

Original Article

Targeted Therapy in Patients with Metastatic Colorectal Cancer Who Underwent Curative Intervention: A Single-center Retrospective Study

Hsin-Ping Tseng¹

Chao-Wen Hsu^{1,2}

Jiu-Ho Wang¹

Yu-Hsun Chen¹

Ming-Hung Lee¹

Ping-Teng Chu¹

Chih-Chien Wu^{1,2}

¹Division of Colorectal Surgery, Department of Surgery, Kaohsiung Veterans General Hospital, Kaohsiung,

²School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

Key Words

Colorectal neoplasms;

Neoplasm metastasis;

Molecular targeted therapy;

Overall survival;

Progression-free survival

Purpose. To evaluate whether adding targeted therapy to chemotherapy improves survival outcomes in patients with resectable metastatic colorectal cancer who have undergone curative-intent resection.

Methods. We retrospectively analyzed 95 patients with metastatic colorectal cancer who were either initially resectable or converted from initially unresectable to resectable status. These patients were diagnosed at Kaohsiung Veterans General Hospital between 2016 and 2020. All underwent curative-intent treatment for both primary and metastatic lesions, and received systemic chemotherapy with or without targeted therapy. Clinical characteristics and treatment patterns were compared between the groups. The primary outcomes were overall survival and disease-free survival.

Results. Of the 95 patients, 80 (84.2%) received chemotherapy plus targeted therapy, and 15 (15.8%) received chemotherapy alone. Patients in the chemotherapy plus targeted therapy group were significantly younger and more likely to receive infusional chemotherapy regimens. Median overall survival was 40.9 months for the chemotherapy plus targeted therapy group and 34.2 months for the chemotherapy-only group ($p = 0.306$). Median disease-free survival was 11.5 vs. 8.8 months, respectively ($p = 0.238$). No statistically significant differences in survival rates were observed.

Conclusions. Among patients with resectable metastatic colorectal cancer who underwent curative-intent resection, the addition of targeted therapy to chemotherapy did not significantly improve survival outcomes. Although targeted agents are effective in advanced, unresectable disease, their benefit in the perioperative setting for resectable metastatic colorectal cancer remains uncertain.

[J Soc Colon Rectal Surgeon (Taiwan) 2026;37:221-233]

Colorectal cancer (CRC) is the third most common cancer worldwide,¹ with a significant proportion of patients presenting at advanced stages and

facing poor prognoses. For patients with metastatic colorectal cancer (mCRC), systemic chemotherapy remains the standard of care. In recent years, targeted

Received: June 24, 2025.

Accepted: August 21, 2025.

Correspondence to: Dr. Chih-Chien Wu, Division of Colon and Rectal Surgery, Department of Surgery, Kaohsiung Veterans General Hospital, No. 386, Ta-Chung 1st Rd., Kaohsiung, Taiwan. Tel: 886-7-342-2121 ext. 73022; Fax: 886-7-342-2288; E-mail: s19101080@gm.ym.edu.tw

therapies, such as vascular endothelial growth factor (VEGF) inhibitors and epidermal growth factor receptor (EGFR) inhibitors, have been approved for use in combination with chemotherapy. Notably, anti-EGFR agents are recommended only for patients with tumors harboring wild-type *KRAS* mutations.^{2,3}

In selected patients with resectable mCRC, surgical resection, either synchronous or staged colectomy with metastasectomy, has become one of the mainstay therapeutic strategies.⁴⁻⁷ However, the role of perioperative systemic therapy, particularly the addition of targeted agents, remains uncertain. Some studies have demonstrated that neoadjuvant chemotherapy combined with agents such as bevacizumab or cetuximab can improve tumor response and survival in patients with initially unresectable mCRC.⁸⁻¹⁰ Conversely, the recent EPOC trial reported that adding cetuximab to perioperative chemotherapy was associated with worse progression-free survival in patients with resectable colorectal liver metastases.¹¹ Given these conflicting findings, the benefit of incorporating targeted therapy into perioperative treatment for resectable mCRC remains unclear. In clinical practice, some patients receive systemic therapy, including chemotherapy, with or without targeted agents, either before or after surgery. To address this uncertainty, we conducted a retrospective study to evaluate whether the addition of targeted therapy to chemotherapy, regardless of the timing (preoperative and/or postoperative), was associated with improved overall survival (OS) and disease-free survival (DFS) in patients with resectable mCRC.

Materials and Methods

Study design and patient selection

We conducted a retrospective cohort study using the Cancer Registry Database of Kaohsiung Veterans General Hospital (KSVGH), a tertiary referral center in southern Taiwan. Patients diagnosed with mCRC who underwent primary tumor resection between January 2016 and December 2020 were identified for the initial screening (n = 244).

Patients were excluded if they:

- Did not undergo treatment for metastatic lesions (i.e., no metastasectomy or local therapy) (n = 123)
- Did not receive any systemic therapy after diagnosis (n = 5)
- Had synchronous colorectal primary tumors (n = 10)
- Were lost to follow-up or followed up at other institutions (n = 11)

After applying these exclusion criteria, 95 adult patients (aged ≥ 18 years) were included in the final analysis. All included patients had histologically confirmed colorectal adenocarcinoma and received curative-intent treatment for both primary and metastatic lesions, including surgical resection and/or local therapies such as tumor ablation and arterially directed embolic therapy (e.g., transarterial chemoembolization [TACE] and hepatic transarterial radioembolization with Yttrium-90 (Y-90) microspheres). All patients also received systemic therapy and chemotherapy with or without targeted agents, administered either before or after surgery. Conversion was defined as achieving resectable status and undergoing curative-intent treatment after systemic therapy in patients with initially unresectable metastatic colorectal cancer.

