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Survival Analysis of the Registered Colorectal Cancer Cases in the Gaza Strip

Murad B. Alrun

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Survival Analysis of the Registered Colorectal Cancer Cases in the Gaza Strip

Prepared by

Murad Basher Alrun

Bachelor of Nursing, Palestine College of Nursing, Gaza-Palestine

Supervisor: Dr. Khaled Ata Thabet

MD-PhD. Clinical Oncology-Cairo University

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Dedication

To my beloved parents who always give us the power, encouragement, and guidance for everything is good.

To my wonderful lovely wife Mona for her endless support, she is a continuous source of motivation, support, love, and hope.

To my amazing son Qais and beautiful daughter Mais who give me bright hope for tomorrow.

To my teachers in school, nursing college, and public health college for their efforts to be active person in our societies.

To my all friend and my all colleagues in the work.

To everyone had help me and contributed to finish this study.

Murad B. Alrun

Declaration

I certify that this thesis submitted for the degree of Master, is the result of my own research, except where otherwise acknowledged, and that this study (or any part of the same) has not been submitted for a higher degree to any other university or institution.

Signed:

Murad Basher Alrun

Date:

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Abstract

Colorectal Cancer (CRC) is the first major common cancer among men in Gaza Strip (GS) and it is considered the second common cancer after breast cancer for both sexes combined. Survival analysis for CRC cases is essential for monitoring and evaluation of health care system effectiveness in managing and fighting CRC. This non-concurrent prospective study was conducted to analyze the survival data for CRC cases who were diagnosed in the period 2008-2010, and to give estimates about overall survival rate, disease free survival rate, progression free survival. Beside exploring main factors may affect on survival rates for CRC in GS.

After some cases were excluded due to various causes, 207 cases were eligible for this study. The main source for data was the medical records for the cases, and data analysis was conducted by using SPSS program version 22. Kaplan-Meier method was used to provide overall survival estimates, survival estimates adjusted to selected prognostic factors and survival curves for subgroups, while the log rank test was used to assess survival differences between the subgroups. Cox regression survival analysis was used to examine the independent effect of study variables on survival data and to estimate the hazard ratio. Statistical significance was defined as P <0.05. The study findings showed that CRC incidence rate in Gaza Strip (GS) was 14/100000 in the study period (2008-2010).

Findings regarding socio-demographic characteristics of study population revealed that the mean of age at diagnosis for cases was 59.6 years, incidence rate among male is slightly higher than female (Male:54.6%, female:45.6%), 16.4% of cases were unmarried at time of diagnosis, while data about education level and work were missed from the majority of medical records. All cases presented with signs and symptoms at time of diagnosis. The common signs and symptoms were bleeding per rectum and abdominal pain 63.3%, 35.3% from all cases respectively. The most common histological type was Non-mucinous adenocarcinomas which accounted 86.7%. More than two third of cases were diagnosed with low grade tumor (grades 1, 2), while more than the half of patients (61.6%) were diagnosed with advanced stages (III, IV). Left-sided colon is the most common site for developing CRC with 52.3% of all cases. It followed with rectal cancer with 25.9%, while right-sided colon accounted only 21.9%. The study revealed that 5-year observed overall survival rate, disease free survival rate, and progression free survival rate probabilities to be 45%, 59% and 19% respectively.

According univariate analysis (log rank test) survival rate was significantly affected by co-morbidity status (P-value: 0.040), smoking (P-value: 0.002), stage at diagnosis (P-value< 0.001), tumor grade (P-value=0.41), tumor site (P-value=0.004), and treatment type (P-value=0.001). While the multivariate analysis (Cox regression) showed that only three prognostic factors had statically significant effect which were stage at diagnosis (P-value<0.001, 95%CI 2.673-9.034), Co-morbidity status (P-value=0.031, 95%CI, 0.434-0.962) and tumor site (P-value0.018, 95%CI, 0.373-0.912). Factors such as main treating hospital, diagnostic delay, treatment delay and place, sites of distant metastasis, gender, age, residency, or family history of cancer were found to be without statically significant effect on survival data for CRC cases in GS.

According the current study results, 5-years survival estimates in GS is poorer than the estimates in the developed countries, which were between 60-70% there. However, they are in line with most the estimates in the Arabic countries where the survival rates between 30-50%.

The study concluded that the absence of a national CRC screening program, poor public awareness and official attention, and absences/shortage of many cancer services in GS may be the main causes for poor CRC survival estimates. Decreasing gaps in the last three issues may contribute to enhance the survival data, prevent premature deaths, and promote the quality of life for CRC cases in GS.

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List of Abbreviation

ACS	American Cancer Society
CBC	Complete Blood Cell
CRC	Colorectal Cancer
CT	Computed Tomography
CEA	Carcinoembryonic Antigen
DFS	Disease Free Survival
DRE	Digital Rectal Examination
EGH	European Gaza Hospital
FAP	Familial Adenomatous Polyposis
GG	Gaza Governorates
GS	Gaza Strip
HNPCC	Hereditary Non-Polyposis Colorectal Cancer
IARC	International Agency for Research on Cancer
MOH	Ministry of Health
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute (American)
NGOs	Non Governmental Organizations
NIH	National Institutes of Health (American)
OS	Overall Survival
OECD	Organisation for Economic Co-operation and Development
PCR	Palestinian Cancer Registry
PFS	Progression Free Survival
PHIS	Palestinian Health Information System
RSPH	Rantesi Specialist Pediatric Hospital
SoP	State of Palestine
TNM	Tumor size, Lymph node, Metastasis
UK	United Kingdom

UNRWA	United Nations Relief and Works Agency for the Refugee of Palestine in the Near East.
USA	United States of America
WAFA	Palestine News & Information Agency West Bank
WB	West bank
WHO	World Health Organization

Chapter (1): Introduction

1.1 Background

Cancer is a major cause of morbidity and mortality worldwide, and its burden rises over recent decades. According to International Agency for Research on Cancer-IARC (2014), Colorectal Cancer (CRC) is one of the most cancer affects both sexes worldwide and it ranks the second most common for female cancer and third male cancer representing about 10% of global cancer incidence in 2012. Even though CRC is more common in developed countries and relates with modern civilization, its incidence is rapidly increase in many countries around the world especially in Asia and Eastern Europe, which reflecting increasing the load of risk factors related to CRC such as obesity, smoking, diet habits and other factors associated with westernization culture (American Cancer Society-ACS, 2015a). In the last 10 years, CRC incidence rates in many Arabic countries have been increasing, even though its figures still lower than the figures in the developed countries (Arafa & Farhat, 2015). On the other hand, many recent studies showed remarkable improvement in CRC survival rate in developed countries which indicated that determining the prognostic factors and modified it will lead to improve overall survival rate from CRC (Zare-Bandamiri et al., 2016).

Palestine as many developing countries is experiencing an epidemiological transition where the burden of the chronic diseases become the greatest. Cancer diseases are considered the second most common chronic diseases after cardiovascular diseases (Mosleh, 2016). Also cancer is considered a public health problem which affecting both sexes with growing incidence rates for certain cancer types such as breast cancer and CRC and the Gaza Strip (GS) in last few years have been experiencing clear steadily increasing trend in cancer diseases incidence. Ministry of Health (MOH) records mentioned that CRC is the first common cancer among males in GG, and the second among both sexes combined (MOH, 2015a). Another MOH reports shows that cancer diseases as overall are the second leading cause of death after cardiovascular diseases in GS (MOH, 2014).

Palestine as many developing and less developed countries lacks to population based survival studies for cancer diseases, and to the best of the researcher knowledge, there was no any studies for CRC survival analysis were done. Survival rate is a useful measure for monitoring the effectiveness of health care management of CRC (Foot and Harrison,

2011). Also survival analysis is main indicator for the efficacy of heath care system delivery. Survival of CRC is affected by many factors such as patient socio- demographic

characteristics, tumor histological type, the stage at diagnosed, and health management factors. Worldwide, there are large differences in survival rates between economically developed and developing countries. Also 5-years survival rates for CRC cases were diagnosed in early stage exceeds 90% compared with 10% for metastatic cases (Waghray et al., 2016). In this study the researcher will give the fist estimation of survival statistics for CRC patients in GS. Beside the study will focus on the main determinants which may affect on survival rate among CRC cases in GS and determined overall survival rate and adjusted survival rate to selected prognostic factors such as stage at diagnosis and metastasis status. Ultimately the study results will provide a baseline of useful information CRC prognosis which helps in detecting gaps in management of CRC to enhance survival of CRC and prevent premature deaths which are attributable to it. Beside that identifying of main factors associated with survival of CRC will help policymakers, health planners and physicians to develop effective strategies and plans to fight CRC and promote survival rate by decreasing suspected gaps in main factors associated with CRC survival rate in the Gaza Strip.

1.2 Research problem

Recent MOH reports showed that the CRC is the first major common cancer among men in GS and it is considered the second major common cancer after Breast cancer for both sexes combined (MOH, 2015a). Furthermore cancer diseases as overall are the second leading cause of death in GS after heart diseases (MOH, 2014). Current situation of cancer management in Palestine is complicated from one hand cancer incidence in increasing trend, and from the other hand many of cancer services is poor or absent such as radiotherapy, PET CT, special palliative therapy especially in Gaza Strip, So that MOH referred routinely many cases to be treated abroad (in East Jerusalem, West Bank, and others). As overall referral for treating cancer only (rather than diagnostic procedures) ranks on the top of the causes for referral abroad which increases the load on health care system in Palestine (MOH, 2016a). Notwithstanding the foregoing and to the best of researcher knowledge survival statistics for CRC patients in GS are not available.

The survival rates and mortality rates are essential for evaluation the effectiveness of health care system in managing CRC and adjusted survival rates according selected prognostic factors such as stage at diagnosis, tumor site, socio-demographic factors, and others are used as evaluation tools for how these factor affecting survival rate for CRC patients in GS.

This currents study will be the first study to estimate CRC survival rate in GS and defining main factors affecting its prognosis, so it will give the baseline of the survival data about CRC in GS which may is used for future improvement plans.

1.3 Justification of the study

Survival analysis is very important tool for monitoring the effectiveness of health care systems, and survival rate is considered main indicator which reflect many factors both in population and health care system delivery. It can used to evaluate the effectiveness of screening program and detecting cancer as early as possible, the effect and success of treatment protocols, and also it used as comparator indicator among different population (Foot et al., 2011). 5-year survival rate is used widely over the world to quantify the burden of CRC mortality. In Gaza Governorates (GG), even though MOH reports in GS is showing increasing trend in CRC incidence, the population-based survival analysis of CRC cases in GG is absent. And to the best of researcher knowledge survival statistics regarding CRC in the Gaza strip is unavailable. So it will be worth and rationale to conduct study to provide estimation of CRC statistics in GS due to survival statistics significance. Accordingly this study will gain more importance because it will be the first study will examine the survival rates and explore the main factors correlated with CRC in GG. Study results will give a baseline of information and opportunities for health care system stakeholders to understand and address inequalities in the management of CRC and define areas for future possible improvement. This will contribute to prevent premature deaths of CRC cases and improving the quality of life for CRC patients in GS.

1.4 Study objectives

1.4.1 General objective

To explore the observed survival rate for colorectal cancer cases, and investigate main factors may associated with Colorectal Cancer (CRC) survival in GS at the period between (2008- 2010).

1.4.2 Specific objectives of the study

1. To determine the overall 5-years survival rate for colorectal cancer cases in GS.
2. To identify adjusted survival rates according to certain prognostic factors such as stage at
   diagnosis, and histological type of tumor.
3. To assess the impact of socio-demographic factors such as gender, age at diagnosis, and
   residency on survival rate .
4. To investigate how healthcare related factors such as delay in diagnosis, treatment type and delay in treatment affect on survival rate of CRC.
5. To develop recommendations that may improve the survival rates and prevent premature deaths from CRC in GS.

1.5 Research question

1. What is the overall five years survival rate for CRC cases in GS?
2. What are main factors correlate with CRC survival rate in GS?
3. How stage at diagnosis affects on the progression of CRC?
4. Is survival rate for CRC cases affected by socio-demographic characteristics of the cases?
5. Are there survival differences between male and female CRC patients in GS?
6. Is diagnostic delay affect on the survival rate for CRC cases?
7. How CRC progression affected by treatment delay?
8. Which are treatment issues related with survival rates for CRC cases in GS?
9. What is overall survival rate for non-metastatic and metastatic cases?
10. hat is disease free survival rate for non-metastatic cases and progression free survival
    rate for metastatic cases?
11. Which are main suggestions to improve the survival rates for CRC cases?

1.6 Study context

1.6.1 Gaza Strip overview

The GS is a small piece of land located in the southern area of State of Palestine (SoP). SoP is a small country with about 27.009 km2. It is located in the west of Asia continent, and in the east of the Mediterranean Sea (Annex 1). It is boarded from the north by Lebanon and Syria, from south by Egypt and the Gulf of Aqaba, and from east by Jordan. GS is divided into five governorates: North Gaza, Gaza, mid zone, Khan Younis, and Rafah (Palestinian Central Bureau of Statistics-PCBS, 2015) (Annex 2).

The total population in Gaza Strip governorates was around 1.82 million in mid-2015, where is considered from the most crowded areas over the world with more than 8,328 individual per square kilometer. Population in GS is characterized by youth bulge with 55% from total population are less than eighteen years old. Average family size in GS is 5.8 individual, 50.8% from total population in GS are male, while 49.2% are female, and life expectancy for males and females is 71.2 and 74.1 respectively. The unemployment rate in GS increases from 37.8% in 2010 to 43.9% in 2014, while the poverty rate was 38% in 2010 (MOH, 2015b).

The World Bank classified the socioeconomic status of GS and WB at the low-middle-income level. GS has sharp economics deterioration in recent years mainly due the military siege and isolation of population (Abed, 2007). According to MOH (2015c) the total number of chronic diseases patients in GS in 2014 was 116762 patients. Hypertension disease accounts 33.4% of total number of chronic disease which considered the most common chronic diseases followed by Diabetes mellitus disease, while cancer diseases accounts 3.3% ranking the fifth in term of number of patients.

1.6.2 Health care system

Palestinian health care system is a complex system due to the health services delivery in Palestine consists from multi-major health care providers: Ministry of Health (MOH), United Nation Relief and Work Agency for the Refugee of Palestine in the Near East (UNRWA), Non- Governmental Organizations (NGOs) and profit private sector. MOH is considered the main health care provider and according to the Palestinian Public Health Law, the main roles and tasks of the MOH are providing, regulating and supervising the

delivery of health care in Palestine. Also, MOH is responsible about the planning the health care services in coordination with different stakeholders, enhancing health promotion to improve the health status, developing human resources in health sector, managing and disseminating health information, and others (MOH, 2016a).

In GS, the Latest MOH report regarding the hospitals in GS in year 2015 which is published in 2016 shows that there is thirty hospitals with 2816 beds are distributed as the follow: 2242 hospital beds in the governmental hospitals and 574 beds in non-governmental sector (MOH, 2016c).

European Gaza Hospital (EGH) and Al-Shifa hospital are two main hospitals provide adult cancer services in GS. Regarding the diagnostic tests and procedures for CRC, they are available in CS which include the endoscopic examinations, Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and others except Positron Emission Tomography–Computed Tomography (PET CT) still unavailable in GS (Thabet, 2017). The same source added that the cancer therapy in GS is facing many difficulties and challenges such as shortage of supply the systemic therapy, unavailability of some important drugs, shortage of training courses for the oncology team, beside the overcrowding of cancer patients in the oncology department. These difficulties long the patient waiting list for chemotherapy which contributes to delay in receiving the chemotherapy also delay in the referral abroad.

1.6.4 Al-Shifa Hospital

Al-Shifa hospital was established on 1946 and developed over years, its buildings over 45.000sq.m and the total number of beds 696 beds. In the fact, Al-Shifa is medical complex that includes three hospitals: Surgery hospital, internal medicine hospital and women's and obstetrics hospital. The hospital has been the key center for the Palestinian population living in Gaza Governorates. It locates in the west part of Gaza city, in the North Rimal district.

Oncology department at Al Shifa hospital was constructed since 1984 with one big room and over years developing and give health services to patients with hem-oncology diseases from age 12 years. It was built at 1992 and rebuilding at 2001, it consists of five normal

rooms with fifteen beds and four isolated rooms with one bed for each isolated room (El Shifa Hospital records, 2013).

1.6.5 European Gaza Hospital

European Gaza Hospital (EGH) was built in 1993 in Khan Yonis governorates at the south of the GS. At the beginning, the management of EGH was delivered by European Union, and then on 15 October 2000 the management authority was transferred to the Palestinian staff.

EGH is considered as referral center and providing secondary care for Rafah and Khan Yonis governorates. The EGH involves adult medical-surgical services, cardiac catheterization, cardiology, outpatient clinics, medical and surgical pediatrics, pediatric intensive care unit, radiology, and adult oncology. The EGH consists of 245 beds and includes computerized network system with quality care for patients and the hospital offers special health services to people from all GG (EGH records, 2013).

1.6.6 Cancer registry in Gaza governorates

Cancer registry is defined as an information system designed for the collection, storage, management, and analysis of data on persons with cancer, usually covering a hospital or group of hospitals. In Palestine, MOH with cooperation of Middle East Council of Churches established the Palestinian cancer Registry (PCR) which considered a population based registry in 1996, and started its regular work in 1998. Defining the burden of the cancer problem and pattern of its occurrence are the main purpose of the PCR. Since lunch of PRC the registrations process in PCR centers have been affected by unrest political circumstances in the Palestinian regions and due to Israeli measures, which divided Northern governorates (West Bank) into 43 separate areas, and continuity of Israeli siege for Gaza strip. Beside other problem which include internal conflicts and political and geographical separation between GS and WB (MOH, 2002). The registry process in Gaza governorates extends from 1995 until present with the registry including all cancer cases from its different sources. Cancer registry collect data from five main sources which include; The first source is governmental hospital which provide cancer services, the second is governmental and private histopathological centers, the third governmental,

UNRWA, and private radiology centers, the fourth is treatment abroad referral records, finally the death certificates (MOH, 2015a).

1.7 Operational definition

Survival analysis

Survival analysis is a set of methods for analyzing data where the outcome variable is the time until the occurrence of an event of interest. The event can be death, occurrence of disease, re-occurrence of disease and others.

Survival rate

"The percentage of people in a study or treatment group who are still alive for a certain period of time after they were diagnosed with or started treatment for a disease, such as cancer. The survival rate is often stated as a five-year survival rate, which is the percentage of people in a study or treatment group who are alive five years after their diagnosis or the start of treatment. Also called overall survival rate" (NCI, 2016a).

Diseases free survival rate (DFS)

“The length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer” (NCI, 2016b).

Progression free survival rate (PFS)

"The length of time during and after the treatment of a disease, such as cancer which a patient lives with the disease but it does not get worse. In a clinical trial, measuring the progression-free survival is one way to see how well a new treatment works "(NCI, 2016c).

The smoker

The patient is defined as smoker if she/he smoked any kind of smoking (Cigarette, hubble bubble…) at any time of his life, while he is defined as non-smoker if he does not smoke any kind of smoking at any time of his life. The smoking is suspected to have negative effect on CRC prognosis and the survival rates.

Obesity status

In current study, the patient is defined as obese if the Body Mass Index (BMI) more than 25 kg/m2, and with normal weight if the BMI less than 25 kg/m2

Interval to diagnosis and diagnostic delay

Interval to diagnosis is defined as the period between first time for appearance of signs and symptoms to date of confirmed diagnosis. The patient is defined to have diagnostic delay if the interval to diagnosis exceeds three months.

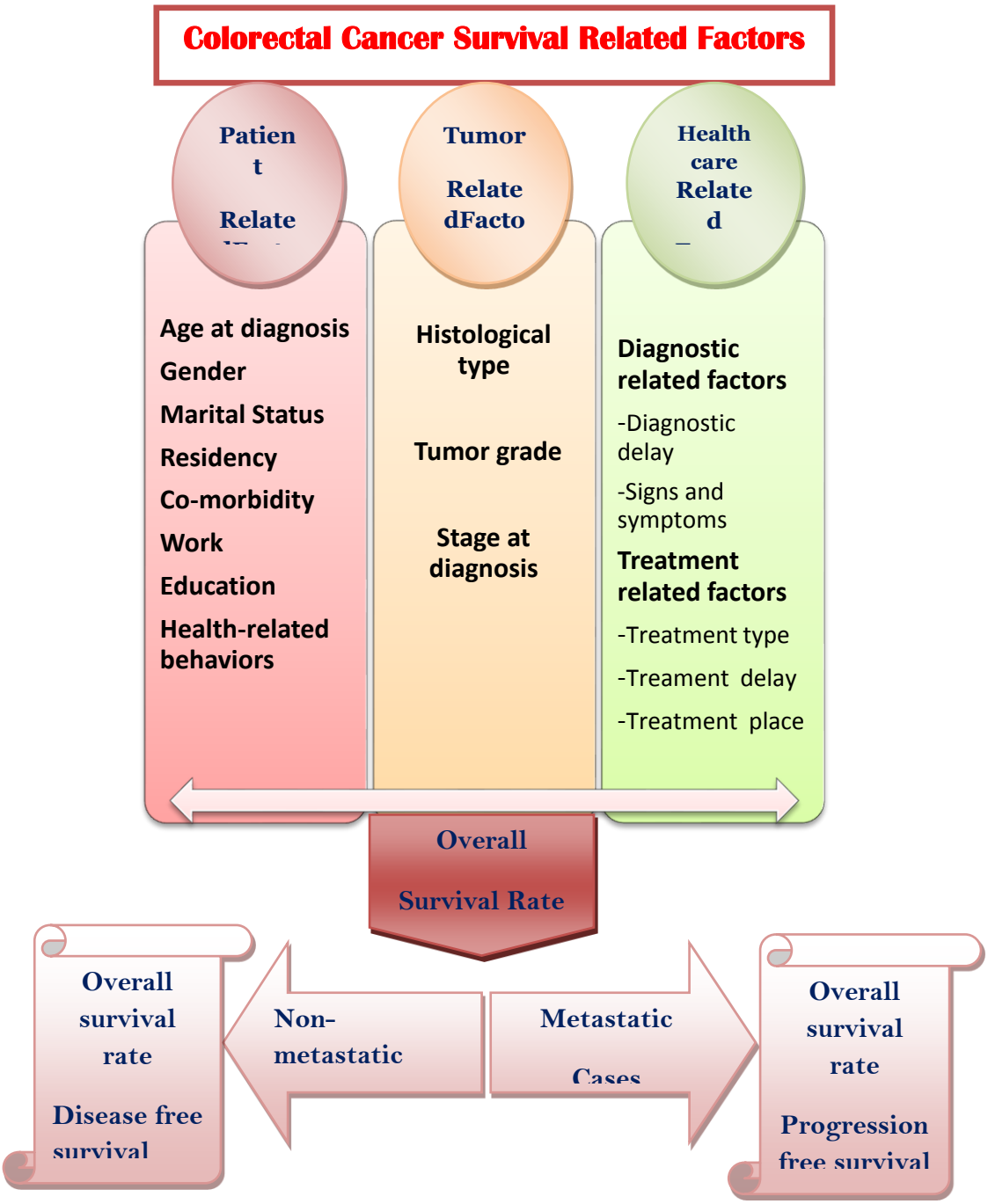
Interval to treatment and treatment delay

Interval to treatment is defined as the time between date of pathological diagnosis, usually via open biopsy, and the date of initial therapy, either surgical or systemic. Treatment delay is divided to two construct: The surgical intervention delay which occurs if the interval to the surgery exceeds fourteen days from date of confirmed diagnosis, while the chemotherapy delay is defined as waiting time for chemotherapy exceeds three months after patient have the surgery.

Chapter (2) Literature review2.1Conceptual Frame work

After the literature was reviewed by the researcher thoroughly with help from the supervisor, he grouped the main factors that may associated with CRC survival in three groups which are considered the main blocks for this current study (figure2.1). The three groups include patient related factors, tumor related factors, and healthcare related factors.

Figure (2.1) Conceptual Framework - Self Developed



2.1.1 Patient Related Factors

Patient related factors include the following factors (Age at diagnosis, Gender, Work, Education, Material status, Residency, Co-morbidity, and Health-related behaviors (smoking, diet, obesity, physical inactivity). The researcher studied how these factors which related to patient himself affect on CRC prognosis and the survival rates. Each variable will be explained in the following paragraphs.

- **Age**

  Age for study population was obtained at date of confirmed diagnosis by biopsy (histopathological study report). Age at diagnosis is suspected to have an effect on CRC prognosis and survival rates.

- **Gender**

  The gender is defined as factor in the current study to explore the impact of cases gender on survival rate, and to examine if there are differences in survival rates between female and male CRC cases.

- **Work**

  The patients work included in this study due to it is expected to affect on CRC prognosis positively or negatively.

- **Education**

  Cases' medical records were assessed for information about education level for cases. As data availability about education level of cases, analysis was done to define impact of education level on survival form CRC.

- **Material status**

  Unmarried and married status of the study cases at date of confirmed diagnosis and journey of treatment were obtained to investigate the suspected relationship between marital status at diagnosis and prognosis of CRC.

- **Residency**

  The place of residency for cases was studied to assess if there are survival variance based on the area of residency. There five governorates in GS which are (North Gaza, Gaza, Mid-Zone, Khan Youis, and Rafah), so the study population are classified to five groups according area of residency (governorate).

- **Co-morbidity**

  The presence of other diseases in addition to CRC correlates with human ability to survive from CRC. Dramatically the other diseases may deplete body ability to fight CRC. In this study two main chronic diseases are studied which combine with CRC (diabetes mellitus (DM) and hypertension (HTN)). These diseases are suspected to have negative effect on CRC prognosis and the survival rates.

- **Health-related behaviors**

  Information about health related behaviors were obtained from available data in the patient's medical records. Health related behaviors include: smoking, diet regime, obesity, and physical activity status of cases at time of confirmed diagnosis of CRC. These variables are studied to define the effect of these behaviors on CRC prognosis and survival rates.

  The patient is defined as smoker if he smoked any kind of smoking (Cigarette, hubble bubble…) at any time of his life, while he is defined as non smoker if he did not smoke any kind of smoking at any time of his life. The smoking is suspected to have negative effect on CRC prognosis and the survival rates.

  About diet, available information in the patients' medical records was collected. Even though the Gazans have same race, same culture, and same dietary norms, some difference may be presented between poor and rich patients especially about the food quality and diversity.

  While regarding physical activity, also available information about physical activity status at time of diagnosis were collected and sorted into three categories (physical active, moderate, and poor activity).

  Height and weight for the study cases were obtained from the medical records to calculate the Body Mass Index (BMI) in order to define the obesity status. The obesity is defined as a factor may an effect on the survival rates for CRC cases.

2.1.2 Tumor Related Factors

Tumor related factors include histological type, tumor grade, stage at diagnosis, and tumor site. The following paragraphs will describe each variable.

- **Histological type**

  There are different histological types of CRC. The most common type is adenocarcinoma and the other less occurred type is mucinous adenocarcinomas. In this study, two main histological types are studied which are non-mucinous adenocarcinomas and mucinous adenocarcinoma as general.

- **Tumor Grade**

  Based on CRC classification of WHO and American Cancer Society (ACS), there are four grades of colorectal carcinomas (grade 1 (G1), grade 2 (G2), grade 3 (G3), and grade 4 (G4)). G1 for cancer looks much like normal colorectal tissue also G1 is called well differentiated, G2 is intermediate grade which is called moderately differentiated, G3 is high grade which is called poorly differentiated, while G4 for cancer looks very abnormal which is called poorly undifferentiated, anaplastic (Fritz et al., 2000; ACS, 2015b).

- **Stage at diagnosis**

  Four main stages derived from TNM classification system of CRC are (stage I, stage II, stage III, and stage IV). Stage I is described when the tumor is localized on the lining of the colon, stage II when The tumor grows into the outer lining of the colon or surrounding tissue, stage III when metastasis to the lymph nodes is present, while stage IV when metastasis to distant organs in the body is present. Stage at diagnosis was determined from data at the medical records where the data were analyzed to see impact of stage at diagnosis on survival from CRC.

  Stage at diagnosis is suspected to be main variable affects on CRC prognosis and the survival rates.

- **Tumor site**

  In this study the cases are divided to three groups according tumor site (patients with right-sided tumors, left-sided tumors, and rectum tumors), in order to investigate the relationship between tumor site and the survival rates from CRC.

2.1.3 Healthcare Related Factors

Healthcare related factors include two main groups of factors (Diagnostic related factors and treatment related factors). The following paragraphs will describe each factor from the two groups.

2.1.3.1 Diagnostic related factors

- **Diagnostic delay:** Is the condition if the interval to confirmed diagnosis exceeds three months from date of signs and symptoms started. Diagnostic delay is defined as prognostic factor in this study and it is suspected to effect negatively on CRC prognosis.
- **Signs and symptoms:** There are many signs and symptoms related to CRC directly or indirectly. The signs and symptoms which are studied in this current study include bleeding per rectum, constipation, abdominal pain, intestinal obstruction, and diarrhea.

