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Risk of death of colon cancer according to the time elapsed between the diagnose and the first surgery in Puerto Rico

By

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Abstract

Background/Objectives: According to the Puerto Rico Central Cancer Registry (PRCCR), during the period 2010-2014, colorectal cancer was the second leading cancer with the highest incidence in both sexes. Previous studies have reported inconsistency on the effects of surgery delay after the cancer diagnose. The main objective of this study is to assess the risks of death according to the time that elapses between the diagnostic and the first surgery among patients with colon cancer, controlling for demographical and clinical characteristics.

Methods: To reach this aim we used the data collected from the PRCCR. The data analyze were from patients with colon cancer diagnosed between the years 2009 to 2012 with a maximum time of observation for death occurrence of 5 years after the first surgery. The surgery delay was defined as the time between the cancer diagnose and the first surgery, which was categorized as follow: 1) 1-14 days, 2) 15-28 days, and 3) 29+ days. The Kaplan-Meier method and the Cox model was used to evaluate the risk of death by different types of delay.

Results: Our final dataset was composed of 1,408 patients with an almost equally distribution of male and female patients; the age mean was 67.0 years ($\pm$12.6). The risk of death for patients with more than 29 days of surgery delay is 29.1% (HR: 0.699, 99.5% CI: 0.477-0.897) lower than patients with surgery within the first two week after diagnose, after adjusting for all characteristics.

Conclusion: It was observed that risk of death is higher among patients who had less

time between diagnose and first surgery. Even though our results do not support our research hypothesis, it supports the ongoing question of the effects of delay in other studies. Future studies should consider the type of surgery (elective or emergency) and different risk factors not studied in this research, such as lifestyle, nutrition and genetic factors.

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Chapter 1

Introduction

Colorectal cancer is any cancer that affects the colon and the rectum that may spread to other part of the body. The American Cancer Society estimates that about 1 in 22 men and 1 in 24 women in the United States of America (USA) will develop colorectal cancer during their lifetime [1]. According to the Puerto Rico Central Cancer Registry (PRCCR), during the period 2010-2014 [2], colorectal cancer was the second leading cancer with the highest incidence in both sexes. During this period in Puerto Rico (PR), colorectal cancer represented the 12.9% of the total cancer cases among men and 11.6% among women; in addition, on average in PR, 1,035 men and 842 women were diagnosed annually with colorectal cancer during this period [2]. During 2016 in PR, there were 15,938 new cases of cancer reported. Among these cases, there were 1,350 cases reported of colon cancer, this represented 8.5% of all new cases of cancer [3].

The American Cancer Society estimates that about 51,020 deaths are caused by colorectal cancer, resulting the second most common cause of cancer death in USA

for 2019 [1]. Colorectal Cancer is the primary cause of death among patients with cancer in PR during the period 2010 to 2014 for both sexes combined; about 13.0% of cancer deaths among men and 13.3% of cancer deaths among women [2]. On average during this period in PR, 387 among men and 312 among women died annually from colorectal cancer [2]. In PR during 2016, 5,152 persons died of some type of cancer in Puerto Rico; among these deaths, 12.4% were due to colon cancer [3].

In PR, colorectal cancer is a leading cause of cancer-related deaths, but screening rates still remain low [5]. According to Serra et al, colorectal cancer is largely preventable through screening [5]. According to the Behavioral Risk Factor Surveillance System in 2016, approximately 57.1% of adults aged 50-75 years residing in PR had a current colorectal cancer screening test. Screening occurred more frequently in men, people aged 65 to 75, and people who were insured, who were more likely insured by Medicare [6]. In PR, colon cancer incidence and mortality rates have stayed relativley constant in the last 15 years [3]; the age-standardized incidence is about 26-29 new cases per 100,000 persons and the age-standardized mortality is 13-14 deaths per 100,000 persons (see table 1.1).

After diagnose of cancer, the first treatment varies according to the type and stage of the cancer; the treatment could be chemotherapy, radiotherapy, combination of these, and surgery. In colon cancer, the first treatment is always surgery, unless the tumor has spread far enough that a surgery will not cure the cancer; for that reason, chemotherapy is used to help the patient live longer [16]. According to Pruitt et al study, patients with colon cancer in the USA usually had their first surgery 13 day after diagnose [7].

Table 1.1: Incidence and Mortality of colon cancer*

Year	**Age-Standardized Incidence (x 100,000)**	**Age-Standardized Mortality (x 100,000)**
2000-2004	26.8	13.8
2005-2009	28.8	13.6
2010-2014	27.8	13.1
*Age-Standardized rate using the Direct Method (USA 2000 as the standard population)		

The purpose of this thesis was to assess how the mortality among patients with colon cancer is affected by delay between the diagnose of this cancer and the first surgery to treat this condition. Previous studies have reported inconsistency on the impact of the delay in treatment after the diagnose of colon cancer [7] [21] [22] [23]. In this study, the delay in treatment among colon cancer was determined by the dates available at the PRCCR during the period of 2009 to 2012. The PRCCR by law receive all the information related to cancer from doctors and hospitals about new cases or deaths [4]. We defined 4 years after the first surgery, as the maximum time of observation for death occurrence. Initially, we describe the survival probabilities at different time periods using the method of Kaplan-Meier (KM), according to demographics and cinical characteristics among patients with colon caner. Then, we used the Cox Proportional-Hazard Regression model to estimate the hazard ratio (HR) between the delay of treatment and the risk of death after controlling for the

following predictors: sex, age, medical plan, marital status, socioeconomic position, stage of colon cancer, grade of tumor and Charlson Comorbidity Index.

Chapter 2

Background

This chapter describes all relevant works related to the primary objective of this research, which is:

> To assess the risks of death according to the time that elapses between the diagnostic and the first surgery among patients with colon cancer, controlling for the following variable: sex, age, medical plan, marital status, socioeconomic position, stage of colon cancer, grade of tumor and Charlson Comorbidity Index

Colorectal cancer is a type of cancer that its primary anatomic location starts in the colon or rectum. The colon is the largest part of the large intestine. It is part of the digestive system in the human body, which helps digest the food we eat and convert it to energy to fuel our bodies [8]. The rectum is located in the last few inches of the colon, which is where the waste or leftover from digestive system is stored until the body is ready to move the waste outside the body throughout the anus [8]. Colon cancer develops when the cells become to grow uncontrollably and are accumulated

in the colon developing a tumor. The main functions of the colon, such as digesting food, can be interfere or disrupted when the tumor grows big enough [10]. The colon and rectal cancer can be grouped together because they shared similar functions and are part of the same organ, but their treatments varied [9]. For this reason, it is recommended to analyze them separately.

Colon cancer is classified by stages in order to identify the severity of the condition and to know the most efficient way to treat it. The stage is affected by different factors, such as the location of the primary tumor, tumor size, regional lymph node involvement, and the number of tumor present [14]. To determine the stage of the colon cancer, the physicians usually analyze how long the primary cancer has spread inside the walls of the intestine; in addition, they examine if the primary cancer has spread to other organs in the body [11]. The first stage is stage 0, also called carcinoma in situ, where the abnormal cells have been found in the innermost lining of the colon; this cells can become cancer and spread into nearby normal tissue. After stage 0, Stage I trough IV followed, each stage getting progressively worse while the cancer spreads more throughout the body. In stage I, the cancer has formed and has spread from the innermost lining of the colon to the middle layers. In stage II and III, colon cancer can be divided by letters A,B and C; where A means a lower stage. For example, a patient classified with having stage IIC colon cancer means the cancer is spread more throughout the body compared to a patient classified with having stage IIA colon cancer. In stage II, the cancer has spread from the muscle layer of the colon wall to nearby organs. In stage III, the cancer has spread to nearby lymph nodes, but has yet to spread to distant parts of the body. In Stage IV, through the

lymph system, the cancer has spread to the liver, lung or other part of the body [12]. The lymph system is a series of lymph vessels and lymph node that are part of the immune system. The lymph vessels carry clear water fluid that are called lymph that pass through the lymph nodes, which are structures that contains immune cells that help combat bacteria that pass through it [13].

The first treatment in cancer patients varies by cancer type, such as chemotherapy, radiotherapy, combination of these, and surgery; however, in colon cancer the first treatment is always surgery [16]. In stage I, the cancer has not spread outside of the colon, so usually a standard surgery is only required to remove the part of the colon that has cancer. In stage II, similar to stage I, a surgery is only required, unless adjuvant chemotherapy is recommended by the doctor. Adjuvant chemotherapy is chemotherapy given after the surgery to reduce the risk of the cancer coming back or recurring [10]. In stage III, surgery and adjuvant chemotherapy are the standard treatments for the patients. However, radiation therapy in combination with chemotherapy may be given to patients who are not healthy enough for surgery [16]. Generally, in stage IV, a surgery will not get rid of the cancer, because it has spread to other part of the body. For this reason, chemotherapy is the main treatment in stage IV. However, surgery may help patients live longer if the cancer has only spreaded to some small area in the liver or lung and it can be removed alongside the colon cancer [16]. In our study, we chose to include only patients diagnosed with colon cancer between stage I to III and excluded patients in stage IV. The reason to exclude patients in stage IV is due to the fact that a surgery will most likely not cure the patients.

As well, the cancerous cells are assigned a grade, which indicates how quickly

the tumor will growth and spread to other parts of the body. The grade of the tumor is divided in 4 grades: I) Grade 1 or Well differentiated (Low Grade), II) Grade 2 or Moderately differentiated (Intermediate grade), III) Grade 3 or Poorly differentiated (high grade) and IV) Grade 4 or Undifferentiated (high grade). In Grade 1, the tumor grows and spreads slowly, while in Grade 3-4 the tumor grows and spread out faster [14]. This is important for the treatment of the patients, because a grade 1 tumor generally gives a better prognosis for the patients, thus the doctor has additional time to planned out the best type treatment. Meanwhile, a tumor in a higher grade indicates worst prognosis, thus the physician has to give immediate or aggressive treatment to the patient. In order to simplify our analysis of tumor grade we divided as follows: 1) Low Grade, 2) Intermediate Grade, and 3) High Grade.

In addition to the grade and stage of the cancer, Charlson Comorbidity Index (CCI) is considered a good indicator of survival [17]. The CCI assigns a weight according to the comorbidities; for example, 1 for diabetes, 2 for tumor or 6 for HIV/AIDS [18]. When the comorbidity disease is absent, the weight is 0 [18]. The CCI is a summary of the weight assigned to each patients; higher index is associated with lower survival. In our study, we decided to divide CCI in two groups: 1) patients with zero comorbidity, and 2) patients with one or more comorbidities. The reasoning was that we wanted to compare patients with colon cancer, as their primary condition, with no additional conditions versus patients with colon cancer, as their primary condition, with additional conditions.

Other indicator that affects a patients survival could be external factors, such as their socioeconomic position (SEP) or their health insurance coverage. As stated by

Galobarde et al, SEP refers to "the social and economic factors that influence what positions individuals or groups hold within the structure of a society" [15]. The SEP can be constructed on different indicators, such as: education, income, occupation or housing characteristics. In our study, the SEP of the patient was based on SEP associated to SEP assigned to the municipality the patients reside. For this study, the SEP was categorized as follows: 1) High SEP (Richest municipality), and 2) Low SEP (Poorest municipality). Health insurance or medical plan can be divided into Non-Government Health Plan (private plans) and Government Health Plan (non-private plans). In Puerto Rico, patients diagnosed with colorectal cancer between 2004-2005 in Non-Government Health Plan had higher 5-year survival compared to patients with Government Health Plan (71% vs 49%) [19]. In our study, to simplify the predictor health plan we divided as follows: 1) private plan, 2) non-private plan (which included Medicaid, Medicare and both), and 3) other.

