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ORIGINAL ARTICLE

Carcinoembryonic antigen reduction after medical treatment in patients with metastatic colorectal cancer: a systematic review and meta-analysis

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Abstract

Purpose The introduction of new drugs and multimodal treatments for the management of patients with metastatic colorectal cancer (mCRC) has reduced the importance of time-to-event endpoints and reported the attention on the response-related endpoints. Furthermore, the prognostic role of the surgical scores before the resection of metastases has not been confirmed for multimodal treatments. The purpose of this research is to perform a meta-analysis of the studies that evaluated the relationship between carcinoembryonic antigen (CEA) response and outcome in patients with mCRC receiving systemic chemotherapy.

Methods A systematic review of the literature on two databases and a selection of studies that evaluated the relationship between CEA response and outcome were performed according to predefined criteria. After, three meta-analyses were carried out on the selected studies, each for each outcome variable.

Results Nineteen studies have been selected. Fourteen studies (1475 patients) have documented a close association between radiological response and CEA response (odds ratio (OR), 9.03; confidence intervals (CIs), 5.14–15.87; I^2 statistic (I^2), 72%). Four studies have reported a longer progression-free survival for patients with a CEA response (hazard ratio (HR), 0.73; CIs, 0.64–0.83; I^2, 23%). Finally, 10 studies (13 study cohorts) have shown a strong relationship between CEA response and overall survival (OS) (HR, 0. 62; CIs, 0.55–0.70; I^2, 35%).

Conclusions CEA response merits further investigation as a surrogate endpoint of clinical trials of first-line medical therapy of patients with mCRC, and should be studied as a prognostic factor for those patients who are candidates for multimodal treatment strategies.

Keywords Colorectal cancer · Carcinoembryonic antigen · Prognosis · Multimodal therapy · Endpoint

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related death among men and the third among women in European Union [1]. Metastases are the most important cause of death for patients with CRC. Treatment of patients with metastatic colorectal cancer (mCRC) by surgical resection of metastases has become the standard of care over the past 20 years, especially for patients with liver and/or lung metastases, resulting in about 20% long-term survivors [2]. Preoperative chemotherapy has proven useful in an integrated therapeutic approach in which most patients receive a complete surgery of metastases. In any case, even after a radical resection of all metastases, more than 30% of patients die from cancer within 2 years [3]. For this reason, an accurate stratification of the risk of recurrence becomes crucial for the selection of patients to be submitted to surgery of metastases, in order to optimize and personalize their treatment. Changing the standard of care for mCRC, from surgery to multimodal therapy, has challenged traditional prognostic factors and surgical scores. The prognostic scores for patients with mCRC were, in fact, largely based on surgical series of pre-chemotherapy era, and did not include variables such as metabolic response or tumor response to chemotherapy [4]. Furthermore, the introduction of biologics has further prolonged the post-progression survival after first-line

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chemotherapy of patients with mCRC, decreasing the relationship of time-to-event endpoints with overall survival (OS) and their efficacy in evaluating the activity of chemotherapy, while correlation between response-related endpoints and OS was maintained [5, 6].

Carcinoembryonic antigen (CEA) is a complex glycoprotein of the membrane surface, which belongs to the immunoglobulin super-family of cell adhesion molecules, also known as CEACAM5 or CD66e [7]. Although CEA production is detectable in 90% of CRCs, an increase in serum CEA levels above the upper normal limits is detectable in just 30–40% of patients diagnosed with CRC at any time. This is due to two reasons for variability, such as the rate of CEA expression by CRCs and the metabolism of CEA after the first passage to the liver in different patients [8]. Despite this, a recent study of 280 patients with CRC concluded that the CEA appears to be the best of four biomarkers, detecting CEA levels about ten times higher in the tumor compared to the normal colon [9]. It can be hypothesized that in patients with mCRC, among those that express high serum concentrations of CEA, the kinetics of tumor growth measured by CEA, before and after chemotherapy, may have a prognostic value independent from that of the clinical, pathological and molecular features, but also with respect to the same baseline serum concentration of CEA. To date, although it is known that patients with a reduction of CEA after chemotherapy have a more favorable outcome, all prognostic scores before the resection of metastases continue to take into consideration only the preoperative serum level of CEA.

