ORIGINAL ARTICLE

Survival Analysis and Prognostic Factors for Metastatic Colorectal Cancer Patients Treated with Chemotherapy

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Background: Currently, there are limited data on prognostic factors in metastatic colorectal cancer (mCRC) patients treated with chemotherapy. Prognostic factors in colorectal cancer remain varied in each situation when considering their use in different contexts.

Objective: To analyze the independent prognostic factors of mCRC in patients receiving chemotherapy.

Materials and Methods: Data from 156 mCRC patients completely treated by first-line chemotherapy were collected between 2013 and 2018. A retrospective observational cohort study was conducted to evaluate the survival analysis and prognostic factors. A univariate and multivariate Cox's proportional-hazards model were used to explore and identify the independent prognostic factors for overall survival. An analysis of the restricted mean survival time (RMST) method was used to estimate the event-free time from zero to 24 months.

Results: Median overall survival was 18.3 months (96% CI 15.31 to 20.95). The multivariate Cox's proportional-hazards model revealed two prognostic factors for decreased survival, poor Eastern Cooperative Oncology Group (ECOG) performance status greater than or equal to 2 (HR 2.05, 95% CI 1.08 to 3.86; p=0.027) and hypoalbuminemia lower than 3.5 g/dL (HR 3.47, 95% CI 2.10 to 5.75, p<0.001). Analysis of the RMST method was used to estimate the event-free time from zero to 24 months in the group receiving first-line oxaliplatin-based chemotherapy, second-line oxaliplatin-based chemotherapy, and second-line irinotecan-based chemotherapy. It was found that only the group receiving second-line oxaliplatin-based chemotherapy had significantly longer survival time than the comparison groups, with an adjusted mean of survival time of 21.12 months (different mean 5.99, 95% CI 3.99 to 8.00, p<0.001).

Conclusion: Poor ECOG performance status greater than or equal to 2, and hypoalbuminemia lower than 3.5 g/dL can be used as prognostic factors in mCRC patients receiving chemotherapy.

Keywords: Survival; Prognostic factors; Metastatic colorectal cancer; Chemotherapy

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Approximately one-third of colorectal cancer (CRC) patients have metastatic disease at the time of diagnosis[1]. Chemotherapy is used for treatment at this stage. Most chemotherapeutic agents consist of 5-fluorouracil (5FU), capecitabine, oxaliplatin, and irinotecan. Previous studies focusing on the prognostic factors of CRC found that these factors associated with age older than 60 years, performance status 3, stage III or IV, and poorly differentiated histology were poor prognostic factors, while complete surgical resection and adjuvant chemotherapy were good prognostic factors[2,3]. This conforms to studies that have found that staging is an important independent prognostic factor affecting survival[4,5].

For metastatic stage CRC, there are data on the independent prognostic factors in CRC patients with liver metastasis. It was found that the most important independent prognostic factors included Dukes stage, number of metastasis, serum concentration of carcinoembryonic antigen (CEA), alkaline phosphatase, worsened performance status, C-reactive protein of more than 5 mg/dL, anemia, anorexia, weight loss of 10% or more, fatigue, hypoalbuminemia, and blood transfusion as poor prognostic factors[1,6]. Studies on prognostic factors in CRC remain varied in each situation when considering their use in different contexts.

Due to the limited data from previous studies, the present study aimed to investigate the specific prognostic factors of patients with advanced stage CRC receiving chemotherapy as a target group of

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interest.

Materials and Methods

The present study was a prognostic research based as a retrospective observational cohort study, which was implemented as follows:

1. The data of potential prognostic predictors of metastatic colorectal cancer (mCRC) patients were collected, such as performance status, pathological report, site of metastasis, disease-free interval, the level serum CEA, pretreatment white blood cell count, the level of pretreatment albumin, receipt of first-line chemotherapy, or receipt of second-line chemotherapy.

2. Data related to dates of death were collected from the database at the Department of Provincial Administration. Only causes of death due to cancer were analyzed.