The effects of surgery delay in the survival among patient's colon cancer diagnositc and first cancer surgery have not been widely explored [20]. There have been evidences where reasonable delay in surgery has no impact on the survival of the patient with colorectal or colon cancer [7] [21] [23]; but, there have also been evidence of the contrary [22]. In the first study, patients with treatment delay of less than 31 days had 18% less survival than patients with treatment delay of more than 30 days [23]. In another study, patients with colon cancer with treatment delay between 25-38 days had 91% more survival than patients with treatment delay of less than 25 days [22]. In general, a delay between the time of diagnose and first surgey has not shown association in improving or worsening the survival of the patient with colorectal can-

cer [24]. Stratifying the patients with colorectal cancer by colon cancer and rectum cancer could revealed an association not shown originally described in this studies of only colorectal cancer patients [24].

A variety of studies in different part of the world differ in what are the best intervals of time to categorize the surgery delay among colon cancer patients [20][22][23]. One study examined treatments delay and survival in Canadian patients with stage I to III colon cancer. The authors stratified the patients in two groups; those who had surgery before 30 days and those who had surgery after 30 days [23]. Other study examined the relationship between the average time that elapsed between survival probability and the diagnostic and the major surgery among the patients with colorectal cancer in the England. The researchers divided the surgery delay in the following three groups: 1) surgery before 25 days, 2) surgery between 25-38 days, and 3) surgery between 39-62 days [22]. Another study used SEER-Medicare database to assess the influence of surgery delay in the survival of patients with colon cancer; this database contains information of United State of America (USA) cancer patients covering 14% of USA population. This research divided the surgery delay in the following four groups: 1) surgery before 15 days, 2) surgery between 15-28 days, 3) surgery between 29-42 days and 4) surgery after 43 days [20].

Additionally, each country has different recommended surgery delay. For example in Canada, the recommended surgery delay for a malignant cancer that is neither very aggressive (spreads very quickly) or indolent (spreads very slowly) is 28 days [25]. For patients with a very aggressive cancer the recommended surgery delay is 14 days, while for patients with a indolent tumor is 84 days [25]. In the United Kingdom, the

preferable time to start treatment after cancer diagnose is within the first month [26]. The current set time is less than 62 days for time between when the hospital receive a referral for suspected cancer and the start for treatment, while the waiting time when the doctor agrees a treatment plan and the start of treatment is less than 31 days [26]. Even though there are guidelines for general cases, the delay can vary because of patient's age, tumor site, or even by patient or surgeon decision. In our study, we divided treatment delay in the following three groups: 1) 1-14 days, 2) 15-28 days, and 3) 29+ days. The reasoning for this grouping is due to the fact that there were no conclusive standard to categorize surgery delay; so, we left the first two intervals of surgery delay time with the same length.

Chapter 3

Problem Statement

The main objective of this study is to assess the risks of death according to the time that elapses between the diagnostic and the first surgery among patients with colon cancer, controlling for demographical and clinical characteristics. The clinical characteristics for this study were: 1) Stage of Colon Cancer, 2) Grade of Tumor and 3) Charlson Comorbidity Index. The demographical characteristics for this study were: 1) Sex, 2) Age, 3) Medical plan, 4) Marital status, 5) Socioeconomic position of the municipality the patient resides. The sex variable was classified as: males and females. The age variable was classified in 3 groups: patients younger than 65 years, patients between 65 and 75 years and patients older than 75 years. The medical plan variable was classified in 2 groups: private and non-private. The marital status variable was classified in 2 groups: married and unmarried. The socioeconomic position index was classified in two groups: high and low. The stage of colon cancer was classified in 3 groups: Stage I, Stage II, and Stage III. The grade of the tumor variable is classified in 3 groups: Low, Intermediate and High. The Charlson Comorbidity Index

variable is classified in 2 groups: no comborbidities (0) and 1+ comorbidities.

This type of study has not been done in Puerto Rico; the studies related with this topic in different countries have given conflicting results. Due to the uncontrollable growth of cancerous cells, we would expect that a delay in the treatment would affect the progression of the cancer and, as consequence, the survival of the patient worsened. Our working hypothesis is that the survival probability is increased among patients when the surgery is reduced. Based on the database of the PRCCR, our study group was composed of patients with colon cancer diagnosed between the years 2009-2012. We had a maximum of 5 years of observations after the first surgery to assess their survival; so, the maximum date of observation was December 31, 2017 for death occurrence.

Chapter 4

Methods

The aim of this study is to estimate the magnitude of association between the treatment delay for colon cancer and the risk of death, controlling for different potential confounders. To reach this aim we used the data collected from the Puerto Rico Central Registry of Cancer (PRCCR). By law number 113 of the year 2010: "*Ley de Registro Central de Cáncer de Puerto Rico*", this registry receives all cases with a diagnosis of cancer in Puerto Rico. In the initial database, there were 2,810 patients with colon cancer as their primary cancer diagnosed between the years 2009 to 2012. We excluded 999 patients with diagnostic date equal or greater than the surgery date and 109 patients with date of last contact equal or lesser than the surgery date; at this point, we had 1702 patients. Moreover, we excluded 39 patients who lasted more than 6 months without receiving a surgery; thus, we have 1663 so far. The reasoning was that the doctor usually plans the surgery within 3 months after the diagnostic of colon cancer [25] [26]. Finally, we excluded patients who had missing values in the demographic or clinical data. Therefore, the final sample size of our study group was

1,408 patients, which means we are left with 50.1% of the initial database.

The purpose of the study is to observe the survival time after the first surgery, under the following treatment delay groups: 1) 1-14 days, 2) 15-28 days and 3) 29+ days. We defined 5 years after the first surgery, as the maximum time of observation for death occurrence; thus, the maximum cutoff date for a patient was December 31st, 2017. Any patient declared dead after this date was considered alive during the study period.

Initially, we describe the survival probabilities at different time periods using the method of Kaplan-Meier (KM), denoted as *S(t)*. In our study, *S(t)* is defined as a survival function, which indicates the probability of surviving at least until t days. We graphically represent *S(t)* using a step function, which means that *S(t)* remains constant until the next time a death occur [27]. Each graph is plotted according to different clinical and demographic characteristics to visually compare survival probabilities. If

$$S(t = 1000 \text{ days}) = 0.8$$

means that 80% of probability that the patients will survive at least until 1000 days after surgery. Additionally, we estimated with a 95% and 99.5 % confidence level for the median survival time t^* $\big(\ \mathrm{S}(t^*) = 0.5\big)$ for each category of the clinical and demographic characteristics. Furthermore, we used the Logrank test to assess the null hypothesis that there is no difference in the survival between the groups of each clinical and demographic characteristics at any time $[H_0 : S_1 = S_2]$; which means that we are assessing if the difference between survival curves are the same during

the study period [31]. This test is only used to test significance, for this reason we used the hazard ratio (HR) to assess the relative difference between the risk of the death and the categories of different factors [31].

So, the hazard function, denoted *h(t)*, was estimated to assess the risk of dying exactly after time t, given that the patient survive until t, using the Cox Proportional Hazard Regression model [27], as follows:

$$h(t; x;) = h_0(t)e^{\beta_D * D + \sum \beta_j X_j}$$

where D indicates the category of treatment delay, x_j indicates potentional confounders (clinical and demographical characteristics), h_0(t) indicates hazard risk at initial condition, and β indicates the coefficients associated to the predictors (D, X'S) [30]. Based on this model, we estimated the magnitude of association of interest using the HR between the two categories of the clinical or demographic characteristics of the study, one of this categories indicates the reference group and the other group was the comparison group, as follows: $HR_{\text{comparison vs reference group}} = e^{\beta_D}$. Then, we explored the HR using the following predictors in the model with the surgery delay variable: 1) surgery delay with demographical variables, 2) surgery delay with clinical variables, and 3) surgery delay with all the predictors. If the HR is greater than 1, indicates higher risk of death in comparison to the reference group; in this case the category of delay with minimum time was using the reference group. If the HR is less than 1, indicates lower risk of deaths in comparison to the reference group. For example: if the HR is 0.75 this means that the comparison group has 25% less

risk of deaths than the reference group; meanwhile, if the HR is 1.5 means that the comparison group has 50% higher risk of death than the reference group.

When interpreting Cox models is necessary to take into account the proportional hazards assumption [28]. This assumption implies that for any two groups of comparison, the hazard function is proportional at any point in time, so the HR does not vary with times [28]. This means that if a group has three times the risk of dying than the reference group at the beginning of the study, then at different time interval the risk of dying for that group compared to the reference group would remain the same. Additionally, if the assumption is true, then the hazard curves are parallel to each other, which mean they are proportional and do not cross. This assumption can be tested either graphically or test-based [28]. One way to test this assumption is to check if the Kaplan-Meier survival curves cross; if they do not cross suggest that the proportional hazard assumption is met. Even if the assumption fails, it may be because of the small sample size in the study that causes error in the estimation of the survival curve [28]. For that reason, it is recommended using a test-based method with a statistical software to calculate the p-value; if the p-value is greater than 0.05, then we have strong evidence to accept the proportional hazard assumption.

In order to estimate the adjusted HR for different predictors, we assessed previously if the magnitude of association of interest (HR) changes in different conditions (different sex, different age groups, public versus private health plans,...); it means assessing if interaction effects are present. If these effects are present, we cannot estimate an adjusted HR. In this case, we have to estimate HR stratified for different conditions; for example, estimate one HR for each stage of the colon cancer, if the

interaction terms between delay and stage were significant. As a consequence, we performed the likelihood ratio test to explore potential interaction terms in the Cox model, formed with delay treatment and each one of the clinical and demographic characteristics. This test compares likelihood of two models, one with interaction terms versus a model without these terms [29]. When the difference between these two models is statistically significant (i.e., p-value < 0.005), then the model that fits the data better is the one with interactions terms.

In order to reach our aims, we used the statistical software STATA 14. This software provides dialogue-windows that facilitate the programming to use different statistical methods. STATA has the option to convert and transfer databases of different formats, such as Excel. STATA has a user-friendly programming for this study, compared to other programming language that need more detailed programming. Additionally, for our statistically significance analysis we will include p-value less than 0.05 and 0.005. Utilizing p-value < 0.05 may result in a false positive, which means that utilizing p-value < 0.005 should improve the reliability and duplicability of our results [32]. For this reason, we will include both p-value in their own separate tables to be able to compare the results and give us a clearer understanding of what is significant.

Chapter 5

Results

5.0.1 Description of the Study Group

Our final dataset was composed of 1,408 patients with colon cancer diagnosed between the years 2009 and 2012. In table 5.1, we assessed potential selection bias by comparing certain characteristics between excluded and included patients. Based on demographic characteristics, we observe significant difference (p-value < 0.05) mainly in medical plan; we found that the excluded patients had lower proportion of private medical plan. Based on clinical characteristics, we observe significant difference (p-value < 0.05) in the stage of colon cancer. Among the excluded patients, we found that around one fifth of all case were in stage I, meanwhile only one fourth of the included patients were in this stage.

