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COLLEGE OF HEALTH SCIENCE

SCHOOL OF MEDICINE

TREATMENT OUTCOME AND ASSOCIATED FACTORS AMONG COLORECTAL CANCER PATIENTS IN TIKUR ANBESSA HOSPITAL, ETHIOPIA: A PROSPECTIVE COHORT STUDY

By: GIRUM TESSEMA ZINGETA, MD

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Full title	Treatment Outcome and Associated Factors Among Colorectal Cancer Patients in Tikur Anbessa Hospital, Ethiopia: A Prospective Cohort Study

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Approval sheet

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DEPARTMENT OF CLINICAL ONCOLOGY

I, the undersigned Clinical Oncology Student, declare that I Have Submitted My Original work titled as Treatment Outcome and Associated Factors Among Colorectal Cancer Patients in Tikur Anbessa Hospital, Ethiopia, 2023 for the examination.

Submitted By:

_____ _____ _____

Name of the student Signature Date

This thesis work has been submitted for examination with my approval as an advisor.

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APPROVAL BY THE BOARD OF EXAMINATION

This thesis by Girum Tessema is accepted in its present form by the board of examiners as satisfying the thesis requirement for the degree of specialty certificate in clinical oncology

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List of Abbreviations and Acronyms

AA----------Addis Ababa

AACCR----------Addis Ababa City Cancer Registry

AAU----------Addis Ababa University

AC----------Adenocarcinoma

ACS----------American Cancer Society

AJCC----------American Join Committee on Cancer

ASC----------Adenosquamous Carcinoma

CAPEOX----------Capecitabine + oxaliplatin

CC----------Colon cancer

CCRT----------Concurrent Chemo Radiotherapy

CHS----------College of Health Science

CI----------Confidence Interval

CR----------Complete response

CRC----------Colorectal cancer

CXR----------Chest X-Ray

CT----------Computed Tomography

CT----------Chemotherapy

DM----------Diabetes mellitus

DM----------Distant metastases

DTI----------Diagnosis to treatment interval

DFT----------Delay in the first treatment

EBRT----------External Beam Radiotherapy

ECOG----------Eastern Cooperative Oncology Group

EP----------Info Epidemiological information (Software Developed by CDC)

FDG-PET----------Fludeoxyglucose-positron emission tomography

FOLFOX----------5-fluorouracil + leucovorin + oxaliplatin

FOLFRIRI----------5-fluorouracil + leucovorin + Irinotecan

FMOH----------Federal Ministry of Health

G----------Grade

Gy----------Gray

GI----------Gastrointestinal

GLOBOCAN----------Global Burden of Cancer

GP----------General Practioner

HDI----------Human development index

HR----------Hazard Ratio

INCTR----------International Network for Cancer Treatment and Research

IR----------Incomplete response

IRAC----------International Agency for Research on Cancer

IV----------Intravenous

LCC----------Left side colon cancer

LN----------Lymph nodes

Leu/5-FU----------Leucovorin + 5-fluoro uracil

LMIC----------Low- and Middle-Income Countries

MDO----------Missed diagnostic Opportunities

MRI----------Magnetic Resonance Imaging

OR----------Odds Ratio

PD----------Progressive disease

PR----------Partial response

RCC----------Right side colon cancer

RC----------Rectal cancer

RECIST----------Response Evaluation Criteria In Solid Tumor

RR----------Relative Risk

RS----------Rectosigmoid

RT----------Radiotherapy

SC----------Sigmoid colon

SCC----------Squamous cell carcinoma

SD----------Stable disease

SPSS----------Statistical Package for Social Science

TASH----------Tikur Anbessa Specialized Hospital

TNM----------Tumor Size, Nodal involvement, Metastasis

UICC----------Union of International Cancer Control

5 – FU----------5 Fluorouracil

----------Fractions

Abstract:

Background: Colorectal cancer (CRC) is the third most common cancer death in both sexes worldwide. Several studies revealed that advanced-stage at diagnosis and treatment delay negatively affects patient outcome. However, in Ethiopia, the treatment outcome, the time to diagnosis, and initiation of treatment have not been well studied before. Therefore, this study aimed to evaluate the treatment outcome and the prognostic factors of CRC patients at Tikur Anbessa Specialized Hospital.

Methods and Materials: An institution-based prospective cohort study was carried out on 209 CRC patients at the Oncology Center of Tikur Anbessa Specialized Hospital (TASH) and those who met the eligibility criteria were included in our study from January 2020 to September 2022. Patient interval, diagnosis interval, and treatment interval of more than 30, 14, and 30 days were used to categorize patient, diagnosis, and treatment delays respectively. Simple descriptive analysis using frequency, proportion, mean with SD, and the median was applied for sociodemographic and clinical characteristics. For overall survival and progression-free survival, the Kaplan-Meier curve is applied. To see the one to one association between dependent and independent variables, we used bivariate cox analysis and a p value of < 0.25 used for further analysis. To find the prognostic indicators for survival, multivariate cox regression is performed, and a statistically significant value is $P < 0.05$.

Result: The mean age of CRC diagnosis was 49.38(SD=15) years. More than half of the patients were male 119(56.9%). More than three fourth of the patients (79.4%) presented with advanced stage. Delay in a patient, diagnosis, surgery, and chemotherapy (CT) were seen in 93.8%, 81.2%, 75.4%, and 85.4% of patients respectively. Overall mortality is 67.46% (95% CI: 61.0, 74.0) and the 1-year overall survival (OS) is 63.16% (95% CI: 56.23, 69.29). The median OS is 17 months and the median progression free survival (PFS) is 11 months. On multivariate cox regression, the poor prognostic factors for overall survival are; Age >40 (HR=1.53, 1.02 - 2.29, P 0.040), Lower level of education (high school & below), (HR=2.20, 1.24-3.90, P 0.007), poor performance status (HR=1.60, (1.03 - 2.48, P 0.035), Hgb $\leq$ 12.5 g/dl (HR=1.55,1.03-2.08, p 0.035), T-4 disease (HR=6.05, 2.28-16.02, p 0.000) and metastases at diagnosis (HR= 8.53, 3.77-19.25, p 0.000).

Conclusion: The overall survival rate of CRC patients' is very poor. The advanced stage upon presentation, poor functional status, and a lack of timely treatment initiation are all key contributors to poor survival. Few patients were diagnosed and treated in a reasonable

timeframe. We recommend that to improve CRC cancer awareness in the community, health professionals to avoid overlooking CRC in symptomatic patients and improve access to diagnostics and timely treatment. The health sector should prioritize the expansion of cancer centers with the goal of cure.

Key Words: CRC, Survival, Ethiopia.

INTRODUCTION

1.1 Background:

Noncommunicable diseases are becoming more prevalent in both developed and developing countries. According to 2020 world cancer report, cancer is the second leading cause of mortality worldwide, accounting for an estimated 9.6 million deaths in 2018 (1). Cancer now kills one out of every six people worldwide, more than HIV/AIDS, TB, and malaria combined (2). Globally, there were predicted to be 10 million cancer deaths (excluding 9.9 million non-melanoma skin cancer) and 19.3 million new cancer diagnoses (18.1 million excluding nonmelanoma skin cancer) in 2020, according to GOLOBOCAN (3). Due to population growth and aging, the worldwide burden of cancer is anticipated to reach 27.5 million new cases and 16.2 million cancer deaths by 2040. The global figure of 14 million new cancer cases in 2012 is expected to increase to nearly 22 million by 2030, with the burden shifting from 59% to 65% of all cancer cases in low and middle-income countries (LMIC) over this time period (2, 4).

The third most frequent cancer in the world for both sexes is colorectal cancer (CRC), 1.8 million new cases in 2018. It has the second-highest mortality rate (880 000 deaths in 2018). However, because the average case fatality is greater in lower HDI settings, there is less variation in the death rates. Colorectal cancer incidence rates are almost three times higher in transitioning than in transitioned countries (2, 5-7). The crude incidence rate of colorectal cancer in sub-Saharan Africa is 4.04 per 100,000 population, with a male-to-female ratio of 1.2:1(8).

Compared to Whites, African Americans have a higher incidence and mortality of colorectal cancer. African Americans experience CRC development at a younger average age than Whites (9).

In Ethiopia, colorectal cancer is becoming more common overall. For men and women, the estimated incidence rates of colorectal cancer are 8.5 and 6.3 per 100,000, respectively (4). Colorectal cancer is the most prevalent cancer in men in Addis Ababa, accounting for 12.4% of all cancers, and the fourth most common case in women, accounting for 5.4% of all cancers in the city (10). Colorectal cancer accounts for 12% of cancer cases at Tikur Anbessa Hospital oncology ward cancer admissions and 7.7% of all cancer cases in Addis Ababa city (11, 12).

1.2 Statement of the problem

By 2050, it is estimated that 24 million people would receive a cancer diagnosis each year, with up to 70% of those individuals residing in LMIC (13). Only 27 of the 43 Sub-Saharan Africa (SSA) nations have structured cancer registration systems; data quality varies, and national coverage is limited. LMIC account for 70% of all CRC-related deaths (14).

Cancer accounts for around 5.8% of total national mortality in Ethiopia. According to the GLOBOCAN, the yearly incidence of cancer is over 60,960 cases, with an annual fatality rate of over 44,000. The Ethiopian National Cancer Control Plan recognizes that the disease cannot be eradicated, but that its effects can be greatly reduced if effective steps to control risk factors, diagnose cases early, and provide adequate treatment to people with the disease (10, 15).

Over the last few decades, screening, advances in cancer treatment, as well as the recent availability of novel therapies and chemotherapy regimens, have resulted in a trend toward better stage-specific survival, particularly for patients with stage II and III diseases. Improvements in patient management and better adherence to treatment recommendations, evident in the increased use of curative surgery, chemotherapy, and radiotherapy, have all contributed to rising survival rates. Patients with poor socioeconomic status, as well as those living in low-income countries, have a more advanced stage at diagnosis, a reduced probability of receiving medical intervention, and a higher risk of having a permanent stoma (5, 13, 15). The overall survival and progression free survival of CRC in Ethiopia is unknown.

1.3 Significance of the study:

CRC is leading cancer in male and 4th in female in AA City, becoming more common in Ethiopia, although accurate data is scarce. According to limited retrospective data, the majority of patients in Ethiopia present at an advanced stage where curative treatment is not an option. There is a scarcity of literature addressing the survival of colorectal cancer patients in Ethiopia. This is the first prospective study of its kind, and it will develop a multi-level assignment in the prevention, diagnosis, management, and follow-up of CRC patients. It will also help to address a gap in CRC research and knowledge, as well as provide a sound foundation for future investigators.

LITERATURE REVIEW

2.1 Epidemiology

CRC is the third most frequent disease in both sexes, with 1.8 million new cases diagnosed in 2018. In terms of mortality, it ranks second, with 880 000 deaths in 2018. Colorectal cancer incidence rates are almost three times higher in transitioned nations compared to transitioning countries; however, with average case fatality greater in lower human development index (HDI) settings, death rates vary less. Most African and South Asian countries have low rates of colon and rectal cancer incidence (2, 5-7). Colorectal cancer has a crude incidence rate of 4.04 per 100,000 population in SSA, with a male to female ratio of 1.2:1(8). Again, the incidence of CRC is lower in SSA than in South East Asian countries (16).

In general, the incidence of CRC is rising in Ethiopia. The estimated colorectal cancer incidence rate for men and women is 8.5 and 6.3 per 100000 populations, respectively. CRC is the most common cancer type in men, accounting for 12.4% of all cancers and the fourth most common cancer in women, accounting for 5.4% of all cancers in the city (8, 10). According to a 12-year analysis of cancer patterns at the Black Lion Cancer Center, GI malignancies, including CRC, account for 12% of all cancers seen (12). According to a two-year retrospective evaluation of all cancer cases seen at Gondar University Hospital, CRC accounts for 4.8% of all cancer cases and is the seventh most prevalent cancer (17).

2.2 Sociodemographic, Clinical Presentation, Stage and Pathologic Characteristics

Of all ethnic groups in the US, African Americans have the highest rates of CRC incidence and mortality (18). CRC is becoming more common among young people of all races. This is especially evident among young African American adults (those under the age of 50), who had more advanced tumors than other races (19). In the United States, CRC in the young population is more aggressive and advanced at diagnosis. The biggest significant increase occurred between the ages of 40 and 44. Age-based colonoscopy screening starting at age 40 is recommended when the incidence matches that of other accepted screened cancers (20).

The presentation of CRC is widely varied among patients. In Ghana, 221 cases of CRC were evaluated over a six-year period, the average age was 54 ±16.8 years, with a range of 16 to 90 years. Weight loss (44.80%), rectal bleeding (39.82%), and abdominal pain (38.91%) were the most frequently reported clinical symptoms. Adenocarcinoma (68.33%) was the most common

histological type observed. The majority of the patients, 89 (40.27%), were classified as late stage (Stage III) (21).

