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ORIGINAL REPORT

Preoperative Versus Postoperative Chemoradiotherapy for Locally Advanced Rectal Cancer: Results of the German CAO/ARO/AIO-94 Randomized Phase III Trial After a Median Follow-Up of 11 Years

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See accompanying editorial on page 1901; listen to the podcast by Dr Hong at www.jco.org/podcasts

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ABSTRACT

Purpose
Preoperative chemoradiotherapy (CRT) has been established as standard treatment for locally advanced rectal cancer after first results of the CAO/ARO/AIO-94 [Working Group of Surgical Oncology/Working Group of Radiation Oncology/Working Group of Medical Oncology of the Germany Cancer Society] trial, published in 2004, showed an improved local control rate. However, after a median follow-up of 46 months, no survival benefit could be shown. Here, we report long-term results with a median follow-up of 134 months.

Patients and Methods
A total of 823 patients with stage II to III rectal cancer were randomly assigned to preoperative CRT with fluorouracil (FU), total mesorectal excision surgery, and adjuvant FU chemotherapy, or the same schedule of CRT used postoperatively. The study was designed to have 80% power to detect a difference of 10% in 5-year overall survival as the primary end point. Secondary end points included the cumulative incidence of local and distant relapses and disease-free survival.

Results
Of 799 eligible patients, 404 were randomly assigned to preoperative and 395 to postoperative CRT. According to intention-to-treat analysis, overall survival at 10 years was 59.6% in the preoperative arm and 59.9% in the postoperative arm ($P = .85$). The 10-year cumulative incidence of local relapse was 7.1% and 10.1% in the pre- and postoperative arms, respectively ($P = .048$). No significant differences were detected for 10-year cumulative incidence of distant metastases (29.8% and 29.6%; $P = .9$) and disease-free survival.

Conclusion
There is a persisting significant improvement of pre- versus postoperative CRT on local control; however, there was no effect on overall survival. Integrating more effective systemic treatment into the multimodal therapy has been adopted in the CAO/ARO/AIO-04 trial to possibly reduce distant metastases and improve survival.

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INTRODUCTION

Historically, the combination of postoperative radiotherapy (RT) and fluorouracil (FU) chemotherapy has been shown to reduce local recurrences and to improve survival for locally advanced rectal cancer.[1,2] The last two decades have witnessed the development of a variety of preoperative RT and chemoradiotherapy (CRT) schedules designed to optimize the sequence of treatment modalities and the most appropriate scheduling of RT and FU-based chemotherapy.[3] 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 and National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03—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 overall survival in the preoperative CRT arm; however, there was no improvement in local control.[4]

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.[5] 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 months in 2004, there was no difference in overall survival rates between the study arms. Here we report long-term results of this trial regarding local recurrence, distant recurrence, and overall survival after a median follow-up of 134 months. Moreover, we provide exploratory subgroup analyses to identify patient-, tumor-, or treatment-related factors that may be associated with the risk of developing local recurrences.

PATIENTS AND METHODS

CAO/ARO/AIO-94 was a multicenter, open-label, randomized, phase III study, approved by the central and local ethics committees. Each patient provided written informed consent before participating in the study. The design of the trial was reported previously.[5]

Patient Eligibility and Treatment Arms

Eligibility criteria included histopathologically confirmed rectal adenocarcinoma with the inferior margin not more than 16 cm above the anal verge as assessed by rigid rectoscopy. The tumor had to have evidence of perirectal fat (cT3-4) or lymph node involvement (cN+) by either endorectal ultrasound or computed tomography. Random assignment was performed centrally (based on permuted blocks of 14) with stratification according to surgeon. Eligible patients between 18 and 75 years of age were randomly assigned to receive pre- or postoperative CRT. In brief, RT consisted of 50.4 Gy radiation in 28 fractions, delivered with a minimum of 6 MV photons through a three- or four-field box technique to the primary tumor and to the mesorectal, presacral and internal iliac lymph nodes. Concurrent chemotherapy was administered as continuous FU infusion in the first and fifths week of RT (1,000 mg/m^2 on days 1 through 5 and days 29 through 33). CRT was identical in both arms except for a boost of 5.4 Gy delivered to the tumor bed in the postoperative group. Total mesorectal excision (TME) surgery was scheduled to take place 4 to 6 weeks after completion of preoperative CRT. Adjuvant chemotherapy started 4 weeks after surgery or after completion of postoperative CRT and

