Title

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Permalink

Journal

ISSN

Authors

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et al.

Publication Date

DOI

Supplemental Material

Peer reviewed

Consolidation mFOLFOX6 Chemotherapy After Chemoradiotherapy Improves Survival in Patients With Locally Advanced Rectal Cancer: Final Results of a Multicenter Phase II Trial

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For the Timing of Rectal Cancer Response to Chemoradiation Consortium

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BACKGROUND: Adding modified FOLFOX6 (folinic acid, fluorouracil, and oxaliplatin) after chemoradiotherapy and lengthening the chemoradiotherapy-to-surgery interval is associated with an increase in the proportion of rectal cancer patients with a pathological complete response.
OBJECTIVE: The purpose of this study was to analyze disease-free and overall survival.
DESIGN: This was a nonrandomized phase II trial. **SETTINGS:** The study was conducted at multiple institutions.

PATIENTS: Four sequential study groups with stage II or III rectal cancer were included.

INTERVENTION: All of the patients received 50 Gy of radiation with concurrent continuous infusion of fluorouracil for 5 weeks. Patients in each group received 0, 2, 4, or 6 cycles of modified FOLFOX6 after chemoradiation and before total mesorectal excision. Patients were recommended to receive adjuvant chemotherapy after surgery to complete a total of 8 cycles of modified FOLFOX6.

MAIN OUTCOME MEASURES: The trial was powered to detect differences in pathological complete response, which was reported previously. Disease-free and overall survival are the main outcomes for the current study.

RESULTS: Of 259 patients, 211 had a complete followup. Median follow-up was 59 months (range, 9–125 mo). The mean number of total chemotherapy cycles differed among the 4 groups (p = 0.002), because one third of patients in the group assigned to no preoperative FOLFOX did not receive any adjuvant chemotherapy. Disease-free survival was significantly associated with study group, ypTNM stage, and pathological complete response (p = 0.004, <0.001, and 0.001). A secondary analysis including only patients who received ≥1 cycle of FOLFOX still showed differences in survival between study groups (p = 0.03).

LIMITATIONS: The trial was not randomized and was not powered to show differences in survival. Survival data were not available for 19% of the patients.

CONCLUSIONS: Adding modified FOLFOX6 after chemoradiotherapy and before total mesorectal excision increases compliance with systemic chemotherapy and disease-free survival in patients with locally advanced rectal cancer. Neoadjuvant consolidation chemotherapy may have benefits beyond increasing pathological complete response rates.

See Video Abstract at http://links.lww.com/DCR/A739.

The current treatment for patients with locally advanced rectal cancer consists of neoadjuvant fluorouracil-based chemoradiotherapy (CRT) followed by total mesorectal excision (TME) and postoperative systemic chemotherapy.[1,2] Although this trimodal therapy provides excellent local tumor control and long-term survival,[1,3,4] it is associated with significant morbidity and long-term impairment of function that compromise the quality of life.[5]

Meanwhile, rectal cancer response to neoadjuvant CRT is variable. Some tumors undergo minimal regression, although others seem to be fully eradicated by CRT.[6] A complete tumor response to CRT has been associated with improved local and systemic tumor control and long-term survival.[7,8] These findings call into question the

added value of surgery in patients who achieve a clinical complete response (cCR) to CRT. Preliminary data suggest that a watch-and-wait approach may be safe for patients who achieve a cCR after neoadjuvant therapy.[9]

The proportion of patients achieving complete response after standard CRT is relatively low, ranging from 8% to 24%.[8] Increasing the rate of tumor response, and therefore expanding the number of rectal cancer patients who could potentially benefit from a watch-and-wait strategy, has been an active area of research for years. The initiatives include radiation dose escalation,[10] intensification of neoadjuvant treatment with induction or consolidation chemotherapy,[11–17] and delaying the time of assessing tumor response after completion of neoadjuvant therapy.[18] However, the effects of these approaches on tumor response and long-term survival are still controversial.[10–18]

The Timing of Rectal Cancer Response to Chemoradiation trial was designed to investigate the effect of adding an increasing number of cycles mFOLFOX6 (folinic acid, fluorouracil, and oxaliplatin) after CRT and lengthening the CRT-to-surgery interval on the rate of pathological complete response (pCR) in patients with locally advanced rectal cancer.[19] The results showed that adding systemic chemotherapy after CRT and delaying surgery increased the pCR rate without increasing surgical complications. In the current study, we analyzed the possible long-term benefit of neoadjuvant chemotherapy for disease-free survival (DFS) and overall survival (OS) in patients in the Timing of Rectal Cancer Response to Chemoradiation trial.

PATIENTS AND METHODS

Patients

The study was a multicenter, open-label, nonrandomized phase II trial (NCT00335816 on ClinicalTrials.gov). Details of the study design and methods were published previously.[19] Eligible patients were ≥18 years of age, with clinical stage II (T3–4, N0) or III (any T, N1–2) invasive rectal adenocarcinoma within 12 cm from the anal verge. Endorectal ultrasonography or MRI was used for staging. Patients were required to have an Eastern Collaborative Oncology Group performance status score of 0 or 1 or a comparable Karnofsky score. Patients with a history of pelvic radiation, polyposis syndromes, IBD, recurrent rectal cancer, metastatic disease, other primary tumors within the previous 5 years, substantial cardiac disease, neurologic disease, or renal, hepatic, or bone marrow dysfunction were ineligible.

