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Association of Timing of Adjuvant Chemotherapy on Survival Outcomes in Colon Cancer

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An abstract of
A Thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health in Epidemiology
2018

Abstract

Association of Timing of Adjuvant Chemotherapy on Survival

Outcomes in Colon Cancer

By Renuka Narayan

Background: Current guidelines regarding the treatment of colon cancer recommend initiation of adjuvant therapy within 120 days of definitive surgery when chemotherapy is needed. The objective of this study was to investigate the association of time to initiation of adjuvant chemotherapy with survival from colon cancer, while controlling for known strong predictors of survival.

Methods: The study cohort consists of stage I-III colon cancer patients from the Georgia Cancer Registry, who underwent definitive surgery followed by adjuvant chemotherapy. Time interval between diagnosis and adjuvant chemotherapy was divided into tertiles; time $\leq$ 46 days, 46 days < time $\leq$ 69 days and time> 69 days. Kaplan – Meier plots were obtained for all-cause and cancer specific survival in the three time tertiles. Multivariate analysis was done using Cox proportional hazard models controlling for potential confounders. Survival in the second and third tertiles were compared to the first to see if there was an association between the timing of adjuvant chemotherapy and outcomes.

Results: 93.4% of the 2106 colon cancer patients in the study cohort received adjuvant chemotherapy within 120 days of diagnosis. Age at diagnosis ($p<0.01$), race ($p<0.01$) and stage ($p<0.01$) were significantly associated with the timing of adjuvant therapy. There was no decrease in all–cause survival in the second vs first tertile (HR = 0.790, $CI_{95\%}$= 0.619, 1.009) or third vs first tertile ((HR = 0.966, $CI_{95\%}$= 0.76, 1.227). Cancer specific survival was significantly better in the second vs first tertile (HR = 0.738, $CI_{95\%}$= 0.56, 0.972).

Conclusion: In this study, delayed initiation of adjuvant chemotherapy was not significantly associated with decreased survival outcomes in stage I-III colon cancer patients.

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ACKNOWLEDGEMENTS

I would like to thank Dr. Kevin Ward, my thesis advisor for his mentorship, support and guidance through all parts of this project.

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CHAPTER I

BACKGROUND

Cancer is the fifth leading cause of death worldwide (1) and the second leading cause of death in the United States (2, 3). One of every four deaths in the United States is due to cancer. Lung cancer is the most common cause of death due to cancer in the United States and globally (1-3). Breast cancer is the most commonly diagnosed cause of cancer in US women irrespective of race or ethnicity (3) and is the second leading cancer cause of death. Colorectal cancer is the third most commonly diagnosed cancer as well as the third most common cause of death due to cancer in both men and women in the United States (3). A combination of local and systemic therapies are employed in the treatment of these cancers (4).

The immediate indicator of response to any cancer therapy is tumor shrinkage. To be clinically valuable, the response must translate into clinical benefit. This is conventionally established by an increase in survival, or at least an increased time to further progression of disease. FDA approval for a chemotherapeutic agent is based on such clinical benefit (5). The success of treatments for patients with advanced cancers at diagnosis or recurrence is often assessed by computing overall response rates and survival from the start of treatment (6). Overall survival (OS), which is defined as the time from randomization to death, is the gold standard of clinical trial endpoints as it is unambiguous and not subject to interpretation bias (5).

If a tumor is limited to a single site, then surgery alone could be curative. Adjuvant chemotherapy is given with an aim to eliminate any remaining cancer cells and metastasis. It is administered only after allowing sufficient time for the patient to recover

from surgery. However, the postsurgical interval is a very favorable environment for tumor metastasis. Surgery can activate dormant occult micro-metastases, stimulate angiogenesis, and facilitate tumor growth. In addition, surgery is immune-suppressive and the wound healing stimulates release of growth factors thus facilitating proliferation of tumor cells (7). Mathematical modeling suggests that the drug sensitivity of tumors is related to their spontaneous mutation rate which is a function of time (8, 9). According to results from animal models, drug resistance, micro-metastasis, and metastasis due to angiogenesis can be inhibited by earlier initiation of adjuvant therapy (10). Thus, it is reasonable to hypothesize that the longer it takes to initiate chemotherapy, the greater the tumor burden to eradicate. This could, in turn, translate clinically into poorer survival outcomes (8).

Conventional chemotherapy agents that mainly target DNA may be used for the treatment of active, clinically apparent cancer. The goal of such treatment in some cases is cure of the cancer, that is, elimination of all clinical and pathologic evidence of cancer and return of the patient to an expected survival no different than the general population (4). If cure is not possible, chemotherapy may be undertaken with the goal of palliating some aspect of the tumor's effect on the host. Non-small cell lung cancer, pancreatic cancer, thyroid cancer and prostate cancer are some types for which palliative chemotherapy is commonly used (4).

Many studies have examined the effect of delayed chemotherapy on survival outcomes, in breast, colon and lung cancers. The studies have also tried to identify the possible predictors of delay in initiation of therapy like age of the patient, stage and grade of the tumor, race/ ethnicity, socio-economic status and site. The results vary depending

on the site of cancer, grade, stage, patient characteristics and preference of health care providers.

Studies about timing of adjuvant chemotherapy following definitive surgery in breast cancer have reported that delay in initiation is associated with lower survival (10, 11). In a population-based study published in 2006, Lohrisch et al observed that from 1989 to 1998, there was a trend towards a reduction in the proportion of patients annually who initiated chemotherapy more than 12 weeks after surgery and an increase in the proportion who started chemotherapy earlier, between 4 and 8 weeks (11). They concluded that adjuvant chemotherapy is equally effective up to 12 weeks after definitive surgery. Initiation of adjuvant chemotherapy more than 12 weeks from surgery remained significantly associated with inferior survival, with a hazard ratio of 1.6 ($CI_{95\%}$, 1.2 to 2.3; P = .005). Alkis et al observed that, in early stage breast cancer, the median time to initiation of adjuvant therapy was 21 days (4 days to 258 days) (10). In their study, early stage breast cancer patients were divided into two groups as starting adjuvant treatment equal to or shorter than 44 days and longer than 44 days (n = 344, 85.6% and vs. n = 58, 14.4%, respectively). Overall survival was significantly better (p = 0.03) in the group that received chemotherapy early (92%) vs those who received it later (83%). DFS was not significantly different between two groups. In a study published in 2010 by Fedewa et al (12) about factors causing delays in adjuvant chemotherapy among breast cancer patients, the authors observed the average time from primary surgery to adjuvant chemotherapy to be 41.14 days (± 24.46 days). Two studies previously showed no benefit by starting chemotherapy earlier (13, 14). This heterogeneity is probably due to the interplay with other significant prognostic factors like age, stage, hormone receptor status, pathologic

subtype or menopausal status (10). It could also be because of the differences in the time intervals for chemotherapy initiation in these studies. For example the study using data from the Danish Breast Cancer Cooperative Group (DBCG) divided the patients into four strata (1-3, 4, 5 and 6-13 weeks from surgery to chemotherapy) and they found no association between timing and survival (14). In the study by Alkis et al, they did find significant association between timing and survival in breast cancer when patients were divided into two groups. The authors however found no association when they divided the same cohort into 5 groups (shorter than 14 days, between days 15–29, between days 30–44, between days 45.-59 and more than 59 days) (10).