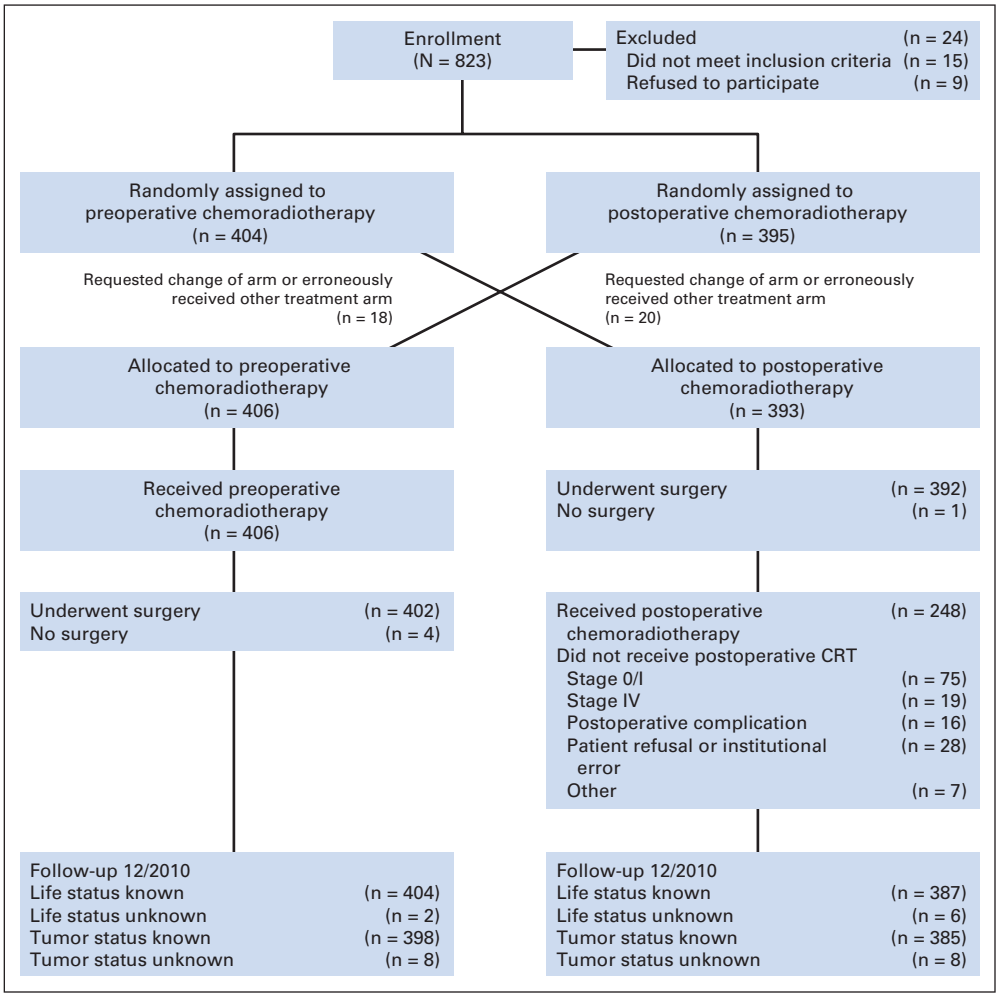

Fig 1. CONSORT diagram showing the flow of participants through each stage of the CAO/ARO/AIO-94 [Working Group of Surgical Oncology/Working Group of Radiation Oncology/Working Group of Medical Oncology of the Germany Cancer Society] trial. CRT, chemoradiotherapy.

comprised four cycles of FU 500 mg/m^2 intravenous bolus on days 1 through 5, repeated on day 29.

Follow-Up

Protocol-specified follow-up occurred at 3-month intervals for 2 years, then at 6-month intervals for 3 years for a total of 5 years. Evaluations consisted of physical examination, a complete blood count, and blood chemistry. Rectoscopy, abdominal ultrasound, computed tomography scan of the abdomen, and chest radiography were also performed according to guidelines of the German Cancer Society.[6] Histologic confirmation of local recurrence, defined as a colorectal cancer within the true pelvis or perineal scar, and distant recurrence was encouraged. Alternate acceptable criteria included sequential enlargement of a mass in radiologic studies.

Follow-up procedures beyond 5 years were not explicitly specified in the original study protocol. To obtain long-term data on survival and tumor status, additional information was collected from all participating hospitals as well as from general practitioners on additional case report forms that were sent to the central data management office at the University of Erlangen, and from German registry offices (which provided data on survival status only).