A central institutional review board and the institutional review boards at each participating institution approved the study protocol. The Memorial Sloan Kettering Cancer Center was responsible for overseeing all of the fiscal and administrative arrangements with the consortium. Patients provided written informed consent for the outcomes included in the original version of the study protocol. The original protocol was amended to include DFS and OS as secondary outcomes after accrual had already started. Long-term follow-up data could be collected only for patients who provided consent for these survival analyses.

Treatment

The trial consisted of 4 sequential study groups (SGs). The protocol schema is shown in Supplemental Figure 1 (http://links.lww.com/DCR/A740). Patients in SG1 underwent fluorouracil-based CRT and TME. Patients in SG2 to SG4 received 2, 4, or 6 cycles of mFOLFOX6 between CRT and TME. Patients in all of the SGs were recommended to receive additional adjuvant chemotherapy to complete a total of 8 cycles of mFOLFOX6. Details of the CRT and mFOLFOX regimens were reported previously.[19] The study recommended delivering adjuvant chemotherapy after surgery to complete a 4-month course of FOLFOX as recommended by the guidelines of the National Comprehensive Cancer Network.[20] Because the initial study design did not include collecting information on adjuvant chemotherapy or long-term survival, some patients in SG1 were not consented for the survival analysis and were not included in this study. Surveillance was done according to the guidelines of the National Comprehensive Cancer Network.[20]

FIGURE 1. Inclusion and exclusion of patients.
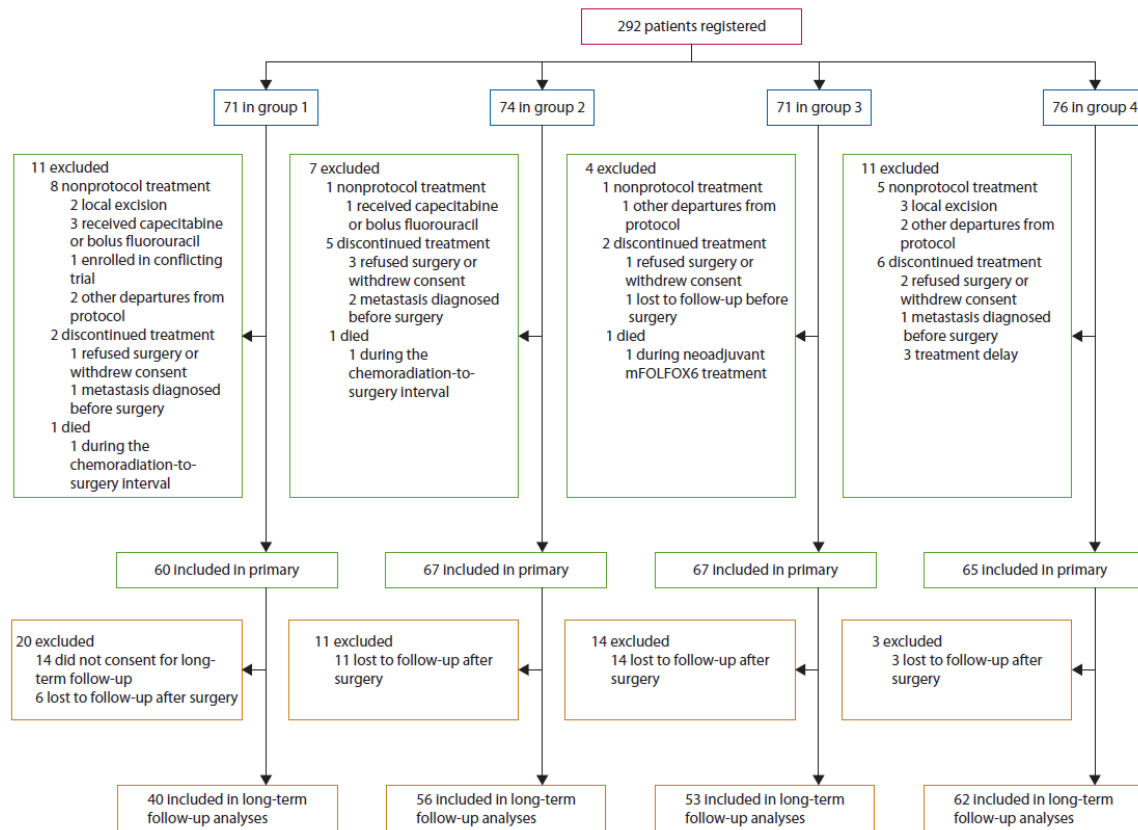
Outcomes

The primary end point of the study, the proportion of patients achieving pCR in each SG, has been reported previously.[19] Here, we report DFS, counting local relapse, distant metastasis, or death as an event, whichever occurred first. We also report OS, counting

death from any cause as an event. Time to event was calculated from the first day of CRT.

