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REVIEW ARTICLE

Prognostic factors for survival with bevacizumab-based therapy in colorectal cancer patients: a systematic review and pooled analysis of 11,585 patients

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Abstract First-line chemotherapy + bevacizumab (BEV) is one of the standards of care in advanced colorectal cancer (CRC). Contrary to anti-*EGFR* agents, it is currently not possible to identify the ideal candidate for BEV-based chemotherapy due to the lack of predictors of outcomes. The aim of this study was to perform a systematic review of risk factors for survival after B-based chemotherapy for CRC. We performed a meta-analysis by searching on the databases PubMed, EMBASE, Web of Science and SCOPUS for a published series that focused on prognostic factors for BEV-based therapy in advanced CRC. Pooled hazard ratios (HR) were calculated by using a random-effects model for parameters that could be considered as potential prognostic factors in ≥3 papers. Twenty-nine studies, which included a total of 11,585 patients, were considered in this analysis. Five parameters were associated with survival in ≥3 papers: (1) a longer progression-free interval [PFS: HR 0.87, 95 % confidence interval (CI) 0.78–0.97; $P = 0.01$]; (2) a single site of metastases (HR 0.63, 95 % CI 0.56–0.71; $P < 0.00001$); (3) elevated lactate dehydrogenase (LDH: HR 2.08, 95 % CI 1.69–2.57; $P < 0.00001$); (4) KRAS mutation (HR 1.66, 95 % CI 1.36–2.03; $P < 0.00001$); and (5) poor performance status (PS: HR 1.99, 95 % CI 1.41–2.82; $P < 0.0001$). Clinical variables associated with prolonged survival, after first-line treatment with chemotherapy + BEV for metastatic CRC patients, included long PFS, low LDH levels, KRAS wild-type status, good PS and a single site of metastasis. They should be considered when stratifying patients for inclusion in randomized trials. Investigations into new prognostic factors based on tumor biology are needed and of high priority.

Keywords Bevacizumab · First-line · Colorectal cancer · Prognostic factors · Meta-analysis

Introduction

Outcomes of patients with advanced colorectal cancer (CRC) have significantly improved with the addition of molecular agents such as anti-EGFR (cetuximab and panitumumab) and anti-angiogenetic monoclonal antibodies [bevacizumab (BEV)] in first-line chemotherapy. Selection of patients for such molecular drugs depends on their performance status (PS) and aim of treatment, the extent of their disease and the clinical or molecular predictors of benefit. It has clearly been demonstrated that anti-EGFR monoclonal antibodies work only if there are no mutations in the RAS protooncogene; in this case, the outcome [overall survival (OS)] is similar or even better than with chemotherapy + BEV [1, 2]. This has been explained by the better deepness of response and early tumor shrinkage associated with anti-EGFR agents [3]. Among patients treated with cetuximab or panitumumab, the development of a skin rash of moderate/severe entity has been associated with a better OS [4]. Conversely, BEV seems to confer a similar magnitude of benefit both in RAS wild-type and in KRAS- or BRAF-mutated tumors [5].

In 2002, Kohne demonstrated, in 19 first-line 5-fluorouracil-based prospective trials, that a clinical risk score based upon four baseline clinical variables such as PS, white blood cells count, alkaline phosphatase and the number of metastatic sites could predict outcome [6]. In four prospective trials, comparing FOLFOX and

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FOLFIRI, Chibaudel et al. [7] showed that serum lactate dehydrogenase (LDH) level was the main prognostic factor in predicting survival, followed by WHO PS. Similar analysis was not performed for patients treated with targeted therapies, in particular those with first-line BEV-based chemotherapy. Among patients treated with first-line BEV, the predictors of survival have not yet been discovered. However, the development of arterial hypertension has been correlated with increased response rate, progression-free survival and OS in BEV-treated patients [8].

