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Prognostic Factor and *KRAS* Mutation Status in Association with Overall Survival in Patients with Colorectal Adenocarcinoma in Hasan Sadikin General Hospital

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ABSTRACT

Introduction
Colorectal adenocarcinoma is a malignant epithelial tumor originating from the colon. Colorectal adenocarcinoma is the most common colorectal carcinoma. We aim to analyze the association between prognostic factors and *KRAS* mutation status with overall survival in patients with colorectal adenocarcinoma in Hasan Sadikin General Hospital.

Methods
This retrospective analysis investigated the prognostic factors and KRAS mutation status in 27 patients with stage III and IV colorectal adenocarcinoma. *KRAS* mutations were assessed using PCR.

Results
A total of 27 cases were collected and analyzed. Patients dominated with female patients (74.1%), with more than half of the patients aged >50 years old (55.6%). Most patients had tumors in their right colon (48.1%) and stage III when they were diagnosed (81.5%). 55.6% of patients had a mutation dominated by *KRAS* codon 12 (25.9%). The median overall survival was 13 months. Age and tumor site were statistically significant to overall survival ($p<0,05$); the median OS was seven months for patients whose diagnosis was <50 years old. The median OS of patients with tumors in the right colon had a median OS of 30.6 months. Gender, *KRAS* mutation, and stage at diagnosis had no statistical significance on overall survival.

Conclusions
Adenocarcinoma colorectal in Hasan Sadikin Hospital from 2016 until 2020 mainly occurred in women over 50 years old, with the most common location being in the right colon and most of the patients were at stage III when they were diagnosed. Most of patient in this study have mutation in *KRAS*. Age and tumor site had statistical significance on overall survival.

Keywords: Adenocarcinoma colorectal, KRAS mutation, overall survival, prognostic factor

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INTRODUCTION

Colorectal carcinoma (CC) is the third most frequent malignancy and the second most deadly cancer globally.[1–3] Most colorectal carcinoma cases, approximately 90%, are adenocarcinomas.[1,2] Colorectal adenocarcinoma is a malignant epithelial tumor originating from the colon, which shows glandular or mucous differentiation.[2,3]

Global Cancer Statistic (GLOBOCAN) 2020 data states that colorectal cancer is increasing globally, with an estimated 1.93 million new cases diagnosed and 0.94 million colorectal cancer cases causing death worldwide in 2020. According to estimates from GLOBOCAN 2020, globally, there were 1.15 million new cases of colon cancer and 0.7 million new cases of rectal cancer. Colorectal cancer is predicted to reach 3.2 million cases by 2040, based on projections of aging, population growth, and human development.[1]

Based on GLOBOCAN 2020 data in Indonesia, colorectal cancer is the third cancer with the highest number of new cases after breast and cervical cancer, which is 8.6%. Colorectal cancer ranks eighth in the number of deaths, with 9,444 cases.[1]

Colorectal carcinoma has a consistently high incidence in populations in high-income countries combined with a sedentary diet and lifestyle. Risk factors for colorectal carcinoma are processed and red meat consumption, alcohol consumption, and excess body fat. Genetic predisposition plays an important role in colorectal carcinoma, depending on the type of Mutation.[1–3]

Colorectal adenocarcinoma, referred to as NOS (not otherwise specified) adenocarcinoma, is the most common colorectal carcinoma, but there are several other histopathologic subtypes of colorectal adenocarcinoma, namely serrated adenocarcinoma, adenoma-like adenocarcinoma, micropapillary adenocarcinoma, mucinous adenocarcinoma, poorly cohesive adenocarcinoma, signet-ring cell carcinoma, medullary adenocarcinoma, adenosquamous carcinoma, undifferentiated carcinoma, carcinoma with sarcomatoid component.[2–5]

