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Clinicopathological Features and Prognosis of Unresectable Colorectal Cancer With the *BRAF V600E* Mutation

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Abstract

Background/Aim: Patients with unresectable advanced and recurrent colorectal cancer (CRC) and the *BRAF V600E* mutation have poor prognosis, and conventional chemotherapy is often ineffective. This study aimed to retrospectively evaluate the clinicopathological features and prognosis of this patient population.

Patients and methods: We examined clinicopathological characteristics and treatment outcomes of 26 patients with *BRAF V600E*-mutated unresectable advanced and recurrent CRC treated between June 2015 and October 2022.

Results: The mean age was 63.1±14.0 years; out of 26 patients, nine (34.6%) were female, 12 (46.2%) had right-sided CRC, and eight (30.8%) had poorly differentiated or mucinous adenocarcinoma. One patient (3.8%) had a *RAS* mutation, and three (11.5%) had high microsatellite instability. The median overall survival (OS) was 12.0 months. The median OS for patients treated with the BEACON regimen (encorafenib plus cetuximab, with or without binimetinib) was 13.3 months, which was significantly better than that of patients treated without it (7.2 months; hazard ratio=4.180, 95% confidence interval=1.036-18.631, p=0.029). The median progression-free survival for patients treated with BEACON regimen was 6.6 months.

Conclusion: The *BRAF V600E* mutation was associated with poor prognosis. The BEACON regimen resulted in improved OS compared with other CRC treatment regimens.

Keywords: Unresectable advanced recurrent colorectal cancer, *BRAF V600E*, mutation, Beacon CRC trial, encorafenib, binimetinib, proto-oncogene, B-raf.

Introduction

Colorectal cancer (CRC) is the third most common type of cancer worldwide (1). The prognosis and risk of recurrence vary based on the tumor stage, determined by factors such as tumor depth, lymph node and distant metastasis. However, CRC has significant clinical differences even within the same pathological tumor stage.

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Genetic tests, including those for all ras2 Kirsten rat sarcoma viral oncogene homolog (*RAS*), v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*), and microsatellite instability (MSI), are used for prognostic purposes and treatment decisions. In particular, *BRAF V600E*-mutated CRC has a poor prognosis (2). Previous studies have examined that unresectable advanced and recurrent cases respond poorly to conventional chemotherapy (1, 2) and well to the regimens used in the BEACON CRC trials (BEACON regimen; encorafenib plus cetuximab, with or without binimetinib) (3, 4). On the other hand, there are still many unknowns regarding treatment methods that can improve prognosis.

In this study, based on the BEACON CRC study (4), CRC patients with the *BRAF V600E* mutation were treated with the BEACON regimen. The prognosis of the patients who received the treatment was then examined. We also evaluated the characteristics of unresectable advanced or recurrent *BRAF V600E mutated* CRC.

Patients and Methods

Patients. A total of 36 Japanese patients with *BRAF V600E*-mutated CRC who were treated in our hospital between June 2015 and October 2022 were included in this retrospective study. Of these, 29 had unresectable advanced and recurrent CRC; three patients who were treated with immune checkpoint inhibitors were excluded, and 26 were ultimately enrolled. All participants provided written informed consent, and the study was approved by the Institutional Review Board of the New Treatment Development Support Center at Kanagawa Cancer Center (approval number: 2022-111).

Patient clinicopathological features. Clinicopathological features, including age, sex, tumor location, histology, metastasis patterns, *RAS*/MSI status, and prognosis, including overall survival (OS) and progression-free survival (PFS), were reviewed. Patients were followed up using computed tomography every 2-3 months if under treatment for recurrence or according to the Japanese Society for Cancer of the Colon and Rectum guidelines 2019 for the treatment of CRC (5) if recurrence-free. Immunohistochemical staining (IHC) was used to determine the presence of *BRAF V600E* mutant proteins in cancer tissues obtained from colonoscopy biopsies or surgical specimens.

Statistical analysis. The primary outcome was to compare OS and PFS between patients treated with or without the BEACON regimen and to examine the treatment methods used for patients with good prognoses. As a secondary outcome, we also evaluated the prognostic factors in CRC patients with the *BRAF V600E* mutation.

