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Association of Race/Ethnicity and Population Density with Disparities in Timeliness of Rectal Cancer Therapy

Susanna S. Hill
University of Massachusetts Medical School

ASSOCIATION OF RACE/ETHNICITY AND POPULATION DENSITY WITH DISPARITIES IN TIMELINESS OF RECTAL CANCER THERAPY

A Masters Thesis Presented

By

Susanna Shan Hill

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The signatures of the Master's Thesis Committee signify completion and approval as to style and content of the Thesis

_____
Robert Goldberg PhD, Chair of Committee

_____
Karim Alavi MD MPH, Member of Committee

_____
Sharina Person PhD, Member of Committee

_____
Mara Epstein ScD, Member of Committee

The signature of the Dean of the Graduate School of Biomedical Sciences signifies that the student has met all master's degree graduation requirements of the school.

_____
Mary Ellen Lane Ph.D.
Dean of the Graduate School of Biomedical Sciences

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Abstract:

Objective:

Access to care is key to effective rectal cancer treatment. We hypothesized that ethnic/racial minorities living in high population density areas would have the greatest delays in cancer care compared to whites living in medium population density areas.

Methods:

Using 2004-2016 National Cancer DataBase data, we identified stage I-III patients with invasive rectal adenocarcinoma who underwent surgery. The data were analyzed by race/ethnicity (whites, blacks, or Hispanics) and population density (metropolitan or urban/rural). Multivariable ANCOVA was performed to evaluate the duration of time from diagnosis to surgery.

Results:

The study population consisted of 76,131 patients: 65,172 Non-Hispanic whites (NHW; 85.6%), 6,167 Non-Hispanic blacks (NHB; 8.1%), and 4,792 Hispanics (6.3%). Of these, 61,363 patients (80.6%) lived in metropolitan areas.

Among direct-to-surgery patients, the greatest difference in mean time from diagnosis to surgery was 20.3 days (urban/rural NHW, 53.3 days, vs. metropolitan Hispanics, 73.6 days). Among patients receiving neoadjuvant therapy, the greatest difference in mean time from diagnosis to surgery was 18.8 days (urban/rural NHW, 136.9 days, vs. metropolitan NHB, 155.7 days).

After multivariable adjustment for several socioeconomic and clinical factors, among direct-to-surgery patients, metropolitan Hispanics had a 16.5-day delay (95% CI 12.9-20.0) compared with urban/rural NHW. In patients receiving neoadjuvant therapy, metropolitan NHB had an 18.1-day delay (95% CI 16.1-20.0) compared to urban/rural NHW.

Conclusion:

The combination of high population density and racial/ethnic minority status was associated with delays in rectal cancer care that persisted after adjusting for other important factors. Understanding which populations are at risk and perceived obstacles to timely care will help inform interventions to minimize treatment access disparities.

Key Words:

Rectal Cancer; Access to Care; Healthcare Disparities

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List of Tables:

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All materials (Figures, Tables, etc.) in this thesis represent original work.

List of Abbreviations:

National Cancer Database (NCDB)

Surveillance, Epidemiology, and End Results (SEER)

Non-Hispanic White (NHW)

Non-Hispanic Black (NHB)

95% Confidence Interval (95% CI)

OR (Odds Ratio)

aOR (adjusted Odds Ratio)

Preface:

Other works that will not be presented as part of this thesis:

Manuscripts:

1. Sarani B, Paspulati RM, Hambley J, Efron D, Martinez J, Perez A, Bowles-Cintron R, Yi F, **Hill S**, Meyer D, Maykel J, Attala S, Kochman M, Steel S, Turnbull RB. A Multidisciplinary Approach to Diagnosis and Management of Bowel Obstruction. Curr Probl Surg. 2018 Oct; 55(10):394-438.
2. **Hill SS**, Davids JS. Surgical Evaluation and Management of Constipation. Dis Colon Rectum. 2019 Jun; 62(6):661-664.
3. Davids JS, **Hill SS**, Lu P, Melnitchouk N. Progress Towards Reducing Implicit Bias – A 2019 American Society of Colon and Rectal Surgery Annual Meeting Update. Dis Colon Rectum. 2019 Dec; 62(12):1411.
4. **Hill SS**, Chung SK, Meyer DC, Crawford AS, Sturrock PR, Harnsberger CR, Davids JS, Maykel JA, Alavi K. Impact of pre-operative care for rectal adenocarcinoma on pathologic specimen quality and post-operative morbidity: a NSQIP analysis. J Am Coll Surg. 2020 Jan; 230(1):17-25.
5. **Hill SS**, Hoang CM, Cheraghi SN, Shabo MR, Resnick AJ, Crawford AS, Melnitchouk N, Harnsberger CR, Alavi K, Sturrock PR, Maykel JA, Davids JS. Data accuracy and predictors of highly rated colon and rectal surgeons on an online physician rating website. Dis Colon Rectum. 2020 Feb; 63(2):226-232.

Abstract Poster and Podium Presentations:

1. Harnsberger CR, **Hill SS**, Wyman A, Hoang CM, Davids JS, Sturrock PR, Maykel JA, Alavi K. A Validated Risk Prediction Model for Readmission following Elective

Colorectal Surgery. Podium presentation at: October 21-25, 2018 at American College of Surgeons Clinical Congress; Boston, MA.

