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EJSO

the Journal of Cancer Surgery

EJSO 41 (2015) 1188–1196

www.ejso.com

Intensified follow-up in colorectal cancer patients using frequent Carcino-Embryonic Antigen (CEA) measurements and CEA-triggered imaging: Results of the randomized "CEAwatch" trial

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Accepted 12 June 2015

Available online 30 June 2015

Abstract

Aim: The value of frequent Carcino-Embryonic Antigen (CEA) measurements and CEA-triggered imaging for detecting recurrent disease in colorectal cancer (CRC) patients was investigated in search for an evidence-based follow-up protocol.

Methods: This is a randomized-controlled multicenter prospective study using a stepped-wedge cluster design. From October 2010 to October 2012, surgically treated non-metastasized CRC patients in follow-up were followed in eleven hospitals. Clusters of hospitals

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http://dx.doi.org/10.1016/j.ejso.2015.06.008

sequentially changed their usual follow-up care into an intensified follow-up schedule consisting of CEA measurements every two months, with imaging in case of two CEA rises. The primary outcome measures were the proportion of recurrences that could be treated with curative intent, recurrences with definitive curative treatment outcome, and the time to detection of recurrent disease.
Results: 3223 patients were included; 243 recurrences were detected (7.5%). A higher proportion of recurrences was detected in the intervention protocol compared to the control protocol (OR = 1.80; 95%-CI: 1.33–2.50; p = 0.0004). The proportion of recurrences that could be treated with curative intent was higher in the intervention protocol (OR = 2.84; 95%-CI: 1.38–5.86; p = 0.0048) and the proportion of recurrences with definitive curative treatment outcome was also higher (OR = 3.12, 95%-CI: 1.25–6.02, p-value: 0.0145). The time to detection of recurrent disease was significantly shorter in the intensified follow-up protocol (HR = 1.45; 95%-CI: 1.08–1.95; p = 0.013).
Conclusion: The CEAwatch protocol detects recurrent disease after colorectal cancer earlier, in a phase that a significantly higher proportion of recurrences can be treated with curative intent.

Keywords: Colorectal cancer; Follow-up; CEA; Stepped-wedge cluster randomized trial (SW-RCT)

Introduction

After curative surgical resection of colorectal cancer (CRC) and termination of adjuvant treatments, patients are offered a follow-up program consisting of imaging, laboratory measurements, and physical examination to detect recurrent disease as early as possible. The use of an intensive follow-up regime results in a modest but statistically relevant improvement in survival compared with a minimal strategy,[1–5] but this conclusion is based on older studies (inclusion period 1983–2001) and most studies were considered to be of poor quality.[6] The survival gain of intensive protocols is considered to be the effect of detecting recurrences at an earlier stage, associated with a higher rate of curative treatment.[6,7]

Routine imaging with ultrasound of the liver is advised twice yearly for the first three years and once annually in years 4 and 5 in the Dutch national guideline (2008) (www.oncoline.nl). Computed Tomography (CT) scanning is an alternative with higher sensitivity,[8] but it is costly and has the potential disadvantages of radiation damage[9] and false positive findings.[10]

The tumour marker Carcino-Embryonic Antigen (CEA) has long been known to be important in signalling recurrent disease in CRC.[11] Intensive follow-up schedules including CEA measurements are correlated with better survival than schedules not using CEA measurements,[7] and serial measurements of CEA are recommended in colorectal cancer follow-up in all international guidelines.[12–14] The rise and doubling time of CEA rather than the absolute value are sensitive in signalling recurrent disease.[11,15] CEA is cheap and available, but is irregularly used in follow-up and has poor protocol adherence.[16,17] No studies of serial CEA measurements and imaging steps in response to significant CEA rise, with special attention to reasonable sensitivity in combination with good specificity, have been performed so far.

There is a need for an evidence-based follow-up guideline defining the optimal frequency and implications of imaging and CEA measurements. A phase-2 trial with monthly CEA measurements showed both high sensitivity and specificity for detection of recurrences using serial CEA rises rather than absolute values.[18] Therefore, a promising solution may be frequent CEA testing with imaging triggered by a significant rise in CEA. The current study compared a new intensified follow-up schedule with care as usual in a randomized multicenter trial and aimed to assess the value of frequent CEA measurements and CEA-triggered imaging in detecting recurrent disease with curative possibilities in CRC patients.

