World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i7.848

World J Gastroenterol 2011 February 21; 17(7): 848-854
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

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Neoadjuvant *vs* adjuvant pelvic radiotherapy for locally advanced rectal cancer: Which is superior?

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Received: August 30, 2010 Revised: September 29, 2010
Accepted: October 6, 2010
Published online: February 21, 2011

Abstract

The treatment of locally advanced rectal cancer including timing and dosage of radiotherapy, degree of sphincter preservation with neoadjuvant radiotherapy, and short and long term effects of radiotherapy are controversial topics. The MEDLINE, Cochrane Library databases, and meeting proceedings from the American Society of Clinical Oncology, were searched for reports of randomized controlled trials and meta-analyses comparing neoadjuvant and adjuvant radiotherapy with surgery to surgery alone for rectal cancer. Neoadjuvant radiotherapy shows superior results in terms of local control compared to adjuvant radiotherapy. Neither adjuvant or neoadjuvant radiotherapy impacts overall survival. Short course versus long course neoadjuvant radiotherapy remains controversial. There is insufficient data to conclude that neoadjuvant therapy improves rates of sphincter preserving surgery. Radiation significantly impacts anorectal and sexual function and includes both acute and long term toxicity. Data demonstrate that neoadjuvant radiation causes less toxicity compared to adjuvant radiotherapy, and specifically short course neoadjuvant radiation results in less toxicity than long course neoadjuvant radiation. Neoadjuvant radiotherapy is the preferred modality for administering radiation in locally advanced rectal cancer. There are significant side effects from radiation, including anorectal and sexual dysfunction, which may be less with short course neoadjuvant radiation.

Key words: Locally advanced rectal cancer; Neoadjuvant radiation; Adjuvant radiation; Rectal neoplasm; Chemoradiotherapy; Neoadjuvant chemoradiotherapy

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Popek S, Tsikitis VL. Neoadjuvant *vs* adjuvant pelvic radiotherapy for locally advanced rectal cancer: Which is superior? *World J Gastroenterol* 2011; 17(7): 848-854 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i7/848.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i7.848

INTRODUCTION

Colorectal cancer is the third most frequent cancer in men and women. In 2009, in the United States 40 000 new cases of rectal cancer alone were diagnosed[1]. The past 2 decades have seen many advances in the treatment of patients with rectal cancer. Surgery remains the mainstay. The standard of surgical care now includes total mesorectal excision (TME), which was shown to significantly decrease local recurrence rates[2]. Evolution of Combined Modality Treatment (CMT) revolutionized care of locally advanced rectal cancer with the most considerable change the introduction of pelvic radiation. Improvements in preoperative staging with endorectal ultrasound and magnetic resonance imaging have allowed experimentation with different regimens of neoadjuvant (preoperative) and adjuvant (postoperative) radiotherapy (RT).

The goals of this review are to provide a critical over-

view of the most relevant clinical trials, and to evaluate the advantages and disadvantages of different RT regimens, in the adjuvant and neoadjuvant setting, for patients with locally advanced rectal cancer (stages ⅡB and C, ⅢA through C).

ADJUVANT RADIATION

RT for rectal cancer was first introduced in the 1980s, in an attempt to decrease rates of local recurrence in patients with locally advanced rectal cancer; at that time, the local recurrence rates after surgical resection were as high as 50%[3].

One of the first randomized controlled trials (RCTs) to demonstrate success in control of local recurrence with the use of adjuvant therapy was published in 1985 by the Gastrointestinal Tumor Study Group[4]. That study randomized 227 patients (data from 202 collected) to 4 arms: (1) no adjuvant therapy (the control arm) (n = 58); (2) adjuvant RT (n = 50); (3) adjuvant chemotherapy (n = 48); or (4) adjuvant CMT (n = 46). Patients in the CMT arm had significantly decreased local recurrence rates ($P < 0.009$), as compared with the control arm, but the overall survival rates did not significantly differ ($P = 0.07$). That 1985 publication ushered in the era of adjuvant therapy with RT for patients with locally advanced rectal cancer.

