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ORIGINAL REPORT

Preoperative Radiotherapy With or Without Concurrent Fluorouracil and Leucovorin in T3-4 Rectal Cancers: Results of FFCD 9203

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ABSTRACT

Purpose
In 1992, preoperative radiotherapy was considered in France as the standard treatment for T3-4 rectal cancers. The present randomized trial compares preoperative radiotherapy with chemoradiotherapy.

Patients and Methods
Patients were eligible if they presented a resectable T3-4, Nx, M0 rectal adenocarcinoma accessible to digital rectal examination. Preoperative radiotherapy with 45 Gy in 25 fractions during 5 weeks was delivered. Concurrent chemotherapy with fluorouracil 350 mg/m^2/d during 5 days, together with leucovorin, was administered during the first and fifth week in the experimental arm. Surgery was planned 3 to 10 weeks after the end of radiotherapy. All patients should receive adjuvant chemotherapy with the same fluorouracil/leucovorin regimen. The primary end point of the trial was overall survival.

Results
A total of 733 patients were eligible. Grade 3 or 4 acute toxicity was more frequent with chemoradiotherapy (14.6% *v* 2.7%; $P < .05$). There was no difference in sphincter preservation. Complete sterilization of the operative specimen was more frequent with chemoradiotherapy (11.4% *v* 3.6%; $P < .05$). The 5-year incidence of local recurrence was lower with chemoradiotherapy (8.1% *v* 16.5%; $P < .05$). Overall 5-year survival in the two groups did not differ.

Conclusion
Preoperative chemoradiotherapy despite a moderate increase in acute toxicity and no impact on overall survival significantly improves local control and is recommended for T3-4, N0-2, M0 adenocarcinoma of the middle and distal rectum.

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INTRODUCTION

In the early 1990s, after randomized trials[1,2] preoperative radiotherapy (RT) was considered in most European countries as standard treatment for T3-4 rectal cancers, which was not in agreement with the National Institutes of Health recommendations.[3] The evaluation of concurrent chemotherapy and radiotherapy (CT-RT) was an attractive field of research. Pilot studies were conducted by European Organisation for Research and Treatment of Cancer (EORTC) to determine the recommended dose of bolus fluorouracil (FU) modulated with leucovorin (LV).[4] The aim of this study was to evaluate if concurrent CT-RT in a neoadjuvant schedule could increase overall survival (OS) when compared with RT alone. The Fédération Francophone de Cancérologie Digestive (FFCD) 9203 trial was launched in 1993 to test this hypothesis.

PATIENTS AND METHODS

Eligibility Criteria and Randomization

Patients were eligible if they presented with a histologically confirmed, previously untreated rectal adenocarcinoma accessible to digital rectal examination; T3 or resectable T4 tumor with no evidence of distant metastases; age younger than 75 years; and WHO performance status of 0 or 1. All patients provided written informed consent and ethical committee permission was obtained. Eligible patients were randomly allocated to either preoperative RT alone or concurrent CT-RT.

Work-Up

Before random assignment, patients underwent direct rigid proctoscopy. The distance from the lower pole of

the tumor was measured to the anal verge. Endorectal ultrasound, pelvic computed tomography scan, liver sonography, or computed tomography scan and chest x-ray were performed. Blood serum analysis included total blood counts, creatinine, and serum carcinoembryonic antigen.

Treatment

RT. RT was delivered with photons from a linear accelerator with an energy level of 8 MV or above. The patient prone position was recommended. A three- or four-field box technique was used. The target volume was restricted to the posterior pelvis including the whole thickness of the sacral bone. The lateral borders of the posterior field were 1.0 cm (or at the limit) lateral to the widest bony margin of the true pelvic side walls. The inferior border was 4.0 to 5.0 cm inferior to the distal, furthest extent of the tumor or the anal verge. The anterior border of the lateral fields was 2.0 to 3.0 cm in front of the rectal wall. The posterior border was at the limit of the posterior bony sacral margin. The superior border was at the promontorium or 1 cm below for distal tumor. In general, field size measured 14 × 13 cm (posterior) and 14 × 12 cm (lateral). Dose display was performed on a minimum of three transverse axial slices from the computed tomography scan or simulator. The dose was specified into the International Commission on Radiation Units (and Measurements) point at the intersection of the beam axis. The dose per fraction was 1.8 Gy and all fields were treated each day with five fractions per week. The total dose was 45 Gy in 25 fractions during 5 weeks.

Concurrent CT. The first CT cycle was administered from days 1 to 5 of the RT treatment. LV 20 mg/m^2/d was delivered intravenously immediately before administration of FU. FU 350 mg/m^2/d was delivered during 20 minutes in 100 mL of saline infusion, 1 hour before RT.

