TAS-102 plus bevacizumab as salvage treatment in colorectal cancer: A retrospective study

KEITA MATSUMOTO, RYOMA YOKOI, CHIKA MIZUTANI, RYUICHI ASAI, JESSE YU TAJIMA, MASAHIDE ENDO, YUJI HATANAKA, TAKESHI HORAGUCHI, MASAHIRO FUKADA, ITARU YASUFUKU, YUTA SATO, YOSHIHIRO TANAKA, KATSUTOSHI MURASE and NOBUHISA MATSUHASHI

Department of Gastroenterological Surgery, Graduate School of Medicine, Gifu University Hospital, Gifu University, Gifu, Gifu 501-1194, Japan

Received August 8, 2025; Accepted October 20, 2025

DOI: 10.3892/ol.2025.15387

Abstract. The current study aimed to evaluate the efficacy and safety of TAS-102 plus bevacizumab therapy as a salvage treatment for colorectal cancer, focusing on the differences between colon and rectal cancers. The present single-center retrospective study enrolled 101 patients treated with TAS-102 between October 2016 and December 2023 (median age, 67 years; 65 men and 36 women). The tumors included 16, 23 and 62 lesions in the right colon, left colon and rectum, respectively. The chemotherapy history included fluoropyrimidine (101 patients, 100%), oxaliplatin (95 patients, 94.1%), irinotecan (82 patients, 81.2%), anti-vascular endothelial growth factor antibody (92 patients, 91.1%) and anti-epidermal growth factor receptor antibody (41 patients, accounting for 87.2% of the RAS wild-type subgroup). The median duration of TAS-102 plus bevacizumab treatment was 184 days. A subsequent line of chemotherapy was administered in 66 patients (65.3%). The progression-free survival (PFS) time was 5.6 months, whereas the overall survival (OS) time was 14.2 months. Colon and rectal cancers exhibited a PFS of 4.0 and 6.9 months, and an OS of 11.0 and 17.6 months, respectively. The results of the present study suggested that TAS-102 combined with bevacizumab in subsequent treatment may have greater efficacy in rectal cancer than in colon cancer, possibly due to the lower frequency of liver metastases in rectal cancer. However, this finding is exploratory and requires further validation via larger prospective studies.

Correspondence to: Dr Keita Matsumoto, Department of Gastroenterological Surgery, Graduate School of Medicine, Gifu University Hospital, Gifu University, 1-1 Yanagito, Gifu, Gifu 501-1194, Japan
E-mail: 10b6.yncc@gmail.com

Abbreviations: CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FTD, trifluridine; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TPI, tipiracil; VEGF, vascular endothelial growth factor

Key words: CRC, colon cancer, rectal cancer, TAS-102 plus bevacizumab, survival

Introduction

Colorectal cancer (CRC) is one of the most prevalent malignancies worldwide, accounting for a significant proportion of cancer-related morbidity and mortality. According to global cancer statistics, CRC is the third most commonly diagnosed cancer and second leading cause of cancer-related deaths (1). Despite advancements in surgical techniques and early detection methods, many patients present with locally advanced or metastatic disease at diagnosis, necessitating systemic chemotherapy to improve outcomes.

For metastatic CRC (mCRC), systemic chemotherapy has been a cornerstone of treatment and is often combined with targeted therapies. The introduction of monoclonal antibodies, including bevacizumab, an anti-vascular endothelial growth factor (VEGF) agent, and epidermal growth factor receptor (EGFR) inhibitors (cetuximab and panitumumab), has significantly improved survival in specific patient subgroups. The combination of fluorouracil, leucovorin, oxaliplatin, and/or irinotecan (FOLFOX, FOLFIRI, or FOLFOXIRI) with targeted agents has effected a median overall survival (OS) >30 months in selected patients (2,3).

However, despite these advancements in CRC treatment, resistance and progression remain major challenges for later-line therapies. TAS-102, an effective treatment for previously treated mCRC, exerts its cytotoxic effects through trifluridine (FTD), which gets incorporated into DNA, thereby disrupting its replication (4). Additionally, preclinical CRC models have demonstrated that adding bevacizumab enhances phosphorylated FTD levels, supporting the rationale for this combination in mCRC (5).

In 2023, the results of the SUNLIGHT trial, a phase III study, showed a significantly better OS for TAS-102 plus bevacizumab compared with TAS-102 alone [10.8 vs. 7.5 months; hazard ratio (HR)=0.61, P<0.001] (6).

Based on the results of the phase 1/2 C-TASK FORCE trial (7) and after undergoing Institutional Review Board approval, we have been actively introducing and administering TAS-102 plus bevacizumab therapy as a backward treatment since October 2016. The results of the SUNLIGHT study were used as the basis for the present retrospective analysis of the results and validity of TAS-102 plus bevacizumab therapy.

