

## The Role of Radiation Therapy for Colorectal Cancer

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**R**adiation therapy (RT) has been used to treat cancers for more than a century. It damages cellular deoxyribonucleic acid (DNA), leading to aborted cellular reproduction and death of the daughter cells. Fractionated treatment (the administration of smaller doses 5 days per week for a number of weeks) was discovered empirically early in the development of RT to be beneficial because fractionation permitted a higher total dose of RT to be administered with improved therapeutic efficacy and less toxicity to adjacent normal tissue.

Modern RT uses X rays produced by a linear accelerator. Depth of penetration is controlled by the energy used to produce the X rays and multiple tungsten leaves are used to shape the irradiated volume. Under computer control, some common RT plans can use seven different beam directions, with nine different beam shapes per direction, for a total of up to  $7 \times 9$  or 63 beams, an advance from the traditional administration of 2 to 4 RT beams. The unit dose is the Gray (Gy) which is the deposition of one joule of energy per kilogram of tissue equivalent water. One centigray (cGy) equals the previously used unit of one rad.

A course of RT administered for curative intent for solid malignancy typically lasts 6 to 8 weeks, depending on the cancer. Adjuvant RT is usually given for 5 to 6 weeks, whereas palliative treatment can be accomplished in from 1 day to 3 weeks. The standard fractionated RT dose administered each day for either primary or adjuvant treatment is typically 1.8 or 2 Gy (called standard course of RT herein). It is usually 1.8 Gy per day for 28 fractions (treatments) administered 5 days per week, for a total dose of 50.4 Gy when used adjuvantly for rectal cancer. When the dose per day is increased, the total number of days is correspondingly decreased to limit the risks for injury to normal tissue from the increasing dose per fraction. “Short-course” RT referred to in this article consists of 5 Gy per day for only 5 days for a total dose of 25 Gy.

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## RECTAL CANCER

### Adjuvant Postoperative Treatment

Postoperative chemotherapy and RT was the standard of care for a number of years in patients who had resected transmural (T3) or lymph node positive (N+) rectal cancer based on three pivotal trials. First, in the Gastrointestinal Tumor Study Group (GITSG), 227 patients were randomized to observation; postoperative RT alone; postoperative 5-fluorouracil (5-FU) and semustine chemotherapy alone; or postoperative RT, 5-FU, and semustine [1]. This trial found that disease-free and overall survival were significantly better in the group receiving combined postoperative RT and chemotherapy [2]. Second, in the National Surgical Adjuvant Breast and Bowel Project (NSABP), 555 patients who had T3 or N+ tumors were randomized to observation, postoperative RT, or postoperative 5-FU with semustine and vincristine [3]. This trial concluded that disease-free and overall survival were better with adjuvant chemotherapy, but that adjuvant RT was associated with only a lower locoregional recurrence rate. Third, in the North Central Cancer Treatment Group (NCCTG), 204 patients were randomized to postoperative RT alone or postoperative RT with 5-FU preceded by 5-FU and semustine [4]. Like the GITSG trial, the NCCTG study found a significant disease-free and survival benefit for adjuvant postoperative combined RT and chemotherapy. All three studies showed that adjuvant postoperative RT with chemotherapy produced the best 5-year survival (Table 1). Moreover, pelvic recurrence rates were the lowest in the adjuvant postoperative RT with chemotherapy arms (Table 2). These three studies prompted the National Institutes of Health (NIH) to recommend in 1990 adjuvant postoperative RT with chemotherapy for patients who have transmural or lymph node–positive rectal cancer, although semustine was recommended only in a research setting because of an increased risk for leukemia and chronic renal toxicity [5]. Indeed, a subsequent trial concluded that semustine was unnecessary [6].

### *Chemotherapy and radiation therapy*

Since 1990, most prospective trials of postoperative therapy for transmural or lymph node–positive rectal cancer have focused on the method of 5-FU delivery during RT and the optimal chemotherapeutic combination before and after RT administration. 5-FU helps sensitize malignant cells to RT [7]. It is therefore logical to combine a 24-hour continuous infusion of 5-FU with RT, so that

**Table 1**

Five-year survival rates for the three key randomized trials supporting adjuvant postoperative radiation therapy with chemotherapy for T3 or N+ rectal cancer

Study	Observation	Adjuvant chemotherapy	Adjuvant RT	Adjuvant chemotherapy + RT
GITSG [1]	43%	56%	52%	59%
NSABP [3]	43%	53%	41%	—
NCCTG [4]	—	—	47%	58%

