Treatment Disparities among elderly colon cancer patients in the United States using SEER-Medicare Data.

By

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A Thesis Presented to

The Department Of Public Health and Preventative Medicine

at the Oregon Health and Science University

School of Medicine in partial fulfillment of the requirement for the degree

of Master of Public Health

December 7th, 2009

Department of Public Health and Preventive Medicine

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CERTIFICATE OF APPROVAL

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ACKNOWLEDGMENTS

I would like to thank many people who helped me through this journey. I would like to thank my thesis committee members Dr. Don Austin, Dr. Daniel Herzig, and Dr. Garnett McMillan, for all their support, suggestions and for sharing their time for this project. Dr. Don Austin was a great thesis chair, his attention to detail and ideas kempt me on track and organized. Dr. Daniel Herzig always brought ideas to the table that I hadn't thought of and he was a great teacher. And finally, Dr. Garnett McMillan was very supportive and patient throughout this entire statistical journey.

Although many of my classmates have graduated I still keep in touch with one. Melissa Curran is always there for me to vent my problems on and give me advice to get through. I also have many close friends who have helped me out along the way. Rebekah and Sara, my wonderful coworkers and dear friends, have been there to cheer me on even when I think it is hopeless.

Lastly and most importantly, I would like to thank my family. This would not have been possible without the financial support from my grandparents Henry and Evelyn Lanxon. And finally, I would like to thank my husband, Devon Shoop for being my constant cheerleader and support. He made it possible and easy for me to go back to school while working full time. I truly could not have done this without him.

ABSTRACT

BACKGROUND: Colorectal cancer (CRC) is the third most common cancer type in the United States and the third-leading cause of deaths among both men and women. The five year survival in colorectal cancer stage II is approximately 80% and in stage III reduced to 50% (1). Colon cancer is also one of the most curable types of cancer if it is diagnosed early.

METHODS: This study is a historic cohort of anonymized secondary data and examines the relationship between increasing age and cancer directed therapy for colon cancer stages I-III, within the Medicare population. The purchased SEER Medicare linked sample provided patients who had a colon cancer diagnosis, identified by ICD-9 diagnosis code, from 2000-2005 with follow-up data through 2005. Patients were categorized by age into five-year increments starting with age 65. The primary goal of this analysis was to examine whether older patients receive less cancer directed therapy than younger patients, stratified by cancer stage. Two multivariate logistic regression models were fit to examine the associations. The first examined the association between older age and receipt of cancer directed therapy, adjusting for demographics and clinical characteristics. The second model looked at the association between older age and the number of lymph nodes examined during surgery. Additionally, adjusted hazard ratios (HR) were estimated using Cox proportional hazards regression, to examine colon cancer specific survival among age groups.

RESULTS: Subjects aged 70-74 were significantly (OR=0.21, 95% CI: 0.13-0.52) less likely to receive cancer directed therapy compared to those aged 65-69. This result was seen at all older age categories. Individuals over the age of 90 were 1.82 times more likely to have inadequate surgery (OR=1.82 95% CI: 1.57-2.21). Interestingly, Blacks (OR=1.16 95% CI: 1.06-1.27), Asians (OR=1.14 95% CI: 1.01-1.30), and Hispanics (OR=1.64 95% CI: 1.35-2.00) were all more likely to have inadequate surgery than Whites. Age was a significant predictor of poor colon cancer survival in all subjects. The largest HR was seen among subjects who did not receive cancer directed therapy.

CONCLUSIONS: After adjusting for patient factors and clinical characteristics elderly patients were significantly more likely to receive less cancer directed therapy and receive inadequate resection. Increased age was strongly associated with colon cancer mortality. However, among subjects who received cancer directed therapy stage of disease was more highly associated with mortality than age. While subjects who did not receive cancer directed therapy were much more likely to die from age than their disease.

Research Question and Specific Aims

Title

Treatment Disparities among elderly colon cancer patients in the United States using SEER-Medicare Data.

Research Question

After accounting for comorbidities and patient factors are older patients more likely to receive cancer directed treatment (as opposed to palliative care) for colon cancer stages I-III than younger patients?

Specific Aims

Use SEER Medicare linked data from 2000-2005 to create six age groups (65-69, 70-74, 75-79, 80-84, 85-89, 90+), then

1. Examine the data and restrict the original sample based upon predetermined exclusion criteria (Table 8), and weight comorbid conditions using the Charlson MACRO provided by SEER.
2. Use multiple logistic regression to build two separate models. Looking at the association between older age and a decrease in cancer directed treatment and number of lymph nodes examined during surgery, controlling for:
    a) Total weighted Charlson comorbid conditions.
    b) Regional differences and income
    c) Other demographic factors and clinical characteristics such as race, gender, and stage of cancer.

3. Using the Kaplan-Meier estimates, and a multivariate Cox proportional hazards model, assess the colon cancer survival benefit between those who did receive cancer directed treatment and those who did not, controlling for:
    a) Total weighted Charlson comorbid conditions
    b) Regional differences and income
    c) Other demographic factors and clinical characteristics such as race, gender, and stage of cancer.

Relevance

Colon cancer is the third leading cause of cancer-related deaths in the United States accounting for about 20 percent of all cancer deaths. One of the most significant risk factors for colon cancer is age. Age was significantly associated with having less cancer directed therapy and inadequate surgery, after adjustment for patient factors and clinical characteristics. Age was more associated with colon cancer mortality among those who did not receive cancer directed therapy. While among those who did receive cancer directed therapy, stage of disease was most highly associated with colon cancer mortality. Indicating that severity of disease is more predictive of mortality than age. This study is one of the few that includes subjects over the age of 80 and adjusts for comorbid conditions and patient factors. It is hoped that these results may spark further analysis in the field of elderly colon cancer treatment.

BACKGROUND

Colon and rectal cancer was projected to afflict 148,810 Americans in 2008 and was estimated to cause more than 49,960 deaths (2). Colorectal cancer (CRC) is the third most common cancer type in the United States and the third-leading cause of deaths among both men and women, still the most important prognostic factor is stage of disease. The five year survival in colorectal cancer stage II is approximately 80% and in stage III reduced to 50% (1). Colon cancer is also one of the most curable types of cancer if diagnosed early. When detected at its earliest stages, chances for a cure are as high as 90 percent. Significant risk factors for colorectal cancer include: age, family history, history of inflammatory bowel disease, racial and ethnic background, obesity, smoking, heavy alcohol use and type II diabetes (2).

The National Cancer institute states that treatment depends upon the stage of cancer (0-IV), whether the cancer has reoccurred, and overall patient health. Stage 0 (also called carcinoma in situ) is categorized as abnormal cells found in the innermost lining of the colon. These abnormal cells may become cancer and spread into nearby normal tissue. In stage I, cancer has formed and spread beyond the innermost tissue layer of the colon wall to the middle layers. Stage II is divided into two subgroup. Stage IIA, the cancer has spread beyond the middle tissue layers of the colon wall or has spread to nearby tissues around the colon or rectum. Stage IIB the cancer has spread beyond the colon wall into nearby organs and/or through the peritoneum. Stage III is divided into three subgroups. Stage IIIA is when the cancer has spread from the innermost tissue layer of the colon wall to the middle layers and has spread to as many as 3 lymph nodes. Stage

IIIB the cancer has spread to as many as 3 nearby lymph nodes and has spread: beyond the middle tissue layers of the colon wall, to nearby tissues around the colon or rectum, or beyond the colon wall into nearby organs and/or through the peritoneum. Stage IIIC the cancer has spread to 4 or more nearby lymph nodes and has spread: to or beyond the middle tissue layers of the colon wall, to nearby tissues around the colon or rectum, or to nearby organs and/or through the peritoneum (3). In stage IV, cancer may have spread to nearby lymph nodes and has spread to other parts of the body, such as the liver or lungs.

Accurate histologic assessment of lymph node involvement is a critical part of staging and it has been suggested that a minimum number of lymph nodes (LNs) should be examined to have confidence that the stage of cancer is correctly identified (4).The number of nodes harvested can be used as a marker for quality of care which may allow for a meaningful comparison of node harvest and stage between populations and demographics (5). In an effort to reduce staging errors, many experts have emphasized a need to evaluate a minimum number of LNs in any colorectal cancer specimen (6-12). The National Quality Forum has recommended that at least 12 nodes be examined as a quality indicator (13).

Patients who do not undergo surgery are clinically staged. Clinically staged cancer is the physician's best estimate of the extent of disease, based upon the results from a physical exam, biopsy, and any imaging tests performed. Pathologic staging done after surgery is likely to be more accurate than clinical staging, as it allows for surgeons to get a firsthand impression of the extent of disease (2). The status and staging of regional LNs is not only a significant prognostic indicator but also a major determinant of the need for adjuvant therapy (14).

Three types of standard treatments are used to treat colon cancer and vary depending upon the stage of cancer. Surgery is the most common treatment for all stages of colon cancer. Removal of the tumor may be done by various types of procedures. Local excision is preformed if the cancer is found at a very early stage; the tumor may be removed without cutting through the abdominal wall. A resection is done if the cancer is larger, a partial colectomy may be performed which is the removal of the cancer and a small amount of the healthy tissue surrounding it. An anastomosis may then be done which is when the healthy portions of the colon are sewn back together. Lymph nodes near the colon are also removed and examined to see whether they contain cancer (3).

Even if all visible cancer is removed at the time of the operation, some patients may be given chemotherapy or radiation therapy after surgery to kill any cancer cells remaining. Treatment given after surgery, to increase the chances of a cure, is called adjuvant therapy (3). Chemotherapy is a cancer treatment that uses potent drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. The last treatment option is radiation therapy which uses high-energy x-rays or other types of radiation to kill cancer cells or keep them from growing. Types of chemotherapy and radiation therapy administered to patients depend upon the stage of the cancer (Table 1).

Table 1- Recommended treatment options based upon staging of tumor

Stage	Recommended treatment
0	Local resection of tumor or resection if the tumor is large
I	Resection of tumor
II	Resection of tumor
III	Resection of tumor to remove as much as possible and adjuvant chemotherapy
IV	Resection of tumor and chemotherapy or radiation therapy for palliative care

One of the most significant risk factors for colon cancer is age. More than half of all new cancers in the United States occur in patients 65 years of age or older (15). The incidence of cancer in this age group is 11 times that in the population under 65 and more than half of all deaths due to cancer occur in patients 65 or older. The increasing longevity of our population makes these statistics especially sobering; by 2030 it is likely that 20 percent of the population of the United States will be 65 or older, as compared with the current 13 percent. Moreover, life expectancy continues to improve. The median survival for healthy women and men who are 70 years old is 15.7 and 12.4 years, respectively, and for those 80 years old it is 8.6 and 6.7 years, respectively (16).

These factors have recently stimulated more research in this age group, but health care decisions for elderly patients are still understudied (17). Much of the data guiding treatment of colon cancer was obtained in studies in which elderly patients were excluded, resulting in variation in treatment especially in those 80 years old and beyond. Some of this discrepancy is based upon uncertain benefits in the elderly population. The MOSAIC trial, which is widely cited to provide the basis for first line chemotherapy in colon cancer, only included patients up to age 75 (18). In addition, adjuvant chemotherapy is inconstantly used in the elderly, despite having well documented survival benefits in the general population (19). Disparities based on age in colon cancer diagnosis and treatments are poorly understood.

One major hurdle in assessing treatment benefits in the elderly population is the high prevalence of comorbid conditions. Many studies lack information on comorbid conditions of patients and therefore cannot truly analyze which treatment is beneficial for older patients with accompanying chronic illnesses. A recent study done using SEER-Medicare linked data found that the probability of a patient being offered chemotherapy significantly decreased with age. And that although comorbidity was associated with an increased risk of death, it did not diminish the relative survival benefit associated with chemotherapy given for colon cancer (20). Indicating that despite the fact that older patients would have increased survival benefits with chemotherapy, they are still not being given appropriate treatment.

Additionally, a population based study done to assess comorbidity and age as predictors of risk of early mortality in colon cancer patients found that 75% of the patients in the cohort had stage III or lower colon cancer, demonstrating that increased age did not signify increased severity of the disease. They concluded that older age (75 +) and the presence of comorbidity were significantly predictive of not receiving surgery (21) even though colon cancer stage was less severe. A study conducted in Italy looked at curative surgery for elderly patients. Within their study, 60% of patients 80 years old and beyond received curative surgery, while those individuals younger than 80 received 73.5%. Inversely, patients older than 80 received 13% more palliative surgery (surgery done to reduce disease severity symptoms) than patients younger than 80 years old (22).

