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Critical Reviews in Oncology/Hematology

Can KRAS and BRAF mutations limit the benefit of liver resection in metastatic colorectal cancer patients? A systematic review and meta-analysis

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ABSTRACT

Background: Clinical trials investigated the potential role of both KRAS and BRAF mutations, as prognostic biomarkers, in colorectal cancer (CRC) patients who underwent surgical treatment of CRC-related liver metastases (CLM), showing conflicting results. This meta-analysis aims to review all the studies reporting survival outcomes (recurrence free survival (RFS), and/or overall survival (OS)) of patients undergoing resection of CLM, stratified according to KRAS and/or BRAF mutation status.
Materials and methods: Data from all published studies reporting survival outcomes (RFS and/or OS) of CRC patients who received resection of CLM, stratified by KRAS and/or BRAF mutation status were collected, according to the PRISMA guidelines. Pooled HRs were calculated for both the OS and/or RFS.
Results: Seven eligible trials (1403 patients) were included. Pooled analysis showed that KRAS mutations predicted a significantly worse both RFS (HR: 1.65; 95% CI: 1.23–2.21) and OS (HR: 1.86; 95% CI: 1.51–2.30) in patients who underwent surgical resection of CLM. BRAF mutations were also associated with a significantly worse OS (HR: 3.90; 95% CI: 1.96–7.73) in this subgroup of patients.
Conclusions: This meta-analysis suggests both KRAS and BRAF mutations as poor, prognostic biomarkers, associated with worse survival outcomes, in patients undergoing hepatic resection of CLM.

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1. Introduction

The liver is the most common metastatic site (Adam et al., 2009) in colorectal cancer (CRC) patients. Twenty to twenty-five percent (20–25%) of patients have clinically detectable colorectal-related liver metastases (CLM) at the initial diagnosis and approximately 50% of the patients develop CLM during their disease course

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(Garden et al., 2006). Resection of the CLM, sometimes in combination with other local treatment modalities, such as radiofrequency ablation (RFA), has become the standard of care, and offers the only potential for cure (Chiappa et al., 2009; Ksienski et al., 2010). The development of new surgical approaches, together with an increasing use of the perioperative systemic therapy, have led to an increase of the percentage of patients potentially eligible for curative liver resection (Rolfo et al., 2014, 2013; Bronte et al., 2015, 2013). In most series, up to 25% of patients presenting with stage IV CRC undergo hepatic resection (Kopetz et al., 2009), with reported 5-year survival rates up to 50% (Taylor et al., 2010; Choti et al., 2002; Chua et al., 2011). However over one-half of patients will develop recurrence within 2 years (de Jong et al., 2009; Fong et al., 1999; Nordlinger et al., 1996), not getting any long-term survival benefit from hepatic resection.

Metastatic colorectal cancer is a very heterogeneous disease, with a strong, both clinical and biological variability, among different patients (Bronte et al., 2014). Therefore difficulties remain in deciding who is a good candidate for liver resection. Many studies have examined several clinical and pathological factors, including number and size of CLM, disease-free interval from primary to CLM, carcinoembryonic antigen (CEA) level, primary tumor stage, synchronous or metachronous CLM, as potential prognostic determinants of survival after surgical resection of CLM, in order to establish a preoperative scoring system that is able to predict the risk of recurrence after resection, and ultimately allows the selection of those patients who may benefit more from surgery (Choti et al., 2002; de Jong et al., 2009; Fong et al., 1999; Nordlinger et al., 1996; Mann et al., 2004; Nagashima et al., 2006a,b).