It can be stated that BEV is associated with an increased risk of hypertension, ischemic heart disease, gastrointestinal hemorrhage and/perforation, other than fatal adverse events. So, it is of outstanding importance to discover clinicopathological variables associated with OS in CRC patients exposed to first-line chemotherapy + BEV [9–11]. This could permit decisions for more or less intensive treatments and allow the stratification of patients with different prognoses in randomized clinical trials.

A systematic review or meta-analysis of predictors of survival with BEV in advanced CRC has not yet been performed. In this study, we systematically analyzed all informative studies related to this topic in order to determine the evidence for clinical, therapeutic, laboratory and genetic predictors of outcomes in stage IV CRC patients with BEV-based chemotherapy.

Methods

This systematic review and meta-analysis are reported in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statements (www.prisma-statement.org) [12].

Eligibility criteria

All clinical, therapeutic, laboratory or genetic variables studied in patients with advanced CRC for its possible association with OS were searched for.

Clinical trials or prospective/retrospective cohort series with adult, stage IV, CRC patients studying the relationship between clinical, therapeutic, laboratory or genetic parameters at the time of starting first-line chemotherapy + BEV and survival (OS) published in the English language, without publication date restrictions, were eligible for inclusion. Only the variables reported as significant predictors in at least 3 papers were pooled.

Studies (1) with <10 pts; (2) where the predictors were not determined at first-line therapy; (3) where the described therapy included other biological agents or chemotherapy alone; (3) where predictors were not evaluated as multivariate analysis; and (4) where there was no full text available, were excluded.

Studies were identified by searching PubMed, EMBASE, Web of Science and SCOPUS databases. The search was performed in November 2014. We searched for the terms (CRC or colorectal carcinoma) and (multivariate or multivariable or 'cox regression') and BEV and (overall survival) and (hazard ratio or HR).

Two investigators (FP and AC) independently screened all results by reviewing the titles and abstracts. All potentially relevant studies were retrieved as full-text manuscripts. FP and AC evaluated all studies for compliance with the inclusion criteria. In case there was any doubt about their eligibility for inclusion, this was discussed with a third independent senior oncologist (SB). Duplicate reports of studies were excluded by checking authors' names, affiliations and titles. Duplicate inclusion of patients participating in more than one study was avoided by systematically evaluating patient recruitment periods and participating centers. A patient could only be evaluated in more than one study if a different predictor was analyzed.

Data extraction

Data extraction from manuscripts was performed by two investigators (FP and AC). The following data were extracted from the included studies: first author, year of publication, number of patients, type of study cohort, first-line chemotherapy, prognostic determinants studied as multivariate analysis and significantly associated with OS, hazard ratios (HRs) and their 95 % confidence interval (95 % CI). HRs were extracted from multivariable analyses where available.

Statistical analysis

The primary aim was to determine the independent prognostic value of clinical variables related to OS. All clinical variables studied were recorded, and results were given for prognostic factors found to be significantly associated with OS in multivariate analysis. HRs of OS were used as the primary effect estimate in this meta-analysis. We calculated the pooled HRs and 95 % CI for all predictors presented in at least three papers. To incorporate heterogeneity between studies, we used generic inverse-variance and the random effect model by the implementing the Mantel–Haenszel method [13] and using the Cochrane statistical package in Review Manager 5.3 (RevMan version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Heterogeneity was assessed using Cochran Q and I^2 statistics. All statistical tests were two-sided, and the statistical significance was defined as $P < 0.05$. Measures of heterogeneity were calculated and included in all forest plots created with RevMan.

Results

Twenty-nine studies [14–39, 43], among 386 retrieved, which encompassed a total of 11,585 patients, were included. An overview of our search and study selection is shown in the flowchart (Fig. 1). Characteristics of the included studies are shown in Table 1; most were published in 2010 or later. Among them, 21 were prospective or retrospective cohort single or multicenter series and 7 were analyses of the prospective phase II ($n = 4$) or III ($n = 3$) studies. Patients ranged from 33 to 3,187.

