International Journal of Colorectal Disease (2020) 35:1513–1527
https://doi.org/10.1007/s00384-020-03589-9

ORIGINAL ARTICLE

The treatment paradigm of right-sided metastatic colon cancer: harboring BRAF mutation makes the difference

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Accepted: 4 April 2020 / Published online: 7 May 2020

Abstract

Purpose BRAF mutations represent the main negative prognostic factor for metastatic colorectal cancer and a supposed negative predictive factor of response to standard chemotherapy. We have explored survival difference in right-sided colon cancer (RCC) patients according to BRAF mutations, with the aim to identify any predictive factors of response to targeted-based therapy.

Methods A retrospective study of RCC patients, with BRAF known mutation status, treated with chemotherapy (CT) from October 2008 to June 2019 in 5 Italian centers, was conducted.

Results We identified 207 advanced RCC patients: 20.3% BRAF mutant and 79.7% BRAF wild type (wt). BRAF-mutant cancers were more likely to be pT4 (50.0% v 25.7%, $p = 0.016$), undifferentiated (71.4% v 44.0%, $p = 0.004$), KRAS wt (90.5% v 38.2%, $p < 0.001$), and MSI-H (41.7% v 16.2%, $p = 0.019$) tumors, with synchronous (52.4% v 31.5%, $p = 0.018$) and peritoneal metastases (38.1% v 22.4%, $p = 0.003$). Median overall survival (OS) was 16 v 27 months in BRAF mutant and BRAF wt ($P = 0.020$). In first-line setting, BRAF-mutant showed a 2ys OS of 80% in clinical trials, 32% in anti-VEGF, 14% in epidermial growth factor receptor (EGFR), and 0% in chemotherapy alone regimens ($P = 0.009$). BRAF-mutant patients demonstrated worse survival, regardless of targeted therapy administered. However, survival difference was statistically significant in the anti-EGFR-treated subgroup (16 v 28 months, $P = 0.005$ in BRAF mutant v BRAF wt, respectively).

Conclusions Our study demonstrated that BRAF status makes the difference in treatment's outcome. Therefore, the anti-EGFR should not be excluded in all advanced RCC but considered on a case-by-case basis.

Keywords Colorectal cancer · RCC · Sidedness · BRAF · Anti-EGFR

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide [1]. In recent years, the sidedness seems to be a well-established and relevant prognostic factor due to distinct differences in epidemiology, pathogenesis, genetic and epigenetic alterations, molecular pathways, and outcome between right (RCC) and left-side colorectal cancer (LCC) [2, 3].

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Moreover, RCC is prevalent among old age patients with iron deficiency anemia at diagnosis [4] and in female gender [5] and is more likely to be diploid and to be characterized by high microsatellite instability [6], CpG island methylation, and BRAF mutations [7–10].

Furthermore, different signaling pathways are involved in the development of colon cancer: in the RCC is more prevalent the serrated pathway [11, 12], in which BRAF mutations develop and CpG island hypermethylation occurs, resulting in gene transcriptional inactivation and loss of gene function by methylation of the promoter region. Otherwise, the conventional pathway with mutations in KRAS, TP53, and APC is associated with LCC.

From this literature data, it is clear how the RCC constitutes a different entity than the LCC. All these factors may contribute to the difference observed in patient prognosis and to explain the relationship between cancer location and mortality. Several population-based studies have explored the prognostic relevance of laterality in CRC, with conflicting results [13–17].

Meguid et al. [13] reported that right-sided cancers had a higher risk of mortality than left-sided colorectal cancers across all stages (HR, 1.04; 95% CI, 1.02 to 1.07); it was also confirmed by a more recent meta-analysis [2], in which LCC were associated with improved survival rather than RCC (HR, 0.82; 95% CI, 0.79–0.84). The association between RCC and higher mortality is strongest for patients with stage III and IV disease [16].

Moreover, the right-sidedness seems to be also a predictive factor of response to first-line treatment in mCRC patients. A retrospective analysis from CRYSTAL and FIRE-3 trials, in patients with RAS wild-type (wt) mCRC treated with chemotherapy and epidermial growth factor receptor (EGFR) targeted agent, found a better response in LCC than RCC patients [18]. Moreover, as shown by the data of CALGB/SWOG 80405 trial, among patients with KRAS wt disease, overall survival (OS) and progression free survival (PFS) were better in those with left-sided primary tumors, while both OS and PFS were better with bevacizumab than with cetuximab in patients with right-sided primary tumors [19].

In general, BRAF mutations are present in about 10% of colorectal cancer cases but over two-thirds of BRAFV600E tumors originate in the RCC v the LCC (68 v 32%) [7]. The RCC negative prognosis seems to be related with the more frequent BRAF mutations [20, 21] which represent the main negative prognostic factor for mCRC, regardless of sidedness and other molecular factors [22]. Indeed, BRAF-mutant CRC has emerged as a distinct biologic entity, refractory to standard chemotherapy regimens approved for the treatment of metastatic CRC and associated with a dismal prognosis [23–25]. An effective therapy has not yet been identified although some positive data have emerged regarding the use of more intensive chemotherapy backbone plus bevacizumab as initial therapy [26] and the more recent multi-targeted therapy combinations [27–30]. Up to date, it is still not clear which is the best therapeutic strategy in RCC tumors, albeit with BRAF mutation. However, clinical trials with combining MAPK pathway targeted therapies are under investigation and could be the best therapeutic strategy [23].

This is a retrospective analysis of metastatic RCC patients referred to 5 Italian centers with the aim to evaluate the outcome of RCC patients according to BRAF status and the treatment performed.

Methods

Patients

A multi-institutional retrospective analysis of clinical data from 207 patients with right mCRC treated with chemotherapy from October 2008 to June 2019 was done. All patients with BRAF known mutation status were included in this analysis. Clinicopathological factors of patients were extrapolated from their clinical data records, including their comorbidity, grouped according to Charlson comorbidity index (CCI). CCI is a well-known method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, such as hospital abstracts data. Each comorbidity category has an associated weight (from 1 to 6), based on the adjusted risk of mortality or resource use, and the sum of all the weights results in a single comorbidity score for a patient. A score of zero indicates that no comorbidities were found. The higher the score, the more likely the predicted outcome will result in mortality or higher resource use. Taking into account surgery procedures, as reported in clinical data records, there were 49 minor liver resections, from solitary metastasectomy to left lateral sectionectomy, combined with right hemicolectomy, without post-operative complications. In total, 162 patients underwent right hemicolectomy at diagnosis, of which 10 laparoscopically. The study was conducted in accordance with the Declaration of Helsinki and Institutional Review Board approval.

