Attachment A
Title Page

The Effect of Rurality and Region of Residence on the Receipt of Adjuvant Chemotherapy in Colon Cancer Patients: A Look at North Carolina

By

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A look at North Carolina

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Introduction

Objective

Social inequalities in cancer outcomes are well documented. The social determinants of these cancer disparities often include factors related to race, age, gender, social capital, socio-economic status, and environment. These determinants often work in combination to create or help sustain the disparities in cancer outcomes that appear to be widespread in the United States. One of the ways that social determinants create inequalities is by promoting differences in the quality of cancer treatment for different patient subgroups. For instance, there is some evidence that colon cancer patients who belong to disadvantaged races, who live in rural areas, or who have low socio-economic status receive recommended adjuvant chemotherapy (ACT) at lower rates than predominant social groups.[1-4] However, studies examining the link between these social factors and the quality of cancer treatment often offer conflicting results.[5]

This study examines the relationship between living in rural areas and the receipt of adjuvant chemotherapy for colon cancer patients in North Carolina. It also examines the relationship between region of residence in North Carolina and the probability of ACT receipt. Patient-level data was acquired from the North Carolina Central Cancer Registry (CCR) to answer the study questions. If a treatment disparity is found it may indicate the need for specific interventions to counter deficiencies in post-operative medical care for rural patients with colon cancer.

Burden of Disease

Colorectal cancer is the third most frequent cancer type and the third leading cause of cancer death in the United States.[6] The American Cancer Society projected that

colon cancer, a subtype of colorectal cancer, was diagnosed in over one hundred thousand Americans in 2007 and that nearly 52,000 cases died last year.[6] These numbers are estimates of the burden of disease, but they are calculated with incidence data from the Surveillance Epidemiology and End Results (SEER) database. The SEER database is the most comprehensive database describing annual incidence of the most common forms of cancer affecting Americans.

The American Cancer society derives its cancer mortality figures from the National Center for Health Statistics (NCHS).[6] Together, raw data from SEER and the NCHS provide the best estimates of national cancer statistics available. Estimates of disease burden in North Carolina also come from come from the North Carolina Central Cancer Registry (CCR).[7] Using similar techniques as the ACS, the registry estimated that 4,425 new cases and 1,645 deaths from colorectal cancer occurred in North Carolina in 2007.[7]

Treatment of Colon Cancer

Surgery is the primary therapy for colon cancer. All patients with stage I to stage III colon cancer (85% of cases) require surgical removal as the major mode of therapy.[8] Adjuvant chemotherapy is recommended for patients with stage III cancer.[9] These cases comprise 22% of all incident colon cancers. The recommended chemotherapy regimen was initially based on results from three clinical trials indicating that 5-fluorouracil and levamisole improved five-year survival in patients with stage III colon cancer compared to those who received levisimole alone, or surgery alone.[9] In particular, adjuvant chemotherapy lowers five-year mortality by 33% and five-year recurrence by 40% when compared to surgery alone.[10]

In 2003 fluorouracil plus leucovorin became the standard therapy following a series of trials proving its superiority to fluorouracil and levamisole. In 2004, Andre et al. demonstrated that adding oxaliplatin to fluorouracil and leucovorin improves five-year survival from 73%, to 78%. These results led to oxaliplatin gaining acceptance as the current standard adjuvant chemotherapy treatment.[9] The results of adjuvant chemotherapy appear even more impressive when one considers an outcomes table (Table 1). As seen in Table 1, stage III colon cancer patients on average have mortality rates reaching 55% over 5 years with only surgery, but with adjuvant chemotherapy five-year mortality may fall to as low as 36.6%.[8,10] Combining the figures derived by the ACS and by Moertel et. al, one can estimate that there are nearly twenty-two thousand patients are diagnosed with stage III cancer a year in the U.S. One can postulate that if these patients are treated with surgical resection alone, on average 12,100 will die within five years.[8] Providing adjuvant chemotherapy to all eligible candidates may lower this number to 8,066 over five years.

In the context of clinical trials, ACT has offered impressive survival benefits for stage III patients. Consequently, adjuvant chemotherapy has gained nationwide acceptance as critical part of post-operative colon cancer treatment. The National Cancer Institute and the National Institute of Health both have issued recommendations reiterating this point, but U.S. cancer patients have experienced low treatment rates for nearly a decade. In 2001, Schrag et al. concluded that only 55% of eligible Medicare patients received adjuvant treatment.[11] Similarly, in 2004, the investigators recording data for the National Cancer Database found that only 45% of eligible patients received adjuvant chemotherapy. More recent figures for all colon cancer patients indicate that

these numbers are on an upward trend, as some demographic groups receive ACT at rates close to 80%, but under-treatment is still present, especially among certain subgroups.[12]

Disparities in Treatment among Colon Cancer Patients

Race

Several studies have explored social factors explaining why some groups receive adjuvant chemotherapy at lower rates than the average and key results have surfaced. Race, age, rural residence, insurance status, socioeconomic status have all been found to be related to the under use of adjuvant chemotherapy, but results have been conflicting for some of these factors. Most recent studies have found no relationship between race and rates of adjuvant chemotherapy use.[1, 2, 12] The most recent study to find otherwise, Baldwin et al., noted that African American patients were just as likely to be offered chemotherapy, but significantly less likely to receive it.[13] This result might indicate differences in patient preference, a problem with physician-patient communication, or problems with access to care for certain racial groups. This is an area which needs further research, but preliminary results indicate that white and black patients may be offered ACT for colon cancer at similar rates.

