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Preliminary Analysis of a Randomized Clinical Trial of Adjuvant Postoperative RT Vs. Postoperative RT Plus 5-FU and Levamisole in Patients With TNM Stage II-III Resectable Rectal Cancer

F. CAFIERO, MD,[1]* M. GIPPONI, MD,[1] A. PERESSINI, MD,[1] S. BERTOGLIO, MD,[2]
R. LIONETTO, MD,[3] AND THE P.A.R. COOPERATIVE STUDY GROUP

[1]*Division of Surgical Oncology, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy*
[2]*Department of Oncology–Biology and Genetics, University of Genoa, School of Medicine, Genoa, Italy*
[3]*Clinical Trial Service, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy*

Objectives: Two-hundred eighteen patients with TNM stage II-III resectable rectal cancer, enrolled into a randomized clinical trial, were assessed for efficacy and toxicity of adjuvant postoperative radiation therapy (RT) vs. those of combined RT and chemotherapy (CT), with 5-fluorouracil (5-FU) plus levamisole. End points were overall survival, disease-free survival, the rate of loco-regional recurrence, and treatment-related toxicity.

Methods: Patients in arm I underwent RT (50 Gy) in daily fractions of 2 Gy, 5 days/week for 5 weeks. Patients in arm II began with 5-FU (450 mg/m^2/day intravenous bolus, days 1–5) plus levamisole (150 mg/day orally, days 1–3); postoperative RT was delivered during week 2 at the same dosage and schedule as in arm I. The other five cycles of CT (5-FU every 28 days and levamisole every 15 days for the length of 5-FU administration) continued after the end of RT if clinical and hemato-biochemical parameters were normal.

Results: RT was completed or modified in 170 (90%) of 189 evaluable patients undergoing RT (both treatment groups). Only 44 (59%) of 75 evaluable patients of arm II completed or had an adjustment of the CT schedule; the remaining 31 patients (41%) had to stop or never started the CT regimen. Patients undergoing combined RT and CT had more severe toxicity (enteritis, $P = 0.03$). There was one CT-related death (gastrointestinal bleeding) in this subset. No significant difference was observed in outcome of patients in the two study groups, nor for pattern of recurrence (heterogeneity $\chi^2 = 4.82$; d.f. $= 2$; $P = 0.08$).

Conclusions: These preliminary findings suggest a similar efficacy, coupled with less morbidity, of postoperative RT alone compared with a combined regimen of postoperative RT and CT in patients undergoing radical surgery for stage II-III rectal cancer.

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KEY WORDS: rectum; adjuvant treatment; radiation therapy; chemotherapy

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P.A.R. (Protocollo Adiuvante Retto) Cooperative Study Group: A. Anfossi, D. Barone, S. Bartolomeo, G. Battistini, G. Becchi, E. Berti Riboli, F. Bistolfi, U. Bonalumi, F. Brema, F. Bruna, G. Castelluccio, P. Cavaliere, E. Ciferri, L. Cogolo, G. D'Ambrosio, C. Dani, F. Falchero, U. Folco, L. Gallo, C. Gatti, G.M. Gazzaniga, A. Gori, S. Mammoliti, M.V. Mari, M.C. Martini, C. Marziano, R. Masini, M.T. Nobile, E. Paganini, P. Percivale, P. Pramaggiore, C. Prior, R. Rosso, V. Rovere, D. Scarpati, C. Schenardi, T. Scolaro, C. Siccardi, A. Siragusa, N. Solari, E. Spagliardi, G. Tallero, P. Torelli, A. Trimarchi, V. Vitale.

*Correspondence to: Ferdinando Cafiero, M.D., Oncologia Chirurgica, Istituto Nazionale per la Ricerca sul Cancro, L.go Rosanna Benzi, 10, 16132 Genoa, Italy.

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INTRODUCTION

Pre- or postoperative radiation therapy (RT) significantly reduces loco-regional recurrence in rectal cancer patients; postoperative chemotherapy (CT), alone or in different combinations with RT, improves both disease-free survival (DFS) time and overall survival (OS). Notably, the optimal modality of RT delivery as well as the toxicity of combination adjuvant regimen with CT have yet to be defined [1–8].

On these grounds, the P.A.R. (Protocollo Adiuvante Retto) Cooperative Group started in 1992 a randomized clinical trial with the aim of assessing the efficacy and toxicity of adjuvant postoperative RT vs. those of combined RT and CT with 5-fluorouracil (5-FU) plus levamisole in patients with TNM stage II-III resectable rectal cancer (pT3-4, pN0, M0; pT1-4, pN1-3, M0). The primary end point was OS; secondary end points were DFS, the rate of loco-regional recurrence, and treatment-related toxicity/morbidity.

