Is Hepatectomy Justified for *BRAF* Mutant Colorectal Liver Metastases?

A Multi-institutional Analysis of 1497 Patients

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Objective: To analyze clinical outcomes and prognostic variables of patients undergoing hepatic resection for *BRAF* mutant (*BRAF*-mut) colorectal liver metastases (CRLM).

Background: Outcomes following hepatectomy for *BRAF*-mut CRLM have not been well studied.

Methods: All patients who underwent hepatectomy for CRLM with complete resection and known *BRAF* status during 2001 to 2016 at 3 high-volume centers were analyzed.

Results: Of 4124 patients who underwent hepatectomy for CRLM, 1497 had complete resection and known *BRAF* status. Thirty-five (2%) patients were *BRAF*-mut, with 71% of V600E mutation. Compared with *BRAF* wild-type (*BRAF*-wt), *BRAF*-mut patients were older, more commonly presented with higher ASA scores, synchronous, multiple and smaller CRLM, underwent more major hepatectomies, but had less extrahepatic disease. Median overall survival (OS) was 81 months for *BRAF*-wt and 40 months for *BRAF*-mut patients ($P < 0.001$). Median recurrence-free survival (RFS) was 22 and 10 months for *BRAF*-wt and *BRAF*-mut patients ($P < 0.001$). For *BRAF*-mut, factors associated with worse OS were node-positive primary tumor, carcinoembryonic antigen (CEA) >200 μg/L, and clinical risk score (CRS) ≥4. Factors associated with worse RFS were node-positive primary tumor, ≥4 CRLM, and positive hepatic margin. V600E mutations were not associated with worse OS or RFS. A case-control matching analysis on prognostic clinicopathologic factors confirmed shorter OS ($P < 0.001$) and RFS ($P < 0.001$) in *BRAF*-mut.

Conclusions: Patients with resectable *BRAF*-mut CRLM are rare among patients selected for surgery and more commonly present with multiple synchronous tumors. *BRAF* mutation is associated with worse prognosis; however, long-term survival is possible and associated with node-negative primary tumors, CEA ≤ 200 μg/L and CRS < 4.

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The potential prognostic relevance of tumor genomics has recently generated great interest. In patients with colorectal cancer liver metastases (CRLM), tumor-related genomic alterations can act as biomarkers supplementing well-known clinicopathological prognostic factors.[1–4] In particular, the role of rat sarcoma viral oncogene homolog (*RAS*) and v-raf murine sarcoma b-viral oncogene (*BRAF*) mutations as new prognosis factors in patients with CRLM has been investigated. Indeed, *RAS* mutations, found in 15% to 35% of patients with resectable CRLM, have been associated with worse overall survival (OS) and recurrence-free survival (RFS) after liver resection.[5–8] In addition, *RAS* mutation status is a validated predictor of response to chemotherapy regimens targeting the epidermal growth factor receptor (EGFR).[6,9–12] *BRAF* mutations are found in 5% to 15% of all colorectal cancer (CRC) patients,[13–16] but small series have documented that only 0.6% to 5% of the patients undergoing liver resection for CRLM exhibit *BRAF* mutations.[5,6,8,17–22] Preliminary data have suggested that a few patients with *BRAF*-mutated (*BRAF*-mut) CRLM are eligible for liver surgery because the majority present with unresectable extrahepatic disease at diagnosis.[23–27] The negative prognostic impact of *BRAF* mutations among all patients with metastatic CRC being treated with palliative chemotherapy is well documented, with reported survivals, on average, half as long as *BRAF* wild-type (*BRAF*-wt) metastatic CRC.[24,25,28] Little data are available regarding oncologic outcomes after liver resection for patients with *BRAF*-mut tumors. Small case series have reported a decrease in the median OS compared with *BRAF*-wt patients,[22,29,30] ranging from 8 to 22 months.[29,30] The impact of *BRAF* mutations on RFS after liver resection has been poorly studied, but early recurrences, especially at extrahepatic sites, have been reported.[29,30] Moreover, the only reported prognostic factor in patients undergoing surgery for *BRAF*-mut CRLM is a non-V600E mutation, which is felt to portend a better prognosis, but represents only 22% of *BRAF* mutations.[31]

Because the available data are based on very small numbers of patients, with limited follow-up and details regarding recurrence, whether hepatectomy is justified over chemotherapy alone in these patients presenting with resectable *BRAF*-mut CRLM remains unclear. Therefore, larger numbers of patients with adequate follow-up are needed to appropriately assess the oncologic outcomes following liver resection for *BRAF*-mut CRLM. The aim of this study was to analyze clinical outcomes and prognostic variables of patients undergoing hepatic resection for *BRAF*-mut CRLM using a large, multicenter prospective database.