2.1.3.2 Treatment related factors

Treatment related factors include treatment delay, treatment type, and treatment location. Each factor is described as the following.

- **Treatment delay:** The patient is defined to have treatment delay if the time from confirmed diagnosis to the surgery exceeds 31 days in this condition is called surgery delay or the time from the surgery to the chemotherapy exceeds 3 months in this condition is called chemotherapy delay. The treatment delay is defined as factors may affect on CRC prognosis negatively.
- **Treatment types**: Include four main types of treatment are provided to CRC cases which are surgical intervention, chemotherapy, radiotherapy, and palliative care.
- **Treatment place:** CRC cases in the GS are treated in different places, and the main places are GS, WB, East Jerusalem, Israel, and Egypt. Treatment place is defined as a variable may affect on the survival rates from CRC.

2.1.4 Overall Survival

This is the percentage of cases with CRC who have not died from any cause during a certain period of time after diagnosis. Five years overall survival rate are calculated for all the study cases. It will be the first estimation of five years survival rate for CRC cases in GS.

2.1.5 Non-Metastatic Cases

Non-Metastatic Cases are defined as CRC cases that are diagnosed with stage I, stage II, or stage III at time of diagnosis without distant metastasis to other organs. The overall survival rate and disease free survival rate are conducted for this group to see the treatment benefits and distant metastasis effects on the overall survival rate.

2.1.6 Disease free survival (DFS) rate

The length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer. In this study DFS is calculated by determining date of surgery (Surgical removal of the tumor) and date of CRC recurrence.

2.1.7 Metastatic Cases

Metastatic cases are defined as CRC cases who are diagnosed with stage IV at time of diagnosis with distant metastasis to other organs such as liver, lung, brain, bone and others.

2.1.8 Progression free survival rate

The length of time during and after the treatment of metastatic CRC which a patient lives with the CRC but it does not get worse. It is calculated by determining date of treatment start and date of disease progression. It used to examine how far the treatment does well.

2.2 Literature review

2.2.1 Anatomy of the colon and the rectum

The colon and the rectum are parts of the digestive system, which they make up the large intestine, annex (3). The colorectum starts from the terminal ileum to the anal canal, and it is divided respectively as the follow: Cecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, recto-sigmoid segment,

rectum, and anal canal. As general, the colorectum is divided into three main parts, the right colon, the left colon, and the rectum. The right colon include cecum, appendix, ascending colon, hepatic flexure, and the right half of transverse colon, while the left colon includes left part of transverse colon, splenic flexure, descending colon, sigmoid colon, and the recto-sigmoid segment is a shared part between the left colon and the rectum, whereas the rectum include the anal canal and the anus (NCI, 2016d; ACS, 2015b).

2.2.2 Colorectal cancer definition

CRC refereed to tumors which start in the colon or the rectum, and they usually grouped together because they have many similar features. Mostly CRC begins as polyps, but not all polyps change to cancer. There are many types of polyps, the two main types are adenomatous polyps which sometimes change to cancer, so they are called a pre-cancerous condition, and the hyperplastic polyps and inflammatory polyps which are the common and rarely change to cancer (ACS, 2015b). The most common origin of CRC is adenomatous polyp, hence the majority of CRC are adenocarcinomas, which constitute about 96% from all types. The others rare types include lymphoma, carcinoid tumors, melanoma and sarcomas (Al Nsour, 2014).

2.2.3 Clinical manifestation of colorectal cancer

According to ACS (2015b), CRC patients sometimes do not complain clearly from symptoms and signs related to CRC especially in the early stages. Major patients with early stage have not symptoms of CRC, and they are diagnosed by screening. Recent studies show that more than 70% up to 90% of CRC cases presented at onset of symptoms at time of diagnosis, hence mostly of CRC cases are diagnosed at advanced stages. The main signs and symptoms of CRC due to local tumor include blood per rectum, abdominal pain, anemia, change in bowel movements, intestinal obstruction, and others, while the patients with metastatic CRC are presented with extra symptoms such as pain at upper quadrant of abdomen, abdominal distention, early satiety, supraclavicular adenopathy, or periumbilical nodules (Macrae et al., 2016).

2.2.4 Risk factors for colorectal cancer

The risk factors for CRC can be divided into non modifiable risk factors and modifiable risk factors. The non-modifiable risk factors include inherited genetic mutations such as Lynch syndrome (hereditary non-polyposis CRC and familial adenomatous polyposis),

personal or family history of CRC, personal history of chronic inflammatory bowel disease, and also the risk for developing CRC increase with age. While the modifiable risk factors for CRC include obesity, physical inactivity, a diet high in red or processed meat, heavy alcohol consumption, and smoking (ACS, 2011).

2.2.5 Staging of colorectal cancer

The first staging system for CRC was developed by Cuthbert Dukes In 1932, and through years dukes staging system was been modified to have more prognostic factors (Fisher, 1989). While the most common used staging system for CRC was developed by American Joint Committee on Cancer (AJCC) which called the Tumor, Node, and Metastasis (TNM) staging system. T is refereed to primary tumor, N is refereed to lymph node, and metastasis is denoted by M. These three letters T, N, and M are followed by number to give further information. Usually the stage of cancer is quoted with Latin number as I, II, III, IV derived from the TNM system value, where the higher number indicate more advance stage (Al Nsour, 2014).

2.2.6 Colorectal cancer grades

The grade of cancer describes the microscopic features of tumor, how it looks like normal tissue.

The scale used for grading CRC is from 1 to 4. The Grade 1 (G1) for cancer looks much like the normal colorectal tissue, and the Grade 4 (G4) for cancer looks very abnormal. Grades 2 and 3 (G2 and G3) for vague it fall somewhere in between G1 and G4 (ACS, 2015b).

Another classification of CRC grades based on International Classification of Diseases-Oncology ICD-O third edition as the follow: Well differentiated = G1, moderately differentiated = G2, poorly differentiated = G3, and undifferentiated anaplastic = G4).

2.2.7 Colorectal cancer screening

According Center for Disease Control and Prevention CDC (2016), the screening test is done to assess the disease in clients without any signs or symptoms related to CRC.

Discovering CRC at early stage is crucial in decreasing mortality rate and increase survival rate (Al Nsour, 2014).

According ACS (2016a) the 5-year survival rate is about 90% if CRC is found at early stage, but unfortunately only 40 % of all CRC cases are found at this early stage. The same source added that only half of people who need CRC screening test, get the needed tests and it is explained that by things such as lack of public and health care providers awareness of screening options, the screening tests costs, and health insurance coverage issues. The American guidelines for CRC screening recommend for men and women to begin the screening tests at age 50. They recommend three main screening tests which the individual at least should to do one of them. The screening tests are colonoscopy (once every 10 years), high-sensitivity fecal occult blood test, and flexible sigmoidoscopy (every 5 years).

2.2.8 Colorectal cancer Diagnosis

According to Canadian Cancer Society (2016), the main diagnostic tests and procedures are used for CRC diagnosis are health history and physical exam, complete blood count (CBC), blood chemistry tests, stool tests, double-contrast barium enema, sigmoidoscopy, colonoscopy, cell and tissue studies, digital rectal exam (DRE), CT scan, PET CT, MRI, and chest x-ray.

2.2.9 Treatment

CRC treatment depends mainly on stage and grade of CRC at diagnosis. Treatment options for CRC include the surgery which is considered the main treatment for CRC without metastasis. The permanent colostomy (creation of an abdominal opening for elimination of body wastes) is very rarely needed for colon cancer and is infrequently required for rectal cancer. Treatment of rectal cancer includes surgery besides chemotherapy alone or with combination with radiotherapy before, after, or both it. Chemotherapy is most used after colon cancer surgical removal for colon which spread to lymph nodes (ACS, 2011). Recent ongoing research in CRC introduces new approaches to control the side effects which related to treatment.

The palliative care is the control of physical symptoms, attention to the social, psychological and spiritual needs of the patient and his family, beside the assessment, early identification, and treatment of pain and other problems of a physical, psychosocial or

spiritual nature to reduce suffering and improves the quality of life of cancer patients and their families (WHO, 2009).

2.2.10 Burden of colorectal cancer

2.2.10.1 Global burden of colorectal cancer

CRC is the third most occurrence cancer in men (it accounts about 10% from all men cancers), and the second in women (it accounts 9.2 % from all women cancers) worldwide. Incidence of CRC differs widely across different regions of the world, almost about 55% of CRC cases occurs in more developed countries with lower mortality rates compared to high mortality rates and increasing incidence trends in less developed countries (IARC, 2017).

ACS (2015a) report show that CRC is the third most common cancer for both sexes, and it ranks the third in terms of mortality from all deaths attributable to cancer in the United State of America (USA). Previous study was done in Denmark showed that CRC is the third most common male cancer and second female cancer in Denmark, like many Western countries (Iversen et al., 2012). Also in United Kingdom (UK) CRC is the third major common cancer in female and males (Cancer Research-United Kingdom, 2013).

2.2.10.2 Burden of colorectal in Eastern Mediterranean Region (EMRO).

WHO (2009) expected that Eastern Mediterranean Region will has the highest increasing incidence rate of CRC among all WHO regions in the coming two decades, while the recent reports show low survival rates for diagnosed CRC in the region comparable with the developed countries. Previous study was carried out in Saudi Arabia, mentioned that CRC is the most common cancer among men and the third commonest among women since 2002 in Saudi Arabia, it added that the overall 5-year survival rate was 44.6% for the period 1994-2004 (Alsanea et al., 2015).

Another previous study was carried out in Lebanon showed that colorectal cancer is the second major cancer in female and ranks the fourth among male cancers (Shamseddine et al., 2014). Recent studies were done in Iran have shown rapid rise in the incidence of CRC making the CRC to become the third most common cancer in Iran (Dolatkhah et al., 2015).

2.2.10.3 Burden of colorectal in Palestine

In the most recent report about cancer in Gaza strip which is prepared by Palestinian Cancer Registry (PCR) and disturbed by MOH in GS, mentioned that the top five cancers in the Gaza strip are breast Cancer, CRC, lung Cancer, leukemia, and lymphoma respectively as shown in annex (4). The same source added that the CRC is the most common type of cancer among men and the second among women after breast cancer, where CRC accounts 10% of all cancer occurred in the period 2009-2014 with incidence rate about 45/100000 (MOH, 2015a).

In the WB, cancer statistics do not significantly differ from statistics in GS, where the breast cancer is the most common cancer with 17.8 % from all registered cancer cases, followed by CRC with 9.4 % in 2015 among both sexes combined, while the lung cancer is the most common cancer among male followed by CRC (MOH, 2016a). Previous Study was done in north West Bank mentioned that the most common cancer for men is CRC which ranks the second for women cancer (Tanjeer, 2010). Cancer is the second most common cause of death in Palestine after cardiovascular diseases with rate 13.8% of all deaths in 2015 (MOH, 2016b). In Gaza strip 10.7% from all deaths occurred in 2015 attributable to cancer which considered the second most common cause of death (PHIC-MOH, 2016). Moreover, due to many cancer services are not available in Palestine particular in GS such as (radiotherapy, many chemotherapy drugs, PET CT, and others), MOH routinely refereed many cancer cases to have treatment abroad (such as East Jerusalem, WB, and others). So cancer diseases are on the top of causes for treatment abroad. In 2015, treatment abroad as overall costed about 147.5 million USD (560,873,668 NIS). Cancer treatment only rather than the diagnostic procedures hauled about third of that number with 40 million USD (150,836,724 NIS) divided as about 10 million USD (36,787,515 NIS) for the cases from GS, and about 30 million USD (114,049,209) for the cases from WB (MOH, 2016).

2.2.11 Colorectal cancer survival

Recent years bear witness to remarkable progress and development on CRC management such as advancement on treatment protocols, improvement in surgical intervention, and

useful screening tools which resulting in improvement of CRC survival rate and more better progression of CRC (Hassan et al., 2016). The 5-years survival rate is the most used indicator for cancer survival which is measured as the proportion of cancer patients who still alive five years after diagnosis of cancer, comparable to five year survival of people in general population at same age and sex. Many factors affect on CRC survival, the most important factors are stage at diagnosis and the early detection of the tumors (ACS, 2011). According ACS (2016a), the 5-years survival rate for patient who are diagnosed at a local stage (stages I, and II) is 90.3%, while for patients who are diagnosed with regional stage (stage III) is about 70.4% and the survival rate declines sharply for patients who are diagnosed with distant-stage (stage IV) with the lowest rate 12.5%.

In USA, about 1.2 million Americans survived from CRC due to the progress in the early detection and the advancement in treatment, besides that there is significant improvement in the overall 5-years survival rate for colon cancer which was 50.6% in 1970 and became 65.4% in 2012, and for the same period the 5-years survival rate for rectal cancer improved from 48.1% to 67.7% (Siegel et al., 2014).

2.2.12 Variances in colorectal cancer survival over the world

There are wide international differences in cancer survival rates especially between the developed countries and the less developed countries. Behind these differences are many factors such as differences in screening, treatment, detection practice, awareness, and data quality. CRC from cancers which is significantly affected by early detection and treatment which are considered the main causes for CRC survival differences between economically developed and developing countries (ACS, 2011).

London School of Hygiene & Tropical Medicine with collaboration from the Union for International Cancer Control launched at 2008 CONCORD program, which is the global program for world-wide surveillance of cancer survival. To date CONCORD program is considered the most comprehensive international comparison of cancer survival, which covers countries in five continents. Two CONCORD studies was conducted which called CONCORD-1 and CONCORD-2 while final work is doing to publish CONCORD-3 study (Cancer Survival Group, 2017).

In CONCORD-1, the focus was on three main cancers (breast cancer, colon cancer, and prostate cancer) for patients who diagnosed in the period 1990–94 and followed up to 1999. CONCORD-1 study showed wide global differences in 5-years survival rate for CRC patients, which were generally high in North America, Australia, Japan, and northern, western, and southern Europe, comparable with low rates in Algeria, Brazil, and eastern Europe (Coleman, 2008). CONCORD-2 studied the 5-years survival for patients diagnosed between 1995 and 2009, using data from 279 cancer registries in 67 countries, and it included ten common types of cancers include CRC. CONCORD-2 like CONCORD-1showed very large variations between countries in survival rates for specific cancer, but it outlined that 5-year survival from CRC has increased steadily in most developed countries, where it reached in many countries 60% (Allemani et al., 2015).

In USA, the overall 5-years survival rate exceeds 64%, while in Asia at approximately 60% with best survival rate in China and the poorest in India. In Korea, reports indicated that the 5-year survival rates was 62.1%, while study conducted in china showed that 5-years survival rate was 62.3%. Furthermore study conducted in Japan showed that 5-years survival rate for CRC was 61.4%. Previous studies in India showed the lowest 5-year survival rate in Asia with rate 31.2% (Moghimi-Dehkordi, and Safaee, 2012). Another Study conducted in Jordan to analyze survival rate for CRC showed that relative 5-years survival rate in Jordan was 57.7% (Al Nsour, 2014). Another study conducted in Iran showed that 5-years survival rate was 58.5% (Zare-Bandamiri et al., 2016). Also another study conducted in Malaysia revealed that 5-year survival rate was 59.1% (Suan et al., 2016).

Annex (5) shows the survival differences in 5-years survival rate from colon cancer. Data was obtained from CONCORD-2 study which provided survival analysis data for cancer diseases in 67 countries (Allemani et al., 2015).

2.2.13 Factors affecting survival rate for colorectal cancer

After systematic review of literature was been done, the researcher classified the main factors which may affect on the survival rates from CRC into three groups. The following paragraphs explain the impact of each factor from the three groups on CRC prognosis and the survival rates.

2.2.13.1 Patient Related Factors

- **Age at diagnosis**

Based on previous studies, the effect of age on prognosis and survival from CRC is argumentative subject. McKay and colleagues (2014) studied the influence of young age on the prognosis of CRC in Canada, and they found that young age is an independent factor for good prognosis and better survival, while the old age associates with poor prognosis because they usually presented with advanced disease and co-morbidity. While van Eeghen and colleagues (2015) have showed different effect of age at diagnosis for colon cancer patients and rectal cancer patients where the age at diagnosis significantly affects on the survival of colon cancer, but there is not significant effect on survival of rectal cancer.

Another study was conducted on USA showed no differences in survival rate among patients aged below 50, or above 50 up to 80 years old, while patients aged above 80 years old experienced with poor survival rate (Steele et al., 2014).

- **Gender**

Many recent studies showed slightly survival differences between female and male CRC patients. Study was done in Germany by analysis of 164966 CRC cases between 1997 to 2006, outlined that age-adjusted five years relative survival rate was slightly greater in women than men, and survival benefits go to those younger than age 45 years old (Majek et al., 2013). Another previous study was done in USA demonstrated significantly longer adjusted survival rates for women rather than men (Paulson et al., 2009). Furthermore previous study conducted in South Korea showed poorer survival rates among women aged over 65 years old than men (Kim et al., 2015).

- **Marital status**

Many research studies through literature showed that marital status has strong association with prognosis of many cancer diseases. Regarding CRC, survival benefits go to married patients rather than unmarried patients (Li et al., 2015). Lai and colleagues (2010) studied the association between marital status and survival rates from colon cancer. They

demonstrated that there are fairly modest survival differences between the married and the unmarried patients with colon cancer. Even though the married patients have slightly better survival rates than the unmarried patients. The authors showed that married patients may have better access to health care system and they diagnosed early, but when cancer stage was controlled, the survival differences decreased between the married and the unmarried CRC patients (Lai et al., 2010).

Another previous study was done in Denmark found that five years survival rate for married colon cancer patients is significantly better than unmarried colon patients, but there were no survival differences regarding the married and the unmarried rectal cancer patients (Johansen et al., 1996).

- **Residency**

A systematic review of the literature points wide survival differences from cancer diseases between countries and regions. These differences extend within the boundaries of a single country itself. Previous study was conducted in South Australia showed that CRC patients who live in the remote areas had significantly poorer prognosis than those live in the urban areas (Beckmann et al., 2016). Another previous study was done in Iran outlined that district residency have a significant impact on 5-year survival rate for colon cancer patients, and it added that , there are survival differences between western and southern regions of Iran (Heidarnia et al., 2013).

- **Co-morbidity**

Co-morbidity is defined as the "coexistence of disorders in addition to a primary disease of interest." (Sarfati et al., 2016). Many previous studies have shown poorer survival rates among cancer patients with co-morbidity. Sogaard and colleagues (2013) have studied the impact of co-morbidity on cancer survival by reviewing more than 2,500 articles related to co-morbidity effect on cancer, and they found that the patients with co-morbidity have poorer survival rates than those without co-morbidity.

Previous study was conducted in Netherland showed that co-morbidity significantly impacted on overall survival from CRC. It's added that co-morbidity affected significantly survival for colon cancer patient, but did not significantly affected for those with rectum cancer (van Eeghen et al., 2015).

- **Work**

Work environment is considered one from the risk factors for CRC (Arbman et al., 1993). CRC affects on the ability of the patients to engage the usual occupational activities during cancer treatment and survivorship periods (Shipp et al., 2015). In this study, the work is defined as a variable may affects on the survival rates from CRC, but the scarcity of data in patients' medical records regarding the patients work impeded the study of work impact on CRC prognosis.

- **Education**

Many previous studies have showed association between the patients' educational level and survival rates from CRC. The previous studies showed that the survival benefits goes to more educated patients, and there is strong and inverse relationship between education level and mortality from CRC. Moreover the overall survival rates from CRC for high educated patients is better than those with low education level (Albano et al., 2007; Antunes et al., 2016; Cavalli-Björkman et al., 2011). In this study, the majority of patients medical records which is considered the main data source for the study, do not contain any data about the educational level for the patients, so study the impact of educational level on survival rate from CRC is unachievable.

- **Health-related behaviors**

There is growing evidence that lifestyle factors which include obesity, physical activity, and diet are associated with CRC prognosis, moreover studies showed that having normal weight, engaging in regular physical activity, and eating healthy diet are potential critical elements and preventive measures to improve survival rate among CRC patients (Lee et al., 2015a).

Even though smoking is considered as risk factor for many cancers including CRC, but the evidence regarding its impact on the prognosis of CRC patients remains sparse. Previous population-based study consists from 3130 CRC patients, showed that smoking associated with decreased survival rates among patients with non-metastatic colon cancer. The authors suggested that the association may be more pronounced in men rather than women (Walter et al., 2015).

Previous study was conducted in USA concluded that long-term smoking increased the risk for death from CRC in both gender. Also the adjusted mortality rates for lifelong non-smokers patients are lower than former or current smokers' patients (Chao et al., 2000).

Another study was conducted in USA outlined that the total tobacco usage early in life may be an important independent prognostic factor for cancer recurrences and death in patients with stage III colon cancer (McCleary et al., 2010).

There is few studies focus on relationship between survival from CRC and diet before or after diagnosis of CRC (Lee et al., 2015a). Previous study was conducted in France to analyze the influence of dietary factors on survival from CRC, showed that five years survival rate was affected by pre-diagnosis diet. Furthermore the authors have showed that high carbohydrate, protein, and lipid intake, is strongly related to increase survival benefits for CRC cases (Dray et al., 2003).

According WHO (2006), the BMI is a simple index of weight-for-height which it is commonly used to classify underweight, overweight and obesity in adults. It is defined as the weight in kilograms divided by the square of the height in meters (kg/m2).

Obesity increase risk for CRC, but there is no conclusive evidence showed that obesity has direct negative effect on survival rate from CRC (Bardou et al., 2013).

Regarding physical activity, many previous studies indicated that physical activity associated with positive effect on colorectal cancer survivors and reduce risk of disease recurrence (Cassileth et al., 2016). Beside that non-metastatic patient who are more physical active have low mortality rate than those with low physical activity (Meyerhardt et al., 2009).

2.2.13.2 Tumor Related Factors

- **Histological type**

According to WHO classification, there are a number of histological types of colorectal carcinomas such as an usual adenocarcinomas, mucinous, signet ring cell, and others (Fleming et al., 2012). Usual adenocarcinomas are the most common colorectal carcinomas constitute about 85%, while the mucinous adenocarcinomas are the second most common type constitute about 10 to 15% from all colorectal carcinomas, whereas the other types are very rare (Lanza et al., 2011).

In this study, the usual and the mucinous adenocarcinomas are studied, so the patients are classified to two groups, the patients with non-Mucinous Adenocarcinomas (non-MAC) and the patients with Mucinous Adenocarcinomas (MAC).

Previous large-scale study was conducted in South Korea enrolled a total of 6475 CRC patients with stage I–III, showed that 95.8% from patients were with non-MAC, and 4.2 % were with MAC. And it demonstrated that major patients with MAC have tumor in right colon and they were younger, tumor sizes larger, and more advanced status than patients with non-MAC. Moreover the study showed that mucinous histology has not an independent effect on prognosis. However, patients with non-MAC have better survival rate than patients with MAC (Park et al., 2015).

- **Tumor Grade**

To date, the most widely used system of defining CRC's histological grade is based on the percentage of tumor glands which are forming the mass. Tumor grade is an important for defining treatment and indication for tumor prognosis.
As general, a lower grade related with better prognosis, while high grade correlated with poor prognosis and need more aggressive treatment (ACS, 2015c). Also Canadian cancer society emphasizes that high grade CRC indicates poor prognosis rather than lower grade (Canadian Cancer Society, 2016).

Previous study showed that tumor grade is associated with survival from CRC, in tumors with stages II, III, IV rather than stage I at date of confirmed diagnosis (O'Connell et al., 2004).

- **Stage at diagnosis**

Stage at diagnosis is considered the main and the strongest factor determines the cancer prognosis. CRC with lower stages associates with better prognosis and higher survival rates rather than CRC with advanced stages (Canadian Cancer Society, 2017). Previous large scale study was conducted in USA included 119363 patients were diagnosed with CRC in the period from 1991to 2000, shows significant differences in 5-years survival rate among patients based on stage of CRC at diagnosis, and it outlined that 5-years survival rate for patients who were diagnosed with stage I was 93.2%, 82.5% for patients with stage II, 59.5% for stage III, and 8.1% for stage IV (O'Connell et al., 2004).

Another previous study was conducted in three European countries (Switzerland, France, Spain) to study impact of stage at diagnosis on survival from rectal cancer outlined that the main factor for survival differences between the three countries was stage at diagnosis (Monnet et al., 1999).

2.2.13.3 Healthcare Related Factors

2.2.13.3.1 Diagnostic related factors

- **Diagnostic delay**

To date, the effect of diagnostic delay on cancer prognosis is still argumentative subject, and there is no clear evidence on this subject. Despite of cancer is progressive disease, so is expected to be affected by delay whether in diagnosis or treatment (Foot and Harrison, 2011). There are different definitions and sub-classifications of diagnostic delay through literature. In this current study, the researcher studied diagnostic delay as the period from onset of symptoms until date of confirmed diagnosis by histo-pathological evidence. Pita-Fernández and colleagues (2016) defined symptom to diagnosis interval (SDI) as the time from the diagnosis of cancer and the first symptoms related to CRC. The authors outlined that short SDI were significantly associated with lower survival rate in rectal cancer, modest effect were observed in colon cancer cases.

- **Signs and symptoms of CRC**

Blooding per rectum, abdominal pain, change in bowel habits constipation/diarrhea, and unexplained anemia are main signs and symptoms associated with CRC cancer. Symptomatic patients at diagnosis usually have advanced disease so dramatically have poor prognosis. There are inverse relationship between number of signs and symptoms and survival from CRC (Macrae et al., 2016).

2.2.13.3.2 Treatment related factors

- **Treatment delay**

Association between survival and waiting time from diagnosis to initiation of treatment is still argumentative issue. Shandiz (2016) defined the interval to treatment as "the time between date of pathological diagnosis, usually via open biopsy, and the date of initial therapy, either surgical or systemic". Previous study was conducted in USA showed that longer interval to treatment up to one year has no strong effect on CRC-specific deaths. The authors suggested that the screening remains the primary goal to reduce CRC mortality (Pruitt et al., 2013).

Another previous study shows that there are not significant relationship between treatment delay and CRC survival rates (Murchie et al., 2014).

- **Treatment places (Gaza Strip, West Bank, East Jerusalem, Egypt, Israel, others)**

MOH purchases many services for cancer management from many places inside Palestine and outside Palestine to treat GS patients who their treatment plan need more advance diagnostic procedures or treatment protocol are not available in MOH hospitals inside GS. The main places for treatment abroad for GS CRC patients are (West Bank, East Jerusalem, Egypt, Israel, and Jordan) (MOH, 2016). In this study the researcher study how different treatment places affect on survival from CRC. Treatment place is divided to two domains: Inside GS, and outside GS.

- **Treatment types**

1. Surgery

Many studies around the world show that the surgery is considered the most effective treatment approach for CRC patients. For patients with stage I and II can cure completely by surgical resection of tumor alone, while for those with stage III need beside surgical intervention chemotherapy.

In the opposite, for those with stage IV with unresectable metastases there is uncertainty about the effectiveness of the surgical resection. However, the palliative surgery may be needed in some conditions such as complete bowel obstruction and uncontrolled bleeding (Biondi et al., 2016).

As the surgical resection remain the only curative method for CRC in the early stages and even with liver metastasis, the multidisciplinary treatment management stills the way to conduct the proper treatment plan and gain the best results (Patrlj et al., 2014).

2. Chemotherapy

Chemotherapy is treatment approach which chemicals such as (5Fluorouracil (5-FU), Camptosar, Xeloda, Eloxatin, and Lonsurf) is used to kill rapid divided cells such as cancer cells. In CRC, used of chemotherapy and its components based mainly on CRC stage. There is no need of chemotherapy in CRC at stage I, while for rectal cancer stage II and high risk patients with colon cancer at stage II, chemotherapy is used. In stage III and IV chemotherapy often is used if there no thing stops it such as patient health status and availability of drugs. The most common used chemotherapy regimens are FOLFOX (leucovorin, 5-FU, and oxaliplatin), FOLFIRI (leucovorin, 5-FU, and irinotecan), CapeOX (capecitabine (Xeloda) and oxaliplatin) and FOLFOXIRI (leucovorin, 5-FU, oxaliplatin, and irinotecan) and there are other combinations and generations (ACS, 2016b). As general use of chemotherapy combination in treating advance CRC is relating with better outcomes (Cancer-Connect, 2017). Furthermore many previous studies have showed that patients with advance CRC who received chemotherapy have more better survival rate than those who did not received chemotherapy, also they suggested that chemotherapy reduce disease recurrences rate, disease relapse, and improved quality of life (Leydon, et al., 2000; Texas Oncology, 2017; Ragnhammar et al.,2001; Milinis et al., 2015).

