

Rectal cancer in young patients: incidence and outcome disparities

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Background: There is an alarming rise in incidence among young patients with rectal cancer. The National Cancer Database (NCDB) and Surveillance, Epidemiology, and End Results Analysis (SEER) databases may help identify population level disparities in incidence and cancer-related outcomes.

Methods: A total of 197,178 patients within the SEER 18 registry and 221,886 patients from the NCDB database with rectal cancer were evaluated in this retrospective cohort study. The analyzed cohort consisted of young (<50), white or African American patients. Indication bias was mitigated by conducting inverse probability of treatment weighted analysis using binary logistic regression modeling to determine propensity score for being white or African American.

Results: A total of 6,144 young patients were identified from the SEER 18 registry and a total of 17,819 young patients were identified from the NCDB. From 1990 to 2016, there was a significant change in rectal cancer incidence, with a steadily increasing APC of 3.06 (P<0.05). The was no overall change in age-adjusted APC among young African American patients (APC 0.00, P=1); however, there was a significant increase among young white patients (APC 2.97, P<0.05). There was an increased incidence for both stage III and IV among young rectal cancer patients, with an age-adjusted APC of 5.35 and 3.83, respectively (P<0.05). After propensity score matching and inverse probability of treatment weighting, young African Americans had worse overall survival in both the NCDB and SEER (HR 1.1–1.3, P<0.05) databases. This disparity was also seen for cancer-specific survival (HR 1.5, P=0.002).

Conclusions: The current study adds to the growing body of literature demonstrating an alarming increase in incidence of rectal cancer among young patients. Moreover, the incidence appears to be increasing particularly among young white patients and driven by stage III disease.

Keywords: Rectal neoplasms; chemoradiotherapy; chemotherapy; adjuvant; propensity score; cohort studies

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Introduction

Excluding skin cancer, colorectal cancer (CRC) is the third most frequent cancer in the United States, with an estimated incidence of 140,250 patients in 2018, with an estimated 43,030 cases being rectal cancers (1). Moreover, CRC is the third most common cause of mortality among both

sexes. However, the incidence of CRC has been steadily decreasing, largely related to colorectal screening. Gilbertsen *et al.* reported in 1978 that annual proctosigmoidoscopic examination and polyp removal prevented 95% of anticipated rectal cancer and, of the cancers that were identified, 80% were minimally invasive with submucosal involvement only (2). Subsequently, the National Polyp

Study Workgroup published a reduction in incidence of CRC with colonoscopic polypectomy (3). Consequently, with implementation of screening colonoscopy in 1997, rectal cancer incidence has decreased overall. However, in recent studies, it has been shown that the incidence of CRC has increased among patients younger than 50 and decreasing among older patients (4). Per the National Cancer Institute (NCI), the number of young-onset (<50 years old) CRC cases have increased by about 51% since 1994 (5) Patients born around 1990 have quadruple the risk of rectal cancer compared to those born in 1950, with an incidence rate ratio of 4.3 (95% CI: 2.2–8.5) (4).

Furthermore, younger patients diagnosed with CRC tend to present with hematochezia, obstruction, and abdominal discomfort (6), and may have a 1.4 fold delay in time to diagnosis, compared to older patients (7). Additionally, younger patients with colon cancer tend to have more aggressive pathological features, including: lymphovascular invasion, T3/T4 tumors, lymph node metastases and stage III disease (8), hence they are more often diagnosed with advanced disease (9).

Until recently, CRC screening was recommended to start at the age of 50 (10,11). However, given the concerning rise in incidence of CRC among young adults, the American Cancer Society (ACS) recently updated their recommendations to start screening patients at 45 years old for individuals with average risk (12). The purpose of this study is to further investigate disparate incidence trends among young rectal cancer patients using the Surveillance, Epidemiology, and End Results Analysis (SEER) database and then evaluate survival outcomes using both the SEER and National Cancer Database (NCDB) databases. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi. org/10.21037/jgo-20-197).

Methods

Data source

The NCDB is a database that records cancer data from >1,500 Commission on Cancer (COC)-accredited facilities nationwide. The database encompasses >70% of newly diagnosed cancer cases and reports a number of clinical parameters, including: demographics, staging, course of treatment and overall survival (OS).

In contrast, the SEER Program collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 34% of the US population. The SEER 9 (1975 to 2016) and SEER 18 (2000 to 2016) registries were used for incidence and

annual percent change (APC) calculations. The specialized Radiation/Chemotherapy Database (SEER 18 Custom Data, November 2017 Submission) was used for clinical outcomes analysis (13).

Cobort analyzed

The selected cohort consisted of young (<50), white or African American patients with International Classification of Disease for Oncology, 3rd Edition (ICD-O-3/WHO 2008) diagnosis of 'Rectum' cancer. Patients with missing or <3 months of follow-up, multiple cancers and nonmalignant pathology were excluded (*Figure 1*).