METHODS

Study Population and Data Collection

We analyzed data from a prospectively maintained database of all the consecutive patients who underwent complete gross resection for CRLM at 3 tertiary centers, between January 2001 and December 2016. Only patients with known *BRAF* mutation status determined from DNA extraction from either the primary tumor or CRLM were included. Patients were excluded if they did not undergo a complete gross resection of both the primary tumor and CRLM, if the CRLM were treated with ablation only, or if there was inadequate follow-up (<3 months). Data regarding demographics, clinicopathologic characteristics, therapeutic features, operative and perioperative details, recurrence, and survival were collected.

Therapeutic Features, Follow-up, and Definitions

All patients were discussed at multidisciplinary tumor board meetings at their respective institutions, and treatments were tailored individually. Perioperative systemic chemotherapy, with or without hepatic artery infusional chemotherapy, was offered on an individual basis after discussion with the involved physicians. Perioperative chemotherapy was defined as treatment within 6 months before and/or after liver resection specifically to treat CRLM. When preoperative chemotherapy was administrated, only patients without significant progression were considered for surgery. There was no general consensus to exclude patients for surgery based on *BRAF* mutation status alone at our 3 institutions.

All patients underwent preoperative, contrast-enhanced, cross-sectional imaging of the chest, abdomen, and pelvis, with a combination of computed tomography (CT) and/or magnetic resonance imaging (MRI). Fluorodeoxyglucose positron emission tomography (FDG-PET) scans were performed at the discretion of the treating physicians. Clinical risk scores (CRS) were calculated using a previously reporting scoring system based on 5 factors: node-positive primary, disease-free interval of CRLM < 12 months (synchronous), > 1 CRLM (multiple), size of the largest CRLM > 5 cm, and carcinoembryonic antigen (CEA) > 200 ng/mL, each scoring 1 point.[1] Patients were deemed resectable when liver resection could achieve a complete gross resection while preserving an adequate future liver remnant. In patients with an anticipated insufficient future liver remnant, preoperative portal and/or hepatic vein embolization and staged hepatectomy were considered.

Liver resections were performed open, laparoscopically, or robotically. Intraoperative ablation was used as an adjunct in patients in whom complete resection leaving an adequate liver remnant was not possible or when maximal parenchymal preservation was desired. The choice of the ablation modality (radiofrequency, cryoablation, microwave, or irreversible electroporation) was at the discretion of the treating surgeon. A major hepatectomy was defined as liver resection including 3 or more segments. Diagnosis of CRLM was confirmed by pathology examination. A positive liver resection margin was defined as the closest margin microscopically involved by the tumor.

All patients were followed up every 3 to 6 months. A physical examination, CEA level determination, and cross-sectional imaging were performed at each visit. Time of recurrence was defined as the time of the first imaging that reported definitive or suspicious new tumors. For patients with biopsy-proven recurrence, the date of positive cytological of histological results was defined as the time of recurrence. OS and RFS were calculated from the time to complete resection to the time of death and first recurrence, respectively. For the purposes of this study, only the initial site of recurrence was recorded. Liver recurrence was defined as recurrence at the margin site only and/or away from the surgical margin. Extrahepatic recurrence sites were recorded as lung, peritoneum, retroperitoneal lymph nodes (including regional portal nodes), or other sites (eg, bones, brain, and anastomosis). Patients with more than 1 site of recurrence, as defined above, were recorded as ''multiple recurrence sites.''

Statistical Analysis

Qualitative and quantitative variables were expressed as number of patients (%) and median (range), respectively. Continuous variables were compared using the Student *t* test or Mann-Whitney test, as appropriate by the type of distribution. Categorical variables were compared using Chi-square or the Fisher exact test depending on the number of observations. A P value ≤ 0.05 was considered significant. Survival outcomes were estimated using the Kaplan-Meier method and were compared using a stratified log-rank test. Patients who did not experience the event of interest by the end of the study period were censored at the time of last follow-up. Multivariate analyses were not possible due to the small number of patients in the *BRAF*-mut group. For the case-control matching analysis, all the *BRAF*-mut were matched (1:1) to *BRAF*-wt patients according to the 5 factors of the previously described CRS,[1] and to other variables with a significant P value after univariate analysis and considered relevant for this study. All statistical analyses were performed using statistical software (SPSS software version 25; Statistical Package for the Social Science, Inc., Chicago, IL).