3. Radiotherapy

Radiotherapy is defined as the use of high-energy rays (such as x-rays) or particles to destroy cancer cells, and to make radiotherapy more effective against some colon and rectal cancers, it is used with combination with chemotherapy, in this case they called chemoradiation (ACS, 2016b). Radiation therapy has assumed an integral role in the treatment of colon and rectal malignancy when combined with potentially curative resection and may be used in either an adjuvant or neo-adjuvant manner (Dixon and Stamos, 2005). According ACS (2016b) radiotherapy is must used for colorectal cancer in many situation either before or after surgery such as treating distant metastasis to bone or brain, partial surgical removal of tumor when it attached to an internal organ, and also is used to palliate ease symptoms such as intestinal blockage, bleeding, or pain in patients with unresectable tumors.

4. Palliative care

In recent years, the palliative care has attracted more attention where the palliative care by controlling of symptoms and decreasing suffering become the goal of treatment, when cure of cancer is not possible. There are many different strategies of non-surgical palliative care methods offered to advanced CRC patients such as (Chemotherapy, radiotherapy, pain management, endorectal metallic stent placement, and laser recanalization) beside the surgical palliation (Dixon and Stamos, 2005). In this current study, the first three methods (Chemotherapy, radiation therapy, and pain management) are studied.

As general, the patients with advanced CRC (Stage IV) who received palliative chemotherapy have prolonged time to disease progression and better survival than those who did not received chemotherapy (Colorectal Cancer Collaborative Group, 2000). Also palliative radiotherapy play an effective role in controlling symptoms such as pain and bleeding. While for non-chemotherapy/non-radiotherapy methods for controlling pain, the oral opioids is considered the first line for patients with an effective effect, this is beside other drugs such as amitriptyline, gabapentin, and other approaches (Dixon and Stamos, 2005).

Another recent study shows a dramatic improvement in the expected survival from 4-6 months to more than two years, for CRC patients with advanced stages who received best supportive palliative care (Costi et al, 2014).

Chapter (3) Methodology

3.1 Study design

Observational analytical retrospective cohort study (non-concurrent prospective) design was used in this study. The researcher analyzed the survival rate of CRC cases who were diagnosed in the period (2008-2010) in GS and follow up them for 5 years to determine the overall 5-years survival rates.

Retrospective cohort studies are suitable for this study, because it allowed the researcher to examine many factors that may affect on the survival rates from CRC in short period relatively and this design of studies is less expensive, that enabling the researcher to achieve the study general and specific objectives in short period and with low cost. Furthermore it is characterized with low bias, because the used data is already collected for other purpose of this study.

3.2 Study population

The study population is all CRC patients who were diagnosed in the period (2008-2010) in GS. List of 255 CRC cases were diagnosed in the period 2008-2010 was retrieved from PCR in GS. According the study inclusion and exclusion criteria, only 184 cases are eligible for this study, where 71 cases are excluded for different causes. The 184 cases are added to them 23 cases from patients' database in Al-Shifa hospital and EGH, hence the total number for the study cases become 207 cases. For more detailed information see annex (7) which describes with details the selection process of the study cases.

3.3 Study setting

The study was population based and conducted in main four areas

1. Al-Shifa hospital (Information technology unit, Central archive, and Histopathological lab).
2. Rantesi Specialist Pediatric Hospital-RSPH (Due to the transfer of adult oncology and hematology services which were in Al-Shifa hospital to RSPH, because of rebuilding in many departments in Al-Shifa hospital).
3. European Gaza Hospital (Oncology and hematology services including archive, and information technology unit).

4. Ministry of Health (Cancer registry center, Central archive, Deaths and births registry directorate)

3.4 Study period

The School of Public Health-SPH at Al-Quds University accepted the study proposal at end of May, 2016. After that proposal copy was sent to Helsinki committee in GS to assign ethical approval for the study. Helsinki Committee approved the study proposal at August, 2016 (annex4). Then Administrative and approval letters with copies of Helsinki approval were sent to MOH (Human Resources Development Directorate) in August, 2016 (Annexes 5, 6). Data collection journey started from cancer registry at beginning of September, 2016 extended to January, 2017.

Data entry on SPSSversion-22 was done alongside data collection. Re-entry of 5% data (11 medical records), re-checking of the missing data and data filtering were finished at beginning of February, 2016. Data analysis and discussion of main findings were consuming about three weeks. The research report was ready at end of March, 2016. As general the study consumed about 14 months, began at March 2016 and finished at May, 2017.

3.5 Eligibility criteria

3.5.1 Inclusion

The study includes all CRC cases who were diagnosed in the period between (2008- 2010), and recorded in Al-Shifa hospital, EGH, or PCR and their medical records are available, except any case met any of exclusion criteria.

3.5.2 Exclusion

1. CRC cases who were diagnosed before 1/1/2008 (2 cases).
2. CRC cases who were diagnosed after 31/12/2010 (8 cases).
3. CRC cases from outside GS and they were been diagnosed inside GS (1 case).
4. Cases who were diagnosed with other cancer rather than CRC (5 cases).
5. CRC cases who were diagnosed in 2008-2010 with unavailable medical records (55 cases).

3.6 Study instruments

The data abstract sheet (Annex 10) is constructed to make the data collection process from the medical records and other data sources more smoothly and more organized. Also the data entry in the analytical programs becomes more easy and smooth.

3.6.1 Main Items for Abstract sheet

- **Socio-demographic information** (Age at diagnosis, gender, marital status, work, area of residency, and education).
- **Patient Health profile** (Patient history, family history, chronic diseases, health risk factors behaviors such as smoking, high fatty diet , physical inactivity ....)
- **Tumor characteristics** (Histological type, stage at diagnosis "TNM", tumor grade).
- **Health care management information**

  - **Diagnosis process:** (Date of initial symptoms and signs related to CRC began to appear, first visit to health care facilities related to symptoms and signs, date of first diagnostic procedure, date of taking the biopsy from the tumor, and date of confirmed diagnosis).

  - **Treatment information:** date of initial treatment (which is surgery, chemotherapy), date of first time of radiotherapy, palliative therapy, and the treatment places.
- **Progression information**

  - **Metastasis information** (Metastatic case/non-metastatic case).
  - **Vital Status information** (Alive/dead).

3.7 Scientific rigor

3.7.1Validity

The abstract sheet was constructed by the researcher with help from the supervisor. The abstract sheet items are enough to cover all needed information for study variables in order to achieve the general and specific objectives of the study.

Data abstract sheet was introduced to health care professional in the oncology department at Al-Shifa hospital and the experts to give their feedback about the abstract sheet contents, arrangement of items in the abstract sheet. Advices and notifies (which relevant to study specific and general objectives) were taken into consideration when the researcher went to prepare final copy of abstract sheet. Also the researcher carried out pilot study before actual data collection to ensure the validity of data abstract sheet content.

3.7.2 Reliability

- Data abstract sheet was standardized and each abstract sheet was coded with serial number.
- Frequent and daily checkup of abstract sheet was done immediately after it is completed at field to find missed data and completeness of abstract sheet.
- Data entry was been in parallel with data collection
- Data collection was done by the researcher himself, and to ensure the accuracy of data entry 5 % of data had been re-entered (11 medical records).
- The medical records are the main source data for data to complete the abstract sheet. In case of unreported items in the medical records, the researcher tried to find the missed information from patients' information database in Al-Shifa hospital, EGH, death certificates, histopathological records.
- To avoid duplication of cases each case is defined by full name, her national identity number and coded with serial number.

3.8 Ethical and administration consideration

The researcher asked for all ethical and administrational considerations which are required to conduct the study, and he was committed to these considerations from the study start till the end. Firstly an academic approval was taken from the Al-Quds University-SPH, was followed by taken an ethical approval from Helsinki Committee to carry out the study (annex 4). SPH sent an administrational letters to MOH (Human Resources Development Directorate and Primary Health Care Directorate), where MOH approved to allow conducting of the study (annexes 5 and 6). The researcher is committed to academic honesty and high confidently precautions over study period (data collection, data entry, analyses and respect to research results).

The researcher set a plan to share the study results locally and international to get maximum benefits from the study. Hard copies form the final study report will be distributed to local university and college, whereas electronic copies will be distributed via international medical journals.

3.9 Pilot study

The pilot study was conducted before actual time of data collection had began, where fifteen medical records were included in the pilot study, which are distributed as the follow (Five medical records for cases who were diagnosed in 2008 year, five cases from 2009 year, and five cases from 2010 year). The pilot study was conducted by the researcher to assure validity of data abstract sheet, and to assess the quality and quantity of data available in the medical records which are considered the source for data in this current study.

The pilot study give chance for examining the reporting status of study variables in the medical records and arrangement of data in them. The pilot study shows different quality and quantity of reporting items between the medical records, but the available data in the medical records is enough to conduct the study.

After the pilot study was finished, minor modifications had been done on data abstract sheet. The fifteen cases which are included in the pilot study, also they are included within the study.

3.10 Data collection

After the final modification on data abstract sheet have been done and the pilot study have been carried out, the researcher himself began to collect data from the main sources which was the medical records for the study cases.

The medical records for CRC cases are present in four places: The oncology outpatient clinic archive in SPH, EGH archive, the main archive in Al-Shifa hospital, and MOH-central archive as described in table (3.1).

Table (3.1) Distribution of medical records for all study cases according their Location

Location of medical records	Living status At time of Data collection	No. of the medical records	(%) percent
Oncology outpatient clinic archive in SPH	Alive	52	24.6%
EGH archive	Alive	36	17.4%
The Main archive in Al Shifa hospital	Dead	27	13%
MOH-Central archive	Dead	92	45%
Total	Alive/Dead	207	100%

3.11 Data entry and analysis

Statistical Package of Social Science (SPSS) program version-22 was used for data entry and analysis. Data entry took place parallel with actual data collection began. All abstract sheet copies were organized and coded with serial number code. Data entry was done by the researcher himself. After data entry had been finished, the researcher re-entered 5% from data abstract sheet copies (11 abstract sheet). Also all entered data on SPSS was reviewed for missing or wrong data (Data cleaning). Data analysis includes the forming of frequency tables, selected graphs, to show main characteristic of study population and main study findings related. Survival analysis was done by using Kaplan-Meier method to estimate overall survival times and rates. A univariate analysis was conducted to show impact of main study variables on the survival data such as stage at diagnosis, treatment type, and place of treatment. Also the log rank test was used to estimate difference between the groups. The researcher considered the variable to have a significant effect if the P-value ≤ 0.05, with 95% confidence interval.

Cox-regression analysis is conducted to verify how far these differences between groups are statistically significant (P-value ≤ 0.05).

After overall survival rate for the entire population was estimated, the cases are divided into two sub-groups, where the first group is non-metastatic cases and the researcher determines the overall survival rate and disease free survival rate for them. The second group is metastatic cases; overall survival rate and progression free survival rate for them were determined.

3.12 Limitation of the study

- Hard access to the medical records, especially for the dead cases.
- Poor quality of documentation and organization of data in the medical records and the missed data in the majority of the medical records with different degrees.
- Weak coordination between hospitals and the central archive and the high number of the missed medical records,
- Absence of computerized archiving system except the central archive.
- Small body of previous research studies in Arabic region including Palestine regarding the survival analysis of CRC and the main aspects and factors which have effect on CRC progression and the survival rate.
- Cases that were eligible for the study were 207 cases, it is small number compared to the international studies.
- Radiotherapy, chemo-radiation, and PET CT, are not available at GS neither governmental nor private sectors, so many medical records miss information about these services.
- TNM staging of CRC are missed in the majority of the medical records. So the researcher with kind help from the supervisors and the oncologist in EGH conducted the TNM staging system for all missing records which consumed additional time, and efforts.
- Study population is limited only to the medical records of the cases, so there is no any contact between the researcher and the study cases or their families to complete any missing data from the medical records.
- This study was first study conducted in GS regarding CRC progression, so the comparison with previous results is not possible.

Chapter (4) Results and Discussion

4.1 Descriptive analysis

4.1.1 Socio-demographic characteristics of study population

Study population is all CRC cases who were diagnosed in the GS at the period (2008-2010), which are 255 cases according list retrieved from PCR. After exclusion of some cases due to for various causes, only 207 patients were eligible for this study Annex (7).

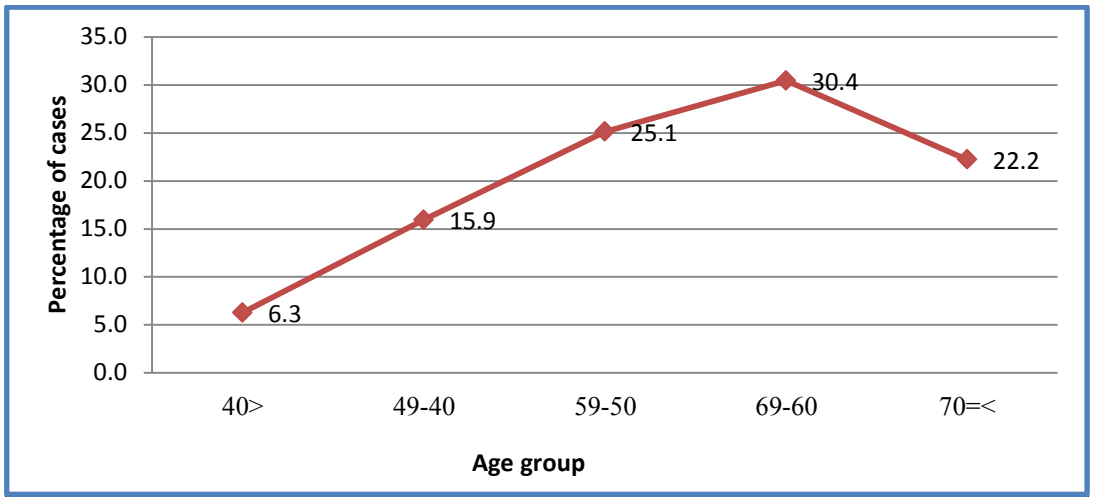
Crude incidence rate for the included CRC cases in GG who were diagnosed at period 2008-2010 was 14 per 100000 (207/1,486,816*100000), which was calculated by dividing the total number of the study cases on GS population at the mid-study period (mid-2009 year) as shown in table (4.2). This finding is lower than the rates according PCR and these differences refereed directly to exclusion of many CRC from this current which decrease the total number of cases. While the age adjusted rate for CRC in GS according PCR is 16.2/100000 (MOH, 2015a).

The following paragraphs will explain the main results and findings regarding the study cases socio-demographic characteristics and how study findings agreed or disagreed with other previous studies.

4.1.1.1 Age at diagnosis

The mean of age for the study population is 59.6, while the most frequent age group is 60-69 years as shown in Table (4.1). Study findings show dramatically increase of CRC incidence with age where more than two third of the study cases occurred after age 50 years old with 77.7%, while 22.3% below age 50 years old (figure 4.1). The literature shows wide global differences about mean of age at diagnosis for CRC cases, but there are compatible results, that the incidence of CRC increases with age especially after age 50 years old. Previous study was conducted in USA have showed high age mean for CRC cases with 65.1 years (Lai and Stotler, 2010). Another previous study was conducted in Iran have showed low mean age with 53.5 comparable with current study findings (Fatemi et al., 2015). Another previous study was conducted in Egypt have showed lower age mean for CRC patients in Egypt with age mean 46 at time of diagnosis (Abu-Zeid et al., 2002).

Figure (4.1): Distribution of colorectal cancer cases according age at diagnosis group in GS (2008-2010)



4.1.1.2 Gender

Study findings show that male cases constituted 54.6% (113 cases) from the study population, while female cases constituted 45.6% (94) as shown in table (4.1). These findings were similar with findings from large scale study which included 164966 colorectal patients in German, where showed that male patients accounted 52.6% and female patients 48.4% (Majek et al., 2013). And else study conducted in USA showed that 53% from colorectal cases were male cases (Lai and Stotler, 2010). Another previous study conducted in Jordan showed similar findings with 54.2% of its population were male, while 45.8% were female (Al Nsour, 2014). In Iran, CRC study was conducted showed that 51.2% from total study population were male patients (Fatemi et al., 2015). Furthermore previous study conducted in Egypt showed slightly high percentage of male patient with 58.8% (Abou-Zeid et al., 2002).

Table (4.1): Socio-demographic characteristics of study population

	Socio-demographic factors	No. of cases	Percent
1.	Age at diagnosis group		
	<40	13	6.3 %
	40-49	33	15.6 %
	50-59	52	25.1 %
	60-69	63	30.4 %
	>=70	46	22.2 %
	Total	207	100 %
2.	Gender		
	Female	94	45.4 %
	Male	113	54.6 %
	Total	207	100 %
3.	Marital Status		
	Married	172	83.1 %
	unmarried	34	16.4 %
	unreported	1	0.5 %
	Total	207	100%
4.	Residency		
	North Gaza	34	16.4 %
	Gaza	77	37.2 %
	Gaza Center	29	14.0 %
	Khan Younis	40	19.3 %
	Rafah	27	13.0 %
	Total	207	100 %
5.	Work		
	Unemployed	16	7.7 %
	Employed	14	6.8 %
	Unreported	177	85.5%
	Total	207	100 %
6.	Education		
	BS.C	8	3.9 %
	Unreported	199	96.1%
	Total	207	100%
The mean of age at diagnosis for the study population is 59.6 years.			

4.1.1.3 Marital Status

As shown in table (4.1), most of study cases have available information about their marital status in the medical records except one case. The study findings show that 83.1% from cases were married at time of diagnosis and 16.4 were unmarried. This percentage of married cases is high if it is compared to many countries in the world. These differences may be refereed to nature of social relationships and culture of Arabic societies.

Lai and Stotler (2010) in their study which was conducted in USA show that 65 % from CRC cases who were diagnosed in 1992-2003 were married at time of diagnosis. Another previous study was conducted in USA have showed that 58.4% from CRC cases were married at time of diagnosis (El-Haddad, 2015). Also low percentage of married CRC cases was showed in previous study was conducted in China with about 55.20% (Li et al., 2015).

4.1.1.4 Residency

According study findings, Gaza governorate records the high number of CRC cases who were diagnosed at the period (2008-2010), and as illustrated in table (4.1) 37.2% of the cases (34 cases) were from Gaza governorate. The least governorate records cases was Rafah with 27 case (13%), while North Gaza, Mid Zone, Khan Younis governorates constituted 16.4%, 14%, and 19.3% respectively. As shown in table (4.2) Gaza governorate had the highest incidence rate with 15.2 per 100000, followed by Khan Younis governorate with rate 14.4 per 100000 while North Gaza governorate had the least incidence rate with 12 per 100000. Incidence rate for colorectal cases per 100000 for Gaza Center and Rafah governorates were 13.4, 13.1 respectively. In term of incidence rate North Gaza had the least incidence among the five GG, but according cases numbers Rafah governorate in the south of GS recorded the least number of cases at study period (2008-2010).

Table (4.2): Incidence rate for study population according Gaza Governorates

Governorate	No. of cases	Population at mid study period (mid-2009)	Incidence rate /100000
North Gaza	34	286,246	12
Gaza	79	519,027	15.2
Mid Zone	29	215,808	13.4
Khan Younis	41	283,286	14.4
Rafah	24	182,449	13.1
total	207	1,486,816	14

4.1.1.5 Work

Information about kind of cases work at time of diagnosis was missed in the majority of the medical records for study population. As shown in table (4.1) 30 medical records out from 207 medical records have information about patients cases work. From 30 cases, 16 are unemployed and 14 are employed at time of diagnosis and there is no any additional information in the medical records. Due to few cases and scarcity of data about the study cases work, the analysis of work effect on the survival rate from CRC cases is not achieved.

4.1.1.6 Education

As shown in table (4.1) information about the educational level of CRC cases is absent in the majority of the medical recodes. There are no any medical records contained any direct information about cases educational level except eight medical records have indirect information about education through type of cases occupation, but it is not enough to conduct the analysis about impact of educational level of cases on survival rate from CRC.

4.1.2 Patient medical profile

Data about the general medical condition for the study cases are collected from the medical records. The main items are checked and analyzed (the presence of co-morbidity, family history of cancer, obesity status, smoking, physical activity status, and diet habits).
Unfortunately no data are found about the diet habits or the physical activity status in the medical records so they are excluded from the analysis.
Regarding the other variables, not all 207 medical records contain data about each variable, but the reported data as general is enough to conduct the survival analysis for theses prognostic variables. Table (4.3) summarized the main finding regarding the cases medical status.

Table (4.3): Distribution of the study cases according selected medical profile items.

	Socio-demographic factors	No. of cases	Percent
1.	Age at diagnosis group		
	<40	13	6.3 %
	40-49	33	15.6 %
	50-59	52	25.1 %
	60-69	63	30.4 %
	>=70	46	22.2 %
	Total	207	100 %
2.	Gender		
	Female	94	45.4 %
	Male	113	54.6 %
	Total	207	100 %
3.	Marital Status		
	Married	172	83.1 %
	unmarried	34	16.4 %
	unreported	1	0.5 %
	Total	207	100%
4.	Residency		
	North Gaza	34	16.4 %
	Gaza	77	37.2 %
	Gaza Center	29	14.0 %
	Khan Younis	40	19.3 %
	Rafah	27	13.0 %
	Total	207	100 %
5.	Work		
	Unemployed	16	7.7 %
	Employed	14	6.8 %
	Unreported	177	85.5%
	Total	207	100 %
6.	Education		
	BS.C	8	3.9 %
	Unreported	199	96.1%
	Total	207	100%
The mean of age at diagnosis for the study population is 59.6 years.			

4.1.2.1 Co-morbidity

Regarding the co-morbidity status, 155 medical records contained information about co-morbidity status of cases. 66 patients (43%) out of 155 patients are found with co-morbidity (HTN, DM, HTN+DM, or others) and 89 cases (57%) have not any other disease rather than CRC. From the 66 cases who have co-morbidity 37.9% had HTN, 33.3% have DM, and 22.7% had DM and HTN together, and 6.1% had other diseases.

In long with other studies, many findings show relatively high rates of co-morbidity among CRC cases. Previous study was conducted in Denmark outlined that about at least one third of cases had co-morbidities (Iversen et al., 2012). Another previous study was conducted in China also showed high percentage of co-morbidities among CRC case, where outlined that about 79% from CRC cases had at least one kind of co-morbidities diseases (Wang, et al., 2016). In the South of the Netherlands, previous study showed that 62% from CRC cases had co-morbidity (Van Leersum, et al., 2013).

4.1.2.2 History of cancer

Patient history data about cancer are found in 129 medical records, 10.8% (14 patients) have history of previous cancer and 89.2% (115 patients) have not history of cancer. While 25.9% from study cases have positive family history of cancer, and 74.1% had negative family history of cancer. This study finding accord with other study conducted in Iran which showed that 24.5% from CRC patients had positive family history of cancer (Karimi et al., 2011). Zell and colleagues study have showed high percentage of positive family history of cancer among CRC cases with about 35 % (Zell et al., 2008).

4.1.2.2 Obesity status

To calculate Body Mass Index (BMI), 207 medical records are checked out for height and weight of patients at time of diagnosis. As overall the researcher found 154 medical records contain data about height and weight of patients.

By using SPSS program, BMI is calculated for the cases who have data about their height and weight. Then the cases were classified to two groups (cases with normal weight-BMI<24.9, and cases with overweight or obesity-BMI>25). The results are as the follow, 66 patients (42.8%) were with normal weight, while 88 patients (57.2%) were over-

weighted or obsess at time of CRC diagnosis (Table 4.3). Relatively these findings accord with Yuan and colleagues study which showed that about the BMI for about 61% of CRC cases were ≥25 kg/m2 at time of CRC diagnosis (Yuan et al., 2013).

4.1.2.3 Smoking

About smoking, as shown in table (4.3) 144 medical records have data about it. The study findings show that 88 patients (61.1%) are non-smoker, while 56 patients are smoker (38.9%). These results are more than results from previous study was conducted in Iran which showed that only 22.4% from CRC patients were smoker at time of diagnosis (Karimi et al., 2011). Also this study results is more than previous study was conducted in China which showed that only 14% from CRC cases were smoker (Yuan et al., 2013). In USA, previous study outlined that about 34% from CRC cases were former or current smoker at time of CRC, these results also lower than current study results with about 4%. These high rates of smoking among the study cases may be more attention to discover the causes behind that.

4.1.3 Tumor characteristics

4.1.3.1 Histological type

Analysis of available data for 201 cases who have data about histological types of colorectal carcinomas show that the most common histological type is usual adenocarcinomas (Non-mucinous) with 86.7%. While mucinous adenocarcinomas accounted 11%, and 2.3% for other histological types (Table 4.4). Compared to other studies, O'Connell and colleagues (2004) have showed similar findings where the most frequent histological type among cases was adenocarcinomas 87.4%, while 11.6% from cases had mucinous adenocarcinoma (O'Connell et al., 2004). Also relatively similar findings in Al-Nsour study, which showed that 84.5% from colorectal carcinomas are adenocarcinomas and 7.8% are mucinous adenocarcinomas (Al-Nsour, 2014). In China, previous study illustrated that adenocarcinomas and mucinous adenocarcinomas accounted 79.2 % and 16.8% respectively (Yuan et al., 2013).

4.1.3.2 Tumor grade

As illustrated at table (4.4), 185 medical records had information about tumor grade, 14 cases were found with tumor grade 1 (7.6%), 140 cases with tumor grade 2 (75.7%), 29 cases with tumor grade 3 (15.7%), and only 2 cases with tumor grade 4 (1%).

The study results are in line with a previous study was conducted in Jordan which has showed that 62.7% from CRC cases with moderate grade and 14.9 with poor grade (Al-Nsour, 2014). Another previous study conducted in China showed relatively similar findings where well, moderate, and poor differentiation grade accounted 25.6%, 43.9%, and 20.1% respectively (Yuan et al., 2013).

In USA, previous study demonstrated that 67.8% from CRC cases has low grade tumors, while 19.4% have high grade tumors (O'Connell et al., 2004)

4.1.3.3 Stage at diagnosis

The study findings regarding the tumor stage at diagnosis show that 190 patients out of 207 patients have enough data about stage of CRC at diagnosis in the medical records. The study results outline that six patients (3.2%) were diagnosed with stage I, 67 patients (35.2%) with stage II, 40 patients (21.1%) with stage III, and 77 (40.5%) patients were diagnosed with stage IV. It is mean that more than the half of patients (61.6%) are diagnosed with advanced stages (III + IV) which directly poor prognosis of CRC in GS. In the other hand these results may give good space for future improvement by decreasing the rate of discovering cases with advanced stages.

In line with other studies, previous study was conducted in Jordan revealed that low percentage of patients diagnosed with stage IV compared to the current study 24%, 40.5% respectively. Even though it showed that stage III and IV accounted 82.5% from all cases which is more than the current study finding which showed that these stages accounted 61.6% from all cases (Al-Nsour, 2014). In the Netherlands, previous study showed that only 22% from CRC cases presented with stage IV lower than current study, while 25% presented with stage III, 33% stage 2, and 14% stage I (Lemmens et al., 2010).

4.1.3.4 Tumor site

Data about tumor site are found in 197 medical records. Analysis of findings showed that Left-sided colon are the most common site for developing CRC with 52.3% of all cases. It

followed with rectal cancer with 25.9%, while right-sided colon accounted only 21.9% from all 197 patients.

Relatively agreed with these findings in Al-Nsour study where showed that the rectum cancer constituted 36.5 % and colon cancer 63.5 % from all CRC cases (Al-Nsour, 2014). Another previous study have provided relatively same results compared to the current study in Qiu and colleagues study where outlined that the colon cancer and rectal cancer accounted 77.9%, 22.1% respectively (Qiu et al., 2015).

Contradicted with the study results, previous study was conducted in the South Korea which showed that the rectal cancer accounted slightly more than the half of all colorectal tumors about 51.8%, where as in this current study the rectal cancer accounted only 25.9% from all colorectal tumors (Kim et al., 2000).

Table (4.4) Distribution of the study cases according selected tumor characteristics

	Socio-demographic factors	No. of cases	Percent
1.	Age at diagnosis group		
	<40	13	6.3 %
	40-49	33	15.6 %
	50-59	52	25.1 %
	60-69	63	30.4 %
	>=70	46	22.2 %
	Total	207	100 %
2.	Gender		
	Female	94	45.4 %
	Male	113	54.6 %
	Total	207	100 %
3.	Marital Status		
	Married	172	83.1 %
	unmarried	34	16.4 %
	unreported	1	0.5 %
	Total	207	100%
4.	Residency		
	North Gaza	34	16.4 %
	Gaza	77	37.2 %
	Gaza Center	29	14.0 %
	Khan Younis	40	19.3 %
	Rafah	27	13.0 %
	Total	207	100 %
5.	Work		
	Unemployed	16	7.7 %
	Employed	14	6.8 %
	Unreported	177	85.5%
	Total	207	100 %
6.	Education		
	BS.C	8	3.9 %
	Unreported	199	96.1%
	Total	207	100%
The mean of age at diagnosis for the study population is 59.6 years.			

4.1.3.5 Distant metastasis status

According the study findings 78 cases out from 207 cases (37.7%) have metastasis to distant organs at time of diagnosis, and is added to them ten cases have developed distant metastasis during treatment journey to make the total number of distant metastatic cases 88 cases with 42.5% from all study cases.