Table 5.1: Data Comparison between included and excluded patients

Characteristics	**Excluded (%)**	**Included (%)**
Sex	P-value = 0.23	
Male	697 (49.9)	735 (52.20)
Female	699 (50.1)	673 (47.80)
Age at Diagnostic	P-value = 0.05	
< 65 years	500 (35.8)	562 (39.9)
65-74 years	438 (31.4)	434 (30.8)
75+ years	458 (32.8)	412 (29.7)
Stage of Colon Cancer	P-value = 0.003	
Stage I	356 (25.50)	283 (20.10)
Stage II	492 (35.24)	540 (38.35)
Stage III	548 (39.26)	585 (41.55)
Grade of the Tumor	P-value = 0.46	
Low	313 (27.2)	359 (25.5)
Intermediate	743 (64.6)	942 (66.9)
High	95 (8.3)	107 (7.6)
Medical Plan	P-value = 0.02	
Private	295 (23.3)	376 (27.5)
Non-Private	969 (76.7)	992 (72.5)

In table 5.2, we summarize the distribution of patients with colon cancer by different demographical characteristics. The sex distribution was almost equally distributed: 52.2% males and 47.8 % females. The average age was 67 ($\pm$12.6) years; there was approximately equal distribution between patients of age 65 to 74 years (30.8%) and patients older or equal to 75 years (29.2%). The vast majority of the patient (73.3%) did not have private medical. Additionally, the majority of patients were married (57%) and resided in a municipality with high socioeconomic position (63.4%).

In table 5.3, we summarize the distribution of patients with colon cancer by different clinical characteristics. The majority of the patients had colon cancer on stage II (38.4%)and III (41.6 %). The tumor of most patients had an intermediate grade with a 66.9%. Around 60% of patients had zero comorbidities; thus, most patient had colon cancer as their primary condition with no additional conditions.

Table 5.2: Demographical Characteristics of Patients with Colon Cancer, Puerto Rico, 2009-2012

Characteristics	**N**	**%**
Sex		
Male	735	52.20
Female	673	47.80
Age at Diagnostic		
< 65 years	562	39.91
65-74 years	434	30.82
75+ years	412	29.26
Mean (± SD)	67.0 (±12.6)	
Marital Status		
Unmarried	521	37.00
Married	803	57.03
Unknown	84	5.97
Medical Plan		
Private	376	26.70
Non-Private	992	70.45
Other	40	2.84
Socioeconomic Position		
Low	515	36.58
High	893	63.42
Total	1,408	100.00

Table 5.3: Clinical Characteristics of Patients with Colon Cancer, Puerto Rico, 2009-2012

Characteristics	**N**	**%**
Stage of Colon Cancer		
Stage I	283	20.10
Stage II	540	38.35
Stage III	585	41.55
Grade of the Tumor		
Low	359	25.50
Intermediate	942	66.90
High	107	7.60
Charlson Comorbidity Index		
0	845	60.01
1+	563	39.99
Total	1,408	100

Table 5.4: Surgery Delay Distribution for Patients with Colon Cancer, Puerto Rico, 2009-2012

Characteristics	**N**	**%**
Surgery Delay		
1-14 days	613	43.54
15-28 days	362	25.71
29+ days	433	30.75
Median (p25,p75)	18 (6,34)	
Total	1,408	100

In table 5.4, we summarize the distribution of patients with colon cancer by different delay. Approximately, 43.5 % of the patients had the first surgery delay in the first two weeks after being diagnosed of colon cancer. The median time for surgery delay after diagnose was 18 days. Additionally, 25% of the patients had surgery between the first 6 days after diagnose and 25% of patient had surgery after 34 days after diagnose.

5.0.2 Survival Probability using Kaplan-Meier Method

In Figures 5.1 to 5.9, we describe the survival probabilities at different time periods using the method of Kaplan-Meier (KM), including the log-rank test for the different demographical and clinical characteristics $[H_0 : S_I(t) = S_{II}(t)]$. In figure 5.1, we observe that patients who had their first surgery within the first 14 days after

diagnose was significantly lower probabilities of survival than the other two surgery delay groups (p-value < 0.005). In figure 5.2, we observe that the probabilities of survival were slight lower in male patients than in female patients; however, the log rank test indicates no significant difference between sexes using p-value >0.005. In figure 5.3, we observed that the probabilities of survival for patients older than 75 years were noticeably less than the other two age groups; we verified this with the log rank test that showed there was significant difference between the age groups (p-value < 0.005). In figure 5.4, we observed that the probabilities of survival for patients that were married were significantly higher compared to patients that were unmarried (p-value < 0.005). In figure 5.5, we observed that the probabilities of survival for patients with private medical plan were significantly lower than patients with non-private medical plan (p-value < 0.005). In figure 5.6, the result suggest that the probabilities of survival did not varied in patients residing in municipalities with high socioeconomic position versus patients residing in municipalities with low socioeconomic position, using p-value > 0.005. In figure 5.7, we observed that the probabilities of survival for patient with cancer stage III were significantly lower than patients with cancer stages I or II (p-value < 0.005). In figure 5.8, we observed the probabilities of survival for patients with had high tumor grade were significantly lower than patients with low or intermediate tumor grades (p-value < 0.005). In figure 5.9, we observed that the probabilities survival curves of Charlson Comorbidity Index crossed, so we did not interpret the log-rank test.

