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No benefit of more intense follow-up after surgery for colorectal cancer in the risk group with elevated CEA levels – An analysis within the COLOFOL randomized clinical trial

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ABSTRACT

Background: Patients with colorectal cancer were examined to determine (1) whether elevated carcinoembryonic antigen (CEA) levels, either before treatment or after surgery, was associated with an increased risk of overall or colorectal cancer-specific mortality or recurrence, and (2) whether high intensity follow-up would benefit those patients.

Materials and methods: Post-hoc analysis based on 2509 patients that underwent surgery for colorectal cancer, stage II or III, in the COLOFOL randomized trial with 5-year follow-up. Serum CEA levels were ascertained before treatment and one month after surgery. Follow-up examinations included computed tomography of the thorax and abdomen and serum CEA sampling. Patients were randomized to examinations at either 6, 12, 18, 24, and 36 months (high-intensity group) or at 12 and 36 months after surgery (low-intensity group). Levels of CEA >5 μg/l were defined as elevated.

Results: Elevated CEA levels before treatment were associated with increased risk of recurrence (hazard ratio [HR], 1.49; 95% confidence interval [CI]: 1.22–1.83), colorectal cancer-specific mortality (HR, 1.44; 95% CI: 1.08–1.91), and overall mortality (HR, 1.38; 95% CI: 1.07–1.78). Elevated CEA levels after surgery were associated with increased colorectal cancer-specific mortality (HR, 1.68; 95% CI: 1.08–2.61) and overall mortality (HR, 1.79; 95% CI: 1.22–2.63). The intensity of the follow-up regimen had no effect on 5-year outcomes in patients with elevated CEA levels.

Conclusion: Both pre-treatment and post-surgery elevated serum CEA levels were associated with increased overall and cancer-specific mortality. Intensified follow-up showed no benefit over low-intensity follow-up in this high-risk group of patients with elevated CEA levels.

Introduction

Colorectal cancer is the second most common cancer in Europe and the second most common cause of cancer death [1]. Almost two thirds of patients have stage II or III disease at diagnosis [2], and a good chance of cure after surgical resection. However, about 20% experience recurrence, which is associated with poor prognosis [3]. Although international and national guidelines provide recommendations on how to follow the patients after surgery [4,5] the

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evidence base of surveillance programs is limited.

The main objective of surveillance programs is to detect recurrences early, which supposedly increase the curative potential, and thus, improve survival [5]. Progress in oncological treatment and resection of metastatic disease has improved the potential of curative treatment for recurrences, and thus, most likely, also improved the probable benefit of follow-up. However, a recent meta-analysis, including 19 randomized controlled trials, among them the COLOFOL trial [6] showed no clear benefit of increasing the frequency of follow-up testing [7].

Several studies have found that elevated carcinoembryonic antigen (CEA) levels (usually >5 μg/l but not always) before [8–10] and after [11] surgery were associated with impaired oncological outcomes, including a shorter recurrence-free interval, reduced cancer-specific survival, and impaired overall survival. These associations were observed when analyzing either CEA alone or CEA in combination with other cancer markers or characteristics [11–13]. The ratio between post- and pre-operative CEA levels has also been associated with survival [14]. The CEA-watch study found that follow-up testing with frequent CEA sampling was associated with earlier detection, and that a somewhat higher proportion of recurrences could be treated with curative intent [15]. No studies have analyzed the effect of different follow-up regimens based on CEA levels.

In the present analysis, COLOFOL trial data were used for a post hoc analysis to examine whether elevated CEA levels (measured before treatment and one month after surgery) were associated with recurrence and mortality. We also investigated whether the follow-up regimen intensity affected mortality and recurrence in subgroups of patients with elevated pre-treatment or post-surgery CEA levels.

Our hypotheses were: (1) patients with elevated pre-treatment or post-surgery CEA levels constitute high-risk groups with increased overall mortality, increased colorectal cancer-specific mortality, and increased colorectal cancer recurrence, and (2) an intensive follow-up would benefit these high-risk groups of patients with elevated CEA levels.

Methods

Participants

In the COLOFOL trial, 2509 patients with colorectal cancer in 24 hospitals in Denmark, Sweden, and Uruguay were randomized (1:1) to a low-intensity or high-intensity follow-up between 2006 and 2010.