RESULTS

Patient Characteristics

Among the 4124 patients who underwent hepatectomy for CRLM during the study period, 1497 patients had gross complete resection and known *BRAF* mutation status (Fig. 1 and Supplementary Figure 1, http://links.lww.com/SLA/B473). Thirty-five (2%) patients were *BRAF*-mut and were compared with 1462 *BRAF*-wt patients. The type of *BRAF* mutation was known for 34 of the *BRAF*-mut patients, and 25 (71%) of them had a V600E mutation. Table 1 lists the patient's clinicopathologic and therapeutic features stratified by *BRAF* mutation status. Compared with *BRAF*-wt patients, *BRAF*-mut patients were older ($P = 0.05$) and had higher American Scores of Anesthesiologists (ASA) score ($P = 0.05$). They more commonly presented with synchronous (77% vs 54%, $P = 0.01$), multiple (83% vs 53%, $P < 0.01$), and smaller ($P = 0.05$) CRLM, and underwent more major

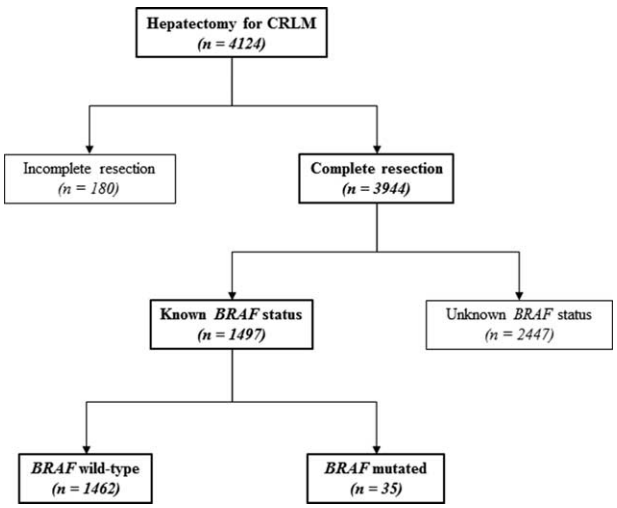

FIGURE 1. Flow chart of the study cohort.

TABLE 1. Clinicopathological and Treatment Features of Patients Who Underwent Complete Gross Resection of CRLM Stratified by *BRAF* Status*

Characteristics	*BRAF* Wild-type (n = 1462)	*BRAF* Mutant (n = 35)	*P*
Median age, y (range)	59 (19–91)	64 (41–85)	**0.05**
Sex			0.74
Male	813 (55.6)	19 (54.3)	
Female	649 (44.4)	16 (45.7)	
Median BMI, kg/m^2, (range)	26 (11–49)	24 (19–41)	0.52
ASA score			**0.05**
1	57 (3.9)	0 (0)	
2	632 (43.2)	14 (40)	
3	438 (30.0)	21 (60)	
4	19 (1.3)	0 (0)	
Unknown	316 (21.6)	0 (0)	
Primary tumor site			0.06
Colon	1051 (71.9)	28 (80.0)	
Right	488 (33.4)	19 (54.3)	
Left	563 (38.5)	9 (25.7)	
Rectum	336 (23.0)	7 (20.0)	
Unknown	75 (5.1)	0 (0)	
Primary tumor nodal status			0.28
Negative	482 (33.0)	10 (28.6)	
Positive	807 (55.2)	25 (71.4)	
Unknown	173 (11.8)	0 (0)	
Synchronous presentation of CRLM			**0.01**
No	668 (45.7)	8 (22.9)	
Yes	794 (54.3)	27 (77.1)	
Median number of CRLM (range)	2 (1–15)	3 (1–8)	**<0.01**
Multiple lesions			**<0.01**
No	683 (46.7)	6 (17.1)	
Yes	779 (53.3)	29 (82.9)	
Median diameter of largest CRLM, cm (range)	3 (0–22)	2 (1–7)	**0.05**
Largest CRLM > 5 cm	329 (22.9)	5 (14.3)	0.22
Median CEA level, μg/L (range)	7 (1–19262)	4 (1–260)	0.61
CEA level > 200 μg/L			0.83
No	1186 (81.1)	33 (94.3)	
Yes	60 (4.0)	2 (5.7)	
Unknown	216 (14.9)	0 (0)	
CRS			0.33
0	36 (2.5)	1 (2.9)	
1	193 (13.2)	3 (8.6)	
2	335 (22.9)	10 (28.6)	
3	451 (30.8)	15 (42.9)	
4	88 (6.0)	6 (17.5)	
5	19 (1.3)	0 (0)	
Incalculable	340 (23.3)	0 (0)	
Extrahepatic disease at presentation			**<0.001**
No	1324 (90.6)	34 (87.1)	
Yes	138 (9.4)	1 (2.9)	
Perioperative chemotherapy			0.77
No	109 (7.4)	1 (2.9)	
Yes	1353 (92.5)	34 (97.1)	0.36
Oxaliplatin-based	886 (60.6)	25 (71.4)	0.48
Irinotecan-based	642 (43.9)	17 (48.6)	0.19
Bevacizumab/Cetuximab	316 (21.6)	12 (34.3)	
Perioperative HAIP chemotherapy			0.54
No	1064 (72.8)	27 (77.1)	
Yes	398 (27.2)	8 (22.9)	
Median number of resected segments (range)	2 (0–7)	2.5 (0–6)	0.06
Major hepatectomy			**<0.001**
No	1026 (70.2)	28 (54.3)	
Yes	436 (29.8)	16 (45.7)	
Ablation associated with hepatectomy			0.96
No	1324 (90.6)	32 (91.4)	
Yes	138 (9.4)	3 (8.6)	
Colorectal synchronous resection			0.45
No	1235 (84.5)	30 (85.7)	
Yes	227 (15.5)	5 (14.3)	