Data collection and outcome measures

Baseline demographic and clinical data were collected from the medical records and cancer registry database of Kaohsiung Veterans General Hospital. The following variables were extracted:

- Tumor characteristics: Year of diagnosis, primary tumor location, histological subtype, and tumor differentiation
- Molecular status: All-RAS mutation status
- Treatment details: Chemotherapy regimen, use of targeted therapy, and type of treatment for metastatic lesions

The primary outcome was OS, defined as the time from the initial diagnosis of mCRC to death from any cause or the last follow-up. The secondary outcome was DFS, defined as the time from the completion of

curative-intent treatment (i.e., resection or local therapy for both primary and metastatic tumors) to the earliest occurrence of disease recurrence (based on imaging studies such as CT, MRI, or PET/CT), death, or last follow-up, whichever occurred first.

All patients were followed until December 31, 2023, or until death.

Statistical analysis

Descriptive statistics were used to compare the baseline characteristics between the chemotherapy-only and chemotherapy plus targeted therapy groups. Categorical variables were analyzed using Fisher's exact test or Pearson's Chi-square test. Continuous variables were compared using either the independent samples t-test or the Mann-Whitney U test, depending on the data distribution.

OS and DFS were estimated using the Kaplan-Meier method, and survival curves were compared using the log-rank test.

All statistical analyses were performed using the IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). Statistical significance was set at a two-tailed p -value < 0.05 .

Results

Patient characteristics

A total of 95 patients with resectable mCRC were included in this study; 80 (84.2%) received chemotherapy plus targeted therapy (CT + TT group) and 15 (15.8%) received chemotherapy alone (CT only group). The median follow-up duration was 38.8 months (range, 7.1-92.0 months).

Patients in the CT + TT group were significantly younger than those in the CT-only group (mean age: 57.8 vs. 70.7 years, $p < 0.001$). There were no significant differences between the groups in terms of sex distribution ($p = 0.578$), history of smoking ($p = 0.870$), alcohol consumption ($p = 0.501$), or betel nut use ($p = 0.790$). The ECOG performance status was similar across the groups ($p = 0.292$).

Tumor features and molecular profile

No statistically significant differences were observed in tumor histology ($p = 0.239$) or tumor differentiation ($p = 0.620$). The all-RAS status, excluding unknowns, did not differ significantly ($p = 1.000$). Regarding tumor location, there was a borderline trend toward more right-sided tumors in the CT-only group ($p = 0.054$).

A significant difference was observed based on the year of diagnosis: patients diagnosed between 2018 and 2020 were more likely to receive CT + TT compared to those diagnosed between 2016 and 2017 ($p = 0.004$).

There was also a significant difference in the distribution of metastatic sites between groups ($\chi^2 = 10.660$, $p = 0.014$). Liver-only metastases were the most common in both groups. Patients with lung-only metastases were more likely to receive chemotherapy alone, while those with multiple or single-site metastases were more likely to receive combination therapy.

The clinical characteristics are listed in Table 1 and Table 2.

Treatment characteristics

The proportion of patients receiving neoadjuvant chemotherapy did not differ significantly between the groups ($p = 0.181$). However, patients in the CT-only group were significantly more likely to have received oral chemotherapy (capecitabine or Ufur). In contrast, those in the CT + TT group predominantly received infusional regimens (FOLFIRI, FOLFOX, or FOLFOXIRI) ($p < 0.001$). The type of metastatic treatment (surgical resection, RFA/local treatment, or TACE/Y-90) was similar between groups ($p = 0.962$). There was a trend toward higher conversion rates among patients receiving chemotherapy plus targeted therapy ($p = 0.081$).

The treatment characteristics are listed in Table 2.

Survival outcomes

The mean OS was 44.7 months (95% confidence interval [CI]: 39.3-50.1) in the chemotherapy plus tar-

Table 1. Clinical characteristics

	CT alone (n = 15)	CT + TT (n = 80)	p value
Age (mean $\pm$ SD)	70.73 $\pm$ 8.36	57.76 $\pm$ 10.46	< 0.001
Sex (Male %)	9 (60.0%)	40 (50.0%)	0.578
ECOG PS			0.292
0-1	14 (93.3%)	79 (98.8%)	
≥ 2	1 (6.7%)	1 (1.3%)	
Year of diagnosis			0.004
2016-2017	9 (60.0%)	17 (21.3%)	
2018-2020	6 (40.0%)	63 (78.8%)	
Tumor sidedness			0.091
Right colon	6 (40.0%)	15 (18.8%)	
Left colon & rectum	9 (60.0%)	65 (81.3%)	
Histologic subtype			0.239
Adenocarcinoma	13 (86.7%)	76 (95.0%)	
Mucinous or Signet-ring	2 (13.3%)	4 (5.0%)	
Tumor grade			0.620
Well / moderately differentiated	12 (80.0%)	72 (90.0%)	
Poor / undifferentiated / high grade in MAC	2 (13.3%)	7 (8.8%)	
Unknown ^a	1 (6.7%)	1 (1.3%)	—
RAS status			1.000 ^b
Wild-type	3 (20.0%)	36 (45.0%)	
Mutation	2 (13.3%)	34 (42.5%)	
Unknown ^b	10 (66.7%)	10 (12.5%)	

CT: chemotherapy; TT: targeted therapy; SD: standard deviation; ECOG PS: Eastern Cooperative Oncology Group performance status; MAC: mucinous adenocarcinoma.