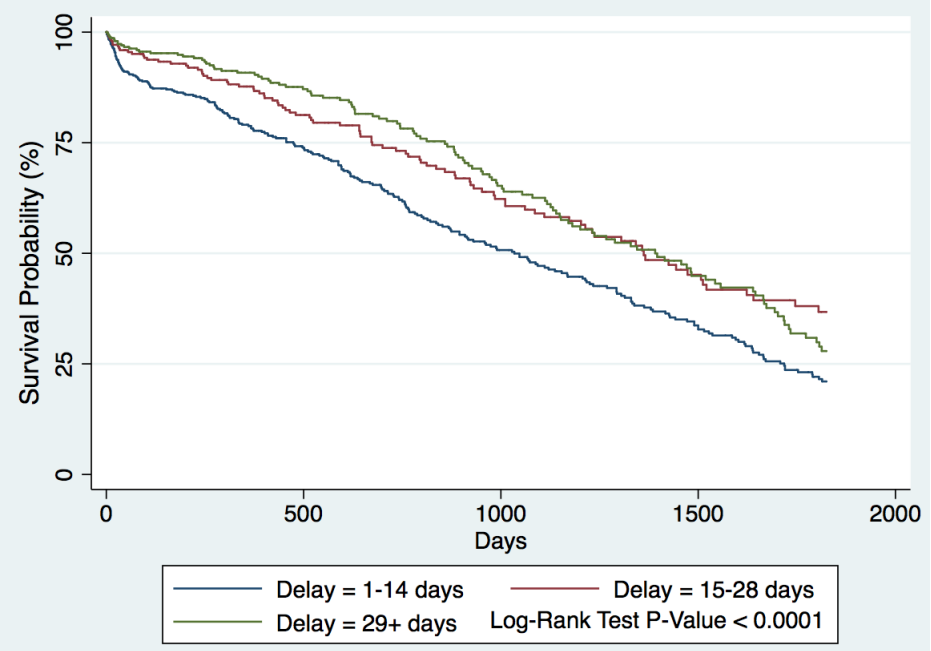

Figure 5.1: Kaplan-Meier Estimator by Surgery Delay

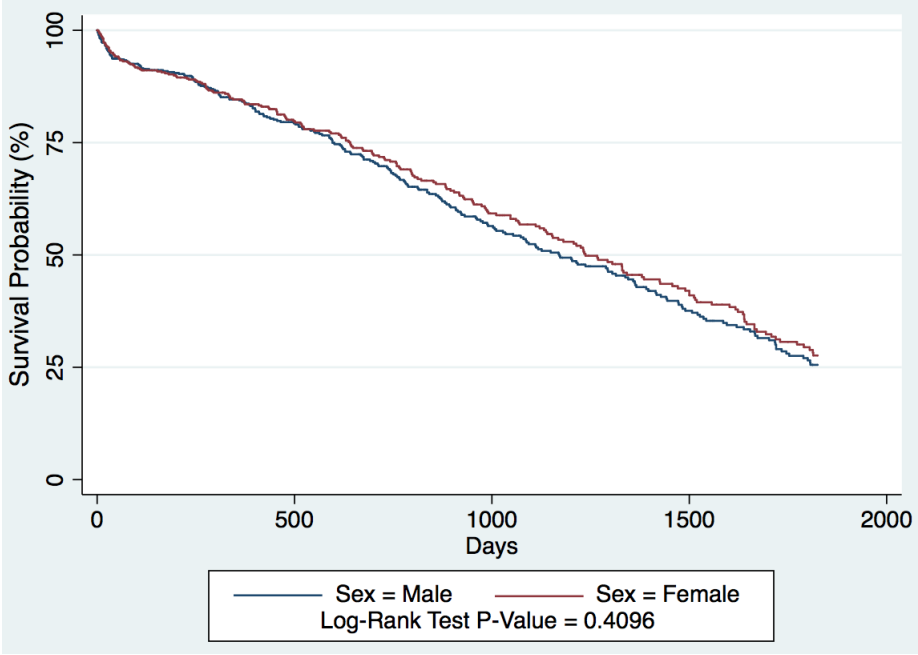

Figure 5.2: Kaplan-Meier Estimator by Sex

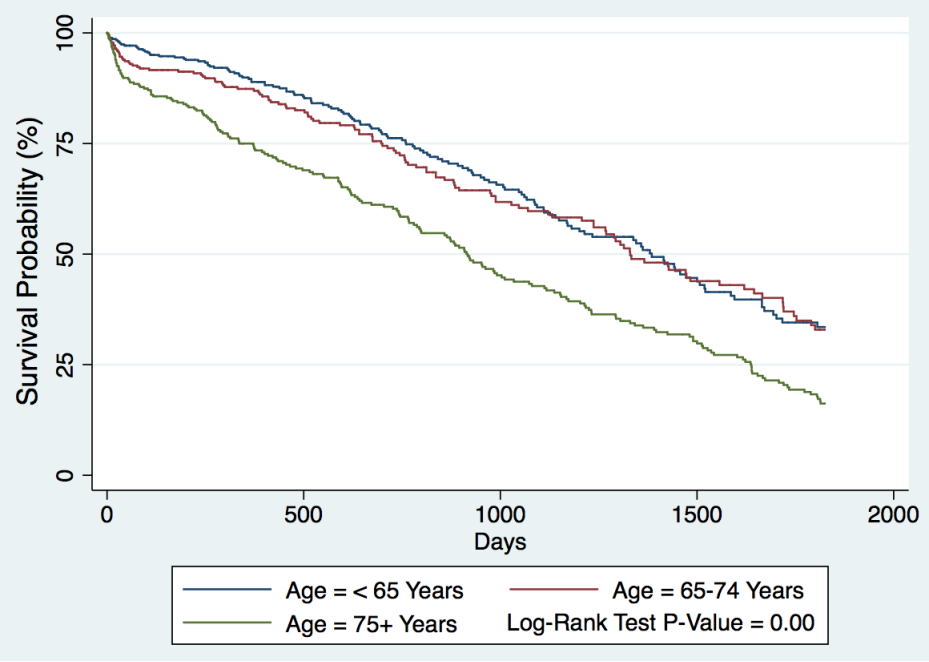

Figure 5.3: Kaplan-Meier Estimator by Age Group

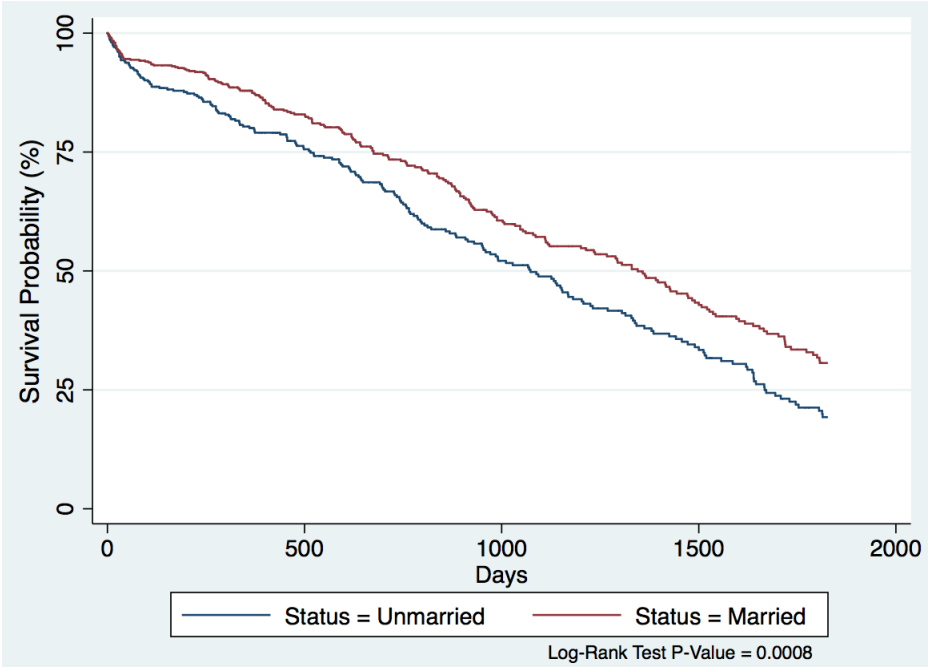

Figure 5.4: Kaplan-Meier Estimator by Marital Status

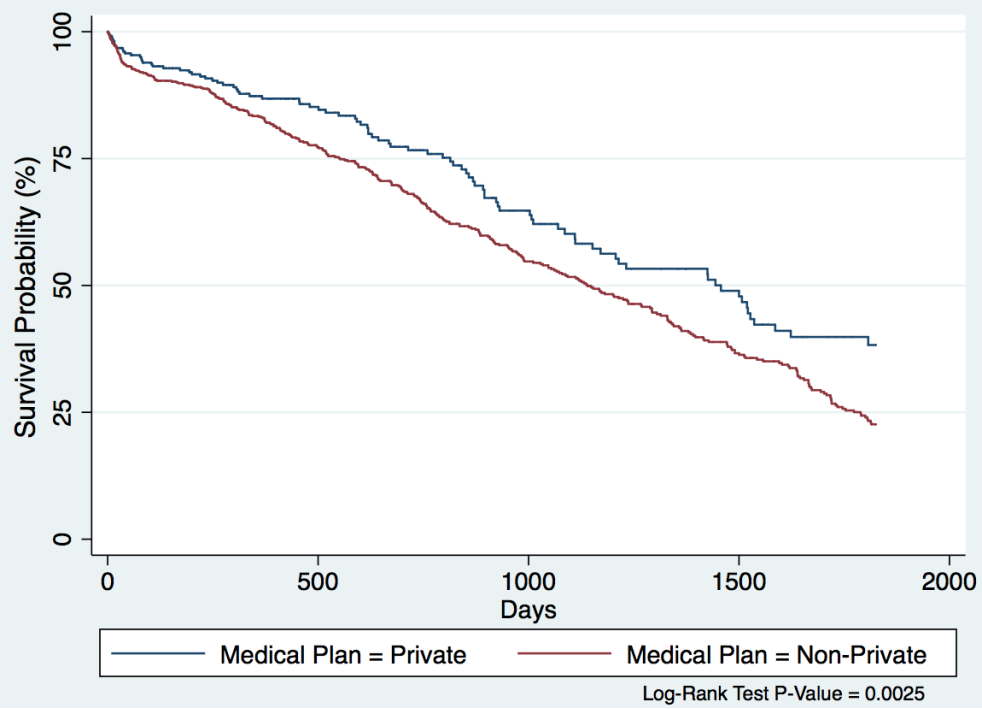

Figure 5.5: Kaplan-Meier Estimator by Medical Plan

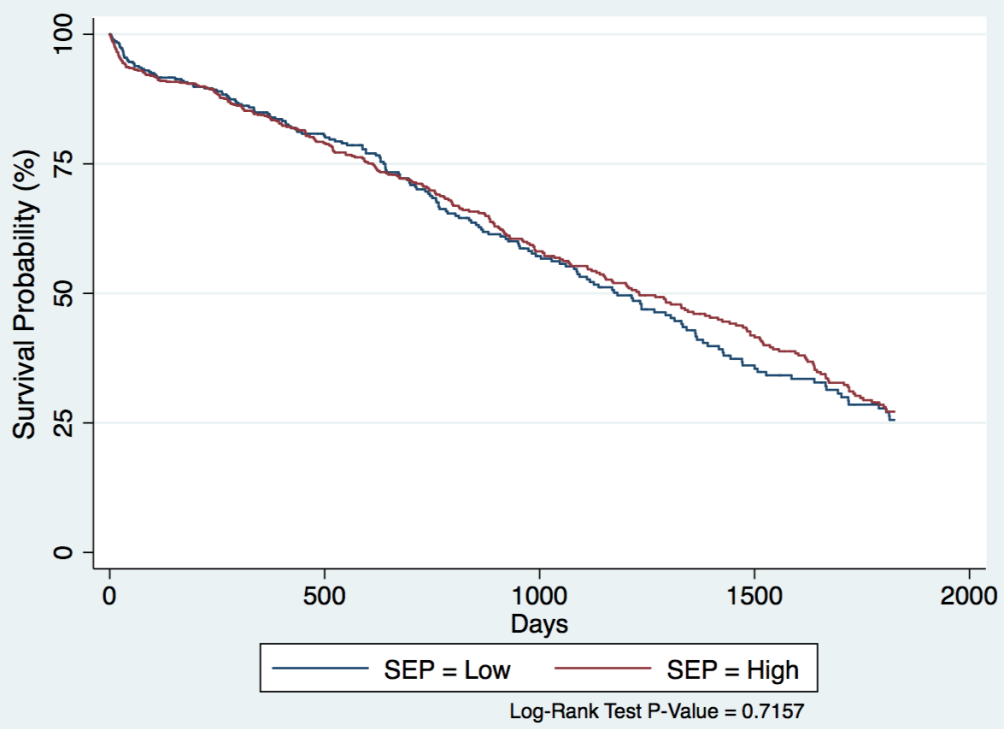

Figure 5.6: Kaplan-Meier Estimator by Socioeconomic Position

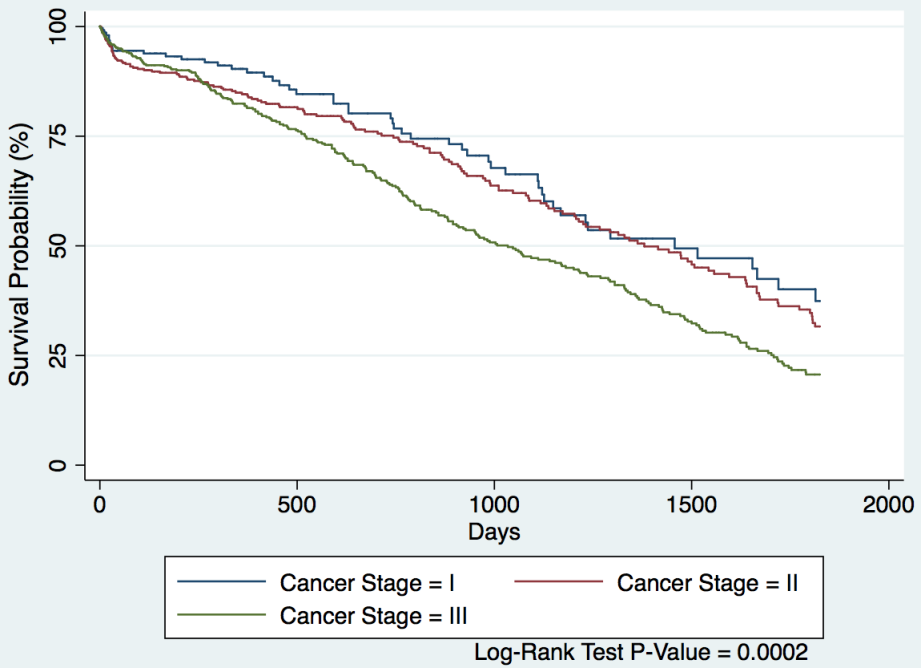

Figure 5.7: Kaplan-Meier Estimator by Stage of Cancer

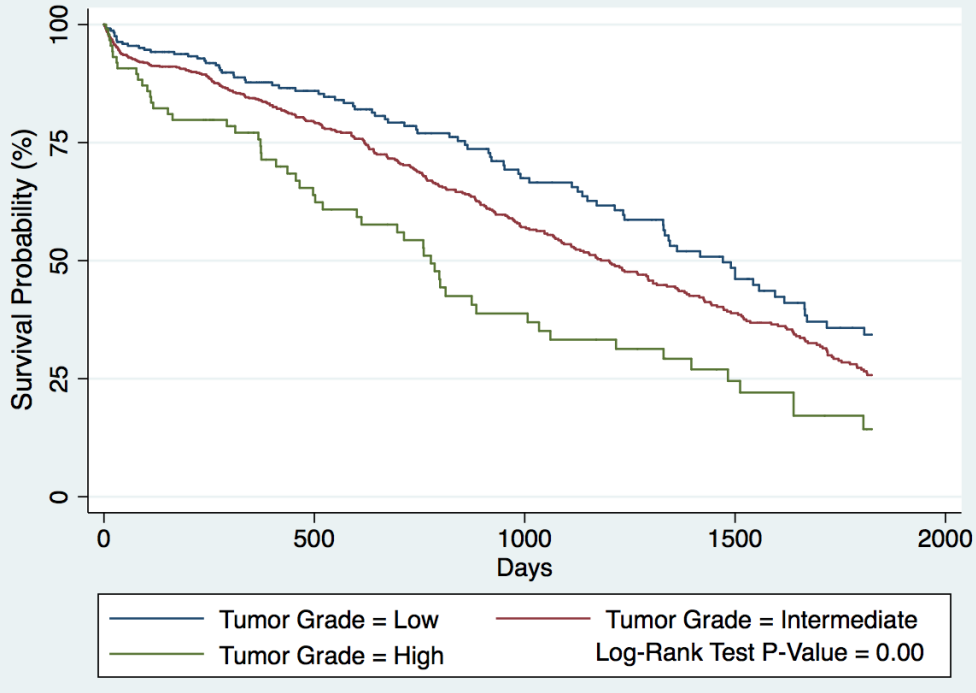

Figure 5.8: Kaplan-Meier Estimator by Tumor Grade

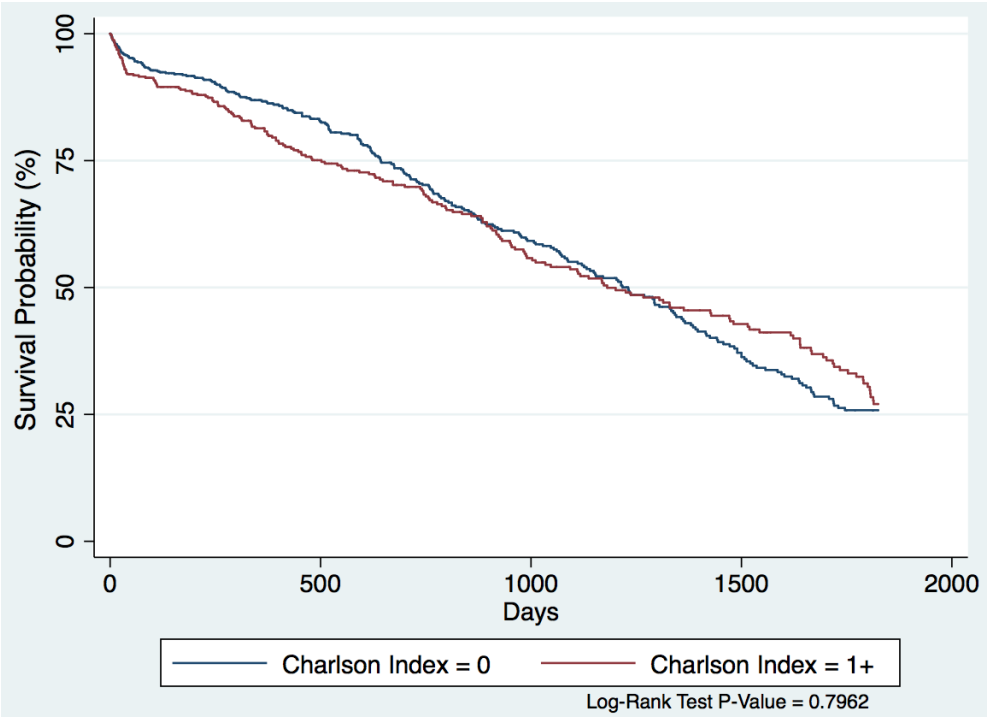

Figure 5.9: Kaplan-Meier Estimator by Charlson Comorbidity Index

In Figures 5.10 to 5.12, we describe the survival probabilities at different time periods using the method of KM according to the delay category among patients in different stages. For each of these graph, we included the log-rank test. The purpose of these graph is to visualize how the stage modifies the relationship between survival and delay. In figure 5.10, we observe no conclusive survival pattern according to the delay among patients with stage I cancer. In figure 5.11, we observe that patients with Stage II who had their first surgery within the first 14 days after diagnose was significantly lower probabilities of survival than the other two surgery delay groups (p-value < 0.0001). In figure 5.12, we observe that patients with Stage III who had their first surgery within the first 14 days after diagnose was significantly lower probabilities of survival than the other two surgery delay groups (p-value < 0.0001).

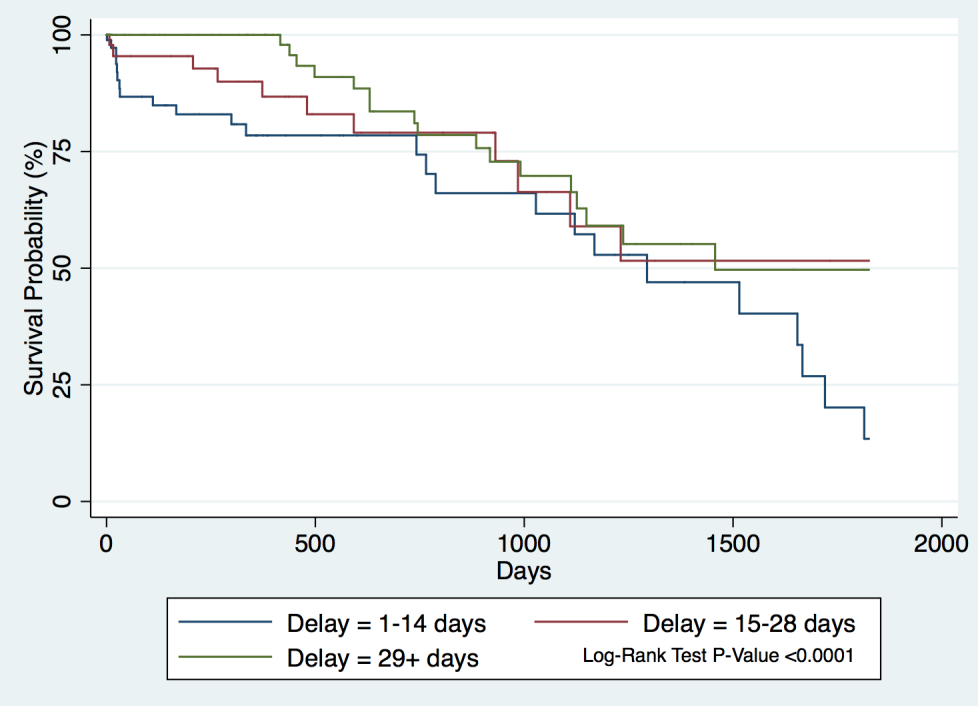

Figure 5.10: Kaplan-Meier Estimator by Delay among Stage I Patients

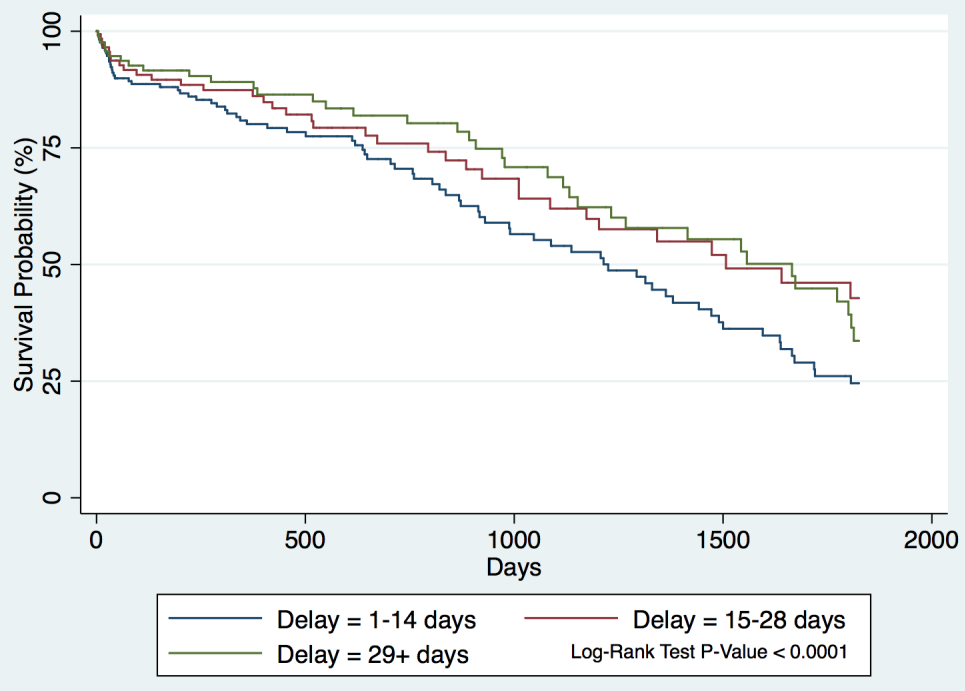

Figure 5.11: Kaplan-Meier Estimator by Delay among Stage II Patients