To date, there are not molecular biomarkers, approved in the clinical setting, that are able to predict such biological differences, favoring the identification of patients, at high risk of relapse (Russo et al., 2009). RAS mutations, including both KRAS and NRAS gene mutations, have been reported in about 50% of primary CRC, and have been associated with resistance to the anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (MoAbs), Cetuximab
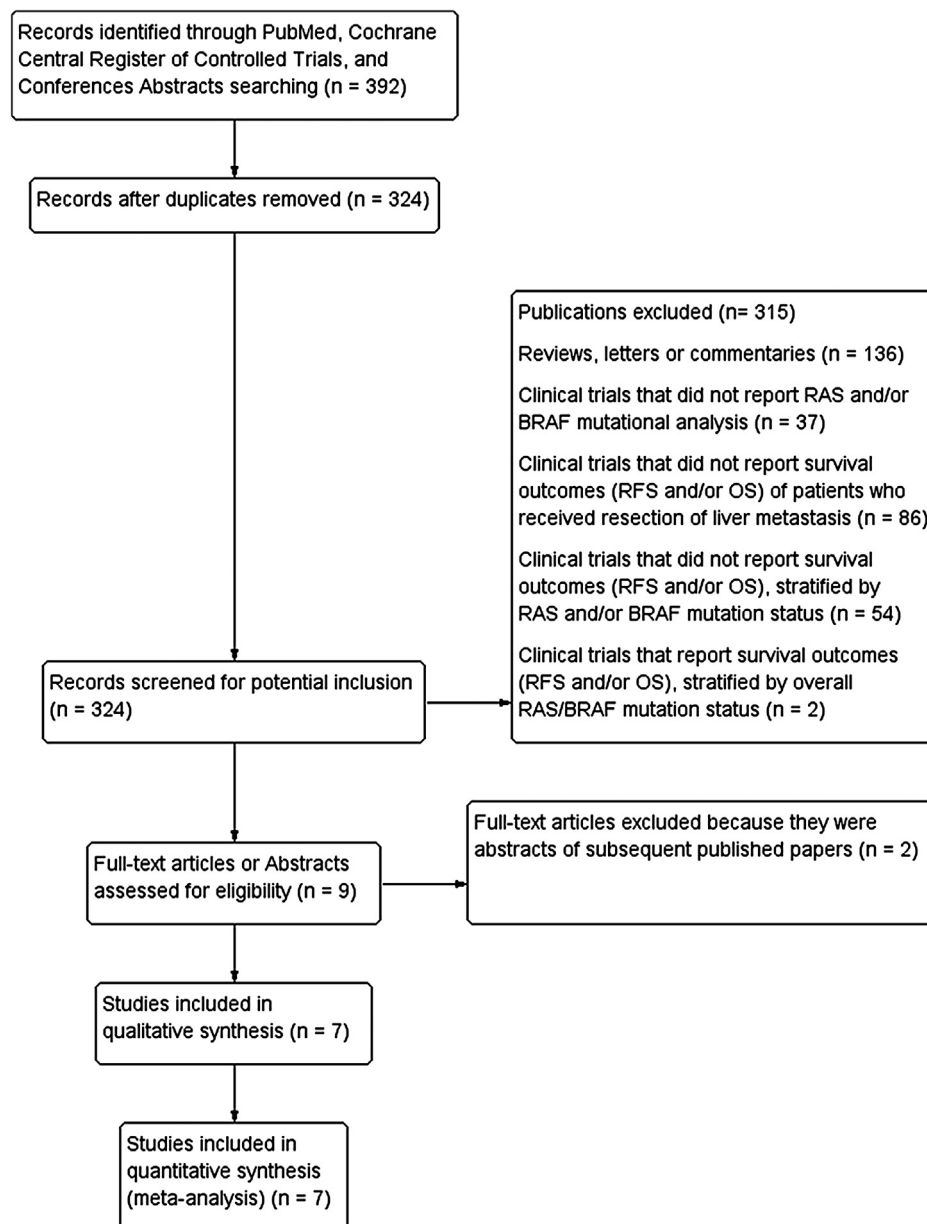

Fig. 1. Flow-chart of studies selection.

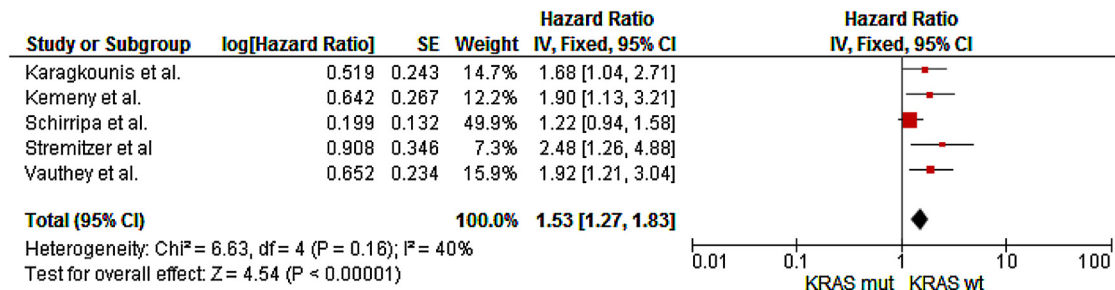| Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Karagkounis et al.	0.519	0.243	14.7%	1.68 [1.04, 2.71]
Kemeny et al.	0.642	0.267	12.2%	1.90 [1.13, 3.21]
Schirripa et al.	0.199	0.132	49.9%	1.22 [0.94, 1.58]
Stremitzer et al	0.908	0.346	7.3%	2.48 [1.26, 4.88]
Vauthey et al.	0.652	0.234	15.9%	1.92 [1.21, 3.04]
Total (95% CI)			**100.0%**	**1.53 [1.27, 1.83]**
Heterogeneity: Chi² = 6.63, df = 4 (P = 0.16); I² = 40%				
Test for overall effect: Z = 4.54 (P < 0.00001)				