^a Two patients had unknown tumor differentiation and were excluded from statistical comparison. ^b Patients with unknown RAS status (N = 20) were excluded from statistical comparison.

Table 2. Treatment characteristics

	CT alone (n = 15)	CT + TT (n = 80)	p value
Neoadjuvant chemotherapy (Yes %)	1 (6.7%)	19 (23.8%)	0.181
Chemotherapy type			< 0.001
Oral	11 (73.3%)	0 (0.0%)	
Infusional	4 (26.7%)	80 (100.0%)	
Targeted agent			—
None	15 (100.0%)	0 (0.0%)	
Anti-VEGF	0 (0.0%)	63 (78.8%)	
Anti-EGFR	0 (0.0%)	17 (21.3%)	
Metastatic site ^a			0.014
Liver only	8 (53.3%)	44 (55.0%)	
Lung only	4 (26.7%)	3 (3.8%)	
Other single ^a	2 (13.3%)	18 (22.5%)	
Multiple	1 (6.7%)	15 (18.8%)	
Metastatic treatment			0.962
Surgical resection	9 (60.0%)	48 (60.0%)	
RFA or other local Tx	5 (33.3%)	28 (35.0%)	
TACE or Y-90	1 (6.7%)	4 (5.0%)	
Conversion (Yes %)	2 (13.3%)	30 (37.5%)	0.081

CT: chemotherapy; TT: targeted therapy; VEGF: vascular endothelial growth factor; EGFR: epidermal growth factor receptor; RFA: radiofrequency ablation; Tx: treatment; TACE: transarterial chemoembolization.

^a "Other single" refers to patients with a single metastatic site limited to the peritoneum, para-aortic lymph nodes, brain, or ovary.

geted therapy group and 53.6 months (95% CI: 35.2-72.1) in the chemotherapy-only group. The median OS was 40.9 months (95% CI: 33.6-48.2) in the CT + TT group and 34.2 months in the CT-only group; however, the confidence interval of median OS for the CT-only group could not be estimated due to censored data. There was no statistically significant difference in the OS between the two groups (log-rank $p = 0.306$).

The mean DFS was 16.9 months (95% CI: 13.1-20.8) in the chemotherapy plus targeted therapy group

and 29.4 months (95% CI: 12.7-46.1) in the chemotherapy-only group. The median DFS was 11.5 months (95% CI: 8.1-14.9) for the CT + TT group and 8.8 months (95% CI: 5.0-12.7) for the CT-only group. Similarly, no significant difference in DFS was observed between the two groups (log-rank $p = 0.238$).

The comparisons for OS and DFS were accomplished by Kaplan–Meier method with log-rank test as depicted in Fig. 1 and Fig. 2, respectively.

In the univariate analysis of overall and disease-

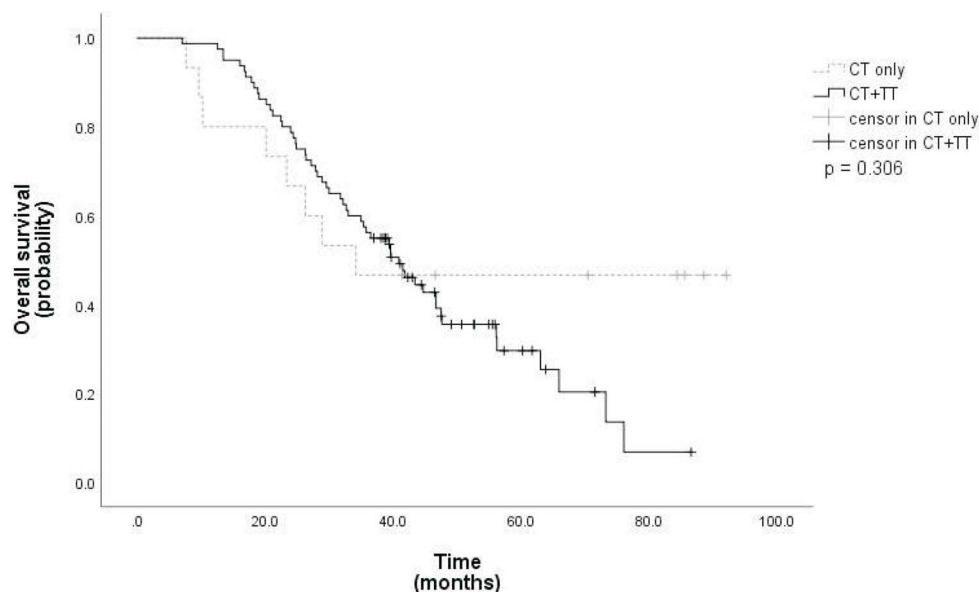


Fig. 1. Kaplan–Meier curves for overall survival, with comparisons between groups performed using the log-rank test.