PATIENTS AND METHODS

Eligibility Criteria

Protocol entry criteria were the following: en bloc resection of all known tumors; the surgical specimen was adequate for TNM staging, and patients had pT3-4, pN0, M0 or pT1-4, pN1-3, M0 primary rectal adenocarcinomas. Excluded patients were those with microscopically positive resection margins; recurrent cancer; second malignancy (except nonmelanomatous skin cancer and in situ cervical cancer); and active infection. Pregnant or nursing women were also excluded. No prior or concurrent chemo-, immuno-, radio-, or endocrine therapy were allowed. Eligible patients were enrolled within 40 days after surgery. The design of the study was a multicenter, randomized clinical trial with two arms of treatment: arm I = postoperative RT; arm II = postoperative RT and CT (5-FU plus levamisole).

In regard to hematobiochemical tests, patients had the following values: hematologic (white blood cells at least 4,000/mm^3, platelets at least 100,000/mm^3); hepatic (bilirubin <1.5 × normal value [N]); alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase <2.5 × N; renal (creatinine <1.25 × N).

Dosage Schedule

Beginning within 60 days from surgery, patients randomized to arm I underwent RT (50 Gy) in daily fractions of 2 Gy, 5 days/week for 5 weeks to the tumor bed and loco-regional lymph nodes (internal iliac and presacral nodes) with four portals (antero-posterior/postero-anterior and right/left lateral fields). External iliac nodes were included in the radiation field if the tumor invaded bladder, prostate, cervix, or vagina. Patients randomized to arm II began the treatment with one cycle of 5-FU (450 mg/m^2/day intravenous bolus on days 1 through 5) plus levamisole (150 mg/day orally on days 1 through 3). Postoperative RT was delivered the next week at the same dosage and schedule as in arm I. The other five cycles of CT (5-FU every 28 days and levamisole every 15 days for the length of 5-FU administration) continued after the end of RT if all clinical and hematobiochemical parameters were within the normal range. This sequence of CT-RT-CT was adopted in order to overcome any possible delay of RT treatment due to loco-regional postoperative complications.

WHO criteria of toxicity were adopted for evaluating toxic effects [9]. Figure 1 describes the dosage adjustment of the CT regimen based on the type and grade of toxic events. In case of RT-related toxic effects (i.e., serious cystitis, ileitis), the administration of RT was temporarily stopped, and the total dose was adjusted by adding one fraction of 2 Gy for every week of postponement.

Randomization, Statistical, and Ethical Considerations

Randomization was performed by phoning a central office. Randomization lists were stratified by participating centers and balanced within blocks of variable size. The primary end point of the study was OS, and the expected 5-year survival rate in RT-treated patients was 50%. Hence, 175 patients should have been enrolled in each arm to have 80% power to detect a 15% increase of 5-year survival rate in RT+CT-treated patients at the 5% significance level. According to the "intention to treat" principle, all randomized patients were included in the analysis. Each patient was informed regarding the modalities of treatment and the aims of the study, and he/she gave oral or written consent. The protocol was approved by the ethics committee of our institution.

Categorical variables were compared by means of χ^2 test or the Fisher exact test, as it applies. DFS and OS were computed using the Kaplan-Meier method. Statistical significance was tested by means of the log-rank test (two-tailed *P* value are provided). DFS is defined as time from randomization until recurrence, death prior to recurrence, or occurrence of a new primary cancer. OS is defined as time from randomization until death from any cause. A Cox multiple regression model (backward procedure) was used to identify independent factors predictive of OS and DFS; all the variables in the model were categorical.

RESULTS

From May 1992 to December 1998, 218 patients were enrolled into the randomized clinical trial (144 men, 74 women; age range 28–75, median 64 years). The characteristics of patients are reported in Table I. Patients in both groups were well balanced in regard to sex, age,