Patients and methods

Patients. This retrospective observational study was approved by the Ethics Committee of Gifu University Graduate School of Medicine (Institutional Review Board approval no. 2024-144) and was conducted in accordance with the national guidelines for human research. The requirement for informed consent was waived by the Ethics Committee due to the retrospective nature of the study.

This study analyzed data from electronic medical records at our hospital. The study included patients with mCRC resistant to at least one of the following: Fluoropyrimidine, irinotecan, oxaliplatin, anti-VEGF therapy, and anti-EGFR therapy (for KRAS wild-type tumors). These patients were administered TAS-102 at our outpatient chemotherapy clinic between October 2016 and December 2023. The median age of the patients was 67 years (range, 24-86 years).

KRAS/NRAS mutation status was analyzed at our institution using a PCR-SSO (sequence-specific oligonucleotide) method routinely performed in the clinical diagnostic laboratory, covering exon 2 (codons 12, 13), exon 3 (codons 59, 61), and exon 4 (codons 117, 146). Primer sequences are proprietary and not disclosed, but the assay is standardized and validated in our institutional diagnostic setting.

Chemotherapy. Patients were administered TAS-102 (35 mg/m^2 body surface area) orally twice daily on days 1-5 and 8-12 of a 28-day cycle, in combination with bevacizumab (5 mg/kg, infused intravenously over 30 min every 2 weeks).

For severe adverse events (grade 3-4 neutropenia), a 10-mg/day dose reduction was applied in subsequent cycles without re-escalation. Treatment was suspended in cases of grade 3-4 neutropenia, thrombocytopenia, febrile neutropenia, elevated bilirubin (>3.0 mg/dl), aspartate aminotransferase/alanine aminotransferase level >150 U/l, creatinine level >1.5 mg/dl, or grade 3-4 non-hematologic toxicities. After resolution, treatment was resumed at a lower TAS-102 dose of 10 mg/day.

Statistical analysis. Statistical analyses were performed using JMP Student Edition version 18 (SAS Institute Inc., Cary, NC, USA). The significance level (α) was set at 0.05 (two-sided). Categorical variables were compared using the χ^2 test (for frequencies), and continuous variables, such as age, were compared using the Wilcoxon rank-sum test. Survival curves were analyzed using both the log-rank test and the Gehan-Breslow-Wilcoxon test; both were included because the log-rank test is more sensitive to proportional hazards, whereas the Gehan-Breslow-Wilcoxon test places more weight on early differences. Median survival times with 95% confidence intervals were calculated, and hazard ratios were estimated using the Cox proportional hazards model. Both univariable and multivariable analyses were performed.

Results

Patient backgrounds. A total of 101 patients with CRC (65 men and 36 women; median age, 67 years) were administered TAS-102 plus bevacizumab during the study period (Table I). Approximately 60% of the patients had a primary rectal tumor,

Table I. Subject and patient background.

Characteristic	Value
Age, years[a]	67 (24-86)
Sex	
Male	65 (64.4%)
Female	36 (35.6%)
Primary diagnosis	
Right-sided colon	16 (15.8%)
Left-sided colon	23 (22.8%)
Rectum	62 (61.4%)
Time from diagnosis of first metastasis to treatment	
<18 months	38 (37.6%)
≥18 months	63 (62.4%)
Number of metastatic sites	
1	55 (54.5%)
2	37 (36.6%)
3	7 (6.9%)
4	2 (2.0%)
RAS status	
Wild type	47 (46.5%)
Mutation	52 (51.5%)
Unknown	2 (2.0%)
BRAF status	
Wild type	66 (65.3%)
Mutation	2 (2.0%)
Unknown	33 (32.7%)
MMR and MSI status	
MMR deficient and high MSI	2 (2.0%)
MMR proficient and stable or low MSI	72 (71.3%)
Unknown	27 (26.7%)
Number of previous treatment regimens	
1	17 (16.8%)
2	63 (62.4%)
≥3	21 (20.8%)
Subsequent therapy	
Yes	66 (65.3%)
Regorafenib	54 (81.8%)[b]
No	35 (34.7%)
Drugs used in the previous treatment regimen	
Fluoropyrimidine	101 (100.0%)
Irinotecan	82 (81.2%)
Oxaliplatin	95 (94.1%)
Anti-VEGF monoclonal antibody	92 (91.1%)
Anti-EGFR monoclonal antibody	41/47 (87.2%)[c]

[a]Data are presented as median (range). All other data are presented as n (%). [b]Percentage of patients who received regorafenib among those with subsequent therapy. [c]Percentage of RAS wild type patients. MMR, mismatch repair; MSI, microsatellite instability; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor.

