

## ORIGINAL ARTICLE

# Chemotherapy with Preoperative Radiotherapy in Rectal Cancer

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## ABSTRACT

**BACKGROUND**

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Preoperative radiotherapy is recommended for selected patients with rectal cancer. We evaluated the addition of chemotherapy to preoperative radiotherapy and the use of postoperative chemotherapy in the treatment of rectal cancer.

**METHODS**

We randomly assigned patients with clinical stage T3 or T4 resectable rectal cancer to receive preoperative radiotherapy, preoperative chemoradiotherapy, preoperative radiotherapy and postoperative chemotherapy, or preoperative chemoradiotherapy and postoperative chemotherapy. Radiotherapy consisted of 45 Gy delivered over a period of 5 weeks. One course of chemotherapy consisted of 350 mg of fluorouracil per square meter of body-surface area per day and 20 mg of leucovorin per square meter per day, both given for 5 days. Two courses were combined with preoperative radiotherapy in the group receiving preoperative chemoradiotherapy and the group receiving preoperative chemoradiotherapy and postoperative chemotherapy; four courses were planned postoperatively in the group receiving preoperative radiotherapy and postoperative chemotherapy and the group receiving preoperative chemoradiotherapy and postoperative chemotherapy. The primary end point was overall survival.

**RESULTS**

We enrolled 1011 patients in the trial. There was no significant difference in overall survival between the groups that received chemotherapy preoperatively ( $P=0.84$ ) and those that received it postoperatively ( $P=0.12$ ). The combined 5-year overall survival 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%.

**CONCLUSIONS**

In patients with rectal cancer who receive preoperative radiotherapy, adding fluorouracil-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. (ClinicalTrials.gov number, NCT00002523.)

\*The institutions that participated in European Organization for Research and Treatment of Cancer (EORTC) Radiotherapy Group Trial 22921 are listed in the Appendix.

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UNTIL THE LATE 1980s, THERE WAS A high risk of local and distant recurrences after resection of rectal cancer.<sup>1-3</sup> Preoperative radiotherapy, with the aim of improving local control, has been extensively evaluated. The following two schedules of treatment have been explored: short-term treatment that delivers 25 Gy in 5 fractions during 1 week, followed immediately by surgery, and conventional schedules that deliver 40 to 50 Gy in 20 to 25 fractions during 4 to 5 weeks, followed by surgery 3 to 6 weeks later. Regardless of the protocol, preoperative radiotherapy decreases local recurrence rates by 50 to 60% as compared with surgery alone.<sup>4-12</sup>

In the early 1990s, postoperative chemoradiotherapy was established as a standard treatment in the United States.<sup>13</sup> We have investigated the effect of preoperative chemoradiotherapy on the outcome of the treatment of rectal cancer. The trial was initiated after the European Organization for Research and Treatment of Cancer (EORTC) Radiotherapy Group showed that a combination of fluorouracil and leucovorin could be given safely during pelvic radiotherapy in patients with locally advanced rectal cancer.<sup>14</sup> In 1993, the EORTC Radiotherapy Group initiated a trial (EORTC 22921) to assess whether preoperative chemoradiotherapy followed by postoperative chemotherapy improves overall and progression-free survival. We report the results of this trial after a median follow-up of 5.4 years.

## METHODS

### ELIGIBILITY AND ENROLLMENT

Eligibility criteria included T3 or resectable T4M0 adenocarcinoma of the rectum (according to the 1987 International Union Against Cancer [UICC] staging system<sup>15</sup>), located within 15 cm of the anal verge; a World Health Organization (WHO) performance status of 0 or 1; and an age of 80 years or less. We excluded patients with a history of cancer (except nonmelanoma skin cancer), angina pectoris, or inflammatory disease of the ileum or colon. The extent of disease was assessed by clinical examination, rigid proctoscopy, chest radiography, and computed tomography of the abdomen and pelvis. Endorectal ultrasonography was optional. Tumor staging was clinical. If tumor staging was not available, the results from endorectal ultrasonography were used. The clinical T-stage definition has been described previ-

ously.<sup>16</sup> The trial was approved by the medical ethics committees of all participating centers. Written informed consent was obtained from all patients before randomization.

### RANDOMIZATION AND TREATMENT

Randomization was performed at the EORTC Center in Brussels with the use of the minimization technique and stratification according to institution, sex, T stage, and distance from the tumor to the anal verge. Patients were randomly assigned to receive one of the following four treatments: preoperative radiotherapy (standard group), preoperative chemoradiotherapy, preoperative radiotherapy and postoperative chemotherapy, or preoperative chemoradiotherapy and postoperative chemotherapy (Fig. 1).

Radiotherapy consisted of 45 Gy delivered to the posterior pelvis in 25 fractions of 1.8 Gy over a period of 5 weeks. Irradiation techniques and treatment volumes have been reported previously.<sup>16,17</sup> Preoperative chemotherapy was delivered in two 5-day courses during the first and fifth weeks of radiotherapy. Fluorouracil was given at a dose of 350 mg per square meter of body-surface area per day, and leucovorin at a dose of 20 mg per square meter per day. Surgery was scheduled to take place 3 to 10 weeks after treatment. A total mesorectal excision was recommended beginning in 1999. Postoperative chemotherapy was scheduled to begin 3 to 10 weeks after surgery and was delivered in four courses, every 3 weeks, with the same scheme and doses that were used preoperatively.