The pathogenesis of colorectal carcinoma mainly develops through the conventional adenoma-carcinoma sequence, and the remainder evolves through hypermutant or ultramutant pathways. This involves transitioning from normal mucosal epithelial stem cells through adenoma to carcinoma, gradually accumulating genetic and epigenetic abnormalities in highly variable patterns in the developing tumor cells. The most frequent and characteristic genetic alterations in the conventional colorectal adenoma-carcinoma pathway include changes in APC, KRAS, TP53, SMAD4, or PIK3CA (84%, chromosomal instability pathway). Mismatch repair genes in MLH1 and MSH2 (13% MSI hypermutant pathway) and POLE (3% ultramutant pathway). Kirsten rat sarcoma (KRAS) is one of the most frequently mutated oncogenes in CRC, with approximately 40% of CRC patients harboring activating missense mutations in KRAS and most of them occurring at codon 12,13 and 61. KRAS plays an essential regulatory role in the cell signal transduction pathways, such as PI3K-Akt and RAS-RAF-MAPK signaling pathways involved in cell proliferation and RAS-GEF signaling pathway related to cytokine production. The constitutive active KRAS causes aberrant and uncontrollable cell growth and cell transformation, promotes cancer metastasis, and increases resistance to chemotherapy. EGFR targeted therapy in many cancer types including CRC. Patients with KRAS-mutant CRC have a poorer prognosis than those with KRAS wild-type CRC, especially in the metastatic setting. In CRC, KRAS mutations are most associated with right-sided colon tumors.[2,6–8]

The prognosis of colorectal cancer is affected by factors such as site of origin, tumor morphology, and metastasis at diagnosis, but also.[9] Based on the above, this study aims to analyze the association between KRAS mutation status and prognostic factors, especially overall survival in patients with colorectal adenocarcinoma in Hasan Sadikin General Hospital.

METHODS

This study used 27 paraffin blocks from patients who had undergone surgical excision and had been diagnosed histopathologically with adenocarcinoma colorectal stage III and stage IV with more than 12 lymph nodes in Hasan Sadikin General Hospital from 2016 until 2020. Paraffin blocks that did not contain more than 10% tumor mass were excluded. Paraffin blocks were cut to a 5 µm thickness, and unstained slides were made for PCR using the Idylla KRAS mutation test with the following procedure: unstained slides containing >10% tumor mass were scraped, and the scraped tissue was positioned between two filter papers (like a sandwich). After that, drip the tissue and filter paper with nuclease-free water and insert the tissue and filter paper into the Idylla™

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KRAS Mutation Asssay (Biocartis NV, Belgium) (Table 1). Next, scan the cartridge barcode with the Idylla™ Platform. Insert the cartridge into the Idylla™ Platform. Confirm the test request on the Idylla™ Platform. Idylla will process the tissue (real-time) automatically for 120 minutes using quantitative polymerase chain reaction (PCR) method. Results will be immediately displayed on Idylla™ Platform and can be downloaded.

Statistical analysis was performed using statistical software: prognostic factors, KRAS mutation, and survival were analyzed using the Kaplan-Meier curve. This study has obtained ethical approval from the Health Research Ethics Committee of Padjajadran University with number 1222/UN6.KEP/EC/2023.

Table 1. KRAS mutation detection using Idylla™ KRAS Mutation Asssay (Biocartis NV, Belgium)

Location mutation	SNP
Codon 12 (exon 2)	G12C (c.34G>T) G12R (c.34G>C) G12S (c.34G>A) G12A (c.35G>C) G12D (c.35G>A) G12V (c.35G>T)
Codon 13 (Exon 2)	G13D (c.38G>A)
Codon 59 (Exon 3)	A59E (c.176C>A) A59G (c.176C>G) A59T (c.175G>A)
Codon 61 (Exon 3)	Q61K (c.181C>A; c.180_181delinsAA) Q61L (c.182A>T) Q61R (c.182A>G) Q61H (c.83A>C; c.183A>T)
Codon 117 (Exon 4)	K117N (c.351A>C; c.351A>T)
Codon 146 (Exon 4)	A146P (c.436G>C) A146T (c.436G>A) A146V (c.437C>T)

RESULTS

A total of 27 cases were included during the study period. Subjects mainly were female (74.1%). More than half of the participants were diagnosed at more than 50 years old (55.6%). The mean age at diagnosis according to their gender was 47.0 ± 13.8 years old in men and 54.8±12.1 years old in women (p=0.167).

Table 1. Characteristics of patients according to age group.