Also study findings reveal that 65 cases out from 88 cases who have distant metastasis, have liver only metastasis, and is added to them 16 cases had liver metastasis concomitant with other metastasis. So the overall percentage of liver metastasis for CRC cases who were diagnosed in 2008-2010 with stage IV is 91.8% from all cases. While 4.5% from cases had lung only distant metastasis and 3.4% with brain only metastasis (Table 4.5).

Previous study was conducted in USA showed that about 31% from distant metastasis are developed after CRC diagnosis, while 69% at time of diagnosis. It added that the liver is the most common site for metastasis with about 68.5% all of metastatic sites (Patanaphan et al., 1993).

Table (4.5) Distribution of CRC cases (2008-2010) according distant metastasis status

	No. of cases	% percent
1. Metastatic status at diagnosis		
non metastatic case	115	55.6 %
metastatic case	78	37.7 %
Unknown	14	6.8 %
Total	207	100 %
2. Developing distant metastasis during treatment		
Yes	10	8.7 %
No	105	91.3 %
Total	115	100 %
3. Distant metastasis to liver only		
Yes	65	73.8 %
No	23	26.2 %
Total	88	100 %
4. Distant metastasis to liver concomitant with other mets.		
Yes	16	18 %
No	72	82 %
Total	88	100 %
5. Distant metastasis to lung only		
Yes	4	4.5%
No	84	95.6 %
Total	88	100%
6. Distant metastasis to brain only		
Yes	3	3.4%
No	85	96.6%
Total	88	100%

4.1.4 Medical management of colorectal cancer in the Gaza Strip.

4.1.4.1 Diagnostic process

- **Diagnostic delay**

Diagnosis delay was defined previously as the condition if the interval to diagnosis exceeds 3 months, where the reviewing of the medical records of the study cases shows that 121 medical records had precise information about time of signs and symptoms related to CRC were experienced by the study cases.

The study findings show 61.9% from the study cases were diagnosed within one month from initiation of signs and symptoms, 16.5% within one month to three months, and 21.6% were diagnosed after three months (Table 4.6).

Table (4.6): Distribution of the study cases according signs and symptoms at diagnosis.

	No. of cases	% percent
1. The presence of signs and symptoms at time of diagnosis		
Yes	139	100%
No	0	0%
Total	139	100%
2. Bleeding per rectum		
Yes	88	63.3%
No	51	36.7%
Total	139	100%
3. Abdominal pain		
Yes	49	35.3%
No	90	64.7%
Total	139	100%
4. Intestinal obstruction		
Yes	17	12.2%
No	122	87.8%
Total	139	100%
5. Bowel habits changes diarrhea constipation		
Yes	22	15.8%
No	117	84.2%
Total	139	100%
6. Anemia		
Yes	26	18.7%
No	113	81.3%
Total	139	100%
7. Duration of signs and symptoms before diagnosis		
Less than one month	86	61.9%
More 1 m up to 3 m	23	16.5%
More than 3 months	30	21.6%
Total	139	100%

- **Main Signs and symptoms related to CRC**

Data about the presence of signs and symptoms at time of diagnosis was found in 139 medical records. These 139 patients (100%) presented with signs and symptoms at time of diagnosis. The researcher suggested that, it is directly refereed due to absence of CRC

screening programs in GS, and it is may indicated for low public awareness and concerns of CRC in GS.

The most frequent signs and symptoms among the 139 patients are as the following: The commonest is bleeding per rectum with 63.3% from all patient, then abdominal pain with 35.3%, then anemia 18.7%, followed by bowel habits changes (diarrhea/constipation) with 15.9% and intestinal obstruction with 12.2 % from all patients (Table 4.6).

The study findings agree with Macrae and colleagues study which showed that 34 % from CRC cases are presented with abdominal pain at time of diagnosis which accords with the study findings. While regarding bleeding per rectum, the current study showed results disagree with Macrae and colleagues study which outlined that only 37% of cases are presented bleeding per rectum. In the other hand, this current study showed slightly lower anemia percentage compared to the same study 18.7%, 23% respectively (Macrae et al., 2016).

Also another previous study conducted in China agreed in some signs and symptoms and disagreed with others. It showed similar findings regarding per bleeding rectum with 65 % where the current study records 63.3%. The same study disagreed regarding intestinal obstruction which showed only 5.2% have this signs from all cases which is lower than the current study ,while it showed higher percentage of bowel habits changes among the cases with 36% more than current study with about a double (Yuan et al, 2013).

Table (4.7): Distribution of the study cases according treatment process

	No. of cases	% percent
1. The presence of signs and symptoms at time of diagnosis		
Yes	139	100%
No	0	0%
Total	139	100%
2. Bleeding per rectum		
Yes	88	63.3%
No	51	36.7%
Total	139	100%
3. Abdominal pain		
Yes	49	35.3%
No	90	64.7%
Total	139	100%
4. Intestinal obstruction		
Yes	17	12.2%
No	122	87.8%
Total	139	100%
5. Bowel habits changes diarrhea constipation		
Yes	22	15.8%
No	117	84.2%
Total	139	100%
6. Anemia		
Yes	26	18.7%
No	113	81.3%
Total	139	100%
7. Duration of signs and symptoms before diagnosis		
Less than one month	86	61.9%
More 1 m up to 3 m	23	16.5%
More than 3 months	30	21.6%
Total	139	100%

4.1.4.2 Treatment process

4.1.4.2.1 Treatment types

Stage at diagnosis is the main factor for defining the treatment model for CRC. As general the study finding show that 83% from cases underwent surgical intervention, 82.6% have chemotherapy, 16.4% have radiotherapy, and 38% had palliative care.

Data analysis regarding the treatment types shows that 26 (13.70) underwent surgery only and those were diagnosed with stage 1, 24 (12.6%) cases have chemotherapy only, 105

(55.5%) cases underwent surgery beside chemotherapy, 27 (14.2) cases underwent surgery beside the chemotherapy and radiotherapy as shown in table (4.7).

4.1.4.2.2Treatment delay

- **Surgery delay**

Data about date of surgery is found in 156 medical records, where the data analysis shows that the mean for waiting time from date of confirmed diagnosis to surgery was 32 day (SD 68.1), while more than 78% from patients who underwent surgery, the surgery was done in the first month of diagnosis and about half of them have the surgery within fourteen days from time of diagnosis. Regarding the surgery delay the study findings show that 21.8 % from the study cases have surgery delay where the surgery underwent after 31 days from date of confirmed diagnosis.

- **Chemotherapy delay**

About waiting time to the chemotherapy initiation after surgery only 52% from cases have chemotherapy within the first month from surgery, 23% within one month to two month, while about 25% time waiting for chemotherapy exceeded 3 months from date of surgery. This means that about quarter of the study cases have chemotherapy delay.

These results are better than what shows in Chan and colleagues study which revealed that more than half of patients failed to have chemotherapy within the first two months from date of surgery. Study findings are on line with previous study results which was conducted in Jordan which showed that about 77.9% from CRC patients underwent surgery within the first month from the diagnosis (Al Nsour, 2014).

4.1.4.2.3 Treatment places

Regarding the main treating hospitals in GS, the study findings show that Al-Shifa hospital is the main hospital for 130 cases (62.8%), while 77 cases (37.2%) are treated at the European Gaza hospital.

Regarding the surgery place, the study findings show that 79.1% from the cases who needed the surgery, have it inside GS, while 20.9 % outside GS.

Regarding chemotherapy place, the studying findings show that about 75% from the cases who need the chemotherapy have it inside GS, while 25% have it outside GS.

In the other hand, the radiotherapy services are not available inside GS, so the patients who need the radiotherapy are referred abroad.

4.1.5 The overall observed survival rate

Previously in this study, the overall observed survival (OS) rate is defined as the percentage of people with a specific type and stage of cancer who have not died from any cause during a certain period of time after diagnosis. In this current study, OS rate was calculated for all study cases (207 CRC cases diagnosed at period 2008-2010) at different time periods from 1-years to 5-years as illustrated at table (4.7). The overall observed OS rate was calculated for each year regardless of any prognostic factors that may be affect on the survival rate such as stage at diagnosis, tumor grade, socio-demographic factors, or management related factors. The best survival rate is seen at the end of first year with 85%, and it gradually declines through years to reach the lowest survival rate at 5-years with 45.1% as illustrated in table (4.7).

Table (4.8) Calculation of observed overall survival rate for the entire study population

Time	1-year	2-year	3-year	4-year	5-year
Alive	171	142	127	116	94
Dead	36	65	80	91	113
Total	207	207	207	207	207
Calculation	171/207*100	142/207*100	127/207*100	116/207*100	113/207*100
Overall Survival rate	82.6%	68.6%	61.4%	56%	45.1%

This trend agrees with the majority of previous studies which showed that the survival rates decline dramatically through years from time of diagnosis (Al-Nsour, 2014; Yuan et al., 2013; Majek et al., 2012). Study findings showed that overall 5-years survival rate for colorectal cancer cases who were diagnosed at the period 2008-2010 and they were eligible for the study was 45.1%. Compared these results to other regions, shows that 5-years survival rate for CRC cases at GS was poorer than many countries in the world and better than few countries (Figure 4.1). In Jordan 5-years survival rate for colorectal cancer cases

was 57.7 % for CRC cases diagnosed at the period 2003-2007 (Al-Nsour, 2014). Previous study In Malaysia, revealed that 5-year survival rate was 59.1% (Hassan et al., 2016). In Iran, there were contraindicated studies, in Moradi and colleagues have showed that the 5-years survival rate was 41% (Moradi et al., 2009), while where at another study 61% (Moghimi-Dehkordi et al., 2008).

Compared with developed countries, the overall OS rate in GS is poorer than all the developed countries. As example the overall 5-year survival rate was 65.2% in USA (O'Connell et al., 2004), In Korea, 61 % (Kim, et al., 2000), In the Netherlands 52% (Van Steenbergen et al., 2010).

CONCORD-2 study provided survival statistics regarding CRC for many countries and outlined that the 5-years survival rate for CRC cases who were diagnosed at period 2005-2009 in Canada, Finland, the Netherlands, Norway, Sweden, and the USA was between 62% to 65% (Allemani et al., 2015). Furthermore Organization for Economic Co-operation and Development-OECD (2015) have demonstrated that Korea and Israel have the best survival rates among OECD countries which reach over 70% (OECD, 2015).

In the other hand study results are better than few countries in Asia like India, with rate 31.2% (Moghimi-Dehkordi, and Safaee, 2012), While it is relatively similar to the overall 5-year survival rate in Saudi Arabia which was 44.6% for the period 1994-2004 (Alsanea et al., 2015).

4.2 Inferential analysis

4.2.1 Observed survival estimates by using Kaplan-Meier method.

4.2.1.1 Overall survival estimates

The total number of the included cases in this current study is 207 CRC cases who were diagnosed at the period 2008-2010 and they met the inclusion criteria for the study (Table 4.8). Each case was followed for complete five years in order to be able to estimate 5-years survival rate by using Kaplan-Meier methods. So cases who were diagnosed in 2008 followed to end of 2012, cases were diagnosed in 2009 followed to end of 2013, while cases who were diagnosed in 2010 followed to end of 2014. As general the start time point for follow up was 1/1/2008 and end time and last contact with cases was 31/12/2014. Survival time was calculated by using Kaplan-Meier method by months and years for all study cases from date of diagnosis till date of death or censoring. By using the Kaplan-Meier test, the 5-year survival rate for CRC patients was found about 45% as shown in

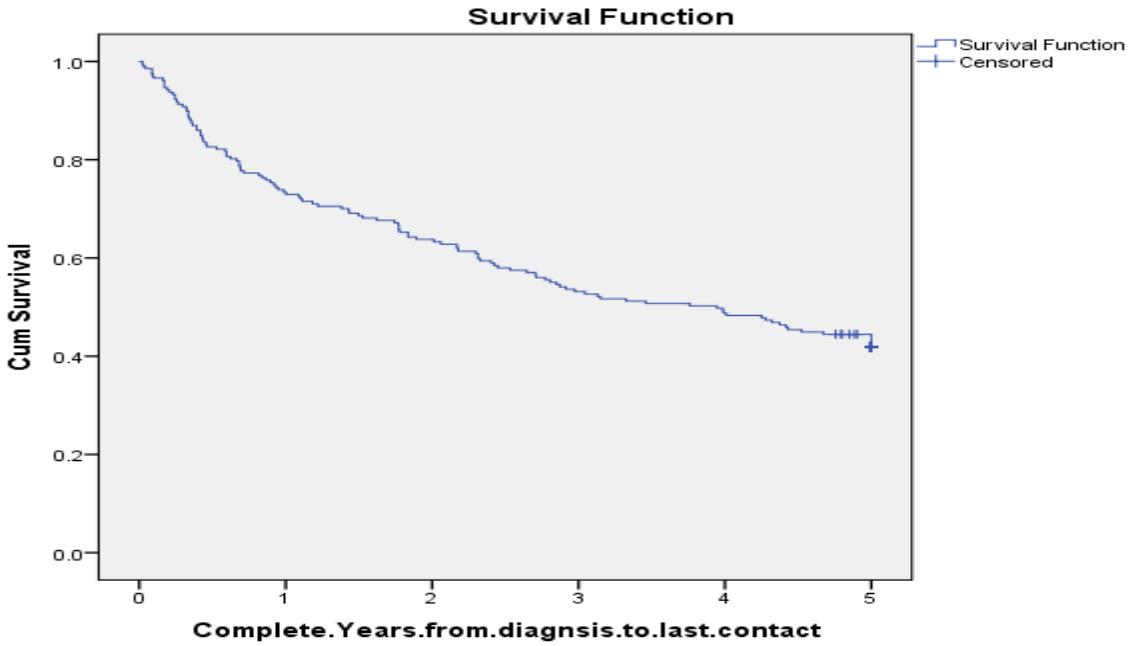
figure (4.2). While as shown in table (4.9) the mean survival time by months was 37.1months (SE=1.65), and by years was 3.1 years (SE=0.15).

These results relatively are lower than many countries over the world as literature shows such as previous study in Iran showed that the mean survival time for CRC cases was 56.5 ±1.9 months (Karimi, et al., 2011). While the current study results showed that median survival time was about four years, it also lower than median survival time in van Eeghen and Colleagues study (2015) which conducted in the Netherlands, where was 5.13 years (van Eeghen et al., 2015).

Table (4.9): Kaplan-Meier survival analysis for all study cases/observed survival rate

Time	1-year	2-year	3-year	4-year	5-year
Alive	171	142	127	116	94
Dead	36	65	80	91	113
Total	207	207	207	207	207
Calculation	171/207*100	142/207*100	127/207*100	116/207*100	113/207*100
Overall Survival rate	82.6%	68.6%	61.4%	56%	45.1%

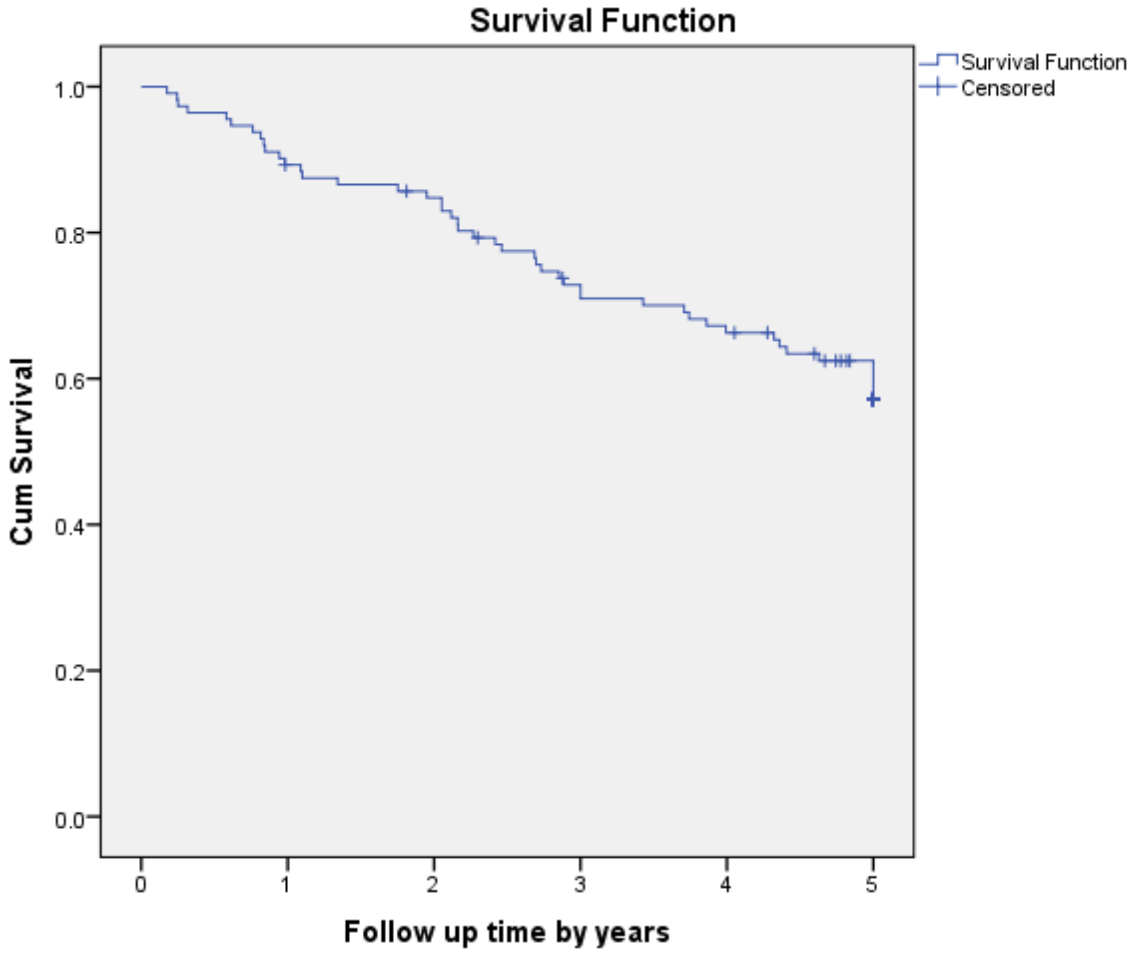
Figure (4.2): Kaplan-Meier survival curve for all CRC cases included in the study (2008-2010) in GS.



4.2.1.2 Disease Free Survival (DFS) estimates for non-metastatic cases

DFS rate was determined for 113 cases who were diagnosed with all stages except stage IV and they have precise data about date of surgery, disease recurrence, and vital status information. As shown at table (4.8) the best DFS rate was at 1-year with 91%, while 5-years DFS rate was 61% (Figure 4.3). These results were relatively low compared to many studies in the literature especially in developed countries. In Grande and colleagues study showed that 5-years DFS rate was 76.7% in Italia (Grande et al., 2013). Another study conducted in the South Korea showed that 5-years DFS rate was 84.4% (Park et al., 1999). But the current study results showed DFS rate in GS was better than DFS rate in Iran where was about 57% (Gunderson et al., 2008).

Figure (4.3): Kaplan-Meier curve for disease free survival estimates/non- metastatic cases

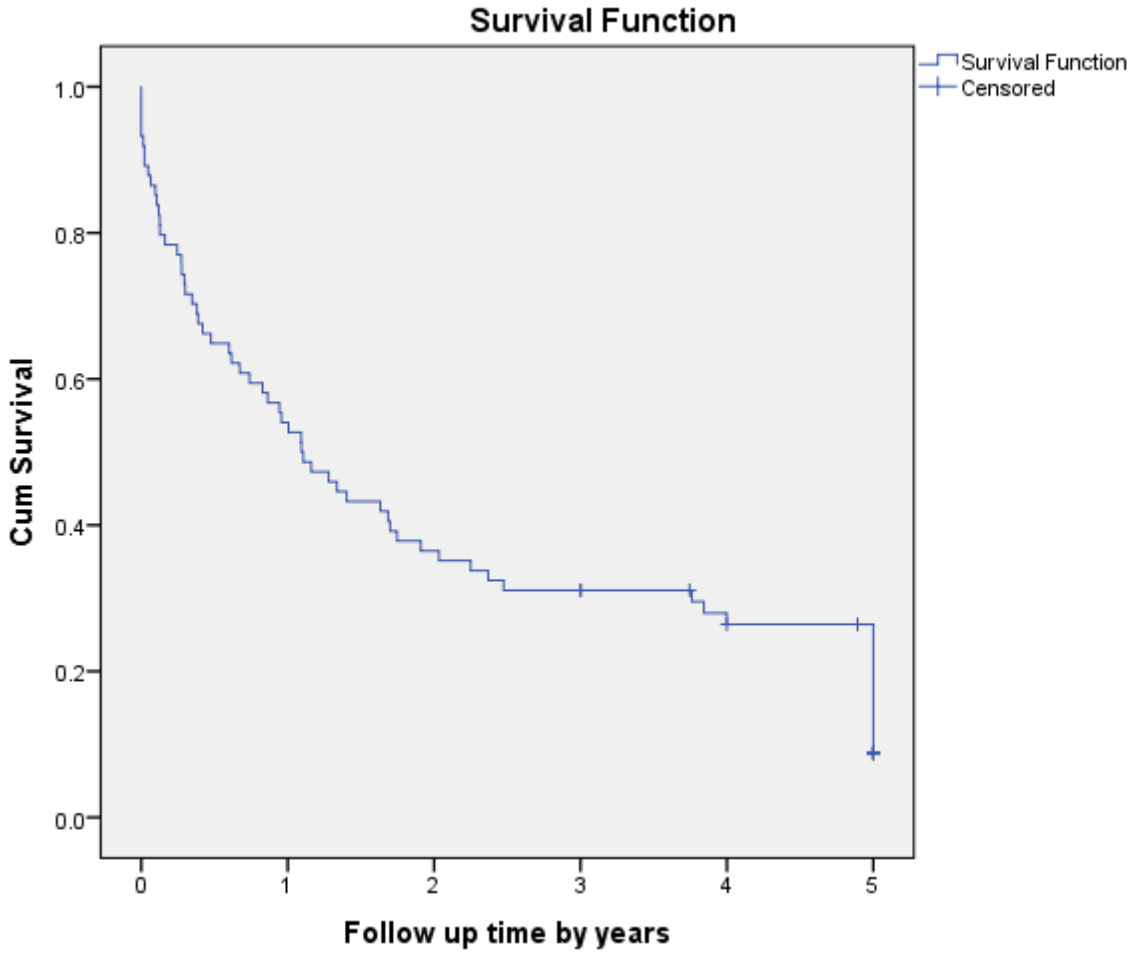


4.2.1.3 Progression Free Survival (PFS) estimates for metastatic cases

Progression Free Survival (PFS) rate was calculated for metastatic cases which were 88 cases and they have enough data about date of start chemotherapy, date of disease progression or the second chemotherapy cycle, and the vital status data.

PFS rate at 1-year survival rate was 54% and 5-years PFS rate was 28% as shown in table (4.9) and illustrated in figure (4.4).

Figure (4.4): Kaplan-Meier curve for Progression free survival estimates of metastatic cases



4.2.2 Effect of patient related factors on overall survival rate

4.2.2.1 Survival analysis according age group

The study cases are divided into three groups according to age at diagnosis: age group-1 <50 years, age group-2 (50-69 years), and age group-3 ≥ 70 years (Figure 4.1).

Kaplan-Meier test by age group shows that the age group-1 have the best mean survival time among the three age groups with about 43 months followed by age group-2 with survival months means about 36.3 months, while the poorest mean survival time is among age group-3 with 32.9 months (Table 4.10).

These survival differences are not statistically significant, but as the overall young age at diagnosis correlate with better survival which is clear in figure (4.5). The literature shows contradicted results for different previous studies. From one hand, there are various studies agreed with current study results where have showed that young age at time of diagnosis

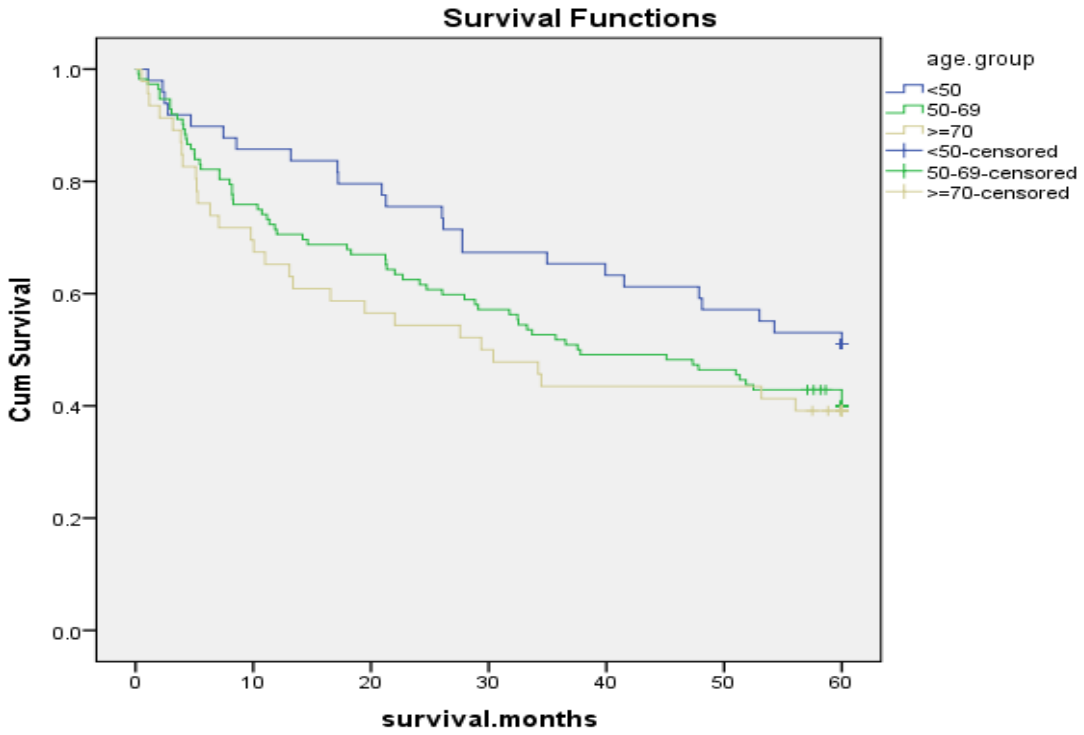
correlated with better survival rate (Jiang et al., 2016; McKay et al., 2014; Steele et al., 2014; Kemppainen et al., 1995).

In the other hand, the current study results contraindicate with results in previous studies such as in Chan and colleagues study where showed that CRC patients less than 40 years olds had poorer survival rate compared with patients >40 years old ($p < 0.05$) (Chan et al, 2010). Also Fu et and colleagues study shows contraindicated results compared with this current study results, where outlined that CRC patients who their age below 35 years old had lower overall survival rate than older patients (Fu et al., 2014). In addition to that previous study In China, showed that there were statistically differences in survival rate among different age group of patients. It showed that age group (60–74) had better survival rate (Yuan et al., 2013). That disagreed with current study results but it agreed with that the poorest survival rate was among age group >75 years old.