**Table 2**

Five-year pelvic recurrence rates for the three key randomized trials supporting adjuvant postoperative radiation therapy with chemotherapy for T3 or N+ rectal cancer

Study	Observation (%)	Adjuvant chemotherapy (%)	Adjuvant RT (%)	Adjuvant chemotherapy + RT (%)
GITSG [1]	25	27	20	11
NSABP [3]	25	21	16	—
NCCTG [4]	—	—	25	14

every dose of radiation would be sensitized as compared with bolus 5-FU infusion, in which RT would be sensitized only for the 10 days of a typical 28-day RT course during which 5-FU was administered. This concept was verified by a randomized trial that showed improved 4-year survival in the continuous infusion arm versus the bolus arm (70% versus 60%) [6]. The pattern of improvement suggested the benefit was due mostly to reduced metastases, however. As a result, another study tested bolus 5-FU infusion before and after continuous 5-FU infusion during RT against continuous infusion of 5-FU before, during, and after RT [8]. A third arm tested whether addition of the biomodulator leucovorin to bolus 5-FU before, during, and after RT could obviate the need for continuous 5-FU infusion. After a median follow-up of more than 5 years, there were no differences in disease-free or overall survival, but less hematologic toxicity in the continuous infusion arm of 5-FU. Biomodulation of 5-FU was also studied in a four-arm trial, using bolus 5-FU in each arm, in a study begun before release of the infusional data [9]. This trial demonstrated that addition of leucovorin, levamisole, or both was not superior to bolus 5-FU alone. On the basis of these randomized trials, the optimal postoperative therapy seemed to be bolus 5-FU infusion for four cycles with continuous infusion of 5-FU during the approximately 5- to 6-week long RT course.

The need for RT has not been definitively established, however, when at least four cycles of adjuvant chemotherapy are given. The original GITSG trial was relatively small: 58 patients were in the observation arm, 48 were in the chemotherapy-alone arm, and 46 were in the combined modality arm [1]. The NCCTG study tested RT only against RT with chemotherapy but did not incorporate a chemotherapy-alone arm [4]. This evidence led the NSABP to perform a randomized trial of postoperative chemotherapy, with or without RT, in 694 patients who had Dukes' stage B (N = 207) or stage C (N = 487) tumors [10]. Although the cumulative incidence at 5 years of locoregional recurrence was significantly lower in the RT group (8% versus 13%), there was no disease-free or overall survival benefit from the addition of RT, in contrast to earlier NIH recommendations [5]. Subgroup analysis provided support that RT benefited patients younger than 60 years old ( $P = .007$  for overall survival) or patients undergoing abdominoperineal resection ( $P = .007$  for relapse-free survival and  $P = .07$  for overall survival) [10].

Adjuvant postoperative RT has been supported by two other recent randomized trials. In one trial, 218 patients who had resected transmural or

lymph node–positive rectal cancer were randomized to receive either RT alone versus RT with concurrent 5-FU and levamisole followed by five additional cycles of chemotherapy [11]. Although this trial lacked a chemotherapy-only arm, the addition of concurrent chemotherapy to RT increased the relative risk for death by 33% ( $P = .18$ ) compared with the RT-only arm [12]. Although this increase may have been related to the increased rate of severe enteritis in the concurrent chemotherapy plus RT arm (14% versus 5%;  $P = .03$ ), there was only one chemotherapy-related death in the chemotherapy plus RT arm, suggesting that other factors were involved [11]. Another recent randomized trial supported use of adjuvant postoperative RT in 308 patients who had resected transmural or lymph node–positive disease who were randomized to chemotherapy (5-FU with leucovorin) plus RT with the RT either given early (during first cycle of chemotherapy) or late (during third cycle of chemotherapy) [13]. During a median follow-up of only 37 months, this study showed a significant increase in disease-free survival for the early RT arm (81% versus 70%) but did not show an overall survival difference. This finding implied that RT did make a difference and that delays in RT administration may negatively impact on efficacy.

#### *Selection of appropriate stages for radiation therapy*

Selected patients may not need adjuvant RT; this may explain discrepancies between trials. A retrospective review of 117 patients who had T3 N0 rectal cancer suggested that neither RT nor chemotherapy was needed in patients treated with resection alone, who had favorable histologic features (well or moderately well differentiated, invading less than 2 mm into the perirectal fat, without lymphatic or venous vessel involvement) [14]. The 25 such patients had 10-year rates of local control and recurrence-free survival of 95% and 87%, respectively, versus 71% and 55% for 88 patients who did not have these features [14]. Data combining 3791 patients from five large North American randomized postoperative trials support the conclusion that adjuvant RT provides no additional survival benefit over adjuvant chemotherapy alone in patients who have T1-2 N1 or T3 N0 rectal cancer (Table 3) [15].