Fig. 2. Forest plot showing hazard ratio for relapse free survival according to KRAS mutation status in colorectal cancer patients who received resection of liver metastasis.

and Panitumumab, in the metastatic disease (Rizzo et al., 2010; Bronte et al., 2011). This has been well exploited by several randomized trials (De Roock et al., 2010; Bokemeyer et al., 2012; Douillard et al., 2013; Heinemann et al., 2014; Schwartzberg et al., 2014; Van Cutsem et al., 2015; Bokemeyer et al., 2015), that have overall shown significant poorer response rates and inferior survival outcomes in RAS-mutated patients receiving chemotherapy plus anti-EGFR MoAbs, compared to RAS-wild type population. RAS mutations represent the only, molecular, predictive biomarker approved for clinical use, while their prognostic role is still debated. Several randomized studies have shown no significant survival differences between KRAS mutated and KRAS wild-type, CRC patients, independently of anti-EGFR therapy (Price et al., 2011; Hecht et al., 2009; Kastrinakis et al., 1995; Russo et al., 1998; Tol et al., 2010), while others have demonstrated a prognostic role of KRAS in advanced disease (Richman et al., 2009; Maughan et al., 2011; Tejpar et al., 2012). BRAF mutations have been described in about 10% of primary CRC, representing a well-known negative prognostic factor, associated with worse survival outcomes, regardless of any treatment received (Ahn et al., 2014).

Several studies have recently investigated the potential role of KRAS and/or BRAF mutations, as prognostic biomarkers, in patients who underwent surgical treatment of CLM. The majority of such studies have shown that both KRAS and BRAF, respectively detected in about 30% and 3% of CLM, are associated with worse survival outcomes of patients undergoing liver resection (Nash et al., 2010; Karagkounis et al., 2013; Vauthey et al., 2013; Stremitzer et al., 2012), while some other studies have not found a significant association (Kemeny et al., 2014; Teng et al., 2012; Schirripa et al., 2015). The aim of this meta-analysis is to combine and analyze simultaneously all the studies reporting the survival outcomes (recurrence free survival (RFS), and/or overall survival (OS)) of patients who received resection of CLM, stratified by KRAS and/or BRAF mutation status, in order to provide a more precise estimation of the prognostic value of both KRAS and BRAF, in patients undergoing surgical therapy for CLM.

2. Materials and methods

2.1. Search for clinical trials

We performed our meta-analysis according to a predefined written protocol. We searched for all published studies, that report the survival outcomes (RFS and/or OS) of patients who received resection of CLM, stratified by KRAS and/or BRAF mutation status. Publications were identified by an electronic search in Medline, using PubMed online service, updated in May 2015. The search for publications was made by other databases including the Cochrane Library and EMBASE. However the search on PubMed allowed the widest collection of publications about this topic. The following search terms were used: "KRAS", "BRAF", "colorectal cancer", "CRC", "prognostic", "liver metastases", "liver resection" "hepatic surgery". The search was limited to human studies in the English language. The results were supplemented with manual searches of American Society of Clinical Oncology meeting proceedings, references of selected articles and published reviews. A systematic review on this topic in the Cochrane database of systematic reviews was not found.

2.2. Selection criteria

According to this search clinical trials were taken into account if they had to fulfill all the following inclusion criteria: (1) only patients with metastatic colorectal cancer were included; (2) only patients who underwent resection of CLM were included (3) studies that report the survival outcomes (RFS and/or OS) of patients who received resection of CLM; (4) studies that report the survival outcomes (RFS and/or OS), stratified by KRAS and/or BRAF mutation status.