Table (4.10): Kaplan-Meier survival analysis by selected patient related factors

Variable	Subgroups	Total no.	Mean survival time	Median survival time	5-years survival rate (%)	Log rank test	
						χ^2	Sig.
Age group	<50	49	42.9		55	2.91	0.233
	50-69	112	36.2	37.5	43		
	≥70	46	32.8	29.3	40		
Gender	Male	113	38.8	56.0	50	1.24	0.265
	Female	94	35.0	33.2	40		
Marital Status	Married	172	37.8	47.8	48	.41	0.518
	Unmarried	34	32.4	32.4	41		
Residency	North Gaza	34	39.3	37.8	58	3.25	0.516
	Gaza	79	37.8	34.4	42		
	Mid Zone	29	38.5	28.8	50		
	Khan Younis	41	32.0	52.5	37		
	Rafah	24	38.3	37.8	53		
Co-morbidity Status	YES	66	28.6	20.9	35	4.23	0.040*
	NO	89	38.3	39.9	43		
Family History of cancer	YES	34	29.9	22.0	36	1.156	0.282
	NO	97	37.3	41.5	43		
classification of BMI	Normal weight BMI <25 kg/m2	66	33.7	30.4	42	4.055	0.044*
	Overweight/ Obese BMI ≥25 kg/m2	88	41.4	-	58		
Smoking	Non-Smoker	88	40.0	-	53	9.204	0.002*
	Smoker	56	28.0	21.3	30		
*Statically significant							

Figure (4.5): Kaplan-Meier survival curves for cases by Age group



4.2.2.2 Survival analysis according Gender

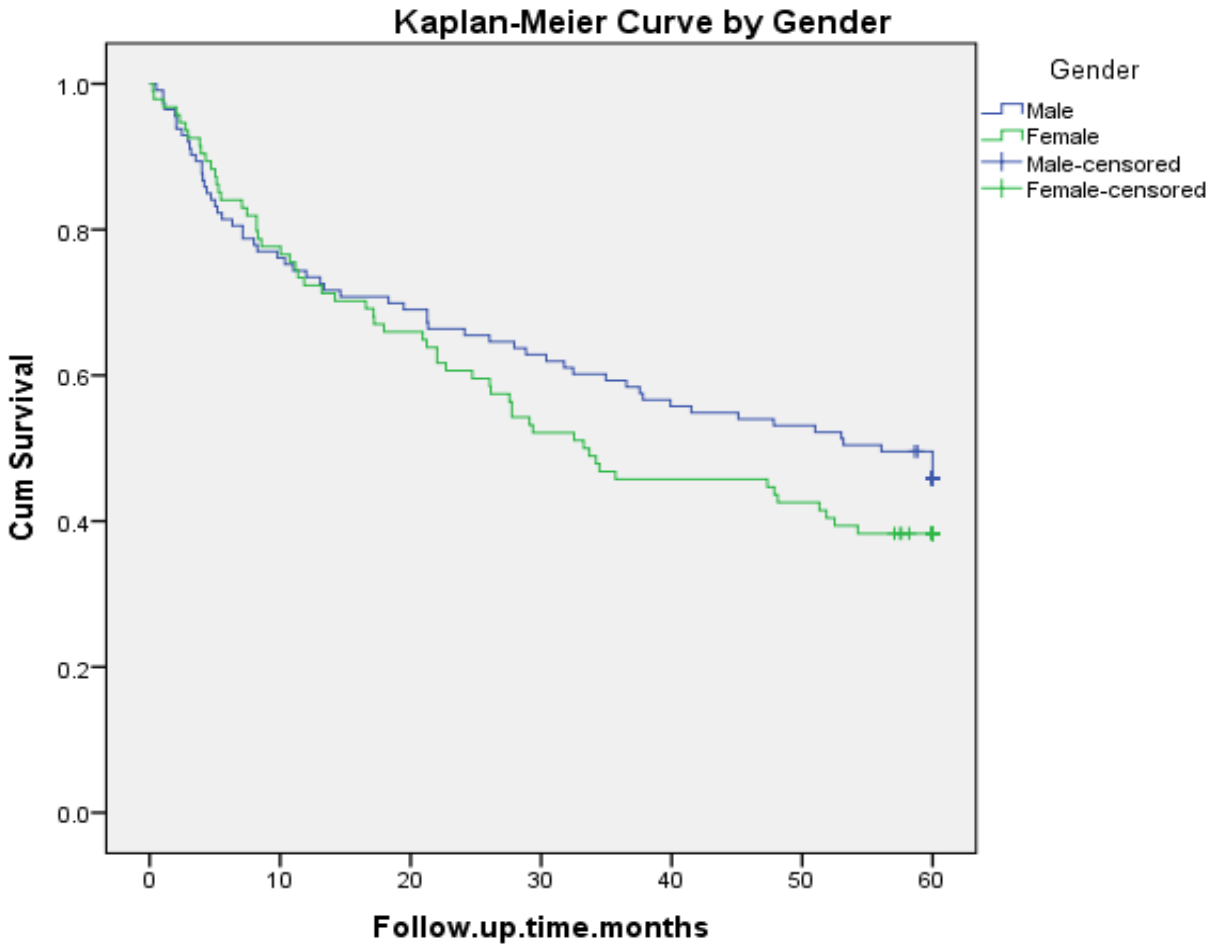
Kaplan-Meier test is used to analyze the survival rates for CRC cases according gender. The test result shows that the male cases have slightly longer survival time than female cases as shown at table (4.10) and figure (4.6).The mean survival time for male cases was about 39 months, while for female was 35 months.

Theses Survival differences between male and female cases are not statically significant (p-value =0256). Even though these survival differences between the female cases and the male cases may referred to many factors such as the culturally barriers for female to seek medical help for bowel diseases in early stages, and the poor health awareness among female rather than male cases in GS.

These findings disagreed with many global studies which show that the female cases have better survival rates from CRC than the male cases. For example, previous study conducted in Jordan showed slightly higher survival rates among females even though these finding were not statically significant (p-value=0.1698) (Al-Nsour, 2014). Another study conducted in China showed that there were no statically significant survival differences between male and female patients, but in the opposite of this current study the female patients in China had better survival rate that male patient about 2 %. (Yuan et al., 2013).

In Korea, female patients had 5-years survival rate about 3% better than male cases (P-value=0.26) (Kim et al., 2000).

Figure (4.6): Kaplan-Meier survival curves for cases by gender



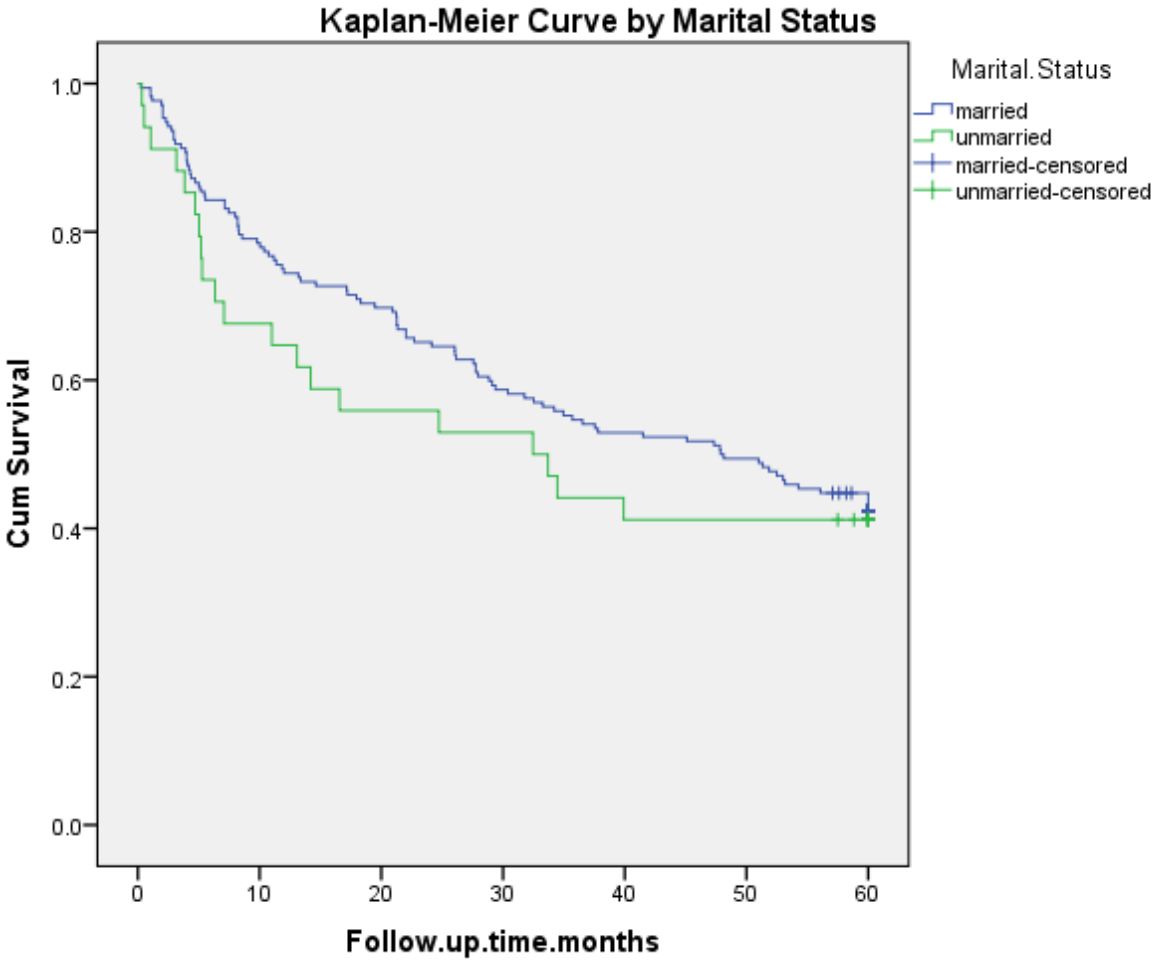
4.2.2.3 Survival analysis according to Marital Status

Kaplan-Meier method is used to investigate the impact of marital status at diagnosis on survival rate from CRC. As shown in figure (4.7) the survival benefits go to the married cases, the mean survival time by months for the married cases was 37.8 months (3.2 years), while for the unmarried cases survival 32.5 months (2.7 years).

These survival differences are not statistically significant (P-value =0.518). These findings are compatible with many previous studies which showed that the married cases have better survival than the unmarried cases (Qingguo et al., 2015; Shi et al., 2016; Wang et al., 2011).

The researcher suggested that the married patients have more chance to discover CRC as early as possible, seek medical help quickly, beside the emotional and psycho-social support for the married cases rather than unmarried.

Figure (4.7): Kaplan-Meier survival curve by Marital Status



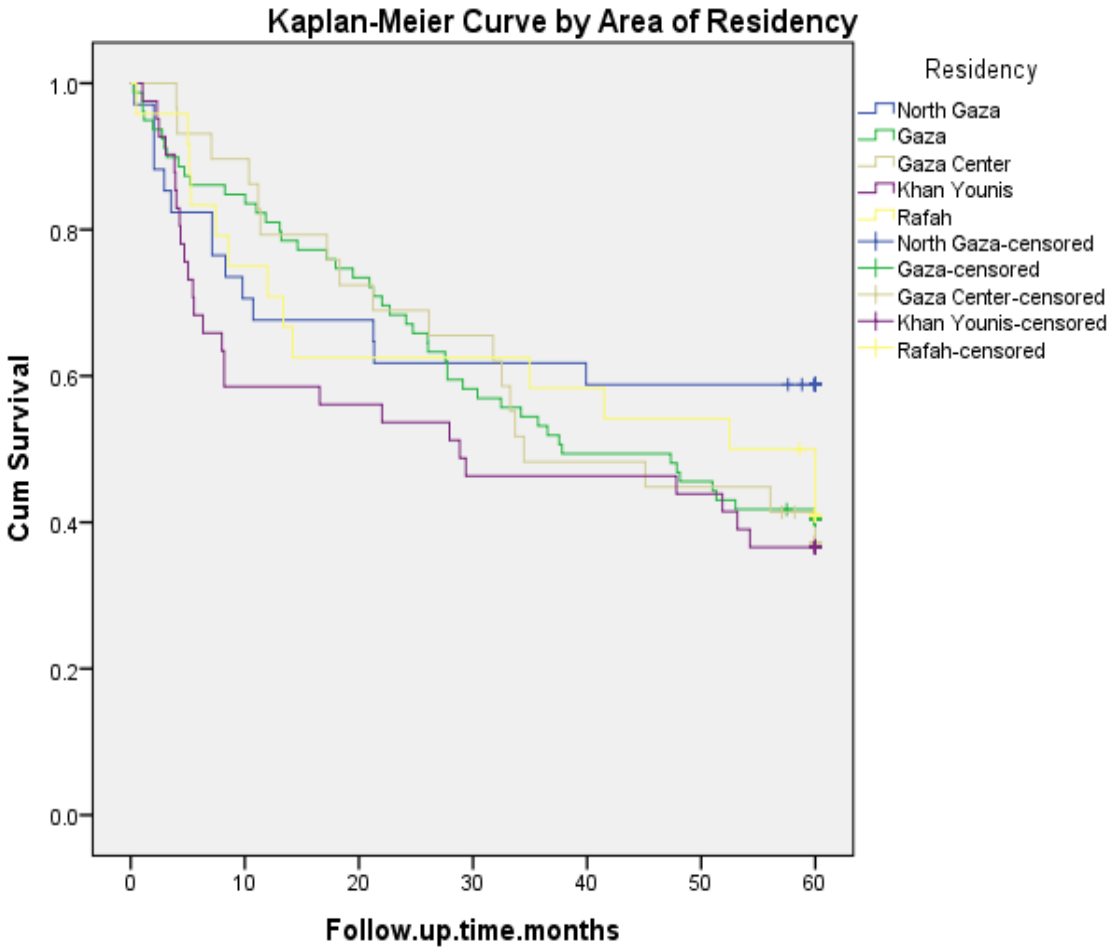
4.2.2.4 Survival analysis according to place of residency for all study cases

The study cases are divided by place of residency to five groups according GG. Then Kaplan-Meier test is used to analyze the survival data for the study cases according place of residency. As illustrated in table (4.10) the cases who are resident in North Gaza have better mean survival time with 39 months while the least mean survival time among the cases from Khan-Younis Governorate.

These Survival differences between GG are not statistically significant. In line with other previous studies, many studies showed survival differences between the same population

according their place of residency within the country borders. In Al-Nsour study which was conducted in Jordan outlined that the cases who were living in the central part of Jordan have the highest survival rate compared to the cases who were living in the northern and southern regions (Al-Nsour, 2014).

Figure (4.8) Kaplan-Meier survival curves by place of residency

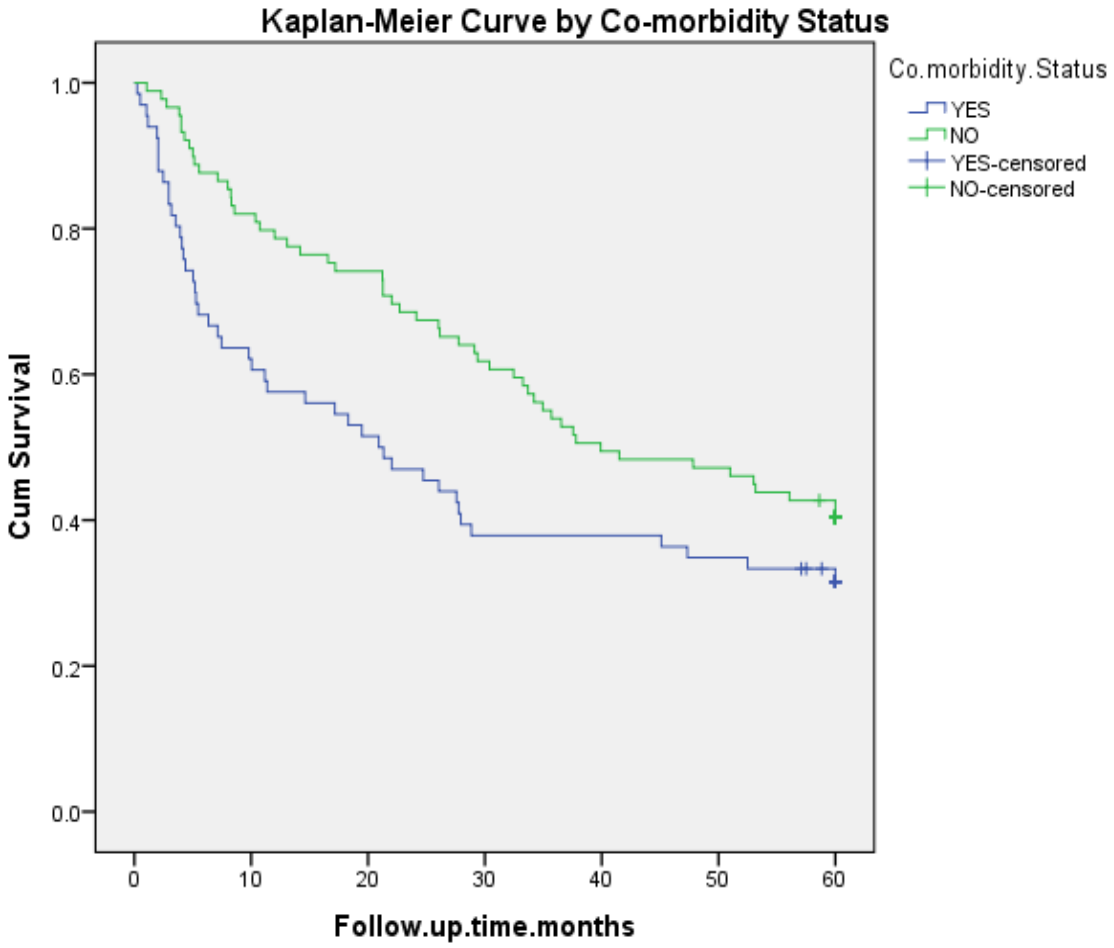


4.2.2.5 Survival analysis according co-morbidity status of cases.

Kaplan-Meier test is used to analyze of co-morbidity impact on survival rate among CRC cases. Test results show statistically significant survival differences between the cases with co-morbid disease and the cases without co-morbid diseases where the P-value is 0.040 and the cases without co-morbidity have mean survival time more than the cases with co-morbidity with about 8 months as shown in table (4.10) and figure (4.9).

In general, the majority of previous studies show that the cancer patients with co-morbidity have poorer survival rates than those without co-morbidity (Sogaard et al., 2013). Previous meta-analysis study has showed that CRC patients with diabetes have poorer survival rate than those without diabetes (Mills et al., 2013). Else previous study revealed that patients who had co-morbidity before time of CRC diagnosis had poorer survival rate than those without co-morbidity (Shack et al., 2010).

Figure (4.9) Kaplan-Meier survival curves by co-morbidity status



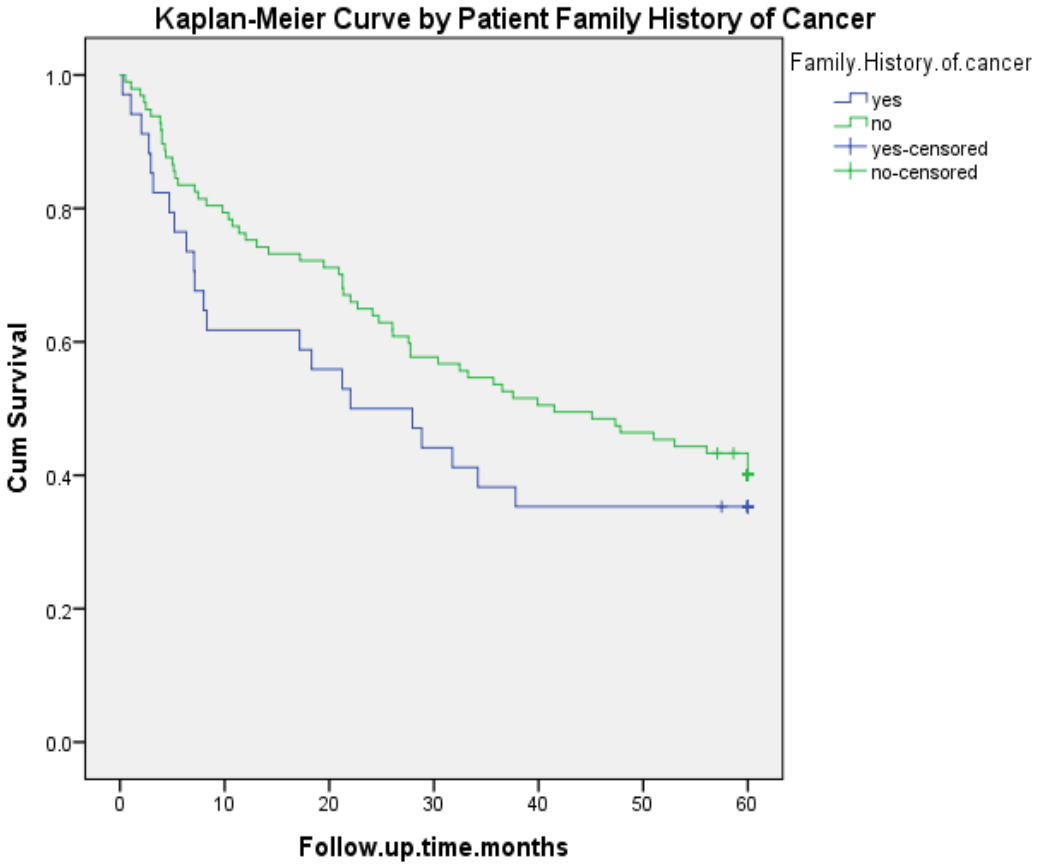
4.2.2.6 Survival analysis according Patient's family history of cancer

Kaplan-Meier method is used in order to analyze the impact of patient's family history of cancer on survival data from CRC and as illustrated in table (4.10) the cases with negative family history of cancer have mean survival time (29.9 months) better than the cases with positive family history of cancer (figure 4.10).

These survival differences are not statically significant where the log rank test shows the P-value= 0.282.

Contraindicated with these findings, previous study was conducted in China have showed that the patient with positive history family cancer have better survival rate than patients with negative family history of cancer. (Yuan et al., 2013).

Figure (4.10) Kaplan-Meier survival curves for cases by patient family history of cancer



4.2.2.7 Survival analysis according Body Mass Index-BMI of the cases.

Kaplan-Meier method was used in order to analyze the impact of obesity (Based on BMI scale) on the survival data for the study cases. The entire study population was divided according BMI to two subgroups. The first group is CRC cases who were diagnosed with BMI <25 kg/m2 (Normal weight), while the second group is those who were diagnosed with BMI ≥25 kg/m2 (Over weight/Obese).

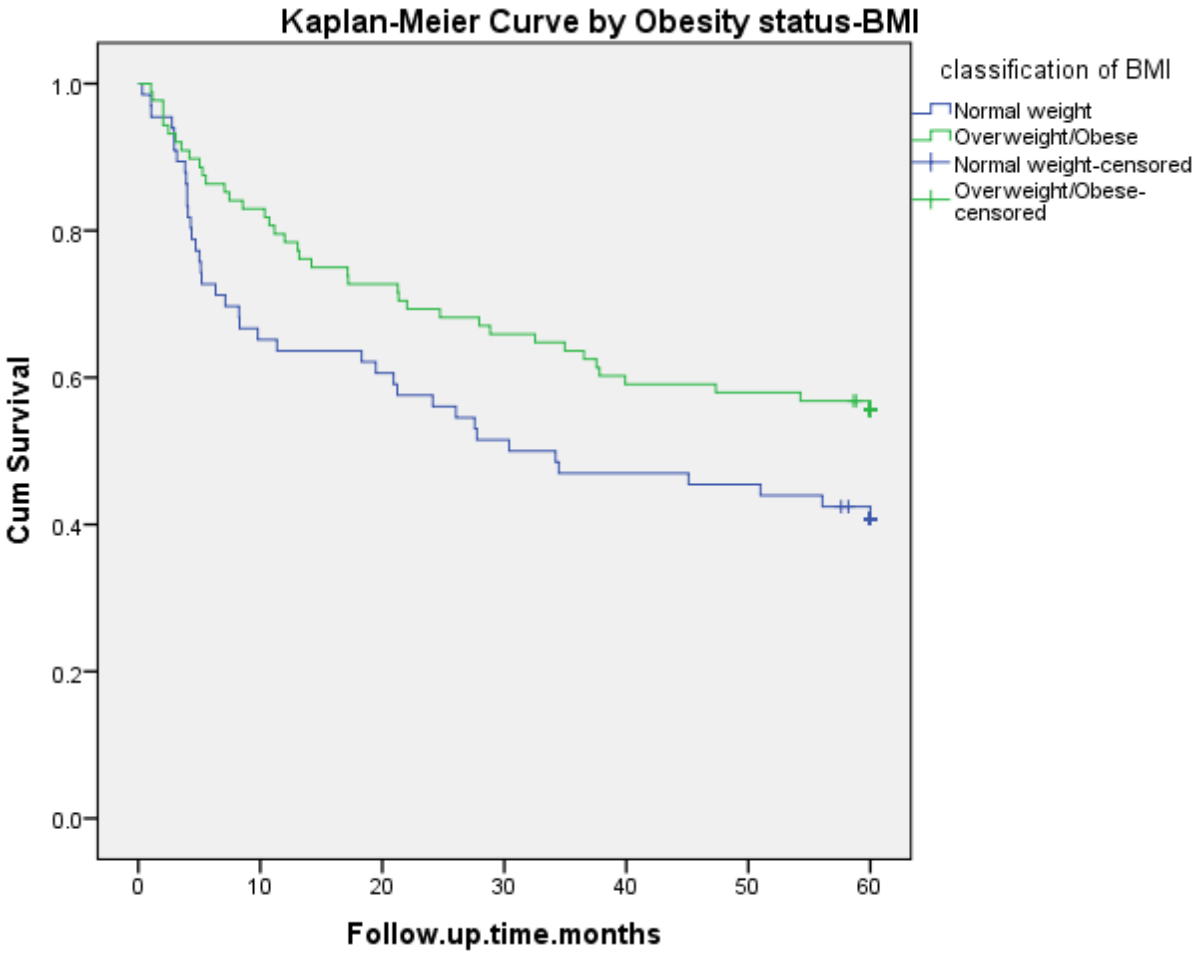
As shown in table (4.10) mean survival time for the cases with normal weight at time of diagnosis (33.4 months) is poorer than the mean survival time for the cases with overweight/obesity at time of diagnosis (41.4 months).

These survival differences are statically significant, where the P-value was 0.044 according the log rank test result. These results accord with Hines and colleagues study which was conducted in USA, where showed that the African American who were overweight/obese have better survival rates than underweight cases.

In the other hand study results disagreed with many previous studies which showed that overweight and obesity associated with poorer survival rate compared with normal weight cases (Murphy et al., 2000; Campbell et al., 2011; Hall, 2006; Lee et al., 2015b).

The researcher suggested that the differences between the current study and the other studies, due to the majority of CRC cases in GS diagnosed with advanced stages.

Figure (4.11): Kaplan-Meier survival curves by Body Mass Index-BMI

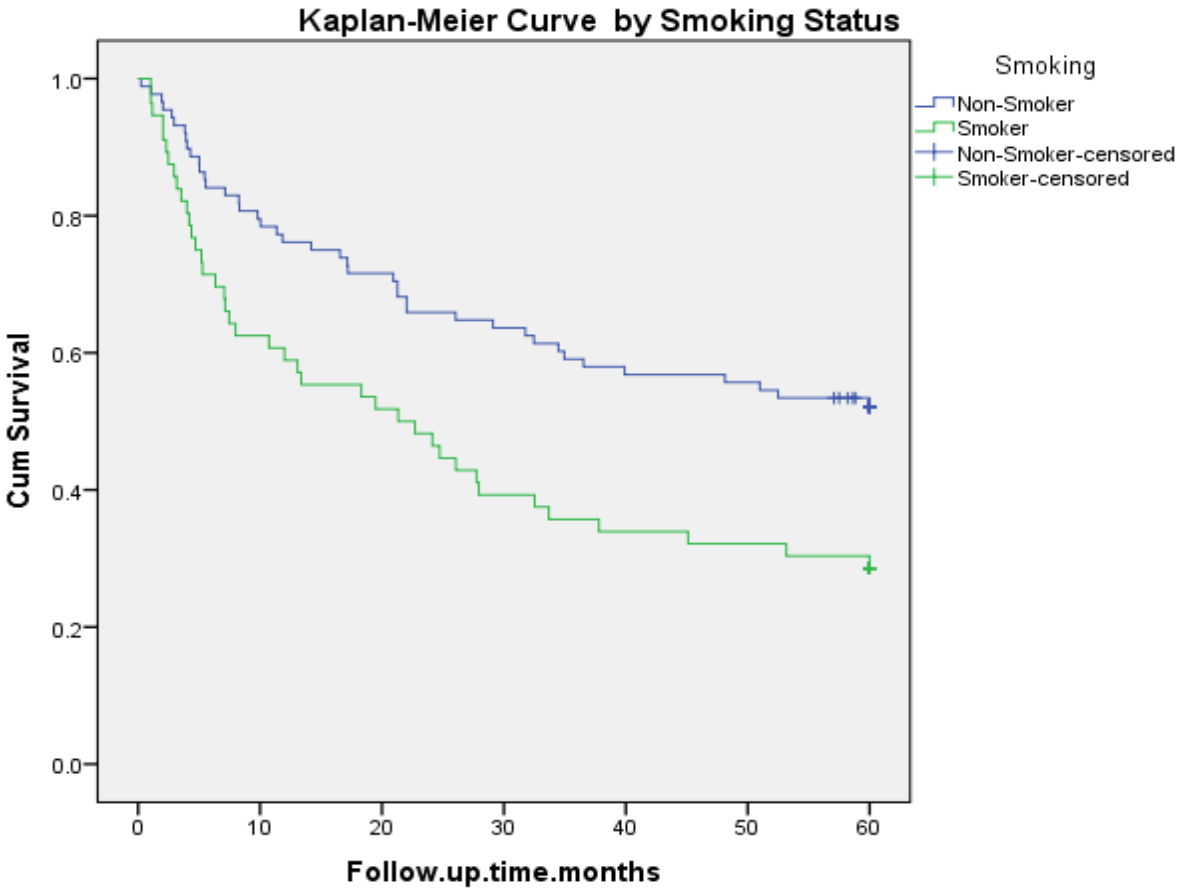


4.2.2.8 Survival analysis according smoking status of the cases

Kaplan-Meier test is used to analyze the effect of smoking on the survival data for the study cases and as illustrated in table (4.10) the non-smoker cases have mean survival about 40 months (SE: 2.543) which is better than smoker cases where the mean survival time is 28 months (SE: 3.228).