Socio-economic Status and Insurance Status

Only one study has found that insurance status and income are related the receipt of adjuvant chemotherapy among colon cancer patients. In 2002, in a study by VanEnwyk, patients with an annual income of less than nine thousand dollars were significantly less likely to receive adjuvant chemotherapy. The study also found that patients with private insurance were more likely to receive adjuvant chemotherapy than patients with Medicare or Medicaid, but the study was unable to control for other factors

like education level, and the measure of insurance status was inexact. Given the weaknesses in this study and the lack of available evidence on the subject, the relationship between socio-economic status, insurance status and colon cancer treatment is inconclusive.[5]

Age

Studies have consistently linked advanced age at cancer diagnosis to low rates of adjuvant chemotherapy receipt. One study estimated that only 69% of patients between the ages of 70 and 79 receive ACT treatment, while only 34% above age 80 receive ACT.[11] Another study published in 2002, found that patients younger than 55 were much more likely to receive adjuvant chemotherapy than patients older than 80 after adjusting for co-morbidities.[5]

There are several possible reasons for this trend. First, the presence of significant co-morbidities among the elderly could play a role. Potosky et al. found that the presence of a co-morbidity using the Charlson co-morbidity scale was inversely related to the receipt of standard adjuvant chemotherapy when adjusting for age.[14] The Charlson morbidity score measures the severity of co-morbid conditions, with higher scores representing more significant health problems. A score of zero represents the healthiest patients and a score of three or more three represents the sickest patients. A more recent study, published in 2006, using SEER data found that 60% of elderly patients (age>65) with a score of zero received adjuvant chemotherapy, while only 51% and 45% of patients with scores of two and three were offered treatment.[15]

Physician reluctance to prescribe the current adjuvant chemotherapy regimen to patients with several co-morbidities may be well-founded, because randomized controlled

trials describing the efficacy of each treatment rarely included patients with significant co-morbidities.[9] Consequently, it is not known whether co-morbidities reduce the survival benefits offered by adjuvant chemotherapy for colon cancer.

In addition, some physicians may not offer elderly patients chemotherapy because of notions that otherwise healthy elderly patients cannot significantly benefit from chemotherapy. Physicians may believe that the elderly have low potential life expectancy or may believe that the elderly do not tolerate chemotherapy well. Studies among the elderly examining these issues are limited in number, but Sargeant et al. published a high-quality study in 2001 indicating that patients taking 5-fluorouracil experienced higher rates of severe organ toxicity and poorer patient tolerability when compared to patients under 65.[14] This study seemed to validate the belief that patient tolerability of chemotherapy declines with age, independent of general health. On the other hand, Jensen et al. in 2006 found that patients 75 years and older, despite requiring lower doses of chemotherapy, still benefited significantly from adjuvant treatment.[15] Furthermore, Jessup et al found in 2005 that colon cancer patients 80 years or older benefited similarly from adjuvant chemotherapy in terms of five-year survival in comparison to younger patients.[12] Consequently, age is currently not accepted as a reason for not offering adjuvant chemotherapy to patients with stage III colon cancer, but physicians must be prepared to vary doses to optimize patient tolerance.

Finally, patient age may relate to patient preference for treatment. In a study of general patient preferences for adjuvant chemotherapy, age was a strong predictor of patient preference with older patients less likely to choose ACT.[16] It is difficult to estimate how much patient preference for treatment is responsible for age's effect on the

receipt of adjuvant chemotherapy. A patient's preference against ACT could explain much of the differences seen in the receipt of ACT among older cancer patients. However, research suggests that patients rely heavily on the advice of physicians; better-informed physician advice may lead to a reduction of the age gap in cancer therapy.

Rural Residence

Only a few studies have examined the relationship between rurality and ACT receipt. One study done by VanEenwyk et al, in 2002 indicated that patients living in rural zip codes in Washington State were 60% less likely to receive adjuvant chemotherapy. The authors were able to adjust for patient co-morbidity, age, sex, race and insurance status.[5] The data used in this study included colon cancer cases diagnosed from 1996 to 1997. Research has suggested that rates of adjuvant chemotherapy for patients with stage III colon cancer have continued to increase since the mid 1990's, so the results of this study may not adequately reflect the current relationship between rural residence and ACT receipt.[12] A second study done by Wu et. al, in 2004, using data from several Louisiana hospitals and medical practices, found no difference in the receipt of ACT between patients living in rural versus urban areas. The authors of this study controlled for confounding factors thoroughly, and their results provide up to date information regarding rurality's effect on ACT receipt. [17] More studies are needed to verify the results put forth by Wu's study.

Research Objective

We will attempt to investigate the relationship between rural residence and ACT receipt for stage III colon cancer cases using data from the North Carolina Central Cancer Registry (CCR). This is a worthwhile study to undertake given that there are few studies

examining the study question we propose, and the studies that have been published offer conflicting results. Additionally, the breadth of information obtainable from the CCR has been improved significantly over the years, and we hope we can answer our study questions adequately and also provide information about regional differences in ACT receipt. The CCR now obtains a higher percentage of information about colon cancer cases in the state than in past years, especially from small community hospitals. The CCR has also added variables related to patient refusal of treatment, and more detailed information about tumor stage, grade and date of treatment.