According to the European Society for Medical Oncology, postsurgical chemotherapy for colon cancer should be initiated as early as possible, starting from the 4^{th} week up to a maximum of 8–12 weeks after resection. Adjuvant chemotherapy should be considered or administered within 4 months (120 days) of surgery to patients under the age of 80 with American Joint Committee on Cancer (AJCC) stage III (lymph node positive) colon cancer according to the guidelines of the Commission on Cancer, American College of Surgeons (ACS) (15). There is no consensus regarding use or benefits of chemotherapy in AJCC stage II cancer. The American Society of Clinical Oncology issued a guideline stating "direct evidence from randomized controlled trials does not support the routine use of adjuvant chemotherapy for patients with stage II colon cancer" (16). A number of studies have been conducted regarding the effect of timing of adjuvant chemotherapy on survival among colon cancer patients. A Dutch study on colon cancer, published in 2015 observed a median interval 5.6 weeks after surgery for start of adjuvant chemotherapy (17). They however found no prognostic significance of a delay

in chemotherapy beyond 8 weeks on either relapse free survival (hazard ratio (HR), 1.08; P = .609) or cancer specific survival (HR, 1.02; P = .893). A study by Gresham et al, using data on colon cancer patients from the British Columbia Cancer Agency (BCCA), found a median postsurgical interval of 8.3 weeks (SD, 18.58) (18). They concluded that initiation of adjuvant therapy at 6 weeks from date of surgery was associated with a significant survival benefit (hazard ratio 0.52, $CI_{95\%}$, =0.31-0.90, P = .017), while no significant association was seen at 4, 8 or 12 weeks (P > .05). Another study also using BCCA colon cancer data published in 2015, by Nachiappan et al, found 7 weeks (2 weeks to 33 weeks) as the median postsurgical interval (19). They divided the study cohort into 5 groups based on timing. Sequentially worse overall survival was observed: <8 weeks: Ref; 8–10 weeks: HR 1.09; 10–12 weeks: HR 1.22; 12–14 weeks HR 1.23 and 14–16 weeks: HR 1.31, $p < 0.001$. A large U.K based study utilizing 15 years of epidemiological data from colorectal cancer patients who underwent resection, observed that 49.3% of patients received adjuvant therapy within 8 weeks (20). A Systematic Review of ten eligible studies was published in 2011 in The Journal of the American Medical Association that used meta-analysis to study the association between timing of adjuvant therapy and survival in colorectal cancer (21). The authors of the review demonstrated that a 4-week increase in time to AC was associated with a significant decrease in both overall survival (HR, 1.14; $CI_{95\%}$, 1.10-1.17) and disease-free survival (HR, 1.14; 95% $CI_{95\%}$, 1.10-1.18). Most studies mention that the 8-week cut off was arbitrary based on many clinical trials.

Forty-five percent of patients with non-small cell lung cancer (NSCLC) present with disease in stages that permit surgical resection (22). Many randomized control trials

have proven the clinical benefit of adjuvant chemotherapy in NSCLC (23-26). There is, however, no defined optimal postsurgical time interval for adjuvant chemotherapy among NSCLC (27). Although some trials suggest the time interval to be 4 to 6 weeks after surgery (28), since patients vary greatly in their ability to tolerate chemotherapy after surgery, this time interval also varies (29). According to a study conducted by Booth et al based on the Ontario Cancer Registry, the most common interval between surgery and cancer was 8-10 weeks (30). Only one study that examined the effect of timing of chemotherapy on outcomes showed that delay in adjuvant therapy beyond 60 days after surgery was associated with worse survival outcomes (31). In contrast, 4 other studies have shown no survival benefit with early initiation of chemotherapy (27-30). Two such studies also conducted sub-group analysis but again could not find any difference by age, race, gender, comorbidities or other possible factors (27, 28). This could be because the effect size in lung cancer might be smaller than that in breast cancer or colorectal cancer, thus requiring higher powered studies. Also, lung cancer patients may differ in significant ways from other cancer patients and surgical resection of lung cancer is a comparatively greater undertaking (30). It could also be that any benefit due to early chemotherapy is offset by competing causes of death (30). Most studies regarding the prognosis of NSCLC are conducted using data from patients who underwent surgical resection. As such, the results are likely to be subject to selection bias due to inclusion of only those patients who were staged by TNM criteria, could undergo complete resection and were able to tolerate surgery (32).

Many variations exist in the timing and receipt of chemotherapy based on medical and nonmedical factors. Increased age, being nonwhite, having Medicaid or no

insurance, lower education, squamous cell carcinoma, undetermined grade, pneumonectomy resection, extended length of stay (>14 days), and unplanned 30-day readmission were significant predictors of delayed initiation of adjuvant chemotherapy in NSCLC (29). Booth et al found county of residence to be a predictor of timing of chemotherapy in lung cancer patients (30)

Age was found to be a significant factor determining timing and receipt of chemotherapy among lung cancer patients (33, 34), breast cancer patients (35) and colon cancer patients (20). This may be because elderly patients are less likely to meet the requirements for therapy and are also less likely to desire aggressive therapy (33).

Race was another very important predictor in the receipt of therapy and survival in lung, breast and colon cancer patients (33, 34, 36-41). A 2000 study on SEER data also found African Americans were less likely to receive chemotherapy for lung cancer comparing to other races with OR 0.70 ($CI_{95\%}$ = 0.55 to 0.88) (33). African American and Hispanic patients also had higher risk of 60-day delay compared to white women (12).

Additionally, some studies examined effect measure modification between a few of the aforementioned predictors. County of residence was associated with treatment disparities in Non-Hispanic black colon cancer patients (40). Yet another study found no modification by insurance on race (41).

The primary objective of this study is to investigate the association of timing to initiation of chemotherapy with survival from colon cancer in patients from the racially and socioeconomically diverse state of Georgia, while controlling for known strong predictors of survival. The findings from this study could help to inform local cancer control plans.

CHAPTER II (MANUSCRIPT)

Association of Timing of Adjuvant Chemotherapy on Survival Outcomes in Colon Cancer

INTRODUCTION

Lung cancer is the most common cause of death due to cancer in the United States and globally (1-3). Breast Cancer is the most commonly diagnosed cause of cancer in women irrespective of race or ethnicity, in the United States (3). Colorectal cancer is the third most commonly diagnosed cancer as well as the third most common cause of death due to cancer in both men and women in the United States (3). A combination of local and systemic therapies are employed in the treatment of these cancers (4).

Surgical resection alone may not remove all of the cancerous cells. Also, there might be micro metastasis to distant sites in most stage 3 and stage 4 cancer. Adjuvant chemotherapy aims to eliminate any remaining cancer cells and metastasis (31). However, the postsurgical interval is a very favorable environment for tumor metastasis due to angiogenesis, immune suppression and growth factors released due to wound healing (7). Mathematical modeling suggests that the drug sensitivity of tumors is related to their spontaneous mutation rate which is a function of time (8, 9). Thus, it is reasonable to hypothesize that a longer postsurgical interval would lead to increase in the tumor burden. This could, in turn, translate clinically into worsening survival outcomes (8).

