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Effect of More vs Less Frequent Follow-up Testing on Overall and Colorectal Cancer–Specific Mortality in Patients With Stage II or III Colorectal Cancer

The COLOFOL Randomized Clinical Trial

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IMPORTANCE Intensive follow-up of patients after curative surgery for colorectal cancer is common in clinical practice, but evidence of a survival benefit is limited.

OBJECTIVE To examine overall mortality, colorectal cancer–specific mortality, and colorectal cancer–specific recurrence rates among patients with stage II or III colorectal cancer who were randomized after curative surgery to 2 alternative schedules for follow-up testing with computed tomography and carcinoembryonic antigen.

DESIGN, SETTING, AND PARTICIPANTS Unblinded randomized trial including 2509 patients with stage II or III colorectal cancer treated at 24 centers in Sweden, Denmark, and Uruguay from January 2006 through December 2010 and followed up for 5 years; follow-up ended on December 31, 2015.

INTERVENTIONS Patients were randomized either to follow-up testing with computed tomography of the thorax and abdomen and serum carcinoembryonic antigen at 6, 12, 18, 24, and 36 months after surgery (high-frequency group; n = 1253 patients) or at 12 and 36 months after surgery (low-frequency group; n = 1256 patients).

MAIN OUTCOMES AND MEASURES The primary outcomes were 5-year overall mortality and colorectal cancer–specific mortality rates. The secondary outcome was the colorectal cancer–specific recurrence rate. Both intention-to-treat and per-protocol analyses were performed.

RESULTS Among 2555 patients who were randomized, 2509 were included in the intention-to-treat analysis (mean age, 63.5 years; 1128 women [45%]) and 2365 (94.3%) completed the trial. The 5-year overall patient mortality rate in the high-frequency group was 13.0% (161/1253) compared with 14.1% (174/1256) in the low-frequency group (risk difference, 1.1% [95% CI, –1.6% to 3.8%]; $P = .43$). The 5-year colorectal cancer–specific mortality rate in the high-frequency group was 10.6% (128/1248) compared with 11.4% (137/1250) in the low-frequency group (risk difference, 0.8% [95% CI, –1.7% to 3.3%]; $P = .52$). The colorectal cancer–specific recurrence rate was 21.6% (265/1248) in the high-frequency group compared with 19.4% (238/1250) in the low-frequency group (risk difference, 2.2% [95% CI, –1.0% to 5.4%]; $P = .15$).

CONCLUSIONS AND RELEVANCE Among patients with stage II or III colorectal cancer, follow-up testing with computed tomography and carcinoembryonic antigen more frequently compared with less frequently did not result in a significant rate reduction in 5-year overall mortality or colorectal cancer–specific mortality.

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Across very high human deprivation index countries, 0.7 million new cases of colorectal cancer are diagnosed annually.¹ Two-thirds of these patients present at tumor stage II or III,² and the majority of whom undergo curative resection and are eligible for subsequent surveillance screening. In most countries, patients undergo follow-up examinations to detect cancer recurrence. However, the question of appropriate follow-up intervals has been controversial, and varying intensity of follow-up has been used within and among countries.^{3,4} The reasons for patient follow-up after colorectal surgery with curative intent include (1) to detect recurrence and adverse effects when curative treatment is still possible, thus improving survival; (2) to assess the quality of the primary treatment; (3) to detect metachronous tumors; and (4) to satisfy a patient's desire for information about prognosis.⁵

From 2005 to the present, approaches for treating recurrence, including resection of liver and lung metastases and improved adjuvant and palliative chemotherapy,⁶ have improved patient outcomes. The availability of better treatment for metastatic disease prompted evaluation of the survival benefit with more-intensive vs less-intensive surveillance after primary surgery. However, systematic reviews and a randomized trial provided inconclusive evidence regarding survival benefit.⁷⁻¹³ This lack of consistency highlights the need for a large contemporary trial to evaluate any survival benefit associated with more intense follow-up.

Given the advances in treatment options, we sought to determine whether intensive frequency of surveillance tests provides a survival benefit after curative resection among patients with stage II or III colorectal cancer (COLOFOL trial). Specifically, this randomized trial was designed to compare surveillance with a more intensive vs a less intensive schedule of follow-up testing with computed tomography (CT) and serum carcinoembryonic antigen (CEA). The hypothesis was that more intense follow-up testing with CT and CEA and a focus on potentially treatable recurrences (eg, lung and liver metastases) would decrease 5-year overall and colorectal cancer-specific mortality rates and extend time to colorectal cancer-specific recurrence.

Methods

Trial Design and Study Setting

The COLOFOL study group was established in 2004 and invited centers in Denmark, Sweden, Ireland, Poland, Hungary, England, the Netherlands, and Uruguay to participate in recruitment.⁵ To take part in the study, each center was supposed to enroll at least 50 patients within 2 years and at least 30% of its eligible patients. These criteria were modified by the steering committee in 2007 after study initiation because smaller centers could not achieve the 50-patient threshold; therefore, the minimum inclusion was reduced to 20 patients within 2 years.⁵

The recruitment centers in Hungary, England, and the Netherlands were never established (mainly due to conflicting national clinical guidelines) and 5 centers in Poland and

Key Points

Question Is intensive follow-up of patients after curative surgery for colorectal cancer effective in reducing mortality?