Statistical analysis

SPSS statistical software, version 24 (SPSS Inc. Chicago, IL, USA) was used. The χ^2 test and t test for unpaired data were applied to compare frequencies and means, respectively. The interaction among clinicopathologic parameters was first analyzed using univariate logistic regression. Survival curves were estimated using the Kaplan-Meier method and the log-rank test was used for the difference assessment. A multivariate Cox-proportional hazard model was used to identify independent prognostic factors for survival. All reported P values are two sided, and P values less than 0.05 are considered statistically significant.

Table 1 All clinicopathologic features (valid cases and percentages)

	Number	Percent
Total	207	100
Age median (range)	66 (38–86)	
Age category		
≤ 70	127	61.4
> 70	80	38.6
Sex		
Male	126	60.9
Female	81	39.1
Charlson comorbidity index		
≤ 8	104	50.2
> 8	96	46.4
Not available	7	3.4
Tumor onset		
Anemia	50	24.2
Intestinal occlusion	42	20.3
Pain	13	6.3
Intestinal perforation	4	1.9
Other (fever, weight loss, asthenia)	54	26.1
Primary tumor resected		
Yes	162	78.3
No	45	21.7
Tumor location		
Ascending and proximal hepatic flexure	90	43.5
Cecum	70	33.8
Distal hepatic flexure and two-third proximal transverse	47	22.7
Stage of disease at diagnosis		
I	2	1.0
II	20	9.7
III	47	22.7
IV	128	66.7
pT		
1	4	1.9
2	1	0.5
3	96	46.4
4	45	21.7
Not available	17	8.2
pN		
0	35	16.9
1	47	22.7
2	67	32.4
Not available	13	6.3
Lymphovascular/perineural invasion		
Yes	87	20.3
No	42	42.0
Tumor grading		
G1	6	2.9
G2	79	38.2
G3	83	40.1
G4	1	0.5

Table 1 (continued)

	Number	Percent
Mucinous histology		
Yes	60	29.0
No	140	67.6
KRAS		
Wild type	101	48.8
Mutated	106	51.2
NRAS		
Wild type	128	61.8
Mutated	7	3.4
BRAF		
Wild type	165	79.7
Mutated	42	20.3
Microsatellite instability		
MSS	66	31.9
MSI-High	19	9.2
Baseline ECOG performance status		
0	149	72.0
≥ 1	58	28.0
Adjuvant chemotherapy		
Yes	51	24.6
No	156	75.4
Adjuvant oxaliplatin		
Yes	43	20.7
Upfront treatment of liver metastases		
Surgery	49	23.7
RFA/TACE	10	4.8
Presentations of metastases		
Synchronous	133	64.3
Metachronous	74	35.7
Site of metastases at diagnosis		
Liver	122	58.9
Lung	22	10.6
Peritoneum	53	25.6
Local relapse	7	3.4
Distant nodes	3	1.4
No. of metastatic sites		
1	81	39.1
≥ 2	126	60.9
First-line chemotherapy (CT) regimen		
CT alone (mono/doublet regimen)	38 (6/32)	18.4 (2.9/15.5)
CT plus anti-VEGF	80	39.0
CT plus anti-EGFR	38	18.4
Triplets CT (plus anti-VEGF/anti-EGFR)	38 (13/2)	18.4 (6.3/1.0)
Clinical trials	5 (5)	2.4
No CT	7	3.4
Second line		
CT alone (mono/doublet regimen)	33 (9/24)	15.9 (7.0/18.8)
CT plus anti-VEGF (Bevacizumab/aflibercept)	68 (46/22)	53.2 (22.2/10.6)
CT plus anti-EGFR	5	2.4

Table 1 (continued)

	Number	Percent
Triplets CT (plus anti-VEGF/anti-EGFR)	9 (2/0)	4.3 (1.0/0)
Clinical trials	9	4.3
Regorafenib	3	1.5
Tas102	1	0.5
Third line		
CT alone (mono/doublet CT)	25 (11/14)	12.1 (5.3/6.8)
CT plus anti-VEGF	7	3.
CT plus anti-EGFR	2	1.0
Triplets CT (plus anti-VEGF/anti-EGFR)	4(2/0)	1.9 (1.0/0)
Clinical trials	3	1.5
Regorafenib	17	8.2
Tas 102	5	2.4
Beyond 3-line treatment		
Yes/rechallenge	35/19	16.9/9.2

RFA radiofrequency ablation, *TACE* transarterial chemoembolization

Results

Clinicopathological characteristics

This study included 207 right-sided metastatic colon cancer patients with known BRAF mutation status. All patients' clinicopathological characteristics are summarized in Table 1. In total, 42 (20.3%) patients had BRAF-mutant tumors and 165 (79.7%) had BRAF-wt tumors. Also, KRAS/NRAS and MSI status were considered for the analysis. According to RAS-status, 40 (20%) patients had undergone a first-line chemotherapy with an anti-EGFR target agent.

Differences in clinicopathological characteristics between BRAF-mutant and BRAF-wt tumors are reported in Table 2. BRAF-mutant RCC was significantly more likely to occur in pT4 (50.0% v 25.7%, $p = 0.016$), undifferentiated (71.4% v 44.0%, $p = 0.004$), KRAS wt (90.5% v 38.2%, $p < 0.001$), MSI-H (41.7% v 16.2%, $p = 0.019$) tumors, with synchronous (52.4% v 31.5%, $p = 0.018$), and peritoneal metastases (38.1% v 22.4%, $p = 0.003$). A higher proportion of BRAF-mutant tumors were observed in female patients, although this was not statistically significant (52.4% v 47.6% in female and male group, respectively). Moreover, the tumor onset with anemia was more common in BRAF-mutant than BRAF-wt tumors (40% v 27.3%, $p = 0.065$). No difference between BRAF statuses was found in right colon tumor location as well as mucinous histology or lymph node involvement.