### FOLLOW-UP

During preoperative treatment, patients were monitored weekly for signs of acute toxic effects, with precautionary adjustments in radiotherapy or chemotherapy made as necessary.<sup>17</sup> During postoperative treatment, patients were assessed every 3 weeks for acute toxic effects. These effects were scored according to WHO criteria for assessing preoperative and postoperative toxic effects.<sup>18</sup> Patients were followed at 6-month intervals until death or for at least 5 years. The 6-month evaluation included clinical examination, abdominal ultrasonography, and chest radiography; colonoscopy was performed annually. Evaluation of late side effects included investigation of small-bowel and rectal complications and the need for additional surgery. Recurrences were confirmed

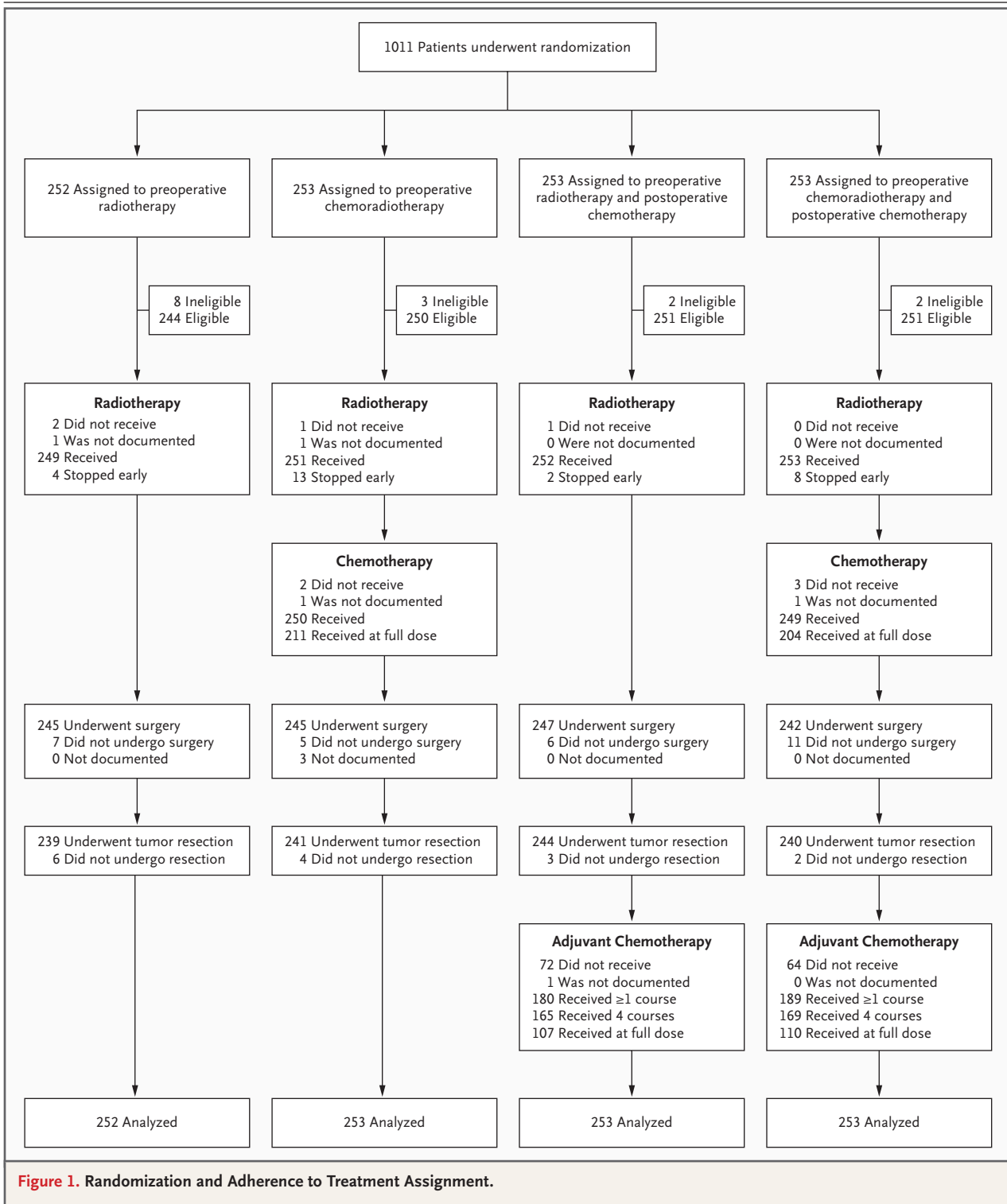


Figure 1. Randomization and Adherence to Treatment Assignment.

radiologically or by biopsy. Local recurrence was defined as tumor regrowth within the pelvis or perineum.