Findings In this randomized clinical trial that included 2509 patients with stage II or III colorectal cancer, follow-up testing with computed tomography and serum carcinoembryonic antigen on 5 vs 2 occasions did not result in a significant difference in the 5-year overall mortality rate (13.0% vs 14.1%, respectively) or colorectal cancer-specific mortality rate (10.6% vs 11.4%).

Meaning Among patients with stage II or III colorectal cancer, increased frequency of follow-up testing did not reduce the 5-year mortality rate.

Ireland did not meet the minimum threshold and were excluded. Twenty-four recruitment centers in Denmark, Sweden, and Uruguay remained in the study. The study was approved by ethics committees in each of the participating countries. The study protocol and statistical analysis plan appear in [Supplement 1](#).

Participants

Inclusion criteria were surgical resection with curative intent for colorectal adenocarcinoma (with or without adjuvant treatment), age of 75 years or younger, provision of written informed consent for participation, a colon and rectum free of neoplasia verified by perioperative barium enema or a colonoscopy within 3 months after surgery, and tumor stage II or III (T3-T4, NO, MO, any N1-N2, MO).

Exclusion criteria were a clinical diagnosis of hereditary nonpolyposis colorectal cancer or familial adenomatous polyposis, local resection of colorectal cancer (eg, transanal endoscopic microsurgery procedure), life expectancy of less than 2 years due to comorbid conditions (eg, cardiac disease, advanced multiple sclerosis with systemic complications, or liver cirrhosis), inability or refusal to provide informed consent, inability to comply with study requirements, inability to tolerate surgery for recurrence, other or previous malignancies (except for nonmelanoma skin cancer), or participation in another clinical trial that was incompatible with this study's follow-up regimen.

Participants were required to have at least 1 imaging procedure (ultrasonography, magnetic resonance imaging, or CT) of the liver and CT or radiography of the lungs prior to surgery. Patients also were required to have testing with CEA at 1 month after surgery. Patients with an elevated CEA level were enrolled only after a completely negative diagnostic workup. Written informed consent for participation was obtained at least 30 days after surgical resection of the primary colorectal cancer.

Intervention

Patients randomized to the high-frequency group were required to have follow-up testing with multislice contrast-enhanced CT of the thorax and abdomen and CEA at 6, 12, 18, 24, and 36 months after surgery. Patients randomized to the low-frequency group were required to have follow-up testing

with multislice contrast-enhanced CT of the thorax and abdomen and CEA at 12 and 36 months after surgery. Testing with a pelvic CT was not required. Participating patients were randomized in block sizes of 10 by computer allocation to 1 of the 2 follow-up regimens.

Endoscopy and examination for pelvic recurrence were allowed in both groups at the discretion of the treating physician. Although permitted in the study, no department used magnetic resonance imaging or chest radiography as part of its surveillance program. An external consultant (Lennart Blomquist, PhD, Karolinska Hospital, Stockholm, Sweden) with extensive experience in abdominal CT certified the quality of the CT scans at each recruitment center (Supplement 1).

After verification of study enrollment criteria, baseline information for each participant (sex, comorbidity, and lifestyle factors such as smoking and alcohol consumption, preoperative diagnosis and staging, type of surgery performed, pathological staging after surgery, postoperative complications, blood transfusions, and adjuvant chemotherapy or radiation therapy) was recorded. At each follow-up surveillance examination, data were collected on symptoms, CT scans, and CEA test results per the trial protocol, and additional examinations were performed for suspected recurrence. In accordance with the study's pragmatic approach, up to 3 months' variability in follow-up intervals was allowed to accommodate local needs for prioritization and patient preferences.

Symptoms leading to interval examinations also were recorded. If a recurrence was not detected during an interval follow-up examination, the patient was allowed to continue in the study. If a recurrence was suspected during any follow-up examination, the case was discussed at a meeting of the local multidisciplinary team and further diagnostic assessment (eg, positron emission tomography or CT) and treatment was undertaken as recommended (eg, surgery for liver or other metastases, referral for chemotherapy or radiation therapy, or both surgery and therapy).

Each center had to follow-up all study participants with surveillance examinations until 3 years after surgery according to the protocol and to report outcomes to the study's coordinating center until 5 years after surgery. Clinically diagnosed recurrences and deaths were reported at the time of the event. All patients were tracked throughout the study by monitoring their inpatient and outpatient records and through linkage with national population and cancer registries (except in Uruguay because only hospital data were available).^{14,15}

Patients known to have emigrated or whose medical records were discontinued were deemed lost to follow-up and censored on the date of their last identifiable data point. Follow-up ended on December 31, 2015. All data were submitted electronically from the recruitment centers to the study's coordinating center in Denmark.