Survival analysis

In our study, BRAF-mutant RCC showed a poorer prognosis than BRAF-wt tumors with a median OS of 16.0 (range 13.72–18.27) v 27.0 (range 21.82–31.17) months, respectively (hazard ratio [HR], 1.60; 95% CI, 1.06–2.41; $P = 0.020$) (Fig. 1a).

Other clinicopathological factors significantly associated with poorer survival included age > 70 years ($P = 0.002$), pT4 ($P = 0.009$), pN2 ($P = 0.034$), G3–4 tumor grading ($P = 0.009$), and lympho-vascular invasion ($P = 0.013$) at the histological exam. Moreover, peritoneum as metastatic site ($P = 0.040$) and the synchronous occurrence of metastases ($P = 0.045$) were associated with a worse survival. On the contrary, a good ECOG PS ($P = < 0.0001$), primary resected tumors ($P = < 0.0001$), and the upfront surgery of liver metastases ($P = 0.001$) were associated with better outcome. At the multivariate analysis, only BRAF status, baseline ECOG PS, and the upfront surgery of metastatic disease were independent prognostic factors of survival (Table 3).

Overall, there was non-significant difference in median OS between first-line treatment with mono or doublet chemotherapy (18.0 months, range 10.5–25.4), triplet chemo regimen (25.0 months, range 18.1–31.8), chemo plus an anti-VEGF (24.0 months, range 13–24.9) or anti-EGFR (26.0 months, range 20.9–31.1) targeted agent, and clinical trials with immunotherapy (not reached) (HR = 0.90, 95% CI 0.81–1.00, $P = 0.072$). (Fig. 2a) However, taking into account the first-line regimen, patients enrolled in clinical trials showed a better median progression free survival (PFS1) than others (17.0 v 6.0 v.13.0 months, in clinical trials, CT plus a target agent and triplet CT group, respectively) (HR = 0.90, 95% CI 0.82–0.99, $P = 0.037$) (Fig. 2b). Beyond first-line treatment, clinical trials and reintroduction of triplet CT regimen performed significantly better than the other treatment strategies (median PFS2 was 16.0 v 15.0 v 7.0 v 5.0 v 4.0 v 2.0 months in clinical trials, triplet CT, CT plus anti-EGFR, CT plus anti-VEGF, CT alone, and regorafenib/lonsurf as second line therapy,

Table 2 Clinicopathologic parameter distribution between BRAF-wild type (wt) and BRAF-mutant tumors

	BRAF-wt	BRAF-mutant	*P*
Total	*N* (%)	*N* (%)	
Age category			
≤ 70	102 (61.8)	25 (59.5)	0.860
> 70	63 (38.2)	17 (40.5)	
Sex			
Male	105 (63.6)	20 (47.6)	
Female	60 (36.4)	22 (52.4)	0.077
Charlson comorbidity index			
≤ 8	80 (49.7)	24 (61.5)	
> 8	81 (50.3)	15 (38.5)	0.213
Tumor onset			
Anemia	35 (27.3)	14 (40.0)	
Intestinal occlusion	33 (25.8)	9 (25.7)	
Pain	14 (10.)	0 (0.0)	0.171
Intestinal perforation	4 (3.1)	0 (0.0)	
Other (fever, weight loss, asthenia)	42 (32.8)	12 (34.3)	
Primary tumor resected			
Yes	129 (78.2)	33 (78.6)	
No	36 (21.8)	9 (21.4)	1.000
Tumor location			
Ascending and proximal hepatic flexure	69 (41.8)	21 (50.0)	
Cecum	60 (36.4)	10 (23.8)	0.308
Distal hepatic flexure and two-third proximal transverse	36 (21.8)	11 (26.2)	
pT			
≤ 3	84 (74.3)	16 (50.0)	
4	29 (25.7)	16 (50.0)	0.016
pN			
0	28 (24.1)	7 (21.2)	
1	39 (33.6)	8 (24.2)	0.433
2	49 (42.2)	18 (54.5)	
Lymphovascular/perineural invasion			
Yes	64 (65.3)	23 (74.2)	
No	34 (34.7)	8 (25.8)	0.389
Tumor grading			
G1–2	75 (56.0)	10 (28.6)	
G3–4	59 (44.0)	25 (71.4)	0.004
Mucinous histology			
Yes	43 (27.2)	16 (38.1)	0.185
No	115 (72.8)	26 (61.9)	
KRAS			
Wt	63 (38.2)	38 (90.5)	
mut	102 (61.8)	4 (9.5)	< 0.0001
NRAS			
Wt	90 (93.8)	38 (97.4)	0.673
Mut	6 (6.3)	1 (2.6)	
Microsatellite instability			
MSS	57 (83.8)	9 (52.9)	
MSI-H	11 (16.2)	8 (47.1)	0.019
Baseline ECOG performance status			

Table 2 (continued)

	BRAF-wt	BRAF-mutant	*P*
0	117 (70.9)	32 (76.2)	
≥ 1	48 (29.1)	10 (23.8)	0.567
Presentations of metastases			
Synchronous	113 (68.5)	20 (47.6)	
Metachronous	52 (31.5)	22 (52.4)	0.018
Site of metastases at diagnosis			
Liver	101 (61.2)	21 (50.0)	
Lung	22 (13.3)	0 (0.0)	0.003
Peritoneum	37 (22.4)	16 (38.1)	
Local relapse	4 (2.4)	3 (7.1)	
Distant nodes	1 (0.6)	2 (4.8)	
No. of metastatic sites			
1	60 (36.4)	21 (50.0)	
≥ 2	105 (63.6)	21 (50.0)	0.114

respectively) (HR = 0.69, 95% CI 0.57–0.85, $P = 0.001$) (Fig. 2c). Although a more intensified chemotherapy regimen seems to give more survival benefit, non-significant difference was found among third-line treatments (HR for PFS3 = 1.0, 95% CI 0.94–1.07, $P = 0.883$) (Fig. 2d).