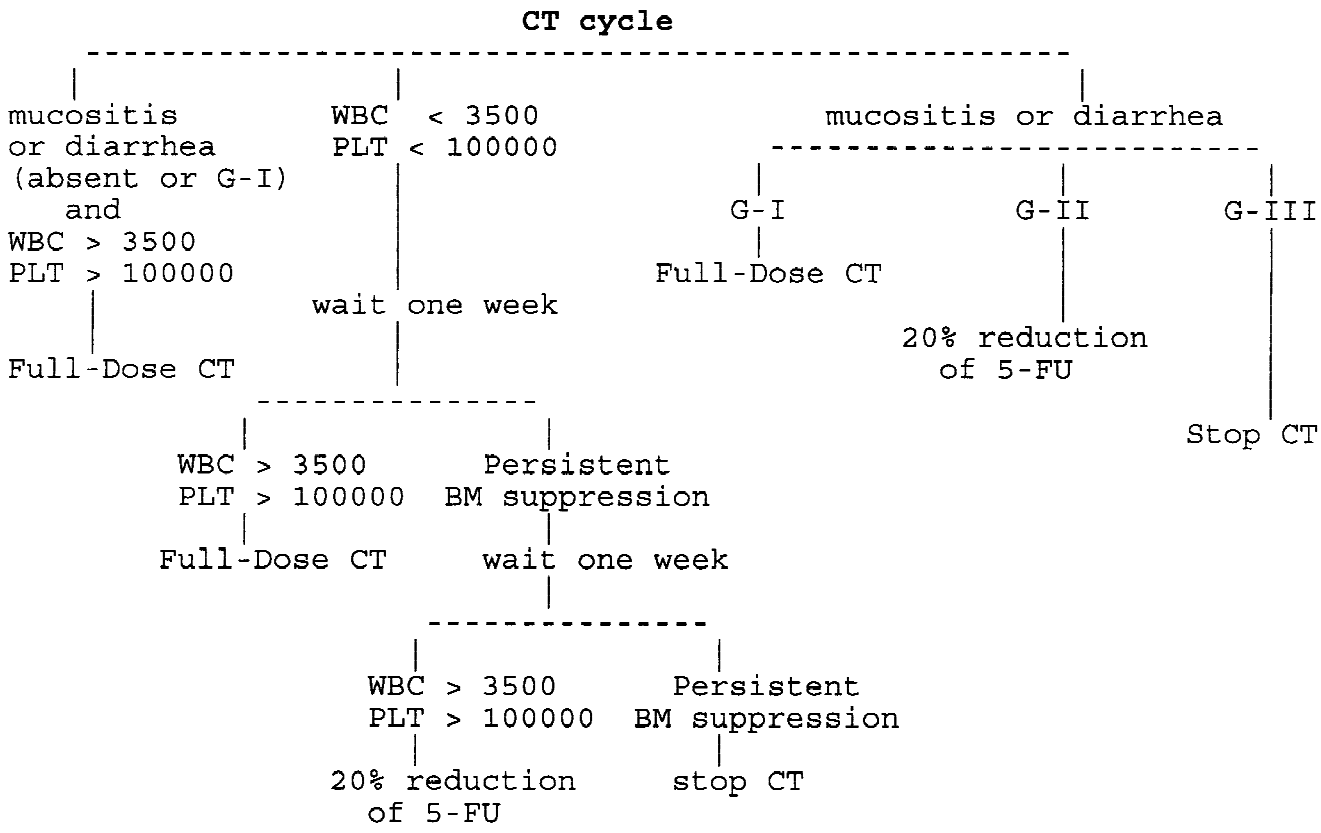

Fig. 1. Adjustment of chemotherapy (CT) regimen related to toxic effects. WBC = white blood cell count; PLT = platelet count; G-I, G-II, G-III = toxicity grades I, II, and III; 5-FU = 5-fluorouracil; BM = bone marrow.

performance status (PS), type of operation (sphincter-saving resection or abdominoperineal resection of the rectum), pT, number of sampled lymph nodes, and tumor grade. A higher number of stage III tumors was observed in arm II.

The median randomization time occurred on the 19th postoperative day (range, 6–24 days). On average, patients began RT 44 and 48 days from surgery (range, 26–106 days) in arm I and arm II, respectively; CT was started 39 days from surgery (range, 21–96 days) in arm II.

In regard to postoperative complications, data were available for 180 of 218 patients (arm I = 87; arm II = 93). No significant difference was observed for any of the complications reported. Patients undergoing abdominoperineal resection of the rectum had a higher rate of wound infections (21.4% and 16.2% in arms I and II, respectively) because perineal infections were included under this item (Table II).

Regarding compliance with the adjuvant treatment protocols, RT was completed or modified in 53 (57%) and 32 (35%) patients in arm I, whereas it was completed or modified in 57 (60%) and 28 (29%) patients in arm II. Therefore, 85 patients in each group underwent an appropriate adjuvant regimen, and there was no significant difference in the compliance with RT. Conversely, only 44 (59%) of 75 evaluable patients of arm II completed or had some adjustment of the CT schedule, whereas the remaining 31 patients (41%) had to stop or never started the CT regimen (Table III).