TABLE 1. (*Continued*)

Characteristics	*BRAF* Wild-type (n = 1462)	*BRAF* Mutant (n = 35)	*P*
Type of *BRAF* mutation			—
V600E	—	25 (71.4)	
Non-V600E	—	9 (25.7)	
Unknown	—	1 (2.9)	
KRAS mutant			**<0.001**
No	920 (63)	35 (100)	
Yes	542 (37.0)	0 (0)	
Positive margin			0.67
No	1353 (92.5)	33 (94.3)	
Yes	109 (7.5)	2 (5.7)	
Median margin, mm (range)	4 (0–70)	6 (0–30)	0.89

*Values in the table are numbers of patients (percentages) unless otherwise indicated.

ASA indicates American Score of Anesthesiologists; BMI, body mass index; CEA, carcinoembryonic antigen; CRLM, colorectal liver metastases; HAIP, hepatic arterial infusion pump.

Bold values correspond to statistically significant results.

hepatectomies (46% vs 30%, $P < 0.001$). Less extrahepatic disease at presentation was observed in patients with *BRAF*-mut CRLM (3% vs 9%, $P < 0.001$). Among the 1462 *BRAF*-wt patients, 542 (37%) had mutated *RAS*. All *BRAF*-mut patients were *RAS* wild-type.

Outcomes After Liver Resection According to BRAF Mutation Status

Twenty-three (1.5%) patients had a < 3 months follow-up, corresponding to patients who died from postoperative complications. The 90-day mortality was similar between *BRAF*-wt and *BRAF*-mut patients (1.5% vs 0.0%, respectively, $P = 0.54$). Ten (0.7%) *BRAF*-wt patients but no *BRAF*-mut patients were lost to follow-up. At a median follow-up for survivors of 60 and 57 months, respectively, median OS was 81 (range 0 to 192) months for *BRAF*-wt and 40 (range 5 to 104) months for *BRAF*-mut patients ($P < 0.001$) (Fig. 2A). Three- and 5-year OS were 51% versus 80% ($P = 0.05$) and 37% versus 67% ($P < 0.01$) for patients with *BRAF*-mut and *BRAF*-wt CRLM, respectively. Among the 13 *BRAF*-mut patients who were alive at last follow-up, there were 6 actual 5-year survivors. Median RFS was 22 (range 0 to 192) and 10 (range 2 to 63) months for *BRAF*-wt and *BRAF*-mut patients ($P < 0.001$), respectively (Fig. 3A). Three- and 5-year RFS were 14% versus 47% ($P < 0.01$) and 8% versus 38% ($P = 0.02$) for patients with *BRAF*-mut and *BRAF*-wt CRLM, respectively. Among the 6 *BRAF*-mut patients with a 5-year follow-up, there was 1 actual 5-year recurrence-free survivor.

The overall recurrence rate was significantly higher in patients with *BRAF*-mut CRLM (91% vs 54%, $P < 0.001$). Table 2 lists the initial recurrence patterns stratified by *BRAF* mutation status. The rate of hepatic recurrence, with the liver as the only site of initial recurrence, was increased in *BRAF*-mut patients (41% vs 26%), a difference that approached statistical significance ($P = 0.08$). The rate of extrahepatic recurrence only was also comparable between *BRAF*-mut and *BRAF*-wt patients (47% vs 54%, $P = 0.40$).