This study aims to perform a systematic review and meta-analysis of published studies, reporting the results of the relationships between CEA response and outcome variables of patients with mCRC who receive systemic chemotherapy.

Methods

Study selection

The purpose of the research was to identify all primary literature by examining the relationship between a CEA response and the outcome indicators of mCRC, such as OS, progression-free survival (PFS), overall radiological response rate (ORR). The research strategy was performed according to the following criteria: "(colon or colic or colorect*) and (carcinoma or adenocarcinoma or cancer or neoplas* or tumor) and (advanced or metasta*) and (prognos* or survival or mortality) and CEA". The search term has been inserted in the PubMed and Web of Science databases, without time limits. Systematic reviews and reference lists have been cross-checked for studies missed by the search term. If the studies were derived from the same data set, the most recent or most complete article was retained. Only the published results were included in this review.

After examining the titles of the articles and the exclusion of duplicates by GC and AV, the titles and abstracts were selected as relevant for the purpose of the review. Afterwards, the abstracts were evaluated by all three authors, the most likely items for inclusion in the analysis were identified, further reducing the number of selected articles. The additional literature was identified through the reference list of these selected articles and other review articles, by GC and AV.

All patients in the selected studies were diagnosed with mCRC and received systemic anti-neoplastic chemotherapy. Full-text articles have been examined with respect to certain quality criteria: a prospective or retrospective design with a well-defined study population; clear description of the methods for calculating the CEA response and its cutoff; reporting of at least one of the three variables of outcome; a number of at least 20 patients included. For each study, some variables were extracted and evaluated as possible moderators of the relationship between CEA response and outcome results: cutoff of the CEA response; age; percentage of male patients; median follow-up; year of publication; retrospective or prospective design.

Statistical analysis

Three meta-analyses have been planned for evaluating the relationship of the CEA response to each of the three outcome measures (ORR, PFS, OS). The null hypothesis tested was the absence of a significant association of CEA response with the outcome. The odds ratios (ORs)/hazard ratios (HRs) and the confidence intervals (CIs) relative to the overall effect size were calculated using a random-effects model meta-analysis. Whenever the HR was not presented in the original publication, it was calculated from the survival curve, as previously reported [10]. For the current analyses, the CEA response cutoff used by the authors of each study was adopted.

The heterogeneity between studies was assessed using the Cochrane's Q-test and the I^2 statistic, defining a significant heterogeneity as p value < 0.10 and/or $I^2 > 50\%$. In the case of significant heterogeneity, the possible role of some variables of the studies on the relationship between CEA response and outcome measure was evaluated. In the case of numerical variables, a meta-reggression was carried out according to the DerSimonian and Laird method, but if there were fewer than 10 studies that reported the explanatory variable(s) of interest, the meta-regression was not performed. In the case of categorical variables, a subgroup analysis was performed when the number of studies allowed it.

To assess the risk of publication bias, the Egger's test was reported. Two-sided p values were calculated, with a p value < 0.05 considered significant for all tests. Finally, meta-regressions for numerical moderators were performed to evaluate the effect of moderators on heterogeneity. All three meta-analyses were conducted using the ProMeta software (version 3.0), meta-regression was done by using the statistical computing language R (version 3.4.0 for Linux).

Results

On November 9, 2017, the search term was entered into the PubMed and Web of Science databases, with no limits, and 904 and 1094 articles were returned respectively. The titles of the articles were examined and duplicates were excluded. From the titles, 353 abstracts were selected. After reviewing the abstracts, 48 potentially suitable full-text articles were retrieved. The reference lists of these articles and the cross-checking of the reference lists of systematic reviews revealed 15 additional articles relevant to the research topic. Only 19 articles out of 63 reported at least one relationship between the CEA response and outcome, and were finally selected [11–29]. The literature search process is resumed in the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flowchart in Fig. 1.

Among the selected studies, an article retrospectively reported the outcomes of 4 independent cohorts of a randomized study, three articles showed results of prospective trials and 14 reported retrospective case series. In 6 of 19 studies, patients received a combination of chemotherapy with a biological agent, bevacizumab or anti-EGFR (anti-epidermal growth factor receptor) monoclonal antibody. In 13/19 studies, the cutoff of the CEA response after chemotherapy consisted of a reduction of CEA serum levels of at least 50%, in a study of at least 75% (Table 1 suppl).

