Addis Ababa University College of Health Sciences

School of Public Health

Department of Epidemiology & Biostatistics

Time to Initiation of Adjuvant Chemotherapy and its Predictors among Adult Colorectal Cancer Patients at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia; a Retrospective Cohort Study 2013-2018.

Principal Investigator: Sisay Lopiso (BSc)

Advisors: Girma Taye [PHD, Associate professor]

Naod Fikru [MD, MPH]

Abigiya Wondimagegn [BSc, MPH, PHD Candidate]

A thesis submitted to the Department of Epidemiology and Biostatistics, School of Public Health, College of Health Science, Addis Ababa University, in partial fulfillment of the requirements for Degree in Masters of Public Health in Epidemiology and Biostatistics.

November, 2023

Addis Ababa, Ethiopia

Approval Sheet

Addis Ababa University College of Health Science

School of Public Health

Time to initiation of adjuvant chemotherapy and its predictors among adult colorectal cancer patients in TASH, Addis Ababa, Ethiopia; A retrospective study 2013-2018.

I undersigned agree to accept all responsibilities for the scientific and ethical conduct of this research project and declare that this thesis is my original work in partial fulfillment of the requirement for the Master of Public Health in Epidemiology and Biostatistics

Name of the principal investigator:

Date: _____

Signature: _____

Approval of the primary advisor

This thesis work has been submitted with our approval as university advisor.

Name of the student: _____

Date: _____

Signature: _____

Approval by Examination Board

This thesis by Sisay Lopiso is accepted in its present form by the board of examiners as satisfying thesis requirements for the review of degree of masters of public health in Epidemiology and Biostatistics.

Name of primary advisor: _____

Date _____Signature _____

Name of external examiner _____

Date _____ Signature _____

Name of internal examiner _____

Date _____ Signature _____

Acknowledgement

My heartfelt thanks go to Addis Ababa University School of Public Health, for their financial support to conduct this study and Wolaita Sodo University for their academic sponsorship.

My deepest acknowledgment also goes to my advisor, Girma Taye [PHD, Associate professor], Naod Fikru (MD, MPH) Abigiya Wondimagegn (BSc, MPH) for their unreserved, timely and constructive comments, which have been very helpful throughout the study.

I would also like to thank Tikur Anbessa Specialized Hospital oncology department head and staff members for their permission of the study and full cooperation afterwards.

Furthermore, my deepest gratitude also goes to data collectors, friends, and families for unreserved support for this work.

Abbreviations and Acronyms

5-FU: 5-Fluorouracil

AAU: Addis Ababa University

ACT: Adjuvant Chemotherapy

ASIR: Age Standardized Incidence Rate

BMI: Body Mass Index

CAPEOX or CAPOX: Capecitabine and Oxaliplatin

CRC: Colorectal Cancer

Co-60: Cobalt 60

COR: Crude Odds Ratio

DALY: Daily Adjusted Life Year

DM: Diabetes mellitus

DR: Disease recurrence

ESMO: European Society for Medical Oncology

FOLFIRI: Fluorouracil, Leucovorin, and Irinotecan

FOLFOX: Fluorouracil, Leucovorin, and Oxaliplatin

GLOBCAN: Global Cancer Observatory

HIC: High Income Countries

LINAC: Linear Accelerator Machine

LMIC: Low and Middle-Income Countries

NACT: Neoadjuvant Chemotherapy

OS: Overall Survival

RUQ: Right Upper Quadrant Pain

RT: Radiation Therapy

SSA: Sub-Saharans Africa

TASH: Tikur Anbessa Specialized Hospital

WHO: World Health Organization

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Abstract

Background: Colorectal cancer (CRC) is world's third most commonly diagnosed cancer type and the second most fatal cancer globally accounting for 10% and 9.4% respectively in 2020.

Objectives: to assess the time to initiation of Adjuvant Chemotherapy (ACT) and its predictors among adults with CRC at Tikur Anbesa Specialized Hospital (TASH), Ethiopia, 2013 -2018.

Methodology: The study was conducted at TASH, an adult oncology unit. An institution-based retrospective cohort study was done to assess the time to initiation of ACT and its predictors among adults with CRC. Data was collected by kobo toolbox and exported to STATA V17 software for analysis. Kaplan–Meier survival curve was employed to estimate the time to initiation of ACT and the overall survival of patients. The existence of significance differences was as checked by using the Log-rank test. Cox-proportional hazard model was used to identify significant factors associated with initiation of ACT and survival of CRC patients.

Result: A total 135 patients were included in this study. Among this, more than half (60%) were males. The median age of the patient was 48. The median time to initiation of ACT among stage II and III CRC patients after surgery was 11 weeks. Underweighted were 56% less likely to initiate ACT compared to patients with those who had normal BMI Having comorbidities and surgical complications were other significant factors for initiation of ACT with hazard ratio of (AHR = 0.62, 95% CI: 0.22-0.64) and (AHR = 0.45, 95% CI: 0.26, 0.78) respectively. Significant association between initiation of ACT and overall survival was observed; those who initiated ACT late had almost three times higher risk of death compared to those who initiated early. In addition, patients with poorly differentiated cancer cells were four times at higher risk of death (AHR=4.05; 95% CI: 1.58, 10.37).

Conclusion; This study revealed that time of initiation ACT was longer than the standard. Comorbidities, post-operative complication, and low BMI were identified factors for late initiation. The overall survival of patients at three- and five-years were low and significant association was found between late initiation of ACT and having poorly differentiated cancer cells. Therefore, actions should be taken targeting those factors delaying timely initiation of ACT and lowering the overall survival of CRC patients both at health facility and policy level.

Keywords; adjuvant chemotherapy, timely initiation, colorectal cancer, overall survival rate, Ethiopia.

1. Introduction

1.1. Background

Cancer is one of the significant elements of the global non communicable disease (NCD) burden, with prevalence estimated to rise to 24.6 million incident cases by 2030(1,2). Colorectal cancer (CRC) is a malignant tumor in the walls of colon and rectum as a result abnormal growth polyps, and overtime time those polyps may develop into cancer (2,3).

CRC is world's third most commonly diagnosed and the second most fatal from all types of cancers, globally accounting for 10% and 9.4% respectively in 2020(1). In America, more than 104,000 estimated new cases of colon and 43,000 cases of rectal cancer were diagnosed in 2020 (2). Eastern part of Asia was the highly affected region in the world, CRC was responsible for more than 275,000 cancer-related deaths and 6·7 million disability-adjusted life years (DALY). In addition, nearly 637,000 new cases of CRC were registered in 2019 (3). The age standardized incidence rate was the lowest in central sub-Saharan Africa 8.7 per 100,000 which nearly equals the ASIR of Ethiopia 7.7 per 100,000 (3–5).

The risk of developing colorectal cancer is higher with increase age. The significantly higher proportion of CRC patients were diagnosed in adults age and older, but younger population was still sharing nearly 18000(12%) of the total newly diagnosed cases. The occurrence of CRC is also slightly different between gender in their lifetime, 1 in 23 men and 1 in 25 women will be diagnosed with CRC(2,3). In addition, family history of CRC, heredity, inflammatory bowel disease(IBD), previous history of exposure to radiation, having adenomatous polyps, individuals with history of certain types of cancers, race, lack of physical exercise and obesity, lack of nutritional dietary fibers, smoking were also associate with the risk of developing colorectal cancer (6–8).

Surgical resection of the cancerous segment of the colorectum is the gold standard treatment mechanism with adjunct pre and postoperative anti-cancer therapeutic measures. The primary goal of treatment of non-metastatic CRC is to cure the disease by surgical resection of the cancerous tumor, so that it would result an excellent prognosis after primary treatment only, and at present there are no studies supporting initiation adjuvant chemotherapy for patients with this early-stage at this disease. In most cases, stage I CRC is entirely treatable with surgery only (8).

Even though, there are some variations in current clinical practices, most studies didn't support the initiation of adjuvant chemotherapy adjuvant chemotherapy for patients diagnosed with the early-stage II. Approximately 25% of CRC cases are diagnosed at advanced stage of disease, and 20% cases develop distance metastasis; therefore, curative surgical resection alone is often challenging, resulting in cancer-related mortality(10,11). Now a days, some advancements on neoadjuvant chemotherapy (NACT) and adjuvant chemotherapy (ACT) have been improved disease-free survival time against CRC (12). It is highly indicated to consider early initiation of ACT after surgical treatment, especially for potentially high-risk stage II and advanced III and IV, to whom it is known to reduce the mortality rate by 22 to 32% and the disease recurrence rate nearly by 30% (1).

Given the potential benefits adjuvant chemotherapy in terms reducing death and disease recurrence, still little is known on time to initiation of ACT among CRC in Ethiopia. So that, it is important to gain better understanding on how much should be the time gap between operation and ACT commencement and potential predicators affecting timely initiation of ACT in terms of improving the survival outcome of the patients. Therefore, this study aims determine time to initiation of ACT and factor associated among CRC patients in Ethiopia. This in turn will help clinicians to provide a quality care with better oncological outcome.

1.2. Statement of the problem

The global burden of cancer is estimated to increase about 3.2 million new cancer cases and 1.6 deaths annually by 2040, with the greatest increases in LMIC (13). Colorectal cancer represents a significant health problem as third most commonly diagnosed type of cancer globally, between 1990 and 2019 the incident cases and the deaths from colorectal cancer were more than doubled, from 842000 to 2.17 million and 518000 to 1.09 million (2,12). Higher incidence (42.43%) is registered in higher income countries recorded than upper-middle-income countries; however, the deaths were significantly lower (36.4%) due to better treatment opportunity they had(1).

In many of LMIC, radiotherapy centres have problems with long waiting time in order to get timely treatment. Even though, there is change towards increment in the number of radiotherapy centre availability in developing countries, accesses to timely initiation of radiotherapy remained to be a big challenge (14). A quick response is therefore essential and NACT, radiotherapy and ACT is a key component but they are vastly under-resourced. According to International Atomic

Energy Agency data in Africa, only two countries (Egypt and South Africa) come had acceptable standard of access to radiotherapy and chemotherapy treatment (15).

Global cancer observatory from country-specific data source for Ethiopia reported that, number of prevalent cancer cases for 5-year were 130, 858 and, the number prevalent 8774(7%) and deaths registered were 51,865, from which 4335(8.4%) deaths were occurred due colorectal cancer (12).The challenge for effective prevention and control of CRC are of many different factors for developing countries like Ethiopia. They emanate from patients, health service providers and health care facilities(16). Now a days, most of those problems could also be explained in terms of disproportionate cancer diagnostic and chemotherapy centers when compared to increasing burden of disease.

In Ethiopia, less attempts towards early detection of cases and delayed initiation of treatments have been a major health problem for non-communicable diseases including cancer (17). On the other hand, early initiation of adjuvant chemotherapy (ACT) for colorectal cancer has been shown to have an invaluable role towards improving the overall survival in patients with stage III CRC and trend toward increased disease-free survival on some of the patients with stage II CRC with high risk of relapse (3,18). In addition to this, most of the studies in Ethiopia were undertaken on magnitude, the overall survival and quality of life among colorectal cancer patients. But there were no studies done in Ethiopia specifically on time to initiation of the adjuvant chemotherapy for CRC and on its predicators.

Therefore, there are there are gaps towards determining the appropriate timing to initiation of adjuvant chemotherapy in Ethiopia. So that, this study aims to assess the optimal time to initiate adjuvant chemotherapy after surgery for colorectal carcinoma by exploring the main factors affecting the timely initiation of the treatment.

