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REVIEW ARTICLE

Early tumor shrinkage after first-line medical treatment of metastatic colorectal cancer: a meta-analysis

Giuseppe A. Colloca[1] · **Antonella Venturino**[1] · **Domenico Guarneri**[1]

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Abstract

Background Early tumor shrinkage (ETS) is a response-related endpoint of clinical trials of chemotherapy (CHT) of patients with metastatic colorectal cancer (mCRC). It identifies a dimensional reduction of tumor size by at least 20–30% after 6–8 weeks of CHT.

Methods A literature search of randomized trials of systemic treatment including CHT with or without antiangiogenics or anti-EGFR inhibitors in patients with mCRC has been conducted, and studies reporting the results of the relationship of ETS with overall survival (OS) and progression-free survival (PFS) were selected.

Results Twelve trials, including 3117 patients, have been included; all data were retrospective and only 72% of the enrolled patients have been evaluated for ETS. Two meta-analyses, each including 20 study cohorts from the selected 12 trials, reported a strong relationship of ETS with OS (HR 0.62; CIs 0.55–0.69) and of ETS with PFS (HR 0.66; CIs 0.60–0.73). However, both meta-analyses displayed a high level of heterogeneity. Among nine possible moderators, three variables (median age, surgery of metastases, and publication year) were able to explain at least a part of this heterogeneity.

Conclusion ETS is a simple and interesting intermediate endpoint for clinical practice and future trials of medical treatments of patients with mCRC, but a large prospective analysis and validation are mandatory.

Keywords Early tumor shrinkage · Chemotherapy · Endpoint · Prognosis · Bevacizumab · Cetuximab

Introduction

Colorectal cancer (CRC) is one of the leading cause of cancer morbidity and mortality worldwide, and an increase in global burden is expected, which will persist until the year 2035 [1]. The median overall survival (OS) of metastatic colorectal cancer (mCRC) is progressively increasing due to surgery of metastases, the introduction of new drugs, and a better understanding of molecular targets. A milestone meta-analysis of cytotoxic chemotherapy in 2004 concluded that the number of drugs received by the patient during the course of the mCRC was more important than the intensity of the first-line regimen [2] in determining a longer OS. This result has made it even more difficult to assess the effectiveness of first-line CHT regimens. Among clinical endpoints of randomized trials, progression-free survival (PFS), considered by many authors for a long time as the reference endpoint [3], has recently proved to be unreliable in predicting OS [4]. This finding has been confirmed in a previous analysis of clinical trials, in which we found that the response-related endpoints performed better than PFS in the most recent phase-3 trials of first-line therapy of mCRC [5].

Early tumor shrinkage (ETS) is particularly interesting among response-related endpoints due to its early and simple determination. ETS has been studied retrospectively by many authors at different cutoffs of tumor size reduction percentages and at different timepoints, with encouraging results, especially in trials of CHT plus anti-epidermal growth factor receptor (EGFR) antibodies [6]. Two individual patient data analyses (IPDA) of the phase-3 trials of the ARCAD database were published in abstract form: the first one included 10,962 patients receiving CHT (16 trials) and reported that ETS is an early predictor of OS, with similar results from 6 to 12 weeks [7]; the second one was a similar analysis on 4776 patients (eight trials) who received a first-line combination of CHT plus antiangiogenics, which

✉ Giuseppe A. Colloca
ga.colloca@europe.com

[1] Department of Oncology, Ospedale Civile di Sanremo, Via G. Borea n. 56, 18038 Sanremo, Imperia, Italy

confirmed the predictive role of ETS on OS [8]. Finally, a pooled analysis, while noting a strong relationship between ETS and OS (HR 0.58), concluded that it is not possible to consider ETS as a surrogate endpoint of OS [9].

The aim of the current paper is to perform a trial-level meta-analysis of studies of first-line medical treatment, with the purpose to evaluate the relationship of ETS with OS and of ETS with PFS in randomized trials of first-line medical therapy of patients with mCRC and to assess the variables moderating such relationships.