Inclusion criteria were: surgical resection with curative intent (R0-resection) for colorectal adenocarcinoma; stage II ($T_{3\text{-}4}N_0M_0$) or III ($T_{any}N_{1\text{-}2}M_0$); age ≤75 years; a negative perioperative barium enema or colonoscopy within three months after surgery; and the provision of written informed consent by participants. Neo-adjuvant treatment was allowed, according to local regimen protocols.

Exclusion criteria were: a clinical diagnosis of hereditary non-polyposis colorectal cancer (HNPCC) or familial adenomatous polyposis (FAP); local resection for colorectal cancer (*e.g.*, transanal endoscopic microsurgery procedure); life expectancy less than two years, due to concurrent diseases (*e.g.*, cardiac disease, advanced multiple sclerosis with systemic complications, or liver cirrhosis); refusal or inability to provide informed consent; inability to comply with the follow-up regimens; participation in other clinical trials that could interfere with the follow-up regimens; and other or previous malignancies (except for non-melanoma skin cancer).

To rule out synchronous metastases, all participants were required to have at least one liver imaging procedure (multi-slice computed tomography [CT], magnetic resonance imaging, or ultrasound) and one lung imaging procedure (CT or X-ray) prior to surgery, performed in certified radiology departments. Patients were also required to undergo CEA testing prior to the start of an oncological treatment or surgery, and another test one month after surgery. The post-surgical CEA level was considered the baseline value.

Intervention

Patients randomized to the high-intensity follow-up group underwent a multi-slice contrast-enhanced CT of the thorax and abdomen and a serum CEA test at 6, 12, 18, 24, and 36 months after surgery. Patients randomized to the low-intensity group underwent the same assessments, but only at 12 and 36 months after surgery.

At follow-up examinations, CEA values were considered normal when they were <5 μg/l or <30% higher than a baseline CEA value >5 μg/l. When a follow-up CEA value was either 5–10 μg/l, in patients with normal baseline CEA levels, or 30%-100% elevated, in patients with elevated baseline CEA levels, a new test was performed after four weeks. At that time, a further increase in the CEA value raised the suspicion of recurrence. When the CEA level was more than 100% higher than baseline, a new test was performed immediately. In case the finding was confirmed, a recurrence was considered probable.

Based on the study protocol, each center had to follow up all participants with surveillance examinations for 3 years after surgery. Moreover, they were expected to report any recurrence or death that occurred within 5 years after surgery.

Details on the data retrieval process were described previously [6].

Statistical analysis

The primary endpoints in this post hoc analysis were 5-year overall mortality and colorectal cancer-specific mortality. The secondary endpoint was colorectal cancer recurrence.

To examine the effects of CEA on the endpoints, we evaluated all patients (regardless of follow-up intensity), based on (1) CEA status before treatment (considered normal if ≤5 μg/l and elevated if >5 μg/l); and (2) CEA status after surgery (normal vs. elevated). To examine the effects of the follow-up intensity, we compared patients with different follow-up regimens (i.e., high-intensity vs. low-intensity). In addition, to determine whether follow-up intensity benefitted only the low- or high-risk group, we compared endpoints in the following patient groups: (1) normal CEA levels and low-intensity follow-up (reference), (2) normal CEA and high-intensity follow-up, (3) elevated CEA levels and low-intensity follow-up, and (4) elevated CEA levels and high-intensity follow-up.

Covariate balance was assessed with descriptive statistics. Overall mortality was analyzed with the Kaplan-Meier method. Cumulative incidence curves were computed as: 1 − the Kaplan-Meier estimate. When analyzing colorectal cancer-specific mortality and recurrence, we included two competing risks: death due to other causes (for cause-specific mortality) and overall death (for recurrence). The cumulative incidence function estimates were calculated accordingly [16]. Cumulative incidence at five years and absolute risk differences were calculated with 95% confidence intervals (CIs). In addition, Cox proportional hazards regression analyses were performed to compute crude and adjusted hazard ratios (HRs) with 95% CIs, as a measure of the relative risks for overall mortality, colorectal cancer-specific mortality, and colorectal cancer recurrence. The HRs were adjusted for the age at colorectal cancer surgery, sex, tumor location in colon or rectum, TNM-stage, diabetes, cardiovascular disease, pulmonary disease, cerebrovascular disease, adjuvant chemotherapy, and smoking.

