World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/esps/
wjgo@wjgnet.com
doi:10.4251/wjgo.v4.i12.230

World J Gastrointest Oncol 2012 December 15; 4(12): 230-237
ISSN 1948-5204 (online)

EDITORIAL

Role of radiation therapy in neoadjuvant era in patients with locally advanced rectal cancer

Georgios V Koukourakis

Georgios V Koukourakis, Department of Radiation Oncology, Anticancer Institute of Athens "Saint Savvas", 11525 Athens, Greece
Author contributions: Koukourakis GV made the literature research and wrote this paper.
Correspondence to: Georgios V Koukourakis, MD, PhD, Senior of Radiation Oncology, Anticancer Institute of Athens "Saint Savvas", 11525 Athens, Greece. gkoyokoyrakis@yahoo.gr
Telephone: +30-21-6409421 Fax: +30-21-6420418
Received: July 16, 2012 Revised: November 1, 2012
Accepted: November 20, 2012
Published online: December 15, 2012

Abstract

Surgery remains the primary determinant of cure in patients with localized rectal cancer, and total mesorectal excision is now widely accepted as standard of care. The widespread implementation of neoadjuvant short-course radiotherapy (RT) or long-course chemoradiotherapy (CRT) has reduced local recurrence rates from 25% to 40% to less than 10%; Preoperative RT in resectable rectal cancer has a number of potential advantages, most importantly reducing local recurrence, and down-staging effect. In this article making a comprehensive literature review searching the reliable medical data bases of PubMed and Cochrane we present all available information on the role of radiation therapy alone or in combination with chemotherapy in preoperative setting of rectal cancer. Data reported show that in locally advanced rectal cancer the addition of radiation therapy or CRT pre surgically has significantly improved sphincter prevention surgery. Moreover, the addition of chemotherapy to radiation therapy in preoperative setting has significantly improved pathologic complete response rate and loco-regional control rate without improvement in sphincter preserving surgery. Finally, the results of recently published randomized trials have shown a significant improvement of pre- *vs* postoperative CRT on local control; however, there was no effect on overall survival.

Key words: Rectal cancer; Locally advanced; Preoperative treatment; Neoadjuvant treatment; Radiation therapy

Peer reviewers: Ralph Schneider, MD, Department of Visceral, Thoracic and Vascular Surgery, Philipps University Marburg, Baldingerstresse, 35043 Marburg, Germany; Asahi Hishida, MD, PhD, Department of Preventive Medicine, Nagoya University Graduate School of Medicine, Tsurumai-cho 65, Showa-ku, Nagoya 466-8550, Japan; Dr. David Tougeron, Department of Gastroenterology, Poitiers University Hospital, 2 rue de la Milétrie, 86000 Poitiers Cedex, France; John Griniatsos, MD, Assistant Professor, Department of Surgery, University of Athens, Medical School, 1st LAIKO Hospital, 17 Agiou Thoma str, GR 115-27 Athens, Greece

Koukourakis GV. Role of radiation therapy in neoadjuvant era in patients with locally advanced rectal cancer. *World J Gastrointest Oncol* 2012; 4(12): 230-237 Available from: URL: http://www.wjgnet.com/1948-5204/full/v4/i12/230.htm DOI: http://dx.doi.org/10.4251/wjgo.v4.i12.230

INTRODUCTION

Rectal cancer is a paradigm for multimodal management, as the combination of surgery, chemotherapy and radiotherapy (RT) is necessary to achieve the optimal outcome[1]. The incidence of rectal cancer in the European Union is approximately 35% of the total colorectal cancer incidence with 15-25/100 000 per year. The mortality is 4-10/100 000 per year with lower rates for females[2].

Surgery remains the primary determinant of cure in patients with localized rectal cancer, and total mesorectal excision (TME) is now widely accepted as standard of care[3,4]. Early-stage rectal cancer (TNM: T1-T2N0M0) is associated with 5-year survival rates greater than 90% after surgery alone; therefore, neoadjuvant treatment is reserved for locally advanced disease.

In recent years, significant advances have been made in the treatment of rectal cancer with new antitumor agents and approaches. Among these approaches, neoadjuvant chemoradiotherapy (CRT) has attracted great attention. For patients with invasive tumors, neoadjuvant therapy has been utilized to promote tumor regression. Several phase Ⅲ studies have compared preoperative CRT to RT alone. The rates of complete pathological response are higher in the combination groups and have been linked to improved long-term outcome.

The widespread implementation of neoadjuvant short-course RT or long-course CRT has reduced local recurrence rates from 25% to 40% to less than 10%; however, only the Swedish Rectal Cancer Trial demonstrated an overall survival (OS) benefit. Despite low local relapse rates, systemic recurrence remains a significant problem, occurring in 30% to 40% of patients[5,6].