Table 1. Patient and Tumor Characteristics According to Treatment Received

Characteristic	Preoperative CRT (n = 406)		Postoperative CRT (n = 248)		No Postoperative CRT (n = 145)	
	No.	%	No.	%	No.	%
Age, years						
Median	62		61		63	
Range	30-77		33-76		40-76	
Sex						
Male	293	72	164	66	91	63
Female	113	28	84	34	54	37
Distance from anal verge, cm						
0-< 5	117	29	59	24	27	19
5-< 10	189	47	102	41	66	46
10-16	85	21	79	32	45	31
Unknown	15	4	8	3	7	5
TNM stage						
pCR/stage 0	36	9	0		2	1
yI/I	111	27	2	< 1	73	50
yII/II	117	29	87	35	28	19
yIII/III	103	25	146	59	21	14
yIV/IV	31	8	13	5	19	13
Unknown	4	1	0		1	< 1
Type of resection						
None	4	1	0		1	< 1
Low anterior	255	63	169	68	105	72
Intersphincteric	36	9	18	7	5	3
Abdominoperineal	109	27	61	25	33	23
Other	2	< 1	0		0	
Unknown	0		0		0	
Completeness of local resection						
Complete local resection (R0)	387	95	240	97	141	97
Without distant metastases	357		228		122	
With distant metastases	30		12		19	
Microscopic incomplete resection (R1)	4	1	8	3	1	1
Without distant metastases	4		7		1	
With distant metastases	0		1		0	
Macroscopic incomplete resection (R2)	3	1	0		1	1
Without distant metastases	2		0		1	
With distant metastases	1		0		0	
Unknown/RX	8	2	0		1	1
No resection	4	1	0		1	1

Abbreviations: CRT, chemoradiotherapy; pCR, pathologic complete response.

Statistical Analysis

The primary end point was overall survival. The study was designed to have an 80% power to detect a difference of 10% in the 5-year overall survival rate, with two-sided $\alpha = .05$. The sample size required to detect this difference was 340 patients per group. Because an estimated 15% dropout rate was expected, the enrollment period was extended to the end of September 2002, at which point 823 patients had been enrolled. Secondary end points included the cumulative incidence of local and distant recurrences and disease-free survival.

All time-to-event end points were measured from the date of random assignment. Overall survival was defined as the time from random assignment to death for any reason or the day of last follow-up. Local recurrence analyses were done on all eligible patients who underwent a macroscopically complete local resection (patients with an R1 resection of the primary tumor or with distant metastases found at surgery were included, whereas patients without surgery or with macroscopically incomplete local resection, R2, were excluded). Distant recurrence analyses were done on all eligible patients, and any occurrence of distant metastasis during CRT, at surgery, or during follow-up was calculated as an event. In accordance with the previous report of this trial, data from patients who were alive and free of recurrences or who died without having had a recurrence were censored in the analyses of disease-free survival and recurrences. In addition, we provided recurrence analysis accounting for death as a competing risk.

Overall and disease-free survival were calculated with the Kaplan-Meier method. Analyses for recurrences were reported as cumulative incidences. Differences were evaluated with the log-rank test. To exclude the possibility of bias according to non–tumor-related deaths, we also performed a competing risk analysis according to Fine and Gray.[7] Hazard ratios and 95% CIs were computed by using the Cox proportional hazards model. We performed multivariate analysis to identify treatment-, patient-, or tumor-related risk factors for local recurrences. A two-sided P value $\leq .05$ was considered significant. Analyses for the main end points were performed on an intention-to-treat basis. All other exploratory analyses for prognostic factors were done according to the actual treatment. All analyses were performed by using the statistical computing environment R and the R package for survival (http://www.r-project.org).

RESULTS

Patient and Tumor Characteristics

A total of 823 patients were randomly assigned to preoperative or postoperative CRT; 24 patients were excluded because they did not meet the inclusion criteria (Fig 1). Of the remaining 799 patients, 404 were randomly assigned to preoperative CRT and 395 to postoperative treatment (intention-to-treat population); 18 and 20 patients, respectively, requested a change in treatment group or erroneously received the treatment of the other arm. Thus, 406 patients were treated according to the preoperative protocol, and 393 patients were treated according to the postoperative protocol (actual treatment arm population). In the postoperative treatment arm, 145 patients did not receive CRT because they had been histopathologically diagnosed as stage 0 to I (n = 75) or as stage IV (n = 19), because of postoperative

