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ORIGINAL ARTICLE

Can carcinoembryonic antigen replace computed tomography in response evaluation of metastatic colorectal cancer?

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ABSTRACT

Introduction: Response Evaluation Criteria in Solid Tumours (RECISTs 1.1) define computed tomography (CT) as the gold standard in response evaluation of patients with metastatic colorectal cancer (mCRC) who are undergoing chemotherapy. The aim of this study was to evaluate whether carcinoembryonic antigen (CEA), which is cheaper and easier to perform, can replace repeated CT.

Material and methods: The study included 66 patients with non-resectable mCRC participating in a phase I–II study. CEA values were determined, and CT images were taken every 2 months. CT images were externally and retrospectively reviewed according to the RECIST 1.1 criteria. Different cut-off values for CEA change in percent (DeltaCEA%) compared with baseline or nadir value underwent testing to find patients with disease control (that is stable disease, partial or complete response) at 2, 4, 6 and 8 months, in order to identify those who could have continued with chemotherapy based on CEA values alone. CT verification is needed in progressive disease (PD), and therefore identifying PD patients was our secondary endpoint.

Results: The results showed that by using a cut-off value of 0 for DeltaCEA%, disease control was seen in all patients at all measuring points (negative predictive value (NPV) = 1.0). Secondarily, increasing CEA was able to identify all PD patients (sensitivity (Se) = 1.0) and in 50–74% of the patients increasing CEA provided a lead time to PD on upcoming CT. It was possible to replace CT with CEA in all patients with decreasing CEA, meaning that 23–47% of CT scans could have been avoided at any given time point.

Conclusion: When the CEA level at a certain measuring point is the same or lower than CEA at baseline or at nadir (the measuring point with the lowest CEA value) during treatment, CEA can replace CT.

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Introduction

Response evaluation of oncological treatments is based mainly on structural imaging with computed tomography (CT) or magnetic resonance imaging (MRI) every two to three months, according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria (that have replaced the WHO criteria) [1]. However, response evaluation based on imaging is not always feasible, because patients may have a disease difficult to measure by CT or MRI such as diffuse peritoneal dissemination, or imaging results may be misleading early in the course of treatment, as in immunotherapy, or the capacity for imaging may be limited as it is resource-demanding. An ideal follow-up of mCRC patients undergoing systemic therapy would include a method that is accurate, reliable, simple, patient-friendly, fast and inexpensive.

Tumor markers offer an alternative or complement to imaging. Carcinoembryonic antigen (CEA) is today the marker of choice for response evaluation in mCRC during systemic therapy. CEA measurement should begin at the start of treatment for metastatic disease and occur every 1–3 months during active treatment [2,3]. Persistently rising values above baseline on three separate occasions suggest progressive disease (PD) even in the absence of corroborating radiographs [2]. Caution is, however, necessary when interpreting a rising CEA level during the first 4–6 weeks of a new therapy, since spurious early rises of CEA may occur especially after oxaliplatin-based chemotherapy [2–8].

In the literature, we found 14 studies comparing CT and CEA for response evaluation in mCRC [9–22]. Settings differed slightly among these studies, as did their end-points. CEA and CT were repeated every 2 months in all but three studies which used 1.5- and 3-month CT intervals, respectively.

We could find no consensus on the cut-off values for CEA to define response, progression or stable disease (SD). The definition of CEA progression varied between 15–200%

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Supplemental data for this article can be accessed here.

increase from the baseline [9,12–17,19,20] and 0–50% CEA decrease compared with baseline for response [9,12,13,15–17,19,22]. SD is defined as between these variable cut-offs. Only two studies have looked at dichotomized response, meaning PD versus disease control, either complete response (CR), partial response (PR) or SD [9,20]. According to the ASCO guidelines, two values above baseline are adequate evidence of PD, but no exact values for increase in CEA appear in either the ASCO or EGTM guidelines [2,3].

The main objective of follow-up of patients receiving palliative oncologic therapy for mCRC is to identify disease progression at the earliest opportunity in order to adjust treatment accordingly. Continuation of non-beneficial treatment is detrimental for both patients and society; it is resource-consuming without providing any quality-of-life or survival gain. In patients receiving palliative therapy, disease control is clinically meaningful [23] and does not need to be characterized meticulously by radiology at short intervals. CEA could replace CT evaluation if a reliable cut-off for disease control could be identified.

Our study comprised 66 patients with mCRC receiving palliative chemotherapy. The primary aim of our study was to find the optimal CEA cut-off value that would identify disease control patients who could continue with chemotherapy without CT verification, and a secondary aim was to find PD patients using CEA, and thus to reduce the need for repeated CT evaluations at short intervals.