Each of the three meta-analyses rejected the respective null hypothesis, detecting a significant association of CEA response with ORR, with PFS and with OS. The global effect sizes of these relationships were consistent, as it is shown in Table 1.

CEA and radiological response

The CEA response is highly correlated with ORR (OR, 9.03; Fig. 2a), but the studies are very heterogeneous (I^2, 72%) and influenced by publication bias (Egger's test of 2.67; p value, 0.004). Details of the selected studies are shown in Table 2.

CEA and progression-free survival

Only 4 studies reported the results of the relationship between CEA response and median PFS after chemotherapy (Table 2). These studies confirm a better PFS for patients with CEA response (HR, 0.73; Fig. 2b), although the relationship was significant only for studies with a CEA response cutoff > 50% or > 75%.

CEA and overall survival

Finally, a strong relationship between CEA response to OS was reported in 10 studies (Table 2), with HR, 0.62 (Fig. 2C). Only 1/3 study cohorts with a CEA response cutoff < 50% showed a significant relationship between the CEA response and OS, while 7/10 with a CEA response cutoff > 50% reported a significant correlation.

Analysis of the heterogeneity of the studies

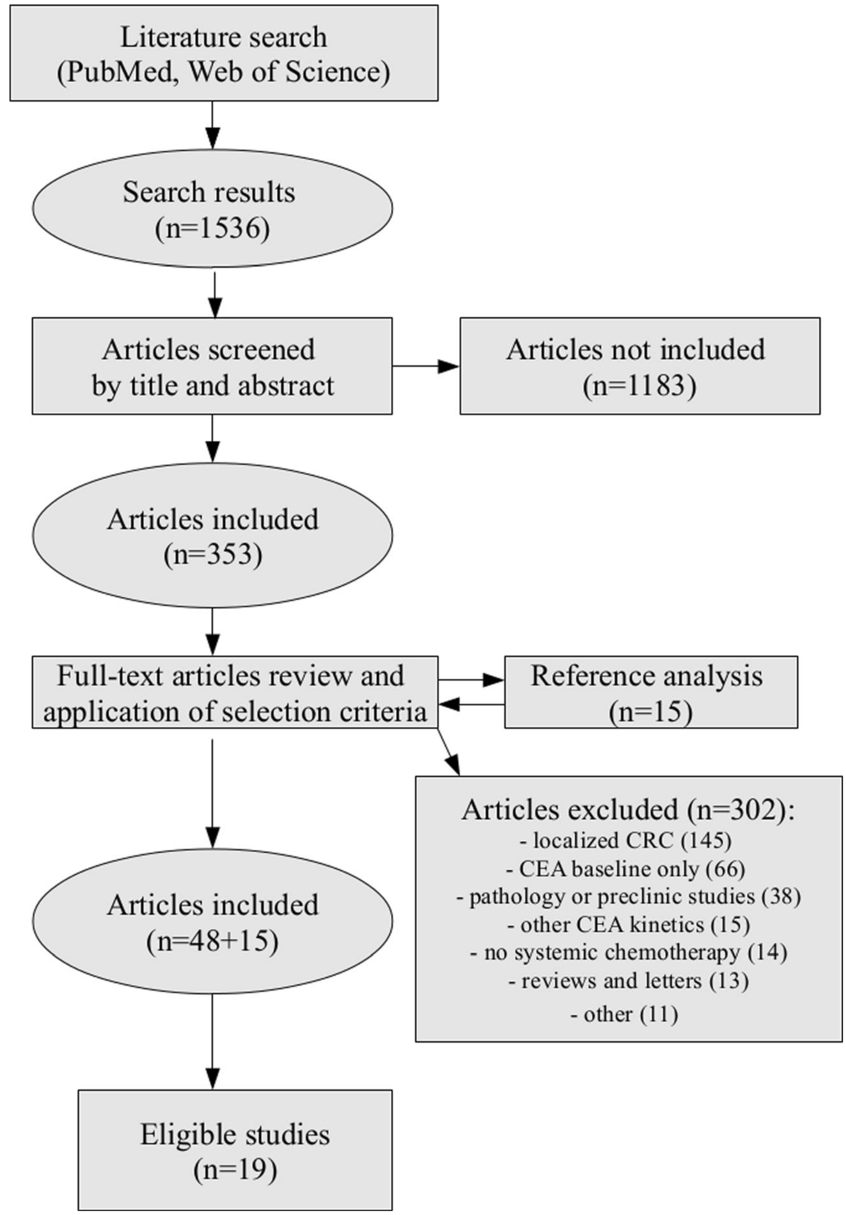
We detect significant heterogeneity in the first meta-analysis, that exploring the relationship of CEA response with radiological response (I^2, 72.22%; Q, 46.80, p value < 0.001), whereas the heterogeneity was limited in the other two meta-analyses, in which CEA response was related to PFS (I^2, 23.15%; Q, 7.77; p value, 0.256) and to OS (I^2, 35.51%; Q, 18.61; p value, 0.098). In order to explain the possible sources of such heterogeneity in the 14 studies that evaluated the relationship between CEA response and ORR, a meta-regression of potential explanatory variables was performed, i.e., patient numbers, baseline CEA cutoff, and age, as resumed in Table 2 suppl. Only age was significantly able to explain the high heterogeneity of the studies: median age spanned from 58.5 to 64.0 years among the studies, and OR halved moving from studies with median younger age to studies with older patients. Conversely, the low number of studies did not allow a subgroup analysis to explore the role of CEA response cutoff, chemotherapy regimen, radiological response assessment criteria and publication year as sources of study heterogeneity. However, in the subgroup of 12 studies with CEA response cutoff ≥ 50%, effect size and heterogeneity did not differ from those of the entire sample of 14 studies (ORR, 7.27; CIs, 4.17–12.67; I^2, 67.32%; Q, 33.66; p value < 0.001).