Patients and methods

Study selection

A literature search of randomized trials of first-line medical treatment in patients with mCRC was conducted on 3 March 2018. This search was performed on the electronic database MedLINE. The criteria used for the research were as follows: "colorectal cancer" and "early tumor shrinkage". The search was limited to randomized prospective studies published from January 2008 to December 2017. Editorials, comments, and letters were excluded, reviews were considered for references, but were not included in the final analysis, as well as non-randomized studies. A manual search was performed for the abstracts presented at the annual meetings of the American Society of Clinical Oncology and of the European Society for Medical Oncology. A first selection of eligible studies was made by GC, who selected by title and abstract, all randomized trials that enrolled patients with mCRC and reported the analysis of the ETS. The candidate articles were then selected for inclusion in the review. This was followed by a further evaluation of the selected articles by GC and AV, and only those that examined OS/PFS and the ETS in relation with OS/PFS were included in the study analysis. Based on the determination of the ETS, the whole trial or two arms per trial were selected for the analysis as separate study cohorts.

Statistical analysis

ETS is defined as a reduction in the initial size of measurable disease after a short period from the beginning of chemotherapy (CHT), usually 6–8 weeks. The summary hazard ratios (HRs) and confidence intervals (CIs) related to the global effect sizes were calculated using random-effects models. Two primary meta-analyses were performed, one exploring the relationship of ETS and OS and another the relationship of ETS and PFS. The null hypotheses tested were the absence of a significant association of ETS with the outcome variables. Meta-analyses included two outcome measures (OS and PFS) and 16 moderator variables for each study cohort (number of patients with an ETS assessment, sex, age, performance status, adjuvant chemotherapy, duration of first-line chemotherapy, patients receiving second-line chemotherapy, response assessment criteria, surgery of metastases after chemotherapy, median follow-up, oxaliplatin- or irinotecan-based chemotherapy, type of fluoropyrimidine, primary endpoint, phase 2 or 3 study, timing of ETS determination, publication year, drug regimen, wild type, or unselected RAS tumors). For the current analyses, the ETS cutoff used by the authors of each study was adopted.

The heterogeneity between studies was assessed by Q test and I^2 statistics defining a significant heterogeneity as p value < 0.10 and/or $I^2 > 50\%$. In the case of numerical variables, a meta-regression was carried out according to the DerSimonian and Laird method, but if there were fewer than ten study cohorts 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 study cohorts allowed it.

To assess the risk of publication bias, the Egger's test was reported for each analysis. Two-sided p values were calculated, with a p value < 0.05 considered significant for all tests. Finally, meta-regressions for numerical moderators

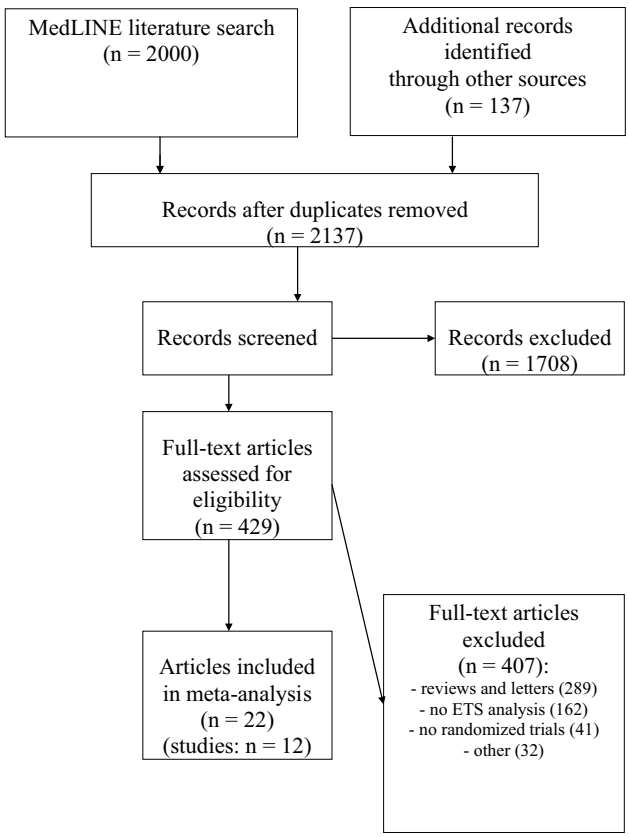

Fig. 1 PRISMA diagram flow

were performed to evaluate the effect of moderators on heterogeneity. All three meta-analyses were conducted using the ProMeta software (version 3.0), and meta-regression was done using the statistical computing language R (version 3.4.0 for Linux).