2.3. Data extraction

Two authors independently selected studies according to the aforementioned inclusion criteria. If these two authors could not
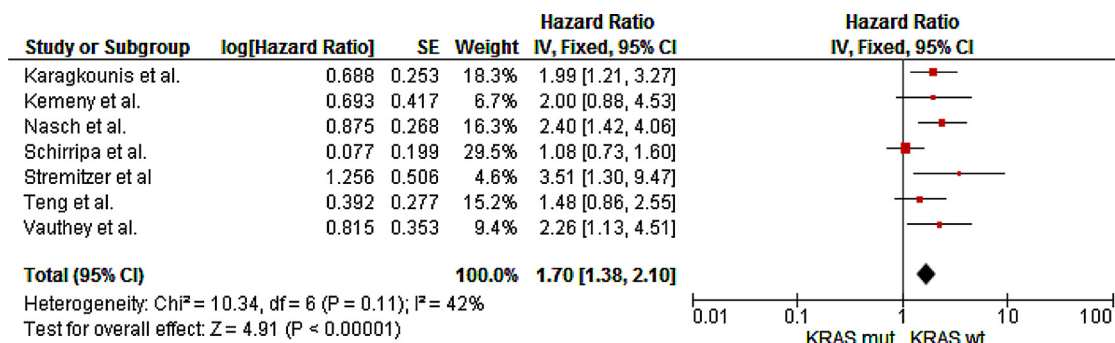
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Karagkounis et al.	0.688	0.253	18.3%	1.99 [1.21, 3.27]
Kemeny et al.	0.693	0.417	6.7%	2.00 [0.88, 4.53]
Nasch et al.	0.875	0.268	16.3%	2.40 [1.42, 4.06]
Schirripa et al.	0.077	0.199	29.5%	1.08 [0.73, 1.60]
Stremitzer et al	1.256	0.506	4.6%	3.51 [1.30, 9.47]
Teng et al.	0.392	0.277	15.2%	1.48 [0.86, 2.55]
Vauthey et al.	0.815	0.353	9.4%	2.26 [1.13, 4.51]
Total (95% CI)			**100.0%**	**1.70 [1.38, 2.10]**
Heterogeneity: Chi² = 10.34, df = 6 (P = 0.11); I² = 42%				
Test for overall effect: Z = 4.91 (P < 0.00001)				

Fig. 3. Forest plot showing hazard ratio for overall survival according to KRAS mutation status in colorectal cancer patients who received resection of liver metastasis.

Table 1
Characteristics of the 7 trials included in the meta-analysis.

Trial (reference)	RAS mut n. (%)	BRAF mut n. (%)	KRAS (mut vs wt) RFS (HR, 95% CI)	KRAS (mut vs wt) OS (HR, 95% CI)	BRAF (mut vs wt) RFS (HR,95% CI)	BRAF (mut vs wt) OS (HR, 95% CI)
Schirripa et al. (2015)	160/309 (52)	12/309 (4)	1.22 (0.94–1.58)	1.08 (0.73–1.59)	2.31 (1.09–4.87)	2.76 (1.12–6.81)
Karagkounis et al. 2013	58/202 (29)	4/202 (2)	1.78 (1.04–2.71)	1.97 (1.20–3.24)	N.A	1.90 (0.60–5.99)
Kemeny et al. (2014)	51/169 (30)	1/162 (0.6)	1.90 (1.12–3.20)	1.99 (0.88–4.51)	N.A	N.A
Nasch et al. (2010)	51/188 (27)	N.A	N.A	2.39 (1.41–4.04)	N.A	N.A
Stremitzer et al. (2012)	15/60 (25)	0/60	2.48 (1.26–4.89)	3.49 (1.29–9.41)	N.A	N.A
Teng et al. (2012)	87/231 (37)	5/231 (2)	N.A	1.48 (0.86–2.54)	N.A	6.23 (1.89–20.61)
Vauthey et al. (2013)	34/193 (18)	N.A	1.92 (1.21–3.03)	2.25 (1.13–4.49)	N.A	N.A

OS indicates overall survival; RFS, relapse free survival; mut, mutated; wt, wild type; *n.*, number of patients.
HR, hazard ratio; CI, confidence intervals; N.A, not available.

reach a consensus, another author was consulted and a final decision was made by consensus. Information was carefully extracted by overall selected studies. The following data were collected and organized from eligible studies: first author name, journal and year of publication, study design, study treatment, baseline characteristics of patients (i.e., age, stage, KRAS status, BRAF status), outcome measures (i.e., RFS and/or OS), and and hazard ratio (HR) with 95% confidence intervals (CIs) for RFS and/or OS, stratified according to KRAS and/or BRAF mutation status. Data extraction was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2010).
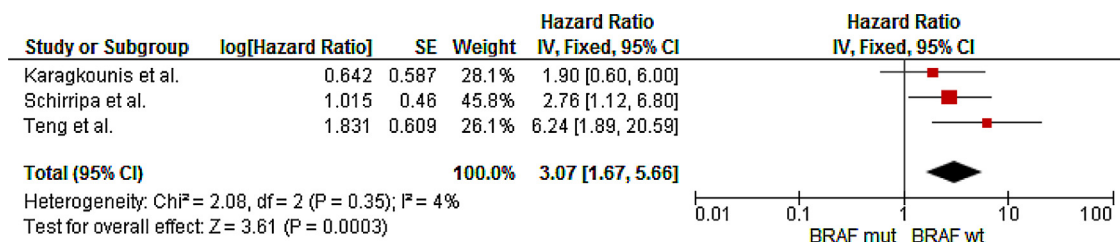
2.4. Statistical analysis