2. **Hill SS**, Hoang CM, Cheraghi SN, Shabo MR, Resnick AJ, Crawford AS, Melnitchouk N, Harnsberger CR, Alavi K, Sturrock PR, Maykel JA, Davids JS. Reaching for the stars: data accuracy and predictors of highly rated colon and rectal surgeons on an online physician rating website. Podium presentation at: American Society of Colon and Rectal Surgeons; 2019 Jun 6-10; Cleveland, OH.
3. Harnsberger CR, **Hill SS**, Crawford AS, Hoang CM, Davids JS, Sturrock PR, Maykel JA, Alavi K. Institutional Validation of a Readmission Risk Calculator for Elective Colorectal Surgery. Podium presentation at: American Society of Colon and Rectal Surgeons; 2019 Jun 6-10; Cleveland, OH.
4. **Hill SS**, Harnsberger CR, Crawford AS, Sturrock PR, Maykel JA, Alavi K, Davids JS. Outcomes of conversion from minimally invasive to open proctectomy for rectal adenocarcinoma: a NSQIP analysis. Poster presented at: American Society of Colon and Rectal Surgeons; 2019 Jun 6-10; Cleveland, OH.
5. Meyer DC, Resnick AJ, **Hill SS**, Harnsberger CR, Davids JS, Alavi K, Maykel JA, Sturrock PR. Prolonged Foley catheterization with pre-removal cystogram after surgical repair of colovesical fistula: are we being too vigilant? Poster presented at: American Society of Colon and Rectal Surgeons; 2019 Jun 6-10; Cleveland, OH.
6. **Hill SS**, Chung SK, Meyer DC, Crawford AS, Sturrock PR, Harnsberger CR, Davids JS, Maykel JA, Alavi K. Impact of a complete pre-operative work-up for rectal adenocarcinoma on pathologic quality and post-operative morbidity: a NSQIP analysis.

Podium presentation at: American College of Surgeons Clinical Congress; 2019 Oct 27-31; San Francisco, CA.

7. Meyer DC, Resnick AJ, **Hill SS**, Crawford AS, Sturrock PR, Harnsberger CR, Davids JS, Maykel JA, Alavi K. Stop over-prescribing opioids following colorectal surgery: more than half of patients don't take them. Podium presentation at: American College of Surgeons Clinical Congress; 2019 Oct 27-31; San Francisco, CA.
8. **Hill SS**, Dore FJ, Em ST, McLoughlin RJ, Meyer DC, Sturrock PR, Harnsberger CR, Maykel JA, Alavi K, Davids JS. Characterization of Twitter Use Among Departments of Surgery with ACGME General Surgery Residency Programs. Poster presented at: American College of Surgeons Clinical Congress; 2019 Oct 27-31; San Francisco, CA.
9. Columbus AB, Lu P, **Hill SS**, Fields AC, Davids JS, Melnitchouk N. In her chair: influences upon the professional success of female surgical department chairs. Poster presented at: Association of Women Surgeons Annual Conference; 2019 Oct 26-29; San Francisco, CA. Second Place Starr Research Award.

Chapter 1: Introduction

Rectal Cancer

Colorectal cancer is the third most common malignancy diagnosed and the fourth leading cause of cancer-related deaths both worldwide[1] and in the United States.[2] The American Cancer Society has estimated that there will be 104,610 cases of newly diagnosed colon cancer and 43,340 new cases of rectal cancer in the U.S. in 2020. There are multiple histologic subtypes of colorectal cancer: adenocarcinoma, carcinoid and other neuroendocrine tumors, gastrointestinal stromal tumor, lymphomas, hamartomas, and mesenchymal tumors. Of these, over 90% exhibit adenocarcinoma histology.[3]

Based on the Surveillance, Epidemiology, and End Results (SEER) data, the American Cancer Society estimates that patients with rectal cancer have an average 5-year survival rate of 67% for all stages combined. [2] After stratification by disease stage, the 5-year relative survival rate was estimated at 90% for localized disease, 71% for regional disease, and 14% for distant disease.

The treatment of rectal cancer is highly complex due to imaging limitations, technical demands of the surgery, and multiple treatment paradigms. The current imaging technology has diagnostic limitations; magnetic resonance imaging, currently the standard of care per the National Comprehensive Cancer Network guidelines,[4] has only a 75% sensitivity for T stage and 71% sensitivity for nodal metastases.[5] This creates the potential for under-staging and undertreatment. of patients with potential rectal cancer. From the surgical perspective, total mesorectal excision, the gold standard for adequate local control, is technically difficult due to the physical constraints of the bony pelvis, several nearby key urogenital structures, and challenging dissection planes. Moreover, treatment is multifaceted with many key decision

points including whether a patient would benefit from neoadjuvant and/or adjuvant chemoradiation, which therapeutic regimen to use, and which surgery to perform accounting for tumor characteristics, location, and patient comorbidities. As such, multidisciplinary tumor boards are essential to maximizing the quality of care a patient receives and should involve physicians from surgery, medical oncology, radiation oncology, and radiology. Given the high level of complexity involved in rectal cancer care, there are multiple pathways through which potential disparities may arise.

Currently available data have shown considerable variability in long-term outcomes of patients with rectal cancer with these rates influenced by factors including hospital volume and compliance with standards of care. Higher-volume surgeons and hospitals have been associated with higher rates of total mesorectal excision, improved lymph node harvest, decreased colostomy rates, and decreased local recurrence.[6-8] To standardize rectal cancer practices, multiple European countries have implemented policies with the Norwegian Rectal Cancer Project,[9] Spanish Rectal Cancer Project,[10] and Dutch Colorectal Cancer Group.[11] All of these programs have shown significant improvements in rates of total mesorectal excisions. In the United States, the National Accreditation Program for Rectal Cancer was created in 2017 through "a collaboration between The OSTRiCh Consortium and the Commission on Cancer, a quality program of the American College of Surgeons" to address these challenges and promote standardization of practices and quality improvement.[12] While a key step towards improving rectal cancer quality, only fifteen sites have been accredited as of April 2020,[13] reaching a small proportion of patients with rectal cancer in limited centers.

Socioeconomic Disparities in Cancer Care and Outcomes

Disparities exist between racial and ethnic groups in terms of the magnitude and prognosis associated with colorectal cancer. A previous SEER study using 1985-2008 data showed increased mortality in blacks at every stage of colorectal cancer, with the largest survival differences (a 1.72 black:white mortality rate ratio) among those with distant stage of disease.[14] The authors speculated that this could be related to differences in early detection and treatment with decreased screening[15] and uneven dissemination of adjuvant chemotherapy for Stage II and III colorectal cancer in black populations.[8, 16] A study using National Cancer Database (NCDB) 1998-2006 data, with propensity matching for clinically significant variables, found that blacks were more likely to present with higher stage rectal cancer.[17] Among patients with resectable stage I-III disease, blacks underwent surgery less frequently than whites (78% vs. 86%), and, even among those who underwent resection, black race was still associated with 20% higher risk of 5-year mortality compared with whites after propensity matching for key clinical and socioeconomic variables.

