Clinicopathologic Features and Prognosis of BRAF Mutated Colorectal Cancer Patients

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Background: BRAF V600E mutation is associated with poor prognosis of colorectal cancer (CRC) patients, but the comparison of clinic-pathologic features between V600E and non-V600E mutation was not well-known in CRC patients. The aim of this study is to evaluate the clinical and pathological features, prognostic value of BRAF mutations in CRC.

Methods: We conducted a retrospective study to characterize the clinical and pathological features and survival of patients with BRAF mutated CRC. Patients were classified according to BRAF status as BRAF V600E mutation and non-V600E mutations. Difference of characteristics and survival between the two groups was analyzed.

Results: There was no significant difference in gender, family history, location of primary tumor, metastatic sites between patients with BRAF-V600E mutation and non-V600E mutations. Patients with V600E mutation were younger than those with non-V600E mutations (p = 0.002). Patients with BRAF V600E mutation showed a poorer outcome than those with non-V600E mutations (23.1 vs. 49.9 months, respectively, p = 0.0024). Lack of CDX2 expression was associated with worse prognosis (mOS: 9.4 m vs. not reached, respectively, p = 0.016). Status of V600E mutation did not affect the mPFS and ORR of first-line or second-line treatment.

Conclusion: BRAF V600E mutation defines a distinct subgroup of CRC with worse prognosis. Lack of CDX2 expression is associated with poor OS. Status of V600E mutation did not affect the mPFS of first-line or second-line treatment.

Keywords: BRAF, V600E, CDX2, colorectal cancer, prognosis

INTRODUCTION

Colorectal cancer (CRC) is the third most prevalent malignancy worldwide (1). CRC is widely recognized as a molecularly heterogeneous disease, resulted from accumulation of genetic and/or epigenetic changes involving several pathways, such as microsatellite instability (MSI), chromosomal instability (CIN), RAS-RAF-MEK-ERK-MAPK pathway. Among them, mutations in RAS and BRAF (v-raf murine sarcoma viral oncogene homolog B) genes are most
widely used in clinical decision making (2). BRAF, a proto-oncogene, plays an important role in cell differentiation, proliferation and survival through MAPK pathway (3). Therefore, its aberrant activation is critical for tumorigenesis in many types of malignancies, such as melanoma, hairy cell leukemia, papillary thyroid carcinoma, non-small cell lung cancer (NSCLC) as well as CRC (4–9). In CRC, the incidence of BRAF mutation is about 3–10% (4, 10–12). The most common BRAF mutation is due to a CTGCAG change in the nucleotide 1,799 of exon 15 (T1799A), which leads to an amino acid substitution from valine to glutamate at codon 600 (p.V600E). This mutation is known as BRAFV600E mutation, which accounts for 56–90% of BRAF mutations (13–16). Many studies have demonstrated the negative prognostic value of BRAF V600E mutation on metastatic CRC patients (4, 8). However, in our clinical practice, we found that not all the BRAFV600E patients had poor prognosis. Moreover, non-V600E BRAF mutations are less common in CRC, and their clinical and pathological features, prognostic and predictive value were less discussed.

Since the behavior of BRAFV600E mutated mCRC is aggressive, the PFS of traditional chemotherapy is poor and only 60% of patients can receive second-line treatment. Hence, intensive combination of targeted therapy and chemotherapy may be effective. FOLFOXIRI plus bevacizumab regimen has demonstrated an improved PFS and OS (17). So, it is recommended during first-line treatment for BRAFV600E mutated mCRC. During second-line treatment, combined approach with several targeted inhibitors against different key components of MAPK pathway has showed promising results, with a median progression free survival (PFS) of 7.7 months by vemurafenib, irinotecan, and cetuximab (18, 19), or 8.0 months by encorafenib, binimetinib, and cetuximab (20). To our knowledge, there are no studies about effectiveness of chemotherapy for Chinese CRC patients with BRAF mutation. In this study, we evaluated these mutations and tried to provide new insights of Chinese BRAF mutations CRC patients.

METHODS

Clinical Data
In this study, we retrospectively review CRC patients with BRAF mutation who were diagnosed between April 2013 to January 2020 at Sun Yat-sen University Cancer Center (Guangzhou, China). All the patients were diagnosed as CRC by hematoxylin and eosin (HE) staining and histologically analysis. Clinic records, including gender, age, primary tumor location, TNM stage at diagnosis, metastatic sites, family history, MSI/MMR status, date of diagnosis and date of last contact, were collected by our medical record system.