The last two decades have witnessed the development of a variety of preoperative RT and CRT schedules designed to optimize the sequence of treatment modalities and the most appropriate scheduling of RT and FU-based chemotherapy[7]. Only the CAOI/ARO/AIO-04 trial demonstrated improvements in pathologic complete response (pCR) (12.8% with CRT *vs* 16.5% with CRT and oxaliplatin, $P = 0.045$) with addition of oxaliplatin in an unplanned exploratory analysis[8]. The objective of the study is to accumulate and present all available information regarding the role of radiation therapy in neoadjuvant era in patients with locally advanced rectal cancer.

IDENTIFICATION OF ELIGIBLE STUDIES

We searched MEDLINE and the Cochrane Central Register of Controlled Trials (last search on June 2012) using combinations of terms, such as: locally advanced rectal cancer, preoperative radiation therapy, preoperative CRT, and surgery. We also checked the abstracts from the major International Cancer Meetings such as American's Society of Clinical Oncology (ASCO) and Gastro-Intestinal Cancer Symposiums during the last decade. We considered all, English written, meta-analyses, randomized controlled trials, research trials providing evidence about the effectiveness of radiation therapy as neoadjuvant treatment on locally advanced rectal cancer, and future directions of ongoing research, as eligible. Due to the fact of the large experience accumulated during the last few years on the use of radiation therapy for treating patients with locally advanced rectal cancer, we believe it is of the interest to endow with a review and summary of the results of the most relevant clinical trials on this issue. We have incorporated those published as full papers in peer-reviewed journals as well as those, in recently reported at the major international cancer meetings such as ASCO end Gastro-Intestinal Cancer Symposium.

DATA EXTRACTION

We extracted information from each eligible study. The data recorded, included author's name, year of publication, number of patients included in the study, combination(s) of treatment used, doses of radiation therapy, sphincter preservation surgery rate, pCR rate, loco-regional control rate, disease free survival (DFS), median time to progression median survival and OS.

PREOPERATIVE RADIATION THERAPY *VS* SURGERY ALONE

Neoadjuvant radiation alone effectively improves local control. Although neoadjuvant radiation with a biologically effective dose > 30 Gy provides significant improvement in local failure [odds ratio (OR) = 0.49], in cancer-specific survival (OR = 0.71) and in OS at 5 years, it does not improve the rate of distant metastasis[9]. Cammà *et al*[10] performed a meta-analysis of all available controlled randomized trials regarding the effectiveness of preoperative RT followed by surgery in the reduction of overall and cancer-related mortality and in the prevention of local recurrence and distant metastases. They managed to analyze 14 randomized controlled trials. The authors have shown that RT plus surgery compared with surgery alone significantly reduced the 5-year overall mortality rate [OR = 0.84, 95% confidence interval (CI): 0.72-0.98, $P = 0.03$], cancer-related mortality rate (OR = 0.71, 95%CI: 0.61-0.82, $P < 0.001$), and local recurrence rate (OR = 0.49, 95%CI: 0.38-0.62, $P < 0.001$). No reduction was observed in the occurrence of distant metastases (OR = 0.93, 95%CI: 0.73-1.18, $P = 0.54$). They concluded that in patients with resectable rectal cancer, preoperative RT significantly improved overall and cancer-specific survival compared with surgery alone.

The Dutch Colorectal Cancer Group (CKVO 95-04) compared short course, neoadjuvant RT followed by TME to TME alone in 1861 matched patients with clinically resectable disease. A total dose of 25 Gy in 5-Gy fractions was delivered over 5 d. Initial data at 2 years showed a decrease in local recurrence (8% *vs* 2%). This difference remained at 5 years, 5.6% in the RT + TME arm and 10.9% for TME alone. The greatest benefit was seen in patients with mid-rectal tumor, negative circumferential margins, and positive nodes. There was no benefit in the RT + TME arm as compared to TME alone on OS, with 64.2% and 63.5%, respectively[11,12].