Studies have shown that the more lymph nodes assessed in lymph node–negative patients, the better the 5-year relapse ( $P = .003$ ) and survival rates ( $P = .02$ ), with the highest 5-year survival rate (82%) in patients who had

**Table 3**

Five-year overall survival rates of patients who have selected stages treated in the five large postoperative randomized trials

Stage	# patients	Adjuvant chemotherapy (%)	Adjuvant chemotherapy + RT (%)
T1/2 N1	355	85	78–83
T3 N0	1060	84	74–80

Data from Gunderson LL, Sargent DJ, Tepper JE, et al. Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: a pooled analysis. *J Clin Oncol* 2004;22:1785–96.

more than 13 lymph nodes assessed [16]. This effect was likely not therapeutic, in that removing more lymph nodes impacted on survival, because there was no similar benefit in lymph node–positive patients. Likely an increased lymph node harvest reflected an improved ability to detect lymph node metastases. Patients who had more than 13 lymph nodes examined were thus much more likely to be truly lymph node–negative. It therefore seems reasonable to consider adjuvant chemotherapy without RT in patients who have T1-2 N1 or T3 N0 rectal cancer if more than 13 lymph nodes were assessed, especially if a total mesorectal excision was done. Prospective studies, however, would be best to test this important change in therapy.

#### *General recommendation for postoperative therapy*

Currently, the most common schedule of adjuvant postoperative chemotherapy with RT is to administer two cycles of 5-FU–based chemotherapy, initiate RT with the third cycle, and follow this with two additional cycles of 5-FU–based chemotherapy [6,8,9]. The National Comprehensive Cancer Network, an alliance of 21 National Cancer Institute designated Comprehensive Cancer Centers, recommends four different alternatives for the initial chemotherapy-only portion of treatment: 5-FU alone, 5-FU with leucovorin, 5-FU with leucovorin and oxaliplatin, or capecitabine, because of disagreements among panel members (Table 4) [17]. Nevertheless, all these choices involve a delay in RT for at least 6 weeks from the initiation of chemotherapy. Because of the above report that RT during the first cycle of chemotherapy, compared with the third cycle, improves disease-free survival [13], further investigation of advancing RT to the first cycle of chemotherapy is warranted. Adjuvant therapy may also need to be individually tailored according to specific surgical staging, intermediate-risk versus high-risk cancers [15], or according to gender [10]. Studies of postoperative RT have been overshadowed by recent developments in preoperative therapy.

#### **Preoperative Treatment**

The concept of preoperative RT for rectal cancer has existed and been tested for decades. The first randomized trial was initiated in 1963 (see [18] for a summary of the randomized trials). Preoperative RT has been given from as few as

**Table 4**  
Commonly accepted regimens for adjuvant chemoradiotherapy

Sequence	Stage	RT dose (total/dose per fraction)	Reference
Preoperative	Resectable	25 Gy/5Gy	[23,30,38]
	uT3/4, cT4, or uN+ <sup>a</sup>	45 to 50.4 Gy/1.8 Gy	[24,28,30,33]
Postoperative	pT3 N0 or pT1/2 N1	None or 50.4 Gy/1.8 Gy	[1,5,6,8,9,15]
	Any pN+	45 to 50.4 Gy/1.8 Gy	[1,5,6,8,9]

All radiation schedules other than the short-course (25 Gy in 5-Gy fractions) should preferentially be given with chemotherapy. Both bolus 5-FU with leucovorin and continuous infusional 5-FU have been shown beneficial in randomized trials. Capecitabine may be equivalent but has not been randomized.

<sup>a</sup>Treatment of uN+ preoperatively is controversial; see text.

one fraction of 5 Gy to as many as 28 fractions and a total dose 50.4 Gy, both with and without chemotherapy [18]. When multiple randomized trials of preoperative RT were reported as negative, enthusiasm waned, and research efforts became focused on the appropriate patient selection and the optimal schedule of treatment for postoperative therapy.