Access to care differences also exist along population density gradients. A rectal cancer study examining 2007-2011 SEER patients found that those living in rural areas were more likely to have their surgeries done by low volume surgeons at low volume hospitals, have a general surgeon compared to a colorectal surgery specialist, and have higher drive times to the hospital.[18] A NCDB study using 2006-2014 data found that patients with rectal cancer living in rural areas had a 42% higher odds of undertreatment with neoadjuvant radiation compared to those living in metropolitan areas.[19] A study on patient ratings of access to care using 1998-2013 SEER-Consumer Assessment of Healthcare Providers & Systems data found non-Hispanic

black and Hispanic breast, lung, and colorectal cancer patients in rural areas rated "getting need care" lower than those living in urban areas.[20]

Overview of the National Cancer Database (NCDB)

The NCDB was created in 1989 and is jointly sponsored by the American Cancer Society and the Commission on Cancer of the American College of Surgeons.[21] This database contains de-identified data from over 1,500 hospitals that hold Commission on Cancer accreditation, representing approximately 70% of all newly diagnosed cases of cancer in the United States It is important to note that the NCDB is hospital-based and not population-based data. All data collection is sourced from hospital cancer registries by certified tumor registrars with over 34 million records in total.

To maintain accreditation, programs are mandated to access, abstract, and conduct follow-up activities for all required tumors diagnosed and/or treated at the abstracting facility. Data have standardized coding definitions based on the Standards for Oncology Registry Entry guidebook[22] (the most recent revision in 2018 reflects the American Joint Committee on Cancer 8th edition staging standards). In addition, there are over 600 automated edit checks and regular audits to ensure data fidelity. Data access is granted only to participants at Commission on Cancer hospital sites after submission of an application that is reviewed by NCDB staff on a bi-annual basis.

Compared with SEER, this database has more granularity regarding diagnosis and treatment variables such as timing and type of surgery, chemotherapy, and radiation. The Commission on Cancer hospitals are the source of the de-identified data used herein; they have

not been verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

Specific Aims

The primary aim of this retrospective study was to examine, among patients with newly diagnosed rectal cancer, if racial/ethnic minority status and living in metropolitan areas was associated with delays in access to care. The secondary aims of the study were to evaluate differences in short-term outcomes (30-day readmission and 30-day and 90-day mortality) according to racial/ethnic minority status and population density groups. This study utilized the NCDB data from 2004-2016 on patients with stage I-III rectal adenocarcinoma to examine these outcomes. Patients with metastatic cancer were excluded because the complex evaluation and timing of potential metastectomy is impossible to evaluate from a retrospective database but this cohort would likely have different timing to definitive resection.

Chapter 2: Methods

Data Source

Using the NCDB, we initially performed a cross-sectional analysis after combining all cases of patients with rectal cancer diagnosed from January 1, 2004 to December 31, 2016.

Case Selection

Patients were included in the study if they had adenocarcinoma histology (ICD-O-3 814, 821, 826, 848, 859), invasive behavior only, and underwent a proctectomy (partial proctectomy, pull through with sphincter preservation, total proctectomy, or proctectomy not otherwise specified).

Patients were excluded if they were clinical stage IV because the NCDB does not clearly delineate extent of metastatic disease beyond location, so it is difficult to tell who is a candidate for metastectomy. Furthermore, even if the patient is a candidate, the timing is highly complex with no clear standard of care for whether this should occur prior, simultaneous to, or following primary disease resection, which would affect the primary outcome of interest. In addition, patients were excluded if they were involved in clinical trials because there could be unconventional timing as they were no longer receiving standard of care therapy. In addition, patients were excluded if they were missing data on the following key variables: clinical stage, exposure variables of interest (race, ethnicity, and county population density), or neoadjuvant chemotherapy or radiation status. Finally, patients were excluded if they underwent non-proctectomy surgeries to create a more homogenous patient population. The local tumor destruction/excision code could include either polypectomies, which may be oncologically insufficient resection, or transanal endoscopic microsurgery, but this level of detail cannot be

determined in this database. In addition, patients who underwent more radical procedures (total proctocolectomy or pelvic exenteration) likely reflected more aggressive locoregional disease that may not be a true stage I-III patient if there was concern for invasion into adjacent structures or other underlying disease pathology necessitating a more aggressive than standard-of-care oncologic procedure.

Independent and Dependent Variables

Race and ethnicity are both highly complex social constructs that have multifaceted components and a single person may possess multiple racial/ethnic identities. For purposes of this study, which seeks primarily to clarify disparities that may be driven by "minority" status, race and ethnicity have been simplified for analysis. NCDB defines their race variable to be analyzed with their Spanish/Hispanic origin variable and both items must be recorded. Patients are identified by the "primary race of the person." Spanish/Hispanic origin is defined by the NCDB to be those of Spanish/Hispanic origin of any race. Patients were stratified based on race/ethnicity groups into three mutually exclusive categories: Non-Hispanic whites (NHW), Non-Hispanic blacks (NHB), and Hispanics. Patients that did not fall into one of these three categories were excluded from analysis due to small sample sizes.

The second key exposure of interest was metropolitan vs. urban/rural status. NCDB determines population density status by matching state and county Federal Information Processing Standard codes of the patient recorded at the time of diagnosis against the 2013 files published by the United States of Department of Agriculture Economic Research Service.[23] Population density was analyzed as either metropolitan (at least 250,000 population), urban (2,500-20,000 or more adjacent to a metropolitan area), and rural (<2,500 population either

adjacent or non-adjacent to a metropolitan area). To simultaneously examine the effects of population density and minority status, and because certain cells for rural patients were less than 10, which violates the NCDB data use agreement, urban and rural were combined for purposes of this analysis.