Materials and methods

Trial design

This was a multicenter stepped-wedge cluster randomized (SW-CRT) trial[19,20] conducted in 11 non-academic teaching hospitals in the Netherlands. These hospitals were randomly grouped into five clusters. Detailed explanation on the motivation of using this trial design is given by Zhan et al.[21]

In an SW-CRT, all clusters cross over from control to intervention at certain time points called switches. Instead of randomizing patients to treatment arms, randomization is used to allocate clusters to predefined switches. For the CEAwatch trial, each of the clusters was randomly switched to change from the usual follow-up schedule (control) to the intensive follow-up schedule (intervention); crossover occurred in one direction only. From October 2010 clusters switched from usual follow-up to intensive follow-up every three months one by one; the length between two consecutive switches was three months (Fig. 1).

Randomization was performed independently by Trial Coordination Center (TCC) Groningen (www.tcc.umcg.nl). CEAwatch (Netherlands Trial Register [NTR] 2182) was approved by the Medical Ethics Committee of the University Medical Centre Groningen (METc-UMCG 2010.064) and the local ethics committees of all participating centres. CEAwatch was sponsored by the Netherlands Organization for Health Research and

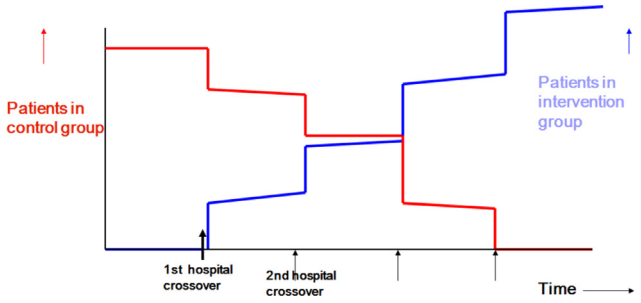

Figure 1. Graphic depiction of the stepped wedge cluster randomized trial.

Development and undertaken in accordance with the principles of Good Clinical Practice.

Participants

Eligible patients were patients with AJCC stage I–III CRC after R0 resection. Patients operated on from 2007 to July 2012 were included. At October 2010, patients who were already in follow-up in the participating hospitals since 2007 were included. Between October 2010 and October 2012, all new patients that entered follow-up in the participating hospitals were included and assigned to the actual protocol of that hospital.

Patients who were not medically fit for metastasectomy, patients diagnosed with other malignancies and patients with metachronous metastases at the start of the study were excluded.

Patient identification and validation

Eligible patients were identified using the diagnosis or operation code(s). At the end of patient recruitment (October 2012), eligibility of all patients was validated using the database of the Dutch Comprehensive Cancer Center (NCCC), a registry of all diagnosed malignancies based on the automated pathological archive (www.iknl.nl).

Patients' characteristics were obtained directly from the Dutch Surgical Colorectal Audit (DSCA) and stored in a password-protected database. DSCA is a national databank gathering all relevant information on surgically treated CRC patients, allowing a valid and complete registration of all CRC patients in the Netherlands (www.clinicalaudit.nl/dsca).

Follow-up schedules

The control or "care-as-usual" protocol consisted of the national guideline in the Netherlands in 2008 (www.oncoline.nl); an outpatient clinic visit every six months for the first three years and an annual visit in years 4 and 5. Liver ultrasound and chest X-ray were recommended at each clinic visit. CEA (half-life: 5 days) was measured every 3–6 months in the first three years and each year in the last two years.

The intervention follow-up protocol adhered to bi-monthly CEA measurements and yearly imaging in the first three years, and 3-monthly CEA measurements in the fourth and fifth years of follow-up. Outpatient clinic visits with imaging of chest and abdomen were performed annually in the first three years. In case of an increase of 20% compared with the previous CEA with CEA value >2.5 ng/mL, another blood sample was drawn four weeks later. If a consecutive rise were was observed, a CT scan of chest and abdomen was advised (Fig. 2). The static normal value of serum-CEA as advised by manufacturers is 2.0–2.5 ng/mL, depending on the actual test.

The coordination and monitoring of this process was supported by an automatic computer system.[22]

Implementation

Patients entering the study before the switch were followed using the control protocol and switched to the intervention after their hospital's switch. Patients entering the study after the randomized switch of a hospital were followed using the intervention protocol only. Patients who met the inclusion criteria on October 1st, 2010, but no longer met these criteria at the switch date participated in the control protocol only. Informed consent was obtained before entering the intervention for all patients as required by the Medical Ethical Committee.