Characteristics	All		<50 years old		≥50 years old	
	n=27	%	n=12	%	n=15	%
Gender						
Males	7	25.9	4	33.3	3	20.0
Females	20	74.1	8	66.7	12	80.0
Tumour site						
Right Colon	13	48.1	7	58.3	6	40.0
Left Colon	5	18.5	2	16.7	3	20.0
Rectum	9	33.3	3	25.0	6	40.0
Stage at diagnosis						
III	22	81.5	9	75.0	13	86.7
IV	5	18.5	3	25.0	2	13.3
Mutation						
Yes	15	55.6	8	66.7	7	46.7
No	12	44.4	4	33.3	8	53.3

Table 1 summarizes the demographic characteristics, tumor site, stage at diagnosis, and mutation status in detail. In this study, most patients had tumors in their right colon (48.1%). Furthermore, most patients were at stage III when diagnosed with the cancer (81.5%). In terms of Mutation, most of the patient's tumors were mutated (55.6%), dominated by KRAS codon 12 (25.9%), followed by KRAS codon 13 (14.8%) and KRAS codon 61 (11.1%).

Overall survival (OS)

During the study, the median OS was 13 months (95% CI [6.2 – 19.8]). According to their gender, the median OS of male patients was seven months (95% CI [0.6 – 13.4]). Male median OS was less than the median OS of female patients, which was 24 months (95% CI [0.0 – 35.6]). There was no difference in OS according to gender ($p = 0.139$).

Furthermore, there was a statistically significant difference in OS according to age at

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diagnosis ($p < 0.05$). Among patients whose age at diagnosis <50 years old, the median OS was seven months (95% CI [1.4 – 12.6]), which was significantly lower than patients whose age at diagnosis ≥50 years old with median OS 15 months (95% CI [0.0 – 35.6]).

In addition, there was a statistically significant OS according to the tumor site, $p < 0.05$. The patients with tumors in the right colon had a median OS of 7 months (95% CI [1.4 – 12.6]), significantly lower than those in the left colon and rectum. The median OS of patients whose tumors were located in the right colon was 30.6 months (95% CI [12.2 – 48.9]), while the median OS of patients whose tumors were located in the rectum was 35.5 months (95% CI [12.7 – 30.4]).

The median OS of participants diagnosed at stage III was 25.3 months (95% CI [14.2 – 36.3]), which was higher than those participants diagnosed at stage IV was 12.0 months (95% CI [4.4 – 19.6]), but not statistically significant ($p = 0.245$).

In terms of the tumor mutation, there was no significant difference in OS between patients which tumor mutated or not, $p = 0.571$. The median OS of participants with mutated tumors was 17.2 months (95% CI [14.2 – 36.3]), which was lower than that of participants with unmutated tumors. Table 2 presents the median OS of the patients stratified by gender, age at diagnosis, tumor site, cancer stage, and mutation status.

Table 2. Median OS of the patients.

Characteristics	Patients (N = 27)	
	Median OS, Months (95%CI)	Statistics
Overall	13 (6.2 - 19.8)	
Age at diagnosis		
<50 years old	7 (1.4 - 12.6)	$p < 0.05$
≥50 years old	15 (0 - 35.6)	
Gender		
Males	7 (0.6 - 13.4)	$p = 0.139$
Females	24 (0 - 49.9)	
Tumor site		
Right Colon	6 (1.3 - 10.7)	
Left Colon	38	$p < 0.05$
Rectum	24 (0 - 56.6)	
Stage at diagnosis		
III	14 (5.1 - 22.9)	$p = 0.245$
IV	13 (0.1 - 25.9)	
Mutation		
Yes	13 (1.1 - 24.9)	$p = 0.571$
No	13 (5.1 - 20.9)	

The 3-years survival rates of the patients were unfortunately poor as the overall was only 11.1%. Interestingly, the result showed that the 1-year survival rate of patients diagnosed at age ≥50 years (66.7%) was higher than those diagnosed at age <50 years old (16.7%). There was a similar 1-year survival rate between male (42.9%) and female patients (45%).

Patients with tumors located in the left colon (60%) and rectum (6.7%) had a higher 1-year survival rate than those with tumors located in the right colon (23.1%). The study also found an interesting result where patients diagnosed with stage III cancer had a 1-year survival rate (40.9%) than those diagnosed with stage IV (60%).

According to their mutation status, there was a slight difference of 1-year survival rate between patients with mutated tumors (40%) and unmutated tumors (50%). Table 3 presents the OS rate evaluated in detail in 1-year, 2-years, and 3-years.