LDH levels

Three studies contributed to the analysis (Fig. 2). No heterogeneity across the studies was detected ($I^2 = 0$; $P = 0.37$). An elevated LDH level was associated with an increased risk of death (HR 2.08, 95 % CI 1.69–2.57; $P < 0.00001$).

Number of metastatic sites

Six studies contributed to the pooled analysis (Fig. 3). No heterogeneity across the studies was detected ($I^2 = 0$; $P = 0.54$). A single metastatic site was associated with a reduced risk of death compared to multiple sites of disease (HR 0.63, 95 % CI 0.56–0.71; $P < 0.00001$).

Performance status

In five studies with data available (Fig. 4), a poor PS was associated with an increased risk of death (HR 1.99, 95 % CI 1.41–2.82; $P < 0.00001$). Significant heterogeneity was observed ($I^2 = 84$ %; $P < 0.0001$).

Progression-free survival/time to progression

Three studies contributed to this analysis. A longer time to progression or PFS was moderately associated with a reduced risk of death (HR 0.87, 95 % CI 0.78–0.97; $P = 0.01$) (Fig. 5). High heterogeneity across the studies was detected ($I^2 = 98$; $P < 0.00001$).

KRAS status

Three studies contributed to this analysis (Fig. 6). KRAS-mutated status was associated with an increased risk of death (HR 1.66, 95 % CI = 1.36–2.03; $P < 0.00001$).