One of the most difficult challenges of this study is adequately defining rural residence. Depending on one's definition of rurality, around 10- 28% of the U.S. population lives in rural areas.[18, 19] On average residents in rural areas in the U.S. have higher rates of unemployment, higher percentages of the elderly and of children, lower population density, higher poverty rates, and higher rates of uninsurance and underinsurance.[18] Many of these characteristics of rural environments play a role in the quality of care patients receive. The prevalence of these factors varies depending on the definition of urbanization that researchers use.

Using rural residence as an independent variable in analytic studies leads to two major problems. The first is that rural areas can vary greatly in terms of culture, economics, demography and environment. As a result, attempting to lump all rural areas together in these types of analyses is difficult and ultimately leads to a more diverse groups that desired.[18] A second problem relates to the possibility that a defined level of urbanization serves only as a marker for more specific social determinants of health. The factors that truly affect health outcomes in rural areas may be classified more clearly by

reporting population density, economic and trade development, environment, pollution, urbanization, relationship to metropolitan areas, penetration and development of medical specialists, or distance to hospital care.[18] As a result, it is useful for researchers to also attempt to evaluate these other variables by either controlling for them or evaluating them individually and including them in the study discussion.

Despite these difficulties, a number of standardized methods for defining urbanization have emerged. The Office of Management and Budget (OMB) has issued one of the more widely accepted systems of defining urbanization.[17, 18] The OMB system is based on assigning all U.S. counties Urban Influence Codes, which were derived from 2000 census figures. These codes classify counties as either metropolitan or non-metropolitan based on population size, population density and proximity to urban areas. This system then subdivides each category based on adjacency to the different size counties created.[19] The Urban Influence Codes put forth by the OMB offer one of most rigorous and conservative methods of delineating rural areas as has been used in many studies in heath care research.[18]

Consequently, we will use OMB urban influence codes in our analysis. We will also examine the relationship between patient region of residence and the receipt of adjuvant chemotherapy, to determine whether there are regions of the state with lower receipt of ACT, regardless of degree of rurality. We believe that these relationships will clearly delineate whether access to care represents a barrier to the receipt of chemotherapy. We will attempt to control for the other factors that are related to rural residence and receipt of ACT.

Methods

Data source

The North Carolina Central Cancer Registry (CCR) collects information on colon cancer cases diagnosed and treated within state boundaries. The CCR records name, gender, age, sex, race/ethnicity, insurance status, and residence geocodes. The CCR also collects information related to disease, including tumor stage, tumor grade, date of diagnosis, initial treatment, use of adjuvant chemotherapy and patient specified reason for refusing treatment. The CCR is licensed to receive information from every cancer diagnosing health care provider within the state. The sources of information most often are hospital based, but they can include physician practices, pathology laboratories and individual death certificates. The goal of the CCR is to monitor the incidence of cancer among various populations over time, and to also report information related to staging, location and treatment. Specifically for colon cancer the CCR obtains over 83% of the desired information. Public health experts, researchers, and members of the state health department analyze the data upon request. The quality of the data is assessed and by the NCCCR, Centers for Disease Control and the North American Association of Central Cancer Registries.

Patients

Our analysis was restricted to state residents diagnosed with colon cancer between 1998 and 2004 in North Carolina. The study included all men and women diagnosed with stage III colon cancer in that time. Staging was accomplished using the tumor, node, metastases staging classification designated by the American Joint Cancer Commission (AJCC). The patients were staged from physical exam, abdominal and chest CT, and intra-operatively. Stage III according to the AJCC includes all patients with colon cancer

extending to one or two lymph nodes but without established metastasis. All patients meeting these criteria were included in the study.[20]

Geocoding Locations

We used Geographic Information Systems (GIS) to provide spatial analysis. Our goal was to accurately determine each patient's residence within a North Carolina county. Traditionally, GIS has been a powerful research tool allowing investigators to process, analyze and visualize ecologic data. In this study, as part of the abstraction of process, the CCR collected information on patient residence. Through GIS, the CCR was able to give each patient a geo-code for residence location. Using these geo-codes, the CCR assigns each patient to a specific county in North Carolina. The CCR is also able to assign a geo-code location for a patient's hospital of diagnosis, surgical treatment and adjuvant chemotherapy treatment. We will use the patient's geocoded data on residence to determine the patient's county urbanization level and geographical region. We will examine the relationships between these factors and the probability of receiving recommended adjuvant chemotherapy and other factors related to receiving appropriate care.

Study Variables

Urbanization

Rural status was defined using urban influence codes which were published by the federal Office of Management and Budget (OMB) in 2003. We grouped the OMB's codes to fit the design of our study. The urban influence codes originally defined by the OMB can be seen in Table 2. The listed classification scheme defines metropolitan counties and then divides the remaining non-metropolitan counties by their size and

adjacency with more urbanized areas. The urbanization scale correlates well with economic development, access to information, finance and many other important social resources. This scale is particularly useful in health access research because the level of urbanization and adjacency to urban areas often correlates well with the proximity of community hospitals and large medical centers. Using this scale, 75% of the nation's land is considered rural, and 17% of the nation's citizens are considered rural residents.[19]