Material and methods

A phase I–II clinical trial included 81 consecutive, eligible and consenting patients at Helsinki University Central Hospital between March 30, 1998, and February 21, 2001. Each received raltitrexed (1.5-) 3.0 mg/m^2 on cycle day one as an intravenous infusion and carmofur 300 (−400) mg/m^2 orally divided into three daily doses on cycle days 2–14, followed by a week of rest. The doses in parenthesis were those for the six patients in the phase I portion of the study, but all other patients received the stated raltitrexed treatment [24,25]. Of these 81 patients, 66 had at least two CEA values and CT scans available at baseline and at 2 months and were included in the study. Of these 66 patients, 47 (71%) received treatment as first line and 19 (29%) as second line. Table 1 shows patient characteristics. Median age was 61 years. A good balance existed between gender and site of primary tumor. Of these 66 patients, 39% had metachronous and 61% synchronous metastases, with liver and lung as the most common metastatic sites. Median number of metastatic sites was 2 (range 1–5). Eastern Cooperative Oncology Group (ECOG) performance status was 0–2 with two thirds being 1.

Serum CEA was determined by the AutoDELFIA® assay (Wallac, Turku, Finland) at the Helsinki University Hospital laboratory in Finland. A CEA level $\leq$5 μg/ml was considered normal.

The study protocol was approved by the local Ethics Committee and the National Agency for Medicines, Helsinki,

Table 1. Patient characteristics in those eligible to receive raltitrexed and carmofur chemotherapy for mCRC as first line or second line treatment.

	All patients ($n = 66$)	First-line 47 (71%)	Second-line 19 (29%)
Median age, years (range)	61 (41–76)	59 (40–73)	64 (45–76)
Gender			
Male	33 (50%)	26 (55%)	7 (37%)
Female	33 (50%)	21 (45%)	12 (63%)
ECOG			
0	9 (14%)	6 (13%)	3 (16%)
1	45 (68%)	32 (68%)	13 (68%)
2	12 (18%)	9 (19%)	3 (16%)
Pre-chemotherapy CEA			
≤5	7 (11%)	3 (6%)	4 (21%)
>5	59 (89%)	44 (94%)	15 (79%)
Primary tumor			
Colon	37 (56%)	23 (49%)	14 (74%)
Rectum	29 (44%)	24 (51%)	5 (26%)
Metastatic disease			
Metachronous	26 (39%)	20 (43%)	6 (36%)
Synchronous	40 (61%)	27 (57%)	13 (68%)
Adjuvant therapy			
None	50 (76%)	32 (68%)	18 (95%)
5-FU-based	16 (24%)	15 (32%)	1 (5%)
Chemotherapy cycles			
Median	8	9	4
Range	2–23	2–23	3–9
Metastatic sites			
Liver	53 (83%)	37 (79%)	16 (84%)
Lung	40 (61%)	28 (60%)	12 (63%)
Distant lymph nodes	16 (24%)	11 (23%)	5 (26%)
Peritoneum	4 (6%)	2 (4%)	2 (4%)
Pelvis	2 (3%)	1 (2%)	1 (5%)
Adrenal glands	2 (3%)	2 (4%)	0 (0%)
Ovaries	2 (3%)	1 (2%)	1 (2%)
Other[a]	3 (4%)	2 (4%)	1 (2%)

[a]Other includes metastases in the spleen (1 patient), kidneys (1 patient) and vagina (1 patient).

Finland, and informed consent was required from all patients.

Response evaluation

Computed tomography of the chest, abdomen and pelvis, together with CEA determination, was performed within 4 weeks before the first chemotherapy cycle and repeated every 2 months. Serum CEA was measured on the last day of the chemotherapy cycle. During the phase I and II studies, CT scans were evaluated by one experienced radiologist. For this retrospective study, CT response was externally reviewed according to the RECIST 1.1 criteria by an experienced gastrointestinal radiologist (E. L.) blinded to outcome, clinical benefit and CEA level [1]. CT response served as the gold standard for evaluation of treatment response.

Statistical analyses

Pearson correlation (*r*) served to evaluate the correlation between CEA and the target sum according to the RECIST at baseline and during the chemotherapy at 2, 4, 6 and 8 months. The distributions of CEA and target sum were skewed to the right and were logarithmically (ln) transformed before analysis. The method of generalized estimating equations (GEE) with linear regression analysis allowed description of the association between logarithmically transformed CEA and target sum when all five measuring points were considered at the same time. Spearman rank correlation (rho) served to correlate changes in CEA and in progression-free survival (PFS).