Patients undergoing RT+CT (Table IV) had a more severe toxicity (enteritis, $P = 0.03$). One CT-related death occurred in arm II, which was due to gastrointestinal bleeding.

The median follow-up time was 28 months. OS and DFS curves are reported in Figures 2 and 3. Median survival time for node-negative patients was not reached in patients treated with RT alone, while it was 1,746 days in patients undergoing RT+CT. Median survival time for node-positive patients was 1,793 and 1,169 days in arms I and II, respectively. Median DFS time for node-negative patients was 1,803 and 1,420 days in arms I and II, respectively, while the corresponding values for node-positive patients were 649 and 549 days.

By means of stratified analysis of OS and DFS in stage II and stage III patients, no significant difference was observed regarding the outcome of patients in the two study groups (Table V). The pattern of recurrence is reported in Table VI, comparing patients without relapse, patients with local recurrence alone, and patients with other events. No significant difference was observed in

TABLE I. Characteristics of Rectal Cancer Patients Enrolled in the Randomized Clinical Trial

	Arm I (RT) (n = 108)		Arm II (RT+CT) (n = 110)	
	n	%	n	%
Sex				
Males	70	64.8	74	67.3
Females	38	35.2	36	32.7
Age				
Median	65.5		63	
Range	34–75		28–75	
PS				
0	91	84.3	95	86.4
1	16	14.8	14	12.7
2	1	0.9	1	0.9
Type of operation				
SSR	65	67	64	62
APER	32	33	39	38
pT				
1	1	1	2	2
2	10	9	17	15.5
3	93	86	85	77
4	4	4	6	5.5
pN				
0	57	52.8	35	31.8
1	35	32.4	49	44.5
2	15	13.9	24	21.8
3	1	0.9	2	1.8
Stage				
I (not eligible)	1	0.9	—	—
II	56	51.9	35	31.8
III	51	47.2	74	67.3
IV (not eligible)	—	—	1	0.9
Tumor grading				
1	9	9.2	11	10.8
2	75	76.5	81	79.4
3	13	13.3	10	9.8
4	1	1.0	—	—

RT = radiation therapy; CT = chemotherapy; arm I = postoperative RT; arm II = postoperative RT+CT; PS = performance status; SSR = sphincter-saving resection; APER = abdominoperineal resection of the rectum.

the two arms of treatment (heterogeneity $\chi^2 = 4.82$; d.f. = 2; $P = 0.08$), although a 17% increase in the distant pattern of recurrence was observed in patients undergoing RT alone.

Univariate and Cox regression analysis on OS and DFS are reported in Tables VII and VIII. Cox multiple regression analysis for OS confirmed what was observed by univariate analysis for all variables but age. The relative risk of death under the experimental treatment (RT+CT) is similar to the control treatment. Older age and positive nodes at surgical intervention define the subgroups with the worst prognosis. The relative risk of having an event is increased 60% for patients undergoing abdominoperineal resection of the rectum compared with conservative treatment. This does not reach statistical significance even after correction for the other prognostic factors. Cox multiple regression analysis for DFS confirmed what was observed by univariate analysis for all variables: The only independent variable in predicting DFS is the positivity of nodes at pathologic staging. The unbalance of stage III tumors observed in the two study groups does not seem to have influenced the analysis since the exponential of the coefficient for the variable "treatment" was similar in the Cox regression model with only "treatment" as an independent variable ($\exp(\beta) = 1.16$), and in the Cox regression model with six independent variables (including "treatment") ($\exp(\beta) = 1.06$). Neither of them were statistically significant. Finally, since 31 patients (41%) in the chemo-radiation arm never started or stopped CT, an analysis by treatment actually received was performed, although it did not show any DFS (log rank = 0.92; d.f. = 1; $P = 0.34$) or OS (log rank = 0.03; d.f. = 1; $P = 0.87$) advantage for patients treated with the combined RT+CT regimen.

DISCUSSION

On March 14, 1991, the National Cancer Institute (Bethesda, MD) recommended combined CT (5-FU) and RT as postoperative adjuvant therapy in clinical practice, outside of clinical trials, for patients with stage II and III resectable rectal cancer [10]. These recommendations were based on the results of available clinical trials (NSABP R-01, GITSG-7175, NCCTG-794751, GITSG-7180) that suggested the advantage of RT+CT over surgery alone and postoperative RT. Moreover, the use of methyl-CCNU did not show any significant improvement but certainly increased the risk of leukemia and chronic renal insufficiency.