Patients were stratified according to KRAS and/or BRAF mutation status into 2 groups: mutant KRAS and/or BRAF and wild-type KRAS and/or BRAF. The outcome measures were OS and RFS, calculated in KRAS and/or BRAF-mutated patients undergoing resection of CLM, compared to KRAS and/or BRAF wild-type population. The correlation between these endpoints and KRAS/BRAF mutations was expressed as an HR of KRAS and/or BRAF-mutated patients over KRAS/BRAF-wild type patients. Thus, an HR more than 1 indicates that KRAS and/or BRAF-mutations are associated with worse OS and/or RFS after CLM resection. The heterogeneity between trials was tested using the Cochran *Q*-test, with a predefined significance threshold of 0.1. A meta-analysis of HRs was performed to calculate a pooled HR for each outcome using a fixed-effect or random-effect, based on statistical significance of *Q*-test, according to Mantel–Haenszel method. Publication bias for both OS and RFS analysis were assessed using Begg's funnel plots and Egger's test. The level of significance was set at 5% ($P < 0.05$ suggested a statistical significant publication bias). If publication bias was found, the Duval and Tweedie nonparametric 'trim and fill' method was used to adjust it. All statistical analyses were performed with Review Manager 5.3.5 (RevMan; version 5.3.5) and Comprehensive Meta-Analysis software (CMA; version 3.0).

3. Results

Our search, according to the aforementioned criteria, performed in May 2015, identified 392 publications. Among these, after a careful selection procedure, only seven studies (1403 patients) met our inclusion criteria and were included in our meta-analysis (Fig. 1). Three of these studies were retrospective series (Vauthey et al., 2013; Kemeny et al., 2014; Francesca Bergamo and Loupakis et al., 2014), while the others were prospective studies (Nash et al., 2010; Karagkounis et al., 2013; Stremitzer et al., 2012; Teng et al., 2012). In these 7 studies, sample sizes of the analyzed population ranged from 60 (Stremitzer et al., 2012) to 309 (Schirripa et al., 2015), while the percentage of KRAS mutated patients ranged from 14% (Stremitzer et al., 2012) to 37% (Teng et al., 2012). BRAF mutations were analysed in four of the seven included studies (Karagkounis et al., 2013; Stremitzer et al., 2012; Teng et al., 2012), and it was found in 2–4% of patients who underwent surgery for CLM. In nearly every trial, patients' characteristics were well balanced between the two arms. A detailed list of the seven selected studies, including molecular genotyping and patients' outcomes, are described in Table 1.

All the included studies analyzed the survival outcomes (OS and/or RFS) of patients undergoing resection of CLM, stratified by KRAS mutation status. Five studies reported HRs with 95% CI data for both RFS and OS (Karagkounis et al., 2013; Vauthey et al., 2013; Stremitzer et al., 2012; Kemeny et al., 2014), while two studies reported only HRs with 95% CI data for OS (Nash et al., 2010; Teng et al., 2012). Pooled analysis showed that KRAS mutations predicted a significant worse both RFS (HR: 1.53; 95% CI: 1.27–1.83) and OS (HR: 1.7; 95% CI: 1.38–2.10) in patients who underwent surgical resection of CLM (Figs. 2 and 3). The pooled HRs for both RFS and OS were calculated using fixed-effect model, because of non-significant heterogeneity between treatment effects (*Q*-test: *P*: 0.16; *P*: 0.11). Only three of the seven included studies analysed the OS of patients who underwent resection of CLM, according to BRAF mutation status (Karagkounis et al., 2013; Teng et al., 2012),

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Karagkounis et al.	0.642	0.587	28.1%	1.90 [0.60, 6.00]
Schirripa et al.	1.015	0.46	45.8%	2.76 [1.12, 6.80]
Teng et al.	1.831	0.609	26.1%	6.24 [1.89, 20.59]
Total (95% CI)			**100.0%**	**3.07 [1.67, 5.66]**

Heterogeneity: Chi² = 2.08, df = 2 (P = 0.35); I² = 4%
Test for overall effect: Z = 3.61 (P = 0.0003)

Fig. 4. Forest plot showing hazard ratio for overall survival according to BRAF mutation status in colorectal cancer patients who received resection of liver metastasis.