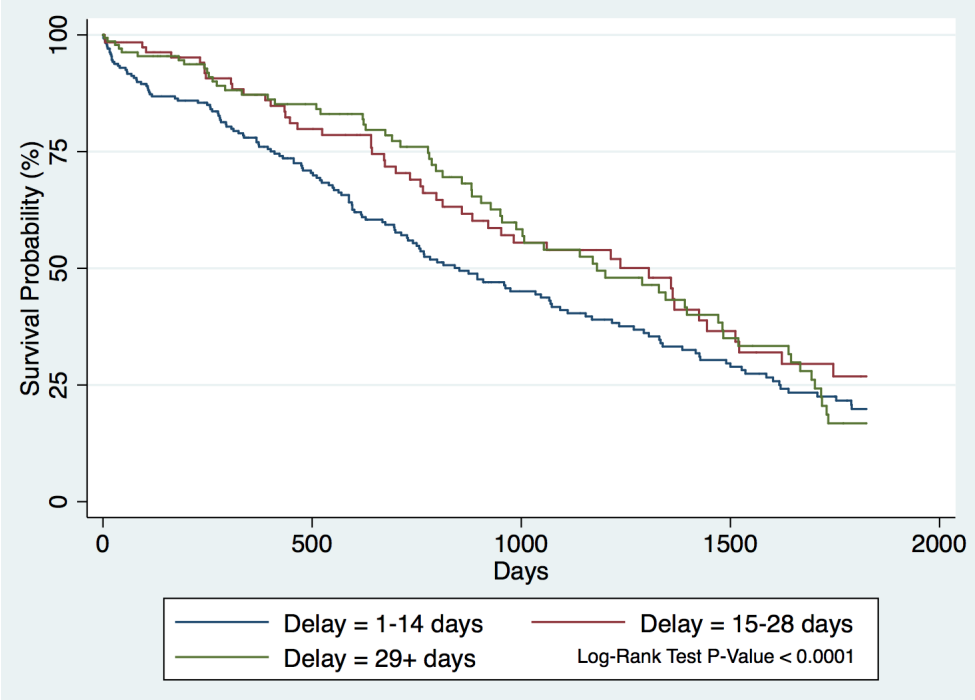

Figure 5.12: Kaplan-Meier Estimator by Delay among Stage III Patients

5.0.3 Median Survival Time

To explore the distribution of survival time in our study group we estimate the median survival time for each demographical and clinical characteristics with a 95% and 99.5% confidence interval (CI). In table 5.5, we observed median survival time increased when the surgery delay is increased. For example, there was 50% of probability that patients with two weeks surgery delay will survive until 1034 days (∼2.8 years) compared to 1391 days (∼3.8 years) for patients that had surgery delay greater than 29 days. So, patients with surgery closer to the diagnosis had worst survival than those who wait longer.

Table 5.5: Median Survival for Surgery Delay Distribution for Patients with Colon Cancer, Puerto Rico, 2009-2012

Characteristics	**Median Survival Time (Days)**	**95% CI**	**99.5% CI**
Surgery Delay			
1-14 days	1034	872-1207	814-1293
15-28 days	1362	1173-1623	1011-1805
29+ days	1391	1152-1639	1126-1667

In table 5.6, we observed the demographical characteristics groups with their median survival days. We observed that male and female patient had similar median survival time as shown in KM graph; the median survival time was 1171 days ($\sim$ 3.2 years) for male patients and 1237 days ($\sim$3.4 years) for female patients. Also, we observed that patients with private medical plan had higher median survival time compared to non-private medical plan; the median survival time was 1457 days ($\sim$ 4.0 years) for patients with private medical plan and 1140 days ($\sim$ 3.1 years) for patients with non-private medical plan. The highest difference in median survival time was between patients younger than 65 years and older than 74 years; the median survival time was 1385 days ($\sim$ 3.8 years) for patients younger than 65 years and 917 days ($\sim$ 2.5 years) for patient older than 74 years.