### *Conversion of unresectable disease*

Preoperative RT, with or without chemotherapy, however, still had a role for patients who had unresectable disease, to render the tumor resectable. The data were not solid because the presence of unresectable disease is relatively subjective and cannot be objective without mandatory exploratory laparotomy before treatment. In two prospective studies of preoperative chemotherapy and RT for patients deemed unresectable, the ultimate rate of curative, margin-negative resection was reported to be 61% (17 of 30 patients) with RT and continuous infusion of 5-FU [19] versus 85% (17 of 20 patients) for RT with bolus 5-FU and leucovorin [20]. The need for chemotherapy with preoperative RT in this setting has not been established, because earlier reports of RT alone found a complete resection rate of 75% (26 of 33 patients) [21]. Despite this uncertainty, however, the obvious efficacy of converting unresectable disease to resectable disease provided evidence of treatment efficacy and justified continued analysis of preoperative treatment. Currently, with more accurate preoperative staging [22], the publication of the Swedish Rectal Cancer Trial (Swedish RCT) [23], and the successful completion of the German Rectal Cancer Study Group (German RCSG) trial [24], the standard of care has shifted to rational application of preoperative therapy [25].

### *Benefits of preoperative treatment*

*Tumor shrinkage.* Preoperative treatment is traditionally believed to have three advantages [25]. First, the tumor shrinks, allowing less radical surgery to be done with consequent preservation of the anal sphincter and a better quality of life. Single institution prospective studies support this concept, with reported conversion rates of 40% to 89% [26,27]. As with the difficulty in establishing the conversion rate from unresectable to resectable disease, determination of conversion to a sphincter-sparing procedure is limited and would ideally require surgical exploration to definitively establish the need for an abdominoperineal resection (APR), a requirement that is impractical. Reported improvement in sphincter preservation could thus reflect patient selection bias or subjectivity by the referring surgeon rather than a true treatment benefit. Other questions regarding the appropriate distal surgical margin, sphincter functionality, and quality of life of very low resections also remain to be answered.

Two published multi-institutional randomized trials of preoperative versus postoperative treatment required a surgical declaration of the intended procedure before randomization, but allowed that declaration to be changed during surgery. Although the NSABP R-03 study was not completed, the

postoperative arm had 26 patients who had a pretreatment declaration that an APR was required and all 26 underwent the planned APR. In the preoperative arm, 22 had an APR planned, but only 16 required APR for a conversion rate of 27% [28]. The much larger, completed, German RCSG trial of preoperative versus postoperative treatment had 15 of 72 patients in the postoperative arm with a pretreatment declaration of APR requirement not undergoing APR, because 19% of patients had sphincter sparing based on improved evaluation with anesthetic relaxation of the pelvis [24]. The preoperative arm of the German RCSG study had 116 patients who had an APR planned, of whom 45 (39%) had a sphincter-sparing procedure after preoperative therapy. It thus appeared that the net conversion rate of patients from an APR to sphincter-sparing surgery because of preoperative treatment was 20% (derived from 39%–19%). It has traditionally been believed that short-course RT (25 Gy in 5 fractions), as given in the Swedish RCT [23], followed 1 week later by resection, did not allow enough time for an effect to permit sphincter-sparing surgery [29]. A randomized trial of preoperative short-course RT versus standard-course RT with chemotherapy found, despite significant downstaging, no evidence of increased sphincter sparing in the standard course group [30], in contrast to the German RCSG standard course experience [24]. This difference likely reflected subjective bias in that surgeons were reluctant to alter their planned procedure depending on tumor response [30].

*Decreased toxicity.* The second major potential benefit of preoperative compared with postoperative therapy is less acute toxicity, primarily less diarrhea [25]. Direct comparison of acute toxicity between studies is hampered by different toxicity criteria and selection bias inherent in nonrandomized trials. Studies of preoperative RT with chemotherapy have reported rates of severe diarrhea of 0%, 3%, or 11% [27,31,32]. These differences were likely partly attributable to the inclusion of chemotherapy and the variable chemotherapeutic agents used. For example, a randomized trial of preoperative RT alone compared with preoperative chemoradiotherapy found rates of severe diarrhea of 17% versus 34%, respectively, using a different toxicity scale than the above reports [33]. Studies of postoperative RT with chemotherapy have usually reported higher rates of severe diarrhea than studies of preoperative therapy, with a 14% to 35% incidence [4,6,9]. The rates also depend on the particular chemotherapeutic agent. When different studies using the same chemotherapy (bolus 5-FU with leucovorin) are compared, the rate of grade 3+ diarrhea was 11% for preoperative treatment [27] but 28% for postoperative treatment [9]. Most of the observed difference in clinical tolerability and diarrhea was attributable to inadvertent radiation of the small bowel during treatment. Based on this observation, routine use of a prone position and small bowel exclusion cradles for RT in rectal cancer is recommended [34]. Recent sophisticated three-dimensional analyses using multiple sets of CT scans in the treatment position during therapy have verified that preoperatively treated patients have significantly less irradiated small bowel than postoperatively treated patients [35].