#### QUALITY CONTROL

Early in the course of the trial an individual case review was performed. Minor deviations from protocol were observed and recommendations to correct them were provided to participating centers; details on this procedure have been reported previously.<sup>19</sup>

#### STATISTICAL ANALYSIS

The primary objective of this trial was to compare the two preoperative and the two postoperative treatments for overall survival. Assuming a total of 340 deaths, we calculated that we would need a sample of 1011 patients in order to have 80% statistical power to detect a difference in survival of 10 percentage points at 5 years, with a two-sided significance level of 0.05. Log-rank tests for interaction were performed to verify the assumptions underlying the two-by-two factorial design. Whenever the assumption was violated, the four treatment groups were compared with the use of a single log-rank test; otherwise, stratified log-rank tests<sup>20</sup> were used to assess the preoperative and the postoperative treatments separately. Kaplan–Meier curves<sup>21</sup> or cumulative incidence curves<sup>22</sup> (in the case of competing risks) were used to estimate the event rates. Chi-square tests were used to compare toxic effects and rates of adherence. The analysis was based on strict application of the intention-to-treat principle.

The trial was designed by Dr. Bosset with the methodologic support of Dr. Collette.

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## RESULTS

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#### PATIENTS

From April 1993 to March 2003, 1011 patients were randomly assigned as follows: 252 to preoperative radiotherapy, 253 to preoperative chemoradiotherapy, 253 to preoperative radiotherapy and postoperative chemotherapy, and 253 to preoperative chemoradiotherapy and postoperative chemotherapy (Fig. 1). Characteristics of the patients and tumors were well balanced among the four treatment groups (Table 1). The tumor was

located 10 cm or less from the anal verge in 938 patients (92.8%). The T stage was assessed clinically in 961 patients. Stage T3 was documented in 910 patients (90.0%).

#### PREOPERATIVE TREATMENT

Figure 1 shows adherence to the assigned treatments. Radiotherapy was delivered as planned in 495 of 505 patients assigned to preoperative radiotherapy (98.0%) and in 483 of 506 patients assigned to preoperative chemoradiotherapy (95.5%). Overall, 415 patients (82.0%) received the planned doses of fluorouracil. Grade 2 acute toxic effects were reported in 29.7% of the patients receiving preoperative radiotherapy and 38.4% of the patients receiving preoperative chemoradiotherapy, and in these two groups grade 3 or higher acute toxic effects occurred in 7.4% and 13.9% of patients, respectively (P for trend <0.001). Diarrhea of grade 2 or higher occurred in 17.3% of patients assigned to preoperative radiotherapy and in 37.6% of patients assigned to preoperative chemoradiotherapy (P<0.001).

#### SURGERY

Thirteen patients in the preoperative-radiotherapy groups and 16 in the preoperative-chemoradiotherapy groups did not undergo surgery. The reasons were refusal (9 patients), disease progression (10), toxicity (3), ineligibility (3), and other (4). The median time from the end of the preoperative treatments to surgery was 5.4 weeks for both treatment protocols. Tumor was resected in 964 of the 979 patients who underwent surgery (95.4% of all 1011 patients). Liver metastases were found in 42 patients. Sphincter-sparing resection was performed in 255 patients who were assigned to preoperative radiotherapy (50.5%) and in 267 patients assigned to preoperative chemoradiotherapy (52.8%) (P=0.47). Six patients died within 30 days after surgery or the last preoperative treatment in the preoperative-radiotherapy groups (1.2%) and 12 died within this period in the preoperative-chemoradiotherapy groups (2.4%). Rates of postoperative complications were 23.3% and 22.8% in the radiotherapy and chemoradiotherapy groups, respectively. Table 1 lists the types of surgical techniques used in this study.

**Table 1. Characteristics of the Patients at Study Entry.\***

Characteristic	Preoperative Radiotherapy (N=252)	Preoperative Chemoradiotherapy (N=253)	Preoperative Radiotherapy and Postoperative Chemotherapy (N=253)	Preoperative Chemoradiotherapy and Postoperative Chemotherapy (N=253)	Total (N=1011)
Age — yr					
Median	63.0	62.0	63.0	63.0	63.0
Range	23.0–79.0	36.0–79.0	27.0–78.0	22.0–78.0	22.0–79.0
Sex — no. (%)					
Male	183 (72.6)	184 (72.7)	185 (73.1)	187 (73.9)	739 (73.1)
Female	69 (27.4)	69 (27.3)	68 (26.9)	66 (26.1)	272 (26.9)
WHO performance status — no. (%)†					
0	202 (80.2)	194 (76.7)	199 (78.7)	199 (78.7)	794 (78.5)
1	50 (19.8)	59 (23.3)	54 (21.3)	54 (21.3)	217 (21.5)
Distance to anal verge — no. (%)					
0–5 cm	125 (49.6)	125 (49.4)	124 (49.0)	129 (51.0)	503 (49.8)
6–10 cm	103 (40.9)	114 (45.1)	112 (44.3)	112 (44.3)	441 (43.6)
>10 cm	24 (9.5)	14 (5.5)	17 (6.7)	12 (4.8)	67 (6.6)
Tumor stage — no. (%)‡					
T3	226 (89.7)	230 (90.9)	228 (90.1)	226 (89.3)	910 (90.0)
T4	26 (10.3)	23 (9.1)	25 (9.9)	27 (10.7)	101 (10.0)
Tumor differentiation — no. (%)					
Well differentiated	104 (41.3)	98 (38.7)	83 (32.8)	94 (37.2)	379 (37.5)
Moderately differentiated	92 (36.5)	98 (38.7)	94 (37.2)	103 (40.7)	387 (38.3)
Poorly differentiated	11 (4.4)	10 (4.0)	14 (5.5)	13 (5.1)	48 (4.7)
Not stated	45 (17.9)	47 (18.6)	62 (24.5)	43 (17.0)	197 (19.5)
Histologic type — no. (%)					
Adenocarcinoma	251 (99.6)	249 (98.4)	251 (99.2)	249 (98.4)	1000 (98.9)
Mucinous	1 (0.4)	4 (1.6)	2 (0.8)	3 (1.2)	10 (1.0)
Other	0	0	0	1 (0.4)	1 (0.1)
Type of surgery — no. (%)					
Total mesorectal excision	87 (34.5)	96 (37.9)	88 (34.8)	101 (39.9)	372 (36.8)
Other	36 (14.3)	28 (11.1)	25 (9.9)	26 (10.3)	115 (11.4)
No surgery or no resection	13 (5.2)	9 (3.6)	9 (3.6)	13 (5.1)	44 (4.4)
Unknown	116 (46.0)	120 (47.4)	131 (51.8)	113 (44.7)	480 (47.5)