From 2009 to 2013, a five-year prospective study was conducted in a Nigerian tertiary hospital. There were 120 CRC patients seen. The majority of the patients (71.7%) had rectal cancer, whereas the remainder 34 (28.3%) had colon cancer. The majority of colon cancer cases were between the ages of 51 and 60. The rectum: colon ratio was 2.5:1, 31% of patients were 40 years or younger, and 37% of those with rectal cancer were 40 years or younger. Only 24% of patients under the age of 40 and 41% of those over the age of 40 with confirmed rectal cancer underwent surgery (22).

Even if the age-standardized ratio is more or less comparable with the industrialized world, the prevalence, incidence, and total burden of CRC in young black Africans is rising. In this group of patients, a high level of suspicion and aggressive management are required. One multicenter prospective study in SSA was carried out in CRC patients under the age of 40 who were managed between 2005 and 2011. There was no difference in gender, and the peak age was in the third decade of life. The vast majority were rural farmers. Symptoms lasted an average of 16 months. The majority of the patients (88.7%) reported with symptoms of acute abdomen and were confirmed to have advanced colorectal tumor upon laparotomy. Histology revealed that 37.5% of the AC were poorly differentiated (23).

From 2006 to 2011, a Tanzanian study analyzed 332 histologically proven CRC patients, accounting for 4.7% of all cancers. The vast majority of patients (96.7%) came late with advanced stages. Distant metastases were present at the time of diagnosis in 24.7% of patients (24).

A two-year retrospective assessment of 120 Colorectal Cancer patients at Tikur Anbessa Cancer Center from 2010 to 2011 revealed that 20% presented as an emergency. Rectal bleeding (63.0%), abdominal pain (54.3%), weight loss (44.9%), tenesmus (39.4%), change in bowel habit (48.0%), and obstructive symptoms (17.3%) were reported. More over half of the study participants were in stages III to IV of the disease. More than 94% of the patients had histologically confirmed AC. Thirty-four percent of the cases had tumors that were inoperable indicating a delayed presentation (25).

2.3 Treatment options

CRC is one of the deadliest cancers. This can be overcome by a variety of approaches depending on the stage of the disease: health promotion, screening programs, and the introduction of nearly individualized treatments based on both patient features and the cancer biology. Unfortunately, applying non-invasive and low-cost testing for population-based screening and early intervention of colorectal cancer in SSA is not feasible for a number of reasons (26).

Surgery, traditional chemotherapy, targeted agents, and radiotherapy are the primary therapeutic options for CRC. However, the treatment choice is highly influenced by the tumor's stage of presentation, several individual patient factors, and, increasingly, the tumor molecular make-up. Most developed countries have advanced in personalized cancer treatment, but cancer management in developing countries remains difficult (27, 28).

A significant barrier to cancer care in SSA is a lack of access to surgical care. Gastroenterologist, Radiologist, Oncologists, pathologists, and other healthcare professionals who are required for cancer treatment are in scarcity, and the expense of such care is another barrier. Due to the lack of expertise in sphincter-preserving surgery, the high expense of the stapling devices required for sphincter preservation, and the inadequacy of therapies that can downstage rectal cancers, surgical treatment of rectal cancer is challenging. The percentage of patients who undergo APR is now less than 25% in high-income nations. Most statistics from sub-Saharan Africa, however, continue to demonstrate that more than 40% of patients still get this type of resection. Stomas are frequently not socially accepted, and they can even increase suicide (13).

Because malignancies are diagnosed at earlier stages in countries with surveillance programs, both the incidence and fatality rates have decreased. In terms of preoperative treatment, the standard of care for rectal cancer differs from that for colon cancer. Treatment options have evolved over time, from single-agent 5-fluorouracil (5 FU) to combination regimens combining 5-FU with Oxaliplatin, irinotecan, or both. The introduction of targeted agents has increased treatment efficacy in the metastatic settings. Recent attempts have concentrated on colorectal cancer molecular classification in order to develop molecularly defined subgroups (28).

In one of the previously cited Tanzanian studies, 326 (98.2%) of 332 CRC patients had surgery. Only 54 of 321 patients (16.8%) received adjuvant treatment. At the end of five years, just nine

of 297 survivors (3.0%) were available for follow-up. Recurrence was reported in 56 of 297 survivors (18.9%) (24).

2.5 Treatment delay

Cancer diagnosis and treatment are difficult in developing countries, including Ethiopia. There are various factors that contribute to this, including advanced stage upon presentation, poor health seeking behavior, delayed cancer diagnosis, and delayed initiation of treatment. The outcome and prognosis of colorectal cancer treatment are strongly dependent on early detection, standard treatment, and additional oncology care. In Ethiopia, studies on diagnosis and treatment delay in breast and cervical cancer are available in part. However, literature on the detection and treatment delays of colon cancer patients in Africa and Ethiopia is scarce. According to various clinical findings and literatures, the delay can be categorized as Patient delay, diagnostic delay and treatment delay (29-33).

A retrospective cohort research with 39,000 newly diagnosed CRC patients was done in China in 2019 to determine the effect of diagnosis to treatment interval (DTI) on overall survival. When compared to DTI 30, the risk of death increased for DTI 31-150 days (HR 1.51;95% confidence range 1.43-1.59) and DTI > 151 days (1.64;1.54-1.76). This risk was maintained at all stages of cancer. Based on these findings, it was recommended that the DTI for all CRC patients, regardless of disease stage, be 30 days or fewer (34).

Missed opportunities for early detection and intervention occur in practically all malignancies; many CRC patients experience missed opportunities. In one study conducted in the US that assessed missed diagnostic opportunities (MDO) for CRC, 92 patients (36.5%) experienced an MDO. Other GI-GU illnesses, such as hemorrhoids and diverticulitis, accounted for over 80% of alternate diagnoses. Age (50) [OR = 2.29 (1.14-4.60), = 0.02] and female sex [OR = 2.19 (1.16-4.16), = 0.03] were independent risk factors for MDO. Each additional physician seen increased the incidence of MDO by more than doubling [OR = 2.05 (1.53-2.74), 0]. .001] (35).

Delays in diagnosis have a negative impact on treatment and, ultimately, treatment outcome. Treatment delays are classified as patient delays, general Practioner (GP) delays, and hospital delays. Total latency can be reduced by reducing all delay intervals. A population-based prospective observational study of 743 Danish CRC patients was conducted. Patient wait times were especially long for RC patients (median 44 days vs.18 days). Although the median G.P. delay was short, 25% of CC-patients experienced a G.P. delay of 59 days or more, and 25% of

RC-patients experienced a G.P. delay of 53 days or more. The fast-track recommendations were not followed; 53% of CC-patients and 39% of RC-patients waited more than 14 days after referral for a diagnosis. A total of 29% of CC patients and 53% of RC patients waited more than 14 days before initiating treatment (36).

Treatment delay has inverse relation with outcome in surgically treated colorectal cancer patients. Report from Harvard medical school analyzed 769 patients, for every treatment delay quartile increase, odds of death decreased by an odds ratio (OR) of 0.78 (p=0.001), and metastatic recurrence by OR 0.78 (p=0.013). Shorter survival duration had a HR of 0.81 (p=0.001) and shorter disease-free survival (DFS) HR 0.72 (p = 0.001). However, multivariate regression adjusting for baseline staging greatly reduces these ratios, and makes them non-significant (37).

Treatment delay in CRC is also influenced by sociocultural factors. In order to optimize treatment attention, the healthcare provider needs to pay more attention to social groups with less formal education. A prolonged treatment delay was documented in 65.5% of cases and was more common among rectal cancer patients, according to a recent prospective study conducted in Spain to evaluate the factors that influence the treatment delay of 2749 CRC patients. Low levels of education, small tumors, ex-smokers, asymptomatic at diagnosis, and following the use of screening were independent predictor variables of DFT in colon cancer patients. Primary school education and being asymptomatic were the corresponding factors among rectal cancer patients (38).

For early identification and management of CRC, a multi-level approach is necessary, including policy-level level intervention, community screening, patient and health professional awareness, and proper treatment facilities. Overall, the evidence suggests that longer wait times may increase the chance of poorer CRC cancer outcomes, which encourages undertaking diagnostic testing as soon as possible after a positive result. Longer diagnostic and treatment wait times may affect disadvantaged groups differently, leading to greater morbidity and mortality, indicating the potential value of specific strategies for these population subgroups (39).

2.6 Survival

The pattern of CRC mortality differs across nations based on HDI and racial characteristics. This is directly or indirectly related to the stage of disease at presentation, patient health-

seeking behavior, and treatment accessibility. CRC mortality is improving in high-income countries, but disease and mortality rates are increasing in low- and middle-income countries. The ratio of CRC mortality to incidence in Sub - Saharan Africa is the highest in the world (13, 14).

According to an Oregon study, recurrence-free survival varies depending on the stage of the disease; for stage II cancer patients, estimated recurrence-free survival rates one, three, five, and seven years after surgery were 98%, 92%, 90%, and 89%, respectively. Only the T stage was found to be strongly related to recurrence. The estimated recurrence-free survival rates for stage III patients after one, three, five, and seven years were 94%, 78%, 70%, and 66%, respectively. Patients who did not receive chemotherapy had a higher recurrence rate (p = 0.023), as well as a larger number of positive nodes (p 0.001) (40).

In China, the three-year survival rate was 74%, while the five-year survival rate was 68%. TNM staging was a prognostic factor (41). A comprehensive population-based study conducted in four European nations (Denmark, England, Norway, and Sweden) also found that the stage of the disease is the most important predictor of CRC survival (42).

A 13-year study in Iran found that survival rates at 1, 3, and 5 years were 90, 70, and 63% for all patients, 89%, 67%, and 58% for RC, and 90%, 74%, and 71% for CC, respectively (P = 0.009). The significant survival predictive factors in Rectal cancers were tumor stages II (P = 0.003, HR:2.45, 95% CI;1.34-4.49), III (P = 0.001, HR:3.46, 95% CI;1.88-6.36), and IV (P = 0.001, HR:6.28, 95% CI;2.73-14.42) and IV (P = 0.003, HR:9.33, 95% CI;1.1-76.37) in colon cancers (15).

In Vietnam, the OS rate fell dramatically to 84.7%, 56.19%, and 45.01% one year, three years, and five years after diagnosis, respectively. The median survival was 48.59 months. Patients with advanced stage had a higher mortality risk (HR, 3.04; 95 CI, 1.79-5.18), were underweight (18.5 kg/m2; HR, 1.65; 95 CI, 1.03-2.65), and had an elevated preoperative carcinoembryonic antigen (CEA) level (>5.0 ng/mL; HR, 1.63; 95 CI, 1.03-2.59). Furthermore, younger patients (50 years old) had worse OS than the middle-aged group (60-69 years) (43).

One study compared the rates of death in African Americans and Caucasians in the United States. Across all data sets, African-Americans had higher overall and stage-specific risks of CRC death and shorter survival than Caucasians. An advanced stage of disease at the time of diagnosis is a primary contributor to the racial discrepancy in survival among African-

Americans. Despite advances in treatment, advancements in the standard of care, and increased screening options, racial disparities in CRC mortality and survival continue (14). Currently, oncologists are convinced that cancer is a genetic disease, but all of the exact causative genetic markers have not been established completely, including the explanation for the racial difference in CRC incidence and mortality for African Americans against whites (44).

Despite medical interventions, most patients in developing countries continue to have poor clinical outcomes and survival. In a retrospective hospital-based study in Gahanna, 221 individuals diagnosed with CRC at the Surgical and Oncological units from 2009 to 2015 were evaluated. The median survival duration was 15 months (95% CI, 11.79–18.21). Over a 5-year period, the overall survival rate for CRC was 16.0%. Survival rates in the first, second, third, fourth, and fifth years were 64%, 40%, 21%, 16%, and 16%, respectively. There was a significant variation in colorectal cancer survival rates according to stage (p=0.0001). The major social and clinical factors influencing overall survival were family history [HR= (3.44), p=0.029)], chemotherapy [HR=(0.23), p=0.0001)], BMI [HR=(1.78), p=0.017)] and both chemo/radiotherapy [HR=(3.63), p=0.042)]. TNM tumor stage (p=0.012), depth of tumor invasion (p=0.036), lymph node metastasis (p=0.0001), and distance metastasis (p=0.00) were all related with poor overall survival (45).

Significant numbers of CRC patients do not receive standard recommended therapies in most low-income countries, including Ethiopia. This is attributable to health-seeking behavior and, more crucially, the scarcity of integrated care. Between 2013 and 2017, a three-year prospective study of 300 CRC patients in Nigeria revealed that 71% of patients received the indicated surgical procedure. When chemotherapy was recommended, approximately half of the patients (50.5%) received it, and 4.1% received radiotherapy when it was recommended as the optimal treatment. The median overall survival with therapy for patients diagnosed with stage III and IV CRC was 24 and 10.5 months, respectively. Patients who received the prescribed treatment had a significantly higher median survival (25 vs. 7 months.01) (46).