The percentage changes in CEA (DeltaCEA%) were calculated from baseline or at nadir, whichever was lower, according to RECIST criteria for target sum.

Receiver operating characteristic (ROC) and waterfall plot curves served to evaluate the cut-off values of 0% and 20% of DeltaCEA% and to find the best cut-off point with the best combination of sensitivity and specificity to differentiate between disease control and progression. The gold standard for response evaluation (disease control (CR, PR or SD) and PD) is the RECIST 1.1 criteria.

We used the following definitions:

DeltaCEA% values $\leq$0% and $\leq$20% were defined as negative and values $>$0% and $>$20% as positive.

Sensitivity (Se) = the proportion of PD patients correctly identified positive by DeltaCEA%.

Specificity (Sp) = the proportion of disease control patients correctly identified as negative by DeltaCEA%.

Positive predictive value (PPV) = the proportion of positive DeltaCEA% patients correctly identified as PD.

Negative predictive value (NPV) = the proportion of negative DeltaCEA% patients correctly identified as disease control.

Accuracy = the proportion of patients correctly identified as disease control or PD.

The aims were to find disease control patients and PD patients. Therefore, high NPV and high sensitivity were the main criteria for optimal cut-off values.

PFS was calculated from inclusion into the trial until disease progression or death from any cause, and overall survival (OS) from study inclusion until death from any cause, unless patients were censored at last day of follow-up at 198 months. The Kaplan–Meier method served to estimate survival curves and median survival times with 95% confidence intervals ($CI_{95\%}$). Cox proportional hazards models and Log rank tests served to compare survival probabilities between patients with different DeltaCEA% categories and in the first vs. second line analysis. Results are given as hazard ratios (HR) with 95% confidence intervals.

Two-tailed *p* values $<$.05 were considered statistically significant. Analysis involved IBM SPSS Statistics for Windows (version 23.0, IBM Corp., Armonk, NY, USA), and Kaplan–Meier statistics with Sigmaplot (version 11.0 SysStat software Inc, San Jose, CA, USA).

Results

Correlation between CEA and target sum according to the RECIST 1.1

A statistically significant linear correlation existed between CEA and the target sum at all measuring points except

Table 2. CEA and target sum and Pearson correlation between them at baseline and during chemotherapy treatment at 2, 4, 6 and 8 months.

	Baseline	2 months	4 months	6 months	8 months
CEA (μg/l)					
N	66	66	44	30	12
GMeana	59.2	48.6	63.2	68.1	64.5
Median	50.0	36.4	49.3	52.8	16.3
IQRb	10–248	7–270	7–359	8–309	11–168
Range	1.6–36,600	1.3–6170	1.7–6790	1.5–12,500	5.9–23,200
Target sum (mm)					
N	66	66	46	30	16
GMean	87.3	79.1	76.6	80.9	64.1
Median	97.0	93.0	89.5	89.0	78.5
IQR	60–140	55.0–128	52–130	60–150	58–112
Range	10–285	10–250	10–247	10–300	10–152
Correlationc					
r	.37	.43	.44	.47	.41
p value	.002	$<$.001	.003	.01	.19

[a]Geometric mean.
[b]Inter-quartile range.
[c]CEA and target sum logarithmically (ln) transformed before analysis.

Table 3. Frequency, negative predictive value (true disease control out of patients with decreasing CEA) and missed progressions (PD patients) in patients with decreasing CEA. Frequency, sensitivity (true PD of patients with increasing CEA), and a lead time to PD on upcoming scan 2 months later in patients with increasing CEA at assessment time- points: baseline, 2, 4, 6 and 8 months. CT scans postponable is percentage of CT scans that may be postponed at a given time point.

		Decreasing CEA (DeltaCEA ≤0%)[a]			Increasing CEA (DeltaCEA >0%)[a]					
Time period	No. of evaluable patients	*N* (%)	NPV	Missed PD patients	*N* (%)	PPV	Lead time to PD on next CT[b]	Se	Sp	Post-ponable CTs
0–2 months	66	31 (47)	31/31 (100)	0 (0)	35 (53)	11/35 (31)	16/24 (67)	11/11 (100)	31/55 (56)	47%
0–4 months	44	10 (23)	10/10 (100)	0 (0)	34 (77)	15/34 (44)	14/19 (74)	15/15 (100)	10/29 (34)	23%
0–6 months	29	1 (3)	1/1 (100)	0 (0)	28 (97)	20/28 (71)	2/3 (67)	20/20 (100)	1/9 (11)	3%
0–8 months	12	0 (0)	–	–	12 (100)	8/12 (67)	2/4 (50)	8/8 (100)	0/4	–