The volume of small bowel irradiated is strongly correlated with the frequency of severe diarrhea [36].

Randomized trials of preoperative versus postoperative combined RT and chemotherapy have provided mixed results regarding diarrhea. Preliminary toxicity data from the NSABP R-03 trial on the first 116 enrolled patients showed that the incidence of grade 3 or worse diarrhea was much higher (23%) in the preoperative than the postoperative group (6%) [28]. The much larger, completed German RCTSG study reported that grade 3 or worse diarrhea occurred in 12% of the preoperative group versus 18% of the postoperative group ( $P = .04$ ) [24]. The same trial also found that the incidence of any grade 3 or worse acute toxicity was 27% for preoperatively treated patients versus 40% in postoperatively treated patients. Additionally, the incidence of any grade 3 or worse chronic toxicity was 14% in the preoperative group versus 24% in the postoperative group. When analyzing toxicity for all patients, however, including patients who for various reasons received no RT, there were no differences in either acute or chronic toxicity between the preoperative and postoperatively randomized groups [24].

*Radiobiologic advantage.* The third argument for preoperative treatment is that the presence of more radiation-sensitive oxygenated cells may be biologically advantageous [25] and may result in reduced tumor seeding, manifesting as lower pelvic and distant recurrence rates and improved survival. This concept is supported by the Swedish RCT [23]. In this study, 1168 patients younger than 80 years old who had resectable rectal cancer were randomized to short-course RT (25 Gy in 5 fractions) followed by surgery within 1 week versus surgery alone. After 5 years of follow-up, the local recurrence rate (11% versus 27%), cancer-specific survival (74% versus 65%), and overall survival (58% versus 48%) were all statistically significantly better in the preoperative RT group compared with the surgery-alone group [23]. Although this result disagreed with previous randomized trials, the Swedish RCT was the largest preoperative trial ever performed and was sufficiently powered to detect a 10% survival difference. Also, the Swedish RCT included more than 50% of eligible patients within Sweden during the enrollment period and was likely to be more generalizable than all other cancer trials [37]. In a meta-analysis, a particular dose of RT, used in both the Swedish RCT and in other trials, of a standard course of 46 Gy in 23 fractions, was associated with a 43% reduction in pelvic recurrence and a 22% reduction in rectal cancer mortality [18].

Total mesorectal excision (TME) instead of traditional blunt pelvic dissection may, however, obviate the observed survival benefit from short-course preoperative RT. In a large randomized study from the Dutch Colorectal Cancer Group (Dutch CCG), more than 1800 patients who had resectable rectal cancer were randomized to preoperative short-course RT, as in the Swedish RCT study, followed by TME versus TME alone with a median follow-up of nearly 5 years [38]. An update of this study reported in 2007 that overall survival rates were identical (64% versus 64%), although local recurrence rates

were slightly different (6% with RT versus 11% without) [39]. Nevertheless, this same study group concluded that if the reduced local recurrence rate led to a survival advantage, short-course preoperative RT was therapeutically efficacious and cost-effective [40]. Another factor that may obviate the need for preoperative RT is selective application of postoperative RT with chemotherapy. The only trial that analyzed this issue was the German RCSG study of preoperative RT for 28 fractions (50.4 Gy) with concurrent chemotherapy compared with the same regimen given postoperatively, both of which were followed by four cycles of chemotherapy alone [24]. In this study, the overall 5-year survival was 76% for preoperative treatment versus 74% for postoperative treatment, although the incidence of local relapse was different at 6% versus 13%, respectively.

*Overall preoperative experience.* In summary, sphincter-sparing surgery was possible in an additional 20% of patients because of preoperative RT with chemotherapy. Toxicity was decreased, with a 6% lower rate of severe diarrhea, a 13% lower incidence of any grade 3+ acute toxicity, and a 10% lower incidence of any grade 3 or greater chronic toxicity [24]. The argument for a biologic advantage was substantiated by a 7% lower pelvic recurrence rate in preoperatively irradiated patients [24], although survival was equivalent for short-course preoperative RT when a TME was performed [38] and for standard-course preoperative RT with chemotherapy when postoperative RT with chemotherapy was given [24]. Commonly accepted regimens for preoperative therapy are shown in Table 4, although the short course (25 Gy in five fractions) is not in widespread use in North America.