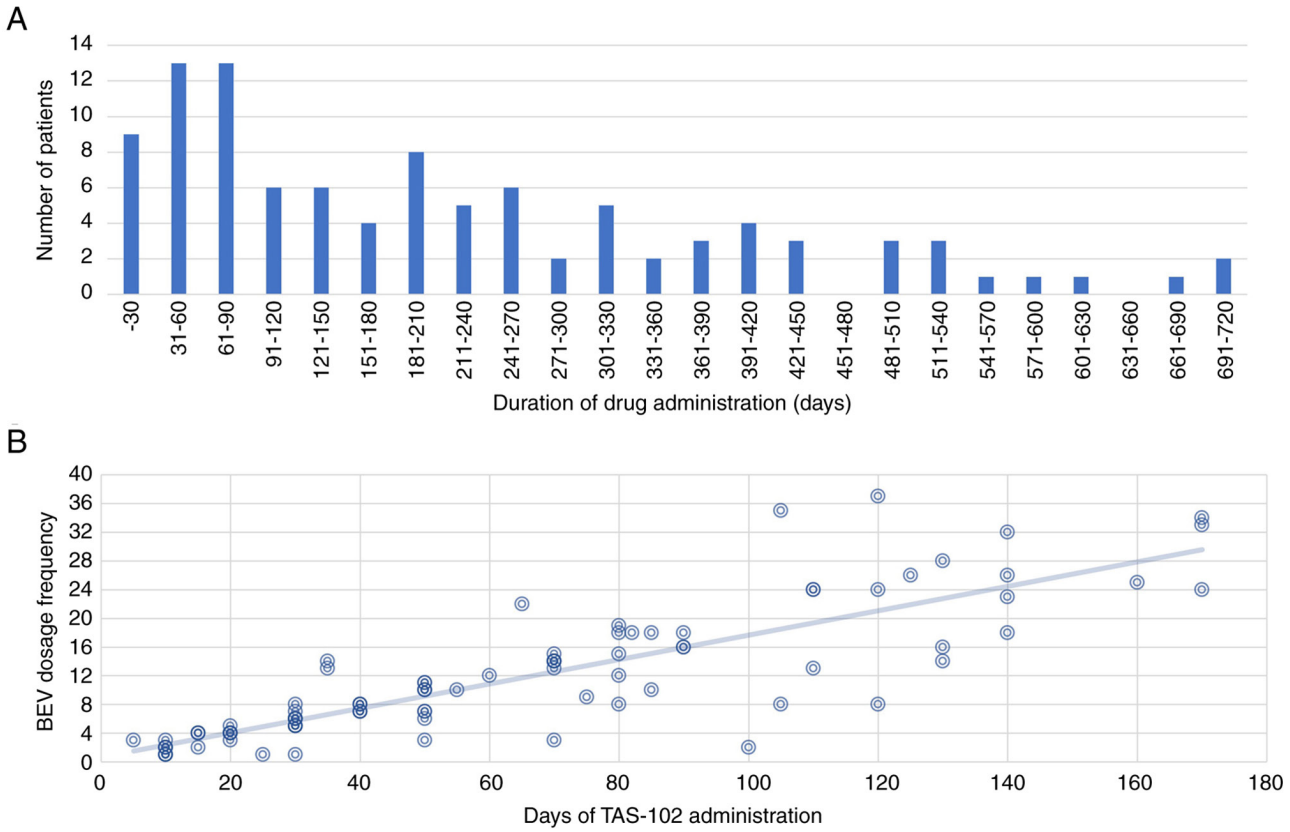

Figure 1. (A) Distribution of TAS-102 plus BEV treatment duration. The median duration was 184 days, with most patients discontinuing the treatment within 9 months and the longest treatment duration lasting nearly 2 years. (B) Relationship between TAS-102 treatment days and BEV administration, with a positive correlation between the two parameters. Generally, patients with a longer TAS-102 treatment course underwent more BEV cycles. BEV, bevacizumab.