Outcomes

The primary outcomes were 5-year overall mortality and 5-year colorectal cancer-specific mortality rates. The secondary outcome was the colorectal cancer-specific recurrence rate during 5 years of follow-up. Potential adverse events were not systematically tracked.

Statistical Analysis

Sample Size Calculation

At the time the study was designed, the results of 2 meta-analyses^{7,8} pointed out an effect in favor of high-intensity follow-up. One of these meta-analyses additionally reported the range of absolute reduction in mortality rate from 9% to 13%.⁷ Given the uncertainty in the evidence, and the inclusion of a surveillance intervention in the comparator group (whereas some older trials had no surveillance intervention in the comparator group), the study was designed to detect an absolute difference in mortality rate of 6% between the low-intensity and high-intensity surveillance groups.

Assuming a 5% risk of type I error and a 15% risk of type II error, 1083 patients needed to be randomized to each group. Given an expected dropout rate of 20%, the planned number of randomized patients was 2500.

Main Statistical Analysis

Participants were characterized by randomization group and by sex, age, clinical variables, comorbidities, and the lifestyle factors of smoking and alcohol consumption. Primary and secondary outcomes data were analyzed using the Kaplan-Meier method and the log-rank test was used for between-group comparisons. In the time-to-recurrence analysis, patients were censored at the time of death. In the intention-to-treat analyses, trial participants were followed up from the date of radical surgery for colorectal cancer until the analyzed study outcome, date of dropout, date when lost to follow-up, or at 5-year follow-up, whichever came first.

In addition, risk differences in the 5-year mortality rate and in the recurrence probabilities were calculated with 95% CIs. The cumulative incidence curves were computed using Kaplan-Meier estimates minus 1. Study results were evaluated on an intention-to-treat basis and on an as-treated per-protocol basis. There were missing data for some key variables for 11 patients (5 in the high-frequency group and 6 in the low-frequency group). Patients who withdrew informed consent or switched to another follow-up regimen remained in their randomized group for the intention-to-treat analysis, but were excluded from the per-protocol analysis.

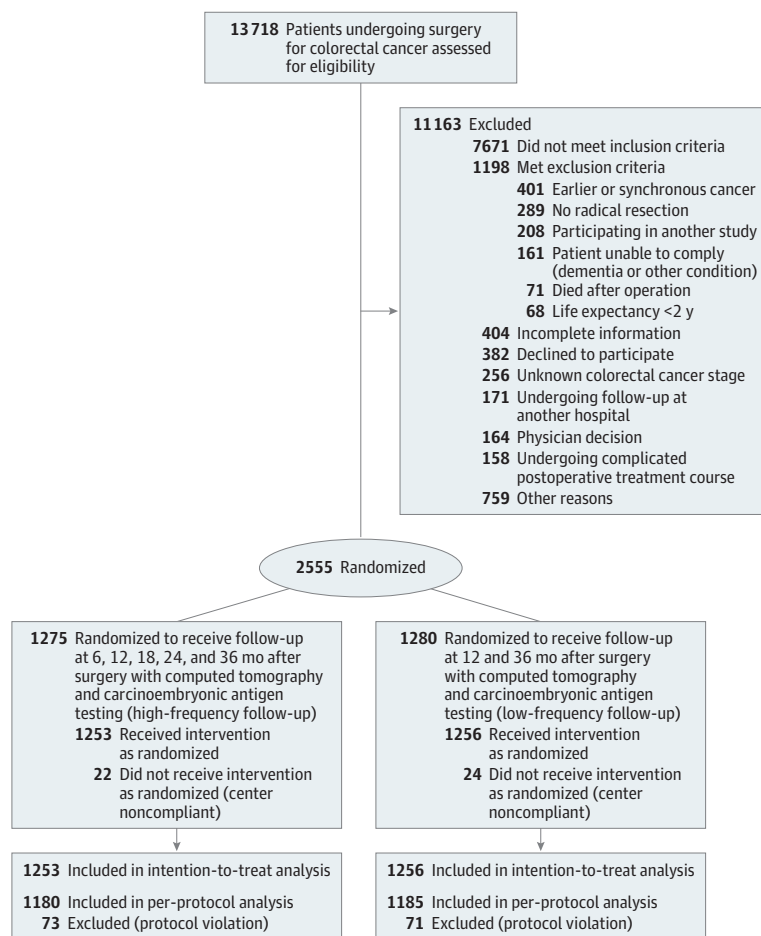
Post Hoc Subgroup Analysis

Post hoc analyses were stratified by cancer stage (stage II or III) and were repeated for patients with rectal cancer who had or did not have preoperative radiotherapy. Moreover, a potential statistical cancer stage \times frequency of follow-up testing interaction was assessed by inclusion of these interaction terms in a Cox regression model.