OBJECTIVE OF THE STUDY

3.0 General Objective

To Assess the Treatment outcome and Factors Associated among Colorectal Cancer Patients at Tikur Anbessa Hospital, Addis Ababa Ethiopia

3.2 Specific objectives

To Evaluate the Overall Survival and Progression-Free Survival of CRC patients

To Determine Factors Associated with Overall survival of CRC patients

METHODS AND MATERIALS

4.1 Study Setting and participants

The study was carried out in the adult oncology department of TASH, under Addis Ababa University. The radiotherapy (RT) center at TASH, established 25 years ago, is still the only center in the country which provides RT services. The center has one linear accelerator (Linac) and one brachytherapy machine. It's the only hospital which provides comprehensive cancer care including surgery, CT, RT, and palliative care services for cancer patients in Ethiopia (11). All pathologically confirmed CRC patients who visited the oncology center at TASH were recruited for the study. CRC patients were assessed to the time interval between manifestation of signs and symptoms and presentation to health facilities. The time to confirmation of diagnosis and available treatment received was obtained from patients' chart. Patients who consented to participate in the study underwent clinical evaluations including diagnostic tests for proper staging. The median patient follow-up duration was 20 months. The minimum follow-up time was 14 months until the end of data collection and the maximum follow up duration was 40 months.

4.2 Study Design

The study is an institutional-based prospective cohort study of CRC patients from TASH oncology department for clinical presentation, histologic types, stage at presentation, diagnosis and treatment delay, and survival. Patients who volunteered to take part in the study were given comprehensive clinical evaluations, including diagnostic tests and proper staging. Treatment details are documented, and patient outcomes are monitored. Patient PFS and death were determined through clinical follow-up and telephone interviews.

4.3 Source population

All colorectal cancer patients seen at Tikur Anbessa Hospital oncology center during the study period.

4.4 Study population

All colorectal cancer patients who started treatment at Tikur Anbessa Hospital oncology center from Jan 01, 2020 to September 10, 2022.

4.5 Inclusion and exclusion criteria

4.5.1 Inclusion criteria: all biopsy confirmed CRC cases**,** who started treatment in TASH oncology center with adequate clinical, laboratory and imaging information

4.5.2 Exclusion criteria: Patients with ambiguous diagnosis of CRC, Patients diagnosed after August 10, 2021, and who didn`t start treatment

4.7 Sample size

All eligible patients with a diagnosis of CRC are included into the study. During the study period, 415 CRC patients were seen at the outpatient department of the oncology center. Out of those, two hundred and nine (209) CRC patients met the inclusion criteria, thereby the final sample size of the study was found to be 209.

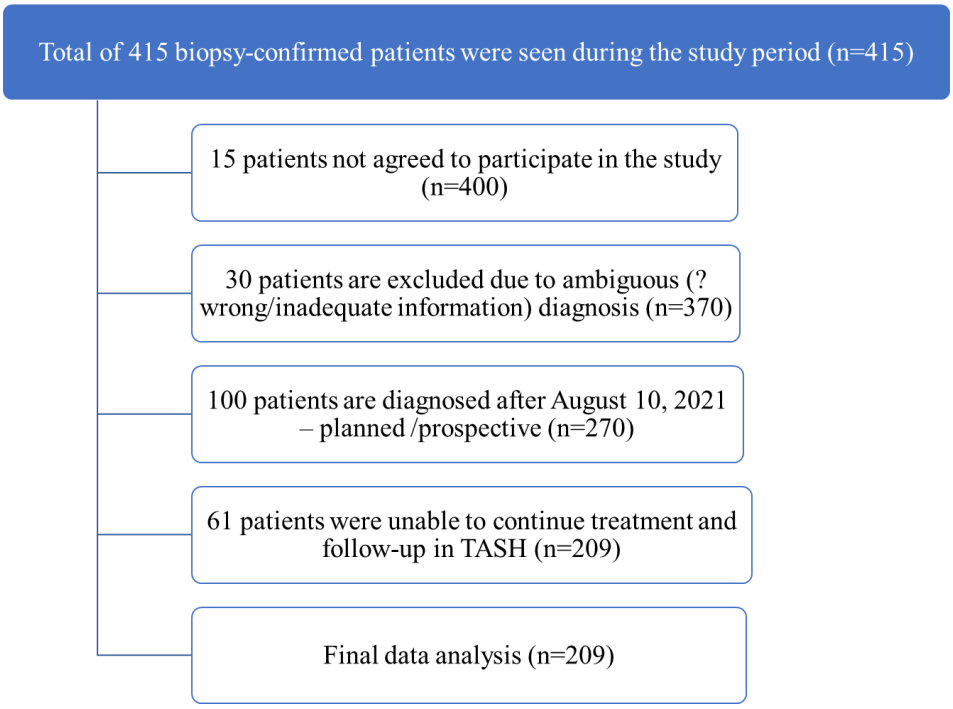

Figure 1: Figure 1: Flow diagram for sample determination of CRC patients in TASH, January 2020 to September 10, 2022.

4.8 Study variables

Dependent variables

- Treatment outcome
    - Alive
    - Death
    - Disease progression

Independent variables

- Sociodemographic factor
    - Age
    - Sex
    - Marital status
    - Educational status
    - Habits
    - Monthly income
    - Comorbidities
- Stage at presentation
- Performance status
- Hemoglobin level
- Delay
    - Health seeking delay
    - Diagnosis delay
    - Treatment delay
- Types of treatments
    - Surgery
    - Chemotherapy
    - Radiotherapy

4.8 Operational definitions

Stage at first presentation: The colorectal cancer at presentation is refers to the stage of the patients based on TNM staging primarily sourced from AJCC cancer staging manual, eighth edition (2017) (47). It is mainly based on imaging if the patient presentation was pre-op or pathological based on histopathological and imaging study if the patient presentation was post op. (Appendix I)

Early stage: Stage-I and Stage-II (48).

Advanced Stage: Stage-III and Stage-IV (48)

Performance status: The scales and criteria are used to assess general well-being and activities of daily life, to determine appropriate treatment and prognosis. We used ECOG performance scale in this study which is simple and widely applicable (49). (Appendix II)

Health seeking delay (patient interval): failed to seek medical attention within 30 days of symptom onset. The patient interval delay in literatures seen is greater than 14 days to 180 days, due to the feasibility in our patients we choose 30 days (50-53).

Diagnosis delay: If failed to made the diagnosis with 14 days of patient presentation to health facility (36).

Treatment delay: Initiation of treatment after 30 or more days of the diagnosis is made (34). For adjuvant chemotherapy, initiation after 8 weeks of surgery (54).

Progression Free survival (PFS): PFS refers to the length of time during and after treatment of CRC that the patient lives without local or distant recurrence, or worsening of the symptoms, death whichever comes first (55).

Overall survival: proportions of patients who are alive after some period (years) among study population (55).

4.9 Data collection tools and procedures

Three oncology resident physicians participated in data collection after going through a two-day training focused on the purpose of the study, data extraction techniques, and codes. The principal investigator and two other supervisors were monitoring the overall data collection process. After customization for the suitability of our patients, patient-centered interview questionnaires (Annex-II) were adopted (56, 57) and used to collect information from patients via phone or in-person interviews. From related studies, data extraction questionnaires were adopted for sociodemographic and clinical characteristics, treatment patterns and outcomes, and survivals (39, 43, 58-60). Pretesting of the data extraction format and interview was done on 10 patients prior to the actual study. Appropriate modifications were made based on the pre-test result. Prior to data collection, each eligible patient's chart was given a unique code number. The demographic data for CRC patients that was collected included socio-demographic status, economic status, stage at presentation, location of disease, care received prior to cancer diagnosis, and health conditions treated before cancer diagnosis. Treatment details are recorded and patients are followed on outcome every 3 months. The PFS and

mortality rate the patients is also assessed through clinical follow up and telephone interview every 3 months.

4.10 Data Analysis

The revised patient record charts were checked for completeness, cleaned manually and entered in to Epidata version 4.60 and then transferred to SPSS windows version 25.0 for further analysis. Different frequency tables, graphs and descriptive summaries are used to describe the study variables like performance status, histologic type of cancer, patterns of delay and stage of cancer at presentation. Categorical variables are compared using chi-square tests. OS is calculated using the Kaplan-Meier method and checked by log rank test. Variables with the log-rank value < 0.05 on Kaplan Meir are considered as having significant association. Those predictor variables which had an association with a p-value ≤0.25 by univariate cox regression analysis were entered into multivariate cox regression and a p-value of less than 0.05 was considered to be statistically significant.

4.11 Dissemination of the result

The findings of this study will be submitted and presented to Addis Ababa University College of medicine and health sciences. The research participant's phone number was collected, and the results of the study will be communicated to each patient through phone call or text message. The broader public will be informed through various local media outlets such as radio, newspapers, and magazines. We will try to publish the study in different national and international journal and disseminate to Health professionals and policy makers.

4.12 Ethical Considerations

This research was conducted to act in the best interests of the study participants. Ethical approval was obtained from the department of clinical oncology, Addis Ababa University. Oral and written consent was also requested from all the participants during data collection. Only approved study personnel had access to this information. After completion of the study, identifier information was set aside, and only study identification numbers (ID no.) were used during the analysis. At the time of enrolment, study participants and their family members were encouraged to contact the data collectors for any concerns they may have. The right to withdraw from the research process at any point in time was respected. There were no interventions undertaken by the investigator in terms of the investigation and treatment.

RESULTS

Sociodemographic characteristics:

Among the 209 patients evaluated, the median age for diagnosis of CRC was 50 years (SD ± 15). Twenty-five percent of the patients were below the age of 38 years and 75% of the patients were below the age of 60 years. Majority of the patients were Orthodox Christian by religion which accounts for 66% (n=138) followed by Protestant and Muslim, at 17.2% (n=36) and 15.8% (n=33) respectively. Most of the patients were from Addis Ababa, comprising 55% (n=115) followed by Oromia and Amhara regions, which accounted for 23.4% (n=49) and 11% (n=23) respectively. Thirty-nine (18.7%) patients had preexisting comorbid illness. Hypertension was recorded in 20 (9.5%) patients, and 14 (6.7%) patients had diabetes. Alcohol usage was recorded in 32 (15.3%) participants and history of smoking was also reported in 11(5.2%) of the patients (Table 1.).

Table 1:Sociodemographic characteristics of CRC patients in TASH, January 2020 to September 10, 2022.

Sociodemographic Characteristics		Frequency	Percentage (%)
Age in years	< 30	21	10.05
	30-39	41	19.6
	40-49	41	19.6
	50-59	41	19.6
	61-69	43	20.5
	≥ 70	22	10.5
Sex	Male	119	56.9
	Female	90	43.1
Educational status	Not at all	45	21.5
	Read and write	32	15.3
	Primary education	43	20.6
	Secondary education	39	18.7
	College and above	50	23.9
Monthly income ETB	Below 1000	7	5.5
	1000-5000	97	75.8
	> 5001-10000	24	18,8
Comorbidity	Yes	39	18.7
	No	170	81.3
Family history	No	209	100
Marital status	Single	25	12
	Married	175	83.7
	Widowed/widower/divorced	9	4.3
Occupation	Farmer	27	12.9
	House wife	63	30.1
	Civil servant in gov't office	46	22
	NGO/private work	16	7.7
	Others*	57	27.2

Habits	Yes	46	22
	No	163	78

* A day laborer, guard men, carpenter, students and no job

Clinical characteristics:

Among the total 209 patients, 128 (61.2%) patients had rectal cancer, while 81 (38.8%) patients had colonic cancer. Nearly two third of the total 209 patients, 134 (64.1%) had presented with bowel habit changes (diarrhea, constipation or tenesmus) and about the same number of patients had presented with rectal bleeding. Among 128 rectal cancer patients, 117(91.4%) patients presented with rectal bleeding, and 82 (64%) had bowel habit changes. Among 81 colonic ca patients only 17 (20.1%) presented with rectal bleeding. Equal numbers (52 each) of colon and rectal cancer patients had presented with abdominal pain. At initial presentation, 49 (38.3%) rectal and 29 (35.8) colonic cancer patients had weight loss. Fifty-six (26.8%) patients had presented with bowel obstruction symptoms at presentation; 34 of them were colonic and the rest were rectal in origin. Ninety-nine (82.5%) patients with rectal cancer had mass on digital rectal examination. Two rectal cancer patients had inguinal lymphadenopathy, while 3 colonic cancer patients had supraclavicular lymphadenopathy (Table. 2)

Table 2: Clinical Characteristics of CRC Patients Seen at TASH, January 1, 2020 to September 10, 2022

Clinical characteristics	Category	Frequency	Percentage (%)
Tumor location	Colon	81	38.8
	Rectum	128	61.2
Hemoglobin	Hgb ≤ 12.5	102	48.8
	Hgb > 12.5	105	51.2
Common presenting Symptoms	Bowel habit change	134	64.1
	Rectal bleeding	134	64.1
	Abdominal pain	114	54.5
	Weight loss	78	37.3
	Bowel obstruction	56	26.79
	Rectal discharge	41	19.6
	Others**	10	4.8
Performance status	ECOG-0	2	1
	ECOG-I	168	80.4
	ECOG-II	31	14.8
	ECOG-III	8	3.8
Histologic types	Adenocarcinoma	179	85.6
	Mucinous	14	6.7
	Signet ring	13	6.2
	Others	3	1.5

** abdominal swelling, cough, easy fatigability.

Stage at presentation

More than three fourth 166 (79.4%) of the patients were found to have advanced disease (stage-III/IV). Out of 104 patients, 56 (53.8%) patients who underwent surgery were not staged preoperatively (Fig 1).

