

Time to death and associated factors of Colorectal Cancer Patients in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

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Abstract

Colorectal cancer (CRC) is a cancer of the large intestine. Anatomically, it also is known as colon cancer or rectal cancer but when both present with similar features they are termed colorectal cancer. It is a common health problem, representing the third most commonly diagnosed cancer worldwide and causing a significant burden in terms of morbidity and mortality. In Ethiopia CRC is the third most common cancer next to breast and uterine cancer for females, but the first most common cancer among the male population. The main objective of the study was to investigate the associated factors that affect the time to death of CRC patients in TASH, Addis Ababa, Ethiopia. The retrospective cohort study was conducted on 325 CRC patients who enrolled between January 1, 2017, and December 30, 2020, in TASH, Addis Ababa, Ethiopia. This study used survival time analysis and comparing the survival curve in different groups of variables.

In this study, out of the total 325 patients, 111(34.15%) died and 214(65.85%) were censored until the end of the study. Large percentages (83.08%) of the patients were diagnosed at late stages and more than three-fifth (61.26%) of the patients that had been diagnosed at stage IV died. The overall Kaplan-Meier plot also showed that the follow-up time of CRC patients increased, the survival probability of patients would be decreased. This indicated that the probability of survival was the highest on the first day of diagnosis of colorectal cancer, but it relatively fell later as follow up time increases. Our finding also showed that Non-alcohol user patients had a higher probability of survival than alcohol user patients. The estimated median survival time of colorectal cancer patients was 23 months. There were significant differences in survival experience among groups of family history, alcohol consumption, comorbidity, physical exercise, stage, tumor grade, and treatment modality.

From our findings, it is better to implement colorectal cancer early screening and detection programs to improve survival outcomes.

Keywords: colorectal cancer, Kaplan-Meier, Log-Rank, Survival time; Tikur Anbessa Specialized Hospital.

I. INTRODUCTION

Cancer is a disease characterized by the unchecked division of abnormal cells. When this type of growth occurs in the colon or rectum, it is called colorectal cancer (CRC). It is the third common cancer and the second cause of mortality among males and females tends to be the major cause of the health-related problem (19). The American Cancer Society (ACS) and American College of Gastroenterology (ACG) documented that CRC starts in the colon or the rectum which originates from pre-cancerous growths or polyps that grow in the colon or rectum, but their progression to CRC could be halted if it is detected early and polyps are removed (9,28).

Clinical presentation of CRC depends on its size, presence, or absence of metastatic and tumor location. Most colorectal cancers occur sporadically and are characterized by a sequenced carcinogenesis process that involves the progressive accumulation of mutations in a period that lasts on average 10–15 years (2,3). Globally, CRC is the third most commonly occurring cancer and the second most common cause of cancer death next to lung cancer in men and breast cancer in women (27). CRC is the third prevalent cancer leading to death in western countries (16). In 2017, about 1,348,087 people living with colorectal cancer in the United States. There are an estimated 50,630 deaths from colorectal cancer (CRC) in 2018 in the US, second only to lung cancer (23).

CRC is the 4th most common cancer in the World Health Organization-Africa region. Recent studies have shown that the incidence and mortality of CRC are increasing in low and middle-income country's (LMIC), especially in Sub-Saharan Africa (10). This rising burden is mirrored in Nigeria, where more than half of the patients die within one year of diagnosis. In the African population, patients with CRC tend to present at a younger age with advanced disease (6). CRC accounted for over 600,000 of those deaths, with 70% occurring in (LMIC) (15).

In Ethiopia, CRC is the third most prevalent cancer among the entire adult population, and patients often present with advanced stages of cancer (17). It becomes prevalent to account (12.2%) in males and (4.4%) in females of all ages (24).

Sex, comorbidity, and stage of the disease are the most important factors for CRC patient mortality (21). Alcohol consumption is also a known risk factor determinant for the onset of CRC at a young age (5). In November 2009, the International Agency for Research on Cancer reported that there is sufficient evidence to conclude that tobacco smoking is a cause of CRC (22).