Statistical Analysis

This phase II study was powered to evaluate pCR in sequentially accrued SGs.[19] DFS and OS were secondary end points. All of the comparisons between SGs were based on intention to treat. A secondary survival analysis was done to exclude patients who did not receive any systemic chemotherapy before or after TME. Descriptive statistics were used to summarize the data overall and by SG. Comparisons were made using ANOVA or the χ^2 test. DFS and OS were analyzed separately using the Kaplan–Meier method and log-rank tests. A multivariate Cox proportional hazards model was fit to each time-to-event end point. These models were based on results from univariate analyses and ensured that 2 highly correlated variables were not simultaneously included in a model. P values <0.05 were deemed statistically significant. All of the analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.1.1 software (https://www.r-project.org/).

RESULTS

A total of 259 eligible patients accrued between March 24, 2004, and November 16, 2012, were included in the primary analysis,[19] but 48 patients (20 in SG1, 11 in SG2, 14 in SG3, and 3 in SG4) were excluded from the survival analyses for various reasons (Fig. 1). We found no differences in demographics, tumor characteristics, or pCR rates between the patients who were included in the survival analyses (n = 211) and the patients who were excluded (n = 48; Supplemental Table 1).

Table 1 lists the patient demographics and tumor characteristics by SG for the 211 patients included in the survival analyses. SG1 had a higher mean age compared with SG2 to SG4, whereas sex, Eastern Collaborative Oncology Group performance status, clinical stage, and distance from the anal verge were similar between the SGs. Early results on pathological response, neoadjuvant chemotherapy–related adverse events, surgery, and postoperative complications were published previously.[19]

TABLE 1. Baseline patient and tumor characteristics

Age, mean ± SD, y	61 ± 13	54 ± 10	56 ± 12	58 ± 9	0.02[a]
Sex, n (%)					0.82
Men	24 (60)	32 (57)	29 (55)	39 (63)	
Women	16 (40)	24 (43)	24 (45)	23 (37)	
ECOG performance status, n (%)					0.09
0	38 (95)	49 (88)	44 (83)	48 (77)	
1	2 (5)	7 (13)	9 (17)	14 (23)	
cT classification, n (%)					0.49
T2	1 (3)	4 (7)	7 (13)	5 (8)	
T3	38 (95)	51 (91)	43 (81)	52 (84)	
T4	1 (3)	1 (2)	3 (6)	3 (5)	
Tx	0	0	0	2 (3)	
cN classification, n (%)					0.07
N0	11 (28)	9 (16)	12 (23)	18 (29)	
N1	27 (68)	44 (79)	34 (64)	34 (55)	
N2	1 (3)	3 (5)	7 (13)	10 (16)	
Nx	1 (3)	0	0	0	
Clinical stage, n (%)					0.37
II	11 (28)	9 (16)	12 (23)	18 (29)	
III	29 (73)	47 (84)	41 (77)	44 (71)	
Distance from anal verge, mean ± SD, cm	6.5 ± 3.2	6.5 ± 3.2	7.4 ± 3.0	6.6 ± 3.3	0.43
Procedure, n (%)					0.19
LAR	30 (75)	45 (80)	41 (77)	41 (66)	
APR	10 (25)	11 (20)	12 (23)	21 (34)	
Ileostomy	24/30	38/45	38/41	35/41	0.74
ypT classification, n (%)					0.84
T0	9 (23)	17 (30)[b]	14 (26)	23 (37)	
Tis	2 (5)	1 (2)	1 (2)	1 (2)	
T1	2 (5)	4 (7)	5 (9)	3 (5)	
T2	10 (25)	18 (32)	13 (25)	15 (24)	
T3	17 (43)	14 (25)	19 (36)	18 (29)	
T4	0	2 (4)	1 (2)	2 (3)	
ypN classification, n (%)					0.06
N0	30 (75)	41 (73)	45 (85)	49 (79)	
N1	4 (10)	9 (16)	7 (13)	12 (19)	
N2	6 (15)	6 (11)	1 (2)	1 (2)	
ypTNM stage, n (%)					0.61
0	10 (25)	16 (29)	15 (28)	24 (39)	
I	11 (28)	17 (30)	16 (30)	14 (23)	
II	9 (23)	8 (14)	14 (26)	10 (16)	
III	10 (25)	15 (27)	8 (15)	14 (23)	
Pathological complete response, n (%)					0.04[a]
Yes	8 (20)	13 (23)	14 (26)	23 (37)	
No	32 (80)	43 (77)	39 (74)	39 (63)	

SG = study group; ECOG = Eastern Collaborative Oncology Group; LAR = low anterior resection; APR = abdominoperineal resection.

[a]Data are significant.

[b]Three patients had residual adenoma after neoadjuvant chemoradiotherapy.

