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Original Research

Factors Affecting Survival of Patients with Synchronous Metastatic Colorectal Cancer in a Tertiary Hospital in Indonesia: A Retrospective Study

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Background and Objective: Despite colorectal cancer (CRC) being one of the most frequent cancers in Indonesia, limited data exists regarding the survival and prognostic factors of Indonesian metastatic CRC patients. This study aimed to investigate the survival outcome and factors influencing local CRC patients presenting with a metastatic stage at diagnosis.

Materials and Methods: A retrospective cohort study was conducted using data from 441 cases of synchronous metastatic CRC treated between January 2016 and December 2019 at Dr. Sardjito Hospital, Yogyakarta, Indonesia. Secondary data were collected from the CRC clinical registry database. Demographic, clinicopathological, and treatment data were collected. Survival status was obtained from the registry database and communication with patients or their families. Kaplan-Meier curves were used to estimate overall survival (OS). The Cox proportional hazards regression model was applied to analyze potential factors affecting survival.

Results: The median follow-up in the study was 17 months. The median overall survival was 13 months. Two-year overall survival was 37%, and the estimated 5-year overall survival was 16.1%. Multivariate Cox analysis identified poor performance status (HR 2.639, 95% CI 1.438-4.842, p = 0.002), elevated carcinoembryonic antigen (CEA) (HR 2.795, 95% CI 1.509-5.176, p = 0.001), and higher histological grade (HR 2.019, 95% CI 1.112-3.667, p = 0.021) as factors associated with poorer overall survival.

Conclusion: Based on the findings, poor performance status, high CEA levels, and higher histological grade were associated with unfavorable overall survival among patients with synchronous metastatic colorectal cancer in Yogyakarta, Indonesia.

Introduction

Colorectal cancer (CRC) is a malignancy with the third most common incidence globally based on the GLOBOCAN database 2020 [1]. In Indonesia, CRC is ranked 4th for cancer incidence and 5th for the cause of death due to cancer [2]. Approximately 22% of CRC patients are diagnosed at stage IV [3]. Stage 4 colorectal cancer patients have poor overall survival, around 10% for five years [3]. A retrospective cohort study using the Surveillance Epidemiology and End Results (SEER) database reported that age at diagnosis, marital status, race, primary tumor site, tumor grade, CEA level, T status, N status, surgery for the primary lesion, chemotherapy, and location of metastases (bone, brain, liver and lung) independently influenced prognosis [4].

There is little information on CRC survival in Indonesia and even less on mCRC. A study in eastern Indonesia reported an association between age, type of histopathology, stage and mode of surgery on overall survival of CRC [5]. Still, it did not focus on patients with metastatic disease. In Yogyakarta province, CRC is the third most common cancer according to the cancer registry data, with 39% of patients have been diagnosed at stage 4 [6]. The purpose of this study is to determine the survival of this group of patients and identify factors affecting it.

Materials and Methods

Data collection

This study used secondary data from the hospital based cancer registry (HBCR) of colorectal in Dr. Sardjito General Hospital Yogyakarta. HBCR abstracted 32 variables using canreg5 software. Based

on initial data from canreg5, more detailed data were collected through medical records as the CRC clinical registry, including patients diagnosed in 2016-2019. The present study recruited all patients with synchronous metastatic disease data from the clinical registry database, including demographic, clinical, pathology and first line treatment information. Data collection was undertaken between August 2020 and February 2022. We included 441 mCRC patients' data from the registry database. The joint ethics committee from the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, has approved this study (reference number KE/FK/0549/E.C./2020). Based on ethical clearance policy, informed consent is not required for retrospective studies

Key Variables

We determined age as "young" if <50 years and "old" if ≥50 years. gender (male versus female), education (<junior high school or ≥junior high school, referred to the 9-years compulsory education in Indonesia), marital status (single, married, or widower/widow), and insurance type (government insurance for the poor, private or premium payer or government insurance for civil servant, or self-pocket). Performance status data was based on Eastern Cooperative Oncology Group (ECOG) scale (0-1, 2, or 3-4) [7]. Body mass index (BMI) was used WHO BMI cut-off for Asian populations (malnutrition <18.5, normal = 18.5-22.9, overweight and obese ≥ 23) [8]. Pretreatment hemoglobin level (<10 or ≥10 g/dL) and CEA level (<=5 ng/mL versus >5 ng/ml) were also collected.