1.3. Significance of the study

In this study, we were interested to see the time to initiation of adjuvant chemotherapy and its predictors among adult colorectal cancer patients and who underwent surgery. So that, the result of this study will be helpful on improving and designing appropriate clinical practices regarding scheduling follow-ups for treatment as early as possible according to the guidelines by taking the main factors affecting early of initiation of chemotherapy into consideration.

The findings could also provide better input to decision-makers, program implementers, monitors, and evaluators, to advance better knowledge to offer ACT timely. It also improves the awareness of the community about most important factors affecting early initiation of adjuvant chemotherapy and the importance of early health care-seeking behavior.

Additionally, the study could be used as baseline-information for future researchers who will be interested to do their research on related topics.

2. Literature Review

2.1. Introduction

After thorough review of various sources related to the issue under study, the literature review was classified into four sections focusing on epidemiology of colorectal cancer at global, regional and national level, time to initiation of adjuvant chemotherapy, survival benefit of ACT and factors associated with initiation of ACT. Relevant publications presented in those sections, databases such as webpages, Google Scholars, PubMed, Journals and papers published within last 10 years were searched. Zotero reference manager was used for citations.

2.2. Epidemiology of colorectal cancer

According to the report from GLOBCAN data, approximately there were about 19.3 million incident of cases and about 10 million cancer deaths were registered in 2020 from which, about 1.93 and 0.94 million further new cases and deaths respectively were contributed only by CRC (1,19). Of this 59.46% new cases and 61.68% of deaths is contributed from cancer arising from the colon in both sexes. Of the 15 million deaths between the ages of 30 and 69 ("premature deaths") in 2018, 4.5 million were due to cancer (1). CRC incidence rates are 30% higher in men than in women. Approximately 64,253 incident cancer cases were estimated for 2015, from which 21,563 and 42,722 incident cases were diagnosed in males and females, respectively. CRC is most common cancer in men age ≥ 15 years and it is the third most common cancer, with (age specific incidence rate) ASIR of 8 per 100,000 (2,20).

A more recent report from population-based cancer registries of American Cancer society revealed that, CRC is the third most commonly diagnosed cancer in both men and women with estimated 106,970 and 46,050 will be newly diagnosed cases of colon and rectal cancer respectively in 2023. The study also reported that, estimated 52,550 will die from those newly diagnosed cases in similar year (21). The incidence rate of CRC was highest in high income countries specially in Australia and New Zealand, and mortality was highest in Eastern Europe (7). Five countries in Asia (China, Japan, Korea, Malaysia and Singapore) were known to have a highest five-year prevalence (each having >46.5 cases per 100,000 population), incidence and mortality rate than other Asian countries (8).

The incidence and death from colon cancer are increasing in developing countries for both males and female, even if it is significantly in high-income countries. The upper-middle-income countries accounted for the highest incidence (45.9%) and the death (49.1%). The incidence of new cases of cancer and mortality occurring disproportionately in low income countries have resulted on significantly worse population outcome, people with low socioeconomic status have poorer health outcomes and are more likely to fall in financial hardship (1,19).

A systematic review and meta-analysis report estimated that the overall ASIR of CRC in Africa per 100,000 population was 5.3. Crude incidence rate of CRC in Sub-Saharan Africa (SSA) was 4.04/100,000 population with higher incidence rate in men (4.4), which was much lower when compared to HIC (19,22). According to study done in Nigeria the trend in prevalence of CRC was increasing ranked as tenth and twelfth most common cancer in 1960 among men and women respectively. But, in 2018 CRC became the second common in men and third most common cancer in women (23).

According to GLOBCAN report in Ethiopia (12), number of new cases cancer in 2020 in both sexes of all age group were 77,352 From these, CRC were the third most newly diagnosed following breast and cervical cancer accounting 7,445 (9.6%) of the total. Study conducted in Ethiopia revealed that the overall six-year mortality rate was 18.3 per 100-person year follow-up (24). Another three-years institution-based retrospective cohort study conducted among colorectal cancer patients at oncology units of Northwest Ethiopia showed that, 27.5% of deaths occurred within the follow-up period, which makes mortality rate of 22.5 per 100 person-years (95% CI: 18.5, 27.38) (12).

The risk of occurrence of colorectal cancer increases with increasing age, that for every subsequent 5-year adds on, the incidence rate approximately doubles until age 50, and thereafter increases by about 30%. Trends are showing that, the majority of cases are occurring in older age groups, masking trends in young adults. The exception is ages 50-54 years versus ages 55-59 years, for which there is only a 15% difference (2,12,26). Decreasing in mortality from CRC were began earlier and were initially more rapid in white than in black people, resulting in a widening racial gap from 1990 to 2015, when death rates were almost 50% higher in blacks (13). However, within the past decade, the black-white mortality disparity has begun to narrow because rapid declines that occurred during the 2000s (of approximately 3% per year) have slowed in whites but persisted in blacks (27). Over the past 10 data years (2008-2017), death

rates declined by 3% per year in individuals aged 65 years and older and by 0.6% per year in individuals aged 50 to 64 years while increasing by 1.3% per year in those younger than 50 years (12). Because of the earlier appearance of symptoms, rectal cancer is diagnosed at a localized stage slightly more often than colon cancer (38% vs 36%), partly explaining the higher overall 5-year survival (67% vs 63%). The lifetime risk of developing CRC was 1 in 20 males and 1 in 26 females (21).

Life style factors associated with increased risk of CRC were, physical inactivity, overweight and obesity, smoking, alcohol consumption, low intake of fruits, vegetables and dietary fiber and increased intake of high-fat diet and processed meats. Other factor associated with risk CRC specially in advanced age group are Inflammatory (IBD) (Crohn's Disease(CD) and ulcerative colitis), family history CRC, accumulated mutation in adenomatous polyposis or hereditary non polyposis (3,6,8).

2.3. Time to adjuvant chemotherapy

The Victorian guideline for time to ACT were developed by the National Health and Medical Research (NHMR) formulated for prioritized cancer groups such as breast, colorectal, lung ovarian cancer and lymphoma. According to this guideline ACT should be commenced within eight weeks after surgery for medically fit CRC patients (28). A population-based study involving 18,491 patients in in China claimed that ACT should be initiated within 8 weeks to decrease the mortality and recurrence rate among patients with colon cancer(29). Another two large scale national population-based cohort studies speculated that patient started ACT after eight weeks of curative resection had worse overall survival (18,30). According study done in South Korea, better oncological outcome among rectal patients was achieved by early initiation of adjuvant chemotherapy within a cut-off point of approximately 3 weeks (31).

The median time between primary surgical treatment and adjuvant chemotherapy was 4 ± 2 weeks according to other retrospective study conducted in China (32). In America the median time for initiation of adjuvant chemotherapy was 9 weeks with an interquartile range of 7-11 weeks (33). According to large scale population-based study in china, as a time to ACT increased, an improvement on overall survival of patients get smaller and those patients who initiated ACT beyond 21 weeks of surgical resection did not significantly improve the overall survival rate when compared with non-user of chemotherapy (29).

2.4. Factors associated with delayed initiation of ACT

Sociodemographic factors: Costs related to chemotherapy are rapidly rising and disproportionately oriented to a minority of patients, at the expense of providing effective established, generic medicines and biosimilars to many more patients (12). The ESMO International Consortium found that many essential cancer medications were unavailable in low income countries (LIC); when they were available, the full cost was paid by patients, limiting their access. Furthermore, many recent targeted therapy agents are available without high out-of-pocket expenditure only in HIC (34,35). Patients with low to moderate income status were 2 times at high risk of delayed initiation of ACT (32). In addition to this, male sex, increased age, cancer care centers far from residential area of the patients, being unmarried, and being noninsured have been associated with delays time to initiation adjuvant chemotherapy (36–39).

Postoperative complications: delayed initiation of adjuvant chemotherapy was high in patients with postoperative complication and intercurrent illness (40). Among the postoperative complications; cardiac arrest, ostomy infection shock and septicemia had strong influences on chemotherapy delay approximately 4 – 11 weeks (29,41). A retrospective study conducted in America demonstrated that, patients with anastomotic leakage had 8.1 times and emergency surgery had 1.9 times higher risk of delayed initiation of ACT (42).

Comorbidities: were strong predictors of chemotherapy non-use and delay, studies reported that anxiety and dementia were highly corelated with late initiation of ACT (43). In addition, patients with congestive heart failure and stroke were 66% and 44% lower chance of initiation of ACT respectively(36,44). Apart from the survival disadvantage of CRC patients with comorbidities, further evidence on the risk–benefit ratio of chemotherapy according to the type and severity of comorbidity. In addition, the extent to which the survival disadvantage of comorbidity could also be explained by less- or non-use or lower tolerability of ACT which needs to foster individualized medical care in those patients. Institution based retrospective study revealed that more than 79.9% of patients with comorbid illnesses were initiated ACT after 4 weeks (44). Another study conducted in china reported that renal failure, pneumonia, pulmonary embolism, anemia and myocardial infarction each responsible for 2-3 weeks delay on ACT initiation (29).

Health care service factors: patient referred to another hospital for adjuvant chemotherapy and prolonged postoperative hospital admission had 1.9- and 4.7-times higher risk of delayed initiation chemotherapy. A multicenter retrospective cohort study in Canada demonstrated that

higher time interval between date of surgery and pathology report was associated with increase in time to ACT (45). Another study done in United Kingdom reported that, longer inpatient stay and admission to intensive care unit was also associated with increased time to adjuvant chemotherapy (43).

Apart from factors explained in earlier sections some clinical factors such as grade, stage, route of administration of chemotherapy and BMI were associated with delayed ACT initiation for more than 6 weeks (46).

2.5. Benefit of adjuvant chemotherapy

A higher risk of recurrence and death will be expected at in late stage II and III colorectal cancer. So that it is highly recommended to start adjuvant chemotherapy in the absence of a medical or psychiatric contraindication (11,27). Timely commencement of ACT maximizes individual patient outcomes in terms of overall survival. In addition, it plays a major diseases free survival role, particularly by reducing the of recurrence rate, specially within first 2 years of adjuvant therapy with some additional benefit to more than 3 to 4 years, so that it reflects the curative role of chemotherapy in those settings. In most cases the recurrence rate after 5 years is less likely (less than 1.5% per year), and after 8 years, they were less than 0.5% per year, so that, long-term follow-up for recurrence provides little value. A significant overall survival (OS) benefit of adjuvant therapy was consistent over the 8-year follow-up period (10,47).

Delayed initiation of ACT has been associated with decreased overall survival rate (48). Each 4 weeks increase in time to adjuvant chemotherapy is associated with a significant decrease in both overall survival with HR of 1.14; 95% CI, 1.10 to 1.17) and disease-free survival (HR 1.14; 95% CI, 1.10 to 1.18). In addition to this, some other studies have also shown that OS decreases with increasing time for commencement of adjuvant chemotherapy, with hazard ratio 1.22, 1.25 and 1.96, for 9–12 weeks, 13–16 weeks, and over 17 weeks delay respectively (29,41,49). In Nigeria a four years prospective study determined that approximately half of the patients (50.5%) received adjuvant chemotherapy regimen in recommended time interval. The median survival time is found to be significantly better nearly 25 and 7 months for patients taking ACT after surgery and, in those patients underwent surgery only, respectively (50). Another retrospective study conducted in Ethiopia at cancer treatment center of Tikur Anbessa Specialized Hospital shown that the risk of death among patients received adjuvant therapy reduced by 36.1% (HR:

0.639 (95% CI: 0.41–0.97)) when compared to that of patients who had an only surgical resection (49).

