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A critical appraisal of the current landscape of resectable BRAF mutated colorectal liver metastases: A systematic review

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Abstract

Background: Patients with surgically resectable *BRAF*-mutated colorectal liver metastases (CRLM) or limited extrahepatic disease constitute a highly selective subgroup among *BRAF*-mutated patients, characterized by a more indolent disease biology. This is evident in their suitability for surgical resection. However, initial studies from a decade ago presented a discouraging outlook for these patients, citing early, frequent, multifocal recurrences and a very limited median overall survival (OS) of less than two years. Our objective was to provide an updated, comprehensive, and critically assessed review of the current literature on the prognostic impact of *BRAF* variants in CRLM, as well as to explore optimal treatment strategies for these patients through a systematic search.

Methods: A systematic literature search of the Medline, Scopus, and CENTRAL databases for studies reporting long-term outcomes of patients with a known *BRAF* status was performed.

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Author contributions

(I) Conception and design: GAM, MD
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(III) Provision of study materials or patients: N/A
(IV) Collection and assembly of data: GAM, DP
(V) Data analysis and interpretation: All authors.
(VI) Manuscript writing: All authors.
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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest: None

Results: A total of 386 unique studies were screened during the study selection process. After applying the exclusion criteria, a total of 18 studies published between 2012 and 2023 were deemed eligible for inclusion.

Conclusions: In contrast to older studies, more recent studies, with larger sample sizes, have revealed that the rate of extrahepatic recurrence is comparable between *BRAF*-mutated and wild-type patients. Furthermore, they have reported significantly improved survival outcomes, with OS extending up to 52 months. Notably, patients with non-V600E *BRAF* mutations may even achieve outcomes comparable to those with wild-type *BRAF* CRLM. Additionally, a few recent studies have compared surgery and systemic therapies, indicating that surgery is associated with improved survival rates, even for patients with the V600E mutation. This challenges the previous belief that *BRAF* mutations are absolute contraindications to surgical treatment. Surgical denial for technically resectable patients may now be reserved for specific clinical scenarios, such as the presence of a *BRAF* V600E mutation and concurrent extrahepatic disease.

Keywords

BRAF mutation; resectable CRLM; systematic review

Introduction

The *BRAF* gene encodes a protein kinase downstream from the *RAS* signaling cascade and forms part of the mitogen-activated protein kinase pathway, an important regulator of cellular growth (1). Somatic *BRAF* mutations have been described in many malignancies and result in constitutive activation of the aforementioned pathway, which in turn drives neoplastic proliferation. Despite being one of the rarest somatic mutations found in patients with resectable colorectal liver metastases (CRLM), *BRAF* mutations have been the focus of numerous studies over the past two decades. The rationale behind this focus lies in the longstanding belief that patients with resectable, *BRAF* mutated (*BRAF*mut) CRLM experience extremely poor survival. Some even proposed the mere presence of a *BRAF* mutation as a 'biological' contraindication in otherwise technically resectable tumors (2). This article's objective is not to present an exhaustive list of relevant studies, as numerous reviews on the topic have already been published in recent years. Instead, our aim is to offer an updated, comprehensive, and critically assessed review of the current literature on the prognostic impact of *BRAF* variants in CRLM, as well as to explore optimal treatment strategies for these patients through a systematic search.

Methods

We conducted a systematic literature search of the Medline, Scopus, and CENTRAL databases for studies reporting outcomes of patients with a known *BRAF* status. The search utilized the terms “colorectal neoplasms,” “metastatic,” “liver resection,” “hepatectomy,” “BRAF,” and “B-RAF,” combined with Boolean operators AND/OR to create a comprehensive search string. After removing duplicate studies, the generated abstract list was independently screened by two authors (DP and JW). Potentially eligible studies were selected for full-text assessment. The reference lists of relevant articles were manually checked for additional studies.