Other patient sociodemographic characteristics examined included age (all patients 90 or older are censored as 90 to protect against potential identification), year of diagnosis (divided into three roughly equivalent categories for analysis), and sex. Insurance status was recorded by NCDB as the primary payor and was categorized for analysis as private, government (including Medicaid, Medicare, and other government), none, or unknown. Both education and income data were defined by census-tract level data by matching the zip code of the patient at the time of diagnosis against files derived from the 2016 American Community Survey data and categorized into equally portioned quartiles among all United States zip codes. Educational attainment was measured as the percentage of adults 25 years and older who did not graduate from high school. Median household income was adjusted for 2016 inflation. Both education and income were analyzed dichotomously (lowest quartile vs. top three quartiles). Distance from residence to treatment facility is recorded by NCDB based on the centroid of the patient's zip code and street address of the hospital facility. For analysis, this was divided into three groups based on previously published NCDB literature[24] as <10 miles, 10-49 miles, >50 miles.

Three facility variables were used in the present analysis. Facility type was assigned by the Commission on Cancer Accreditation program[25] as Community Cancer Program, Comprehensive Community Cancer Program, Academic/Research Program including National Cancer Institute-designated comprehensive cancer centers, or Integrated Network Cancer Programs. Facility location was categorized by census regions:[26] Northeast (New England,

Middle Atlantic), South (South Atlantic, East South Central, West South Central), Midwest (East North Central, West North Central), and West (Mountain, Pacific). A facility volume variable was created using facility identification codes and number of incident cases to divide this variable into tertiles. To account for potential yearly variance, the total number of cases was summed over the most recent 5 years of the database (i.e., 2011- 2016 data). The facilities were divided into high (29-412 cases / 5 years), medium (12 – 28), and low (1 – 11) volume.

Clinical comorbidity was evaluated in NCDB with the Charlson-Deyo score,[27] which is a well-validated research tool that is a composite score of ten equally-weighted diagnoses (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, moderate or severe liver disease, and AIDS). This was then recorded in the database as a value of 0, 1, 2, and 3 or more.

Clinical stage grouping was defined based on the Cancer Staging Manual published by the American Joint Committee on Cancer. These designations were determined based on a patient's T, N, and M (depth of invasion, nodal involvement, metastatic disease, respectively) status, which were required by NCDB standards to be copied from a standardized document found in the record that was recorded by the managing physician. These were analyzed as stage I, II, or III rectal cancer.

Order of treatment was determined using the NCDB Systemic Surgery Sequence and Radiation Surgery Sequence variables. Neoadjuvant treatment was defined by receipt of both systemic chemotherapy and radiation prior to surgery as this is the standard of care per NCCN

guidelines for stage II and III rectal cancer patients.[4] Patients who did not receive neoadjuvant therapy were treated as the direct-to-surgery group.

Statistical Analysis

All univariate comparisons were done between the three racial/ethnic groups. Continuous variables are shown as means with standard deviations and tested for significance with ANOVA. Categorical variables are shown as frequencies and tested for significance with the chi square test.

Using the three race/ethnicity designations (NHB, NHW, vs. Hispanic) and the two population density designations (metropolitan vs. urban/rural), six different combinations were created to compare patients from these groups in the analysis for the primary outcome of timing from diagnosis to definitive surgery. Two separate univariate ANOVA models were used to evaluate the association between race/ethnicity-population density group and time to definitive surgery among patients who: (1) received neoadjuvant treatment or (2) were direct-to-surgery. The reference group was chosen based on which race/ethnicity-population density group had the shortest time interval. These ANOVA models were also evaluated using an interaction term between for race/ethnicity group and population density. Results are reported as beta coefficient (95% confidence interval, 95% CI). Two separate ANCOVA models were fit using backwards stepwise selection based on variables that were different at $p < 0.20$ on univariate comparison between race/ethnicity groups with variables that were significant at $p < 0.05$ were kept in the final model.

To evaluate the secondary aim of short-term outcomes, univariate logistic regression analyses were carried out to examine the association between exposure (race/ethnicity-population density group) and outcomes (30-day unplanned readmission, 30-day death, and 90-

day death). For ease of comparison, reference group was carried over from the primary outcome. Three separate multivariable logistic regressions were fit using backwards stepwise regression based on variables that were different at $p < 0.20$ on univariate comparison between race/ethnicity groups with variables that were significant at $p < 0.05$ kept in the final model. Results are reported as odds ratio (OR) or adjusted odds ratio (aOR) with 95% CI and the p-values reported are for the maximum likelihood estimate. All statistics were performed using SAS software (version 9.4, Cary, NC). Statistical significance was defined as $p < 0.05$.

Sensitivity Analysis for Missing Information on Clinical Stage

A sensitivity analysis was performed examining the primary study outcome (i.e., timing from diagnosis to definitive surgery) stratified by race/ethnicity and population density among patients excluded from the main analysis for having missing data on the clinical stage of their malignancy. These groups were compared by whether they received neoadjuvant therapy or were direct-to-surgery with their respective groups in the main study analysis.

Ethical Considerations:

The Institutional Review Board at the University of Massachusetts Medical School deemed this study non-human subjects research and exempt from IRB review due to the de-identified nature of the data. In compliance with the NCDB data use agreement, this study suppresses all non-zero counts that are less than ten unless they are in the “missing” or “unknown” categories to prevent potential identification of subjects.

Chapter 3: Results

There was a total of 290,015 cases of rectal cancer during the period under study (2004-2016) (Figure 1). The study cohort excluded patients with non-adenocarcinoma histology (n = 35,896), non-invasive tumor biology (n = 12,091), missing information on clinical stage (n = 71,555), and stage IV patients (n =3 7,398). Patients were excluded if they were missing information on the exposures of interest (race, ethnicity, or population density, n = 15,772) or the outcome (timing to definitive surgery, n = 21,517). Patients in clinical trials were excluded (n = 60) because this likely would affect timing of therapy. Finally, only patients who underwent surgical resection of the rectum (i.e., partial or total proctectomy) were included because this reflects the oncologic standard-of-care procedure (all other procedures, n = 19,595).