Urban influence codes divide all state counties into a total of 12 groups. As mentioned above, counties are first determined to be either metropolitan (metro) or non-metropolitan. Metro areas are defined using population and commuting data from the 2000 census. The definition depends on the census definition of an urbanized area. The census bureau defines urban areas as those with a nucleus of at least 50,000 residents, which may or may not contain individual cities. In general, urban areas must have a population density of 1,000 persons per square mile and may contain adjoining territory with at least 500 persons per square mile.[19]

According to the OMB counties are counted as metro areas if they are central counties with one or more urbanized areas, or they outlying counties that are economically tied to the core counties by work commuting. Outlying counties are included if at least 25 percent of workers living in the county commute to the central counties, or if 25 percent of the employment in the county consists of workers coming from the central counties. Metropolitan areas are further divided into two groups by their population size. Large metro areas are those with more than a million people, and small metro areas have less than one million residents.[19]

Non-metro counties are divided into two main groups. The first group is entitled micropolitan (micro) areas which consist of any non-metropolitan area with an urban cluster of at least 10,000 residents. Surrounding counties can be included in the micro area by considering the amount of inter-county commuting, which is defined in the same way as for metro areas which is detailed above. These micro areas are further divided into three groups depending on their adjacency or non-adjacency to large, small, or no metro areas. The second group of non-metro counties is called non-core counties. They are divided into seven groups by their adjacency to a metro or a micro area and whether or not they contain a town of at least 2,500 residents. Non-core counties containing more than 2,500 resident are referred to as having their "own town".[19]

Using patient geo-codes for county residence each patient was placed in one of the 12 areas detailed above and also illustrated in Table 2. For the purposes of this study, we consolidated urban influence codes into three groups. 1) NC Metropolitan Areas which were any area designated as metro using UIC codes (UIC codes 1 and 2). 2) NC Non-metropolitan areas were areas designated as non-metropolitan according to UIC codes and non-adjacent to metropolitan areas (UIC codes 8-12). 3) NC Adjacent areas were defined as areas with UIC codes indicating a non-metropolitan status but areas adjacent to metro areas (UIC codes 3-7). The UIC coded regions were grouped in order to capture the proximity to metropolitan areas. We believe that the distance each patient encountered in attempting to reach a metropolitan area is the most relevant factor to explore in regards receipt of chemotherapy.

North Carolina Region

The North Carolina Cancer Partnership, an organization committed to the improvement of cancer outcomes for patients in North Carolina, divided the state into several regions based geography and each region's perceived major center of health care. The regions are as follows: the Asheville Region, Greensboro Region, Charlotte Region, Raleigh Region, Wilmington Region, and Greenville Region. The counties of each region are depicted in Figure 1. We will use patient geo-codes to stratify patient residence based on the region in which they live. We will then analyze patient region versus the probability of not receiving adjuvant chemotherapy and the other outcomes we outline below

Receipt of care

We will use several variables to provide information about the receipt of adjuvant chemotherapy among the study population. The NC Central Cancer Registry collects information on whether patients with stage III colon cancer receive chemotherapy. Patients for whom there is no record of chemotherapy having been received are assigned one of the following codes: chemotherapy not recommended (1); chemotherapy contraindicated (2); chemotherapy treatment of choice, not administered, no reason given (6), chemotherapy refused by patient, family member or guardian (7); chemotherapy recommended, unknown if given (8); and reason for no chemotherapy unknown (9). We grouped these variables to create several new variables, to give us a more complete picture of whether patients were being offered and receiving care consistent with current guidelines. We considered it to be consistent with current guidelines to withhold chemotherapy if it was contraindicated or refused by the patient; we therefore created a variable "received adjuvant chemotherapy if not contraindicated or refused" that includes

patients who received chemotherapy and those for whom chemotherapy was contraindicated or refused (codes 2 and 7). We also created a variable "offered adjuvant chemotherapy if not contraindicated," which includes those patients who received chemotherapy, those to whom chemotherapy was offered but for whom there was incomplete data on whether it was received (codes 6 and 8), and those for whom chemotherapy was contraindicated or refused (codes 2 and 7). We compared these variables to "chemotherapy not recommended," a group for whom it could be clearly determined that care was not consistent with current guidelines.

Statistical Analysis

Statistical analyses were performed with the help of several biostatisticians at the North Carolina Central Cancer Registry. We used the total number of cases of Stage III colon cancer occurring between 1998 and 2004 as our study population. We geocoded to a specific street address. We geocoded patients who provided non-street addresses to census block groups. Finally, we geocoded patients who provided county of residence data only. It is important assign as many patients to street level addresses as possible to be able to control for some of the confounding variables we will detail below.

In our analysis, we compared patient residence in Metropolitan Areas, Non-Metropolitan Areas, and Adjacent Areas to the receipt of adjuvant chemotherapy. We compared region of residence using NC Cancer Partnership regions to the receipt of ACT. Specifically we used Chi-square analysis to examine our primary and secondary questions in the study. We had concerns that the data were not normally distributed and we felt that a chi-square test for statistical significance would provide a more valid result.

We will also perform multivariate analysis to determine the effect of that the potentially confounding variables. Because we did not have patient-level data on income we used mean census tract income as a proxy for patient income. For patients for whom a street address was not available, we used median county income as a proxy for patient income. Those variables will include race, patient age at diagnosis, and sex. We will use mean census tract income as crude measure to control for patient income.