In a bivariate analysis where BRAF status was stratified by treatments, there was no significant survival differences between first-line CT with anti-EGFR or anti-VEGF targets in BRAF-wt tumors (Fig. 1b), while, in BRAF-mutant tumors, 2ys OS was 80% v 32% v 14% v 0% in clinical trials, anti-VEGF, anti-EGFR, and CT alone regimen, respectively (HR = 0.63, 95% CI 0.45–0.89, $P = 0.009$) (Fig. 1c). In the reverse analysis where anti-EGFR- and anti-VEGF-based chemotherapies were stratified by BRAF status, we demonstrated poorer survival for BRAF-mutant tumors regardless of targeted therapy administered even if there was a significantly difference only in the subgroup of patients treated with CT plus anti-EGFR target agents, where BRAF-mutant showed a significant lower OS (HR for anti-EGFR = 16 v 28 months in BRAF-mutant v BRAF-wt tumors, $P = 0.005$; HR for anti-VEGF = 18 v 26 months in BRAF-mutant v BRAF-wt tumors, $P = 0.509$) (Fig. 3a, b).

Discussion

By now we know that RCC is a completely different entity with a different embryological origin, molecular pathways (harboring BRAF, PIK3CA, and KRAS mutations, more frequently with MSI-H phenotype), and poorer outcome than LCC [2, 12]. Furthermore, different signaling pathways are involved in the development of colon cancer: in the RCC is more prevalent the serrated pathway [11, 12], in which BRAF mutations develop and CpG island hypermethylation occurs, resulting in gene transcriptional inactivation and loss of gene function by methylation of the promoter region. Otherwise, the conventional pathway with mutations in KRAS, TP53, and APC is associated with LCC.

The worse prognosis of RCC is confirmed irrespective of the therapeutic strategy [22, 31, 32], although a triplet chemotherapy backbone plus bevacizumab as initial therapy [26] and especially a multi-targeted therapy combination seems to be the best future therapeutic choice [27–30].

Moreover, the right-sidedness seems to be also a predictive factor of response to first-line treatment in mCRC patients. On the basis of retrospective analysis of CRYSTAL, FIRE-3, and CALGB/SWOG 80405 trials, among patients with KRAS wt disease [18, 19], NCCN guidelines recommend choosing anti-EGFR plus chemo as first-line chemotherapy only in left-sided mCRC [33]. However, the NRAS and/or BRAF status was not considered in these trials.

Therefore, a better understanding of RCC behavior is crucial to explain the different response to chemotherapy and the available targeted agents.

We conducted a multi-institutional retrospective analysis of advanced RCC patients with known BRAF status and available treatment data with the aim to identify predictive factors for survival and the difference between target agents compound in first-line chemotherapy choice.

The proportion of BRAF-mutant tumors (42/207 patients) was consistent across this population and more large-scale cohorts' study (57/201 patients), including RCC [7]. According to the recently published largest series of V600E BRAF-mutated mCRC [34], our study confirmed a median overall survival in BRAF-mutant tumors of less than 20 months and significantly worse OS in patients with an ECOG PS > 1 ($P = < 0.0001$), G3–4 tumor grading ($P =$

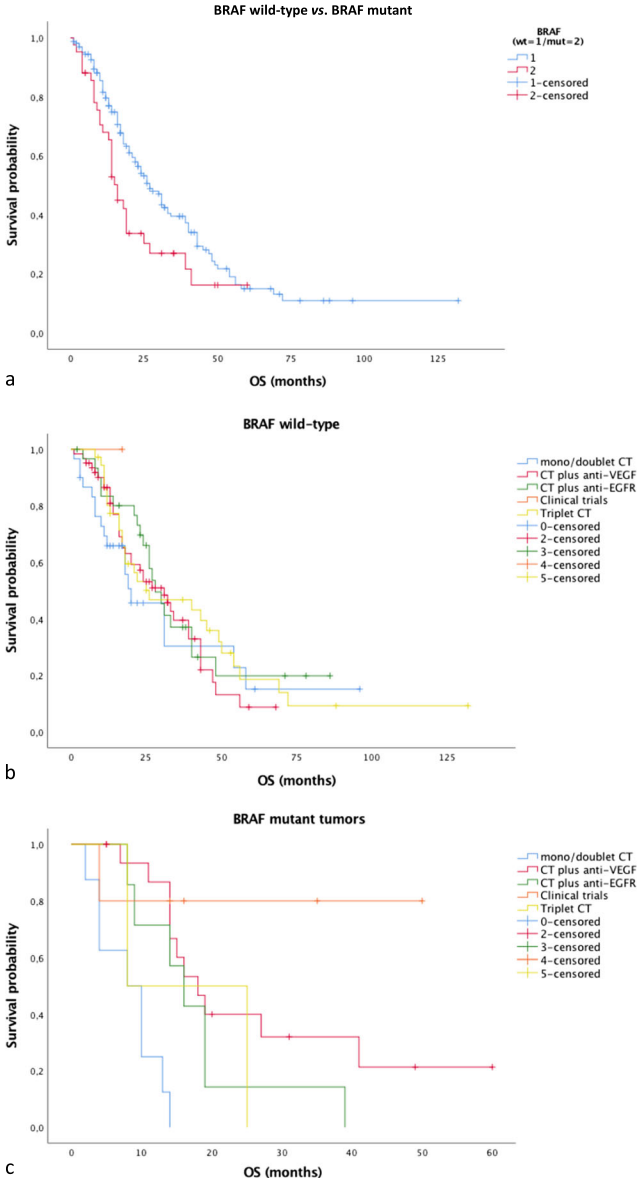


Fig. 1 **a**–**c** Overall survival (OS) according to BRAF status (**a**). OS in BRAF-wild type tumors (**b**) and BRAF-mutant tumors (**c**) according to first-line chemotherapy performed

0.009), with lympho-vascular invasion ($P = 0.013$), not having the primary tumor resected ($P = < 0.0001$).

Moreover, according to the largest stage IV colon cancer analysis for survival [14], our study showed older age ($P = 0.002$), pT4 ($P = 0.009$), pN2 ($P = 0.034$), peritoneum as metastatic site (0.040), and the synchronous occurrence of metastases ($P = 0.045$), independent of the number of metastatic site, as significantly negative prognostic factor of survival. Actually, advanced RCC is a different entity from LCC, with a significant correlation with known negative prognostic factors such as advanced pT and pN stage, dedifferentiated tumor grading, metachronous, and peritoneal metastases. All these clinicopathological factors may contribute to the difference observed in patient's prognosis with increasing pooled data demonstrating a shorter survival for patients with RCC than LCC [35]. On the contrary, the upfront surgery of liver metastases ($P = 0.001$) was associated with better outcome. Literature data showed that surgery plays an important role in the treatment of patients with limited metastatic disease of colorectal cancer [36]. Indeed, long-term survival and cure is reported in 20–50% of highly selected patients with oligometastatic disease who underwent surgery. The goal of surgery should be to resect all metastases with negative histological margins while preserving sufficient functional hepatic parenchyma. The treatment plan requires multidisciplinary evaluation and actually, as confirmed by our analysis, the surgery of primary tumor (univariate analysis) and even more the upfront surgery of liver disease (multivariate analysis) in metastatic CRC have to be always discussed with surgeons because they offer a great chance for prolonged survival in patients affected with metastatic RCC.