The second cycle was administered from days 29 to 33 of the RT treatment using the same schedule. Doses were adapted according to toxicity. For grade ≥ 3 toxicity, RT and/or CT were interrupted.

Surgery. Surgery was planned between 3 and 10 weeks after the end of the preoperative RT (± CT). The choice between abdominoperineal resection or sphincter-saving surgery was left to the surgeon. Total mesorectal excision (TME) was recommended but no specific training or monitoring of this type of surgery was performed. A 2-cm distal clearance from the gross tumor was required in case of sphincter-saving surgery. A diverting stoma was recommended in case of low colorectal or colo-anal anastomosis.

Adjuvant CT. Patients in both arms were scheduled to receive adjuvant CT. Four cycles were administered at 4-week intervals using the same schedule as in the preoperative setting.

Pathologic Examination

Tumor regression was staged in three categories: sterilized specimen (no visible cancer cells), few residual isolated tumor cells, or residual evolutive tumor. The pathologic stage (ypTN) was recorded according to the International Union Against Cancer TNM system. The surgeon and the pathologist were to describe the resection as gross complete or incomplete (R2). The circumferential rectal margin was measured according to each pathologic laboratory technique and was considered as positive if the microscopic tumor extension reached the margin. Central quality control for pathologic examinations was not performed.

Follow-Up

All patients were observed every 6 months for 5 years and annually thereafter. Evaluation included clinical examination, abdominal ultrasonography or computed tomography scan, chest x-ray, and serum carcinoembryonic antigen level. Adverse events were codified using the WHO criteria.

Sample Size

The primary end point was OS. Compared with RT alone, the hypothesis was to increase the 5-year OS by 10% with preoperative concurrent CT-RT (52% *v* 62%). To detect such a difference, with $\alpha = .05$ (two tailed) and $\beta = .2$, it was required to observe 323 deaths and to recruit 762 eligible patients. Secondary end points were complete sterilization defined as ypT0N0, sphincter preservation, local control, progression-free survival (PFS), and acute toxicities according to WHO criteria. After inclusion criteria were checked, random assignment was performed centrally at the FFCD central office by telephone, using a minimization method. Stratification was performed according to four criteria: center, sex, cT3 versus cT4, and distance from anal verge (≤ 5 *v* > 5 cm).

Organization of the Trial

The investigation, collection of data, management, and analyses were performed by the FFCD office. The article was written by the investigators.

Statistical Analysis

All eligible patients were included in the analysis according to the intention-to-treat principle. χ^2 tests or Fisher's exact tests were used to compare proportions. Student's *t* tests or Mann-Whitney tests were used to compare quantitative variables. Univariate analyses of survival were carried out by the Kaplan-Meier method, and the evaluation of differences between the two groups was performed with the log-rank test. The Cox proportional hazards model was used to calculate hazard radios and 95% CIs in the univariate analyses. Cumulative incidence of relapse was determined according to the Breslow and Day method.

The starting point for the analyses of survival and relapse was the date of random assignment. Survival was censored at the time of the last follow-up. The rate of local recurrence was calculated on the basis of the number of eligible patients who underwent a macroscopically complete local resection, and by taking as the end point all local recurrences without or with associated distant metastasis. Local recurrence was defined as any clinically proven tumor relapse within the pelvis or perineum. The PFS was calculated on the basis of the number of eligible patients. The events taken into account in PFS were any death and any local or distant relapse of cancer.

RESULTS

Between April 1993 and November 2003, 762 patients were randomly assigned. At the time of analysis (May 2005), the median follow-up time was 81 months (range, 17 to 145 months).

Patient Characteristics and Protocol Violation

Out of the 762 patients randomly assigned, 14 were found ineligible because of protocol violation (patient not able to receive CT or past history of cancer; Fig 1) and six were lost to follow-up immediately. The analysis was performed on 742 eligible patients. Patient characteristics were well balanced between both arms (Table 1). Patients were enrolled from 54 French and Belgian institutions.