The Swedish Rectal Cancer Trial randomized 1168 patients with resectable, rectal cancers to 25 Gy in five fractions preoperatively *vs* surgery alone. The 5-year recurrence rates for preoperative RT *vs* surgery alone were 12% and 27%, respectively. An absolute OS benefit of 10% favoring the preoperative RT arm was noted. This trial has been criticized for lacking TME in the surgery only arm, leading to the high failure rate[5,13].

van Gijn *et al*[14] investigated the value of preoperative short-term RT in combination with TME. Actually, this is the Dutch Colorectal Cancer Group trial which results were reported after a median follow-up of 12 years. They randomized 1861 patients with resectable rectal cancer without evidence of distant disease to TME preceded by

Table 1 Randomized trials comparing the role of radiation therapy as preoperative treatment *vs* surgery alone in patients with locally advanced rectal cancer

Ref.	*n*	Treatment arms	Local recurrence	Overall survival
Kapiteijn *et al*[11], 2001 (the Dutch colorectal cancer group)	1861	Arm 1(924 patients): preoperative RT (5 Gy × 5 d) followed by TME Arm 2 (937 patients): TME alone	2 yr of follow-up 2.4% in the RT + S group 8.2% S only group ($P < 0.001$)	2-yr survival rate 82.0% RT + S 81.8% S alone ($P = 0.84$)
Pahlman[5], 1997 (Swedish rectal cancer trial)	1168	Arm 1 (553 patients): preoperative RT (25 Gy delivered in five fractions in 1 wk) followed by S Arm 2 (557 patients): S alone	5 yr of follow-up 11% in the RT + S group 27% S only group ($P < 0.001$)	5-yr survival rate 58.0% RT + S 48.0% S alone ($P = 0.004$)
van Gijn *et al*[14], 2011	1805	Arm 1 (897 patients): preoperative RT (5 Gy × 5 d) followed by TME Arm 2 (908 patients): TME alone	10 yr of follow-up 5% in the RT + S group 11% S only group ($P < 0.0001$)	10-yr survival rate 50% RT + S 40% S alone ($P = 0.032$)

TME: Total mesorectal excision; RT: Radiation therapy; S: Surgery.

5 × 5 Gy RT or TME alone. The primary endpoint was local recurrence, analysed for all eligible patients who underwent a macroscopically complete local resection. Ten-year cumulative incidence of local recurrence was 5% in the group assigned to RT and surgery and 11% in the surgery-alone group ($P < 0.0001$). The effect of RT became stronger as the distance from the anal verge increased. However, when patients with a positive circumferential resection margin were excluded, the relation between distance from the anal verge and the effect of RT disappeared. Patients assigned to RT had a lower overall recurrence and when operated with a negative circumferential resection margin, cancer-specific survival was higher. OS did not differ between groups. For patients with TNM stage Ⅲ cancer with a negative circumferential resection margin, 10-year survival was 50% in the preoperative RT group *vs* 40% in the surgery-alone group ($P = 0.032$). The authors concluded that for all eligible patients, preoperative short-term RT reduced 10-year local recurrence by more than 50% relative to surgery alone without an OS benefit. For patients with a negative resection margin, the effect of RT was irrespective of the distance from the anal verge and led to an improved cancer specific survival, which was nullified by an increase in other causes of death, resulting in an equal OS. Nevertheless, preoperative short-term RT significantly improved 10-year survival in patients with a negative circumferential margin and TNM stage Ⅲ. Table 1 summarizes the results of the randomized trials comparing the role of radiation therapy as preoperative treatment *vs* surgery alone in patients with locally advanced rectal cancer.

PREOPERATIVE RADIATION THERAPY *VS* SURGERY ALONE FOCUSING ON THE TIME OF SURGERY AFTER RT AND THE SHORT OR LONG COURSE OF RT

Pach *et al*[15] enrolled a randomized study in order to establish the influence of time interval between preoperative hypo-fractionated RT (5 × 5 Gy) and surgery on long-term OS (5 years) and recurrence rate in patients with locally advanced rectal cancer operated on according to TME technique. Between 1999 and 2006, 154 patients with locally advanced rectal cancer were qualified to preoperative RT 5 × 5 Gy and then randomly assigned to subgroups with different time intervals between RT and surgery: one subgroup consisted of 77 patients operated on 7-10 d after the end of irradiation, and the second subgroup consisted of 77 patients operated on after 4-5 wk. The results of this trial have shown that 5-year survival rate in patients operated on 7- 10 d after irradiation was 63%, whereas in those operated on after 4-5 wk, it was 73%. The difference was not statistically significant (log rank, $P = 0.24$). A statistically significant increase in 5-year survival rate was observed only in patients with downstaging after RT. 90% in comparison with 60% in patients without response to neoadjuvant treatment (log rank, $P = 0.004$). Recurrence was diagnosed in 13.2% of patients. A lower rate of systemic recurrence was observed in patients operated on 4-5 wk after the end of irradiation (2.8% *vs* 12.3% in the subgroup with a shorter interval, $P = 0.035$). No differences in local recurrence rates were observed in both subgroups of irradiated patients ($P = 0.119$). The longer time interval between RT and surgery resulted in higher downstaging rate (44.2% *vs* 13% in patients with a shorter interval, $P = 0.0001$) although it did not increase the rate of sphincter-saving procedures ($P = 0.627$) and curative resections ($P = 0.132$). The authors have concluded that longer time interval after preoperative RT 25 Gy does not improve the rate of sphincter-saving procedures and curative resections (R0) despite higher downstaging rate observed in this regimen.