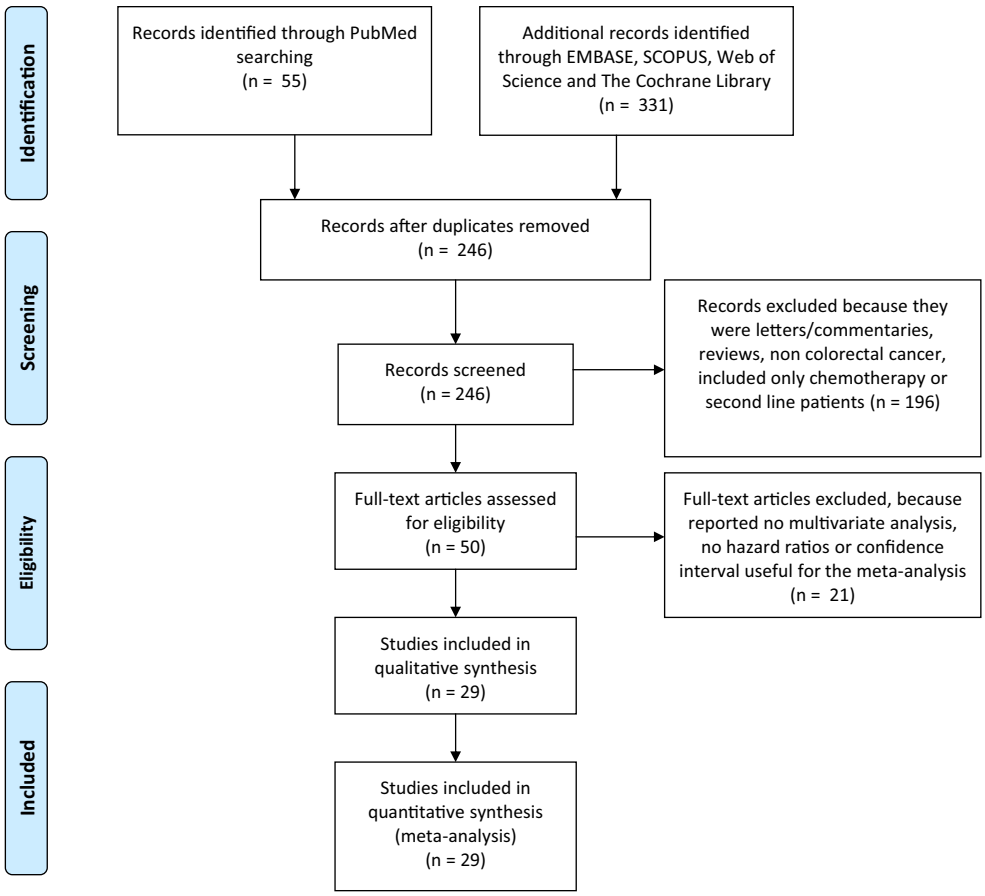

Fig. 1 PRISMA flow diagram of included studies

Table 1 Characteristics of included studies

References	Type of study	No of pts	Treatment regimen	Median follow-up (months)	Median OS (months)	Prognostic factor of increased OS by multivariate analysis
Koutras et al. [28]	Phase III	173	FOLFIRI + B versus XELIRI + B	29.7	26.2 and 20.1	VEGF-1154 AA + GA polymorphism, PS 2–3
Moscetti et al. [40]	Retrospective cohort	220	Oxaliplatin- or irinotecan-based + B	18	22.5	Objective response
Kim et al. [27]	Phase II	61	FOLFIRI-3 + B	46.7	24.5	Angiopoietin-2
Lastoria et al. [29]	Phase II	33	FOLFIRI + B	30	38	Highest SUV max, total SUV max, total lesions glycolysis, SUV max by lesion
Sastre et al. [36]	Phase III	158	XELOX + B	NA	NA	KRAS mutated, CTC ≥/7.5 ml blood
Boisen et al. [16]	Retrospective cohort	667	CAPEOX + B	NA	NA	Sigmoid colon, rectum, sigmoid colon + rectum
Loupakis et al. [30]	Phase II	424	FOLFIRI + B	24	29.9	Ps 1–2, left colon, rectum No of M + sites >1
Diaz-Rubio et al. [22]	Phase III	393	XELOX + B	NA	26.73 and 17.98 in KRAS wt and mut	LDH, No of M + sites >1, KRAS mut
Malka et al. [33]	Phase II	99	FOLFIRI + B versus XELIRI + B	36	26.1 and 19.8 for < vs > 23 CEC at baseline	Low and intermediate risk according to Kohne score
Gerger et al. [24]	Retrospective cohort	132	FOLFOX + B or XELOX + B	42	25.9	EGF rs444903 A > G, IGF-1 rs6220 A > G
Matsusaka et al. [41]	Prospective series	33	FOLFOX + B	NA	NA	CEC > 65, peritoneal metastasis
Aoyagi et al. [14]	Prospective series	46	FOLFOX-6 + B	NA	NA	sVEGFR-1
Guiu/2009	Retrospective cohort	80	FOLFIRI or FOLFOX + B (92.5 %)	24	Not reached	PS 1, PS 2, visceral fat area
Boisen et al. [15]	Retrospective cohort	333	CAPEOX + B	NA	19 and 21.9 (screening and validation cohort)	26 miRNA
Budai et al. [18]	Prospective series	85	FOLFIRI + B	NA	NA	Hypertension grade >1, CC-SHMT1 1420
Grothey et al. [25]	Prospective observational study	1,445	FOLFOX or FOLFIRI + B (70 %), IFL (9.7 %), XELOX (4.8 %)	19.6	25.1	PS 1, PS ≥ 2, albumin, alkaline phosphatase, rectum, TTP, PR, SD, BBP, no second line therapy
Slavicek et al. [37]	Population-based registry	3,187	FOLFO/XELOX + B or FOLFIRI/XELIRI + B (90 %)	17	26.9 and 27.5 for <65 and 65–75 years old patients	No of 2 and 3 M + sites, rectum, synchronous M+
Cartwright et al. [19]	Retrospective cohort	573	FOLFO/XELOX + B or FOLFIRI/XELIRI + B (92 %)	NA	24.5	Time to progression, BMI, BEV beyond progression
Crea et al. [21]	Retrospective cohort	110	FOLFIRI + B	18.9	23.3	Mucinous histology, EZH2 rs3757441 C/C variant
Cetin et al. [20]	Retrospective cohort	170	FOLFIRI- or XELIRI- or IFL + B	NA	18	Neutrophils, PFS <6 months, LDH