Incidence analysis

Age-adjustment was performed using the 2000 U.S. Standard Population. APC was calculated and heteroscedasticity accounted for using weighted least squares regression (14). Modified gamma and F intervals for confidence interval estimation was performed using the Tiwari modification (15) in SEER*Stat [Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/ seerstat) version 8.3.5]. In order to better fit the APC trends over time, Joinpoint regression modeling was performed with log-linear transformation and final model selection via Monte Carlo Permutation method (16) (Joinpoint Regression Program, Version 4.6.0.0. April, 2018; Statistical Research and Applications Branch, National Cancer Institute). If the number of incident cases were low, a 0 joinpoint curve was selected. Percent changes were calculated using 1-year for each endpoint.

Outcomes analysis

Patient characteristics were evaluated before and after matching by using a combination of Chi square analysis and standard mean difference (SMD), with a SMD >0.1 determined to be imbalanced (17). Univariate analysis (UVA) of clinical parameters effect on OS was performed using the Kaplan-Meier (KM) method, with the log rank method to assess for significance (18). Statistical significance was accepted at P<0.05 and 2-sided tests were used for all analyses. The following clinical parameters were evaluated: age, facility type, insurance, income, percent with no



Figure 1 CONSORT diagram demonstrating the inclusion and exclusion criteria used to select young rectal cancer patients using SEER 18 (A) and NCDB (B).

high school diploma, population density, Charlson/Deyo Comorbid Conditions (NCDB only), marital status (SEER only), percent under poverty level (SEER only) sex, year of diagnosis, grade, stage, circumferential margin status, chemotherapy, radiation therapy, and surgery.

Multivariable analysis (MVA) of clinical parameters and OS was performed using Cox proportional hazards regression modeling. For SEER 18 patients, cancer-specific survival (CSS) was also determined. Covariates included in the final MVA model were selected via backward elimination, excluding covariates with P>0.1.

In order to reduce indication bias, binary logistic regression was used to calculate propensity scores (PS) for being white or African American (19). Subsequently, inverse probability of treatment weights (IPTW) were calculated as 1/PS and 1/(1-PS) (20). Finally, IPTW-adjusted UVA KM and doubly robust MVA cox proportional hazards regression modeling was performed (21-23). Subgroup analyses were assessed for heterogeneity using I2. Cases with incomplete/ missing data were excluded.

Statistical analysis

All statistics were completed using SEER*Stat (v8.3.5, The Surveillance Research Program of the Division of Cancer Control and Population Sciences, National Cancer Institute), Joinpoint Regression Program (v4.7.0.0, Statistical Research and Applications Branch, National Cancer Institute), SPSS (v24, IBM), RStudio (v1.2.1335). The following R packages were used: survminer, survival, ggplot2, tableone, ipw, IPWsurvival, and olsrr. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The SEER and NCDB registries provide de-identified data. Consequently, this study does not require Institutional Review Board (IRB) review or approval. R markdown and data for all analyses are available upon request.

Results

Patient characteristics

A total of 6,144 young (<50 years old), white or African American patients from 2004 to 2012 were identified from the SEER 18 registry with an ICD-O-3 site code of C209, corresponding to rectal cancer (Figure 1A) and a total of 17,819 young white or African American patients from 2004 to 2012 were identified from the NCDB (Figure 1B). The median follow-up for the NCDB and SEER cohorts were 44 months (range, 3–130.5 months) for and 58 months (range, 3–143 months), respectively. Patient characteristics for both cohorts are shown in Table 1 (unadjusted and adjusted characteristics or the NCDB and SEER cohorts, stratified by race, can be found in Tables S1,S2, respectively). The median age at diagnosis was 44 for both cohorts, and the majority of patients were white in the NCDB (87.6%) and SEER (88.5%) cohorts. There was a male predominance in both NCDB and SEER, 56.9% and 58.1%, respectively. Similarly, most patients were diagnosed with Stage III rectal cancer in the NCDB (32.6%) and SEER (35.2%) cohorts.

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 Table 1 Baseline characteristics of the NCDB (N=17,819) SEER (n=6,144) patients