Studies about timing of adjuvant chemotherapy following definitive surgery in breast cancer patients (10, 11) and colon cancer patients have reported that delay in initiation is associated with lower survival (8, 17-20). Although many randomized control trials have proven the clinical benefit of adjuvant chemotherapy in NSCLC (23-26), only one study has shown that a delay in adjuvant therapy beyond 60 days after surgery was associated with worse survival outcomes (31).

Many medical and non-medical factors have been examined as possible predictors of delay in receipt of adjuvant therapy. Increased age, being nonwhite, having Medicaid or no insurance, lower education, squamous cell carcinoma, undetermined grade, pneumonectomy resection, extended length of stay (>14 days), and unplanned 30-day readmission were significant predictors of delayed initiation of adjuvant chemotherapy in NSCLC (29). In addition to race, insurance type, stage, comorbidity, and facility type were found to be associated with adjuvant chemotherapy delay among breast cancer patients (12). Low socioeconomic status and increased travel burden were barriers to care disproportionately experienced by Non-Hispanic Black colon cancer patients (40).

The main objective of this study is to investigate the association of timing of chemotherapy initiation with survival in patients from the racially and socioeconomically diverse state of Georgia, while controlling for known strong predictors of survival.

METHODS

The primary hypothesis for this study was that earlier initiation of adjuvant chemotherapy in colon cancer patients will result in better survival outcomes compared to later initiation of adjuvant chemotherapy.

Study design

This is an observational retrospective cohort study. Time to event was calculated for both all–cause and cancer specific survival and multivariate hazard ratios were obtained controlling for potential confounders.

Setting

The study used data on colon cancer patients collected by the Georgia Cancer Registry (GCR (42). The study period was from January 1st 2010 through December 31st 2014. Follow-up ended December 31st 2015. Demographic data included, the patients' age at diagnosis (in years), sex, race, area-based socioeconomic status, primary payer of insurance at diagnosis and county of residence at diagnosis. Clinical data included the number of tumors in each patient, primary site, laterality, histology, behavior, stage and grade. Data regarding the patient's treatment included type of surgery, chemotherapy, sequence of surgery and chemotherapy, dates of diagnosis, surgery, and chemotherapy, and date of last contact.

Data Sources

The GCR is a statewide population-based cancer registry collecting all cancer cases diagnosed among Georgia residents. The study was approved by the Institutional Review Board of the Georgia Department of Public Health, in accordance with the expedited review procedures. The observations were all coded in accordance to the SEER

Program Coding and Staging Manual 2016 (43). The manual is based on North American Association of Central Cancer Registries (NAACCR) codes.

Study subjects

Colon cancer patients diagnosed during the study period were identified from the registry based on the ICD-O-3 topography codes. All patients with codes C180 through C189 were identified as colon cancer cases. Eligible subjects had only one tumor during their lifetime identified by a sequence number of 00. Any patients who had more than one tumor were excluded. Eligible patients also had definitive surgery followed by adjuvant chemotherapy. All those who underwent definitive surgery of the primary site were identified using sites specific surgery codes 20 through 80. The administration of adjuvant chemotherapy was identified using a surgery/systemic sequence code of 3. Patients were excluded if they had neoadjuvant chemotherapy, more than one surgery, only surgery or only chemotherapy. The data set contained a few cases with grades higher than 4, indicating Lymphoid or Hematologic malignancies. Cases with histology codes 9050 – 9055, 9140 and 9590 – 9992 were excluded, which also excluded all those with grades higher than 4. Late stage colon cancer patients were identified by AJCC storage codes ≥ 700 and were excluded. The cohort also excluded patients with missing demographic information on age at diagnosis, sex, race or socioeconomic status along with those missing dates for diagnosis, surgery, chemotherapy or last contact. Any patients with implausible dates were also excluded or if the interval between surgery and chemotherapy was too long to be considered first course therapy as defined by registry coding rules. **Figure 1** summarizes the steps to final cohort selection. The final study sample size was 2106.

Variables

The main exposure of interest was the time interval between date of diagnosis and initiation of chemotherapy. Diagnosis date was chosen as the starting point instead of date of definitive surgery as this is the traditional measure used by organizations defining quality standards for colon cancer patients. In addition, diagnosis date and surgery dates can be very close together for colon cancer following data collection rules. Procedures like a polypectomy or excisional biopsy may be diagnostic and therapeutic and thus considered as definitive surgery by the SEER manual (43). Dividing patients into 2 groups based on the median time interval was thought to create much variability within each group. Instead, it was decided to classify the study cohort into 3 groups based on tertiles of time in the study cohort (**Table 1**).

Survival time in days was calculated as the time from diagnosis until death, 5 years, the time at which the patient was lost to follow-up, or the study endpoint, whichever came first. A new survival variable was created that included the survival times for all patients in the dataset.

The outcomes of interest were:

1. All–cause survival: The event was death due to any cause, within 5 years from diagnosis. A new status variable was created for overall survival. Patients experiencing death prior to the study endpoint were considered events. Patients lost to follow-up prior to the study endpoint and those with less than 5 years of complete follow up by the time of the study endpoint were censored.
2. Cancer specific survival: The event was death due to cancer, within 5 years of diagnosis. Cause of death as cancer was identified using ICD-10 codes beginning

with “C”. Cancer death was considered as cause specific death as the study cohort only includes those with single cancer during lifetime, identified by the sequence number 00. A second status variable was created for cancer specific survival. Patients experiencing death due to cancer prior to the study endpoint were considered events. Patients lost to follow-up prior to the study endpoint and those with less than 5 years of complete follow up by the time of the study endpoint were censored.

Age at diagnosis was the patient’s age in completed years of life at the time of their cancer diagnosis. Sex of the patients was coded as 1 for males and 2 for females. All patients in the final study cohort were in either one of the 2 groups.

Socioeconomic status was defined using a Census Tract Poverty Indicator. This is coded according to the neighborhood poverty level based on the census tract of the address at diagnosis. Cases diagnosed since 2005 are assigned a code based on the American Community Survey data that is published annually using the diagnosis year. A new 3 level variable was created. The first level included all patients with code 1 (0% - <5% poverty). The second level included all those with codes 2 and 3 (5% - <20% poverty). The third level included all those with codes 4 (20% to 100% poverty) which meets the federal definition of a poverty area, where at least 20 percent of residents were below the federal poverty level (44).

Race and ethnicity were defined by specific physical, hereditary and cultural traditions or origins, not necessarily by birthplace, place of residence, or citizenship. ‘Origin’ is defined by the U.S. Census Bureau as the heritage, nationality group, lineage, or in some cases, the country of birth of the person or the person’s parents or ancestors

before their arrival in the United States. A new 3 level variable was created for analysis. All those with code 1 in the dataset were coded as “White”, all those with code 2 were coded as “Black” and all others were coded as “Other”.

Stage in the dataset was coded in accordance to American Joint Committee on Cancer (AJCC) 7th edition. A new 2 level stage variable was created. The first level included all patients up to and including stage 2 and the second level included only stage 3 cases. Finally, a new 2 level Grade variable was created, the first level included grades 1 and 2, and the second included grades 3 and 4.