Post Hoc Sensitivity Analysis

To test the robustness of the risk estimates, 3 additional sensitivity analyses were performed. First, Cox proportional hazard regression was used to compute hazard ratios (HRs) with 95% CIs for overall mortality rate, colorectal cancer-specific mortality rate, and colorectal cancer-specific recurrence rate. The analysis was adjusted for age at colorectal cancer surgery, sex, colorectal cancer type, cancer stage,

Figure 1. Patient Flow Through the COLOFOL Trial



diabetes, cardiovascular disease, pulmonary disease, cerebrovascular disease, preoperative radiation, adjuvant chemotherapy, and smoking.

Second, the main analysis was repeated for the primary and secondary outcomes and compared the outcomes among the 3 participating countries of Denmark, Sweden, and Uruguay.

Third, a frailty model analysis was performed for the primary and secondary outcomes by introducing random effects in the model to account for associations and unobserved heterogeneity due to participation of different centers.¹⁶

The level of significance was $P < .05$ with a 2-sided test. The Bonferroni correction was used to account for multiple comparisons in the post hoc subgroup analysis.¹⁷ Each individual hypothesis was tested at a significance level of α divided by n , where α was the critical P value level for significance and n was the number of different tests. Instead of setting the critical P level for significance at $.05$, a new significance level of $.02$ ($P = .05/3$) was defined given the 3 end points. The statistical analyses were conducted using the SAS version 9.4 (SAS Institute Inc).

Results

Of the 13 718 patients who underwent surgery for colorectal cancer between January 2006 and December 2010 at participating recruitment centers, 2 555 were randomized, and 2 509 were included in the intention-to-treat analysis. The number of participants assessed for eligibility and the reasons for exclusion appear in **Figure 1**. There were 1 253 patients in the high-frequency group and 1 256 patients in the low-frequency group who were included in the intention-to-treat analysis.

The demographic characteristics of the patients and the clinical risk factors appear in the **Table**. The 2 groups were well balanced, with no major differences observed between patients in the high-frequency and low-frequency groups. Patients in the high-frequency group should have had CT on 5 occasions and the median number was 5 (mean, 4.3); patients in the low-frequency group should have had CT on 2 occasions and the median number was 2 (mean, 1.8).

The proportion of patients with no protocol violations was 94.2% in the high-frequency group and 94.3% in the

Table. Demographic Characteristics and Clinical Prognostic Factors

	Intention-to-Treat Analysis		Per-Protocol Analysis	
	High-Frequency Follow-up Group (n = 1253)	Low-Frequency Follow-up Group (n = 1256)	High-Frequency Follow-up Group (n = 1180)	Low-Frequency Follow-up Group (n = 1185)
Men, No. (%)	706 (56.3)	675 (53.7)	663 (56.2)	634 (53.5)
Age group, y, No. (%) ^a				
≤50	85 (6.8)	98 (7.8)	80 (6.8)	93 (7.8)
51-60	247 (19.7)	274 (21.8)	235 (19.9)	259 (21.9)
61-70	620 (49.5)	573 (45.6)	580 (49.2)	547 (46.2)
>70	301 (24.0)	311 (24.8)	285 (24.2)	286 (24.1)
Age, median (IQR), y	65.2 (59.6-69.7)	64.7 (58.6-69.9)	65.2 (59.5-69.7)	64.6 (58.6-69.8)
Type of cancer, No. (%) ^a				
Rectal	428 (34.2)	456 (36.3)	412 (34.9)	433 (36.5)
Right side of colon	355 (28.3)	357 (28.4)	325 (27.5)	331 (27.9)
Transverse colon	68 (5.4)	47 (3.7)	63 (5.3)	44 (3.7)
Left side of colon	416 (33.2)	419 (33.4)	392 (33.2)	398 (33.6)
Type of treatment, No. (%)				
Preoperative radiation	247 (19.7)	276 (22.0)	238 (20.2)	258 (21.8)
Adjuvant chemotherapy	591 (47.2)	581 (46.3)	561 (47.5)	543 (45.8)
Cancer stage II (T3-4, N0, M0), No. (%) ^b	675 (53.9)	677 (53.9)	625 (53.0)	641 (54.1)
Medical history, No. (%)				
Diabetes	117 (9.3)	107 (8.5)	108 (9.2)	99 (8.4)
Cardiovascular disease	383 (30.6)	414 (33.0)	363 (30.8)	384 (32.4)
Pulmonary disease	77 (6.1)	66 (5.3)	69 (5.8)	60 (5.1)
Cerebrovascular disease	36 (2.9)	39 (3.1)	34 (2.9)	36 (3.0)
Other major disease	61 (4.9)	61 (4.9)	59 (5.0)	58 (4.8)
Current smoker ^c	198 (15.8)	212 (16.9)	185 (15.7)	201 (17.0)
Consume >3 alcohol drinks/d	59 (4.7)	53 (4.2)	53 (4.5)	51 (4.3)
Unplanned CT, No. (%)	75 (6.0)	100 (8.0)	68 (5.8)	88 (7.4)
CT during follow-up, No. of occasions				
Mean (SD)	4.3 (1.5)	1.8 (0.6)	4.4 (1.4)	1.8 (0.6)
Median (IQR)	5.0 (5.0-5.0)	2.0 (2.0-2.0)	5.0 (5.0-5.0)	2.0 (2.0-2.0)

Abbreviations: CT, computed tomography; IQR, interquartile range.