Table 2 lists the data on chemotherapy received in different SGs. Consistent with the trial design, the mean number of neoadjuvant mFOLFOX6 cycles received per patient increased across SGs. Also consistent with the study design, the mean interval from completion of CRT to TME increased across SGs, from 8.6 ± 4.5 weeks in SG1 to 12.9 ± 4.5 weeks in SG2, 15.4 ± 2.4 weeks in SG3, and 19.3 ± 4.1 weeks in SG4. Adjuvant chemotherapy information was missing for 17 patients (8%): 8 in SG1, 5 in SG2, 2 in SG3, and 2 in SG4. Of the 194 patients with complete information on adjuvant chemotherapy, 130 patients (67%) started adjuvant chemotherapy. Although the study recommended FOLFOX as the preferred postoperative adjuvant chemotherapy, some patients received different treatment regimens, including FOLFOX (116 patients), fluorouracil with folinic acid (5 patients), FOLFIRI (folinic acid, fluorouracil, and irinotecan; 3 patients), XELOX (capecitabine and oxaliplatin; 3 patients), capecitabine (2 patients), or oxaliplatin (1 patient). The remaining 64 patients (33%) did not receive any adjuvant chemotherapy because of postoperative complications, adverse reactions to

neoadjuvant chemotherapy, and/or patient refusal. The mean number of total chemotherapy cycles (neoadjuvant and adjuvant) per patient differed significantly among the SGs, because 31% of patients in SG1 did not receive any adjuvant chemotherapy as planned (p = 0.002; Table 2).

TABLE 2. Chemotherapy by SG

| | Neoadjuvant chemotherapy | | Adjuvant chemotherapy | | Any chemotherapy | |
SG (n)	No. of patients (%)	No. of cycles[a]	No. of patients (%)[b]	No. of cycles[a]	No. of patients (%)[b]	Total no. of cycles[a]
SG1 (40)	NA	0	22 (69)	4.9±4.4	22 (69)	4.9±4.4
SG2 (56)	50 (89)	1.8±0.7	41 (80)	5.5±3.4	51 (100)	7.3±3.4
SG3 (53)	50 (94)	3.6±1	34 (67)	3.0±2.6	51 (100)	6.5±2.4
SG4 (62)	54 (87)	5.1±2	33 (55)	1.9±2.4	58 (97)	7.1±2.4

NA = not available; SG = study group.
[a]Data show mean ± SD.
[b]Data on adjuvant chemotherapy were not available for 17 patients: 8 in SG1, 5 in SG2, 2 in SG3, and 2 in SG4. Therefore, the percentages are based on the total number of patients with complete data on adjuvant chemotherapy in each SG.

With a median follow-up of 59 months (range, 9–125 mo), a total of 42 patients (20%) experienced tumor recurrence (13 [6%] local, 39 [18%] distant, and 10 [5%] both local and distant), 21 patients died from rectal cancer, and 5 patients died from causes unrelated to rectal cancer. Only 5 patients (2%) had a positive circumferential resection margin. Age, sex, clinical stage, and sphincter-preserving surgery were not correlated with DFS or OS. ypTNM stage was associated with both DFS and OS (p < 0.0001; Fig. 2 and Table 3). Of the 211 patients, 58 (27.5%) had a pCR. Patients with a pCR had higher rates of DFS (p = 0.0001) and OS (p = 0.005) than patients without a pCR (Fig. 2 and Table 3). DFS differed significantly between the SGs (p = 0.004; Fig. 3 and Table 3) because of a lower DFS rate in SG1 than in SG2 to SG4. There were no differences in DFS rates among SG2, SG3, and SG4 (Fig. 3). OS did not differ between the SGs (p = 0.37; Fig. 3 and Table 3). A multivariable Cox regression model found that both ypTNM and SG were independently correlated with DFS (p < 0.0001 and p = 0.002; Table 4).