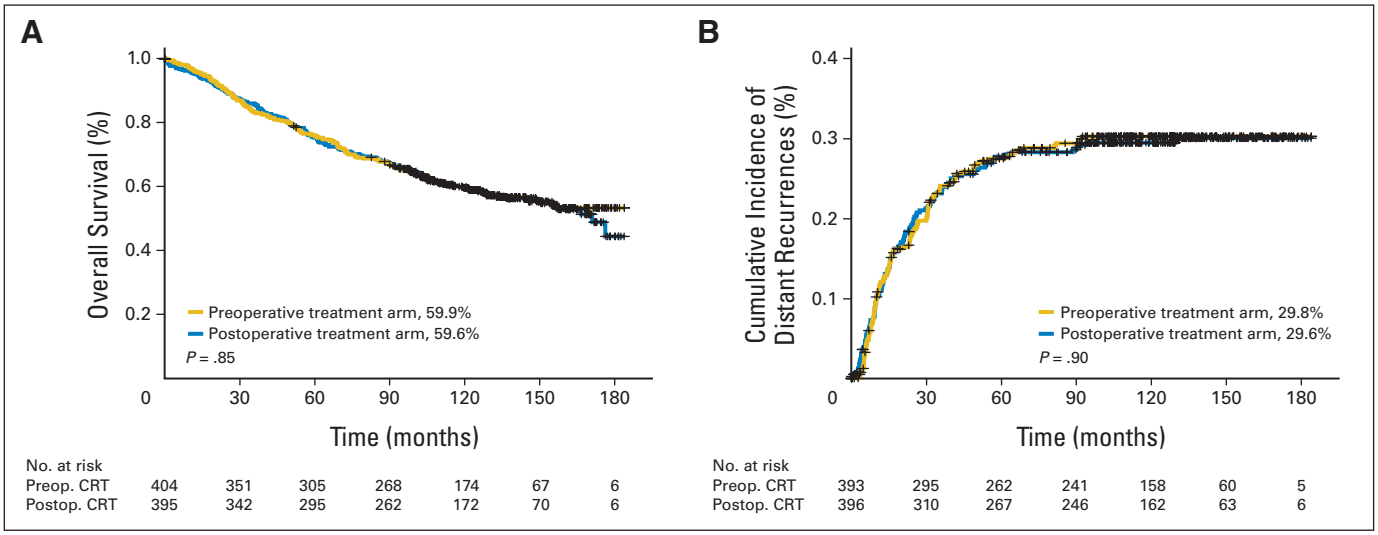

Fig 2. (A) Overall survival and (B) cumulative incidence of distant recurrences in the intention-to-treat population. CRT, chemoradiotherapy; preop, preoperative; postop, postoperative.

complications (n = 16), because of refusal to receive treatment or institutional error (n = 28), and other (n = 7). Patients and tumor characteristics according to the actual treatment received, including surgical and pathologic data, are summarized in Table 1.

Follow-Up and Events

As of December 2010, 450 surviving patients had been followed for a median of 134 months (range, 90 to 184 months). Of these 450 patients, 100% were followed for at least 5 years, 98% for at least 8 years, and 71% for at least 10 years. A total of 341 deaths occurred during follow-up: 223 were related to rectal cancer (206, disease progression; 17, treatment-related), 21 to secondary nonrectal cancer, and 87 to other causes; for 10 patients the cause of death was unknown. No long-term follow-up data were available for eight patients. Local recurrence after macroscopically complete local resection (R0/R1) occurred in 60 patients: 17 (28%) had local recurrence alone, and 43 (72%) also had distant metastases. A total of 183 patients developed distant metastases alone.

Overall and Disease-Free Survival

The overall survival at 10 years in the intention-to-treat population was 59.6% (95% CI, 54.9% to 64.7%) in the preoperative arm and 59.9% (95% CI, 55.2% to 65.1%) in the postoperative arm ($P = .85$; Fig 2A). The hazard ratio (HR) for death in the preoperative versus the postoperative group was 0.98 (95% CI, 0.79 to 1.21). If the analysis was performed for the actual treatment arm population, the respective numbers were 60.1% and 59.3% at 10 years (HR, 0.95; 95% CI, 0.77 to 1.17; $P = .61$). Disease-free survival after macroscopically complete resection of the primary rectal cancer for the intention-to-treat population was 68.1% (95%