Eitta *et al*[16] enrolled a prospective randomized trial on 29 patients with resectable rectal cancer in order to compare two different approaches of preoperative RT, either short course or long course RT. These patients received preoperative RT and were randomized into two arms: arm 1, short course preoperative RT 25 Gy/wk/5 fractions followed by surgery within 1 wk, and arm 2,

Table 2 Randomized trials of preoperative radiation therapy in locally advanced rectal carcinoma focusing on time of surgery after radiation therapy

Author, year published	*n*	Treatment arms-Time to S	Tumor down-staging rate	Overall survival
Pach *et al*[15], 2011	154	Arm 1 (77 patients): preoperative RT (5 Gy × 5 d) followed by TME on d 7-10 after RT Arm 2 (77 patients): T preoperative RT (5 Gy × 5 d) followed by TME on after 4-5 wk	13% in Arm 1 *vs* 44.2% in Arm 2 ($P < 0.001$)	5-yr survival rate 63.0% in Arm 1 *vs* 73.0% in Arm 2 ($P = 0.24$)
Eitta *et al*[16], 2010	32	Arm 1 (16 patients): preoperative SCRT (5 Gy × 5 d) followed by S on one week after SCRT Arm 2 (16 patients): T preoperative LCRT (45 Gy/5 wk/ 25 fractions) followed by S on 4-6 wk after LCRT	21.4% in Arm 1 *vs* 60% in Arm 2 ($P = 0.008$)	2-yr survival rate 64.0% RT + S *vs* 66.0% S alone ($P = 0.389$)

TME: Total mesorectal excision; RT: Radiation therapy; S: Surgery; SCRT: Sort course radiation therapy; LCRT: Long curse radiation therapy.

long course preoperative RT 45 Gy/5 wk per 25 fractions followed by surgery after 4-6 wk. Adjuvant chemotherapy was given 4-6 wk after surgery according to the postoperative pathology. The results have shown that three patients experienced local recurrence, two out of 14 (14.2%) in arm 1 and one out of 15 patients (6.7%) in arm 2 ($P = 0.598$). Three patients developed distant metastases [two in arm 1 (14.2%) and one in arm 2 (6.7%), $P = 0.598$]. Two-year OS rate was 64% ± 3% and 66% ± 2% ($P = 0.389$), and the 2-year DFS rate was 61% ± 2% and 83% ± 2% for arms 1 and 2, respectively ($P = 0.83$). Tumor downstaging was more achieved in long course preoperative radiation therapy arm with a statistically significant difference, but did not reach statistical significance in node down-staging. Sphincter Sparing Procedure was more available in long course preoperative radiation therapy arm but with no statistically significant difference ($P = 0.082$). The authors have concluded that there was no statistically significant difference between short and long course of preoperative radiation therapy as regard local control, distant metastasis, and rate of sphincter sparing procedure, OS and DFS, while there was a statistically significant difference as regard down-staging in favour of long course of preoperative radiation therapy.

Pettersson *et al*[17] in non randomized retrospective study analyzed on 112 patients with locally advanced rectal cancer who had short course radiation therapy (SRT) and delayed surgery (4-8 wk after radiation therapy). The aims of the study were to examine early toxicity, response to RT and short-term outcomes of short course RT-delay. The results of the study have shown that severe radiation therapy-induced toxicity was noted in six patients (5.4%). Signs of tumour regression were seen on magnetic resonance imaging in 74% of patients reassessed after radiation therapy. Pathological stage (44.9% *vs* 60.7% stage 0-Ⅱ, $P < 0.001$), tumour category (11.9% *vs* 29.4% T0-T2, $P < 0.001$) and node category (45.8% *vs* 63.6% N0, $P = 0.014$) were significantly lower than those at initial assessment. Nine patients (8%) had a complete pathological response. The authors have concluded that the SRT-delay schedule was a feasible alternative with low toxicity. The study indicated a downstaging effect of SRT if surgery was delayed.

The characteristics of the trials that report on the role of preoperative radiation therapy in locally advanced rectal carcinoma as short or long course and the time of surgery after radiation therapy are summarized in Table 2.