Discussion

The results of the three meta-analyses confirm the prognostic role of CEA kinetics after medical therapy in patients with mCRC and suggest an effect of the CEA response on each of the three outcome variables. Despite the heterogeneity of the 14 studies reporting the relationship between CEA response and radiological response, the overall effect size appears to be pronounced (OR, 9.03). In contrast, the studies that analyzed the relationship of the CEA response with PFS and of the CEA response with OS showed a low rate of heterogeneity and a good effect size, with HR of 0.73 and 0.62, respectively.

However, the current study has some limitations. First, the bibliographic searches were performed only on two databases. The selected studies are predominantly retrospective, with wide heterogeneity regarding radiologic responses, which

Fig. 1 PRISMA diagram flow



have been evaluated by the World Health Organization (WHO) criteria in 8/19 trials and by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria in other 8/19. Furthermore, given the trial-level character of the analysis, the CEA response cutoff ranges vary widely between a reduction > 20% and > 75%, and only one study defined the cutoff of CEA response by performing the receiver operating characteristic analysis, identifying a reduction in the concentration of CEA of at least 75% as the best threshold [29]. Also, the duration of study follow-up was variable, ranging from 17 to 35 months. Another problem with the heterogeneity of the studies derives from the report of some studies: the data of the CEA response in some randomized studies have been reported by arm or by other stratification criteria, as it appears for the FIRE3 trial, which reported the data per arm of treatment (chemotherapy plus cetuximab compared to chemotherapy plus bevacizumab) and extension of the analysis of mutations of rat sarcoma family (RAS) genes. The levels of baseline CEA cutoff for enrollment were different between studies depending on the local laboratory, ranging from 3.1 to 10.0 ng/mL (see Table 1 suppl), they were not reported in 5 studies, while in one study the CEA response was analyzed regardless of the baseline level [29]. Finally, many HRs were not reported so that they were derived from the Kaplan-Meier curves.

