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Do Tumor Locations and Stages at Diagnosis Predict the 5-Year Survival Outcome in Patients with Colorectal Cancer?

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Abstract

BACKGROUND: Globally, colorectal cancer (CRC) ranks as the third most common cancer. CRC cases are generally discovered at a more advanced stage, so the patients' life expectancy is low. The prognostic factors that affect the survival outcome in CRC patients are still limited.

AIM: This study aimed to identify factors associated with the 5-year overall survival of CRC patients at Dr. Saiful Anwar Regional General Hospital, Malang.

MATERIALS AND METHODS: This study used a retrospective cohort design and obtained data from patients diagnosed with CRC at Dr. Saiful Anwar Regional General Hospital Malang between January and December 2015. The 5-year prognosis factors, tumor clinical characteristics, disease progression, and demographic details were analyzed using Kaplan Meier and Cox regression.

RESULTS: Kaplan–Meier analysis showed differences in the survival function based on surgery ($p = 0.028$) and stages ($p = 0.002$). There were no differences in the survival function based on gender ($p = 0.455$), age ($p = 0.484$), tumor location ($p = 0.114$), carcino embryonic antigen (0.459), histopathology ($p = 0.842$), tumor recurrence ($p = 0.268$), chemotherapy response ($p = 0.06$), and response description ($p = 0.086$). Based on the Cox proportional hazard regression, the tumor stage was the only variable that affected the risk of mortality ($p = 0.014$) with an HR value of 3.500 (CI 95%).

CONCLUSION: The tumor stage is a significant predictor of survival, suggesting that higher stages may require more attention and more aggressive treatment than lower stages.

Introduction

Colorectal cancer (CRC) is a malignancy originating from the colon tissue, consisting of the colon (the longest part of the large intestine) with or without the involvement of the rectum (the last part of the large intestine before the anus) [1]. CRC represents the third most common malignancy worldwide and the second leading cause of death regardless of gender [2].

In Indonesia, CRC cases are only discovered at an advanced stage, resulting in low life expectancy despite the number of therapies. It is due to a lack of public knowledge about cancer, and people only carry out medical check-ups if the symptoms interfere with their activities [3]. The transformation of the normal colonic epithelium into precancerous lesions (adenomas), which later become invasive carcinomas, depends on genetic mutations, either acquired or inherited [4]. Clinical evidence showed that CRC often presents as an adenomatous polyp and usually undergoes dysplastic changes in a 10–15-year period before progressing into invasive carcinoma, and early detection of polyp removal reduces the incidence of CRC [5].

The majority of all CRCs are carcinomas, of which more than 90% are adenocarcinomas and others are less common (adenosquamous, spindle, squamous, and undifferentiated). CRC adenocarcinomas can be differentiated into cribriform comedo, medullary, micropapillary, serrated, mucinous, and stamp ring-type cells. In addition, adenocarcinomas were categorized based on the percentage of glandular formation, which are well-differentiated (more than 95%), moderate (more than 50%), and poor (<49%), but were further divided into two grades, low-grade (well-moderate) and high-grade (poor) with prognostic significance [6]. Complete surgical resection (R0) with all negative circumferential resection margins is essential to avoid local-distant recurrence and improve survival. Palliative systemic chemotherapy is offered to non-surgical candidates with locally advanced inoperable disease

or high metastatic burden to improve quality of life and prolong life expectancy. However, studies on the relationship between clinical characteristics, disease progression, and demographics on patient outcomes are still limited. This study aimed to identify the factors associated with the 5-year overall survival (OS) of CRC patients at dr. Saiful Anwar Regional General Hospital, Malang.

Methods

This retrospective cohort study used data from dr. Saiful Anwar Regional General Hospital, Malang, which is a type A hospital. Data on patients with CRC between January and December 2015 were collected, and biopsies were performed for histopathological analysis, surgery, chemotherapy, and palliative care. The patients were treated according to the applicable standard protocol and prospectively monitored to assess their 5-year survival. Ethics and permissions for conducting this study were obtained from Saiful Anwar Regional General Hospital Malang under the ethical clearance letter number 400/254/K.3/302/2020.

Details of patient information from medical and pathological records, whether from the medical record center unit, cancer clinic, or pathology laboratory, were screened. Data on age at diagnosis, sociodemographic details (marital and educational status), pathological diagnosis, clinical stage, tumor size, histologic type, tumor location, tumor recurrence, and treatment were also collected. The survival status of the patients was obtained from medical records at the end of 5 years of diagnosis. Telephone interviews were conducted for those who did not have a living status in the medical record. The patient's nuclear family members were considered as respondents if the patient had died. Data were considered lost if the authors could not collect live status data from medical records or no responses from three attempts to contact the patient.