PREOPERATIVE RADIATION THERAPY *VS* PREOPERATIVE RADIATION THERAPY COMBINED WITH CHEMOTHERAPY IN LOCALLY ADVANCED RECTAL CARCINOMA

The randomized trial of Fédération Francophone de Cancérologie Digestive 9203[18] was performed in order to compare preoperative RT with CRT in patients who presented a resectable T3-4, Nx, M0 rectal adenocarcinoma accessible to digital rectal examination. Preoperative RT with 45 Gy in 25 fractions during 5 wk was delivered. Concurrent chemotherapy with fluorouracil (FU) 350 mg/m^2 per day during 5 d, together with leucovorin, was administered during the first and fifth week in the experimental arm. Surgery was planned 3 to 10 wk after the end of RT. All patients have received adjuvant chemotherapy with the same FU/leucovorin regimen. The primary end point of the trial was OS. Seven hundred and thirty-three patients were eligible to participate to the study and the results have shown that grade 3 or 4 acute toxicity was more frequent with CRT (14.6% *vs* 2.7%, $P < 0.05$). There was no difference in sphincter preservation. Complete sterilization of the operative specimen was more frequent with CRT (11.4% *vs* 3.6%, $P < 0.05$). The 5-year incidence of local recurrence was lower with CRT (8.1% *vs* 16.5%, $P < 0.05$). Overall 5-year survival in the two groups did not differ. The authors have concluded that preoperative CRT despite a moderate increase in acute toxicity and no impact on OS significantly improves local control and is recommended for T3-4, N0-2, M0 adenocarcinoma of the middle and distal rectum.

The EORTC Radiotherapy Group Trial 22921 enrolled a randomized phase Ⅲ trial[19] in order to evaluate the addition of chemotherapy to preoperative RT and the use of postoperative chemotherapy in the treatment patients with clinical stage T3 or T4 resectable rectal cancer. RT consisted of 45 Gy delivered over a period

of 5 wk. One course of chemotherapy consisted of 350 mg of FU per square meter of body-surface area per day and 20 mg of leucovorin per square meter per day, both given for 5 d. Two courses were combined with preoperative RT in the group receiving preoperative CRT and the group receiving preoperative CRT and postoperative chemotherapy; four courses were planned postoperatively in the group receiving preoperative RT and postoperative chemotherapy and the group receiving preoperative CRT and postoperative chemotherapy. The primary end point was OS. A total of 1011 patients were enrolled. The results have shown that there was no significant difference in OS between the groups that received chemotherapy preoperatively (P = 0.84) and those that received it postoperatively (P = 0.12). The combined 5-year OS rate for all four groups was 65.2%. The 5-year cumulative incidence rates for local recurrences were 8.7%, 9.6%, and 7.6% in the groups that received chemotherapy preoperatively, postoperatively, or both, respectively, and 17.1% in the group that did not receive chemotherapy (P = 0.002). The rate of adherence to preoperative chemotherapy was 82.0%, and to postoperative chemotherapy was 42.9%. The authors have concluded that in patients with rectal cancer who receive preoperative RT, adding FU-based chemotherapy preoperatively or postoperatively has no significant effect on survival. Chemotherapy, regardless of whether it is administered before or after surgery, confers a significant benefit with respect to local control.

Bujko *et al*[20] performed a randomized controlled study on 312 patients with locally advanced T3-T4 resectable rectal cancer. The aim of the study was to compare survival, local control and late toxicity of patients who received short course preoperative radiation therapy with survival, local control and late toxicity of patients who received long course preoperative radiation therapy and chemotherapy. The authors have demonstrated that early radiation toxicity was higher in the chemoradiation group (18.2% *vs* 3.2%, P < 0.001). The actuarial 4-year OS was 67.2% in the short-course group and 66.2% in the chemo-radiation group (P = 0.960). Disease-free survival was 58.4% *vs* 55.6% (P = 0.820), crude incidence of local recurrence was 9.0% *vs* 14.2% (P = 0.170) and severe late toxicity was 10.1% *vs* 7.1% (P = 0.360), respectively. The conclusion of the study was that neoadjuvant chemo-radiation did not increase survival, local control or late toxicity compared with short-course RT alone. This study had some limitations that worthwhile to be mentioned. The study was unlikely to detect small differences, as it has been powered to detect differences of 15 per cent or more. The duration of follow-up was not long enough to assess late toxicity. Furthermore, postoperative chemotherapy was administered more often in the short-course group than in the chemo-radiation group, which might be a confounding factor. This difference was probably related to the down-staging effect of chemo-radiation which has, in consequence, resulted in decreasing the number of patients for whom this treatment was considered beneficial (those with node-positive disease). According to the protocol, only patients with cT3/T4 disease were eligible. However, in the short-course group, 39.5% of patients actually had pathological (p) T1/T2 disease. This may have resulted partly from a down-staging effect of the short-course RT, observed if the time between the start of RT and surgery is more than 10 d.