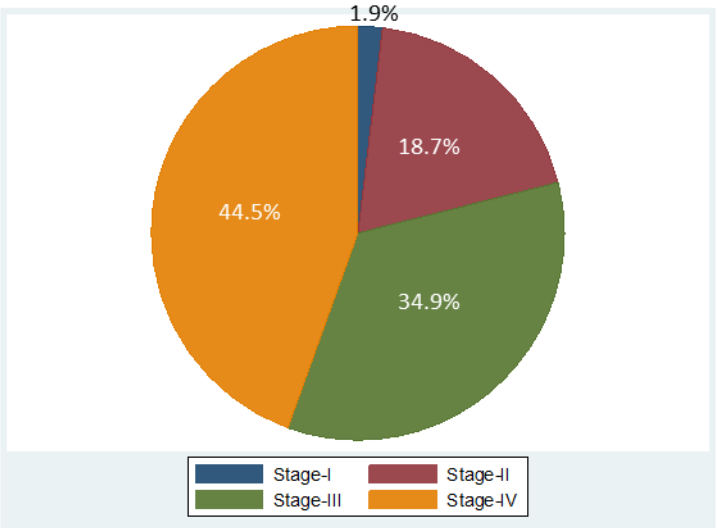

Figure 2:Stages of cancer at presentation for CRC patients in TASH, January 2020 to September 10, 2022.

Previous treatment profile

Among the 209 patients evaluated, 185 (88.5%) of the patients had MDO, i.e., they visited different health care facilities before the diagnosis of cancer was confirmed. Only 24 (11.5%) patients were diagnosed with cancer in their first facility visit for their symptoms. The most common health care facilities that patients visited before their cancer diagnosis were private clinics accounting 132 (63.2%) followed by public health centers, 103 (49.3%) (Table 3).

The median number of health care facilities (HCF) visited among 185 patients was 3 and about 25% of the patients visited 4 or more facilities.

Among the total 209 patients, 184 (88%) were treated for other benign diseases before the diagnosis of cancer was confirmed. The most common condition was intestinal parasitosis, which accounted for 108 (48.8%) followed by amoebic dysentery, 98 (46.4%), dyspepsia, 80 (38.2%) and others (UTI, STI, typhoid fever, etc.) accounts for about 30 (14.3%) patients. In terms of the location of cancer, intestinal parasitosis and dyspepsia were commonly treated in 55 (42.9%) of rectal and 50 (61.7%) of colonic cancer patients, respectively. In patients with rectal cancers, hemorrhoid was the most common condition that was diagnosed in about 80

(38.3%) of the patients, followed by dysentery in about 76 (36.4%) patients. The median number of diseases was 2. Sixty-four (30.6%) patients were treated for 3 or more conditions (Table 3).

Table 3: Previous treatment characteristics of CRC Patients Seen at TASH, January 2020 to September 10, 2022.

Previous HCF visits and treatment characteristics	Category	Frequency	Percentage
Types of HCF visited before the diagnosis of cancer were confirmed	No visit	24	11.5
	Private clinic	132	64
	Government HC	103	49.3
	General Hospital	73	34.9
	Primary hospital	71	33.9
	Tertiary hospital	21	10
	Private clinic	132	64
The number of HCF visited before the diagnosis of cancer was confirmed	0	25	11.5
	1	26	12.4
	2	62	29.7
	3	39	18.7
	4	38	18.2
	5	10	4.8
	≥ 6	10	4.8
Types of disease treated before the diagnosis of cancer were confirmed	Intestinal parasitosis	102	48.8
	Amoebic dysentery	97	46.4
	Hemorrhoids	88	42.1
	Dyspepsia	80	38.2
	Others***	30	14.3
The number of treatments given before the diagnosis of cancer was confirmed(n=209)	0	25	11.5
	1	48	23
	2	72	34.4
	3	43	20.6
	≥ 4	21	10

*** Constipation, acute gastroenteritis (AGE), pelvic inflammatory disease (PID), typhoid

The median time interval of health seeking after the patient experienced initial symptom was 22 weeks. The minimum interval was 1 day and the maximum interval reached up to 173 weeks. Around 25% of the patients waited ≥ 30 weeks to consult a health care provider. The median time interval for the cancer diagnosis after consultation of the first health care provider was 25 weeks. The time from cancer diagnosis to surgery was assessed in 57 patients who underwent surgery. The median time interval to surgery was 66 days with 25% of the patients needing to waiting >114 days to undergo curative surgery. The time interval for adjuvant chemotherapy was evaluated in 82 patients and the mean time interval was 128 days and the median were 105 days.

Patient, diagnosis and treatment delay

Overall, around 93.8% of cases were delayed at presentation and only 13 (6%) patients sought care within 30 days of the symptom onset as shown in fig 2. Among 209 patients, only 38 (18.2%) of them were diagnosed to have cancer within 14 days of health care provider consultation for their symptoms and more than 80% of them had a diagnosis delay. About 47 (22.48%) patients underwent surgery prior to diagnosis being confirmed, and 57 (54.8%) underwent surgery after diagnosis was established, the majority of patients (75.4%) had a delay in receiving curative surgery. Only 14 (24.6%) had the surgery within 30 days of diagnosis. Among 82 patients, 70 (85.4%) experienced delay in receiving adjuvant CT after curative surgical resection; Among the total participants, 50 patients (23.9%) received CT before any other oncologic treatment, 42 (84.0%) patients were late in starting treatment; the average wait time was more than 30 days (Fig 2).

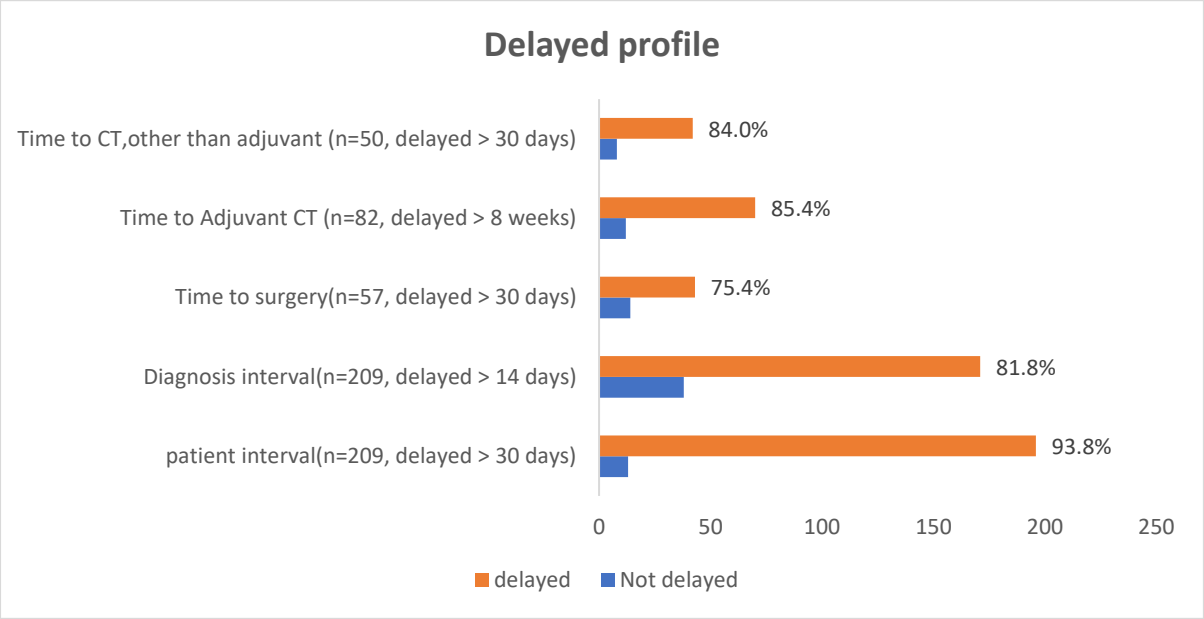

Figure 3: Delay profile of CRC patients in TASH, January 2020 to September 10, 2022.

Treatment delivered:

The treatment status of 209 patients was evaluated, with 138 (66%) having an indication for curative surgery but 34 (16.3%) patients did not received as planned. The majority of the procedures were performed on an elective basis, 69 (66.3%) and with 35 patients (33.7%) undergoing emergency surgery. Twenty-six patients (12.4%) had a palliative diversion stoma. Among patients who needed chemotherapy, 67 (32.1%) did not receive the planned chemotherapy, and 51 (38.9%) did not finish their recommended chemotherapy regimens. A total of 77 rectal cancer patients had been booked for RT with curative intent; however, only 15 (7.2%) of the patients received treatment until the end of the study period. In total, 56 patients (26.8%) did not get any sort of oncologic treatment (Table.4.)

Table 4: Treatment profile of CRC Patients Seen at TASH, January 2020 to September 10, 2022.

Type of treatment given	Category	Frequency	Percentage (%)
Surgery(n=209)	Planned and done	104	49.8
	Planned but not done	34	16.3
	Not planned and not done	45	21.5
	Palliative diversion stoma	26	12.4
Timing of surgery (n=104)	Elective	69	66.3
	Emergency	35	33.7
Chemotherapy(n=209)	Planned and given	135	64.6
	Planned but not given	63	30.1
	Not planned and not given	11	5.3
Completed the prescribed cycles of CT(n=135)	Yes	82	60.7
	No	53	39.3
RT/CCRT	Planned and given	15	7.2
	Planned but not given	62	29.7
	Not planned and not given	132	63.2

Survival

Overall 141 patients (67.46%) died with 95% CI (61%, 74%) between the time of diagnosis and the time of data analysis. A total of 11 (25%) of 44 patients with early-stage disease, 81 (87.09%) of 93 stage-IV patients and 49 (68.05%) of 72 stage-III patients died. The median OS is 17 months (SD, ±10), with a range of 2 to 32 months. For patients who are still alive, the minimum follow-up period until data analysis is 14 months, and the maximum follow-up period is 40 months (Fig.3.). The 1year OS for our patients is 63.16% with 95% CI (56.23%, 69.29%). In terms of staging, the 1-year survival is 91%, 69% and 41% for stage I/II, stage-III, and Stage-IV respectively.

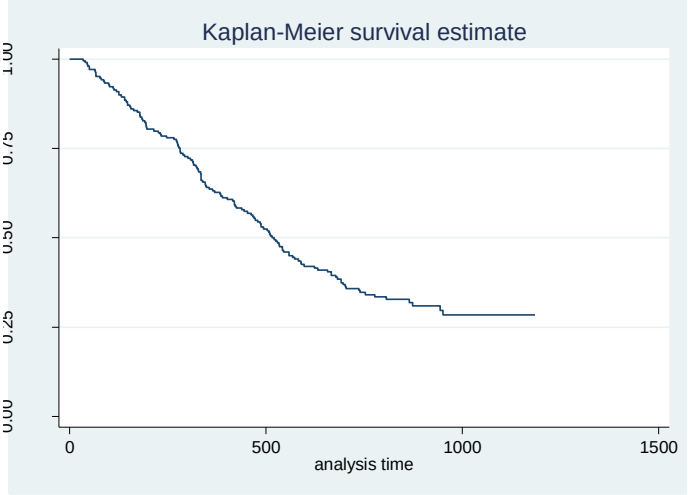

Figure 4: Kaplan Meir overall survival function of CRC patients in TASH, January 2020 to September 10, 2022.

The MS is 19 months for patients with good performance status at presentation versus 10 months for those with poor performance status. The MS for patients with early disease is found to be 33.2 months, whereas the MS for patients with advanced disease is found to be 19 months. Patients who underwent the planned surgical intervention have had MS for 26 months, compared to 16 months for those who did not. The average MS survival time for those in the CT group is 22 months, compared to just 12 months for those who did not follow the recommended chemotherapy regimen (Table.5.)