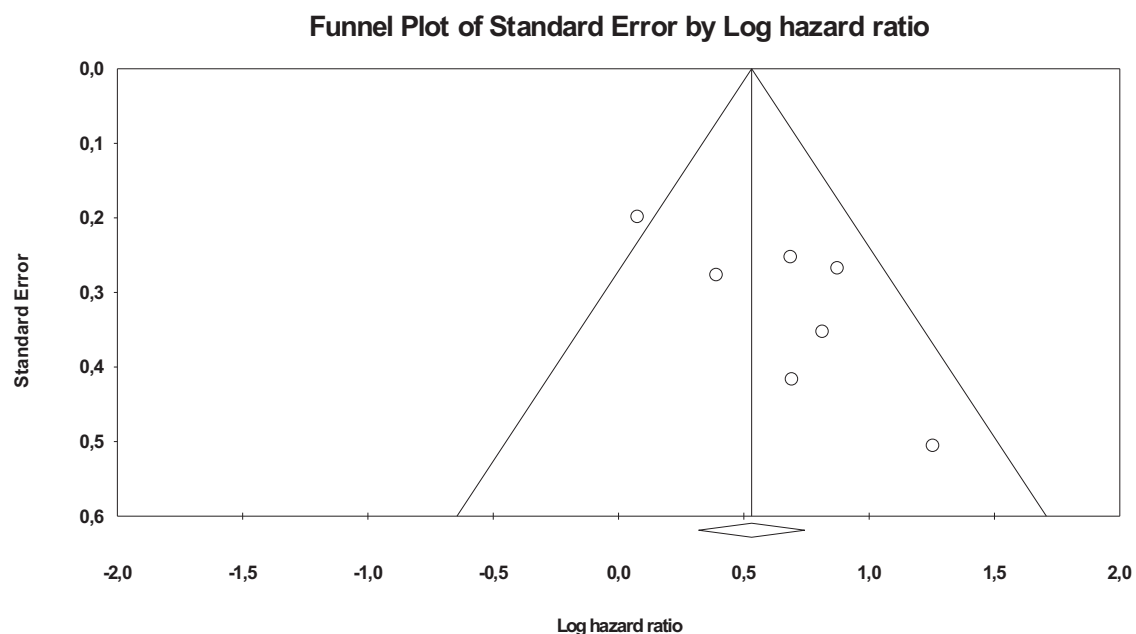## Funnel Plot of Standard Error by Log hazard ratio
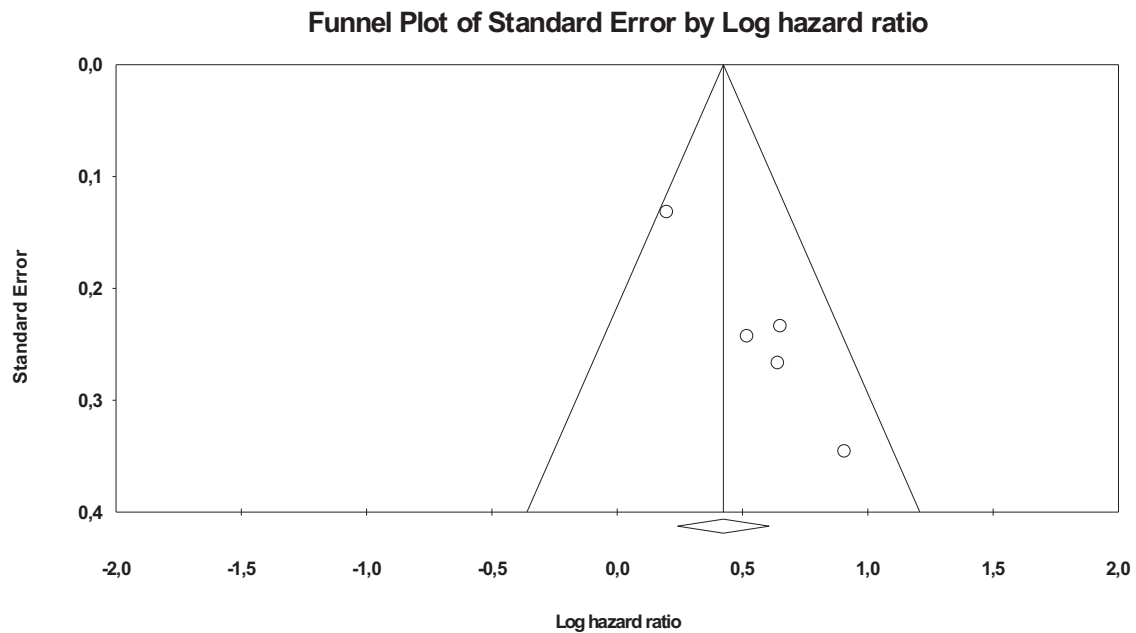
Fig. 5. Funnel plot of log hazard ratio (horizontal axis) and the standard error for the log hazard ratio (vertical axis) for relapse free survival according to KRAS mutation status in colorectal cancer patients who received resection of liver metastasis. Each study is represented by one circle- the vertical line represents the pooled effect estimate.