To guide study selection, we applied predetermined eligibility criteria: 1) clinical studies, irrespective of design; 2) studies reporting patient *BRAF* mutational status; 3) studies involving patients with CRLM amenable to surgical treatment. We also employed exclusion criteria: 1) experimental or non-clinical studies involving adult human patients; 2) studies exclusively focusing on patients with colorectal metastases in sites other than the liver; 3) studies analyzing *RAS* and *BRAF* status as a single variable.

The data of interest included the number of patients with *BRAF* mutations or wild-type status, year of publication, country of origin, study type, and key findings. Relevant articles were evaluated in full text by two authors (DP and JW), with a senior author (GAM) resolving any disagreements regarding eligibility. This systematic review adheres to PRISMA guidelines, however no prospective registering was pursued.

Results

A total of 386 unique studies were screened during the study selection process. After applying the exclusion criteria, a total of 18 studies published between 2012 and 2023 were deemed eligible for inclusion (Fig. 1). The study and patient characteristics are reported in Table 1.

Discussion

BRAF V600E is the most common *BRAF* mutation in colorectal cancer (CRC); its prevalence has been reported to range between 8 to 15% in patients with metastatic CRC (mCRC) and is generally much lower among patients with resectable CRLM than those treated with systemic therapy alone (2%-4% vs 5%-10%, respectively) (2-4). This has been attributed to the fact that patients with *BRAF*mut mCRC more frequently exhibit a disease course characterized by diffuse extrahepatic spread often including peritoneal carcinomatosis, which renders them ineligible for surgical resection, although conversion of initially unresectable CRLM is possible in up to 25% of those with borderline or unresectable liver-only disease (5, 21). Thus, patients with resectable, *BRAF*mut CRLM including those with limited extrahepatic disease may represent a highly select subset of patients with more favorable biology, which is reflected by their technical resectability.

Nonetheless, the first studies from a decade ago reported poor outcomes of surgically treated patients with *BRAF* mutations. Specifically, they noted early, frequent, multifocal recurrence and a very limited median overall survival (OS) of up to 22 months (17, 20, 22). Interestingly, more recent studies have reported better outcomes for these patients, with one study noting a median OS of 52 months (12, 13, 16). This likely reflects the fact that most recent studies have larger sample sizes, which allows for a more accurate estimate of median OS. For example, the four studies that included fewer than 10 patients with surgically treated *BRAF*mut CRLM reported median OS of 7, 8, 14, and 16 months (20, 22-24). In contrast, the four larger studies reported median OS of 26, 31, 47, and 52 months (11-13, 16). Notably, a recent meta-analysis that included the newer studies reported a hazard ratio (HR) of 2.80 (95% CI: 2.09-3.77) for OS and 2.29 (95% CI: 2.09-3.77) for recurrence free survival (RFS) for surgically treated patients with *BRAF*mut CRLM compared to their

wild-type counterparts (25). In contrast, an earlier meta-analysis performed in 2016 reported a much higher HR of 3.90 (95% CI: 1.96-7.73) for OS, while RFS was not reported since only a few studies at this time had reported this outcome (26).

In addition to differences in reported OS, patterns of recurrence are another key discrepancy between the larger and the smaller studies. For example, while smaller studies reported a diffuse (intrahepatic and extrahepatic) pattern of recurrence following surgery for *BRAF*mut CRLM, a recent study from the MD Anderson Cancer Center revealed no difference in the patterns of recurrence between *BRAF*mut and *BRAF* wild-type CRLM (8). Similarly, one of the largest studies by Gagniere et al showed that the rate of extrahepatic recurrence was comparable between *BRAF*mut and wild-type patients (47% vs 54%, p = 0.40) (12, 27). They also reported a trend toward a higher rate of liver-only recurrences in *BRAF*mut patients (41% vs 26%, p = 0.08). Importantly, the more favorable patterns of recurrence, which may be amenable to repeat hepatectomy, may underlie the better median OS reported in this study.