Ethics and Consent Statement
The studies involving human participants were reviewed and approved by ethics committee of Sun Yat-sen University Cancer Center. The patients provided written informed consent to participate in this study.

RESULTS

Patients Characteristics
From April 2013 to January 2020, 74 Chinese CRC patients with BRAF mutations were investigated in Sun Yat-sen University Cancer Center. Fifty four (73.0%) were BRAFV600E mutated. Most patients were diagnosed at advanced stage (59/74, 79.7% at stage IV). There were 26 (35.1%) right-sided (cecum to transverse colon) and 19 (25.7%) left-sided (splenic flexure to sigmoid colon) cases, and the rest were in rectum (29/74, 39.2%). Patients with V600E mutation were much younger than those with non-V600E mutations (48.1 vs. 58.8 years old, \(p = 0.002\)). The most common sites of non V600E mutations are codon 469, 464, and 594. There was no significant difference in gender, family history, location of primary tumor, metastatic sites, CDX2 status, MSI status or TMB level between V600E and non-V600E groups. Though RAS and BRAF genes were thought to be mutually exclusive, 4 cases with RAS and BRAF co-mutations were found.
in our study. All of them were non-V600E mutated. The clinical and pathological features are shown in Table 1.

Eight patients with negative CDX2 expression were found in our study. The median age was 47.3 (30–69) years. Most of them (6/8, 75%) were male. Seven (87.5%) of them were BRAF V600E mutated. In terms of primary tumor location, there were 3 cases on each side of colon, and the rest 2 cases were located in the rectum. No remarkable difference of age, gender, location, differentiation, metastatic site was found in patients with negative CDX2 compared to those with positive CDX2 expression.

### Treatment

All patients at stage I, II, and III (9/54 in V600E group and 6/20 in non-V600E group, respectively), received radical surgery. Sixty-five patients received first-line therapy and 58 of them were evaluable. Forty-eight patients with BRAF V600E mutation received first-line treatment, and the regimen mostly used was bevacizumab plus two or three-drug chemotherapy (Table 2). Besides, 2 patients received local therapies for primary tumor and metastatic sites in the condition of disease controlled after systemic treatment. Among the 20 cases with BRAF non-V600E mutation, 17 patients received first-line treatment, including 10 cases with chemotherapy alone, 5 with chemotherapy plus cetuximab, and 2 with chemotherapy plus bevacizumab. Two patients received local therapies for liver/lung metastasis. Median progression free survival (mPFS) and objective response rate (ORR) of patients with BRAF V600E mutation was 7.3 months (95%CI: 4.6–9.1 months) and 30.1%, while patients with non-V600E mutations had an mPFS of 7.6 months (95%CI: 6.4–12.5 months) and an ORR of 37.5%. DFS and ORR during first-line treatment was not affected by status of V600E mutation (p = 0.90, Figure 1). PFS of different regimens for BRAF V600E mutated patients is showed in Table 2. It seems that regimens with Bevacizumab + chemotherapy had a better PFS than chemotherapy alone or chemotherapy plus cetuximab, but the statistical significance was not reached.

Thirty three patients received second-line therapy. the regimens mostly used for patients with BRAF V600E mutation were VIC (vemurafenib, irinotecan and cetuximab) and bevacizumab plus chemotherapy (Table 3). Among patients with BRAF non-V600E mutation, only 8 patients (8/17, 47%) received second-line treatment. Four of them received chemotherapy alone, 3 received bevacizumab plus chemotherapy, and 1 patient received cetuximab plus chemotherapy. mPFS for patients with BRAF V600E and non-V600E mutations was 2.9 months (95%CI: 1.7–8.7 months) and 4.6 months (95%CI: 1.8–12.5 months), respectively (p = 0.30, Figure 2). The ORR of BRAF V600E and non-V600E mutations was 14.3 and 12.5%, respectively, p = 0.90.