This study was a retrospective observational study. Patient characteristics were analyzed using descriptive statistics. Continuous variables were expressed as mean±standard deviation (SD). OS was calculated from the time of recurrence to death and PFS from the time of diagnosis to disease progression. OS and PFS were analyzed using the Kaplan-Meier method, and survival curves were compared using the log-rank method. The Cox proportional hazards model was used to control for multiple risk factors that have been shown to influence CRC survival. Statistical significance was set at $p<0.05$. All analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Results

The clinicopathological features of patients with the *BRAF V600E* mutation are summarized in Table I. The median OS of patients with CRC and the *BRAF V600E* mutation in our hospital was 12.0 months (Figure 1). The median OS of patients treated with and without the BEACON regimen was 13.3 and 7.2 months, respectively, and this difference was significant [hazard ratio (HR)=4.18; 95% confidence interval (CI)=1.04–18.6; $p=0.03$] (Figure 2). The median PFS of patients receiving the BEACON regimen was 6.6 months (Figure 3).

Of the six patients with OS ≥20 months, four underwent surgery and one was treated with heavy-ion therapy (Table II). Thus, we examined patients who underwent surgery in addition to chemotherapy and found that 8/26 underwent

Table I. *Clinicopathological features of patients with BRAF V600E-mutated colorectal cancer (CRC) who were treated in our hospital.*

Age at diagnosis (mean±SD)		63.1±14.0
Sex	Male	17 (65.4%)
	Female	9 (34.6%)
Location of primary tumor	Right-sided	12 (46.2%)
	Left-sided	10 (38.4%)
	Rectum	4 (15.4%)
Histology	Well-differentiated	5 (19.1%)
	Moderately-differentiated	10 (38.4%)
	Poorly differentiated/mucinous	8 (30.8%)
	Unknown	3 (11.5%)
Metastatic sites	Liver	13 (50.0%)
	Lung	12 (46.2%)
	Peritoneum	12 (46.2%)
	Other	15 (57.7%)
Number of metastatic sites	1	12(46.2%)
	2	6 (23.1%)
	3	4 (15.4%)
	≥4	4 (15.4%)
Metastatic resection	Yes	8 (30.8%)
	No	18 (69.2%)
KRAS status	Wild	25 (96.2%)
	Mutation	1 (3.8%)
MSI status	MSS	21 (80.8%)
	MSI-high	3 (11.5%)
	Unknown	2 (7.7%)

SD, Standard deviation; MSI, microsatellite instability; MSS, microsatellite stable.

surgery for recurrent disease. The median OS in the surgery group was 20.4 months, whereas that in the non-surgery group was 10.1 months (HR=2.2, 95% CI=11.4-39.6, p=0.25).

The BEACON regimen was used in 4/8 cases who underwent surgery. These four patients had particularly favorable prognoses (Table III); the median OS with and without BEACON regimen was 25.1 and 11.9 months, respectively (HR=3.68, 95% CI=18.6-36.8, p=0.28).

Discussion

The *BRAF V600E* mutation is present in 5-21% of all CRC cases (4, 6-8). CRC with the *BRAF V600E* mutation has a predilection towards female sex, advancing age, right-sided colonic localization, poorly differentiated histology, and MSI-high phenotype (6, 9). The *V600E* mutation accounts

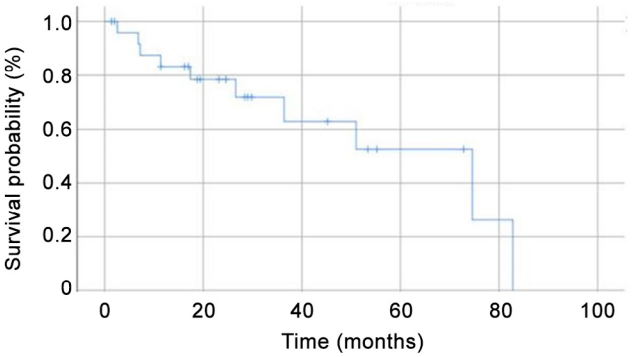

Figure 1. *Median overall survival (OS) of patients with colorectal cancer (CRC) and BRAF V600E mutation.*

for 80% of the *BRAF* mutations in CRC; this mutation may be biologically distinct from other infrequent *BRAF* mutations because cancer cells with the *V600E* mutation can grow without a functional RAS gene (7).

BRAF genes predominantly mutate independently of *RAS* genes, and coincident mutations in these genes rarely occur in CRC, with an incidence of 0.001% (10). However, in such cases, the presence of a *RAS* mutation is expected to reactivate the mitogen-activated protein kinase pathway, making the BEACON regimen less effective. Thus, the prognosis may be worse than that of CRC with only the *BRAF V600E* mutation.