2.6. Conceptual Framework

Different literatures mentioned that there are different factors associated with the risk of delayed initiation of adjuvant chemotherapy for colorectal cancer. Sociodemographic factors like age, sex, marital status, income and residence is among most important predicators. In addition to this, health care service factors and some clinical factors related to comorbidities and postoperative complications were also are the hypothesized factors to affect the commencement of the chemotherapy. The time to initiation of adjuvant chemotherapy in turn hypothesized to affects the overall survival rate of the patient (29,36,51,52).

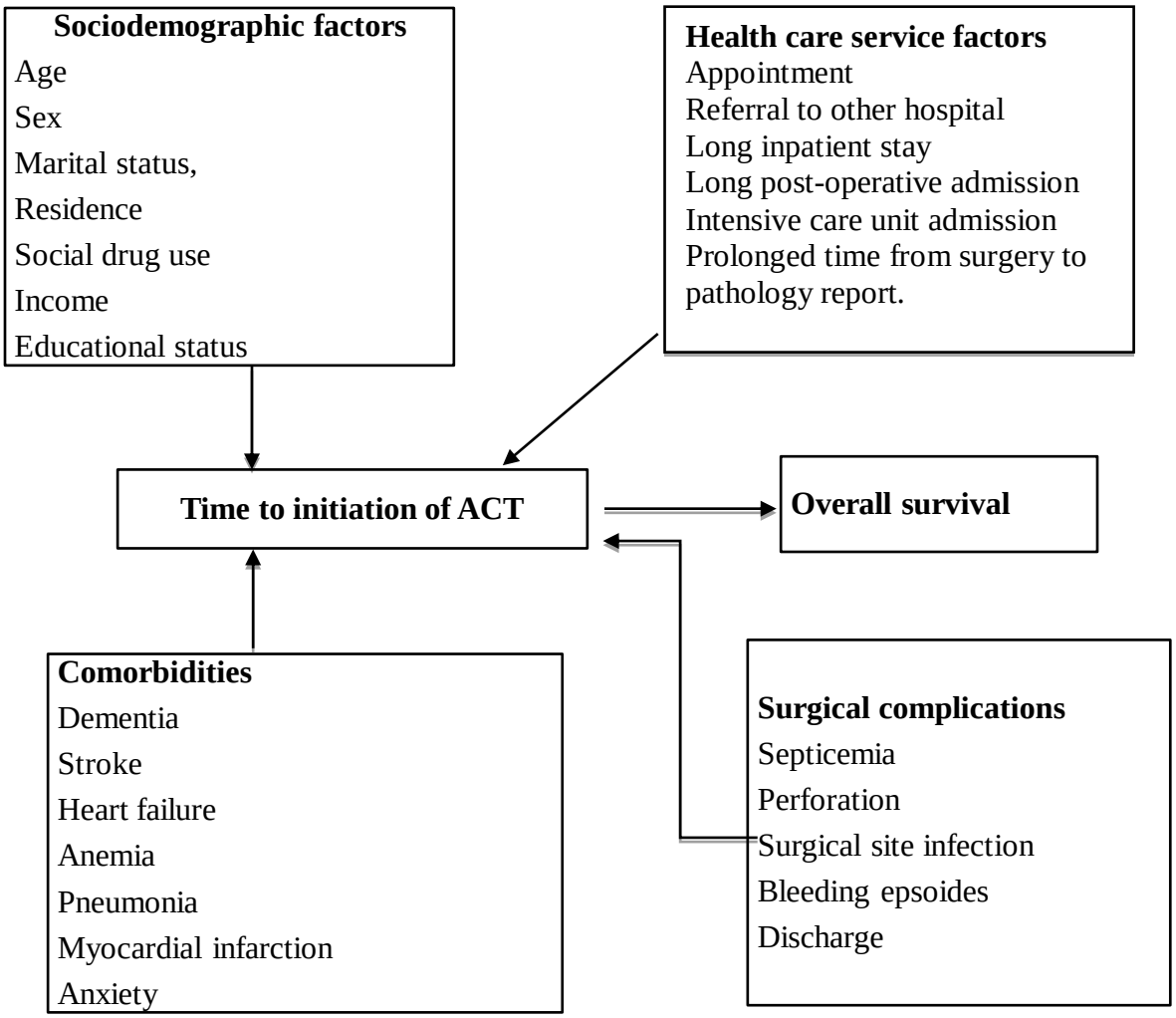

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Figure 2.1. Conceptual framework showing factors affecting early initiation of adjuvant chemotherapy and its potential outcome.

3. Objective

3.1. General objective

- To assess the time to initiation of adjuvant chemotherapy and its predictors among adults with colorectal cancer at TASH, Ethiopia, between 2013 -2018.

3.2. Specific objectives

- To determine time to initiation of ACT among II & III CRC patients at TASH.

- To identify factors associated with initiation of ACT among II & III CRC patients at TASH.
- To assess the association between overall survival and time of initiation of ACT among adult II & III CRC patients at TASH.

4. Methods

4.1. Study setting

This study was conducted at TASH, adult oncology unit. The hospital was established in around 1972 and it is the largest teaching hospital located in Lideta Sub-city, Addis Ababa, Ethiopia. This institution is well known in Ethiopia for rendering comprehensive clinical services that are not easily available in most of other private and / public heath institutions. The oncology center was started to function in 1990, providing chemotherapy treatment, with more than 19 bed for inpatient and more than 10 beds for outpatient clinical services. In addition to this, it has one radiotherapy machines (cobalt-60), high dose rate brachytherapy unit, one CT simulator, one

Linear Accelerator Machine (LINAC) and two colorectal surgeons. The department is also equipped with one computed tomography scans and one magnetic resonance imaging unit(24).

4.2. Study design and period

An institution-based retrospective cohort study was conducted by reviewing the medical chart of CRC patients. The study was conducted between May 7, 2022 and June 5, 202.

4.3. Population

4.3.1. Source population

All patients with colorectal carcinoma at TASH oncology center.

4.3.2. Study population

All patients diagnosed with CRC between January 1, 2013 to December 31, 2018 at TASH and with complete medical records. We purposively selected this time frame for our third objective which is to compare five-year survival status of patients based on initiation of ACT.

4.4. Eligibility criteria

4.4.1. Inclusion criteria

Medical charts of adults above 18 years with pathologically confirmed CRC and who were booked for treatment with ACT after surgery were included in the study.

4.4.2. Exclusion criteria

Patients who had stage I and IV CRC, incomplete medical record more than 15 % and/ lacking key information specially regarding date of surgery and diagnosis were excluded.

4.5. Sample size determination & Sampling procedure

4.5.1. Sample size determination

Sample size for the first objective

For a given effect size (Δ) = 1.48,(29) level of significance α=.05, and power (1 - β) =0.9, the number of events(d).

The required for both groups combined is given(53).

$$d = \left(\frac{\left(Z\frac{\alpha}{2}+\beta\right)(\Delta+1)}{\Delta-1}\right)^2 ,(53)$$

$$\left(\frac{(1.96+1.281)(1.481+1)}{(1.481-1)}\right)^2 = 280$$

When we calculate for 10% non-response rate; $\frac{209}{1-0.1}$ = 308.

Sample size for the second specific objective; $d = \left(\frac{\left(Z\frac{\alpha}{2}+\beta\right)(\Delta+1)}{\Delta-1}\right)^2 ,(53)$

Table 4-1: The sample size calculated using factors associated with delayed initiation of ACT.

Given	Previous study	Variables associated with delayed ACT	AHR (Δ)	Numbers of events
$Z\frac{\alpha}{2}$ =1.96 Power =90=1.28 Add 10%, non-response rate	(36)	Surgical complication	0.55	139
		Comorbidity	0.43	75
		Age >70	0.34	49

Sample size for the third specific objective

Given the hazard of death is 1.63 times higher among initiators of chemotherapy 8 weeks, level of significance α=.05, and power (1 - β) =0.9, the number of events(d). The required for both groups combined is given (30).

$$d = \left(\frac{\left(Z\frac{\alpha}{2}+\beta\right)(\Delta+1)}{\Delta-1}\right)^2 ,(53)$$

$$\left(\frac{(1.96+1.28)(1.63+1)}{(1.63-1)}\right)^2 = 184$$

After adding 10% non-response rate the overall sample size will be 199.

Therefore, the sample size for the first specific objective (n =308) should be taken as the total number of subjects participating in this study, as it is the largest of sample size for the other specific objectives, but 310 subjects were studied.

4.5.2. Sampling technique and procedures

The information was obtained from every subject who fulfill the inclusion criteria during the study period.

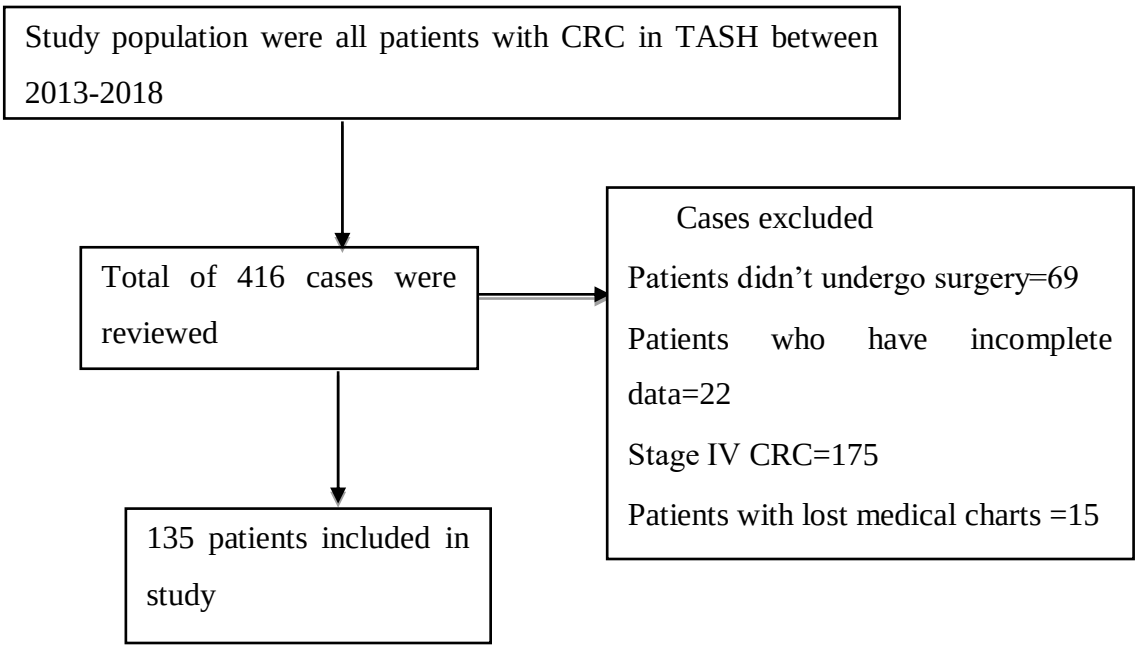

Figure 4.1. Flowchart showing the procedures of medical record abstraction process of the study population.

Even though, the largest sample size calculated for this study was 308, only 135 of subjects with stage II and III CRC had fulfilled the inclusion criteria.