\* Percentages may not sum to 100 because of rounding.

† WHO denotes World Health Organization.

‡ Tumor staging was clinical, if available, and was otherwise determined by endorectal ultrasonography.

#### **PATHOLOGY**

Results of pathological examination of the tumor specimens have been detailed previously.<sup>16</sup> Tumors were smaller after preoperative chemoradiotherapy than after preoperative radiotherapy alone ( $P<0.001$ ) and had less advanced pathologic

tumor stages ( $P<0.001$ ) and pathological nodal status ( $P<0.001$ ). After preoperative chemoradiotherapy, there were fewer examined nodes ( $P=0.05$ ) and less frequent lymphatic, venous, and perineural invasion ( $P=0.008$ ) than after preoperative radiotherapy alone.

### POSTOPERATIVE TREATMENTS

Among the 506 patients who were randomly assigned to postoperative chemotherapy, 136 (26.9%) never started the treatment. Reasons were postoperative complications (33 patients), disease progression (30), patient refusal (25), no surgery or no tumor resection (22), toxic effects of preoperative treatment (7), and other (19). Only 217 patients (42.9%) received 95 to 105% of the planned dose of fluorouracil without delay. Acute toxic effects of any grade were observed in 214 patients (57.8%). Patients with grade 2 or higher toxic effects included 54 patients with diarrhea, 25 with vomiting, 19 with neutropenia, and 13 with infection. There were no deaths from toxic effects.

### LATE SIDE EFFECTS

Grade 2 or higher diarrhea was reported in 97 of the 1011 patients who underwent randomization (9.6%). Among the 522 patients in whom sphincter-sparing surgery was performed, 47 (9.0%) reported some form of fecal incontinence; 2 patients required colostomy for this complication. Thirty-one patients had a stricture of the anastomosis, which required colostomy in 11 patients. Surgery for small-bowel complications was required in 14 patients (1.4%). There was no significant difference in the incidence of late side effects among the four treatment groups.

### EVENTS DURING FOLLOW-UP

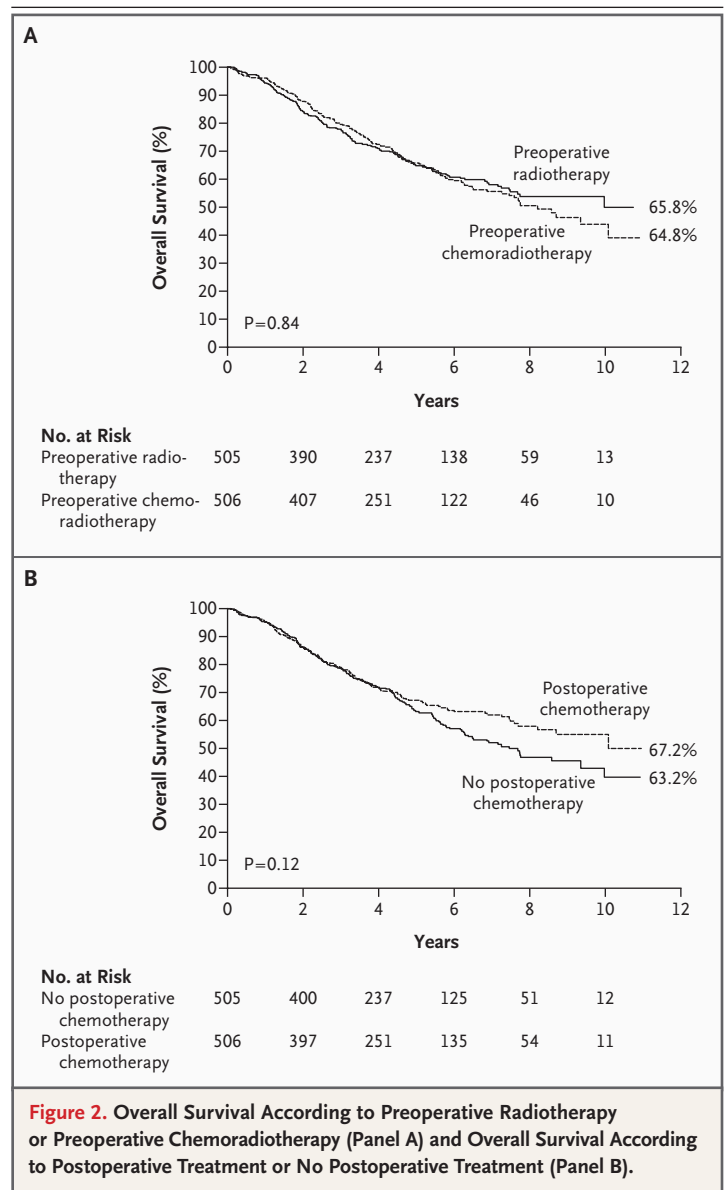
As of April 2005, surviving patients had been followed for a median of 5.4 years (range, 4.0 months to 10.9 years). The follow-up did not differ significantly among treatment groups ( $P=0.96$ ). No data were available for 12 patients. Of the 347 deaths that occurred during follow-up, 264 (76.1%) were due to rectal cancer, 12 were due to other malignant conditions, 13 to toxicity of the treatment, 41 to other causes, and 17 to unknown causes. Local recurrences occurred in 127 patients, and distant recurrences in 326.