Characteristics	Values	Characteristics
NCDB characteristics (N=17,819)		Percent no HS degree
Age (years), median (range)	44 (18 to 49)	≥21%
Sex		13–20.9%
Male	10,132 (56.9)	7–12.9%
Female	7,687 (43.1)	<7%
Race		Urban status
White	15,602 (87.6)	Metro
African American	2,217 (12.4)	Urban (20,000+)
Year of diagnosis		Urban (2,500–19,999)
2004–2008	9,265 [52]	Rural
2009–2012	8,554 [48]	Unknown
Charlson/Deyo Score		Stage
0	16,083 (90.3)	I
1	1,479 (8.3)	Ш
2+	257 (1.4)	III
Primary payer		IV
Not insured	1,400 (7.9)	Grade
Private	13,034 (73.1)	I
Medicaid	2,066 (11.6)	Ш
Medicare	710 [4]	Ш
Other government	237 (1.3)	IV
Unknown	372 (2.1)	Unknown
Facility type		CRM margin status
Community	1,328 (7.5)	0–1 mm
Comprehensive	5,982 (33.6)	1.1–2 mm
Academic	5,225 (29.3)	2.1–5 mm
Integrated	985 (5.5)	5.1–10 mm
Other	4,299 (24.1)	>10 mm
Median income		Negative CRM
<\$38,000	3,202 [18]	No resection
\$38,000-\$47,999	4,249 (23.8)	Unknown
\$48,000-\$62,999	4,797 (26.9)	Surgery
\$63,000+	5,562 (31.2)	No surgery
Unknown	9 (0.1)	Excision

Table 1 (continued)

Table 1 (continued)

Table 1 (continued)

Values

3,323 (18.6) 4,796 (26.9) 5,651 (31.7) 4,049 (22.7)

14,577 (81.8)

1,057 (5.9)

1,526 (8.6) 328 (1.8) 331 (1.9)

4,952 (27.8) 3,664 (20.6) 5,812 (32.6) 3,391 [19]

1,569 (8.8) 10,616 (59.6) 2,524 (14.2) 198 (1.1) 2,912 (16.3)

> 744 (4.2) 230 (1.3) 253 (1.4) 119 (0.7) 199 (1.1)

2,362 (13.3) 1,396 (7.8) 12,516 (70.2)