Table 5: Factors Associated with survival of CRC Patients Seen at TASH using log rank test, January 2020 to September 10, 2022.

Variable	Category	Cross tab		Median OS	P value
		Censored	Dead	(95%CI)	
Sex	Male	42	77	19.0(14.9, 23.0)	0.393
	Female	26	64	17.0(14.7, 19.3)	
Age	≤ 40 years	21	46	17.0(15.3, 18.7)	0.697
	> 40 years	47	95	19.0(15.6, 22.4)	
Marital status	Not married	12	22	17.0(13.2, 20.9)	0.887
	Married	56	119	18.0(15.4, 20.5)	
Education level	Not read at all, read and write	20	57	16.0(19.8, 12.2)	**0.033***
	Primary school	12	31	17.0(11.5, 22.5)	
	Secondary school	12	27	17.0(11.2, 22.8)	
	College and above	24	26	**30.0**(21.3, 38.7)	
Region	Addis Ababa	40	75	19.0(16.2, 21.8)	0.296
	Out of Addis Ababa	28	66	17.0(14.5, 19.5)	
Comorbidity	Yes	14	25	20.0(11.8, 28.2)	0.483
	No	54	116	17.0(19.2, 14.8)	
HCF visit before	Yes	61	124	17.0(14.1, 19.9)	0.848
diagnosis made	No	7	17	18.0 (15.1, 20.9)	
Number of HCF visits	1 HCF	8	17	19.0(16.1, 21.9)	0.654
	> 1 HCF	60	124	17.014.3, 19.7)	

Patient Interval	Not delayed	27	35	21.0(14.9, 27.1)	**0.038***
	Delayed	41	106	16.0(13.1,18.9)	
Diagnosis interval	Not delayed	55	101	19.0(15.9, 22.1)	**0.024***
	Delayed	13	40	14.0(10.4, 17.6)	
Time to surgery	Not delayed	35	36	29(26.0,32.4)	0.125
	Delayed	20	11	32.0(28.4, 34.3)	
Time to Adjuvant CT	Not delayed	9	5	33(28.1, 38.2)	0.381
	Delayed	37	33	32(29.9, 35.7)	
Time to CT	Not delayed	6	11	17.0(9.5, 24.5)	0.140
	Delayed	49	72	23.0(18.9, 27.1)	
ECOG	ECOG 0-1	63	107	19.0(15.9, 22.3)	**0.001****
	ECOG >=2	5	34	10.0(6.9, 13.1)	
Hemoglobin level	Hgb <=12.5	26	76	14.0(10.5, 17.5)	**0.006***
	Hgb>12.5	42	65	20.0(15.8, 24.2)	
Site of cancer	Colon	30	50	18.0(13.7, 22.3)	0.331
	Rectum	38	91	18.0(15.5, 20.5)	
Group staging	**Stage-I/II**	**33**	**11**	**33.2(30.7, 35.8)**	**0.001****
	Stage-III	23	49	19.0(16.8, 21.2)	
	Stage-IV	12	81	11.0(9.3, 12.7)	
T staging	**T-2**	**11**	**6**	**26.3(23.6, 32.1)**	**0.001****
	T-3	**37**	**42**	**25.0(17.7. 32.3)**	
	T-4	20	93	12.0(9.2, 14.8)	
N staging	N1 & N2	34	118	15.0(12.2, 17.8)	**0.001****
	N0 & Nx	34	23	25.0(22.3, 29.6)	
Surgery	Planned and done	56	49	26.0(24.2, 33.1)	**0.001****
	Planned but not done	8	24	16.0(10.7, 21.3)	
Surgery timing	Elective	41	29	32.0(27.7, 33.2)	**0.043***
	Emergency	15	20	24.0(15.8, 32.2)	
Chemotherapy	Planned and given	55	80	22.0(17.9, 26.1)	**0.001****
	Planned but not given	9	54	12.0(9.7, 14.3)	
Completed cycles of the prescribed CT	Yes	45	37	32.0(30.4, 35.4)	**0.001****
	No	10	44	12. 0(9.3, 14.7)	
The overall duration of CT	< = 6 months	38	20	31.0(28.9, 34.8)	**0.012***
	> 6 months	12	20	24.0(21.5, 26.5)	
Radiation or chemoradiation	Planned and given	8	7	32.0(10.4, 53.6)	0.114
	Planned but not given	21	41	19.0(16.8, 21.2)	
Number of CT cycle	<=2 cycle	3	26	10.0(6.0, 13.9)	**0.001****
	>2 cycle	49	52	26.0(19.9, 32.1)	

* statistically significant in the Log-rank test with a p-value of <0.05

** Highly statistically significant in Log-rank test with a P value of < 0.001

OS: overall survival

Progression free survival (PFS) analysis was done on 205 patients who met the criteria. Of them, 147 (71.70%) patients are known to have progressed at some point in their lives. Among these, the event of death was considered as a progression for 96 (45.93%) patients, and 109 (52.15%) patients experienced either local or distant recurrences. Multiple site recurrence at a time (local, liver, lung, bone, etc.), liver-only metastases, and local recurrence occur most frequently in 19, 15, and 10 patients respectively. These 205 participants had a median PFS of 11 months (SD ± 0.7), ranging from 2 to 20 months. (Fig.4.)

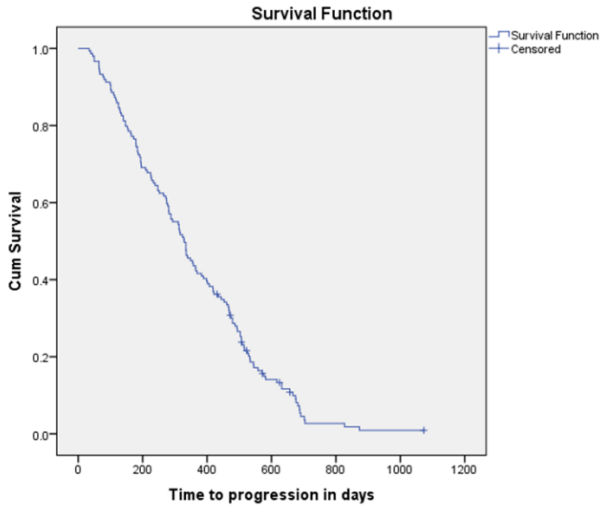

Figure 5: Kaplan Meir progression free survival function of CRC patients in TASH, January 2020 to September 10, 2022.

Factors affecting overall survival

Age over 40 increases the risk of death by 53% when compared to younger age groups (HR=1.53, 1.02 - 2.29, P 0.040). Patients with poor performance status (ECOG-III & IV) had a 60% greater likelihood of dying than those with good functional status, HR=1.60, (1.03 - 2.48, P 0.035). In patients with hemoglobin levels less than 12.5 g/dl, the risk of death is 1.5 times higher (1.03-2.08, p 0.035) than in those without anemia. Tumor depth of invasion is an independent predictive predictor for survival, with T-4 disease increasing the probability of mortality by a factor of 6 (2.28-16.02, p 0.000) when compared to T1 and T2 disease, metastases at diagnosis is associated with a more than eight-fold (3.77-19.25, p 0.000) increased risk of death as compared to early stage cancer (stage I/II). The inability to deliver recommended surgery and chemotherapy are also poor prognostic factors (Fig.5.)

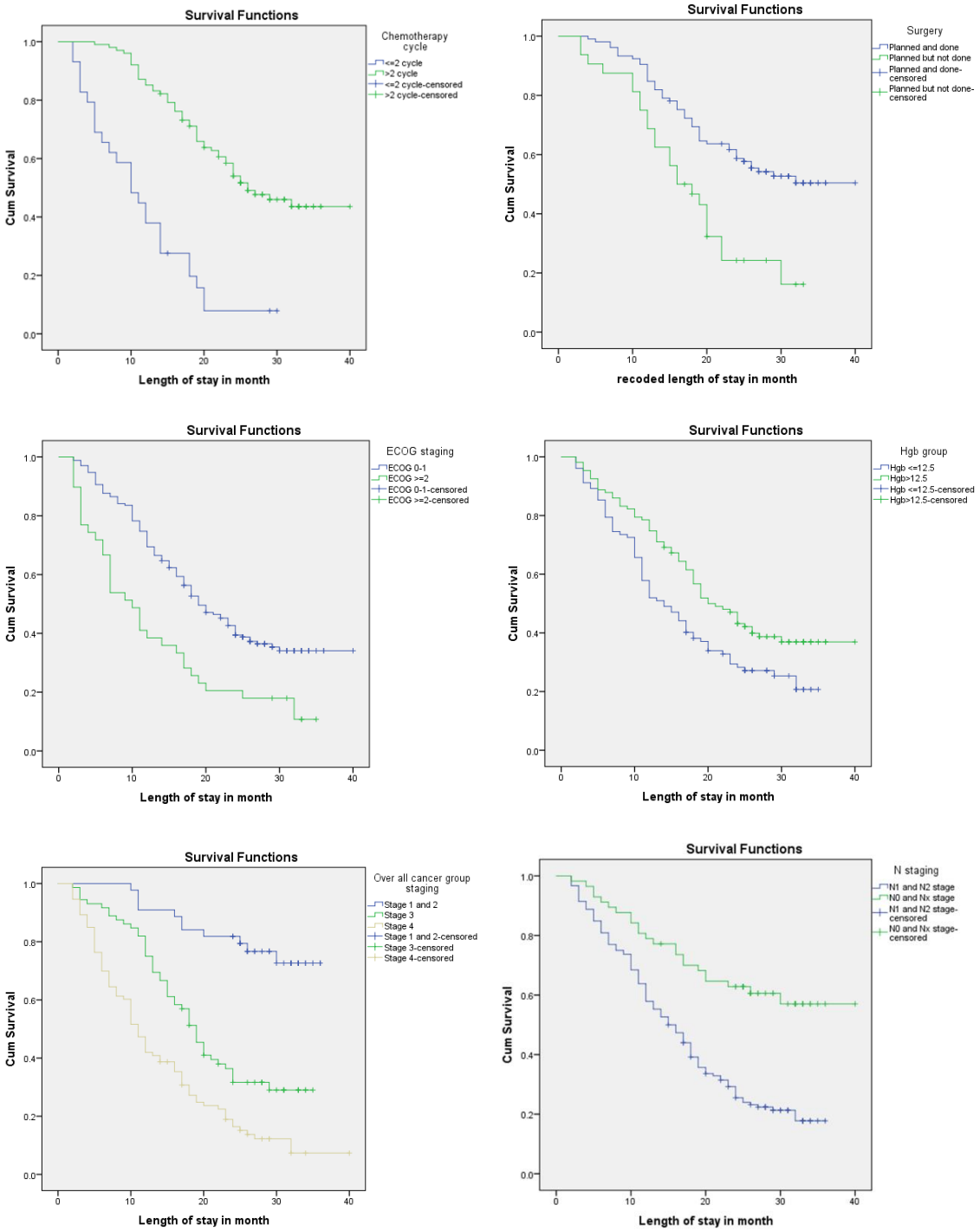

Figure 6: Factors associated with survival of CRC Patients with log-rank test Seen at TASH using Cox regression analysis, January 2020 to September 10, 2022

Table 6: Factors Associated with survival of CRC Patients Seen at TASH using Cox regression analysis, January 2020 to September 10, 2022.