Compliance With Preoperative Treatment

RT was delivered with a linear accelerator in 99% of patients, with three- or four-field techniques in 97% of patients. The dose administered into the International Commission on Radiation Units (and Measurements) point was 45 Gy ± 10% in 96.5% of patients in the RT

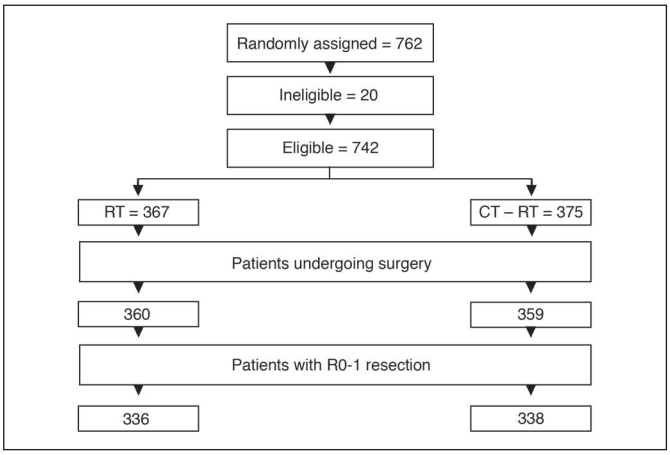

Fig 1. Flow diagram of the study. RT, preoperative radiotherapy; CT-RT, chemotherapy and radiotherapy.

Table 1. Baseline Patient Characteristics

Characteristic	RT Alone (n = 367) No. of Patients	%	CT-RT (n = 375) No. of Patients	%
Age, years				
Median	63		64	
Range	27-79		28-81	
Sex (male/female)	1.98		1.95	
WHO performance status				
0	230	62.7	226	60.3
1	121	33.0	139	37.1
Missing data	16	4.4	10	2.6
Tumor histology				
Adenocarcinoma	367		375	
Differentiation				
Well differentiated	167	45.5	170	45.3
Moderately differentiated	158	43.1	153	40.8
Undifferentiated	8	2.2	16	4.4
Not stated	25	6.8	25	6.7
Missing value	9	2.5	11	2.9
Colloid type	12	3.3	18	4.8
Location, cm from anal verge				
0-5	183	49.9	192	51.2
> 5	178	48.5	180	48.0
Clinical stage				
T3	314	85.6	332	88.5
T4	41	11.2	37	9.9
Ultrasound tumor stage				
T				
uT2	4	1.4	6	1.6
uT3	232	63.2	232	61.9
uT4	27	7.4	19	5.1
Not classified	13	3.5	11	2.9
Not done	91	24.8	107	28.5
N				
uN0	71	25.4	71	25.6
uN+	107	38.2	105	37.9
Unknown	102	36.4	101	36.5

Abbreviations: RT, radiotherapy; CR-RT, chemotherapy and radiotherapy.

Table 2. Acute Toxicity of the Preoperative Regimens

Toxicity	RT (n = 367) No. of Patients	%	CT-RT (n = 375) No. of Patients	%
Overall toxicity				
Grade				
0	134	38.8	92	25.0
1	122	35.4	139	37.8
2	79	22.9	82	22.3
3	10	2.9	47	12.8
4	0	0	8	2.2
Missing data	22		7	
Grade 0-2	335	97.1	313	85.1
Grade 3-4	10	2.9	55	14.9
Overall nonhematologic toxicity				
Grade				
0	200	55.2	146	39.6
1	85	23.5	101	27.4
2	69	19.1	72	19.5
3	8	2.2	46	12.5
4	0	0	4	1.1
Grade 0-2	354	97.8	319	86.5
Grade 3-4	8	2.2	50	13.5

NOTE: $P = .000$ for all categories.
Abbreviations: RT, radiotherapy; CR-RT, chemotherapy and radiotherapy.

arm and 97.1% in the CT-RT arm. In the CT-RT arm, the two cycles of FU-LV were administered to 93% of the patients and the full protocol dose of FU-LV was delivered in 78.1% of patients. The overall rate of grade 3 to 4 toxicities according to the WHO scale was significantly higher in the CT-RT arm (14.9%) than in the RT arm (2.9%; $P < .0001$; Table 2). The four cycles of FU-LV were administered to 70% of the patients (n = 261) in the CT-RT arm and to 65% of the patients (n = 239) in the RT arm ($P = .175$).

Surgical Procedures and Toxicities

Of 719 patients undergoing surgery, abdominoperineal resection was performed in 41.7% and 42.3% in the RT and CT-RT arm, respectively. Details of the surgical procedures are listed in Table 3.

There was no difference in postoperative death either at 30 or 60 days after surgery (2% at 60 days in both arms). The overall rate of complication due to surgery (fistula, pelvic abscess, hemorrhage, myocardial infarction, pulmonary embolism) was 26.9% (97 patients) and 20.9% (75 patients) in the RT and CT-RT groups, respectively. Fistula after anterior resection was observed in 7.6% (14 patients) after RT and 7.4% (14 patients) after CT-RT.

Pathologic Characteristics

The pathologic complete sterilization rate was significantly increased in the CT-RT arm (11.4% *v* 3.6%; $P < .0001$). No difference in the rate of ypN1-2 stage was observed. Details of the pathologic findings are listed in Table 3.