Table 1 continued

References	Type of study	No of pts	Treatment regimen	Median follow-up (months)	Median OS (months)	Prognostic factor of increased OS by multivariate analysis
Silvestris et al. [43]	Retrospective cohort	139	Oxaliplatin (55 %) or irinotecan-based (45 %) CT + B	NA	24.5 and 18.6 for low and high LDH levels	LDH, fibrinogen
Formica et al. [23]	Retrospective cohort	106	FOLFIRI + B	28	41 and 12 months for NLR < and >3.5	NLR, PCR
Vincenzi et al. [39]	Retrospective cohort	116	FOLFIRI + B (41 %) or FOLFOX + B (59 %)	21	28	PS, No of M + sites >1, low Dicer
Loupakis et al. [31]	Retrospective cohort	111	FOLFIRI + B	13.6	27.3, 20.5 and 18.6 for C/C, C/T and T/T VEGF polymorphism	Leukocytosis, mucinous histology, VEGF 1498 T/T polymorphism
Vauthey et al. [39]	Prospective series	193	Oxaliplatin or irinotecan-based CT + B	33	NA	RAS mutations, viable tumor cells ≥50 % after neoadjuvant CT
Buchler et al. [17]	Population-based registry	2,191	FOLFOX + B (55.6 %) or XELOX + B (44.4 %)	15.9	27 and 30.6 for FOLFOX + B and XELOX + B	Synchronous M + , No of M + sites 2 or ≥3
Maillet et al. [33]	Retrospective cohort	80	FOLFIRI + B (30 %) or FOLFOX + B (51 %)	14	20.1, 11.4 and 6.5 for GPS 0,1 and 2	Glasgow prognostic score
Ryanne Wu et al. [36]	Retrospective cohort	84	B-based CT	11	29	Hypertension
Pectasides et al. [35]	Phase III	143	FOLFIRI + B versus XELIRI + B	42	25.3 and 20	PS, no of M + sites 2 or ≥3, high osteopontin level

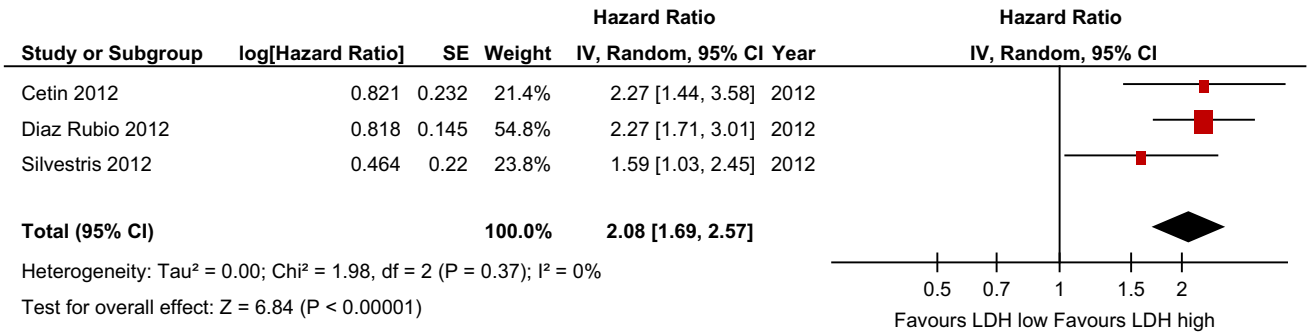

Fig. 2 Forest plot showing hazard ratio for LDH levels (high vs. low)