As previously described [34], BRAF-mutant RCC tumors was significantly reported in pT4 ($P = 0.016$), G3–4 tumor grading ($P = 0.004$) KRAS-wt ($P < 0.0001$), MSI-H ($P = 0.019$), metachronous ($P = 0.018$), and especially peritoneal metastases ($P = 0.003$).

Several trials on metastatic setting have found worsen outcomes in RCC patients rather than LCC and a different therapeutic response to the anti-EGFR targeted agents [37]. Effectively, a chemotherapy doublet or triplet plus bevacizumab was indirectly approved by retrospective, post-hoc analysis mainly focused on describing differences between RCC and LCC [38–41], as the new standard first-line chemotherapy for metastatic RCC, regardless of RAS status.

Non-significant difference was found between treatment arms, irrespective of anti-VEGF or anti-EGFR target agent first-line therapy used, although patients enrolled in clinical trials showed a better median PFS1 than CT plus target agent as well as triplet CT group (17.0 v 6.0 v.13.0 months, respectively).

In account of other molecular aspects, RCC patients are characterized by a MSI-high cancer more frequently than LCC [6] and by a higher total number of harvested lymph nodes [42] but with lower rates of node positivity [43]. The reasons for these node status differences were both anatomic and molecular: it has been shown that the right-sided colon mesentery contains a more complex lymphatic system, leading to an enhanced immune response and an increased number of lymph nodes examined after surgery [44, 45]. In our retrospective analysis, a small number of patients with MSI-H phenotype were enrolled in clinical trials with an anti-PD1 and actually reported a significant better outcome than patients who were not enrolled in clinical trials. (HR for PFS1 = 0.90, 95% CI 0.82–0.99, $P = 0.037$; HR for PFS2 = 0.69, 95% CI 0.57–0.85, $P = 0.001$). As we know by the available literature data, MSI-H CRCs have a better prognosis compared to MSS tumor and do not benefit from 5-

Table 3 The correlation between clinicopathological factors and overall survival (OS) of study patients

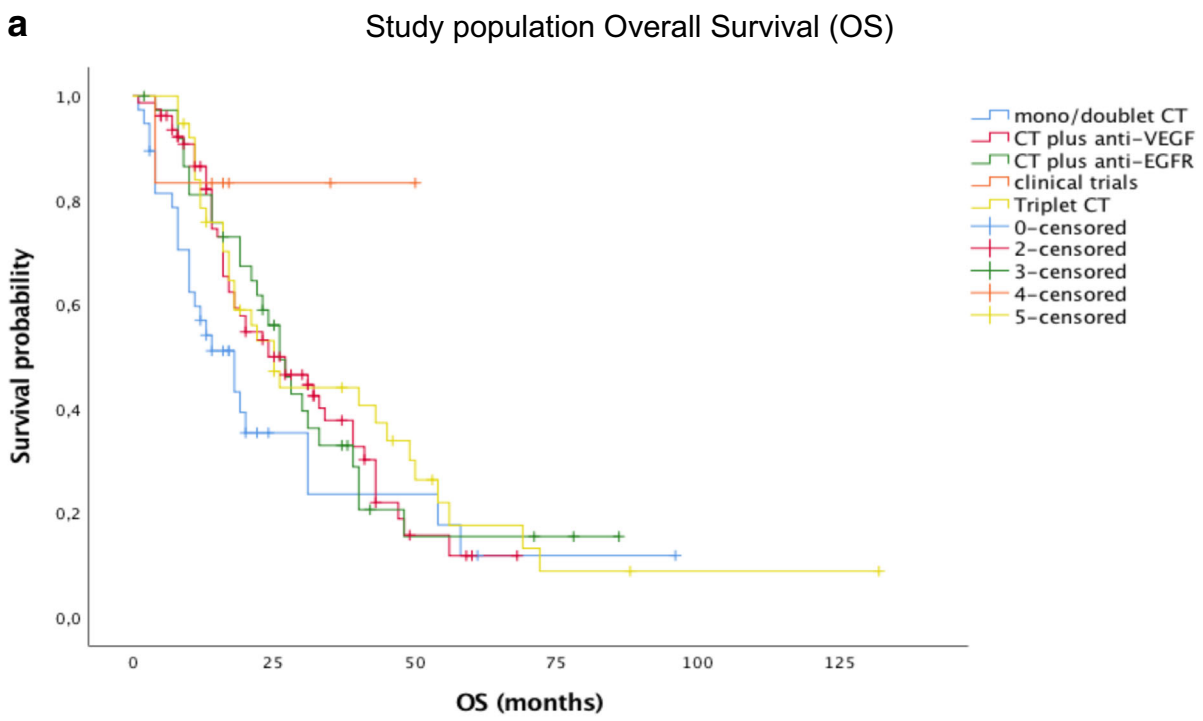
Factors	Univariate analysis			Multivariate analysis	
	OS (months)	HR (95% CI)	*P*	HR (95% CI)	*P* value
Age > 70 v ≤ 70 years	19 v 31	1.73 (1.22–2.46)	0.002	1.35 (0.78–2.35)	0.274
Sex male v female	25 v 21	0.97 (0.69–1.37)	0.881		
CCI > 8 v ≤ 8	23 v 27	1.28 (0.90–1.81)	0.159		
Onset with anemia v intestinal symptoms	19 v 27	1.39 (0.83–2.33)	0.199		
Cecum v ascending v transverse colon cancer	22 v 23 v 27	1.01(0.89–1.15)	0.824		
pT 4 v ≤ 3	19 v 40	1.82 (1.16–2.86)	0.009	1.37 (0.76–2.44)	0.287
pN 2 v 1 v 0	21 v 41 v 43	1.34 (1.02–1.77)	0.034	1.11 (0.77–1.59)	0.563
Mucinous histology YES v NO	26 v 24	0.95 (0.65–1.39)	0.823		
Grading 3-4 v 1-2	19 v 32	1.65 (1.13–2.42)	0.009	0.93 (0.52–1.65)	0.810
LVI YES v NO	23 v 43	1.84 (1.13–2.98)	0.013	1.57 (0.88–2.82)	0.126
KRAS mut v wt	23 v 26	0.97 (0.69–1.37)	0.896		
NRAS mut v wt	14 v 25	1.62 (0.58–4.47)	0.350		
BRAF mut v wt	16 v 27	1.60 (1.06–2.41)	0.020	1.97 (1.02–3.81)	0.043
MSI-H v MSS	41 v 28	0.60 (0.29–1.32)	0.231		
Surgery of primary tumor yes v no	31 v 16	0.38 (0.25–0.57)	< 0.0001	1.08 (0.32–3.65)	0.181
Baseline ECOG PS 1–2 v 0	16 v 31	2.09 (1.4–3.0)	< 0.0001	1.74 (1.02–2.96)	0.040
Metachronous v synchronous metastases	33 v 21	0.68 (0.47–0.99)	0.045	0.72 (0.43–1.29)	0.273
Metastases of peritoneum v others	20 v 26	1.22 (1.1–1.46)	0.040	1.29 (0.96–1.73)	0.084
No. of metastatic site ≥ 2 v 1	21 v 31	1.41 (0.99–2.01)	0.054		
Upfront surgery of liver metastases yes v no	43 v 20	0.46 (0.30–0.71)	0.001	0.37 (0.20–0.67)	0.001