This study utilizes data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI). The SEER-Medicare data reflect the linkage of two large population-based sources of data that provide detailed information about elderly persons with cancer. The SEER data set includes information regarding patient mortality, treatments given, comorbid conditions, survival after diagnosis, age, cancer staging and numerous demographic variables. The purpose of this study was to examine associations related to the receipt of cancer directed surgery in older patients after accounting for demographics other than age, and for other chronic illnesses, stratified by cancer staging.

Preliminary Studies

The surgery department at Oregon Health and Sciences University (OHSU) has conducted preliminary data analysis on diagnosis and treatment of colon cancer in octogenarians (patients aged 80-89) (23). The Oregon State Cancer Registry (OSCaR) was queried for colon cancer patients during 1998-2004. The registry provides mandatory reporting of cases, demographics and initial therapy given to patients. Patients with colonic neoplasm were partitioned into two age categories (less than 80 and 80 years old and beyond) and the demographics of patients were examined. Patients' ≥ 80 years old were significantly more likely to be female and less likely to live in a rural county than younger patients (Table 2). Chemotherapy is given to patients' ≥ 80 years old significantly less often than younger patients for every stage of colon cancer (Figure 1). This study showed that predictors of receiving chemotherapy were different for both age groups. Predictors in older patients included age, worse stage of disease, and living in an urban environment but predictors in younger patients were worse stage and having fewer lymph nodes surgically removed.

Additionally I conducted an analysis for the OHSU surgery department examining surgical approaches for colon cancer patients nationwide. Colonic malignancy is increasingly being treated laparoscopically, which yields less recovery time and lower costs. I performed a retrospective review of data from the National Inpatient Sample including (NIS) 141,562 elective colectomies from 2000 through 2005 performed for benign or neoplastic colon disease. Information regarding demographics, diagnosis, hospital stay and costs were assessed. Multivariate analysis revealed that predictors of having a laparoscopic colectomy included zip code with the highest level of income, being privately insured, having their operation in later years, being in an urban or teaching hospital, and being male. Despite similar costs and shorter hospital stays, determinants of having a laparoscopic colectomy remain highly dependent on socioeconomic factors including health insurance, income, hospital type, age, and gender.

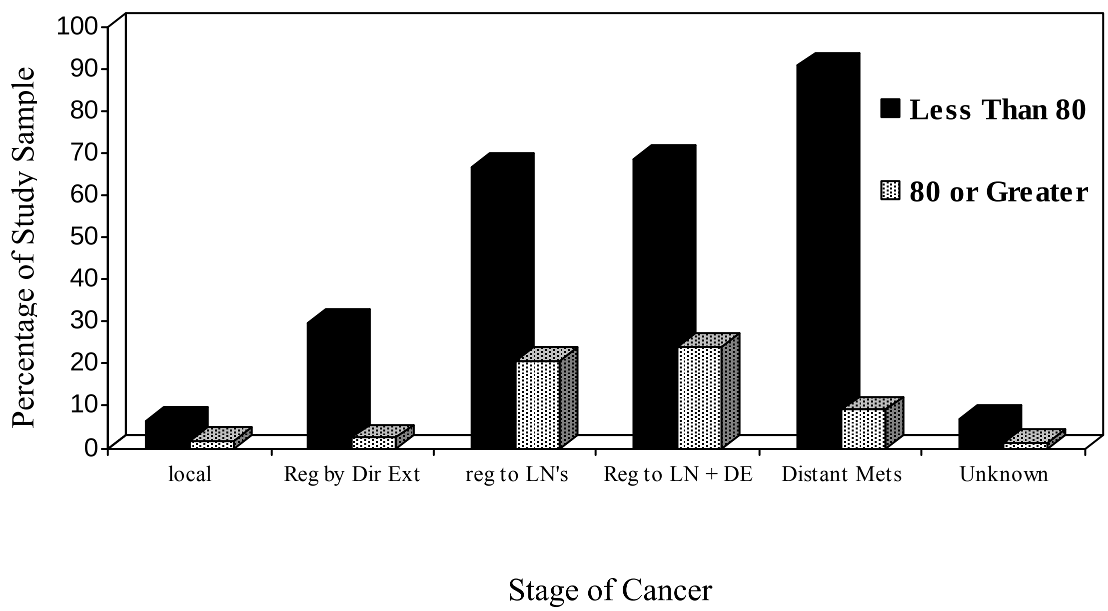
Table 2-Demographics among the Oregon State Cancer Registry colon cancer patients

Covariate	Less than 80	Greater than 80
Sex (Female %)	48	58*
Percent living in a rural community	35	31*

*= P<.001

Most studies conducted omit patients older than 80 years old. The two preliminary studies performed by our team indicate that increasing age is a major factor in treatment outcome. Limitations in the first study included lack of information on patient mortality and comorbidities. The SEER-Medicare data provides a vast amount of colon cancer patients with information regarding survival, mortality and comorbidities. This enabled us to properly examine treatment for colon cancer patients among the elderly.

Figure 1- Percentage of chemotherapy given by stage of cancer among age groups



METHODS

Overview

This study is a historic cohort of anonymized secondary data. The study examines the relationship between increasing age and cancer directed treatment (CDT) for colon cancer stages I-III, within the Medicare population. The purchased SEER Medicare linked sample provided patients who had a colon cancer diagnosis, identified by ICD-9 diagnosis code, from 2000-2005 with follow-up data through 2005. Patients were categorized by age into five-year increments starting with age 65. The primary goal of this analysis was to examine whether older patients receive less CDT than younger patients, stratified for cancer stage.

SEER Database

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) is an authoritative source of information on cancer incidence and survival in the United States. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 26 percent of the US population (24). The SEER program registries routinely collect data on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up for vital status. The SEER program is the only comprehensive source of population-based information in the US that includes stage of cancer at the time of diagnosis and patient survival data (24).

SEER began collecting data on cancer cases on January 1, 1973, in the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii and the metropolitan areas of Detroit and San Francisco-Oakland. SEER then quickly expanded to include other areas that included a more racially diverse population. In 2001, the SEER Program expanded coverage to include Kentucky and the remaining counties in California (Greater California); in addition, New Jersey and Louisiana once again became participants. For the expansion registries (Kentucky, Greater California, New Jersey, and Louisiana), NCI funds are combined with funding from the Centers for Disease Control and Prevention (CDC) through the National Program of Cancer Registries and with funding from the states (24).Several of the primary objectives of the SEER program included: to collect complete and accurate data on all cancers, periodically report on the cancer burden as it relates to cancer incidence and mortality and patient survival overall and in selected segments of the population, and describe temporal changes in cancer incidence.

The SEER-Medicare linked files being used for this analysis include MEDPAR, PEDSF, outpatient and NCH for colon cancer patients. The files from 2000-2005 were combined into one dataset which included over 125,000 patients. The variables of interest included: tumor staging, observed survival time from diagnosis, mortality, CDT, comorbidity and patient demographics.

Subject Selection

The SEER data containing only patients with a colon cancer diagnosis were purchased. Additionally, these data apply to only individuals with Medicare benefits.

Only subjects over the age of 65 were included and partitioned into categories of five year increments.

Patients with colon cancer stages 0-III still have a good chance of recovery and long-term survival. However, patients that have stage 0 colon cancer tend to receive less surgery for their disease than higher staged individuals and may often be misclassified with regard to malignancy and were therefore omitted from the study population. Additionally, advanced stage colon cancer has a poorer prognosis and patients generally receive palliative treatments to lessen disease severity as opposed to procedures with curative intent. Therefore, patients who had stage IV colon cancer were also omitted from the study.

The SEER database does not give staging coded as 0-IV. Instead, the American Joint Committee on Cancer (AJCC) staging system uses three basic descriptors that are then grouped into stage categories. The first component is a “T”, which describes the extent of the primary tumor. The next component is an “N”, which describes the absence or presence and extent of regional lymph node metastasis. The third component is “M”, which describes the absence or presence of distant metastasis. The final stage groupings (determined by the different permutations of A, T and N) range from Stage 0 through Stage IV. The stage group is generated when specific criteria are met in the TNM system. The Collaborative Staging System is based on, and compatible with, the terminology and staging in the sixth edition of the AJCC Cancer Staging Manual, published in 2002. The general rules of the TNM system have been incorporated into the general rules for Collaborative Staging (25). Based upon the SEER modified AJCC stage information, subjects were combined into stage groups and only those subjects with stages I-III were included (Table 3).

Table 3- Staging information and category creation

SEER AJCC classifications	Re-categorized stage
1, 1A-C, 1NOS	Stage I
2, 2A-C, 2NOS	Stage II
3, 3A-C, 3NOS	Stage III

Additionally patients with missing information on key variables of interest such as race, gender, income, location and tumor staging were eliminated. This ensured that only patients with complete data were used for analysis.

Variables

Primary Predictor Variable

The age at diagnosis of the Medicare patients across all 13 registries was the main predictor variable of interest. Age was partitioned into 6 categories. The first group includes colon cancer patients aged 65-69 at diagnosis. The other groups were partitioned in 5 year increments. Preliminary studies done at OHSU looked at patients that were partitioned into two categories (below the age of 80 and 80 and beyond). Two age categories may obscure significant findings and therefore six age categories were chosen.

Covariates

Adjustments for the following variables were preformed: comorbidity, stage of cancer, patient location, gender, race and income. Decisions for which variables to adjust were based upon previous studies. A national population based study using SEER data was conducted in 1997(21). The study examined co-morbidity and age as predictors of risk for early mortality in colon cancer patients. They found that although staging of cancer is a crucial determinant of patient outcome, comorbidity increases the complexity of cancer management and affects overall survival duration (21).

The method developed by Charlson et al. was used to assess comorbidity. Their comorbidity index was developed empirically, based on the 1-yr mortality from an inception cohort study in 1984. The method assigns a weighted index of 1, 2, 3 and 6 for each of the existing comorbid diseases to derive a total score (26). The weighted comorbid conditions are given in Table 4; subjects with conditions not included in the list were given a comorbidity score of 0. For the purposes of this study a window of one year from diagnosis was used to weight the comorbid condition related to colon cancer. If subjects did not have a diagnosis of a comorbid condition within one year after diagnosis the subject was assigned a comorbidity score of 0. Additionally, subjects without comorbid conditions one year prior to the cancer diagnosis were given a score of zero. Finally both the prior and post comorbidity score were combined for a total comorbidity score over the two year window. This measures the effect of weighted comorbid conditions on treatment outcome.

Table 4- Weighted index of comorbidity

Assigned weights for diseases	Conditions
1	Myocardial Infarct
	Congestive heart failure
	Peripheral Vascular disease
	Cerebrovascular disease
	Dementia
	Chronic Pulmonary disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2	Hemiplagia
	Moderate or severe renal disease
	Diabetes with end organ damage
	Any tumor
	Leukemia
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS

(Adapted from Charlson et al.)

Yancik et al also noted that weighted comorbidities differed across gender and age groups. I adjusted for the effect of gender in this analysis. Income quartiles were chosen based upon a previous study done using the National Inpatient Survey Data, (NIS) which span the same time period as this study. Patient locations were categorized as Big Metro, Metro, Urban, and Less Urban, Rural, and Unknown (see Table 5 for population sizes per category). These variables were included as covariates because all were significant predictors in the preliminary studies discussed previously. The variable of survival time was given in months after diagnosis with a maximum follow-up of 5 years for those patients diagnosed in 2000.

Outcome Variables

Cancer Directed Treatment

The SEER database provides information on cancer directed surgery received by subjects. Initially the variable had nine categories: surgery performed, surgery not recommended, surgery not recommended due to other conditions, surgery not performed because patient died before surgery, surgery was recommended but not performed due to unknown reasons, recommended but patient refused surgery, and an unknown category that included death certificate or autopsy information as the primary source of information. For the purposes of this analysis the unknown patients were eliminated and subjects were partitioned into two categories. Subjects either received cancer directed treatment (CDT) or they did not (Table 5).

Surgical Adequacy

The SEER database provides information on the number of LNs examined during surgery. This information speaks to the extent of the surgery. The more lymph nodes examined the more adequate the surgery. This variable had reliable data from 2000 through 2002, and therefore a separate sub-analysis was done that was restricted by year and eliminates patients diagnosed in 2003 to 2005. Previous studies have recommended a minimum number of nodes, ranging between 6 and 17, for accurate staging (12, 27). The variable was partitioned into two categories: 0-11 lymph nodes examined and 12+ LNs examined during surgery (Table5). For the purposes of this study 12 or more lymph nodes removed during surgery will indicate that adequate surgery was performed.