Results are given as number of patients (%).
[a]In relation to lowest value at baseline or nadir during treatment, according to RECIST principles.
[b]Increasing CEA without progression on CT at the measurement time point, but with progression on the upcoming CT two months later.

at 8 months with its low number of cases (Table 2). GEE analysis including all five measuring points simultaneously found a significant ($p < .001$) linear association: ln(target sum) $= 3.736 + 0.180 \times$ ln(CEA). A positive correlation was observed between DeltaCEA% and Delta target sum% at all measuring points independently, whether the change was calculated from baseline (Spearman's rho coefficients .68–.80, p values $< .002$) or from nadir value (Spearman's rho coefficients .36–.67, p values $\leq .05$).

Baseline CEA within the normal range

Seven patients (11%) had a pre-chemotherapy CEA value within the normal range (CEA ≤5.0 μg/l), but none had a value under the detection limit (CEA <1.0 g/l). All patients with baseline CEA within the normal range had a significant CEA elevation upon progression. CEA elevation was within the normal range in three cases and above normal in four cases upon progression.

Optimal CEA cut-off for finding patients with disease control

ROC curves at 2, 4 and 6 months showed that DeltaCEA% compared with baseline gave a greater area under the curve (AUC) than did absolute CEA values or change in CEA (data not shown). At 2 months, a cut-off value of 31% gave the best sensitivity and specificity combination when CEA at 2 months was compared to baseline. For 4, 6 and 8 months, when compared only to baseline CEA value, the cut-offs were 57%, 23% and 19%, respectively. Thereby, we chose a 20% increase as the cutoff for further testing.

When CEA was compared with lowest measured CEA level, either baseline or nadir value, then significantly higher values were noted (32%, 154%, 210% and 489%). ROC curves for comparison between baseline and 4 months or baseline/nadir and 4 months are presented in Supplementary Figure 3.

Waterfall plots visualize the correlation between Delta target lesion sum % and DeltaCEA% (Supplementary Figure 4). We noted that all PR patients according to imaging had decreasing CEA, and all PD patients had increasing CEA. Of 36 cases, in 16 (44%) with SD according to RECIST, increasing CEA provided lead time to PD on upcoming imaging. Thus, 0% of DeltaCEA% was chosen as the arbitrary second cut-off for further testing.

Decreasing CEA and disease control

In the group with decreasing CEA, meaning DeltaCEA% ≤ 0%, compared with baseline or nadir value, disease control on CT was apparent in all patients (100%) at 2, 4 and 6 months (Table 3). Treatment thus could have been continued without CT verification in 47%, 23% and 3% of patients on treatment at 2, 4 and 6 months, respectively. None of the patients with decreasing CEA had PD according to target sum ≥20% or due to new lesions on CT (Table 3, Supplementary Figure 4).

The highest NPV, 1.0, was evident at the measuring points 2, 4 and 6 months when DeltaCEA% was ≤0% (Figure 1 and Supplementary Table 4(A)). Cut-off 20% yielded similar NPV results (Figure 1 and Supplementary Table 4(B)). The ROC-curve-defined best cut-offs yielded NPV estimates of 0.98, 0.90, and 0.57 (Figure 1 and Supplementary Table 4(C)).

Specificity was 0.11–0.56 at measuring points 2, 4 and 6 months for cut-off 0%, 0.33–0.75 for cut-off 20%, and 0.78–0.90 for ROC-curve-defined cut-offs (Figure 1 and Supplementary Table 4(A–C)).

Accuracy was low for both cut-off points, (0.57–0.72 for 0% and 0.68–0.79 for 20%) and highest for ROC-defined cut-offs (0.76–0.86; Figure 1 and Supplementary Table 4(A–C)).

Increasing CEA and disease progression or lead time to progression

The ability to identify PD patients in the group with increasing CEA according to RECIST principles (DeltaCEA% ≤0%) was 100% at 2, 4, 6 and 8 months, respectively. A CEA increase at a given time point without progression on CT provided lead time to progression on the next assessment 2 months later in 67%, 74%, 67% and 50%, respectively. A CEA surge was still noticeable at 9 weeks in one patient (2%), but was apparent in more patients at 3 and 6 weeks (frequency not calculable as data not available for all patients).