Results

On 3 March 2018, the search resulted in 2000 hits on MedLINE database and 137 abstracts from ASCO/ESMO congresses. The review process has been summarized in the diagram flow of Fig. 1, and the final analysis included 18 selected articles and four abstracts, for a total of 22 reports about the results of 12 RCTs [4, 6, 10–29].

The characteristics and results of the selected studies are listed in Table 1. ETS has been separately analysed in 20 study cohorts, derived from the arms of the 12 selected trials, considering that 3/12 trials reported results of ETS for the whole sample and not by randomization arm [13, 18, 23]. All reports on the ETS came from retrospective analyses of the studies. The definition of ETS was different in the studies: six studies analyzed a reduction of at least 20% at week 8, one study a reduction of at least 20% or 30% at week 8, and another a reduction of at least 30%, two studies a reduction of at least 20% at week 6, and finally another study a reduction of at least 20% at week 7.

Table 2 reports the relationships of ETS with OS and of ETS with PFS by study cohorts. ETS was available for 3117/4327 (72%) of the patients enrolled in the studies. Each of the two meta-analyses found a significant association between ETS and outcome measure, with a significant global effect size for both relationships, with OS (HR 0.62; CIs 0.55 to 0.69), and with PFS (HR 0.66; CIs 0.60 to 0.73). However, meta-analyses were characterized by a high level of study heterogeneity, for OS (Q test 64.38, p value < 0.001; I^2 70.49%) and for PFS (Q test 105.75, p value < 0.001; I^2 82.03%). Likewise, publication bias was consistent. The results are resumed in Table 3a, Figs. 2 and 3. A more detailed analysis of the relationship between ETS and OS by type of pharmacological regimen (CHT plus anti-EGFR versus CHT plus anti-angiogenetics versus CHT) is reported in Table 3b: despite the low number of study cohorts, the HRs were 0.54, 0.57, and 0.72, respectively.

Table 1 Results of trials and patients' characteristics

Trial [ref]	Trial arms	No. pts	ORR (%)	RAS	DCR (%)	PFS (m)	OS (m)
Phase III							
CRYSTAL [6, 10]	FOLFIRI + C	316	57.3[a]	wt	88.9	9.9[a]	23.5[a]
	FOLFIRI	350	39.7		86.0	8.4	20.0
PRIME [11, 12]	FOLFOX + P	325	57[a]	wt	86	10.0[a]	23.9
	FOLFOX	331	48		84	8.6	19.7
FIRE 1 [13, 14]	mIROX	241	41	uns	68	8.2	19
	FUFIRI	238	41		81[a]	7.2	22
Chinese [15, 16]	CHT + C	70	57.1[a]	wt	78.0	10.2[a]	30.9[a]
	CHT	68	29.4		63.2	5.8	21.0
FIRE 3 [4, 17]	FOLFIRI + C	297	62.0	wt	80.0	10.0	28.7[a]
	FOLFIRI + B	295	58.0		87.0	10.3	25.0
TRIBE [18, 19]	FOLFOXIRI + B	256	65.1[a]	uns	89.7	12.1[a]	31.0
	FOLFIRI + B	252	53.1		85.1	9.7	25.8
WJOG4407G [20, 21]	FOLFIRI + B	197	64	uns	92	12.1	31.4
	FOLFOX + B	198	62		92	10.7	30.1
Phase II							
OPUS [6, 22]	FOLFIRI + C	61	61[a]	wt	92[a]	7.7	22.8[a]
	FOLFIRI	73	37		78	7.2	18.5
AIO KRK 0104 [23, 24]	CAPIRI + C	89	46.1	uns	74.2	6.2	21.1
	CAPOX + C	88	47.7		77.2	7.1	23.5
ACCORD 13 [25, 26]	XELIRI + B	72	62	uns	83	9	23
	FOLFIRI + B	73	63		86	9	23
PEAK [27, 28]	FOLFOX + P	142	57.8	wt	89.8	10.9	34.2
	FOLFOX + B	143	53.5		85.5	10.1	24.3
PLANET TTD [29]	FOLFOX + P	38	74	wt	NR	13	37
	FOLFIRI + P	39	67		NR	14	41