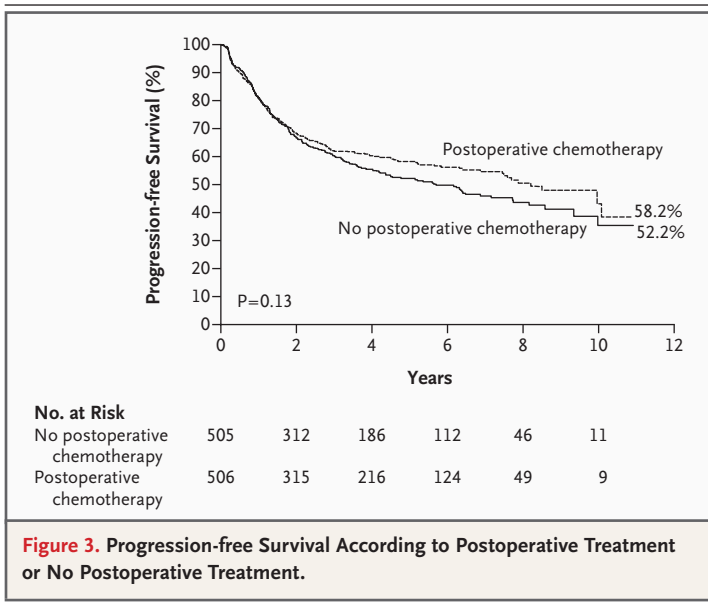
### SURVIVAL

There was no significant interaction between the effects of the preoperative and postoperative treatments on overall or disease-free survival ( $P=0.43$  and  $P=0.50$ , respectively). The 5-year overall survival rate was 64.8% in the two groups receiving preoperative radiotherapy and 65.8% in the two groups receiving preoperative chemoradiotherapy. The survival curves did not differ significant-

ly ( $P=0.84$ ) (Fig. 2A). The hazard ratio for death in the preoperative-chemoradiotherapy groups as compared with the preoperative-radiotherapy groups was 1.02 (95% confidence interval [CI], 0.83 to 1.26). The 5-year overall survival rate was 63.2% in the two groups that did not receive adjuvant chemotherapy and 67.2% in the two groups that did ( $P=0.12$ ) (Fig. 2B). The hazard ratio for death in the adjuvant-chemotherapy groups was 0.85 (95% CI, 0.68 to 1.04).

The 5-year disease-free survival rate was 54.4% in the two preoperative-radiotherapy groups and 56.1% in the two preoperative-chemoradiotherapy groups. The disease-free survival curves did





**Figure 3. Progression-free Survival According to Postoperative Treatment or No Postoperative Treatment.**

not differ significantly ( $P=0.52$ ); the hazard ratio was 0.84 (95% CI, 0.78 to 1.13) for preoperative chemoradiotherapy as compared with radiotherapy. The 5-year disease-free survival rates were 52.2% and 58.2% in the no-adjuvant-treatment groups and the adjuvant-treatment groups, respectively ( $P=0.13$ ) (Fig. 3), with a hazard ratio of 0.87 (95% CI, 0.72 to 1.04) for adjuvant chemotherapy as compared with no adjuvant chemotherapy.

#### LOCAL AND DISTANT RECURRENCES

Because of indications of an interaction between preoperative and postoperative chemotherapy ( $P=0.09$ ), local recurrences are reported separately in the four treatment groups. The cumulative incidences of local recurrences as a first event at 5 years were 17.1% (95% CI, 12.3 to 21.9) in the preoperative-radiotherapy group, 8.7% (95% CI, 4.9 to 12.6) in the preoperative-chemoradiotherapy group, 9.6% (95% CI, 5.7 to 13.5) in the group receiving preoperative radiotherapy and postoperative chemotherapy, and 7.6% (95% CI, 4.2 to 11.0) in the group receiving preoperative chemoradiotherapy and postoperative chemotherapy ( $P=0.002$  for the comparison between the group receiving preoperative radiotherapy alone and the other three groups) (Fig. 4). Although tested with low statistical power, the treatment effect seemed homogeneous, regardless of the distance from the tumor to the anal verge ( $\leq 5$  cm vs.  $> 5$  cm,  $P=0.74$ ).

The cumulative incidence of distant metastases

did not differ significantly according to the preoperative or postoperative treatment ( $P=0.14$  and  $P=0.62$ , respectively). Overall, the 5-year cumulative incidence of distant metastases was 34.4% (95% CI, 31.3 to 37.6%).