Sensitivity was 1.0 at 2, 4 and 6 months when the cut-off 0% was used for DeltaCEA% (Figure 1 and Supplementary Table 4(A)). A cut-off of 20% also yielded a sensitivity of 1.0 (Figure 1 and Supplementary Table 4(B)). Thus, cut-offs 0% and 20% gave equal sensitivity, whereas

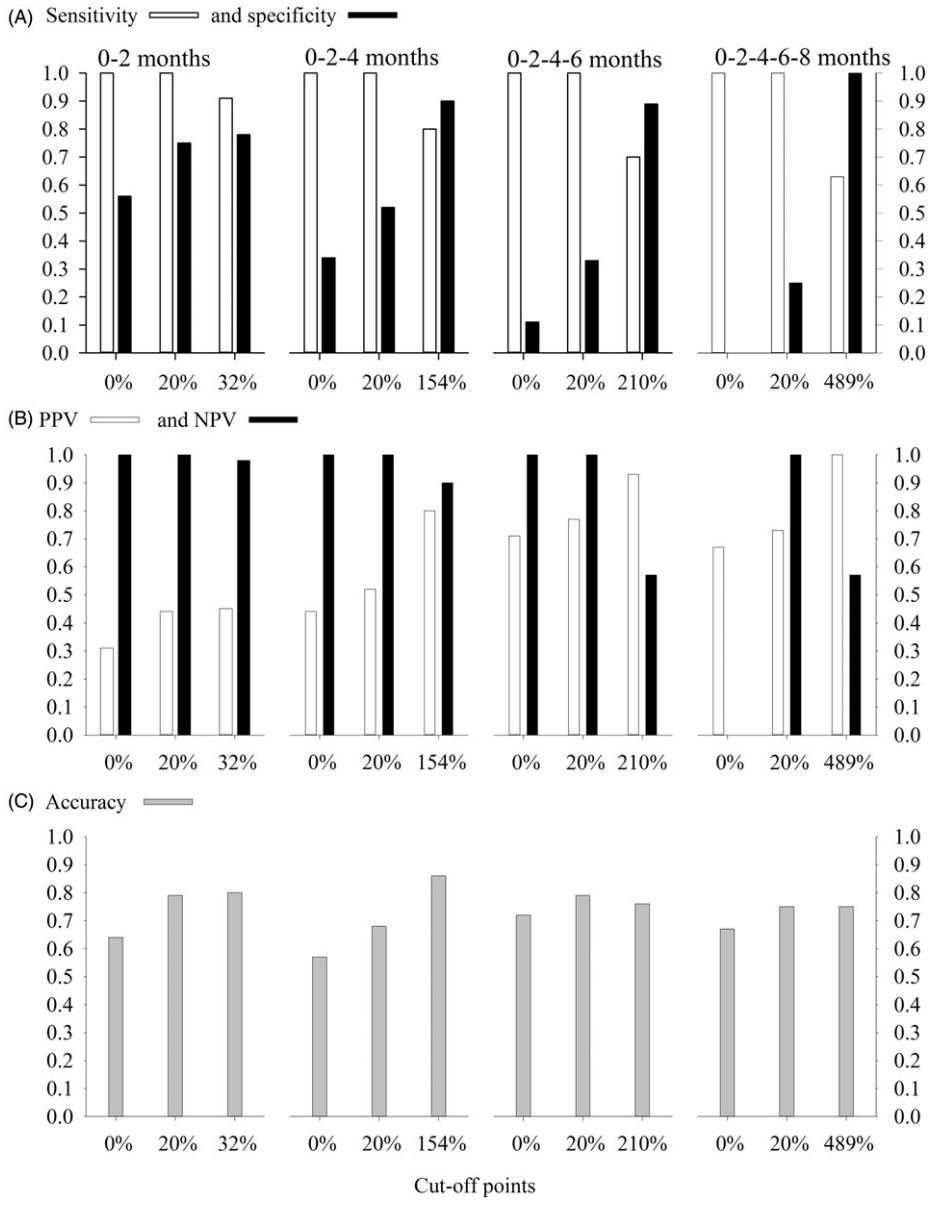

Figure 1. Sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and accuracy for percentage change in CEA (DeltaCEA%) to detect progression (PD) during time-intervals 0–2 ($n = 66$), 0–4 ($n = 44$), 0–6 ($n = 29$) and 0–8 months ($n = 12$). DeltaCEA% was calculated from baseline or from the nadir during treatment, whichever the lowest. Selected cut-off points for DeltaCEA% were 0%, giving the highest sensitivity, and NPV based on the waterfall plot, and were 20%, giving the highest sensitivity, and NPV based on ROC curves. The third cut-off point was based on the ROC analysis giving the best combination of sensitivity and specificity.

the ROC-curve-defined cut-off yielded lower sensitivity (Figure 1 and Supplementary Table 4(C)).