B bevacizumab, *C* cetuximab, *CHT* cytotoxic chemotherapy, *DCR* disease control rate, *NR* not reported, *ORR* overall response rate, *OS* overall survival, *P* panitumumab, *PFS* progression-free survival, *uns* unselected, *wt* wild type

[a]Difference statistically significant

To explain the possible sources of the high level of heterogeneity among the 20 study cohorts that evaluated the relationship between ETS and OS and between ETS and PFS, two meta-regressions of some possible explanatory variables were performed, as shown in Table 4. Nine of the 16 variables, which were extracted from the studies, were selected as possible moderators (number of patients, percentage of male, age, percentage of ECOG PS 0–1, percentage of patients who received adjuvant chemotherapy, percentage of patients who received a second-line chemotherapy, percentage of patients with a radical resection of metastatic disease, median follow-up, and publication year). Among these, only three variables were significantly able to explain a part of the heterogeneity of the studies. A younger age was related to a stronger relationship of ETS with OS and PFS. Studies reporting lower rates of patient receiving a post-chemotherapy radical surgery of metastases have explained a reduced association between ETS and survival. Finally, the first published studies showed a stronger relationship of ETS with the outcome. To verify if this last result could be influenced by the different cutoffs of ETS, the subgroup analysis of the seven studies (12 study cohorts) with a tumor size reduction of at least 20% after 8 weeks was performed, without reporting significant differences of the global effect size for OS (HR 0.75; CIs, 0.67–0.83) and PFS (HR 0.69; CIs, 0.60 to 0.78), and of heterogeneity for OS (I^2 75.16%; Q 44.29, p value < 0.001) and PFS (I^2 77.66%; Q 49.24, p value < 0.001).

Discussion

The current meta-analyses have confirmed that ETS is a good predictor of survival. This happens despite the increasing post-progression survival has reduced the reliability of PFS as an intermediate endpoint of trials of first-line CHT. Therefore, a one-dimensional reduction > 20% at 8 weeks after the start of the first-line treatment could become an easy intermediate endpoint for phase 2 studies, pending the necessary validation of the ETS as a surrogate endpoint of OS in prospective studies, by type of medical treatment.

Many clinical experiences outside of randomized trials have reported for ETS a predictive role on OS [30–34], whereas other studies did not [35, 36]. This is not surprising in trials of second- and third-line chemotherapy. A recent study concluded that after the first-line medical treatment, the optimal cutoff for ETS remains a dimensional reduction of > 20% after 8 weeks, which appears to be the one most related to OS [37]. The performance of the early response in predicting survival appears similar to the best overall response rate by RECIST, and an IPDA meta-analysis of the