Table 5- Summary of variables

Variable	Type of variable	Description	Additional information
Cancer directed therapy	Outcome	Cancer Directed Surgery	0= Cancer Directed surgery received 1= No cancer directed surgery received
Surgical adequacy	Outcome	Assesses adequacy of surgery performed	1= 0-11 LNs examined 2=12+ LNs examined
Age category	Primary Independent	Age group 1: 65-69 Age group 2: 70-74 Age group 3: 75-79 Age group 4: 80-84 Age group 5: 85-89 Age group 6: 90+	
Comorbidity	Covariate/Potential Confounder	Evaluated by ICD-9 diagnosis code.	Patient's chronic conditions will be given numerical values based upon the Charlson comorbidity index. Subjects will be categorized as follows. 0= No comorbidity 1=1 comorbid condition 2=2 comorbid conditions 3=3+ comorbid conditions
Stage of cancer	Covariate/Potential Confounder	Stages I-III	Described previously in the methods. Based upon the SEER TNM staging system See Table 3.
Patients location	Covariate/Potential Confounder	Category defined by population size of residence.	Large Metro > 1,000,000 Metro= 250,000-1,000,000 Urban=20,000-249,000 Less Urban= 2,500-19,999 Rural < 2,500
Race	Covariate/Potential Confounder	Black, white, Asian, Hispanic, Native American, other	
Gender	Covariate/Potential Confounder	Male or Female	
Income quartile	Covariate/Potential Confounder	Median household income	1= ≥$36,999 2=$37,000-45,999 3=$46,000-60,999 4=$61,000+
Survival time after diagnosis	Covariate	Continuous variable	Survival time in months after cancer diagnosis.

Statistical Analysis and Data Management

Statistical analyses were performed using SAS software 9.1 (SAS Institute Inc., Cary, NC). Both univariate and multivariate logistic regression were used to analyze the relationship between independent variables and CDT or surgical adequacy.

Descriptive Analysis

Frequencies were initially calculated for all categorical variables of interest. Cross-tabulations were examined for each independent and outcome variable. Differences between the proportions were determined with the χ^2 statistic. The only continuous variable of interest was survival time in months from date of diagnosis. The mean survival time was evaluated for covariates.

Univariate Regression

Univariate logistic regression models were analyzed for each possible covariate with a dichotomous outcome of CDT or surgical adequacy. The Wald F statistics and their associated p values were used to determine statistical significance. All variables with a p value of .10 or lower were considered a variable of interest for model building. Variables that were possible confounders such as patient location or race were considered during the modeling phase regardless of significance level.

Multiple Regression

Due to the advanced age of the study population these patients are likely to suffer from other chronic illnesses. To properly answer the research question, comorbidity of colon cancer patients must be adjusted for with multiple logistic regression. After assessing the univariate logistic regression results, multiple regression analysis was preformed to evaluate associations. Modeling the probability of receiving cancer directed therapy and adjusting for covariates and confounders. Using the stepwise approach all variables were entered into a model. Independent variables were eliminated one by one beginning with the least significant until all remaining variables were significant ($p<.05$). After the stepwise approach confounding variables were added back into the model. If coefficients were changed by more than 10% after the addition of a variable than that variable was considered a confounder.

Interaction terms between remaining variables in the model were assessed. Only univariate interaction terms that were significant ($p<.10$) were considered for the final model. The Hosmer and Lemeshow goodness-of-fit test statistic was used to assess the fit of the final models. A secondary analysis that models the probability of having inadequate surgery (0-11 LNs) was also built following the same principles already explained.

Survival Analysis

Survival time was measured in months after primary diagnosis of colon cancer to death or the end of the study period. The SEER database contained a variable that indicates whether the Medicare and SEER date of death match. Only patients with agreement of “still alive at end of study” or “date of death” were considered for analysis. Survival time was calculated by subtracting the date of death from the date of cancer diagnosis. For censored individuals still alive at the end of the study (2005) the date of

January 1st, 2006 was used as the stop date to calculate their survival time. Individuals with a cause of death not attributable to colon cancer were also censored, and those patients with unknown cause of death. Patients with an ICD-10 cause of death code of C18 and C26 are those who died from cancer causes of the colon excluding the rectum. This will provide cause specific survival rates. Table 6 provides the breakdown of censored individuals in the sample.

Univariate analysis of survival was performed using Kaplan-Meier estimates. Adjusted hazard ratios (HR) were estimated using Cox proportional hazards regression. Independent variables considered for the multivariate model were assessed using stepwise selection already described for the multiple logistic regression models.

Table 6 - Cause of death information for the study sample

Cause of death	Frequency	Percentage
Alive at the end of the study period	37186	63.37
Unknown cause of death	181	0.31
Colon Cancer ICD-10 code of C18 and 26	10037	17.10
All other causes of death	11278	19.22

Sample Size and Statistical Power

The SEER database with colon cancer cases diagnosed during 2000-2005 had over 125,000 subjects with Medicare coverage. A previous study (22) examined the rates of curative surgery for colorectal cancer among age groups in Italy. They found that approximately 72% of patients younger than 80 years old received curative surgery. In patients older than 80 only 60% received surgery with curative intent. In order for this study to achieve these results with 90% power only 326 subjects are required in each age group. However each age group needs to be stratified by cancer stage. The total sample size needed with 90% power would then be 3,573 (Table 7). As the cancer stage increases we predicted that the difference in receiving cancer directed treatment would increase between age groups.

Table 7 - Power and sample size calculations

Strata	Percent difference between groups	Age 65-69	70-74	75-79	80-84	85-89	90+	Size needed for 90% power	Number of subjects after restriction
Stage I	12%	326	326	326	326	326	326	1956	18,209
Stage II	17%	167	167	167	167	167	167	1002	23,070
Stage III	22%	102	102	102	102	102	102	612	17,403

PASS software was used to conduct the analysis.

RESULTS

Initially 125,060 subjects were provided by SEER in the Medicare linked data that had a colon cancer diagnosis from 2000-2005. Table 8 includes all restriction criteria and the number of subjects eliminated from the original sample. Individuals that were below the age of 65 were excluded (N=20,206). Additionally some subjects had a diagnosis date before the year 2000 and they were also excluded (N=5,518). For this analysis we were only interested in subjects with primary colon cancer diagnosis, therefore 873 subjects were eliminated who were categorized as having a secondary or subsequent tumor. To ensure that the survival and comorbid data were reliable 1,342 subjects with primary information from autopsy or death certificate were excluded. Next, subjects that were categorized as cancer stage 0 and IV were excluded (N=29,274).

Because survival analysis was being performed the date of death needed to be confirmed. The SEER dataset contained a variable that determined whether or not the SEER and Medicare date of death matched. Subjects where there was no agreement between the date were excluded (N=8,933). And finally, after looking at covariates with unknown information, subjects with missing race information (N=109) and LNs examined during surgery (119) were excluded. The number of subjects excluded from the initial sample was 66,378 which left a total of 58,682 subjects for analysis. It is also of importance to note that the sub-analysis done to compare surgical adequacy only applied to subjects who had information regarding how many LNs were examined during surgery (N=32,963).

Table 8- Restriction criteria for data set

Restriction criteria	Patients excluded	Number before restriction	Number after restriction
Patients age at diagnosis if younger than 65	20,206	125,060	104,854
Patients diagnosed before 2000	5,518	10,4854	99,336
Patients with second or subsequent tumor, or in situ when the patient also has an invasive tumor	873	99,336	98,463
Source reporting: autopsy and death certificate eliminated	1,346	98,463	97,117
SEER modified AJCC stage year 2000-2003: dropped stage 0 and IV	20,188	97,117	76,929
SEER modified AJCC stage year 2003-2005: dropped stage 0 and IV	9,086	76,929	67,843
Number of lymph node exam: if number unknown then excluded	119	67,843	67,724
If date of death did not agree between the SEER and Medicare files	8,933	67,724	58,791
Unknown race	109	58,791	58,682
Total number excluded	66,378		

Sample Characteristics

Demographic and Clinical Characteristics

The demographics and clinical characteristics of the final study population (N=58,682) are summarized in Table 9. Subjects with stage II disease were the most prevalent (39.31%), in the sample, while stages I (31.03%) and II (29.66%) were similar. The six age categories were not equal in size. The largest age group was 75-79 years old (23.73%), the other age categories are as follows: 65-69 (18.27%), 70-74 (21.50%), 80-84 (19.94%), 85-89 (11.56%) and 90+ (5.01%). Women comprised a larger proportion of the cohort than men (54.88% vs. 45.12%). Of the subjects with known race, 84.02% were white, 8.10% were black, and 7.89% were of other races. The majority of subjects lived in large metropolitan/metropolitan areas (87.50%); with 4.77% living in urban areas, 6.33% in less urban areas and 1.40% living in rural areas, which is to be expected by the way SEER areas are selected.

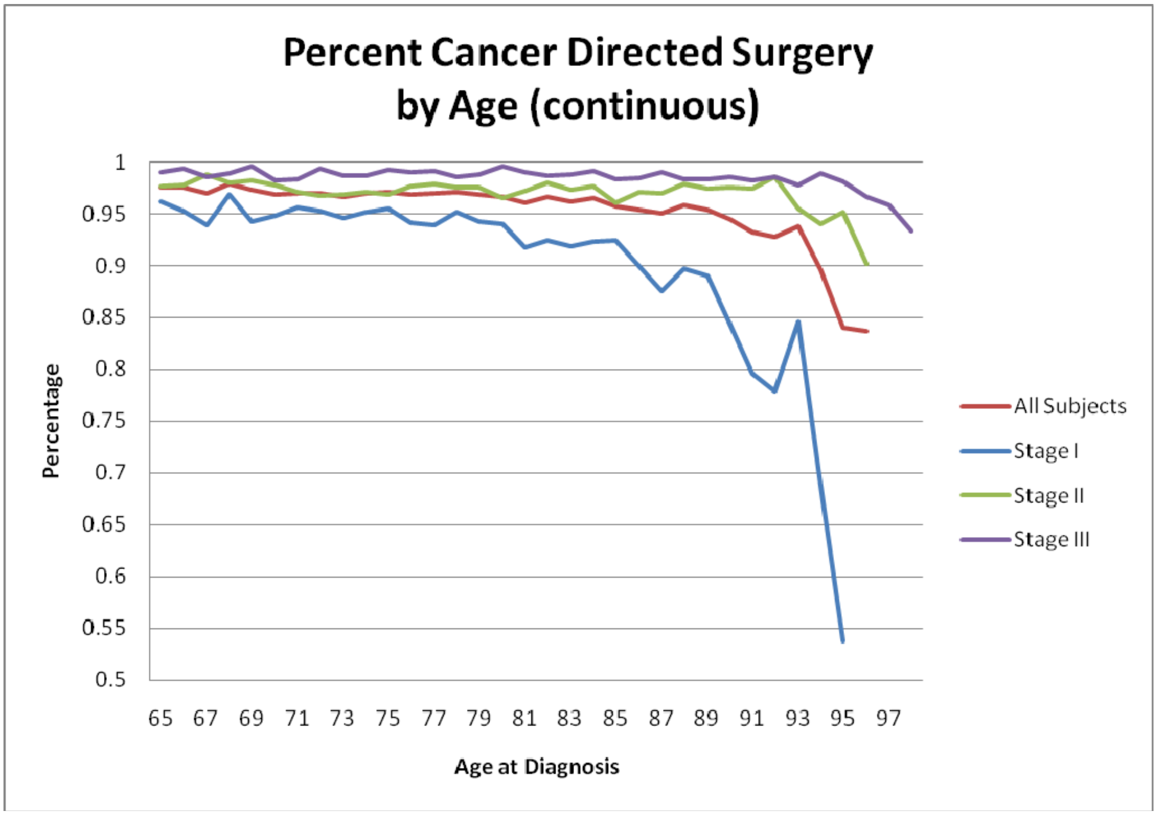
Additionally, the percentage of the cohort diagnosed with colon cancer declined each year; from 2000 (18.98%) to 2005 (15.52%). An annual household income of less than $37,000 (USD) was the most common among Medicare subjects (28.20%). The rest of the study sample was evenly split with 20.56% earning $37,000-45,999; 26.43% earned $46,000-60,999, and 21.07% earned over $61,000 annually. Moreover, an overwhelming percentage of this Medicare population received CDT (96.49%) compared to those who did not (3.51%). Subjects primarily had inadequate surgery (35.11%) compared to those with adequate surgery (21.06%). The majority of subjects had a total comorbidity score of zero (71.29%) or only one (17.17%). Those with a score of 2 (6.76%) were more common than those with a score of 3+ (4.78%).

Percentage of CDT received was examined by age for each stage of disease. Figure 2 shows that subjects with stage I colon cancer received less CDT compared to other stages. Percentage of stage I subjects receiving CDT decreased at age 86. This was not seen among subjects with advanced stages of disease. The decline in percentage of CDT received for stage II subjects was seen at age 92 and 94 for stage III subjects.