CCI Charlson comorbidity index, *LVI* lymphovascular invasion, *PS* performance status

fluorouracile adjuvant chemotherapy [46]: indeed, they have much more active immune microenvironment with severe infiltration of intra-tumor cell infiltrating-lymphocytes and furthermore showed upregulation of inhibitory checkpoints [47]. The majority of data about the prognostic impact of MSS/MSI status is in the setting of localized disease; only few studies have investigated the role of mismatch repair status in metastatic setting, mainly because of the prevalence of MSI is low, about 4% of mCRC. Although in some reports, this survival advantage seems to be independent of tumor stage [48, 49]; in others, it seems to be confined to stage II or stage III [50, 51], so the debate remains open whether MSI-H is a good prognostic factors in advanced disease. Popat and colleagues, in a meta-analysis evaluated 1277 MSI-H stage I–IV CRC patients from a total of 32 eligible studies, found that effect of MSI on prognosis was maintained in both the early and advanced settings, with a 35% reduction in the risk of death (HR 0.65, 95% CI 0.59–0.71) [52]. Our data support this hypothesis that MSI-high phenotype in the metastatic setting could have a positive prognostic role as well as it may be a positive predictive factor of response to immunotherapy.

With regard to the second-line CT, we did not find any differences between anti-VEGF or anti-EGFR target agents, with the exception of significant better survival in clinical trials and in which cases of patients resulted to be fit for reintroduction of triplet CT regimen (median PFS2 was 16.0 v 15.0 v 7.0 v 5.0 v 4.0 v 2.0 months in clinical trials, triplet CT, CT plus anti-EGFR, CT plus anti-VEGF, CT alone and regorafenib/lonsurf as second line therapy, respectively) (HR = 0.69, 95% CI 0.57–0.85, *P* = 0.001).

Actually, BRAF-mutant RCC patients in this study reported a median OS of 16 months (range 13.7–18.3) which was not so far from median OS reported in BRAF-mutant patients enrolled in the TRIBE trial [26], with a worse survival than BRAF-wt patients, both in anti-VEGF and anti-EGFR target agent treatment groups. In the bivariate analysis, where BRAF status was stratified by treatments, there was showed non-significant survival differences between first-line CT with anti-EGFR or anti-VEGF targets in both BRAF and RAS wt tumors (28.0 v 26.0 months, respectively. *P* = 0.427) (Fig. 1b). But if we looked at only BRAF-mutant tumors, 2ys OS was significantly higher in clinical trials group (80% v 32% v 14% v 0% in clinical trials, anti-VEGF, anti-EGFR plus CT, and CT alone or triplet backbone regimen, respectively; HR = 0.63, 95% CI 0.45–0.89, *P* = 0.009) (Fig. 1c). At the reverse analysis where anti-EGFR- and anti-VEGF-based chemotherapies were stratified by BRAF status, we demonstrated that BRAF-mutant tumors reported a poorer survival than BRAF-wt tumors, regardless of targeted therapy administered. However, RAS wt tumors treated with CT plus anti-EGFR showed a