3,081 (17.3) 1,683 (9.4) 884

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Characteristics Values Characteristics Values Partial proctectomy 8,109 (45.) \$25,000-\$40,000 1,467 (23.9) Colonal anastomosis 1,043 (5.9) \$40,001-\$60,000 3,754 (61.1) Total proctectomy 3,031 (17) \$60,000 787 (12.8) Pelvic exenteration 409 (2.3) Percent no HS degree 2,248 (38.2) Chemotherapy given 13-20.9% 2,283 (46.4) No 3,686 (20.7) 7-12.9% 2,283 (46.4) No 3,686 (20.7) 7-12.9% 2,283 (46.4) Unknown 264 (1.5) Percent below poverty 20 (0.3) Unknown 264 (1.5) Percent below poverty 1,242 (28.4) Overall survival 5.873 (33] 15-25% 1,940 (31.6) Vers 1.0-14.9% 1,742 (28.4) 2,928 (37.3) Overall survival 2.873 (13.1) 10-14.9% 2,928 (37.3) Alive 12,784 (71.7) Maritel status 3,956 (58.5) SEER characteristics (N=6,144) Divocred 66 (8.9) Sea	Table 1 (continued)		Table 1 (continued)				
Partial proctectomy 8,109 (45.5) \$25,000-\$40,000 1,467 (23.9) Coloanal anastomosis 1,043 (5.9) \$40,001-\$60,000 3,754 (61.1) Total proctectomy 3,031 [17] \$60,000 767 (23.9) Palvic exentration 409 (2.3) Percent no HS degree 2,348 (38.2) Surgery, NOS 463 (2.6) 221% 2,353 (46.4) No 3,686 (20.7) 7-12.9% 233 [15] Yes 13,269 (77.8) <7% 203 [15] Yes 13,869 (77.8) <7% 228 [15] No 5,873 [33] 15-25% 173 (2.8) No 5,873 [33] 15-25% 1,440 (31.6) Yes 11,946 [67] 10-14.9% 1,742 (28.4) Overall survival 12,784 (71.7) Marital status 1582 [68.5] SEER characteristics (N=6,144) Separated 99 (1.6) 3589 [68.5] SEER characteristics (N=6,144) 140 [10 49] Divorced 668 (9.9) Ale 3,567 (58.1) Unknown 258 [68.5] Fernale 2	Characteristics	Values	Characteristics	Values			
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Total proctectomy 3,031 [17] >\$60,000 787 (12.8) Pelvic exenteration 409 (2.3) Percent no HS degree 2,348 (38.2) Surger, NOS 436 (2.6) ≥21% 2,348 (38.2) Chemotherapy given 13-20.9% 283 (46.4) No 3.686 (20.7) 7-12.9% 923 [15] Yes 13,869 (7.8) <7%	Coloanal anastomosis	1,043 (5.9)	\$40,001-\$60,000	3,754 (61.1)			
Pelvic exenteration 409 (2.3) Percent no HS degree Surgery, NOS 463 (2.6) \approx 21% 2,348 (38.2) Chemotherapy given 13-20.9% 2,853 (46.4) No 3,686 (20.7) 7-12.9% 923 [15] Yes 13,669 (77.8) <7%	Total proctectomy	3,031 [17]	>\$60,000	787 (12.8)			
Surgery, NOS 463 (2.6) $\simeq 21\%$ 2.348 (38.2) Chemotherapy given 13-20.9% 2,853 (46.4) No 3.686 (20.7) 7-12.9% 923 [15] Yes 13,869 (77.8) <7%	Pelvic exenteration	409 (2.3)	Percent no HS degree				
Chemotherapy given 13-20.9% 2,853 (46.4) No 3,686 (20.7) 7-12.9% 923 [15] Yes 13,869 (77.8) $<7\%$ 20 (0.3) Unknown 264 (1.5) Percent below poverty 20 (3.1) Radiation given $>25\%$ 173 (2.8) No 5,873 [33] 15-25% 1,940 (31.6) Overall survival $<109\%$ 228 (37.3) Alive 12,784 (71.7) Marital status Dead 5,035 (28.3) Single 1,548 (25.2) Follow-up (months), median (range) 44 (3 to 130.5) Married 3,596 (58.5) SEER characteristics (N-6,144) Separated 99 (1.6) Age (years), median (range) 44 (16 to 49) Divorced 608 (9.9) Sex Widowed 35 (3.6) 1 1,445 (23.5) Male 3,567 (58.1) Unknown 2,161 (35.2) Year of diagnosis I 1,445 (23.5) 1,445 (23.5) Year of diagnosis I 1,445 (23.5) 1,445 (23.5) Primary payer <td>Surgery, NOS</td> <td>463 (2.6)</td> <td>≥21%</td> <td>2,348 (38.2)</td>	Surgery, NOS	463 (2.6)	≥21%	2,348 (38.2)			
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Unknown 264 (1.5) Percent below poverty Radiation given >25% 173 (2.8) No 5,873 [33] 15–25% 1,940 (31.6) Yes 11,946 [67] 10–14.9% 1,742 (28.4) Overall survival <10%	Yes	13,869 (77.8)	<7%	20 (0.3)			
Radiation given >25% 173 (2.8) No 5,873 (33) 15-25% 1,940 (31.6) Yes 11,946 (67) 10-14.9% 1,742 (28.4) Overall survival <10%	Unknown	264 (1.5)	Percent below poverty				
No 5,873 [33] 15-25% 1,940 [31.6] Yes 11,946 [67] 10-14.9% 1,742 (28.4) Overall survival <10%	Radiation given		>25%	173 (2.8)			
Yes 11,946 [67] 10-14.9% 1,742 (28.4) Overall survival <10%	No	5,873 [33]	15–25%	1,940 (31.6)			