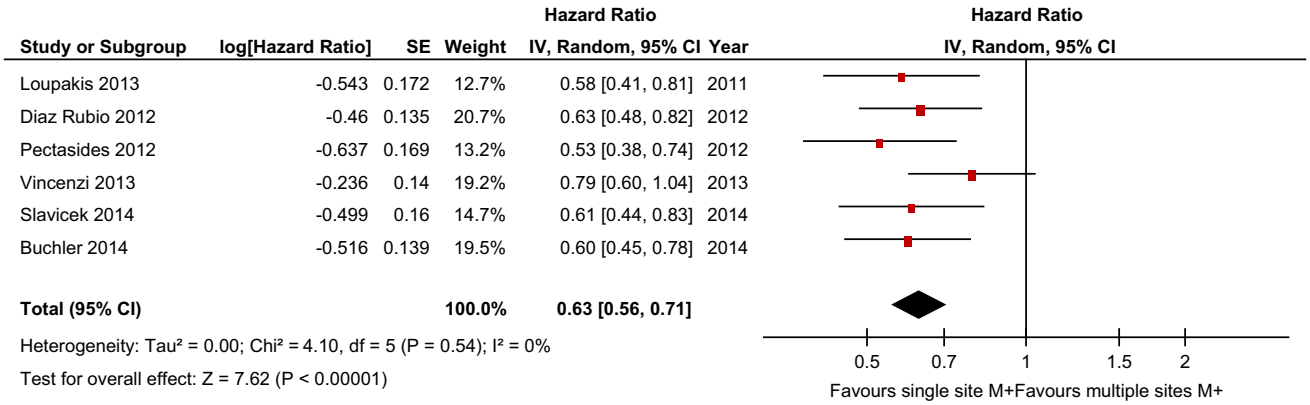

Fig. 3 Forest plot showing hazard ratio for number of sites of metastases (1 vs. >1)

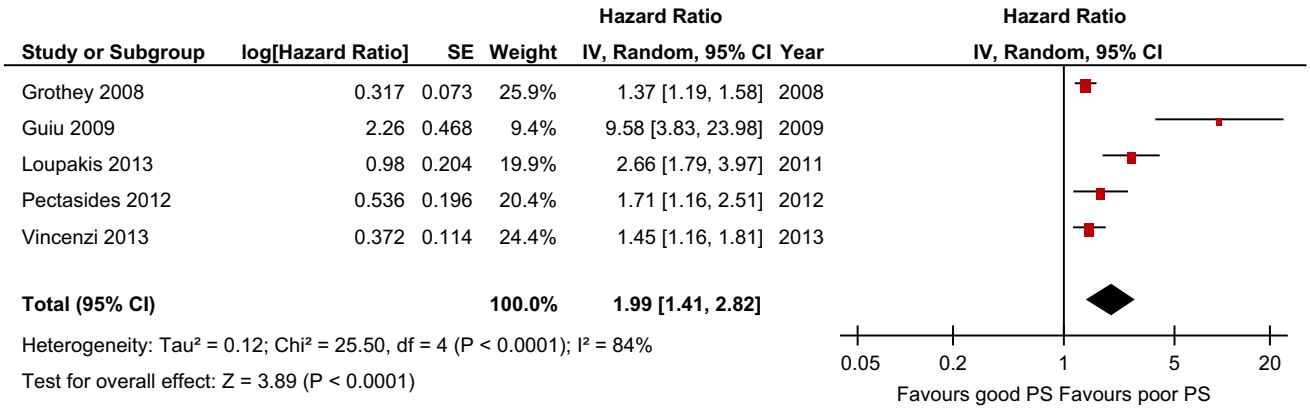

Fig. 4 Forest plot showing hazard ratio for performance status (good vs. poor)

No heterogeneity across the studies was detected ($I^2 = 0$; $P = 0.8$).

Discussion

The data presented here provide robust prognostic information regarding more than 11,000 patients with CCR who underwent first-line chemotherapy including BEV. Three clinicopathological parameters clearly emerged as significant predictors of poor outcomes for patients treated with BEV: high LDH level, poor PS and KRAS mutation. The presence of each of these three variables increases the probability of death by about a factor of two. Conversely, a prolonged time to progression during first-line therapy and a single metastatic site were associated with an improved outcome. To our knowledge, this systematic multivariate analysis represents the largest meta-analysis that identifies