Tumor location was categorized into right sided colon (caecum, ascending colon, hepatic flexure, and transverse colon) and left sided colon (splenic flexure, descending colon, sigmoid colon and rectosigmoid colon). Other tumor parameters included histological grade (1, 2, 3, or 4), morphological subtypes (adenocarcinoma, mucinous carcinoma, or signet ring cell carcinoma), T status (1, 2, 3, 4, and X if it was not determined or unknown), N status (0, 1, 2, and X if it was not determined or unknown), M status (0, 1, and X if it was not determined or unknown), and metastatic stage (A or B-C). Disease stage was determined according to TNM classification of the 8^{th} edition American Joint Committee of Cancer (AJCC) [9]. Primary tumor resection was categorized into two, namely yes and no.

Chemotherapy treatments were categorized into non-oxaliplatin based and oxaliplatin based regimens. Included in the non-oxaliplatin based regimens are single capecitabine (common dose: 2000-2500 mg/m^2/day day 1-14 every 21 days for 8 cycles), De gramont or 2FU/LV (common dose: fluorouracil 400 mg/m^2 IV bolus days 1-2, fluorouracil 600mg/m^2 continuous IV days 1-2, folinicacid 200 mg/m^2 every 14 days for 12 cycles), and FOLFIRI (common dose: irinotecan 180 mg/m^2 day 1, folinic acid 200 mg/m^2 day 1, fluorouracil 400-800 mg IV bolus day 1, fluorouracil 2400-3000 mg/m^2 IV continuously for 36 hours, every 14 days for 6-8 cycles). In comparison, the oxaliplatin based regimens are FOLFOX (common dose: oxaliplatin 85 mg/m^2 day 1, folinic acid 200 mg/m^2 day 1-2, fluorouracil 400 mg/m^2 IV bolus day 1-2, fluorouracil 600 mg/m^2 continuous IV for 22 hours days 1-2, repeated every 14 days for 12 cycles) and CAPOX (common dose: oxaliplatin 135 mg/m^2 day 1, capecitabine 2000-2500 mg/m^2 day 1-14, repeated every 21 days for 8 cycles). The use of targeted therapy was categorized into no targeted therapy and with targeted therapy. Targeted therapy referred to bevacizumab (5 mg/kg day 1, usually administered with FOLFOX 12 cycles maximum or cetuximab (400 mg/kg on first administration, then 200 mg/kg, repeated every week, 12 cycles maximum (based on Indonesia national insurance regulation) according to the KRAS mutation status. The addition of bevacizumab or cetuximab was based on the consideration of the oncologist.

Overall survival (O.S.) was determined as months difference between date of diagnosis and date of death from any causes or the date from current information from medical record. If the patients did not visit the outpatient clinic for more than six months, we contacted them or their families by telephone or mail. We used estimation date in 7 patients who died and the family could only remember the year of death. We determined Jun 30 of the death year as the date of death. While we

could not contact the patients or their families, their survival status was determined by the date of their last visit to the hospital.

Statistical analysis

Variables were compared by Cox proportional hazards regression model. Variables with a p-value <0.05 were included in the multivariate analysis. The Kaplan-Meier method was used to calculate the O.S. Comparisons between groups of interest were analyzed using a log-rank test. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS statistical software (IBM SPSS Statistics for Windows, version 28 (IBM Corp., Armonk, N.Y., USA).

Results

We analyzed 441 eligible patients. The majority of subjects were ≥50 years old (318, 72.1%), males (244, 55.3%), ≥ junior high school educational attainment (245, 55.6%) and being married (391, 88.7%). Sixty-seven percent had private or premium payer or government insurance for a civil servant. Most subjects had ECOG 0-1 performance status (228, 51.7%). At total of 183 cases (41.5%) had 18.5-23 kg/m^2 BMI and 310 cases (70.3%) had a pretreatment hemoglobin level ≥10 g/dL. CEA level >5 ng/mL were in 227 subjects (51.5%). Most subjects had left-sided tumor (333, 75.5%) and histological grading 1 (152, 34.5%). Adenocarcinoma was the prominent morphological subtypes (n =390, 88.4%). T3 was the majority of tumor status (213, 48.3%) and N1 was the majority of N status (142, 32.2%). A total of 257 (58.3%) patients did not undergo primary tumor resection, 291 patients received targeted therapy (66.0%). and 335 patients (76.0%) had a IV-A metastatic disease. The baseline characteristics of study subjects are listed in Table 1.