Overall survival <10% 2,289 (37.3) Alive 12,784 (71.7) Marital status Dead 5,035 (28.3) Single 1,548 (25.2) Follow-up (months), median (range) 44 (3 to 130.5) Marriad 3,596 (58.3) SEER characteristics (N=6,144) Separated 99 (1.6) Age (years), median (range) 44 (16 to 49) Divorced 608 (9.9) Sex Widowed 58 (0.9) 58 (0.9) Male 3,567 (58.1) Unknown 235 (3.8) Female 2,577 (41.9) Stage 1445 (23.5) Mite 5,437 (88.5) II 1,445 (23.5) Vhite 5,437 (88.5) II 1,445 (23.5) Quot-2008 3,281 (53.4) Grade 200 2004-2008 3,281 (53.4) Grade 33 (66.2) Primary payer II 3,866 (62.9) 348 (7.3) Insured 3,33 (5.1) III 3,866 (62.9) Not insured 3,231 (52.6) N 94 (1.5) Medicaid 638 (10	Yes	11,946 [67]	10–14.9%	1,742 (28.4)			
Alive 12,784 (71.7) Marital status Dead 5,035 (28.3) Single 1,548 (25.2) Follow-up (months), median (range) 44 (3 to 130.5) Married 3,596 (58.5) SEER characteristics (N=6,144) Separated 99 (1.6) Age (years), median (range) 44 (16 to 49) Divorced 608 (9.9) Sex Widowed 58 (0.9) 58 (0.9) Male 3,567 (58.1) Unknown 235 (3.8) Female 2,577 (41.9) Stage 1445 (23.5) Race I 1,448 (73.5) 1,448 (73.5) White 5,437 (88.5) II 1,448 (73.2) Year of diagnosis 707 (11.5) III 2,161 (35.2) Q004-2008 3,281 (53.4) Grade 3806 (62.9) Primary payer II 3,866 (62.9) 1,992 (51.9) Not insured 313 (5.1) III 3866 (62.9) Insurance 3,231 (52.6) NV 94 (1.5) Medicaid 638 (10.4) Unknown 761 (12.4)	Overall survival		<10%	2,289 (37.3)			
Dead 5,035 (28.3) Single 1,548 (25.2) Follow-up (months), median (range) 44 (3 to 130.5) Married 3,596 (58.5) SEER characteristics (N=6,144) Separated 99 (1.6) Age (years), median (range) 44 (16 to 49) Divorced 608 (9.9) Sex Widowed 58 (0.9) 58 (0.9) Male 3,567 (58.1) Unknown 235 (3.8) Female 2,577 (41.9) Stage 1,445 (23.5) Mite 5,437 (88.5) II 1,445 (23.5) White 5,437 (88.5) III 2,161 (35.2) Year of diagnosis 707 (11.5) III 2,161 (35.2) 2004-2008 3,281 (53.4) Grade 3,306 (62.9) Primary payer II 3,866 (62.9) 3,866 (62.9) Not insured 313 (5.1) III 3,866 (62.9) Insurance 3,231 (52.6) N 94 (1.5) Medicaid 638 (10.4) Unknown 761 (12.4) Unknown 1,962 (31.9) CRM margin status 761 (1	Alive	12,784 (71.7)	Marital status				
Follow-up (months), median (range) 44 (3 to 130.5) Married 3,596 (58.5) SEER characteristics (N=6,144) Separated 99 (1.6) Age (years), median (range) 44 (16 to 49) Divorced 608 (9.9) Sex Widowed 58 (0.9) Male 3,567 (58.1) Unknown 235 (3.8) Female 2,577 (41.9) Stage 1 Race I 1,445 (23.5) White 5,437 (88.5) II 1,148 (18.7) African American 707 (11.5) III 2,161 (35.2) Year of diagnosis V 1,390 (22.6) 1 2009-2012 2,863 (46.6) I 448 (7.3) Primary payer II 3,866 (62.9) 3,866 (62.9) Not insured 313 (5.1) III 975 (15.9) Insurance 3,231 (52.6) IV 94 (1.5) Medicaid 638 (10.4) Unknown 761 (12.4) Unknown 1,962 (31.9) CFM margin status 761 (12.4) Median income 0-1 mm <td>Dead</td> <td>5,035 (28.3)</td> <td>Single</td> <td>1,548 (25.2)</td>	Dead	5,035 (28.3)	Single	1,548 (25.2)			
SEER characteristics (N=6, 144) Separated 99 (1.6) Age (years), median (range) 44 (16 to 49) Divorced 608 (9.9) Sex Widowed 58 (0.9) Male 3,567 (58.1) Unknown 235 (3.8) Female 2,577 (41.9) Stage 1,445 (23.5) Race I 1,445 (23.5) 1,148 (18.7) Mite 5,437 (88.5) II 2,161 (35.2) Year of diagnosis 707 (11.5) III 2,161 (35.2) 2004-2008 3,281 (53.4) Grade 448 (7.3) Primary payer I 3,866 (62.9) 3,866 (62.9) Not insured 313 (5.1) III 975 (15.9) Insurance 3,231 (52.6) IV 94 (1.5) Medicai in come 3(3 (1.0.4) Unknown 761 (12.4) Unknown 1,962 (31.9) CRM margin status 761 (12.4) Medicai income 0-1 mm 226 (3.7) 64 [1]	Follow-up (months), median (range)	44 (3 to 130.5)	Married	3,596 (58.5)			
Age (years), median (range) 44 (16 to 49) Divorced 608 (9.) Sex Widowed 58 (0.9) Male 3,567 (58.1) Unknown 235 (3.8) Female 2,577 (41.9) Stage 1 Race I 1,445 (23.5) 1 White 5,437 (88.5) II 1,148 (18.7) African American 707 (11.5) III 2,161 (35.2) Year of diagnosis IV 1,390 (22.6) 2004-2008 3,281 (53.4) Grade 2009-2012 2,863 (46.6) I 448 (7.3) Primary payer II 3,866 (62.9) 1 Not insured 313 (5.1) III 975 (15.9) Insurance 3,231 (52.6) IV 94 (1.5) Medicaid 638 (10.4) Unknown 761 (12.4) Unknown 1,962 (31.9) CRM margin status 226 (3.7) Median income 0-1 mm 226 (3.7) 64 [1]	SEER characteristics (N=6,144)		Separated	99 (1.6)			
Sex Widowed 58 (0.9) Male 3,567 (58.1) Unknown 235 (3.8) Female 2,577 (41.9) Stage 1,445 (23.5) Race I 1,445 (23.5) 1,448 (18.7) White 5,437 (88.5) II 1,148 (18.7) African American 707 (11.5) III 2,161 (35.2) Year of diagnosis IV 1,300 (22.6) 2004-2008 3,281 (53.4) Grade 2009-2012 2,863 (46.6) I 448 (7.3) Primary payer II 3,866 (62.9) 3,866 (62.9) Not insured 313 (5.1) III 975 (15.9) Insurance 3,231 (52.6) IV 94 (1.5) Medicaid 638 (10.4) Unknown 761 (12.4) Unknown 1,962 (31.9) CRM margin status 26 (3.7) Median income 0-1 mm 226 (3.7) 64 [1]	Age (years), median (range)	44 (16 to 49)	Divorced	608 (9.9)			