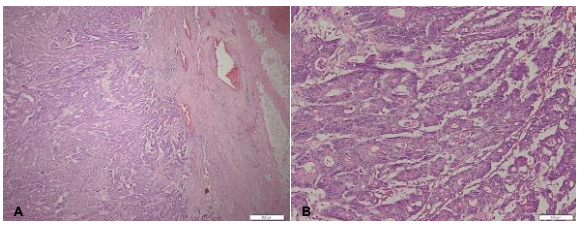

Figure 1. Adenocarcinoma Colorectal stage III stained with hematoxylin and eosin. A. 100 times magnification B. 200 times magnification.

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Table 3. 1-Year, 2-Years, and 3-Years overall survival rate.

Characteristics	Patients (N=27)		
	1-Year OS Rate, % (95% CI)	2-Years OS Rate, % (95% CI)	3-Years OS Rate, % (95% CI)
Overall	44.4 (25.7 - 70.1)	18.5 (3.9 - 22.4)	11.1 (0.0 - 10.4)
Age at diagnosis			
<50 years old	16.7 (-4.4 - 37.8)	0	0
≥50 years old	66.7 (42.8 - 90.5)	33.3 (9.5 - 57.2)	20 (0.0 - 40.2)
Gender			
Males	42.9 (6.2 - 79.5)	0	0
Females	45.0 (23.2 - 66.8)	25 (6.0 - 44.0)	15 (0.0 - 30.6)
Tumor site			
Right Colon	23.1 (0.2 - 46)	0	0
Left Colon	60 (17.1 - 102.9)	40 (0.0 - 82.9)	20 (0.0 - 55.1)
Rectum	66.7 (35.9 - 97.5)	33.3 (2.5 - 64.1)	22.2 (0.0 - 49.4)
Stage at diagnosis			
III	40.9 (20.4 - 61.5)	22.7 (5.2 - 40.2)	13.6 (0.0 - 28.0)
IV	60 (17.1 - 102.9)	0	0
Mutation			
Yes	40 (15.2 - 64.8)	20 (0.0 - 40.2)	13.3 (0.0 - 30.5)
No	50 (21.7 - 78.3)	16.7 (0.0 - 37.8)	8.3 (0.0 - 24.0)