Patients

The data were from mCRC patients treated in the Division of Medical Oncology, Department of Internal Medicine, Buddhasothorn Hospital between 2013 and 2018. The authors conducted retrospective medical chart review in accordance with the principles of the Declaration of Helsinki. The present study protocol was approved by the Institutional Review Board of Buddhasothorn Hospital (number BSH-IRB 041/2563). The IRB determined that formal consent was not required.

Inclusion criteria

1. The data of patients aged 18 years or older.
2. Pathologically confirmed diagnosis with CRC stage IV with de novo metastasis or recurrent patients.
3. Complete clinical history data such as patients' basic data, data of diagnosis.

Exclusion criteria

1. New patients with incomplete or missing data.
2. Patients receiving incomplete chemotherapy as planned.
3. Patients treated with targeted therapy.

Research objectives

1. To study the independent prognostic factors of mCRC patients receiving chemotherapy
2. To analyze survival time at 24 months of treatment by chemotherapy, with group comparison as follows:

2.1 The group receiving first-line chemotherapy with an oxaliplatin-based regimen and the other group with a single-agent regimen.

2.2 The group receiving second-line chemotherapy with the irinotecan-based regimen and the group without the irinotecan-based regimen.

2.3 The group receiving second-line chemotherapy with the oxaliplatin-based regimen and the group without the oxaliplatin-based regimen.

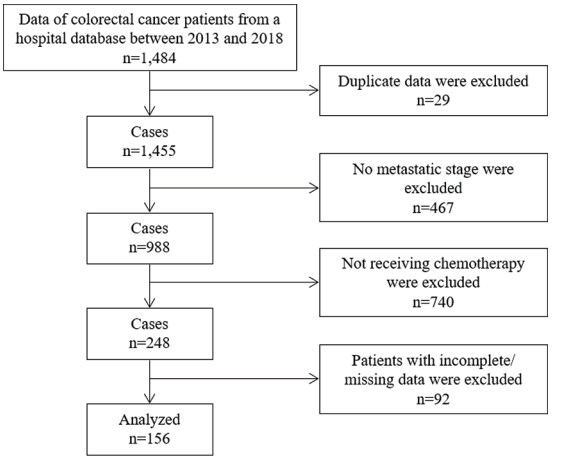

Figure 1. Patient selection flow chart.

Statistical analyses

Step 1: Potential prognostic predictors were analyzed by univariate Cox's proportional hazards regression analysis and multivariate Cox's proportional hazards regression analysis to find the independent prognostic factors. The significance level or alpha level was 0.05.

Step 2: Survival analysis was conducted for receipt of first-line chemotherapy with the oxaliplatin-based regimen, and second-line chemotherapy with the irinotecan-based regimen, or oxaliplatin-based regimen at 24 months by restricted mean survival time (RMST) analysis.

Statistical analyses were performed using Stata Statistical Software, version 16 (StataCorp LLC, College Station, TX, USA).

Results

Data were collected from 156 mCRC patients treated with chemotherapy. The patient selection flowchart is shown in Figure 1. The mean age was 60.9 years and standard deviation (SD) was 10.8 years. The mean albumin level was 4.00 g/dL, SD was 0.81 g/dL. The mean neutrophil-to-lymphocyte ratio (NLR) was 3.81 and SD was 3.46. Baseline characteristics data are show in Table 1, and chemotherapy data in Table 2. The Kaplan-Meier

Table 1. Baseline characteristics in patients with metastatic colorectal cancer (mCRC) treated with chemotherapy (n=156)