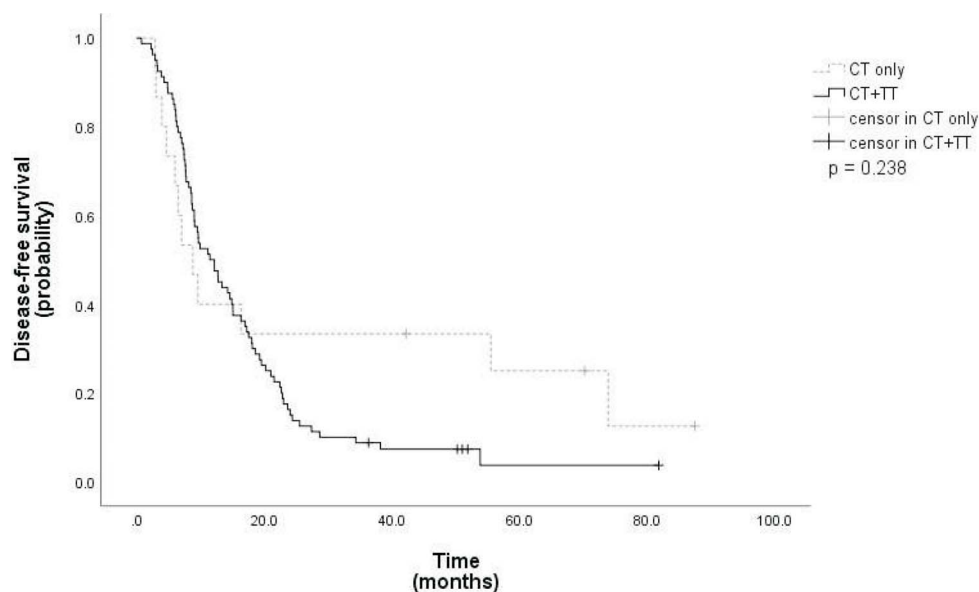


Fig. 2. Kaplan–Meier curves for disease-free survival, with comparisons between groups performed using the log-rank test.

free survival, only the type of metastatic treatment demonstrated a statistically significant association with DFS ($p = 0.003$). Compared with surgical resection, RFA or other local therapies, and TACE or Y-90 were associated with significantly inferior disease-free survival (hazard ratio [HR], 1.548; $p = 0.048$, and HR, 4.636; $p = 0.002$, respectively). No other variables were significantly associated with OS or DFS. Nevertheless, given their clinical relevance, all variables, including age, tumor sidedness, RAS status, metastatic site classification, type of metastatic treatment, and systemic therapy (chemotherapy with or without targeted therapy) were included in the multivariate Cox regression analysis. Because a substantial proportion of patients had unknown RAS status ($N = 20$), accounting for 66.7% of the CT-only group (10 of 15 patients), we retained this category in the multivariate analysis to avoid introducing selection bias.

No variables were statistically significant for OS. Although not statistically significant, patients with

metastatic disease treated with TACE or Y-90 showed a trend toward worse overall survival (HR 2.852, 95% CI, 1.00-8.120; $p = 0.050$) than those who underwent surgical resection.

These two factors were statistically significant for DFS. Patients treated with RFA or other local therapies had inferior DFS compared to those undergoing surgical resection (HR 1.722, 95% CI: 1.016-2.917, $p = 0.043$), and those treated with TACE or Y-90 had significantly worse DFS (HR 3.821, 95% CI: 1.352-10.800, $p = 0.011$).

The multivariate analyses of the predictive factors for overall survival and disease-free survival are listed in Table 3.

Subgroup analysis for anti-VEGF and anti-EGFR

There was no statistically significant difference in age (mean age: 58.6 vs. 54.5 years, $p = 0.152$), year of

Table 3. Multivariate analysis on predicting factors for OS and DFS

Variables	Overall survival		Disease-free survival	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Age	0.999 (0.970-1.029)	0.957	0.984 (0.959-1.009)	0.198
Tumor sidedness				
Right colon	1		1	
Left colon & rectum	1.587 (0.781-3.226)	0.202	1.145 (0.652-2.012)	0.638
RAS status		0.206		0.025
Wild-type	1		1	
Mutation	1.529 (0.797-2.933)	0.202	1.410 (0.855-2.325)	0.178
Unknown	1.968 (0.861-4.495)	0.108	0.465 (0.210-1.029)	0.059
Metastatic site ^a		0.165		0.648
Liver only	1		1	
Lung only	0.800 (0.245-2.610)	0.712	1.089 (0.386-3.075)	0.872
Other single ^a	1.899 (0.903-3.993)	0.091	1.138 (0.591-2.190)	0.699
Multiple	1.788 (0.872-3.667)	0.113	1.486 (0.812-2.722)	0.199
Metastatic treatment		0.145		0.015
Surgical resection	1		1	
RFA or other local Tx	1.163 (0.591-2.286)	0.662	1.722 (1.016-2.917)	0.043
TACE or Y-90	2.852 (1.002-8.120)	0.050	3.821 (1.352-10.800)	0.011
CT or CT + TT				
CT only	1		1	
CT + TT	1.230 (0.436-3.470)	0.696	0.591 (0.225-1.552)	0.285

CT: chemotherapy; TT: targeted therapy; HR: hazard ratio; CI: confidence interval; RFA: radiofrequency ablation; Tx: treatment; TACE: transarterial chemoembolization.

^a "Other single" refers to patients with a single metastatic site limited to the peritoneum, para-aortic lymph nodes, brain, or ovary.

diagnosis ($p = 0.103$) and metastatic site ($p = 0.467$ by Pearson's Chi-square test) between patients receiving anti-VEGF and anti-EGFR therapy.

A statistically significant association was found between tumor sidedness and the type of targeted therapy ($p = 0.032$). Anti-EGFR agents were exclusively used for left-sided or rectal tumors, whereas all patients with right-sided tumors received anti-VEGF therapy only.

There was a statistically significant association between the type of metastatic treatment and the type of targeted agent used ($p = 0.026$, Pearson's chi-square test). A higher rate of anti-EGFR use was observed in patients who underwent TACE/Y90 (75.0%). However, the sample size in this subgroup was small, and 33.3% of cells had expected counts of less than 5, which should be interpreted with caution.