Variables	Frequency (N)	Percentage (%)
Age (years)		
<50	123	27.9
≥50	318	72.1
Gender		
Male	244	55.3
Female	197	44.7
Education		
< junior high school	134	30.4
≥ junior high school	245	55.6
Unknown	62	14.1
Marital status		
Single	12	2.7
Married	391	88.7
Widower/widow	31	7
Unknown	7	1.6
Insurance		
Government insurance for the poor	114	25.9
Private insurance, premium payer, or government insurance for civil servant	297	67.3
Self-pocket	23	5.2
Unknown	7	1.6
ECOG		
0-1	228	51.7
2	94	21.3
04-Mar	46	10.4
Unknown	73	16.6

BMI (kg/m2)		
<18.5	146	33.1
18.5-23	183	41.5
≥23	81	18.4
Unknown	31	7
Hemoglobin level (g/dL)		
<10	98	22.2
≥10	310	70.3
Unknown	33	7.5
CEA (ng/mL)		
≤5	56	12.7
>5	227	51.5
Unknown	158	35.8
Tumor location		
Right	82	18.6
Left	333	75.5
Unknown	26	5.9
Histological grading		
1	152	34.5
2	131	29.7
04-Mar	46	10.4
Unknown	112	25.4
Morphological subtypes		
Adenocarcinoma	390	88.4
Mucinous carcinoma	19	4.3
Signet ring cell carcinoma	8	1.8
T status		
1	4	0.9
2	23	5.2
3	213	48.3
4	120	27.2
X	81	18.4
N status		
0	138	31.3
1	142	32.2
2	50	11.3
X	111	25.2
Targeted therapy		
No	291	66
Yes	150	34
Resection of primary tumor		
No	257	58.3
Yes	75	17
Unknown	109	24.7
Metastatic stage		
IVA	335	76
IVB	91	20.6
IVC	15	3.4

Table 1. Baseline Characteristics of Study Subjects (n=441).

Note, ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; CEA, carcinoembryonic

antigen, T, tumor; N, nodal.

The median duration of follow-up for the whole cohort was 17 months (ranged 0.0-72 months). The median overall survival was 13 months. The 2-year survival was 37%, and the estimated 5-year survival was 16.1% (Figure 1).

Figure 1. Kaplan-Meier curve of OS in mCRC.

Univariate cox regression showed that ECOG, BMI, CEA, hemoglobin, tumor location, histological grading, N status, resection of the primary tumor, targeted therapy and metastatic stage were potential survival predictors.

Multivariate cox regression demonstrated that ECOG 3-4 was associated with poorer prognosis (HR =2.639, 95% confidence interval/CI 1.438-4.842, p 0.002). A higher CEA level was associated with increased mortality (HR = 2.795, 95% CI 1.509-5.176, p = 0.001).

A higher histological grade was also associated with poorer survival (histological grade 3-4, HR 0.021, 95%CI 1.112-3.667, p = 0.021). Due to missing data, only in 177 cases (40.1%) can multivariate analysis be performed. The univariate and multivariate analyses for overall survival are listed in Table 2.

Variables		Univariate analysis			Multivariate analysis	
	HR	95% CI	p*	HR	95% CI	p*
Age (years)						
<50						
≥50	1.179	0.877-1.584	0.275			
Gender						
Male						
Female	1.037	0.802-1.341	0.781			
Education						
<junior high school						
≥junior high school	1.043	0.777 -1.402	0.778			
Marital status						
Single						
Married	0.952	0.563-1.609	0.855			
Widower/Widow	1.085	0.481-2.447	0.844			
Insurance type						
Government insurance for the poor						
Private insurance, premium payer, or government insurance for civil servant	0.998	0.737-1.351	0.99			
Self-pocket	0.727	0.359-1.471	0.375			
ECOG						
0-1						
2	1.336	0.955-1.87	0.091	1.245	0.734-2.111	0.417
04-Mar	2.471	1.655-3.688	0	2.651	1.444-4.865	0.002