PPV was 0.31, 0.44 and 0.71 at the respective measuring points with cut-off 0% and was slightly better (0.44–0.77) for 20% (Figure 1 and Supplementary Tables 4(A) and 4(B)). The ROC-curve-defined cut-offs yielded the best PPV (0.45–0.93, Figure 1 and Supplementary Table 4(C)).

Progression-free and overall survival with raltitrexed and carmofur combination treatment

Median PFS was 5.9 ($CI_{95\%}$ 5.0–6.7) months for all 66 patients, and OS 11.7 ($CI_{95\%}$ 9.2–14.2). The corresponding figures for the 47 PFS first-line patients were 6.6 ($CI_{95\%}$ 5.9–7.2) months and for the 19 second-line patients 3.9 ($CI_{95\%}$ 1.6–6.3) months ($p < .001$, Supplementary Figure 5). The median OS for the first-line patients was 13.4 ($CI_{95\%}$ 9.2–17.6) months and for the second-line patients 8.0 ($CI_{95\%}$ 3.1–13.0) months ($p = .030$, Supplementary Figure 6). Six patients stopped treatment early due to toxicity and further line treatment was given to the seven first-line patients (15%), with irinotecan to five, FOLFOX to one, and fluoropyrimidines to one. Updated toxicities were in line with the previous reports of the phase I [24] and II [25] studies.

Decreasing CEA as a prognostic marker

DeltaCEA% at 2 months was negatively correlated with longer PFS (rho −.44; $p < .001$). Patients with a decreasing CEA at 2 months had significantly longer PFS, 6.6 versus 4.3

months (HR 0.51 [$CI_{95\%}$ 0.31–0.83], $p = .006$; Figure 2(A)) and longer OS, 15.5 versus 10.9 months, (HR 0.58 [$CI_{95\%}$ 0.35–0.97], $p = .036$; Figure 2(B)). To control for guarantee time bias, analysis with the landmark method at two months was performed and significance was noted for both PFS and OS (data not shown). At no other time-points, did a correlation appear with OS or PFS.

Discussion

According to our findings, a reduction of CEA compared with baseline or nadir level, whichever is lower, is associated with disease control in 100% of the cases. Secondly, an increasing CEA level identifies 100% of PD patients, and provided a lead-time to progression in 50–74% of the others. At 2 months, a reduction is possible in the number of CT scans of 47% and at 4 months of 23%.

The growing cost of medical care is a challenge for society today. We need to find new and more cost-efficient ways to care for our patients without reducing care quality. We thus find it surprising that, to the best of our knowledge, only 14 studies have reported on comparison of CEA and CT in evaluation of treatment response in mCRC [9–22]. Some suggest that CEA is better than CT for response evaluation in patients with peritoneal carcinomatosis [11]. Trillet-Lenoir et al. found that CT could be avoided in 13% when progression is defined as a >200% rise in CEA [14]. De Haas et al. claim that CEA could be sufficient for response evaluation in a palliative chemotherapy setting with disease control as the endpoint, but give no figures for omitting CT [9]. Kim et al. note that CEA >20% could be useful in monitoring tumor progression during palliative chemotherapy, but give no figures for omitting CT [15]. Wang et al. report a sensitivity of elevated CEA for prediction of progressive disease of 70–81% and accuracy of 85–90% [12,13]. Hanke et al. report a CEA rise by at least 50% as differentiating between PD and disease control with a sensitivity of 76% and specificity of 90% [20].

We would like to challenge these reports. We claim that CEA can replace CT in larger contexts than described. Instead of trying to diagnose disease progression by CEA increase or limiting ourselves to patients with conditions difficult to distinguish on CT, we focused on finding a cut-off value for CEA that would identify patients with disease control on CT.

Among several cut-off values tested for a CEA increase, the optimal value turned out to be 0%. CEA at the same level or decreasing compared to the lowest measured CEA value, either baseline or nadir, identifies all our patients with disease control on CT. To our knowledge, we are the first to use 0% as cut-off and the second to use nadir values [17]. NPV is 1.0 both with cut-off at 0% and at 20%. When CEA comparison is made only with baseline values, NPV is significantly lower, 0.55–0.94.