#### *Drawbacks of preoperative treatment*

The primary drawback in routine preoperative treatment is overstaging leading to overtreatment. There is no controversy regarding patients who have fixed tumors because preoperative treatment has a well-established role in converting unresectable to resectable tumors. For other patients, clinical staging is usually accomplished by endorectal ultrasound. Preoperative treatment is offered to patients who have ultrasound-staged transmural extension (uT3) or lymph node involvement (uN+) [41]. Endorectal ultrasound is relatively accurate (80% accuracy) for T staging and N staging [22]. A pooled analysis of 11 studies, including T stage in 873 patients and N stage in 571 patients, reported that endorectal ultrasound was very accurate for T stage but only moderately accurate for N stage [42]. In this study, only 11% of uT3 patients, who would be offered preoperative treatment, were pathologically pT1 or pT2. The risk for overtreatment based on endorectal ultrasound for T staging was thus only about 10%, because 15% of pT2 patients would be expected to be eligible for postoperative therapy based on lymph node involvement. Overstaging of lymph node status was a potential issue, because 24% of uN+ patients ultimately were pathologically N0 [42]. The risk for overstaging the T stage at endorectal ultrasound may be much higher than 11%. In the largest single institution experience involving 545 patients, 28% of patients who were uT3

were pathologic T2 and 48% of patients who were uN+ were pathologic N0 [43]. This finding was not because of a learning curve: 88% of the endorectal ultrasounds were performed by colorectal surgeons highly experienced in rectal ultrasonography. If 15% of patients who were pT2 actually had lymph node involvement, as many as 25% of patients could be overtreated because of overstaging. The clinical experience in the German RCSG trial was intermediate between the 11% and 25% rates, with an overstaging incidence of 18% in the postoperative arm using the best available clinical staging [24].

#### *Decision making for preoperative therapy*

These data lead to a dilemma for physicians and patients in deciding between preoperative versus postoperative therapy. Does a 10% to 15% reduction in toxicity, a 20% improvement in sphincter sparing, and a 7% improvement in pelvic control justify a 20% chance that the patient is overstaged and overtreated? This question becomes even more problematic if one accepts that patients who are T3 N0 treated with a TME with an acceptable lymph node harvest may not need irradiation [15,16], and that preoperatively irradiated patients have the same survival as postoperatively irradiated patients [24]. Aside from overstaged uT3 patients, accurately staged uT3 patients who ultimately will be N0 need to be added to the overtreated group, likely around 28% [43], leading to a total of up to 50% of all patients who are uT3 who will be overtreated with RT, although they will still need chemotherapy. This issue should be investigated using sophisticated analysis, but this investigation seems unlikely given the difficulty in recruiting patients in the preoperative versus postoperative studies that led to failure to complete two of the three trials. The issue currently seems to be settled based on the German RSCG and Dutch CCG preoperative trials [24,38].

#### **Surgery and Radiation Therapy**

Surgical developments have impacted on the role of RT, especially the lower local recurrence rate reported with TME [24,38]. The Dutch CCG trial of short-course preoperative RT [38] and the German RCSG trial of preoperative versus postoperative standard-course RT with chemotherapy [24] required use of TME and found that local recurrence rates were improved by about 5% when preoperative treatment was used (Table 5). The ultimate rate of local recurrence may actually be higher, depending on the length of follow-up and the stage of disease. In the Swedish RCT study, the local recurrence curve did not plateau until after 7 years [23]. In the German RCSG trial, local recurrences were observed 5 years after treatment [24]. Aside from length of follow-up, the patient stage was also related to local recurrence rate, with N0 patients and N+ patients in the Swedish RCT exhibiting a 13% and a 20% lower local recurrence rate with RT, respectively [23]. An 11% benefit in N+ patients was also found in the Dutch CCG trial, with an overall 15% rate of local recurrence in the N+ group randomized to surgery only [38,39].