BMI (kg/m2)						
<18.5						
18.5-22.9	0.878	0.651-1.183	0.392	0.782	0.502-1.217	0.276
≥23	0.774	0.53-1.13	0.185	0.904	0.508-1.609	0.731
CEA (ng/mL)						
<=5						
>5	1.854	1.214-2.83	0.004	2.762	1.49-5.121	0.001
Hemoglobin (mg/dL)						
<10						
≥10	0.524	0.384-0.716	<0.001	0.767	0.446-1.319	0.338
Tumor location						
Right						
Left	0.819	0.595-1.126	0.219	0.728	0.417-1.271	0.264
Histological grading						
1						
2	0.81	0.587-1.116	0.198	0.755	0.482-1.184	0.221
04-Mar	1.428	0.945-2.157	0.091	2.01	1.107-3.649	0.022
Pathological morphology						
Adenocarcinoma						
Mucinous carcinoma	0.962	0.51-1.813	0.904			
Signet ring cell carcinoma	1.12	0.278-4.515	0.874			
T status						
1						
2	0.661	0.148-2.957	0.588			
3	0.637	0.157-2.587	0.528			
4	0.818	0.2-3.342	0.78			
x	0.804	0.193-3.346	0.764			
N status						
0						
1	1.057	0.767-1.456	0.734	0.807	0.5-1.304	0.382
2	1.195	0.766-1.863	0.432	0.93	0.482-1.795	0.829
x	1.528	1.078-2.166	0.017	1.053	0.57-1.944	0.869
Resection of primary tumor						
No						
Yes	1.374	0.976-1.934	0.068	1.197	0.676-2.12	0.536
Unknown	1.023	0.661-1.583	0.919	1.41	0.641-3.103	0.393
Targeted therapy						
No						
Yes	0.787	0.605-1.023	0.073	1.066	0.704-1.615	0.762
Metastatic stage						
A						
B-C	1.544	1.544-2.098	0.006	1.345	0.817-2.215	0.243

Table 2. Univariate and Multivariate Analyses for Overall Survival.

Statistical analysis performed by Cox proportional hazard model with p*< 0.05; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; CEA, carcinoembryonic antigen, T, tumor; N,

nodal.

Kaplan-Meier curves also showed statistically significant differences based on ECOG, CEA, and histological grade (Figure 2-4).

Figure 2. Kaplan-Meier Curve of OS in ECOG 0-1, 2, and 3-4. OS, Overall Survival, ECOG, Eastern Cooperative Oncology Group.

Figure 3. Kaplan-Meier Curve of OS Based on CEA Level. OS, Overall Survival; CEA, Carcinoembryonic Antigen.

Figure 4. Kaplan-Meier Curve of OS Based on BMI. OS, overall survival; BMI, body mass index.

Discussion

Metastatic CRC is still a challenge in the field of oncology. In Yogyakarta, Indonesia, nearly 40% of CRC patients present at stage 4 (6). To the best our knowledge, this is the first study conducted to determine the factors that affect the overall survival of mCRC patients in Yogyakarta. We analyzed 411 mCRC patients treated at Dr. Sardjito Hospital, a tertiary hospital in Yogyakarta.

Five years O.S. in this study was 16.1% with a median survival of 13 months. There 41% of participants did not receive targeted therapy. The addition of targeted therapy was at the discretion of the oncologist. The reasons why these patients did not receive targeted therapy were not investigated further in this study. Although the resources for cancer services in Indonesia were limited, as was often found in developing countries, the 5-year overall survival in this study was comparable to the Surveillance, Epidemiology, and End Results (SEER) report, which showed 5-year O.S. for metastatic colorectal cancer in the USA was 14.7% [10,11]. Meanwhile, in Europe, the 5-year overall survival for mCRC was 22% [12].

Based on multivariate cox regression, the variables that independently affect overall survival were ECOG score, CEA and histological grade. The ECOG score, an assessment of performance status, has been known to be one of the most influencing factors for survival in cases of metastatic colorectal cancer [13]. In this study, patients with ECOG 3-4 were independently associated with a worse prognosis with HR 8,472 ($p < 0.001$, 95% CI: 3.748-19151). Since cases with metastases usually present with poor performance status associated with visceral crisis, clinicians tend to give less aggressive therapy or reduced chemotherapy doses [13]. However, we did not record whether the patients received a reduced dose or not in this study.

CEA can be measured in serum quantitatively and can be used as a diagnostic and prognostic marker [14]. Increased preoperative CEA has been known to be associated with poorer overall survival [15], as confirmed by our study. The relationship between histological grade based on tumor differentiation and disease prognosis has also been well-recognized, supporting our findings [16]. Those with colorectal adenocarcinomas that are grade 3 often have a worse prognosis than patients whose tumors are grade 1 or 2. Patients with grade 3 colorectal adenocarcinomas had a 45.5% 5-year survival rate, while the 5-year survival rate of grades 1 and 2 were 71.4% and 59.5%, respectively [17].