4.6. Study variables

Outcome variable/dependent variable

- ✓ Time to initiation of adjuvant chemotherapy.
- ✓ Survival status of the patients

Independent variables

Sociodemographic factors

- ✓ Age
- ✓ Sex
- ✓ Marital status,
- ✓ Residence

- ✓ Religion
- ✓ Occupation

Clinicopathological factors

- ✓ BMI
- ✓ Level of differentiation
- ✓ Stage of disease during diagnosis
- ✓ Mode of treatment used
- ✓ Type of surgery performed
- ✓ Comorbidities
- ✓ Surgical complication

4.7. Operational definition

BMI: is classified according to disease prevention and control as, underweight (BMI <18.5 kg/m²) normal weight (BMI 18.5-24.9 kg/m²), overweight (BMI 25-29.9 kg/m²) and obese (BMI ≥30 kg/m²) (54).

Comorbidity: According components of Charlson Comorbidity Index used during data collection, any of these conditions co-occur with colorectal cancer at the time of diagnosis, it is referred to as comorbidity and is marked with a yes response (55).

Adjuvant chemotherapy: is a therapy given after surgical resection which is first-line treatment of a cancerous tumor, especially it is done for the latter (advanced) stage II & III of colon cancer (56).

Event: There are two events in this study.

1. Initiation of ACT.
2. Death due to CRC.

Follow up time:

1. **Time to initiation ACT**; this is defined as time in days between surgery to the first dose of any kinds of adjuvant chemotherapy received in the form of either single or a combination of chemotherapeutic agents (36). Early initiation according to most studies is defined as to begin within first four to eight post-operative weeks (29,30,42,52). But some suggest starting ACT within first 4 weeks to have better oncologic outcome

(31,57). Therefore, in this study we categorized time of initiation of ACT in to three groups (<4, 4-8 and >8 weeks), to assess the existence of significant difference between the three treatment arms.

2. **Time to death;** this is a time from first pathologically confirmed diagnosis of CRC date of to death.

Censored:

1. Stage II & III CRC patients booked for but, who did not take any form of ACT at the end of the follow-up period and those who were died, lost to follow-up, and transfer to another health care unit during the study before taking adjuvant chemotherapy will be defined as censored (36).
2. Patients who did not develop the outcome of interest (death) at the end of the follow-up period (24).

Major in hospital medical events: are hematological adverse effects (neutropenia, anemia and thrombocytopenia), hospital acquired pneumonia, hypovolemia, DVT and/ it could be any other complications resulting major from comorbid diseases(58–60).

4.8. Data collection

The study was conducted by using secondary data by using kobo toolbox app for data collection. Colorectal cancer patients were identified from other types of cancer patients by using their medical records. Consequently, the process of data abstraction was made using an English version check-list from all eligible patients with colorectal cancer who underwent surgery. Data was collected by two oncology unit nurses after giving them one day training on how to perform data collection. Some informations which are not available in patients records regarding patient's current status (ascertaining whether he/she is alive or dead) were obtained by phone interview.

4.9. Data quality assurance

In order to ensure data quality, high emphasis was given to minimize errors using the following strategies: -

- ✓ The questionnaire was pretested by using 5% of sample size. Patients registered for

adjuvant chemotherapy before the actual study period was employed after identifying their medical recording number and those subjects were not be included in study sample and subsequent correction and modification was done.

- ✓ The data collectors were trained on the data collection technique.
- ✓ The collected data was reviewed, and checked for completeness and consistency before data entry.

4.10. Data analysis procedure

Data was collected by using by kobo toolbox. After considering for the completeness and consistency of the data, then it was exported to STATA version 17 statistical software for analysis. Descriptive statistics was performed for sociodemographic and clinicopathological data and the results were presented using tables and texts. Time to initiation of adjuvant chemotherapy and survival was measured and coded as 1 for the event and 0 for censored; time to initiation of ACT was determined by subtracting the date of surgery from first adjuvant chemotherapy start date. Kaplan–Meier survival curve was employed to estimate the time to initiation, overall survival and comparison between different groups. Investigation of the existence of significant differences in survival and time to initiation was done by using the Log-rank test.

The association between dependent (time to initiation ACT and death) and independent variables was assessed by Cox-proportional hazard model. All potential predicators with p-value <0.25 in the bivariable Cox-proportional analysis were included in the multivariable analysis. Kaplan Meier curve illustration between categories of variables was found to be parallel against time, which implies that the proportional hazard assumption was satisfied for this data. Also, the null hypothesis claiming proportional hazard assumption was not rejected as the global test for the models were insignificant. Cox–Snell residual test were used to check the goodness of fit. The adjusted hazard ratio (AHR) with a 95% confidence interval (CI) was reported to show the strength of association and a two-sided p-value less than 0.05 was considered as to be statistically significant. The missing value of variables of the interest was less than 10% which is handled by using replacement of most frequently occurring value for categorical data.

4.11. Ethical considerations

The ethical issues were handled throughout the study by considering the basic ethical research principles specifically confidentiality of the information obtained from patient records and logbooks used only for the purpose of this research was assured. Ethical clearance was obtained from the Ethical Review Board of AAU College of health science and permission to conduct the study was obtained from the TASH oncology unit.

4.12. Dissemination of finding

The result of the study will be submitted to the TASH oncology unit, AAU, College of Health Science SPH. Finally, publication of the result on the scientific journals will be considered after peer review and presentation at different meetings/ conferences will be done.

5. Result

5.1. Socio-demographic characteristics of study subjects

A total of 416 medical records of patients who underwent surgery after diagnosis of CRC were reviewed for the study. Two hundred and eighty-one of them were excluded from the study due to lack of complete medical record/missing of key information. Out of those 135 study participants, males comprised (81, 60.00%) and the median age of the subjects was 48.03. Of the total number of participants, 109(80.74%) were Christian religion followers and 115(85.19%) were married. Concerning address, half of the patients were from Addis Ababa 71(52.59%) followed by Oromia 28(20.74%), SNNPR 15(11.11%) and Amhara 14(10.37%). Regarding to their occupational status, 50(37.04%) were government employees followed by private work

27(20.00%), housewives 27(20.00%) and farmer 16(11.85). Thirty-nine (25.19%) were social drug users, of this 16(47.06%) drunk alcohol (Table 5-1).

Table 5-1: Socio-demographic characteristics of CRC patients at TASH, Addis Ababa, Ethiopia 2023.

Variables	Categories	Frequency n (%)
Age group	18-30	14(10.37)
	31-40	27(20.00)
	41-50	29(21.48)
	51-60	27(20.00)
	61-70	27(20.00)
	>71	11(8.15)
Gender	Female	54(40.00)
	Male	81(60.00)

Address	Addis Ababa	71(52.59)
	Amhara	14(10.37)
	Oromia	28(20.74)
	SNNPR	15(11.11)
	Others	7(5.19)
Marital status	Divorced	4(2.96)
	Married	115(85.19)
	Single	13(9.63)
	Widowed	3(2.22)
Religion	Christian	109(80.74)
	Muslim	26(19.26)
Job occupation	Farmer	16(11.85)
	Gov't employee	50(37.04)
	Housewife	27(20.00)
	Retired	6(4.44)
	Self-employee	27(20.00)
	Student	9(6.67)
Substance use	Yes	34(25.19)
	No	101(74.81)

⁎ others include Afar, Benishangul Gumuz, Diredawa Gambella, Harar, Somalia and Tigray

5.2. Clinical characteristics of patients.

The body mass index of the patients was calculated; three fourth 91(72.59%) of the subjects were within normal range, 26(19.26%) underweight and 11(8.15%) overweight. One fourth 32(23.70%) of the total patients have comorbid illness, from which hypertension and diabetes mellitus account for 10(29.41%) and 18(23.53%) respectively.

The most commonly mentioned clinical presentation were rectal bleeding, 41(30.37%) followed by abdominal pain 30(22.22%), combination abdominal pain, rectal bleeding and constipation 28(20.74%), and signs of large bowel obstruction 18(13.33%). As mentioned below in Table 5-2 more than two-third 91(67.41%) of the study participants were diagnosed at stage three, the remaining 44(32.59%) were diagnosed with stage two CRC.

One third 42(31.11%) of the study subjects have experienced at least one major in hospital event throughout their follow up time, but only severe anemia comprised half 21(50.00%) of the total events occurred followed by, neutropenia 14(33.33%), hypovolemic shock 4(9.52) and hospital acquired pneumonia 3(7.14%). With respect to surgical complications, about twenty-nine (21.48%) of the patients were developed surgical complication, 12(41.38%) had surgical site infection, 9(31.03%) perforation, and 8(27.59%) major bleeding episodes. One hundred seventy (54.8%) cancer sites were of colon involvement, rectum, 103(32.6%) and colorectum, 39(12.6%). Regarding to the level of differentiation of the disease 87(64.44%) were well differentiated, 32(23.70%) moderately differentiated and 16(11.85 %) poorly differentiated. As illustrated in Table 5-2, almost all of the histologic type was mucinous adenocarcinoma.

Table 5-2: Clinical characteristics of CRC patients in TASH, Addis Ababa, Ethiopia 2023.

Variables	Categories	Frequency (%)
BMI	< 18.5	26(19.26)
	18.5-24.9	91(72.59)
	25-30	11(8.15)
Comorbidity	Yes	32(23.70)
	No	103(76.30)
Clinical presentation	Abdominal pain/RUQ pain	30(22.22)
	Intestinal obstruction	18(13.33)

	Rectal bleeding	41(30.37)
	Rectal bleeding and constipation	12(8.9)
	Rectal bleeding, constipation and RUQ pain	28(20.74)
	Others	6(4.44)
Major in hospital events	Yes	42(31.11)
	No	93(69.89)
Complications	Yes	29(21.48)
	No	106(78.52)
Tumor location	Colon	76(56.30)
	Colorectum	16(11.85)
	Rectum	43(31.85)
Stage	Stage II	44(32.59)
	Stage III	91(67.41)
Level of differentiation	Moderately differentiated	32(23.70)
	Poorly differentiated	16(11.85)
	Well differentiated	87(64.44)

⁎ others include constipation, mass/swelling and tenesmus

5.3. Treatment related characteristics

In terms of treatment modalities used, 119(88.1%) subjects with stage II and III treated with a combined adjuvant chemotherapy and surgery. From those patients who had treatment with adjuvant chemotherapy 106(89.1%) of them took less than six cycles of first line adjuvant chemotherapy. Two third of patients 75(69.8%) took FOLFOX based adjuvant chemotherapy. From all surgical procedures undertaken before chemotherapy, hemicolectomy 101(32.6%) was the most common surgical procedure employed followed by colostomy 82 (26.5%), abdominoperineal resection 54(17.4%) and anterior resection 40(12.6%). (Table 5-3)

Table 5-3: Treatment characteristics of CRC patients in TASH, Addis Ababa, Ethiopia 2023.

Variables	Categories	Frequency (%)
Stage II & III patients initiated ACT	Yes	119(88.15)
	No	16(11.85)
Type of surgery	Abdominoperineal resection	30(22.22)
	Anterior resections	15(11.11)
	Colostomy/bypass/no surgery	28(20.74)
	Hemicolectomy	51(37.78)
	Sigmoid colectomy	11(8.15)
Rout drug administration	Intravenous	109(91.60)
	Oral	10(8.40)
Initiation ACT for stage II & III CRC	Within 8 weeks	48(40.68)
	After 8 weeks	71(59.32)

5.1. Time to initiation of Adjuvant chemotherapy

From total of 135 stage II and III subjects 119 had initiated ACT chemotherapy over 1,929 person weeks, whereas 16 were censored. The median time to initiation of adjuvant chemotherapy is 11 weeks with IQR of 7 & 22.