Male 3,567 (58.1) Unknown 235 (3.8) Female 2,577 (41.9) Stage 1,445 (23.5) Race I 1,445 (23.5) 1,448 (18.7) White 5,437 (88.5) II 1,148 (18.7) African American 707 (11.5) III 2,161 (35.2) Year of diagnosis IV 1,390 (22.6) 2004-2008 3,281 (53.4) Grade 2009-2012 2,863 (46.6) I 448 (7.3) Primary payer II 3,866 (62.9) Not insured 313 (5.1) III 975 (15.9) Insurance 3,231 (52.6) IV 94 (1.5) Medicaid 638 (10.4) Unknown 761 (12.4) Unknown 1,962 (31.9) CRM margin status 226 (3.7) Median income 0-1 mm 226 (3.7) <\$25,000	Sex		Widowed	58 (0.9)			
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Race I 1,445 (23.5) White 5,437 (88.5) II 1,148 (18.7) African American 707 (11.5) III 2,161 (35.2) Year of diagnosis IV 1,390 (22.6) 2004-2008 3,281 (53.4) Grade 2009-2012 2,863 (46.6) I 448 (7.3) Primary payer II 3,866 (62.9) Not insured 313 (5.1) III 975 (15.9) Insurance 3,231 (52.6) IV 94 (1.5) Medicaid 638 (10.4) Unknown 761 (12.4) Unknown 1,962 (31.9) CRM margin status 226 (3.7) Kedian income 0 136 (2.2) 1.1–2 mm 64 [1]	Female	2,577 (41.9)	Stage				
White 5,437 (88.5) II 1,148 (18.7) African American 707 (11.5) III 2,161 (35.2) Year of diagnosis IV 1,390 (22.6) 2004-2008 3,281 (53.4) Grade 2009-2012 2,863 (46.6) I 448 (7.3) Primary payer II 3,866 (62.9) Not insured 313 (5.1) III 975 (15.9) Insurance 3,231 (52.6) IV 94 (1.5) Medicaid 638 (10.4) Unknown 761 (12.4) Unknown 1,962 (31.9) CRM margin status 226 (3.7) Median income 0-1 mm 226 (3.7) 64 [1]	Race		I	1,445 (23.5)			
African American 707 (11.5) III 2,161 (35.2) Year of diagnosis IV 1,390 (22.6) 2004–2008 3,281 (53.4) Grade 2009–2012 2,863 (46.6) I 448 (7.3) Primary payer II 3,866 (62.9) Not insured 313 (5.1) III 975 (15.9) Insurance 3,231 (52.6) IV 94 (1.5) Medicaid 638 (10.4) Unknown 761 (12.4) Unknown 1,962 (31.9) CRM margin status 226 (3.7) Median income 0-1 mm 226 (3.7) 64 [1]	White	5,437 (88.5)	Ш	1,148 (18.7)			
Year of diagnosis IV 1,390 (22.6) 2004–2008 3,281 (53.4) Grade 2009–2012 2,863 (46.6) I 448 (7.3) Primary payer II 3,866 (62.9) Not insured 313 (5.1) III 975 (15.9) Insurance 3,231 (52.6) IV 94 (1.5) Medicaid 638 (10.4) Unknown 761 (12.4) Unknown 1,962 (31.9) CRM margin status 226 (3.7) <	African American	707 (11.5)	Ш	2,161 (35.2)			
2004–2008 3,281 (53.4) Grade 2009–2012 2,863 (46.6) I 448 (7.3) Primary payer II 3,866 (62.9) Not insured 313 (5.1) III 975 (15.9) Insurance 3,231 (52.6) IV 94 (1.5) Medicaid 638 (10.4) Unknown 761 (12.4) Unknown 1,962 (31.9) CRM margin status 226 (3.7) 436 (2.2) 1.1–2 mm 64 [1]	Year of diagnosis		IV	1,390 (22.6)			
2009–2012 2,863 (46.6) I 448 (7.3) Primary payer II 3,866 (62.9) Not insured 313 (5.1) III 975 (15.9) Insurance 3,231 (52.6) IV 94 (1.5) Medicaid 638 (10.4) Unknown 761 (12.4) Unknown 1,962 (31.9) CRM margin status 226 (3.7) <	2004–2008	3,281 (53.4)	Grade				
Primary payer II 3,866 (62.9) Not insured 313 (5.1) III 975 (15.9) Insurance 3,231 (52.6) IV 94 (1.5) Medicaid 638 (10.4) Unknown 761 (12.4) Unknown 1,962 (31.9) CRM margin status 226 (3.7) Median income 0–1 mm 226 (3.7) <\$25,000	2009–2012	2,863 (46.6)	1	448 (7.3)			
Not insured 313 (5.1) III 975 (15.9) Insurance 3,231 (52.6) IV 94 (1.5) Medicaid 638 (10.4) Unknown 761 (12.4) Unknown 1,962 (31.9) CRM margin status 226 (3.7) Median income 0–1 mm 226 (3.7) <\$25,000	Primary payer		Ш	3,866 (62.9)			
Insurance 3,231 (52.6) IV 94 (1.5) Medicaid 638 (10.4) Unknown 761 (12.4) Unknown 1,962 (31.9) CRM margin status 226 (3.7) Median income 0–1 mm 226 (3.7) <\$25,000	Not insured	313 (5.1)	Ш	975 (15.9)			
Medicaid 638 (10.4) Unknown 761 (12.4) Unknown 1,962 (31.9) CRM margin status Median income 0–1 mm 226 (3.7) <\$25,000	Insurance	3,231 (52.6)	IV	94 (1.5)			
Unknown 1,962 (31.9) CRM margin status Median income 0–1 mm 226 (3.7) <\$25,000	Medicaid	638 (10.4)	Unknown	761 (12.4)			
Median income 0–1 mm 226 (3.7) <\$25,000	Unknown	1,962 (31.9)	CRM margin status				
<\$25,000 136 (2.2) 1.1–2 mm 64 [1]	Median income		0–1 mm	226 (3.7)			
	<\$25,000	136 (2.2)	1.1–2 mm	64 [1]			