and 90% had ≤2 metastatic organs. The metastatic organs included 48 livers, 47 lungs, 25 lymph nodes, 11 local, and 6 others. Approximately 60% and <20% of the patients were administered the study treatment as third- and second-line therapies, respectively. Wild-type RAS was present in approximately half of the patients, and mutant BRAF and low microsatellite instability (MSI) were observed in two patients each. The chemotherapy history included fluoropyrimidine (101 patients, 100%), oxaliplatin (95 patients, 94.1%), irinotecan (82 patients, 81.2%), anti-VEGF antibody (92 patients, 91.1%), and anti-EGFR antibody (41 patients, accounting for 87.2% of the RAS wild-type subgroup). Subsequent therapy was administered in 66 patients (65.3%), and regorafenib was used in 54 patients, accounting for 81.8% of those who received subsequent therapy. The median duration of TAS-102 plus bevacizumab treatment was 184 days (Fig. 1A). The longest treatment duration was approximately 2 years, but most cases lasted for 9 months. Although most patients were administered the same regimen, those who skipped FTD/tipiracil (TPI) and received more bevacizumab and those who skipped bevacizumab and received more FTD/TPI were approximately the same (Fig. 1B). The most frequent grade ≥3 adverse event was neutropenia [25 (24.8%) grade 3 and 18 (17.8%) grade 4], followed by leukopenia [25 (24.8%)], anemia [16 (15.8%)], and thrombocytopenia [6 (5.9%)]. Among non-hematological toxicities, grade 3 hypertension [12 (11.9%)], proteinuria [8 (7.9%)], and diarrhea [6 (5.9%)] were observed. Notably, no grade 5 treatment-related adverse events occurred (Table II).

OS and progression-free survival (PFS). Overall, the median PFS and OS were 5.6 and 14.2 months, respectively (Fig. 2). Regarding the primary tumor site, the median PFS was 4.0 months for colon cancer and 6.9 months for rectal cancer, and the median OS values were 11.0 and 17.6 months, respectively. Baseline characteristics of patients with colon and rectal cancers are summarized in Table III. Concerning survival curve comparison, the Gehan-Breslow-Wilcoxon test showed a statistically significant difference in favor of rectal cancer (PFS: P=0.035; OS: P=0.025), whereas the log-rank test did not show a statistically significant difference (PFS: P=0.54; OS: P=0.65). In the multivariable Cox regression analysis adjusting for RAS mutation, primary site, anti-VEGF antibody administration, number of treatment lines, and liver metastasis, primary site was not identified as an independent prognostic factor for either PFS or OS (Table IV).

Comparisons based on the presence or absence of RAS mutations, history of anti-VEGF antibody administration, and treatment line showed numerically longer OS in patients without prior anti-VEGF antibody administration and a trend toward longer PFS in the second-line treatment group; however, none of these differences were statistically significant in Gehan-Breslow-Wilcoxon, log-rank, or Cox analyses (Fig. 3; Table IV). In addition, comparisons according to the presence or absence of liver metastasis are shown in Fig. 4, and the corresponding patient characteristics and outcomes are summarized in Table V.

Table II. Treatment-related adverse events of grade ≥3.

Adverse event	Grade 3, n (%)	Grade 4, n (%)	Total, n (%)
Neutropenia	25 (24.8)	18 (17.8)	43 (42.6)
Leukopenia	25 (24.8)	0	25 (24.8)
Anemia	16 (15.8)	0	16 (15.8)
Thrombocytopenia	6 (5.9)	0	6 (5.9)
Hypertension	12 (11.9)	0	12 (11.9)
Proteinuria	8 (7.9)	0	8 (7.9)
Diarrhea	6 (5.9)	0	6 (5.9)

Data are presented as n (%).

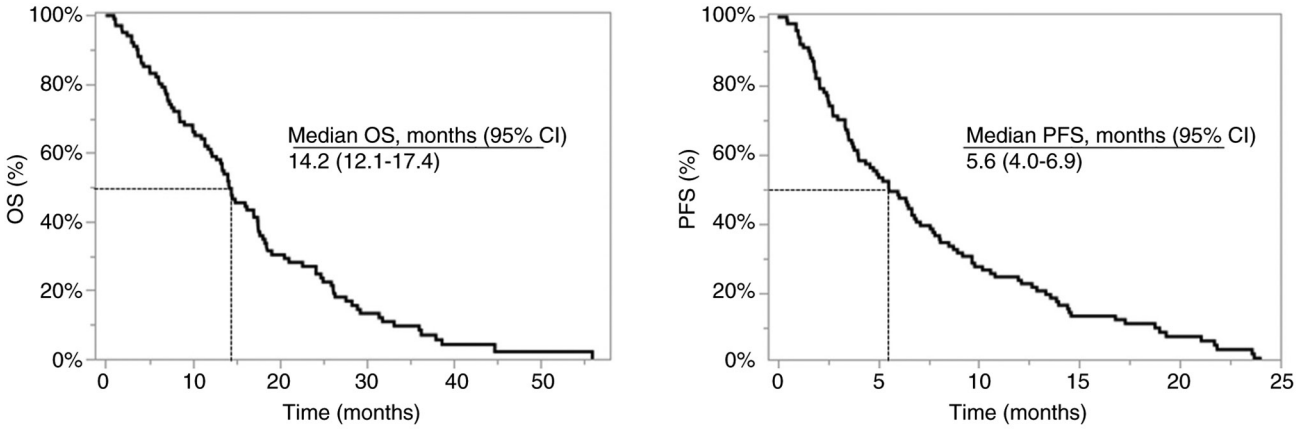

Figure 2. Kaplan-Meier curves of OS and PFS in 101 patients with colorectal cancer treated with TAS-102 plus bevacizumab. The median OS was 14.2 months (95% CI, 12.1-17.4), and the median PFS was 5.6 months (95% CI, 4.0-6.9). OS, overall survival; PFS, progression-free survival; CI, confidence interval.