In our study, the median OS of patients with CRC and the *BRAF V600E* mutation was 12.0 months, which was consistent with the previously reported OS of 11.0–18.8 months (5). Notably, this duration is significantly worse than the median OS of 24-30 months for all patients with unresectable advanced and recurrent CRC (2, 10-13).

Xu *et al.* (13) demonstrated that tumor differentiation, primary tumor resection, ECOG score, liver metastasis, and bone metastasis were prognostic factors for OS in patients with *BRAF V600E* mutations. Accordingly, the authors classified patients into three risk categories, with significantly different median OS: 39.3 months for low-risk, 18.2 months for intermediate-risk, and 10.7 months for high-risk patients. The median OS for low-risk patients was similar to that for all patients with unresectable advanced and recurrent CRC.

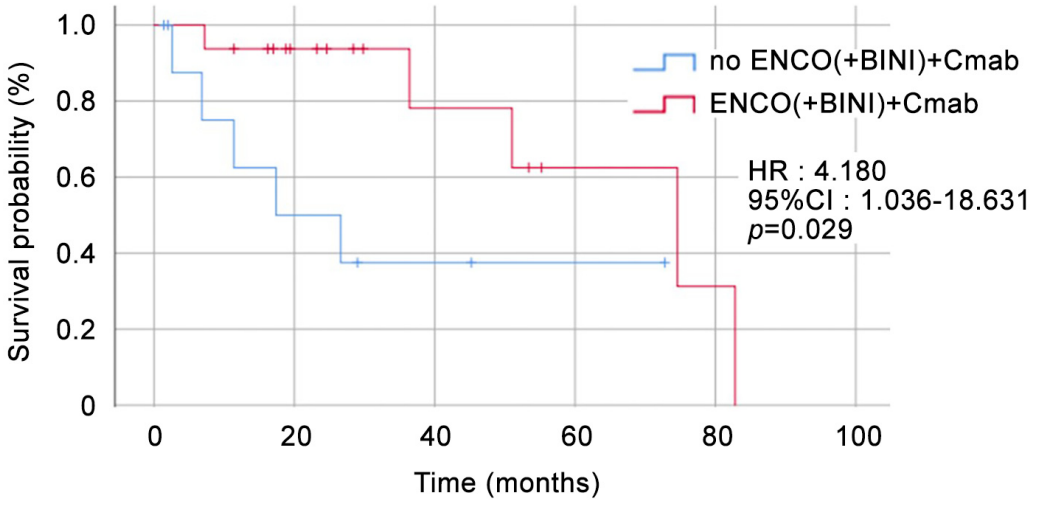

Figure 2. *Median overall survival (OS) of patients treated with or without the BEACON regimen.*

However, in the present study, tumor differentiation and liver metastasis showed no prognostic effect on OS; moreover, the primary tumor was respected in all but one patient.

The BEACON CRC trial investigated whether the BEACON regimen could prolong OS compared with standard therapy [cetuximab and FOLFIRI (folinic acid, fluorouracil, and irinotecan)] in patients with *BRAF V600E*-mutated metastatic CRC (4); the median OS in the BEACON regimen and control groups was 9.3 and 5.9 months, respectively (3, 4). In our study, the median OS with and without BEACON regimen was 13.3 and 7.2 months.

Notably, the prognosis in our study was better than that in previous reports. This may be explained by the start date used to define OS. Existing reports often use the BEACON regimen start date as the OS start date; however, the BEACON regimen may be used as either the first or second line of recurrence treatment. Thus, OS tended to be longer in this study than previously reported. Another possible reason is that our hospital implemented multi-disciplinary treatment (surgery and heavy-ion therapy). Of the six patients with the best prognosis, four underwent surgery and one received heavy-ion therapy (Table II). Although the OS between the surgery and non-surgery groups was not significantly different, the prognosis tended to be better in the surgery group. Furthermore, the BEACON regimen was used in half of the patients who underwent surgery, and these patients also tended to have a better prognosis.