^b Remaining patients had stage III (T1-4, N1-2, M0) cancer.^a Category may not sum to 100% due to rounding.^c Daily or only occasionally.

low-frequency group. The rates and reasons for protocol violations were similar in the groups (eTable 1 in Supplement 2). The most common reason was missing follow-up visits (45 patients). Seven patients were lost to follow-up.

Primary Outcomes

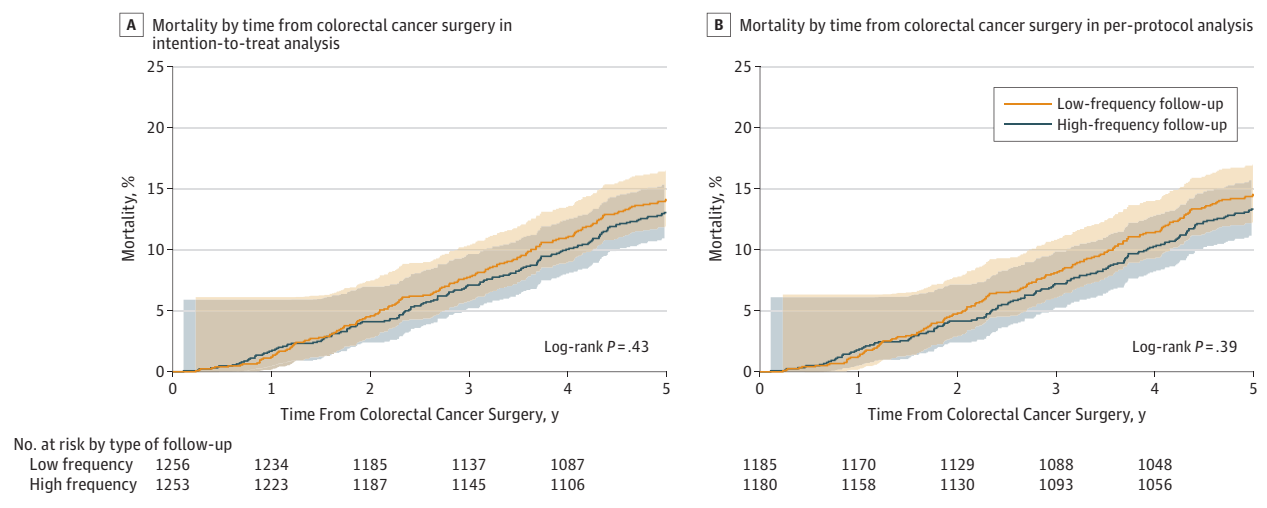
Among all participants, the 5-year overall mortality rate was 13.6%. The 5-year overall mortality rate was 13.0% (95% CI, 11.3% to 15.1%; n = 161) among the 1253 patients in the high-frequency group vs 14.1% (95% CI, 12.3% to 16.2%; n = 174) among the 1256 patients in the low-frequency group in the intention-to-treat analysis (risk difference, 1.1% [95% CI, -1.6% to 3.8%]; *P* = .43). Cumulative incidence plots appear in Figure 2. In the per-protocol analysis, the 5-year mortality rate was 13.3% (95% CI, 11.5% to 15.4%; n = 157) among the 1180 patients in the high-frequency group vs 14.5% (95% CI, 12.6% to 16.7%; n = 172) among the 1185 patients in the low-frequency group (risk difference, 1.2% [95% CI, -1.6% to 4.0%]; *P* = .39; Figure 2).

There were no significant between-group differences in the 5-year colorectal cancer-specific mortality rate in the intention-to-treat and per-protocol analyses (Figure 3). The colorectal cancer-specific mortality rate was 10.6% (95% CI, 9.0% to 12.5%; n = 128) among the 1248 patients in the high-frequency group vs 11.4% (95% CI, 9.7% to 13.3%; n = 137) among the 1250 patients in the low-frequency group in the intention-to-treat analysis (risk difference, 0.8% [95% CI, -1.7% to 3.3%]; *P* = .52). In the per-protocol analyses, the 5-year colorectal cancer-specific mortality rate was 10.8% (95% CI, 9.2% to 12.8%; n = 125) among the 1176 patients in the high-frequency group vs 11.7% (95% CI, 10.0% to 13.7%; n = 136) among the 1179 patients in the low-frequency group (risk difference, 0.9% [95% CI, -1.7% to 3.5%]; *P* = .46).