In the United States, the first official recommendation for the use of adjuvant chemoradiation in patients with rectal cancer came from the National Institutes of Health (NIH) consensus statement, published in 1990[5]. The NIH set the standard of care for patients with stage Ⅱ and Ⅲ rectal cancer to include adjuvant chemoradiation without specifying the optimal regimen. Subsequently, extensive research has been conducted on the most advantageous timing and dosage of pelvic RT in patients with locally advanced rectal cancer (Table 1). In 1997, the Norwegian Adjuvant Rectal Cancer Project Group published the results of one of the early trials evaluating the chemotherapy dose in adjuvant chemoradiation for patients with locally advanced rectal cancer[6]. Previous studies had shown improved locoregional control with adjuvant RT, but high toxicity and poor compliance with adjuvant CMT[4,7]. The Norwegian trial addressed the important issue of clinically significant complications in the setting of adjuvant CMT for rectal cancer. In that trial, 144 patients were randomized to surgery alone or to adjuvant CMT (chemoradiation with long-course RT and short-term 5-fluorouracil (5-FU)-based chemotherapy). The short-term chemotherapy was tolerated by patients without sacrificing the benefits of improved local control. The minimum follow-up time was 4 years. The 5-year recurrence free rates significantly differed (64% in the CMT arm *vs* 46% in the surgery alone arm, $P = 0.01$), as did the 5-year survival rates (64% in CMT arm *vs* 50% in surgery alone arm, $P = 0.05$). Further, a meta-analysis in 1988 reviewed all RCTs evaluating adjuvant therapy (8 RT *vs* surgery alone, 17 chemotherapy *vs* surgery alone) with the endpoint of overall survival and found only a small improvement in the adjuvant chemotherapy arm [odds ratio (OR), 0.83, 95% CI: 0.70-0.98]. No effect on survival was found in the RT arm[8].

NEOADJUVANT RADIATION

Efforts aimed at improving local control and long term survival stimulated experimentation with adjuvant RT in the 1990s and gave birth to the concept of neoadjuvant RT. Initial reports from small studies suggested that efficacy with neoadjuvant RT was comparable or improved compared to adjuvant RT, and toxicity was less severe. Delineating the veracity of these small studies intrigued investigators over the subsequent decade. Specifically two different regimens of neoadjuvant RT were being assessed: (1) long course RT, used mainly in the United States; and (2) short course RT, used mainly in Europe.

The European Organization for Research and Treatment of Cancer (EORTC) designed a study to evaluate the efficacy and toxicity profile of neoadjuvant RT (long-course). Four hundred and sixty-six patients were enrolled: 175 were ultimately randomized to surgery alone, and 166 randomized to neoadjuvant RT followed by surgery. Patients in the neoadjuvant arm tolerated the treatment adequately, had significantly decreased local recurrence rates (15% *vs* 30%, $P = 0.003$), but had no improvement in overall survival[9]. The Swedish Rectal Cancer Trial[10] was the first major trial to demonstrate significant improvement in local control with short-course RT (25 Gy in 5 consecutive daily fractions) followed by surgery, compared with surgery alone (11% local recurrence rate with short-course RT *vs* 27% without, $P < 0.001$). In addition, the Swedish trial was the only trial to demonstrate improved 5-year survival rates for patients in the neoadjuvant arm (58% with short-course RT *vs* 48% without, $P = 0.004$). The patient population included those with stage I rectal cancer as well as locally advanced disease. Note that the results of that trial, published in 1997, preceded surgical standardization to TME; hence, one of its drawbacks was the lack of standardization in surgical technique.