Table 2 Results of early tumor shrinkage retrospective analyses

Trial [refs.]	Trial arms	No. pts	ETS (no/yes)	PFS (HR; CIs)	OS (HR; CIs)
Phase III					
CRYSTAL [6, 10]	FOLFIRI + C	299	115/184	0.72; 0.67–0.78	0.85; 0.80–0.90
	FOLFIRI	322	159/163	0.92; 0.81–1.05	0.90; 0.80-1.00
PRIME [11, 12]	FOLFOX + P	221	62/159	0.62; 0.45–0.85	0.47; 0.35–0.65
	FOLFOX	221	95/126	0.67; 0.50–0.85	0.50; 0.37–0.66
FIRE 1 [13, 14]	mIROX / FUFIRI	201	107/94	0.78; 0.59–1.05	0.58; 0.42–0.80
Chinese [15, 16]	CHT + C	68	23/45	0.22; 0.12–0.39	0.33; 0.18–0.60
	CHT	64	47/17	0.46; 0.27–0.79	0.51; 0.29–0.91
FIRE 3 [4, 17]	FOLFIRI + C	157	50/107	0.59; 0.41–0.85	0.52; 0.34–0.80
	FOLFIRI + B	173	88/85	0.71; 0.52–0.97	0.49; 0.35–0.71
TRIBE [18, 19]	FOLFOXIRI/FOLFIRI + B	443	187/256	0.66; 0.52–0.79	0.54; 0.39–0.67
WJOG4407G [20, 21]	FOLFIRI + B	179	66/113	0.61; 0.43–0.85	0.58; 0.38–0.89
	FOLFOX + B	175	75/100	0.85; 0.61–1.19	0.85; 0.57–1.30
Phase II					
OPUS [6, 22]	FOLFIRI + C	78	36/42	0.68; 0.57–0.81	0.77; 0.67–0.88
	FOLFIRI	90	49/41	0.92; 0.81–1.05	0.90; 0.80-1.00
AIO KRK 0104 [23, 24]	CAPIRI/CAPOX + C	76	31/45	0.37; 0.23–0.60	0.48; 0.29–0.82
ACCORD 13 [25, 26]	XELIRI/FOLFIRI + B	143	56/87	0.84; 0.59–1.20	0.59; 0.36–0.97
PEAK [27, 28]	FOLFOX + P	80	20/60	0.46; 0.25–0.86	0.38; 0.20–0.69
	FOLFOX + B	74	28/46	0.60; 0.36–1.01	0.42; 0.24–1.30
PLANET TTD [29]	FOLFOX + P	27	6/20	0.20; 0.10–0.50	0.30; 0.10–0.80
	FOLFIRI + P	26	5/17	0.70; 0.20–2.20	0.30; 0.10-1.00

B bevacizumab, *C* cetuximab, *CHT* cytotoxic chemotherapy, *CIs* confidence intervals, *ETS* early tumor shrinkage, *HR* hazard ratio, *NR* not reported, *OS* overall survival, *P* panitumumab, *PFS* progression-free survival

ARCAD database has recently underlined the uselessness of a late response or the confirmation of the response [7].

The most important limitation of the present trial-level meta-analyses is the presence of retrospective and partial data on 3117 of 4327 patients enrolled in the selected studies. This exposes our study to a possible inhomogeneity of the study arms, but should not interfere with the analysis of the individual study cohorts that was performed.

Differences in ETS have been detected between the combination of CHT plus anti-EGFR inhibitors versus CHT, but poor data are available between CHT plus anti-angiogenetics versus CHT. From the results of the current analysis, it is interesting to note that the relationship between ETS and OS is stronger for any association of CHT plus biological agent versus CHT alone and that there is not a big difference between anti-EGFR inhibitors and anti-angiogenetics (HR 0.54 versus 0.57).

ETS has been less studied after drug combinations based on anti-angiogenetics, because the mechanism of action of these drugs is theoretically more inclined to promote an increase of the time-to-tumor growth and time-to-event endpoints rather than increasing the dimensional reduction of the tumor, and the radiological dynamics of the response supports greater utility of the morphological response after CHT plus antiangionetics compared to ETS. However, among patients with metastatic renal cell carcinoma an ETS > 10% at the first radiologic evaluation after antiangiogenics alone was the endpoint that best predicted OS, in comparison with RECIST, Choi criteria, and reduction of lesion density [38]. In addition, from the studies conducted on patients with mCRC, the response-related endpoints showed a correlation with OS similar to that of PFS with OS [5, 36].

Contrary to what is reported in individual studies [39] in our meta-analysis, the relationship between ETS and OS does not seem to be more robust for anti-EGFR inhibitors than for anti-angiogenetics, but the difference is between CHT plus biologic agent compared to CHT alone. In addition, this result is not surprising, given the higher remission rates reported compared to CHT alone [40].