A significant association was observed between

conversion status and type of targeted therapy ($p = 0.051$). Among patients who underwent conversion from an initially unresectable to a resectable status, a higher proportion received anti-EGFR agents than those who were resectable at diagnosis.

Because only patients with wild-type RAS tumors were eligible to receive anti-EGFR agents, no direct comparisons were made between the anti-EGFR and anti-VEGF subgroups in the full cohort.

There were no statistically significant differences in OS or DFS between patients receiving anti-VEGF and those receiving anti-EGFR agents. The median OS was 40.9 months in the anti-VEGF group and 41.5 months in the anti-EGFR group, respectively ($p = 0.954$). The median DFS was 11.5 and 12.2 months, respectively ($p = 0.415$). Subgroup analyses are presented in Table 4.

We further stratified the patients according to pri-

Table 4. Subgroup analysis

	CT + Anti-VEGF (n = 63)	CT + Anti-EGFR (n = 17)	<i>p</i> value
Age (mean $\pm$ SD)	58.63 $\pm$ 10.41	54.53 $\pm$ 10.31	0.152
Year of diagnosis			0.103
2016-2017	16 (25.4%)	1 (5.9%)	
2018-2020	47 (74.6%)	16 (94.1%)	
Tumor sidedness			0.032
Right colon	15 (23.8%)	0 (0.0%)	
Left colon & rectum	48 (76.2%)	17 (100.0%)	
RAS status			— ^a
Wild-type	19 (30.2%)	17 (100.0%)	
Mutation	34 (54.0%)	0 (0.0%)	
Unknown	10 (15.9%)	0 (0.0%)	
Metastatic site ^b			0.467
Liver only	33 (52.4%)	11 (64.7%)	
Lung only	3 (4.8%)	0 (0.0%)	
Other single ^b	16 (25.4%)	2 (23.5%)	
Multiple	11 (17.5%)	4 (23.5%)	
Metastatic treatment			0.026
Surgical resection	39 (61.9%)	9 (52.9%)	
RFA or other local Tx	23 (36.5%)	5 (29.4%)	
TACE or Y-90	1 (1.6%)	3 (17.6%)	
Conversion (Yes %)	20 (31.7%)	10 (58.8%)	0.051
Overall survival (median [95% CI])	40.9 (31.3-50.5)	41.5 (37.8-45.2)	0.954
Disease-free survival (median [95% CI])	11.5 (7.9-15.1)	12.2 (4.1-20.3)	0.415

CT: chemotherapy; VEGF: vascular endothelial growth factor; EGFR: epidermal growth factor receptor; SD: standard deviation; RFA: radiofrequency ablation; Tx: treatment; TACE: transarterial chemoembolization; CI: confidence interval.

^a Only patients with RAS wild-type tumors were eligible for anti-EGFR therapy; therefore, intergroup comparisons were not performed. ^b "Other single" refers to patients with a single metastatic site limited to the peritoneum, para-aortic lymph nodes, brain, or ovary.

mary tumor sidedness and the type of targeted agent. The subgroups included CT + anti-VEGF for right-sided tumors, CT + anti-VEGF for left-sided tumors, CT + anti-EGFR for left-sided tumors, and CT. Median overall survival was 47.6 months of patients receiving anti-VEGF for right-sided tumors, 35.8 months for anti-VEGF for left-sided tumors, 41.5 months for anti-EGFR for left-sided tumors, left-sided tumors, and 34.2 months in the CT only groups. No statistically significant difference in overall survival was observed between the subgroups (log-rank test, $p = 0.760$). For disease-free survival, the median durations were 14.6 months for anti-VEGF in right-sided tumors, 11.2 months for anti-VEGF in left-sided tumors, 12.2 months for anti-EGFR in left-sided tumors, and 8.8 months in the CT only group. Again, no significant differences were observed (log-rank test, $p = 0.571$). Kaplan–Meier curves with log-rank tests for OS and DFS by subgroup are shown in Figs. 3 and 4.

Discussion

In this retrospective study, we evaluated the impact of adding targeted therapy to chemotherapy on survival outcomes in patients with resectable mCRC

who underwent curative-intent resection of both primary and metastatic lesions. Our analysis revealed no significant differences in OS or DFS between patients treated with chemotherapy plus targeted therapy (CT + TT group) and those treated with chemotherapy alone (CT-only group). Univariate and multivariate Cox regression analyses incorporating clinically relevant variables failed to identify any statistically significant independent predictors of overall survival or disease-free survival.

Treatment patterns changed over time, with patients diagnosed between 2018 and 2020 more likely to receive chemotherapy plus targeted therapy (CT + TT) than those diagnosed earlier. This likely reflects evolving clinical practice and greater availability of biological agents in Taiwan. However, despite this shift, we did not observe an associated survival benefit in our cohort. These findings contribute to the ongoing debate on the role of targeted therapy in the peri-operative management of resectable mCRC.