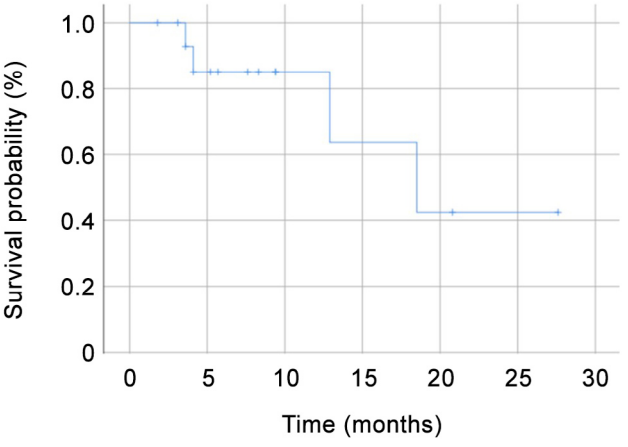

Figure 3. *Median progression-free survival (PFS) of patients treated with the BEACON regimen.*

Two recent retrospective studies showed that median OS was significantly prolonged in patients with *BRAF V600E* metastatic CRC when liver resection with curative intent was performed (14). In addition, a recent case-

Table II. *Patients with the best prognosis.*

	Age /Sex	OS (months)	Primary tumor location	Metastatic sites	Recurrence resection	BEACON regimen	Treatment (after recurrence)
1	68/F	37.9	Cecum	Peritoneum	Yes	No	Surgery (peritoneum) Chemotherapy
2	30/M	37.3	Descending	Lung, peritoneum	No	Yes	Chemotherapy
3	79/M	28.6	Rectum	Liver, lung	Yes	Yes	Surgery (liver) Chemotherapy
4	65/M	27.6	Ascending	Liver, lung, peritoneum	Yes	Yes	Surgery (liver, peritoneum) Chemotherapy Heavy particle therapy
5	40/F	25.5	Descending	Peritoneum	No	Yes	Chemotherapy
6	74/F	22.6	Descending	Lung, pleura	Yes	Yes	Surgery (lung) Chemotherapy

Table III. *Patients who underwent surgery.*

	Age /Sex	OS (months)	Primary tumor location	Metastatic sites	BEACON regimen	Treatment (after recurrence)
1	79/M	28.6	Rectum	Liver, lung	Yes	Surgery (liver, lung) Chemotherapy
2	65/M	27.6	Ascending	Liver, lung, peritoneum	Yes	Surgery (liver, peritoneum) Chemotherapy - Heavy particle therapy
3	74/F	22.6	Descending	Lung, pleura, adrenal glands	Yes	Surgery (lung) Chemotherapy
4	74/M	18.2	Sigmoid	Lung, local	Yes	Surgery (local) Chemotherapy
5	68/F	37.9	Cecum	Peritoneum	No	Surgery (peritoneum) Chemotherapy
6	66/F	14.5	Transverse	Brain	No	Surgery (brain)
7	59/M	9.2	Sigmoid	Testis, lung, lymph node, prostate, skin	No	Surgery (testicular) Chemotherapy
8	72/M	8.7	Transverse	Lymph node	No	Surgery (local, lymph node) Chemotherapy

matched study demonstrated that *BRAF* mutations did not increase the risk of subsequent relapse (15). In contrast, significantly shorter OS in patients with *BRAF V600E* mutations who underwent radical liver or lung resections have also been reported (16). The recurrence rate after liver resection may be as high as 93%, suggesting that chemotherapy should be considered even for resectable metastases (16, 17). No studies have reported on the outcomes of combined surgery and chemotherapy for recurrent disease. In our study, OS tended to be better in the recurrent resection group treated with BEACON during the perioperative period.

Study limitations. Firstly, this was a retrospective, single-center study with a small sample size. Secondly, the follow-up time was relatively short, even for advanced cancer cases. Additionally, some patients were transferred to other hospitals without follow-up. Lastly, some patients were transferred from other hospitals, and the details of their initial treatment were unclear. Despite these

limitations, these results suggest that combination therapy with chemotherapy may improve the prognosis of *BRAF V600E*-mutated metastatic CRC.

Conclusion

Our study underscores the challenging prognosis associated with *BRAF V600E*-mutated CRC. Notably, the BEACON regimen demonstrated significantly improved outcomes, emphasizing its potential as a promising therapeutic approach. Further studies considering the ongoing NEXUS trial (Observational currently ongoing study on the long term prognosis in A Multicenter Phase II Clinical Study Evaluating the Efficacy and Safety of Neoadjuvant and Adjuvant Chemotherapy with Encorafenib, Binimetinib Plus Cetuximab in Patients with Surgically Resectable BRAF V600E Mutant Colorectal Metastasis) are warranted.

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Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

Yukari Ono: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing - original draft. Kenta Iguchi: Writing - review & editing. Mamoru Uchiyama: Writing - review & editing. Masahiro Asari: Writing - review & editing. Koji Numata: Methodology; Writing - review & editing. Sho Sawazaki: Writing - review & editing. Aya Saito: Writing - review & editing. Manabu Shiozawa: Writing - review & editing.

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