The strength of this study is that it is the first study on factors affecting survival in mCRC in Indonesia. Missing data is a weakness of retrospective studies; this study was no exception. There

were 16.6% missing data on ECOG, 35.8% on CEA and 25.4% on histological grading. Thus only 40.1% of cases could be done multivariate analysis (n=177). Another limitation was that it was unknown why patients did not receive targeted therapy and whether patients with poor performance status received reduced chemotherapy doses. Despite these limitations, we found that ECOG score, CEA and histological grading showed their prognostic ability. In conclusion, this study showed ECOG score, CEA levels and histological grade were independent factors affecting survival in mCRC.

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Institutional Review Board Statement

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Conflicts of Interest

All authors declare that they have no conflicts of interest.

References

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: a cancer journal for clinicians.* 2021; 71(3)DOI
2. World Health Organization. Cancer Incident in Indonesia. *Int Agency Res Cancer.* 2020; 858:1-2.
3. Wang J, Li S, Liu Y, Zhang C, Li H, Lai B. Metastatic patterns and survival outcomes in patients with stage IV colon cancer: A population-based analysis. *Cancer Medicine.* 2020; 9(1)DOI
4. Liu Z, Xu Y, Xu G, Baklaushev VP, Chekhonin VP, Peltzer K, Ma W, Wang X, Wang G, Zhang C. Nomogram for predicting overall survival in colorectal cancer with distant metastasis. *BMC gastroenterology.* 2021; 21(1)DOI
5. Labeda I, Lusikooy RE, Mappincara, Dani MI, Sampetoding Sa, Kusuma MI, Uwuratuw JA, et al. Colorectal cancer survival rates in Makassar, Eastern Indonesia: A retrospective Cohort Study. *Annals of Medicine and Surgery.* 2021; 74DOI
6. RKBR Maret 2021. 2021;(8 July 2021). *Available from: https://canreg.fk.ugm.ac.id/laporan-data/registrasi-kanker-berbasis-rumah-sakit-dr-sardjito-fkkmk-ugm/rkbr-maret-2021/.*
7. ECOG Performance Status Scale The ECOG Performance Status Scale circulates in the public domain and is therefore available for public use . Comparing the ECOG Performance

Status and the Karnofsky Performance Status Scales. ECOG-ACRIN [Internet]. 2022;0–1. *Available from: https://ecog-acrin.org/resources/ecog-performance-status/.*
8. WHO/IASO/IOTF . The Asia-Pacific perspective: redefining obesity and its treatment. Health Communications Australia; Melbourne: 2000. 2000;.
9. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Gershenwald JE, et al. AJCC Cancer Staging Manual (8th edition). Springer International Publishing: American Joint Commission on Cancer; 2017. 2AD. 2017 p.
10. Countries L, Souza JA De, Hunt B, Asirwa FC, Adebamowo C, Lopes G. Global Health Equity : Cancer Care Outcome Disparities in. 2016; 34(1):4-6.
11. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER, Cancer Stat Facts: Colorectal Cancer 2011-2017. Accessed 4. 2022;(April):2022..
12. Cardoso R, Guo F, Heisser T, De Schutter H, Van Damme N, Nilbert MC, Christensen J, et al. Overall and stage-specific survival of patients with screen-detected colorectal cancer in European countries: A population-based study in 9 countries. *The Lancet Regional Health. Europe.* 2022; 21DOI
13. Stillwell AP, Ho YH, Veitch C. Systematic review of prognostic factors related to overall survival in patients with stage IV colorectal cancer and unresectable metastases. *World Journal of Surgery.* 2011; 35(3)DOI
14. Lee JH, Lee SW. The Roles of Carcinoembryonic Antigen in Liver Metastasis and Therapeutic Approaches. *Gastroenterology Research and Practice.* 2017; 2017DOI
15. Baqar AR, Wilkins S, Staples M, Angus Lee CH, Oliva K, McMurrick P. The role of preoperative CEA in the management of colorectal cancer: A cohort study from two cancer centres. *International Journal of Surgery (London, England).* 2019; 64DOI
16. Ueno H, Mochizuki H, Hashiguchi Y, Ishiguro M, Kajiwara Y, Sato T, Shimazaki H, Hase K, Talbot IC. Histological grading of colorectal cancer: a simple and objective method. *Annals of Surgery.* 2008; 247(5)DOI
17. Takeuchi K, Kuwano H, Tsuzuki Y, Ando T, Sekihara M, Hara T, Asao T. Clinicopathological characteristics of poorly differentiated adenocarcinoma of the colon and rectum. *Hepato-Gastroenterology.* 2004; 51(60)