Another notable shift in the literature was how studies handled *BRAF* mutational status. Specifically, while older studies treated it as a binary variable (*BRAF*mut vs wild-type), contemporary studies distinguished between V600E and non-V600E *BRAF* mutations. Importantly, they demonstrated that these sub-types are associated with distinct survival outcomes. Specifically, Margonis et al were the first to show that V600E but not non-V600E *BRAF* mutation was associated with worse OS on multivariable analysis (16). Of note, this study included only six patients with non-V600E mutations, and the authors advised that the findings may be the byproduct of random variations of a small cohort. However, a few years later, another study confirmed this finding in a much larger cohort of 47 patients with non-V600E mutations (3). In addition, they demonstrated that not only did patients with non-V600E mutations fare better than those with V600E mutations, but these patients also had better survival compared to historical rates seen in those with wild-type *BRAF* CRLM; interestingly, similar findings have been reported for patients with non-V600E *BRAF* mutations who were treated with systemic therapy alone (28, 29). The aforementioned study also investigated for the first time several more topics regarding the prognosis of surgically treated patients with *BRAF*mut CRLM (3). For example, they showed that a concomitant *BRAF/KRAS* mutation can occur, dismissing previous beliefs that *BRAF* and *KRAS* mutations are mutually exclusive. Importantly, they also demonstrated that this co-mutation is not associated with worse outcomes than a single *BRAF* mutation. This may reflect a biological redundancy of the *BRAF/KRAS* co-mutation given that the products of both genes are sequential effectors in the EGFR pathway. Finally, this study also showed that patients with *BRAF* mutated MSI tumors experienced superior RFS than those with MSS tumors; a similar difference for OS did not reach statistical significance.

One may hypothesize that the biologic and prognostic differences between *BRAF*mut and *BRAF* wild-type CRLM may mandate different management approaches. For example, it has long been postulated that the mere presence of a *BRAF* mutation should be considered a contraindication to surgery since these patients fared so poorly.(2, 24) As noted above, the first studies supported this notion by reporting median OS of 7-16 months for surgically treated patients with *BRAF*mut CRLM, which was similar to historical rates seen in

patients with unresectable mCRC (30). However, subsequent studies reported much better OS, which questions the dogma that *BRAF* mutations are contraindications to surgical treatment. However, these studies did not stratify patients by disease presentation, which is significant since some patients have more unfavorable disease presentations, such as those with concurrent extrahepatic disease. Importantly, the largest study to date performed a sub-analysis of patients with the V600E mutation and concurrent extrahepatic disease and found that these patients had a median OS of 6.5 months with no patients surviving beyond 18 months (3). Although these results were limited by the small sample size of that subgroup of patients, it is unlikely that surgery offers a clinically significant benefit in these extremely high-risk patients.

To better answer the question of whether *BRAF* mutations should be a contraindication to surgery in patients with liver-limited CRLM, one could consider screening a large surgical cohort to find patients with a similar disease profile as medically treated patients and then comparing outcomes between the two groups. Indeed, an approximate matching of surgically vs medically treated patients with *BRAF*mut CRLM was recently performed by the authors of this review and is in the revisions stage of publication. Specifically, they performed propensity score matching for 51 surgically and 51 medically treated patients based on tumor burden and disease characteristics, and showed that the former fared better than the latter. Notably, these results contradict a recent study from Japan which concluded that the mere presence of a V600E *BRAF* mutation should be an absolute contraindication to surgery in patients with technically resectable CRLM (24). However, these authors did not account for confounding variables and based their conclusion on the fact that the 5 patients in the surgical cohort had a very poor median OS of only 14 months. As stated above, survival estimates based on such small cohorts are prone to the effects of random events and may not be truly representative of reality. Another study that investigated the outcomes of surgically vs medically treated patients with V600E *BRAF*mut CRLM reported a much longer median OS for the surgical group (10). Although the authors did not perform a matched analysis, they did conduct a multivariate analysis that suggested a positive association between surgical treatment and OS. Collectively, according to the current evidence, it appears that surgery should be considered for patients with technically resectable V600E *BRAF*mut CRLM even in the presence of adverse prognostic factors (with exception to extrahepatic disease). Future studies should investigate whether the presence of other biomarkers might identify patients with liver-only V600E *BRAF*mut CRLM who do not benefit from surgery.