Such considerations were drawn on the results obtained in no more than 1,000 patients recruited into clinical trials, notwithstanding that colorectal cancer represents the second-leading cause of cancer deaths in Western societies with more than 155,000 new cases diagnosed in the United Stated each year [11]. Furthermore, those trials had some problems regarding the optimal dosage of the radiation programme, their statistical power, and the toxicity of the combined treatment with up to 61% severe acute toxicity, as reported in GITSG-7175.

In 1992, we started a randomized clinical trial to assess the efficacy and toxicity of adjuvant postoperative RT vs. combined RT and CT (5-FU plus levamisole) in patients with TNM stage II-III resectable rectal cancer. The chemo-radiation regiment we used was based on a sequential administration of CT-RT-CT, thus differing from the concurrent schedule suggested by the NCI clinical announcement. Moreover, 41% of patients treated with the combined regimen had to stop or never started CT. We stopped the recruitment of patients at the end of 1998 and made the following observations: first, both

TABLE II. Postoperative Complications in the Two Study Groups by Type of Surgery: Sphincter-Saving Resection (SSR) or Abdominoperineal Resection of the Rectum (APER)

Postoperative complications	Arm I (n = 87)		Arm II (n = 93)		P^a
	SSR (n = 59) n (%)	APER (n = 28) n (%)	SSR (n = 56) n (%)	APER (n = 37) n (%)	
Intraoperative site infections					
No	57 (96.6)	22 (78.6)	51 (91.0)	31 (83.8)	0.37
Yes					
Wound	1 (1.7)	2 (7.1)	3 (5.4)	3 (8.1)	
Perineal	—	4 (14.3)	—	2 (5.4)	
Wound and perineal	—	—	—	1 (2.7)	
Abdominal abscess	1 (1.7)	—	1 (1.8)	—	
Peritonitis	—	—	1 (1.8)	—	
Extraoperative site infections					
No	57 (96.6)	28 (100)	52 (92.8)	37 (100)	0.37
Yes					
Pulmonary	1 (1.7)	—	2 (3.6)	—	
Urinary tract	1 (1.7)	—	2 (3.6)	—	
Stomal complications					
No	—	28 (100)	—	36 (97.3)	0.51
Yes	—	—	—	1 (2.7)	
Anastomotic dehiscence					
No	55 (93.2)	—	53 (94.6)	—	0.46
Yes	4 (6.8)	—	3 (5.4)	—	
Urinary dysfunction					
No	59 (100)	25 (89.3)	55 (98.2)	33 (89.2)	0.39
Yes					
Retention	—	2 (7.1)	1 (1.6)	3 (8.1)	
Incontinence	—	1 (3.6)	—	1 (2.7)	

[a]One-tailed Fisher exact test.

TABLE III. Compliance With Radiation Therapy and Chemotherapy Within the Two Study Groups: Arm I (RT) and Arm II (RT+CT)

	Arm I		Arm II		
	No. of patients	%	No. of patients	%	P^a
Compliance with RT[b]					
Completed	53	57.0	57	59.4	0.42
Modified	32	34.4	28	29.2	0.26
Stopped	4	4.3	2	2.1	0.32
Never started	4	4.3	9	9.3	0.13
Compliance with CT[b]					
Completed			24	32.0	
Modified			20	26.7	
Stopped			24	32.0	
Never started			7	9.3	

RT = radiation therapy; CT = chemotherapy.
[a]One-tailed Fisher exact test.
[b]Data have been analyzed for 189 evaluable patients undergoing RT and 75 evaluable patients undergoing CT.

loco-regional and distant site progressions were not reduced by the combined regimen; second, the number of deaths was similar in the two arms of treatment; third, the compliance to RT was similar in both groups of patients but there was a rather low compliance to the CT regimen; fourth, toxicity was higher in patients undergoing the combined adjuvant treatment mostly regarding enteric toxicity.

Certainly, at least in our country, the use of adjuvant treatments in resectable rectal cancer has been generally disappointing, and only recently have surgeons become aware of the value of RT, both in the preoperative and postoperative setting. Some difficulties, however, still exist regarding the standard use of CT. This fact, coupled with the rather serious toxicity observed in the combined treatment arm, may have conditioned the compliance to the CT regimen.