In response, the Dutch colorectal group performed a similar investigation, with the notable exception of standardizing surgery to TME[11]. Again, patients were randomized to either short course neoadjuvant RT followed by surgery within 1 wk (n = 695) or surgery alone (n = 719). A significant decrease in local recurrence rates was found at 2 years in the neoadjuvant RT arm (2.4% *vs* 8.2%, $P < 0.001$), but no difference in overall survival (82% *vs* 81.8%, $P = 0.84$). An additional variable examined in this study was the import of a positive circumferential margin (CRM). Positive CRM was significantly correlated with an increased risk of local recurrence; and patients with positive CRM received post operative long course RT. The Dutch colorectal group confirmed the findings of the Swedish rectal trial in terms of local control, contradicted findings of improved survival, and raised a new question regarding the role of selective adjuvant RT with positive CRM. That question was addressed with the Medical Research Council (MRC) CR07 trial, whose results were

Table 1 Randomized control trials evaluating timing and dose of radiation therapy

Trial (year results published)	Study design	Patients	Follow-up (mo)	Treatment	Outcome: overall survival	Outcome: local recurrence
Swedish Rectal Cancer Trial (1997)[10]	RCT	1168	60	Neoadjuvant short-course RT *vs* surgery alone	58% *vs* 48% (P = 0.004)	11% *vs* 27% (P < 0.001)
Dutch TME Trial (2001)[11]	RCT	1861	24	Neoadjuvant short-course RT (standard TME) *vs* surgery alone	82% *vs* 81.8% (P = 0.84)	2.4% *vs* 8.2% (P < 0.001)
German Rectal Cancer Study Group (2004)[14]	RCT	799	60	Neoadjuvant long-course RT + chemotherapy *vs* adjuvant long-course RT + chemotherapy	76% *vs* 74% (P = 0.80)	6% *vs* 13% (P = 0.006)
Polish Colorectal Group (2006)[16]	RCT	312	48	Neoadjuvant short-course RT *vs* neoadjuvant long-course RT	67.2% *vs* 66.2% (P = 0.96)	14.2% *vs* 9% (P = 0.17)
MRC-NCIC (2009)[17]	RCT	1350	60	Neoadjuvant short-course RT *vs* selective adjuvant long-course RT + chemotherapy	70% *vs* 67.9% (HR 0.91, 95% CI: 0.73 to -1.13, P = 0.40)	4% *vs* 11% (HR 0.39, 95% CI: 0.27 to 0.58, P < 0.0001)
NSABP R-03 (2009)[18]	RCT	267	60	Neoadjuvant long-course RT + chemotherapy *vs* postoperative long-course RT + chemotherapy	74.5% *vs* 65.6% (P = 0.065)	10.7% *vs* 10.7% (P = 0.69)
Stockholm Ⅲ (2010)[1]	RCT	303	Ongoing	Neoadjuvant short-course RT + surgery within 1 wk *vs* neoadjuvant short-course RT + surgery 4 to 8 wk later *vs* neoadjuvant long-course RT + surgery 4 to 8 wk later		Ongoing

[1]Interim results. RCT: Randomized control trial; RT: Radiotherapy; TME: Total mesorectal excision; MRC-NICI: Medical Rectal Council-National Cancer Institute of Canada; NSABP: National Surgical Adjuvant Breast and Bowel Project; HR: Hazard ratio.

published in 2009 (see below).