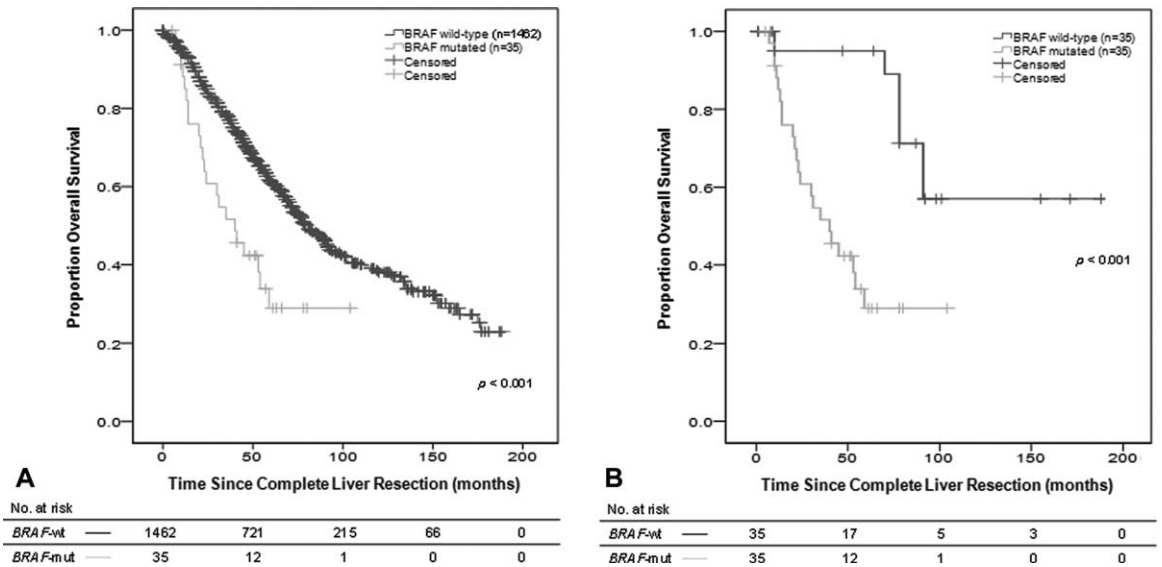

FIGURE 2. A, Overall survival after CRLM resection by *BRAF* mutation status, and (B) after case-control matching analysis (1:1) according to node-positive primary, synchronous CRLM, multiple CRLM, size of the largest CRLM > 5 cm, CEA > 200 ng/mL, the presence of extrahepatic disease at presentation, and the realization of a major hepatectomy.

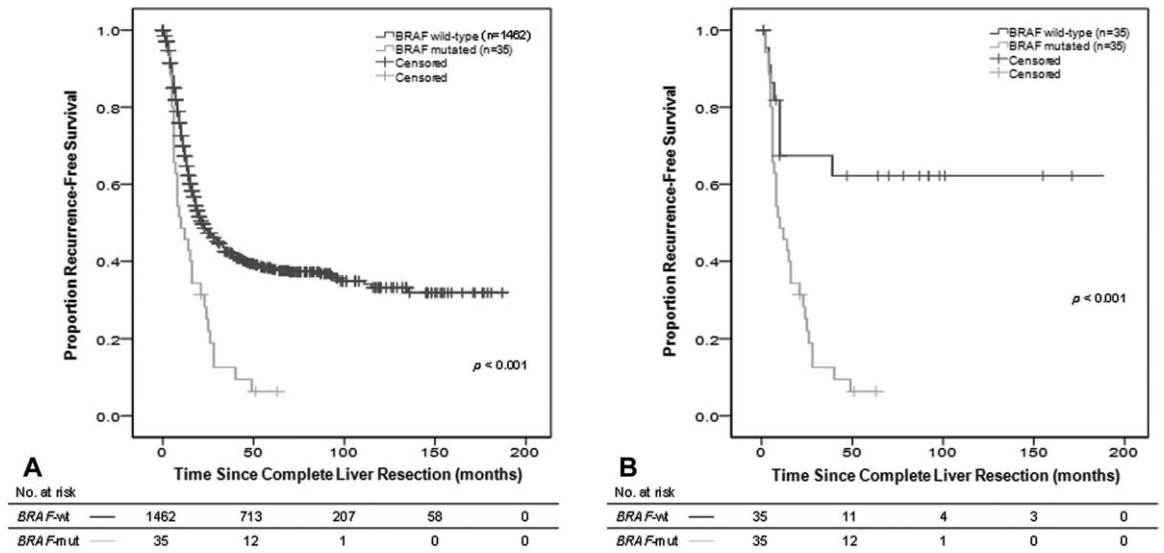

FIGURE 3. A, Recurrence-free survival after CRLM resection by *BRAF* mutation status, and (B) after case-control matching analysis (1:1) according to node-positive primary, synchronous CRLM, multiple CRLM, size of the largest CRLM > 5 cm, CEA > 200 ng/mL, the presence of extrahepatic disease at presentation, and the realization of a major hepatectomy.