Table 9- Descriptive statistics of study population after restriction criteria applied

Characteristic	Category	Number of patients (N=58,682)	Percentage (%)
Age Group	65-69	10,723	18.27
	70-74	12,618	21.50
	75-79	13,923	23.73
	80-84	11,699	19.94
	85-89	6,781	11.56
	90+	2,938	5.01
Race	White	49,305	84.02
	Black	4,751	8.10
	Other	1,348	2.30
	Asian	2,099	3.58
	Hispanic	1,037	1.77
	Native American	142	0.24
Urban Vs. Rural	Big Metropolitan	35,947	61.26
	Metropolitan	15,398	26.24
	Urban	2,800	4.77
	Less Urban	3,717	6.33
	Rural	820	1.40
Gender	Male	26,479	45.12
	Female	32,203	54.88
Year of Diagnosis	2000	11,140	18.98
	2001	10,914	18.60
	2002	10,254	17.47
	2003	9,742	16.60
	2004	8,696	14.82
	2005	7,936	13.52
Cancer Stage	I	18,209	31.03
	II	23,070	39.31
	III	17,403	29.66
Income Category	0-36,999	16,548	28.20
	37,000-45,999	12,065	20.56
	46,000-60,999	15,507	26.43
	61,000+	12,362	21.07
Lymph Nodes examined during surgery	0-11 lymph nodes	20,605	35.11
	12+ lymph nodes	12,358	21.06
	Unknown number	710	1.21
	Missing Info	25,009	42.62
Total Comorbidity score	0	41,835	71.29
	1	10,075	17.17
	2	3,967	6.76
	3+	2,805	4.78
Cancer Directed surgery	Yes	56,624	96.49
	No	2,058	3.51

Figure 2- Percentage of cancer directed therapy received by age and stage



Cancer Directed Treatment Outcome

Demographic and clinical characteristics differences among subjects based upon CDT are shown in Table 10. Due to the large sample size all variables showed a significant difference between subjects who did or did not receive CDT. Age between the two groups was similar except in the highest and lowest age categories. There were fewer subjects aged 65-69 among those who did not receive CDT. The largest difference was seen in the oldest age category; 8.65% of subjects who did not receive CDT were over the age of 90, which is higher than the average for all age groups (3.51%). Racial differences between the treatment groups were small. Of the 4,751 black and 142 Native

American subjects in the study, 5.60% and 5.63% did not have CDT; the average for all races was 3.51%.

Differences between patient locations were negligible among the two groups. One striking difference between the two treatment groups was gender. Among those who did not receive CDT 4.53% were male and only 2.67% were women. Additionally, the same trend by year of diagnosis was seen in both groups. Fewer patients were diagnosed with colon cancer in 2005, (N=7,936) compared to the year 2000 (N=11,140).

There was a striking and counterintuitive difference in cancer stage between the two treatment groups. Of the 18,029 subjects with stage I colon cancer, 6.83% did not receive CDT, which is higher than the average for all stages (3.51%). Additionally, of those with stage III colon cancer (17,403) only 1.14% did not receive CDT. Income category was negligibly different between the two treatment groups.

The total comorbidity score was similar among groups. Subjects receiving CDT were more likely to have had no comorbid conditions (96.78%). Of the 2,805 subjects with 3 comorbid conditions or more, 5.88% received no CDT, again slightly higher than the average of 3.51%. Lymph nodes examined during surgery were very different between each group. Data on this variable were collected through 2002, when SEER stopped collecting information on this variable. Subjects diagnosed after 2002 were missing information which explains the large discrepancy between the groups. This was examined further in a separate analysis done on this variable.

Table 10- Descriptive statistics partitioned by cancer directed therapy (yes/no)

Characteristic		Yes 96.49% (N=56,624)	No 3.51% (N=2,058)	Total (N=58,682)	p-value
Age Group	65-69	97.45(10,450)	2.55 (273)	18.27(10,723)	p<0.0001
	70-74	96.92 (12,229)	3.08 (389)	21.50 (12,618)	
	75-79	96.99 (13,504)	3.01 (419)	23.73 (13,923)	
	80-84	96.44 (11,283)	3.56 (416)	19.94 (11,699)	
	85-89	95.47 (6,474)	4.53 (307)	11.56 (6,781)	
	90+	91.35 (2,684)	8.65 (254)	5.01 (2,938)	
Race	White	96.65 (47,652)	3.35(1,653)	84.02 (49,305)	p<0.0001
	Black	94.40 (4,485)	5.60 (266)	8.10 (4,751)	
	Other	96.74 (1,304)	3.26 (44)	2.30 (1,348)	
	Asian	97.47 (2,046)	2.53 (53)	3.58 (2, 099)	
	Hispanic	96.72 (1,003)	3.28 (34)	1.77 (1,037)	
	Native American	94.37 (134)	5.63 (8)	0.24 (142)	
Urban Vs. Rural	Big Metro	96.31 (34,621)	3.69 (1,326)	61.26 (35,947)	p<0.0001
	Metropolitan	96.94 (14,927)	3.06 (471)	26.24 (15,398)	
	Urban	95.64 (2,678)	4.36 (122)	4.77 (2,800)	
	Less Urban	96.61 (3,591)	3.39 (126)	6.33 (3,717)	
	Rural	98.41 (807)	1.59 (13)	1.40 (820)	
Gender	Male	95.47 (25,280)	4.53 (1,199)	45.12 (26,479)	p<0.0001
	Female	97.33 (31,344)	2.67 (859)	54.88 (32,203)	
Year of Diagnosis	2000	95.92 (10,686)	4.08 (454)	18.98 (11,140)	p<0.0001
	2001	96.34 (10,515)	3.66 (399)	18.60 (10,914)	
	2002	96.31 (9,876)	3.69 (378)	17.47 (10,254)	
	2003	96.12 (9,364)	3.88 (378)	16.60 (9,742)	
	2004	97.01 (8,436)	2.99 (260)	14.82 (8,696)	
	2005	97.62 (7,747)	2.38 (189)	13.52 (7,936)	
Cancer Stage	I	93.17 (16,966)	6.83 (1,243)	31.03 (18,209)	p<0.0001
	II	97.33 (22,454)	2.67 (616)	39.31 (23,070)	
	III	98.86 (17,204)	1.14 (199)	29.66 (17,403)	
Income Category	0-36,999	96.13 (2,099)	4.59 (640)	28.20 (16,548)	p=0.0005
	37,000-45,999	96.71 (11,668)	3.87 (397)	20.56 (12,065)	
	46,000-60,999	96.78 (15,008)	3.29 (499)	26.43 (15,507)	
	61,000+	96.59 (11,941)	3.41 (421)	21.07 (12,362)	
Lymph Nodes Examined	0-11	93.83 (19,333)	6.17 (1,272)	35.11 (20,605)	p<0.0001
	12+	100.00(12,358)	0.00 (0)	21.06 (12,358)	
	Unknown No.	100.00 (710)	0.00 (0)	1.21 (710)	
	Missing Info	96.86 (24,223)	3.14 (789)	42.62 (25,009)	
Total Comorbidity Score	0	96.78 (40,489)	3.22 (1,346)	71.29 (41,835)	p<0.0001
	1	96.32 (9,704)	3.68 (371)	17.17 (10,075)	
	2	95.56 (3,791)	4.44 (176)	6.76 (3,967)	
	3+	94.12 (2,640)	5.88 (165)	4.78 (2,805)	

Surgical Adequacy Outcome

The sub-analysis performed on subjects who had information regarding the number of lymph nodes examined during surgery (N=32,936) excludes patients with an unknown number examined and those with missing information (25,764). Similar trends were seen in this partitioned data set in terms of income, patient location, gender, cancer staging, race and comorbidity score. Table 11 shows the differences in demographics and covariates partitioned by the number of lymph nodes examined during surgery, which evaluates surgical adequacy.

Once again due to the large sample size the differences between the groups were statistically significant for all variables. All age categories had similar percentages between the two groups. Of the 1,631 subjects over the age of 90, only 31.39% had adequate surgery, compared to 37.50% for all age groups. In this subset of patients, Hispanics were more likely to have inadequate surgery (26.85%) than all other races (37.50%). There were negligible differences among subjects in terms of patient location and income category. Additionally, of those that had an inadequate surgery 64.98% (vs. 60.47%) were male

Differences among colon cancer stages were seen between groups. Of the 9,440 subjects with stage I colon cancer 76.82% had inadequate surgery, which is higher than the average among cancer stages 62.50%. The inverse was seen among stage III subjects (N=9,690), 47.40% had adequate surgery, which is approximately 10 percent higher than the average of 37.50%. Additionally, subjects with three or more comorbid conditions (N=1,430) were more likely to have had inadequate surgery (69.51%) when compared to the average for all comorbid conditions (62.50%).

Table 11-Descriptive statistics partitioned by surgical adequacy

Variable		Inadequate 62.50% (20,605)	Adequate 37.50% (12,358)	*Total (N=32,936)*	p-value
Age Group	65-69	61.32(3,631)	38.68(2,290)	17.96(5,921)	p <.0001
	70-74	61.79(4,457)	38.21(2,756)	21.88(7,921)	
	75-79	62.24(4,946)	37.76(3,001)	24.11(7,947)	
	80-84	62.65(3,980)	37.35(2,373)	19.27(6,353)	
	85-89	63.42(2,472)	36.58(1,426)	11.83(3,898)	
	90+	68.61(1,119)	31.39(512)	4.95 (1,631)	
Race	White	61.99(17,286)	38.01(10,598)	84.59(27,884)	p <0001
	Black	66.22 (1,764)	33.78 (900)	8.08(2,664)	
	Other	58.88 (401)	41.12 (280)	2.07 (681)	
	Asian	63.60 (711)	36.40 (407)	3.39 (1,118)	
	Hispanic	73.15 (395)	26.85 (145)	1.64 (540)	
	Native American	63.16 (48)	36.84 (28)	0.23 (76)	
Urban Vs Rural	Large Metro	61.69(12,504)	38.31 (7,766)	61.49(20,270)	p<.0001
	Metropolitan	63.22 (5,494)	36.78 (3,196)	26.36 (8,690)	
	Urban	70.00 (1,078)	30.00 (462)	4.67 (1,540)	
	Less Urban	61.62 (1,267)	38.38 (789)	6.24 (2,056)	
	Rural	64.37 (26)	35.63 (145)	1.23 (407)	
Gender	Male	64.98 (9,679)	35.02 (5,217)	45.19(14,896)	p<.0001
	Female	60.47(10,926)	39.53 (7,141)	54.81(18,067)	
Cancer Stage	I	76.82 (7,868)	23.18 (2,374)	31.07(10,242)	p<.0001
	II	58.63 (7,640)	41.37 (5,391)	39.53(13,031)	
	III	52.60 (5,097)	47.40 (4,593)	29.40 (9,690)	
Income Category	0-36,999	65.60 (6,193)	34.40 (3,247)	28.64 (9,440)	p<.0001
	37-45,999	64.19 (4,323)	35.81 (2,412)	20.43 (6,735)	
	46 -60,999	60.61 (5,313)	39.39 (3,453)	26.59 (8,766)	
	61,000+	59.20 (4,087)	40.80 (2,817)	20.94 (6,904)	
Total Comorbidity Score	0	61.83(14,953)	38.17 (9,233)	73.37(24,186)	p<.0001
	1	62.48 (3,335)	37.52 (2,003)	16.19 (5,338)	
	2	65.85 (1,323)	34.15 (686)	6.09 (2,009)	
	3+	69.51 (994)	30.49 (436)	4.34 (1,430)	

Logistic Regression

Univariate Regression Cancer Directed Outcome

All independent covariates were highly significantly related to receiving CDT ($p<.001$). The unadjusted relative odds and p-values for covariates are found in Table 12. As age increases (compared to subjects 65-69) the likelihood of having CDT significantly decreases. For subjects 90+ the likelihood of having CDT is 1.28 times those who are 65-69 years old. Race was also a significant predictor of CDT. Blacks were less likely to receive CDT compared to Whites (OR=0.59, 95% CI: 0.51-0.67). Asians were significantly more likely to CDT compared to Whites (OR=1.34, 95% CI: 1.02-1.77).

Gender was significantly associated with the receipt of CDT. Being a woman was associated with a greater likelihood of receiving CDT (OR=1.73, 95% CI: 1.58-1.89). Additionally, as cancer stage increased, the probability of receiving CDT also increased when compared with stage I colon cancer subjects. The same was true for subject income. Higher income compared to the referent ($0-36,999) resulted in a higher probability of receiving CDT. However, the increase in comorbidity score was associated with a progressive decrease in the likelihood of CDT when compared to subjects with no comorbid condition.