Variables	n (%)
Sex	
Male	85 (54.49)
Female	71 (45.51)
Elderly age >70 years	27 (17.31)
ECOG PS	
Good ECOG 0-1	141 (90.38)
Poor ECOG PS	15 (9.62)
Location of cancer	
Right-sided colon	24 (15.38)
Left-sided colon	66 (42.31)
Rectum	66 (42.31)
Tumor grading	
Well differentiated	22 (14.10)
Moderately differentiated	128 (82.05)
Poorly differentiated	6 (3.85)
Initial site of metastasis	
Liver	99 (63.46)
Lung	63 (40.38)
Brain	9 (5.77)
Number of metastatic site	
Single organ metastasis	122 (78.21)
Two organ metastasis	30 (19.23)
Multiple organ metastasis	4 (2.56)
First-line chemotherapy	
Single agent (5FU, capecitabine)	69 (44.23)
Oxaliplatin-based regimen	85 (54.49)
Irinotecan-based regimen	2 (1.28)
Second-line chemotherapy	
None	89 (57.05)
Single agent (5FU, capecitabine)	16 (10.26)
Oxaliplatin-based regimen	28 (17.95)
Irinotecan-based regimen	23 (14.74)

Poor ECOG PS=Eastern Cooperative Oncology Group Performance Status greater than or equal to 2; 5FU=5-fluorouracil

curve of overall survival of mCRC patients treated with chemotherapy is shown in Figure 2. The median overall survival was 18.3 months (96% CI 15.31 to 20.95).

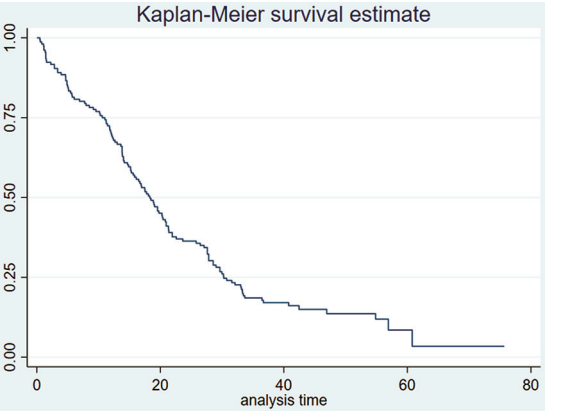

Figure 2. Kaplan-Meier curve of overall survival in the metastatic colorectal cancer patients treated by chemotherapy.

Then, prognostic factors from potential variables were analyzed such as gender, elderly age older than 70 years[7-9], Eastern Cooperative Oncology Group Performance Status (ECOG PS), tumor grading, anatomical distribution of CRC, hypoalbuminemia of less than 3.5 g/dL, NLR greater than 5[10-12], site of initial metastasis such as brain metastasis, lung metastasis, or liver metastasis, and first-line chemotherapy regimen or second-line chemotherapy regimen by univariate Cox's proportional hazards regression analyses. It was found that hypoalbuminemia of less than 3.5 g/dL, NLR greater than 5, and not treated by second-line chemotherapy were poor prognostic factors, while second-line chemotherapy with the oxaliplatin-based regimen was a protective prognostic factor (Table 3).

However, multivariate Cox's proportional hazards regression analysis revealed that six variables tended to affect the survival outcomes. These were independent prognostic factors divided into two poor prognostic factors, which were ECOG PS greater than or equal to 2, and hypoalbuminemia of less than 3.5 g/dL. In addition, four other protective prognostic factors were found, including right-sided colon cancer, left-sided colon cancer, initial liver

Table 2. Data for treatment by first-line chemotherapy regimen and second-line chemotherapy regimen (n=156)

First-line treatment; number	Second-line treatment; number				
	None received	Single agent*	Oxaliplatin-based	Irinotecan-based	Total
Single agent*	39	6	24	0	69
Oxaliplatin-based	48	10	4	23	85
Irinotecan-based	2	0	0	0	2
Total	89	16	28	23	156

* Single agent: 5FU, capecitabine

Table 3. Univariate and multivariate Cox's proportional hazards regression analysis for exploratory potential prognostic variables