Calculations were performed on an intention-to-treat basis and

on a per-protocol basis. Here, we present the results of the intention-to-treat analyses; the results of the per-protocol analyses are presented in the supplement. No imputations were performed in the multivariate analyses. Hence, patients with missing data were excluded from the analyses.

In the intention-to-treat analyses, all patients were followed from the date of surgery for colorectal cancer to the occurrence of the study outcome examined, the drop-out date, the date of loss to follow-up, or for 5 years, whichever came first. Patients that withdrew informed consent or switched to another follow-up regimen remained in the original randomized arm for the intention-to-treat analysis but were excluded in the per-protocol analysis.

For analyses of post-operative CEA levels, follow-up started four weeks after surgery to avoid conditioning on the future. Two patients died within the first month of follow-up and were excluded from all analyses of post-operative CEA levels.

Statistical analyses were performed with SAS version 9.4 (SAS Institute Inc). The study was approved by the Ethics Committee in Uppsala, Sweden (2004: M-453) and Copenhagen and Frederiksberg Scientific committee in Denmark (KF 01–194/04). The clinicaltrials.gov registry number is NCT00225641.

Results

Cohort and patient characteristics

A total of 2509 randomized patients were included in the study and constituted the intention-to-treat cohort. Of these, 1256 patients were in the low-intensity follow-up group and 1253 patients were in the high-intensity follow-up group [6]. The group characteristics were well balanced, as described previously [6]. Protocol violations were recorded for 144 patients, also described previously [6]. The per-protocol cohort thus comprised 2365 patients. Fourteen patients had additional examinations. Seven of these patients were in the low-intensity follow-up group, and of these, 3 patients experienced a recurrence. A flowchart of the complete patient selection process was presented previously [6].

Pre-treatment CEA values were available for 85% of patients, and one-month postoperative CEA values were available for 87% of patients (Table 1 and Fig. 1). The distributions of patients with normal and elevated pre-treatment and post-surgery CEA values were balanced between the randomized arms (Table 2). In our cohort, patients with elevated CEA levels were more likely to be smokers than patients with normal CEA levels. Other health-related variables, including co-morbidity, were well balanced between the groups (Table 2).

Associations between elevated pre-treatment CEA and 5-year recurrence and mortality

The cumulative incidence of colorectal cancer recurrence at five years was higher among patients with elevated pre-treatment CEA values, compared to patients with normal CEA values. The absolute risk difference was 7.83 (CI: 3.88–11.79; Table 3). Adjusted Cox proportional hazards regression models showed an association between the risk of recurrence and elevated pre-treatment CEA levels (HR, 1.49; 95% CI: 1.22–1.83; Table 4).

The cumulative incidence for colorectal-cancer specific death at five years was higher among patients with elevated pre-treatment CEA values compared to patients with normal values. The absolute risk difference was 4.24 (CI: 1.24–7.23; Table 3). Adjusted Cox proportional hazards regression models showed an association between the risk of colorectal cancer-specific death and elevated pre-treatment CEA levels (HR, 1.44; 95% CI: 1.08–1.91; Table 4).

The cumulative incidence of overall mortality after five years of follow-up was higher among patients with elevated pre-treatment CEA values compared to patients with normal values. The absolute risk difference was 4.74 (CI: 1.51–7.97; Table 3). Adjusted Cox proportional hazards regression models showed an association between the risk of overall mortality and elevated pre-treatment CEA levels (HR, 1.38; 95% CI: 1.07–1.78; Table 4).

Associations between elevated post-surgery CEA and 5-year recurrence and mortality

The cumulative incidence of colorectal cancer recurrence at five years was not significantly increased in patients with elevated post-surgery CEA values compared to patients with normal values (Table 3). The absolute risk difference was 8.44 (CI: 0.48–16.41). The adjusted Cox proportional hazards regression model showed no association between an elevated risk of recurrence and elevated post-surgery CEA levels (HR, 1.37; 95% CI: 0.95–1.96; Table 4).