Outcomes

The primary outcome measures were the number of recurrences per follow-up arm, the proportion of recurrences that could be treated with curative intent, the proportion of recurrences with definitive curative treatment outcome (R0 resection of all recurrent disease), and the time to detection of recurrent disease.

Power calculation

The expected percentage of resectable recurrences was 10% in the control protocol and 25% in the intensified protocol.[23,24] Given a significance level of 5% and a power of 80%, 115 patients with recurrent disease in both groups were needed. Given an expected recurrence rate of 25%,[25] 460 patients per group were needed. Given the cluster randomization, we assumed a correlation of 0.1 between hospitals, yielding a correction factor of 1.71.[26] Therefore, a minimum of about 800 patients per group was needed.

Data analysis

Differences in patients' baseline characteristics between the care as usual follow-up and the intensified follow-up

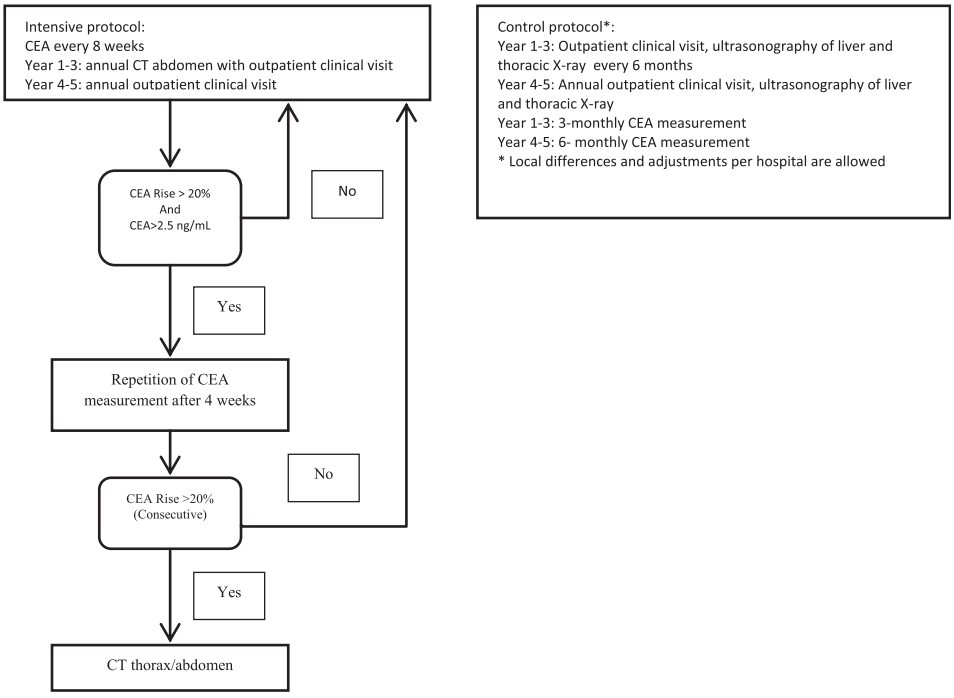

Figure 2. Follow-up schedules.

protocol were calculated using ANOVA and Chi-Square tests.

For each of the three outcomes (recurrence, recurrence with curative intent and recurrence with definite curative treatment outcome), pooled logistic regression was performed to compare the proportion of each outcome between the control follow-up protocol and the intensified follow-up due to the fact that standard statistical technique cannot address the dynamic settings of the follow-up protocol. The study duration was divided into six intervals by the five switch moments. The conditional probability of the outcome measures in each interval, given that this did not happen prior to this interval, was modelled as the dependent variable and the follow-up protocol of each interval was modelled as the independent variable. Meanwhile generalized estimation equation (GEE) was used to allow flexible assumptions of the correlations between each interval. Odds Ratios (OR) with 95% confidence intervals (95%-CIs) were reported for the effects of the intensified follow-up protocols on the detection of recurrences, detection of recurrences treated with curative intent and recurrences with definitive treatment outcome. The Cox proportional hazard model was used to investigate the differences in time till detection of recurrent disease between the follow-up protocols. The follow-up protocols were used as a time-dependent variable since the time in follow-up was dynamic. The time from operation to participation in the study created left truncated data for a subset of patients. Stratification for hospitals was applied. The intervention effect was corrected for gender, age, AJCC stage, and location of the primary tumour and it was reported as hazard ratios (HR) with 95%-CIs. Statistical modelling was performed with SAS statistical software, version 9.3.