Variables	Crude hazard ratio	95% CI (univariate Cox's analysis)	p-value (crude)	Adjusted hazard ratio	95% CI (multivariate Cox's analysis)	p-value (adjusted)
Sex						
Male	1.26	0.89 to 1.78	0.194	1.23	0.83 to 1.83	0.305
Female	1	Reference	-	1	Reference	-
Age						
>70 years	1.12	0.72 to 1.77	0.610	0.78	0.44 to 1.37	0.389
≤70 years	1	Reference	-	1	Reference	-
ECOG PS						
Poor ECOG PS	1.52	0.88 to 2.60	0.129	2.05	1.08 to 3.86	0.027*
Good ECOG 0-1	1	Reference	-	1	Reference	-
Location of cancer						
Right-sided colon	0.92	0.58 to 1.48	0.747	0.51	0.28 to 0.92	0.028*
Left-sided colon	0.87	0.61 to 1.24	0.447	0.54	0.36 to 0.82	0.004*
Rectum	1.20	0.85 to 1.70	0.303	1	Reference	-
Hypoalbuminemia						
<3.5 g/dL	2.97	1.97 to 4.49	<0.001*	3.47	2.10 to 5.75	<0.001*
No hypoalbuminemia	1	Reference	-	1	Reference	-
NLR						
>5	1.59	1.05 to 2.41	0.029*	1.11	0.70 to 1.78	0.652
≤5	1	Reference	-	1	Reference	-
Tumor grading						
Well differentiated	0.63	0.38 to 1.03	0.067	0.69	0.23 to 2.02	0.495
Moderately differentiated	1.45	0.93 to 2.27	0.100	1.22	0.45 to 3.34	0.691
Poorly differentiated	1.10	0.45 to 2.68	0.842	1	Reference	-
Liver metastasis	0.88	0.62 to 1.26	0.496	0.59	0.38 to 0.91	0.017*
Lung metastasis	1.00	0.70 to 1.41	0.989	0.95	0.62 to 1.45	0.802
Brain metastasis	1.11	0.56 to 2.20	0.755	1.54	0.72-3.30	0.271
First-line chemotherapy						
Single agent (5FU, capecitabine)	1.09	0.77 to 1.53	0.629	0.82	0.18 to 3.74	0.802
Oxaliplatin-based regimen	0.89	0.64 to 1.26	0.522	0.53	0.12 to 2.41	0.414
Irinotecan-based regimen	1.87	0.46 to 7.59	0.383	1	Reference	-
Second-line chemotherapy						
None	1.74	1.23 to 2.46	0.002*	1	Reference	-
Single agent (5FU, capecitabine)	1.08	0.64 to 1.83	0.761	0.72	0.38 to 1.34	0.298
Oxaliplatin-based regimen	0.56	0.36 to 0.88	0.013*	0.32	0.18 to 0.54	<0.001*
Irinotecan-based regimen	0.70	0.43 to 1.15	0.159	0.65	0.36 to 1.17	0.151

CI=confidence interval; NLR=neutrophil-to-lymphocyte ratio; 5FU=5-fluorouracil; Poor ECOG PS=Eastern Cooperative Oncology Group Performance Status greater than or equal to 2

* Statistically significant, $p<0.05$

metastasis, and second-line chemotherapy with an oxaliplatin-based regimen (Table 3).

According to survival comparison between the group receiving first-line chemotherapy with an oxaliplatin-based regimen and the group without an oxaliplatin-based regimen by RMST method analysis, the means of survival time between the two groups at 24 months were compared by displaying the crude mean of survival and adjusted mean of survival that adjusted the confounding factors, such as gender, NLR greater than 5, age older than 70 years, hypoalbuminemia of less than 3.5 g/dL, poor ECOG PS greater than or equal to 2, anatomical distribution of CRC, tumor grading, and site of initial metastasis such as brain metastasis, lung metastasis, and liver metastasis. It was found that the means of survival time between the two groups were not significantly different (Table 4).