As more data became available, two meta-analyses were published in 2000 and 2001 asking two important questions. First, what is the efficacy of neoadjuvant RT in improving survival, and decreasing local recurrence rates[12] and second, what is superior in improving survival and decreasing local recurrence: adjuvant or neoadjuvant therapy[13]? Cammà *et al*[12] addressed the first question; their analysis included 14 RCTs and found that neoadjuvant RT significantly improved the 5-year survival rates (OR, 0.84, 95% CI: 0.72-0.98, P = 0.03), the cancer-related mortality rates (OR, 0.71, 95% CI: 0.61-0.82, P < 0.001), and the local recurrence rates (OR, 0.49, 95% CI: 0.38-0.62, P < 0.001). The Colorectal Cancer Collaborative Group evaluated 22 RCTs (involving a total of 8507 patients) to determine the answer to the second question. The RCTs compared neoadjuvant therapy, adjuvant therapy, or surgery alone and included both short-course and long-course RT. The group found a significant improvement in the yearly local recurrence rate in the neoadjuvant RT arm (a 46% decrease *vs* surgery alone, P = 0.00001) and in the adjuvant RT arm (a 37% decrease *vs* surgery alone, P = 0.002). But the 5-year survival rate (45% with RT *vs* 42.1% with surgery alone) and the overall survival rate (62% with RT *vs* 63% with surgery alone, P = 0.06) did not significantly differ. Of note, 30 Gy was identified as the biologically active dose of RT.

The issue of neoadjuvant *vs* adjuvant RT is further clouded by the inclusion of chemotherapy into treatment regimens. In 2004, the German Rectal Cancer Group compared neoadjuvant CMT with adjuvant CMT in patients with locally advanced rectal cancer[14]. Patients were randomly assigned to 2 arms: (1) neoadjuvant CMT (n = 421); and (2) adjuvant CMT (n = 402). All patients received long-course RT and 5-FU-based chemotherapy. The 5-year survival rates (76% with neoadjuvant CMT *vs* 74% with adjuvant CMT, P = 0.8) did not significantly differ. But the local recurrence rates significantly improved in the neoadjuvant arm (6% with neoadjuvant CMT *vs* 13% with adjuvant CMT, P = 0.006). The adjuvant arm had higher rates of acute and long-term toxicity (acute: 27% with neoadjuvant CMT *vs* 40% with adjuvant CMT, P = 0.001; long-term: 14% *vs* 24%, P = 0.01). Another important finding was that overstaging of patients resulted in unnecessary administration of neoadjuvant CMT.

In 2005, Law *et al*[15] contributed to the controversy surrounding overstaging and overtreatment by suggesting that low risk stage Ⅱ patients do not benefit from neoadjuvant therapy. They reported data on 224 patients with stage Ⅱ disease who underwent TME surgery without neoadjuvant or adjuvant CMT. They hypothesized that the benefit of treating stage Ⅱ disease with adjuvant therapy was less than the risk of complications or toxicity from CMT. Median follow up was 43 mo. Five years recurrence rate was reported as 6% which is comparable to previously reported values for patients undergoing neoadjuvant RT and surgery (2.4%-14.2%, Table 1)[10,11,14,16-18]. Overall survival was reported as 71% which is also similar to data from previous trials for patients undergoing neoadjuvant RT and surgery (58%-82%, Table 1)[10,11,14,16-18]. They conclude that there is no advantage to treating low risk stage Ⅱ rectal cancer patients with negative margins with neoadjuvant therapy. There was an emphatic response to this statement from many authors who felt that that not treating stage Ⅱ patients with neoadjuvant CMT was egregious[19].

Once short-course neoadjuvant RT was established to

be safe and effective, the next step was to compare its efficacy with that of long-course neoadjuvant RT. In 2006, the Polish Colorectal Study Group randomized 312 patients to either (1) neoadjuvant short-course RT, surgery within 1 wk, and optional adjuvant chemotherapy or (2) neoadjuvant long-course RT, neoadjuvant chemotherapy, and surgery 6 to 8 wk later. Early RT toxicity was higher in the long-course RT arm (18.2% with long-course RT *vs* 3.2% with short-course RT, $P < 0.001$), but the 5-year survival rates (66% *vs* 67%, $P = 0.96$) and the local recurrence rates (9% *vs* 14%, $P = 0.17$) did not significantly differ. The study concluded that short-course and long-course RT had comparable efficacy, but short-course RT remains the standard of care in Poland because of the lower toxicity distribution and higher compliance rates. In 2009, Guckenberger *et al*[20] introduced a new regimen for short-course RT, administering twice-daily doses of 2.9 Gy for 1 wk (total dose, 29 Gy) to 118 patients. That regimen lowered the single dose and allowed a 6-h tissue recovery period between treatments, but the daily dose was the same as with standard short-course RT (5 Gy daily × 5 d). The 188 patients had clinical stage Ⅱ (50%), Ⅲ (41.5%), and Ⅳ (8.5%) rectal cancer; they all received adjuvant 5-FU-based chemotherapy. The median follow-up time was 46 mo. Late toxicity (grade Ⅱ) occurred in 11% of the patients. The local control rate was 92%. The 5-year survival rate of 67% compared favorably with previously reported rates in randomized trials that also evaluated daily dosing of short-course RT (58%-82%, Table 1)[10,11,16].