Finally, Latkauskas *et al*[21] conducted a randomized controlled trial in eighty-three patients with resectable stage Ⅱ and Ⅲ rectal adenocarcinoma. The aim of the study was to compare the down staging achieved after long-course CRT and short-term RT followed by delayed surgery. Surgery was performed 6 wk after preoperative treatment in both groups. Between 2007 and 2010, 46 patients were randomized to long-course CRT and 37 patients to short-course RT. CRT was consisted of: RT 50 Gy/25 fractions, 1.8-2 Gy per fraction over 5 wk with chemotherapy 5-Fu/Lv (400 mg/m^2 5-FU, 20 mg/m^2 Leucovorine) during the first and last week of RT, whereas the short-term radiotherapy of: 25 Gy/5 fractions, 5 Gy per fraction over 5 d. They found that the R0 (negative margins at resection) resection rate was 91.3% in the chemo-radiation arm and 86.5% in the SRT group (P = 0.734). Sphincter preservation rates were 69.6% *vs* 70.3% (P = 0.342) and postoperative complication rates were 26.1% *vs* 40.5% (P = 0.221). There were more patients with early pT stage [pT0 (complete pathological response) pT1] in the chemo-radiation group [21.8% *vs* 2.7% (P = 0.03)] and more patients with pT3 disease in the short-term RT group (75.7% *vs* 52.2%, P = 0.036). There were no differences in pN stage and lymphatic or vascular invasion in either group. Pathological down-staging (stage 0 and Ⅰ) was observed in eight (21.6%) patients in the short-term RT group and in 18 (39.1%) in the chemo-radiation group (P = 0.07). Tumours were smaller after preoperative chemo-radiation (2.5 cm *vs* 3.3 cm, P = 0.04). The authors have concluded that the long-course preoperative chemo-radiation resulted in greater statistically significant tumour downsizing and down-staging compared with short-term radiation, but there was no difference in the R0 resection rates. Similar postoperative morbidity was observed in each group.

The characteristics of the trials that report on the role of preoperative radiation therapy in locally advanced rectal carcinoma in combination with chemotherapy are summarized in Table 3.

PREOPERATIVE *VS* POSTOPERATIVE CRT FOR LOCALLY ADVANCED RECTAL CANCER

Historically, the combination of postoperative RT and FU chemotherapy has been shown to reduce local recurrences and to improve survival for locally advanced rectal cancer. The last two decades have witnessed the development of a variety of preoperative RT and CRT schedules designed to optimize the sequence of treatment modalities and the most appropriate scheduling

Table 3 Randomized trials of preoperative radiation therapy combined with chemotherapy in locally advanced rectal carcinoma

Author, year published	*n*	Treatment arms	Local recurrence	Overall survival
Gérard *et al*[18], 2006 (FFCD-9203)	742	Arm 1 (367 patients): preoperative RT (45 Gy/25 fractions/5 wk) followed by TME between 3-10 wk after RT Arm 2 (375 patients): preoperative RT (45 Gy/25 fractions/5 wk) + CH (2 cycles: first on days 1-5 of RT and the second on days 29-33 of RT) followed by TME between 3-10 wk after CHRT	At 5 yr follow-up 16.5% Arm 1 8.1% Arm 2 (P = 0.004)	5-yr survival rate 67.9% Arm 1 67.4% Arm 2 (P = 0.684)
Bosset *et al*[19], 2006 (the EORTC Radiotherapy Group Trial 22921)	1011	Arm 1 (252 patients): preoperative RT (45 Gy/25 fractions/5 wk) followed by TME between 3-10 wk after RT Arm 2 (253 patients): Same RT as in Arm 1 + 2 cycles of CH (days 1-5 and 29-33 of RT) + TME between 3-10 wk after CHRT Arm 3 (253 patients): Same RT as in Arm 1 + TME between 3-10 wk after RT + 4 cycles of CH postoperative Arm 4 (253 patients) Same RT as in Arm 1 + 2 cycles of CH (days 1-5 and 29-33 of RT) + TME between 3-10 wk after CHRT + 2 cycles of CH postoperative	5 yr of follow-up 17.1% Arm 1 8.7% Arm 2 9.6% Arm 3 7.6% Arm 4 (P = 0.002)	5-yr survival rate 63.2% Arm 1 63.2% Arm 2 67.2% Arm 3 67.2% Arm 4 (P = 0.12)
Bujko *et al*[20], 2005	312	Arm 1 (155 patients): preoperative RT (5 Gy × 5 d) followed by TME at 7 d after RT Arm 2 (157 patients): preoperative RT (45 Gy/25 fractions/5 wk) + 2 cycles of chemotherapy on weeks 1 and 5 of RT) followed by TME between 4-6 wk later. The cycle consisted of leucovorin 20 mg/m^2 per day and, 10-20 min later, 5-fluorouracil 325 mg/m^2 per day, both administered as rapid infusion on 5 consecutive days	4 yr of follow-up 59% Arm 1 14.2% Arm 2 (P = 0.170)	4-yr survival rate 67.2% Arm 1 66.2% S alone (P = 0.960)