OS

At the time of analysis, of 742 eligible patients, 124 and 128 deaths were observed in the RT and CT-RT arms, respectively. There was no difference in the 5-year OS rate between both arms (67.9% *v* 67.4%; $P = .684$). The hazard ratio of death for CT-RT was 0.96 (95% CI, 0.73 to 1.27).

PFS

There was no difference between both arms for 5-year PFS: 55.5% *v* 59.4%, respectively, in RT versus CT-RT group (hazard ratio = 0.96; 95% CI, 0.77 to 1.20). Isolated distant metastases were found in 71 patients with RT alone and in 91 patients with CT-RT.

Local Recurrence

Among 674 patients who underwent a macroscopically complete resection, four and nine patients, respectively, are without follow-up in the RT and CT-RT arms. A total of 49 local recurrences in the RT group were observed; 21 recurrences were isolated and 28 recurrences were associated with distant metastases. In the CT-RT group, 25 local recurrences were observed, including 16 with distant metastases. The 5-year cumulative local recurrence rate was 16.5% in the RT arm and 8.1% in the CT-RT arm ($P = .004$; Fig 2). The relative risk of local recurrence was 0.50 (95% CI, 0.31 to 0.80) in patients who received CT-RT. A subgroup analysis was performed to compare the cohort of patients operated on between 1993 and 98 (360 patients) and the cohort operated on between 1999 and 2003 (301 patients). The

Table 3. Surgical Procedures and Pathologic Staging

Group	RT No. of Patients	RT %	CT-RT No. of Patients	CT-RT %	P
Eligible patients	367		375		
Surgery					
Yes	360	98.1	359	95.7	.16
No	4	1.1	11	3.0	
Missing data	3	0.8	5	1.3	
Patients undergoing surgery	360		359		
Surgery performed					
Abdominoperineal resection	150	41.7	152	42.3	.837
Anterior resection	185	54.4	188	52.4	
Other surgery	22	6.1	17	4.7	
Missing data	3	0.8	2	0.6	
Stoma					
No	64	17.8	69	19.2	.785
Temporary	134	37.2	131	36.5	
Permanent	160	44.4	156	43.5	
Other	1	0.3	0		
Missing data	1	0.3	3	0.8	
Gross complete resection					
Yes (R0-R1)	336	93.3	338	94.2	.791
No (R2)	20	5.6	15	4.2	
No resection	3	0.8	5	1.4	
Missing data	1	0.3	1	0.3	
Sterilization					
Complete sterilized specimen	13	3.6	41	11.4	.000
Few residual cells	37	10.3	67	18.7	
Evolutive residual cells	304	84.4	241	67.1	
Missing data	6	1.7	10	2.8	
ypN0	234	65.0	239	66.6	.847
ypN1-2	122	34.0	117	32.6	
Missing data	4	1.1	3	0.8	
Patients with gross complete resection	336		338		
ypT0	13	3.9	41	12.1	.000
ypT1	27	8.0	14	4.1	
ypT2	84	25.0	98	29.0	
ypT3	207	61.6	182	53.8	
Missing data	5	1.5	3	0.9	
CRM*					
Negative	188	56.0	185	54.7	.132
Positive	23	6.8	21	6.2	
Not assessable	83	24.7	69	20.4	
Missing data	42	12.5	63	18.6	

Abbreviations: RT, radiotherapy; CR-RT, chemotherapy and radiotherapy; CRM, circumferential rectal margin.
*Considered as positive if the microscopic tumor extension reached the margin.

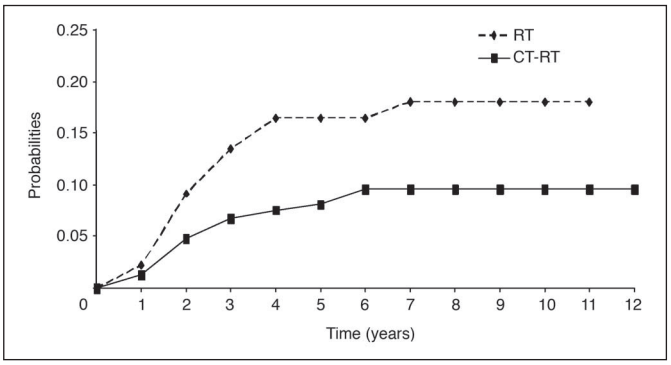

Fig 2. Cumulative incidence of local recurrence among 661 patients with treatment randomly assigned between preoperative radiotherapy (RT) and preoperative chemotherapy and radiotherapy (CT-RT). Estimate performed for patients who underwent surgery with a gross complete resection (R0-1).

difference appeared during the two periods in favor of the CT-RT arm. During the last period, the difference in favor of the CT-RT group was significant (5.1% *v* 14.5%; $P = .007$).