In the United States, the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03 trial also compared neoadjuvant CMT and adjuvant CMT in patients with locally advanced rectal cancer[18]; the NSABP R-03 trial was similar to the German rectal cancer group trial published in 2004[14]. Both arms of the NSABP R-03 trial used long-course RT, and the chemotherapy regimen was 5-FU-based with leucovorin. The study was initially powered for a sample size of 900, but had to close early due to poor accrual. In all, 123 patients were randomized to neoadjuvant CMT and 131 to adjuvant CMT. The surgical technique was not standardized, but rather left to the discretion of the surgeon. Primary endpoints were the disease-free survival and overall survival rates. The overall survival rates (74.5% with neoadjuvant CMT *vs* 65.6% with adjuvant CMT, $P = 0.065$) and the locoregional recurrence rates [Hazard ratio (HR), 0.86, 95% CI: 0.41-1.81, $P = 0.693$] did not significantly differ - in contrast to the 5-year disease-free survival rates (64.7% *vs* 53.4%, $P = 0.011$). Of note, the rate of complete pathologic response was 15% in the neoadjuvant CMT group but the rates of sphincter preservation (48% with neoadjuvant CMT *vs* 39% with adjuvant CMT) did not significantly differ, per the opinion of the operating surgeon. It is difficult to draw conclusions from the NSABP R-03 trial, because it was underpowered and not standardized in operating technique.

In 2009, the MRC and National Cancer Institute of Canada (NCIC) combined CR07/CTG C016 trial[17] addressed the issue of selective adjuvant CMT based on operative margins. The trial randomized 1 350 patients to 2 arms: (1) neoadjuvant short-course RT; or (2) initial surgery with selective adjuvant long-course RT and 5-FU-based chemotherapy based on circumferential (CRM) involvement. The surgical technique was not standardized. Median follow-up time was 4 years; the primary outcome measure was local recurrence. In the selective adjuvant arm, 12% of the patients had a positive CRM, 78% of whom then underwent adjuvant RT. In the neoadjuvant arm, a 61% relative risk reduction (HR, 0.39, CI: 0.27-0.58, $P < 0.0001$) was found for local recurrence, and a 24% improvement (HR, 0.76, CI: 0.62-0.93, $P = 0.013$) was found for disease-free survival. But the 2 arms did not significantly differ in overall survival rates. The MRC CR07/NCIC-CTG C016 investigators concluded that neoadjuvant short-course RT was effective therapy in patients with operable rectal cancer.

BENEFITS OF NEOADJUVANT RT

With the advent of neoadjuvant therapy, reliable methods to evaluate its efficacy and to determine the significance of response to treatment have been necessary. Pathologic tumor response has risen to the forefront, although several tumor grading systems are currently in use. Two recent prospective studies evaluated the impact of tumor response on overall survival in patients with locally advanced rectal cancer[21,22]. Both studies concluded that tumor downstaging was the only variable that significantly and independently correlated with improved survival.