The cumulative incidence of colorectal cancer-specific death after five years was significantly higher in patients with elevated post-surgery CEA values compared to patients with normal values (Table 3). The absolute risk difference was 9.40 (CI: 2.67–16.14). The adjusted Cox proportional hazards regression model showed a positive association between the risk of colorectal cancer-specific death and elevated post-surgery CEA levels (HR, 1.68; 95% CI: 1.08–2.61; Table 4).

The cumulative incidence of overall mortality after five years was higher in patients with elevated post-surgery CEA values compared to patients with normal values (Table 3). The absolute risk difference was 13.45 (CI: 6.35–20.56). The adjusted Cox proportional hazards regression model showed an association between an elevated risk of overall mortality and elevated post-surgery CEA values (HR, 1.79; 95% CI: 1.22–2.63; Table 4).

Associations between follow-up intensity, elevated pre-treatment CEA, and 5-year recurrence and mortality

We compared low-intensity to high-intensity follow-up testing in patients with elevated pre-treatment CEA levels. We found no statistically significant differences regarding risk for recurrence, colorectal cancer-specific death, or overall death (Tables 3 and 4 and Fig. 2).

Table 1
Numbers of stage II and III colorectal cancer patients with normal, elevated, or missing data on CEA levels before treatment and one month after surgery.

		CEA-levels after surgery			
		≤5 μg/l	> 5 μg/l	Missing	Total (%)
CEA-levels before treatment	≤5	1307	13	208	1528 (61)
	>5	426	94	84	604 (24)
	Missing	314	18	45	377 (15)
	Total (%)	2047 (82)	125 (5)	337 (13)	2509 (100)

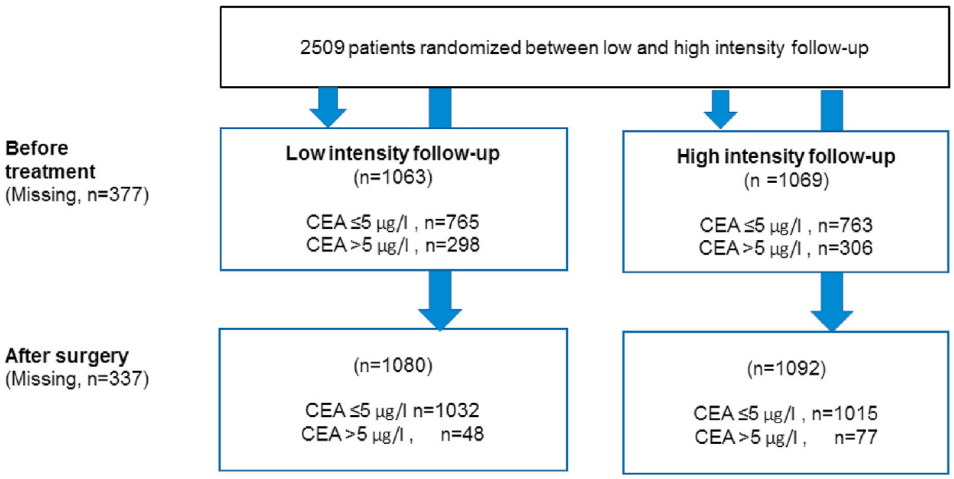

Fig. 1. Numbers of patients randomized to low-intensity and high-intensity follow-up testing. Additionally, within these groups, the numbers of patients with normal, elevated, or missing CEA values are shown for measurements taken before treatment and after surgery.

Table 2
Characteristics of patients randomized to low- or high-intensity follow-up, stratified on CEA levels before treatment and one month after radical surgery for colorectal cancer [number (percent)].