Results

The North Carolina Central Cancer registry reported that 5,474 patients were diagnosed with colon cancer in North Carolina between 1999 and 2004. Of these 5,306 patients were designated as state residents. The remaining 169 cases were eliminated from the study. Demographic characteristics of original sample of patients can be seen in Table 3. Of the 5,306 patients who were North Carolina residents, the registry had data on chemotherapy treatment and county of residence for 4,432 of the patients diagnosed with colon cancer in the time period, and as Table 4 shows, these patients were included in the study. This was 83.5% of the North Carolina patients diagnosed with Stage III colon cancer. For the remaining 874 patients, the registry did not have adequate treatment data. It is unknown how or if these patients were managed. Consequently, they were not included in the study. Depending on how these patients were dispersed in the state and the treatments they received, they could have affected the results of our analysis significantly.

Geocoding Results

The geocoded results were originally completed for patients diagnosed with colon cancer in North Carolina. Of the 5,306 patients geocoded, only 4945 had treatment data

on available to the NCCR. Only these cases were included in the final analyses. Of the cases diagnosed among North Carolina residents, the North Carolina Central registry had a unique recorded address for 4740 cases. If the cases provided a valid street address they were geocoded to that address. If the cases provided a post office box as an address they were geocoded to a 2000 census census block group. This step allowed us to better classify their location within their listed county. The remaining cases, 566 or 10% of the total, could not be geocoded to either street address or census block group, so they were geocoded to their residential county.

Care received results

A total of 2,582 patients with Stage III colon cancer received ACT between 1998 and 2004. This represented 58% of the study population. Twenty-eight percent of the patients did not receive a recommendation for ACT, without any indication that ACT was contraindicated or refused. A total of 72% of the study population patients was offered ACT if it was not contraindicated, and 63% received chemotherapy if it was not contraindicated or refused (Table 5). Consequently, the majority of patients in North Carolina received care consistent with current treatment recommendations, and a larger percentage were at least offered ACT when appropriate, although we do not have complete data on whether they received it or the reasons for why they did not receive it.

For the patients who did not receive ACT, we have some data that sheds some light onto the possible reasons. Three patients in the study population died prior to the decision to treat or not treat with adjuvant chemotherapy. This was less than 0.01% of the study population and was not likely a significant factor in the interpretation of the results. For one percent of patients, ACT was contraindicated due to another medical illness. For

272 patients, 6.1% of the study population, treatment was recommended and either not given or it is unknown if treatment was given.

Chemotherapy regimen results

The exact chemotherapy regimen received by each patient remains unknown. The drugs were not recorded by members of the NCCCR, but they did record the number of agents each patient received. Based on the prevalent recommendations at the time, patients should have received at least two chemotherapeutic agents to maximally benefit from adjuvant chemotherapy.[9] In the study population, it is known that nearly 55.3% of treated patients received only one chemotherapeutic agent. Only 16.6% of patients received two or more chemotherapeutic agents and the regimen. This suggests significant under-treatment among even those who received adjuvant chemotherapy. Additionally, the data indicates that there is significant heterogeneity of treatment received by patients in the study population. It is unknown whether the appropriate chemotherapeutic drugs were administered at appropriate doses in a timely manner.

Level of urbanization vs. Receipt of Care

The results describing the relationship between receiving appropriate care and urbanization level are listed in Table 6. As described earlier, urbanization level was divided into three groups based on metropolitan status or proximity to a metropolitan area. On all statistical analyses a chi-square analysis was used due to Non-Gaussian distribution of data.

Patients living in metropolitan areas, non-metropolitan/adjacent areas, and non-metropolitan/non-adjacent areas received ACT at very similar rates (59.0%, 58.3%, 54.4%) and chi-square analyses revealed no significant differences between groups

(p=0.37). The rates of receiving ACT if not refused or contraindicated (63.7%, 61.3%, 55.5%) and being offered ACT if not contraindicated (72.9, 71.3, 70.1) were very similar as well and no significant difference with discernable on univariate or multivariate analysis.

Region vs. receipt of care

The results describing the relationship between region of residence and treatment can be seen in Table 7. Again, North Carolina was divided into six regions in this analysis: Asheville, Charlotte, Greensboro, Greenville, Raleigh and Wilmington areas (Figure 1). Patients in Asheville, Charlotte and Greenville were less likely to receive, ACT and to be offered ACT than patients in the other NC regions. The relationship between treatment and region was statistically significant ($p<0.0001$) on the univariate analysis. On multivariate analysis including the aforementioned variables, the relationship was no longer significant. To perform this analysis we used multivariate logistic regression with receipt and non-receipt as the two outcome variables. We did this analysis for each of the three dependent variables we analyzed.

Discussion

This study was done to determine if rurality affects the probability of receipt of ACT for stage III colon cancer patients in North Carolina. First, we wanted to determine the overall level of statewide prescription of ACT for stage III colon cancer between 1998 and 2004. We hoped that the results would indicate whether colon cancer patients in North Carolina suffered from under-receipt of treatment. We also hoped that this study would add some clarity to the issue of whether patients with colon cancer in rural areas

receive differing rates or if region of residence in North Carolina affected the probability of ACT receipt.