The contribution of TME to local control rates is not entirely clear. In one surgeon's personal experience of 532 resections done with diathermy or

**Table 5**

Local recurrence rates in selected studies

Study	TME used	RT course	Chemotherapy	Local recurrence rate (%)
Swedish RCT [23]	No	No	No	27
	No	25 Gy preop	No	11
Dutch CCG [38,39]	Yes	No	No	11
	Yes	25 Gy preop	No	6
German RCSG [24]	Yes	50.4 Gy preop	Yes	6
	Yes	55.8 Gy postop	Yes	13

*Abbreviations:* postop, postoperative treatment; preop, preoperative treatment; TME, total mesorectal excision.

scissors, without the sharp dissection required for TME, the 5-year local recurrence rate was only 7% [44]. With such a large sample size, adjuvant RT in only 33 patients (6%) and adjuvant chemotherapy in only 1 patient, the results likely reflected the surgical procedure itself. As with TME studies, there was a relationship between nodal positivity and local recurrence, with a local recurrence rate of 17% in the 190 lymph node–positive patients.

#### *Assessment of pelvic control*

Local recurrence rates may reflect symptomatic pelvic recurrences and may therefore understate the true pelvic failure rate. None of the prospective randomized trials required periodic CT assessment of the asymptomatic pelvis [8,9,23,24,38]. Instead, follow-up always included clinical evaluation, with [9,24] or without [23] blood chemistries. Because abnormal liver function tests lead to evaluation of the asymptomatic liver, a direct comparison of distant failure rates to pelvic failure rates essentially compares rates of asymptomatic distant failure with symptomatic pelvic failure. Frankly, if comparisons of pelvic failure rates are used to compare effectiveness of therapies, then pelvic assessment should be optimized, or comparisons should be strictly limited to straightforward survival comparisons. A reasonable remedy would be to require pelvic assessment in prospective trials when either distant failure or pelvic symptoms were observed. Use of PET scans may remedy this problem because distant and pelvic failure can be assessed with this single study.

#### *Complete clinical response to preoperative treatment*

The appropriate surgical management of patients who have a complete clinical response to preoperative treatment is unknown. Because studies have reported residual microscopic disease in 70 of 93 patients who have a clinical complete response [45], radical surgery is still usually recommended. This approach is unproved, however. Some clinical data suggest, contrariwise, that complete pathologic response in the primary is associated with no lymph node metastases [46]. For example, a randomized trial of preoperative standard-course RT with chemotherapy found that patients who had a pathologic complete response or a partial response to a T1 tumor had a low rate of lymph node

metastases on radical resection (5% and 8%, respectively) [47]. In one prospective clinical study of 71 patients who had a complete clinical response, including a negative biopsy during proctoscopy 8 weeks after treatment, patients not undergoing radical surgery had a 5-year survival rate of 100% (92% disease-free survival), which was comparable to the 88% 5-year survival (83% disease-free survival) of 22 patients who had an incomplete clinical response, but a pathologic complete response in the specimen [48]. Alternatively, local excision after preoperative therapy is supported by retrospective evidence in responding T3 tumors [49] and by preliminary data from a prospective study of uT2 tumors [50]. More clinical studies are necessary before this can be recommended, even if the concept is attractive.

#### *Radiation therapy after wide local excision*

It is unknown whether postoperative RT with chemotherapy can replace radical resection in patients who have T2 tumors undergoing wide local excision. No randomized trials are available, but two prospective multi-institutional, non-randomized trials are relevant. In the first trial, patients were randomized to observation or one of two treatment arms combining RT with chemotherapy, depending on the presence of several adverse pathologic features [51]. The pelvic failure rate in T2 patients was 4 of 25 (16%) and in T3 patients was 3 of 13 (23%) during a median follow-up of 6 years. The second trial registered 51 patients who had T2 tumors treated with RT and bolus 5-FU chemotherapy [52]. With a median follow-up of 4 years, 7 patients (14%) who had T2 tumors had pelvic failure. This failure rate was higher than that reported for radical surgery, especially TME (see Table 5). These data raise concerns that this approach may increase the risk for local failure in some patients. Some data suggest that radical surgery is more appropriate even for T1 tumors. A single-institution, retrospective study reported that in T1 tumors with similar risk profiles, the estimated local recurrence rate at 5 years was 15% for patients treated with local excision alone versus 3% for radical surgery [53]. Nevertheless, the availability of a sphincter-preserving option for patients who have selected distal rectal tumors and the success of surgical salvage [51,52] has to be integrated into the clinical decision.