Discussion

Combination therapy with TAS-102 and bevacizumab has demonstrated improved survival outcomes compared to TAS-102 monotherapy in patients with mCRC. Across multiple studies, the median PFS for this combination ranged from 4.29 to 5.6 months, whereas the median OS spanned 9.3 to 14.4 months (4,5,8-11) (Table VI).

Although TAS-102 plus bevacizumab therapy has shown promising results in mCRC, to date, no study has specifically analyzed or reported outcomes for patients with rectal cancer separately from those for CRC as a whole. All existing studies have combined data for CRC (including both colon and rectal cancers) without a subgroup analysis for rectal cancer. This lack of differentiation represents a significant gap in current research and limits the ability to assess potential differences in treatment efficacy or safety profiles between rectal and colon cancers.

Although both colon and rectal cancers are classified as CRC, they differ in prognosis, recurrence patterns, and treatment responses. Several studies have investigated the survival rates and prognostic factors of these two malignancies, revealing key differences in their outcomes.

Historically, colon cancer has demonstrated a mildly better prognosis than rectal cancer, particularly in the early stages. Population-based studies indicate that five-year survival rates for colon cancer have improved from 51-57% to 62-66%, whereas rectal cancer survival has increased from 44-51% to 59-65% (12-14). These improvements are partly attributable to advances in systemic therapy for colon cancer and preoperative chemoradiotherapy and surgical techniques for rectal cancer (14-16). Thus, the survival gap between colon and rectal cancers has narrowed over time.

Additionally, survival rates differ with disease recurrence. Colon cancer has a high propensity for liver metastasis, whereas rectal cancer more frequently metastasizes to the lungs, and local recurrence remains a major challenge (17-20). These distinct metastatic patterns may partly explain the survival differences observed in our cohort. Nevertheless, the effect of primary tumor site on prognosis in patients with refractory mCRC should be considered hypothesis-generating, and confirmation through larger prospective datasets or pooled analyses is warranted.

In our study, the comparison between rectal and colon cancers revealed no significant differences in age, sex, RAS or BRAF mutation status, MSI status, number of previous treatment regimens, subsequent therapies, or the number of metastatic sites. However, similar to the results of previous surveys, liver metastases were less common in patients with rectal cancer than in those with colon cancer, whereas lung metastases and local recurrence were more common (Table III).

Table III. Comparison of patient backgrounds in the colon and rectum.

Characteristic	Colon (n=39)	Rectum (n=62)	P-value
Age, years[a]	64.7±13.8	65.6±10.7	0.7340
Male sex	22 (56.4%)	43 (69.4%)	0.1860
RAS mutation	20 (51.3%)	33 (54.1%)	0.8490
BRAF mutation	2 (8.0%)	0 (0.0%)	0.1463[b]
MSI high	1 (3.6%)	1 (2.2%)	>0.999[b]
Number of previous treatment regimens			0.3718
1	4	13	
2	26	37	
≥3	9	12	
Subsequent therapy			0.2858[c]
Yes	23	43	
Regorafenib	19	35	
No	16	19	
Number of metastatic sites			0.1662
1	21	34	
2	12	25	
≥3	6	3	
Sites of metastasis[d]			0.0103[b]
Liver	28	20	
Lung	13	34	
Lymph node	7	18	
Local	2	9	
Bone	0	1	
Others	2	3	

[a]Age is presented as mean ± SD. Other data are presented as n or n (%). [b]P-values for BRAF mutation, MSI high and sites of metastasis were calculated using Fisher's exact test due to small expected cell counts. [c]Comparison of yes and no. [d]Overlapping responses included. MSI, microsatellite instability.

Table IV. Multivariable Cox proportional hazards analysis.