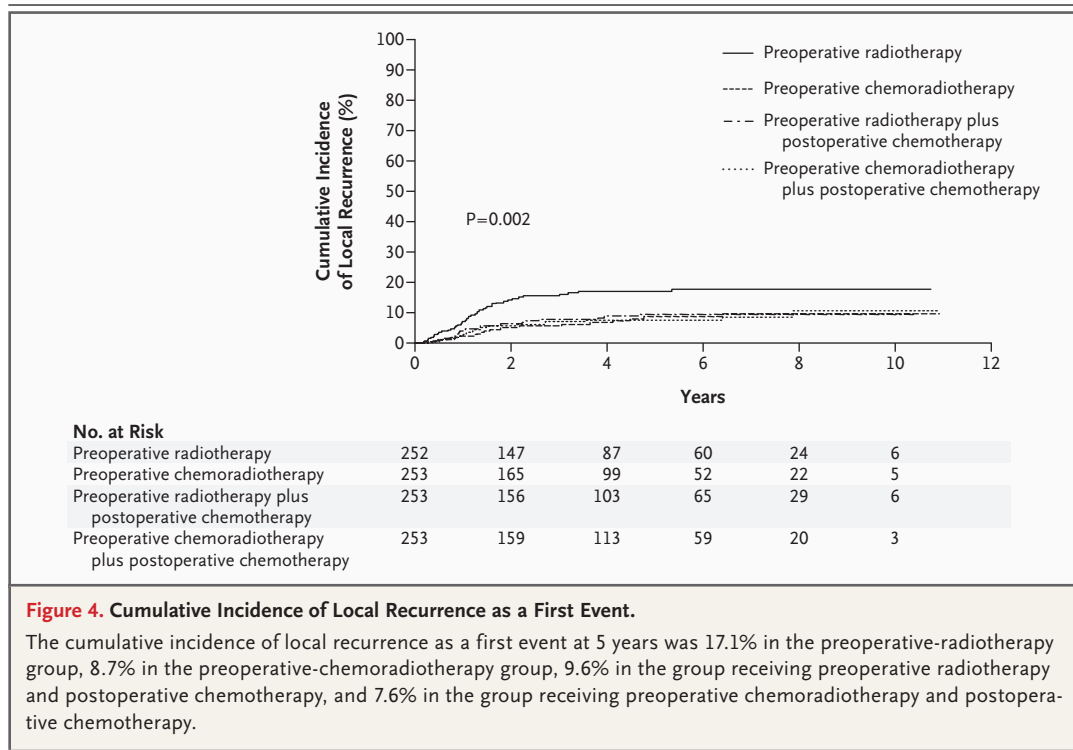
#### DISCUSSION

There were two assumptions underlying the design of our trial. One was that adding chemotherapy to preoperative radiotherapy could augment the local effect of the radiotherapy, and the other was that preoperative or postoperative chemotherapy or both could improve survival.

Adherence to preoperative chemotherapy was excellent. Adding chemotherapy to preoperative radiotherapy slightly increased the incidence of acute toxic effects but did not affect adherence to radiotherapy, the feasibility of surgery, the rate of postoperative complications, or the rates of adherence to postoperative chemotherapy.<sup>17,23</sup> Chemoradiotherapy resulted in downsizing and down-staging of tumors, as well as changes in their histologic characteristics.<sup>16</sup> These effects were associated with a significant increase in local control but no improvement in progression-free or overall survival.

Adherence to postoperative chemotherapy was poor. Less than 50% of the patients assigned to this treatment received it according to protocol. There were no significant effects of adjuvant treatment on progression-free or overall survival, but the survival curves for patients who received adjuvant treatment and those who did not diverged after 2 years (progression-free survival) and 4 years (overall survival). More follow-up is needed to determine whether these differences will continue. The 5-year local recurrence rates were 17.1% among patients who received no chemotherapy and about 8.6% among those who received some form of chemotherapy; this effect did not diminish with time. The assumption of no interaction between preoperative and postoperative chemotherapy on local control was not validated, and there was no evidence that giving both preoperative and postoperative chemotherapy is beneficial.

A meta-analysis of randomized trials that compared preoperative radiotherapy with surgery alone before the introduction of total mesorectal excision showed a decrease in the 5-year rate of local recurrence from 22.2% with surgery alone



to 12.5% with preoperative radiotherapy in clinical stage T1, T2, or T3 disease.<sup>24</sup> The 17% local failure rate we observed in our study in the group receiving only radiotherapy may be related to a more advanced disease stage and to suboptimal rectal excision.

A randomized study conducted by the Dutch Colorectal Cancer Group addressed the value of short-term preoperative radiotherapy in patients with clinical stage T1, T2, or T3 disease who underwent a total mesorectal excision.<sup>25</sup> With preoperative radiotherapy, the 5-year local recurrence rates decreased significantly, from 11.4% to 5.8%, but subgroup analyses showed that radiotherapy was ineffective in patients with tumors in the low rectum.<sup>26</sup> In our study the local effect of radiotherapy and chemotherapy was of the same magnitude regardless of the location of the tumor in the rectum.