DISCUSSION

This multicenter trial was able to accrue 742 patients. The main results can be summarized as follows: concurrent CT-RT, 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 PFS; and increases local control, which is the major clinically relevant result of this trial.

These results should be analyzed keeping in perspective the weak points of this trial, which are mainly related to its long inclusion period (10 years). First, the CT regimen used in this trial may not be considered as optimal at present, especially delivery of the FU as a bolus injection.[5-7] Second, the surgery was not standardized and the concept of sharp dissection of the whole mesorectum (TME surgery), although described in the protocol, was not performed routinely.[8] It is probable that during the more recent period of this trial, TME surgery was more frequent. Third, the pathologic analysis of the operative specimen, regarding the scoring of the circumferential rectal margins, was not standardized.

Given that neoadjuvant treatments are not meant to compensate for suboptimal surgery, the main discussion should be related to the potential benefit of preoperative concurrent CT-RT on local control when used in combination with TME surgery. The Dutch trial[9] demonstrated that a short course of RT (25 Gy in five fractions for 5 days) immediately before TME surgery significantly decreases the 5-year local relapse rate from 11.4% to 5.8% ($P < .001$).[10] This trial differs from ours in many respects: tumors of the upper rectum and T2 tumors were included; for tumors with positive (R1) circumferential rectal margins postoperative irradiation (50.4 Gy in 30 fractions for 6 weeks) was recommended and was administered in 52 of 96 patients with R1 resection. In the present trial, only T3-4 tumors of the lower and middle rectum were included, and the rate of local relapse at 5 years in the period between 1999 and 2003 when TME surgery was performed more frequently, is less than 6%. For all of these reasons, it can be suggested that even with TME surgery, concurrent CT-RT is superior to RT alone to improve local control.

Notably, in many trials[7,11-16] the use of concurrent CT-RT increased significantly the rate of complete sterilization of the operative specimen. This is closely related to the pathologic technique used to analyze the specimen,[15,17] and the interval between the preoperative treatment and surgery.[14,15,18] Moreover, it is probable, according to the present results, that the rate of complete tumor response on the operative specimen is closely related to local control and could become a surrogate end point.

Despite an increase in the pathologic complete tumor response, the rate of sphincter preservation did not improve with CT-RT. This is in agreement with the Polish trial.[14] The EORTC 22921 trial[11-13] found a 3% increase in anterior resection with CT-RT. The Chirurgische Arbeitsgemeinschaft Onkologie/Arbeitsgemeinschaft der RadioOnkologen (CAO/ARO) trial[15] showed no difference in sphincter preservation in patients randomly assigned between preoperative and postoperative CT-RT. Only in a subgroup analysis in tumors "deemed to necessitate abdomino perineal resection," was a difference found in favor of preoperative CT-RT. All of these results are not fully comparable because the location of the tumors in the rectum differed from one trial to another. The question of improved sphincter preservation with neoadjuvant treatment remains complex and surgeon dependent. At present, single-agent FU CT used concomitantly with RT does not increase the probability of sphincter preservation probably because the clinical tumor response is often insufficient to modify the surgeon's decision.[19,20]

This trial, as for all of the other preoperative randomized trials, with the exception of the trial in Sweden,[21] failed to show an improvement in OS. It is possible that the local relapse rate less than 15% observed in the more recent trials is too low to influence survival. A longer follow-up time could also be necessary to observe a survival benefit.

The EORTC 22921 trial was similar to this trial with the addition, using a factorial plan design, of a second randomization for adjuvant CT after surgery. Its results regarding local recurrence are similar to ours, showing at 5 years a rate of 17% with RT alone versus 8% with RT-CT.[12]

This trial, in agreement with the EORTC 22921[12] and CAO-ARO[15] trials, despite a moderate increase in acute toxicity, supports the idea that in T3-4 resectable cancers of the lower and middle rectum, concurrent CT-RT should be considered as a standard. However, in the long term, bowel and sexual functions can be adversely affected by these preoperative regimens.[22] Better selection could be considered to try to individualize the preoperative treatment, possibly using magnetic resonance imaging.[23,24] Smaller irradiated volumes could also improve the cost-benefit ratio.[25] Furthermore, phase II trials using new polychemotherapy,[26] biotargeting drugs,[27] and a radiation dose increase above 45 Gy[28] have shown an increased rate of pathologic complete response close to 20%, which could lead to better local control.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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