These survival differences are statically significant (P-value: 0.002). These results accord with many previous studies which showed that the smoking as general decrease the chances to survive longer from CRC, as result for this the non-smokers cases have better mean survival time (Walter et al., 2014; Yang et al., 2015; Walter et al., 2015; Boyle et al., 2013).

Figure (4.12): Kaplan-Meier survival curves by smoking status



4.2.3 The effect of tumor related factors on survival estimates

4.2.3.1 Survival analysis according stage at diagnosis

Kaplan-Meier test was used to analyze the survival data for cases according CRC stage at diagnosis. As shown in table (4.11) mean survival time by months for cases with stages I, II, III, and IV was 60, 53.6, 39.5, and18.7 respectively. The best mean survival time was for cases who diagnosed with stage I, while the worst mean survival time was for cases diagnosed with stage IV. These survival differences are statistically significant (P-value: 0.001). These finding accord with the majority of previous studies where outlined that stage at diagnosis has statically significant effect on survival time, and added that survival time for low stages was better than survival time for advanced stages (Fu et al., 2014; Yuan et al., 2013; O'Connell et al., 2004; Al-Nsour, 2014).

Figure (4.13): Kaplan-Meier survival curve according satge at diagnosis.

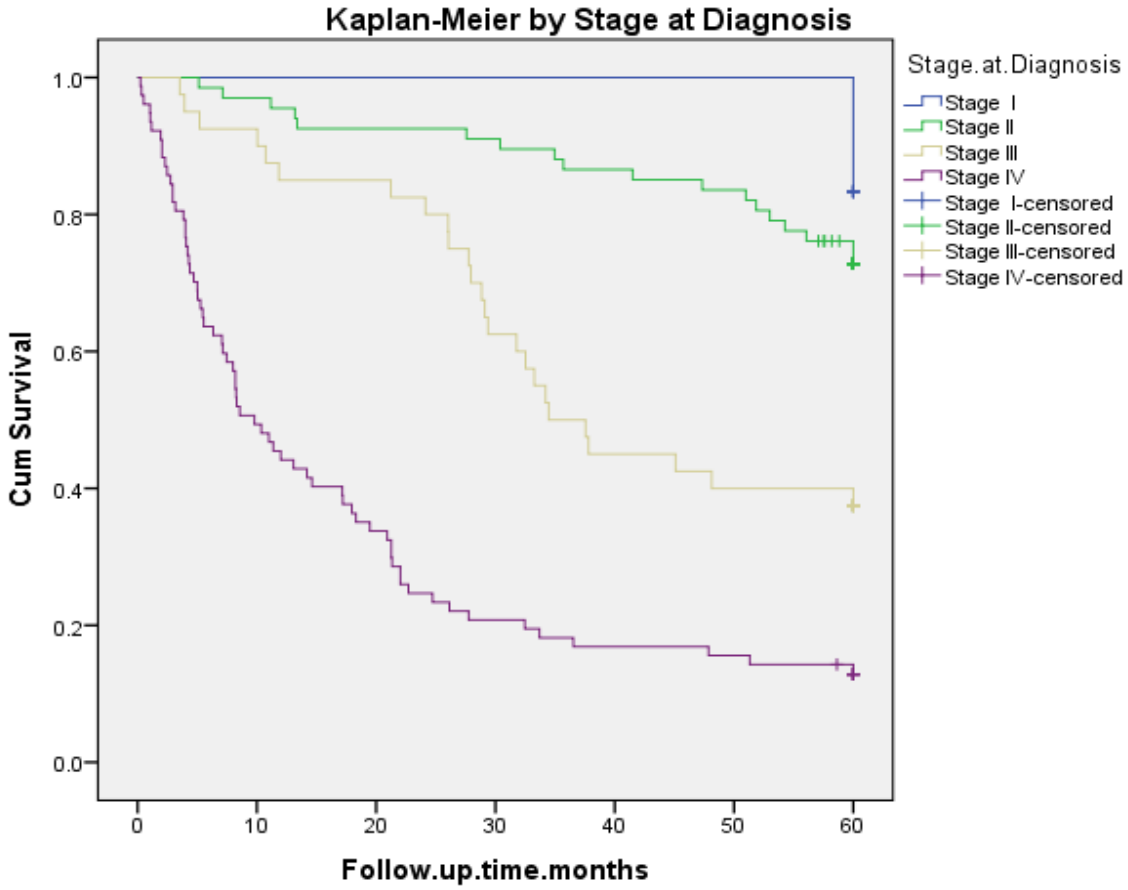


Table (4.11): Kaplan-Meier survival analysis according selected tumor related factors

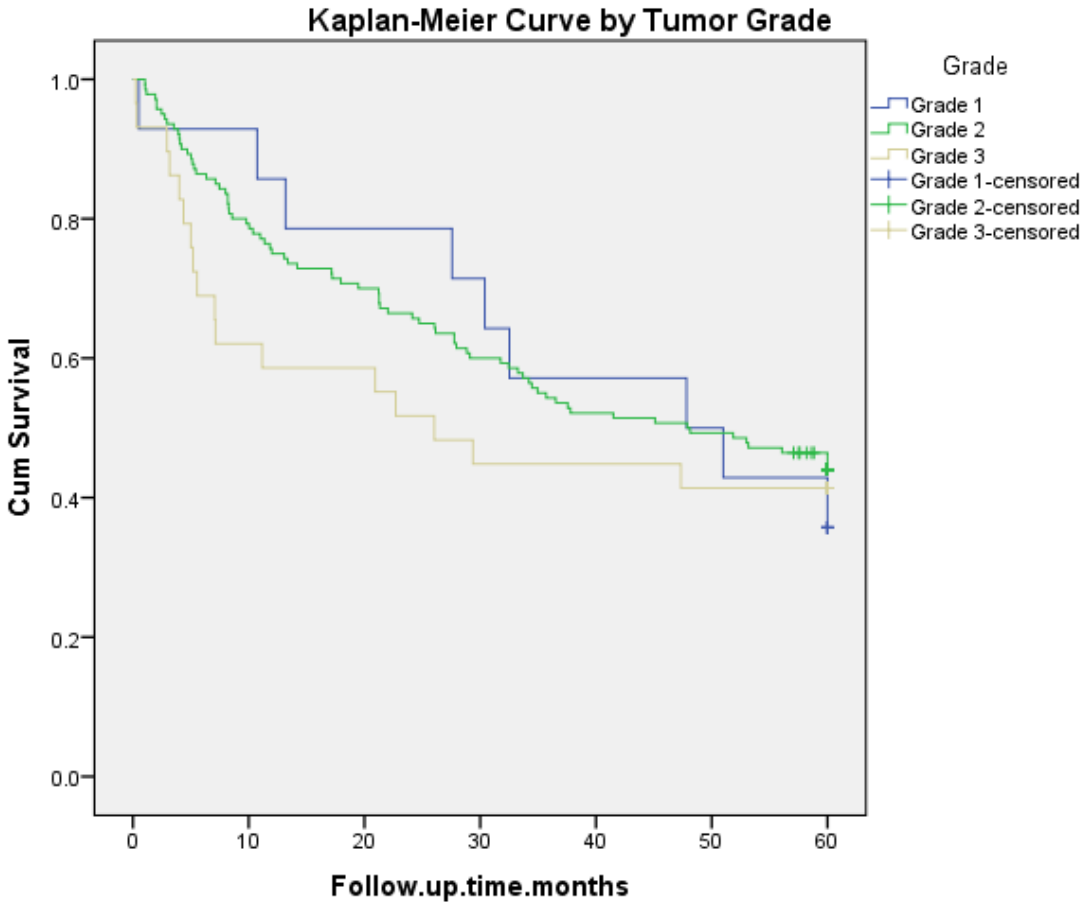
Variable	Subgroups	Total no.	Mean survival time by months	Median survival time by months	5-years survival rate (%)	Log Rank	
						χ^2	p-value
Stage at Diagnosis	Stage I	6	60.0	60	100	93.6	0.001*
	Stage II	67	53.6	43.8	78		
	Stage III	40	39.5	34.4	40		
	Stage IV	77	18.7	9.8	16		
Grade	Grade 1	14	40.9	47.8	50	0.745	0.041*
	Grade 2	140	38.2	47.8	46		
	Grade 3	29	31.8	26.0	41		
Tumor site	Rt. Colon	43	25.2	12.0	32	11.16	0.004*
	Lt. colon	103	40.2	60.0	48		
	Rectum	51	40.7	51.8	50		
Sites of Distant Metastasis	Liver only metastasis	62	21.7	11.0	19	4.730	0.094
	Liver mets. concomitant with other mets.	14	16.1	10.3	8		
	Other distant metastasis	8	9.0	5.2	0		
*Statically significant							

4.2.3.2 Survival analysis according tumor grade

Kaplan-Meier test was used to analyze impact of tumor grade on survival from CRC. Results showed statistically significant survival differences based on tumor grade (P-value= 0.041). Grade-1 and Grade-2 had the best mean survival by months about 41, 38.2

respectively while Grade-3 and Grade-4 had the worst mean survival by months about 32 as shown on table(4.11). These findings were agreed with many previous studies findings which showed that low tumor grade is related with better survival time from CRC (Yuan et al., 2013; O'Connell et al., 2004; Al-Nsour, 2014).

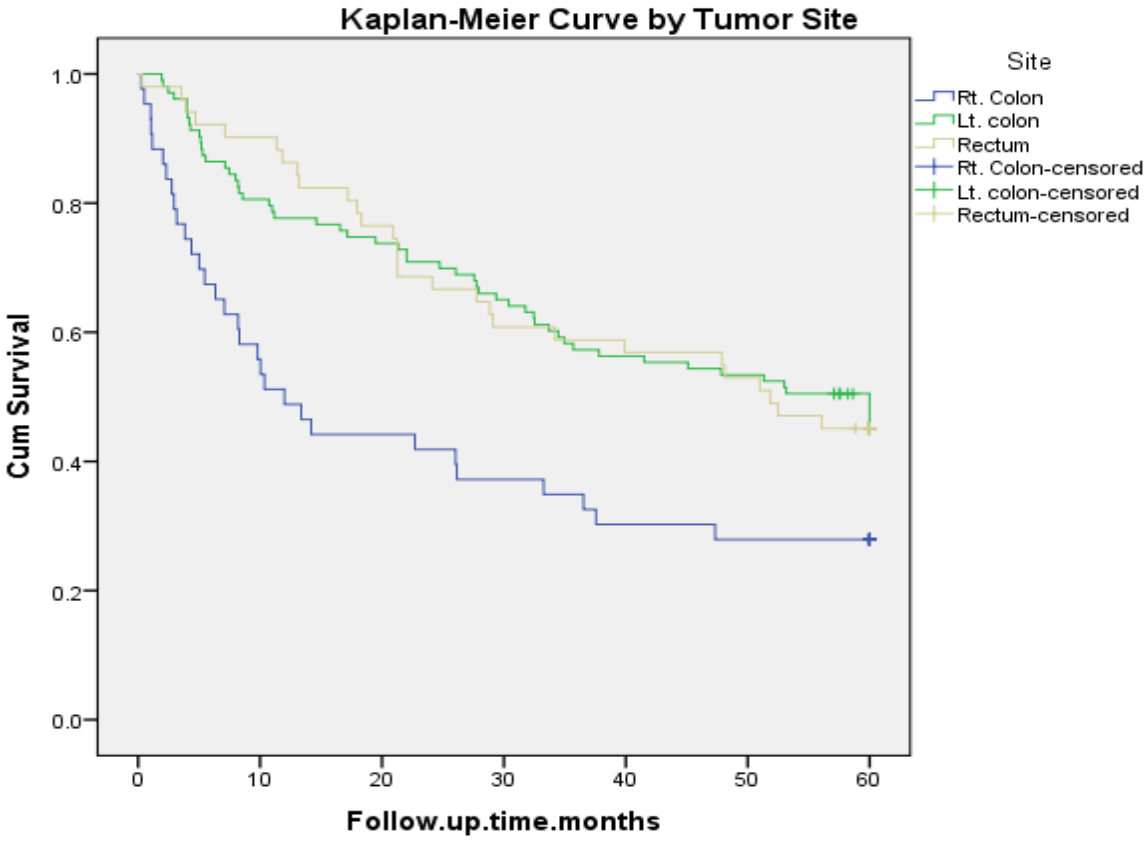
Figure (4.14): Kaplan-Meier survival curves according tumor grade



4.2.3.3 Survival analysis according tumor site.

Kaplan-Meier test showed statistical differences between cases according tumor site, where tumors developed in rectum correlated with the best mean survival time followed by tumors developed in Lt. Colon. While tumors developed in Rt. Colon had the poorest mean survival time as illustrated at table (4.11). Figure (4.16) shows Kaplan-Meier survival curves according tumor site.

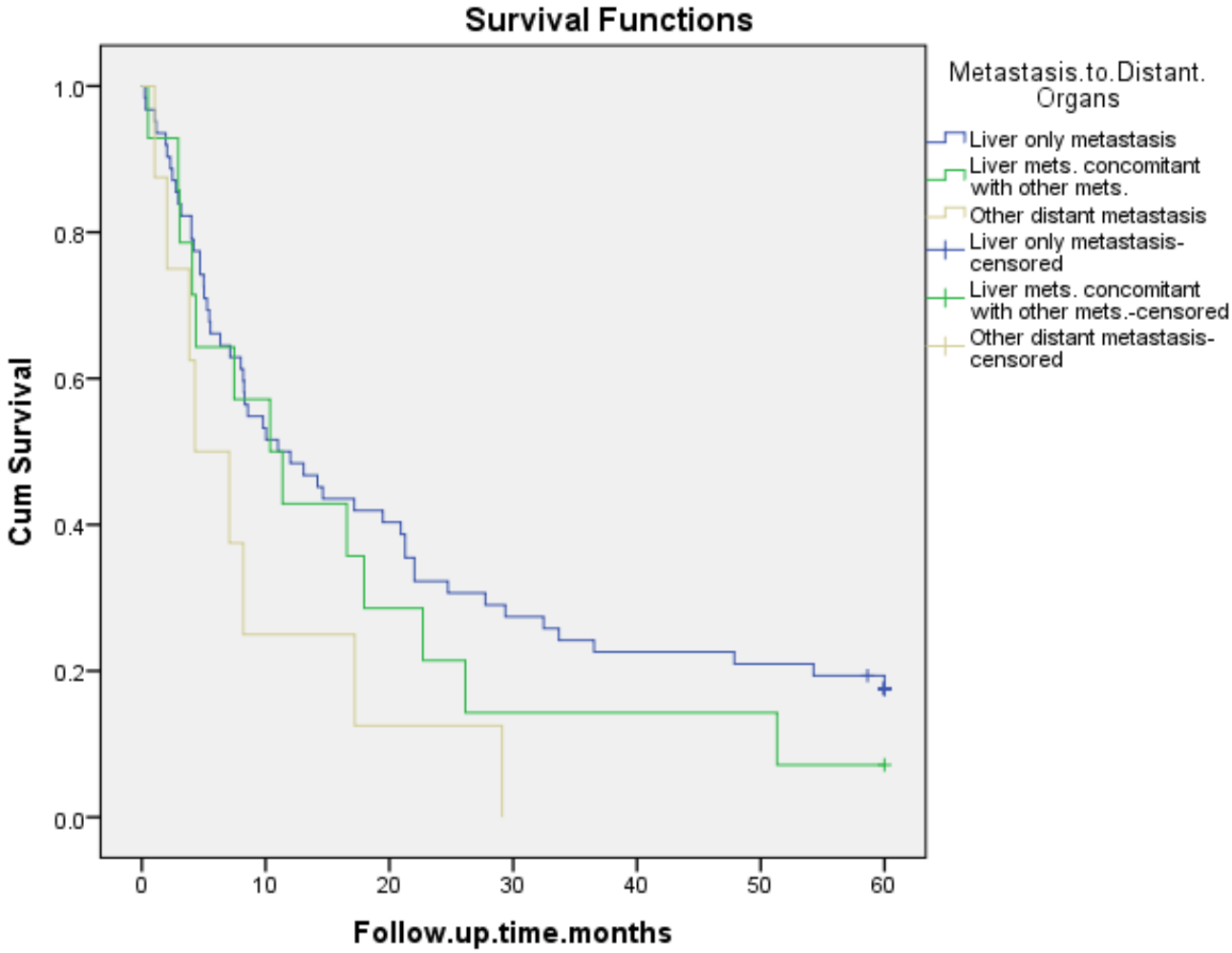
Figure (4.15): Kaplan-Meier survival curves according tumor site



4.2.3.4 Survival analysis according distant metastasis sites

Kaplan-Meier test was used to analyze the impact of different metastasis sites on survival data for metastatic cases. Metastasis sites were divided into three subgroups as the follow: Liver only metastasis, Liver mets. Concomitant with other mets., and other distant metastasis as shown in table (4.11). Test results showed that metastatic cases with liver only metastasis had slightly longer survival time than other metastatic cases (Figure 4.17), but these survival differences were not statistically significant (P-value= 0.094).

Figure (4.16): Kaplan-Meier survival curves according distant metastasis sites



4.2.4 The effect of healthcare related factors on survival estimates.

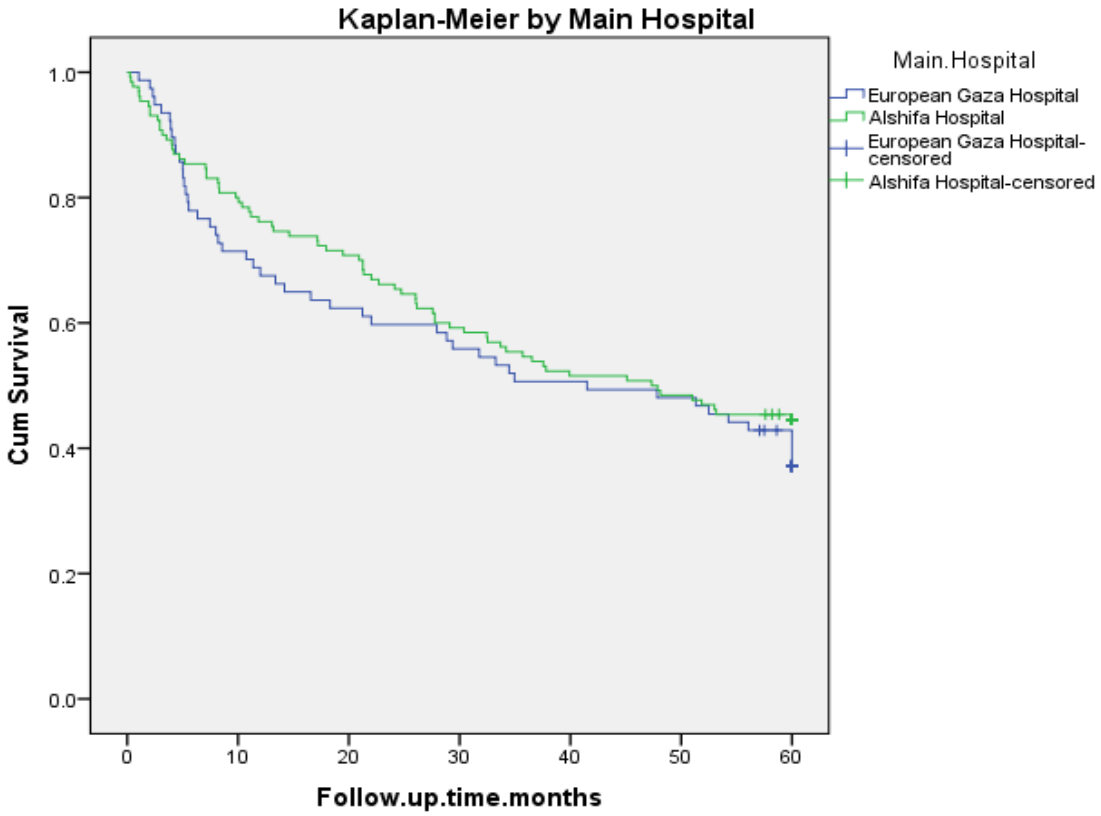
4.2.4.1 Survival analysis according main treating hospital.

As shown in table (4.12) there were no statically differences on survival data between cases based on their main hospital. Even though cases who were treated at Al-Shifa hospital had slightly longer survival time than cases who were treated at EGH with about 2 months. The researcher suppose the absence of survival differences as shown in figure (4.17) between the two hospitals due to the two hospital are governmental hospitals and relatively they provided the same services.

Table (4.12): Kaplan-Meier survival analysis according healthcare related factors.

Variable	Subgroups	Total no.	Mean survival time by months	Median survival time by months	5-years survival rate (%)	Log Rank	
						χ^2	Sig.
Main Hospital	EGH Hospital	77	35.7	41.500	44	0.830	0.362
	Al-Shifa Hospital	130	37.9	47.333	46		
Diagnostic Delay	Delayed (>3 months)	30	41.7	-	54	0.739	0.390
	No delay (<3 months)	109	37.9	51.3	48		
Treatment Type	Surgery only	26	41.7	-	58	17.22	0.001*
	Chemo. only	24	22.2	14.200	18		
	Surgery + Chemo.	105	40.3	54.267	48		
	Surgery+Chemo.+Radio	27	42.3	-	50		
Surgery Place	Inside Gaza Strip	124	42.5	60.0	52	1.646	0.200
	Outside Gaza Strip	33	34.3	28.8	42		
Surgery Delay	Delayed surgery(>31days)	34	37.2	37.8	39	2.682	0.101
	No delay(<31days)	122	42.1	49.2	55		
Chemotherapy place	Inside Gaza Strip	117	38.8	48.1	42	3.520	0.061
	Outside Gaza Strip	33	28.3	21.2	28		
Chemotherapy delay	Delayed Chemotherapy (>3m after surgery)	30	38.322	42.1	42	0.098	0.754
	No Delay (< 3m after surgery)	93	41.5	53.2	45		
*statically significant							

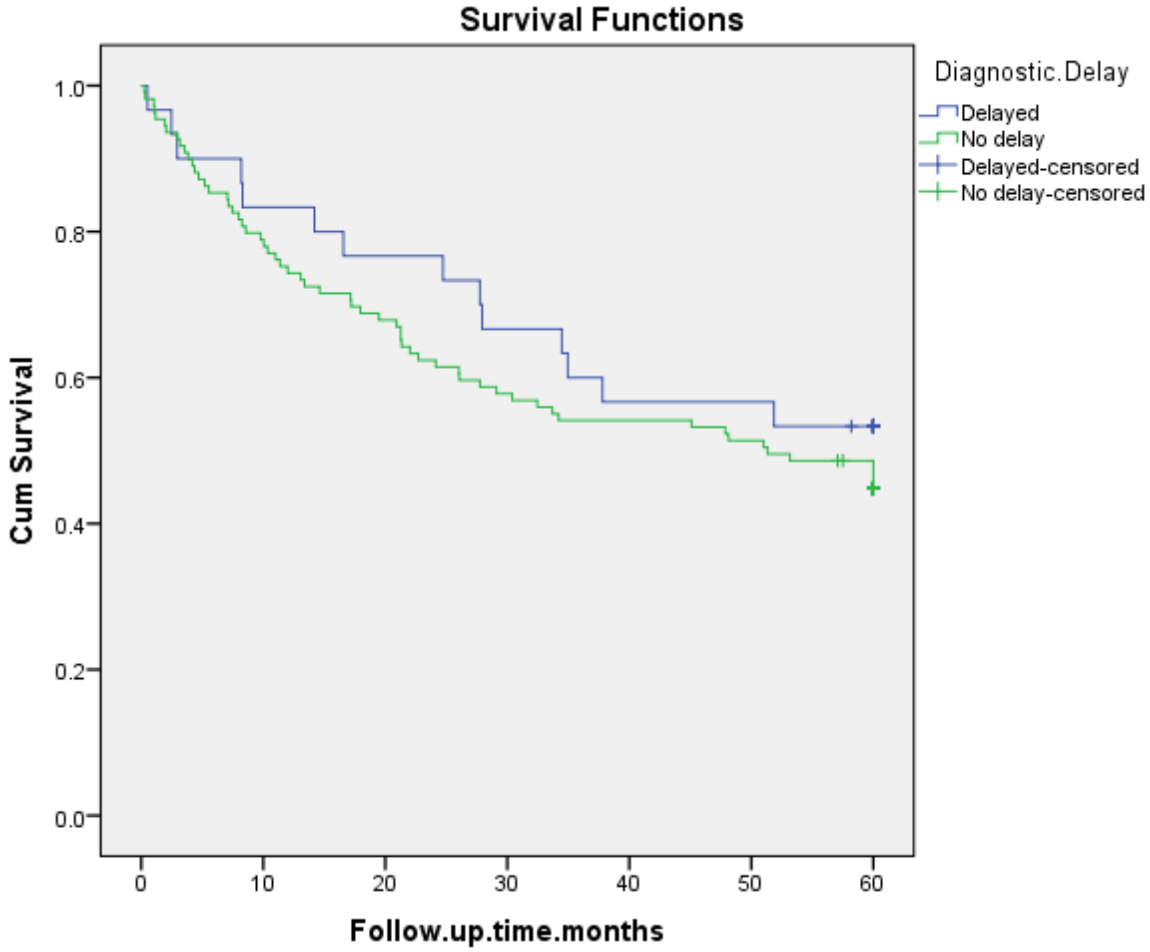
Figure (4.17): Kaplan-Meier survival curve according main treating hospital for cases



4.2.4.2 Survival analysis according diagnostic delay.

Information about signs and symptoms which related to CRC starting date was found in 139 medical records out from 207 records. Thirty cases from the 139 cases have diagnostic delay while 109 were diagnosed within one month. Kaplan-Meier test is used to analyze effect of diagnostic delay on survival data, where the log rank test results shows that there were no statically significant differences between the subgroups (P-value= 0.390). However patients who had delay in diagnosis had slightly better mean survival time than those without delay in diagnosis with about four months as shown in (figure 18). These results accord with many previous studies. For example, study conducted in Australia showed that delayed diagnosis had not statically significant affect on survival from colorectal cancer, and added that short interval for diagnosis was associated with worse survival (Pita-Fernández et al., 2016)

Figure (4.18): Kaplan-Meier survival curves for cases according diagnostic delay



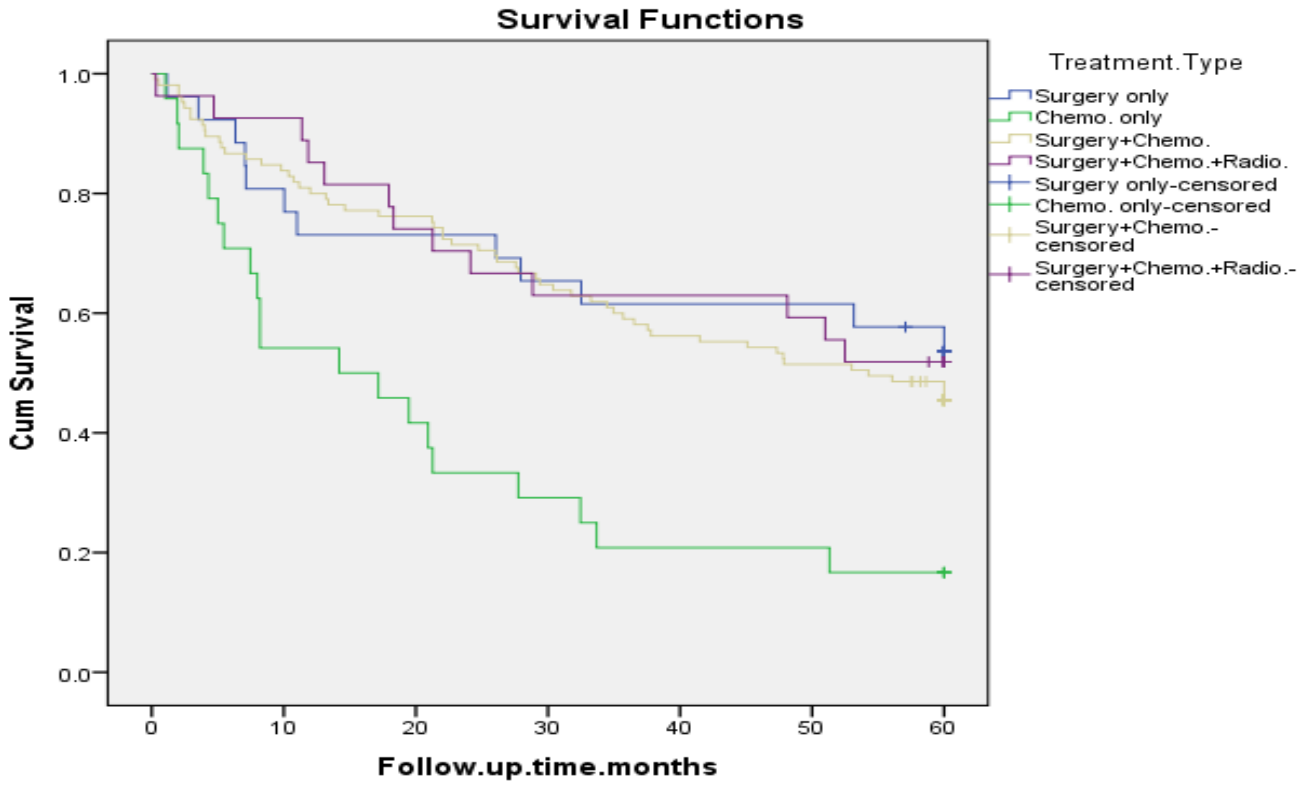
4.2.4.3 Survival analysis according the main treatment type.

