ORIGINAL ARTICLE

Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer

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ABSTRACT

BACKGROUND

Postoperative chemoradiotherapy is the recommended standard therapy for patients with locally advanced rectal cancer. In recent years, encouraging results with preoperative radiotherapy have been reported. We compared preoperative chemoradiotherapy with postoperative chemoradiotherapy for locally advanced rectal cancer.

METHODS

We randomly assigned patients with clinical stage T3 or T4 or node-positive disease to receive either preoperative or postoperative chemoradiotherapy. The preoperative treatment consisted of 5040 cGy delivered in fractions of 180 cGy per day, five days per week, and fluorouracil, given in a 120-hour continuous intravenous infusion at a dose of 1000 mg per square meter of body-surface area per day during the first and fifth weeks of radiotherapy. Surgery was performed six weeks after the completion of chemoradiotherapy. One month after surgery, four five-day cycles of fluorouracil (500 mg per square meter per day) were given. Chemoradiotherapy was identical in the postoperative-treatment group, except for the delivery of a boost of 540 cGy. The primary end point was overall survival.

RESULTS

Four hundred twenty-one patients were randomly assigned to receive preoperative chemoradiotherapy and 402 patients to receive postoperative chemoradiotherapy. The overall five-year survival rates were 76 percent and 74 percent, respectively (P=0.80). The five-year cumulative incidence of local relapse was 6 percent for patients assigned to preoperative chemoradiotherapy and 13 percent in the postoperative-treatment group (P=0.006). Grade 3 or 4 acute toxic effects occurred in 27 percent of the patients in the preoperative-treatment group, as compared with 40 percent of the patients in the postoperative-treatment group (P=0.001); the corresponding rates of long-term toxic effects were 14 percent and 24 percent, respectively (P=0.01).

CONCLUSIONS

Preoperative chemoradiotherapy, as compared with postoperative chemoradiotherapy, improved local control and was associated with reduced toxicity but did not improve overall survival.

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N Engl J Med 2004;351:1731-40.

Adjuvant radiotherapy with or without chemotherapy has been used widely to improve outcomes in patients with rectal cancer. For locally advanced disease, postoperative chemoradiotherapy significantly improves both local control and overall survival as compared with surgery alone or surgery plus irradiation.[1,2] This information prompted a National Institutes of Health consensus conference, convened in 1990, to recommend postoperative adjuvant chemoradiotherapy as standard treatment for patients with rectal cancer classified as tumor–node–metastasis (TNM) stage II (i.e., a tumor penetrating the rectal wall, without regional lymph-node involvement) or stage III (i.e., any tumor with regional lymph-node involvement).[3]

Several randomized studies have found lower rates of local failure with preoperative radiotherapy than with surgery alone. However, only the Swedish Rectal Cancer Trial, which evaluated a short course of preoperative irradiation (25 Gy, delivered in five fractions), found an advantage in overall survival.[4] The authors of a subsequent meta-analysis also concluded that the combination of preoperative radiotherapy and surgery, as compared with surgery alone, significantly improves local control and overall survival.[5] The Dutch Colorectal Cancer Group reported that the addition of short-course preoperative radiotherapy to optimal surgery with total mesorectal excision reduced the rate of local recurrence but did not improve two-year survival.[6]

Given the potential advantages of preoperative radiotherapy and the finding that the addition of chemotherapy to radiotherapy improves survival in the adjuvant setting, we conducted a trial to compare preoperative conventionally fractionated radiotherapy and concurrent fluorouracil chemotherapy with the same treatment given postoperatively in patients with locally advanced rectal cancer. We present the results after a median follow-up of 45.8 months.

METHODS

ELIGIBILITY FOR ENROLLMENT

We initiated the trial in 1994; patients were enrolled beginning in February 1995, and enrollment was extended through September 2002. Eligibility criteria included histopathologically confirmed, resectable adenocarcinoma with the inferior margin within 16 cm from the anal verge. Endorectal ultrasonography and computed tomographic (CT) scanning of the abdomen and pelvis were performed to rule out TNM stage I tumors and distant metastases. Patients were excluded if they were older than 75 years of age, had previously had cancer other than nonmelanoma skin cancer, had previously received chemotherapy, had previously received radiotherapy to the pelvis, or had contraindications to chemoradiotherapy. The trial was approved by the medical ethics committees of all the participating hospitals.