Kaplan–Meier constructs were conducted to estimate the OS level. Five-year patient survival time refers to the number of months from the date of diagnosis to the date the patient died, the date to follow-up, or the end date of the study for living patients. All data were analyzed using SPSS version 26. Before analyzing, data were entered, cleaned, edited, and coded in Microsoft Excel. Survival analysis was conducted by examining the assumption of proportional hazard (PH), bi-variable, and multivariable analysis. The assumption of PH was determined using the Kaplan–Meier curve for the variables that meet the assumption of PH with a significant level of $p < 0.05$. Furthermore, the prognostic factor of clinical characteristics, disease progression, and demographic details was analyzed using Cox regression with a significant level of $p < 0.05$.

Results

A total of 40 patients were evaluated and were diagnosed with CRC. From the data, the number of patients was 25 male (62.5%) and 15 women (37.5%). Patients above 40 years old during the first diagnosis were five patients (12.5%), while patients younger than 40 years old were 35 patients (87.2%). There were 30 patients (75%) who obtained palliative treatment, while ten patients (25%) obtained resurrection treatment. Further, among the patients, 25% suffered CRC in the ascending colon, 20% was in the sigmoid colon, 2.5% was in transverse colon, 37.5% was in distal 1/3 rectum, 5% was in proximal 1/3, and 10% was in rectum 1/3 middle. The number of patients diagnosed as Stage 3 at the beginning of diagnosis was 8 people (21.6%), while those diagnosed as Stage 4 were 29 people (78.4%). Patients with carcino embryonic antigen (CEA) <10 iu/L were 5 (12.5%) and CEA >10 iu/L were 35 (87.5%). In terms of histopathology, there were six patients (15%) with well-differentiated features, nine people (22.5%) with undifferentiated features, 16 (40%) with poorly differentiated features, and nine people (22.5%) with moderately differentiated. Patients with tumor recurrence were 36 people (90%), while those without tumor recurrence were four people (10%). For the response to chemotherapy, six patients responded (15%), and 34 patients did not respond (85%). Based on the response information, there were five patients (12.5%) with complete response, two patients (5%) died, one patient (2.5%) had a partial response, 16 patients (40%) were progressive, and 16 patients (40 patients) were at stable disease.

Based on the Kaplan–Meier analysis, it was found that based on gender, p-value obtained was 0.455, so there was no difference in the survival function according to gender. Meanwhile, based on age, p-value obtained was 0.484, so there was no difference in the survival function based on age. Based on the action, p-value obtained was 0.028, meaning that there were differences in the survival function based on the action. In addition, the average survival of subjects with tumor resection (12.25) was higher than subjects with palliative measures (7.3). Based on the location, p-value obtained was 0.114, so there was no difference in the survival function according to the location (Figure 1). Based on the stage, p-value obtained was 0.002; thus, there was a difference in the survival function based on stage (Figure 2). The average survival of subjects with Stage 3 (13.5) was higher than subjects with Stage 4 (6.655). Based on the CEA, p-value obtained was 0.459, so there was no difference in survival function based on CEA. Based on Histo PA, p-value obtained was 0.842, so there was no difference in survival function based on Histo PA. Based on tumor recurrence, p-value obtained was 0.268, so there was no difference in survival function based on tumor recurrence. According to the response to chemotherapy, p-value obtained was 0.06, so there was no difference in survival function based

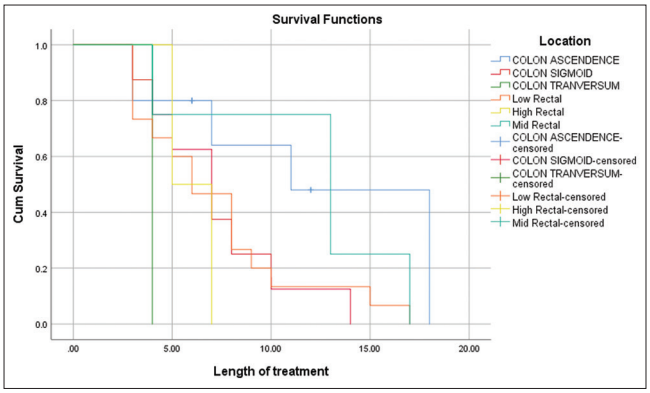

Figure 1: Chart of survival time based on location

on chemotherapy response. Based on the response information, p-value obtained was 0.086, so it can be concluded that there was no difference in the survival function based on the response information (Table 1).

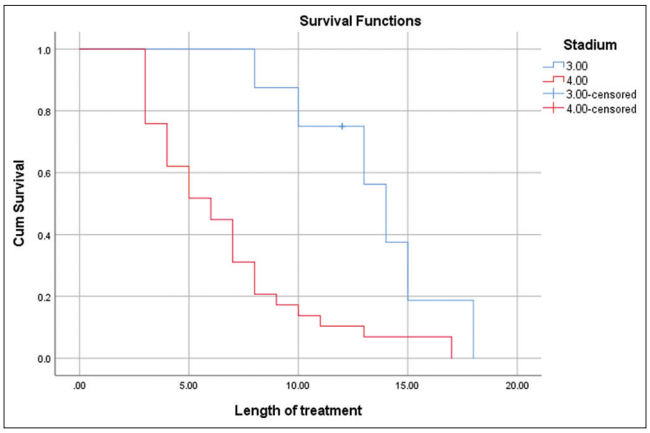

Figure 2: Chart of survival time based on staging

The test of PH assumption did not meet the survival chart based on the variables of gender, age, surgery, tumor location, CEA, histopathology, and response description. However, PH assumptions were met on the survival chart based on tumor stage, tumor recurrence, and chemotherapy response variables. Meanwhile, based on the Cox PH Regression, only tumor stage variable affected the risk of death (p = 0.014) with an HR value of 3.500 (95% CI). This shows that subjects with Stage 4 have a 3.5 times higher risk of death than those with Stage 3.