#### **Functional Outcome and Quality of Life**

Because survival outcomes were equivalent [24], comparisons of preoperative to postoperative therapy and strategies of downstaging to less radical surgical procedures depend on the functionality of the retained sphincter and impact on quality of life (QOL). The reported results of overall long-term bowel function in irradiated patients are mixed. Acceptable bowel complication rates were reported in the German RCSG randomized trial of preoperative standard course treatment versus postoperative treatment [24]. This landmark trial found long-term gastrointestinal side effects in 9% of the preoperatively treated group versus 15% of the postoperatively treated group, including a 2% and 1% rate of reoperation, respectively. The incidence of anastomotic strictures was markedly different, with 9% in the preoperative group versus 15% in the

postoperative group. Although these differences favor preoperative treatment, the rate of long-term effects was essentially identical when all patients were included, including those not eligible for postoperative treatment because of the pathologic findings [24]. Similarly, the randomized trial examining all four possible combinations of preoperative versus postoperative treatment with RT or chemotherapy found no significant differences in the incidence of late side effects among the four treatment groups [33]. In both trials, however, all patients received some form of RT.

Other studies have reported higher rates of long-term bowel dysfunction in irradiated versus unirradiated patients. Using a telephone questionnaire approximately 3.5 years after surgery, patients who had been irradiated reported a median of seven bowel movements per day versus two for patients who had not been irradiated, with occasional incontinence in 39% versus 7%, respectively [54]. In a mailed questionnaire to 400 patients who did not have recurrent or metastatic disease in the national rectal cancer database for Norway (80% questionnaire completion rate) patients who had been irradiated who had an anterior resection had a significantly higher median number of bowel movements per day than patients who had not been irradiated (6 versus 2.5), more incontinence, and reduced well-being [55]. Similar findings were reported in the Swedish RCT study and the Dutch CCG studies of short-course preoperative RT [56,57]. Thirty percent of patients who had been irradiated reported that they had an impaired social life because of bowel dysfunction versus 10% in the surgery-alone group [56]. This difference may not affect a person's overall health-related QOL, however, which was reported to be equivalent between the preoperative RT and surgery-only arms of the Dutch CCG study [58].

These reports are subject to limitations. Selection bias is always present in surveys, given that some questionnaires are not returned and patients who have complaints are more likely to return the questionnaires than patients who feel well. Another source of bias is that assessment of QOL was done in patients free of disease. Ideally, a comparison of different therapeutic strategies would include simultaneous assessment of QOL in patients who have disease recurrence to determine whether the negative QOL aspects of treatment are counterbalanced by the positive QOL aspects of disease control.

Objective data using anorectal manometry have been inconclusive. In one study of 21 patients irradiated with short-course preoperative RT versus 43 treated with surgery alone, the irradiated patients had significantly lower resting and squeeze pressures and evidence of anal sphincter scarring [59]. Another study using anorectal manometry before and after treatment found no significant difference in resting or squeeze pressures among 20 patients treated with standard course preoperative RT [60].

## COLON CANCER

In retrospective reviews, adherence or invasion of colon cancer to adjacent structures and involvement of the resected margin are associated with high

rates of local cancer treatment failure. In a large single institution review, patients who had resected T4 N0 and T4 N1 colon cancer had local failure rates of 31% and 53% with surgery alone, which was reduced to only 7% and 28%, respectively, with the addition of adjuvant RT [61]. The only randomized study of this issue closed after recruitment of only 187 of 700 planned patients, but did report identical local recurrence rates of 19% with or without RT [62]. Aside from early study closure, another confounding issue in this trial is optional use of abdominopelvic CT scans, so that the actual incidence of local failure may have been higher in both groups. Nevertheless, survival was equivalent between arms during a median follow-up of more than 6 years, suggesting that any potential benefit of improved local control was unassociated with improved survival.

## SUMMARY

Postoperative RT with chemotherapy has been the standard of care for a number of years for transmural or lymph node-positive rectal cancer. The use of postoperative treatment has been overshadowed by recent research results in preoperative RT with chemotherapy. Preoperative RT with chemotherapy can downstage low rectal cancer, allowing more frequent sphincter-sparing surgery, reducing toxicity, and possibly improving pelvic control. Recent developments in surgery with TME and chemotherapy may require reevaluation of this strategy, however. Studies in colon cancer have also led to questioning of routine RT for T3 or T4 tumors because of no evident survival advantage, although the optimal use remains to be defined in T4 or margin-positive colon cancer.

## Acknowledgments

The author wishes to acknowledge Maria M. Hardy, RN, MSN, for editing and proofreading assistance.

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