates of diarrhea in the combined modality group. Despite this increased toxicity, there was no difference in compliance with the radiation protocol between the 2 groups. In updated results at the recent American Society of Clinical Oncology (ASCO) meeting, it was reported that pathologic T and N stage, lymphatic, venous and perineural invasion, and tumor size were all significantly reduced in the patients who had received preoperative chemoradiation compared with those who had received radiation alone.³⁴ The impact on local control or survival remains to be seen.

Comparison of Preoperative Versus Postoperative Therapy

Three major randomized studies have been designed to directly compare survival for preoperative and postoperative multimodality therapy. The NSABP R-03 study is a phase III study designed to evaluate the optimal timing of adjuvant chemoradiation.³⁵ Patients randomized to the preoperative arm received 1 cycle of bolus 5-FU/leucovorin, 2 cycles of 5-FU/leucovorin with concurrent radiation therapy (45 Gy), and then surgery followed by 4 additional cycles of 5-FU/leucovorin. The postoperative group received the same regimen but all therapy was administered after surgery. The planned sample size was 900 patients but the study closed after 237 patients were enrolled because of slow accrual. As a result, the study is underpowered to detect a difference in overall survival as an endpoint. Of the patients receiving preoperative therapy, those who had a complete pathologic response at surgery have demonstrated an improved survival as compared to those with a partial response or maintaining stable disease (100% compared to 95% and 83%, $P=.02$ for complete response compared to less than complete response).³⁶ An Intergroup trial similarly designed to compare preoperative to postoperative adjuvant therapy also closed secondary to slow accrual.

The CAO/ARO/AIO-94 trial was designed by the German Rectal Cancer Group to compare the efficacy of postoperative versus preoperative combined modality therapy.³⁷ Eight hundred twenty-three patients were randomized to chemoradiation with 50.4 Gy and concurrent continuous infusion 5-FU during weeks 1 and 5 of radiation in the preoperative or postoperative setting. All patients then received 4 additional cycles of 5-FU adjuvant chemotherapy. At a median follow-up of 43 months, there was a significant reduction in local recurrence in the neoadjuvant group (7% compared to 11%, $P=0.02$) as well as a higher rate of sphincter-sparing surgery possible for the neoadjuvant patients for those who preoperatively had been deemed to need an APR (39% compared to 20%, $P=.004$). Neoadjuvant therapy resulted in a reduction in chronic anastomatic stenosis in addition to statistically significant decrease in overall acute toxicity. Though there is no difference in overall survival, with 74% overall survival in both groups at 43 months, these results do contribute to the growing body of evidence that preoperative combined therapy has significant benefits in terms of both acute and late toxicity as well as a sphincter preservation advantage.

Although a survival benefit has not been demonstrated for preoperative combined modality therapy, there are advantages which should not be overlooked. In addition to a significant reduction in local recurrence, neoadjuvant therapy may offer tumor downstaging by T and N criteria and the opportunity for a sphincter-preserving surgery.³⁸ The data on whether there is an actual increase in sphincter preservation with preoperative combined therapy is limited. The short-term preoperative radiation therapy of 5×5 Gy employed

in Europe, while decreasing local recurrence rates, does not lead to tumor downstaging despite a decrease in tumor size and recovered lymph nodes at surgery.³⁹ A number of studies have since specifically focused on sphincter preservation as one of the defined endpoints. Investigators in Poland sought to evaluate whether preoperative combined modality therapy offered an advantage in sphincter preservation compared with short-term preoperative radiation. Three hundred sixteen patients with T3 or T4 disease were randomized to chemoradiation with 50.4 Gy with 2 courses of bolus 5-FU/LV during weeks 1 and 5, followed by TME 4–6 weeks after therapy, or preoperative radiation to 5 Gy times 5 fractions, with TME within 7 days of radiation.²⁸ While there was a significant downsizing effect due to chemoradiation, as well as a 16% pathologic complete response in the combined modality group, there was not a statistical difference in sphincter-sparing procedures performed. Criticism of this study raised concerns about potential surgeon bias in that surgeons may have been performing a more extensive procedure based on pretreatment tumor volume, not on tumor status at the time of surgery.

Conclusions

Since 1990, when the NIH issued the consensus statement, adjuvant therapy with systemic 5-FU and concurrent 5-FU with radiation has been considered the standard of care for stage II and III rectal cancer. Since this statement, the staging of rectal tumors has changed to reflect the importance of depth of tumor invasion and actual number of lymph nodes involved. In addition, the surgical resection has been standardized and shown to decrease the incidence of local recurrence irrespective of adjuvant therapy. The contribution of local therapy in the setting of TME with T1 or T2 tumors is unknown. Concurrent chemotherapy and radiation has been shown to decrease local recurrence, but has not demonstrated an impact on overall survival. Local recurrence of rectal tumors is a therapeutic challenge. Given the proximity to the sacral nerve plexus, they can be associated with a great deal of pain. Rarely is re-operation an option.

Preoperative chemotherapy and radiation has demonstrated a decrease in the size of the primary tumor, and in one study, an increase in the number of patients able to undergo sphincter-sparing surgery, with a favorable long-term toxicity profile. The German Rectal Cancer Trial was powered sufficiently for overall survival, but did not detect a survival advantage between pre- and postoperative therapy. The greatest disadvantage to preoperative chemotherapy and radiation is the inability to accurately stage the tumor based on the surgical specimen. After combined modality therapy, both the T stage and the N stage may be altered, and the number of lymph nodes recovered is often decreased. This may affect the decision to administer further adjuvant therapy.