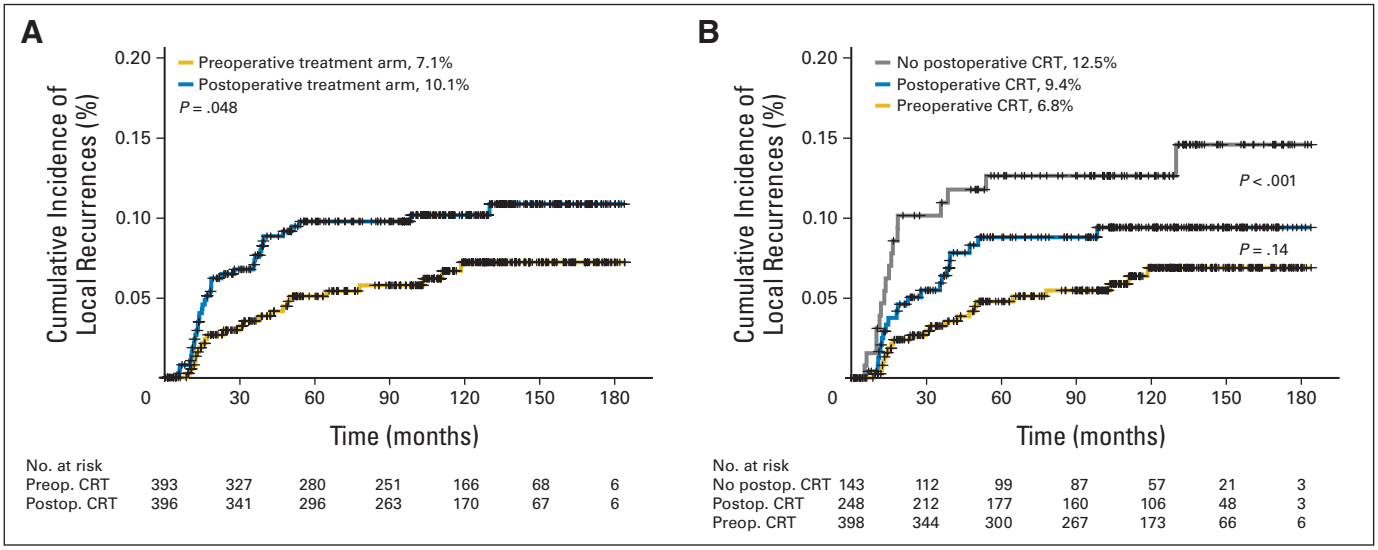

Fig 3. Cumulative incidence of local recurrences after macroscopically complete local tumor resection in the intention-to-treat population (A) and according to treatment received (B). CRT, chemoradiotherapy; preop, preoperative; postop, postoperative.

CI, 63.6% to 73.2%) at 10 years in the preoperative arm and 67.8% (95% CI, 63.3% to 72.8%) at 10 years in the postoperative arm (HR, 0.94; 95% CI, 0.73 to 1.21; $P = .65$). The respective numbers for the actual treatment arm population were 68.5% versus 67.5% (HR, 0.92; 95% CI, 0.72 to 1.19; $P = .54$).

Cumulative Incidence of Local and Distant Recurrences

Local recurrences after macroscopically complete resection of the primary rectal cancer occurred in 23 of 397 patients randomly assigned to preoperative CRT (four patients without surgery and three patients with R2 local resection excluded), and in 37 of 393 patients randomly assigned to postoperative CRT (one patient without surgery and one patient with R2 local resection excluded). The cumulative incidence of local recurrence at 5 and 10 years in this intention-to-treat population was 5% and 7.1% in the group assigned to preoperative CRT and 9.7% and 10.1% in the group assigned to postoperative CRT (HR, 0.60; 95% CI, 0.4 to 1.0; $P = .048$; Fig 3A). In our analysis, only local recurrence was counted as an event, and death was censored. We also performed a competing risk analysis by using the proportional subdistribution hazards regression model with death considered as a competing event. This resulted in a P value of .051 for the intention-to-treat population. When analyzed according to the actual treatment arm (22 local recurrences occurred in the actual preoperative and 38 in the postoperative treatment arm), the 10 year rates were 6.8% and 10.5%, respectively (HR, 0.54; 95% CI, 0.3 to 0.9; $P = .02$). Competing risk analysis according to actual treatment arm resulted in a P value of .024.