RANDOMIZATION AND TREATMENT

After written informed consent had been obtained, eligible patients were randomly assigned to receive either postoperative chemoradiotherapy or preoperative chemoradiotherapy. Randomization was performed by the study center in Erlangen, Germany, and was based on permuted blocks of 14, with stratification according to surgeon. Beginning in October 1998, prerandomization according to the double-consent design of Zelen[7] was permitted at the request of 16 of the 26 participating centers. According to this design, informed consent is sought after the patient is told the result of randomization and, as suggested by the term "double," the result is disclosed to patients in both groups. According to this design, data must be analyzed according to the result of randomization and any decisions made by patients to receive the alternative treatment must be disregarded with respect to the analysis.

Radiotherapy consisted of a total of 5040 cGy delivered (as at least 6-MV photons) in 28 fractions of 180 cGy, five times weekly, to the pelvis with individually shaped portals and the use of a three-field or four-field box technique. During the first and fifth weeks of radiotherapy, fluorouracil was given as a 120-hour continuous infusion at a dose of 1000 mg per square meter per day. Treatment was identical in both groups except for a 540-cGy boost delivered to the tumor bed in the postoperative-treatment group. In patients who were assigned to preoperative treatment, surgery was scheduled to take place six weeks after the completion of chemoradiotherapy. Four cycles of bolus fluorouracil (500 mg per square meter per day, five times weekly, every four weeks) were started four weeks after surgery (in the preoperative-treatment group) or four weeks after chemoradiotherapy (in the postoperative-treatment group). Irradiation techniques and treatment volumes have been described in detail elsewhere.[8]

SURGERY

Total mesorectal excision was performed in all the patients according to a standardized technique. To rule out potential bias with respect to the quality of surgery and the commitment to sphincter preservation, patients were stratified according to surgeon. Assessment of the intended surgical procedure before randomization (i.e., whether sphincter preservation was deemed possible or not) was included to evaluate the efficacy of preoperative chemoradiotherapy in permitting sphincter-sparing surgery in patients with low-lying tumors.

FOLLOW-UP

During therapy, patients were monitored weekly for signs of acute toxic effects, with appropriate adjustments in chemotherapy and radiotherapy made as necessary; long-term toxic effects were assessed at one, three, and five years. Acute and long-term toxic effects were graded according to a German classification system[9] that corresponds to the World Health Organization criteria for assessing the toxicity of chemotherapy and that is compatible with the criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer with respect to the acute and late adverse effects of radiotherapy. Perioperative and 30-day postoperative complications assessed included anastomotic leakage, perineal complications, bleeding, ileus, fistulas, and death.

Patients were followed at three-month intervals for two years and then at six-month intervals for three years. Evaluations consisted of physical examination, a complete blood count, and blood chemical analysis. Proctoscopy, abdominal ultrasonography, CT of the abdomen, and chest radiography were also used, according to guidelines of the German Cancer Society.[10] Histopathological confirmation of local recurrence (defined as a tumor within the pelvis or the perineal scar) and of distant recurrence was encouraged; acceptable alternative approaches included sequential radiologic studies to detect the enlargement of a mass. The physicians evaluating patients' relapse status were aware of the treatment assignments.

QUALITY CONTROL

A quality-assurance program controlled the information submitted on enrollment forms. Reference institutions for surgery (the Department of Surgery, Medizinische Hochschule Hannover), chemotherapy and radiotherapy (the Departments of Radiation Therapy, University of Erlangen and University of Rostock), and pathology (Institute of Pathology, University of Leipzig) obtained copies of original treatment records and could request any other information to confirm compliance with the protocol. All resection specimens were examined according to a standardized protocol that included Union Internationale contre le Cancer TNM categories and staging groups, the number of examined and involved lymph nodes, and the status of oral, aboral, and circumferential resection margins.[11] The quality of each specimen obtained by total mesorectal excision was not formally assessed; however, the distance from the tumor to the resection margins was recorded.