Most significantly the addition of neoadjuvant radiation has resulted in significant downsizing and downstaging of low locally advanced rectal cancers making sphincter preserving procedures feasible and with good oncologic outcomes. Weiser *et al*[23] performed a retrospective analysis of 148 patients with locally advanced rectal cancer (within 6 cm of the anal verge) who were treated with neoadjuvant CMT (long-course RT) and selective adjuvant chemotherapy. The decision to perform sphincter-preserving surgery was made intraoperatively. The likelihood of sphincter-preserving surgery was associated with significant tumor downstaging. They concluded that neoadjuvant CMT facilitated sphincter-preserving surgery in addition to intersphincteric resection.

However, short course neoadjuvant radiation does not seem to offer the same results. Sauer *et al*[14] did not find a significant difference in the rates of sphincter-preserving surgery between their neoadjuvant and adjuvant treatment arms. However, they did note that, within the subgroup of patients deemed to require abdominoperineal resection preoperatively ($n = 194$), the number of abdominoperineal resections actually performed was significantly lower in the neoadjuvant arm ($P = 0.004$). Bujko *et al*[24] specifically looked at whether neoadjuvant short-course RT offered a benefit for sphincter preservation over neoadjuvant CMT in 316 patients and found no significant difference:

61% of patients in the RT arm and 58% in the CMT arm underwent sphincter-preserving surgery (P = 0.57). In conclusion, although short-course RT improves local control, no strong evidence exists that it also improves rates of sphincter-preserving surgery indicating short-course neoadjuvant RT does not have a significant effect on preoperative tumor downsizing or downstaging.

A significant benefit of neoadjuvant RT is patient compliance with treatment. Adjuvant RT has been associated with higher rates of treatment interruption. Lebwohl *et al*[25] assessed for principle factors associated with treatment interruption in 113 RT patients. Patients in the adjuvant arm had a significantly increased chance of RT interruption, as compared with the neoadjuvant RT arm (OR, 14.08, CI: 1.55-127.87). Development of an adverse event was also significantly correlated with RT interruption (OR, 20.66, CI: 1.76-242).

ANORECTAL FUNCTION OUTCOMES

One of the most important variables evaluating quality of life in rectal cancer is anorectal function, specifically bowel function and sexual function[26]. This is affected by both chemoradiation and surgical technique. The Dutch colorectal group assessed anorectal functional outcomes after short-course preoperative RT and TME and found significant differences between patients who did *vs* did not undergo RT[27]. RT patients had higher rates of fecal incontinence (62% with RT *vs* 38% without, $P < 0.001$), pad wearing as a result of incontinence (56% *vs* 33%, $P < 0.001$), and anal blood loss (11% *vs* 3%, $P = 0.004$). RT patients also reported significantly lower satisfaction with bowel function.

A second prospective study randomized 316 patients to (1) short-course neoadjuvant RT or (2) long-course neoadjuvant chemoradiation[26]. The goal was to evaluate anorectal and sexual dysfunction and quality of life. Early complications were more common in the chemoradiation arm, but no significant differences were found in the degree of anorectal and sexual function or in quality of life.

In addition to bowel and sexual dysfunction, RT patients may experience acute and late RT toxicity, including nausea/vomiting, postoperative hernia, femoral neck fracture, skin problems (nonhealing perineal wounds), ileus, anastomotic stricture, and fistula. The Dutch colorectal group assessed RT toxicity, intraoperative and postoperative complications, and other variables in patients who underwent short-course neoadjuvant RT *vs* TME alone[27]. No differences were found in operative time, intraoperative complications, or hospital stay; however, the amount of intraoperative blood loss was higher in the RT arm ($P < 0.001$). Rates of perineal complications were also higher (29% with RT *vs* 18% with TME alone, $P = 0.008$). But no significant differences were found in the rate of abdominal wound complications (4.0% with RT *vs* 3.3% with TME alone) or in the overall postoperative mortality rate.