TME: Total mesorectal excision; RT: Radiation therapy; CHRT: Chemo-radiation therapy; CH: Chemotherapy (Leukovorin 20 mg/m^2 per day was delivered intravenously immediately before administration of Fluorouracil and Fluorouracil 350 mg/m^2 per day was delivered during 20 min in 100 mL of saline infusion, 1 h before RT).

of RT and FU based chemotherapy. Three prospective randomized trials comparing the efficacy of preoperative with postoperative CRT were initiated between 1993 and 1994. Two trials were performed in the United States [Radiation Therapy Oncology Group (RTOG) 94-01 trial and National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03 trial] and one was initiated by the German Rectal Cancer Study Group [CAO/ARO/AIO-94 (Working Group of Surgical Oncology/Working Group of Radiation Oncology/Working Group of Medical Oncology of the Germany Cancer Society)]. Unfortunately, the RTOG 94-01 trial accrued only 53 patients and was closed prematurely. The NSABP R-03 trial accrued 267 patients between 1993 and 1999, when it was terminated short of the planned goal of 900 patients. With a median follow-up of 8.4 years, this trial showed a significantly improved disease-free survival and a trend toward improved OS in the preoperative CRT arm; however, there was no improvement in local control[22].

The German study was completed, and 5-year results were reported in 2004. Compared with postoperative CRT, the preoperative approach was superior in terms of treatment compliance, toxicity, downstaging, sphincter preservation in patients judged by the surgeon to require an abdominoperineal resection, and 5-year local control[6]. Given these advantages, preoperative CRT has become the preferred treatment for patients with stage Ⅱ or Ⅲ rectal cancer in Germany, most parts of Europe, and the United States. However, with a median follow-up of 46 mo in 2004, there was no difference in OS rates between the study arms. The long term results of this trial regarding local recurrence, distant recurrence, and OS after a median follow-up of 134 mo was recently reported by Sauer *et al*[23]. The authors have concluded that there is a persisting significant improvement of pre- *vs* postoperative CRT on local control; however, there was no effect on OS. Integrating more effective systemic treatment into the multimodal therapy has been adopted in the CAO/ARO/AIO-04 trial[8] to possibly reduce distant metastases and improve survival.

The characteristics of the trials that compare preoperative CRT with post-operative CRT in locally advanced rectal carcinoma are summarized in Table 4.

DISCUSSION

The available evidence is sufficient to provide that: preoperative radiation therapy as a single adjuvant therapeutic approach reduces overall and cancer related mortality. The risk of local recurrence is definitely reduced by irradiation. The rate of distant metastases is probably not influenced by preoperative RT as a single adjuvant. Postoperative mortality is not significantly increased by irradiation despite the higher rate of adverse effects. Both short- and long-course RT with delayed surgery result in clinical (ultrasound) and histopathological downstaging. Downstaging assessed by pre- and post treatment rectal ultrasound was significantly greater after long course CRT. In addition, downstaging assessed by histopathological examination of the resected specimen was significantly greater after long-course CRT. There was no difference between short- and long course RT in sphincter preservation, morbidity or completeness of surgical resection.

An improved 5-year OS rate is observed only in patients with down-staging after a preoperative RT dose of

Table 4 Randomized trials of preoperative chemo-radiotherapy *vs* postoperative chemo-radiotherapy in locally advanced rectal carcinoma