Table 1. Baseline Characteristics of the 799 Eligible Patients, According to Randomly Assigned Treatment Group.*

Characteristic	Preoperative Chemoradiotherapy (N=405)	Postoperative Chemoradiotherapy (N=394)	P Value
Age — yr			0.35
Median	62	62	
Range	30–76	33–76	
Sex — no. (%)			0.21
Male	286 (71)	262 (66)	
Female	119 (29)	132 (34)	
Clinical tumor category — no. (%)			0.16
T1 or T2	19 (5)	18 (5)	
T3	277 (68)	262 (66)	
T4	23 (6)	10 (3)	
Unknown	86 (21)	104 (26)	
Clinical nodal category — no. (%)			0.88
Node-negative	168 (41)	153 (39)	
Node-positive	217 (54)	202 (51)	
Unknown	20 (5)	39 (10)	
Distance of tumor from anal verge — no. (%)			0.008
<5 cm	157 (39)	117 (30)	
5–10 cm	166 (41)	168 (43)	
>10 cm	47 (12)	69 (18)	
Unknown	35 (9)	40 (10)	

* Because of rounding, not all percentages total 100.

STATISTICAL ANALYSIS

The primary end point was overall survival. The study was designed to have 80 percent power to de-

Table 2. Compliance with the Protocol and Protocol Violations.*

Variable	Preoperative Chemoradiotherapy	Postoperative Chemoradiotherapy	P Value
Randomly assigned — no.	421	402	
Included in full analysis population — no.	405	394	0.12
Requested change in treatment group — no.	9	19	0.05
Included in treated population — no.	415	384	
Received full dose of radiotherapy — no. (%)	380 (92)	206 (54)	<0.001
Received full dose of chemotherapy — no. (%)	369 (89)	193 (50)	<0.001
Did not receive chemoradiotherapy — no. (%)			
Stage I disease	NA	71 (18)	<0.001
Other reason†	1 (<1)	39 (10)	<0.001
Received radiotherapy with modification — no. (%)‡	19 (5)	31 (8)	0.04
Received chemotherapy with modification — no. (%)‡	23 (6)	26 (7)	0.47
Protocol violations — no. (%)§			
Radiotherapy	13 (3)	33 (9)	0.001
Chemotherapy	15 (4)	49 (13)	<0.001
Missing data — no. (%)			
Radiotherapy	2 (<1)	4 (1)	0.36
Chemotherapy	7 (2)	6 (2)	0.89

* NA denotes not applicable.
† Other protocol-specified reasons for not receiving postoperative chemoradiotherapy included intraoperative detection of distant disease and postoperative complications or death.
‡ Modifications included dose reductions because of toxicity or alterations in treatment because of distant disease detected during treatment.
§ The protocol was considered violated when patients declined or erroneously did not receive radiotherapy or chemotherapy or did receive non–protocol-specified radiotherapy or chemotherapy.

tect an absolute difference of 10 percentage points in the five-year overall survival rate, with a two-sided alpha level of 0.05. The sample size required to detect this difference was 340 patients per group. Because an estimated 15 percent 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 were disease-free survival, local and distant recurrences, postoperative complications, acute and long-term toxic effects, and sphincter preservation. All eligible and consenting patients (the full analysis population) were included in the analyses of overall and disease-free survival and the cumulative incidence rates of local and distant recurrences, according to the intention-to-treat principle. End points were measured beginning at the time of randomization. Patients who received any neoadjuvant or adjuvant radiotherapy were assessed for acute and delayed toxic effects according to their actual treatment group.

Chi-square tests were used to compare proportions. Mann–Whitney tests were used to compare quantitative and ordinal variables. Univariate analyses of survival were carried out by the Kaplan–Meier method, and the evaluation of differences was performed with the log-rank test. Data from patients who where alive and free of recurrence or who died without having had a recurrence were censored in the analyses of disease-free survival and recurrence.