Table 12-Unadjusted odd ratios modeled on the probability that cancer directed treatment was received

Variable		Odds Ratio	95% CI	p-value
Age Category	65-69	Referent		p<.0001
	70-74	0.82	(0.70-0.96)	
	75-79	0.84	(0.72-0.98)	
	80-84	0.71	(0.61-0.83)	
	85-89	0.55	(0.47-0.65)	
	90+	0.28	(0.23-0.33)	
Race	White	Referent		p<.0001
	Black	0.59	(0.51-0.67)	
	Other	1.03	(0.76-1.39)	
	Asian	1.34	(1.02-1.77)	
	Hispanic	1.02	(0.73-1.45)	
	Native American	0.58	(0.28-1.19)	
Urban/Rural	Large Metro	Referent		p<.0001
	Metropolitan	1.21	(1.09-1.35)	
	Urban	0.84	(0.70-1.02)	
	Less urban	1.09	(0.91-1.32)	
	Rural	2.38	(1.37-4.12)	
Gender	Male	Referent		p<.0001
	Female	1.73	(1.58-1.89)	
Cancer Stage	I	Referent		p<.0001
	II	2.67	(2.42-2.95)	
	III	6.33	(5.45-7.37)	
Income Category	>36,999	Referent		p=0.0005
	37,000-45,999	1.18	(1.04-1.34)	
	46,000-60,999	1.21	(1.07-1.36)	
	61,000 +	1.14	(1.01-1.29)	
Total Comorbidity Category	0	Referent		p<.0001
	1	0.87	(0.77-0.98)	
	2	0.72	(0.61-0.84)	
	3+	0.53	(0.45-0.63)	

Univariate Regression for Surgical Adequacy Outcome

In the sub-analysis evaluating the adequacy of surgery performed, all covariates were statistically significant (p<.01). The relative odds and p-values of the unadjusted associations are summarized in Table 13. Age category was a significant predictor of surgery adequacy. Subjects 90+ were more likely to have inadequate surgery when compared to 65-69 year olds. Hispanics (OR=1.67, 95% CI: 1.38-2.02) and Blacks

(OR=1.20, 95% CI: 1.11-1.31) were also more likely to have inadequate surgery compared to their white counterparts.

Gender was a significant predictor of surgical adequacy. Women were more likely to have adequate surgery when compared to men (OR=0.83, 95% CI: 0.79-0.86). Increasing cancer stage was associated with a higher probability of having adequate surgery when compared to stage I. Additionally, when compared to the referent ($0-36,999), increasing income was also associated with a higher likelihood of having adequate surgery. Inversely, as comorbidity score increased, the likelihood of having inadequate surgery increased when compared to subjects with no comorbidity.

Table 13-Unadjusted odds ratios modeled on the probability that subjects received inadequate surgery

Variable		Odds Ratio	95% CI	p-value
Age Category	65-69	Referent		p<.0001
	70-74	1.02	(0.95-1.10)	
	75-79	1.04	(0.97-1.11)	
	80-84	1.06	(0.98-1.14)	
	85-89	1.09	(1.01-1.19)	
	90+	1.38	(1.23-1.55)	
Race	White	Referent		p<.0001
	Black	1.20	(1.11-1.31)	
	Other	0.88	(0.75-1.03)	
	Asian	1.07	(0.95-1.21)	
	Hispanic	1.67	(1.38-2.02)	
	Native American	1.05	(0.66-1.68)	
Urban/Rural	Large Metro	Referent		p<.0001
	Metropolitan	1.07	(1.01-1.13)	
	Urban	1.45	(1.30-1.62)	
	Less urban	0.99	(0.91-1.10)	
	Rural	1.12	(0.91-1.38)	
Gender	Male	Referent		p<.0001
	Female	0.83	(0.79-0.86)	
Cancer Stage	I	Referent		p<.0001
	II	0.43	(0.40-.45)	
	III	0.34	(0.32-0.36)	
Income Category	>36,999	Referent		p<.0001
	37,000-45,999	0.94	(0.88-1.00)	
	46,000-60,999	0.81	(0.76-0.86)	
	61,000 +	0.76	(0.71-0.81)	
Total Comorbidity Category	0	Referent		p<.0001
	1	1.03	(0.97-1.09)	
	2	1.19	(1.08-1.31)	
	3+	1.41	(1.25-1.58)	

Mulivariate Regression Cancer Directed Therapy Outcome

All unadjusted variables were previously significant (p<.001) and were all considered for the preliminary model. Table 14 summarizes the preliminary multivariate model before the addition of interaction terms. After adjusting for all covariates each variable remained significantly associated with the outcome of CDT. The relative odds ratio for variables remained similar in effect and interpretation to the unadjusted odds ratios. Prior to the addition of interaction terms age was significantly associated with a decrease in the likelihood or receiving CDT.

Table 14- Preliminary multivariate logistic regression results modeled on the probability of receiving cancer directed treatment

Variable		Odds Ratio	95% CI	p-value
Age Category	65-69	Referent		p<.0001
	70-74	0.80	(0.68-0.93)	
	75-79	0.79	(0.67-0.92)	
	80-84	0.62	(0.53-0.72)	
	85-89	0.46	(0.38-0.54)	
	90+	0.21	(0.17-0.25)	
Race	White	Referent		p<.0001
	Black	0.58	(0.50-0.68)	
	Other	0.92	(0.68-1.26)	
	Asian	1.29	(0.98-1.71)	
	Hispanic	1.06	(0.74-1.50)	
	Native American	0.52	(0.25-1.08)	
Urban/Rural	Large Metro	Referent		p<.0001
	Metropolitan	1.24	(1.12-1.40)	
	Urban	0.91	(0.74-1.11)	
	Less urban	1.16	(0.95-1.42)	
	Rural	2.44	(1.40-4.27)	
Gender	Male	Referent		p<.0001
	Female	1.87	(1.71-2.05)	
Cancer Stage	I	Referent		p<.0001
	II	2.80	(2.54-3.10)	
	III	6.46	(5.55-7.52)	
Income Category	>36,999	Referent		p=0.0125
	37,000-45,999	1.13	(0.99-1.30)	
	46,000-60,999	1.18	(1.04-1.35)	
	61,000 +	1.14	(0.99-1.31)	
Total Comorbidity Category	0	Referent		p<.0001
	1	0.92	(0.82-1.04)	
	2	0.79	(0.67-0.93)	
	3+	0.64	(0.54-0.76)	

There were significant (p<.001) interactions between gender and age, as well as gender and stage of cancer. These were then added to the preliminary model and both retained their significance level. The results of the final model are shown in Table 15**.**

After adjusting for covariates, age category was still a significant predictor of receiving CDT ($p<.001$). Asians no longer had a significantly elevated odds ratio when compare to whites. However, after adjusting for all covariates Blacks were approximately 43% less likely to receive CDT when compared to Whites (OR=0.57, 95% CI: 0.50-0.66).

Patient location was still a significant predictor of CDT. The most significant association in this category was seen between large metropolitan and. rural subjects. Subjects with a rural status have a higher likelihood of receiving CDT when compared to subjects in a large metropolitan area (OR=2.41, 95% CI: 1.38-4.23). Women had a significantly higher likelihood of receiving CDT when compared to men, after adjustment (OR=2.42, 95% CI: 1.85-3.18).

Income category became slightly less significant after adjustment ($p<.001$ vs. $p=.019$). Only subjects that earned $46,000-60,999 were significantly more likely to receive CDT compared to those in the lowest income bracket (OR=1.18, 95% CI: 1.03-1.34). After adjustment, the total comorbidity score for subjects who scored 2 and higher were significantly less likely to receive CDT compared to those with no comorbidity.

Due to the interaction terms added to the model the covariates included in those terms must be assessed within that interaction and not the main effects of the variable. Table 16 shows the calculated relative odds for subjects broken up by gender, stage and age. Generally, for men and women as age increased the likelihood of having CDT decreased for all stages. The largest decrease for men in the likelihood for CDT was seen among 90+ year old subjects with stages I and II colon cancer. Women aged 90 + were drastically less likely to receive CDT when compared to the referent category for all stages. While the decreased likelihood of having CDT was negligible for men with stage III disease

After addition of the interaction terms into the final model the Hosmer and Lemeshow goodness-of-fit test gives a χ^2=8.28 (p=0.41), which indicates there is no lack of fit to the model.

Table 15- Adjusted odds ratios of receiving cancer directed surgery

Variable		**Odds Ratio**	**95% CI**	**p-value**
Age Category	Main effects			p<.0001
Race	White	Referent		p<.0001
	Black	0.57	(0.50-0.66)	
	Other	0.91	(0.67-1.24)	
	Asian	1.27	(0.96-1.69)	
	Hispanic	1.07	(0.75-1.53)	
	Native American	0.53	(0.25-1.13)	
Urban/Rural	Large metro	Referent		p<.0001
	Metropolitan	1.24	(1.11-1.39)	
	Urban	0.90	(0.74-1.10)	
	Less urban	1.15	(0.94-1.40)	
	Rural	2.41	(1.38-4.23)	
Gender	Main effects			p<.0001
Cancer Stage	Main effects			p<.0001
Income Category	>36,999	Referent		p=0.0194
	37,000-45,999	1.14	(0.99-1.30)	
	46,000-60,999	1.18	(1.03-1.34)	
	61,000 +	1.13	(0.98-1.30)	
Total Comorbidity Category	0	Referent		p<.0001
	1	0.93	(0.83-1.05)	
	2	0.79	(0.67-0.93)	
	3+	0.66	(0.55-0.78)	

Table 16- Odds ratios for interaction terms modeled on the probability that cancer directed therapy was received

	Men			Women		
Age Group	Stage I	Stage II	Stage III	Stage I	Stage II	Stage III
65-69	1.00	1.00	1.00	1.00	1.00	1.00
70-74	0.91	0.62	0.60	1.06	0.72	0.70
75-79	0.85	0.74	0.80	0.76	0.66	0.71
80-84	0.63	0.72	0.94	0.46	0.53	0.69
85-89	0.47	0.67	0.60	0.31	0.44	0.39
90+	0.25	0.31	0.81	0.08	0.10	0.11

Mulivariate Regression for Surgical Adequacy Outcome

All unadjusted variables were previously significant ($p<.001$) and were all considered for the preliminary model. Table 17 summarizes the preliminary multivariate model before the addition of interaction terms. After adjusting for all covariates each variable remained significantly associated with surgical adequacy. The odds ratios for covariates remained similar in effect and interpretation to the unadjusted odds ratio. Prior to the addition of interaction terms increased age was significantly associated with a higher likelihood of having inadequate surgery.

Table 17- Preliminary multivariate logistic regression results modeled on the probability of receiving inadequate surgery

Variable		Odds Ratio	95% CI	p-value
Age Category	65-69	Referent		p<.0001
	70-74	1.02	(0.95-1.10)	
	75-79	1.05	(0.98-1.13)	
	80-84	1.12	(1.04-1.21)	
	85-89	1.17	(1.08-1.28)	
	90+	1.54	(1.36-1.73)	
Race	White	Referent		p<.0001
	Black	1.16	(1.06-1.27)	
	Other	0.90	(0.76-1.05)	
	Asian	1.14	(1.01-1.30)	
	Hispanic	1.64	(1.35-1.99)	
	Native American	1.06	(0.66-1.72)	
Urban/Rural	Large Metro	Referent		p<.0001
	Metropolitan	1.02	(0.97-1.08)	
	Urban	1.34	(1.19-1.51)	
	Less urban	0.89	(0.80-0.99)	
	Rural	0.99	(0.80-1.22)	
Gender	Male	Referent		p<.0001
	Female	0.83	(0.79-0.87)	
Cancer Stage	I	Referent		p<.0001
	II	0.42	(0.40-0.45)	
	III	0.33	(0.31-0.35)	
Income Category	>36,999	Referent		p<.0001
	37,000-45,999	0.95	(0.73-0.95)	
	46,000-60,999	0.82	(0.88-1.02)	
	61,000 +	0.77	(0.72-0.83)	
Total Comorbidity Category	0	Referent		p<.0001
	1	1.00	(0.94-1.07)	
	2	1.15	(1.04-1.26)	
	3+	1.32	(1.17-1.48))	

There was a significant (p<.001) interaction between gender and age. This variable was then added to the preliminary model and retained its significance level. The results of the final model are shown in Table 18**.** After adjusting for covariates (Table 18), Blacks, Hispanics, and Asians were more likely to receive inadequate surgery when compared to their White counterparts. Women were 0.76 times less likely to have inadequate surgery then men (OR= 0.76, 95% CI: 0.68-.85). Interestingly, increased income was independently associated with a lower likelihood of having inadequate surgery.