Our study was similar to prior studies done by Wu and VanEenWyk, but key differences do exist between our study and prior studies investigating rurality versus ACT receipt for colon cancer. First, our study data is considerably more recent and covers a greater time span than previous studies. We used statewide data from 1998 to 2004, while the Wu used data from a single year, 2001, and VanEnwyk used data from 1996-1997. Consequently, we hoped that our results we provide a more up to date estimate of the patterns of ACT receipt for stage III colon cancer patients. Second, the aforementioned studies were completed in Louisiana and Washington State respectively, and we felt that investigating the relationship between rurality and ACT receipt in North Carolina would be more relevant to our local health systems.[5, 17] Finally, we hoped that including additional dependent variables in our study would allow us to make more precise conclusions about the patterns of ACT receipt in North Carolina. For example, we included variables describing rates of ACT refusal and contraindication which allowed us to investigate the relationship between region and rurality and the probability of being offered ACT.

Overall ACT Receipt for Colon Cancer Patients with Stage III Disease

Ultimately, our results allow us to draw a few conclusions about the treatment of colon cancer among North Carolinians. First, nearly forty percent of eligible patients in the state still do not receive ACT. This supports prior publications indicating that ACT is under prescribed. For example, Scharg et al. and data from the National Cancer Database indicate that only 55% and 45% of Stage III colon cancer patients receive ACT

respectively. [8, 11] These results highlight the need for continued emphasis on the prescription of ACT for all eligible patients in North Carolina. The efforts to improve the rates of ACT receipt could take the form of statewide initiatives to make ACT for stage III colon cancer patients a measure of cancer treatment quality among all cancer treating hospitals in North Carolina. A similar initiative could also be incorporated into the North Carolina's Cancer Partnership's overall mission to improve the cancer outcomes among state residents. Such an initiative would be worthwhile because data from clinical trials suggest that outcomes could improve collectively for all stage III patients if more eligible patients received the appropriate treatment.

Our data also indicate that between 1998 and 2004 there was not clear standard of care ACT treatment for followed for eligible patients. Nearly 55.3% of patients only received one chemotherapeutic agent. Only 16.6% of patients received multi-drug therapy, while for 11% of patients the exact number of drugs used was not recorded. This indicates that the current and past standard of care treatments, meaning the treatment regimens supported by landmark clinical trials were not used for the majority of patients. Those studies support the use of at least two chemotherapeutic agents as a part of ACT. [9, 10] Again, this is an indication that under treatment was pervasive in the study period, and a statewide initiative to improve the level of recommended ACT might be beneficial.

Rurality vs. ACT Receipt

Our study results indicate that rural residence does not affect the probability of ACT receipt in the North Carolina. The results trended towards higher rates of ACT receipt being associated with metropolitan and adjacent to metropolitan areas, but these results were not significant on univariate and multivariate analysis. Our other variables

of interest, which included the probability of receiving ACT if not contraindicated or refused and the probability being offered ACT if not contraindicated, also did not vary with rurality significantly. Environment, as defined by rurality, likely has no effect on the probability that stage III colon patients in North Carolina receive ACT. It is possible that our study did not have enough power to produce a significant test result. Still, the absolute difference in probabilities across levels of rurality would not have been clinically significant regardless of the p value obtained. The groups differed only slightly in regards to the probability of ACT receipt, being offered ACT if not contraindicated, and receiving ACT if not contradiccated or refused.

In addition, it is possible that the OMB-defined urban influence codes did not adequately capture rural-urban differences in receipt of ACT. In some cases counties were defined as part of a metropolitan area if 25% or more of residents commuted to an adjacent metropolitan area, but access to heath care in these counties on the periphery of the metropolitan area may in be different from that of counties at the center of the metropolitan area. If counties that were actually more rural in character were misclassified as urban, differences between rural and urban areas would have been obscured.

Results from prior studies investigating rurality's effect on ACT receipt offered conflicting results. VanEwyk found that rurality lowers the probability of ACT receipt for stage III colon cancer patients.[5] The most recent data, from our study and fromWu et al, both agree that rurality has no effect.[17] Consequently, it possible that over time the quality of care available to patients in rural environments in terms of post-operative management of stage III colon cancer improved between 1997 and 2001.

Region of residence vs. ACT receipt

Our study also showed that region of residence significantly affects the probability of receiving ACT, the probability of being offered ACT and the probability of receiving ACT if not refused or contraindicated. This significant difference disappeared upon multivariate analysis when race, age, and income were taken into account. These results indicate that patients receive differing care depending on the region. Patients residing in the Asheville, Charlotte and Greenville regions are offered and receive ACT much less often than the other regions of North Carolina. This is most likely explained by other factors related to each region. Income, race, and age could be confounding the relationship between region and ACT receipt. Other factors like distance to National Cancer Institute funded cancer centers may also act as a confounder in the relationship between region and ACT receipt.

There have not been any prior studies investigating region of residence versus receipt of ACT for stage III colon cancer. Consequently, there is no body of evidence available to substantiate or oppose our findings. Investigating the patterns associated with differing quality of cancer treatment in North Carolina is a worthwhile issue. In future studies, if the same regions continually have inferior treatment rates for recommended cancer treatments, then it would signal for the need of significant interventions to improve cancer care in those regions.

Study Limitations

The study is hampered by several significant weaknesses. The first group of shortcomings relates to the potential for misclassification of treatment and race. For example, race in this study was limited to white, black and other. It is likely that these

classifiers do not accurately represent a significant proportion of the actual study population. It is unclear from our system how many patients with colon cancer are Hispanic, American Indian or of Asian descent. This is significant because over ten percent of the North Carolina population is made up of non-white, non- black races. [21] Patients of these other races may receive ACT at differing rates, making racial misclassification a significant issue.