Variables	Crosstab		Unadjusted				Adjusted			
	Censored	Death	HR	95% CI		p-value	HR	95% CI		P-value
Age										
≤ 40	21	46	1							
>40	47	95	. 93	.65	1.31	0.671	1.53	1.02	2.29	**0.040***
Educational level										
College and higher	24	26	1				1			
Not at all, read & write	20	51	1.95	1.22	3.10	0.005	1.48	0.89	2.45	0.134
Primary school	12	31	1.80	1.06	3.04	0.027	2.01	1.15	3.53	**0.015***
Secondary school	12	27	1.78	1.04	3.06	0.036	2.20	1.24	3.90	**0.007***
ECOG										
0-I	63	107	1				1			
II-III	5	34	2.18	1.47	3.21	0.000	1.60	1.03	2.48	**0.035***
Hgb at presentation										
> 12.5			1				1			
≤ 12.5	26	76	1.59	1.14	2.22	0.006	1.55	1.06	2.25	**0.022***
T-staging										
T-1/2	11	6	1				1			
T-3	37	42	1.71	.73	4.03	0.217	2.42	.92	6.34	0.072
T4	20	93	4.43	1.93	10.15	0.000	6.05	2.28	16.02	**0.000****
N-staging										
N-0	23	18	1				1			
N-1	15	43	2.12	1.22	3.67	0.008	.99	.52	1.93	0.998
N-2	19	75	2.83	1.67	4.75	0.000	1.07	.57	2.02	0.832
Nx	11	5	.64	.24	1.73	0.378	1.58	.55	4.56	0.393
Group staging						0.000				
Stage I-II	33	11	1				1			
Stage-III	23	49	4.12	2.13	7.95	0.000	3.65	1.54	8.62	**0.003***
Stage - IV	12	81	8.25	4.36	15.57	0.000	8.53	3.77	19.25	**0.000****
Patient interval										
Not delayed	8	15	1				1			
Delayed	60	136	2.67	1.09	6.52	0.031	1.20	.45	3.19	0.709
Diagnosis interval										
Not delayed	14	24	1				1			
Delayed	54	117	1.32	.85	2.05	0.214	.72	.45	1.17	0.182
Chemotherapy										
Planed and given	55	80	1				1			
Planned but not given	9	54	2.35	1.66	3.34	0.000	2.11	1.44	3.09	**0.000****
Not planned not given	4	7	1.39	.64	3.02	0.401	2.84	1.17	6.90	0.021*

* statistically significant in the multivariate cox-regression with a p-value of < 0.05

** Highly statistically significant in the multivariate cox-regression with a P value of < 0.001

HR: Hazard Ratio

DISCUSSION

CRC is one of the most common causes of cancer morbidity and mortality worldwide. Population based screening, early diagnosis and treatment is required to improve outcome This institutional based prospective study looked at the overall survival and the contributing factors (the pattern of patient presentation, diagnosis and treatment delay). Similar literature is hardly available in the country or even in Africa.

In this study, 67.46 % with 95% CI (61%, 74%) of patients died in a median follow-up duration of 20 months in range of 14 to 40 months. The 1-year overall survival rate is 63.13% with 95% CI (56.23%, 69.29%). This is similar to a finding a retrospective study in Gahanna, where the 1-year survival rate was 64% (61). Comparatively to other regions, SSA has a low rate of CRC survival, where the recently reported metanalysis found the 1-year survival is 74%, even lower in lower income countries like Ethiopia (60). Our finding is far lower than many other studies performed in different parts of the world. Recently reported a large study from brazil where 2,279 CRC cases were analyzed and the 5-year OS was 63.5% and 60.6% for colonic and rectal malignancies, respectively (48). Surprisingly, in one Chinese study reported that 3 and 5-year overall survival is 74 and 68% respectively which is greater than 1-year survival of our patients (41). In a similar study in Vietnam, the 1, 3 and 5 OS survival showed 84.7%, 56% and 45% respectively (43).

The median survival time observed in our patient is 17 months, and 11 months for stage IV disease, which is comparable to a previous study in Gahanna, MS, which is 15 months, where lack of treatment delivery was the main reason for poor survival, and a similar explanation with our patients (61). However, for stage -III patients MS we found is 19 months this finding is lower than a report from Nigeria, MS for stage-III is 24 months, because of curative treatment delivery is relatively better in such locally advanced cases(46). In compared to the survival rate of Vietnamese patients, the median survival time was 48.59 months (39.34 -57.93 months) (43). This stark disparity resulted from varying stage distribution and type of treatment delivery.

Progression-free survival is established as a surrogate marker for overall survival (55, 62). The median PFS is 11 months, and only 58 (27.8%) patients have no progression at the end of the study period. For stage 2 and stage 3 cases, median PFS is 16 and 13 months respectively. However, the 5 years PFS of stage II/III patients in a study done in Oregon is 90%, Proper

adjuvant CT is identified as a protective factor for recurrence (40). It is true for our patients who have not received the appropriate treatment recommendations which results in early disease recurrence or death. The 5 years PFS of stage-II disease in Italy is 78.4%, which showed the relevance of timely initiation of adjuvant chemotherapy (63). The time interval to start adjuvant CT is recommended within 6 to 8 weeks of definitive surgery and delay after 8 weeks is associated with poor outcome (54, 59). In our study, 64 (84.2%) patients had to wait more than 8 weeks to receive adjuvant CT because the mean waiting time for CT in our setup is more than double compared to the standard time recommendation. It is due to the limited number of CT centers in the city.

There are several factors that could affect patient survival seen in many studies. In our assessment, a significant number of patients, 67 (32.06%), were under the age of 40 at the time of diagnosis. we found that the probability of death increased with age greater than 40 years (HR 1.53, 1.02-2.29 p 0.040). A Canadian study that found that young age (45 years) was an independent predictor of better survival supports our finding (64). However, early-onset (age 50) CRC has a poor prognosis due to its advanced stage at diagnosis and poorly differentiated histologies (65). Colonoscopy screening at age 45 and flexible sigmoidoscopy screening at age 40 is beneficial in identifying more patients with early-onset CRC in individuals who are at average risk (66). The difference in prognosis between the two groups could be attributed to the aggressive nature of tumor biology in the younger age group, whereas multiple comorbidities and frailty in the older age group resulted in a barrier to initiating recommended cancer therapy.

Despite advances in cancer treatment, socioeconomic inequities continue to play a significant impact on all types of cancer survival. Socioeconomically disadvantaged groups are at a higher risk of death (67). In the Netherlands, highly educated cancer patients had better survival with low-educated counterparts (68). In our investigation, the median survival time for patients with a college or higher education was 30 months (21.3-38.7, log-rank: p 0.033) and 17 months for those with primary education. In multivariate, high school graduates have a doubled risk of death, HR 2.2 (1.24-3.90, p0.007), compared to college and above graduates. This is consistent with a Swedish study, Patients with lesser levels of education had worse 5-year relative survival (57.9% vs 63.8% in colon cancer, 58.7% to 69.1% in rectal cancer) (68). Better health awareness and early diagnosis, higher income, and good follow-up care could all explain this.

Advanced stage is the most important predictor of CRC patient outcome (69). In our study, the stage of the disease is an independent prognostic factor for lower survival, HR=8.53 ($p<0.000$) for the stage-IV disease relative to early-stage disease (stage 1/II). Stage as a prognostic factor was confirmed in earlier study done on Chinese patients (41) and recently reported large study from Iran (15). A comprehensive population-based study conducted in four European nations (Denmark, England, Norway, and Sweden) also found that the stage of the disease is the most important predictor of CRC survival (42). Furthermore, various factors influence the stage of the disease including sociographic characteristics of patient, biology of the disease and delay.

Ideally, patients should consult a physician within a reasonable time period after symptom initiation for early diagnosis and treatment. Studies recommend that patients seek medical care within 2 weeks of symptom development. A higher symptom awareness is associated with a decrease in the delay of diagnosis (70, 71). In our study, the vast majority of the patients (94%) were late in seeking care, they had waited more than 30 days. This is far beyond the projected data when compared to different studies. In Spain, 28% of the patients waited more than 30 days to consult a health care provider (50). In middle income setup like Malaysia, where a nation-wide study was done, the anticipated health seeking delay for rectal bleeding was 6.1% (72). In US, the anticipated health seeking delay for rectal bleeding was 9.1% (73). Even though further investigation is needed, the likely reason for the differences in health seeking behavior in different countries might be due to the variation in sociocultural, economic and health awareness. In our study, the median patient interval was 22 weeks (154 days) for any cancer symptoms. In Denmark, the median patient interval was 28 days for rectal bleeding, 61 days for bowel habit changes, and 31 days for abdominal pain. The presence of rectal bleeding was associated with a longer patient interval delay (51). A multicenter Asian study had shown more or less similar outcome with our study, with a patient interval delay for abdominal pain seen in 71.4-87.0% of patients as implicated by a lower health awareness in the population (74).

Any cancer can have a chance of missed opportunity for early diagnosis and treatments(35). The delay in the diagnosis and treatment interval increases the risk of poor outcomes in CRC patients (39). Once a patient consults a physician after experiencing a red flag symptom of CRC, the care provider should be vigilant and needs to have a high index of suspicion for malignancy. Health professionals sometimes fail to recognize the symptoms and refer to specialist (75). Practioner also need to be aware that repeated digestive complaints warrant rethinking an alternative diagnosis (56). In our study, the median time to diagnosis interval is

180 days and 90.4% of the patients experienced a delay in diagnosis of cancer. This result was significantly different when compared to other studies in different countries. A study in Spain showed that the median diagnosis interval was 66 days and 38.3% of the patients had waited more than 30 days for the diagnosis (50). In Danish study, diagnosis delay was found in 53% of colonic and 39% of rectal cancer patients(36).

A missed opportunity to diagnose CRC is common despite the presence of different clues to suspect malignancy. In one USA retrospective study, a MDO was seen by 31.4% of patients (76). In our study, 88.5% of the patients had at least one or more MDO in health care facilities. The common conditions that patients were treated for prior to their cancer diagnosis include intestinal parasitosis (48.8%), Amoebic dysentery (46.4%), hemorrhoids (42.1%) and dyspepsia (38.2%). Alternative diagnosis including hemorrhoids, diverticulitis and stomach pain and anemia were also seen in 80% of patients who had a MDO (36.5%) (35). In another cohort study from USA, the MDO was identified in 65% of patients; however, the majority (38%) of the cases were due to patient related factors and only 10% of the cases were due to failure to screen by the health care providers (77). In a Spanish study, the diagnostic clues for patients with MDO were anemia, rectal bleeding, and abdominal pain and the main reason for missing the cancer diagnosis was due to failure to order a diagnostic test (43.3%) (57). Our study revealed similarities in symptom presentation, diagnostic clues, and the failure to pursue a diagnostic investigation as a reason for missed diagnosis. Unavailability of imaging and colonoscopy, even simple fecal occult test at the periphery when there is suspicion of cancer and the poor tier of referral system and catchment-related issues further lengthen the time to a definitive diagnosis.

The vast majority of patients in this study had visited several HCF including public health centers, private clinics and various levels of private and public hospitals; however, the opportunity for diagnosis was still missed despite red flag symptoms and signs. For instance, most (82.5%) of the patients with rectal cancer had palpable mass on rectal examination during oncologic evaluation. Although there needs to be further investigation to outline root causes of missed or delayed diagnosis, it seems like the suspicion of cancer in symptomatic patients, early referral to specialist, as well as the practice of digital rectal exam is poor among frontline health care providers. Additionally, the recommended population based colorectal screening, which significantly prevents morbidity and mortality through early detection of cancer for average risk individuals above the age of 45, is lacking in Ethiopia due to economic and resource issues (78).

Poor PS is an indication of cancer burden and has been shown to reduce survival for a wide range of reasons (79). In our study in patients with an ECOG of III/IV, the risk of death increased by almost 60% (p 0.035). This is because patients are unable to tolerate cancer treatment, and only supporting measures are possible.

Low hemoglobin level in cancer patients can be caused by cancer itself or by a combination of factors; however, it has a significant impact on cancer treatment and patient survival in the long run due to its ability to predict advanced disease(80). In this study, we observed that Hgb levels less than or equal to 12.5 mg/dl were related to poor overall survival, with an HR of 1.55 (1.06-2.25, p=0.022). Despite differences in magnitude and patient demographics, its prognostication potential is similar to other studies. Preoperative normocytic anemia is associated with a generally lower survival rate in Finland (multivariate HR 1.61, 1.07-2.42, p = 0.023) (81). Furthermore, the impact of lower hemoglobin level is more pronounced in in black African Americans (82) .

After cancer is diagnosed, treatment should be initiated as soon as possible considering tumor progression with time as well as psychological stress in patients.

The median waiting time to surgery in our study was 66 days, which is more than two times higher than the standard recommendations. In Norway, the median waiting time to colorectal surgery is 21 days (83). Time to surgery that is longer than 30 says is associated with poor oncologic outcome (84). In our study, among the 57 patients who underwent surgery after the confirmation of their cancer diagnosis, 43(75.5%) of the patients had to wait more than 30 days for intervention. This delay in intervention usually leads to disease progression, sometimes to the point where the cancer is unresectable and death.

In our study, lack of chemotherapy was statistically associated with poor survival by two times (HR 2.11, 1.44-3.09, p=0.000) in multivariate cox regression when compared to those who received as indicated. The protective effect of chemotherapy is also seen in a study from Gahanna (HR 0.23, 0.13-0.41, p=0.0001) (61). In a Nigerian study, patients who got the recommended treatment had a significantly higher median survival (25 versus 7 months) (46). It has been found in various investigations that timely treatment initiation is crucial for patient survival. Treatment delays of more than 30 days increase the risk of death, as determined by a large study conducted in Taiwan (HR: 1.51; 95% CI: 1.43-1.59) (34). Unfortunately, in our investigation, 32.1% patients did not receive the prescribed CT at all. Until the time of data

analysis, only 14 patients had received RT as recommended among the 76 rectal cancer patients due to the prolonged RT wait time. Currently, the wait time for RT is more than 24 months in TASH and there is no other RT center in the county. Our data is not consistent with any of the existing studies. In Norway, the median waiting time for RT is 14-50 days (83). In Taiwan, about 90.5% of CRC patients received the recommended oncologic treatment within 30 days (34). Furthermore, due to a lack of resources in Ethiopia, 56 (26.8%) CRC patients did not receive any form of oncologic intervention. This should be the primary explanation for our patients' increased CRC case fatality rate. However, most patients with locally advanced resectable or metastatic cancers in developed countries undergo standard-of-care treatments such as surgery, CT, and RT as deemed appropriate given well-equipped cancer treatment centers and experienced healthcare professionals, resulting in a CRC cure (27, 84, 85).