Results

Inclusions

From 1-1-2007 till 01-10-2010, 5604 patients from 11 hospitals with stage AJCC I–III colorectal cancer were registered by the Netherlands Cancer Registration; 118 patients were not identified in the hospitals. Of these patients, 2318 met the inclusion criteria; their follow-up data were prospectively collected from 01-10-2010. During the control period, there were 589 eligible new patients identified before the switch dates; 116 patients reached an endpoint (not fit for metastasectomy, recurrent disease before switch date, or other) during the control period. A total of 2791 patients were asked for informed consent prior to the switch dates. Of these, 1725 patients provided written informed consent. For the remaining 1066 patients, prospective data collection of follow-up data ended on the switch dates. During the intervention period, an additional 316 patients gave written informed consent to participate in the intensive follow-up protocol.

A total of 3223 patients were included. 1725 patients participated both in the control protocol and in the intervention protocol, 1182 patients participated only in the control protocol, and 316 patients participated only in the intervention protocol (Fig. 3).

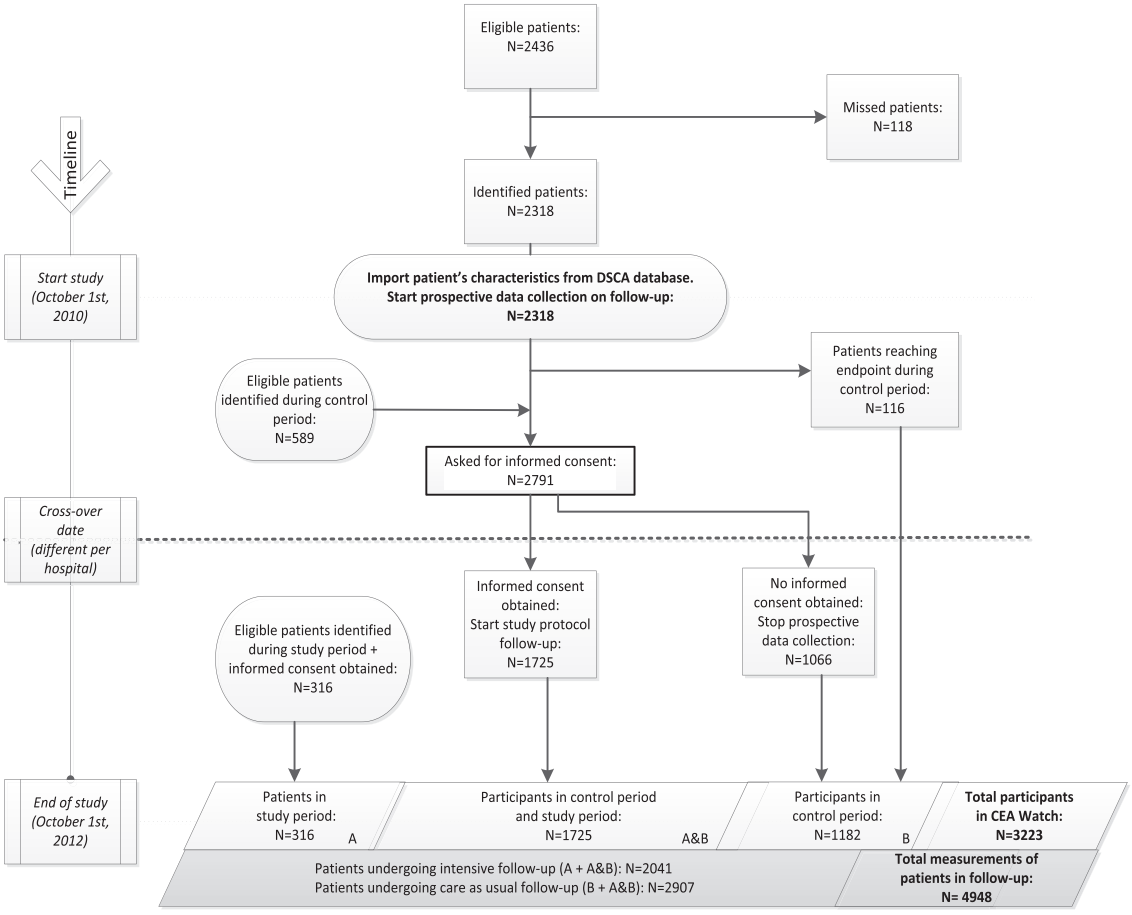

Figure 3. Inclusions.