In the postoperative treatment arm, 17 of 38 local recurrences occurred in the 145 patients who did not receive CRT, and 21 local recurrences occurred in the 248 patients who did receive postoperative CRT. The cumulative incidence of local recurrence at 10 years was 9.4% in postoperative CRT group (HR for preoperative CRT, 1.6; 95% CI, 0.9 to 2.8; $P = .14$) and 12.5% in no postoperative CRT group (HR for preoperative CRT, 2.4; 95% CI, 1.3 to 4.5; $P < .001$; Fig 3B). The median time to local recurrence was 15.1 months for the 17 patients without postoperative CRT, 18.7 months for the 21 patients with postoperative CRT (Wilcoxon test $P = .17$), and 30.7 months for the 22 patients after preoperative CRT ($P = .05$). Of note, seven (12%) of 60 local recurrences occurred beyond 5 years of follow-up: five (23%) of 22 in the preoperative arm and two (5%) of 38 in the postoperative arm.

The cumulative incidence of distant metastases at 10 years in the intention-to-treat population was 29.8% in the preoperative and 29.6% in the postoperative arm (HR, 0.98; 95% CI, 0.76 to 1.28; $P = .9$; Fig 2B). Data for the actual treatment population were also not significantly different (HR, 0.98; 95% CI, 0.76 to 1.28; $P = .91$). Seventeen (7.6%) of 226 distant metastases occurred beyond 5 years of follow-up: nine (7.8%) of 115 in the preoperative arm, and eight (7.2%) of 111 in the postoperative arm.

Table 2. Influence on Local Recurrence Risk of Different Covariables Based on the Received Therapy

	Preoperative CRT			Postoperative CRT			No Postoperative CRT		
		Cumulative Local Recurrence Rate (%)			Cumulative Local Recurrence Rate (%)			Cumulative Local Recurrence Rate (%)	
Variable	No. at Risk	At 5 Years	At 10 Years	No. at Risk	At 5 Years	At 10 Years	No. at Risk	At 5 Years	At 10 Years
Overall	398	4.7	6.8	248	8.8	9.4	143	12.5	12.5
Age, years									
≤ Median	198	6.3	7.1	137	8.8	8.8	60	16.3	16.3
> Median	200	3.0	6.6	111	8.8	10.2	83	9.7	9,7
Sex									
Male	287	3.7	6.6	164	9.5	10.5	90	16.8	16.8
Female	111	7.2	7.2	84	7.5	7.5	53	5.9	5.9
Distance from anal verge, cm									
0-< 5	116	10.1	10.1	59	16.1	16.1	27	4.5	4.5
5-< 10	185	1.2	4.9	102	7.8	9.3	64	18.7	18.7
10-16	83	2.5	4.3	79	2.7	2.7	45	10.4	10.4
Type of resection									
Low anterior	253	2.6	4.7	169	3.9	3.9	104	15.2	15.2
Intersphincteric	36	2.8	6.0	18	23	23	5	40	40
Abdominoperineal	108	10.4	12.3	61	18.2	20.7	33	0	0
(y)TNM stage									
pCR/0	36	2.9	2.9	0			2	0.0	0.0
yI/I	111	1.0	3.4	2	50	50	73	6.1	6.1
yII/II	116	2.8	4.2	87	3.6	3.6	28	20	20
yIII/III	102	9.5	11.0	146	10.9	12	20	32.0	32.0
yIV/IV	30	18.7	45.8	13	16.7	16.7	19	6.7	6.7
Completeness of local resection									
R0	387	4.6	6.7	240	7.7	8.3	141	12	12
R1	4	25.0	—	8	48.6	48.6	0		

Abbreviations: CRT, chemoradiotherapy; pCR, pathologic complete response.

Univariate and Multivariate Analyses of Local Recurrences

We performed exploratory, nonprotocol-specified subgroup analyses to identify patient-, tumor-, or treatment-related factors that may be associated with the risk of developing local recurrences after macroscopically complete resection of the primary tumor (Table 2). Multivariate Cox regression analysis for the entire group of patients revealed that incomplete local resection (R1) and not receiving CRT at all were significantly associated with a higher local recurrence risk (Table 3). An increased HR was also confirmed for patients with (y) stage III or IV and for those patients who had surgery that included intersphincteric or abdominoperineal resection.

Figure 4 shows a forest plot analysis with HRs for patients who actually received preoperative compared with those who actually received postoperative CRT. For almost all subgroups of patients, the HR increased after postoperative CRT. The strongest difference of risks for developing local recurrences occurred in patients who had surgery that included intersphincteric or abdominoperineal resection who showed a significantly higher risk after postoperative CRT compared with preoperative CRT (HR, 2.24; 95% CI, 1.07 to 4.71; $P = .03$).