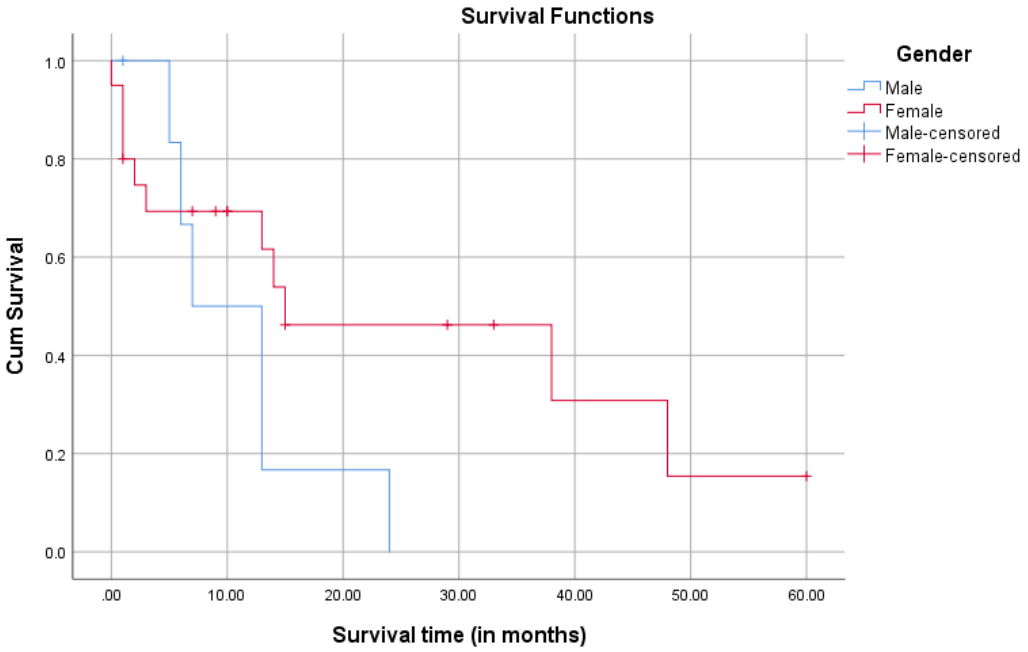

Figure 2. Survival function based on gender. Cum Survival: Cumulative Survival

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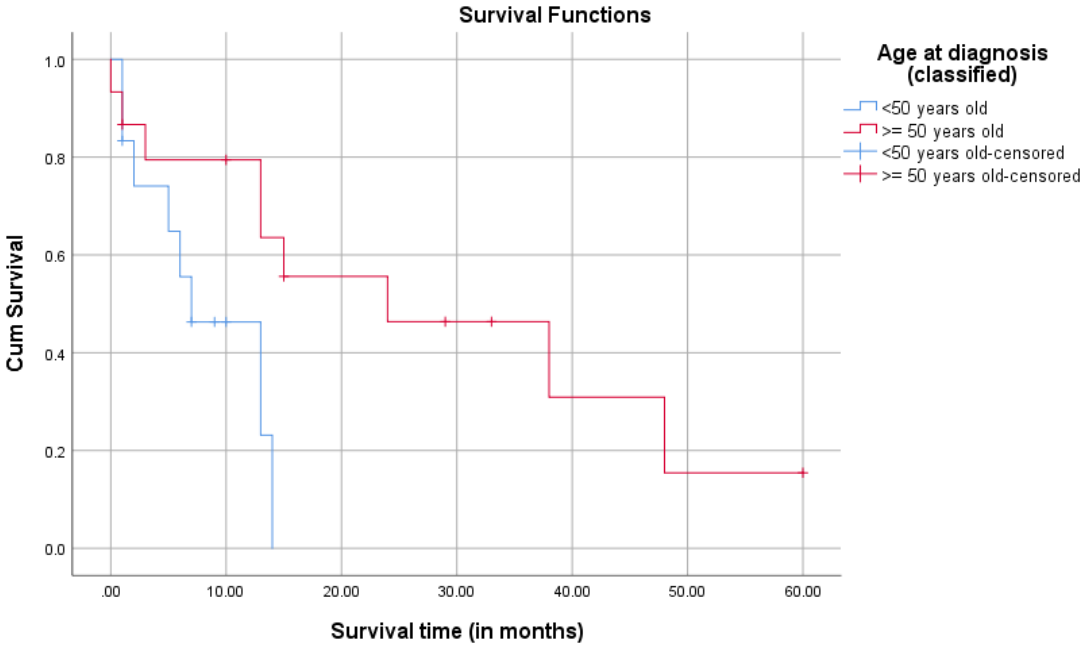

Figure 3. Survival function based on age at diagnosis. Cum Survival: Cumulative Survival