	CEA before treatment				CEA after surgery			
CEA levels by randomized assignment to low- vs high-intensity follow-up	≤ **5** µg/l	≤ **5** µg/l	> **5** µg/l	> **5** µg/l	≤ **5** µg/l	≤ **5** µg/l	> **5** µg/l	> **5** µg/l
	Low-intensity	High-intensity	Low-intensity	High-intensity	Low-intensity	High-intensity	Low-intensity	High-intensity
	(n = 765)	(n = 763)	(n = 298)	(n = 306)	(n = 1030)	(n = 1015)	(n = 48)	(n = 77)
Gender, female	346 (45)	315 (41)	136 (46)	147 (48)	473 (46)	450 (44)	25 (52)	37 (48)
Age at operation								
≤50 years	56 (7)	51 (7)	22 (7)	14 (5)	82 (8)	68 (7)	1 (2)	4 (5)
51–60 years	171 (22)	150 (20)	67 (22)	63 (21)	237 (23)	198 (20)	6 (13)	14 (18)
61–70 years	341 (45)	386 (51)	133 (45)	150 (49)	462 (45)	496 (49)	23 (48)	40 (52)
>70 years	197 (26)	176 (23)	76 (26)	79 (26)	249 (24)	253 (25)	18 (38)	19 (25)
Location of cancer								
Right side colon	211 (28)	214 (28)	84 (28)	85 (28)	285 (28)	290 (29)	27 (56)	34 (44)
Transverse colon	32 (4)	40 (5)	10 (3)	17 (6)	37 (4)	59 (6)	1 (2)	2 (3)
Left side colon	250 (33)	230 (30)	102 (34)	107 (35)	350 (34)	330 (33)	10 (21)	27 (35)
Rectal cancer	286 (37)	287 (38)	110 (37)	103 (34)	375 (36)	349 (34)	12 (25)	16 (21)
Tumor stage								
Stage II(T3-4, N0, M0)	422 (55)	419 (55)	150 (50)	164 (54)	545 (53)	542 (53)	18 (38)	41 (53)
Stage III(T1-4, N1-2, M0)	343 (45)	344 (45)	148 (50)	142 (46)	485 (47)	473 (47)	30 (63)	36 (47)
Oncological treatment								
Preop chemotherapy	82 (11)	67 (9)	28 (9)	30 (10)	107 (10)	92 (9)	3 (6)	3 (4)
Preop radiation	167 (22)	161 (21)	66 (22)	60 (22)	244 (24)	214 (21)	6 (13)	5 (6)
Adjuvant chemotherapy	326 (43)	342 (45)	148 (50)	140 (46)	482 (47)	486 (48)	31 (65)	37 (48)
Comorbidity								
Diabetes	54 (7)	69 (9)	38 (13)	33 (11)	85 (8)	97 (10)	10 (21)	6 (8)
AMI, hypertension or other heart diseases	253 (33)	232 (30)	104 (35)	90 (29)	331 (32)	305 (30)	20 (42)	26 (34)
Pulmonary disease	43 (6)	46 (6)	17 (6)	18 (6)	53 (5)	60 (6)	3 (6)	10 (13)
Multiple sclerosis	2 (0)	1 (0)	1 (0)	1 (0)	3 (0)	2 (0)		
Cerebrovascular disease	23 (3)	25 (3)	11 (4)	8 (3)	29 (3)	27 (3)	6 (13)	4 (5)
Other major disease	37 (5)	29 (4)	13 (4)	17 (6)	50 (5)	44 (4)	2 (4)	9 (12)
Lifestyle								
Smoking	84 (11)	91 (12)	61 (20)	66 (22)	142 (14)	140 (14)	16 (33)	30 (39)
daily								
occasionally	18 (2)	6 (1)	3 (1)	1 (0)	19 (2)	6 (1)		1 (1)
non smoker	624 (82)	627 (82)	213 (71)	220 (77)	816 (79)	810 (80)	29 (60)	43 (56)
unknown	39 (5)	39 (5)	21 (7)	19 (6)	53 (5)	59 (6)	3 (6)	3 (4)
Alcohol consumption								
3 or more drinks	31 (4)	30 (4)	12 (4)	18 (6)	41 (4)	44 (4)	1 (2)	5 (6)
<3 drinks	175 (23)	165 (22)	61 (20)	56 (18)	199 (19)	185 (18)	11 (23)	16 (21)
none	473 (62)	481 (63)	183 (61)	192 (63)	670 (65)	660 (65)	30 (63)	48 (62)
unknown	86 (11)	87 (11)	42 (14)	40 (13)	120 (12)	126 (12)	6 (13)	8 (10)

Table 3
Cumulative incidence and absolute risk differences (95% confidence intervals) for 5-year colorectal cancer recurrence, colorectal cancer-specific mortality, and overall mortality in patients randomized to low- or high-intensity follow-up, depending on CEA levels before treatment and one month after surgery for colorectal cancer.