FIGURE 2. Kaplan–Meier curves of disease-free survival (DFS) and overall survival (OS) are shown, with numbers of subjects at risk indicated. A and B, DFS and OS in relation to ypTNM stage. C and D, DFS and OS in relation to pathological complete response (pCR).
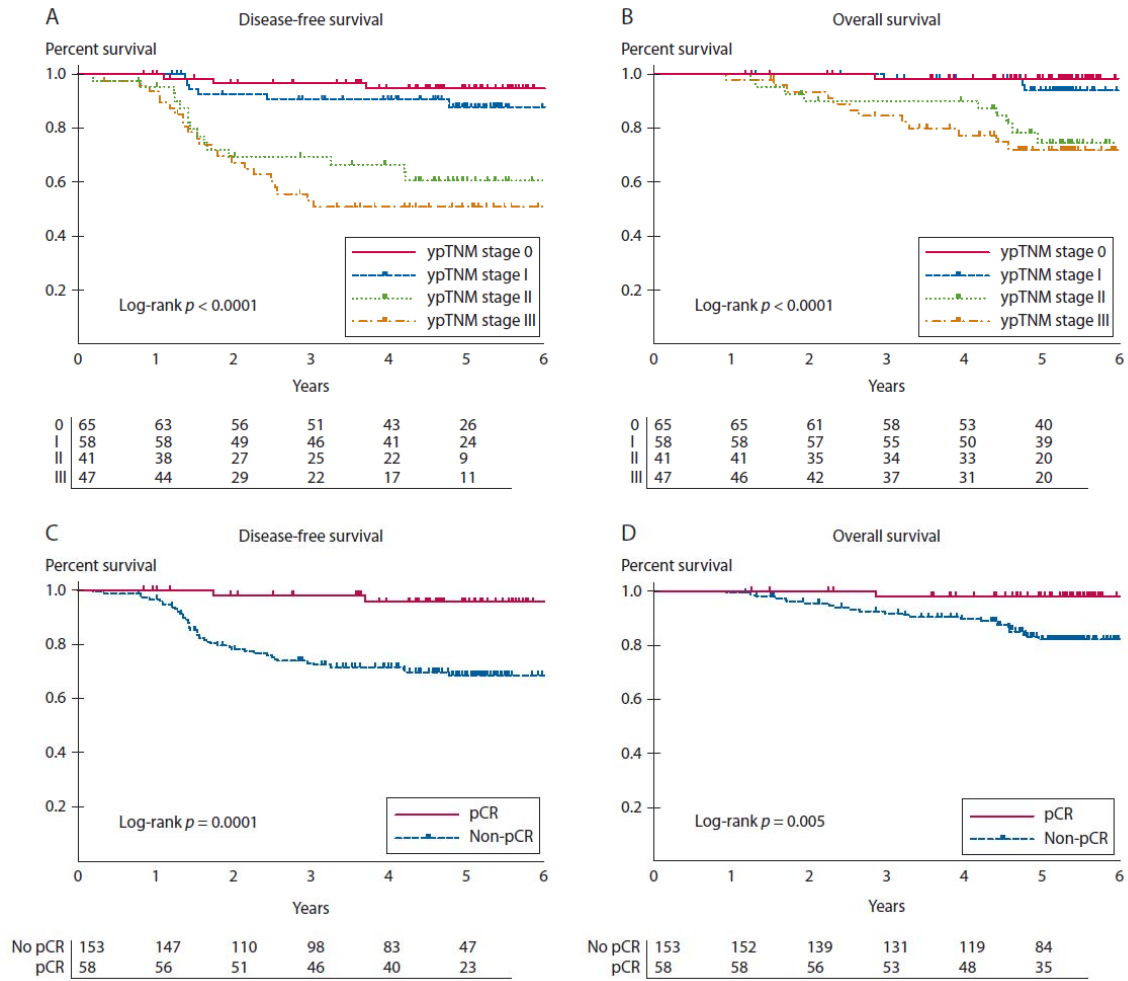

A — Disease-free survival

	0	1	2	3	4	5
0	65	63	56	51	43	26
I	58	58	49	46	41	24
II	41	38	27	25	22	9
III	47	44	29	22	17	11

B — Overall survival

	0	1	2	3	4	5
0	65	65	61	58	53	40
I	58	58	57	55	50	39
II	41	41	35	34	33	20
III	47	46	42	37	31	20

C — Disease-free survival

	0	1	2	3	4	5
No pCR	153	147	110	98	83	47
pCR	58	56	51	46	40	23

D — Overall survival

	0	1	2	3	4	5
No pCR	153	152	139	131	119	84
pCR	58	58	56	53	48	35

FIGURE 3. Kaplan–Meier curves of disease-free survival (DFS) and overall survival (OS) are shown in different study groups (SGs), with numbers of subjects at risk indicated. SG1, CRT + TME; SG2, CRT + mFOLFOX6 (2 cycles) + TME; SG3, CRT + mFOLFOX6 (4 cycles) + TME; SG4,CRT + mFOLFOX6 (6 cycles) + TME. CRT = chemoradiotherapy; TME = total mesorectal excision.
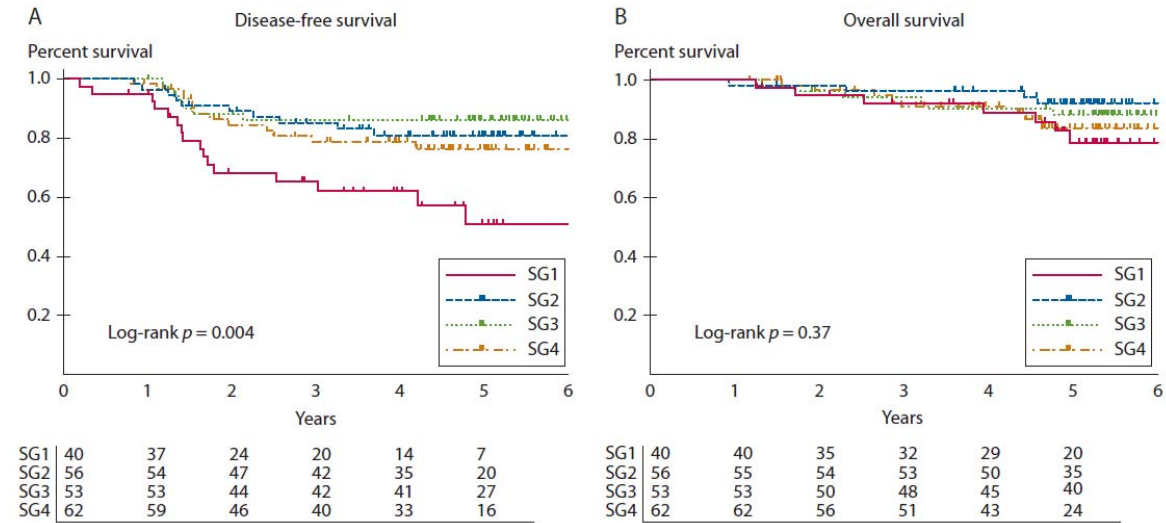