### Table 1 | Clinical characteristics of colorectal cancer patients with BRAF mutation.

|                   | V600E N = 54 | Non-V600E N = 20 | P-value |
|-------------------|-------------|-----------------|---------|
| Gender            |             |                 | 0.653   |
| Female            | 22 (40.7)   | 7 (35.0)        |         |
| Male              | 32 (59.3)   | 13 (65.0)       |         |
| Age               |             |                 | 0.002   |
| Mean ± SD         | 48.1 ± 13.1 | 58.8 ± 11.2     |         |
| Median            | 48          | 63              |         |
| Family history    |             |                 | 0.566   |
| No                | 39          | 16              |         |
| Lung cancer history | 8         | 3               |         |
| Colorectal cancer history | 2 | 1              |         |
| Other cancer history | 5        | 0               |         |
| Location          |             |                 | 0.076   |
| Right-sided colon | 22          | 4               |         |
| Left-sided colon  | 15          | 4               |         |
| Rectum            | 17          | 12              |         |
| RAS               |             |                 | 0.001   |
| Wild type         | 54          | 16              |         |
| Mutation          | 0           | 4               |         |
| PI3K              |             |                 | 0.348   |
| Wild type         | 46          | 14              |         |
| Mutation          | 8           | 6               |         |
| MSI status        |             |                 | 0.401   |
| MSS/MSI-L         | 44          | 12              |         |
| MSI-H             | 1           | 1               |         |
| Unknown           | 9           | 7               |         |
| TMB               |             |                 | 0.440   |
| Mean ± SD         | 7.3 ± 3.6   | 8.4 ± 1.7       |         |
| Median            | 7.1         | 8.2             |         |
| CDX2              |             |                 | 0.453   |
| Positive          | 21          | 7               |         |
| Negative          | 7           | 1               |         |
| Unknown           | 26          | 12              |         |
| TNM stage         |             |                 | 0.356   |
| I                 | 0           | 1               |         |
| II                | 2           | 1               |         |
| III               | 7           | 4               |         |
| IV                | 45          | 14              |         |
| Metastasis site   |             |                 | 0.732   |
| Liver             | 30          | 12              |         |
| Lung              | 13          | 8               | 0.177   |
| Peritoneal        | 23          | 7               | 0.555   |
| Bone              | 1           | 3               | 0.058   |
| Distant lymph node| 20          | 6               | 0.685   |

### Table 2 | First line therapy for patients with BRAF V600E mutated colorectal cancer.

| Regimen                          | Partial response | Stable disease | Progression disease | mPFS (months) |
|----------------------------------|------------------|----------------|---------------------|---------------|
| Bevacizumab + FOLFOXIRI (N = 11) | 6                | 3              | 2                   | 8.8           |
| Bevacizumab + FOLFOX/ FOLFIRI/XELOX (N = 9) | 2 | 5              | 2                   | 9.1           |
| FOLFIRI/XELOX/FOLFIRI/ XELOX (N = 19) | 4 | 8              | 7                   | 4.6           |
| Cetuximab + FOLFOX/FOLFIRI (N = 2) | 0                | 2              | 0                   | 4.3           |
FIGURE 1 | First-line PFS of CRC patients with BRAF V600E and non-V600E mutation (ECOG = 0–2).

TABLE 3 | Second line chemotherapy for patients with BRAFV600E mutated colorectal cancer.

| Regimen                        | Partial response | Stable disease | Progression disease | mPFS (months) |
|--------------------------------|------------------|----------------|---------------------|---------------|
| VIC (N = 8)                    | 1                | 5              | 2                   | 2.9           |
| Bevacizumab + FOLFOXIRI/FOLFIRI (N = 8) | 1                | 4              | 3                   | 9.7           |
| FOLFOXIRI/FOLFIRI (N = 2)      | 0                | 0              | 2                   | 1.2           |
| Regorafenib/Fruquintinib (N = 3) | 1                | 1              | 1                   | 1.8           |

The effect of different regimens for patients with BRAFV600E mutation is presented in Table 3. Bevacizumab + chemotherapy seemed to have an improved PFS (9.7 months) compared to other regimens, though it was not statistically different.

Among the 8 patients with loss of CDX2 expression, 6 patients received first-line treatment. Two of them were treated with bevacizumab plus chemotherapy, and the other 4 patients used chemotherapy alone. The ORR was 16.7% (1/6) and mPFS was 3.2 months.

Survival Analysis

The median overall survival (OS) of all patients was 27.4 months in our study. Patients with BRAFV600E mutation showed a poorer outcome than those with non-V600E mutations (23.1 vs. 49.9 months, \( p = 0.0024 \), Figure 3). There were 15 patients diagnosed at early stage (stage I, II, and III; 9/54 with V600E mutation and 6/20 with non-V600E mutation). All of them received radical surgery and 10/15 received adjuvant chemotherapy. The median disease-free survival (DFS) was 15.3 months (3.0–63.9 months). No statistical difference was found between V600E/non-V600E patients (14.0 vs. 15.3 m, respectively, \( p = 0.257 \)). However, Non-V600E mutant type at early stage showed better OS than V600E mutant type (not reached vs. 26.1 m, respectively, \( p = 0.05 \)).