	OS			PFS		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
Ras status (wild type vs. mutation)	0.62	0.34-1.65	0.38	0.56	0.31-1.29	0.37
Primary site (rectum vs. colon)	1.20	0.65-1.78	0.65	1.18	0.73-1.82	0.54
Anti-VEGF therapy (yes vs. no)	1.29	0.61-2.98	0.51	1.46	0.67-3.54	0.35
Liver metastasis (yes vs. no)	1.08	0.71-2.08	0.75	1.36	0.87-2.12	0.18
Treatment line number	1.02	0.64-1.47	0.95	0.92	0.67-1.37	0.82

HR, hazard ratio; CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Various studies have also reported prognostic differences based on metastatic and recurrent sites in CRC. For instance, some studies have suggested that solitary lung metastases are associated with a better prognosis (21-23); however, these analyses often included cases in which the metastases were surgically resected. In our study, likely owing to the small sample size, no significant prognostic differences were observed among cases with solitary metastases based on the metastatic site.

The present study is the first to evaluate the differences in prognosis after salvage therapy. Contrary to previous reports, most patients receiving the salvage line did not have resectable distant metastases. In our analysis, patients with liver metastases tended to have poorer OS and PFS compared with those

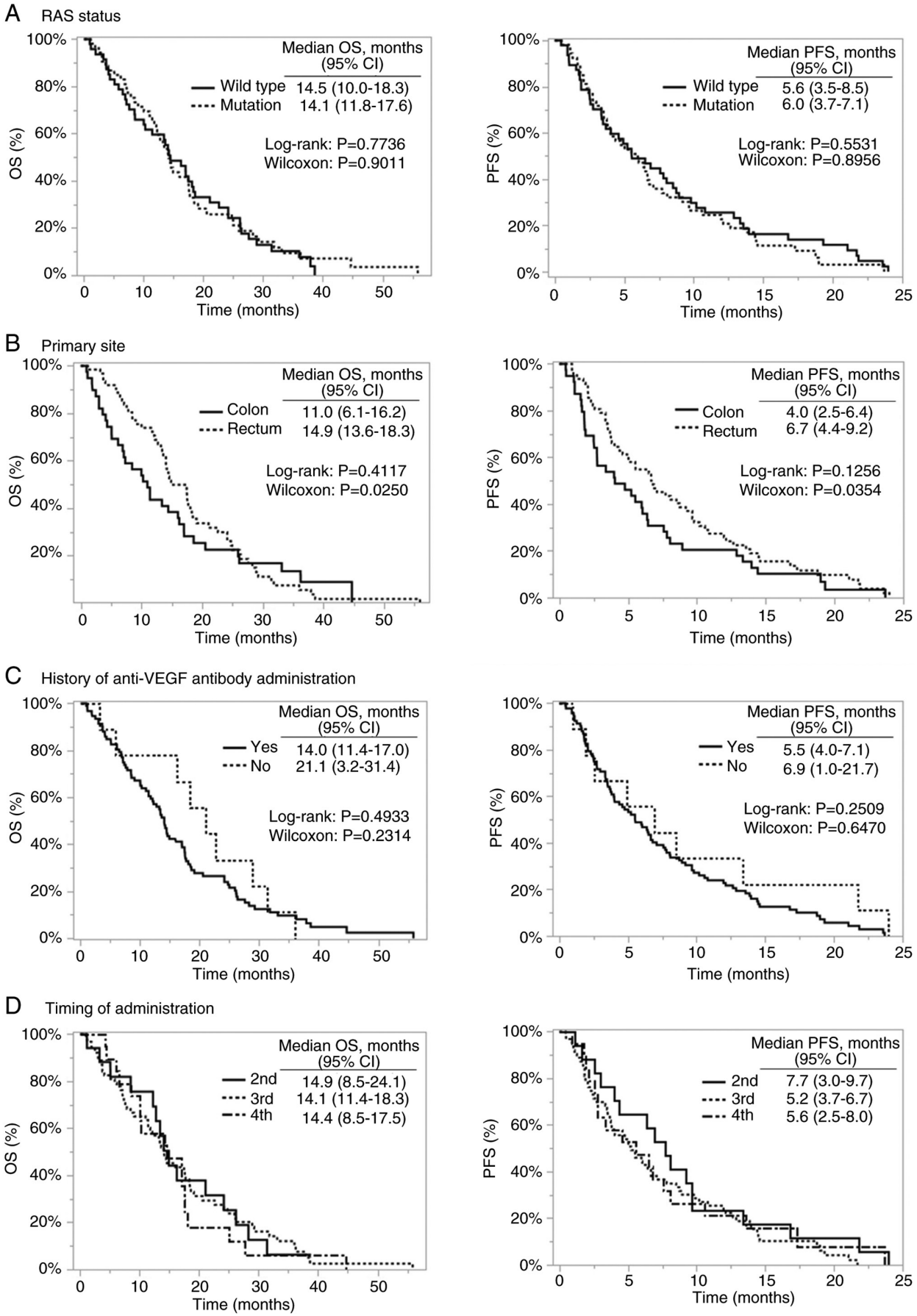

Figure 3. Comparison of OS and PFS according to (A) RAS status, (B) colon or rectal cancer, (C) history of anti-VEGF antibody administration and (D) timing of treatment administration. Median survival times with 95% CIs and hazard ratios were estimated using the Cox proportional hazards model (univariable analysis). Survival curves were compared using the log-rank and Gehan-Breslow-Wilcoxon tests. OS, overall survival; PFS, progression-free survival; VEGF, vascular endothelial growth factor; CI, confidence interval.