None of the patients with decreasing CEA has PD; sensitivity is thus 1.0 at all measuring points when compared to the nadir value, but 0.75–0.93, when compared only to baseline. This is in line with previous findings 0.50–1.00, using cut-offs −50% to +50% compared with baseline [9,12,13,15,19,20].

Our results show that 23–47% of our patients could continue their chemotherapy based on CEA evaluation alone and that no CT verification is necessary at their early time points, which is in line with the 55% reported by Hanke et al [20], but not reported in the majority of other studies.

PPV at different time points is 0.31–0.71, which is slightly lower than in studies choosing a higher cut-off for CEA. The low PPV is not a concern, since we are not trying to identify PD patients with increasing CEA, as PD patients need a CT for decision-making as to their further treatment (if to be given). Specificity is 0.56–0.75 with a cut-off of 0%, and 0.25–0.75 with cut-off 20%. This is in line with previous findings 0.47–1.00, with cut-off −30% to +50% compared with baseline [9,12,15,19,20]. The specificity is of no concern in this setting, since a lead time to progression occurred in the majority of cases with disease control on imaging, and patients with an increasing CEA value would require a CT scan for further treatment evaluation.

A decreasing CEA at 2 months correlated with longer OS and PFS, also in line with most earlier findings [13,16–18,21,22]. Diverse results have been published, Bystrom et al. conclude that baseline CEA is more informative than the CEA slope confounded by for example CEA surge and lead time to progression [10]. According to de Haas et al., preoperative CEA change is not prognostic for survival at 3 and 5 years after metastasectomy [9].

CEA within the normal range is not negative in the same sense as a negative CA19-9 value, which in 10% of Caucasian patients is not expressed due to their lack of the Lewis antigen [26]. Several studies find that CEA monitoring is likely to underestimate disease progression if baseline CEA is within the normal range [15,17,21,22]. In our study, 11% of the patients had initially normal CEA, in line with 10–27% in other studies [12–15,19,21]. CEA is above the reference range at progression in 57%, also in line with others' findings [12–15,19,21]. We identify all disease control and PD patients with the cut-off value for CEA at 0% and evaluating change in per cent. This cut-off worked even within the reference range. With higher cut-offs, some PD patients are missed [9,12,13,15,19]. Fluoropyrimidines, especially with oxaliplatin or to a lesser extent with irinotecan, cause an initial transient CEA rise, called a flare or surge, in 11–18% [6–8,10,27], and so also in this patient cohort [28]. The peak is reported at 2–3 weeks and its duration is 8–9 weeks [5,6]. As opposed to constant rise in CEA, a surge reflects non-progression [5,7]. Tumor-marker surge is not of significant concern when interpreting results of this study, because a CEA increase would automatically lead to CT assessment, as recommended by Sorbye et al. [4]. Secondly, marker surge is mostly over (2%) at 2 months.

Our study comprised 66 patients, which is comparable to others' studies with their median of 90 (range 33–265) patients [9–22]. The strengths of our study are that treatment is the same for all patients (it varied in 10 of the other studies) and laboratory tests and CT imaging took place prospectively at a single institution as part of a phase I–II study, as in the substudy of the Nordic VI (94 patients with CEA) [10], or as in the study by Ward (33 patients taking part in a multicentre study) [19], as opposed to retrospective assessments