Interestingly, the post-hepatectomy surveillance and the role of adjuvant systemic therapies for these patients after surgery has not been well studied. To our knowledge, only one study can be used to indirectly inform post-hepatectomy surveillance and guide decisions on adjuvant therapy. Specifically, a study from Johns Hopkins that utilized conditional survival analysis showed that while the presence of a *BRAF* mutation at baseline is associated with an adverse prognosis, patients with *BRAF*mut CRLM who surpass the first postoperative year may no longer exhibit a worse prognosis compared to those with *BRAF* wild-type tumors (14). Periodic updates of prognostic assessments for such patients could guide decisions on adjuvant therapy and potentially influence surveillance intensity. Future studies should investigate the impact of systemic chemotherapy and HAI on patients with surgically

treated *BRAF*mut CRLM, as well as identify patient subgroups who are most likely to benefit from these treatments. Finally, an important question arises regarding whether patients with *BRAF*mut CRLM can achieve a 'cure,' defined as survival beyond 10 years after CRLM resection (31). In a recent study, despite the association of a *BRAF* mutation with the highest hazard ratio among all prognostic factors linked to 10-year survival, patients with a *BRAF* mutation could still achieve a cure, demonstrated by their 10-year overall survival of 22% (95% CI 11–46%) (6).

Conclusions

In summary, the first meta-analysis that investigated the outcomes of patients with *BRAF*mut CRLM reported poor survival after surgery and questioned the benefit of liver resection in the presence of a *BRAF* mutation. However, more recent studies have contested these findings. Specifically, they have demonstrated that despite the well-established negative prognostic role of *BRAF* mutations, the average patient with liver-limited *BRAF*mut CRLM will rarely experience diffuse recurrence after resection and has better survival compared to historical rates seen in patients treated with systemic therapies alone. Remarkably, up to one-fifth of these patients can attain a 'cure,' defined as survival beyond 10 years following CRLM resection. Even those with initially unresectable disease, once converted to resectable status, exhibit favorable outcomes (3). The first large study that directly compared surgically vs medically treated patients with *BRAF*mut liver-only CRLM was recently performed and confirmed that the mere presence of a *BRAF* mutation, even if it is of the V600E subtype, should not be an absolute contraindication to surgery for these patients. Nevertheless, there remains the possibility that when combined with other tumor characteristics, the V600E subtype may lead to such a poor prognosis that surgery becomes futile. Future investigations should draw upon counterfactual literature to estimate prognosis with systemic therapies alone versus surgery. Subsequently, the application of machine learning methods, specifically training decision trees, can help identify subgroups where surgery may or may not be beneficial. On a broader note, the more recent studies also serve to emphasize not only the importance of having adequate statistical power in observational studies, but also the importance of international collaborations especially when investigating rare biomarkers. Finally, there is currently a gap in knowledge with regard to the optimal post-surgical management of these patients. This is hardly surprising given the general lack of consensus on perioperative chemotherapy in CRLM as well as the rarity of patients with resectable *BRAF*mut CRLM.

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• Key findings

The adverse prognostic significance of *BRAF* mutations has been overstated; a ‘cure’ rate as high as 22% has been reported for *BRAF* mutants.

The mere presence of a *BRAF* mutation should not serve as a contraindication to surgery in patients with liver-limited *BRAF*mut CRLM.

- Patients with *BRAF*mut CRLM who surpass the first postoperative year may no longer demonstrate a worse prognosis compared to those with *BRAF* wild-type tumors. Therefore, regular updates of prognostic assessments for such patients could inform decisions regarding adjuvant therapy and potentially impact surveillance intensity.What is known and what is new?

It is widely acknowledged that patients with *BRAF* mutations fare worse than their wild-type counterparts, and *BRAF* has been suggested to serve as a ‘biological’ contraindication for surgery.