Table V. Comparison with and without liver metastasis.

Characteristic	With liver metastasis (n=48)	Without liver metastasis (n=53)	P-value
Age, years[a]	64.0±13.3	66.5±10.6	0.3097
Male sex	34 (70.8%)	31 (58.5%)	0.1959
Primary diagnosis			0.0001
Colon	28 (58.3%)	11 (20.8%)	
Rectum	20 (41.7%)	42 (79.2%)	
RAS mutation	24 (50.0%)	30 (56.6%)	0.5063
BRAF mutation	2 (4.2%)	0 (0.0%)	0.2234[b]
MSI high	2 (4.2%)	0 (0.0%)	0.2234[b]
Number of previous treatment regimens			0.0211
1	3	14	
2	35	28	
≥3	10	11	
Subsequent therapy			0.2701[c]
Yes	34	32	
Regorafenib	29	25	
No	14	21	
Number of metastatic sites			0.1534[b]
1	23	32	
2	14	19	
≥3	7	2	

[a]Age is presented as mean ± SD. Other data are presented as n or n (%). [b]P-values for BRAF mutation, MSI high and sites of metastasis were calculated using Fisher's exact test due to small expected cell counts. [c]Comparison of yes and no. MSI, microsatellite instability.

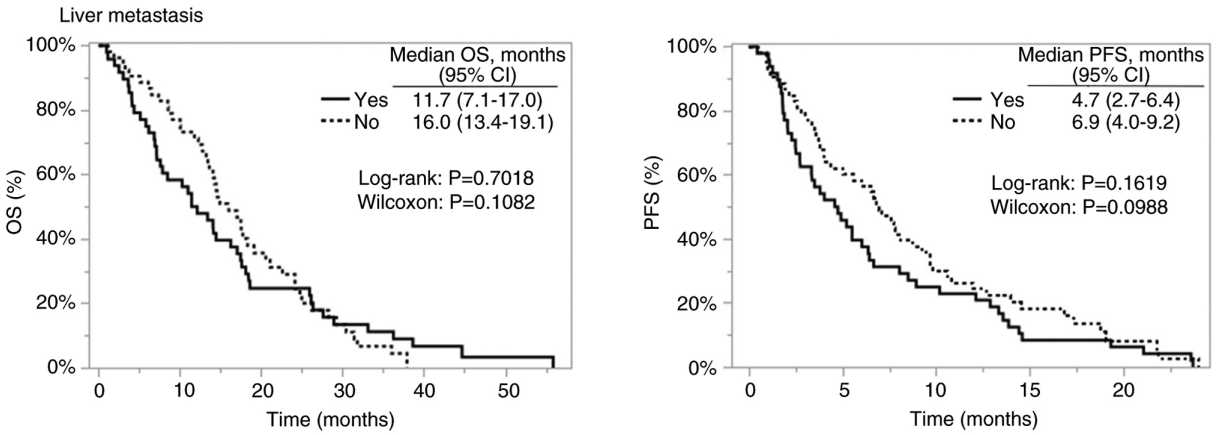

Figure 4. Comparison of OS and PFS according to liver metastasis status. Median survival times with 95% CIs and hazard ratios were estimated using the Cox proportional hazards model (univariable analysis). Survival curves were compared using the log-rank and Gehan-Breslow-Wilcoxon tests. OS, overall survival; PFS, progression-free survival; CI, confidence interval.

without metastases (Fig. 4). Comparison of patient characteristics based on liver metastasis status revealed that colon cancer was significantly more frequent and the proportion of patients receiving second-line treatment was significantly higher in patients with liver metastases. Although the number of metastatic sites in three or more organs was numerically higher in the liver metastasis group, the difference was not statistically significant (Table VI). Notably, although the proportion of patients receiving second-line treatment with a good treatment response was higher in the liver metastasis group, the OS and PFS still tended to be poorer in patients with liver metastasis.