The final study cohort consisted of 76,131 cases of clinical stage I-III invasive rectal adenocarcinoma. In terms of race/ethnicity, 65,172 were NHWs (85.6%), 6,167 NHBs (8.1%), and 4,792 Hispanics (6.3%) and 61,363 patients (80.6%) lived in metropolitan areas and 14,768 in urban/rural areas. The average age of the study cohort was 62 years old and 38.5% were women.

Patient Characteristics According to Race/Ethnicity

In examining differences in selected characteristics according to race/ethnicity, NHWs were significantly older, more likely to have private insurance, receive care at a comprehensive community cancer program, be treated at facilities in the Midwest, and to be treated at high volume surgical centers than NHBs or Hispanics (Table 1). In addition, NHWs were significantly less likely to live in metropolitan areas, live in areas of the lowest education and

income quartiles, and live within 10 miles of the treatment facility. NHBs had a significantly higher proportion of females compared with NHWs and Hispanics.

Timing of Diagnosis to Definitive Surgery

Timing from diagnosis to definitive surgery was analyzed according to whether patients were direct-to-surgery or underwent neoadjuvant therapy. For those in the direct-to-surgery group, the greatest difference in mean time from diagnosis to surgery was 20.3 days (urban/rural NHWs, 53.3 days, vs. metropolitan Hispanics, 73.6 days; Table 2). Among patients receiving neoadjuvant therapy, the greatest difference in mean time from diagnosis to surgery was 18.8 days (urban/rural NHWs, 136.9 days, vs. metropolitan NHBs, 155.7 days).

Timing of Diagnosis to Definitive Surgery in the Direct-to-Surgery Group

Compared to the reference group, urban/rural NHWs, the average length of time from diagnosis to definitive surgery in NHB patients was 14.5 days longer among those living in urban/rural areas (95% CI 6.4-22.6) and 13.1 days longer for those living in metropolitan areas (95% CI 10.0-16.2; Table 3). Compared to the same reference group, for Hispanic patients, the average time did not signficantly differ in urban/rural areas but was 20.3 days longer for those living in metropolitan areas (95% CI 17.0-23.6). Among NHWs living in metropolitan areas, the average time was not significantly different from urban/rural NHWs.

After adjusting for age, year of diagnosis, insurance status, education level, distance to treatment facility, facility type, facility location, facility volume, and clinical stage group, the average length of time to surgery in NHB patients was 14.5 days longer for those living in urban/rural areas (95% CI 6.6-22.4) and 15.2 days longer for those living in metropolitan areas

(95% CI 11.9-18.5) compared to urban/rural NHWs. For Hispanic patients living in urban/rural areas did not significantly differ in time from diagnosis to surgery from urban/rural NHWs; however, Hispanics in metropolitan areas did significantly differ from urban/rural NHWs (16.5 days longer, 95% CI 12.9-20.0). For the metropolitan NHWs, the average time to surgery was 4.6 days longer than for urban/rural NHWs (95% CI 2.5-6.7).

Timing of Diagnosis to Definitive Surgery in the Neoadjuvant Therapy Group

Compared to the reference group, urban/rural NHWs, the average length of time from diagnosis to definitive surgery in NHB patients was 14.3 days longer for those living in urban/rural areas (95% CI 10.1-18.5) and 18.8 days longer for those living in metropolitan areas (95% CI 17.0-20. 6; Table 4). Compared to the same reference group, for Hispanic patients, the average time was 7.7 days longer for those living in urban/rural areas (95% CI 1.8-13.6) and 16.4 days longer for those living in metropolitan areas (95% CI 14.5-18.3). For metropolitan NHWs, the average time was 3.6 days longer than urban/rural NHWs (95% CI 2.5-4.6).

After adjusting for age, year of diagnosis, insurance status, education level, distance to treatment facility, facility type, location, and volume, comorbidity status, and clinical stage, the average length of time to surgery in NHB patients was 12.7 days longer for those living in urban/rural areas (95% CI 8.4-17.0) and 18.1 days longer living in metropolitan areas (95% CI 16.1-20.0) compared to urban/rural NHWs. For Hispanic patients, the difference from urban/rural NHWs was non-significant in urban/rural areas but significant in metropolitan areas (11.8 days longer, 95% CI 9.6-13.9). For metropolitan NHWs, the average time was 3.7 days longer than urban/rural NHWs (95% CI 2.5-4.9).

Interaction Between Race/Ethnicity and Population Density

In direct-to-surgery patients, an interaction term between race/ethnicity group and population density was not statistically significant for time from diagnosis to definitive surgery. However, in patients receiving neoadjuvant therapy, an interaction term between race/ethnicity and population density was statistically significant for time from diagnosis to definitive surgery ($p = 0.01$). In this model, rural/urban location was associated with a shorter mean time interval from diagnosis to definitive surgery in Hispanics (35.9 vs. 40.6 days with metropolitan location). However, rural/urban location was associated with a longer mean time interval in NHBs (41.5 vs. 40.7 days for metropolitan) and in NHWs (33.9 vs. 33.7 days for metropolitan).

Sensitivity Analysis of Excluded Missing Clinical Stage Patients

Among the 71,555 patients excluded for missing information on the clinical stage of their disease, 23,394 patients met all the other inclusion/exclusion criteria and had data regarding the receipt of neoadjuvant therapy, which is critical for evaluating timing to definitive surgery.

In the direct-to-surgery group, a total of 12,578 patients were excluded for missing data on clinical stage, and these patients were compared to the 26,916 patients included in the final analysis. Mean time to surgery in the excluded patients was significantly shorter at 26.2 days (95% CI 25.6-26.8) compared to the analysis patients' mean of 56.7 days (95% CI 56.0-57.4); these differences were statistically significant within every race/ethnicity-population density group. Mean time to surgery was as follows for excluded (vs. analysis) patients by race/ethnic-population density groups: urban/rural NHB 28.9 days (vs. 67.8); metropolitan NHB 28.0 days (vs. 66.4); urban/rural Hispanic 18.3 days (vs. 63.9); metropolitan Hispanic 28.9 days (vs. 73.6); urban/rural NHW 25.1 days (vs. 53.3); metropolitan NHW 26.3 days (vs. 55.0). This appeared

to be driven by the high proportion of patients who underwent surgery almost immediately after diagnosis: 2,340 (18.6%) patients within a day of diagnosis and 3,676 (29.2%) within a week of diagnosis.