This review offers an update on this patient group, emphasizing recent studies that have reported more favorable recurrence patterns and significantly improved survival outcomes. Moreover, emerging evidence suggests that patients with non-V600E *BRAF* mutations may achieve outcomes comparable to those with wild-type *BRAF* CRLM. Additionally, our review includes insights from recent studies comparing surgery and systemic therapieswhich indicate that surgery is in general associated with improved survival rates for patients with liver-limited disease.

- What is the implication, and what should change now?

These findings challenge the previous notion that *BRAF* mutations should serve as absolute contraindications to surgical treatment. Surgical denial for technically resectable patients may now be reserved for specific clinical scenarios, such as the coexistence of a *BRAF* V600E mutation and extrahepatic disease.

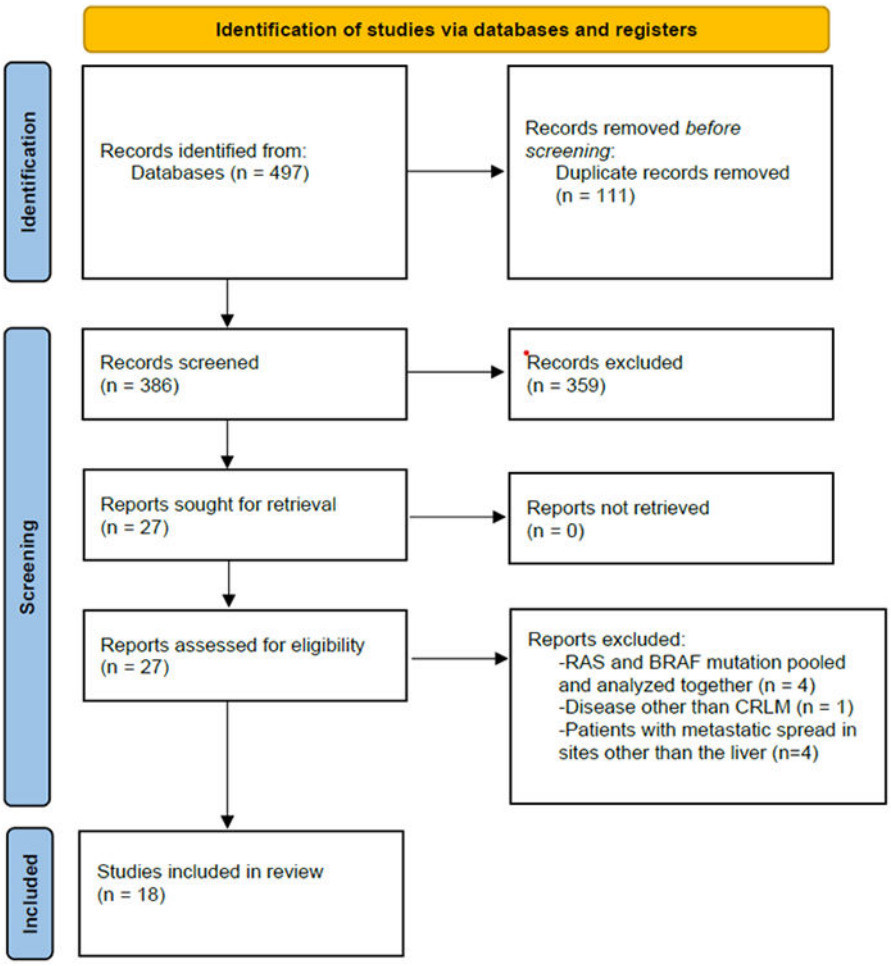

Figure 1.
Prisma flowchart of study selection process.

Table 1.

Characteristics of studies reporting outcomes of patients with a known BRAF status. mutBRAF= mutated BRAF status, wtBRAF= wild-type BRAF status, DFS= Disease-Free Survival, OS= Overall Survival, RFS= Recurrence-Free Survival. *Studies have overlapping patient populations, CRLM= Colorectal Liver Metastases.