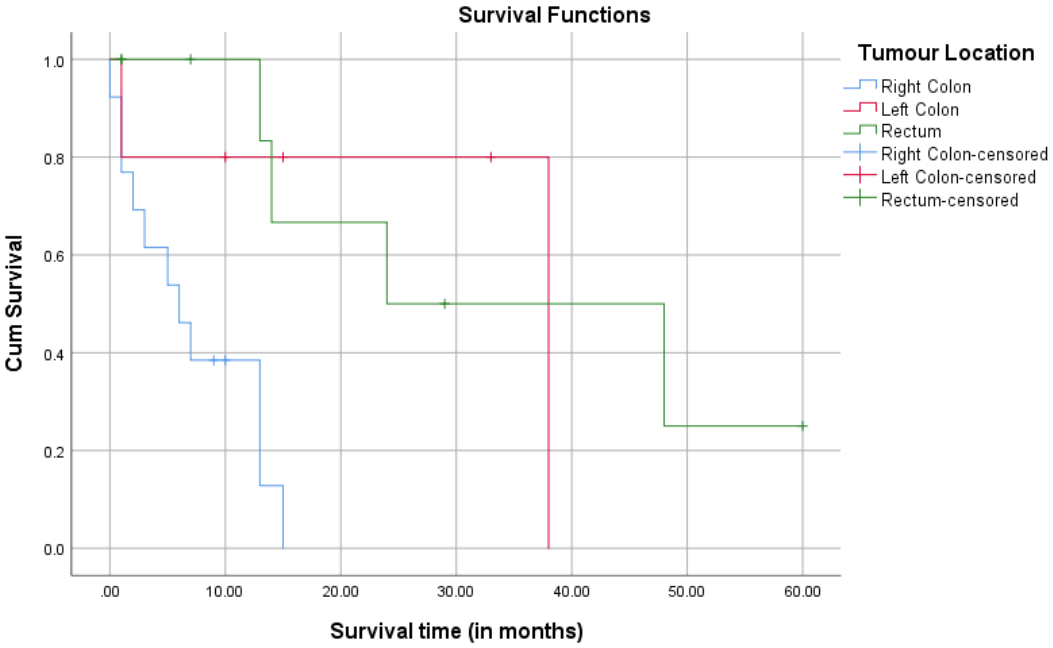

Figure 4. Survival function based on tumor location. Cum Survival: Cumulative Survival

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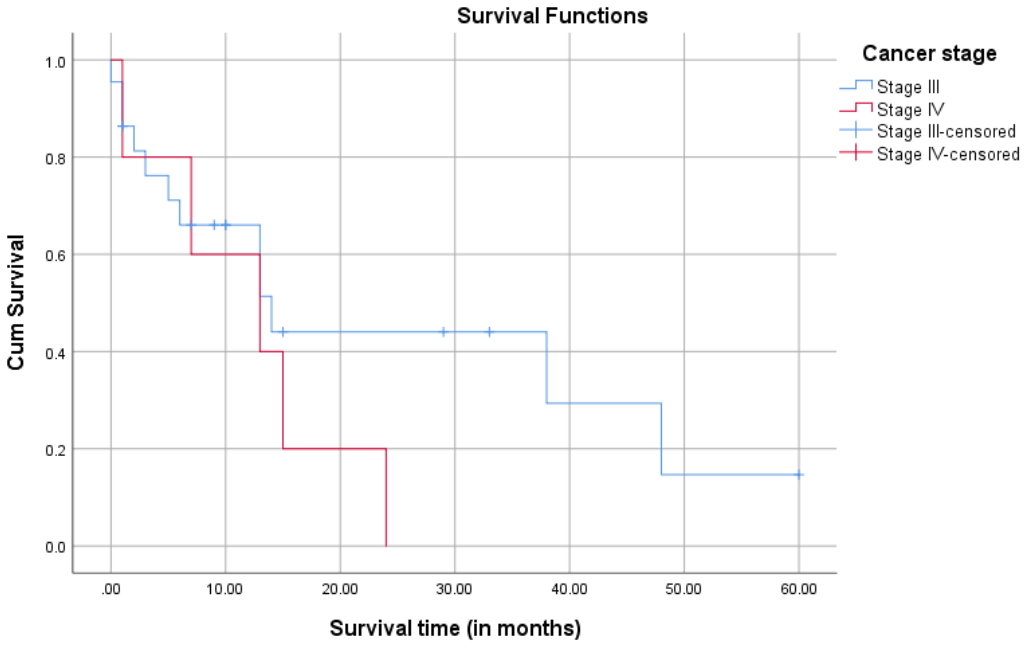

Figure 5. Survival function based on cancer stage at diagnosis. Cum Survival: Cumulative Survival