Statistical analysis

Software

Initial selection of colon cancer patients who had definitive surgery followed by adjuvant chemotherapy, complete demographic variables and a single tumor was done using Microsoft Access. This access table was then imported into SAS, version 9.4 (Cary, N.C, USA). Further selection criteria as outlined in Figure 1 were applied using data steps and if-then statements in SAS. All baseline, Kaplan Meier survival and multivariate analyses were performed in SAS.

Time tertiles

A new continuous variable was created for time to adjuvant chemotherapy from date of diagnosis. Using proc univariate in SAS, the 33.33 and 66.66 percentile points were obtained for the time interval between diagnosis date and chemotherapy in days (**Table 1**). A new three level categorical variable was created using the cut-points. Time tertile 1 included all those who received chemotherapy $\leq$ 46 days from diagnosis. Time tertile 2 included all those with time interval 46 to 69 days and all those with interval $\geq$

69 days were grouped into time tertile 3 (see **Table 1**). Time tertile 1 is used as the reference group for univariate analysis and Cox proportional hazard models.

Baseline

Baseline characteristics were compared among patients who were in the three time tertiles. The continuous variable age was compared using ANOVA. The categorical variables stage, grade, sex, race and socioeconomic status were compared using Chi square tests.

Kaplan Meier Curves

Kaplan Meier (KM) plots were obtained for all–cause survival using the new status variable that coded death due to any cause as the event of interest (**Figure 2**). KM plots were also similarly obtained for cancer specific survival, using the new status variable that coded only death due to cancer as the event of interest (**Figure 3**). Log rank test was performed to assess any difference in survival among the three groups at an alpha of 0.05.

Cox Proportional Hazards Model

The proportional hazards assumption was assessed for the exposure of interest and each of the covariates of interest using Log–Log survival curves, Goodness of Fit test and time dependent variable testing. If at least two out of the three tests showed that there was no violation of the proportional hazards assumption, then the variable was accepted as meeting the assumption and thus included in the final model. Cox proportional hazard models were run separately for all–cause survival and cancer specific survival to obtain hazard ratios. Interaction assessment was performed using a chunk test followed by backwards elimination for all the covariates.

RESULTS

Patient characteristics

Out of the 14,778 patients with colon cancer identified from the GCR, 3195 cases had definitive surgery followed by adjuvant chemotherapy. 2142 of these patients had tumors staged 1 to 3 and grades 1 through 4. 36 patients were excluded for missing demographic information, missing dates or implausible dates for diagnosis, surgery, chemotherapy or last contact. Of the 2106 colon cancer patients in the study cohort, 395 (18.8%) patients died within 5 years from date of diagnosis and within the study endpoint. 315 (15%) patients died within 5 years of the date of diagnosis specifically due to cancer, within the study endpoint. The median time interval was 55 days. The 33.33^{th} percentile time interval was 46 days and the 66.66^{th} percentile was 69 days (**Table 1**). There were 703, 709 and 694 patients in the first, second and third time tertile groups respectively.

Baseline characteristics

Age at diagnosis, race, and stage were significant predictors of time interval between date of diagnosis and receipt of adjuvant chemotherapy among colon cancer patients in this data. The mean age increased from time tertile 1 to time tertile 3 ($p < 0.01$). Race distribution was significantly different among the three groups ($p < 0.01$). Stage was also significantly different among the three groups ($p < 0.01$). The proportion of white patients progressively decrease from first to third tertile, while the proportion of black patients progressively increased from first to third tertile. White patients were more likely to receive adjuvant chemotherapy in the first time tertile compared to the third time tertile (69.3% vs 57.9%) Black patients were more likely to receive treatment in the third

time tertile as opposed to the first tertile (40.3% vs 26.9%). Sex, socioeconomic status and tumor grade were not significantly different between the three groups (**Table 2**).

Kaplan Meier Curves

Unadjusted KM curves for all–cause survival for the 3 time tertiles (**Figure 2**) were not significantly different from each other (Log rank p = 0.1962). Unadjusted KM curves for cancer specific survival for the 3 time tertiles (**Figure 3**) were also not significantly different from each other (Log rank p = 0.1013).

Cox Proportional Hazards model

The proportional hazards assumption was met for the exposure variable and also all the covariates of interest. Chunk test and backwards elimination was performed for interaction assessment between exposure variable and each of the covariates. No significant interaction was detected between exposure and any of the covariates at an alpha of 0.05.

1. All–cause survival: After controlling for age, sex, socio-economic status, race, stage and grade, there was no decreased survival seen in time tertile 2 vs. time tertile 1 or time tertile 3 vs. time tertile 1. (**Table 3**)
2. Cancer specific survival: After controlling for age, sex, socio-economic status, race, stage and grade the risk of death in time tertile 2 was significantly lower than what was seen in time tertile 1 (HR = 0.738, $CI_{95\%}$ = 0.56, 0.972). But there was no decreased hazard in time tertile 3 Vs time tertile 1. (**Table 3**)

Age at diagnosis was significantly associated with both all–cause survival (1.024, $CI_{95\%}$ = 1.015, 1.032) and cancer specific survival (1.017, $CI_{95\%}$ =1.008, 1.027), while adjusting for all other variables. Stage 3 colon cancer had significantly lower all–cause survival

(1.47, $CI_{95\%}$ = 1.128, 1.916) and lower cancer specific survival (1.566, $CI_{95\%}$ = 1.158, 2.119) compared to reference group, controlling for all other variables. Tumor grades 3 and 4 had significantly lower all–cause survival (2.099, $CI_{95\%}$ = 1.694, 2.602) and lower cancer specific survival (2.452, $CI_{95\%}$ = 1.94, 3.099) compared to the reference group controlling for all other variables. There was no significant association of sex, race or socioeconomic status with all–cause survival or cancer specific survival.

DISCUSSION

This study tested the hypothesis that shorter time interval between diagnosis and adjuvant chemotherapy would improve survival outcomes in stages I, II and III colon cancer patients.

The study subjects were divided into 3 groups based on tertiles of time interval and the all–cause and cancer specific survival of tertiles 2 and 3 were compared to those in tertile 1. The median time interval in the cohort was 55 days, which is similar to the findings from previous studies (17-20).

The result of the analyses showed no significant decrease in all–cause survival in the later time tertiles compared to the first. This result is not consistent with a number of previous studies that have demonstrated improved survival with earlier initiation of adjuvant therapy (17, 19-21). The main driving factor that could account for this result could be that 1966 out of 2106 patients in the study cohort received chemotherapy within 120 days of diagnosis. The ACS guidelines recommend that adjuvant chemotherapy should be started within 120 days of surgery (15). Since 93.4% of this study cohort received timely adjuvant therapy, the difference in survival may have been too small an effect to be detected.

There was decreased risk of cancer specific death in the second tertile compared to the first, but no difference in cancer specific outcome between the third and first tertile. This finding could be because, those given adjuvant therapy very quickly have more advanced disease, thus urging the need for immediate delivery of therapy. This could have driven the higher mortality in first tertile. This phenomenon is known as confounding by indication and is commonly associated with non-randomized survival

analyses. It is said to be "a most stubborn bias" (45). There could also be some residual confounding within the strata for stage or some other uncontrolled confounding.