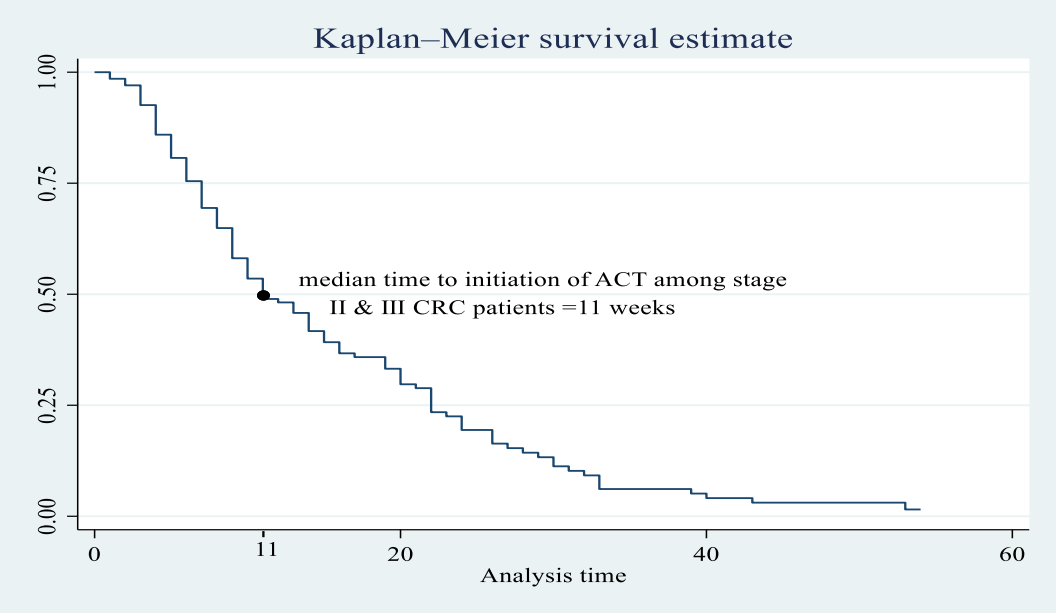

Figure 5.1. Show the overall Kaplan Meir survival function curve estimate of time to initiation of ACT chemotherapy among II & III CRC patients in TASH.

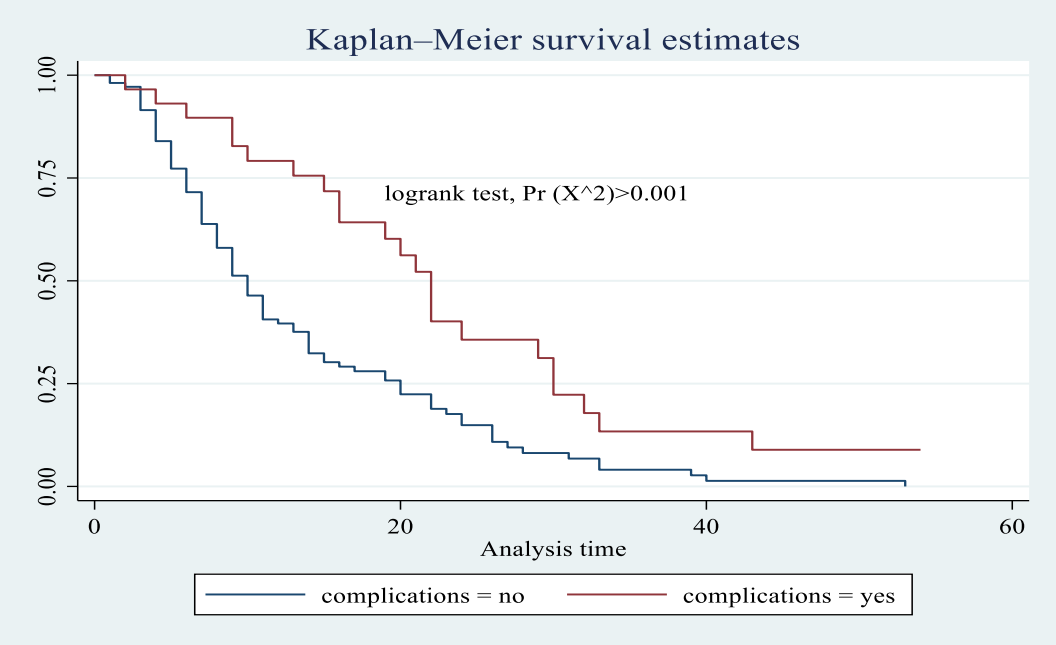

Figure 5.2 Kaplan Meir survival function curve estimate of time to initiation of ACT chemotherapy based on presence of complication among CRC patients in TASH.

The result from log rank test below in Table 5-4 shown, if there could be existence significance difference on time to initiation of chemotherapy between groups of different variables. So that, significant was observed between groups of variables such as comorbidity ($Pr(X^2)>0.001$), BMI

(Pr(X^2)>0.001), major in hospital events (Pr(X^2)>0.044) and surgical complication (Pr(X^2)>0.001).

Table 5-4: Log-rank test for time to initiation of chemotherapy among stage II & III CRC patients, TASH, Addis Ababa, Ethiopia.

Variable	Category	Observed events	Expected events	Chi-squared (X^2)	Pr (X^2)
Religion	Christian	93	99.25	2.58	0.108
	Muslim	26	19.75		
Marital status	Married	101	96.12	2.79	0.425
	Single	12	15.28		
	Divorced	4	3.14		
	Widowed	2	4.46		
Address	Addis Ababa	63	61.46	0.09	0.768
	Outside	56	57.54		
Substance use	Yes	86	82.04	0.68	0.411
	No	33	36.96		
Comorbidity	Yes	28	44.02	10.87	**0.001***
	No	91	74.98		
BMI	<18.5	19	21.83	15.13	**0.001***
	18.5-24.9	90	71.08		
	25-29.9	19	16.09		
Differentiation	Well differentiated	81	78.46	0.60	0.742
	Moderately differentiated	30	30.37		
	Poorly differentiated	8	10.17		
Primary site	Colon	72	63.08	2.93	0.231
	Colorectum	13	15.76		
	Rectum	34	40.16		
Major in-hospital events	Yes	35	44.36	3.42	**0.044***
	No	84	74.64		

Complications	Yes	96	79.41	11.69	**0.001***
	No	23	39.59		

Religion, marital status, occupation, BMI, clinical presentation, comorbidities, surgical complication, in-hospital medical events and primary site of tumor were enrolled into the final model to assess the predicators of initiation of ACT chemotherapy among stage CRC patients. From the multivariable cox regression model result presented in Table 5-5, body mass index, comorbidity and presence of surgical complications were found to be significant predictors on time to initiation of chemotherapy among CRC patients at a 5% level of significance. The hazard of starting chemotherapy early was decreased by 66% (AHR= 0.44, 95% CI: 0.25-0.79) among underweighted (BMI < 18.5) patients than patients with normal BMI. The hazard of starting chemotherapy was decreased by 62% (AHR= 0.38, 95% CI: 0.22, 0.64) among CRC patients with comorbidity than CRC patients without comorbidity. The hazard of early initiation of chemotherapy was decreased by 55% (AHR= 0.45, 95% CI: 0.26, 0.78) among patients with surgical complications than those patients without surgical complications.

Table 5-5: A multivariable survival model analysis for predictors of initiation of ACT chemotherapy among II & III CRC patients in TASH, Addis Ababa, Ethiopia 2023.

Variables	Categories	CHR (95%CI)	AHR (95%CI)	p-value
Religion	Christian	1.00	1.00	
	Muslim	1.41 (0.91, 2.20)	1.31 (0.78, 2.21)	0.308
Marital status	Single	1.00	1.00	
	Divorced	1.63 (0.53, 5.09)	0.78 (0.23, 2.65)	0.689
	Married	1.34 (0.74, 2.45)	0.65 (0.27, 1.55)	0.331
	Widowed	0.56 (0.12, 2.54)	0.83 (0.13, 5.49)	0.844
Occupation	Farmer	1.00	1.00	.
	Gov't employee	1.17 (0.63, 2.18)	1.52 (0.70, 3.32)	0.289
	housewife	1.17 (0.59, 2.33)	1.38 (0.59, 3.21)	0.458
	Retired	1.01 (0.38, 2.68)	2.21 (0.67, 7.31)	0.193
	Self-employee	1.77 (0.89, 3.50)	1.97 (0.83, 4.67)	0.125

	Student	0.68 (0.28, 1.65)	0.37 (0.12, 1.13)	0.080
Comorbidity	No	1.00	1.00	.
	Yes	0.49 (0.32, 0.77)	**0.38 (0.22, 0.64)**	**0.001**
BMI	18.5-24.9	1.00	1.00	.
	25-30	0.42 (0.21, 0.85)	0.45 (0.20, 1.01)	0.053
	< 18.5	0.42 (0.25, 0.71)	**0.44 (0.25, 0.79)**	**0.006**
Clinical presentation	Abdominal pain/RUQ pain	1.00	1.00	.
	Constipation	0.44 (0.10, 1.89)	0.80 (0.17, 3.88)	0.782
	Intestinal obstruction	0.96 (0.52, 1.75)	0.81 (0.41, 1.60)	0.537
	Mass/swelling	4.93 (0.65, 37.42)	8.75 (0.99, 76.94)	0.051
	Rectal bleeding	1.13 (0.68, 1.86)	1.59 (0.85, 2.99)	0.148
	Rectal bleeding and constipation	0.91 (0.44, 1.88)	0.92 (0.40, 2.07)	0.831
	Rectal bleeding, constipation and RUQ pain	0.96 (0.56, 1.66)	1.07 (0.58, 1.96)	0.833
	Tenesmus	0.51 (0.07, 3.75)	0.64 (0.07, 5.53)	0.682
Primary site	Colon	1.00	1.00	.
	Colorectum	0.72 (0.40, 1.31)	0.55 (0.28, 1.07)	0.077
	Rectum	0.74 (0.49, 1.11)	.83 (0.49, 1.39)	0.472
Complication	No	1.00	1.00	.
	Yes	0.47 (0.29, 0.74)	**0.45 (0.26, 0.78)**	**0.005**
In hospital events	No	1.00	1.00	.
	yes	0.70 (0.47, 1.04)	0.83 (0.52, 1.32)	0.427

5.2. Survival pattern of the patients

Sixty-nine (51.11%) patients were died due to colorectal cancer during six year follow up period (3,929 person-months). The median follow-up time was 25 months with IQR of 18–64 months.

The overall event rate was 17.57 per 1000 person-months (95%CI: 13.87 to 22.24). The overall colorectal cancer specific one, three and five-year survival rate was 91.53% (95%CI: 85.22–95.22%), 51.15% (41.13–60.30%) and 31.85% (21.71–42.44%) respectively. The overall survival curve is shown in figure 5.2. The median survival time was 38 months with 95%CI of 31 to 45.