Risk is believed to increase with increased BMI since there's an increase in circulating estrogens and a decrease in insulin sensitivity; therefore, this is assumed to influence CRC risk (20). People with a first-degree relative (parent, sibling, or child) who has been diagnosed with CRC have 2 to 4 times the risk of developing the disease compared to people without this family history, with a higher risk for diagnosis before age 50 and/or multiple affected relatives (12). Studies suggest a dose-response effect, that reflects the regularity and intensity of physical activity which is inversely related to CRC, and studies find as little as 7 hours a week could lower the risk of CRC (7). The gold standard treatment in non-metastatic disease is surgery, with 5-year survival rates ranging from 44% to 93% depending on the stage (18).

2. Data and Methodology

2.1. Study Area

Data were used from Addis Ababa Population-Based Cancer Registry (AAPBCR), which was established in 2011 under the TASH radiotherapy center. TASH is a tertiary-level hospital equipped with cancer diagnostic and treatment facilities and is one of the cancer treatment centers in Ethiopia. TASH is a teaching, central tertiary generalized referral hospital with approximately 800 inpatient beds. It is the largest and well-known public hospital which was built in the early 1960s. The hospital

hosts a Cancer Treatment Center. The registry uses hospitals, higher diagnostic clinics, and pathology services as the main source of cases. The Hospital is geographically located between 900'0" to 9010'0" north latitude and 38040'0" to 38050'0" east longitude with an altitude of 2379 meters above sea level.

2.2. Source of Data and Study Population

All CRC patients in the TASH Oncology unit were used as a source of data for this study which was obtained from the TASH oncology unit, Addis Ababa of Ethiopia and the population of the study was all medical records of CRC patients in the TASH Oncology unit who were diagnosed January 1, 2017, up to December 30, 2020, who fulfill eligibility criteria.

2.3. Study Design

A hospital-based Retrospective cohort study was applied to obtain data on CRC patients that was recorded in the oncology department of TASH, Addis Ababa, Ethiopia.

2.4 Survival Data Analysis

Survival analysis is a set of methods for analyzing data where the outcome variable is the time until the occurrence of an event of interest. It was used in analyzing the time-to-event data arising in several applied fields like medicine, biology, public health, epidemiology, demography (1). Censoring is an important issue in survival analysis, it present when we have some information about a subject's event time, but we don't know the exact event time. There are three categories of censoring such as right censoring, left censoring, and interval censoring (11). The presence of the patient in the data set who have not yet experienced a failure by the end of the study period.

Non –Parametric Estimation of Survivorship Function

In practice, when using actual data, we usually obtain the estimated survivor function and obtain curves that are step functions, rather than smooth curves.

Kaplan-Meier Estimate of the Survival Function

The number of observed events at $t_{(j)}$, $j = 1 \dots r$. Then the K-M estimator of $S(t)$ is defined as the Kaplan-Meier estimator is the standard non-parametric estimator of the survival function used for estimating the survival probabilities from observed survival times both censored and uncensored (8).

Suppose that r individuals have failures in a group of individuals, let $0 \leq t_{(1)} \leq \dots \leq t_{(r)} < \infty$ be the observed ordered death times. Let $r_{(j)}$ be the size of the risk set $t_{(j)}$ where risk set denotes the collection of individuals alive and uncensored just before $t_{(j)}$. Let $d_{(j)}$ be the number of observed events at $t_{(j)}$ $j=1 \dots r$. Then the K-M estimator of (t) is defined by:

$$\hat{S}(t) = \prod_{j:t_{(j)} < t} \left[1 - \frac{d_{(j)}}{r_{(j)}} \right]$$

The cumulative hazard function of the KM estimator can be estimated as:

$$\hat{H}_{KM}(t) = -\ln(\hat{S}_{KM}(t))$$

Where $S(t)$ is KM estimator

Log-rank test

The log-rank test, developed by Mantel and Haenszel, was a non-parametric test for comparing two or more independent survival curves. Since it was a nonparametric test no assumption about the distributional form of the data was required. This test was most power full in detecting a higher cured proportion in one group than other groups (14). The log-rank test can also be extended for comparing three or more groups of survival experience.