In total, the control period comprised 2907 patients and the intervention period comprised 2041 patients. Patient's characteristics are given in Table 1. The differences between eligible patients who decided to participate and eligible patients who decided not to participate in the intervention protocol are shown in Table 2.

Recurrences

A total of 243 (7.5%) recurrences were detected during the study (Table 3). 104 (43%) recurrences were found while the patient participated in the control protocol and 139 (57%) recurrences were detected while the patient participated in the intervention protocol. 90 (37.0%) of all recurrences could be treated with curative intent.

The proportion of detected recurrences eligible for curative treatment during the intervention protocol was higher than in the control protocol (42.0% versus 30.0%). Further analysis with results of real pathology (treatment outcome instead of treatment intent) showed that and 70 (78%) of all detected recurrences treated with curative intent had definite curative treatment outcome based on pathology: the proportion of curative treatment outcome was also higher in the intervention than in the control (35% versus 22%).

The location of detected recurrences ($p = 0.134$), AJCC stage of the primary tumour ($p = 0.978$) and the location of the primary tumour ($p = 0.261$) were not different in both follow-up protocols.

Pooled logistic regression showed statistically significant higher proportion of recurrences in the intervention protocol compared to the control protocol (OR = 1.80, 95%-CI: 1.33–2.50, p-value: 0.0004). The proportion of recurrences that could be treated with curative intent was also statistically significant higher in the intervention protocol (OR = 2.84, 95%-CI: 1.38–5.86, p-value: 0.0048).

The OR of recurrences with definite curative treatment outcome was also higher in the intervention protocol (OR = 3.12, 95%-CI: 1.25–6.02, p-value: 0.0145).

The time to diagnosis of recurrent disease, corrected for age, gender, AJCC stage and location of the primary tumour, and stratified by hospital using the Cox proportional hazard model, decreased with the intervention follow-up protocol as compared to the control protocol (HR: 1.45; 95%-CI: 1.08–1.95; $p = 0.013$). This was also shown for the recurrences treated with curative intent

Table 1
Patient's and tumour characteristics (N (%)).

Characteristic	Patients only in control period	Patients in control and intervention period	Patients only in intervention period	Total	p-value[a]
Total (%)	**1182 (37)**	**1725 (53)**	**316 (10)**	**3223 (100)**	
Gender					<0.01
Male	603 (51)	1024 (59)	180 (57)	1807 (56)	
Female	579 (49)	701 (41)	136 (43)	1416 (44)	
Age at diagnosis (years)					<0.01
Median (range)	73 (26–95)	69 (30–93)	67 (29–92)	70 (26–95)	
AJCC stage[b]					<0.01
I	281 (24)	504 (29)	92 (29)	877 (28)	
II	462 (39)	670 (39)	137 (43)	1269 (39)	
III	439 (37)	551 (32)	87 (28)	1077 (33)	
Location primary tumour					0.4
Colon	754 (64)	1068 (62)	206 (65)	2028 (63)	
Rectum	428 (36)	657 (38)	110 (35)	1195 (37)	
Adjuvant chemotherapy[c]	299 (43)	337 (49)	55 (8)	691 (100)	0.04
Yes	187 (63)	249 (74)	45 (82)	481 (70)	
No	112 (37)	88 (26)	10 (18)	210 (30)	
Patients with comorbidity[d]	370 (31)	768 (56)	225 (17)	1363 (100)	0.06
None	145 (39)	369 (48)	95 (42)	609 (45)	
Minor	195 (53)	341 (44)	114 (51)	650 (48)	
Major	30 (8)	58 (8)	16 (7)	104 (7)	

[a] These p-values were calculated using ANOVA and Chi-Square tests.
[b] AJCC: American Joint Committee on Cancer.
[c] For adjuvant chemotherapy, only patients with stage III colon cancers are shown.
[d] For comorbidity, only patients with known comorbidity are shown. P-value is calculated for the group with no comorbidity versus minor or major comorbidity.

Table 2
Comparison between patients deciding to participate in the intervention follow-up protocol and patients deciding not to participate in the intervention protocol.