The Cox proportional-hazards model was used to calculate hazard ratios and 95 percent confidence intervals. Cumulative incidence was determined according to the method proposed by Breslow and Day.[12] Statistical comparisons of cumulative incidence rates were performed with the use of a Poisson regression model, with the assigned treatment group (according to the intention to treat) as a categorical covariate. A two-sided P value of less than or equal to 0.05 was considered to indicate statistical significance. No interim analyses of efficacy end points were performed.

Table 3. Postoperative Pathological Tumor Stage, Type of Surgery, and Completeness of Resection, According to Actual Treatment Given.*

Variable	Preoperative Chemoradiotherapy (N=415)	Postoperative Chemoradiotherapy (N=384)	P Value
Histopathological finding (%)			<0.001
Complete response	8	0	
TNM stage			
I	25	18	
II	29	29	
III	25	40	
IV	6	7	
Unknown	6	6	
Type of resection (%)			0.45
Low anterior, intersphincteric	69	71	
Abdominoperineal	26	23	
Other	3	2	
Unknown	2	3	
Completeness of local resection (%)			0.69
Complete			
Without distant metastasis	91	90	
With distant metastasis	2	4	
Incomplete†			
Without distant metastasis	3	3	
With distant metastasis	3	4	

* Because of rounding, not all percentages total 100.
† Positive radial margins (defined as direct invasion of the resection margin by tumor cells on microscopical evaluation) were found in 2 percent of the patients in the preoperative-treatment group and in 3 percent of those in the postoperative-treatment group (P=0.68).

RESULTS

PATIENTS

A total of 823 patients from 26 hospitals were randomly assigned to one of the two treatment groups. Randomization was performed according to the double-consent design in the cases of 146 of the 823 patients. Of the 421 patients randomly assigned to preoperative chemoradiotherapy and the 402 randomly assigned to postoperative chemoradiotherapy, 16 and 8 patients, respectively, were not included in the full analysis population because they withdrew consent to participate (5 and 4 patients, respectively) or because, as a result of institutional errors, they did not meet the inclusion criteria: 2 patients in each group had distant metastases at the time of randomization, 1 patient in each group did not have adenocarcinoma, 2 patients in the preoperative-treatment group and 1 in the postoperative-treatment group presented with fixed, inoperable tumors, and 6 patients in the preoperative-treatment group either had a contraindication to fluorouracil or had previously had cancer. For the most part, the baseline characteristics of the 799 patients in the full analysis population were similar in the two groups (Table 1). Significantly more patients in the preoperative-treatment group than in the postoperative-treatment group had tumors located 5 cm or less from the anal verge.

TREATMENT

Of the 405 patients randomly assigned to preoperative chemoradiotherapy and the 394 randomly assigned to postoperative chemoradiotherapy (i.e., the full analysis population), 9 and 19 patients, respectively, requested a change in treatment group (Table 2). Thus, 415 patients were treated according to the preoperative protocol and 384 patients

Table 4. Rates of Sphincter-Sparing Surgery in 194 Patients Determined by the Surgeon before Randomization to Require Abdominoperineal Resection, According to Actual Treatment Given.

Variable	Preoperative Chemoradiotherapy (N=415)	Postoperative Chemoradiotherapy (N=384)	P Value
Abdominoperineal resection deemed necessary — no. (%)	116 (28)	78 (20)	
Sphincter-preserving surgery performed — no./total no. (%)	45/116 (39)	15/78 (19)	0.004

Table 5. Grade 3 or 4 Toxic Effects of Chemoradiotherapy, According to Actual Treatment Given.*

Type of Toxic Effect	Preoperative Chemoradiotherapy (N=399)	Postoperative Chemoradiotherapy (N=237)	P Value
	% of patients		
Acute			
Diarrhea	12	18	0.04
Hematologic effects	6	8	0.27
Dermatologic effects	11	15	0.09
Any grade 3 or 4 toxic effect	27	40	0.001
Long-term			
Gastrointestinal effects†	9	15	0.07
Strictures at anastomotic site	4	12	0.003
Bladder problems	2	4	0.21
Any grade 3 or 4 toxic effect	14	24	0.01

* All patients who received any preoperative or postoperative radiotherapy according to protocol were included in this analysis. Some patients had more than one toxic effect.