Looking at the different studies and considering the 16 variables of the meta-analyses, the relationship between ETS and survival appears different between the study cohorts receiving a first-line chemotherapy with oxaliplatin-based versus irinotecan-based regimens, for OS (HR 0.50 versus 0.76, data not reported) and for PFS (HR 0.59 versus 0.73; data not reported); however, the low number of cohorts does not allow a reliable analysis of the subgroups. The reason

Table 3 Results of the meta-analyses

A. ETS and overall survival and ETS and progression-free survival		
Overall survival	Overall survival	Progression-free survival
No. study cohorts	20	20
No. patients	3112	3112
Effect size (HR)	0.62	0.66
Confidence interval	0.55–0.69	0.60–0.73
p value	< 0.001	< 0.001
Heterogeneity		
Q (*p* value)	105.75 (< 0.001)	64.38 (< 0.001)
I^2	82.03%	70.49%
Publication bias		
Egger's test (*p* value)	− 2.77 (< 0.001)	− 1.73 (0.004)

B. ETS and overall survival among study cohorts grouped by drug regimen			
Parameter	CHT + anti-EGFR	CHT + anti-VEGF	CHT alone
No. study cohorts	9	6	5
No. patients	1027	1187	898
Effect size (HR)	0.54	0.57	0.72
Confidence interval	0.43–0.69	0.48–0.67	0.59–0.88
p value	< 0.001	< 0.001	0.001
Heterogeneity			
Q (*p* value)	43.39 (< 0.001)	5.59 (0.359)	26.27 (< 0.001)
I^2	81.56%	0.00%	84.72%

CHT chemotherapy, *EGFR* epidermal growth factor receptor, *ETS* early tumor shrinkage, *HR* hazard ratio, *VEGF* vascular endothelial growth factor