Furthermore, a significant difference in the distribution of metastatic sites was observed between the CT-only and CT + TT groups ($p = 0.014$). Patients in the CT-only group were more likely to present with lung-only metastases (26.7%), while the CT + TT group had a higher proportion of multiple (18.8%) or other

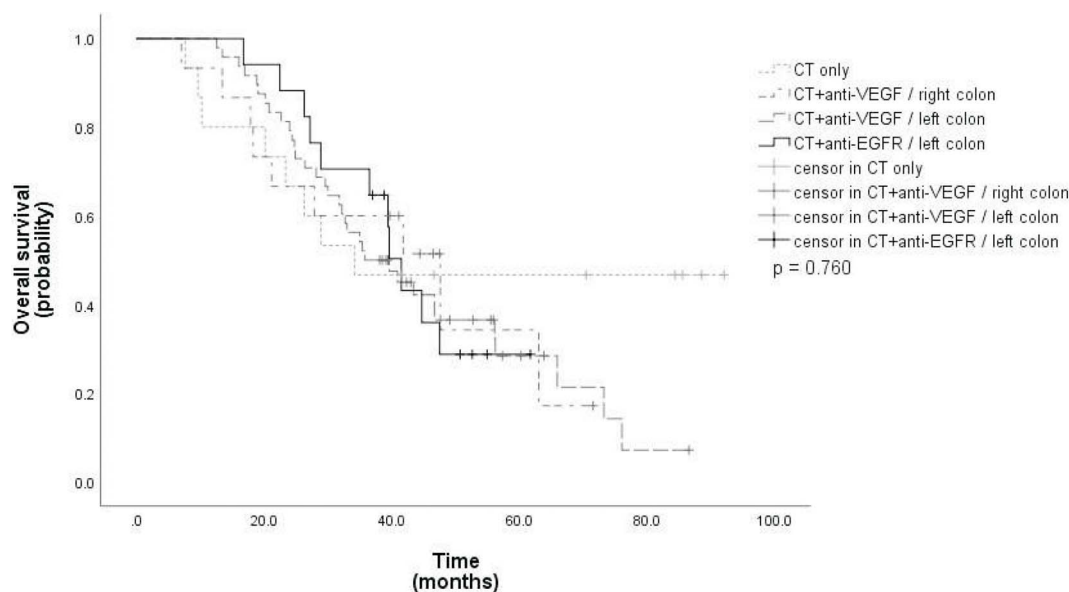


Fig. 3. Kaplan–Meier curves for overall survival by subgroup, with comparisons between groups performed using the log-rank test.

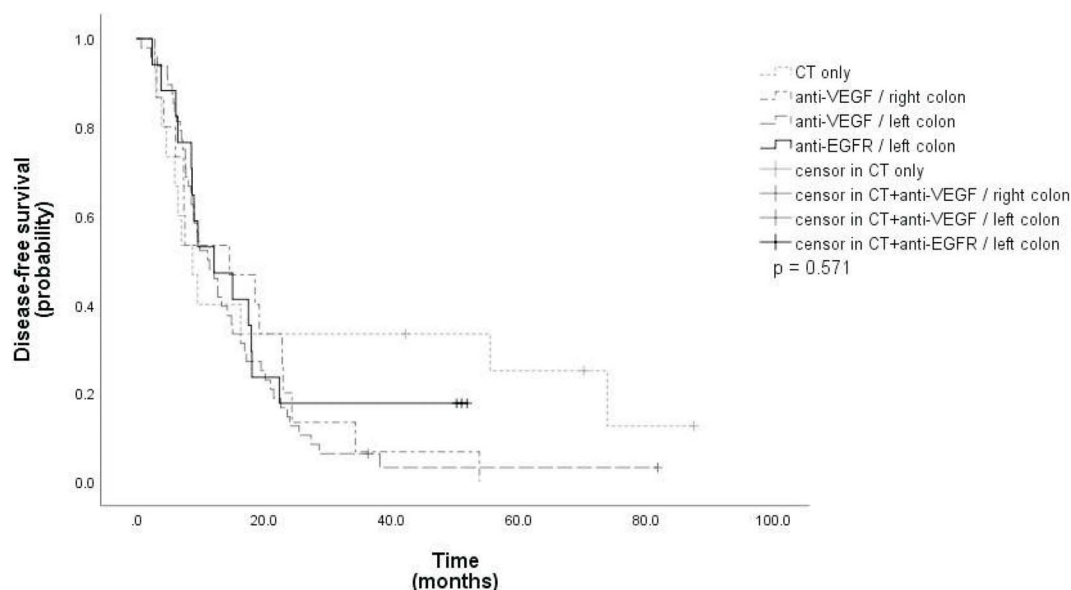


Fig. 4. Kaplan–Meier curves for disease-free survival by subgroup, with comparisons between groups performed using the log-rank test.

single-site metastases (22.5%). This suggests that disease burden and pattern may have influenced treatment selection, with clinicians potentially favoring more intensive systemic therapy for patients with more complex metastatic presentations. These differences may also confound comparisons of treatment outcomes between the groups.

Previous studies also reported conflicting results. Some reports suggest that neoadjuvant cetuximab combined with chemotherapy can improve outcomes,^{8,10} while the recent EPOC trial found that adding cetuximab to chemotherapy actually shortened progression-free survival in patients with resectable liver metastases.¹¹ Similarly, bevacizumab did not improve progression-free or overall survival in patients who underwent resection of hepatic and pulmonary metastases from colorectal cancer.^{12–14} One retrospective study in Taiwan examined perioperative targeted therapy for resectable mCRC and found no improvement in overall or progression-free survival when anti-EGFR or anti-VEGF agents were added to chemotherapy.¹⁵ Although not prospective, this real-world data reinforces the lack of clear benefits of perioperative targeted therapy in resectable disease.

Multivariate analysis revealed that the type of metastatic treatment was a significant predictor of DFS. Compared with surgical resection, patients treated with

RFA or other local treatments and those receiving TACE or Y-90 experienced significantly shorter DFS. These results underscore the importance of achieving complete resection whenever possible in resectable mCRC, as non-surgical local therapies may be associated with inferior oncological outcomes. This finding is consistent with those of previous studies that reported that patients treated with liver resection achieved better PFS and OS than those treated with RFA.¹⁶

In our cohort, tumor sidedness and RAS mutation status did not independently predict OS or DFS in the multivariate analysis. Although previous studies have highlighted these factors as important prognostic markers, their effects may be attenuated by curative-intent treatments following resection. Additionally, the sample size and inclusion of patients with unknown RAS status may have introduced heterogeneity and reduced statistical power.