TABLE 3. Univariable analysis of survival

| | | 5-y DFS | | 5-y OS | |
Variable	No. of patients (%)	% (95% CI)	p	% (95% CI)	p
Clinical stage					
II	50 (24)	77 (60–87)	0.58	89 (74–95)	0.57
III	161 (76)	76 (68–82)		86 (79–91)	
Procedure					
LAR	157 (74)	77 (69–83)	0.80	89 (82–93)	0.28
APR	54 (26)	73 (57–84)		81 (66–90)	
ypTNM					
0	65 (31)	94 (83–98)	<0.0001	98 (89–100)	<0.0001
I	58 (27)	88 (74–94)		94 (82–98)	
II	41 (19)	60 (42–74)		75 (56–86)	
III	47 (22)	51 (35–64)		72 (55–83)	
Pathological complete response					
No	153 (73)	69 (60–76)	0.0001	82 (75–88)	0.005
Yes	58 (27)	96 (83–99)		98 (88–100)	
Total number of chemotherapy cycles[a]					
≤4 cycles	49 (25)	73 (61–84)	0.9	87 (73–94)	0.81
>4 cycles	145 (75)	78 (69–84)		87 (80–92)	
Study group					
SG1	40 (19)	50 (30–68)	0.004	79 (60–89)	0.37
SG2	56 (27)	81 (67–89)		92 (81–97)	
SG3	53 (25)	86 (73–93)		88 (76–95)	
SG4	62 (29)	76 (62–85)		84 (70–92)	
Trial arm					
Control (SG1)	40 (19)	50 (30–68)	0.0005	79 (60–89)	0.20
Experimental (SG2–SG4)	171 (81)	81 (74–86)		88 (82–92)	

DFS = disease-free survival; OS = overall survival; LAR = low anterior resection; APR = abdominoperineal resection; SG = study group.
[a]Only patients with complete adjuvant chemotherapy data (n = 194) were included. A cutoff of 4 cycles was used because it represents 50% of the recommended total number of cycles. The total number of cycles did not affect survival with different quartile cutoff numbers.

TABLE 4. Multivariable analysis of disease-free survival

Variable	HR (95% CI)	p
Study group		
SG1	1	0.002
SG2	0.30 (0.13–0.67)	
SG3	0.23 (0.10–0.58)	
SG4	0.40 (0.19–0.84)	
ypTNM stage		
0	1	<0.0001
I	2.10 (0.52–8.40)	
II	9.80 (2.83–33.93)	
III	13.39 (3.99–44.91)	

The overall p values were based on a type III test.
SG = study group.

A total of 182 (94%) of the 194 patients with complete systemic chemotherapy data received ≥1 chemotherapy cycle as consolidation chemotherapy after CRT, as adjuvant chemotherapy after TME, or as both. Twelve patients (6%) did not receive any chemotherapy cycles after CRT: 10 patients in SG1 and 2 in SG4. Patients who did not receive any chemotherapy cycles had reduced DFS compared with those who received ≥1 chemotherapy cycle (p = 0.02; Supplemental Figure 2.

To investigate whether the differences in DFS among SGs were exclusively attributable to compliance with chemotherapy, we performed a secondary survival analysis only for patients who received any systemic chemotherapy after CRT (n = 182). The mean numbers of chemotherapy (neoadjuvant and/or adjuvant) cycles were not different across the 4 SGs (7 ± 3 cycles in SG1, 7 ± 3 cycles in SG2, 7 ± 2 cycles in SG3, and 7 ± 2 cycles in SG4; p = 0.31). SG1 still had worse DFS compared with SG2 to SG4 within the subset of patients who received ≥1 chemotherapy cycle after CRT (p = 0.03; Fig. 4).

FIGURE 4. Kaplan–Meier curves of disease-free survival, with numbers of subjects at risk shown in different study groups (SGs) for patients who received ≥1 chemotherapy cycle, either as consolidation chemotherapy after chemoradiotherapy (CRT), as adjuvant chemotherapy after total mesorectal excision (TME), or both. SG1, CRT + TME + ≥1 cycle of adjuvant chemotherapy; SG2, CRT + mFOLFOX6 (2 cycles) + TME ± adjuvant chemotherapy; SG3, CRT + mFOLFOX6 (4 cycles) + TME ± adjuvant chemotherapy; SG4, CRT + mFOLFOX6 (6 cycles) + TME ± adjuvant chemotherapy.