Table 1 (continued)

Table 1 (continued)

Table 1 (continued)

Characteristics	Values
2.1–5 mm	75 (1.2)
5.1–10 mm	48 (0.8)
>10 mm	100 (1.6)
Negative CRM	657 (10.7)
No resection	564 (9.2)
Unknown	4,410 (71.8)
Surgery	
No surgery	1,136 (18.5)
Excision	460 (7.5)
Partial proctectomy	3,070 [50]
Coloanal anastomosis	230 (3.7)
Total proctectomy	1,047 [17]
Pelvic exenteration	123 [2]
Surgery, NOS	78 (1.3)
Chemotherapy given	
No/unknown	1,294 (21.1)
Yes	4,850 (78.9)
Radiation given	
No	1,947 (31.7)
Yes	4,197 (68.3)
Overall survival	
Alive	3,861 (62.8)
Dead	2,283 (37.2)
Follow-up (months), median (range)	58 (3 to 143)

The data are represented by n (%) or median (range).

Rectal cancer incidence

Analysis of the SEER 9 registries revealed that the incidence of rectal cancer among young patients did not change significantly from 1975 to 1990, with an age-adjusted APC of -0.67 (P=0.3). However, from 1990 to 2016, there was a significant change in rectal cancer incidence, with a steadily increasing APC of 3.06 (*Figure 2A*, P<0.05). Similarly, analysis of the SEER 18 registries confirmed a significant increase from 2004 to 2015 in rectal cancer incidence among young patients with an APC of 2.58 (*Figure 2B*, P<0.05). Interestingly, there was no overall change in ageadjusted APC among young African American patients (APC 0.00, P=1); however, there was a significant increase among young white patients (*Figure 2C*, APC 2.97, P<0.05). As depicted in *Figure 2D*, there was an overall reduction in stage I disease (APC -1.96, P<0.05) and stable incidence of stage II disease (APC 1.26, P=0.1). Additionally, there was an overall increase for both stage III and IV among young rectal cancer patients, with an age-adjusted APC of 5.35 and 3.83, respectively (P<0.05). After stratifying by race there remained an increase in age-adjusted incidence of stage III (APC 5.57, P<0.05) and IV (APC 4.66, P<0.05) rectal cancer among young white patients (*Figure S1A*) and also an overall increase in age-adjusted incidence of stage III cancer for 2010 to 2015 (APC 14.57, P<0.05) among young African American patients (*Figure S1B*).

Cobort characteristics and univariate analysis

The baseline characteristics among young white and African American patients in the NCDB and SEER cohorts are depicted in *Tables S2,S3*, respectively. After PS matching and IPTW-adjustment, baseline factors were comparable between both databases.

The impact of patient, tumor and treatment characteristic on OS were assessed using IPTW-adjusted KM (*Table S3*). Prior to PS-matching and IPTW-adjustment, the following covariates significantly impacted OS in the NCDB cohort: age, sex, race, CDCC, insurance status, facility type, median income, percent no HS degree, urban location, stage, grade, circumferential margin (CRM) status, type of surgery, chemotherapy and radiation therapy. Within the SEER cohort: age, sex, race, insurance, income, percent no HS degree, marital status, stage, grade, CRM status, type of surgery, chemotherapy and radiation therapy had an impact on OS.