Subjects with increasing colon cancer stage were more likely to have adequate surgery, when compared to subjects with stage I disease. And finally, subjects with comorbidity scores of 2 or more were associated with a higher likelihood of having inadequate surgery, when compared to individuals with no comorbid conditions.

Due to the interaction term added to the final model the covariates included in those terms must be assessed within that interaction and not simply the main effects of the variable. Table 19 shows the calculated relative odds for subjects broken up by age and gender (p=0.003). The results for men at all age groups were close to the null value. The highest odds ratio was 1.10 for men over the age of 90, indicating that they have a slightly increased chance of having inadequate surgery when compared to men 65-69. The results for women were more prominent. As age increased for women they were more likely to have inadequate surgery. The most noticeable difference was again seen in the higher age categories. Women 90+ were 1.82 times more likely to have inadequate surgery compared to women 65-69.

The Hosmer and Lemeshow goodness-of-fit test gives a χ^2=9.66 (p=0.30), which indicates a good overall fit of the final model.

Table 18- Adjusted odds ratio modeled on the probability of having inadequate surgery

Variable		Odds Ratio	95% CI	p-value
Age Category	Main Effects			p=0.196
Race	White	Referent		p<.0001
	Black	1.16	(1.06-1.27)	
	Other	0.90	(0.76-1.05)	
	Asian	1.14	(1.01-1.30)	
	Hispanic	1.64	(1.35-2.00)	
	Native American	1.06	(0.66-1.72)	
Urban/Rural	Large Metro	Referent		p<.0001
	Metropolitan	1.02	(0.97-1.08)	
	Urban	1.34	(1.19-1.51)	
	Less urban	0.89	(0.80-0.99)	
	Rural	0.98	(0.79-1.22)	
Gender	Main effects			p<.0001
Cancer Stage	I	Referent		p<.0001
	II	0.42	(0.40-0.45)	
	III	0.33	(0.31-0.35)	
Income Category	>36,999	Referent		p<.0001
	37,000-45,999	0.95	(0.88-1.02)	
	46,000-60,999	0.82	(0.76-0.87)	
	61,000 +	0.77	(0.72-0.83)	
Total Comorbidity Category	0	Referent		p<.0001
	1	1.01	(0.94-1.07)	
	2	1.15	(1.04-1.26)	
	3+	1.32	(1.17-1.49)	

Table 19- Interaction term for age and gender modeled on the probability of having inadequate surgery

Age Group	Men	Women
65-69	1.00	1.00
70-74	0.96	1.10
75-79	1.05	1.07
80-84	1.06	1.18
85-89	1.10	1.24
90+	1.11	1.82

Survival Analysis

Kaplan-Meier

The survival for subjects was assessed on key variables. The colon cancer specific survival difference among age groups (Figure 3**),** cancer directed treatment (Figure 4**),** and cancer stage (Figure 5**)** were all significant (Log-rank Test, p<.0001). Mean survival times among categories are summarized in Table 20. Average survival time decreased with increasing age category. The same trend was seen with increased cancer stage. The colon cancer specific survival was different between those that received CDT and those that did not.

Table 20- Colon cancer survival statistics among covariates

Variable		**Mean Survival (months)**	**% Censored**	**Log-Rank Test p-value**
Age Group	65-69	60.62	88.87	p<0001
	70-74	60.50	86.46	
	75-79	57.89	84.31	
	80-84	53.80	79.98	
	85-89	50.84	75.31	
	90+	38.95	68.14	
Cancer Stage	I	65.33	92.43	p<0001
	II	58.44	85.43	
	III	47.36	69.56	
Cancer Directed Treatment	Yes	58.64	83.64	p<0001
	No	40.63	62.36	

Figure 3-Colon cancer survival time among age groups

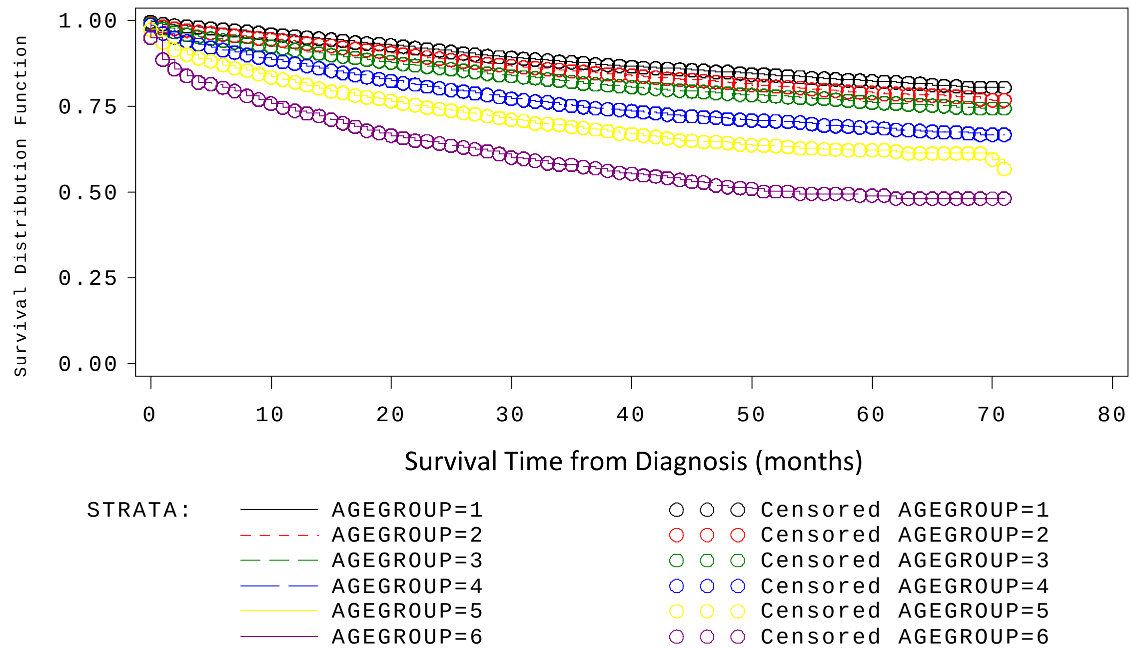


Figure 4- Colon cancer survival time stratified by cancer directed surgery

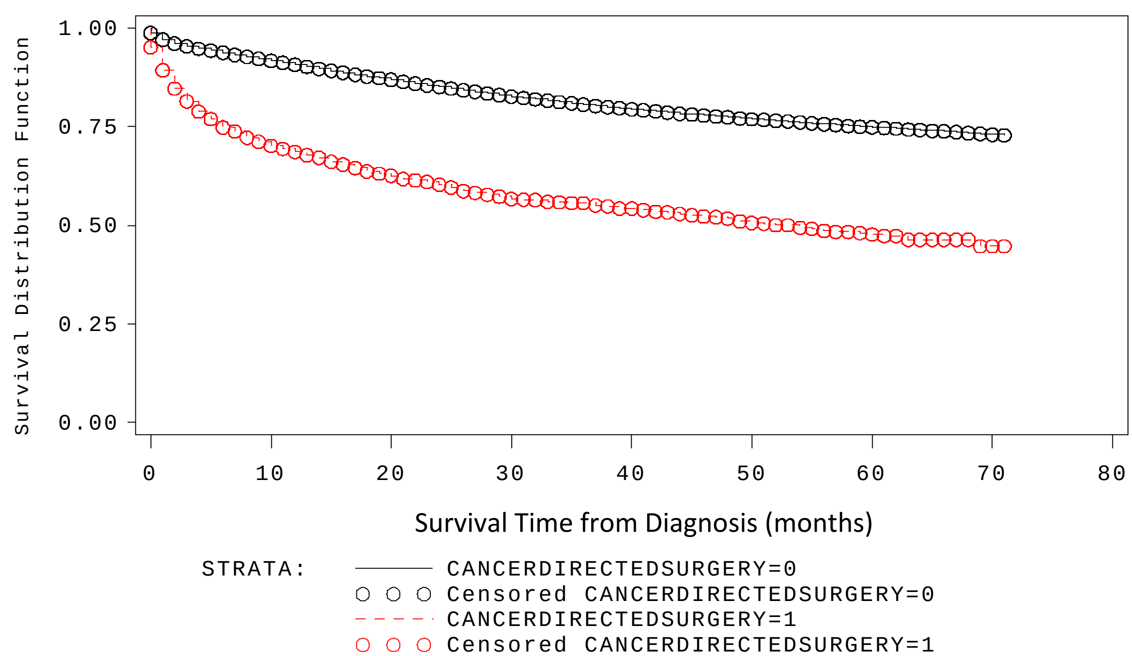
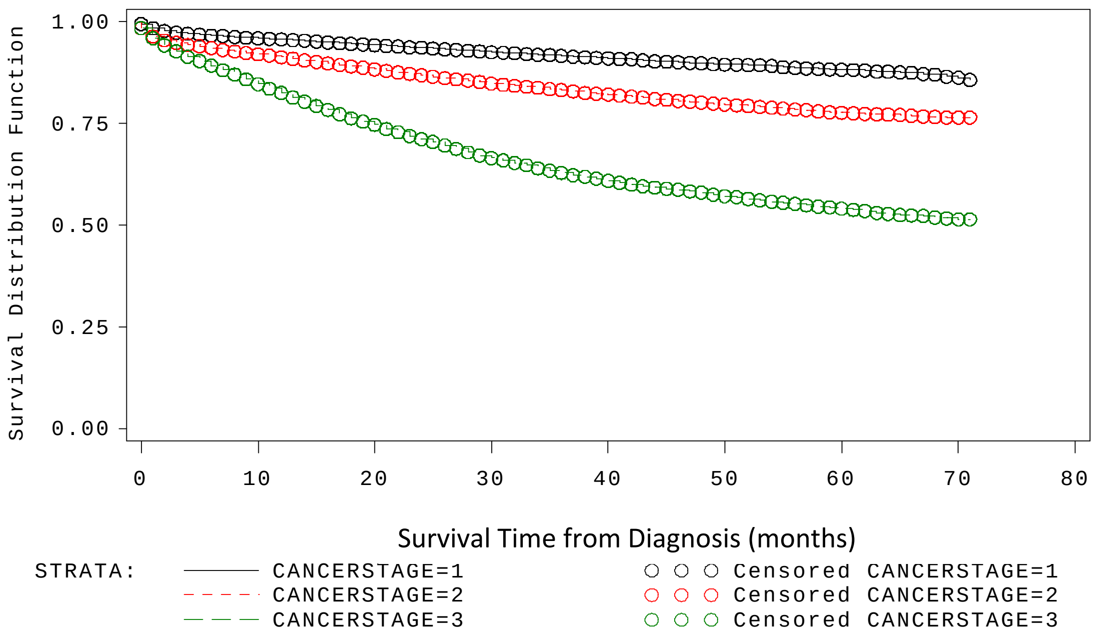


Figure 5-Colon cancer survival time among cancer stages I-III



Cox Regression Analysis

On univariate analysis, factors associated with colon cancer specific survival included demographic and clinical characteristics such as age, comorbidity score, race, cancer stage, income, and CDT (yes/no) ($p<.001$). Gender and patient location were not significant at the .05 level. However, both variables were entered into the preliminary models due to their clinical importance. Table 21 summarizes the univariate survival statistics for the sample population. Survival statistics were then evaluated between subjects who received CDT and those that didn't.

Age groups were significantly associated with lower colon cancer survival. The same trend was seen among comorbidity categories. As the number of weighted comorbid conditions increased so did the likelihood of mortality, Asians were 20% less likely to die from colon cancer than Whites (HR=0.80, 95% CI: 0.75-0.94). While Blacks were 25% more likely to die from colon cancer than Whites (HR=1.25, 95% CI: 1.17-1.34).

Increasing stage of cancer was also a significant predictor of colon cancer mortality. Interestingly, as subjects' income increased the likelihood of mortality from colon cancer decreased significantly. And finally, subjects who did not receive CDT were much more likely to die from colon cancer than subjects who received CDT (HR=3.07, 95% CI: 2.86-3.31).