When comparing rectal and colon cancers, survival curve analysis showed a significant difference in favor of rectal cancer with the Gehan-Breslow-Wilcoxon test but no significant difference with the log-rank test. Moreover, primary tumor site was not identified as an independent prognostic factor in the multivariable Cox regression model. This suggests that patients with rectal cancer may experience better outcomes during the early

Table VI. Treatment outcomes of TAS-102 plus bevacizumab therapy.

First author, year	Median OS, months (95% CI)	Median PFS, months (95% CI)	(Refs.)
Satake *et al*, 2020	10.86	4.29	(5)
Chida *et al*, 2021	11.5 (9.9-13.9)	4.4 (3.7-5.4)	(8)
Fujii *et al*, 2020	14.4	5.6 (TTF)	(9)
Joarder *et al*, 2025	10.9 (8.9-12.8)	4.4 (3.1-5.7)	(10)
Liu *et al*, 2021	10.41 (8.40-12.89)	4.35 (3.05-6.20)	(11)
Martínez-Lago *et al*, 2022	9.3 (6.6-12.1)	4.3 (3.4-5.1)	(4)
Present study, 2025	14.2 (12.1-17.4)	5.6 (4.0-6.9)	-

OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.

Table VII. Comparison of patient backgrounds in the SUNLIGHT trial and this study.

Characteristic	SUNLIGHT trial (n=246)	Our cases (n=101)
Age, years[a]	62 (20-84)	67 (24-86)
Male sex	122 (49.6%)	65 (64.4%)
Primary diagnosis		
Colon	180 (73.2%)	39 (38.6%)
Rectum	66 (26.8%)	62 (61.4%)
Number of metastatic sites		
1 or 2	152 (61.8%)	92 (91.1%)
≥3	94 (38.2%)	9 (8.9%)
RAS status		
Wild type	75 (30.5%)	47 (46.5%)
Mutation	171 (69.5%)	52 (51.5%)
Unknown	0 (0.0%)	2 (2.0%)
Number of previous treatment regimens		
1	11 (4.5%)	17 (16.8%)
2	229 (93.1%)	63 (62.4%)
≥3	6 (2.4%)	21 (20.8%)
Drugs used in the previous treatment regimen		
Fluoropyrimidine	246 (100.0%)	101(100.0%)
Irinotecan	246 (100.0%)	82 (81.2%)
Oxaliplatin	241 (98.0%)	95 (94.1%)
Anti-VEGF monoclonal antibody	178 (72.4%)	92 (91.1%)
Anti-EGFR monoclonal antibody[b]	67/71 (94.4%)	41/47 (87.2%)

[a]Data are presented as the median (range). Other data are presented as n (%). [b]Percentage of RAS wild type patients. VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor.

phase of treatment; however, these differences diminish over time and may be confounded by other clinical factors.

Taken together, these findings suggest that liver metastasis is associated with a poor prognosis in salvage therapy, and the lower frequency of liver metastases in rectal cancer may partially explain the relatively favorable outcomes in this subgroup. However, these results should be interpreted with caution. The observed survival advantage in rectal cancer is hypothesis-generating, and thus confirmation is required via larger prospective datasets or pooled analyses.

The proportion of elderly patients in the present study was higher than that reported in the SUNLIGHT study. As a result, irinotecan was administered less frequently, with a trend towards the use of the less invasive TAS-102 plus bevacizumab regimen as second-line therapy. Similarly, the rate of anti-EGFR antibody administration was low, with a trend towards a higher rate of bevacizumab combination therapy (Table VII). In addition, the high proportion of patients with rectal cancer may have resulted in a relatively good prognosis. Although the patient backgrounds differed from those in the SUNLIGHT

study and other previous reports, similar results were obtained in the present study, indicating the efficacy of TAS-102 plus bevacizumab therapy across different patient populations.

In conclusion, in the present study, TAS-102 combined with bevacizumab in subsequent treatments showed greater efficacy against rectal cancer than against colon cancer. This may be because rectal cancer is associated with fewer liver metastases than colon cancer. However, these results should be interpreted with caution.

The limitations of this study include its retrospective single-center design, potential selection bias, relatively small sample size, and insufficient statistical power for subgroup analyses. In particular, the lack of significant differences in many subgroup comparisons is likely due to the limited number of patients in each subgroup. Therefore, the observed survival advantage for rectal cancer should be considered hypothesis-generating, and further investigations using larger prospective or pooled datasets are required to validate these findings.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

KMa and NM conceptualized the study, performed data analysis, wrote the original draft and reviewed and edited the manuscript. RY, CM, RA, JYT, ME, YH, TH, MF, IY, YS, YT and KMu contributed to data acquisition, clinical supervision, and interpretation of the data. KMa and NM confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval and waiver of informed consent were obtained from the Ethics Committee of Gifu University Graduate School of Medicine (approval no. 2024-144).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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