Another driving factor for these results could be differences in the selection of time intervals for the studies (17). Time intervals were stratified differently in previous studies and consequently the definition of delayed adjuvant chemotherapy initiation varied. Some previous studies used the arbitrary 8-week cutoff point to dichotomize time (8, 18).

In this study, on average, stage does significantly vary across the time tertiles ($p<0.01$) and is also known to be an independent predictor of survival (16). Some studies restricted analysis to stage III cases, since the use of adjuvant chemotherapy is not routine for stage II (8, 16-18). This study does include 459 patients with stage I and II. The stage II cases that do receive chemotherapy are at higher-than-average risk for recurrence (including those with anatomic features such as tumor adherence to adjacent structures, perforation, and complete obstruction) (16). Additionally, some studies included colorectal and rectal cancer patients in analysis (8, 18). These differences could also account for there being no significant decrease in survival in later time tertiles.

The study also found that age at diagnosis, stage and race are significantly associated with delay in receipt of adjuvant therapy. Also, stage, grade and age at diagnosis were associated with both all–cause survival and cancer specific survival. Both these findings are consistent with previous studies.

Limitations

1. This is an observational study with retrospective design. Questions regarding timing however cannot be looked at prospectively or with a randomized control trial due to ethical constraints.
2. As with all observational survival analyses, this study is prone to confounding by indication which cannot be sufficiently addressed by multivariable Cox proportional hazards model (45). Instrumental variables or propensity scores may be effective in some situations (45). But they were not used in this study.
3. This study controlled for age, race, sex, socio-economic status, grade of tumor, stage of cancer. But there are many more independent prognostic factors that are associated with survival in addition to these covariates. A major limitation of this study was that it could not control for all these factors in multivariate analysis.
4. Another limitation for this study is that it did not examine interaction between the covariates that were controlled for in the analysis.
5. The reasons for delay in adjuvant chemotherapy were not addressed in this study. Postoperative complications and recovery time are known to be associated with delayed adjuvant therapy as well as survival. However, since data was not available regarding postoperative events they could not be controlled for in the analysis.
6. The study could not account for the type and class of chemotherapy agents used as this information is not captured by the registry.
7. The study could not ascertain an optimal interval following diagnosis or surgery within which adjuvant therapy would be most beneficial. It could not establish a

cut point beyond which adjuvant chemotherapy is definitely not beneficial and should not be considered.

The key strengths of the study were that the sample size was sufficiently large, and the study population was very diverse with regards to race, sex and socio-economic status.

Conclusion

In stage I-III colon cancer patients, this study could not find improved all–cause survival or cancer specific survival with earlier initiation of adjuvant chemotherapy. Age at diagnosis, race and stage varied significantly across tertiles of timing but only age and stage were independently associated with survival. The majority of patients (93.4%) in Georgia received chemotherapy within 120 days, as per the ACS guidelines. This is encouraging news for those involved in cancer control planning.

REFERENCES

1. *Top 10 causes of death worldwide*. 2017; Available from: http://www.who.int/mediacentre/factsheets/fs310/en/.

2. Nichols, H. *The top 10 leading causes of death in the United States*. 2017; Available from: https://www.medicalnewstoday.com/articles/282929.php.

3. *Statistics for Different Kinds of Cancer*. 2014; Available from: https://www.cdc.gov/cancer/dcpc/data/types.htm.

4. Dennis Kasper, D., et al., *Harrison's Principles of Internal Medicine*. 19th ed. 2015: McGraw-Hill Education.

5. DeVita Jr., V.T.M., T.S.M. Lawrence, PhD, , and S.A.M. Rosenberg, PhD, *Cancer: Principles & Practice of Oncology*. 10th ed.

6. Anderson, J.R., K.C. Cain, and R.D. Gelber, *Analysis of survival by tumor response and other comparisons of time-to-event by outcome variables.* J Clin Oncol, 2008. **26**(24): p. 3913-5.

7. Harless, W. and Y. Qiu, *Cancer: A medical emergency.* Med Hypotheses, 2006. **67**(5): p. 1054-9.

8. Czaykowski, P.M., et al., *Adjuvant chemotherapy for stage III colon cancer: does timing matter?* Dis Colon Rectum, 2011. **54**(9): p. 1082-9.

9. Goldie, J.H., et al., *A mathematical and computer-based model of alternating chemotherapy and radiation therapy in experimental neoplasms.* Antibiot Chemother (1971), 1988. **41**: p. 11-20.

10. Alkis, N., et al., *Optimal timing of adjuvant treatment in patients with early breast cancer.* Med Oncol, 2011. **28**(4): p. 1255-9.

11. Lohrisch, C., et al., *Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer.* J Clin Oncol, 2006. **24**(30): p. 4888-94.

12. Fedewa, S.A., et al., *Delays in Adjuvant Chemotherapy Treatment Among Patients With Breast Cancer Are More Likely in African American and Hispanic Populations: A National Cohort Study 2004-2006.* Journal of Clinical Oncology, 2010. **28**(27): p. 4135-4141.

13. Shannon, C., S. Ashley, and I.E. Smith, *Does timing of adjuvant chemotherapy for early breast cancer influence survival?* J Clin Oncol, 2003. **21**(20): p. 3792-7.

14. Cold, S., et al., *Does timing of adjuvant chemotherapy influence the prognosis after early breast cancer? Results of the Danish Breast Cancer Cooperative Group (DBCG).* Br J Cancer, 2005. **93**(6): p. 627-32.

15. *NQF Endorses Additional Cancer Measures*. 2012, National Quality Forum (NQF): Washington, DC.

16. *PDQ Cancer Information Summaries*, in *PDQ Adult Treatment Editorial Board*. 2018: Bethesda (MD): National Cancer Institute (US).

17. Bos, A.C.R.K., et al., *Timing of adjuvant chemotherapy and its relation to survival among patients with stage III colon cancer.* European Journal of Cancer, 2015. **51**(17): p. 2553-2561.

18. Peixoto, R.D.A., et al., *Effect of Delay in Adjuvant Oxaliplatin-Based Chemotherapy for Stage III Colon Cancer.* Clinical Colorectal Cancer, 2015. **14**(1): p. 25-30.

19. Gresham, G., et al., *Time to adjuvant chemotherapy and survival outcomes among patients with stage 2 to 3 rectal cancer treated with preoperative chemoradiation.* Clin Colorectal Cancer, 2015. **14**(1): p. 41-5.

20. Nachiappan, S., et al., *The impact of adjuvant chemotherapy timing on overall survival following colorectal cancer resection.* European Journal of Surgical Oncology (EJSO), 2015. **41**(12): p. 1636-1644.

21. Biagi, J.J., et al., *Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis.* JAMA, 2011. **305**(22): p. 2335-42.

22. Varlotto, J.M., et al., *Factors associated with local and distant recurrence and survival in patients with resected nonsmall cell lung cancer.* Cancer, 2009. **115**(5): p. 1059-69.