A second potential weakness of our study relates to the method we used to control for income. We used mean census tract income as surrogate value for patient income. It is difficult to determine how well census tract income represented patient-level data. Potentially if patient income is related to the development of colon cancer, then mean census tract income would not accurately represent patient income. For example, if patients with less income develop colon cancer more often than wealthier patients, then the mean census tract income would overestimate patient-level income data. Again, using census tract income was a potential source of misclassification of our confounding variables and unfortunately we can not predict how this potential error could have affected our results.

Finally, our study's most significant weakness was that we did not have treatment data for a large sum of patients in our original sample. The NCCCR did not have treatment data for nearly nine hundred patients (16.5%) in the original sample of North Carolina residents with Stage III colon cancer. This lack of treatment data potentially could have biased our results if these patients were distributed in the state unequally. For example if the majority of unknown treatment cases came from rural areas, or from specific regions in North Carolina, the exclusion of these cases would alter our results

significantly if these patients also received ACT at different rates than we found in the study.

Future Research

As mentioned earlier this study indicates that patients with stage III colon cancer receive ACT less often in the Charlotte, Greenville and Asheville regions. One potential confounder of this relationship is patient distance to National Cancer Institute (NCI) funded cancer center and patient distance to American College of surgeon certified cancer treatment. These centers have to meet specific standards related to cancer treatment quality and are monitored closely by state and Federal agencies. American college of Surgeon and NCI centers are scattered throughout North Carolina and it is possible that patients who live closest to these treatment centers receive ACT at higher percentages than patients who live far away. We feel that this is an important question that needs to be answered. It may give the medical community in North Carolina more insight about how well these centers are performing in delivering care to all patients in North Carolina, as well as how distance to these centers relates to region of residence and the receipt of recommended ACT receipt for patients in this study.

Ultimately, the results of this study may mimic those describing the relationship between rurality and ACT receipt results. The majority of ACOS treatment centers and comprehensive cancer centers are located in metropolitan and or non-metropolitan/adjacent areas. The close relationship between these variables may indicate that they are also closely related in terms of their effect on adjuvant chemotherapy receipt.

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Tables and Figures

Table 1.

Outcomes Table of 5 Year Survival for Patients with Stage III Colon Cancer
Mortality figures derived from Moertel et al. 1995

No. of Cases/yr	5 year Mortality with Surgery Alone		5 year mortality with ACT and Surgery		Deaths prevented w/ ACT	
Stage III	No.	Percentage	No.	Percentage	No.	
22,000	12,100	55%	8066	36.6	4034	

Table 2. Urban Influence Code (UIC) Groupings

UIC		# of NC Counties
Metropolitan		**40**
1	Large metro area of >1 million residents	6
2	Small metro area of < 1million residents	34
Metropolitan adjacent		**40**
3	Micropolitan area adjacent to large metro area	6
4	Noncore adjacent to large metro area	1
5	Micropolitan area adjacent to small metro area	19
6	Noncore adjacent to small metro area and contains a town of at least 2,500 residents	9
7	Noncore adjacent to small metro area and does not contain a town of at least 2,500 residents	6
Non-metropolitan, non-adjacent		**19**
8	Micropolitan area not adjacent to a metro area	6
9	Noncore adjacent to micro area and contains a town of at least 2,500 residents	2
10	Noncore adjacent to micro area and does not contain a town of at least 2,500 residents	4
11	Noncore not adjacent to metro or micro area and contains a town of at least 2,500 residents	2
12	Noncore not adjacent to metro or micro area and does not contain a town of at least 2,500 residents	5

Table 3. Demographic Characteristics of Source Population

	Metro n (%)	**Non-metro Adjacent n (%)**	**Non-metro Non-adjacent n (%)**	**Total n (%)**
Race				
White	2589	1294	250	4133
African American	644	331	89	1064
Other	48	38	6	92
Sex				
Male	1614	783	159	2556
Female	1667	880	185	2732
Mean age	67.57	67.64	68.59	67.66
Mean income	$51,897.38	$42,403.49	$38,451.76	$48,021.02

Table 4. Receipt of Adjuvant Chemotherapy: Study Population

	n	%
Chemotherapy administered	**2582**	**58%**
Chemotherapy not administered	**1850**	**42%**
Chemotherapy not recommended	1228	28%
Chemotherapy contraindicated	68	2%
Chemotherapy was treatment of choice, not administered, no reason given	137	3%
Chemotherapy refused by patient, family member, or guardian	135	3%
Chemotherapy recommended, unknown if given	282	6%
Total	**4432**	

Table 5. Adjuvant Chemotherapy Treatment Categories

	n	%
Received adjuvant chemotherapy	2582	58%
Received adjuvant chemotherapy if not contraindicated or refused	2785	63%
Offered adjuvant chemotherapy if not contraindicated	3204	72%
Not offered adjuvant chemotherapy	1228	28%