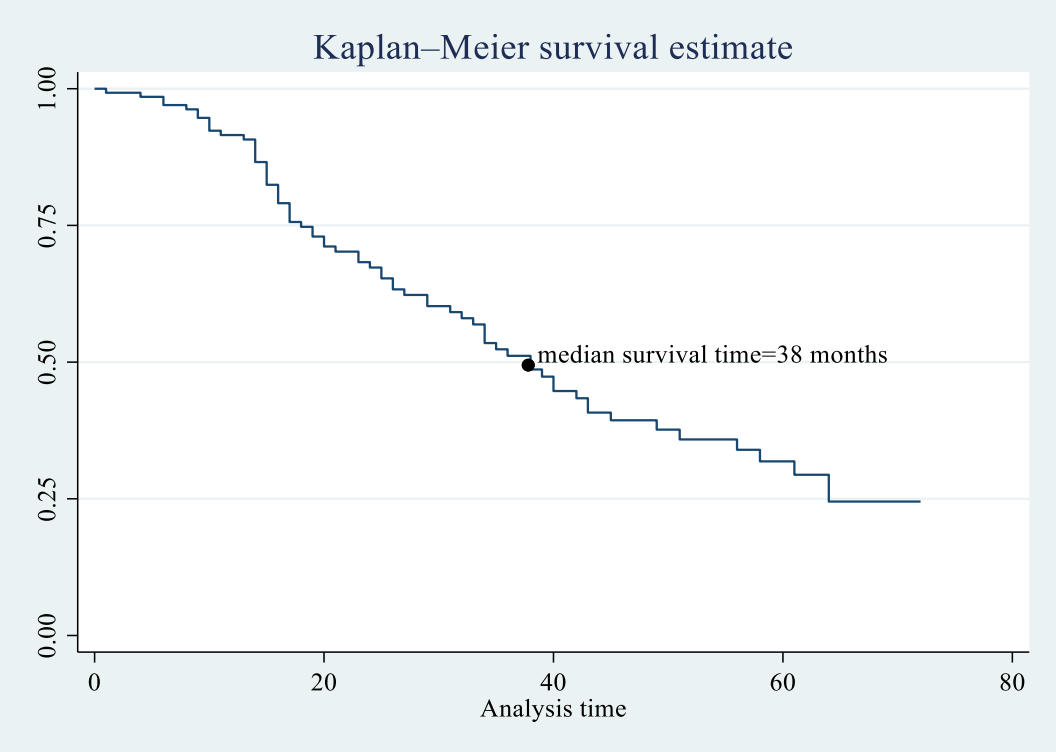

Figure 5.3. Kaplan Meir survival curve estimate of the overall survival rate among CRC patients in TASH.

The overall survival rate was lower for CRC patients initiating adjuvant chemotherapy after 8 weeks of surgery, as depicted in figure 5.3.

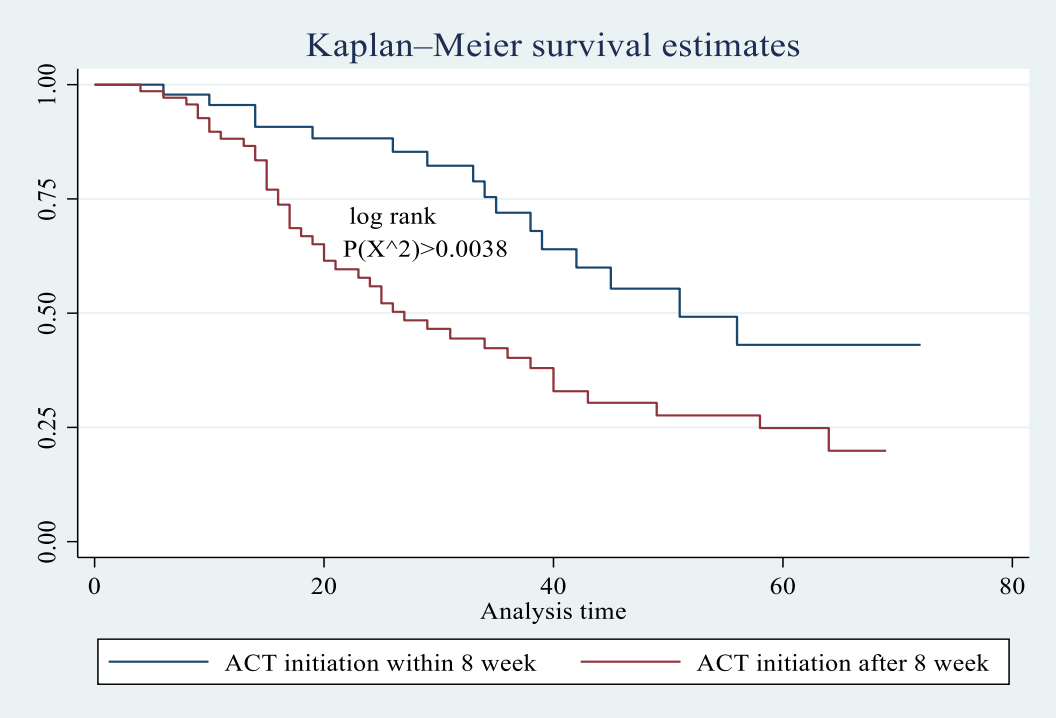

Figure 5.4. Kaplan Meir survival curve estimate of survival between stage II and III CRC patients in terms of the time to initiation of ACT.

Table 5-6: A multivariable survival model analysis on association between time to initiation of ACT and survival among stage II & III CRC patients at TASH, Addis Ababa, Ethiopia.

Variables	Categories	CHR (95% CI)	AHR (95%CI)	P-value
Occupation	Farmer	1.00	1.00	
	Gov't employee	0.78 (0.35, 1.75)	0.77(0.23, 2.53)	0.665
	housewife	1.20 (0.51, 2.81)	1.02 (0.31, 3.39)	0.966
	Retired	3.34(0.99, 11.34)	2.14(0.40, 11.30)	0.368
	Self-employee	0.96 (0.39, 2.36)	0.74 (0.23, 2.38)	0.617
	Student	1.77, (0.64, 4.89)	0.89 (0.19, 4.02)	0.881
Substance use	No	1.00	1.00	
	Yes	0.73 (0.41, 1.30)	0.61 (0.30, 1.25)	0.206
Comorbidity	No	1.00	1.00	
	Yes	1.55 (0.92, 2.61)	1.61 (0.77, 3.35)	0.180
Clinical	Abdominal	1.00	1.00	

presentation	pain/RUQ pain			
	Intestinal obstruction	0.92 (0.42, 2.04)	0.59(0.21, 1.66)	0.319
	Rectal bleeding	0.69 (0.35, 1.33)	0.90 (0.32, 2.53)	0.843
	Rectal bleeding & constipation	0.56 (0.21, 1.47)	0.35 (0.09, 1.43)	0.146
	Rectal bleeding, and RUQ pain	0.86 (0.41, 1.80)	0.65(0.24, 1.76)	0.406
Level of differentiation	Well	1.00	1.00	
	Moderate	1.95(0.91, 4.19)	1.16(0.59, 2.27)	
	Poor	0.70 (0.41, 1.21)	**4.05(1.58, 10.37)**	**0.003**
Stage	II	1.00	1.00	
	III	1.47(0.89, 2.43)	1.03(0.54, 1.94)	0.940
Type of surgery	Abdominoperineal resection	1.00	1.00	
	Anterior resections	0.76 (0.31, 1.86)	0.39 (0.11, 1.34)	0.819
	Colostomy/bypass/no surgery	1.56 (0.78, 3.11)	1.41 (0.55, 3.60)	0.848
	Hemicolectomy	1.20 (0.63, 2.31)	1.08 (0.41, 2.88)	0.865
	Sigmoid colectomy	2.36 (0.90, 6.22)	1.85(0.48, 7.05)	0.368
Timing of ACT initiation	Within 8 weeks	1.00	1.00	
	After 8 weeks	**1.82 (1.07, 3.09)**	**3.06(1.50, 6.28)**	**0.002***

As illustrated above in table 5.6, variables such as, occupation, substance use, comorbidity, clinical presentation, stage of the disease, level of differentiation and type of surgery were recruited through a bivariable cox-proportional hazard model to explore the effect of time of initiation ACT on overall survival rate of stage II & III colorectal patients. According to the results from multivariate cox regression analyses, patients initiating adjuvant chemotherapy after 8 weeks of surgery had three times higher risk of death (AHR=3.06, 95%CI: 1.50, 6.28) when compared patients of their counter parts. In addition, the hazard of death among poorly differentiated CRC cases were four times higher than that of patients who had well differentiated CRC cells (AHR=4.05, 95% CI: 1.58, 10.37).

6. Discussion

The retrospective study demonstrated that median time to initiation of adjuvant chemotherapy after surgery was 11 weeks among stage II and III colorectal cancer patients. Subjects with BMI <18.5 kg/m² were 56% less likely to initiate ACT compared to patients with those who had normal BMI. The hazard of starting adjuvant chemotherapy was decreased by 62% (AHR= 0.38, 95% CI: 0.22, 0.64) among CRC patients with comorbidity than CRC patients without comorbidity. Surgical complications were also significant factor, those with complication were 55% less likely to initiate ACT with AHR = 0.45, 95% CI: 0.26, 0.78. The overall survival of CRC patients at three- and five-year was 51.15% and 31.85% respectively. Furthermore, significant association was found between initiation of ACT and overall survival; those who initiated ACT after 8 weeks after surgery had three times at higher risk of death compared to those who initiated after 8 weeks. Having poorly differentiated cancer cells was almost four times higher risk of death (AHR=4.05, 95% CI: 1.58, 10.37).

The median time for initiation of ACT among stage II & III in this study was 11 weeks. This finding was higher compared with studies conducted in China (4 weeks), America (5 weeks) and Canada (7 weeks) (32,61,62). Most studies declare that it is acceptable to begin ACT within first 4 to 8 post-operative weeks, so as improve the overall survival rate and to prevent the disease recurrence (33,46,47). Possible explanation behind this difference could be limited number of chemotherapy centres in the country while the incidence of the disease is increasing. When the treatment facility gets smaller patient waiting time will be longer on those few existing centres, so that timely initiation of the treatment could be harder to achieve. Another possible explanation behind this discrepancy could also be population of the interest, which is different in terms of economic and educational status, as well as access and availability to the modernized infrastructure for health care services.

In this study, patients with lower BMI were more likely to initiate ACT late than those with normal BMI. Even though this evidence were not supported by other studies, but some suggested anticancer therapies result on hematological toxicities, specially they are associated with anemia and neutropenia in those patients(63). In addition to this, preterm discontinuation of the treatment is more frequent in patients with lower BMI(64). This result may be linked with the fact that patients may experience the above medical conditions during ablation therapy or

neoadjuvant chemotherapy so that, they may not be motivated to initiate the treatment earlier. On the other hand, time taken for recovery after surgery for these patients could also be longer, so as to proceed to the next treatment course.

Another significant predicator associated with delayed initiation of adjuvant chemotherapy in this study was comorbidity. This is comparable with the findings of studies conducted in America and UK(38,43). Potential explanation behind this could be, patients might fear pill burden as the side effect of chemotherapy drugs alone would be higher and it could also be harder to make the decision to continue as early as possible. In the other side, time taken for surgical wound healing for patients with comorbidity could also be longer, so that it might become difficult for them to commence the treatment early on time. Limited to health care service, patient's ability to afford and increased waiting time could be another problem in our country. In contrary, a study done in Canada (41) revealed that there is no significant association between comorbidity and time to initiation of adjuvant chemotherapy. This might be due to difference in population under the study in terms of health care seeking behavior, availability and accessibility of resources.