23. Arriagada, R., et al., *Cisplatin-Based Adjuvant Chemotherapy in Patients with Completely Resected Non–Small-Cell Lung Cancer.* New England Journal of Medicine, 2004. **350**(4): p. 351-360.

24. Douillard, J.-Y., et al., *Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB–IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association (ANITA)): a randomised controlled trial.* The Lancet Oncology. **7**(9): p. 719-727.

25. Kato , H., et al., *A Randomized Trial of Adjuvant Chemotherapy with Uracil–Tegafur for Adenocarcinoma of the Lung.* New England Journal of Medicine, 2004. **350**(17): p. 1713-1721.

26. Winton, T., et al., *Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer.* N Engl J Med, 2005. **352**(25): p. 2589-97.

27. Zhu, Y., et al., *Exploration of optimal time for initiating adjuvant chemotherapy after surgical resection: A retrospective study in Chinese patients with stage IIIA non-small cell lung cancer in a single center.* Thorac Cancer, 2016. **7**(4): p. 399-405.

28. Liu, Y., et al., *Is there an optimal time to initiate adjuvant chemotherapy to predict benefit of survival in non-small cell lung cancer?* Chin J Cancer Res, 2017. **29**(3): p. 263-271.

29. Salazar, M.C., et al., *Association of delayed adjuvant chemotherapy with survival after lung cancer surgery*. JAMA Oncology, 2017. **3**(5): p. 610-619.

30. Booth, C.M., et al., *Time to adjuvant chemotherapy and survival in non-small cell lung cancer: a population-based study.* Cancer, 2013. **119**(6): p. 1243-50.

31. Wang, B.Y., et al., *Impact on Survival on Interval between Surgery and Adjuvant Chemotherapy in Completely Resected Stage IB-IIIA Lung Cancer.* PLoS One, 2016. **11**(11): p. e0163809.

32. Brundage, M.D., D. Davies, and W.J. Mackillop, *Prognostic factors in non-small cell lung cancer: a decade of progress.* Chest, 2002. **122**(3): p. 1037-57.

33. Earle, C.C., et al., *Who gets chemotherapy for metastatic lung cancer?* Chest, 2000. **117**(5): p. 1239-46.

34. Potosky, A.L., et al., *Population variations in the initial treatment of non-small-cell lung cancer.* J Clin Oncol, 2004. **22**(16): p. 3261-8.

35. Hershman, D.L., et al., *Delay of adjuvant chemotherapy initiation following breast cancer surgery among elderly women.* Breast Cancer Res Treat, 2006. **99**(3): p. 313-21.

36. Hardy, D., et al., *Racial disparities and treatment trends in a large cohort of elderly black and white patients with nonsmall cell lung cancer.* Cancer, 2009. **115**(10): p. 2199-211.

37. Bach, P.B., et al., *Racial differences in the treatment of early-stage lung cancer.* N Engl J Med, 1999. **341**(16): p. 1198-205.

38. Shugarman, L.R., et al., *Race and sex differences in the receipt of timely and appropriate lung cancer treatment.* Med Care, 2009. **47**(7): p. 774-81.

39. Gwyn, K., et al., *Racial differences in diagnosis, treatment, and clinical delays in a population-based study of patients with newly diagnosed breast carcinoma.* Cancer, 2004. **100**(8): p. 1595-604.

40. Jones, L.A., et al., *Examining racial disparities in colon cancer clinical delay in the Colon Cancer Patterns of Care in Chicago study.* Annals of Epidemiology. **27**(11): p. 731-738.e1.

41. Murphy, C.C., et al., *Race and Insurance Differences in the Receipt of Adjuvant Chemotherapy Among Patients With Stage III Colon Cancer.* Journal of Clinical Oncology, 2015. **33**(23): p. 2530-2536.

42. *Georgia Comprehensive Cancer Registry*. The Georgia Comprehensive Cancer Registry (GCCR) is a statewide population-based cancer registry collecting all cancer cases diagnosed among Georgia residents since January 1, 1995. This information furthers our understanding of cancer and is used to develop strategies and policies for prevention, control, and treatment. The availability of this data at the state level allows health researchers to analyze geographic, racial, and other differences that provide clues that point to risk factors. This data also helps in determining where early detection, educational, or other programs should be directed.

The Georgia Department of Public Health has designated the Georgia Center for Cancer Statistics (GCCS) at the Rollins School of Public Health at Emory University as

its agent for the purpose of collecting and editing cancer data.). Available from: https://dph.georgia.gov/georgia-comprehensive-cancer-registry.

43. Adamo, M., L. Dickie, and J. Ruhl, *SEER Program Coding and Staging Manual 2016.*, U.S.D.o.H.a.H.S.N.I.o.H.N.C. Institute, Editor. 2016, National Cancer Institute: Bethesda, MD 20850-9765.

44. *POVERTY AREAS*. 1995, Economics and Statistics Administration.

45. Bosco, J.L., et al., *A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies.* J Clin Epidemiol, 2010. **63**(1): p. 64-74.

TABLES

Table 1. Percentiles of time interval in days between diagnosis date and initiation of adjuvant chemotherapy.

Percentile	Days
0	2
25	42
33.33	46
50	55
66.66	69
75	77
100	501

Table2. Clinical and demographic characteristics of colon cancer patients in the state of Georgia, stratified by time interval between diagnosis and adjuvant chemotherapy.

Patient characteristic		First Tertile time ≤ 46 d (n=703)		Second Tertile 46 d < time ≤ 69 d (n=709)		Third Tertile time > 69 d (n=694)		p-value
		n	%	n	%	n	%	
Sex								
	Male	373	(53.1)	345	(48.7)	375	(54)	0.09
	Female	330	(46.9)	364	(51.3)	319	(46)	
Race								
	White	487	(69.3)	484	(68.3)	402	(57.9)	
	Black	189	(26.9)	207	(29.2)	280	(40.3)	<0.01
	Other	27	(3.8)	18	(2.5)	12	(1.7)	
SES								
	Low	74	(10.5)	61	(8.6)	65	(9.4)	
	Middle	381	(54.2)	375	(52.9)	340	(49)	0.13
	High	248	(35.3)	273	(38.5)	289	(41.6)	
Stage								
	I-II	122	(17.4)	141	(19.9)	196	(28.2)	<0.01
	III	581	(82.6)	568	(80.1)	498	(71.8)	
Grade								
	1,2	563	(80.1)	571	(80.5)	573	(82.6)	0.5
	3,4	140	(19.9)	138	(19.5)	121	(17.4)	
Age (mean and SD)		58	(±12.8)	60	(±11.7)	61	(±11.6)	<0.01

Table 3. Cox Proportional Hazards model of variables associated with survival in colon cancer patients, who underwent definitive surgery followed by adjuvant chemotherapy, from the Georgia Cancer Registry, 2010 to 2014