The German Rectal Cancer Study Group conducted a randomized study that compared preoperative chemoradiotherapy with postoperative chemoradiotherapy for patients with clinical stage T3 or T4 disease.<sup>27</sup> Chemotherapy consisted of a continuous infusion of fluorouracil. The radiotherapy dose was about 50 Gy, and total mesorectal excision was recommended. Four courses

of adjuvant fluorouracil were added in each group. There was no difference in overall survival between the group receiving preoperative chemoradiotherapy and the group receiving postoperative chemoradiotherapy. The 5-year local recurrence rate was significantly reduced in the preoperative-treatment group (6% vs. 13%). Adherence was better with preoperative treatment, and it had fewer acute and long-term toxic effects. Our results with preoperative chemoradiotherapy are consistent with those of the German trial.

Given the high rate of local control obtained with preoperative chemoradiotherapy and the lack of effect on survival, it seems unnecessary to intensify this regimen in an attempt to further decrease local recurrences or to prevent metastases. In our study, the 5-year cumulative incidence of distant metastases was about three times that of local recurrences, indicating that future trials should focus on eradicating micrometastases. The role of postoperative chemotherapy is not yet defined and adherence to it is poor. We believe, therefore, that preoperative chemotherapy is an option worth considering for some patients.<sup>28</sup>

In our trial, the rate of fecal incontinence af

ter conservative surgery was 9%. In the Swedish Rectal Cancer Trial and in the trial conducted by the Dutch Colorectal Cancer Group,<sup>25</sup> the rate of fecal incontinence increased from 27% and 39% after surgery alone to 62% and 64% after preoperative radiotherapy, respectively.<sup>29,30</sup> The discrepancy between these two trials and ours may be related to the use of different radiotherapy protocols, as well as differences in the irradiated volumes and in the methods for assessing long-term toxic effects. In our study, fecal incontinence was scored by the treating physician, whereas it was self-reported in the two other trials. Exclusion of the anal canal from the irradiated volume for tumor in the midrectum may have helped reduce long-term toxic effects in our study. An increased fraction size in radiotherapy has a negative effect on normal tissue tolerance,<sup>31,32</sup> but whether a protocol of short duration has more long-term toxic

effects than a conventional protocol is unknown. Quality of life will become an increasingly relevant end point in new trials.

We conclude that in patients with stage T3 or T4 resectable rectal cancer treated with preoperative radiotherapy, 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.

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No potential conflict of interest relevant to this article was reported.

The views expressed are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

#### APPENDIX

The following institutions participated in the EORTC Radiotherapy Group Trial no. 22921: **France** — Centre Hospitalier Universitaire (CHU) de Besançon, Besançon; CHU de Tours—Hôpital Bretonneau, Tours; Clinique Sainte Catherine, Avignon; Centre Georges-François Leclerc, Dijon; Hôpital Jean Bernard, Poitiers; Centre René Gauducheau, Nantes; Centre Paul Strauss, Strasbourg; CHU de Grenoble-la-Tronche, Grenoble; Centre Saint-Yves, Vannes; CHU de Limoges; Polyclinique Clairval, Marseille; Clinique du Valdegour, Nîmes; Clinique de la Rochebelle, Alès; Centre Hospitalier Général de Belfort, Belfort; Centre Paul Papin, Angers; CHU Henri Mondor, Créteil; Clinique Sainte Clotilde, La Réunion; CHU de Brest, Brest; Centre Oscar Lambret, Lille; CHU Caen; **Belgium** — Hôpital Universitaire Erasme, Brussels; Intercommunale de Santé Publique du Pays de Charleroi, Charleroi; Hôpital de Jolimont, La Louvière; CHU de Tivoli, La Louvière; Clinique Sainte Elisabeth, Namur; Institut Jules Bordet, Brussels; **the Netherlands** — University Medical Centre Nijmegen, Nijmegen; Dr. Bernard Verbeeten Instituut, Tilburg; Arnhem's radiotherapeutisch Instituut, Arnhem; **Spain** — Hospital General Vall d'Hebron, Barcelona; Ciudad Sanitaria Universitaria de Bellvitge-Hospital Princesps d'Espanya (now Institut Català d'Oncologia, Llobregat), Barcelona; Hospital General Universitario Gregorio Marañón, Madrid; **Germany** — Heinrich-Heine Universitätsklinik Düsseldorf, Düsseldorf; Allgemeines Krankenhaus Hagen, Hagen; **Poland** — Medical University of Gdansk, Gdansk; **Israel** — Rambam Medical Center, Haifa; **Serbia** — Institute of Oncology and Radiology, Belgrade; **Turkey** — Dokuz Eylul University School of Medicine, Izmir; **Switzerland** — Universitaets Spital, Zurich; Kantonsspital Winterthur, Winterthur.