while RFS data have not been reported in any of such studies. Pooled analysis showed that BRAF mutations predicted a significant worse OS (HR: 3.07; 95% CI: 1.67–5.66) in this subgroup of CRC patients (Fig. 4). The pooled HR for OS was calculated using fixed-effect model, because of non-significant heterogeneity between treatment effects (Q-test: P: 0.35). Publication bias have not been found by Begg's test for both RFS and OS (P: 0.11), according to KRAS mutation status, while Egger's tests for both RFS and OS (HRs) analysis, resulted positive for bias (P: 0.0017; P: 0.02). Funnel plots for HRs of both RFS and OS stratified by KRAS mutations are reported in Figs. 5 and 6. However, analysis with the 'trim and fill' method did not draw remarkably different conclusions, confirming the sig-

nificant association between KRAS mutations and worse patients' outcomes, including both OS (adjusted HR: 1.39, 95% CI: 1.16–1.66) and RFS (adjusted HR: 1.31, 95% CI: 1.12–1.53). Publication biases were not found for BRAF status and OS by both Begg's (P: 0.5) and Egger's tests (P: 0.39).

4. Discussion

This meta-analysis, including seven studies, which evaluated the survival outcomes (OS, and/or RFS) of patients undergoing hepatic resection of CLM, stratified by KRAS and/or BRAF mutation status, has shown that both KRAS and BRAF mutations are asso-

Funnel Plot of Standard Error by Log hazard ratio

Fig. 6. Funnel plot of log hazard ratio (horizontal axis) and the standard error for the log hazard ratio (vertical axis) for overall survival according to KRAS mutation status in colorectal cancer patients who received resection of liver metastasis. Each study is represented by one circle- the vertical line represents the pooled effect estimate.

ciated with worse patients' survival outcomes, compared to KRAS and BRAF wild-type population. Indeed both the risk of recurrence and death are significantly higher in both KRAS and BRAF mutated compared to KRAS and BRAF wild-type patients, suggesting a negative prognostic value of such molecular biomarkers in this subgroup of patients. Currently, few clinical-pathological factors are considered to predict the recurrence risk and outcomes of patients undergoing resection of CLM in clinical practice, but our ability to identify patients who may benefit more from surgical therapies still very poor, and very little is known about the biology underlying the tumor heterogeneity. The role of molecular biomarkers, such as KRAS and BRAF, is well established in the advanced and unresectable disease, but its potential application in CRC patients with liver metastases candidate to resection has not been defined yet. The results of our work suggest both KRAS and BRAF mutations as negative prognostic biomarkers in patients undergoing surgical therapy for CLM, supporting the evaluation of such molecular biomarkers together with the other clinical-pathological factors, in order to more accurately predict, both recurrence risk and survival of patients undergoing resection of CLM, and ultimately select only the best candidates for surgery. Indeed it's possible that both KRAS and BRAF mutations are associated with a worse biology and a more rapid and aggressive metastatic behavior of CLM, discouraging surgeons to perform surgical resection, independently of clinical resectability. This interpretation is consistent with the evidence that the percentage of KRAS mutated patients ranged from 14% (Stremitzer et al., 2012) to 37% (Teng et al., 2012) in all seven included studies, compared to 35-45% reported in metastatic and unresectable CRC, suggesting a significant association between KRAS mutations rates and tumor behavior, as described in preclinical studies (Suchy et al., 1992; Tanaka et al., 1994; Varghese et al., 2002; Webb et al., 1998). Some clinical series have also shown that KRAS mutations are associated with an increased risk of developing lung and liver metastases compared to wild-type population (Vauthey et al., 2013; Kemeny et al., 2014). Others have shown a higher incidence of lung metastases/recurrence than liver metastases/recurrence in KRAS mutated patients (Vauthey et al., 2013; Tie et al., 2011; Kim et al., 2012). Even if KRAS mutations rate in CLM usually corresponds with the mutation status of the primary tumor (Tie et al., 2011; Vakiani et al., 2012), it seems to be different among different metastatic sites, with a higher percentage of mutations in lung and brain metastases, than in liver metastases (Tie et al., 2011; Kim et al., 2012), suggesting specific RAS-related patterns of recurrence, with potential implication in the clinical management of CRC patients, but these trends need to be investigated in larger, prospective studies. As regards BRAF mutations, even if evaluated in a small subgroup of patients, our findings are consistent with the most part of published studies which have validated BRAF mutations obtained from primary tumour specimens as a strong negative prognostic biomarker in metastatic CRC (Ahn et al., 2014), showing a more aggressive and chemo-refractory behavior compared to wild-type tumours (Tran et al., 2011). However it's interesting to observe that the percentages of BRAF mutations (2–4%) in all the included studies is lower than those reported in the literature (5–10%) (Sridhar et al., 2005; Di Nicolantonio et al., 2008), likely due to the clinical selection of patients included in such studies. Indeed, because of their peculiar metastatic spread, BRAF-mutated tumours are usually detected as an advanced disease, rarely candidate for liver surgery. The low percentage of BRAF mutations in such subgroup of CRC patients, could limit its clinical application as prognostic biomarker for routinary use, but does not affect neither its scientific relevance, nor its potential implications for individual patients.