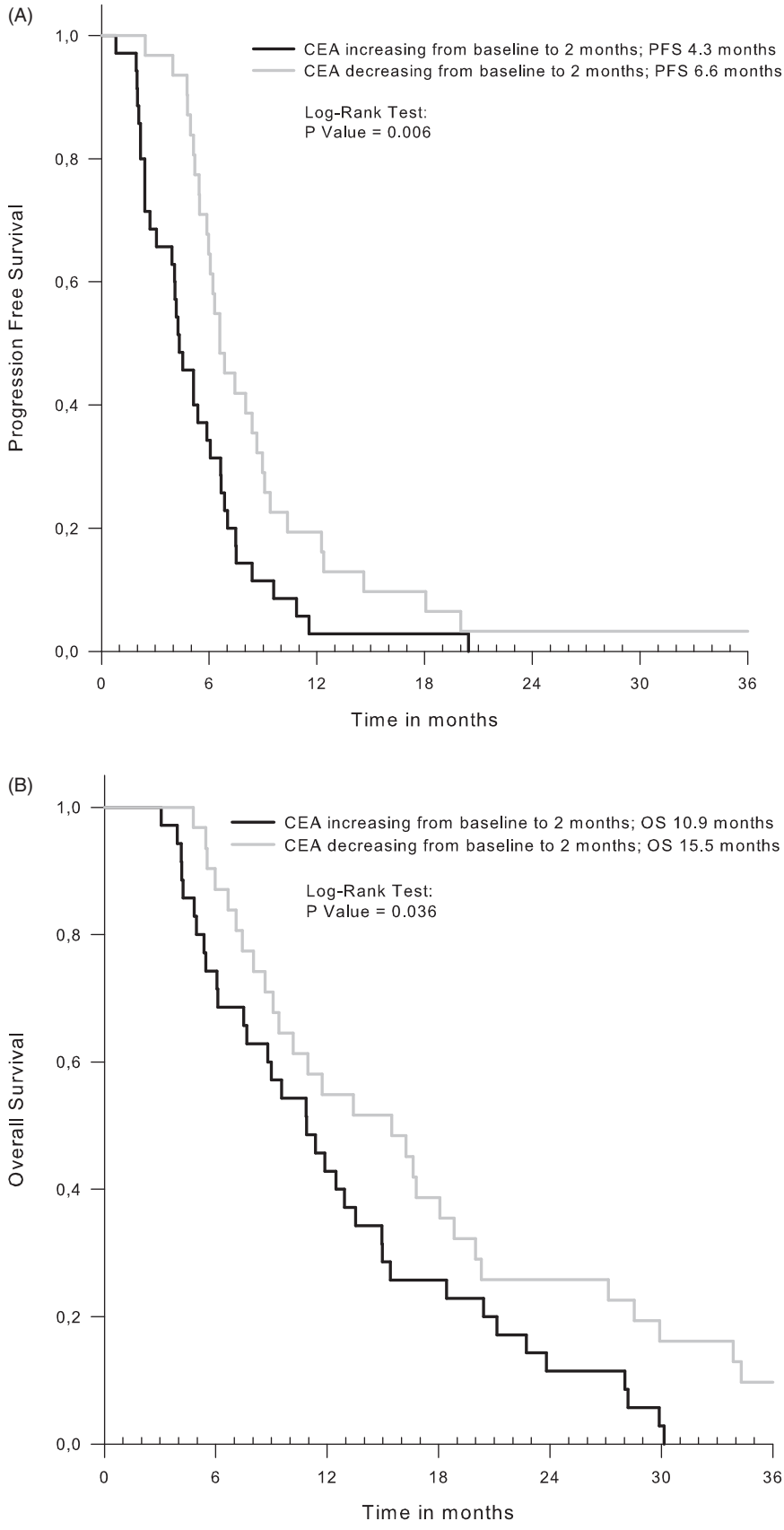

Figure 2. (A) Kaplan–Meier curve for progression-free survival (PFS), divided by increasing or decreasing CEA at 2 months: first-line treatment ($n = 47$, 71%) and second-line ($n = 19$, 29%). (B) Kaplan–Meier curve for overall survival (OS) divided by increasing or decreasing CEA at 2 months: first-line treatment ($n = 47$, 71%) and second-line ($n = 19$, 29%).

of patient series in the 12 other studies [9,11–18,20–22]. The CT scans of our study underwent external review by an experienced gastrointestinal radiologist, in a blinded manner, according to RECIST 1.1 criteria; to our knowledge, this is not the case in the other studies. We and Grem et al. are the only researchers to compare RECIST principles both for CT and CEA assessment with nadir value or baseline, whichever is lower [17]. We also present comparison data for each measuring point separately, whereas some studies used only baseline plus one measuring point during treatment [9,15].

The day that tumor marker assessment occurs is also valid, as it is the last day of the chemotherapy cycle immediately before the next cycle (one day before or same morning as cycle starts), as mentioned in Grem et al [17]. Significant fluctuation may occur in the middle of the cycle [28], which may contaminate CEA assessment if performed during mid-cycle with nadir full-blood counts. Cycle day of CEA measurement is not mentioned in the majority of the studies.

Some limitations of our study are that the chemotherapy combination is old-fashioned, and we use no targeted agents. Raltitrexed in combination with a fluoropyrimide, in this case carmofur, was promising in the late 1990s [29,30], as well as in the present phase I–II studies [24,25]. Smoking is not recorded, but most of our patients are non-smokers.

In conclusion, when CEA level at a certain measuring point is the same or lower than CEA at baseline or nadir, it can replace CT in response evaluation. This would mean a reduction of 23–47% in CTs needed. However, because of the scarcity of studies in this field, we strongly propose confirming this by studies with modern chemotherapy and targeted agents. If our findings can be verified, they can change clinical practice with a benefit for both patients and hospitals.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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