† The gastrointestinal effects were chronic diarrhea and small-bowel obstruction. The incidence of small-bowel obstruction requiring reoperation was 2 percent in the preoperative-treatment group and 1 percent in the postoperative-treatment group (P=0.70).

according to the postoperative protocol. In the preoperative-treatment group, 92 percent received the prescribed radiotherapy and 89 percent completed preoperative chemoradiotherapy as planned. In the postoperative-treatment group, 28 percent were excluded from receiving postoperative chemoradiotherapy according to the protocol specifications, either because of stage I disease (18 percent) or because of intraoperatively detected distant metastases or postoperative complications or death (10 percent). Overall, there were modifications in the radiotherapy or chemotherapy regimens, mainly due to toxic effects, in 5 to 8 percent of the patients. Protocol violations occurred more frequently in the postoperative-treatment group and were mainly due to patients' refusal to receive radiotherapy or chemotherapy (Table 2).

HISTOPATHOLOGICAL TUMOR STAGING AND SURGICAL PROCEDURES

After preoperative chemoradiotherapy, there was a significant shift toward earlier TNM stages (P<0.001): 8 percent of the patients in this group had a complete response, according to histopathological examination of the tumor specimen, and only 25 percent (as compared with 40 percent in the postoperative-treatment group) had positive lymph nodes (TNM stage III) (Table 3). Eighteen percent of the patients in the postoperative-treatment group had TNM stage I disease on histopathological examination of their resected specimen; all 18 percent had previously been found to have stage T3 or T4 or node-positive disease on endorectal ultrasonography.

The rates of complete resection and sphincter-

sparing surgery did not differ between the groups when the 799 patients in the full analysis population were considered (Table 3). However, among the 194 patients with tumors that were determined by the surgeon before randomization to require an abdominoperineal excision, a statistically significant increase in sphincter preservation was achieved among patients who received preoperative chemoradiotherapy (Table 4).

POSTOPERATIVE MORBIDITY AND TOXICITY OF CHEMORADIOTHERAPY

In-hospital mortality was 0.7 percent in the preoperative chemoradiotherapy group (3 of the 415 treated patients died while hospitalized) and 1.3 percent in the postoperative-treatment group (5 of the 384 treated patients died while hospitalized; P=0.41). The overall rate of postoperative complications was 36 percent in the preoperative-treatment group and 34 percent in the postoperative-treatment group (P=0.68). The rate of anastomotic leakage of any grade was 11 percent in the preoperative-treatment group and 12 percent in the postoperative-treatment group (P=0.77). The rates of delayed sacral-wound healing (10 percent in the preoperative-treatment group vs. 8 percent in the postoperative-treatment group, P=0.10), postoperative bleeding (3 percent vs. 2 percent, respectively; P=0.50), and ileus (2 percent vs. 1 percent, respectively; P=0.26) did not differ significantly between the groups.

Grade 3 or 4 acute and long-term toxic effects that occurred among patients who received preoperative or postoperative radiotherapy are summarized in Table 5. The overall rates of acute and long-term side effects were lower with the preoperative approach than with the postoperative approach, especially with respect to acute and chronic diarrhea and the development of strictures at the anastomotic site. When the toxicity analyses were performed for all patients, including the 110 patients in the postoperative-treatment group who, for various reasons, received no radiotherapy (Table 2), no significant differences between the two groups were noted (overall rate of acute toxic effects, 25 percent in the preoperative-treatment group vs. 24 percent in the postoperative-treatment group; P=0.78; overall rate of long-term toxic effects, 14 percent vs. 15 percent, respectively; P=0.85).