	0	1	2	3	4	5
SG1 ≥1 cycles	22	21	19	15	12	8
SG2 ≥1 cycles	51	51	49	45	41	22
SG3 ≥1 cycles	51	51	47	44	42	27
SG4 ≥1 cycles	58	58	50	45	36	18
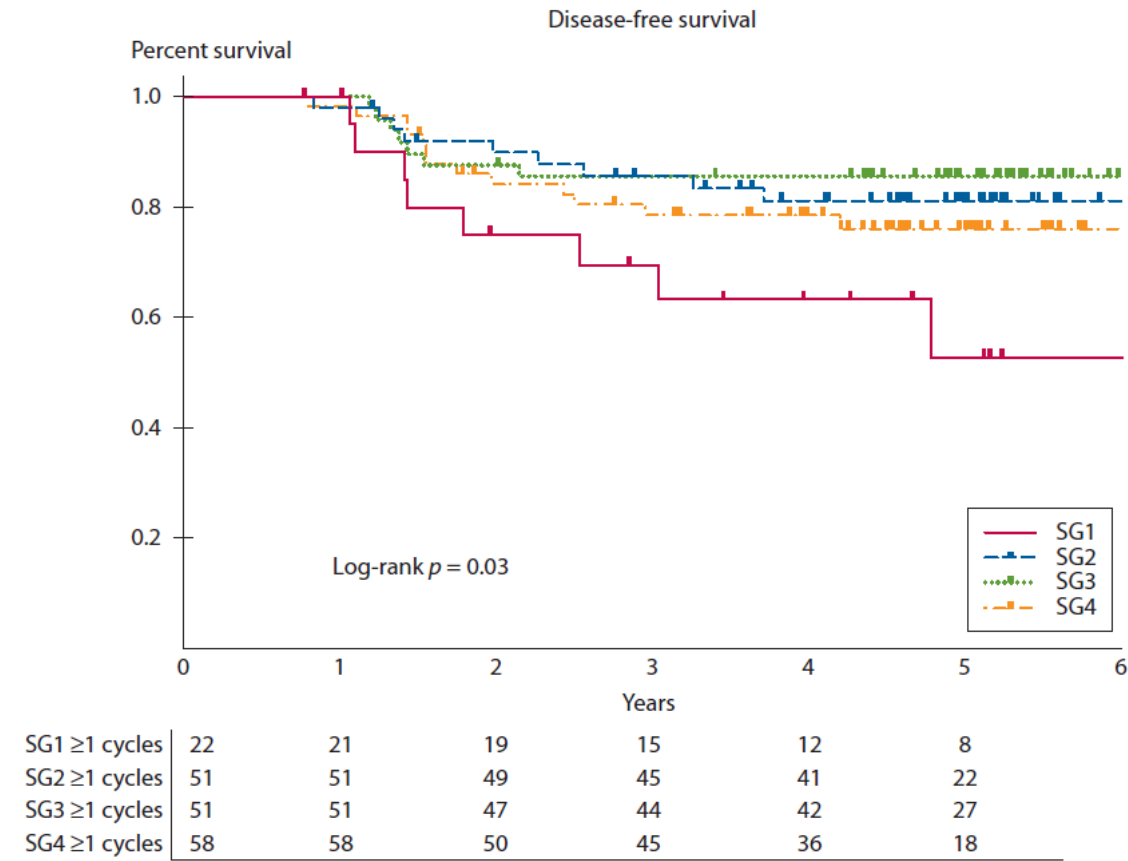
DISCUSSION

The results of this phase II trial indicate that adding neoadjuvant mFOLFOX6 after CRT and increasing the time interval between CRT and surgery not only increases the rate of pCR response but also improves DFS. The study also shows that the proportion of patients receiving any systemic chemotherapy and the number of cycles of chemotherapy were higher for the SGs scheduled to receive chemotherapy before surgery (p = 0.002). This could be explained by the fact that 31% of patients in SG1 did not receive any adjuvant chemotherapy. This rate is similar to the proportion of patients not receiving any scheduled adjuvant chemotherapy in phase III rectal cancer trials.[21,22]

   Lower compliance with adjuvant chemotherapy could explain at least in part the differences in survival between SGs.[23] However, our study also shows that the differences in DFS between SGs persisted when patients who received no systemic chemotherapy after CRT were excluded. Because the mean numbers of total chemotherapy cycles were similar in all of the SGs in this subset of patients, our data

suggest that delivering systemic chemotherapy after CRT and before surgery may be more effective than conventional postoperative chemotherapy beyond compliance with the planned regimen.

Our study also confirms previous observations that pCR is a strong predictor of survival and that ypTNM stage is also associated with survival in multivariable analysis.[7,8] Considering the close relationship between SG and pCR, we were surprised to find no differences in survival in SG2 to SG4. However, the design of the Timing of Rectal Cancer Response to Chemoradiation trial did not allow for determination of whether the increase in pCR observed in an SG was secondary to the lengthening of the CRT-to-surgery interval or the number of cycles of FOLFOX added during the waiting period. Although our current results could be interpreted as an indication that pCR depends more on the CRT-to-surgery interval and that survival depends more on adding some cycles of FOLFOX during the waiting period, it is possible that the differences in pCR between groups were too small to impact survival.