3. Results

3.1. Socio-Demographic Characteristics of the Study Participants

A total of 325 colorectal cancer patients treated in Tikur Anbessa Specialized Hospital from January 1, 2017, up to December 30, 2020. Two hundred fourteen (65.85%) of the patents

censored in the study period while the remaining 111(34.15%) were died.

About 203(62.46%) of study participants were males and 60.31% were from urban areas. Out of those 116(35.69%), participants had a family history and the remaining 209 (64.31%) were not having a family history. As we have been considered the age of patients, 107(32.92%), 64(19.9%), 80 (24.62%), 74(22.77%) of patients were less than 40, 40 to 49, 50 to 59, and the age of 60 and above years old respectively. When we have been considered

the smoking status of participants, we observed that 96(29.54%) of the participants were smokers, of which 33.33% have died and 59(27.57 %) were censored. Slightly more than half of (52.31%) the participants were in the normal condition (healthy weight) of BMI, out of which 123(57.48) patients were censored and 48(43.24) died. More than one quarter (29.5%) had comorbid conditions, of which 36.94% have died. About 129 (39.69%) patients were alcohol consumers, out of those patients 72(64.86%) were died.

Table 3.1:- socio-demographic characteristics of colorectal cancer patients in TASH

Variable	Category	Survival status		Total No. %
		Death No. (%)	Censored No. (%)	
Sex	Male	68(61.26)	135(63.08)	203 (62.46)
	Female	43(38.76)	79(36.92)	122(37.54)
Age of patients	< 40	36(32.43)	71(33.18)	107(32.92)
	40-49	23(20.72)	41(19.16)	64(19.69)
	50-59	28(25.23)	52(24.30)	80(24.62)
	>=60	24(21.62)	50 (23.36)	74(22.77)
Alcohol consumption	Yes	72(64.86)	57 (26.64)	129 (39.69)
	No	39(35.14)	157(73.36)	196 (60.31)
Family history	Yes	30(27.03)	86(40.19)	116(35.69)
	No	128 (59.81)	128 (59.81)	209 (64.31)
Smoking status	Smoking	37(33.33)	59(27.57)	96(29.54)
	Non Smoking	74(66.67)	155(72.43)	229(70.46)
Residence	Urban	69(62.16)	127(59.35)	196(60.31)
	Rural	42(37.84)	87(40.65)	129(39.69)
Marital status	Single	20(18.02)	28(13.08)	48(14.77)
	Married	91(81.98)	186(86.92)	277(85.23)
	Under weight	47(42.34)	62(28.97)	110(33.85)
BMI	Healthy weight	48(43.24)	123(57.48)	170(52.31)
	Over weight	16(14.41)	29 (13.55)	45(13.85)
Comorbidity	Yes	41(36.94)	56(26.17)	97(29.85)
	No	70(63.06)	158(73.83)	228(70.15)
physical exercise	Yes	11(9.91)	67(31.31)	78(24.00)
	No	100(90.09)	147 (68.69)	247(76.00)
Religious	Orthodox	72(64.86)	125(58.41)	197(60.62)
	Muslim	22(19.82)	45(21.03)	67(20.62)
	Protestant	17(15.32)	44(20.56)	61(18.77)

TASH: Tikur Anbesa Specialized Hospital.

3.2. Clinical and pathological and treatment-related characteristics

More than half (52%) of the primary site of the tumor was found to be rectal. Of those patients, 48.65% died. A large percentage (83.08%) of the patients were diagnosed at late stages

(28.00% at stage III, and 55.08 % at stage IV). Slightly more than three-fifth (61.26%) of the patients that had been diagnosed at stage IV died. 61.85% of the tumor grade was well-differentiated; about 229 (70.46%) were adenocarcinoma type. Concerning the type of

treatment given, 115(35.38%) of the cases were given chemotherapy alone, of which 41(36.94%) have died and 27.38% of the cases were served surgery plus chemotherapy out of those patients 42(37.84%) were died.