With EUS, the ability to accurately stage rectal tumors based on depth of tumor invasion and the involvement of local lymph nodes has improved dramatically. This has allowed precise pretreatment staging prior to surgical resection. The

course of adjuvant therapy to be dispensed should be based on the stage of disease prior to any therapy being administered. With EUS in experienced hands, appropriate adjuvant therapy is more likely to be recommended. Patients with tumors that are found to be T1 or T2 with enlarged but reactive lymph nodes by echogenic characteristics (stage I disease) have not been shown to benefit from any adjuvant therapy and should undergo definitive surgical resection. Conversely, patients with T3 or T4 tumors, or any tumor with malignant appearing lymph nodes by EUS may benefit from neoadjuvant therapy. Preoperative chemotherapy and radiation may allow for sphincter-sparing surgery, and has been shown to cause fewer long-term local complications. With EUS, the risk of mistaging patients based on the post-treatment pathologic stage is diminished.

Future Directions

Future research in rectal cancer will focus on improving overall survival and local control, as well as addressing important quality-of-life concerns. Infusional 5-FU remains the standard choice for either neoadjuvant or adjuvant chemotherapy in the setting of combined modality treatment of locally advanced rectal cancer, but newer agents are under investigation. The recently published MOSAIC trial compared standard adjuvant treatment of colon cancer with 5-FU/leucovorin to the regimen of oxaliplatin/5-FU/leucovorin (FOLFOX), which has become the first-line treatment of metastatic disease. At 3 years, the rate of disease-free survival in the FOLFOX group was 78.2%, compared to 72.9% in the standard treatment arm ($P=.002$).⁴⁰

The use of newer agents in the adjuvant treatment of rectal cancer is being pursued. Eastern Cooperative Oncology Group (ECOG) trial 3201 is a phase III randomized trial comparing postoperative systemic therapy with irinotecan (Camptosar, Pharmacia)/5-FU/leucovorin (FOLFIRI) or FOLFOX to standard 5-FU and leucovorin for stage II and III patients with rectal cancer. Patients will have received neoadjuvant therapy with radiation and continuous infusion 5-FU or immediate postoperative therapy with radiation and continuous infusion 5-FU, based on physician choice. Although FOLFOX therapy has shown a favorable disease-free survival advantage in the adjuvant colon setting, this study will address whether the toxicity will be too great with FOLFOX or FOLFIRI in patients who have already received concurrent 5-FU and pelvic radiation. The primary endpoint in this study is overall survival; however, prospective evaluations of rectal function and problems with bowel function as perceived by the patient are important issues that will be monitored.

Vascular endothelial growth factor (VEGF) plays an important role in angiogenesis, and inhibitors of VEGF are under investigation as potential important antitumor agents. Bevacizumab (Avastin, Genentech), a monoclonal antibody against VEGF, was combined with irinotecan and 5-FU in a randomized study of 813 patients with metastatic colorectal cancer. The combination of bevacizumab with chemotherapy

showed a survival advantage compared with chemotherapy alone (20.3 vs 15.6 months, $P<.001$). There is interest in combining chemotherapy with bevacizumab in the adjuvant setting for both colon and rectal cancer. There is currently a proposal to revise ECOG 3201 to incorporate bevacizumab into the randomized design.⁴¹

A recent phase I study integrated bevacizumab into standard neoadjuvant chemoradiation for patients with locally advanced rectal cancer and evaluated VEGF inhibition on tumor physiology, tumor response, and overall systemic effect. The 6 patients enrolled in this study received a dose of bevacizumab, followed 2 weeks later by bevacizumab with 5-FU and concurrent radiation as part of a neoadjuvant combined modality treatment plan. There was a demonstrable decrease in markers of tumor vascularity, including tumor perfusion and microvascular density, supporting the role of this biologic agent in further studies with rectal cancer.⁴²

Previously, ECOG trial 1297 accrued 16 patients to a phase I study of preoperative oxaliplatin with standard concurrent radiation/5-FU therapy with the ultimate goal of improving resectability, sphincter preservation, and pathologic response rates.⁴³ The regimen was well tolerated, and more than half of the patients showed a complete pathologic response or microscopic residual disease at the time of surgery. The Cancer and Leukemia Group B conducted a similar pilot study evaluating weekly oxaliplatin during radiation, demonstrating similar results. The NSABP R-04 trial is currently accruing and randomizing patients to either standard preoperative therapy with continuous infusion 5-FU during radiation or to the oral 5-FU prodrug capecitabine with concurrent radiation, evaluating its effect on radiation and sensitization and local recurrence rates. R-04 will be revised to include a 2 × 2 design implementing oxaliplatin.

Irinotecan has been studied in preoperative combined modality therapy. Mitchell et al⁴⁴ conducted a phase II study of 106 patients comparing preoperative continuous-infusion 5-FU with concurrent radiation to continuous-infusion 5-FU, irinotecan, and concurrent radiation. The endpoint was pathologic complete response, and both treatment regimens demonstrated similar pathologic complete response rates (30% and 26%, respectively) with similar toxicity profiles and tolerability.

Identifying molecular markers of response to therapy and of survival is another important area of study. In patients with high-risk stage II or stage III colon cancer, loss of heterozygosity at chromosome 18q was a poor prognostic factor for survival.⁴⁵ It remains to be seen whether similar molecular prognostic factors will be identified in rectal cancer, and, more important, if they will have real clinical utility in the care of patients with rectal cancer.

The care of the patient with locally advanced rectal cancer continues to evolve. The goals of care should be continued improvement in overall survival, focusing on newer agents, both chemotherapeutic and biologic, and a reduction in local recurrence, which relies on good surgical technique and may

also be improved with neoadjuvant therapy offering a pathologic complete response.

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