Table 5.6: Median Survival for Demographical Characteristics of Patients with Colon Cancer, Puerto Rico, 2009-2012

Characteristics	**Median Survival Time (Days)**	**95% CI**	**99.5% CI**
Sex			
Male	1171	1028-1345	971-1396
Female	1237	1132-1425	1047-1500
Age at Diagnostic			
$<$ 65 years	1385	1171-1519	1111-1665
65-74 years	1330	1237-1620	1047-719
75+ years	917	788-1073	742-1152
Marital Status			
Unmarried	1073	930-1203	858-1305
Married	1345	1117-1483	1061-1527
Medical Plan			
Private	1457	1111-1586	1070-.
Non-Private	1140	1011-1293	974-1330
Socioeconomic Position			
Low	1181	1028-1333	954-1380
High	1231	1111-1425	1034-1483

Table 5.7: Median Surival for Clinical Characteristics of Patients with Colon Cancer, Puerto Rico, 2009-2012

Characteristics	**Median Survival Time (Days)**	**95% CI**	**99.5% CI**
Stage of Colon Cancer			
Stage I	1457	1126-1814	1110-.
Stage II	1380	1203-1595	1117-1665
Stage III	1034	895-1201	852-1289
Grade of the Tumor			
Low	1471	1237-1665	1149-1718
Intermediate	1201	1073-1305	1011-1385
High	777	520-1007	456-1061
Charlson Comorbidity Index			
0	1231	1088-1342	1061-1385
1+	1181	990-1471	952-1543

In table 5.7, we observed the clinical characteristics groups with their median survival days. We observed that patient with no comorbidities and patient with comorbidities had similar median survival time; the median survival time was 1231 days ($\sim$ 3.4 years) for patients with no comorbidities and 1181 days ($\sim$3.2 years) for patients with comorbidities. In addition, we observed that patients with Stage III cancer had higher median survival time compared to patient with stage I cancer; the

median survival time was 1457 days ($\sim$ 4.0 years) for patients with stage I cancer and 1034 days ($\sim$ 2.8 years) for patients with Stage III cancer. The highest difference in median survival time was between patients with low grade tumor and high grade tumor; the median survival time was 1471 days ($\sim$ 4.0 years) for patients with low grade tumor and 777 days ($\sim$ 2.1 years) for patient with high grade tumor.

5.0.4 Magnitude of association between risk of death and different characteristics

To assess the magnitude of association between the risk of death and different characteristics, we estimated the hazard ratio (HR) with 95% and 99.5% confidence interval; the result were summarize in table 5.8. The risk of dying in female patients was 7.4% (HR: 0.926) lower than the risk of dying in male patients. The risk of dying in patients who were older than 75 years is 79.5% (HR: 1.795) higher than the risk of dying in patients who were younger than 65 years. The risk of dying in patients who where married was 27.8% (HR: 0.722) lower than the risk of dying in patients who where unmarried. The risk of dying in patients with non-private medical plan was 42.3% (HR: 1.423) higher than the risk of dying in patients with private medical plan. The risk of dying in patients who had stage III of colon cancer is 65.3% (HR: 1.653) higher than the risk of dying in patients who had stage I of colon cancer. The risk of dying in patients who had a high tumor grade is two times (HR: 2.182) higher than the risk of dying in patients who had a low tumor grade. In table 5.11, it shows that the risk of dying in patients who had a delay between 15 to 28 days is 34.2%

(HR: 0.658) lower than the risk of dying in patients who had a delay within the first two weeks. In table 5.12, it shows that the risk of dying in patients who had a delay of more than 29 days is 34.4% (HR: 0.656) lower than the risk of dying in patients who had a delay within the first two weeks.

To test the risk of death is affected by the combination of different factors, we first fitted different Cox models with surgery delay and different demographical and clinical characteristics to estimate their hazard ratio with different confidence interval. Secondly, we fitted three Cox model with different combination of predictors to estimate their hazard ratio with different confidence interval; the specifics predictors of the models were: 1) surgery delay and the demographical characteristics, 2) surgery delay and clinical characteristics, and 3) surgery delay with demographical and clinical characteristics. Previously, we assessed if interaction effects are present under different conditions (different sex, different age groups, different cancer stage, different tumor grade,...). Due to the fact that if the HR for surgery delay and risk of death is modified for each category of these predictors we cannot estimate an adjusted HR.

As a consequence, in table 5.9 and 5.10 we included the likelihood ratio test to compare the likelihood of a model with interaction terms versus the likelihood of a model without these terms. When the p-value for each model was higher than 0.05 and subsequently higher than 0.005, suggest that the model that fits the data better is the one without interactions terms. Additionally, in table 5.9 and 5.10 we included the p-value for the proportional hazards assumption. Utilizing p-value $<$ 0.005 for significance, we have that there is strong evidence to accept proportional

hazard assumption for every model, except for surgery delay with Charlson Comorbidity Index. Utilizing p-value < 0.05 for significance, we have that there is strong evidence to accept proportional hazard assumption for only two models: 1) delay and the demographical characteristics, and 2) delay with demographical and clinical characteristics. Thus, for our model with all the predictors there is a very strong evidence to accept the proportional hazards assumption, which means that the HR of interest does not vary with survival times. After checking the results of the likelihood ratio test and proportional hazards assumption, we can assess the HR for the different Cox models.

Table 5.8: Magnitude of the association between risk of death and different characteristics among colon cancer patient in Puerto Rico, 2009-2012

Characteristics	**Hazard Ratio**	**95% CI**	**99.5% CI**
Sex			
Female vs. Male[(1)]	0.926	0.770-1.113	0.711-1.205
Age at Diagnostic			
65-74 years vs. $<$ 65 years[(1)]	1.083	0.848-1.382	0.764-1.535
75+ years vs. $<$ 65 years[(1)]	1.795**	1.444-2.231	1.315-2.451
Marital Status			
Married vs. Unmarried[(1)]	0.722**	0.597-0.874	0.550-0.949
Medical Plan			
Non-Private vs. Private[(1)]	1.423**	1.131-1.790	1.024-1.976
Socioeconomic Position			
High vs Low[(1)]	0.966	0.800-1.166	0.737-1.265
Stage of Colon Cancer			
Stage II vs. Stage I[(1)]	1.203	0.877-1.650	0.765-1.891
Stage III vs. Stage I[(1)]	1.653**	1.227-2.228	1.078-2.534
Grade of the Tumor			
Intermediate vs. Low[(1)]	1.352*	1.063-1.720	0.958-1.908
High vs. Low[(1)]	2.182**	1.550-3.072	1.337-3.562
Charlson Comorbidity Index			
1+ vs. 0[(1)]	1.025	0.851-1.234	0.786-1.336
(1) = Reference Group; * = p-value $<$ 0.05; ** = p-value $<$ 0.005			

Table 5.9: Assessment of Interaction Terms in the Cox Models with 2 predictors and evaluation of the proportional hazard assumption

Predictors of Cox Models	**Likelihood Ratio Test (p-value)**	**Test of Proportional Hazard Assumption (p-value)**
Delay	-	$> 0.005*$ (0.008)
Delay + Sex	> 0.005 (0.219)	$> 0.005*$ (0.021)
Delay + Age	> 0.005 (0.932)	$> 0.005*$ (0.019)
Delay + Marital Status	> 0.005 (0.744)	$> 0.005*$ (0.015)
Delay + Medical Plan	> 0.005 (0.060)	$> 0.005*$ (0.037)
Delay + SEP	> 0.005 (0.360)	$> 0.005*$ (0.017)
Delay + Cancer Stage	> 0.005 (0.687)	$> 0.005*$ (0.035)
Delay + Tumor Grade	> 0.005 (0.575)	$> 0.005*$ (0.032)
Delay + Charlson Index	> 0.005 (0.541)	< 0.005 (0.002)

Table 5.10: Assessment of Interaction Terms in the Cox Models with more than 2 predictors and evaluatio of the proportional hazard assumption

Predictors of Cox Models	**Likelihood Ratio Test (p-value)**	**Test of Proportional Hazard Assumption (p-value)**
Delay + Age + Sex + Medical Plan + Marital Status + SEP	> 0.005 (0.307)	> 0.005 (0.133)
Delay + Cancer Stage + Tumor Grade + CCI	> 0.005 (0.785)	$> 0.005*$ (0.022)
Delay + Age + Sex + Medical Plan + Marital Status + SEP + Cancer Stage + Grade + CCI	> 0.005 (0.627)	> 0.005 (0.177)
*** = p-value $<$ 0.05**		

In table 5.11, we include the HR estimation for comparing surgery after the first two week of the diagnostic versus surgery delay after 15-28 day of the diagnostic. The Cox models predictors were surgery delay with each one of the demographical and clinical characteristics; each model suggested significant results (p-value<0.005). For the model with surgery delay and sex, it shows that the risk of dying in patients who had a delay between 15 to 28 days is 34.5% (HR: 0.655) lower than the risk of dying in patients who had a delay within the first two weeks after adjusted for sex. For the model with surgery delay and age, it shows that the risk of dying in patients who had a surgery delay between 15 to 28 days is 33.8% (HR: 0.662) lower than the

risk of dying in patients who had a surgery delay within the first two weeks after adjusted for age. For the model with surgery delay and medical plan, it shows that the risk of dying in patients who had a surgery delay between 15 to 28 days is 31.4% (HR: 0.686) lower than the risk of dying in patients who had a surgery delay within the first two weeks after adjusted for medical plan. For the model delay with cancer stage, it shows that the risk of dying in patients who had a surgery delay between 15 to 28 days is 31.7% (HR: 0.683) lower than the risk of dying in patients who had a surgery delay within the first two weeks after adjusted for cancer stage. For the model delay with tumor grade, it shows that the risk of dying in patients who had a surgery delay between 15 to 28 days is 34.0% (HR: 0.660) lower than the risk of dying in patients who had a surgery delay within the first two weeks after adjusted for tumor grade.

Table 5.11: Magnitude of the association between surgery delay and risk of death for different characteristics adjusted with one predictor: 15-28 days vs. 1-14 days

Predictors of Cox Models	**$HR_{15\text{-}28 \text{ days vs. } 1\text{-}14 \text{ days}}$**	**95% CI**	**99.5% CI**
Delay	0.658**	0.519-0.835	0.468-0.925
Delay + Sex	0.655**	0.516-0.830	0.466-0.920
Delay + Age	0.662**	0.522-0.840	0.471-0.932
Delay + Marital Status	0.677**	0.534-0.860	0.481-0.953
Delay + Medical Plan	0.686**	0.540-0.871	0.487-0.966
Delay + SEP	0.658**	0.519-0.835	0.468-0.925
Delay + Cancer Stage	0.683**	0.538-0.868	0.486-0.962
Delay + Tumor Grade	0.660**	0.521-0.838	0.470-0.929
Delay + Charlson Index	0.657**	0.518-0.833	0.467-0.923
**** = p-value < 0.005**			

In table 5.12, we include the HR estimation for comparing surgery after the first two week of the diagnostic versus surgery after 29 day of the diagnostic, adjusting for one predictor. The Cox models predictor were surgery delay with each one of the demographical and clinical characteristics; each HR was statistically significant (p-value < 0.005). For the model with delay and sex, it shows that the risk of dying in patients who had a delay after 29 days is 35.2% (HR: 0.648) lower than the risk of dying in patients who had a delay within the first two weeks after adjusted for sex. For the model with delay and age, it shows that the risk of dying in patients who had

a delay after 29 days is 34.0% (HR: 0.660) lower than the risk of dying in patients who had a delay within the first two weeks after adjusted for age. For the model with delay and medical plan, it shows that the risk of dying in patients who had a delay after 29 days is 33.2% (HR: 0.668) lower than the risk of dying in patients who had a delay within the first two weeks after adjusted for medical plan. For the model with delay and cancer stage, it shows that the risk of dying in patients who had a delay after 29 days is 31.2% (HR: 0.688) lower than the risk of dying in patients who had a delay within the first two weeks after adjusted for cancer stage. For the model with delay and tumor grade, it shows that the risk of dying in patients who had a delay after 29 days is 34.5% (HR: 0.655) lower than the risk of dying in patients who had a delay within the first two weeks after adjusted for tumor grade.