In both univariate and multivariate logistic cox regression, sex, marital status, comorbidities, cancer location (rectum vs colon), and frequency of HCF visits had no statistically significant association with survival.

Conclusion: our patient's 1-year survival rate is very low, and overall mortality rate is also very high. The advanced stage upon presentation, poor functional status, and a lack of timely treatment initiation are all key contributors to poor survival. The vast majority of the patients in this study exhibited all levels of delay, which would explain the advanced stage. Few patients were diagnosed and treated in a reasonable timeframe. A significant number of patients were unable to receive the recommended treatment. We recommend that to improve the awareness of our community towards health-seeking behavior.

Recommendation: We recommend increasing our community's awareness of health-seeking behavior towards CRC symptoms. We also recommend that physicians avoid overlooking colorectal cancer in symptomatic patients. Oncology training programs should be included in medical schools. The responsible government and NGO should prioritize the expansion of cancer treatment centers, which would eventually allow for curative treatment without any form of delay.

Strength of the study: The study was conducted at the largest and only comprehensive oncology center in Ethiopia and the prospective nature of this study.

Limitation of the study: We are limited in considering CEA level as a determinant factor in this study because the majority of the patients were investigated after some type of intervention. The COVID-19 pandemic made patient follow-up difficult, and many patients were excluded from the final analysis, making it impossible to determine some variables for prognostic logistic regression due to the small number of patient proportions in cohorts.

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ANNEXES

7.1: ANNEX I: Data abstraction tools

Data Abstraction Tool for the Treatment Outcome of CRC Patients Seen in Tikur Anbessa Hospital, Ethiopia: Prospective Cohort Study from January 2020 to September 2022.

MRN			
I care No.			
Phone No.			
Socio-demographic data			**Comments**
100.1	Age		
100.2	Sex	1. Male 2. Female	
100.3	Occupation	1. Farmer 2. House wife 3. Civil servant in gov't office 4. NGO/private work 5. Merchant 6. Student (except post graduate) 7. Daily labourer 8. Others	
100.4	Marital status	1. Single 2. Married 3. Divorced 4. Widowed/widower	
100.5	Region	1. AA 2. Oromia 3. Amhara 4. Tigray 5. SNNPR 6. Other(specify)	
100.06	Religion	1. Muslim 2. Orthodox 3. Protestant 4. Catholic 5. Other	
100.07	Co morbidity	1. No 2. HTN 3. DM 4. RVI 5. Cardiac	

		6. Renal 7. Other	
100.08	Habits	1. No 2. Alcohol 3. Smoking 4. Chat 5. Other	
100.09	Educational status	1. Not at all 2. Read and write 3. Primary education 4. Secondary education 5. College and above	
100.10	Monthly income	----------birr	
100.11	Family history of CRC	1. YES 2. NO	

Clinical data			**Comments**
200.01	Date of diagnosis(dd/mm/yy) /date of biopsy report	---------/--------/--------	
200.02	Patients complaints at presentation (specify the duration)	1. Abdominal pain 2. Bowel habit change (D, C, T) 3. Rectal bleeding 4. Rectal discharge 5. LBO 6. Abdominal swelling 7. Cough 8. Bone pain 9. Weight loss 10. Incidental finding while on medical check up 11. Other (specify)	
200.05	Type of health facility visited prior to visit to the one where diagnosis was made (more than one facility is possible)	1. Government HC 2. Private clinic/hospital 3. Primary hospital 4. General hospital 5. Tertiary hospital	
200.06	Number of health care providers (HPC) visited prior to visit to the one where diagnosis was made	----------	
200.07	History of treatment for before the diagnosis was made	1. IP 2. Dysentery 3. Haemorrhoids 4. Dyspepsia 5. None	

200.08	Duration initial symptom to first health facility visit	---------- Days	
200.09	Duration of first health facility visit to diagnosis	---------- Days	
200.10	Duration of diagnosis to surgery	---------- Days	
200.11	Duration of surgery to adjuvant chemotherapy/RT/CRT	---------- Days	
200.12	If surgery is not done, duration of diagnosis to CT/RT/CRT	---------- Days	

Physical examination findings						**Comments**
200.13		At presentation	At mid C	At end C	At last FU	
	ECOG	1. 0 2. I 3. II 4. III 5. IV	1. 0 2. I 3. II 4. III 5. IV	1. 0 2. I 3. II 4. III 5. IV	1. 0 2. I 3. II 4. III 5. IV	
200.14	Pertinent P/E findings	1. LAP (inguinal/supraclav) 2. Chest findings(specify) 3. Abdominal mass/Organomegaly 4. Ascites 5. Rectal mass on PR 6. Edema 7. Other (specify)				

Work UP				Comments
200.15	Diagnostic work up	1. CBC 2. RFT 3. LFT 4. CEA 5. Colonoscopy 6. CXR 7. Abd-Pel US		
		8. CT	1. Chest 2. Abdomen 3. Pelvic	
		9. MRI	1. Abdomen 2. Pelvic	
		10. Type of biopsy	1. colonoscopy 2. sample from while doing diversion colostomy/exploration 3. surgically resected specimen	
200.16	Histologic sub type	1. AC, NOS 2. Mucinous 3. Medullary 4. Signet ring 5. Others(specify) 6. Not reported		
200.17	If AC, NOS grade	1. AC, Grade I (well differentiated) 2. AC, Grade II (mod differentiated) 3. AC, Grade III (poorly differentiated) 1. AC, Grade not reported		
200.18	Margin status (proximal, distal or both)	2. Free 3. Involved 4. Not reported		
200.19	CRM	1. Free 2. Involved 3. Not reported		
200.20	MSI	1. Not done 2. High 3. Low 4. Stable		

200.21	LVSI	1. Invasion not seen 2. Invasion seen 3. Not reported			
200.22	PNI	1. Invasion not seen 2. Invasion seen 3. Not reported			
200.23	Tumor Budding	1. Invasion not seen 2. Invasion seen 3. Not reported			
Pathologic staging					**Comments**
200.24	T				
200.25	N				
200.26	No of nodes harvested				
200.27	No of +ve nodes				
200.28	Pathologic staging at presentation	1. stage I 2. Stage II a. IIA b. II B c. II C	3. Stage III a. III A b. III B c. III C	4. Stage IV a. IVA b. IVB c. IVC	
200.29	CT/MRI findings	1. Mass (site and size) 2. Adjacent organ involved (T-staging) 3. LN (no) 4. Mets 5. Ascites 6. Others			
200.30	If mets, site of mets (including CXR/US/FNAC)	1. Liver 2. Lung 3. Bone 4. LN 5. Peritoneum 6. Other			
200.31	clinical group staging at presentation (based on imaging)	5. stage I 6. Stage II a. IIA b. II B c. II C	7. Stage III a. III A b. III B c. III C	8. Stage IV a. IVA b. IVB c. IVC	

Colonoscopy (31,32)				**Comments**
200.31	Site from the anal verge	1. Cecal 2. AC 3. HF 4. TC 5. SF 6. DC	7. SC 8. RS 9. Rectal (subsite by MRI)	
200.32	Colonoscopy Findings	1. Mass 2. Ulcer 3. Stricture 4. Others (specify)	The full report _____ _____ _____	

Lab values						**Comments**
200.33	**Lab**	Before CT	At mid C	At end C	At last FU	
	Hgb					
	Plt					
	ANC					
	AST					
	ALT					
	ALP					
	Bil –D					
	Bil-T					
	Alb					
	Cr					
	CEA					

Treatment			**Comment**
300.01	Frist treatment decision	1. MDT 2. Surgeons 3. Oncologists	
300.02	Type of treatment planned (> 1 possible)	1. Surgery 2. CT 3. CRT 4. RT	
300.03	Type of treatment given (> 1 possible)	1. Surgery 2. CT 3. CRT 4. RT	
			date(mm/dd/yy)/comment
300.04	Surgery	1. Emergency	---------/--------/-------

		2. Elective	
300.05	Type of Surgery if colon	1. Rt hemicolectomy/extended 2. Lt hemicolectomy/extended 3. Transverse colectomy/extended 4. Sigmoid resection 5. Enbloc resection 6. Others (specify) 7. Inoperable and only diversion colostomy	
300.06	Type of surgery if rectum	1. Trans-anal mucosal excision 2. APR 3. LAR 4. + TME 5. Inoperable and only diversion colostomy	
300.07	Chemotherapy if given	1. Adjuvant 2. NA 3. Palliative	---------/----------/----------
300.08	Type of CT if given	1. Single agent Capecitabine 2. CAPOX 3. 5-FU/leucovorin 4. FOLFOX 5. FOLFRI 6. Others	
300.09	Cycles of CT planned	----------	
300.10	Cycles of CT given	----------	
300.11	RT if given	1. Adjuvant CRT 2. NA CRT 3. Palliative	initiated-------/-------/---- completed------/------/-----
300.12	Dose/fractionation of RT planned		
300.13	Dose/fractionation of RT given		
300.14	Sequence of treatment given (surgery is only definitive)	1. CT alone 2. Surgery →CT 3. Surgery→CCRT→CT 4. NACT →Surgery→CCRT 5. NA-CCRT→Surgery→CT 6. Surgery →CCRT 7. CT→RT 8. CCRT→CT 9. Surgery alone	started------/------/-------- completed-----/------/------

Treatment outcome			
400.01	Mid cycle work- up	1. CEA 2. CXR 3. Abd-pel US 4. CT/MRI 5. Not done at all	**Comments**
400.02	Mid cycle response	1. Complete response 2. Partial response 3. Stable 4. Progression	
400.03	If progression	1. Local progression 2. Distant mets a. Liver b. Lung c. Bone d. LN e. Other	--------/--------/------
400.04	Mid cycle plan	1. Continue the same Rx 2. Second line CT 3. RT(CRT) 4. Palliative care	
400.05	End cycle work-up	1. CEA 2. CXR 3. Abd-pel US 4. CT/MRI 5. Not done at all	
400.06	End cycle response	1. Complete response 2. Partial response 3. Stable 4. Progression	
400.07	If progression	3. Local progression 4. Distant mets a. Liver b. Lung c. Bone d. LN e. Other	-------/--------/-------
400.08	End cycle plan	1. Follow up 2. Second line CT 3. RT(CRT) 4. Palliative care	
400.09	New recurrence on follow up	1. No 2. Yes	

		3. Unknown	
400.10	If new recurrence	1. Local 2. Distant 3. Both	----------/-------/----
400.11	If distant metastases on follow up	1. Liver 2. Lung 3. Bone 4. LN 5. Other	
400.12	Clinical Ass't on last FU	1. Stable disease 2. Local Progressive disease 3. New distant mets	date:_____/_____/_____
400.13	Outcome 3 month of Dx	1, Alive 2, Lost to follow up 3, Died	date____/___/___
400.14	Out come at 6 months of Dx	1, Alive 2, Lost to follow up 3, Died	date____/___/___
400.15	Out come at 12 months of Dx	1, Alive 2, Lost to follow up 3, Died	date____/___/___
400.16	Out come at 18 months of Dx	1, Alive 2, Lost to follow up 3, Died	date____/___/___
400.17	Out come at 24 months of Dx	1, Alive 2, Lost to follow up 3, Died	date____/___/___
400.18	Out come at 30 months of Dx	1, Alive 2, Lost to follow up 3, Died	date____/___/___
400.19	Out come at 36 months of Dx	1, Alive 2, Lost to follow up 3, Died	date____/___/___

7.2: ANNEX II: Questioner Amharic version

ለታካሚዎች የተዘጋጀ የቃለመጠይቅ ፎርም

Code: CRC_____	MRN_____	I care_____	
የስነማህበረሰባዊ ሁኔታ በተመለከተ			
100.03	ስራዎት ምንድነው		
100.09	የትምህርት ደረጃዎት ስንት ነው		
100.10	የወር ገቢዎ ስንት ነው 1. _____ 2. *መመለስ አልፈልግም*		
100.11	በቤተሰዎ ተመሳሳይ አይነት ካንሰር አለ/ነበር		
200.02	ከመጀመርያ ጀምሮ የታየቦት የበሽታ ምልክት ምንድን ናቸው(በዝርዝር ይናገሩ)		
የህክምና መዘግየት በተመለከተ			
200.05	ካንሰር እንዳለቦት ካረጋገጠው ተቃም በፊት፣ በየትኛው ተቃም ታይተው ነበር(ከአንድ በላይ ይቻላል)	6. ጤና ጣቢያ 7. የግል ክሊኒክ 8. የመጀመርያ ሆስፒታል	9. አጠቃላይ ሆስፒታል 10. ሪፈራል ሆስፒታል 11. ተርሸሪ ሆስፒታል
200.06	ካንሰር እንዳለቦት ካረጋገጠው ተቃም በፊት ስንት ተቃም ጎብኝተዋል		
200.07	ካንሰር እንዳለቦት ከማወቆ በፊት ለየትኛው በሽታ ታክመዋል	1. የአንጀት ትላትል 2. አሜባ 3. ኪንታሮት	4. ጨጋራ 5. ሌላ 6. የላም
200.08	የመጀመርያ ምልክት ካዩ በሁላ፣ በስንት ሳምንታት ውስጥ ነው ሀኪም ቤት የሄዱት ----------		
200.09	ለመጀመርያ ጊዜ ሀኪም ቤት በሄዱ በስንት ሳምንታት ውስጥ ነው ካንሰር እንዳለቦት የተነገሮት ------		

7.3: ANNEX III: Consent form (English version)

Information Sheet and consent process for patients

Principal investigator: Dr Girum Tessema

Title: Treatment Outcome and associated factors among Colorectal Cancer Patients Seen in Tikur Anbessa Hospital, Ethiopia:

I have been given information about treatment Outcome and associated factors Among Colorectal Cancer Patients Seen in Tikur Anbessa Hospital and discussed the research project with Dr. Girum Tessema who is conducting this research as part of partial fulfilment of specialty certificate in clinical oncology supervised by Dr. Mathewos Assefa in the department of oncology at the Addis Ababa university.