Characteristic	All patients eligible for intervention protocol	Patients not crossing over to intervention protocol[a]	Patients crossing over to intervention protocol	p-value[b]
Total	**2791 (100)**	**1066 (38.2)**	**1725 (61.8)**	**NA**
Gender				NA
Male	1562 (56)	538 (50)	1024 (59)	
Female	1229 (44)	528 (50)	701 (41)	
Age at diagnosis (years)				0.001
Median (range)	70 (26–95)	73 (26–95)	69 (30–93)	
AJCC stage primary tumour[c]				0.44
I	767 (27)	263 (25)	504 (29)	
II	1093 (39)	423 (40)	670 (39)	
III	931 (34)	380 (35)	551 (32)	
Location primary tumour				0.45
Colon	1744 (63)	676 (63)	1068 (62)	
Rectum	1047 (37)	390 (37)	657 (38)	
Adjuvant chemotherapy				0.13
Yes	737 (26)	295 (28)	442 (6)	
No	2054 (73)	771 (72)	1283 (74)	
Patients with comorbidity[d]	1121 (100)	353 (32)	768 (68)	0.01
None	509 (45)	140 (40)	369 (48)	
Minor	528 (47)	187 (53)	341 (44)	
Major	84 (8)	26 (7)	58 (8)	

[a] These were all the patients eligible to cross over who did not consent to cross-over to the new follow-up regimen.
[b] These p-values were calculated using ANOVA and Chi-Square tests.
[c] AJCC: American Joint Committee on Cancer.
[d] For comorbidity, only patients with known comorbidity are shown. p-value is calculated for the group with no comorbidity versus minor or major comorbidity.

Table 3
Location and treatment of recurrences in control and intervention protocol (N; %).

Variable	Total	Control period	Intervention period	p-value[a]
Recurrent disease	243 (8)	104 (43)	139 (57)	<0.001
Treatment for recurrent disease				0.03
Curative	90 (37)	31 (30)	59 (42)	
Palliative	153 (63)	74 (70)	79 (58)	
Location of recurrent disease				0.13[b]
Liver	89 (36)	41 (39)	48 (35)	
Local recurrence	44 (18)	13 (13)	31 (22)	
Lymph nodes	15 (6)	8 (8)	7 (5)	
Lung	48 (20)	17 (16)	31 (22)	
Other	24 (10)	15 (14)	9 (7)	
Combination	23 (10)	10 (10)	13 (9)	
AJCC stage primary tumour				0.98[c]
I	23 (9.5)	10 (9.6)	13 (9)	
II	89 (36.6)	36 (34.6)	53 (38)	
III	131 (53.9)	58 (55.8)	73 (53)	
Location primary tumour				0.26
Colon	145 (60)	68 (65)	77 (55)	
Rectum	98 (40)	36 (35)	62 (45)	

[a] These p-values were calculated with a logistic regression stratified for centre.
[b] This p-value was calculated by comparing recurrences in liver versus in other locations, stratified for centre.
[c] This p-value was calculated by comparing AJCC stage I and II versus III, stratified for centre.

(HR: 1.76; 95%-CI: 1.07–2.90; $p = 0.027$) and recurrences with definite curative treatment outcome (HR: 6.27; 95%-CI: 3.82–10.30; $p < 0.0001$).

Discussion

In the current study including 3223 patients, it is shown that an intensified follow-up schedule with frequent CEA measurements, CEA slope analyses instead of absolute values and imaging in case of two subsequent CEA rises detects recurrences with higher rate of curable options (42% versus 30%), higher rate of definitive treatment outcome (35% versus 22%) and less time-to-detection compared to a care as usual follow-up protocol. To date there has been no randomized trial for colorectal cancer follow-up with so many participants.