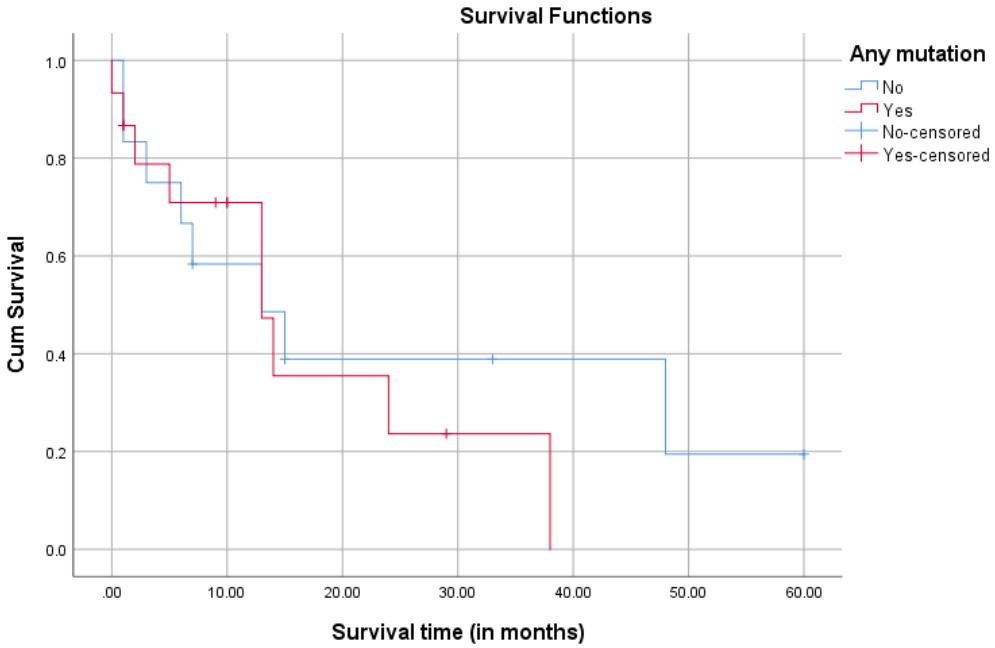

Figure 6. Survival Function based on mutation of the tumor. Cum Survival: Cumulative Survival

DISCUSSION

The International Agency for Research on Cancer (IARC) 2018 states that colorectal carcinoma is more common among men than women.[1] Epidemiology data from GLOBOCAN 2020 colorectal carcinoma became the third leading cause of cancer-related deaths in both genders worldwide, with an estimated 515,637 deaths among males and 419,536 deaths among females in 2020.[1] In this study of colorectal adenocarcinoma from registry data, we recorded 27 cases of stage III and IV

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adenocarcinoma colorectal throughout 2016 until 2020. More than half were diagnosed at more than 50 years old (55.6%), mainly in female patients (74.1%). Overall survival declined from one to three years, with three years of overall survival only 11.1%. Overall survival was statistically different according to age and tumor site. Mutation, gender, and stage at diagnosis had no statistical effect on overall survival. Most patients were at stage III when diagnosed with the cancer (81.5%).

KRAS mutation occurs in approximately 30 to 45% of CRC and mostly in codon 12 or 13.[6–8,10,11] The association between KRAS mutation and patients' survival remained controversial. A clinical trial showed that KRAS mutation was linked to worse survival in CRC patients.[8] In this study shows that most of the patient's tumors were mutated (55.6%), dominated by Mutation in KRAS codon 12 (25.9%), followed by KRAS codon 13 (14.8%) and KRAS codon 61 (11.1%), this result is in concordance with the research of Xue-lian et al. There was no significant difference in OS between patients whose tumors were mutated or not; the median OS of participants with mutated tumors was 17.2 months. There was a slight difference in the 1-year survival rate between patients with KRAS-mutated tumors (40%) and not KRAS-mutated tumors (50%). Some studies have shown that KRAS mutations do not have a prognostic value or any association with survival in patients with metachronous or synchronous metastatic CRC.[10]

The most common location in this study is the right colon (48.1%), and this site impacts overall survival with a median overall survival of seven months. This is similar to a study in Norway 2021; the most common location is the right colon, which found that left colorectal carcinoma had significantly better overall survival than right colorectal carcinoma.[12] The 5-years OS was 40.9% for LCC and 40.5% for RCC. Viviana et al and Cassia et al also stated that the right colon was associated with lower survival rates. Our study's median overall survival for right colorectal carcinoma is 30.6 months.[9,13]

In this study, age at diagnosis had a statistically significant influence on overall survival, with median overall survival in patients whose age at diagnosis ≥50 years old is 15 months. In the study of Clarisse Joachim et al based on the Martinique Cancer Registry, there was a statistically significant difference in overall survival based on age at diagnosis.[14] But in Clarisse Joachim's study, age <50 years old had a better overall survival; this is discordant with this study.

CONCLUSION

Adenocarcinoma colorectal in Hasan Sadikin Hospital from 2016 until 2020 occurs mainly in women over 50. The most common location is right-sided colorectal cancer; most patients were at stage III when they were diagnosed. Most of the patient's tumors were KRAS-mutated, especially in codons 12 and 13. Age and tumor location had a statistically significant effect on overall survival. As for KRAS, the mutation has no statistical impact on overall survival, but patients with mutations have lower overall survival than patients without mutations.

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