Secondary Outcome

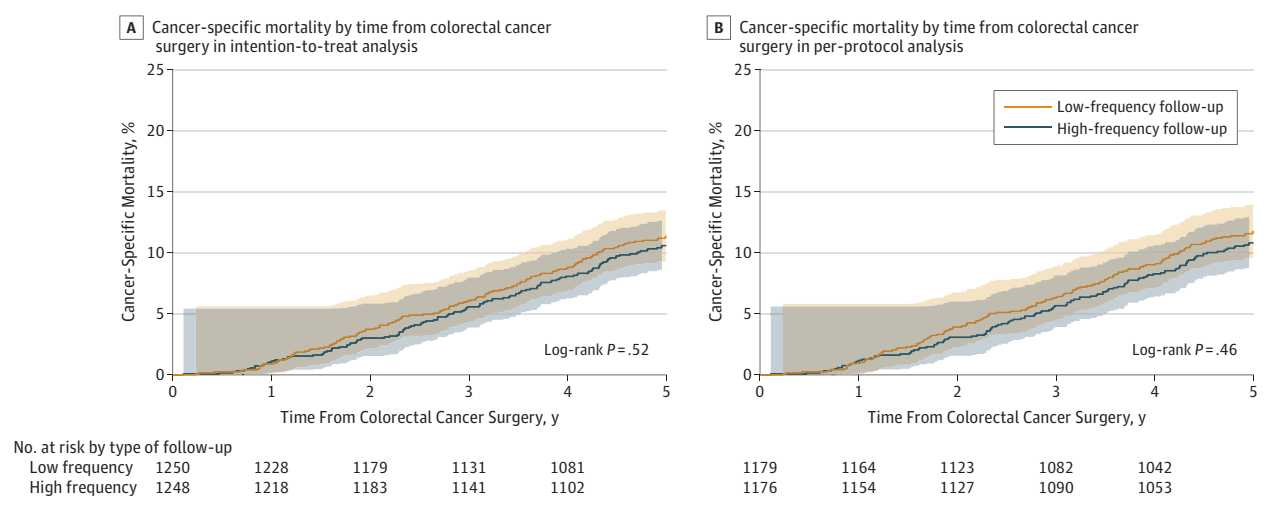
The risk of detected colorectal cancer-specific recurrence was not significantly increased at 21.6% (95% CI, 19.4% to 24.0%; n = 265) among the 1248 patients in the high-frequency group

Figure 2. Primary Outcome of Overall Mortality by Time From Colorectal Cancer Surgery for the Intention-to-Treat and Per-Protocol Analyses



The median follow-up time was 5 years (interquartile range, 5-5 years) in each study group. Tinted area indicates 95% confidence interval.

Figure 3. Primary Outcome of Colorectal Cancer-Specific Mortality by Time From Colorectal Cancer Surgery for the Intention-to-Treat and Per-Protocol Analyses



The median follow-up time was 5 years (interquartile range, 5-5 years) in each study group. The No. at risk sample sizes differ from Figure 2 because 11 patients (6 from the low-frequency group and 5 from the high-frequency group)

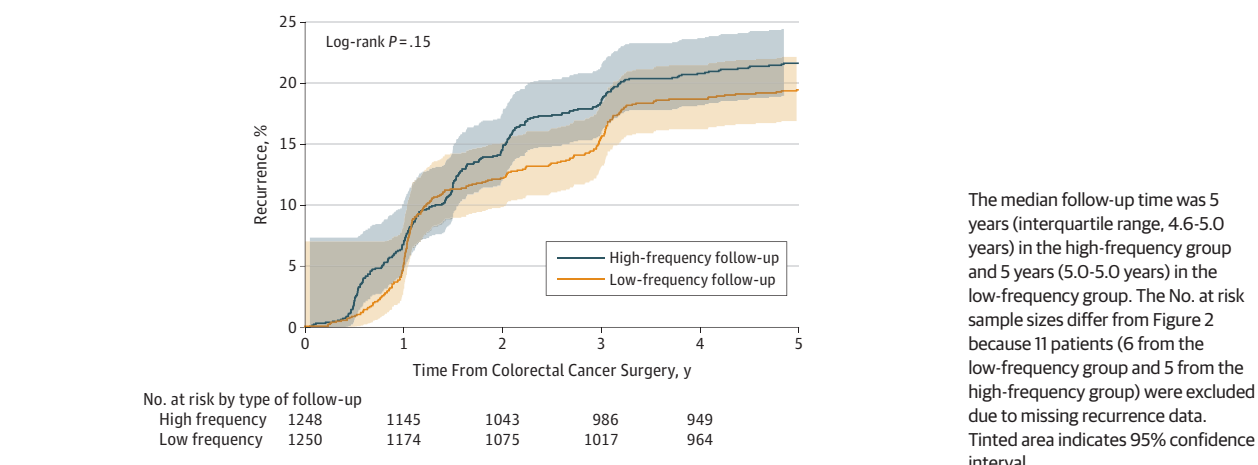
were excluded due to missing recurrence data. Tinted area indicates 95% confidence interval.

vs 19.4% (95% CI, 17.3% to 21.8%; n = 238) among the 1250 patients in the low-frequency group in the intention-to-treat analysis (risk difference, 2.2% [95% CI, -1.0% to 5.4%]; P = .15; Figure 4). However, the rate of colorectal cancer-specific recurrence was higher for the high-intensity group during the time intervals in which patients in the low-intensity group had no examinations (after 6 months and again at 18 and 24 months). The same pattern was observed in the per-protocol analyses with a colorectal cancer-specific recurrence rate of 22.1% (257/1176) in the high-frequency group vs 19.8% (231/1179) in the low-frequency group (risk difference, 2.3% [95% CI, -1.0% to 5.6%]; P = .15).