Table 21 -Univariate analysis of colon cancer survival

Variable		Hazard Ratio	95% Hazard Ratio Confidence Limits	p-value
Age Group	65-69	Referent		p<.0001
	70-74	1.25	(1.16-1.34)	
	75-79	1.52	(1.42-1.63)	
	80-84	2.19	(2.04-2.35)	
	85-89	3.01	(2.79-3.24)	
	90+	4.70	(4.31-5.12)	
Comorbidity Score	0	Referent		p<.0001
	1	1.30	(1.23-1.36)	
	2	1.50	(1.39-1.62)	
	3+	1.94	(1.79-2.11)	
Race	White	Referent		p<.0001
	Black	1.25	(1.17-1.34)	
	Other	0.80	(0.69-0.92)	
	Asian	0.84	(0.75-0.94)	
	Hispanic	1.07	(0.93-1.24)	
	Native American	1.34	(0.95-1.89)	
Urban/Rural	Large Metropolitan	Referent		p=0.28
	Metropolitan	0.96	(0.92-1.01)	
	Urban	1.00	(0.91-1.10)	
	Less Urban	0.98	(0.90-1.06)	
	Rural	1.12	(0.96-1.32)	
Gender	Male	Referent		p=0.39
	Female	1.10	(1.06-1.15)	
Cancer Stage	I	Referent		p<.0001
	II	2.06	(1.93-2.19)	
	III	4.18	(4.54-5.11)	
Income Category	0-36,999	Referent		p<.0001
	37,000-45,999	0.90	(0.85-0.95)	
	46,000-60,999	0.84	(0.80-0.88)	
	61,000 +	0.81	(0.77-0.86)	
Cancer Directed Surgery	Received	Referent		p<.0001
	Not received	3.07	(2.86-3.31)	

After adjustment for all covariates, age was significantly associated with colon cancer survival (Table 22). All age categories were associated with poorer colon cancer survival compared to those 65-69. Increasing comorbidity score was still a significant predictor of poorer survival.

Blacks were still significantly associated with poorer survival when compared to Whites (HR=1.17, 95% CI: 1.09-1.27). Asians were slightly less likely to die from colon cancer than Whites after adjustment (HR=0.82, 95% CI: 0.73-0.92). The patient location variable was significant after adjusting for covariates, although the results were barely noteworthy.

Interestingly, higher income (on all levels) was significantly associated with better survival rates for colon cancer when compared to the lowest income category. The receipt of CDT for colon cancer survival became even more significant after adjustment (HR=4.58, 95% CI: 4.23-4.95). The same happened for the variable of cancer stage as well, the HR increased slightly for both stages when compared to stage I.

Table 22 -Adjusted colon cancer hazard ratio for all subjects

Variable		Hazard Ratio	95% Hazard Ratio confidence limits	p-value
Age Group	65-69	Referent		p<.001
	70-74	1.21	(1.19-1.30)	
	75-79	1.51	(1.41-1.63)	
	80-84	2.17	(2.02-2.33)	
	85-89	2.98	(2.76-3.22)	
	90+	4.43	(4.05-4.84)	
Co-morbidity Score	0	Referent		p<.001
	1	1.21	(1.14-1.27)	
	2	1.37	(1.27-1.48)	
	3+	1.83	(1.09-1.26)	
Race	White	Referent		p<.001
	Black	1.17	(1.09-1.23)	
	Other	0.83	(0.71-0.96)	
	Asian	0.82	(0.73-0.92)	
	Hispanic	1.09	(0.94-1.26)	
	Native American	1.16	(0.79-1.25)	
Urban/Rural	Large Metropolitan	Referent		p=0.019
	Metropolitan	0.94	(0.89-0.99)	
	Urban	0.96	(0.87-1.06)	
	Less Urban	0.89	(0.81-0.97)	
	Rural	0.98	(0.82-1.15)	
Gender	Male	Referent		p=0.518
	Female	0.98	(0.94-1.02)	
Cancer Stage	I	Referent		p<.001
	II	2.23	(2.08-2.38)	
	III	5.71	(5.37-6.08)	
Cancer Directed	Yes	Referent		p<.001
	No	4.66	(4.30-5.03)	
Income Category	0-36,999	Referent		p<.001
	37,000-45,999	0.93	(0.88-0.99)	
	46,000-60,999	0.87	(0.82-0.92)	
	61,000 +	0.83	(0.78-0.89)	

Subjects who did not receive cancer directed surgery

Among patients who did not receive CDT, significant factors associated with colon cancer survival were age, gender, and cancer stage ($p<.0001$) (Table 23). After adjustment, race, patient location (urban vs. rural) and income categories were not significantly associated with colon cancer survival in this population. Among these individuals, all age categories were significantly more likely to die from colon cancer compared to the youngest group.

Women who did not receive CDT were 60% more likely to die from colon cancer than men (HR= 1.60, 95% CI: 1.36-1.87). It is important to note that these subjects' cancer stage was assessed clinically and not pathologically. Subjects with stage II disease were the more likely to die from colon cancer than those with stage I (HR=1.96, 95% CI: 1.67-2.30). Subjects with stage III disease were also more likely to die from colon cancer (HR=1.40, 95% CI: 1.08-1.82) but the likelihood was smaller than those with stage 2 disease.

Table 23- Adjusted hazard ratios for subjects who did not receive cancer directed therapy

Variable		Hazard Ratio	95% Hazard Ratio Confidence Limits	p-value
Age Group	65-69	Referent		p<.0001
	70-74	1.46	(1.02-2.08)	
	75-79	1.88	(1.34-2.64)	
	80-84	3.26	(2.34-4.54)	
	85-89	4.81	(3.44-6.73)	
	90+	6.46	(4.55-9.18)	
Co-morbidity Score	0	Referent		p=0.237
	1	1.06	(0.88-1.29)	
	2	1.16	(0.89-1.50)	
	3+	1.31	(0.99-1.73)	
Race	White	Referent		p=0.557
	Black	1.09	(0.86-1.39)	
	Other	0.60	(0.33-1.16)	
	Asian	1.11	(0.74-1.71)	
	Hispanic	1.28	(0.71-2.27)	
	Native American	1.04	(0.39-2.81)	
Urban/Rural	Large Metropolitan	Referent		p=0.506
	Metropolitan	0.97	(0.81-1.16)	
	Urban	1.25	(0.92-1.70)	
	Less Urban	1.02	(0.73-1.41)	
	Rural	0.67	(0.21-2.10)	
Gender	Male	Referent		p<.0001
	Female	1.60	(1.36-1.87)	
Cancer Stage*	I	Referent		p<.0001
	II	1.96	(1.67-2.30)	
	III	1.40	(1.08-1.82)	
Income Category	0-36,999	Referent		p=0.755
	37,000-45,999	0.91	(0.73-1.13)	
	46,000-60,999	0.94	(0.75-1.16)	
	61,000 +	0.89	(0.71-1.13)	

** Clinically staged*

Subjects who did receive cancer directed surgery

Among patients who received CDT, all variables were significantly associated with colon cancer survival, which was not the case among those who did not receive CDT (Table 24).

As seen in the population that did not receive CDT, age was a strong predictor of colon cancer mortality. Additionally, those with increased comorbidity scores also had poorer colon cancer survival when compared to those without comorbid conditions. In this sub-analysis race was significant. Blacks had poorer colon cancer survival compared to Whites (HR=1.19, 95% CI 1.11-1.29). However, Asians (HR=0.80, 95% CI: 0.71-0.90) experienced better survival when compared with Whites. Subjects who lived in metropolitan (HR=0.95, 95% CI: 0.90-0.99) and less urban (HR=0.88, 95% CI: 0.80-0.97) areas had better colon cancer survival than those in a large metropolitan area.

Interestingly, women (HR=0.94, 95% CI: 0.90-0.98) had slightly better colon cancer survival in this population when compared to men. Increasing cancer stage was significantly associated with poorer survival when compared to subjects with stage I cancer. And finally, subjects with increased income had better colon cancer adjusted survival rates when compared to those in the lowest income bracket.

Table 24- Adjusted hazard ratios for subjects who received cancer directed therapy

Variable		Hazard Ratio	95% Hazard Ratio Confidence Limits	p-value
Age Group	65-69	Referent		p<.001
	70-74	1.21	(1.12-1.31)	
	75-79	1.51	(1.40-1.62)	
	80-84	2.12	(1.96-2.28)	
	85-89	2.88	(2.66-3.11)	
	90+	4.19	(3.81-4.60)	
Co-morbidity Score	0	Referent		p<.001
	1	1.21	(1.14-1.27)	
	2	1.38	(1.27-1.49)	
	3+	1.88	(1.71-2.06)	
Race	White	Referent		p<.001
	Black	1.19	(1.11-1.29)	
	Other	0.83	(0.72-0.97)	
	Asian	0.80	(0.71-0.90)	
	Hispanic	1.08	(0.92-1.26)	
	Native American	1.12	(0.75-1.67)	
Urban/Rural	Large Metropolitan	Referent		p=0.024
	Metropolitan	0.95	(0.90-0.99)	
	Urban	0.94	(0.85-1.04)	
	Less Urban	0.88	(0.80-0.97)	
	Rural	0.99	(0.84-1.17)	
Gender	Male	Referent		p=0.017
	Female	0.94	(0.90-0.98)	
Cancer Stage	I	Referent		p<.001
	II	2.42	(2.25-2.61)	
	III	6.50	(6.06-6.97)	
Income Category	0-36,999	Referent		p<.001
	37,000-45,999	0.94	(0.88-0.99)	
	46,000-60,999	0.87	(0.82-0.92)	
	61,000 +	0.83	(0.78-0.89)	

CONCLUSIONS

Discussion

Cancer Directed Therapy

The results from this study show that after adjustment for many covariates there is a significant difference between the likelihood for older subjects receiving CDT compared to younger subjects. One income category was a significant predictor of CDT. Subjects with a household income of $46,000-60,999 were 1.18 times (OR=1.18 95% CI: 1.03-1.34) more likely to receive CDT compared to individuals making than $37,000. Race was also a strong predictor for CDT.

Blacks were 0.57 times (OR=0.57, 95% CI: 0.50-0.66) as likely to receive CDT after accounting for age and other patient factors. Additionally, women were over twice as likely to receive CDT compared to men (OR=2.42, 95% CI: 1.85-3.18). These findings indicate a gender and racial inequality may exist when determining whether or not CDT will be given to colon cancer patients.

Stage of cancer was still highly associated with receipt of CDT after adjustment. When compared to stage I subjects, stage II (OR=8.60, 95% CI: 6.22-11.90) and III (OR=18.58, 95% CI: 11.85-31.81) patients were much more likely to receive CDT after accounting for age and comorbid conditions. This may indicate that disease severity weighs heavily in determining treatment regardless of age and other conditions.

A significant association was only seen in subjects with 2 or more comorbid conditions. Subjects with 2 conditions were 0.79 times (OR=0.79, 95% CI: 0.67-0.93) less likely to receive CDT. And subjects with 3+ conditions were 0.66 times (OR=0.66, 95% CI: 0.55-0.78) less likely to receive treatment.

The interaction between age, stage, and gender provided significant results. Men with stage I and II disease were much less likely to receive CDT as age increased. However, men with stage III colon cancer were only slightly less likely to receive CDT compared to the youngest age group. Indicating, that stage may be more important than age when determining whether or not to undergo CDT among those with stage III disease. Similarly, women had a much lower likelihood of receiving CDT as age increased for stages I and II colon cancer. However, women over the age of 84 with stage III colon cancer were just as likely to receive CDT as those with stage I and II disease. This may indicate that even though the stage of disease is worse, age may be a limiting factor when deciding if CDT should be performed in women.

This study showed that age was a significant predictor of a lower likelihood of receiving CDT for all age categories. Racial and gender inequalities still exist when determining care for colon cancer patients. Moreover, stage and comorbidity are still significant predictors of CDT regardless of age and demographics.

Surgical Adequacy

These results are only applicable to subjects diagnosed from 2000-2002. The reason for this separate analysis was to examine the extent of surgery being performed on colon cancer patients, more lymph nodes examined is taken as a measure for more adequate surgery. In this sub-analysis increasing age was a significant predictor of inadequate surgery for subjects. Interestingly, Blacks (OR=1.16, 95% CI: 1.06-1.27), Asians (OR=1.14, 95% CI: 1.01-1.30), and Hispanics (OR=1.64, 95% CI: 1.35-2.00) were all more likely to have inadequate surgery than Whites, regardless of age and disease stage.

Additionally, the higher the weighted comorbid condition in subjects, the more likely they were to have inadequate surgery. Subjects with 2 conditions were 1.15 times (OR=1.15, 95% CI: 1.04-1.26) more likely to have inadequate surgery. And those with 3+ comorbid conditions were 1.32 times (OR=1.32, 95% CI: 1.17-1.49) more likely to have inadequate surgery. An income trend was seen after adjustment. Increasing income ($46,000+) was significantly associated with adequate surgery. Indicating that the more money a person makes the more adequate the surgery performed.