This study demonstrated that the presence of surgical complication was significant predictor for time to initiation of ACT. This is in line with previous study conducted in China (32) which reported as patients who had surgical complication ended up with delayed initiation of adjuvant chemotherapy. This result is also in agreement with another retrospective study conducted in America(29) from the database by SEER-Medicare for patients diagnosed with primary colon adenocarcinoma. Findings from other studies done Canada and UK reported similar results (41,43). This could be explained by the fact that patients with post-operative complications need to buy more time for recovery after surgery in order to start adjuvant chemotherapy.

A three- and five-year survival in this study was 41.62% and 23.12% respectively. The estimated median survival time in this study was 32 months. This finding is within similar range of values of survival when compared to previously conducted study in Ethiopia (24) and systematic review in sub-Sharan Africa (65). This may be due to the population of the interest shares similar sociodemographic features in terms of economy, educational status and access and availability to health care service. However, this result has slightly different when compared to the study undertaken in Malaysia, at which the three and five-year survival rate is relatively higher ranging 52.1-53.7% and 40.4-45.4% respectively(66). Countries like Korea and Israel achieved a highest

survival rate, that over 70% colorectal cancer patients remain alive after 5 years(67). This indicates that there is readily available technological advancement for screening, diagnosis and treatment of colorectal cancer across the countries.

The result of this study revealed that the overall survival is worse among late initiator of adjuvant chemotherapy after 8 weeks of surgical resection is 2.4 times higher. This is consistent with finding from other studies in China, South Korea (18,29,30,33,51). This is may be due to waiting longer time than this duration could facilitate angiogenesis of the malignant tumor and further metastasis of the disease, consequently causing weaker response against the treatment. This in turn could lead failure of achievement of curation and subsequent death.

Survival benefit of commencement of treatment within four weeks of surgery is similar when compared with patients initiating between five to eight weeks. This is in line with study done in Netherlands and China that there was no difference on efficacy of ACT between the two groups (29,42). Possible explanation for this might be that body's immune system needs to be reconstructed, because the stress resulting from surgery and anesthesia by itself is immune-suppressive. In addition to this, the action chemotherapeutic agents act against the body's immune system within first four postoperative weeks. Hence, the combination of the above factor may override the survival benefit of initiating in first month after primary treatment.

Poorly differentiated tumor cells were another significant predicator associated with decreased overall survival rate according to the result of this study. This result is similar with another study done in Ethiopia and Switzerland (24,68). Poor differentiation of the cells is among one of important adverse histopathological prognostic marker in colorectal cancer patients(69), such type of cancer cells found at latter stage of disease and they tend to easily metastasize to lymph nodes, peritoneum, liver and lung so as to cause death.

In this study age, comorbidity, surgical complications were not significantly associated with overall survival rate.

7. Strength and limitation

7.1. Strength of the study

Even though, there were some shortcomings in this study, this study gives insight on the effect of timing of initiation of adjuvant chemotherapy on overall survival rate of patients with colorectal cancer, which aids the physicians for making a prompt decision during prescription of chemotherapeutic drugs. Besides, estimation of time to initiation of adjuvant chemotherapy and the overall survival among patients of different follow-up time was done using a multivariable Cox regression analysis by taking account of censored data. The software kobo toolbox used for data collection played an important role to control the quality of the data by minimizing some problems encountering during collection and entry of the data.

7.2. Limitation of the study

This study was undertaken on patients who were diagnosed and treated only at TASH and patients from private hospital were not included in this study to make the finding more generalizable. There was incomplete registration of some clinical information specially regarding date of surgery which was frequently observed on referral cases. Furthermore, as the nature of the study is retrospective, some important sociodemographic factors (educational status and income of the patients) and health care service factors were not assessed, even if they were expected to be associated with the outcome variables. The sample size used for this study were small.

8. Conclusion and recommendation

8.1. Conclusion

In this study, time to adjuvant chemotherapy among II & III was much longer when compared to other studies. The study demonstrated that being underweighted, presence of post-operative complication and comorbid illnesses were significantly associated with delayed initiation of adjuvant chemotherapy. In addition, the three- and five-year survival rate were also low. Presence of poorly differentiated tumor cells and initiation of chemotherapy after eight weeks of surgery were associated with higher risk of mortality among colorectal cancer patients in Ethiopia.

8.2. Recommendation

Quality care during primary surgical treatment should be tailored in hospitals towards minimizing postoperative complications by taking preventive measures, teamwork and communication between health care providers throughout pre-, intra- and postoperative course of the patient in order to reduce time to adjuvant chemotherapy.

Clinicians should make appropriate decision for patients with lower body mass index and comorbid illnesses while ordering and administering adjuvant chemotherapy by taking the pill burden, side effect and drug-drug interaction in to consideration. In addition to this, scheduling of follow-ups and adjunct counselling could also be invaluable.

Policy makers, should strive to promote awareness campaigns about risk factors, signs and symptoms and possible preventive measures of CRC to the community and encouraging patients diagnosed with colorectal carcinoma enable them present at early stage of the disease. In addition to this, expansion of cancer treatment centers has to be done in order to decrease patient waiting time for chemotherapy.

Prospective study involving multiple cancer treatment centers should be done, in order to determine the effect of waiting time, drug adherence and sociodemographic factors such as economic status and level of education on overall survival of colorectal cancer patients.

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Annex- I Data extraction tool

Serial no	Variable	category
	MRN	
	Age	
	Sex	1. Male 2. Female
	Residence	1. Addis A baba 2. Amhara 3. Oromia 4. Tigray 5. SNNPR 6. Gambella 7. Benishangul Gumuz 8. Harar 9. Diredawa 10.Somalia 11. Afar
	Marital status	1. Single 2. Married 3. Divorced 4. Widowed
	Level of education	1. No formal education 2. Primary level 3. Secondary education 4. Higher level education

	Year of diagnosis	1. 2013-2014 2. 2014-2015 3. 2015-2016 4. 2016-2017 5. 2017-2018
	History of major comorbid diseases	1. Yes 2. No 3. Unknown
	If yes for comorbidities	1. DM 2. HTN 3. DM plus HTN 4. HF 5. Asthma 6. Other, specify
	Body mass index (kg/m2)	1. < 18.5 2. 18.5-24.9 3. 25-30 4. ≥ 30
	Initial clinical presentation	1. Rectal bleeding 2. Intestinal obstruction 3. Tenesmus 4. Abdominal pain/RUQ pain 5. Constipation 6. Rectal bleeding and constipation 7. RUQ pain and constipation 8. Rectal bleeding, constipation and RUQ pain 9. Other specify
	Histologic cell type	1. Adenocarcinoma 2. Squamous Cell Cancer 3. Others (specify): ……

	Level of histological cell differentiation (Histological Grade)	1. Well differentiated 2. Moderately differentiated 3. Poorly differentiated 4. Unknown/Unspecified
	Cancer location	1. Colon 2. Rectal 3. Colorectal
	Stage of the disease at diagnosis (TNM classification)	1. II 2. III 3. Not known/ unspecified
	Date of commencement of treatment	_____/_____/_____
	Mode of treatment used	1. Surgery 2. Radiotherapy 3. Chemotherapy 4. Chemo-radiation 5. Surgery and chemotherapy 6. Surgery, radiotherapy and chemotherapy
	Type of surgery performed	1. Hemicolectomy 2. Transverse colectomy 3. Sigmoid colectomy 4. Anterior resections 5. Abdominoperineal resection 6. Colostomy/bypass/no surgery 7. Other: _____

	Adjuvant chemotherapy regimen	1. FOLFOX 2. FOLFRI 3. CapOx 4. FOLFOXIRI 5. Fluorouracil plus Leucovorin 6. Capecitabine (Xeloda) 7. VEGF, (bevacizumab, ziv-aflibercept, or ramucirumab) added 8. EGFR (cetuximab or panitumumab) added 9. Irinotecan
	Route of administration of chemotherapy	1. Oral 2. Intravenous
	Days within which ACT commenced after surgical resection:	
	Major in-hospital medical event.	1. Yes 2. No 3. Unknown
	If yes; Major in-hospital medical event type:	1. Neutropenic 2. Anemia 3. Hypovolemic shock 4. Others Specify: _____
	Was there surgical complication/s	1. Yes 2. No 3. Unknown
	If yes; surgical	1. Perforation

	complication type:	2. Major bleeding episodes 3. SSI (Surgical Site infection) 4. Discharge 5. Others; Specify_____
	Disease recurred	1. Yes 2. No 3. Unknown
	Status of the patient?	1. Alive 2. Dead 3. unknown
	If dead; time of death (month)	

Annex II: Information sheet

English version

Title; Time to initiation of Adjuvant Chemotherapy and its predictors among adult colon cancer patients; A 5 years Retrospective Study, Ethiopia, 2023

Name of principal investigator: Sisay Lopiso

Name of the sponsor: Addis Ababa University

Introduction

This information sheet is prepared for Tikur Anbesa Specialized Hospital. The aim of the form is to make the institution clear about the purpose of the research, data collection procedures and finally to get permission to conduct the research.

Purpose of the research project

First of all, the final the result of these study will be submitted to the Department of Epidemiology and Biostatistics, School of Public Health, College of Health Science, Addis Ababa University, in partial fulfillment of the requirements for Degree in Masters of Public Health in Epidemiology and Biostatistics. In addition to this there are very few studies were undertaken so far in this area specially in our country Ethiopia in determining an optimal time to initiate adjuvant chemotherapy for colorectal cancer patients. Some studies from abroad provide little information regarding time of initiation of adjuvant chemotherapy. Late initiation of adjuvant chemotherapy is found to be a very important to predictors to cause the rising mortality and morbidity from colorectal cancer. In the other hand, there is no a clear-cut time frame adjustment made for those patients in our country which is compatible to our local contexts. Thus, the finding of this study will contribute its part in filling the information gap regarding appropriate timing of initiation of adjuvant chemotherapy and factors affecting it. So that, it will contribute its own part for policy makers focusing on prevention of recurrence of colorectal cancer, reducing mortality, providing appropriate care and treatment guidelines.

Procedure: patient record and registries of those who are under follow up from 2011 to 2011 in Tikur Anbesa specialized hospitals were selected and a review of the required information from the records will be made using questionnaire.

Risk: There will be no risk at all on patients whom their records are reviewed.

Benefits: the participants have not obtained direct benefit for involving in this study. Indeed, they will benefit indirectly from the research when the result of the study is used for program in designing appropriate clinical practice in colorectal cancer treatment. Thus, this research will

have a remarkable direct benefit for health care planners and managers working on cancer prevention, care and treatment guidelines.

Confidentiality: All patient rights were highly respected. Patients name was be used, instead, number codes were used for every patient. Patient's information was kept confidentially so as no other parties can obtain except the principal investigator and it was locked with password in a computer.

Person to contact: This research project will be reviewed and approved by the institutional review board of College of Medicine and Health Sciences, Addis Ababa University. In case, if you want to know more information about the research and its undertakings, you can contact the committee through the following address.

Addis Ababa University College of Medicine and Health Science Research Review Committee
Tel: +251-115157701 or +251-115-513-099.

Permission: Therefore, you are kindly requested to permit and forward your permission to concerned body in your organization so that the researcher can get cooperation from data clerks and other responsible bodies.

Kinds regard!

To be filled by Medical Directors:

I have properly examined the objective of the study, understood patient rights are respected patient confidentiality is assured and there will be no risks on patients related to the study.