Only 1 previous study reported long-term outcomes in patients with rectal cancer treated with CRT and consolidation chemotherapy. That retrospective study included patients with clinically staged T3 rectal cancer treated with a standard neoadjuvant regimen (50.4 Gy of radiation and 2 cycles of infusional fluorouracil/leucovorin) and an extended neoadjuvant regimen (54 Gy of radiation and 3 cycles of infusional fluorouracil/leucovorin, followed by 3 additional cycles of fluorouracil/leucovorin).[14] The study found no difference in distant metastasis–free survival between the standard-regimen group and the extendedregimen group. However, the doses of infusional fluorouracil used during and after radiation were significantly lower than in our trial. Specifically, the total dose of fluorouracil scheduled after CRT was less than one half of the dose scheduled during a single cycle of FOLFOX. In addition, the study did not use oxaliplatin after CRT, whereas oxaliplatin is now commonly combined with fluorouracil in neoadjuvant or adjuvant chemotherapy regimens for locally advanced rectal cancer.[23] Finally, tumors in the extended-regimen group were larger than and twice as likely to have nodal metastasis as tumors in the standardregimen group.

Few studies have reported survival outcomes in patients treated with short-course radiation (SCR) and consolidation chemotherapy for locally advanced rectal cancer. Myerson et al[15] found that a regimen of 5 fractions of pelvic radiation (5 Gy/day for 5 consecutive days) followed by 4 cycles of FOLFOX resulted in a 25% pCR rate and an 87% rate of absence of disease relapse after a median follow-up of 30 months. A subsequent study from the same institution compared the outcomes of patients treated with total neoadjuvant therapy (5 Gy/day for 5 consecutive days followed by 4 cycles of FOLFOX) and patients treated with standard CRT (45 Gy of radiation in 25 fractions with concurrent fluorouracil or capecitabine and scheduled adjuvant FOLFOX).[16] Similar to our study, patients who underwent total neoadjuvant therapy received more cycles of chemotherapy, achieved higher pCR rates (28% vs 16%), and had a higher rate of 3-year DFS (85% vs 68%) than matched control subjects treated with CRT. Although the dose and fractionation of radiation were different, these studies lend support to the idea that delivering chemotherapy after radiation improves tumor response and DFS.

In a recently completed Polish Colorectal Study Group trial, patients with cT3 or cT4 rectal cancer were randomly assigned to either preoperative 5 × 5 Gy irradiation followed by 3 cycles of FOLFOX-4 or 50.4 Gy of radiation in 28 fractions of 1.8 Gy each

concomitantly with oxaliplatin, boluses of fluorouracil, and folinic acid.[17] These regimens were chosen to ensure equivalent treatment time and interval from initiation of radiation to surgery. The proportion of patients with an R0 resection or a pCR was greater among patients who received SCR and consolidation chemotherapy than among patients who received long-course radiation and concomitant chemotherapy, but the differences did not reach statistical significance. Toxicity was lower and the OS rate was higher in patients who received SCR and consolidation chemotherapy. Although the cumulative rates of local failure, distant failure, and death from noncancer-related causes at 3 years were similar between groups, cumulative incidence of death in patients with tumor relapse was lower in the group treated with SCR and consolidation chemotherapy than in the group treated with long-course radiation and concomitant chemotherapy (23% vs 31%; p = 0.049). The reasons for those differences were unclear, and the authors indicated that a longer follow-up was needed to clarify the issue. The ongoing phase III Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation trial, with patients randomly assigned to either SCR and consolidation chemotherapy before TME or CRT, TME, and adjuvant chemotherapy, will provide additional information about the effects of consolidation chemotherapy on tumor response and patient survival.

The strengths of our study include its prospective design with predefined inclusion and exclusion criteria and uniform CRT in all SGs. Among the limitations are the fact that, because the study was powered to detect differences in pCR rates, it may have been underpowered to detect differences in survival between SGs. Patient demographics and tumor characteristics were similar in all of the SGs, but because of the lack of randomization, the possibility of selection bias between SGs cannot be completely excluded. Other potential limitations are the lack of data on MRI-identified circumferential resection margins, MRI-identified extramural venous invasion, TME quality, and lymphatic or perineural invasion (MRI was not routinely used for locoregional staging of rectal cancer at the time the study opened to accrual, TME procedures in all of the groups were performed by the same highly experienced surgeons, and lymphatic and perineural invasion cannot be reliably detected in pretreatment biopsies). Lastly, almost one third of the patients in SG1 were not consented for survival analysis and could not be included. Other patients were excluded for a variety of reasons. Although patient demographics and tumor characteristics did not differ between patients who were included and patients who were excluded, the impact of the exclusion on the study outcomes cannot be fully ascertained.

CONCLUSIONS

The findings of our study indicate that adding neoadjuvant consolidation chemotherapy after CRT is a safe approach that can lead to higher pCR rates, increased compliance with systemic chemotherapy regimens, and longer DFS. This neoadjuvant regimen may be particularly attractive for patients with very distal rectal cancer who may be interested in organ preservation via a watch-and-wait approach.

ACKNOWLEDGMENTS

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