Table 4. Event-free time (RMST) in patients receiving first-line chemotherapy with the oxaliplatin-based regimen and the group with single agent regimen at 24 months (n=154)

Event-free time (based on 24 months)	Single agent chemotherapy (n=69); mean±SE	Oxaliplatin-based chemotherapy (n=85); mean±SE	Different mean	95% CI	p-value
RMST (month)					
Crude	15.22±0.97	17.00±0.80	1.79	–0.65 to 4.22	0.151
Adjusted	15.61±0.89	16.80±0.76	1.19	–1.22 to 3.61	0.334

CI=confidence interval; SE=standard error; RMST=restricted mean survival time

Table 5. Event-free time (RMST) in patients receiving second-line chemotherapy with the irinotecan-based regimen and the group without the irinotecan-based regimen at 24 months (n=156)

Event-free time (based on 24 months)	Non-irinotecan-based chemotherapy (n=133); mean±SE	Irinotecan-based chemotherapy (n=23); mean±SE	Different mean	95% CI	p-value
RMST (month)					
Crude	15.59 ± 0.70	19.69 ± 1.22	4.10	1.27 to 6.92	0.004*
Adjusted	15.89 ± 0.64	18.76± 1.44	2.87	–0.25 to 5.99	0.071

CI=confidence interval; SE=standard error; RMST=restricted mean survival time

* Statistically significant, p<0.05

Table 6. Event-free time (RMST) in patients receiving second-line chemotherapy with the oxaliplatin-based regimen and the group without the oxaliplatin-based regimen at 24 months (n=156)

Event-free time (based on 24 months)	Non-oxaliplatin-based chemotherapy (n=128); mean±SE	Oxaliplatin-based chemotherapy (n=28); mean±SE	Different mean	95% CI	p-value
RMST (month)					
Crude	15.16 ± 0.71	20.97 ± 0.94	5.80	3.54 to 8.07	<0.001*
Adjusted	15.12 ± 0.62	21.12 ± 0.81	5.99	3.99 to 8.00	<0.001*

CI=confidence interval; SE=standard error; RMST=restricted mean survival time

* Statistically significant, p<0.05

Survival analysis between the group receiving second-line chemotherapy with an irinotecan-based regimen and the group without an irinotecan-based regimen by RMST method analysis at 24 months showed that the group receiving an irinotecan-based regimen as second-line chemotherapy had a crude mean of survival time 19.69 months, significantly longer than the group without an irinotecan-based regimen by 15.59 months (different mean 4.10, 95% CI 1.27 to 6.92, p=0.004). However, no difference was observed between the two groups after adjusting for confounding factors (different mean 2.87, 95% CI 0.25 to 5.99, p=0.071) (Table 5).

Analyses of the restricted median survival time method at 24 months between the group receiving an oxaliplatin-based regimen and the group not receiving an oxaliplatin-based regimen as second-line chemotherapy showed that the group receiving second-line chemotherapy with an oxaliplatin-based regimen had a significantly longer survival time 20.97 months (different mean 5.80, 95% CI 3.54 to 8.07, p<0.001). When confounders were adjusted, significance was also observed with an adjusted mean of survival time 21.12 months (different mean 5.99, 95% CI 3.99 to 8.00, p<0.001) (Table 6).

Discussion

There are studies concerning the prognostic factors in mCRC patients receiving first-line chemotherapy. It was found that poor performance status and multiple sites of metastasis were independent prognostic factors[13,14]. There is also data of biomarkers related to the predictive markers for chemotherapy and prognostic factors, and progression-free survival (PFS) such as albumin-to-globulin ratio (AGR), the fibrinogen-to-albumin ratio (FAR), the prealbumin-to-globulin ratio (PGR), and the fibrinogen-to-prealbumin ratio (FPR). Nonetheless, it is only a univariate analysis[15].

These research findings were based on multi-variate analysis. It was found that there were six independent prognostic factors affecting the survival of mCRC patients receiving chemotherapy. The factors were divided into two poor prognostic

factors as poor ECOG PS greater than or equal to 2, and hypoalbuminemia of less than 3.5 g/dL, and four protective prognostic factors, as right-sided colon cancer, left-sided colon cancer, initial liver metastasis, and receipt of second-line chemotherapy with an oxaliplatin-based regimen. When the survival analysis in each group with the different chemotherapy regimens was examined by RMST method analysis at 24 months, along with the adjusted confounders, it was found that the means of survival time were significantly different between the group receiving an oxaliplatin-based regimen as second-line chemotherapy and the group not receiving an oxaliplatin-based regimen as second-line chemotherapy. This was consistent with multivariate proportional Cox's proportional hazards regression analysis, which showed that they were independent protective prognostic factors.