Factors Associated With Outcomes After Liver Resection in BRAF-mut Patients

For *BRAF*-mut patients, factors associated with worse OS were node-positive primary tumor ($P < 0.01$), CEA level > 200 μg/L ($P = 0.02$), and clinical risk score ≥ 4 ($P < 0.001$) (Table 3). A CRS of 3 was not a prognostic cut-off for OS in *BRAF*-mut patients ($P = 0.11$). Factors associated with worse RFS were node-positive primary tumor ($P = 0.05$), ≥ 4 CRLM ($P = 0.04$), and positive hepatic margin ($P < 0.01$) (Table 3). A V600E *BRAF* mutation was not associated with worse OS [31 (range 5 to 104) months vs "not reached," $P = 0.16$] or RFS [8 (range 2 to 51) vs 16 (range 6 to 63) months, $P = 0.14$]. After a median follow-up of 51 months (range 21 to 63), 3 *BRAF*-mut patients did not recur, and 2 of them had a V600E *BRAF* mutation.

Case-control Matching Analysis of Outcomes According to BRAF Mutation Status

The 35 *BRAF*-mut patients were matched with 35 *BRAF*-wt patients according to the 5 factors of the previously described CRS (node-positive primary, synchronous CRLM, multiple CRLM, size of the largest CRLM > 5 cm, and CEA > 200 ng/mL),[1] the presence of extrahepatic disease at presentation, and the performance of a major hepatectomy. At a median follow-up for survivors of 57 and 83 months, respectively, median OS was significantly decreased in *BRAF*-mut compared with *BRAF*-wt patients [40 (range 5 to 104) months vs "not reached," $P < 0.001$] (Fig. 2B). Median RFS was also not reached for matched *BRAF*-wt and 10 (range 2 to 63) months for *BRAF*-mut patients ($P < 0.001$) (Fig. 3B).

TABLE 2. Recurrence Patterns of Patients Who Underwent Complete Gross Resection of CRLM Stratified by *BRAF* Status*

Characteristics	*BRAF* Wild-type (n = 1462)	*BRAF* Mutant (n = 35)	*P*
Recurrence			**< 0.001**
No	603 (41.2)	3 (8.6)	
Yes	789 (54.0)	32 (91.4)	0.40
Liver	359 (45.5)	17 (53.1)	0.08
Liver only	209 (26.5)	13 (40.6)	**0.03**
Extrahepatic	582 (73.8)	18 (56.3)	0.40
Extrahepatic only	430 (54.5)	15 (46.9)	0.06
Lung only	216 (27.4)	4 (12.5)	0.62
Peritoneum only	6 (0.8)	0 (0)	0.11
Retroperitoneal lymph nodes only	30 (3.8)	3 (9.4)	0.48
Other only	79 (10.0)	2 (6.3)	0.97
Multiple	249 (31.6)	10 (31.3)	0.27
Median number of recurrence sites	1 (1–4)	1 (1–4)	—
Unknown	70 (4.8)	0 (0)	

*Values in the table are numbers of patients (percentages) unless otherwise indicated.

TABLE 3. Univariate Analysis of Potential Predictive Factors of Overall survival (OS) and Recurrence-free (RFS) Survival for BRAF-mutated patients Who Underwent Intent-to-treat Liver Resection for CRLM

Potential Predictor	*P* for OS	*P* for RFS
Age	0.172	0.654
Sex	0.355	0.327
BMI	0.802	0.185
ASA score	0.147	0.169
Primary tumor site	0.649	0.787
Node-positive primary tumor	**0.005**	**0.050**
Synchronous presentation of CRLM	0.526	0.142
Multiple lesions	0.436	0.154
≥3	0.584	0.244
≥4	0.161	**0.038**
≥5	0.076	**0.042**
≥6	0.133	**0.001**
≥7	0.245	**0.028**
Diameter of largest CRLM	0.204	0.466
Largest CRLM > 5 cm	0.191	0.282
CEA level > 200 μg/L	**0.017**	0.820
CRS		
0	0.256	0.085
≥1	0.256	0.085
≥2	0.150	0.153
≥3	0.113	0.078
≥4	**<0.001**	0.209
Extrahepatic disease at presentation	0.268	0.276
Perioperative chemotherapy	0.863	0.134
Oxaliplatin-based	0.958	0.706
Irinotecan-based	0.263	0.746
Bevacizumab/Cetuximab	0.066	0.181
HAIP	0.378	0.102
Number of resected segments	0.551	0.466
Major hepatectomy	0.111	0.078
Colorectal synchronous resection	0.504	0.323
V600E *BRAF* mutation	0.162	0.138
Positive margin	0.413	**0.003**