Our subgroup analyses did not reveal any statistically significant differences in survival between patients receiving anti-VEGF and anti-EGFR agents. However, anti-EGFR agents were exclusively administered to patients with left-sided or rectal tumors, consistent with the current guideline recommendations.¹⁷ Furthermore, a higher proportion of patients who underwent conversion from an initially unresectable disease received anti-EGFR therapy, suggesting the po-

tential benefits of anti-EGFR agents in this setting. We also observed a significant difference in the distribution of metastatic treatment modalities ($p = 0.026$).

Among the patients receiving anti-EGFR therapy, a higher proportion underwent TACE or Y-90 therapy (17.6%) than those receiving anti-VEGF therapy (1.6%). Conversely, surgical resection remained the most common approach in both groups but was slightly less frequent in the anti-EGFR group (52.9% vs. 61.9%). Given that non-surgical treatments such as TACE or Y-90 were associated with inferior DFS in our multivariate analysis, the higher proportion of such treatments in the anti-EGFR group may have confounded comparisons of survival outcomes between the targeted therapy subgroups. This factor should be considered when interpreting the observed lack of a difference in survival.

Our study has some limitations. The retrospective design may have introduced selection bias, and the sample size of the CT-only group was relatively small. Owing to censored data and limited events in the CT-only group, the confidence interval for the median overall survival could not be estimated. Because RAS testing was not reimbursed by the National Health Insurance in Taiwan until 2021, and RAS testing was not routinely performed at our institution during the study period, a substantial portion of the CT-only group had unknown RAS status (66.7%). These may have reduced the precision of survival comparisons, limited the statistical power of analyses, may mask potential clinical differences.

Conclusions

In this retrospective cohort of patients with resectable metastatic colorectal cancer undergoing curative-intent resection, the addition of targeted therapy to chemotherapy did not demonstrate a significant survival benefit in the overall population. Although a higher proportion of patients treated with anti-EGFR agents had initially unresectable disease and underwent conversion therapy, they were also more likely to receive local rather than surgical treatment for metastases, which may substantially affect prognosis.

Further studies are warranted to clarify the role of perioperative targeted therapy in this patient population.

Acknowledgements

We would like to express our gratitude to the Department of Colorectal Surgery at Kaohsiung Veterans General Hospital for valuable discussions and support.

Sources of Financial Support

None.

References

1. Roshandel G, Ghasemi-Kebria F, Malekzadeh R. Colorectal cancer: epidemiology, risk factors, and prevention. *Cancers (Basel)* 2024;16(8).
2. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350(23):2335-42.
3. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004;351(4):337-45.
4. Fong Y, Cohen AM, Fortner JG, Enker WE, Turnbull AD, Coit DG, et al. Liver resection for colorectal metastases. *J Clin Oncol* 1997;15(3):938-46.
5. McAfee MK, Allen MS, Trastek VF, Ilstrup DM, Deschamps C, Pairolero PC. Colorectal lung metastases: results of surgical excision. *Ann Thorac Surg* 1992;53(5):780-5; discussion 785-6.
6. Headrick JR, Miller DL, Nagorney DM, Allen MS, Deschamps C, Trastek VF, et al. Surgical treatment of hepatic and pulmonary metastases from colon cancer. *Ann Thorac Surg* 2001;71(3):975-9; discussion 979-80.
7. Khatib J, Goksu SY, Reddy S, Chowattukunnel N, Sanford NN, Sanjeevaiah A, et al. Metastasectomy in colorectal cancer patients with concurrent lung and liver metastasis: trends in utilization and impact on survival. *J Clin Oncol* 2022;40(4_suppl):53.
8. Chen HH, Lin JK, Chen JB, Chuang CH, Liu MC, Wang JY, et al. Neoadjuvant therapy of bevacizumab in combination with oxaliplatin and capecitabine (XELOX) for patients with metastatic colorectal cancer with unresectable liver meta-

- stases: a phase II, open-label, single-arm, noncomparative trial. *Asia Pac J Clin Oncol* 2018;14(1):61-8.
9. Ye LC, Liu TS, Ren L, Wei Y, Zhu DX, Zai SY, et al. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. *J Clin Oncol* 2013;31(16):1931-8.
 10. Kim SA, Kim JW, Suh KJ, Chang W, Kim JW, Oh HK, et al. Conversion surgery after cetuximab or bevacizumab plus FOLFIRI chemotherapy in colorectal cancer patients with liver- and/or lung-limited metastases. *J Cancer Res Clin Oncol* 2020;146(9):2399-410.
 11. Primrose J, Falk S, Finch-Jones M, Valle J, O'Reilly D, Siriwardena A, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. *Lancet Oncol* 2014;15(6):601-11.
 12. Rong Z, Martel G, Vandenbroucke-Menu F, Adam R, Lapointe R. Impact of peri-operative bevacizumab on survival in patients with resected colorectal liver metastases: an analysis of the LiverMetSurvey. *HPB (Oxford)* 2014;16(4):342-9.
 13. Turan N, Benekli M, Koca D, Ustaalioglu BO, Dane F, Ozdemir N, et al. Adjuvant systemic chemotherapy with or without bevacizumab in patients with resected liver metastases from colorectal cancer. *Oncology* 2013;84(1):14-21.
 14. Turan N, Benekli M, Dane F, Unal OU, Kara HV, Koca D, et al. Adjuvant systemic chemotherapy with or without bevacizumab in patients with resected pulmonary metastases from colorectal cancer. *Thorac Cancer* 2014;5(5):398-404.
 15. Su YC, Wu CC, Chen YH, Su CC, Chang YC, Hsieh MC, et al. Assessing the effectiveness of targeted agents in adjuvant therapy for patients with metastatic colorectal cancer undergoing surgical resection: a retrospective cohort study. *Ther Adv Med Oncol* 2024;16:17588359241246427.
 16. Hao W, Binbin J, Wei Y, Kun Y. Can radiofrequency ablation replace liver resection for solitary colorectal liver metastasis? A systemic review and meta-analysis. *Frontiers in Oncology* 2020;10.
 17. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Colon Cancer V.4.2025. Available from: https://www.nccn.org/guidelines/category_1 [Accessed 23rd July, 2025].