Table 5.12: Magnitude of the association between surgery delay and risk of death for different characteristics adjusted with one predictor: 29+ days vs. 1-14 days

Predictors of Cox Models	**$HR_{29+ \text{ days vs. } 1\text{-}14 \text{ days}}$**	**95% CI**	**99.5% CI**
Delay	0.656**	0.527-0.818	0.479-0.900
Delay + Sex	0.648**	0.520-0.809	0.472-0.890
Delay + Age	0.660**	0.529-0.823	0.481-0.905
Delay + Marital Status	0.679**	0.544-0.847	0.494-0.932
Delay + Medical Plan	0.668**	0.536-0.833	0.487-0.917
Delay + SEP	0.657**	0.527-0.819	0.479-0.901
Delay + Cancer Stage	0.688**	0.551-0.859	0.500-0.946
Delay + Tumor Grade	0.655**	0.525-0.816	0.478-0.897
Delay + Charlson Index	0.654**	0.525-0.815	0.477-0.897
**** = p-value < 0.005**			

In table 5.13, we include the HR estimation for comparing surgery delay after the first two week of the diagnostic versus surgery between 15 to 28 days of the diagnostic, adjusting for one more than one predictor. The Cox models includes surgery delay with all demographical characteristics, surgery delay with all clinical characteristics and surgery delay with all characteristics; each model showed significant results, except the model adjusted for Charlson index for p-value < 0.005. For the model with delay and all demographical characteristics (age, sex, medical plan, marital status, socioeconomic position), it shows that the risk of dying in patients who had a delay

between 15 to 28 days is 31.2% (HR: 0.688) lower than the risk of dying in patients who had a delay within the first two weeks after adjusted for all demographical characteristics. For the model with delay and all clinical characteristics (cancer stage, tumor grade, charlson grouped index), it shows that the risk of dying in patients who had a surgery delay between 15 to 28 days is 31.8% (HR: 0.682) lower than the risk of dying in patients who had a delay within the first two weeks after adjusted for all clinical characteristics. For the model with surgery delay and all characteristic, it shows that the risk of dying in patients who had a delay between 15 to 28 days is 27.9% (HR: 0.721) lower than the risk of dying in patients who had a surgery delay within the first two weeks after adjusted for all characteristics.

Table 5.13: Magnitude of the association between surgery delay and risk of death after adjusted for different combination of predictors: 15-28 days vs. 1-14 days

Predictors of Cox Models	**$HR_{15\text{-}28 \text{ days vs. } 1\text{-}14 \text{ days}}$**	**95% CI**	**99.5% CI**
Delay + Age + Sex + Medical Plan + Marital Status + SEP	0.688**	0.541-0.876	0.487-0.972
Delay + Cancer Stage + Tumor Grade + CCI	0.682**	0.537-0.865	0.484-0.960
Delay + Age + Sex + Medical Plan + Marital Status + SEP + CCI + Cancer Stage + Grade	0.721*	0.565-0.918	0.509-1.020
*** = p-value $<$ 0.05; ** = p-value $<$ 0.005**			

In table 5.14, we include the HR estimation for comparing surgery delay after the first two week of the diagnostic versus surgery delay after 29 day of the diagnostic. The Cox models includes surgery delay with all demographical characteristic, surgery delay with all clinical characteristics and surgery delay with all characteristic; each model was statistically significant (p-value $<$ 0.005). For the model with surgery delay and all demographical characteristics, it shows that the risk of dying in patients who had a delay after 29 days is 32.8% (HR: 0.672) lower than the risk of dying in patients who had a delay within the first two weeks, after adjusted for demographical

characteristics. For the model with delay and all clinical characteristic, it shows that the risk of dying in patients who had a delay after 29 days is 31.7% (HR: 0.683) lower than the risk of dying in patients who had a surgery delay within the first two weeks, after adjusted for clinical characteristics. For the model with delay and all characteristic, it shows that the risk of dying in patients who had a delay after 29 days is 30.1% (HR: 0.699) lower than the risk of dying in patients who had a delay within the first two weeks, after adjusted for all characteristics.

Table 5.14: Magnitude of the association between surgery delay and risk of death after adjusted for different combination of predictors: 29+ days vs. 1-14 days

Predictors of Cox Models	**$HR_{29+ \text{ days vs. } 1\text{-}14 \text{ days}}$**	**95% CI**	**99.5% CI**
Delay + Age + Sex + Medical Plan + Marital Status + SEP	0.672**	0.537-0.840	0.488-0.925
Delay + Cancer Stage + Tumor Grade + CCI	0.683**	0.546-0.853	0.496-0.939
Delay + Age + Sex + Medical Plan + Marital Status + SEP + CCI + Cancer Stage + Grade	0.699**	0.558-0.875	0.506-0.965
**** = p-value $<$ 0.005**			

Chapter 6

Conclusion and Recommendations

Throughout the Kaplan-Meier method we were able to validate if our database had correct information and if the data exclusion had negative effects on it. We assessed if the survival curves behave according to the scientific literature. For example, patients that you will expect to have worse prognosis in clinical characteristics (higher cancer stage, higher tumor grade) or in demographical characteristics (older patients, non-private health plans) had worst survival compared to the other groups [16] [14] [19] [22]. Additionally, we verified that the hazard ratio estimation was higher than one in the mentioned characteristics. Overall, the most relevant results for the risk of death were found in the following characteristics: 1) Age [higher risk of death increased with age], 2) Medical Plan [higher risk of death increased among non-private health plan], 3) Stage of Colon Cancer [higher risk of death increased with worse stage], 4) Grade of the Tumor [higher risk of death increased with worse stage].

The median surgery delay among colon cancer patients was 18 days, slightly higher than reported by Pruitt et al [7]. In our study, approximately, 43.5% of pa-

tient had surgery in the first two weeks after diagnose; they reported a 52.1% of patient in the same interval. This means that the patients with colon cancer are waiting longer for surgery in Puerto Rico. To verify our working hypothesis we assessed the risk of death under different surgery delays, controlling for different risk factors for colon cancer. First, our crude HR estimation suggest that surgery delay affects positively patients survival; it means that patients with more than 29 days of surgery delay have 34.4% lower risk of death than patients with surgery within the first two weeks after diagnose. Even though these results seem contradictory, similar findings has been previously reported. Wanis et al (2017) reported that patients with more than 30 days of surgery delay have 18% lower risk of death than patients with surgery within the first month (HR: 0.82; 95% CI: 0.631.1) [23]. Redaniel et al (2014) reported that patients with less than 25 days of surgery delay had 78% higher excess risk of death than patients with surgery delay between 25-38 days [22].

Our finding suggest that with individual confounders we did not observe confounding changes in the association between surgery delay and risk of death. We used the 10% cutoff for assessing confounding effect by comparing the point estimates of the crude HR versus the adjusted HR with one confounder [33]. When we compared the surgery delay between 29+ days versus 1-14 days, the point estimate of the crude HR (HR: 0.656) is similar to the points estimates of the adjusted HR's (HR Range: 0.648-0.688). Individually each confounder did not show any confounding effect; therefore, we proceeded to adjust for all potential confounders simultaneously. Our finding suggest that after adjusting for all potential confounders simultaneously, we also did not observe confounding changes in the association between surgery delay

and risk of death. Similarly, we used the 10% cutoff for assessing confounding effect by comparing crude HR versus adjusted HR by all potential confounders simultaneously. When we compare the surgery delay between 29+ days versus 1-14 days, the point estimate of the crude HR (HR: 0.656) is similar to the point estimates adjusted HR by all potential confounders simultaneously (HR: 0.699).

When the HR is adjusted by all potential confounders simultaneously, the estimation suggest that surgery delay also affects positively patients survival; it means that patients with more than 29 days of surgery delay have 29.1% lower risk of death than patients with surgery within the first two weeks after diagnose. As we mentioned, similar results have been published previously, there also have been conflicted results. Simunovic et al reported that patients with surgery between the first 2 week have 20% lower risk of death than patients with surgery after 42 days of diagnose (HR: 1.2; 95% CI: 1.1-1.3); this HR estimation was adjusted for age, sex, race, median household income group, admission type, comorbidity score and hospital procedure volume [20]. Additionally, they reported an adjusted HR of 1 (95% CI: 0.9-1.1) when comparing patients with surgery between the first 2 week and 1) patients with surgery delay between 15 to 28 days, and 2) patient with surgery delay between 29 and 42 days. However, Redaniel et al reported that after adjusting by age, sex, region of residence, stage, grade, morphology, deprivation quintile and period, that patients with less than 25 days of surgery delay had 60% higher excess risk of death than patients with surgery delay between 25-38 days [22].

Even though our results did not support our research hypothesis that the survival probability is increased among patients when the surgery delay is reduced, it

supports the ongoing question of the effects of delay in other studies. So, if our main result is real (short delay, lower survival), the medical practice for determining the surgery in patients with colon cancer should be reassessed. Early intervention with poor medical care could do more harm than good; Pruitt et all remarked that: "timeliness and quality of colorectal cancer care are not synonymous" [7]. The reasoning for this was that the standard of care for preparing the patient for the surgery entails several medical procedures.

Future studies should consider the type of surgery (elective or emergency), lifestyle, nutrition and genetic factors. Additionally, if the cancer is located in the abdomen, it might cause bowel obstruction; this is a blockage, which prevents food and waste to pass through. This obstruction may create a perforation that causes the contents of the intestine to leak into the abdominal cavity leading to a severe infection [34]. Furthermore, a larger database is recommended to be able to increase the categories of surgery delay after one month with enough number of patients. Other possible explanations for our main result are that we need more time of observation after first surgery and we should take into consideration cancer damage (such as obstruction and perforation) and surgeon specialty (general vs. colorectal surgeon). Also, it is recommended to consider the type of treatment received after surgery, particularly if chemotherapy was given. In addition, we recommend to reduce the missing data to reduce possible selction bias [35]. For these reasons, its necessary to have further studies to explain the effects of treatment delay and survival.