Baseline CEA has been suggested as an integration to the TNM staging system [30] and, according to some authors, the kinetics of the CEA after chemotherapy could provide prognostic information similar to that of the RECIST criteria [28]. The results of our analysis support this hypothesis and strongly recommend future prospective studies with the

Table 1 Results of the meta-analyses

Parameter	Result
CEA response and radiologic response rate	
No. study cohorts	14
No. patients	1475
Effect size (OR)	9.03
Confidence interval	5.14–15.87
p value	< 0.001
Heterogeneity	
Q (*p* value)	46.80 (< 0.001)
I^2	72.22%
Publication bias	
Egger's test (*p* value)	2.67 (0.004)
CEA response and progression-free survival	
No. study cohorts	7
No. patients	959
Effect size (HR)	0.73
Confidence interval	0.64–0.83
p value	< 0.001
Heterogeneity	
Q (*p* value)	7.77 (0.256)
I^2	23.15%
Publication bias	
Egger's test (*p* value)	−1.28 (0.588)
CEA response and overall survival	
No. study cohorts	13
No. patients	1926
Effect size (HR)	0.62
Confidence interval	0.55–0.70
p value	< 0.001
Heterogeneity	
Q (*p* value)	18.61 (0.098)
I^2	35.51%
Publication bias	
Egger's test (*p* value)	1.49 (0.121)

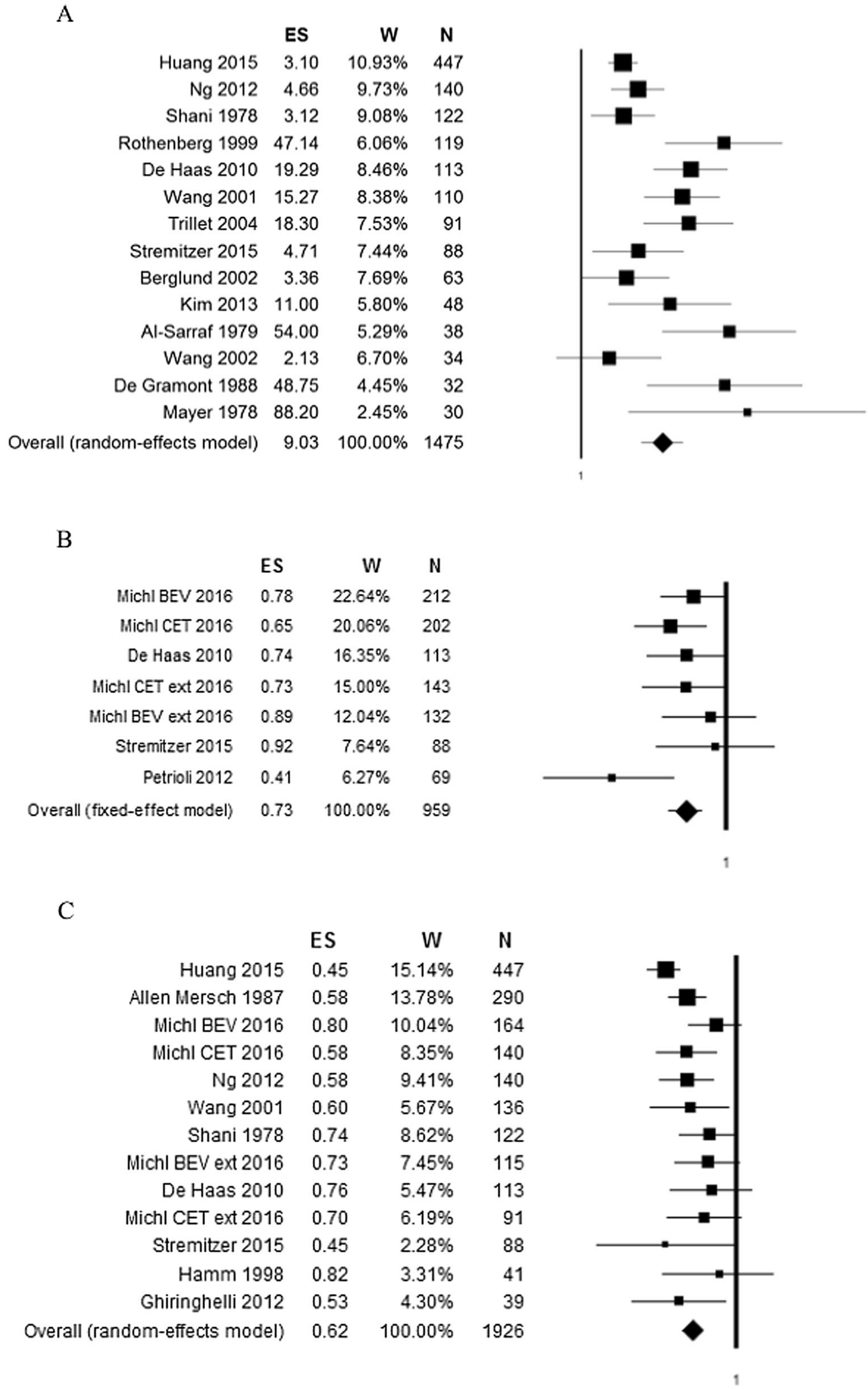
simultaneous assessment of the radiological response rate by RECIST criteria and of CEA response in patients with mCRC receiving systemic chemotherapy. In our opinion, the timing of CEA determination after chemotherapy for the definition of the serological response deserve a lot of attention in future research, since the importance of time for the serological response is similar to that for radiological response, as recently highlighted for radiologic response by the role of early tumor shrinkage after chemotherapy in patients with mCRC. Moreover, for the CEA, it is necessary to take into account the phenomenon of the surge, avoiding too early CEA determinations, and assuming that the optimal timing could be between 8 and 12 weeks after the beginning of chemotherapy. Similarly to the radiological response, for a better evaluation of the serological response, the depth of the response and the time for the maximum reduction should also be considered, as suggested by some authors [29].