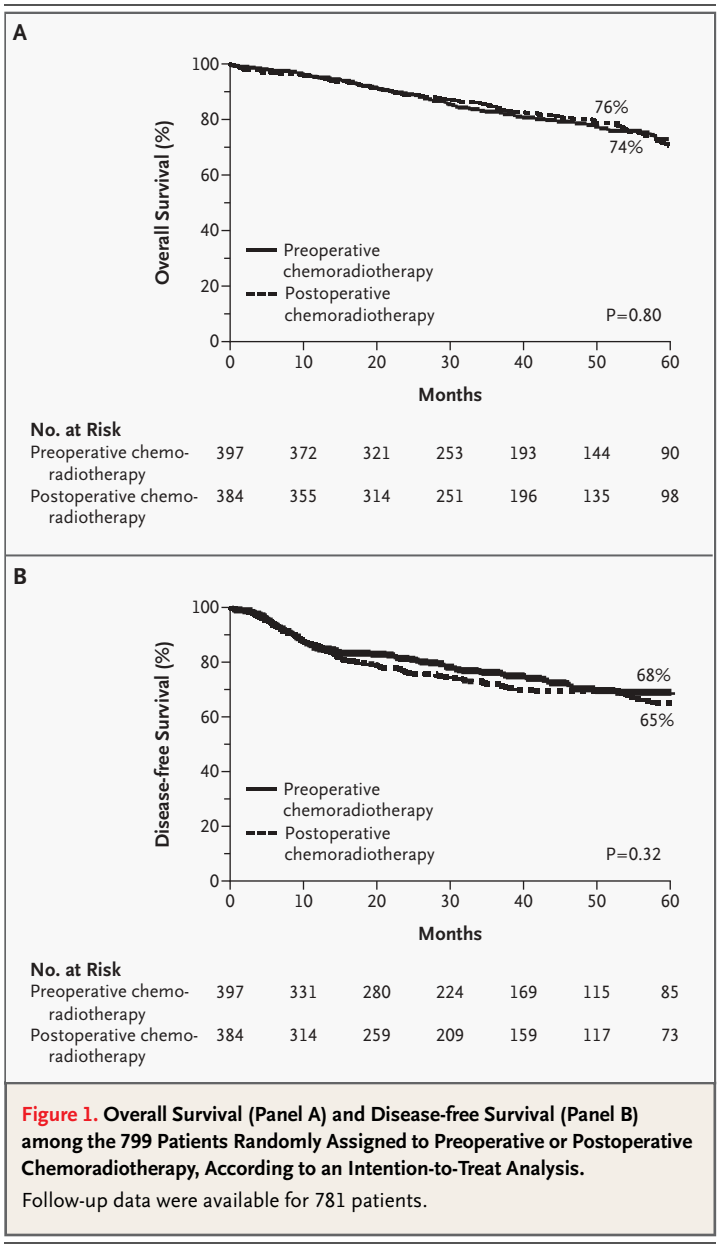

Figure 1. Overall Survival (Panel A) and Disease-free Survival (Panel B) among the 799 Patients Randomly Assigned to Preoperative or Postoperative Chemoradiotherapy, According to an Intention-to-Treat Analysis.

Follow-up data were available for 781 patients.

EVENTS DURING FOLLOW-UP

As of November 2003, surviving patients had been followed for a median of 46 months (range, 3 to 102). Of these 642 patients, 67 percent were followed for at least three years, 48 percent for at least four years, and 32 percent for at least five years. The median follow-up time was 45 months (range, 5 to 101) among the patients assigned to preoperative chemoradiotherapy and 49 months (range, 3 to 102) among those assigned to postoperative chemoradiotherapy; no follow-up data were available for 8 and 10 patients, respectively. Of the 157 deaths that occurred during follow-up, 109 were related to rectal cancer and 35 to other causes; in 13 cases the cause of death was unknown. Local recurrence occurred