In the neoadjuvant group, the 10,816 patients excluded for missing clinical staging were compared to the 49,215 patients included in the final analysis. Mean time to surgery in the excluded patients was significantly shorter at 105.0 days (95% CI 104.2-105.8) compared to the analysis patients' mean of 107.1 days (95% CI 106.7-107.4). When stratified by race/ethnicity-population density groups, mean time to surgery significantly differed only within the metropolitan NHW groups (excluded mean 103.7 vs. analysis mean 106.8 days).

Short-Term Outcomes

Unplanned readmissions within 30-days of surgical discharge differed between groups with the lowest rate observed among rural/urban Hispanics (5.9%) and the highest rate in rural/urban NHBs (9.0%, $p < 0.001$). The odds of 30-day unplanned readmission were higher for urban/rural NHBs (OR 1.36, 95% CI 1.04-1.79) compared to rural/urban NHWs (Table 5). After adjustment for year of diagnosis, sex, insurance, distance to treatment facility, facility region, facility volume, and comorbidity status, odds of readmission were still higher for urban NHBs (aOR 1.36, 95% CI 1.03-1.79) compared to rural/urban NHWs. In contrast, odds of 30-day unplanned readmission were lower for metropolitan NHWs (OR 0.90, 95% CI 0.83-0.97) compared to rural/urban NHWs. After adjustment for the same clinical and socioeconomic factors, odds of readmission were still lower for metropolitan NHW (aOR 0.88, 95% CI 0.80-0.96).

All-cause mortality at 30-days after definitive surgery did not differ between our principal study groups with the lowest rate observed in rural/urban Hispanics (0.7%) and the highest rate in metropolitan NHBs (1.3%, p = 0.63). The odds of dying at 30-days were not significantly different for any racial/ethnic-population density group when compared to rural/urban NHWs. After adjustment for age, sex, insurance, facility volume, and comorbidity status, there were still no significant differences for any racial/ethnic-population density group.

All-cause mortality at 90-days after definitive surgery differed significantly between various comparison groups with the lowest rate observed in metropolitan Hispanics (1.8%) and the highest rate in rural/urban NHBs (4.1%, p = 0.003). The odds of 90-day mortality were higher for urban/rural NHBs (OR 1.77, 95% CI 1.16-2.68) compared to rural/urban NHWs. After adjustment for age, sex, insurance, facility region, facility volume, comorbidity status, and clinical stage, odds were 90-day mortality were still higher compared to rural/urban NHWs with increased magnitude (aOR 2.21, 95% CI 1.44-3.41). Conversely, the odds of dying within the first 90 days after definitive surgery were lower for metropolitan Hispanics (OR 0.76, 95% CI 0.58-0.99; aOR 0.97, 95% 0.73 – 1.28) compared with rural/urban NHWs.

As I noted earlier, you might want to try to carry out a multivariable adjusted logistic regression analysis on all or some of these short-term outcomes and see if it changes either the magnitude or direction of your unadjusted findings.

Chapter 4: Discussion

This study utilized data from the NCDB to evaluate the association of race/ethnicity and population density with delays in timing of definitive surgery in patients with resectable rectal cancer. After adjusting for a variety of clinical and socioeconomic factors, over two week delays from diagnosis to surgery were seen in the neoadjuvant and direct-to surgery settings for NHB patients living in both rural/urban areas and metropolitan areas and Hispanic patients in metropolitan areas compared to urban/rural NHW patients. While 30-day all-cause mortality did not differ between groups, NHB patients living in metropolitan and urban/rural areas were at geratest risk for dying within 90 days following definitive surgery.

The World Health Organization defines Social Determinants of Health as "the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life."[28] A key intent of this study was to begin to deconstruct access to care inequalities that arise from beyond a single socioeconomic construct. Inasmuch, we examined race/ethnicity with population density in tandem. Timing from diagnosis to definitive surgery served as a proxy measure in this study for potential access to care disparities. To identify which patients have increased vulnerability to access issues that can stem from underlying social and economic conditions,[29] it is critical to interpret information obtained from patients in a larger context, especially using sources of data that are potentially generalizable to broader populations, such as the NCDB .

We found that racial/ethnic minority status was associated with delays in receipt of definitive surgery. These delays persisted after adjusting for other key potentially confounding socioeconomic factors that have been previously shown to be linked to survival differences

including insurance status,[30, 31] education level,[32] and facility volume.[33] In addition, these delays in timing did not seem to worsen with addition of more complex care (i.e., neoadjvuant therapy).

While impossible to disentangle the causality of the findings of our observational study, our results suggest that the observed delays may lie with initial access rather than coordination of care. Both NHB and Hispanic minority groups experienced care delays in the metropolitan setting. While this may be contrary to our initial thinking that access would be easier with increased density of cancer centers, delays among minority patients who live in metropolitan settings have been shown in other studies. A study of colorectal cancer patients in California showed that a lower proportion of minority patients used high volume hospitals for colorectal cancer care despite a higher proportion living nearby.[34] Increased distance and travel time have been found in black female breast cancer patients for radiotherapy facility access in both Atlanta[35] and Detroit[36] metropolitan areas. While a different disease process, these challenges with radiotherapy access likely reflect systemic access disparities to onocologic facilities.