The overall survival after recurrence or metastasis was 18.9 months in BRAFV600E group and not reached in BRAFnon-V600E group (\( p = 0.051 \)). Multivariate analysis was showed in Table 4 and BRAFV600E was an independent prognostic factor for survival. The univariate analysis showed that only CDX2 expression was related with prognosis of BRAFV600E mutation patients, while gender, age, tumor location, tumor mutational burden (TMB) level and TNM stage were not (Table 5). Patients with negative CDX2 expression have worse outcome compared to those with positive CDX2 (mOS: 9.4 months vs. not reached, \( p = 0.016 \), Figure 4).

There were 3 BRAFV600E patients who were alive for more than 40 months. One was a 66-year old male diagnosed as at stage II in 2013, who received radical surgery. The immunohistochemistry of primary tumor showed CDX2 positive and dMMR (MSH2 deficient). He got single lung metastasis after...
5 years and received resection of the metastatic tumor and oral S1 as chemotherapy. He had multiple brain metastasis and received local radiotherapy in 2019. This patient was still in the follow-up. The other two patients were diagnosed at stage IV with pMMR and unknown CDX2 status. One got tumor located in rectum, with concurrent lung and peritoneum metastasis. The other one got left-sided colon cancer with peritoneum metastasis. Both patients received XELOX as first-line treatment and bevacizumab plus FOLFIRI regimen as second-line treatment.

DISCUSSION

It has been reported that BRAF mutated CRC patients have specific clinical, pathological and molecular characteristics, compared to patients with wild-type BRAF (14). Clinically, BRAF mutated CRCs are more often seen in elderly women, located in right-sided colon, and accompany with peritoneal and/or distant lymph node metastasis (4, 24). Regarding to pathological features, BRAFV600E mutated CRCs are characterized by mucinous components, poor differentiation and highly aggressive behavior (14). In addition, BRAFV600E mutation is associated with MSI-H/dMMR status, and mutually exclusive with RAS mutations (25–27). However, few studies have described the clinical, pathological and molecular features of non-V600E mutations. We tried to summarize the similarities and differences between V600E and non-V600E mutations in our single institution in China. The frequency of non-V600E mutations was 27% (20/74) in our study, similar with the rates reported in other literatures (15). Patients with non-V600E mutations showed no difference in gender, family history, metastatic sites, CDX2 status or TMB level compared with patients with V600E mutation. Regarding primary tumor sidedness, some studies demonstrated that CRC with non-V600E mutations might be more often on left side, but others found no relation between sidedness and non-V600E mutations (15, 16, 28). In this study, we found most of non-V600E mutated CRC located on left colon and rectum, but due to the small sample size, the difference was not statistically significant. Besides, we found 4 cases (4/20, 20%) with concomitant presence of both BRAF non-V600E and RAS mutations, though BRAF mutation was thought to be mutually exclusive with RAS mutations. Jones et al. also reported that patients with non-V600E mutant CRC were more likely with concomitant RAS mutation (15). According to previous literatures, though some subtypes of BRAF mutations had impaired or no kinase activity, they might retain oncogenic function by co-expression with other mutations, such as RAS/EGFR mutations (29). In fact, some researchers have identified BRAF mutations as three classes according to their acting pattern and RAS dependency: class 1 (V600 mutations) is activated monomers when RAS activity is low; class 2 (codon 464, 469, 597 and 601) acts as a RAS-independent dimer; class 3 (codon 287, 459, 466, 467, 469,
581, 594, 595, and 596) acts as a dimer with impaired kinase activity, so the oncogenic potential is RAS-dependent (29, 30). This may explain the concomitant presence of BRAF non-V600E and RAS mutations in some cases.

It has been broadly demonstrated that $\text{BRAF}^{\text{V600E}}$ mutation is associated with poor prognosis of CRC patients regardless of stage (25, 31). According to our analysis, patients with non-V600E mutations had better OS than those with V600E mutation ($p = 0.0239$), especially for patients diagnosed at early stage. Shimada et al. reported V600E mutant type showed poorer OS than non-V600E mutant type after R0 resection ($p = 0.038$), which was consistent with our result. However, the prognostic value of non-V600E mutations is still controversial due to limited clinical data of this subgroup. Cremolini et al. found that some subtypes of non-V600E mutations (codon 594 and 596) might indicate a favorable outcome (28). More recently, Jones et al. reported a longer OS in patients with $\text{BRAF}$ non-V600 mutations (60.7 months), which not only exceeded the OS of 11.4 months for patients with $\text{BRAF}^{\text{V600E}}$ mutation, but also the survival of 43.0 months for patients with wild-type $\text{BRAF}$ gene (15). Besides, they explored if the kinase activity (which was discussed above) would influence the OS of $\text{BRAF}^{\text{non-V600E}}$ mutant patients. It turned out there was no significant difference in OS for patients with activated vs. impaired kinase ($p = 0.544$) (15). Hence the non-V600E mutated CRC may be a totally different subtype of CRC regarding to prognostic value.