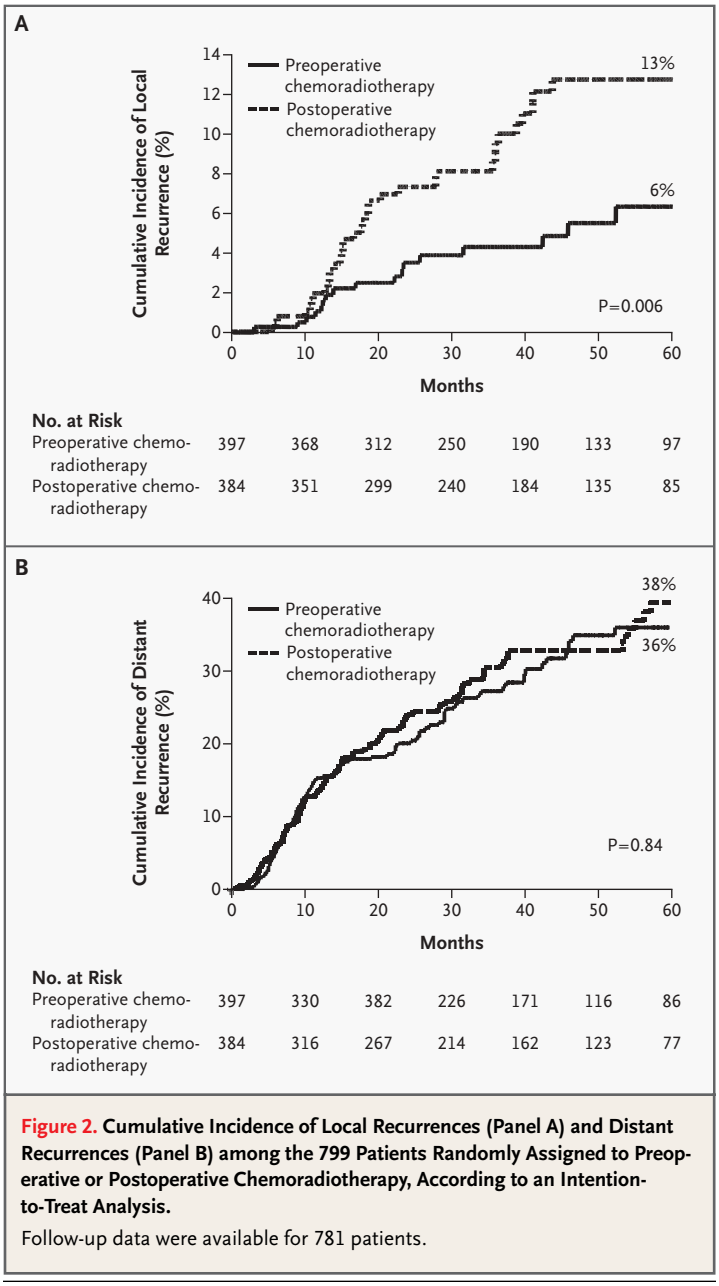

Figure 2. Cumulative Incidence of Local Recurrences (Panel A) and Distant Recurrences (Panel B) among the 799 Patients Randomly Assigned to Preoperative or Postoperative Chemoradiotherapy, According to an Intention-to-Treat Analysis.

Follow-up data were available for 781 patients.

in 53 patients: 15 (28 percent) had local recurrence alone, and 38 (72 percent) also had distant recurrences. A total of 160 patients had only distant recurrences.

OVERALL AND DISEASE-FREE SURVIVAL

In the full analysis population, 102 of the 405 patients assigned to preoperative chemoradiotherapy had a relapse and 77 died. The corresponding outcomes among the 394 patients assigned to postoperative chemoradiotherapy were 111 relapses and 80 deaths. The overall survival at five years was 76 percent in the preoperative-treatment group and 74 percent in the postoperative-treatment group (P=0.80) (Fig. 1A). The hazard ratio for death in the preoperative-treatment group, as compared with the postoperative-treatment group, was 0.96 (95 percent confidence interval, 0.70 to 1.31). The five-year rate of disease-free survival was 68 percent in the preoperative-treatment group and 65 percent in the postoperative-treatment group (P=0.32) (Fig. 1B), and the hazard ratio for disease-free survival in the former group, as compared with the latter, was 0.87 (95 percent confidence interval, 0.67 to 1.14).

LOCAL AND DISTANT RECURRENCES

Of the 405 patients assigned to receive preoperative chemoradiotherapy, local and distant recurrences occurred in 17 and 99 patients, respectively; of the 394 assigned to postoperative chemoradiotherapy, local and distant recurrences occurred in 36 and 99, respectively. The cumulative incidence of local recurrences at five years was 6 percent in the group assigned to preoperative chemoradiotherapy and 13 percent in the group assigned to postoperative chemoradiotherapy (P=0.006) (Fig. 2A). On analysis with a Poisson regression model, the relative risk of local recurrence in the preoperative-treatment group, as compared with the postoperative-treatment group, was 0.46 (95 percent confidence interval, 0.26 to 0.82). The cumulative incidence of distant recurrences at five years was 36 percent in the preoperative-treatment group and 38 percent in the postoperative-treatment group (P=0.84; relative risk, 0.97; 95 percent confidence interval, 0.73 to 1.28) (Fig. 2B).