		Recurrence		CRC-specific mortality		Overall mortality	
CEA before treatment		**Cumulative incidence**	**Absolute risk difference**	**Cumulative incidence**	**Absolute risk difference**	**Cumulative incidence**	**Absolute risk difference**
≤5 μg/l	Both groups	17.67 (15.79–19.64)	Reference	8.97 (7.59–10.49)	Reference	11.46 (9.95–13.18)	Reference
>5 μg/l	Both groups	25.50 (22.07–29.06)	7.83 (3.88–11.79)	13.21 (10.62–16.08)	4.24 (1.24–7.23)	16.19 (13.46–19.41)	4.74 (1.51–7.97)
≤5 μg/l	Low intensity follow-up	16.08 (13.55–18.80)	Reference	9.51 (7.54–11.75)	Reference	12.39 (10.23–14.97)	Reference
	High intensity follow-up	19.26 (16.53-22.16)	3.18 (-0.67-7.04)	8.43 (6.58-10.56)	-1.08 (-3.98-1.82)	10.52 (8.53-12.94)	-1.87 (-5.12-1.39)
>5 μg/l	Low intensity follow-up	24.95 (20.14–30.02)	8.87 (3.35–14.38)	12.76 (9.23–16.89)	3.25 (−0.93–7.44)	16.09 (12.34–20.84)	3.70 (−0.85–8.25)
	High intensity follow-up	26.06 (21.25-31.10)	9.98 (4.46-15.50)	13.63 (10.04-17.77)	4.12 (-0.11-8.36)	16.29 (12.57-20.97)	3.90 (-0.63-8.42)
CEA after surgery							
≤5 μg/l	Both groups	19.96 (18.24–21.73)	Reference	10.54 (9.25–11.94)	Reference	12.93 (11.53–14.47)	Reference
>5 μg/l	Both groups	28.40 (20.63–36.64)	8.44 (0.48–16.41)	19.95 (13.36–27.50)	9.40 (2.67–16.14)	26.38 (19.45–35.19)	13.45 (6.35–20.56)
≤5 μg/l	Low intensity follow-up	18.88 (16.53–21.35)	Reference	10.95 (9.11–12.97)	Reference	13.65 (11.68–15.93)	Reference
	High intensity follow-up	21.04 (18.58-23.62)	2.16 (-1.33-5.66)	10.14 (8.36-12.11)	-0.81 (-3.50-1.88)	12.19 (10.31-14.38)	-1.46 (-4.41-1.49)
>5 μg/l	Low intensity follow-up	27.08 (15.51–40.03)	8.20 (−3.63–20.04)	20.83 (10.76–33.17)	9.89 (−0.39–20.16)	27.08 (16.72–42.03)	13.43 (2.82–24.04)
	High intensity follow-up	29.17 (19.18-39.88)	10.29 (-0.00-20.58)	19.37 (11.23-29.17)	8.42 (0.03-16.81)	25.91 (17.38-37.58)	12.26 (3.43-21.09)

Associations between follow-up intensity, elevated post-surgery CEA, and 5-year recurrence and mortality

We compared low-intensity to high-intensity follow-up testing among patients with elevated post-surgery CEA levels. We found no statistically significant differences regarding the risk of recurrence, 5-year colorectal cancer-specific mortality, or 5-year overall mortality (Tables 3 and 4 and Fig. 2).

Discussion

Although major progress has been made in treating colorectal cancer recurrences, no survival benefit has been shown with intensified follow-up testing. However, no large study has focused on high-risk patient subgroups in which, theoretically, it would be more likely to detect a benefit. The present study was undertaken to address this knowledge gap. This follow-up study analyzed more than 2500 patients treated for colorectal cancer in a multicenter randomized trial. We evaluated the effect of low-vs. high-intensity follow-up testing in patients with different serum CEA levels. Elevated pre-treatment and post-surgery CEA levels in patients with colorectal cancer were associated with high-risk of over-all mortality and cancer-specific mortality. In addition, elevated pre-treatment levels were associated with high risk of recurrence. High-intensity follow-up provided, however, no survival benefit over standard follow-up in this group of patients at high-risk of recurrence and mortality.