Table 4.2:- Clinical and pathological and treatment-related factors of colorectal cancer patients in TASH

Variable	Category	Survival status		Total No. (%)
		Death No. (%)	Censored No. (%)	
primary site of tumor	Colon	57(51.35)	99(46.26)	156(48.00)
	Rectal	54(48.65)	115(53.74)	169(52.00)
Stage	Stage I and II	10(9.01)	45 (21.03)	55(16.92)
	Stage III	33(29.73)	58(27.10)	91(28.00)
	Stage IV	68 (61.26)	111 (51.87)	179(55.08)
Tumor grade	Well-differentiated	62(55.86)	139(64.95)	201(61.85)
	Moderately differentiated	17(15.32)	46(21.50)	63(19.38)
	Poorly differentiated	32(28.83)	29(13.55)	61(18.77)
Histology type	Adenocarcinoma	74(66.67)	155(72.43)	229(70.46)
	Mucinous/signet ring cell carcinoma	59(27.57)	37(33.33)	96(29.54)
Treatment modality	Radiotherapy alone	11(9.91)	37 (17.29)	48 (14.77)
	Surgical treatment alone	2(1.80)	34 (15.89)	36 (11.08)
	chemotherapy alone	41(36.94)	74(34.58)	115(35.38)
	surgery plus chemo	42(37.84)	47(21.96)	89(27.38)
	radiation + surgery+ chemo	15(13.51)	22(10.28)	37(11.38)

TASH: Tikur Anbesa Specialized Hospital.

3.3. Non-parametric Survival Analysis

3.3.1The Kaplan- Meier Survival Estimate for Time to Death of Colorectal Cancer Patients in TASH

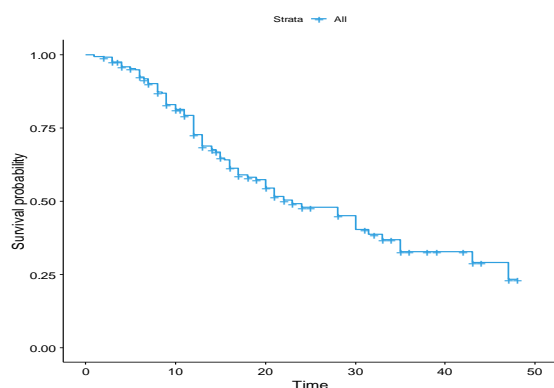


Figure 3.1: Overall Kaplan-Meier estimation of survival functions of colorectal cancer patients

From Figure 3.1, we have observed that the probability of survival was highest at the first month of diagnosis of colorectal cancer, but it relatively declined later as follow-up time increased.

3.3.2. The Overall Median Survival Time of Colorectal Cancer Patients

Table 3.3 showed that the overall median survival time of colorectal cancer patients was 23 months with [95% CI: 20–33].

Table 3.3:- Estimation of overall median survival time of colorectal cancer patients

No of observation	No of events	Median survival time in a month	95% CI Lower	Upper
325	111	23.0	20.0	33

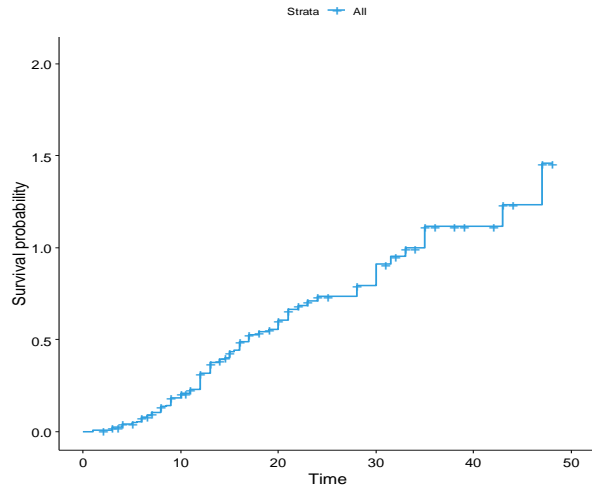


Figure 3.2: Overall Kaplan-Meier estimation of hazard functions of colorectal cancer patients

From Figure 3.2 we observed that the probability of hazard is the lowest at the first month of diagnosis of colorectal cancer, but it relatively highest as follow up time increases.