The interaction between age and gender was significantly associated with adequacy of surgery after adjustment. Women were more likely to have inadequate surgery as their age increased. Women 90+ were 1.82 times more likely to have an inadequate surgery for colon cancer compared to those 65-69. However, this finding was not seen among men.

This study showed that being White, staged II+ disease and subjects making over $64,000 a year are significantly more likely to receive adequate care. The only finding that made individuals more likely to have inadequate surgery was an increase in (2+) comorbid conditions, gender and increasing age.

Colon Cancer Survival

Overall Survival

Overall colon cancer survival was significantly associated with increasing age, comorbidity, being Black, cancer stage, CDT, and income. Blacks were more likely to have poorer colon cancer survival by 17% (HR=1.17, 95% CI: 1.09-1.26) compared to Whites. Comorbid conditions (1+) were significantly associated with poorer survival rates that those with no conditions. Additionally, subjects who did not receive CDT had very poor colon cancer survival rates compared to those who had CDT (HR=4.58, 95% CI: 1.23-4.95).

Survival Among Subjects Who Received Cancer Directed Treatment

Age was a significant predictor of colon cancer survival at all levels in this population ($p<.001$). As age increase survival for colon cancer gets much worse. For those subjects 80-84 years old a two-fold increase in colon cancer mortality was seen (HR=2.12, 95% CI: 1.96-2.28). Again, increasing comorbidity was associated with poorer colon cancer survival rates. This was seen on all levels of weighted comorbid conditions when compared to those with no comorbid conditions.

Being Black was also associated with poorer colon cancer survival rates in this population (HR=1.19, 95% CI: 1.11-1.29). And again Asians had better colon cancer survival compared to Whites (HR=0.80, 95% CI: 0.71-0.90). Women who received CDT had slightly better colon cancer survival rates compared to men (HR=0.94, 95% CI: 0.90-0.98).

Overall, Blacks, men, advanced disease, and increased comorbidity were all associated with poorer colon cancer survival. The most significant predictor of colon cancer survival in this population was cancer stage. Increased stages had a much poorer colon cancer survival rate, after adjusting for demographics and clinical characteristics.

Survival Among Subjects Who Did Not Received Cancer Directed Treatment

In subjects who did not receive CDT age was a highly significant predictor of colon cancer survival. Subjects who were 80-89 had poorer colon cancer survival compared to those 65-69 years old (HR=4.81, 95% CI: 3.44-6.73). Comorbidity was not significantly associated with colon cancer survival in this group of subjects (p=0.237) which differed from those who did receive CDT. Moreover, race (p=0.577), patient location (p=0.506) and income (p=0.755) were not associated with colon cancer survival either.

Significant predictors of colon cancer survival among subjects who did not receive CDT were age, gender and cancer stage. Women who did not receive CDT had poorer colon cancer survival when compared to men (HR=1.60, 95% CI: 1.36-1.87). Cancer stage was still a significant predictor of colon cancer survival. However, the hazard ratios were much smaller in this group compared to those who received CDT. Overall in this population poor colon cancer survival was associated with gender, disease severity and all age groups.

Strengths and Limitations

We have planned and implemented an original and important study that suggests there may be inequality by race and age in the treatment of colon cancer. This may change treatment standards for elderly colon cancer patients in the United States. We were able to control for many confounders associated with age and treatment outcomes. Additionally our sample size was very large and provided ample power to perform the analyses.

Historical cohort studies come with small inherent limitations. Generally there is less control over subject selection and measurement of variables. There are few limitations to the SEER database used in this study. The entire sample is made up of Medicare aged patients. Therefore the results will only be applicable to those 65 years of age or older. This is not a major concern because the median age of colon cancer diagnosis is 71 years of age (24). While older patients are the vast majority of colon cancer patients, this sample is not representative of all US patients, particularly those with other forms of health insurance (e.g., managed care or private pay).

Comorbidity information in the SEER database use ICD-9 codes and the potential for inaccuracy exists. However, the lack of ambiguity regarding colon cancer diagnosis coupled with the fact that complete coding for major surgical procedures favorably affects hospital physician reimbursement suggests that the claims-based approach used should be accurate (28). Additionally there was no information given on obesity, which is a known risk factor for colon cancer. Obesity is a major confounder for whether surgical procedures are performed or not. The comorbidity code that was used for this analysis did not include obesity ICD-9 codes. However in a recent study, there were no differences found in the number of LNs removed from obese compared to nonobese patients (29). Additionally the average number of LNs removed was above 12 for both groups, indicating that subjects both obese and nonobese received adequate surgery.

There is one major limitation to this study. We discovered that elderly Medicare subjects receive less cancer directed therapy. However, we cannot ascertain from our study if that is due to physician or patient discrimination. Patients may choose not to undergo surgery because of their age and the perceived complications that accompany surgical procedures. Additionally, physicians may base the decision for a patient to receive CDT based solely upon age. Our study can only capture that a bias exists but we cannot explicitly say what that bias is due. Future studies should be performed to discover why this bias exists.

Public Health Significance

This research adds a new source of information to the field of colon cancer research. Age seems to be significantly associated with the receipt of cancer directed therapy in colon cancer patients. Increasing age is associated with a lower likelihood of receiving cancer directed therapy after adjusting for demographic and clinical characteristics. Comorbidities are often left out of studies. This study adjusted for various comorbid conditions and age was still significantly associated with less cancer directed therapy indicating that ageism may be the reason why older healthy subjects are receiving less cancer directed therapy. This possibility should be explored further.

Additionally, older subjects were more likely to have inadequate surgery compared to younger subjects after accounting for demographic and clinical characteristics. The reason for a decreasing number of LNs examined in elderly patients is still not clear. One hypothesis could be that LNs may undergo a process of involution with increasing age (30). Blacks, Asians and Hispanics were also more likely to have fewer LNs examined during surgery, which may indicated a genetic variability in the number of LNs present between races.

This study contributes to the existing literature on survival in colon cancer by focusing solely on older patients and by using the latest available data. Poor colon cancer specific survival rates among elderly patients were seen in both populations. However, poorer colon cancer survival rates were much higher in those who did not receive cancer directed therapy. Moreover, in subjects who did receive cancer directed therapy, cancer stage was the most highly associated with poor survival. It is hoped that discovering this age discrepancy may lead to more information which may influence care in the elderly colon cancer population. Additionally, the racial and gender inequalities found in this study should also be examined in the colon cancer field.

Future Research

This study provided data that will be useful to physicians and quality of care evaluators nationwide. The likelihood of cancer directed treatment received by each age group after accounting for co-morbidities addressed treatment inequalities among the elderly population. Future research should try to explain why elderly patients receive less cancer directed therapy. A prospective research study that combines interviews with physicians to help ascertain why the decision for cancer directed treatment was made would help fill in this gap. In this study we can only speculate that it was due to an age prejudice by the physician or the patient.

The LN data yielded important findings. However, a better evaluation looking at the mean number of LNs examined during surgery as an outcome would be helpful. This would effectively examine the mean number of LNs examined across all covariates in this study and would give a better interpretation of how age and the total number of LNs for each age group interact with one another.

In the elderly population there are few well conducted clinical trials that address treatments tolerated by older patients. Hopefully this study will encourage more research among the elderly and would help to establish consistent guidelines for colon cancer treatment in this population.

References

1. Edler D, Ohrling K, Hallstrom M, Karlberg M, Ragnhammar P. The number of analyzed lymph nodes - a prognostic factor in colorectal cancer. Acta Oncologica. 2007;46:975.

2. American Cancer Society. 2009. http://www.cancer.org/docroot/home/index.asp/

3. National Cancer Institute. 2009. Available from: http://www.cancer.gov/.

4. Maurel J, Launoy G, Grosclaude P, et al. Lymph node harvest reporting in patients with carcinoma of the large bowel: A french population study. Cancer. 1998;82:1482.

5. Tekkis M.D. PP, Smith JJ, Heriot AG, Darzi AW, Thompson MR, Stamatakis JD. A national study on lymph node retrieval in resection surgery for colorectal cancer. Dis Colon Rectum. 2006(49):1673.

6. Chang GJ, Rodruiguez-Bigas M, Skibber J, et al. Lymph node evaluation and survival after curative resection of colon cancer: Systematic review. Journal of National Cancer Institute. 2007;99:433.

7. Simunovic M, Baxter NN. Lymph node counts in colon cancer surgery: Lessons for users of quality indicators. Journal of National Cancer Institute. 2007;298:2194.

8. Ricciardi R, Baxter N. Association versus causation versus quality improvement: Setting benchmarks for lymph node evaluation in colon cancer. Journal of National Cancer Institute. 2007;99:414.

9. Bilimoria K, Stewart A, Edge S, et al. Lymph node examination rate, survival rate and quality of care in colon cancer. JAMA. 2008;299:896.

10. Frankel K. Minimum number of lymph nodes to be recovered from colorectal resection specimens. American Journal of Clinical Pathology. 1997;107:494.

11. Cainchi F, Palomba A, Boddi V, et al. Lymph node recovery from colorectal tumor specimens: Recommendation for a minimum number of lymph nodes to be examined. World Journal of Surgery. 2002;26:384.

12. Goldstein N, Sanford W, Coffey M, Layfield L. Lymph node recovery from colorectal resection specimens removed for adenocarcinoma. trends over time and a recommendation for a minimum number of lymph nodes to be recovered. American Journal of Clinical Pathology. 1996(106):209.

13. Appendix A: Specifications of the national voluntary consensus standards for breast and colon cancer.[homepage on the Internet]. . 2009. Available from: http://www.qualityforum.org/.

14. Wang JM, PhD, Kulaylat MM, Rockette HP, Hassett JM, Rajput AM, Dunn KBM, et al. Should total number of lymph nodes be used as a quality of care measure for stage III colon cancer? Annals of Surgery. 2009;249(4):559.

15. Trimble, E.L, Christian,M.C. Cancer treatment and the older patient. Clin. Cancer Res. 2006(12):156-1959.

16. Walter LC CK. Cancer screening in elderly patients: A framework for individualized decision making. JAMA. 2001(285):2750-6.

17. Murthy VH, Krumholz HM,Gross CP. Participation in cancer clinical trials: Race-,sex-, and age-based disparities. JAMA. 2004;291(22):2720-6.

18. Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J,Hickish T et al. Oxalipalatin, fluorouacil, and leucovarin as adjuvant treatment for colon cancer. NJEM. 2004;350(23):2343.

19. Jessup JM, Stewart A, Greene FL,Minsky BD. Adjuvant chemotherapy for stage III colon cancer: Implications of Race/Ethnicity, age, and differentiation. JAMA. 2005;294(21):2703-11.

20. Gross CP, McAvay GJ, Guo Z,Tinetti ME. The impact of chronic illness of the use of effectiveness of adjuvant chemotherapy for colon cancer. Cancer;109:2410-9.

21. Yancik R., Wesley MN. Rives L., Long S., Edwards BK.,Yates JW. Comorbidity and age as predictors of risk for early mortality of male and female colon carcinoma patients. American Cancer Society. 1997(82):2123-34.

22. Violi V., Pietra N., Grattarola M., Sarli L., Choua O., Roncoroni L.,Peracchia A. Curative surgery for colorectal cancer: Long-term results and life expectancy in the elderly. Dis Colon Rectum. 1998(41):291-8.

23. Hardiman M.D, PhD, Karin M., Cone M.D, Molly, Sheppard MD BC, Herzig M.D. DO, Disparities in the treatment of colon cancer in octogenarians. The American Journal of Surgery. 2009;197:624.

24. Surveillance, epidemiology and end results cancer registry. 2009. Available from: http://seer.cancer.gov/.

25. Johnson CH , Adamo M. SEER program coding and staging manual 2007. National Cancer Institute. 2007;07-5581.

26. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. Journal of Chronic Disease. 1987;40(5):373.

27. Caplin S, Cerottini J, Bosman F, Constanada M, Givel J. For patients with dukes B (TNM stage II) colorectal carcinoma, examination of six or fewer lymph nodes is related to poor prognosis. Cancer. 1998;86:666.

28. Schrag D., Cramer LD., Bach PB., Cohen AM., Warren JL.,Begg CB. Influence of hospital procedure volume on outcomes following surgery for colon cancer. JAMA. 2000;284(23):3028-35.

29. Damadi M.D. AA, Julien M.D. L, Arrangoiz M.D. R, Raiji M.D. M, Weise M.D. PhD D, Saxe M.D. AW. Does obesity influence lymph node harvest among patients undergoing colectomy for colon cancer. The American Surgeon. 2008;74:1073.

30. Schmuker D, Owen R, Outenreath R, Thoreux K. Basis for the age-related decline in intestinal mucosal immunity. Clinical Developmental Immunology. 2003(10):167.