This literature-based meta-analysis confirms the results achieved in the majority of included studies, suggesting both KRAS and BRAF mutations as, negative, prognostic biomarker, in patients who underwent surgical resection of CLM; however, it has some limitations. The patients cohorts included in the seven studies of our meta-analysis are quite heterogeneous, because of different selection criteria, as well as a variable origin (primary tumor vs liver metastases) of tissue available for the mutational analysis. Indeed the mutation status was determined from liver metastasis for the majority of patients, while it was determined from the primary tumor in about 20% of patients included in both the Kemeny et al. (2014) and Schirripa et al. (2015) studies. Almost all seven studies included, performed the evaluation of the most common KRAS mutations in the extracted DNA (codon12/13); only two studies (Vauthey et al., 2013; Schirripa et al., 2015) evaluated both KRAS and NRAS mutations (codon12/13/61), stratifying patients according to all RAS mutation status. However, NRAS mutations account for only 10–20% of all RAS-mutated patients, representing a very small subgroup of patients included in both studies, likely not influencing final study results. Almost all the patients included in our meta-analysis had received peri-operative, 5-FU-based, systemic chemotherapy, with or without bevacizumab. Only a small percentage of patients had received anti-EGFR MoAbs (11.8% in the study of Teng et al. (2012), 5% in the study of Schirripa et al. (2015), and 13 of 28 wild-type *KRAS* patients who developed recurrence, in the study of Stremitzer et al. (2012)). Furthermore two of the seven studies, included also patients who received loco-regional treatments after liver resection, such as adjuvant hepatic arterial infusion (HAI) (Kemeny et al., 2014), and tumour ablation (Karagkounis et al., 2013). The above described heterogeneity among the different patients' cohort, does not reduce the clinical and statistical significance of our results, which reveal both KRAS and BRAF as poor prognostic biomarker in patients who underwent surgical resection of CLM, but limits, of course, any generalization to the overall CRC population, as well as its current use as predominant factor for the upfront patients selection in clinical practice. Indeed, the lack of a larger individual patient analysis, including also the other known clinical-pathological prognostic factors, such as the number and size of CLM, the disease-free interval from primary to CLM, CEA level, primary tumor stage, etc., does not allow to consider both KRAS and BRAF mutations as independent prognostic biomarkers for clinical decision models. Finally, long-term survival outcomes (10–20 year RFS/OS rate) should be known before to definitively exclude CRC patients from surgery, but such data were not reported in any of included studies. Therefore further clinical trials are urgently needed to investigate if KRAS/BRAF mutated patients undergoing hepatectomy for CLM, have significantly lower RFS/OS rates compared to the wild type, after a long-term follow-up, and ultimately recommend, as suggested by our work, the surgical treatment of CLM only to the wild type population. In conclusion our meta-analysis confirm both KRAS and BRAF mutations as a strong, prognostic biomarkers, associated with worse both OS and RFS, in patients undergoing hepatic resection of CLM. Certainly, these interesting evidences represent the first step towards a deeper understanding of molecular mechanisms underlying the tumor behavior and patients' outcomes in a clinical-selected subgroup of CRC patients, supporting the introduction of new treatment decision models, taking into account the tumor molecular profile, together with the other clinical-pathological factors, in order to predict the outcomes of patients undergoing resection of CLM, and individualize both systemic and loco-regional treatment strategies.

Conflict of interest

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