Author	Year	Country	Study design	Total patients	Number of mutBRAF patients			Findings
				n	*Total*	*V600E*	*Non-V600E*	
Margonis et al.(3) *	2023	USA	Retrospective multicenter	240	240 (100%)			mutBRAF patients with the V600E mutation demonstrated significantly shortened OS but not RFS relative to their non-V600E counterparts
Tseng et al.(4)	2023	Taiwan	Retrospective	65	2 (3.1%)	n/a	n/a	mutBRAF was an independent predictor of poor survival in patients with concurrent extrahepatic disease and surgically treated CRLM
Uutela et al.(5)	2023	Finland	Prospective	672	54 (8%)	54 (100%)	excluded	mutBRAF patients with the V600E mutation and initially borderline or unresectable CRLM had a secondary resection/local ablative treatment rate as high as 25%
Buisman et al.(6)	2022	USA/ Netherlands	Retrospective multicenter	4112	55 (4%)	n/a	n/a	mutBRAF was an independent predictor of reduced 10-year OS
Narayan et al.(7)	2022	USA	Retrospective	333	13 (3.9%)	n/a	n/a	mutBRAF was an independent predictor of poor survival in both early and standard onset CRLM
Nishioka et al.(8)	2022	USA	Retrospective	552	17 (3%)	n/a	n/a	No association between BRAF status and survival
Han et al.(9)	2022	China	Retrospective	50	10 (20%)	10 (100%)	n/a	mutBRAF was an independent predictor of poor OS in patients with disease converted to resectable
Javed et al.(10)	2022	France	Retrospective multicenter	105	105 (100%)	105 (100%)	n/a	Median OS of 34 months among mutBRAF patients
Kobayashi et al.(11)	2020	Japan	Retrospective multicenter	33	33 (100%)	33 (100%)	n/a	Median RFS of 5.3 months and median OS of 31.1 months among mutBRAF patients
Gagnière et al.(12) *	2020	USA	Retrospective, case-matched multicenter	1497	35 (2.3%)	25 (71%)	10 (29%)	mutBRAF patients exhibited shortened OS and RFS relative to wtBRAF patients.
Bachet et al.(13) *	2019	France	Retrospective multicenter	253	66 (26.1%)	55 (83.3%)	11 (26.7%)	mutBRAF was an independent predictor of poor OS but not DFS and was associated with multisite disease recurrence
Margonis et al.(14) *	2019	USA	Retrospective	1099	47 (5.5%)	n/a	n/a	mutBRAF status was associated with worse OS during the first year after surgery, with a non-significant impact thereafter
Lin et al.(15) *	2018	China	Retrospective	139	10 (7.2%)	10 (100%)	n/a	mutBRAF status was independently associated with worse OS and DFS among patients with synchronous CRLM who underwent R0 resections
Margonis et al.(16) *	2018	USA	Retrospective	853	43 (50.4%)	33 (76.7%)	10 (23.3%)	V600E mutations, but not non-V600E, were independent predictors of poor OS and DFS

Author	Year	Country	Study design	Total patients	Number of mutBRAF patients			Findings
				n	*Total*	*V600E*	*Non-V600E*	
Schirripa et al.(17)	2015	Italy	Retrospective	309	11 (4%)	11 (100%)	n/a	mutBRAF was an independent predictor of poor OS and RFS and conveys a larger detriment to survival than RAS mutational status
Lin et al.(18) *	2014	China	Retrospective	154	14 (9.1%)	n/a	n/a	mutBRAF was an independent predictor of poor OS and DFS in patients undergoing synchronous resections of CRLM and primary tumors
Yaeger et al.(19)	2014	USA	Retrospective	201 (sub-analysis)	23 (11%)	n/a	n/a	All patients had single-organ–limited metastatic disease (n=18 underwent hepatectomy); BRAF mutation was found to be a poor prognostic marker for potentially curable disease, even in the presence of a low CRS.
Teng et al.(20)	2012	Taiwan	Retrospective	292	6 (2.1%)	4 (66.7%)	2 (33.3%)	mutBRAF was independently associated with worse OS in