Post Hoc Subgroup Analysis

The analyses stratified by cancer stage yielded no significant between-group differences (eTable 2 in Supplement 2). Patients with rectal cancer constituted a special subgroup. In the intention-to-treat analysis, the 5-year overall mortality rate was 13.7% (95% CI, 10.8%-17.4%; n = 58) among the 428 patients with rectal cancer in the high-frequency group vs 15.0% (95% CI, 12.0%-18.7%; n = 67) among the 456 patients with rectal cancer in the low-frequency group. Among these 884 patients, 510 received preoperative radiotherapy. There was no between-group difference in the 5-year overall mortality rate.

Figure 4. Secondary Outcome of Colorectal Cancer–Specific Recurrence



The median follow-up time was 5 years (interquartile range, 4.6-5.0 years) in the high-frequency group and 5 years (5.0-5.0 years) in the low-frequency group. The No. at risk sample sizes differ from Figure 2 because 11 patients (6 from the low-frequency group and 5 from the high-frequency group) were excluded due to missing recurrence data. Tinted area indicates 95% confidence interval.

Among the patients in the intention-to-treat population who received radiotherapy, the 5-year overall mortality rate was 14.9% (35/239) in the high-frequency group vs 14.0% (37/271) in the low-frequency group ($P = .84$). Among the patients in the intention-to-treat population who did not receive radiotherapy, the 5-year overall mortality rate was 12.3% (23/189) in the high-frequency group vs 16.5% (30/185) in the low-frequency group ($P = .27$). Among the patients in the per-protocol population who received radiotherapy, the 5-year overall mortality rate was 14.8% (34/230) in the high-frequency group vs 14.3% (36/253) in the low-frequency group ($P = .91$). Among the patients in the per-protocol population who did not receive radiotherapy, the 5-year overall mortality rate was 12.6% (23/182) in the high-frequency group vs 16.1% (29/180) in the low-frequency group ($P = .38$). There was no significant cancer stage \times frequency of follow-up testing interaction observed for the 5-year overall mortality rate ($P = .64$ for interaction).

Post Hoc Sensitivity Analysis

In the intention-to-treat analysis, no significant associations with the primary outcomes were found in a Cox regression analysis controlling for covariates when patients in the high-intensity group were compared with patients in the low-intensity group for the 5-year overall mortality rate (adjusted HR, 0.90; 95% CI, 0.73-1.12) or the colorectal cancer–specific mortality rate (adjusted HR, 0.92; 95% CI, 0.72-1.17). The risk of detected recurrence was not significantly increased in the high-intensity group compared with the low-intensity group (adjusted HR, 1.15 [95% CI, 0.97-1.38]; eTable 3 in Supplement 2).

No significant differences were observed in the sensitivity analysis of the 3 participating countries (eFigure in Supplement 2). No significant between-group differences were found in the frailty analysis (eTable 4 in Supplement 2).

Discussion

In this trial of more than 2500 patients with colorectal cancer who underwent surgery with curative intent, no significant rate

differences in 5-year overall mortality or colorectal cancer–specific mortality were found when the intensity of postoperative colorectal cancer follow-up was increased from 2 to 5 examinations during the 3 years after surgery and with 5 years of follow-up. In the high-intensity group, colorectal cancer–specific recurrence was detected earlier, but this did not translate into a reduced mortality rate.

The data extend former research on the utility of postoperative colorectal cancer follow-up. Systematic reviews conducted in 2002, 2003, and 2007 (including meta-analyses of randomized trials comparing intensive vs less intensive follow-up) indicated that more intense regimens were associated with improved survival.⁷⁻¹⁰ Only use of testing with CEA and CT of the liver demonstrated significant efficacy in detecting recurrence.⁷⁻¹⁰ The included studies were heterogeneous and cancer-specific survival data were not statistically significant. Furthermore, the survival benefit might not have been related to earlier detection and treatment of recurrent disease.¹⁸ In addition, most studies were conducted during the era before the availability of advanced imaging techniques, multimodal treatment of metastatic disease, or both, which is reflected by a very high local recurrence rate and a high proportion of detected metachronous primary tumors.