Supplementary Material

Supplementary Table 1. Clinical characteristics and treatment for patients with multiple metastatic sites

No.	Year of diagnosis	Age	Sex	Tumor site	RAS	Regimen	Metastatic sites	Treatment for metastases
1	2020	50	M	Ascending colon	Wild type	Avastin + FOLFOXIRI	Liver, lung, para-aortic LN	Curative-intent surgery, RFA for liver and lung
2	2020	54	M	Descending colon	Wild type	Erbitux + FOLFIRI	Liver, para-aortic LN	Curative-intent surgery, RFA for liver
3	2020	75	F	Rectum	Mutation	Avastin + FOLFIRI	Liver, lung	RFA for liver and lung
4	2020	48	F	Sigmoid colon	Wild type	Erbitux + FOLFIRI	Para-aortic LN, Rt ovarian	Curative-intent surgery
5	2020	61	M	Rectum	Mutation	Avastin + FOLFIRI	Liver, peritoneum	Curative-intent surgery, RFA for liver
6	2020	52	M	Sigmoid colon	Wild type	Avastin + FOLFIRI	Liver, peritoneum	Curative-intent surgery, RFA for liver
7	2020	48	M	Sigmoid colon	Wild type	Erbitux + FOLFIRI	Liver, para-aortic LN	Curative-intent surgery, TACE
8	2020	54	F	Descending colon	Wild type	Panitumumab + FOLFIRI	Liver, peritoneum	Curative-intent surgery
9	2019	70	M	Sigmoid colon	Mutation	Avastin + FOLFIRI	Liver, lung	Curative-intent surgery
10	2019	57	M	Sigmoid colon	Wild type	Avastin + FOLFIRI	Liver, lung	Curative-intent surgery, RFA for lung
11	2019	49	M	Rectum	Mutation	Avastin + FOLFIRI	Liver, lung, para-aortic LN	Curative-intent surgery, RFA for liver and lung
12	2019	52	M	Descending colon	Mutation	Avastin + FOLFIRI	Liver, lung	Curative-intent surgery, RFA for liver and lung
13	2018	70	F	Cecum	Unknown	Avastin + FOLFIRI	Peritoneum, Bil. ovarian	Curative-intent surgery
14	2018	37	F	RSJ	Mutation	Avastin + FOLFIRI	Liver, peritoneum	Curative-intent surgery
15	2017	65	F	Rectum	Unknown	FOLFIRI	Lung, brain	Gamma knife radiosurgery, RFA for lung
16	2016	67	M	Rectum	Wild type	Avastin + FOLFIRI	Liver, lung	RFA for liver and lung

LN: lymph node(s); RFA: radiofrequency ablation; Rt: right; Bil.: bilateral; RSJ: rectosigmoid junction; GKRS: Gamma-Knife radiosurgery.

原 著

可切除的轉移性大腸直腸癌患者之標靶治療： 單一醫學中心回溯性研究

曾馨平¹ 許詔文^{1,2} 王瑞和¹ 陳禹勳¹ 李明泓¹ 朱炳騰¹ 吳志謙^{1,2}¹高雄榮民總醫院 大腸直腸外科²國立陽明交通大學 醫學系

目的 本研究旨在評估針對接受根治性手術的可切除轉移性大腸直腸癌 (mCRC) 患者，化學治療加上標靶治療是否能改善其存活結果。

方法 本回溯性研究分析 2016 年至 2020 年間於高雄榮民總醫院診斷之 95 位轉移性大腸直腸癌患者，包含初始可切除及經治療後轉變為可切除者。所有患者皆接受原發腫瘤與轉移病灶之根治性治療，並接受化學治療，部分合併標靶治療。比較兩組病人的臨床特徵與治療模式。主要研究結果為整體存活期 (OS) 與無病存活期 (DFS)。

結果 95 位患者中，80 位 (84.2%) 接受化學治療合併標靶治療，15 位 (15.8%) 僅接受化學治療。合併標靶治療組患者顯著年輕，且較常接受輸注型化療，其整體存活期中位數為 40.9 個月；化療單獨組為 34.2 個月 ($p = 0.306$)。無病存活期分別為 11.5 與 8.8 個月 ($p = 0.238$)。兩組間存活率無統計學差異。

結論 在接受根治性手術的可切除轉移性大腸直腸癌患者中，化療合併標靶治療未顯示顯著存活效益。雖然標靶治療在無法手術的轉移性大腸直腸癌患者中有效，但其在可切除的轉移性大腸直腸癌患者的應用效果仍待進一步釐清。

關鍵詞 大腸直腸腫瘤、腫瘤轉移、分子標靶治療、整體存活率、無病存活期。