Intensity of colorectal cancer follow-up schedules has been the subject of discussion for decades but in the studies performed to date both the use of CEA and imaging are heterogeneous between studies.[1,2,4,5,8,27] All performed studies so far lack a description of a systematic plan of action in case of a CEA rise resulting in the impossibility to describe the best combination of techniques for the ideal CRC follow-up.[7] The expanding options for curing liver metastases show that intensive systematic searching for liver metastases is worthwhile.[28,29] At least as important is the growing evidence that limited extrahepatic diseases as well as local recurrent disease are no longer an absolute contraindication for intended curative treatment.[30,31] However, the definition of curable or resectable recurrences is difficult and differs per hospital, especially for Radio-Frequent Ablation options and stereotactic radiation therapy.[32]

An optimal follow-up schedule should detect recurrences in an early stage. The balance between false positive findings as a result of a too sensitive test reflecting normal CEA variations or not yet detectable recurrent disease and the too late detection is crucial. An analysis on older data using CEA showed a lack of survival improvement for second-look operations based on CEA rise.[33] The FACS trial, a randomized trial comparing minimal and intensive follow-up, recently confirmed that regular CEA measurements, CT scanning and CEA with CT scanning result in significantly higher rates of curable recurrences compared to minimum follow-up (resp 7.6%, 9.5%, 7.3% and 1.5).[34] However there was no survival improvement between the different follow-up protocols in this study. A recent systematic review and meta-analysis included next to the FACS trial all old studies; a modest survival improvement for intensified protocols was shown.[6] However, it can be questioned whether this estimate is unbiased since the incidence of recurrences is lowering and the options for cure of recurrences are expanding, and only one recent study was included in the meta-analysis. Data from two other prospective trials (the COLOFOL trial[35] and the GILDA trial,[36] both comparing overall and disease-specific survival between different follow-up schedules) will become available.

Relatively few recurrences (7.5%) were found in the here presented study; the expected recurrence rate for AJCC stages I–III of colorectal carcinomas is about 20%.[37] In the FACS study this percentage is also lower in comparison with the older literature, namely 16%. The Dutch national guideline on routine preoperative staging with CT scan seems to result in more synchronous and less metachronous metastases.[38] Hereby the intention of the study is to cover a period of five years of follow-up and patients with a disease-free period before the schedule started were included. The prospective data collection of these patients started sometimes 2–3 year after resection, decreasing the expected recurrence rate. The total number of patients included was high enough to detect statistically significant differences.

A strong point in this study is the high data integrity, as all data on patients' and tumour characteristics were exported from a national audit which is known to be filled out for up to 97% of all colorectal cancer patients (www.clinicalaudit.nl). Data monitoring was performed through a secondary validation using the NCCC, which is the complete cancer registration in the Netherlands. Another strong point of this study was the uniformity of the intervention protocol and high adherence to the protocol. This was the result of a software-support system for the management

of all patients in the intervention group, an intranet-based software system written to support clinicians working with patients in follow-up. The software support has been shown to be safe and efficient.[22]

Internationally, CT scanning is common practice and ultrasound with thoracic X-ray which seem a bit old-fashioned. However this study is performed to compare the usual follow-up with a new schedule; the study was performed during the time that the 2008 Dutch national guideline was used and this guideline advised X-ray and ultrasound.

The SW-CRT has not previously been used for the purposes of a follow-up study. Advantages of the design are the inclusion of large patient groups in a short time period and the avoiding of in-hospital protocol contamination. On the other hand, patients participating in both follow-up protocols are always later in the intervention protocol than in the control protocol, which makes the SW-CRT not a pure RCT. Meanwhile, the incidence of recurrence tends to change over time during follow-up. Most recurrences are found in the first two years of follow-up, but retaining percentages of recurrences are seen in the years thereafter.[29] Thus, it can never be known whether the observed effects are completely due to the intervention. However, as shown in the results, the increase in resectable recurrences was not entirely due to the increases of recurrences since the effect size of the intervention is much larger for resectable recurrences.

The current study shows that an intensified protocol with CEA and assessment on CEA rise rather than absolute value detects recurrences earlier than the standard protocol, which is related to an increase in curable recurrence rate. The results advocate an intensification of CEA measurements and more frequent action at CEA rises in follow-up. The FACS study is using an absolute CEA cut-off point of 7 μg/l compared to baseline instead of slope analyses; in the discussion the authors advocate further analyses on this matter, but in the current results of this study, already addressing CEA changes, no further conclusions on this topic can be drawn. The final proof of the value and strength of this new protocol will be if the effects of the intensified CEA-based follow-up strategy will result in higher disease-specific and overall survival, with acceptable quality of life and cost-effectiveness rates.

Conflict of interest statement

All authors declare that there is no conflict of interest.

Acknowledgements

This trial was sponsored by the Netherlands Organization for Health Research and Development (project number: 171002209). Registration: Netherlands Trial Register NTR 2182.

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