Though $\text{BRAF}^{\text{V600E}}$ mutation was associated with poorer survival in CRC, it has been observed that some patients with $\text{BRAF}^{\text{V600E}}$ mutation have a relatively poorer outcome than others. Loupakis et al. classified patients with $\text{BRAF}^{\text{V600E}}$

### TABLE 4 | Multivariate analysis for patients with $\text{BRAF}$ mutated colorectal cancer.

| Characteristics            | $N$ | Overall survival | HR | 95% CI    | $P$  |
|----------------------------|-----|------------------|----|-----------|------|
| Mutational status          |     |                  |    |           |      |
| $\text{BRAF}^{\text{V600E}}$ | 54  | 1                |    |           |      |
| $\text{BRAF}$ non-$\text{V600E}$ | 20  | 0.34             | 0.14–0.84 | 0.019 |
| Age                        |     |                  |    |           |      |
| <49 year                   | 32  | 1                |    |           |      |
| ≥49 year                   | 42  | 1.98             | 0.87–4.48 | 0.102 |
| Gender                     |     |                  |    |           |      |
| Male                       | 45  | 1                |    |           |      |
| Female                     | 29  | 1.28             | 0.61–2.69 | 0.523 |
| Primary tumor site         |     |                  |    |           |      |
| Right colon                | 26  | 1                |    |           |      |
| Left colon/rectum          | 48  | 1.38             | 0.61–3.12 | 0.436 |
| Stage                      |     |                  |    |           |      |
| I, II, III                 | 15  | 1                |    |           |      |
| IV                         | 59  | 1.75             | 0.73–4.21 | 0.212 |

**FIGURE 3** | Overall survival of CRC patients with $\text{BRAF}^{\text{V600E}}$ and non-$\text{V600E}$ mutation.
mutation as three different prognostic groups according to ECOG score, CA19-9 and LDH level, grade of tumor, status of metastasis (lung, liver and lymph nodes) (32). Prognosis of

TABLE 5 | Survival analysis for patients with \( \text{BRAF}^{V600E} \) mutated colorectal cancer.

|                        | mOS (months) | \( P \)-value |
|------------------------|--------------|---------------|
| Gender                 |              |               |
| Male                   | 24.7         | 0.8116        |
| Female                 | 23.1         |               |
| Age                    |              |               |
| <49                    | 24.8         |               |
| >48                    | 23.0         | 0.4016        |
| Location               |              |               |
| Right-sided colon      | 26.1         |               |
| Left-sided colon       | 24.8         |               |
| Rectum                 | 22.4         | 0.6703        |
| TMB (Mut/Mb)           |              |               |
| <7.2                   | 29.4         | 0.5491        |
| >7.1                   | NA           |               |
| CDX2                   |              |               |
| Negative               | 9.4          | 0.016         |
| Positive               | NA           |               |
| TNM stage              |              |               |
| II                     | NA           |               |
| III                    | 23.1         |               |
| IV                     | 22.4         | 0.3134        |

patients with \( \text{BRAF}^{V600E} \) mutation could be related to MMR/MSI status, or some genetic events occurring in pathogenesis of CRC (29, 30, 33). Recently, it was reported that CDX2 might play a significant role in prognosis of CRC (34, 35). CDX2 is a transcription factor and a specific marker of differentiation of intestine, which could be used to identified tumors originating from intestine (36). Aasebo et al. reported that CDX2 expression, which accounts for 53% of patients with \( \text{BRAF} \) mutation in their study, was associated with much better prognosis (34). Our study also demonstrated that loss of CDX2 expression indicated worse survival in patients with \( \text{BRAF}^{V600E} \) mutation \((p = 0.016)\). Therefore, the loss of CDX2 expression may define a subgroup of poor prognosis in CRC patients, especially those with \( \text{BRAF}^{V600E} \) mutation.