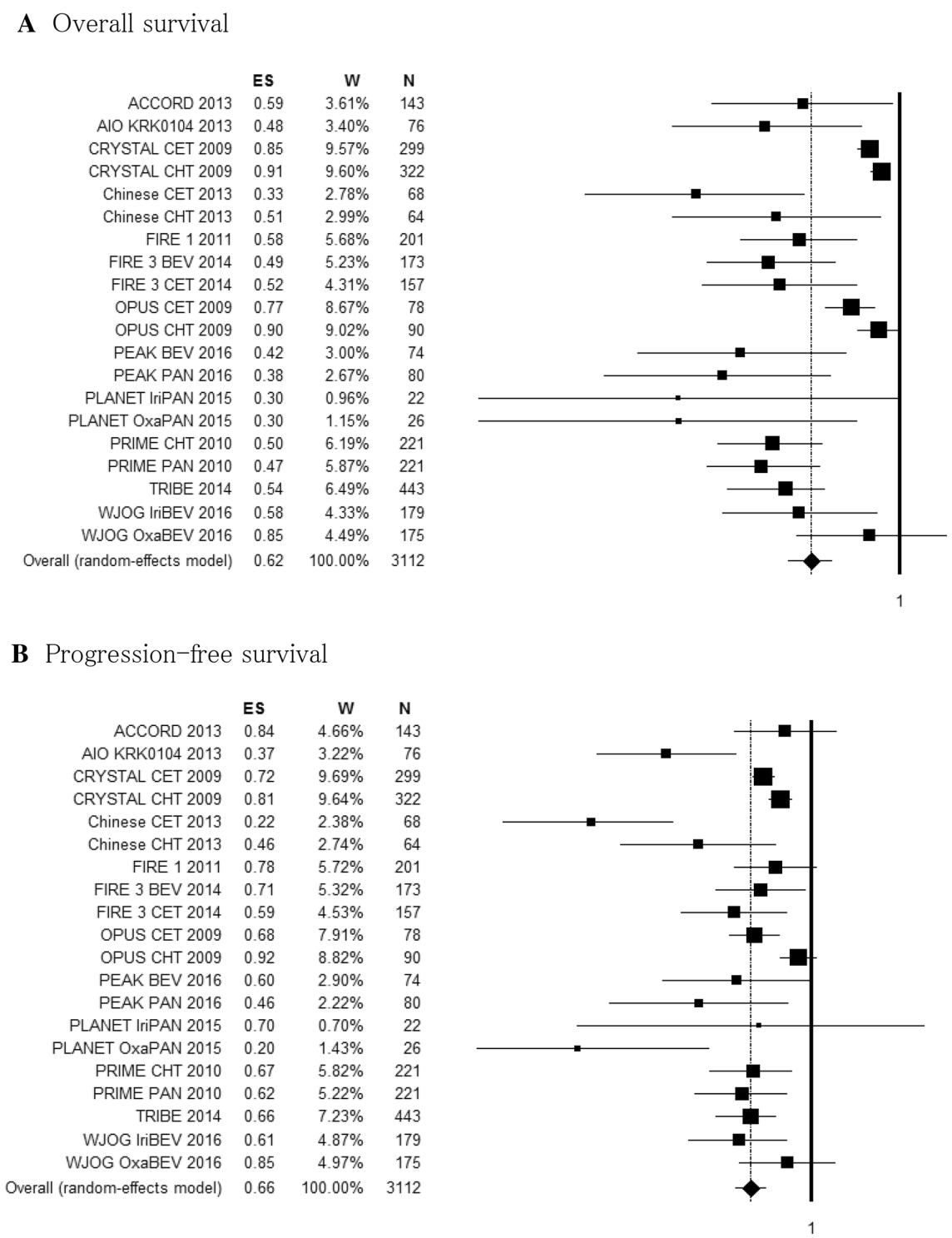

Fig. 2 Results of meta-analysis of the relationship of early tumor shrinkage with outcome. **a** Overall survival. **b** Progression-free survival

for this association is not clear, as indeed a previous meta-analysis reported that oxaliplatin was less effective than irinotecan in association with anti-EGFR inhibitors [41]. This data should be confirmed by prospective studies, and it would be interesting to verify if it is a bias related to the fact that the population receiving oxaliplatin had not performed adjuvant chemotherapy.

Selection of the study sample using RAS mutations did not interfere on the relationship between ETS and outcome, which is similar between the studies that enrolled mCRC