More recent clinical trials, such as the NCCTG-864751 and the Intergroup-0114, have tried to define the optimal CT regimen to be combined with postoperative RT. The NCCTG trial showed that a protracted venous infusion of 5-FU during pelvic radiation significantly reduces both loco-regional and distant failures and produces a 10% improvement in overall tumor-free survival and mortality compared with a standard programme of bolus 5-FU [12]. The Intergroup study had a median follow-up time of 48 months and reported no statistically significant advantage of any of the modulated 5-FU regi-

TABLE IV. Crude Toxicity Rates in the Two Study Groups: Arm I (Postoperative RT) and Arm II (Postoperative RT+CT)

	Arm I[a]				Arm II[a]				
	Grade of toxicity				Grade of toxicity				
Toxic effect	I	II	III	IV	I	II	III	IV	P^b
Nausea/vomiting	2%	—	—	—	18%	15%	—	—	n.d.
Enteritis	22%	16%	5%	—	18%	26%	12%	2%	0.03
Leukopenia	6%	—	—	—	8%	8%	2%	2%	0.07
Anemia	—	—	—	—	—	1%	—	—	n.d.
Thrombocytopenia	1%	—	—	—	3%	—	—	—	n.d.
Cystitis	24%	7%	1%	—	26%	4%	—	—	0.48
Fever	—	—	—	—	1%	2%	—	—	n.d.
Asthenia	—	—	—	—	1%	3%	—	—	n.d.
Vulvitis	—	—	—	—	—	—	1%	—	0.52
Radiodermatitis	16%	9%	5%	—	17%	8%	7%	—	0.19
Proctitis	24%	5%	—	—	22%	12%	1%	—	0.49
Tenesmus	—	3%	—	—	1%	1%	—	—	n.d.
Stomatitis					21%	15%	5%	—	0.07
Alopecia					12%	2%	—	—	n.d.
Conjunctivitis					15%	—	—	—	n.d.
Dermatitis					5%	2%	2%	—	0.43

RT = radiation therapy; CT = chemotherapy; n.d. = not done.
[a]Data have been analyzed for 88 evaluable patients undergoing RT in arm I and 87 patients undergoing RT and 68 patients undergoing CT in arm II.
[b]One-tailed Fisher exact test.