Though the prognostic value was widely discussed in many studies, the predictive role of \( \text{BRAF} \) mutation in CRC patients received chemotherapy or targeted therapy remains unclear. Some studies showed \( \text{BRAF}^{V600E} \) mutated patients had worse PFS during first-line chemotherapy (10, 37); on the contrary, other studies reported that \( \text{BRAF} \) mutation was not associated with PFS of first-line treatment (8, 11, 38). The ambiguous results might depend on the small number of patients enrolled in the studies. Due to the aggressive behavior observed in \( \text{BRAF}^{V600E} \) mutated CRC, intensive chemotherapy combined with targeted therapy was used in first-line treatment and proved to be effective (39). It has been reported that FOLFOXIRI plus bevacizumab showed an improved response rate and PFS.
compared to chemotherapy alone in BRAF mutated CRC (17). In our study, bevacizumab plus chemotherapy regimen had a better response rate and longer median PFS compared to chemotherapy alone in BRAF\textsuperscript{V600E} mutated CRC patients, though the statistical significance was not reached. The response rate of bevacizumab plus FOLFOXIRI was 54.5%, which was an inspiring result considering the aggressiveness of BRAF\textsuperscript{V600E} mutated CRC.

Regimens including specific inhibitors against BRAF mutation and other components of MAPK pathway were proved to be effective in second-line treatment. The phase II SWOG S1406 trial showed that combination of vemurafenib, irinotecan and cetuximab (the “VIC” regimen) for BRAF\textsuperscript{V600E} mutant, RAS wild-type mCRC had an improved PFS compared with irinotecan plus cetuximab regimen (4.4 vs. 2.0 months) (18). Recently, the phase III BEACON trial proved an advantage of response rate and overall survival for combination of the BRAF inhibitor (encorafenib), MEK inhibitor (binimetinib) and cetuximab (20). Since MEK inhibitor was not available in China, we recorded only eight patients receiving the VIC regimen during second-line treatment. The ORR was 12.5% (1/8) and PFS was 2.9 months. The potential predictive value of different BRAF subtypes was less explored. Our studies showed that the subtypes of BRAF mutations had no significant impact on PFS during first-line or second-line treatment ($p = 0.51$ and 0.30, respectively).

There are some limitations of our study. First, it is a retrospective study and patients are from a single institution; hence selection bias inevitably exists. Most patients in this study were diagnosed at advanced stage, so the frequency of BRAF mutation in early staged CRC might be underestimated and its prognostic and predictive value is not clear. Second, given the rareness of BRAF mutation, especially non-V600E mutation, the prognostic and predictive value is not clear. Second, given the罕见的BRAF mutation，尤其是非V600E突变，其 prognostic and predictive value is not clear. Finally, the sample size is too small to summarize the whole picture of CRC patients with BRAF mutation. Third, we were limited by lack of complete follow-up and treatment information for some patients.

**CONCLUSION**

In summary, the clinical and pathological features and outcomes of BRAF mutated CRC patients are heterogeneous. While BRAF\textsuperscript{V600E} mutation is related with poor prognosis, non-V600E mutations define a subgroup of CRC patients with better outcome. Besides, some molecular basis like CDX2 status may affect the prognosis. So, it could be valuable to further classify BRAF mutated CRCs according to their molecular basis. The predictive value of BRAF mutation in CRC is still controversial; combination of different therapies may have better response compared to traditional chemotherapy. More efforts are needed to explore the molecular mechanism of BRAF mutation.

**DATA AVAILABILITY STATEMENT**

The data from this study can be found at the following link: http://download.omicsbio.info/files/BRAF_mut/.

**ETHICS STATEMENT**

The studies involving human participants were reviewed and approved by ethics committee of Sun Yat-sen University Cancer Center. The patients provided written informed consent to participate in this study.

**AUTHOR CONTRIBUTIONS**

M-ZQ, F-HW, and R-HX: study design. W-LG and M-ZQ: literature search and writing. W-LG, M-ZQ, L-QY, YJ, Z-QW, Y-HL, F-HW, and R-HX: data collecting. C-YH: gene mutations testing. W-LG, M-ZQ, F-HW, and R-HX: data analysis, figure, and tables. All authors contributed to the article and approved the submitted version.

**FUNDING**

This work was supported by National Natural Science Foundation of China (Grant numbers. 82073377, 81772587); the third outstanding young talents training plan and Medical Scientist program of Sun Yat-sen University Cancer Center.

**ACKNOWLEDGMENTS**

The authors thank the patients and their families.

**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found at: https://www.frontiersin.org/articles/10.3389/oncology.2020.563407/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.