Frykholm *et al*[28] looked at long-term complications (minimum follow-up time, 5 years) after either neoadjuvant short-course RT (n = 255) or adjuvant long-course RT (n = 127), as compared with surgery alone (control group, n = 82). Long-term complications (defined as occurring at least 6 mo postoperatively) included recurrent abdominal pain, diarrhea, fecal incontinence, ileus, cystitis, paresthesias, delayed wound healing, and any neurologic dysfunction. The percentage of patients with small bowel obstruction did not significantly differ between the neoadjuvant RT group and control group. In the adjuvant RT group, the risk of developing a small bowel obstruction was significantly higher ($P < 0.01$). Overall, the frequency of complications possibly related to RT in the neoadjuvant group was 20%; in the adjuvant group, 41%. However, in the control group, the percentage of similar complications was 23%. In addition to finding a significant decrease in local recurrence after neoadjuvant short-course RT (13% in the neoadjuvant group *vs* 22% in the adjuvant group, $P = 0.02$), the cumulative risk of bowel obstruction was significantly higher in the adjuvant group.

Minsky *et al*[29] also demonstrated significantly lower rates of adverse events and improved compliance in patients treated with neoadjuvant CMT compared to patients treated with adjuvant CMT. Despite receiving higher doses of chemotherapy, the neoadjuvant arm experienced a 13% incidence of acute grade 3 or 4 toxicity compared to a 48% incidence in the adjuvant arm ($P = 0.045$). A meta-analysis by Birgisson *et al*[30] found that the most common late adverse effects of RT were bowel obstruction, bowel dysfunction (fecal incontinence), and sexual dysfunction. Several different RT regimens were included in the meta-analysis, offering some insight into how complications correlated with dosage. Overall, in the more recent studies which used lower doses and better techniques, the rates of adverse events were lower. Unfortunately, to date, no specific markers have been identified that might help predict which patients have a higher risk of acute RT toxicity. Further work is needed in this important area of ongoing research.

CONCLUSION

Patients with locally advanced rectal cancer clearly benefit, in terms of locoregional control, from both neoadjuvant and adjuvant RT; and patient compliance is better with neoadjuvant RT. No definitive evidence demonstrates the superiority of using short *vs* long-course RT.

The current standard treatment for patients with locally advanced rectal cancer in the United States consists of neoadjuvant radiation (45 to 55 Gy administered over 5 to 6 wk), followed by neoadjuvant chemotherapy (5-FU-based infusion + leucovorin), surgery 6 to 8 wk after completion of chemotherapy, and additional adjuvant chemotherapy after surgery[31]. In contrast, the standard regimen in most of Europe is now neoadjuvant short-course RT. The most recent European Rectal Cancer Consensus Conference concluded that neoadjuvant short-course RT (25 Gy administered over 1 wk), especially when combined with

5-FU-based chemotherapy, improved local control for patients with locally advanced rectal cancer[32].

Several important trials are currently in progress. The next interim analysis from Stockholm Ⅲ should provide some clues in the debate concerning short-course neoadjuvant RT and timing of surgery. Given the lack of data supporting improved overall survival rates with neoadjuvant or adjuvant RT, treatment failure in patients with stage Ⅱ and Ⅲ rectal cancer likely arises from distant metastases.

Current research trials focus on evaluating the impact of chemotherapy regimens on systemic disease in patients with locally advanced rectal cancer. The NSABP R-04 trial (radiation therapy and either capecitabine or fluorouracil with or without oxaliplatin before surgery in treating patients with resectable rectal cancer is designed to compare capecitabine (with or without oxaliplatin) *vs* 5-FU (with or without oxaliplatin) in patients with operable rectal cancer who undergo neoadjuvant RT. The EORTC is also currently enrolling patients in a similar trial comparing neoadjuvant CMT and adjuvant chemotherapy with (1) capecitabine and oxaliplatin *vs* (2) capecitabine alone in patients with locally advanced rectal cancer (PETACC-6).

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