DISCUSSION

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

with the former approach.[13] Retrospective, nonrandomized studies have also found reduced toxicity with preoperative treatment.[14]

Prospective, randomized trials comparing the efficacy of preoperative chemoradiotherapy with that of standard, postoperative chemoradiotherapy for rectal cancer were initiated in the United States by the RTOG (trial 94-01) and the National Surgical Adjuvant Breast and Bowel Project (protocol R-03).[15] Unfortunately, both studies suffered from low enrollment and were closed prematurely.

In our study, we confirmed that preoperative chemoradiotherapy, given as planned (i.e., without any modification or dose reduction) in most of the patients assigned to this group (89 percent), significantly reduced rates of local failure and acute and long-term toxic effects. Among patients with tumors judged by the surgeon to require an abdominoperineal excision, the rate of sphincter-preserving surgery was more than doubled after preoperative chemoradiotherapy. Postponing surgery for a six-week course of neoadjuvant treatment plus a six-week interval to allow tumor shrinkage and recovery from side effects did not result in an increased rate of surgical complications or an increased incidence of tumor progression.

Our trial was designed to show an absolute difference of 10 percentage points in overall survival between standard postoperative and preoperative chemoradiotherapy. It was based on the hypotheses that starting systemic treatment as early as possible might effectively treat systemic micrometastases and that the combination of chemotherapy and radiotherapy given preoperatively reduces rates of local failure. Although the latter hypothesis was clearly confirmed, no statistically significant difference in the incidence of distant recurrence or in the rates of disease-free or overall survival could be demonstrated. Given that the rate of local recurrence with preoperative chemoradiotherapy and total mesorectal excision was only 6 percent, it is possible that further progress in the prevention of distant recurrences might be accomplished with more effective chemotherapy. Phase 1 and 2 trials of preoperative radiotherapy with concurrent capecitabine and oxaliplatin have been completed by our group.[16] This combination regimen should be tested against standard fluorouracil-based chemoradiotherapy in subsequent trials.

With the increasing use of preoperative treatment in patients with rectal cancer, accurate staging is needed to avoid unnecessary treatment of early-stage tumors. The accuracy of endorectal ultrasonography is reported to be 67 to 93 percent for the assessment of rectal-wall penetration and 62 to 83 percent for the determination of nodal status.[17] In our study, endorectal ultrasonography was mandatory for pretreatment evaluation of the tumor. Eighteen percent of patients in the postoperative-treatment group, determined preoperatively to have tumor penetration through the bowel wall (stage T3 or T4 disease) or lymph-node metastasis, were found to have stage T1 or T2, node-negative tumors (i.e., TNM stage I disease) on pathological examination of the resected specimen. As experience with this technique increases, the accuracy of staging should improve. Moreover, innovative approaches, including three-dimensional endosonography and magnetic resonance imaging, may further improve the accuracy of staging.[18,19]

In conclusion, although no survival benefit was achieved with preoperative as compared with postoperative chemoradiotherapy, we suggest that preoperative chemoradiotherapy is the preferred treatment for patients with locally advanced rectal cancer, given that it is associated with a superior overall compliance rate, an improved rate of local control, reduced toxicity, and an increased rate of sphincter preservation in patients with low-lying tumors.

Supported by a grant (70-587) from Deutsche Krebshilfe.

Dr. Rödel reports having received consulting fees from Roche, Sanofi-Synthelabo, and Merck and lecture fees from Roche.

We are indebted to Petra Lietzau, Karin Zecho, and Sabrina Petsch (all of the Erlangen Tumor Center) for data monitoring and documentation and to Richard Herrmann (Basel) for helpful discussions.

APPENDIX

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