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Chapter 8

Appendix

8.0.1 STATA Do File

```
********** DATABASE **********
use "Colon Data.dta", clear
quietly: do "Do File Labels.do"
do "Do File Dates.do"
stset time, fa(vitalstatus==0)

*Table 5.1
local var sex agedxg marital2 primary_payer2 sep2
foreach y of loc var {
tab1 `y'
}
sum agedx

*Table 5.2
local var stage_ajcc tumorg2 grpci2
foreach y of loc var {
tab1 `y'
}

*Table 5.3
tab delayp
sum delayp, detail

**Kaplan-Meier survival curves (Figure 5.1-5.9)
sts graph, by (delayp)
sts test delayp

sts graph, by (sex)
sts test sex
```

```
sts graph, by (agedxg)
sts test agedxg

sts graph if marital2 !=9, by (marital2)
sts test marital2 if marital2!=9

sts graph if primary_payer2!=3, by (primary_payer2)
sts test primary_payer2 if primary_payer2!=3

sts graph, by (sep2)
sts test sep2

sts graph, by (stage_ajcc)
sts test stage_ajcc

sts graph, by (tumorg2)
sts test tumorg2

sts graph, by (grpci2)
sts test grpci2

**Kaplan-Meier survival curves (5.10-5.12)
sts graph if stage_ajcc==1, by (delayp)
sts test delayp

sts graph if stage_ajcc==2, by (delayp)
sts test delayp

sts graph if stage_ajcc==3, by (delayp)
sts test delayp

*Table 5.4 (Median Survival for delay)
stci, median by(delay3)
stci, median by(delay3) level(99.5)

*Table 5.5 (Median Survival for demographical characteristic)
local var sex agedxg marital2 primary_payer2 sep2
foreach y of loc var {
stci, median by(`y')
stci, median by(`y') level(99.5)
}

*Table 5.6 (Median Survival for clinical characteristic)
local var stage_ajcc tumorg2 grpci2
foreach y of loc var {
```

```
stci, median by('y')
stci, median by('y') level(99.5)
}

*Hazard Ratio (Table 5.7)
local var sex agedxg marital2 primary_payer2 sep2 stage_ajcc
tumorg2 grpci2
foreach y of loc var {
xi: stcox i.'y', cformat(%5.3f) nolog
xi: stcox i.'y', cformat(%5.3f) level(99.5) nolog
}

*Table 5.8
**Test of Proportional Hazard Assumption (stphtest)
**Likelihood Ratio Test

quietly xi: stcox i.delayp*i.agedxg
estimate store m1
quietly stcox i.delayp  i.agedxg
lrtest m1 .

quietly xi: stcox i.delayp*i.stage_ajcc
estimate store m1
quietly stcox i.delay3  i.stage_ajcc
lrtest m1 .

quietly xi: stcox i.delayp*i.sex
estimate store m1
quietly stcox i.delayp  i.sex
lrtest m1 .

quietly xi: stcox i.delayp*i.tumorg2
estimate store m1
quietly stcox i.delayp  i.tumorg2
lrtest m1 .

quietly xi: stcox i.delayp*i.grpci2
estimate store m1
quietly stcox i.delayp  i.grpci2
lrtest m1 .

quietly xi: stcox i.delayp*i.sep2
estimate store m1
quietly stcox i.delayp  i.sep2
lrtest m1 .
```

```
quietly xi: stcox i.delayp*i.primary_payer2
estimate store m1
quietly stcox i.delayp  i.primary_payer2
lrtest m1 .

quietly xi: stcox i.delayp*i.marital2
estimate store m1
quietly stcox i.delayp  i.marital2
lrtest m1 .

*Table 5.9 (Likelhood Ratio Test)
quietly xi: stcox i.delayp*i.agedxg i.delayp*i.sex
i.delayp*i.primary_payer2 i.delayp*i.marital2 i.delayp*i.sep2
estimate store m1
quietly stcox i.delayp i.agedxg i.sex i.primary_payer2
i.marital2 i.sep2
lrtest m1 .

quietly xi: stcox i.delayp*i.stage_ajcc i.delayp*i.grpci2
i.delayp*i.tumorg2
estimate store m1
quietly stcox i.delayp i.stage_ajcc i.grpci2 i.tumorg2
lrtest m1 .

quietly xi: stcox i.delayp*i.agedxg i.delayp*i.sex
i.delayp*i.primary_payer2 i.delayp*i.marital2 i.delayp*i.sep2
i.delayp*i.stage_ajcc i.delayp*i.grpci2 i.delayp*i.tumorg2
estimate store m1
quietly stcox i.delayp i.agedxg i.sex i.primary_payer2 i.marital2
i.sep2 i.stage_ajcc i.grpci2 i.tumorg2
lrtest m1 .

*Table 5.10 and 5.11
xi: stcox i.delay3, cformat(%5.3f) nolog
xi: stcox i.delay3, cformat(%5.3f) level(99.5) nolog
stphtest

local var sex agedxg marital2 primary_payer2 sep2 stage_ajcc
tumorg2 grpci2
foreach y of loc var {
xi: stcox i.delay3 i.`y', cformat(%5.3f) nolog
xi: stcox i.delay3 i.`y', cformat(%5.3f) level(99.5) nolog
stphtest
}
```

```
*Table 5.12 and 5.13
xi: stcox i.delay3 i.agedxg i.sex i.primary_payer2 i.marital2
i.sep2, cformat(%5.3f) nolog
xi: stcox i.delay3 i.agedxg i.sex i.primary_payer2 i.marital2
i.sep2, cformat(%5.3f)level(99.5) nolog
stphtest

xi: stcox i.delay3 i.stage_ajcc i.grpci2 i.tumorg2,
cformat(%5.3f) nolog
xi: stcox i.delay3 i.stage_ajcc i.grpci2 i.tumorg2,
cformat(%5.3f) level(99.5) nolog
stphtest

xi: stcox i.delay3 i.agedxg i.sex i.primary_payer2 i.marital2
i.sep2 i.stage_ajcc i.grpci2 i.tumorg2, cformat(%5.3f) nolog
xi: stcox i.delay3 i.agedxg i.sex i.primary_payer2 i.marital2
i.sep2 i.stage_ajcc i.grpci2 i.tumorg2, cformat(%5.3f) level(99.5)
stphtest
```

8.0.2 STATA Do File Dates

```
*************************************************************
********** CREATING DATES FOR SURVIVAL ANALYSIS *************
*************************************************************

*DATE OF CANCER DIAGNOSIS
gen dx_yy=(substr(dxdate,1,4))
destring dx_yy, replace

gen dx_mm=(substr(dxdate,5,2))
destring dx_mm, replace
recode dx_mm (.=6)

gen dx_dd=(substr(dxdate,7,2))
destring dx_dd, replace
recode dx_dd (.=15)

gen date_dx=.
replace date_dx=mdy( dx_mm, dx_dd, dx_yy)
format date_dx %td

*DATE OF SURGERY DATE (surgery_date)
* fromdate = dates from surgery from CLAIMS
* rxdatesurg = dates from surgery from CRS
```

```
* surgery_date --> uses surgery dates from CLAIMS (fromdate)
* and replaces missing values from surgery dates of CRS (rxsurgdate)

drop surgery_date

tostring fromdate, replace
gen fromdate2 = date(fromdate, "YMD")
format fromdate2 %td

tostring rxdatesurg, replace
gen rxdatesurg2 = date(rxdatesurg, "YMD")
format rxdatesurg2 %td

gen surg_date=fromdate2
format surg_date %td
replace surg_date=rxdatesurg2 if surg_date==.

drop if surg_date==.

*DATE OF LAST CONTACT
tostring datelastcontact, replace

gen last_yy=(substr(datelastcontact,1,4))
destring last_yy, replace
drop if last_yy==.

gen last_mm=(substr(datelastcontact,5,2))
destring last_mm, replace
recode last_mm (.=6)

gen last_dd=(substr(datelastcontact,7,2))
destring last_dd, replace
recode last_dd (.=15)

gen dlc=.
replace dlc=mdy( last_mm, last_dd, last_yy)
format dlc %td
count

*ELIMINATE PATIENTS WITH DX => SURGERY DATE
drop if date_dx >= surg_date

*ELIMINATE PATIENTS WITH DLC = SURGERY DATE
drop if dlc <= surg_date
```

```
*OUTCOME VARIABLE = DELAY (TIME BETWEEN CANCER DX AND
*FIRST SURGERY)
gen delay = surg_date - date_dx

*Evaluate only the patients who had surgery the first
*6 months after cancer dx
drop if delay >180

*Creating Delay Variable
gen delayp = delay
recode delayp (1/14 =1) (15/28 =2) (29/max =3)
label define delp 1 "1-14 days" 2 "15-28 days" 3 "29+ days"
label value delayp delp

//////////////////////////////////////////////////////////
**** DECLARE DATA TO BE SURVIVAL-TIME DATA OF 5 YEARS*******
//////////////////////////////////////////////////////////
rename encryptedid id

gen t =(dlc-surg_date)

replace vitalstatus = 1 if t>1825 & vitalstatus == 0
gen time = .

replace time = 1825  if vitalstatus==1 & t>1825
replace time = t    if  t<=1825

drop if tumorg2 ==.
drop if grpci2 ==.
drop if marital ==.
```

8.0.3 STATA Do File Characteristcs Labels

```
*AGE AT CANCER DIAGNOSIS
gen agedxg = agedx
recode agedxg min/64 = 1 65/74=2 75/max = 3
label define ag 1 "< 65 yrs" 2 "65-74 yrs" 3 "75+ yrs"
label value agedxg ag

*SEX
label define sex 1 "male" 2 "female"
label value sex sex

*AJCC STAGE - Group I, II Y III -
gen stage_ajcc = ajcc
```

```
recode stage_ajcc 10/15=1 30/34=2 50/54=3
label define ajc 1 "stage 1" 2 "stage 2" 3 "stage 3"
label value stage_ajcc ajc

*HEALTH INSURANCE
gen primary_payer = pripayer
recode primary_payer 20/21=1 31/35=2 60/63=3 64=4 65/66=5
67=6 68=7 10=8 1/2=9 99=10
replace primary_payer=10 if primary_payer==.

*Simplified Health Insurance
gen primary_payer2 = primary_payer
recode primary_payer2 1 = 1 2/4=2 5/10=3
label define pri2 1 "private" 2 "non-private" 3 "other"
label value primary_payer2 pri2

*MARITAL STATUS
gen marital2= marital
recode marital2 (1 3 4 5=0) (2=1)
label variable marital2 "Marital States"
label define maritalx 0 "Unmarried" 1 "Married" 9 "Unknown"
label values marital2 maritalx

*TUMOR GRADE
gen tumorg2=grade
recode tumorg2(1=1) (2=2) (3/4 =3)  (9 = 9)
label variable tumorg2 "Tumor Grade"
label define tumorsgrade2 1 "Low Grade" 2 "Intermediate Grade"
3 "High Grade"  9 "Unknown"
label values tumorg2 tumorsgrade2
replace tumorg2=. if tumorg2==9

*VITAL STATUS
label define vit 1 "alive" 0 "dead"
label value vitalstatus vit

*SEP
gen sep=dxcounty
recode sep(1 39 45 55 73 81 83 87 93 95 101 107 111 141 147 149 =1)
(11 15 17 19 47 54 59 75 79 99 103 109 123 131 133 =2)
(3 5 29 43 57 65 71 105 115 117 121 129 143 151 153 =3)
(7 9 13 23 27 33 35 77 85 89 91 97 113 119 125 145 =4)
(21 25 31 37 41 49 51 53 61 63 67 69 127 135 137 139 =5)
label variable sep "SEP"
```

```
*HIGH = Rich vs. LOW = Poor
gen sep2=sep
recode sep2 (1/3=1) (4/5=2)
label define sep2x 1 "LOW"  2 "HIGH"
label values sep2 sep2x

*CHARLSON INDEX
gen grpci2 = grpci
replace grpci2=9 if claims==0
recode grpci2(0 = 1)  (1/2 = 2)
label variable grpci2 "Grouped Charlson Index"
label define grpci2 1 "0" 2 "1+" 9 "Unknown"
label values grpci2 grpci2
replace grpci2=. if grpci2==9
```