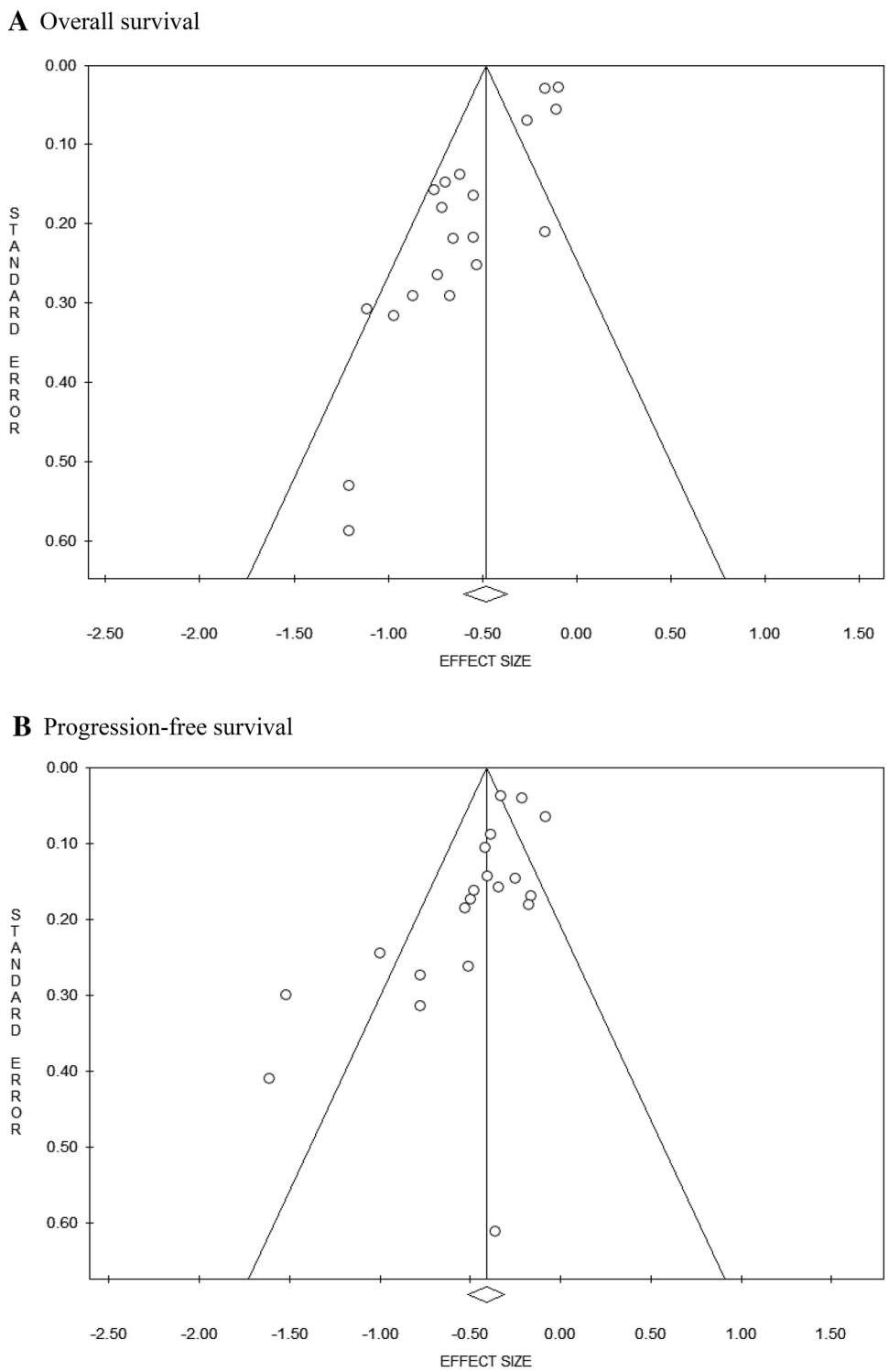

Fig. 3 Funnel plots. **a** Overall survival. **b** Progression-free survival

patients with wild-type RAS compared to those that randomized patients without any RAS selection. Few experiences report data by molecular subgroups, and some authors suggest that the role of ETS as a predictor of OS may be more relevant among patients with RAS-mutated tumors [36], a phenomenon attributed to the low number of therapeutic options after the first-line CHT, thus to a lower post-progression survival of patients with RAS-mutated mCRC. However, even in the 6 study cohorts of CHT plus anti-angiogenetics, the relationship of ETS with OS was strong in both the four cohorts with RAS unselected and in the two ones with wild-type RAS (HR 0.61 versus 0.47; data

Table 4 Results of meta-regressions of moderators of the relationship of ETS with OS (A) and PFS (B)

Moderator	No. of study cohorts	R^2	Standardized beta	*p* value
A				
Number of pts	20	0.041	0.202	0.392
Sex	20	0.001	−0.003	0.990
Age	20	0.232	−0.482	0.031
ECOG PS	15	0.022	−0.149	0.597
Pts receiving adjuvant CHT	16	0.002	−0.044	0.872
Pts receiving 2nd line CHT	14	0.018	0.135	0.646
Surgery of metastases	18	0.452	−0.672	0.002
Median follow-up	20	0.049	0.222	0.348
Publication year	20	0.489	−0.699	0.001
B				
Number of pts	20	0.006	0.078	0.744
Sex	20	0.122	−0.350	0.130
Age	20	0.347	−0.589	0.006
ECOG PS	15	0.082	−0.286	0.301
Pts receiving adjuvant CHT	16	0.128	−0.360	0.175
Pts receiving 2nd line CHT	14	0.001	0.016	0.956
Surgery of metastases	18	0.555	−0.745	< 0.001
Median follow-up	20	0.068	0.260	0.268
Publication year	20	0.605	−0.778	< 0.001

CEA carcinoembryonic antigen, *CHT* chemotherapy, *ECOG PS* eastern cooperative oncology group performance status, *ETS* early tumor shrinkage, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival, *Pts* patients, R^2 proportion of heterogeneity explained

not reported). This contrasts with the results reported by a previous pooled analysis, in which a possible surrogacy of ETS was excluded based only on partial retrospective data of six studies [9].

Despite the interesting results of new endpoints related to therapeutic strategies and the definition of subgroups of mCRC with different prognosis and sensitivity to treatments, we believe that the development of response-related endpoints remains indispensable for clinical practice and clinical trials, beyond any possible negative future results as a surrogate of OS [9, 35]. Indeed, tumor shrinkage may be a simply and early measurable true endpoint for trials of early and late lines of medical treatments, considering that patients with mCRC who report a radiologic response to the first line of medical treatment most frequently have a tumor response to the further lines [42].

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Compliance with ethical standards

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

Ethical statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent For this type of study, formal consent is not required.

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