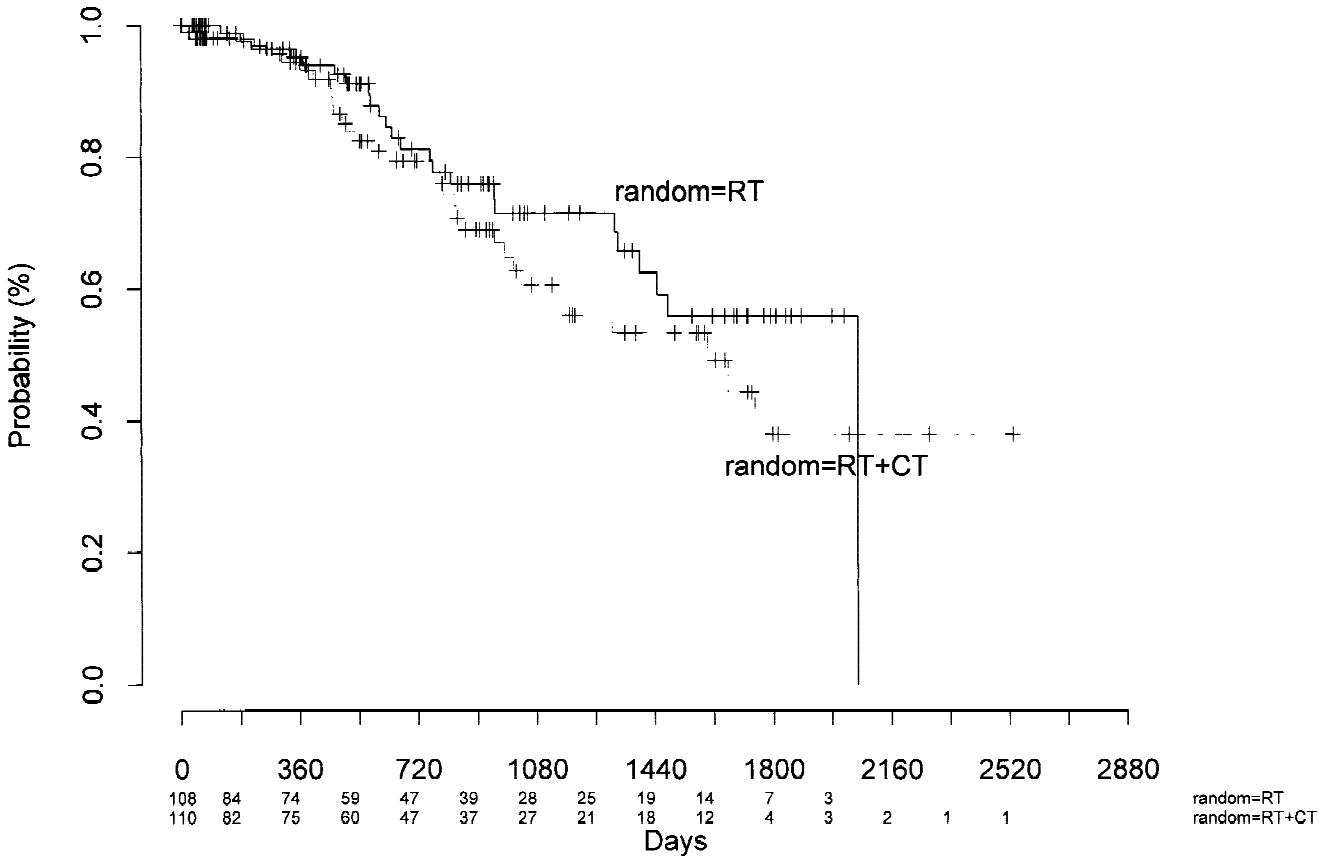

Fig. 2. Overall survival in randomized rectal cancer patients treated postoperatively with radiation therapy (RT) or RT plus chemotherapy (CT).

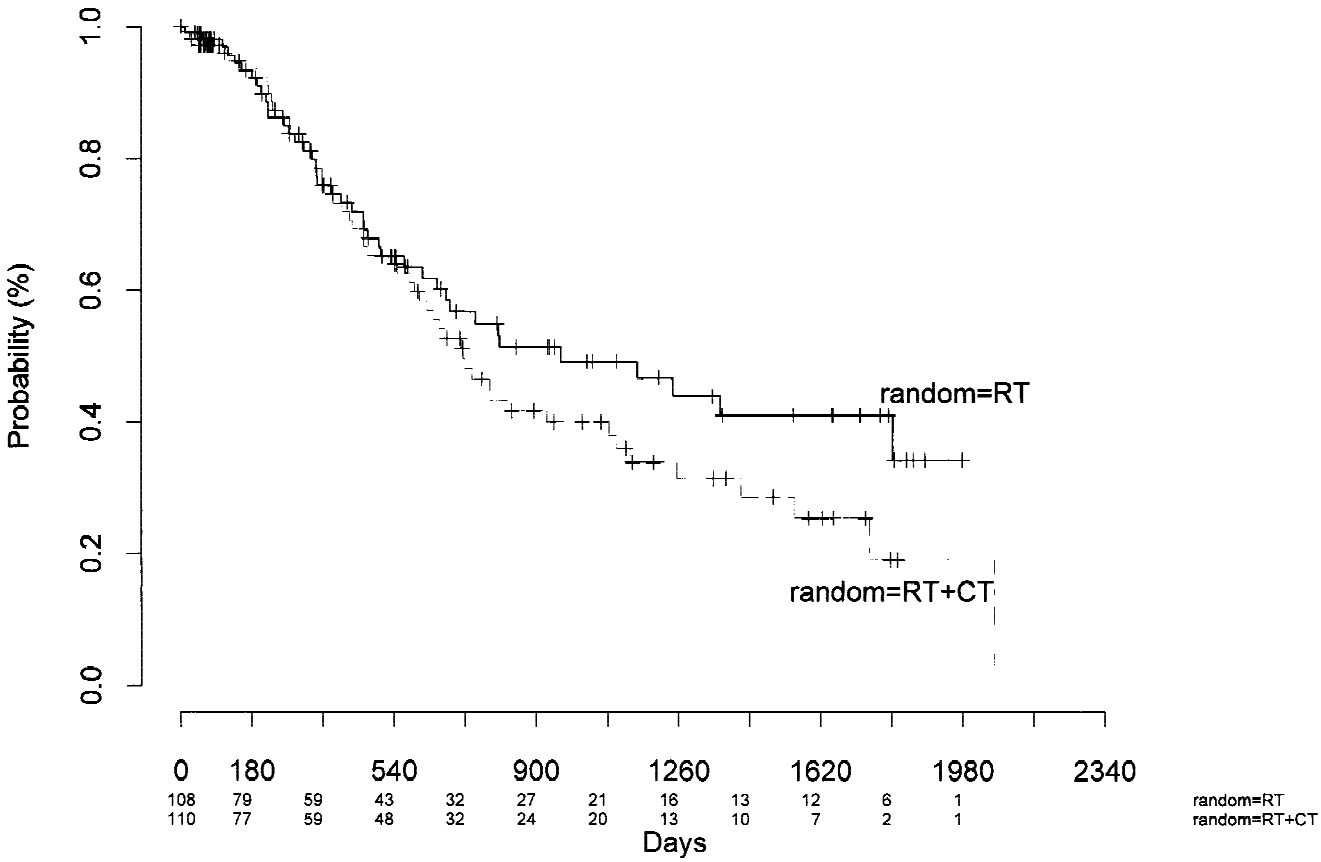

Fig. 3. Disease-free survival in randomized rectal cancer patients treated postoperatively with radiation therapy (RT) or RT plus chemotherapy (CT).