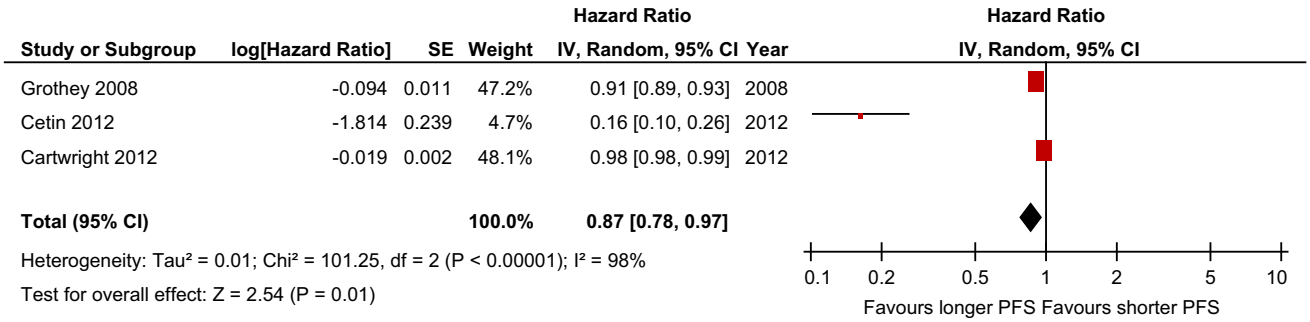

Fig. 5 Forest plot showing hazard ratio for progression-free survival (longer vs. shorter)

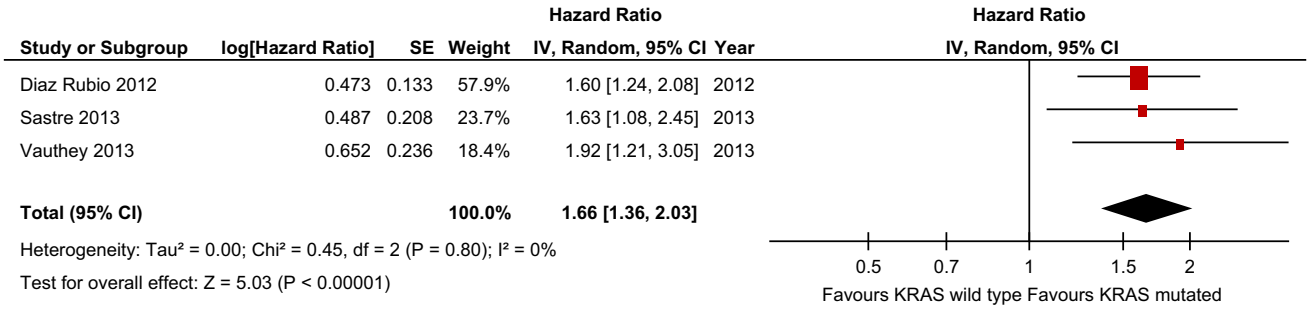

Fig. 6 Forest plot showing hazard ratio for KRAS (mutated vs. wild-type)

the clinicopathological prognostic factors for patients with metastatic CCR treated with BEV-based chemotherapy. It derives from the inclusion of 29 studies published in the last decade, when BEV was approved for use in advanced CRC. BEV targets the angiogenesis pathway through circulating VEGF but actually lacks any predictive factors, so an evaluation of predictors of outcome could permit oncologists to select the best candidate for the combination of chemotherapy plus BEV.

An examination of some of these parameters usually belongs to the clinical routine practice before a patient starts any chemotherapy regimens for stage IV CRC. PS and an evaluation of the extent of disease, other than serum chemical analysis including LDH levels, are usually checked at baseline evaluation. KRAS mutation status may also exclude patients from anti- to EGFR therapy, as commonly stated in the clinical guidelines, and it identifies metastatic CRC patients with a poor prognosis, even those treated with BEV [42].