		All-cause survival			Cancer specific survival		
Covariate		Hazard Ratio (95% CI)		p-value	Hazard Ratio (95% CI)		p-value
Time interval							
in days	1st Tertile	1			1		
	2nd Tertile	0.790	(0.619, 1.009)	0.0588	0.738	(0.56,0.972)	0.031
	3rd Tertile	0.966	(0.76, 1.227)	0.7739	0.965	(0.74,1.259)	0.793
Age		1.024	(1.015, 1.032)	<.0001	1.017	(1.008,1.027)	0.0003
Race							
	White	1			1		
	Black	1.056	(0.84, 1.326)	0.642	1.085	(0.842, 1.399)	0.527
	Other	0.978	(0.483, 1.979)	0.950	1.063	(0.5, 2.263)	0.874
SES							
	Low	1			1		
	Middle	1.233	(0.838, 1.814)	0.2888	1.173	(0.767, 1.794)	0.462
	High	1.484	(0.997, 2.207)	0.0516	1.436	(0.928, 2.222)	0.105
Stage							
	1	1			1		
	2	1.47	(1.128, 1.916)	0.0044	1.566	(1.158, 2.119)	0.004
Grade							
	1, 2	1			1		
	3, 4	2.099	(1.694, 2.602)	<.0001	2.452	(1.94, 3.099)	<.0001
Gender	Male	1			1		
	Female	0.853	(0.698, 1.044)	0.1225	0.886	(0.707, 1.109)	0.292

FIGURES

Figure 1. Diagram of the steps leading up to the study cohort

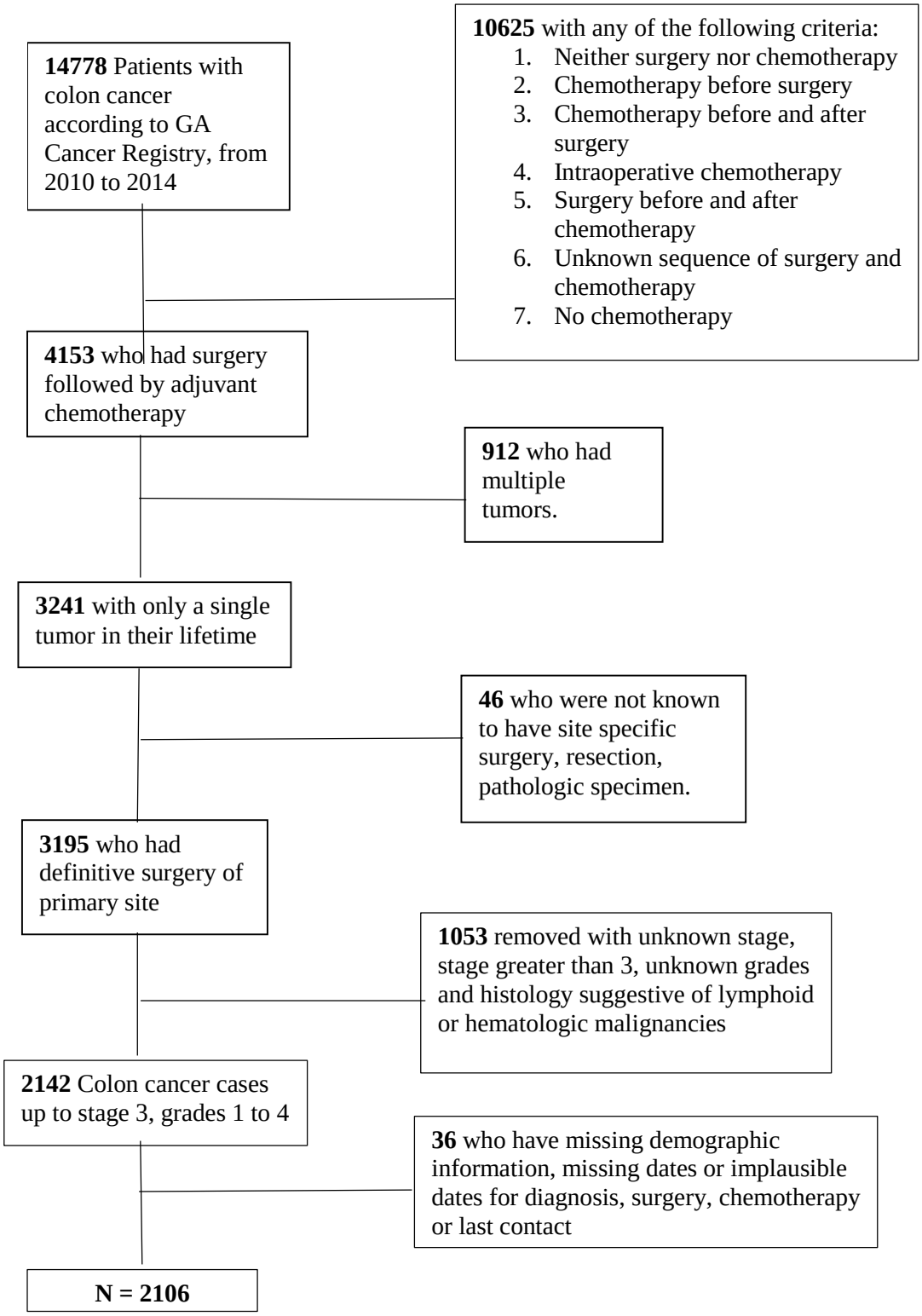


Figure 2. Kaplan–Meier curves of all cause survival by time interval from diagnosis date to initiation of adjuvant chemotherapy in colon cancer patients