Therefore, I gave a formal permission for the study to begin on behalf of the Tikur Anbesa Specialized Hospital.

Medical Director Name:

Signature:

Annex III. Training guide for medical chart data extraction

From the beginning, the guide was developed by identifying potentially challenging areas during data collection. After that, the principal investigator used the guide for training of the data

collectors, while data collectors are abstracting data from the medical records, during or before telephone interview and interviewing of colorectal cancer patients in TASH. This guide will explain; source of data for every variable, the most frequently used abbreviations by physicians in the hospital, protocols and steps for data collection from records. Therefore, data collectors were easily performing their tasks with this reference.

Objective of the study

To assess the time to initiation of adjuvant chemotherapy and its predictors among adults with colon cancer at Tikur Anbesa Specialized Hospital, Ethiopia, between 2011 -2018.

Study population

Patients who underwent surgery at TASH or elsewhere for colorectal carcinoma after pathologically confirmed colon cancer and treatment with ACT at TASH from January 1, 2011 to December 31, 2017.

Inclusion criteria; Patients aged beyond 18 years were included in the study.

Exclusion criteria; Patients who had incomplete medical record more than 15 % and/ lacking key information regarding the study were excluded from the study.

Sources of data: Medical records, Data base, log book

Criteria for data collectors and Supervisor: data collectors and supervisor are going to be experienced in data collection and have smart phone.

Part I: Data collection from Medical records

Time required: a maximum of 25-30 minutes for every patient chart

How each variable is extracted?

1. Socio-demographic variables

Sex and age: are usually written in the patient chart

Place of residence: this can be fully or partially available on the cover page of patient chart. Family history, are not usually available on the patient chart However, if there is a nursing process sheet in the chart, you can record from it.

2. Clinical data

Time to death: will be determined by calculating date of first diagnosis of CRC to death**.**

Time to initiation ACT; will be obtained by subtracting the date of first initiation of ACT from the date of surgery.

3. **Comorbidities**: this variable is going to be filled from discharge diagnosis of the patients.

Annex IV: Supplementary files

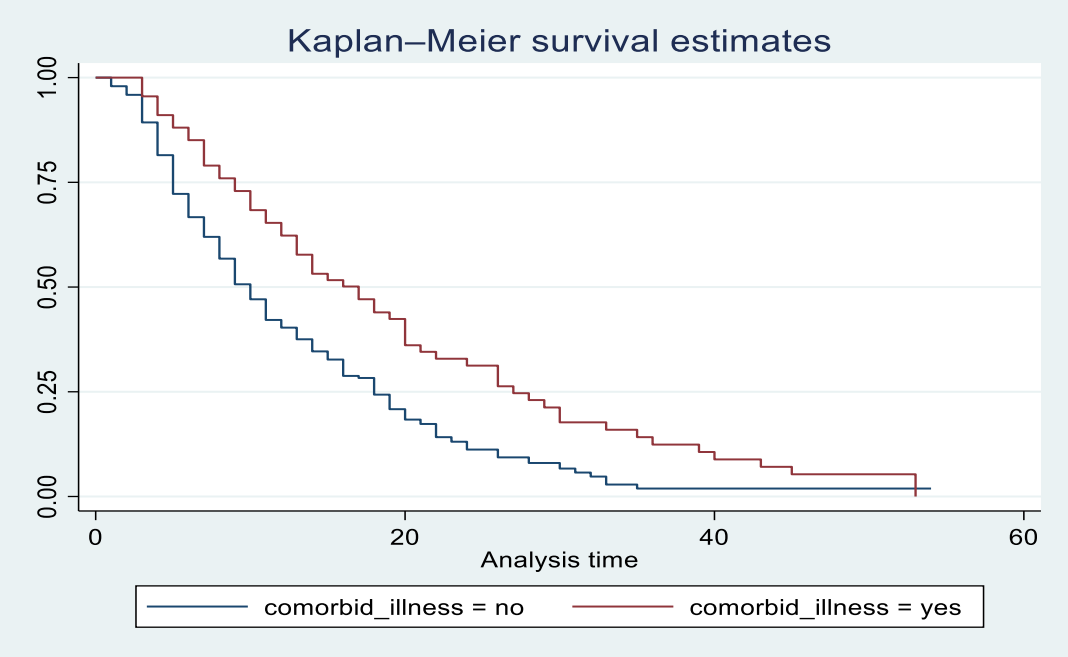

Figure 0.1. Kaplan Meir survival curve estimate of time to initiation of adjuvant chemotherapy between CRC patients with and without comorbidity in TASH.

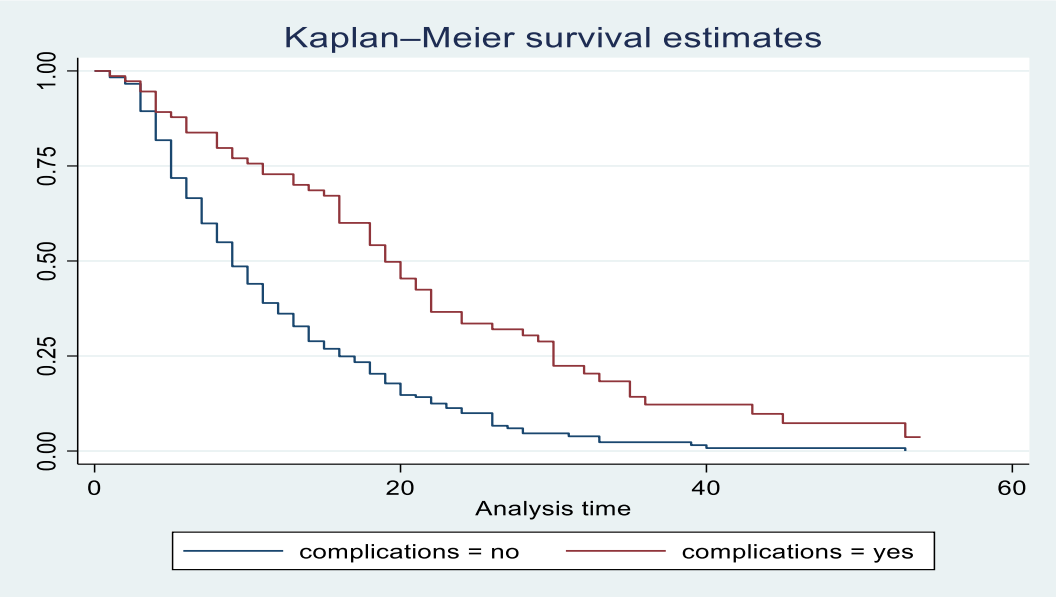

Figure 0.2. Kaplan Meir survival curve estimate of time to initiation of adjuvant chemotherapy between CRC patients with and without surgical complications in TASH.

Cox proportional hazard assumption for time to ACT

The Schoenfeld residual global test showed overall full model satisfies the proportionality on ime to ACT assumption ($X2$= 16.85, P < 0.9515). Again, the Cox Snell residual plot below showed was the assumption was satisfied (Figure 9).

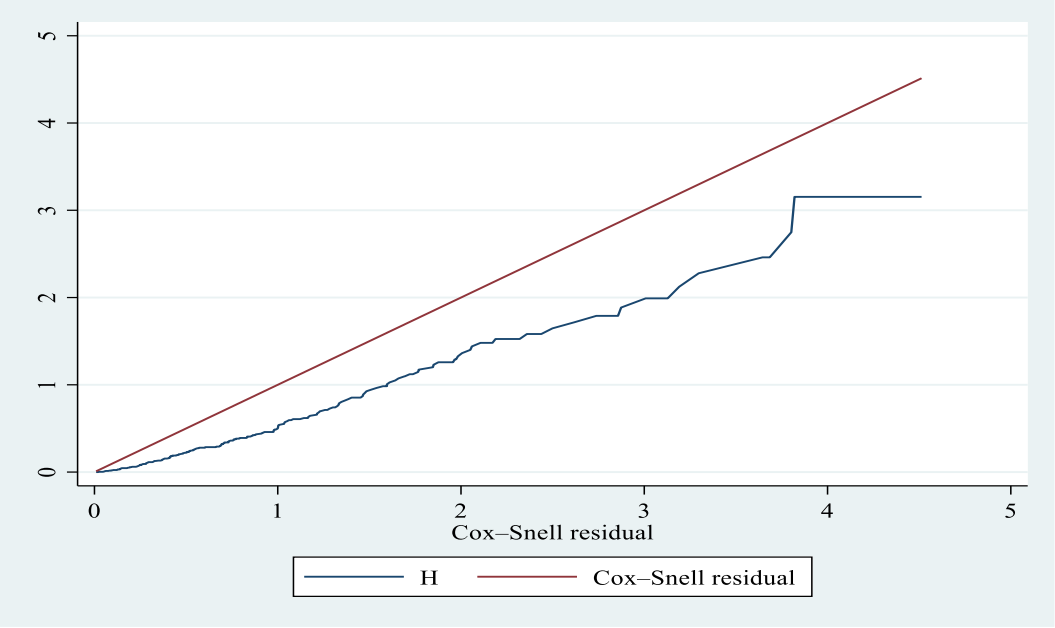

Figure 0.3: Cox-residual assumption graph for overall model fitness for time to initiation of ACT.

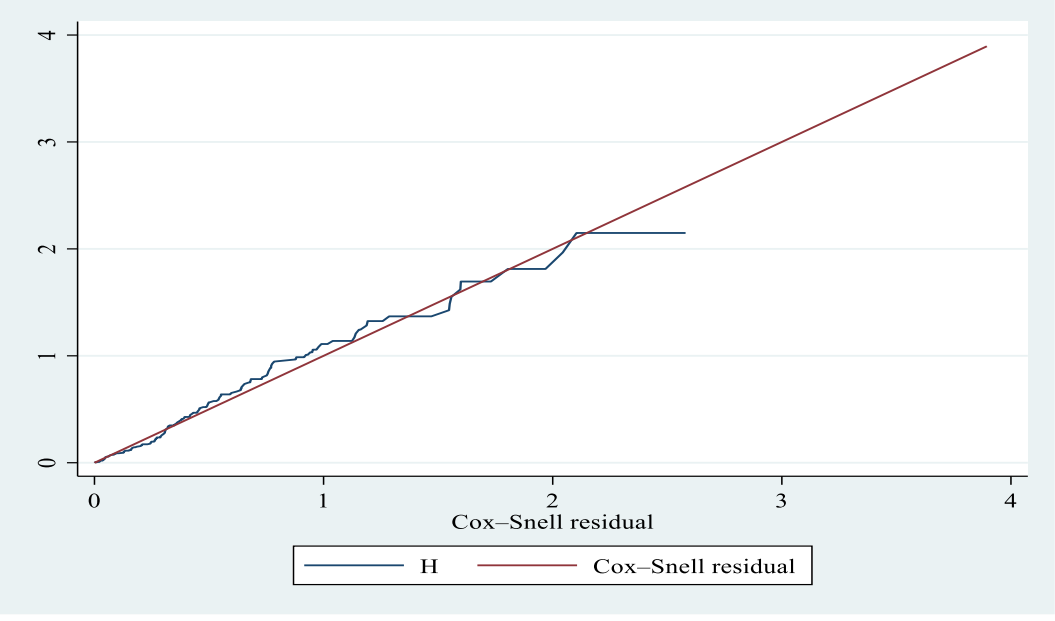

Figure 0.4 Cox-residual assumption graph for overall model fitness on survival of the patients.