The definition of these prognostic factors has several implications in clinical practice. The PS other than the sites of metastases permits the validation of the scope of cure (palliative or curative) in a metastatic setting. A liver-confined disease in a fit and young patient should induce the start of a neoadjuvant course of chemotherapy (plus a biological agent?) with the aim of the resection of hepatic metastases. Conversely, in unfit patients with widespread metastatic disease and KRAS-mutated status, the intensity of cure can be attenuated with sequential mono- or poly-chemotherapy alone, which could represent the preferable choice. In a CRC setting, LDH has assumed rising importance in defining the prognosis of patients treated with anti-VEGF(R) agents. Recently, Silvestris and colleagues [43] showed a statistically significant association between high pretreatment LDH levels and progressive disease compared to low basal LDH patients. Furthermore, the median PFS was 7.3 versus 10.8 months for high and low LDH levels, respectively. High LDH levels have been correlated with intratumoral gene expression of VEGFA and VEGFR1, thus supporting the hypothesis that serum LDH levels may serve as a surrogate marker for activation of the hypoxia-inducible factor-related genes in the tumor [44]. Finally, progression-free survival or time to progression have already been validated as surrogate endpoints in advanced CRC with targeted therapies [45] and are also common predictors of better outcomes in patients treated with first-line therapy in many other solid tumors.

There are several limitations to the present study, and our results should be interpreted cautiously because there is a possibility of bias regarding selection criteria. The study, also, should not be taken as advocacy for excluding some patients from BEV therapy. Rather, it highlights the importance of selection criteria for intensive therapy including chemotherapy + BEV for advanced disease. In addition, there is likely to be substantial variation among the included series in terms of the timing of disease

evaluation and median follow-up. We observed significant heterogeneity for two out of five parameters: first, PS meta-analysis includes comparisons of PS 0–1 versus PS $\geq$ 2 or PS 1 versus PS > 1. Second, significant heterogeneity was present for the PFS analysis. This finding might be explained by the fact that imaging studies could have been performed differently in clinical studies versus cohort studies. Finally, the results of this meta-analysis do not provide a predictive significance for patients treated with BEV, and the aim of this study was restricted to the observation of prognostic risk factors for survival.

Other prognostic variables have been investigated in patients exposed to BEV. Among them, the development of hypertension seems a reliable prognostic parameter with anti-angiogenetic agents. A meta-analysis previously published confirmed the favorable prognostic significance of hypertension development in CCR studies [8]. The occurrence of BEV-induced hypertension in patients was highly associated with improvements in PFS (HR 0.57, 95 % CI 0.46–0.72; $P < 0.001$), OS (HR 0.50; 95 % CI 0.37–0.68; $P < 0.001$) and response rate (relative risk = 1.57, 95 % CI 1.07–2.30, $P < 0.05$), as compared to patients without hypertension. Monitoring hypertension during treatment is of medical and clinical importance in preventing fatal events and is likely to reassure patients as a result of its prognostic significance. This clinical parameter, however, needs to be prospectively investigated. Inflammation parameters have also acquired prognostic importance. The level of neutrophils and the ratio between neutrophils and lymphocytes have been correlated with poor prognosis in CRC according to a meta-analysis of cohort studies [46]. In our meta-analysis, few trials reported a significant association of hypertension and neutrophils count or neutrophil/lymphocyte ratio and outcome, and as such were not included in the final analysis.

This meta-analysis can be of paramount importance for medical oncologists treating CRC patients with first-line chemotherapy. It defines, in fact, a portrait of an ideal candidate for first-line treatment with chemotherapy and BEV for advanced CRC in clinical practice. Fit patients, with a low burden of disease and normal LDH levels, probably obtain the greater benefit from first-line BEV. However, the need for rapid tumor shrinkage with a neo-adjuvant treatment, or for a symptomatic palliation of symptoms in the presence of a high burden of disease, could lead to the preference of anti-EGFR agents.

In conclusion, we found five reliable predictors of survival for (first-line) BEV-treated CRC patients. These parameters should be considered when selecting first-line therapy and stratifying patients for inclusion in future randomized trials including BEV for managing stage IV CRC patients.

Conflict of interest None.

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