3.3.3. Survival Function of Different Categorical variables

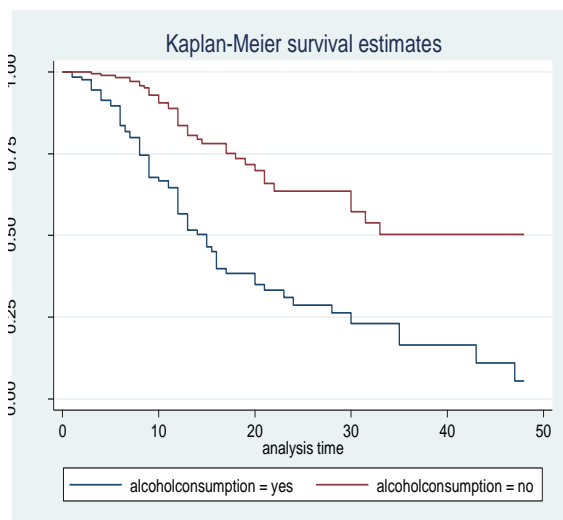


Figure 3.3: Plot of Kaplan-Meier Estimates for alcohol consumption

The survival curves in Figure 3.3 showed that non-alcohol user patients lying above as compared to alcohol user patients. It indicated

that non-alcohol user patients had a higher probability of survival than alcohol user patients.

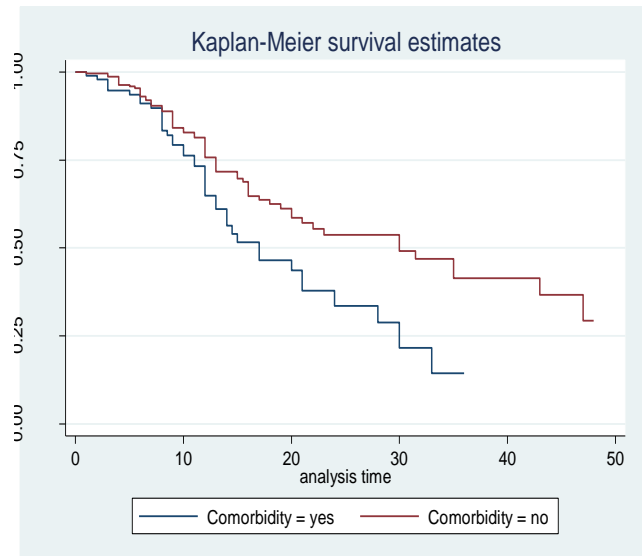


Figure3.4: Plot of Kaplan-Meier Estimates for comorbidity

Figure 3.4 revealed that the survival of the patients having non-comorbid conditions had better survived as compared to the survival of the patients that had a comorbid condition. It showed that comorbid condition patients had a lower probability of survival than non-comorbidity illness patients.

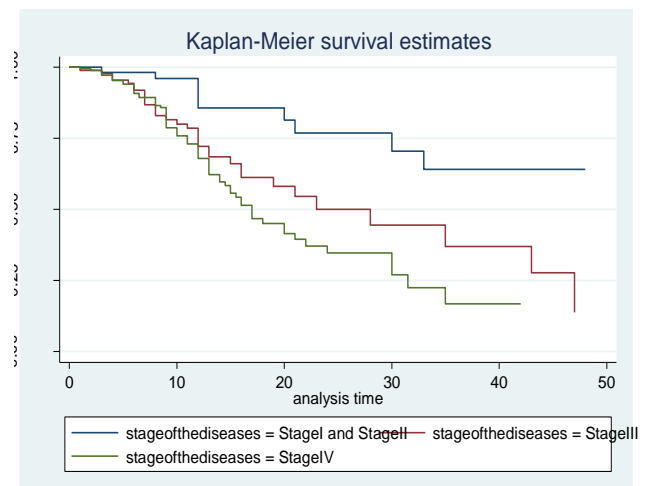


Figure 3.5: Plot of Kaplan-Meier Estimates for the stage

The survival function against survival time for time to death of colorectal cancer patients by stage of the diseases was shown in Figure 3.5. This plot indicated that patients who were diagnosed at stages I and II have a higher probability of survival than stage III and stage IV and patients who were diagnosed at stage III had a higher probability of survival than stage IV.