TABLE V. Stratified Analyses for Overall Survival (OS) and Disease-Free Survival (DFS)

	Log rank	d.f.	*P*
OS			
Stage II	0.01	1	0.90
Stage III	0.08	1	0.77
Pooled	0.03	1	0.85
DFS			
Stage II	0.16	1	0.69
Stage III	0.42	1	0.51
Pooled	0.40	1	0.52

TABLE VI. Pattern of Recurrence in the Two Study Groups (Arm I (RT) and Arm II (RT+CT)

	Arm I (n = 108)		Arm II (n = 110)		
	n	%	n	%	*P*
Disease progressions					
Yes	37	34.0	53	48.0	
No	71	66.0	57	52.0	
Site of relapse					
Local	10	27.0	11	21.6	0.49
Distant	18	48.7	16	31.4	0.06
Multiple	6	16.2	12	23.5	0.45
II cancer	1	2.7	4	7.8	0.33
Death[a]	2	5.4	8	15.7	0.15
Unknown site	—	—	2	—	
Death					
Yes	25	23.0	30	27.0	
No	83	77.0	80	73.0	

RT = radiation therapy; CT = chemotherapy.
[a]Death without progression.

mens (5-FU + leucovorin; 5-FU + levamisole; 5-FU + leucovorin + levamisole) compared with single-agent bolus 5-FU. Notably, the combination of levamisole and leucovorin significantly increased the toxicity and the number of treatment-related deaths [13].

Postoperative RT has a serious impact on local tumor control after radical resection of rectal cancer, and this may be improved by CT, used either as a radiosensitiser or in a standard adjuvant setting. The benefit of an adjuvant regimen, however, should not be outweighed by its toxicity, and as our preliminary findings seem to suggest (the short duration of the trial notwithstanding), there is the need to get further information from ongoing clinical trials in regard to the type and optimal sequence of surgery, RT and CT. Our experience suggests a similar efficacy, coupled with less morbidity, for postoperative RT alone compared with combined postoperative RT and CT.

TABLE VIII. Univariate Analysis and Cox Regression Analysis for Disease-Free Survival

	Univariate analysis				Cox regression	
Variable	Obs/Tot	χ^2	d.f.	*P*	Exp (coeff)	*P*
Random						
RT	37/108				1	
RT+CT	53/110	1.94	1	0.16	1.12	0.60
Dukes stage						
B	26/92				1	
C	64/126	15.41	1	0.0001	2.44	0.0001
PS						
0	74/186				1	
1+2	16/32	0.02	1	0.89	0.97	0.92
Gender						
Male	58/144				1	
Female	32/74	0.98	1	0.32	1.12	0.63
Age						
≤60 years	29/75				1	
>60 years	61/143	0.01	1	0.92	1.14	0.56
Surgical procedure						
SSR	55/129				1	
APER	35/71	0.45	1	0.50	1.25	0.30

RT = radiation therapy; CT = chemotherapy; Obs = observed; Tot = total; PS = performance status; SSR = sphincter-saving resection; APER = abdominoperineal resection of the rectum.

TABLE VII. Univariate Analysis and Cox Regression Analysis for Overall Survival

	Univariate analysis				Cox regression	
Variable	Obs/Tot	χ^2	d.f.	*P*	Exp (coeff)	*P*
Random						
RT	25/108				1	
RT+CT	30/110	0.31	1	0.58	1.04	0.9
Dukes stage						
B	15/92				1	
C	40/126	8.96	1	0.0028	2.66	0.0015
PS						
0	42/186				1	
1+2	13/32	0.48	1	0.49	1.07	0.83
Gender						
Male	33/144				1	
Female	22/74	1.54	1	0.22	1.18	0.56
Age						
≤60 years	14/75				1	
>60 years	41/143	2.41	1	0.12	1.88	0.04
Surgical procedure						
SSR	32/129				1	
APER	23/71	2.05	1	0.15	1.58	0.09

RT = radiation therapy; CT = chemotherapy; Obs = observed; Tot = total; PS = performance status; SSR = sphincter-saving resection; APER = abdominoperineal resection of the rectum.

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