I have been advised that there is no significant risk, burden or additional cost associated with this research and have had an opportunity to ask Dr Girum Tessema any questions I may have about the research and my participation.

I have been selected because I have the disease. I have been informed that there is no payment for being participated, there will not be data sharing other than the principal investigator, and all the data will be kept safe and confidential. I am not going to receive any direct benefit from being participated in this study but I will have the opportunity of close follow up for treatment complications, disease progression and timely intervention.

I understand that my participation in this research is voluntary, I am free to refuse to participate and I am free to withdraw from the research at any time. My refusal to participate or withdrawal of consent will not affect my treatment in any way.

If I have any enquiries about the research, I can contact Dr Girum Tessema (phone no.0966732950) and Dr Mathewos Assefa or if I have any concerns or complaints regarding the way the research is or has been conducted, I can contact the ethical committee of AAU.

By signing below, I am indicating my consent to (please tick)

- ☐ Bring already done workups
- ☐ Having oral or Phone interview if the investigator wants

I understand that the data collected from my participation will be used for purpose like journal publication and I consent for it to be used in that manner.

code: ……SIGN……

DATE……

7.4: ANNEX IV: Consent process (Amharic version)

የተሳታፊዎች የመረጃና የስምምነት ቅፅ

ዋና ጥናት አድራጊ፡ ዶ/ር ግሩም ተሰማ

የጥናቱ አርዕስርት፡ በ አዲስ አበባ ዩኒቨርሲቲ ጥቁር አንበሳ ሆስፒታል የትልቁ አንጀት ካንሰር ታካሚዎች

የህክምና ሁኔታ እና ውጤት

እኔ ስለ የትልቁ አንጀት ካንሰር የህክምና ሁኔታ እና ውጤት በተመለከተ ስለሚጠናው የጥናት ፕሮጀክት በተመለከተ በ አዲስ አበባ ዩኒቨርሲቲ ጥቁር አንበሳ ሆስፒታል የካንሰር ህክምና ትምህርት የመመረቂያ ጽሁፉን በሚሰራው ዶ/ር ግሩም ተሰማ እና በአማካሪው ዶ/ር ማቴዎስ አሰፋ በቂ መረጃ ወስጃለሁ፡፡

በጥናቱ በመሳተፌ ምንም አይነት ጉዳት ወይም ተጨማሪ ወጪ እንደማይኖረው ተገልጾልኛል፤እንደውም በሽታዬን በተመለከተ ተጨማሪ መረጃ ከዶ/ር ግሩም ሁሌ ማግኘት እንደምችል ተገንዝቤአለሁ፡፡

እኔ ለጥናቱ የተመረጥኩት በሽታው ስላለብኝ ብቻ ነው፡፡ ለዚህ ተብሎ የሚከፈለኝ ምንም ነገር እንደሌለ እና ማንኛውም መረጃ ከጥናት አድራጊዎች ውጪ ሚስጥራዊነቱ በእጅጉ የተጠበቀ እንደሆነ ተነግሮኛል፡፡ በተጨማሪም የቅርብ ክትትል እድል እንደሚኖረኝ አውቃልሁ፡፡

የማደርው ተሳትፎ ሙሉ በሙሉ በእራሴ ፈቃድ ላይ የተመሰረተና በፈለኩበት ሰዓት የማቋረጥ መብቴ የተጠበቀ እንደሆነ ተረድቻለሁ፡፡ ያለመሳተፍ ወይም ማቋረጥ በዚህ ሆስፒታል በማገኘው ሕክምና ላይ ምንም ዓይነት ተጽእኖ አያሳድርም፡፡

ስለጥናቱ ተጨማሪ መረጃ ከፈለግኩ፣ማንኛዉም ጥያቄ ካለኝ ዶ/ር ግሩም ተሰማ (ስልክ፡ 0966732950) እና ዶ/ር ማቴዎስ አሰፋ(ስልክ፡ 0911240521) በማንኛዉም ጊዜ ማነጋገር እችላለኑ፡፡ በኋላም ማንኛዉም ጥያቄ ካላኝ የጥናቱ ተመራማሪዎች ከታች በተጠቀሱት አድራሻዎች መጠየቅ እችላለሁ፡፡ ማንኛውም ቅሬታ ካለኝ ለአዲስ አበባ ዩኒቨርሲቲ ህክምና ኮሌጅ ስነምግባር ኮሚቴ ማቅረብ እችላለሁ(ስልክ፡251-118-96-13-96)፡:

በሚከተሉት ላይ በመፈረም መስማማቴን አረጋግጣለሁ(ሳጥኑ ላይ ምልክት ያድርጉ)

- ◯ ለምርመራ የተሰሩ ውጤቶች ለመስጠት
- ◯ የቃል ወይም የስልክ ቃለመጠይቅ ለማድረግ

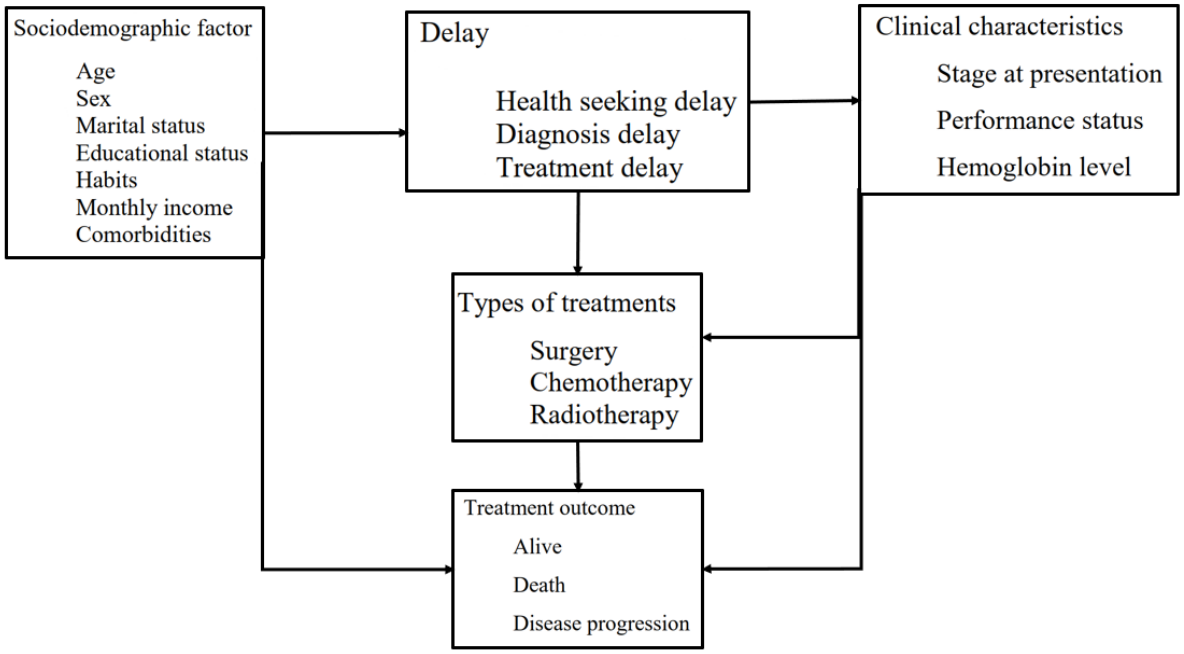
በእኔ ተሳትፎ የተሰበሰበ መረጃ ለጥናት ህትመት እና ጥቅም ላይ እንደሚውል ተስፋ አደርጋለሁ፡፡

ኮድ፡_____

ፊርማ፡_____

ቀን:_____

ANNEX V: Conceptual frame work



APPENDIX

8.1 APPENDIX I: TNM STAGING OF CRC, AJCC 8TH EDITION, 2017 (47).

T category		Description
Tis:		CIS or invasion into lamina propria without extension to the muscularis mucosae
T1:		Invades submucosa (muscularis mucosae)
T2		Invades muscularis propria
T3		Invades through muscularis and into pericolorectal tissues
T4	T4a	Penetrates surface of visceral peritoneum (including gross bowel perforation)
	T4b	Invades or adheres to adjacent organs
N category		Description
N1	N1a	1 regional LN
	N1b	2–3 regional LNs
	N1c	Tumor deposits in subserosa, mesentery, or non peritonealized pericolic or perirectal tissues without regional LN mets
N2	N2a	4–6 regional LNs
	N2b	≥7 regional LNs
M category		Description
M1	M1a	Mets to single organ/site (e.g., liver, lung, non-regional LNs) without peritoneal mets
	M1b	Mets to ≥2 organs/sites without peritoneal mets
	M1c	Mets to peritoneal surface with or without additional organ/site mets
Group staging		Description
Stage I:		T1–2N0
Stage II	IIA	T3N0
	IIB	T4aN0
	IIC	T4bN0
Stage III	IIIA	T1–2N1 or N1c; T1N2a

8.2: APPENDIX II: Eastern Cooperative Oncology Group (ECOG, Zubrod, World Health Organization) performance scale (49).

Performance status	Definition
ECOG-0	Fully active; no performance restrictions
ECOG-I	Strenuous physical activity restricted; fully ambulatory and able to carry out light work
ECOG-II	Capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours.
ECOG-III	Capable of only limited self-care; confined to bed or chair >50% of waking hours.
ECOG-IV	Completely disabled; cannot carry out any self-care; confined to bed or chair.

8.3: APPENDIX III: Response Evaluation Criteria in Solid Tumors (RECIST) (86, 87)

Response assessment	RECIST guideline, version 1.0[1]	RECIST guideline, version 1.1[2]
Target lesions		
CR	Disappearance of all target lesions	Disappearance of all target lesions and reduction in the short axis measurement of all pathologic lymph nodes to ≤10 mm
PR	≥30 percent decrease in the sum of the longest diameter of the target lesions compared with baseline	≥30 percent decrease in the sum of the longest diameter of the target lesions compared with baseline
PD	≥20 percent increase in the sum of the longest diameter of the target lesions compared with the smallest sum of the longest diameter recorded since treatment started **OR** The appearance of one or more new lesions	≥20 percent increase of at least 5 mm in the sum of the longest diameters of the target lesions compared with the smallest sum of the longest diameter recorded **OR** The appearance of new lesions, including those detected by FDG-PET
SD	Neither PR nor PD	Neither PR nor PD
Non-target lesions		
CR	Disappearance of all non-target lesions and normalization of tumor marker levels	Disappearance of all non-target lesions and normalization of tumor marker levels
IR, SD	Persistence of one or more non-target lesions and/or the maintenance of tumor marker levels above normal limits	Persistence of one or more non-target lesions and/or the maintenance of tumor marker levels above normal limits
PD	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions	The appearance of one or more new lesions or unequivocal progression If patient has measurable disease, an increase in the overall level, or substantial worsening in non-target lesions, such that tumor burden has increased, even if there is a SD or PR in target lesions If no measurable disease, an increase in the overall tumor burden comparable in magnitude to the increase that would be required to declare PD in measurable disease (eg, an increase in pleural effusions from trace to large, or an increase in lymphangitic disease from localized to widespread)