Author, year published	*n*	Treatment arms	Disease free survival-local relapse	Overall survival
Roh *et al*[22], 2009 (NSABP R-03)	267	Arm 1 (130 patients): preoperative CHRT: Chemo cycle 1: FU 500 mg/m^2 once per week for 6 wk + LV 500 mg/m^2 once per week for 6 wk followed by RT: 45 Gy in 25 fractions with a 5.4 Gy boost within the original margins of treatment + 2 cycles of FU 325 mg/m^2 for 5 d LV 20 mg/m^2 for 5 d (1st and 5th week of RT) followed by chemo cycles 4-7 as cycle 1 Arm 2 (137patients): postoperative CHRT: same as in Arm 1	At 5 yr follow-up 64.7% DSF in Arm 1 53.4% DSF in Arm 2 (P = 0.011)	5-yr survival rate 74.5% Arm 1 65.6% Arm 2 (P = 0.065)
Sauer *et al*[6], 2004 (German study)	823	Arm 1 (421 patients): preoperative CHRT: 50, 4 Gy/28 fractions/ 5 fractions weekly + FU 1000 mg/m^2 120 h continuous infusion in first and fifth week of RT followed by 4 cycles of FU 500 mg/m^2 per day/five times weekly every 4 wk followed by TME 6 wk after CHRT Arm 2 (402 patients): postoperative CHRT: same as in Arm 1 except a 5.4 Gy boost in RT	5 yr of follow-up 6.0% LR in Arm 1 13% LR in Arm 2 (P = 0.006)	5-yr survival rate 76.0% Arm 1 74.0% Arm 2 (P = 0.80)
Sauer *et al*[23], 2012 (CAO/ARO/AIO-94 trial: results after 10 yr follow-up)	823	Arm 1 same as in above trial Arm 2 same as in above trial	10-yr of follow-up 7.1% LR in Arm 1 10.1% in Arm 2 (P = 0.48)	10-yr survival rate 59.6% in Arm 1 59.9% in Arm 2 (P = 0.85)

RT: Radiation therapy; CHRT: Chemo-radiation therapy; FU: Fluorouracil; LV: Leukovorin; DFS: Disease free survival; LR: Local relapse.

25 Gy. A longer time interval between RT and surgery increases the down-staging rate in patients with locally advanced rectal cancer. Preoperative RT 25 Gy does not improve the rate of sphincter-saving procedures and potentially curative resections (R0). Appropriately defining high-risk patients with advanced rectal cancer is crucial in providing neoadjuvant treatment only to those who would benefit mostly from irradiation.

The studies have also showed that SRT-delay schedule is a feasible alternative not only for older patients, and those with severe co-morbidity and advanced tumours; younger patients with less co-morbidity and tumours that were not locally advanced also fared well with this treatment. Potential advantages of SRT-delay compared with immediate surgery are fewer postoperative complications and a down-staging effect. Much is left to explore concerning SRT-delay. Short- and long term adverse effects of RT, differences between immediate and delayed surgery with regard to postoperative complications, down-staging effects and local recurrences are all endpoints in the ongoing Stockholm Ⅲ trial[24].

Interest in preoperative CRT for patients with resectable rectal cancer is based not only on the expected survival benefit achieved with this treatment, but also on the potential advantages of delivering both agents preoperatively. These advantages include improved compliance with the CRT regimen if it is given before major surgery, as well as down-staging, which may enhance the rate of curative surgery and permit sphincter preservation in patients with low-lying tumors. In addition, because tumor oxygenation is better with preoperative treatment than with postoperative treatment, irradiation seems to be more effective with the former approach[9]. Retrospective, nonrandomized studies have also found reduced toxicity with preoperative treatment[25].

Prospective, randomized trials comparing the efficacy of preoperative CRT with that of standard, postoperative CRT for rectal cancer were initiated in the United States by the RTOG (trial 94-01) and the NSABP (protocolR-03). Unfortunately, both studies suffered from low enrolment and were closed prematurely.

The German study confirmed that preoperative CRT, given as planned in most of the patients assigned to this group, 89%, significantly reduced rates of local failure and acute and long-term toxic effects. Among patients with tumors judged by the surgeon to require an abdominoperineal excision, the rate of sphincter-preserving surgery was more than doubled after preoperative CRT. Postponing surgery for a 6-wk course of neoadjuvant treatment plus a 6 wk interval to allow tumor shrinkage and recovery from side effects did not result in an increased rate of surgical complications or an increased incidence of tumor progression.

Concurrent CRT, when compared with RT alone, in T3-4 resectable cancers of the low or middle rectum increases moderately early preoperative toxicity; increases sterilization of the operative specimen; does not modify sphincter preservation and OS or progression free survival; and increases local control, which is the major clinically relevant result of the trials.

It is evident that in patients with stage T3 or T4 resectable rectal cancer treated with preoperative RT, adding fluorouracil-based chemotherapy preoperatively or postoperatively has no significant effect on survival. Regardless of timing, chemotherapy provides a significant benefit with respect to local control.

CONCLUSION

Although no survival benefit was achieved with preoperative as compared with postoperative CRT, we suggest that preoperative CRT is the preferred treatment for patients with locally advanced rectal cancer, given that it is associated with a superior overall compliance rate, an

improved rate of local control, reduced toxicity, and an increased rate of sphincter preservation in patients with low-lying tumours.

The magnitude of the overall effect is small but clinically relevant. Further large-scale multicenter randomized controlled trials may prove useful to substantiate the benefit on OS.

Finally, a significant DFS benefit was achieved with preoperative compared with postoperative CRT and is the recommended treatment for patients with locally advanced rectal cancer.

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