However, among patients with mCRC, those for whom the prognostic role of CEA response is more interesting are those who are susceptible to a radical resection of metastases. One of the recent studies has not documented any relationship between CEA response and pathological response of metastases after chemotherapy, but confirmed the close relationship between CEA response and ORR and between CEA response and OS [28]. Among patients with mCRC, the baseline CEA was included in several scores and nomograms to evaluate the prognosis before resection of liver metastases [31]. In contrast, the prognostic role of CEA response after preoperative chemotherapy has been poorly studied, although it may provide additional prognostic information, which could be included in scores or nomograms.

Recently, some authors have studied the prognostic importance of the baseline CEA serum concentration and have found that it is independent of the tumor stage, and have reported that it improved the prediction of prognosis when associated with the stage compared to the 7th AJCC staging system alone [30, 32]. At each stage, a high concentration of serum CEA at baseline was associated with a worse survival [32–36]. In most of the selected studies, among patients with a mCRC, the serum concentration of CEA at baseline was related to a poor prognosis [37, 38], and patients with mCRC and normal CEA generally reported longer OS after chemotherapy, regardless of performance status and tumor burden [38, 39]. However, within metastatic disease, there are several levels of CEA expression, as it has been hypothesized for so long [40], and a different pattern of expression has been reported in metastatic sites, with lung metastases expressing low levels of CEA [41, 42].

In addition, the CEA acts as a time-dependent variable throughout the course of the CRC, regardless of treatments, and appears to correlate with the number of circulating tumor cells [38, 43]. According to some authors, it is not the serum concentration of CEA but the slope of the CEA after chemotherapy that is related to the prognosis [44, 45]. This kinetic variable probably expresses further prognostic information, and today the complex relationship between the CEA level and the prognosis of mCRC can no longer be explained simply as an effect of a "subclinical metastatic disease" [35, 36, 46]. In fact, it would be more appropriate to associate the high CEA level with an activated molecular pathway than with the disseminated stage. A recent study on the expression of mRNA of tumors expressing CEA has documented that at least 100 genes have changed their expression profile, and at least four pathways have been involved, with the induction of the epithelial-mesenchymal transition [47]. At the same time, the clinical features of CEA-positive CRCs appear different,

Fig. 2 Trials exploring the relationship between CEA response and ORR (**A**), CEA response and RFS (**B**), and CEA response and OS (**C**)



with tumors expressing very aggressive metabolic behaviors, as suggested by the high sensitivity of the 18-fluoro-deoxy-glucose positron emission tomography (^{18}FDG PET) examination in patients with mCRC and elevated CEA [48–50].