#### REFERENCES

- Phillips RK, Hittinger R, Blesovsky L, Fry JS, Fielding LP. Local recurrence following 'curative' surgery for large bowel cancer: I. The overall picture. *Br J Surg* 1984;71:12-6.
- Minsky BD, Mies C, Recht A, Rich TA, Chaffey JT. Resectable adenocarcinoma of the rectosigmoid and rectum. I. Patterns of failure and survival. *Cancer* 1988;61:1408-16.
- Galandiuk S, Wieand HS, Moertel CG, et al. Patterns of recurrence after curative resection of carcinoma of the colon and rectum. *Surg Gynecol Obstet* 1992;174:27-32.
- Gerard A, Buyse M, Nordlinger B, et al. Preoperative radiotherapy as adjuvant treatment in rectal cancer: final results of a randomized study of the European Organization for Research and Treatment of Cancer (EORTC). *Ann Surg* 1988;208:606-14.
- Reis Neto JA, Quilici FA, Reis JA Jr. A comparison of nonoperative vs. preoperative radiotherapy in rectal carcinoma: a 10-year randomized trial. *Dis Colon Rectum* 1989;32:702-10.
- Dahl O, Horn A, Morild I, et al. Low-dose preoperative radiation postpones recurrences in operable rectal cancer: results of a randomized multicenter trial in western Norway. *Cancer* 1990;66:2286-94.
- Cedermark B. The Stockholm II trial on pre-operative short term radiotherapy in operable rectal carcinoma: a prospective randomised trial. *Proc Am Soc Clin Oncol* 1994;13:198. abstract.
- Marsh PJ, James RD, Schofield PF. Adjuvant preoperative radiotherapy for locally advanced rectal carcinoma: results of a prospective, randomized trial. *Dis Colon Rectum* 1994;37:1205-14.
- Goldberg PA, Nicholls RJ, Porter NH, Love S, Grimsey JE. Long-term results of a randomised trial of short-course low-dose adjuvant preoperative radiotherapy for rectal cancer: reduction in local treatment failure. *Eur J Cancer* 1994;30A:1602-6.
- Cedermark B, Johansson H, Rutqvist LE, Wilking N. The Stockholm I trial of preoperative short term radiotherapy in operable rectal carcinoma: a prospective randomized trial. *Cancer* 1995;75:2269-75.
- Medical Research Council Rectal Cancer Working Party. Randomised trial of surgery alone versus radiotherapy followed by surgery for potentially operable locally advanced rectal cancer. *Lancet* 1996;348:1605-10.
- Swedish Rectal Cancer Trial Group. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med* 1997;336:980-7. [Erratum, *N Engl J Med* 1997;336:1539.]
- NIH Consensus Conference: adjuvant therapy for patients with colon and rectal cancer. *JAMA* 1990;264:1444-50.
- Bosset JF, Pavy JJ, Hamers HP, et al. Determination of the optimal dose of

- 5-fluorouracil when combined with low dose 5-FU, leucovorin and irradiation in rectal cancer: results of three consecutive phase II studies. *Eur J Cancer* 1993;29A:1406-10.
15. Sobin LH, Witteking C. TNM classification of malignant tumours. Geneva: International Union Against Cancer, 1987.
16. Bosset JF, Calais G, Mineur L, et al. Enhanced tumoricidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results — EORTC 22921. *J Clin Oncol* 2005;23:5620-7.
17. Bosset JF, Calais G, Daban A, et al. Preoperative chemoradiotherapy versus preoperative radiotherapy in rectal cancer patients: assessment of acute toxicity and treatment compliance — report of the 22921 randomised trial conducted by the EORTC Radiotherapy Group. *Eur J Cancer* 2004;40:219-24.
18. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207-14.
19. Kouloulas VE, Bosset JF, van Tienhoven G, et al. Quality assurance in the EORTC 22921 trial on preoperative radiotherapy with or without chemotherapy for resectable rectal cancer: evaluation of the individual case review procedure. *Eur J Cancer* 2002;38:1849-56.
20. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966;50:163-70.
21. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
22. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: John Wiley, 1980:163-78.
23. Musat E, Bosset JF, Calais G, et al. Serious adverse events in the EORTC randomized phase III trial 22921 comparing preoperative pelvic irradiation to preoperative chemo-irradiation with or without postoperative adjuvant chemotherapy for T3-T4 resectable rectal cancer. *Eur J Cancer* 2005;2:Suppl 3:171. abstract.
24. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. *Lancet* 2001;358:1291-304.
25. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;345:638-46.
26. Marijnen CAM, Peeters KCMJ, Putter H, et al. Long term results, toxicity and quality of life in the TME trial. *Radiother Oncol* 2004;73:Suppl 1:S127.
27. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;351:1731-40.
28. Chau I, Brown G, Cunningham D, et al. Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer. *J Clin Oncol* 2006;24:668-74.
29. Dahlberg M, Glimelius B, Graf W, Pahlman L. Preoperative irradiation affects functional results after surgery for rectal cancer: results from a randomized study. *Dis Colon Rectum* 1998;41:543-9.
30. Peeters KC, van de Velde CJ, Leer JW, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients — a Dutch Colorectal Cancer Group study. *J Clin Oncol* 2005;23:6199-206.
31. Barendsen GW. Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. *Int J Radiat Oncol Biol Phys* 1982;8:1981-97.
32. Turesson J, Notter G. The influence of fraction size in radiotherapy on the late normal tissue responses. *Int J Radiat Oncol Biol Phys* 1984;10:593-606.

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**CORRECTION**

**Chemotherapy with Preoperative Radiotherapy in Rectal Cancer**

Chemotherapy with Preoperative Radiotherapy in Rectal Cancer . In Figure 2 (page 1119), the percentage labels for the lines in Panel A were reversed. The solid line should have read 65.8%, and the dashed line should have read 64.8%. The figure has been corrected on the *Journal's* Web site at [www.nejm.org](http://www.nejm.org).