3.3.4. Comparison of Survival Experiences between Groups

By using log-rank tests there were significant differences in survival experience among groups of family history, alcohol consumption, comorbidity, physical exercise, stage, tumor grade, and treatment modality shown in Table 3.4. These showed that those categorical variables had statistically significant differences in survival probabilities.

Table 3.4:- Results of log-rank test for each categorical variable

Covariates /factors	DF	Log-rank test	
		Test statistics	p- value
Age	3	1.39	0.7072
Sex	1	0.1	0.8
Family history	1	7	0.008*
Alcohol consumption	1	42	<0.0001***
Residence	1	0.6	0.4
Marital status	1	2.13	0.1442
Smoking status	1	1.7	0.2
BMI	2	2.95	0.2290
Comorbidity	1	7.5	0.006*
Physical exercise	1	13.7	< 0.0001***
Religion	2	1.3	0.2
Primary site of tumor	1	0.001	0.9
Stage	2	18.19	0.00011**
Tumor grade	2	11.3	0.004*
Histology type	1	0.75	0.3866
Treatment modality	4	17.51	0.0015*

4. Discussions

This study aimed to estimate the survival probability of CRC patients in TASH enrolled from January 1, 2017, to December 30, 2020. Covariates that were included in the study were age, sex, Marital status, Family history, alcohol consumption, smoking status, BMI, comorbidity, physical exercise, residence, Religion, Site of a tumor, Stage of disease, Tumor grade, Histology type, and treatment modality.

In this study, out of the total 325 patients, 111(34.15%) died and 214(65.85%) were censored until the end of the study. Large percentages (83.08%) of the patients were

diagnosed at late stages and more than three-fifth (61.26%) of the patients that had been diagnosed at stage IV died. This result almost similar to the result reported by (4), which implies that large percentage (65.7%) of the patients were diagnosed at late stages (39.3% at stage III, and 26.4% at stage IV). Three-fifth (60.4%) of the patients that had diagnosed at stage IV died.

The overall Kaplan- Meier plot also showed that the follow-uptime of CRC patients increased, the survival probability of patients would be decreased. This was consistent with (4,25), which indicated that the probability of survival was the highest on the first day of diagnosis of colorectal cancer, but it relatively fell later as follow up time increases. A study conducted by (4) showed that CRC patients

who smoke cigarettes' and alcohol user were less probability of survival than non-smokers and non-alcohol users respectively. Our finding also showed that Non-alcohol user patients had a higher probability of survival than alcohol user patients.

5. Conclusions

This study was based on colorectal cancer (CRC) patient's data set which was obtained from the TASH oncology unit in Addis Ababa, Ethiopia. The major objective of the study was to investigate the associated factors that affect the time to death of CRC patients in TASH enrolled from January 1, 2017, to December 30, 2020. Based on the descriptive result out of the total 325 patients 111(34.15%) died and 214(65.85%) were censored.

The Kaplan-Meier curve plot of CRC patient's shows as the follow-up time increases the survival probability of patient's decreases. The estimated median survival time of colorectal cancer patients was 23 months. There were significant differences in survival experience among groups of family history, alcohol consumption, comorbidity, physical exercise, stage, tumor grade, and treatment modality.

Conflict of interest statement

The authors have declared that no competing interests exist.

Creators' commitment

Yesewzer had made generous commitment to origination and plan, or securing of information, or investigation and translation of the information; Fekade had been engaged with drafting the composition or amending it basically for significant scholarly substance; and had given last endorsement of variant to be distributed.

Subsidizing

The creators have no help or subsidizing to report.

Accessibility of information and materials

The datasets utilized and broke down during the current investigation are accessible from the comparing creator on sensible solicitation. Ethics approval and consent to participate has been approved by DebreBerhan University.

Morals endorsement and agree to take an interest

Moral freedom ethical Approval was taken from DebreBerhan University; school Post Graduate coordination moral audit board and authority letter was composed by the division of insights to in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia so as to acquire the information from the emergency clinic before arranging and beginning information assortment. Official letter was given for concerned bodies to conduct the research and afterward privacy of the data was guaranteed from all perspectives.

Consent for publication

Not applicable.

Acknowledgment

The authors are generally grateful to Tikur Anbessa Specialized Hospital permitting us to utilize patients recorded information for this investigation.

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