It follows that CEA response after chemotherapy is a variable linked to the kinetics of the CEA, and probably to the basal slope of the CEA, and as such, should be interpreted from a biological point of view. The studies

Table 2 Studies evaluating CEA response-related variables and their relationship with outcome measures after chemotherapy in patients with metastatic colorectal cancer receiving chemotherapy

Year	Author	No pts. evaluated	CHT	CEA-R (yes vs not)	OR	CIs	*p* value
1978	Mayer	30	F	4/26	88.20	3.60–2160.50	0.006
1978	Shani	122	F	33/89	3.12	1.31–7.44	0.010
1979	Al-Sarraf	38	F	9/29	54.00	8.87–328.82	< 0.001
1988	De Gramont	32	F	15/17	48.75	5.99–396.51	< 0.001
1999	Rothenberg	119	O	29/90	47.14	9.71–228.77	< 0.001
2001	Wang	136	F	34/102	15.27	5.49–42.38	< 0.001
2002	Berglund	63	F	20/43	3.36	1.04–10.90	0.043
2002	Wang	34	F	17/17	2.13	0.52–8.76	0.293
2004	Trillet	78	F	26/52	18.30	5.44–61.56	< 0.001
2010	De Haas	113	FO	75/38	19.29	7.06–52.71	< 0.001
2012	Ng	140	FOB	76/64	4.66	2.27–9.57	< 0.001
2013	Kim	48	FO	14/34	11.00	2.10–57.50	0.004
2015	Huang	447	FOB	228/219	3.10	2.08–4.62	< 0.001
2015	Stremitzer	88	FOB	61/27	4.71	1.37–16.17	0.014
Year	Author	No. pts. evaluated	Follow-up (m)	PFS (m)	HR	CIs	
2010	De Haas	75 v 38	34	9 v 7	0.74	0.54–1.02	
2012	Petrioli	38 v 31	16.7	12.2 v 7.6	0,41	0.24–0.67	
2015	Stremitzer	61 v 27	34.3	12 v 11	0.92	0.58–1.47	
2016	Michl BEV ex2	104 v 108	39	7.4 v NR	0.78	0.60–1.03	
2016	Michl BEV ext	88 v 44	39	NR	0.89	0.61–1.28	
2016	Michl CET ex2	124 v 78	33	11.8 v NR	0.65	0.49–0.87	
2016	Michl CET ext	72 v 71	33	NR	0.73	0.52–1.01	
Year	Author	No. pts. evaluated	Follow-up (m)	OS (m)	HR	CIs	
1978	Shani	33 v 89	NR	8.5 v 6.5	0.74	0.53–1.03	
1987	Allen-Mersch	206 v 84	NR	12 v 8.8	0.58	0.47–0.72	
1998	Hamm	9 v 32	NR	16 v 10	0.82	0.44–1.53	
2001	Wang	34 v 102	48	28 v 13	0.60	0.38–0.93	
2010	De Haas	75 v 38	34	33 v 33	0.76	0.48–1.20	
2012	Ghiringhelli	29 v 10	11	14 v 7	0.53	0.31–0.90	
2012	Ng	76 v 64	33.6	16 v 7.8	0.58	0.42–0.78	
2015	Huang	228 v 219	20.1	30 v 17	0.45	0.37–0.54	
2015	Stremitzer	61 v 27	34.3	108 v 48	0.45	0.21–0.98	
2016	Michl BEV ex2	78 v 86	39	29.4 v 23.6	0.80	0.59–1.06	
2016	Michl BEV ext	56 v 59	39	30.8 v 22.3	0.73	0.50–1.05	
2016	Michl CET ex2	78 v 62	33	36.6 vs 21.3	0.58	0.41–0.81	
2016	Michl CET ext	55 v 36	33	38.3 v 23.7	0.70	0.46–1.07	

B, biologic drug (bevacizumab or cetuximab); BEV, bevacizumab; CEA-R, carcinoembryonic antigen response; CET, cetuximab; CIs, confidence intervals; CHT, chemotherapy; ex2, KRAS exon 2 wild-type arm; ext, RAS extended wild-type arm; F, fluoropyrimidine-based chemotherapy; HR, hazard ratio; m, months; NR, not reported; O, other cytotoxic drug (irinotecan or oxaliplatin); OR, odds ratio; OS, overall survival; PFS, progression-free survival

included in this analysis found that post-chemotherapy CEA response is correlated with the CEA at baseline, lymphovascular invasion and degree of differentiation, the type of chemotherapy and the RECIST response, but has an independent relationship with OS [27], although for some other authors the prognostic role would be limited to cases who received a surgery of metastases [22].