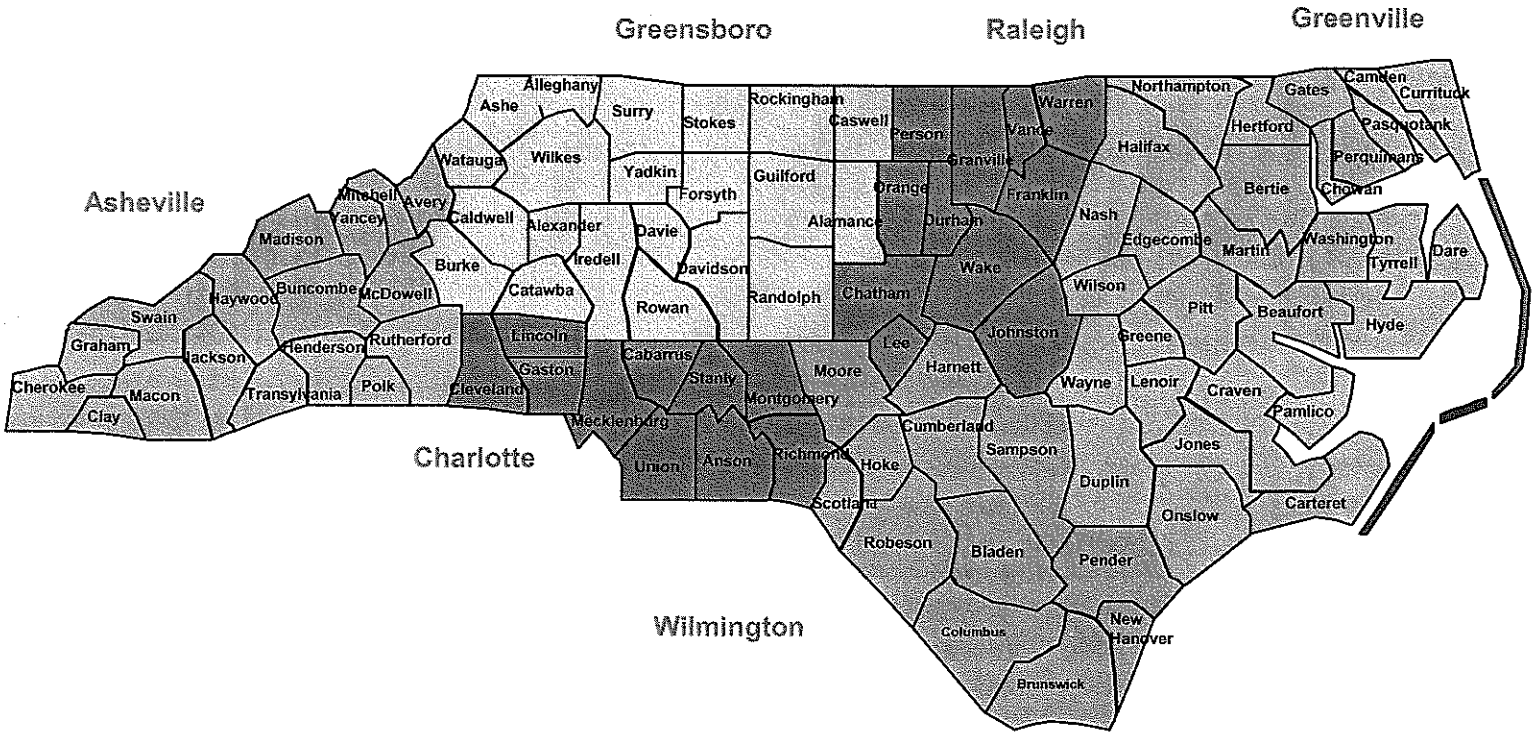
Table 6. Receipt of ACT vs. UIC Groupings

Receipt of Chemotherapy	**Metro n=2688** n (%)	**Non-metro Adjacent n=1448** n (%)	**Non-metro Non-adjacent n=281** n (%)	**X^2** (p value)	**Total n=4417** n (%)
Received ACT	1585 (59.0)	844 (58.3)	153 (54.4)	1.99 (0.37)	2582 (58.5%)
ACT if not contraindicated or refused	1713 (63.7)	887 (61.3)	156 (55.5)	3.72 (0.16)	2756 (62.4%)
ACT if not contraindicated	1959 (72.9)	1033 (71.3)	197 (70.1)	1.77 (0.41)	3189 (72.2%)
Not offered ACT	729 (27.1)	415 (28.7)	84 (29.9)	NA	1228 (27.8)

Table 7. Receipt of ACT by Region of Residence

	Asheville n=430 n(%)	Charlotte n= 729 n(%)	Greensboro n=1373 n(%)	Greenville n = 796 n(%)	Raleigh n = 541 n(%)	Wilmington n = 569 n(%)	Total n=4438 n (%)	X2 (p value)
Received ACT	191(44.4)	386(53.0)	861 (62.7)	430 (54.0)	358(66.2)	367 (64.5)	2593(58.4%)	64.9 (0.0001)
Received ACT if not contraindicated or refused	211(49.1)	422(57.9)	917 (66.8)	447 (56.2)	373(69.0)	399 (70.1)	2769(62.4%)	60.2 (0.0001)
Offered ACT if not contraindicated	273(63.5)	474(65.0)	980 (71.4)	617 (77.6)	414(76.5)	445 (78.2)	3203(72.1%)	61.9 (0.0001)
Not offered ACT	157(36.5)	255(35.0)	393 (28.6)	179 (22.5)	127(23.5)	124 (21.8)	1235(27.8%)	NA

Figure 1. NC Cancer Partnership Regions



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