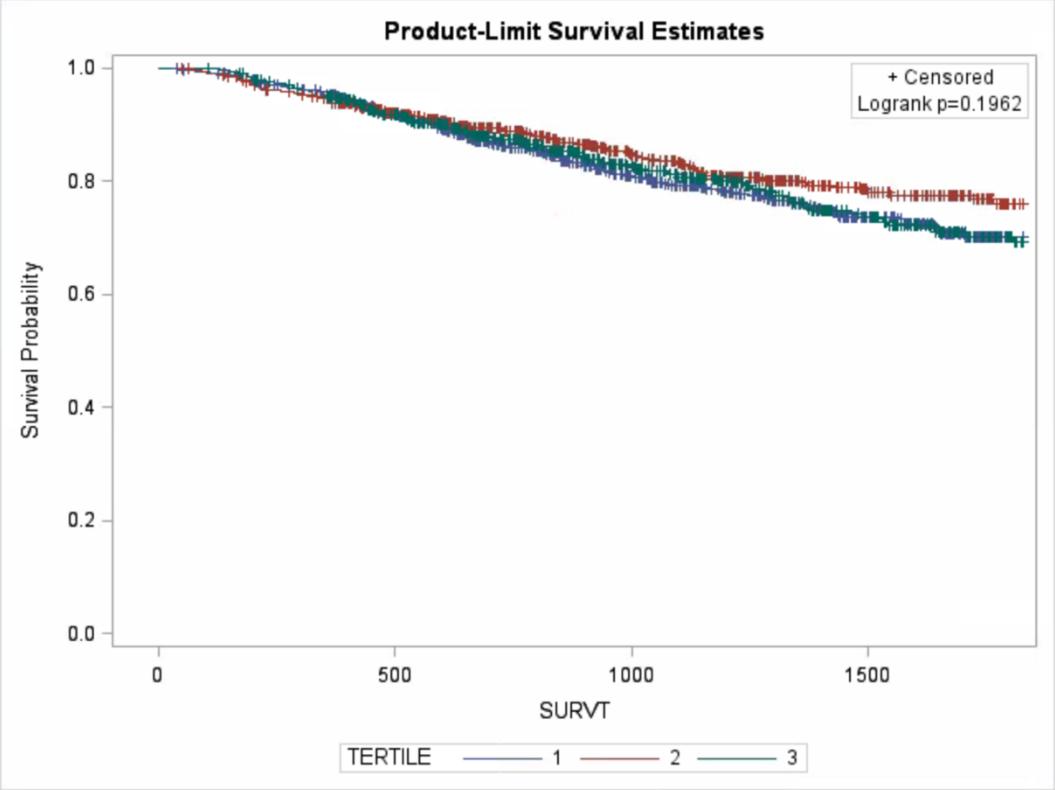
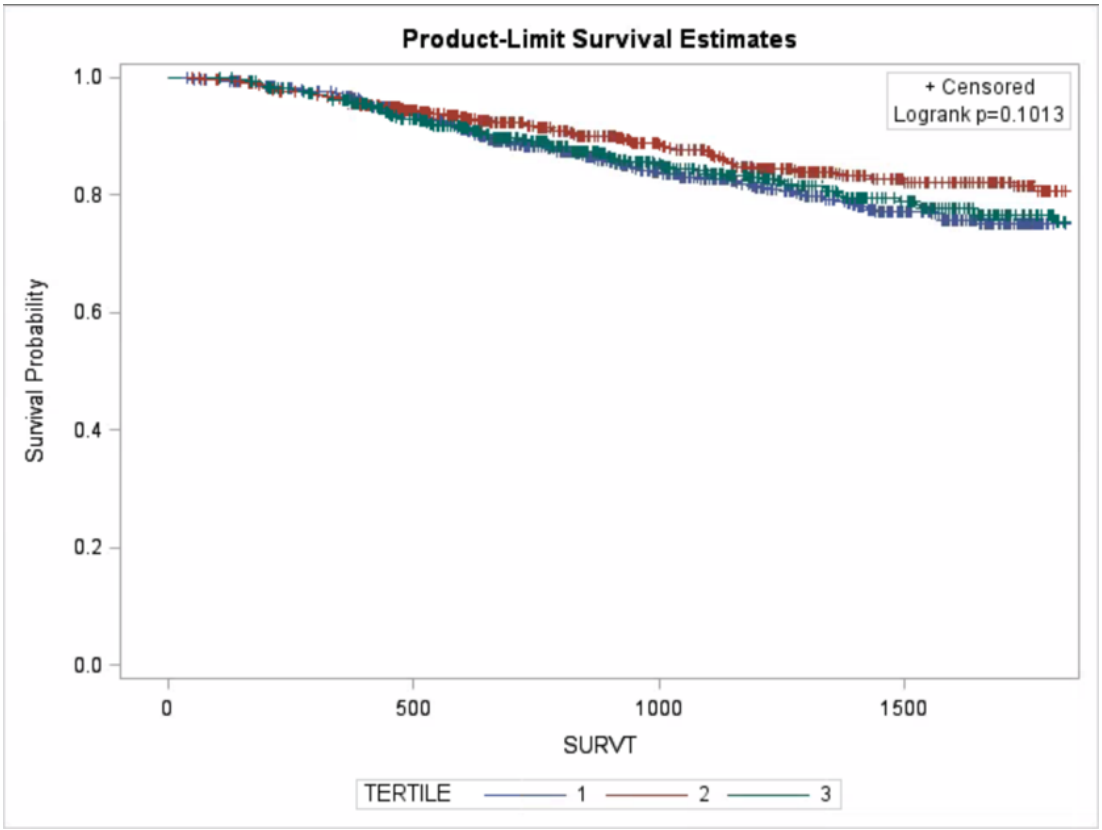


Figure 3. Kaplan–Meier curves of cancer specific survival by time interval from diagnosis date to initiation of adjuvant chemotherapy in colon cancer patients



CHAPTER III

SUMMARY, PUBLIC HEALTH IMPLICATIONS, POSSIBLE FUTURE DIRECTIONS

Summary

The findings from this study do not suggest improved all–cause survival by earlier initiation of adjuvant chemotherapy for colon cancer patients in the state of Georgia. The study noted significantly better cancer specific survival in the second time tertile compared to first tertile. These findings may have been driven mainly by the fact that majority of patients in the study cohort received timely chemotherapy according to ACS guideline of 120 days. Also, the study included stage II patients who do not routinely receive adjuvant chemotherapy.

The study found that age a diagnosis, stage and race varied across time tertiles. Also, age, stage and grade were significantly associated with both all–cause and cancer specific survival. No significant interaction was found between exposure and any of the covariates that were included in the multivariate analysis.

The major limitations of the study were related to the observational nature and retrospective design. Also, the study did not control for all possible predictors of survival in multivariate analysis. All the reasons for delay in adjuvant therapy were not examined in detail.

Public health implications and future directions

The optimal interval for initiation of adjuvant chemotherapy for colon cancer is not yet known. Also unknown is an absolute cut off point beyond which chemotherapy is

no longer beneficial. The mathematical model by Harless and Qiu suggests that such a cut off probably exists (7). But none of the studies so far have been able to ascertain that. A prospective study or a randomized control trial would be needed to answer such a question, neither of which are ethically feasible at this point.

Efforts should be made to ensure that all patients receive timely chemotherapy as per guidelines and this is definitely happening for colon cancer patients in the state of Georgia. Factors associated with delay should be investigated further. While there were significant racial differences in the timing of chemotherapy initiation, there were no differences by socioeconomic status. Neither race nor socioeconomic were independently associated with outcomes among this cohort of patients who received definitive surgery followed by chemotherapy. This is promising news for cancer control planners within Georgia.

The decision to use adjuvant chemotherapy for patients with stage II colon cancer is complicated and requires thoughtful consideration by both patients and their physicians (16). High – risk stage II patients should be encouraged to participate in clinical trials.

APPENDICES

Georgia Department of Public Health

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November 8, 2017

Renuka Narayan
Graduate Student
568 Emory Oaks Way
Decatur GA

Project: 171102 - Timing of chemotherapy and survival outcomes in cancer

Project Status: Approved Until 11/08/2018

Dear Researcher,

The above-refereneced project was reviewed by the DPH Institutional Review Board in accordance with expedited review procedures outlined in 45 CFR 46.110(b)(1), category(ies) **5**
The Board has **approved** this study until **11/08/2018**

If you wish to continue this project beyond the current approval period, please submit a "Continuing Review Application" before the above expiration date. If you do not submit a renewal application before the expiration date, the approval of your project will automatically terminate. Any involvement with human subjects must cease on the above date unless you have received approval from the Board to continue the project. It is the investigators responsibility to track the deadline.

This approval applies only to the protocol described in your application. IRB review and approval is required before implementing any changes in this project except where necessary to eliminate apparent immediate hazards to human subjects.

If you have any questions regarding this letter or general procedures, please contact the DPH IRB at irb@dhr.state.ga.us. Please reference the project # in your communication.

Best wishes in your research endeavors,