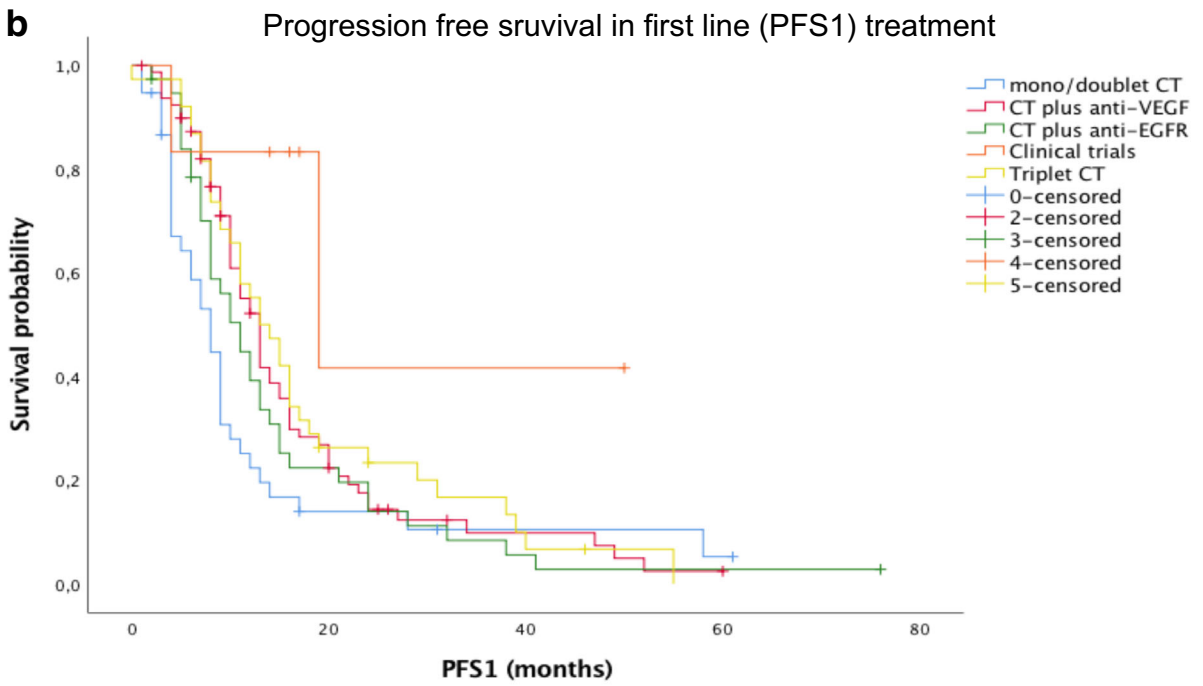


Fig. 2 **a**–**d** Study population OS according to first-line chemotherapy performed (**a**). Progression free survival according to first-line (PFS1) (**b**), second-line (PFS2) (**c**), and third-line (PFS3) therapies (**d**)

significant difference in survival according to BRAF mutation (HR for anti-EGFR = 16 v 28 months in BRAF-mutant v BRAF-wt tumors, $P = 0.005$; HR for anti-VEGF = 18 v 26 months in BRAF-mutant v BRAF-wt tumors, $P = 0.509$). (Fig. 3a, b). These data, taking into account the prevalence of BRAF mutation in RCC, may explain the more pronounced lower effect in RCC than LCC, reported in post-hoc analysis of clinical trials focused on anti-EGFR therapy in the first-line

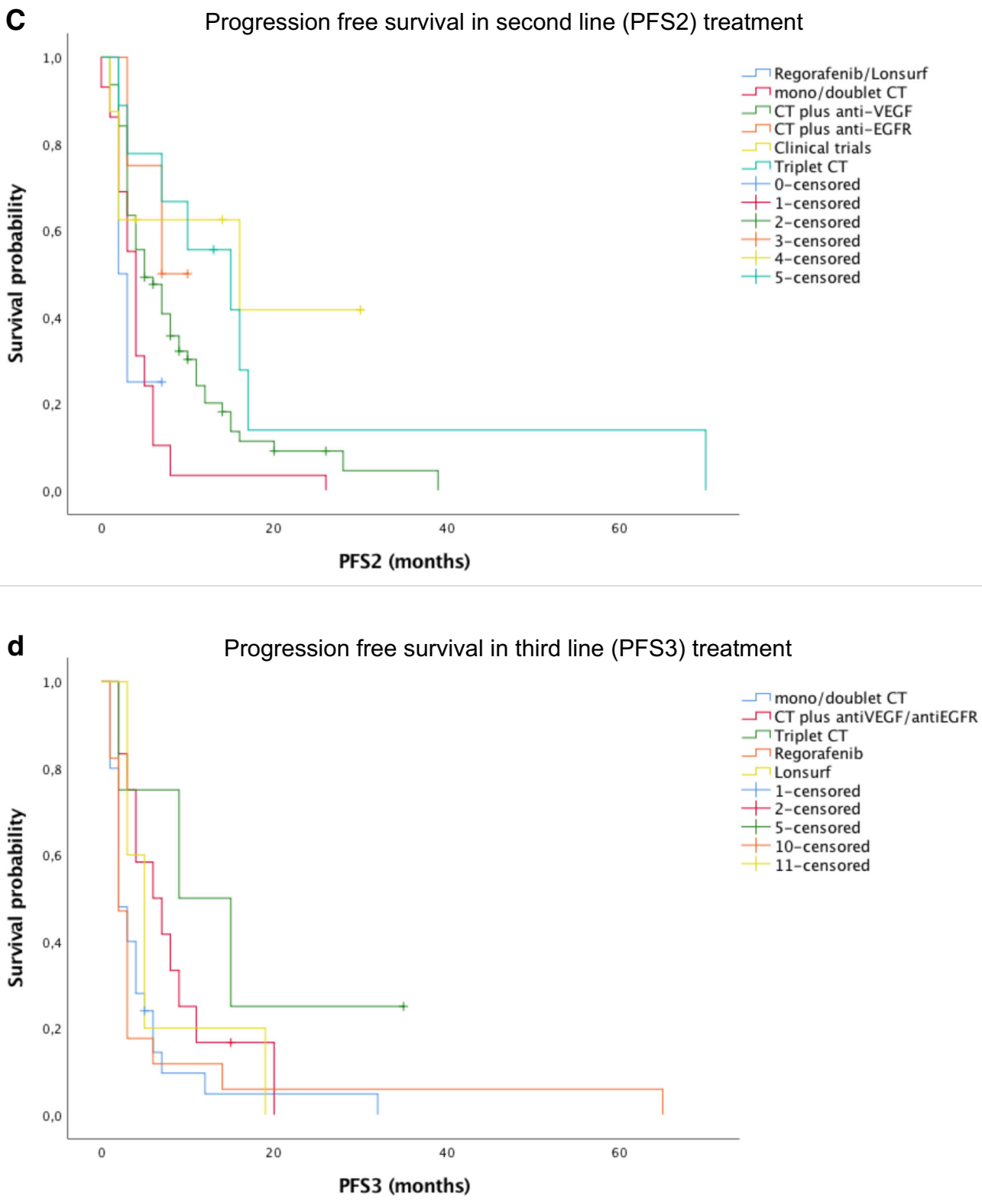


Fig. 2 (continued)

setting [53]. Indeed, it is clear that mutations not only in codon 12 or 13 of the KRAS [54, 55] but also in other downstream effectors of the EGFR signaling pathway, such as BRAF, NRAS, and PI3 kinase, might have a negative effect on