Kaplan-Meier test was used to analyze the effect of treatment types and combination of them on the survival data for CRC cases. Table (4.7) showed the distribution of study cases according the received treatment type. The test results have showed statically significant survival differences between the cases groups (P-value= 0.001) as illustrated in table (4.12). Where the mean survival time for cases who received the surgical intervention, chemotherapy and radiotherapy is the best with 42.3 months while the worst survival time for cases who received only chemotherapy.

The same results are found in Wiegering and colleagues study, where they have demonstrated that a combination between treatment (surgery, chemotherapy, and radiotherapy) is associated with better overall survival rate for CRC patient with all stages (Wiegering et al., 2014). The surgical resection remains the only hope for complete cure

from CRC and one of the most common palliation methods in the patients with incurable CRC (Shankar et al., 1999). Xu and colleagues study revealed that the surgical resection of primary tumors associated with better survival rate even in cases even with unresectable stage IV CRC (Xu et al., 2015).

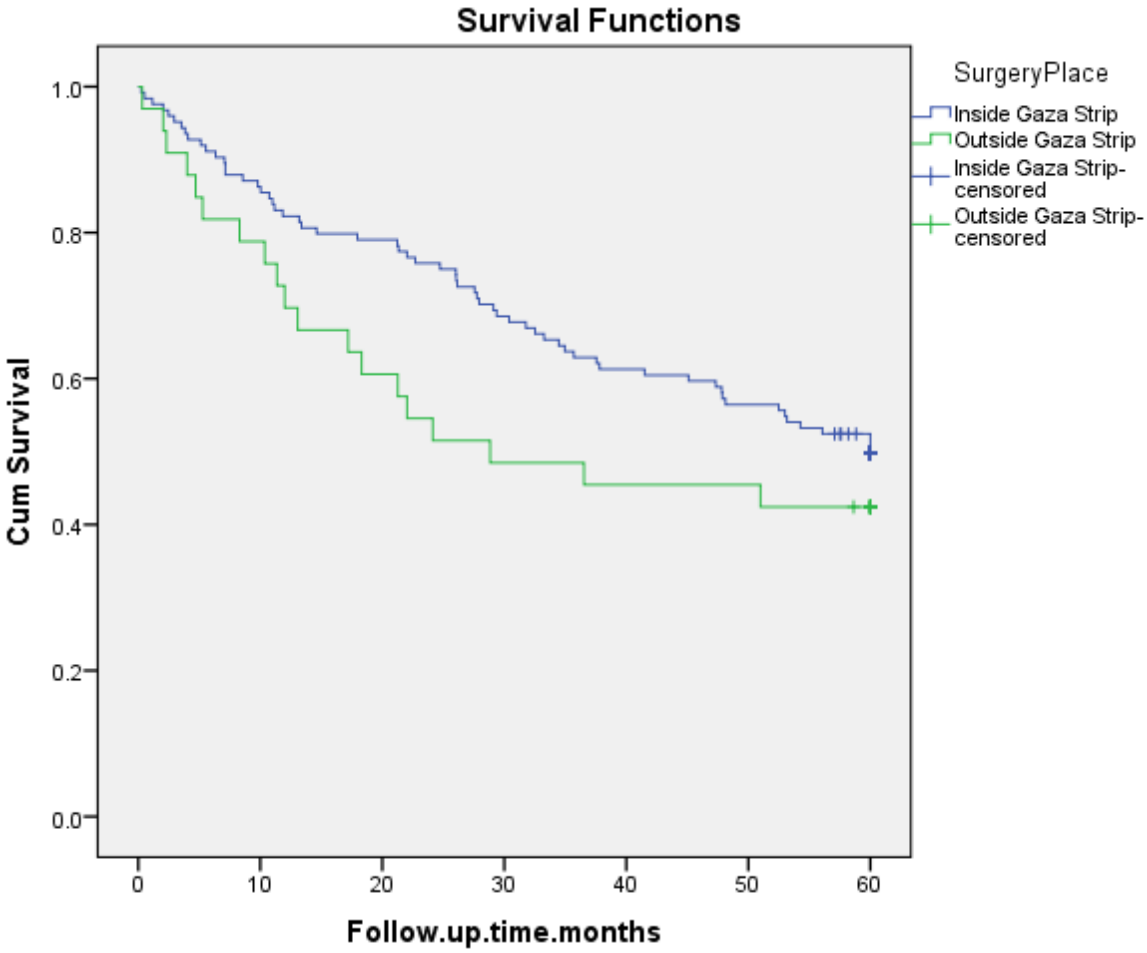
Figure (4.19): Kaplan-Meier survival curves for study cases by treatment type.



4.1.4.4 Survival analysis according surgical intervention place.

Kaplan-Meier test was used to explore the effect of the surgical place on survival data for cases who were underwent surgical resection (4.12). The log rank test shows no statically significant differences between cases who had surgery inside GS and cases who had surgery outside GS. However, cases who were underwent surgery inside GS had slightly better mean survival time with about 8 months (Figure 4.20). Theses difference may be referred due to the most of cases who had surgery outside GS were with advance stage of CRC.

Figure (4.20): Kaplan-Meier survival curves for cases according surgical intervention place.

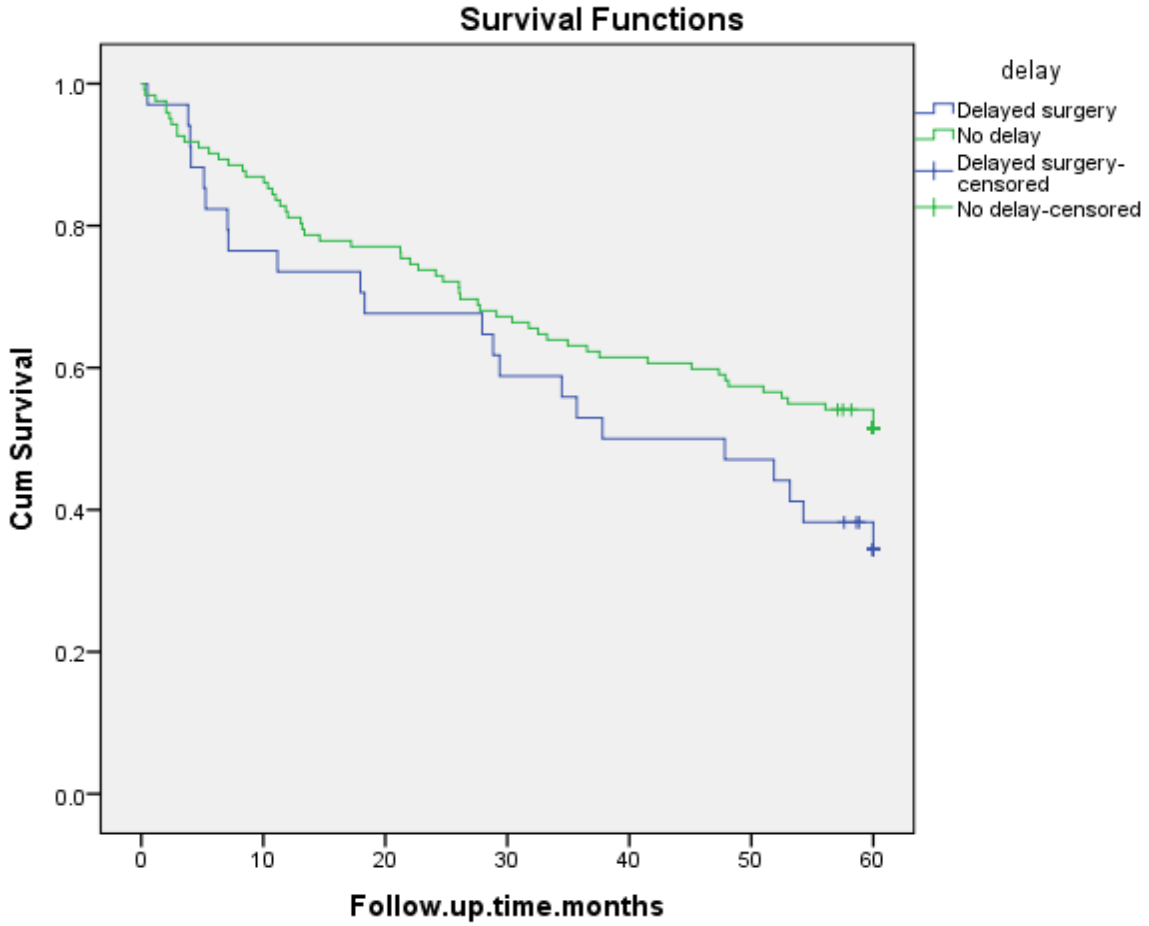


4.2.4.5 Survival analysis according surgery delay.

Kaplan-Meier test is used to analyze the effect of surgery delay on survival data for the study cases who underwent surgical intervention. The cases were divided into three subgroups according waiting time for surgery as shown in table (4.7). The log rank test shows no statically significant survival differences between the study cases according waiting time for surgery (P-value=0.101). However, short time for surgery associated with better survival rates, whereas cases who were underwent surgery before 14 day since confirmed diagnosis have the best survival time with mean 44.3 while cases with delayed surgery (>31 days after confirmed diagnosis) have the worst survival time with mean 37.2 as shown in table (4.12) and illustrated in figure (4.21). Agreed with the researcher findings in previous study conducted in Canada where outlined that there are no significant relationship between the surgery delay and the survival from CRC (Simunovic et al.,

2009). Another previous study showed that treatment delay is not associated with poor survival of CRC patients and reasonable surgery delay dose not worse the survival rate where it permits more scheduling flexibility and proper evaluation of the condition (Amri et al., 2014).

Figure (4.21): Kaplan-Meier survival curves for cases according surgery delay

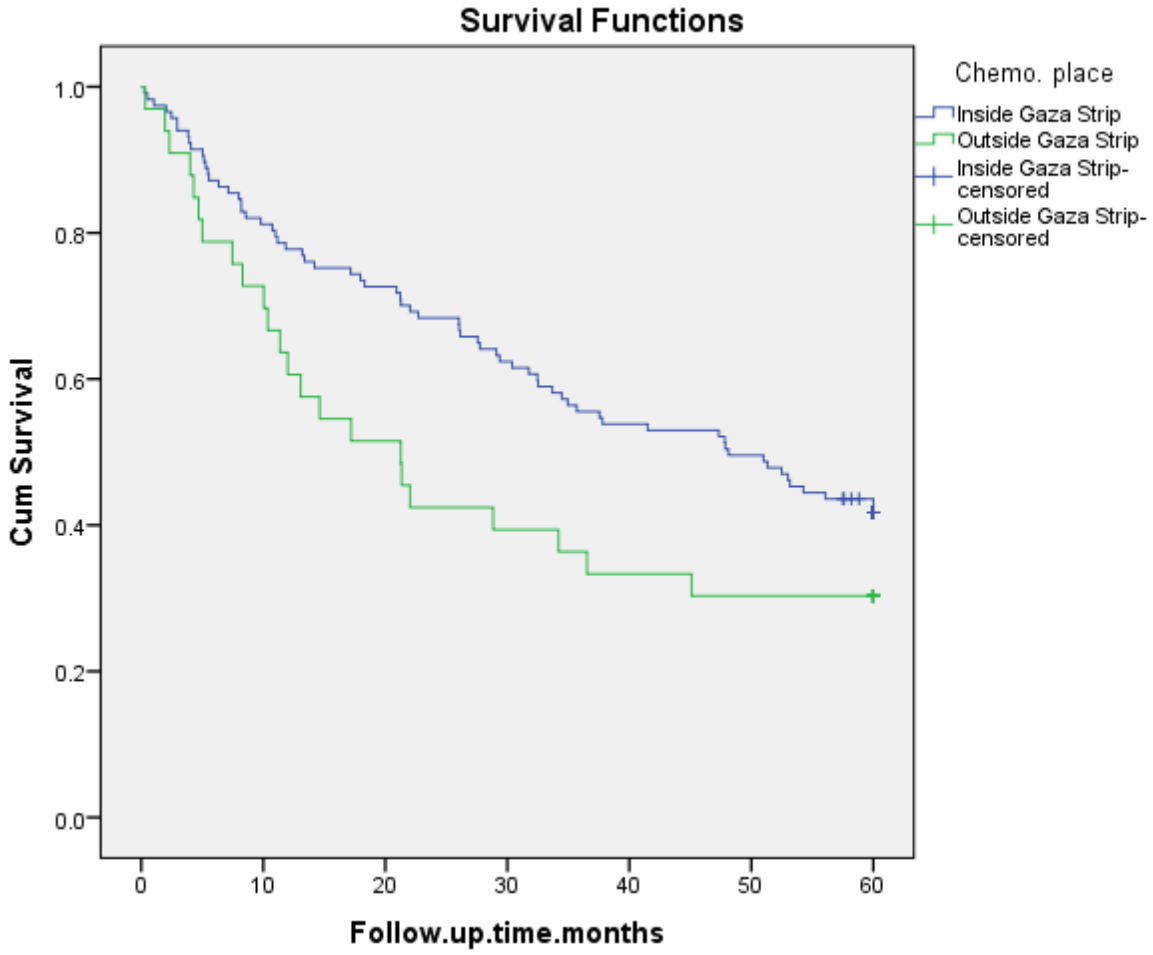


4.2.4.6 Survival analysis according chemotherapy place.

Kaplan-Meier test is used to explore the impact of chemotherapy place on survival data for the study cases who need the chemotherapy (Table 4.12). According the log rank test results, there are no statically significant differences in survival data between the study cases who were treated with chemotherapy inside GS or outside GS (P-value = 0.61). However, cases who were treated outside GS had poorer survival time than the study who were treated inside GS. The researcher suggested these differences may be due to most of

cases who treated outside GS were with more advance stages and chemotherapy drugs for these advance stages were not available inside GS in most of time.

Figure (4.22): Kaplan-Meier survival curves for cases according chemotherapy place

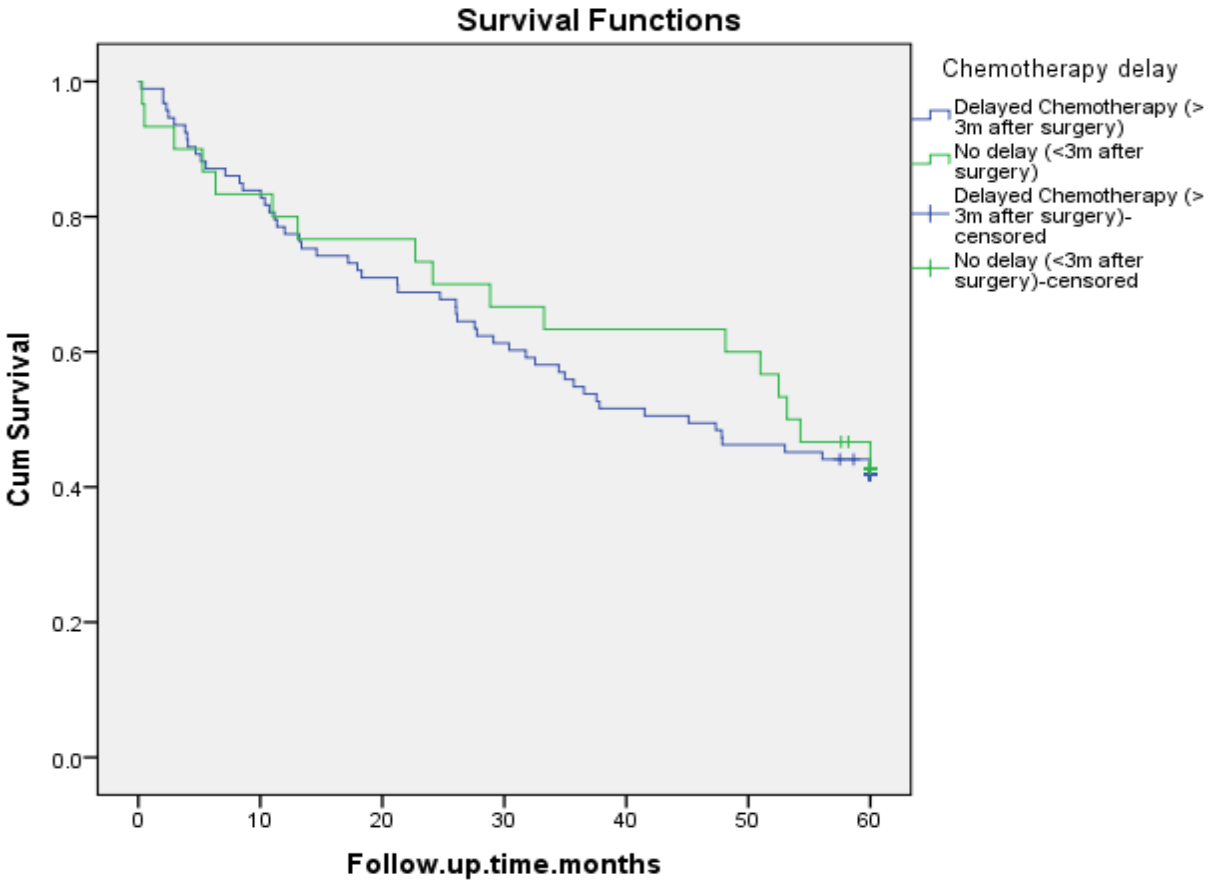


4.2.4.7 Survival analysis according chemotherapy delay

Kaplan-Meier test is used to examine the impact of chemotherapy delay on survival data for cases who need the chemotherapy cycles. The cases that need the chemotherapy are divided into two subgroups in term of chemotherapy. As shown in table (4.12), there are thirty cases with delayed chemotherapy (>3months after surgery), and 93 cases have not delayed chemotherapy. The log rank test shows no statically significant survival differences between the two subgroups (P-value= 0.754). However, the cases without chemotherapy delay had slightly better survival time than cases with delayed chemotherapy with about 3 months. In line with the literature, Xu and colleagues study agrees with the researcher findings where shows that the chemotherapy delay associated

with poorer survival rate but it showed statically significant association (P-value <0.001) (Xu et al., 2014). Previous systematic review and meta-analysis study demonstrated that longer time to chemotherapy is associated with worse overall survival rate (Biagi et al., 2011). Another pervious study conducted in USA showed the same results where the delayed chemotherapy correlated with poorer survival rate (Bayraktar et al., 2011). The researcher supposes that the current result is not statically significant due to small size of study sample beside the effect of missing data in the medical records which were the main source of data.

Figure (4.23): Kaplan-Meier survival curves for cases according chemo-therapy delay



4.2.5 Cox Regression survival analysis

Cox regression survival analysis is conducted to explore the independent effect of the different study variable on the survival rates from CRC. Table (4.13) illustrates the test

results for each entered factors. From the analyzed factors, only three factors have statically significant effect which are stage at diagnosis (P-value<0.001, 95% CI 2.673-9.034), Co-morbidity status (P-value=0.031, 95%CI0.434-0.962) and tumor site (P-value 0.018, 95%CI, 0.373) as shown in the table (4.13).The hazard ratio for co-morbidity (HR=0.646) which means that the risk for death decreased by 36% if the patient had not co-morbidity. The study results accord with many previous studies where showed the same results. Malaysian study conducted Cox regression survival analysis of CRC illustrated that staging at diagnosis was the prognostic factor with significant effect (p<0.001). These results agreed with the current study result (Suan et al, 2016). The multivariate analysis results in Yuan and colleagues study showed that only the TNM staging system had a statistically significant (P < 0.0001) effect on CRC patients survival when all the study variables were included in the analysis (Yuan et al., 2013). In Jordan, previous study illustrated that the Cox regression analysis of prognostic factors of CRC showed more prognostic factors had statically significant effect on CRC which were age, place of residency, extent of disease, and morphology (Al-Nsour, 2014). Else five studies from different countries showed that stage at diagnosis had statically significant effect on CRC survival by using the Cox regression analysis (Mehrkhani et al., 2009; Al-Shamsi et al., 2011; Park et al., 1999; Yeole et al., 2001; Ghazali et al., 2010). The five studies showed site of tumor lost its significant effect in the multivariate analysis while the co-morbidity status was not studied in these studies.

Table (4.13): Cox regression survival analysis of colorectal cancer in the Gaza Strip (2008-2010)

Variable	Hazard ratio	95.0% CI for Exp(B)		P-value
		Lower	Upper	
Gender	1.259	0.880	1.802	0.208
Age	1.009	0.996	1.023	0.188
Marital Status	0.858	0.502	1.466	0.575
Residency	1.001	0.856	1.171	0.991
Family History of cancer	0.582	0.291	1.165	0.127
Obesity status	0.518	0.266	1.010	0.054
Smoking	1.516	0.826	2.782	0.179
Co-morbidity Status	0.646	0.434	0.962	0.031*
Tumor site	0.584	0.373	0.912	0.018*
Grade	1.051	0.442	2.501	0.910
Stage at diagnosis	4.914	2.673	9.034	<0.001*
Histological Type	2.917	0.743	11.456	0.125
Main hospital	1.287	0.202	8.210	0.789
Chemotherapy Place	0.721	0.240	2.172	0.562
Surgery place	1.798	0.605	5.345	0.291
Radiotherapy place	0.474	0.055	4.083	0.497
Treatment type	0.924	0.822	1.039	0.186
Surgery delay	1.356	1.010	1.821	0.143
Chemotherapy delay	1.154	0.854	1.558	0.351
*Statically significant				

Chapter (5) Conclusion and Recommendation

5.1 Conclusion

This study is conducted to explore the observed survival rate for CRC cases, and to investigate main factors may relate with CRC prognosis and the survival in GS at the period between (2008- 2010). The study defines three main groups of factors are suspected to have an effect on CRC prognosis and the survival rates. The first group is patient related factors which includes factors such as age at diagnosis, gender, marital status, and health related behaviors, the second group is the tumor related factors which includes factors such as histological type, tumor grade, stage at diagnosis, and tumor site, while the third group is healthcare related factors which is divided into two constructs: the first construct is diagnostic related factors which include two factors, Diagnostic delay and Signs and symptoms while the second construct is treatment related factors which include the factors, treatment delay, treatment types, and treatment places.

The researcher used self-constructed data abstract sheet to collect data from the medical records which is considered the main source for data in this current study. A total of 207 cases were enrolled after exclusion of some cases for various causes.

In this current study, the Kaplan-Meier method is used to conduct the survival analysis for the study cases and to determine the overall survival rates. A univariate analysis was conducted to show impact of main study variables on the survival data such as stage at diagnosis, treatment type, and place of treatment. Also the log rank test was used to estimate difference between the groups. The researcher considered the variable to have a significant effect if the P-value ≤ 0.05, with 95% confidence interval. Also Cox-regression analysis is conducted to verify how far these differences between groups are statistically significant (P-value ≤ 0.05).

One of the main obstacles was faced the researcher is incomplete and missing data in the medical records. So factors such as education level and occupation types were not studied due to absences of information in the medical records.

Study findings showed that the mean of age at diagnosis for the entire study population was 59.6 years, and more than two third of cases occurred after age 50 with 77.7% from all cases. 54.6% from cases were male and 45.6% female. Regarding tumor characteristics adenocarcinomas (Non-mucinous) accounted 86.7% from histological type. More than two third of cases diagnosed with low grade tumor (grades 1+2), while more than the half of patients (61.6%) were diagnosed with advanced stages (III + IV). Left-sided colon is the

most common site for developing CRC with 52.3% of all cases. It followed with rectal cancer with 25.9%, While Right-sided colon accounted only 21.9%.

The study results reveal that all of the study cases were presented with signs and symptoms at time of diagnosis, mainly due to absent of CRC screening program in GS. The main and symptoms are bleeding per rectum with 63.3% from all cases, then abdominal pain with 35.3%, then anemia 18.7%, followed by bowel habits changes (diarrhea/constipation) with 15.9% and intestinal obstruction with 12.2 % from all cases. Furthermore around 21% from the cases are diagnosed after 3 months from onset of signs and symptoms.

Regarding the treatment of CRC in GS, the study finding show that about 13.70 underwent surgery, 12.6% cases have chemotherapy only, 55.5% cases underwent surgery beside chemotherapy, 27 (14.2) cases underwent surgery beside the chemotherapy and radiotherapy as shown in table have chemotherapy delay and surgery delay

The survival analysis for 5-years follow up showed that the 5-years overall survival rate, disease free survival rate, progression free survival rate were 45.1%, 61%, and 28% respectively. These rates are considered very poor compared to developed countries which reach in many counties the ends of 60%. However, 5-years survival rate in GS was in line with survival rates in the neighbor countries such as Jordan and Saudi Arabia. The univariate analysis (Log Rank test) shows that the factors (Co-morbidity, obesity status, smoking, stage at diagnosis, tumor site, treatment type) were statically significant affect on the survival rate of CRC. While Cox regression survival analysis showed that only three factors prognostic factors had statically significant effect which were stage at diagnosis (P-value<0.001, 95% CI 2.673-9.034), Co-morbidity status (P-value=0.031,95% CI0.434-0.962) and tumor site (P-value0.018,95%CI, 0.373).

The survival figures show that the conditions such as the non-smoker, males, and married have better survival figures than others but without statically significant differences.

The study provides the baseline of the survival data regarding CRC in GS, and the study findings need immediate actions to enhance the prognosis of CRC in GS and improve the quality of life of CRC survivors by discovering the cases early as possible and decrease the rates of patients who are diagnosed with late stages.

5.2 Recommendation

5.2.1 The study Recommendation

1. An urgent need for a national CRC screening program and launch national campaigns for increasing the public and official awareness regarding CRC.
2. Providing GS hospitals with missing cancer services and new treatment models will contribute to enhance the overall survival rate
3. Develop appropriate protocols and guidelines for documentation of the medical records and staging system for cancer diseases.
4. Empowering the national center for cancer registry, in order to improve and promote completeness and quality of the recorded data.
5. Empowering the archiving system of the medical records to decrease the missed records.

5.2.2 Recommendation for further research

1- Conduct research studies to explore the main risk factors for developing CRC in GS.

2- Carry out additional research studies to confirm the current results in large sample at national level including cases from West bank and for longer period. Beside that including other prognostic factors such as status of resection and serum CEA level.

3- Conduct other research studies to analyze the survival rates from other common cancer in GS.

4- Conduct economical studies concerning cancer services in the Gaza Strip.