DISCUSSION

After a median follow-up of 134 months, preoperative CRT was still associated with a significantly reduced cumulative incidence of local recurrences in both the intention-to-treat (7.1% *v* 10.1% at 10 years) and actual treatment population (6.8% *v* 10.5% at 10 years). In our first report published in 2004[5] with a median follow-up of 46 months, the 5-year cumulative incidence of local recurrences was reported as 6% in the preoperative and 13% in the postoperative arm (intention-to-treat analysis $P = .006$). The discrepancy between these incidence numbers, especially for the postoperative treatment arm, can be attributed to the fact that, in the first analysis, follow-up information on local control beyond 5 years was available for only 32% of the patients, whereas in the updated analysis, 75% of patients had follow-up information on local control beyond 5 years. Thus, the number of patients censored for the Kaplan-Meier estimations during the first 5 years of follow-up markedly decreased in the updated analysis. Moreover, the proportion of local recurrences detected beyond 5 years was five (23%) of 22 after preoperative CRT and only two (5%) of 38 in the postoperative arm.

Interestingly, 17 of 38 local recurrences in the postoperative arm occurred in those 145 patients who did not receive CRT, and the median time to local recurrence for this group was only 15.1 months. Median time to local recurrence was higher for those patients who received postoperative CRT (18.7 months) and was almost twice as long for patients after preoperative CRT and surgical resection (30.7 months). Thus, the relative risk reduction for local recurrences decreased over the follow-up period. This indicates that, for a certain proportion of patients, preoperative CRT may at least postpone, although not completely avoid, local recurrences. This is in contrast to recently updated data from the Dutch TME trial,[8,9] reporting a stable relative risk reduction for local recurrences for preoperative short-course RT plus TME versus TME alone after 12 years compared with 6 years of follow-up (both approximately 50%). In this trial, the proportion of local recurrences presenting more than 5 years after surgery was 11% (11 of 97) in the TME-alone group and 9% (four of 46) in the irradiated group. On the basis of our data, we recommend long-term follow-up beyond 5 years, especially for patients after preoperative CRT and surgical resection.[10] The occurrence of late local recurrences beyond 5 years should also be considered in future clinical trial design and interpretation.

As demonstrated by multivariate Cox regression analysis, treatment-related factors (ie, noncomplete local resection [R1] and not receiving CRT at all) were independent risk factors for local recurrence. However, the HR for local recurrences was not significantly different for those patients who actually received pre- versus postoperative CRT in univariate (Fig 3B) and multivariate analyses (Table 3). Although such unplanned subgroup analyses should always be interpreted with caution, it is tempting to speculate that the overall significant advantage of preoperative CRT on local control, as demonstrated in the intention-to-treat and actual treatment arm populations, is a composite effect of both better compliance and improved biologic efficacy of the preoperative approach. Indeed, forest plot analysis showed increased HRs for local recurrences for almost all subgroups for patients actually treated with postoperative as compared with preoperative CRT (Fig 4), with the strongest difference in patients who had surgery involving intersphincteric or abdominoperineal resection (HR, 2.24; 95% CI, 1.07 to 4.71; $P = .03$). For the latter group of

Table 3. Multivariate Cox Regression Analysis of Local Recurrence Risk Among Patients With Macroscopically Complete Local Resection

Variable	HR	95% CI	*P*
Treatment received			
Preoperative CRT	1.0		
Postoperative CRT	1.01	0.51 to 1.98	.98
No postoperative CRT	3.86	1.93 to 7.72	< .001
Age, years			
≤ Median	1.0		
> Median	0.71	0.41 to 1.23	.22
Sex			
Male	1.0		
Female	0.73	0.40 to 1.33	.30
Distance from anal verge, cm			
0-< 5	1.0		
5-< 10	0.83	0.42 to 1.65	.60
10-16	0.62	0.24 to 1.59	.32
Type of resection			
Low anterior	1.0		
Intersphincteric	2.09	0.88 to 4.94	.09
Abdominoperineal	1.34	0.46 to 2.81	.45
(y)TNM stage			
pCR/0	1.0		
(y)I	1.07	0.13 to 8.82	.95
(y)II	1.85	0.24 to 14.57	.56
(y)III	4.14	0.55 to 31.54	.17
(y)IV	4.72	0.57 to 24.19	.15
Completeness of local resection			
R0	1.0		
R1	8.75	3.16 to 24.19	< .001

Abbreviations: CRT, chemoradiotherapy; HR, hazard ratio; pCR, pathologic complete response.