The data correspond with the Follow-up After Colorectal Surgery (FACS) trial and a 2016 meta-analysis.¹¹⁻¹³ The FACS trial included 1202 patients who had undergone curative treatment for Duke colorectal cancer stages A to C in 39 hospitals in the United Kingdom. The patients were allocated to 1 of 4 study regimens: minimum follow-up, CEA testing only, CT only, or CEA testing plus CT. Serum CEA level was measured every 3 months for 2 years and then every 6 months for 3 years. Computed tomography of the chest, abdomen, and pelvis was done every 6 months for 2 years and then annually for 3 years. Those in the minimum follow-up and CEA testing only groups had a CT only once during 12 to 18 months of follow-up. Mortality during follow-up was 18.2% in the combined intensive follow-up groups compared with 15.9% in the combined minimum follow-up groups. The authors¹³ concluded that (1) the survival advantage of any intervention was small and (2) the trial lacked sufficient

power to assess whether improved detection of treatable recurrences achieved by intensive follow-up leads to a reduced overall mortality rate.

Likewise, the 2016 review did not suggest any overall survival benefit from intensifying patient follow-up after curative surgery for colorectal cancer.¹¹ This updated review included 5403 participants enrolled in 15 earlier studies and in 2 new studies. The review concluded that more participants were treated with salvage surgery with curative intent in the intensive follow-up group, but this was not associated with improved survival. Harms related to intensive follow-up and salvage therapy were not well reported.

Survival was higher than expected in both the present trial and in the FACS trial.¹² The differences in survival might reflect the lower proportion of emergency procedures in the present study and the better outcomes expected for patients recruited to a randomized trial compared with patients receiving routine clinical care.¹⁹ Another likely explanation is that the design of the study, which required (based on FACS results¹²) a colon and rectum free of neoplasia and a meticulous preoperative workup excluding synchronous metastases, reduced the rate of residual cancer disease at study entry. Furthermore, survival improved during the study period in the general population with colorectal cancer in both Sweden and Denmark,²⁰⁻²² probably due to improved adjuvant treatment and centralized surgery. Based on national cancer registry data, corresponding survival figures for the same period and using the same inclusion criteria were 86.4% in Denmark and 85.0% in Sweden. This also may explain the discrepancy in this trial's findings compared with those of the meta-analyses.⁷⁻¹⁰ In the studies included in the meta-analyses, residual disease rather than recurrence could have been detected during follow-up. This is consistent with an analysis of randomized patients vs eligible patients in the present study, which showed no difference in distribution of age and sex.

However, more patients with colon cancer were randomized compared with nonparticipating eligible patients (56% vs 51%, respectively) and had stage II cancer (56% vs 49%).⁵ It is also unlikely that more aggressive tumor biology had an effect. In the subgroup analyses based on cancer stage, no improved efficacy of high-intensity follow-up among patients with stage III disease vs patients with stage II disease or any difference due to tumor site (ie, colon or rectum) were detected.

Progress in the diagnosis and treatment of colorectal cancer has intensified the discussion of how and when to follow-up patients after resection with curative intent. Testing of CEA levels, which has long been considered to be central to surveillance,⁴ was questioned in a study based on 20-year follow-up of the first large CEA trial.⁷ However, the

results of another study led to CEA testing being recommended by Verberne et al.²³ For luminal recurrence, the follow-up method of choice is colonoscopy. However, luminal recurrence seldom occurs and detection programs have shown no effect.²⁴

Limitations

This study has several limitations. First, turnover of responsible investigators and staff in many recruitment centers during a long study period is a possible weakness because any non-adherence to the protocol would most likely bias this trial's findings toward the null.^{19,25,26} However, the adherence to the follow-up protocol was good and similar to the FACS trial.¹² A second concern is that due to the nature of the study design, it was not possible to blind patients and physicians to the frequency of the follow-up examinations.¹⁴ Third, an intention-to-treat analysis will tend to underestimate an effect,^{19,25,27} but such bias was likely small because the per-protocol analysis produced similar results. Fourth, survival was higher than expected in both the present trial and in the FACS trial.¹² With fewer outcomes than expected, the statistical power to detect a small significant between-group difference was reduced. Fifth, lack of systematic recording of potential adverse events might have led to underestimation of these events.

When this study was initiated in 2005, Danish guidelines²⁰ advocated follow-up corresponding to that received by the current trial's low-frequency group. In Sweden, no surveillance programs were used and regimens varied between no follow-up to yearly follow-up for 5 years. In the national guidelines released by the Swedish National Board of Health and Welfare in 2014, no specific recommendation was presented instead there was a statement noting that studies were under way.²¹ The Swedish national medical program for colorectal cancer that was released in 2016 advocated use of the current trial's low-frequency group regimen in the interim.²¹ No national guidelines existed in Uruguay at the time of study initiation.

The low-intensity follow-up tested in this clinical trial is less than the recommended guidelines from the National Comprehensive Cancer Network and the American Society of Clinical Oncology.^{28,29} The results of this trial should be considered as the evidence base for updating these clinical guidelines.

Conclusions

Among patients with stage II or III colorectal cancer, follow-up testing with computed tomography and carcinoembryonic antigen more frequently compared with less frequently did not result in a significant rate reduction in 5-year overall mortality or colorectal cancer-specific mortality.

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