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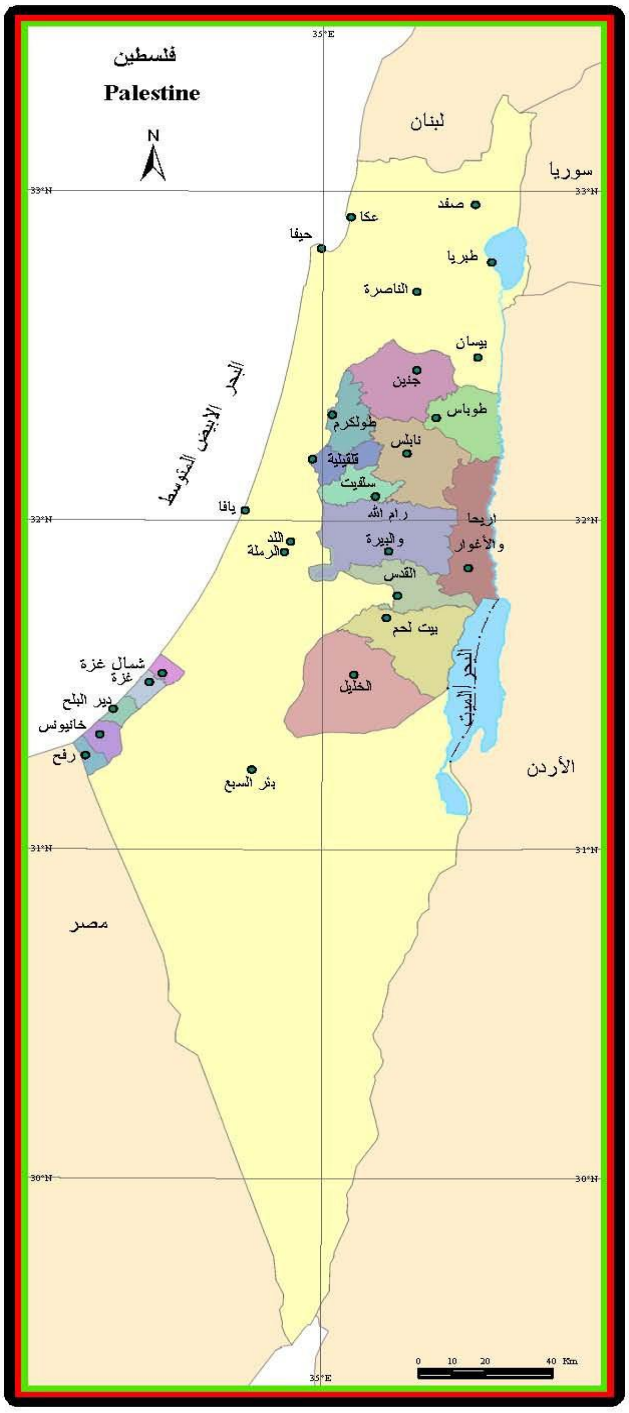
Annex (1): Palestine map

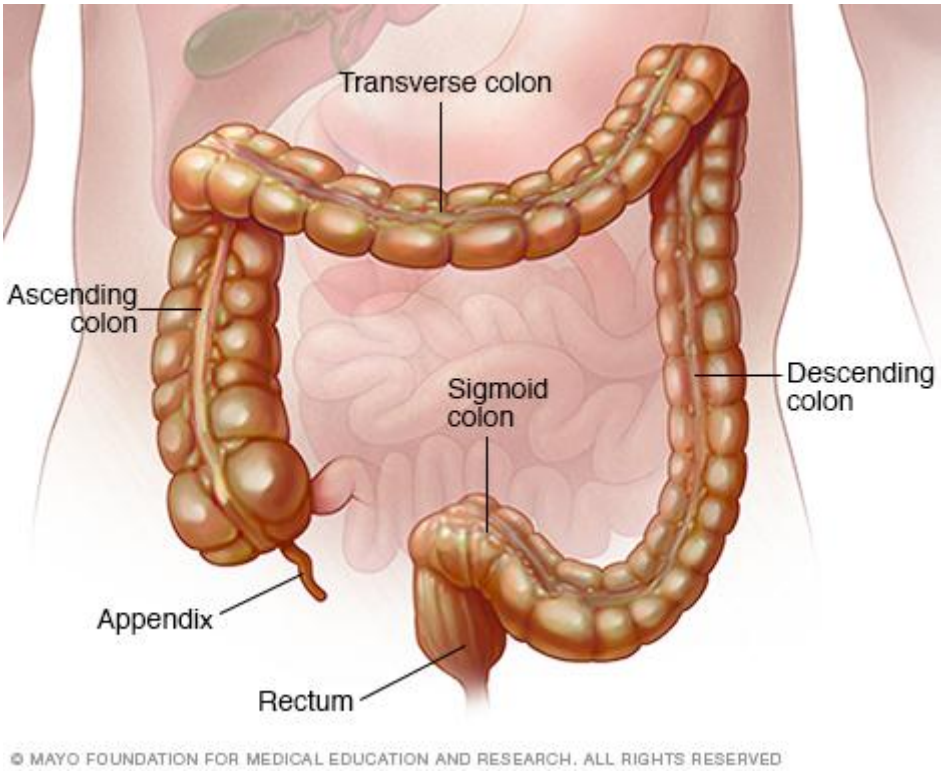


Source: (PCBS, 2015)

Annex (2): Gaza strip map

Source: (Palestine question and answer, 2015)

Annex (3): A diagram of normal colon and rectum anatomy

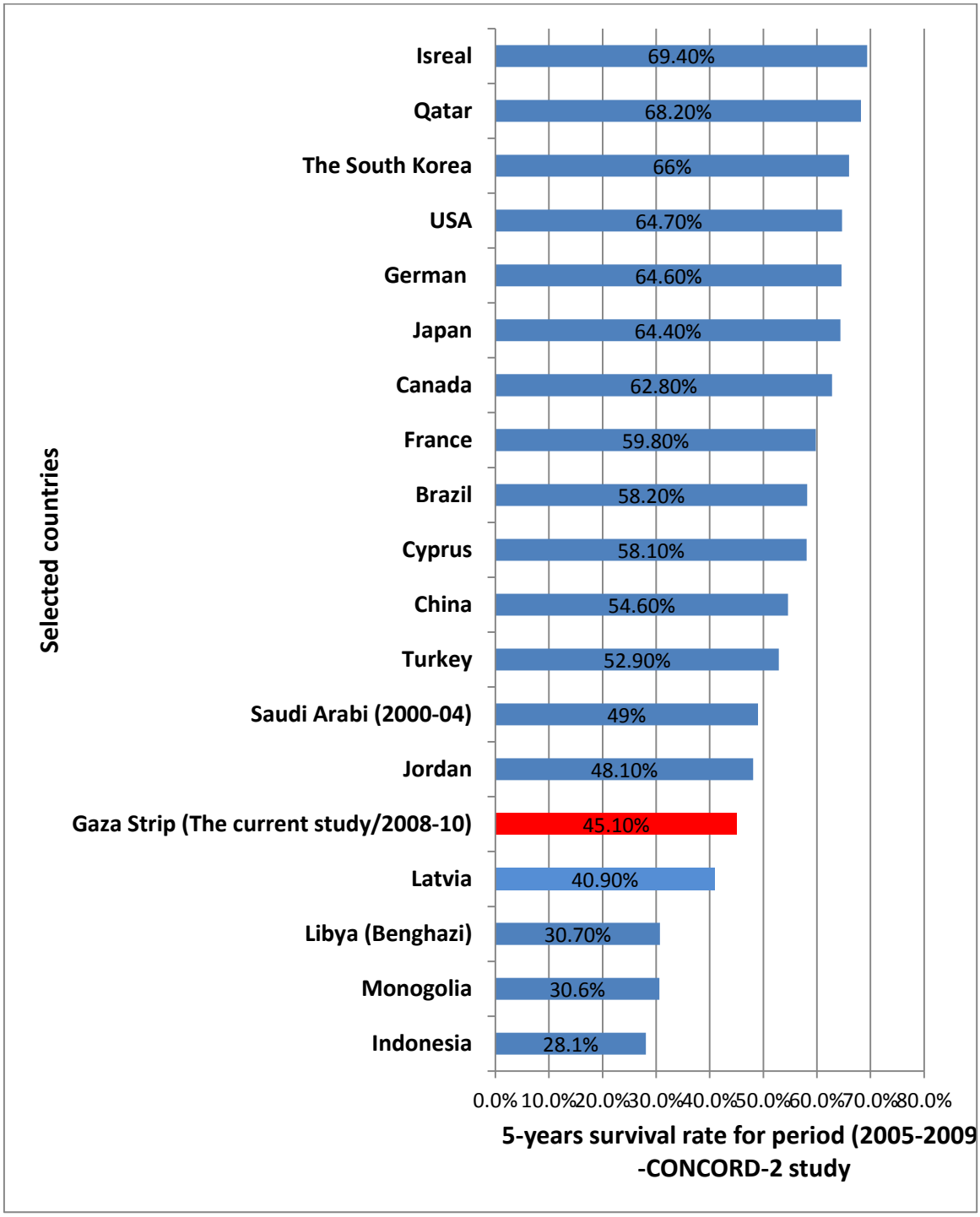


Source: (Mayo clinic, 2017)

Annex (4): Top Five Cancer among Gaza Strip population at period (2009-2014)

	Type of cancer	Cases No.	% of all cancers
1	**Breast Cancer**	1283	18.1
2	**Colorectal Cancer**	709	10
3	**Lung Cancer**	522	7.3
4	**Leukemia Cancer**	490	6.9
5	**Lymphoma Cancer**	409	5.8

Annex (5): Global survival difference in 5-years survival rate from CRC compared to the current study result (Gaza Strip)



Source: Data retrieved from CONCORD-2 study, and the current study result regarding GS, while the figure is self-constructed.

Annex (6): An official letter of approval from the Helsinki Committee in the Gaza Strip

المجلس الفلسطيني للبحث الصحي

Palestinian Health Research Council

تعزيز النظام الصحي الفلسطيني من خلال مأسسة استخدام المعلومات البحثية في صنع القرار

Developing the Palestinian health system through institutionalizing the use of information in decision making

Helsinki Committee

For Ethical Approval

Date: 01/08/2016 **Number:** PHRC/HC/149/16

Name: MURAD B. ELRON **الاسم:** مراد بشير الرن

We would like to inform you that the committee had discussed the proposal of your study about:

نفيدكم علماً بأن اللجنة قد ناقشت مقترح دراستكم حول:

Survival Analysis of the Registered Colorectal Cancer Cases in The Gaza Strip

The committee has decided to approve the above mentioned research. Approval number PHRC/HC/149/16 in its meeting on 01/08/2016

و قد قررت الموافقة على البحث المذكور عاليه بالرقم والتاريخ المذكوران عاليه

Signature

1 Member

Member

Chairman

Genral Conditions:-

1. Valid for 2 years from the date of approval
2. It is necessary to notify the committee of any change in the approved study protocol.
3. The committee appreciates receiving a copy of your final research when completed

Specific Conditions:-

E-Mail:pal.phrc@gmail.com

Gaza - Palestine غزة - فلسطين

شارع النصر - مفترق العيون

Annex (7): Official letter from Al Quds University to the Ministry of Health

Al-Quds University
Jerusalem
School of Public Health

جامعة القدس
القدس
كلية الصحة العامة

التاريخ: 2016/10/26

حضرة الدكتور/فؤاد العيسوي المحترم
الوكيل المساعد–وزارة الصحة

تحية طيبة وبعد،،،

الموضوع: مساعدة الطالب مراد الرن

نرجو تكرم سيادتكم بالعلم بأن الطالب المذكور أعلاه يقوم بإجراء بحث بعنوان:

"Survival Analysis of the Registered Colorectal Cancer Cases in the Gaza Strip"

كمتطلب للحصول على درجة الماجستير في الصحة العامة–مسار الإدارة الصحية، وعليه نرجو التكرم بمساعدة الطالب في الحصول على كشف بشهادات الوفاة لحالات الوفاة من سرطان القولون.
علماً بأن الطالب حاصل على موافقة هلسنكي

و اقبلوا فائق التحية و الاحترام،،،

د. بسام أبو حمد
منسق عام برامج الصحة العامة
فرع غزة

نسخة
- الملف

Jerusalem Branch/Telefax 02-2799234
Gaza Branch/Telefax 08-2644220 -2644210
P.O. box 51000 Jerusalem

فرع القدس / تلفاكس 02-2799234
فرع غزة / تلفاكس 08-264420-2644210
ص.ب. 51000 القدس

Annex (8): Official approval letter from Ministry of Health

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State of Palestine

Ministry of health

دولة فلسطين

وزارة الصحة

التاريخ:16/08/2016

السيد : ناصرالدين رافت مصطفى ابوشعبان حفظه الله
مدير عام بالوزارة/الإدارة العامة لتنمية القوى البشرية - /وزارة الصحة
السلام عليكم ورحمة الله وبركاته ,,,

الموضوع/ تسهيل مهمة باحث/ مراد الرن

التفاصيل //

بخصوص الموضوع أعلاه، يرجى تسهيل مهمة الباحث/ **مراد بشير الرن** الملتحق ببرنامج ماجستير الادارة الصحية – كلية ... الصحة العامة - جامعة القدس أبوديس في إجراء بحث بعنوان

" Survival Analysis of the Registered Colorectal Cancer Cases in the Gaza Strip"

حيث الباحث لبيانات الحالات التي أصيبت بمرض سرطان القولون في الفترة مابين (2008-2010) من وحدة نظم المعلومات، تم الاطلاع على الملف الطبي لهؤلاء المرضى أرشيف أقسام الأورام في مجمع الشفاء الطبي ومستشفى غزة الأوربي بإشراف د.خالد ثابت رئيس قسم الأورام في مجمع الشفاء الطبي مع العلم أن البحث المذكور قد حصل على موافقة لجنة أخلاقيات البحث الصحي(لجنة هلسنكي)، والباحث قد وقع مع المشرف والجامعة على الحفاظ على سرية البيانات و المعلومات التي يحصل عليها، بما لا يتعارض مع مصلحة العمل وضمن أخلاقيات البحث العلمي ، دون تحمل الوزارة أي أعباء

...وتفضلوا بقبول التحية والتقدير

محمد ابراهيم محمد السرساوي
- مدير دائرة/الإدارة العامة لتنمية القوى البشرية

التحويلات

- محمد ابراهيم محمد السرساوي(مدير دائرة)
- كمال صبحي عبدالحميد موسى(مدير اداري)
- عبد اللطيف محمد محمد الحاج(مدير عام بالوزارة)
- عبد اللطيف محمد محمد الحاج(مدير عام بالوزارة)
- يوسف فوزي اسماعيل العقاد(طبيب رئيس قسم)
- يوسف فوزي اسماعيل العقاد(طبيب رئيس قسم)
- ناصرالدين رافت مصطفى ابوشعبان(مدير عام بالوزارة)
- هاني بسطان ارميح الوحيدي(مدير وحدة)
- ناصرالدين رافت مصطفى ابوشعبان(مدير عام بالوزارة)

ناصرالدين رافت مصطفى ابوشعبان(مدير عام بالوزارة) ←	إجراءاتكم بالخصوص
رائد يوسف احمد عبد الرازق(رئيس قسم اداري) ←	لعمل اللازم
منجت عباس خضر حسن (مدير عام بالوزارة) ←	إجراءاتكم بالخصوص
يوسف فوزي اسماعيل العقاد(طبيب رئيس قسم) ←	إجراءاتكم بالخصوص
اتحاد شكري شاكر شبير(رئيس قسم اداري) ←	لعمل اللازم
كمال صبحي عبدالحميد موسى(مدير اداري) ←	لعمل اللازم
عبد اللطيف محمد محمد الحاج(مدير عام بالوزارة) ←	إجراءاتكم بالخصوص
خالد حمدي خليل الدهشان(مدير عام بالوزارة) ←	للإطلاع و توجيهاتكم بالخصوص
منجت محمد يوسف محيسن(وكيل وزارة مساعد) ←	إجراءاتكم بالخصوص

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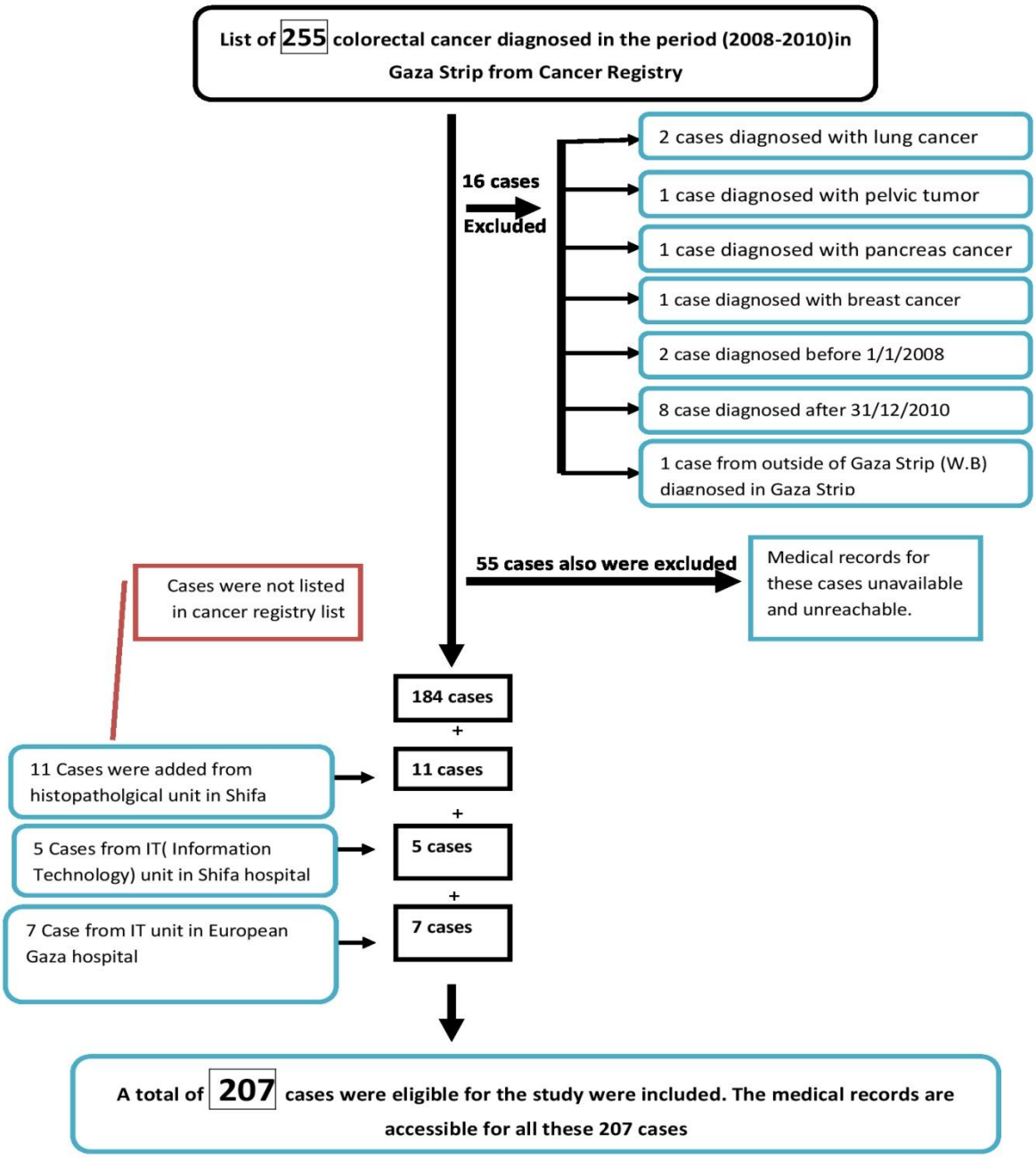
Annex (9): Inclusion and exclusion process for cases of the study population



Annex (10): The main steps for data collection with detailed information.

- **The First Step:** At start, the researcher got on a list for colorectal cancer cases who were diagnosed in the period (2008-2010) from PCR which contained 255 cases. Each case was defined with full name, ID no., and date of diagnosis. The list was reviewed for repeated cases and validity of ID no. The researcher found two repeated cases (were removed from the list) and 55 cases with wrong ID number. But by use of Palestinian civilian record version-2009 the ID numbers were corrected except 3 cases. (Theses 3 cases removed from the list). Annex (7) explains selection of cases in detail and causes for exclusion some of cases.
- **The Second Step:** In parallel with first step the researcher reviewed all histopathological reports which were done at the period 2008-2010 in Al-Shifa hospital, the reports were not computerized, so it was hard to access the CRC cases. So the researcher asked for help from team of three nurses who trained on reviewing histopathological report and help from histopathological team. About 3000 histopathological report were reviewed to find all cases had colorectal carcinomas biopsies in the period 2008-2010. As result of this reviewing, the researcher found 98 cases with colorectal carcinomas. Matching these cases with the main list from cancer registry, eleven cases were not listed in the list, so they added to the list and other repeated cases were removed.
- **The third step:** In EGH, Information technology unit has records for each case treated in the hospital. The researcher asked IT unit for list of patients which were defined with full name and ICD-10 (C18: colon cancer, C19: recto-sigmoid junction, C20: rectum cancer, C21: anal canal). IT unit supplied the researcher a list containing 114 cases. This list was matched with main list to remove the repeated cases. Finally 75 cases were not listed at main list (Cancer registry list), but when the researcher reviewed the medical records for these 75 cases found the majority of medical records had other diagnosis rather than which were recorded in IT unit and coded with ICD-10 except 7 cases found with correct diagnosis comparable to recorded ICD-10. These cases were included in the study.
- **The fourth step:** The researcher obtained vital status for cases listed for the study to know the location of medical records for each case, from Births and Deaths Directorate in MOH. As showed at tables (3.1) there were four places for the medical records for cases and the researcher began with cases in oncology outpatient clinic

archive in SPH and finished with cases in the central archive in MOH. All medical records were reviewed carefully to complete abstract sheet items and needed information for the study such as present health status of patient, medical history, date of confirmed diagnosis (Histopathological report) histological type, tumor site, stage at diagnosis, signs and symptoms and duration before date of confirmed diagnosis, treatment information, type of treatment, place of treatment and others. TNM staging at diagnosis as described in table (2.1) was not available in the majority of medical records, so the researcher with kind help from supervisor (supervisor is oncologist and director of oncology department of Al-Shifa hospital) assigned the TNM staging for all cases as possible as information were present about tumor size, nodal status, and metastatic status.

- **The fifth step:** As overall the main list of cases contained 262 cases. At time of finishing all available medical records, found that 55 cases out from 262 cases their medical records were not available in the four places of medical records stores. So they were excluded, the final number for eligible cases and included in the study was 207. The excluded 55 cases who had not medical records, the researcher went to cancer registry and asked him if there are any additional information about these cases especially date of confirmed diagnosis. Cancer registry has the date of confirmed diagnosis for these 55 cases were recorded in the cancer registry but it was the same date of death of the cases. Cancer registry justified that by that they did not find the medical records for these cases and they took information about cause of death from death certificate for cases. Regarding this current study, case without correct date of confirmed diagnosis was not eligible for the study.
- **The sixth step:** prepared and organized all completed abstract sheet for 207 eligible cases for entering in SPSS program version-22.

Annex (11): Data abstract sheet

Data Abstract Sheet

Serial number .....

Patient Socio-demographic Data (at diagnosis)

Patient ID		Gender	
Patient Birth Date		Age	
Education Level		Marital Status	
Work		Residency	

Patient Health Profile

Co-morbidity Status:	☐ Yes	☐ No	☐ Unreported		
If Yes, Specify	☐ DM	☐ HTN	☐ Others		
Patient History of cancer:	☐ Yes	☐ No	☐ Unreported		
If Yes, Specify.....					
Family History of cancer:	☐ Yes	☐ No	☐ Unreported		
If Yes, Specify.....					
Weight ☐ kg	Height ☐ cm	BSA ☐			
Obesity:	☐ Non-Obese	☐ Obese	Unreported ☐		
Smoking:	☐ Non-Smoker	☐ Smoker	Unreported ☐		
Physical activity status					
Diet:					

Tumor characteristics

Date of Confirmed diagnosis	.....				
Histological Type	☐ Non mucinous	☐ Mucinous	☐ Unknown	☐ Others.....	
Stage at Diagnosis (TNM)	☐ Stage I	☐ Stage II	☐ Stage III	☐ Stage IV	☐ Unknown
Grade	☐ Grade 1	☐ Grade 2	☐ Grade 3	☐ Grade 4	☐ Unknown
Site	☐ Rt. Colon	☐ Lt. colon	☐ Rectum		

Disease Free Status

☐ **Non metastatic case**	☐ **Metastatic case**	
Date of surgery: ☐	Distant Metastasis to	Date
Date of disease recurrences:		
Notes:.....		
	Date of disease progression :.....	

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Healthcare information

Main Hospital: ☐ European Gaza Hospital ☐ Alshifa Hospital

Diagnosis process

First signs and symptoms related to colorectal cancer .

☐ Bleeding/rectum ☐ Constipation ☐ Abdominal pain ☐ Intestinal obstruction
☐ Diarrhea ☐ Others,..... Date:

Endoscopy examination

Endoscopy type: ☐ Colonoscopy ☐ others , ...
Date:
Where done: _____
Endoscopy results: _____

Medical management

☐ **Surgery**	Surgery procedure: _____ Date: _____ Place: _____
☐ **Chemotherapy** Date: _____ Place: _____	Chemotherapy protocol : ☐ Folfox ☐ Folfiri ☐ Avastin ☐ Xeloda ☐ Erbitux ☐ others,..... Notes: _____
☐ **Radiotherapy** Date: _____ Place: _____	☐ Definitive Radiotherapy ☐ Palliative Radiotherapy Notes: _____
☐ **Chemoradiotherapy**	Date: _____ Place: _____
☐ **Palliative care** Date: _____ Place: _____	☐ Chemotherapy ☐ Radiotherapy ☐ Symptomatic (Non-chemotherapy, Non-radiotherapy)

Vital Status Information

☐ Alive	
☐ Dead	Date of Death: _____
☐ Other causes of Death, specify:	_____
☐ Unknown	Note: _____

Notes:

Annex (12): Arabic abstract

تحليل معدلات البقاء على قيد الحياة لدى مرضى سرطان القولون والمستقيم في قطاع غزة.

اعداد الباحث/ مراد بشير درويش الرن

إشراف / د. خالد عطا ثابت

ملخص الدراسة:

مقدمة

يشهد قطاع غزة تحولا وبائيا يتمثل في زيادة عبء الامراض الغير المعدية، حيت تعتبر أمراض القلب و أمراض السرطان أكثر الامراض شيوعا. ويعتبر سرطان القولون والمستقيم واحدا من اكثر أنواع السرطان شيوعا في العالم وقطاع غزة. حيث تفيد تقارير وزارة الصحة في غزة بان سرطان القولون والمستقيم يحتل المرتبة الاولى في السرطانات الاكثر شيوعا بين مجتمع الذكور والمرتبة الثانية لكلا الجنسين بعد سرطان الثدي.

معرفة مقاييس معدلات البقاء على قيد الحياة لمرضى السرطان و تحليل محدداتها اساسي وضروري لتقييم فعالية النظام الصحي ككل في التعامل مع سرطان القولون والمستقيم من حيث الاكتشاف المبكر، التشخيص، والعلاج .هذه المقاييس تستخدم بشكل واسع حول العالم خاصة في الدول المتقدمة.

هذه الدراسة الاولى من نوعها لدراسة وتحليل محددات البقاء على قيد الحياة لمرضى سرطان القولون والمستقيم في قطاع غزة، على ان تساهم نتائج الدراسة في تحسين فعالية النظام الصحي في مواجهة سرطان القولون والمستقيم من خلال تقديم بيانات أولية حول معدلات البقاء على القيد لدى المرضى.

الهدف من الدراسة

الهدف العام من هذه الدراسة هو معرفة معدلات البقاء على قيد الحياة لمرضى سرطان القولون والمستقيم الذين تم تشخيصهم خلال الفترة (2010-2008)، بالإضافة الى دراسة أهم العوامل المؤثرة فيها.

منهجية الدراسة

الدراسة شملت جميع مرضى سرطان القولون والمستقيم الذين تم تشخيصهم خلال الفترة (2008-2010) والمسجلين في المركز الوطني لرصد الاورام وعيادات الاورام في مستشفيات قطاع غزة . العدد الاجمالي للحالات المقبولة في الدراسة 207 حالة بعد أن تم استثناء 71 حالة لأسباب مختلفة.

حصل الباحث على كافة الموافقات الادارية من وزارة الصحة لتسهيل العمل في مرافقها كما التزم الباحث بكافة المعايير الاخلاقية البحثية والامانة العلمية والحفاظ على سرية معلومات المرضى حيث تم الحصول على موافقة لجنة هلسنكي. قام الباحث بنفسه بجمع البيانات من ملفات المرضى وتفريغها في نموذج صمم مسبقا لتسهيل عملية جمع البيانات وتحليلها حيث تم مراجعة ملفات المرضى في ارشيف عيادة الاورام في مستشفى د. عبد العزيز الرنتيسي التخصصي للأطفال، ارشيف مستشفى غزة الأوروبي، الارشيف المركزي في مستشفى الشفاء، والارشيف المركزي في وزارة الصحة. تم استخدام برنامج SPSS نسخة 22 للتحليل الإحصائي وتم حساب معدلات البقاء على قيد الحياة باستخدام طريقة كابلان-ماير حيث أظهر بان معدل البقاء على قيد الحياة بعد خمس سنوات من اكتشاف سرطان القولون بلغ 45% هذا المعدل يتماشي مع النتائج المتوفرة من دول الجوار كالسعودية والأردن ولكنه يقل بشكل واضح عما هو الحال في غالبية الدول المتقدمة. ومن جهة أخرى اظهر التحليل الاحصائي للمتغير الواحد (univariate) بان هناك عدة عوامل لها دلالة احصائية وهي المرض المصاحب، السمنة، التدخين، مرحلة المرض عند التشخيص، النوع النسيجي للورم، مكان نشأة المرض ونوعية العلاج. وبالرغم من ذلك اظهر التحليل متعدد العوامل (Cox regression-multivariate) بان ثلاثة عوامل فقط لها دلالة احصائية في التأثير على معدلات البقاء على قيد الحياة لدى مرضى السرطان القولون والمستقيم وهي (مرحلة المرض عند التشخيص، المرض المصاحب، نوعية العلاج).

اهم التوصيات:

توصي الدراسة بضرورة اطلاق برنامج وطني شامل للكشف المبكر عن سرطان القولون والمستقيم خاصة للأشخاص فوق عمر الخمسين سنة وذوي عوامل الخطر، بالإضافة الى اطلاق حملات توعوية لزيادة الاهتمام الرسمي والشعبي حول مدى عبء سرطان القولون والمستقيم ومعرفة مسبباته وأهم عوامل الخطر بهدف الوقاية منه. ومن الجيد اجراء دراسات اخرى تشمل عينة اكبر من المرضى ودراسات أخرى تهتم بخدمات السرطان المقدمة في قطاع غزة.