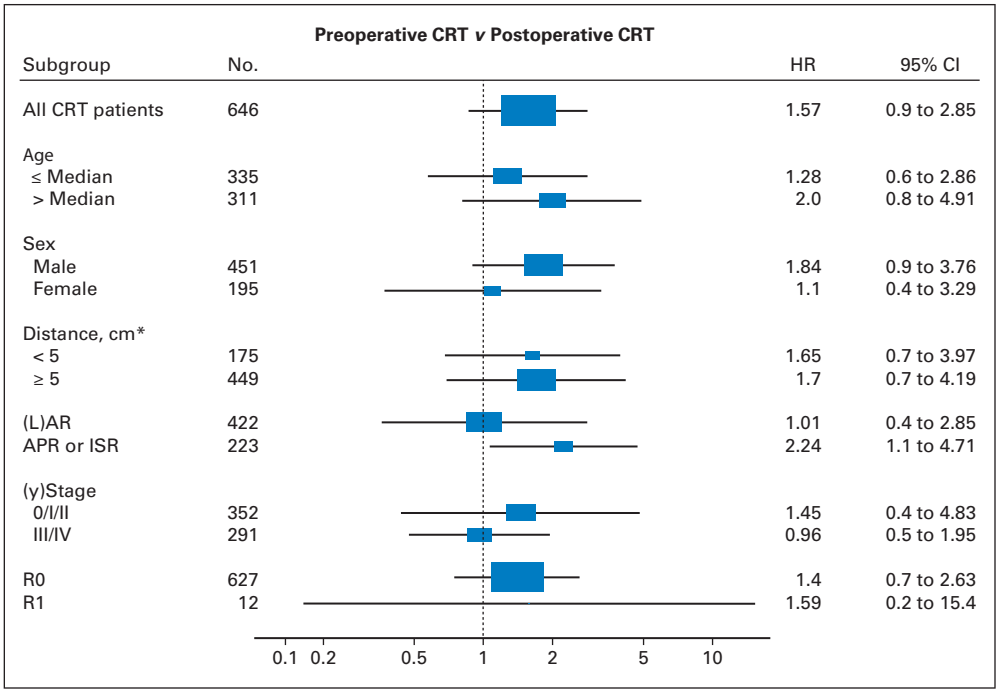

Fig 4. Forest plot analysis of local recurrences after macroscopically complete local tumor resection for different subgroups of patients who actually received chemoradiotherapy (CRT). The subgroups are analyzed individually in different Cox proportional hazards models comparing preoperative versus postoperative CRT. Hazard ratios (HRs) and 95% CIs are shown. (*) Distance from anocutaneous verge. APR, abdominoperineal resection; ISR, intersphincteric resection; (L)AR, (low) anterior resection.

low-lying tumors, the rates of local recurrences increased to 20.7% to 23% at 10 years despite postoperative CRT but could be reduced to 6% to 12.3% when treated preoperatively (Table 2).

Consistent with our previous report, preoperative CRT had no effect on distant recurrences (30% at 10 years in both arms). Overall, 17 (7.5%) of 226 distant metastases occurred beyond 5 years of follow-up with no difference between treatment groups. Notably, 43 (72%) of 60 local recurrences also had distant metastases, indicating that isolated local recurrences occur only rarely after TME surgery and CRT. These findings, together with the small absolute reduction of local recurrences after 10 years (3%) explain why the improvement in local control achieved with the preoperative approach could not translate into an improved overall survival. This is in line with all other recently published randomized trials on multimodal treatment for rectal cancer by using either preoperative RT alone or preoperative RT combined with FU. Although local control was consistently improved, none of these trials could show a significant improvement in overall survival.[9,11-13]

Evidently, any improvement in overall survival rates will require better control of systemic disease. Integrating more effective systemic therapy into multimodal therapy has been the challenge.[14] Recently, a phase III trial (CAO/ARO/AIO-04) by our group has completed accrual with more than 1,250 patients recruited. This study randomly assigned patients to either the best arm of CAO/ARO/AIO-94 (ie, FU-based preoperative CRT, surgery, and four cycles of postoperative FU chemotherapy) or to the investigational arm, which incorporated oxaliplatin into both preoperative CRT and postoperative chemotherapy. First results were recently presented and indicate that the addition of oxaliplatin to preoperative FU-CRT was well tolerated and associated with increased pathologic complete response rates.[15] The primary end point of CAO/ARO/AIO-04 is disease-free survival. Results on this primary end point will be available in late 2013.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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