While the focus of our study was patients undergoing surgery to evaluate timing differences, it is important to acknowledge that disparities exist throughout the quality of oncologic care received as well. Black race and rurality have been found to be independent predictors of who refuses rectal cancer surgery, and this could be a key contributor to survival differences observed between races and different population densities.[37] Prior studies have found a higher odds of inadequate radiation dosing in rectal cancer patients of race other than NHW, NHB, Hispanic, Asian-Pacific Islander and those living in rural settings[19] and that blacks were less likely to receive standard adjuvant therapy.[16] Importantly, multiple studies have shown that black patients tend to present with higher stages of rectal cancer as well, a key prognostic indicator of a worse outcome.[14, 38, 39]

Important future directions of this research include to determine how these combined socioeconomic factors contribute to disparities in survival and whether these gaps arise at specialist referral stage, patient understanding of time urgency and gravity of disease, lack of social and financial support structure, and unequal effects of insurance and scheduling issues. In addition, further examination and identification of other socioeconomic factors that increase vulnerability in accessing medical care may be important including age, health literacy, psychosocial factors, and the distance to treatment centers. Finally, it will be important to perform qualitative research within at-risk communities and prospective institutional level research to determine how best to mitigate these delays in access to care.

Study Strengths and Limitations

A strength of this study is the joint examination of two key components of socioeconomic status, race/ethnicity and population density, which reflects a more comprehensive approach to disparities research. In addition, the large size of this dataset allows for the study of subsets of patients, namely urban/rural minority patients, receiving surgical care. Furthermore, the data granularity within the NCDB allows evaluation of timing differences as a proxy measure for care access, which has not been captured in other data sets.

A limitation of this study was our inability to look specifically at rural minority patients due to limited sample size in the NCDB population, likely reflecting how NCDB only collects data from Commission on Cancer-accredited hospitals that may not include rural patients. To better examine the interplay of rurality and race, utilization of a different database such as SEER may be more beneficial. In addition, since this is an observational study, it was not possible to determine the causality of why there was additional time to receipt of definitive surgery in some

groups of patients; this would need to be conducted on a prospective local level. Furthermore, unmeasured and residual confounding are possible as there are variables not captured in this database that could be key to understanding reasons for delay and difficulty with access of care. These variables include factors such as health literacy, a more accurate reflection of financial liquidity, patients' support networks, and facility and referral network capacity. Closer examination of these additional factors could be important avenues of future study on an institutional and more granular level to improve access for these vulnerable patient populations. Finally, a large proportion of the dataset had to be excluded for missing clinical staging information. While a sensitivity analysis was performed to examine the characteristics of these patients, it is not clear why excluded direct-to-surgery patients had significantly shorter intervals to surgery. While NCDB lacks an emergency surgery variable, given the proximity of time from diagnosis to surgery, likely a large subset of these patients required urgent or emergent surgery and did not undergo neoadjuvant therapy or proper staging work-up.

Chapter 5: Conclusions

Minority status and metropolitan living location were associated with delays from diagnosis to definitive surgery in patients with resectable rectal cancer that persisted after adjusting for other important clinical/socioeconomic factors. Identification of which components of socioeconomic determinants of health place patients at increased risk of delays could be instrumental to mitigating and actively addressing obstacles to the timely access to care among these patients .

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Tables:

Table 1: Patient Demographic and Clinical Characteristics According to Race/Ethnicity

	Non-Hispanic Black (n=6,167)	Hispanic (n=4,792)	Non-Hispanic White (n=65,172)	p-value
County type				<0.001
Metropolitan	5476 (88.8)	4460 (93.1)	51427 (78.9)	
Urban/Rural	691 (11.2)	332 (7.0)	13745 (21.1)	
Age at diagnosis, years, mean (SD)	60 (12)	59 (13)	62 (13)	<0.001
Year of diagnosis				<0.001
2004-2008	1593 (25.8)	1156 (24.1)	17832 (27.4)	
2009-2012	2143 (34.8)	1566 (32.7)	22336 (34.3)	
2012-2016	2431 (39.4)	2070 (43.2)	25004 (38.4)	
Sex, male	3584 (58.1)	3045 (63.5)	4023 (61.7)	<0.001
Insurance Status				<0.001
Private	2599 (42.1)	1996 (41.7)	32200 (49.4)	
Government	3031 (49.2)	2157 (45.0)	30282 (46.5)	
None	445 (7.2)	549 (11.5)	1903 (2.9)	
Unknown	92 (1.5)	90 (1.9)	787 (1.2)	
Lowest Education Quartile	2513 (40.8)	2568 (53.6)	10403 (16.0)	<0.001
Lowest Income Quartile	2788 (45.2)	1269 (26.5)	9925 (15.2)	<0.001
Distance to Facility				<0.001
<10 miles	3770 (61.1)	2864 (59.8)	27844 (42.7)	
10-50 miles	1944 (31.5)	1532 (32.0)	27919 (42.8)	
>50 miles	450 (7.3)	392 (8.2)	9346 (14.3)	
Facility Type				<0.001
Community Cancer Program	373 (6.4)	357 (8.0)	5608 (8.9)	
Comprehensive Community Cancer Program	2029 (34.5)	1736 (38.8)	27250 (43.4)	
Academic/Research Program	2614 (44.5)	1813 (40.5)	21027 (33.5)	
Integrated Network Cancer Program	862 (14.7)	571 (12.8)	8905 (14.2)	
Facility Location				
Northeast	891 (14.5)	805 (16.8)	12515 (19.2)	
South	3463 (56.2)	1643 (34.3)	21029 (32.3)	
Midwest	1229 (20.0)	450 (9.4)	19535 (30.0)	
West	295 (4.8)	1579 (33.0)	9711 (14.9)	
Facility Volume (cases/5-year)				<0.001
Low (1-11)	536 (8.7)	474 (9.9)	5424 (8.3)	
Medium (12-28)	1474 (24.0)	1068 (22.3)	14143 (21.8)	
High (29-412)	4146 (67.4)	3246 (67.8)	45469 (69.9)	
Charlson-Deyo Score				0.005
0	4670 (75.7)	3709 (77.4)	50221 (77.1)	
1	1125 (18.2)	855 (17.8)	11338 (17.4)	
2	245 (4.0)	157 (3.3)	2591 (4.0)	
3+	127 (2.1)	71 (1.5)	1022 (1.6)	
Clinical stage group				<0.001
Stage 1	1340 (21.7)	961 (20.1)	15689 (24.1)	
Stage 2	2174 (35.3)	1577 (32.9)	23575 (36.2)	
Stage 3	2653 (43.0)	2254 (47.0)	25908 (39.8)	

All values given are n (col%) unless otherwise specified.