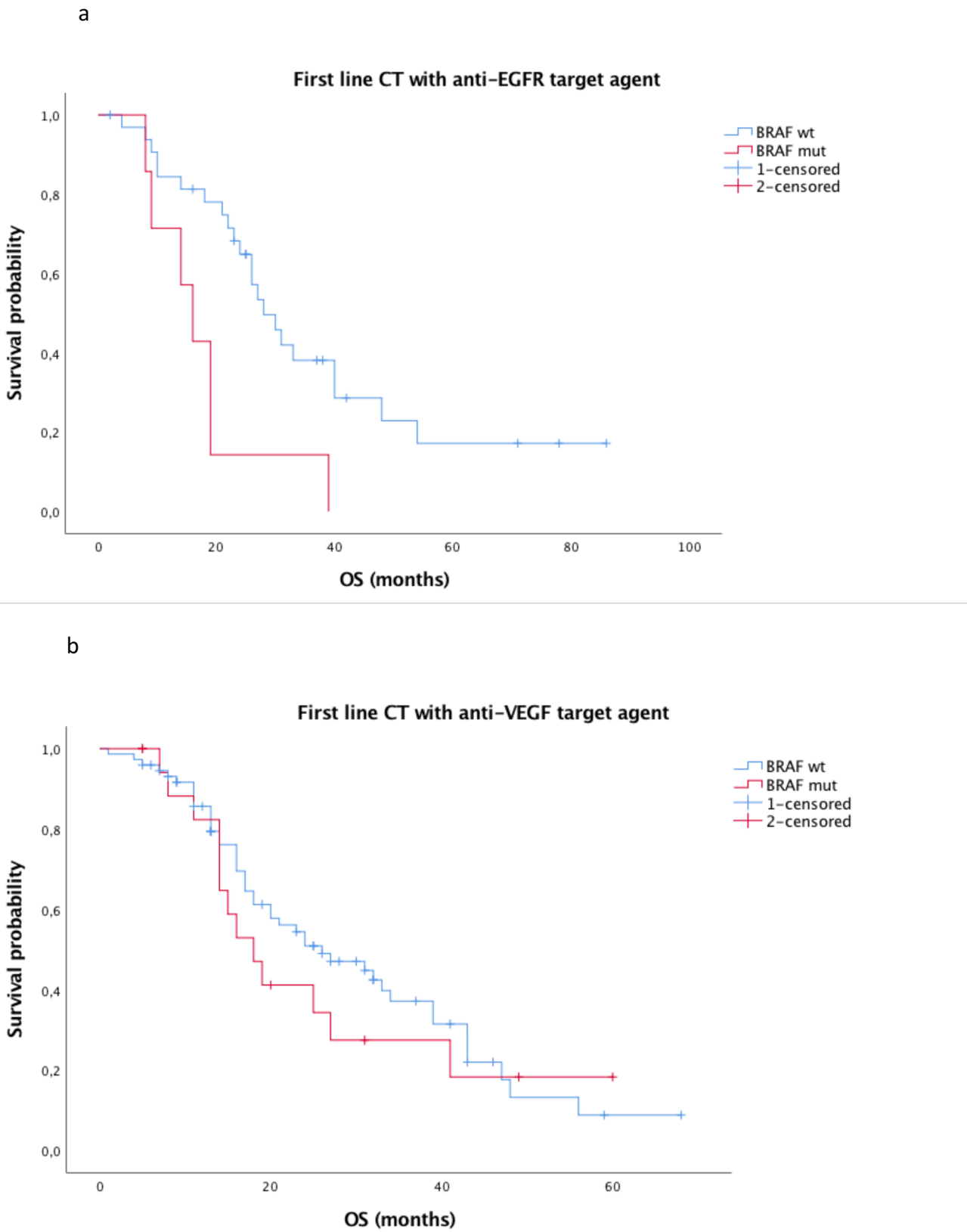


Fig. 3 **a**, **b** The reverse analysis of OS where (**a**) anti-EGFR- and (**b**) anti-VEGF-based therapies were stratified by BRAF status

response to anti-EGFR antibodies [54, 56, 57]. This fact accounts for the dismal advantage in survival found in RCC,

BRAF-mutant patients treated with anti-EGFR targets. Although anti-EGFR seems to be overall ineffective in this population, recent studies have been demonstrated that anti-EGFR combined with BRAF and MEK inhibitors could be a great opportunity of better responses in patients with metastatic BRAFV600E-mutated CRC beyond first-line chemotherapy [30]; however, despite advances, OS remains far inferior for these patients compared to their BRAF-wt counterparts and the development of combination therapies to impede signaling through the MAPK pathway remains an area of active investigation.

Finally, RCC was associated with consensus molecular subtypes (CMS) different from LCC [58–60] and these molecular patterns may also explain the different response to targeted agents. Indeed, a retrospective analysis of the CALGB/SWOG 80405, which compared the efficacy of cetuximab v bevacizumab when added to standard first-line chemotherapy, found that RAS wt patients with CMS1 (mostly RCC patients) benefitted significantly more if they had been randomized to bevacizumab compared to cetuximab, whereas a trend towards better outcomes was observed for CMS2 patients if they had been randomized to cetuximab.

This article is limited by retrospective reporting bias of heterogeneous data regarding clinicopathological characteristics as well as different treatments. Nevertheless, we decide to describe also patients included in clinical trials due to the impressive outcome reported by these patients, whose sample number was small but actually BRAF-mutant metastatic RCC was a relatively rare and an orphan-in-drug disease. However, this small sample of patients included in this study does not affect the principle aim of our study to emphasize the negative prognosis of BRAF-mutant tumors regardless of anti-EGFR or anti-VEGF targets used. Moreover, we have reported survival curve of patients included in clinical trials, although they were a few also to raise awareness that metastatic RCC patients with BRAF-mutant status should be enrolled in clinical trials in respect to standard available treatment since their first-line chemotherapy.

Based on these observations and given the real-life results of our analysis, further studies are needed to determine if molecular signatures according to sidedness are crucial predictive markers of response to specific targeted agents and also to definitively answer the question about the best first-line chemotherapy in RAS-wt, BRAF-mutant, and RCC patients.

Conclusions

Although the limit of sample size, our study demonstrated that BRAF status makes the difference for treatment response. Therefore, a first-line CT plus an anti-EGFR targeted agent should not to be excluded in all RCC cases in advance but considered on a case-by-case basis. Meanwhile, RCC patient with BRAF-mutant tumors or with MSI-H phenotype should be enrolled in clinical trials. Certainly, a better knowledge of the main predictive factors and prospective clinical trials stratifying participants according to primary tumor location would be for helping physician to make the best therapeutic choice.

Compliance with ethical standards

The study was conducted in accordance with the Declaration of Helsinki and Institutional Review Board approval.

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

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