CEA as a prognostic factor

An association between elevated CEA levels at diagnosis and impaired survival was noted, consistent with previous studies

Table 4
Hazard ratios (95% confidence intervals) for 5-year colorectal cancer recurrence, colorectal cancer-specific mortality, and overall mortality in patients randomized to low or high intensity follow-up, depending on CEA levels before treatment and one month after surgery for colorectal cancer. HRs are adjusted for age at colorectal cancer surgery, sex, location to colon or rectum, TNM-stage, diabetes, cardiovascular disease, pulmonary disease, cerebrovascular disease, adjuvant chemotherapy, and smoking.

		Adjusted HR (95% CI)		
		Recurrence	CRC-specific mortality	Overall mortality
CEA before treatment				
≤5 μg/l	Both groups	Reference	Reference	Reference
>5 μg/l	Both groups	1.49 (1.22–1.83)	1.44 (1.08–1.91)	1.38 (1.07–1.78)
≤5 μg/l	Low intensity follow-up	Reference	Reference	Reference
	High intensity follow-up	1.22 (0.96–1.56)	0.85 (0.61–1.20)	0.82 (0.61–1.11)
>5 μg/l	Low intensity follow-up	1.54 (1.15–2.07)	1.26 (0.84–1.89)	1.23 (0.86–1.75)
	High intensity follow-up	1.77 (1.33–2.36)	1.39 (0.94–2.05)	1.27 (0.89–1.80)
CEA after surgery				
≤5 μg/l	Both groups	Reference	Reference	Reference
>5 μg/l	Both groups	1.37 (0.95–1.96)	1.68 (1.08–2.61)	1.79 (1.22–2.63)
≤5 μg/l	Low intensity follow-up	Reference	Reference	Reference
	High intensity follow-up	1.16 (0.95–1.41)	0.90 (0.69–1.19)	0.86 (0.68–1.10)
>5 μg/l	Low intensity follow-up	1.26 (0.71–2.23)	1.51 (0.78–2.95)	1.56 (0.87–2.81)
	High intensity follow-up	1.70 (1.07–2.70)	1.69 (0.95–2.99)	1.75 (1.07–2.88)