Discussion

The survival rate of CRC patients in Indonesia is still rarely analyzed. Based on research conducted by Labeda *et al*., the OS of CRC patients was according to age, histopathology, stage, and history of definitive surgery [7]. Meanwhile, research conducted by Li stated that age, gender, tumor location, and histopathological type influenced the survival of CRC patients [8].

This research collected data on patients diagnosed with CRC between January and December 2015 and biopsies were performed for histopathological analysis, surgery, chemotherapy, and palliative care. Subjects with Stage 4 (higher) had a 3.5 times higher risk of death than subjects at Stage 3. This result is in line with a study conducted in Korea [9], that according to the stage determined by the AJCC 6th edition system, the specific survival for Stage 5 years was 91% for Stage I, 81% for Stage IIa, 83% for Stage IIb, 100% for Stage IIIa, 64% for Stage IIIb, 37% for Stage IIIc, and 4% for Stage IV. In this case, 5-year survival was significantly higher for patients with Stage IIIb (64%) than patients with Stage IIIc (37%).

However, this research was not comparable to the study in China that the survival paradox between Stage IIB/IIC and Stage IIIA colon cancer was based on the latest staging criteria [10]. Another study by Jeo and Subrata Feyona showed that the OS rate of CRC within 5 years at Dr. Cipto Mangunkusumo Hospital was 43% [11]. Factors that affected patient survival were clinical stage and definitive surgery in the form of resectioning the primary tumor mass.

This research showed significant differences in patients with CRC who underwent palliative care and patients with tumor resection. Meta-analysis of clinical trials in previous studies showed that colectomy surgery with laparoscopy or open laparotomy gave similar results for 5-year OS (69% vs. 68%) and disease-free survival (76% vs. 75%) [12]. These differences were probably caused by the differences in the number of subjects.

In this research, there was no significant difference in the location of tumor growth. In a previous study, the survival of CRC patients with tumor location on the right side was relatively lower than tumors growing on the left side of the colon [12]. Another study found that CRC in the ascending colon has a worse prognosis than CRC in the descending colon, except for the cecum. In addition, the OS in the left colon is better than in the right colon and rectum [13].

The estimation of survival rates varied according to the follow-up period, study population, quality of data, statistical methods used, and possible bias. This suggests that comparisons of survival rates should be interpreted with caution. However, such information is missing from this study, although data have been collected from many sources. Thus, many factors that can affect survival cannot be determined accurately. One factor that primarily affects the low survival of CRC patients is that most cases are already at high stages when the diagnosis is carried out. It is vital to carry out routine screening, early detection, and education, followed by treatment, to increase the survival of CRC patients [14].

The limitation of this research is the small population, so further research is needed with larger

Table 1: Kaplan–Meier analysis for survival time of colorectal cancer

Variable	Mean survival time (month)	p (test log) rank	Description
Gender		0.455	No significant difference
Women	9.45		
Men	7.732		
Age (years old)		0.484	No significant difference
<40	9.2		
>40	8.142		
Treatment		0.028	Significant difference
Palliative	7.3		
Tumor resection	12.25		
Location		0.114	No significant difference
Colon ascendence	12.12		
Colon sigmoid	7.25		
Colon tranversum	4		
Rectum 1/3 distal	7.2		
Rectum 1/3 proximal	6		
Rectum 1/3 medial	11.75		
Stage		0.002	Significant difference
3	13.5		
4	6.655		
CEA (ng/mL)		0.459	No significant difference
<10 (iu/L)	8.4		
>10 (iu/L)	8.189		
Histo PA		0.842	No significant difference
Well diff	7.5		
Undiff	8.556		
Poorly diff	7.25		
Moderate diff	9.778		
Tumor recurrence		0.268	No significant difference
−	10.25		
+	8.122		
Chemotherapy response		0.06	No significant difference
No response	7.794		
Response	11		
Response description		0.086	No significant difference
Died	4		
Partial response	6		
Progressive	9.313		
Stable disease	6.75		

CEA: Carcinoembryonic antigen.

subjects. This research was also conducted only from January to December 2015, so further research should be done in a longer periode.

Conclusion

The overall 5-year survival rate for CRC patients is relatively low. In this case, the implementation of screening, improvement of diagnostic approaches, and access to treatment will improve patient survival. Among many prognostic factors, the tumor stage is a significant predictor of survival, suggesting that higher stages may require more attention and more aggressive treatment than lower stages.

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