Table 2: Mean Time in Days from Diagnosis of Rectal Cancer to Definitive Surgery

	Non-Hispanic Black (n=6,167)		Hispanic (n=4,792)		Non-Hispanic White (n=65,172)		p-value
Patient Treatment Group	Rural/Urban (n=691)	Metropolitan (n=5,476)	Rural/Urban (n=332)	Metropolitan (n=4,460)	Rural/Urban (n=13,745)	Metropolitan (n=51,427)	
Direct-to-Surgery	67.8 (61.7)	66.4 (71.9)	63.9 (60.9)	73.6 (71.2)	53.3 (52.2)	55.0 (55.9)	<0.001
Neoadjuvant	151.2 (52.7)	155.7 (57.1)	144.6 (57.2)	153.3 (49.0)	136.9 (40.5)	140.5 (45.6)	<0.001

All values given are mean (standard deviation).

Table 3 –Delay from Diagnosis to Definitive Surgery Among Direct-to-Surgery Patients

	Univariate			Multivariable		
Patient Group	Beta-Coefficient	95% CI	p-value	Beta-Coefficient	95% CI	p-value
NHB						
Urban/rural	14.5	6.4 – 22.6	<0.001	14.5	6.6 – 22.4	<0.001
Metropolitan	13.1	10.0 – 16.2	<0.001	15.2	11.9 – 18.5	<0.001
Hispanic						
Urban/rural	10.6	-1.4 – 22.5	0.08	4.4	-7.5 – 16.2	0.47
Metropolitan	20.3	17.0 – 23.6	<0.001	16.5	12.9 – 20.0	<0.001
NHW						
Urban/rural	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Metropolitan	1.7	-0.2 – 3.5	0.08	4.6	2.5 – 6.7	<0.001

The multivariable ANCOVA is adjusted for age, year of diagnosis, insurance status, education level, distance to treatment facility, facility type, facility location, facility volume, and clinical stage group.

Table 4 –Delay from Diagnosis to Definitive Surgery Among Neoadjuvant Patients

	Univariate			Multivariable		
Patient Group	Beta-Coefficient	95% CI	p-value	Beta-Coefficient	95% CI	p-value
NHB						
Urban/rural	14.3	10.1 – 18.4	<0.001	12.7	8.4 – 18.0	<0.001
Metropolitan	18.8	17.0 – 20.6	<0.001	18.1	16.1 – 20.0	<0.001
Hispanic						
Urban/rural	7.7	1.8 – 13.6	0.01	3.9	-2.1 – 9. 8	0.20
Metropolitan	16.4	14.5 – 18.3	<0.001	11.8	9.6 – 13.9	<0.001
NHW						
Urban/rural	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Metropolitan	3.6	2.5 – 4.5	<0.001	3.7	2.5 – 4.9	<0.001

The multivariable ANCOVA is adjusted for age, year of diagnosis, insurance status, education level, distance to treatment facility, facility type, facility location, facility volume, comorbidity status, and clinical stage group.

Table 5 –Short Term Outcomes Stratified by Race/Ethnicity-Population Density Groups

	Univariate			Multivariable		
Patient Group	OR	95% CI	p-value	aOR	95% CI	p-value
30-Day Unplanned Readmission After Discharge						
NHB						
Urban/rural	1.36	1.04 – 1.79	0.01	1.36	1.03 – 1.79	0.01
Metropolitan	1.05	0.93 – 1.18	0.52	0.97	0.85 – 1.11	0.72
Hispanic						
Urban/rural	0.85	0.53 – 1.35	0.39	0.87	0.54 – 1.42	0.54
Metropolitan	0.95	0.83 – 1.09	0.39	0.95	0.82 – 1.10	0.54
NHW						
Urban/rural	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Metropolitan	0.90	0.83 – 0.97	0.03	0.88	0.80 – 0.96	0.02
30-Day All-Cause Mortality After Definitive Surgery						
NHB						
Urban/rural	0.98	0.46 – 2.10	0.83	1.37	0.63 – 2.96	0.59
Metropolitan	1.17	0.87 – 1.57	0.14	1.53	1.13 – 2.06	0.09
Hispanic						
Urban/rural	0.59	0.15 – 2.39	0.47	0.88	0.21 – 3.58	0.66
Metropolitan	0.86	0.60 – 1.23	0.80	1.15	0.80 – 1.66	0.94
NHW						
Urban/rural	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Metropolitan	0.96	0.80 – 1.16	0.70	1.02	0.84 – 1.24	0.46
90-Day All-Cause Mortality After Definitive Surgery						
NHB						
Urban/rural	1.77	1.16 – 2.68	0.01	2.21	1.44 – 3.41	0.01
Metropolitan	1.21	0.99 – 1.49	0.32	1.51	1.22 – 1.87	0.17
Hispanic						
Urban/rural	1.05	0.49 – 2.24	0.89	1.42	0.65 – 3.07	0.78
Metropolitan	0.76	0.58 – 0.99	0.004	0.97	0.73 – 1.28	0.02
NHW						
Urban/rural	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Metropolitan	1.00	0.88 – 1.14	0.27	1.06	0.92 – 1.22	0.02

The multivariable logistic regression for the 30-day unplanned readmission after discharge outcome was adjusted for year of diagnosis, sex, insurance, distance to treatment facility, facility region, facility volume, and comorbidity status.

The multivariable logistic regression for the 30-day all-cause mortality outcome after definitive surgery was adjusted for age, sex, insurance, facility volume, and comorbidity status.

The multivariable logistic regression for the 90-day all-cause mortality outcome after definitive surgery was adjusted for age, sex, insurance, facility region, facility volume, comorbidity status, and clinical stage.

Figures

Figure 1—Study Flow Diagram