According to the poor prognostic factors by univariate analysis and multivariate analysis, the data conformed to the previous studies that found hypoalbuminemia affected worsening survival. Hypoalbuminemia was a marker that indicated the nutritional status of patients[16,17]. Another interesting biomarker was NLR, which has been proposed as a simple marker of systemic inflammatory response in many diseases and various cancers[18-21]. The systematic review and meta-analysis by Jie et al. found that NLR of more than 5 could predict the prognosis of patients with CRC[10]. The results showed that univariate analysis also associated NLR greater than 5 with prognostic factors. In addition, the study also highlighted the relationship between survival and anatomical distribution of cancer in mCRC patients receiving chemotherapy. To clarify, when comparing the rectal cancer group with the colon cancer group, regardless of whether it was right-sided or left-sided colon cancer, a significant survival-protective effect was observed in colon cancer compared with rectal cancer (right-sided, adjusted HR 0.51, 95% CI 0.28 to 0.92, p=0.028; left-sided, adjusted HR 0.54, 95% CI 0.36 to 0.82, p=0.004). Previous data on this issue are limited. In addition, there is also an interesting independent protective prognostic factor for initial liver metastasis. When compared with other potential variables in multivariate analysis, it was found to be a protective prognostic factor. Further studies are needed to determine whether the site of metastasis is related to differential survival.

Regarding the prognostic factors of the chemotherapy regimens, it was found that univariate analysis revealed a poor prognosis in the group of patients who did not receive second-line chemotherapy. However, multivariate analysis revealed that only the group receiving second-line chemotherapy with an oxaliplatin-based regimen was an independent prognostic protective factor. When the data in Table 2 were examined, it was found that the group receiving second-line chemotherapy with an oxaliplatin-based regimen included most patients who had previously received a single agent as first-line chemotherapy. More than half of mCRC patients or 57%, did not receive further second-line chemotherapy. Therefore, only one-third of patients continued oxaliplatin-based therapy as second-line treatment. This group might have less severe disease. Therefore, the results of protective prognostic factors might need careful interpretation, which is still a limitation of the present study and requires further studies.

The investigators hope that the findings from the present study on prognostic factors, especially those with poor prognostic factors, can be applied and help with decision-making regarding treatment plans for mCRC patients receiving chemotherapy.

What is already known on this topic?

In the past, it was found that the prognostic factor for CRC were cancer stage, number of metastasis, serum concentration of CEA, alkaline phosphatase, worsened performance status, C-reactive protein greater than 5 mg/dL, anemia, anorexia, weight loss of 10% or more, fatigue, hypoalbuminemia, and blood transfusion as poor prognostic factors. However, in the context of metastatic patients receiving chemotherapy, there is no such information.

What this study adds?

In this study, poor ECOG PS greater than or equal to 2, and hypoalbuminemia of less than 3.5 g/dL were poor prognostic factors. Right-sided colon cancer, left-sided colon cancer, initial liver metastasis, and receipt of second-line chemotherapy with an oxaliplatin-based regimen were protective prognostic factors in patients with metastatic stage CRC receiving chemotherapy.

Acknowledgment

The present study protocol was approved by the Institutional Review Board of Buddhasothorn Hospital (number BSH-IRB 041/2563).

Authors' contributions

(I) Conception and design: CC, (II) Administrative

support: CC, (III) Provision of study materials or patients: CC, (IV) Collection and assembly of data: CC, WP, (V) Data analysis and interpretation: CC, (VI) Manuscript writing: All authors, (VII) Final approval of manuscript: All authors.

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Conflicts of interest

The authors declare no conflicts of interest.

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