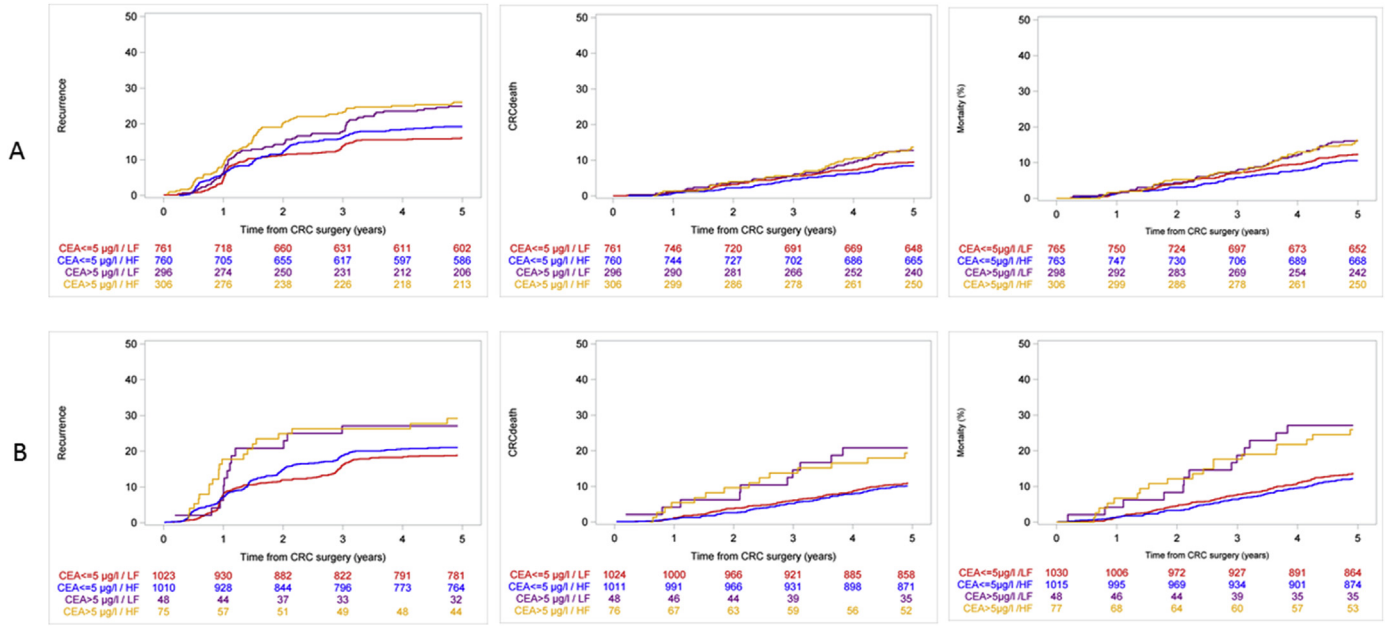

Fig. 2. Colorectal cancer recurrence (*left*), colorectal cancer-specific mortality (*middle*), and overall mortality (*right*) for the two randomization arms, grouped by CEA status. (A) CEA measured before the start of treatment: (B) CEA measured 4 weeks after surgery. Start date: time of surgery for primary colorectal tumor; low CEA: ≤5 μg/l; elevated CEA: >5 μg/l; LF: Low intensity follow-up; HF: high intensity follow-up.

[8–10,12,13]. An association between recurrence and elevated CEA was only observed for elevated pre-treatment CEA levels but not in patients with elevated post-surgery CEA levels. This is in contrast to a previous study [11], but might be associated to a type II error as the risk estimate was imprecise (CI: 0.48–16.41). It has been reported that smokers have higher levels of CEA than non-smokers and also that increased CEA levels can be due to various benign diseases [17]. Hence, an alternative explanation might be that the group of patients with increased CEA after surgery includes patients with other reasons for increased CEA than cancer, which might explain the association with mortality but not with recurrence.

The impact of follow-up intensity in patients with elevated CEA levels

Although patients with elevated CEA levels constituted a high-risk group for poor oncological outcome, the high-intensity follow-up did not affect survival. This lack of effect was consistent with findings from several previous randomized studies [6,15,18], which used different protocols for low-vs. high-intensity follow-up testing, and the Cochrane analyses from 2019 [7]. The Cochrane analysis concluded that salvage surgery with a curative intent was performed more frequently among patients with high- compared to low-intensity follow-up testing after curative surgery for colorectal cancer. Interval recurrences were found less frequently among patients with high- compared to low-intensity follow-up testing. However, no difference in colorectal cancer-free survival or overall survival was seen among patients with high- compared to low-intensity follow-up testing.

These findings indicate that the earlier detection of recurrences did not lead to a cure in a large proportion of these patients, despite the increased ability of treatment with curative intent. This lack of effect might be due to the presence of more aggressive biology in this subgroup of patients. Hence, it is important to identify predictive biomarkers for this group of patients, to enable individualized, aggressive adjuvant treatment.

Although elevated CEA levels have been repeatedly associated with a worse prognosis and a high prevalence of recurrences in colorectal cancer [8–13], no trial has demonstrated a survival benefit of measuring CEA in surveillance regimens. The Cochrane analysis compared 6 studies in which CEA measurements were included in the follow-up programs to one study not including CEA. No difference in overall survival was found [7]. In conclusion, the existing evidence brings into question the routine use of CEA measurements in a follow-up surveillance program after resected colorectal cancer.

Strength and limitations

The main strength of this study was that more than 2500 patients were followed in a randomized trial setting with prospectively collected standardized data. Furthermore, there were only 14 unplanned follow-up testing during the study.

The main limitation was that the randomization was not based on CEA levels, which is a shortcoming when interpreting the results. Furthermore, the number of patients was small in some subgroups. In particular, the group with elevated CEA after surgery included only 125 patients. Thus, although a large study population, caution must be taken when interpreting the results in some of the subgroup analyses due to small sample sizes with subsequent imprecise estimates, especially regarding the group with elevated postoperative CEA. Another limitation was that CEA levels were missing in 15% of patients before treatment and 13% of patients after surgery. The reasons for missing data were probably random, rather than systematic, thus, the presence of missing data was not expected to affect the study results significantly.

Conclusion

Although patients with elevated pre-treatment and post-surgery CEA levels were at high risk of mortality, we found no benefit of an intensive follow-up testing for these groups of patients.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2021.03.235.

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