ASA indicates American Score of Anesthesiologists; BMI, body mass index; CEA, carcinoembryonic antigen; CRLM, colorectal liver metastases; HAIP, hepatic arterial infusion pump.

DISCUSSION

The determination of tumor molecular biology has recently generated great interest in predicting response to chemotherapy and oncologic outcomes in CRC.[32] Besides the commonly used clinicopathological factors,[1–4] biomarkers are now commonly used as predictive and prognostic factors in patients with CRLM,[32–34] but most of them have not been well validated enough to impact clinical decision making in resectable patients. Nevertheless, *RAS* mutation status is now a validated predictor of response to chemotherapy regimens targeting the EGFR,[6,9–12] and *RAS* mutations have already been associated with poor survivals after liver resection,[5–8] especially when combined with other clinicopathological risk factors, with reported survival comparable to *RAS* mutated metastatic CRC treated with chemotherapy alone.[35] *BRAF* mutations have also been strongly associated with poor survival in patients with metastatic CRC being treated with palliative chemotherapy,[24,25,28] and available data now support the use of *BRAF* mutation as a negative predictive biomarker for anti-EGFR antibodies activity in clinical practice.[36–38] However, the role of *BRAF* mutations in patients with resectable CRLM, for whom surgery offers the only chance of cure and long-term survival, is less well defined despite 2 recent meta-analyses on this topic.[29,30] Indeed, the negative impact of *BRAF* mutations on OS has been reported after liver resection for CRLM,[22,29,30] but mostly in a small series, not specifically focused on *BRAF*-mut, with inadequate follow-up to appropriately assess long-term survival. Early recurrences after liver resection, especially at extrahepatic sites, have also been reported,[29,30] but the impact of *BRAF* mutations on both RFS and recurrence patterns has been poorly studied. On the basis of very limited data, it has also been suggested that a non-V600E *BRAF* mutation is associated with better outcomes after liver resection for CRLM.[31] Therefore, given the limited and small series published to date, we sought to use our multi-institutional prospective databases to provide larger numbers of patients with adequate follow-up to define the incidence of *BRAF* mutation in patients with resectable CRLM and to appropriately assess its prognostic impact following liver resection more definitively, especially specifying recurrence patterns.

In analyzing the impact of *BRAF*-mut in the largest cohort of resected CRLM with long-term follow-up, we confirmed that *BRAF*-mut patients are rare among patients selected for liver resection, representing 2% of this population in our institutions, less than the 7% to 10% of *BRAF* mutations reported in all metastatic CRC patients.[39–42] This underscores the fact that *BRAF*-mut patients with CRLM do not typically present with resectable disease.[23–26] It is interesting that we found an unexpected lower rate of extrahepatic disease at presentation in our *BRAF*-mut patients, which may be a reflection of the restrictive selection of *BRAF*-mut patients eligible for surgery. We also found that resected *BRAF*-mut patients did not present with dramatically different clinical features compared with *BRAF*-wt patients, with some tendency to have more multiple, smaller, and synchronous tumors. Interestingly, *BRAF*-mut patients more commonly presented with ASA scores ≥ 3. This could be explained by the older age seen among *BRAF*-mut patients and/or by potential adverse effects of preoperative treatments in these patients who could have a long history of systemic chemotherapy.