CEA influences the biology of tumor cells through autocrine mechanisms, leading to an increase of cell survival and an inhibition of tumor cell differentiation, and by paracrine regulations, with activation of endothelial cells and tumor angiogenesis [51, 52]. CEA is a driver of tumor angiogenesis independent of the vascular endothelial growth factor (VEGF) pathway. Soluble CEA is sufficient to induce pro-angiogenic endothelial cell behaviors, and tumor microvascularization appears higher among patients with higher levels of serum CEA [51]. Soluble CEA has been shown to perform various functions [51], such as inhibiting the differentiation and apoptosis of tumor cells in vivo [53], cooperating with various cellular processes that promote tumorigenesis and metastasis [53–55]. In studies conducted on cell lines, it has been documented that the expression of CEA on the cellular membrane was higher in tumor stem cells than in the normal colon, and the suppression of CEA expression induced a clear reduction in proliferation and clonogenic potential [56]. The expression of CEA could eventually trigger or promote a tumor-favoring state of immunosuppression [36, 57].

To complicate the interpretation of the kinetics of the CEA is the surge phenomenon: it consists of a transient increase of the serum CEA, which occurs within 2–4 weeks and falls back after 8–12 weeks, which is associated with a clinical benefit from systemic therapy [39, 58]. For this reason, the timing for the evaluation of CEA response would be theoretically optimal after at least 12 weeks from the beginning of chemotherapy, contrary to what has been proposed in the past and in some studies selected for the current analysis [19].

Although the trend of the CEA after chemotherapy is related to that of the disease, regardless of the radiological response [36], the relationship between drugs and the expression of CEA is poorly studied [59]. It appears that the high basal serum concentration of CEA is associated with resistance to fluorouracil-based chemotherapy [60] and anti-angiogenic drugs [61, 62]. Data on the relationship between baseline levels and the kinetics of CEA with the efficacy of a treatment with monoclonal antibodies are even more limited. Given the complex relationship between radiological response and outcome after regimens including anti-angiogenic drugs, the role of CEA response in these patients may be relatively more important [63, 64], while the relationship between CEA response and outcome after anti-EGFR therapy in patients with a mCRC appears similar to that between ORR and outcome [29]. In our study, the relationship between CEA response and ORR was stronger when considering the cohorts of prospective studies (3 study cohorts; OR, 19.65; data not reported) compared to retrospective ones (11 study cohorts; OR, 7.60; data not reported). This could be attributable to the more restrictive criteria of response evaluation, moving from WHO to RECIST, or to different chemotherapy regimens, as suggested by the different OR among the studies with fluoropyrimidine alone regimens (8 study cohorts, OR, 10.48; data not reported) and those with doublets plus a biologic drug (3 study cohorts, OR, 3.50; data not reported). However, we think that restrictive criteria for evaluation of radiologic response could be more important than drugs in reflecting a different prognosis, also data of the association between CEA response and OS, which was closer in prospective studies (6 study cohorts; HR, 0.59; data not reported) compared to retrospective (7 study cohorts; HR, 0.67; data not reported), also suggest.

Conclusions

In conclusion, CEA response with a cutoff of a reduction of at least 50% the baseline (75% in patients with mCRC and RAS wild-type) after chemotherapy is a valid prognostic factor and a possible secondary endpoint of clinical trials. For patients with mCRC who receive a multimodal treatment, it deserves further evaluation as a surrogate endpoint of OS and as a stratification factor for patients undergoing surgery of metastases. A possible role of CEA kinetics instead of RECIST criteria for tumor assessment after chemotherapy has been suggested by some authors [28, 65] and the present analysis supports this consideration, strongly recommending a prospective study evaluating the radiological response rate according to RECIST criteria compared to CEA response in patients with mCRC receiving systemic chemotherapy, as well as a retrospective evaluation of clinical trials reporting both responses to pre-established time points. Likewise, in the future studies, an assessment of CEA response cutoffs should be performed for patients with CRC with mutated RAS or with different intrinsic subtypes of CRC, as well as a definition of the optimal time for its determination.

Authors' contributions All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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