Although surgery remains the only potentially curative treatment for patients presenting with CRLM, it is legitimate to question whether it is worth the risk of postoperative complications and alterations of the quality of life in patients with poor prognosis, while modern systemic therapies could offer long-term survivals.[43] Especially, when considering extensive liver resections associated with significant postoperative morbidity and mortality,[44–47] appropriate selection of CRLM patients who could really benefit from surgery appears crucial. The present study helps to define the role of *BRAF* mutation in selecting CRLM patients eligible for surgery, reporting its negative impact on clinical outcomes after liver resection, especially when associated with other risk factors. Indeed, we demonstrated that *BRAF* mutations were associated with worse survival and high rates of recurrence after liver resection. However, long-term survival appeared possible among the highly selected *BRAF*-mut patients, and was associated with node-negative primary tumors, low CEA levels, and low CRS.[1] Moreover, median OS for our *BRAF*-mut patients (40 months) was still higher than median OS reported in *BRAF*-mut metastatic CRC treated with chemotherapy alone (10 to 14 months),[24,25,28,31] and surgery was associated with long-term OS in 17% of our *BRAF*-mut patients. Considering these results, it appears difficult not to propose surgery for resectable CRLM patients exhibiting *BRAF* mutations. However, even if postoperative 90-day mortality appeared to be similar between *BRAF*-mut and *BRAF*-wt patients, the ratio benefit/risks must be carefully weighted in these *BRAF*-mut patients with altered prognosis, especially when extensive resections are considered, and they should be highly selected for surgery using neoadjuvant chemotherapy.

We found a lower rate of extrahepatic disease at presentation in our *BRAF*-mut patients and did not detect any difference in outcomes between V600E and non-V600E *BRAF* mutations, as it

has been previously reported.[31] These inconsistencies raise questions about the representativeness of our cohort and may imply that there were different selection influences among the *BRAF*-mut patients brought to surgery in our institutions. Moreover, it appeared that the median OS for *BRAF*-mut patients presenting with at least 2 of the factors associated with worse OS in this study (node-positive primary tumor, CEA level $> 200\,\mu g/L$, and clinical risk score ≥ 4) was 13 months (data not shown), which more likely corresponds to the previously reported median OS for resected *BRAF*-mut patients, ranging from 8 to 22 months.[29,30] Therefore, especially due to the scarcity of *BRAF* mutations and the small samples used for these statistical analyses, definitive conclusions cannot easily be reached, but *BRAF*-mut patients eligible for CRLM surgery should probably be highly selected and considered for neoadjuvant strategies if multiple poor prognostic factors coexist.

Despite an increased rate of overall recurrence in *BRAF*-mut patients in this study, the recurrence patterns analysis failed to determine a particular recurrence profile for *BRAF*-mut patients, especially regarding extrahepatic recurrences that have been reported to be increased in these patients after liver resection.[29,30] We observed a higher rate of liver recurrence in *BRAF*-mut than in *BRAF*-wt patients, as the only site of recurrence in almost 41% of the patients, a difference that approached significance. If confirmed on larger cohorts, this result would suggest that a large proportion of *BRAF*-mut patients who will recur after liver resection may be eligible for potentially curative repeated hepatectomy if appropriately selected. This is different from most publications on this topic, which have suggested that there is a poor prognosis of resected *BRAF*-mut patients, with early and multiple extrahepatic recurrence ineligible for further potentially curative treatments.[29,30] Moreover, as the rate of liver-only recurrence appeared high in the *BRAF*-mut patients, adjuvant hepatic arterial infusional chemotherapy could be considered in these patients.[48]

This study has other limitations. First, the retrospective design makes the study susceptible to unmeasurable selection biases. Second, there was a lack of data in our cohort regarding the number of cycles of chemotherapy performed before liver resection. Prolonged neoadjuvant chemotherapy has been associated with a group of patients with poor outcomes after resection.[49] Third, *BRAF* mutation status was known for only 36% of the patients who underwent hepatectomy for CRLM in our institutions during the study period, which could alter the representativeness of our cohort. Lastly, *BRAF* mutation profiling was done from both primary tumor and CRLM tissue samples, which may vary in terms of mutational abnormalities, especially after administration of chemotherapy. However, very high concordance has been shown for *BRAF* mutation status between primary CRC and corresponding CRLM.[50]

In conclusion, patients with *BRAF*-mut CRLM are rare among patients selected for liver resection. A subset of *BRAF*-mut patients can present with resectable CRLM, but they tend to more commonly present with multiple, synchronous, and small tumors, and to be older patients with more comorbidities. *BRAF* mutation is associated with high rates of liver recurrence after surgery for CRLM, and adjuvant regional hepatic strategies should probably be considered in *BRAF*-mut patients. Furthermore, although *BRAF*-mut patients have a worse prognosis, the presence of a *BRAF* mutation does not preclude long-term survival. Better outcomes among *BRAF*-mut patients are associated with node-negative primary tumors, CEA $\leq 200\,\mu g/L$, and CRS < 4. Therefore, with current evidence, *BRAF*-mut patients who present with resectable CRLM should be considered for liver surgery but should probably be highly selected and counseled about the high risk of recurrent disease.

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