Multivariable analysis

A complete summary of the doubly robust IPTW-adjusted MVA analysis is shown in *Table 2*. Factors that were strongly protective in the NCDB cohort include: female sex (HR 0.82, 95% CI: 0.78–0.87, P<0.001), private insurance (HR 0.73, 95% CI: 0.66–0.8, P<0.001), negative CRM (HR 0.54, 95% CI: 0.44–0.66, P<0.001), any surgery, and radiation therapy (HR 0.87, 95% CI: 0.81–0.94, P<0.001). Factors strongly associated with worse OS in the NCDB cohort: African American race (HR 1.17, 95% CI: 1.1–1.3, P<0.001), CDCC 2+ (HR 1.5, 95% CI: 1.2–1.8, P<0.001),

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Figure 2 Age-adjusted annual percent change of incidence among young (<50) rectal cancer patients using the SEER 9 (A) and SEER 18 (B) registries. Age-adjusted annual percent change of incidence among young rectal cancer patients using the SEER 18 registry, stratified by race (C) and stage at diagnosis (D).

stage III (HR 3.6, 95% CI: 3.2–4.1, P<0.001) and stage IV (HR 12.7, 95% CI: 11.2–14.5, P<0.001).

Covariates that were strongly protective in the SEER cohort include: female sex (HR 0.87, 95% CI: 0.8–0.95, P<0.001), married status (HR 0.72, 95% CI: 0.65–0.79, P<0.001), negative CRM (HR 0.44, 95% CI: 0.32–0.6, P<0.001). Moreover, factors strongly associated with worse OS include: African American race (HR 1.4, 95% CI: 1.2–1.6, P<0.001), stage III (HR 2.7, 95% CI: 2.2–3.2, P<0.001) and stage IV (HR 9.6, 95% CI: 8–11.5, P<0.001).

Overall survival

After propensity score matching, the 5- and 10-year OS for the entire NCDB cohort was 69.4% and 56.4%,

respectively. For the entire SEER cohort, the 5- and 10year OS was 65.6% and 56.3%, respectively. Young African American rectal cancer patients had worse overall survival in both the NCDB (HR 1.1, 95% CI: 1.1–1.2, P=0.01) and SEER (HR 1.3, 95% CI: 1.1–1.4, P=0.002) databases. However, after stratifying by stage at diagnosis, only stage III patients were found to have an overall survival disparity between whites and African Americans (*Figure 3*). Within the NCDB stage III cohort, the median overall survival for whites was not reached compared to 120 months among African American patients (HR 1.4, 95% CI: 1.3–1.7, P<0.001). Similarly, within the SEER stage III cohort, the median overall survival was not reached compared to 96 months among African American patients (HR 1.6, 95% CI: 1.3–2, P<0.001).

Table 2 Factors associated with survival on doubly robust, propensity score matched, and inverse probability of treatment V

Table 2 ((continued)
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Ρ

0.787

0.005

< 0.001

0.665

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< 0.001

< 0.001

< 0.001

_ 0.560

< 0.001

< 0.001

0.235

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0.085

0.119

0.003

0.177 < 0.001

0.015

0.002

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< 0.001

< 0.001

< 0.001

< 0.001

< 0.001

< 0.001

weighted multivariable analysis			Adjusted			
Multiuniahla analusia	Adjusted	Ŀ	Multivariable analysis	HR (95% CI)		
Multivariable analysis	HR (95% CI)	Р	\$38,000-\$47,999	1.01 (0.93–1.1)		
NCDB: multivariable analysis			\$48,000-\$62,999	0.89 (0.82–0.96)		
Age, years			\$63,000+	0.79 (0.72–0.86)		
<30	-	-	Unknown	1.24 (0.47–3.26)		
30–39	0.91 (0.79–1.04)	0.155	Stage			
40–44	0.85 (0.26–2.8)	0.794	I	-		
45+	0.81 (0.25–2.65)	0.723	II	2.46 (2.14–2.82)		
Sex			III	3.64 (3.2–4.14)		
Male	-	-	IV	12.74 (11.18–14.52)		
Female	0.82 (0.78–0.87)	<0.001	Grade			
Race			I	-		
White	-	-	II	1.04 (0.92–1.17)		
African American	1.17 (1.08–1.27)	<0.001	III	1.81 (1.59–2.07)		
Year of diagnosis			IV	2.29 (1.81–2.9)		
2004–2008	-	-	Unknown	1.08 (0.95–1.24)		
2009–2012	0.98 (0.9–1.06)	0.613	CRM margin status			
Charlson/Deyo Score			0–1 mm	-		
0	-	-	1.1–2 mm	0.69 (0.45–1.05)		
1	1.11 (1–1.22)	0.042	2.1–5 mm	0.73 (0.49–1.08)		
2+	1.46 (1.2–1.78)	<0.001	5.1–10 mm	0.3 (0.14–0.66)		
Primary payer			>10 mm	0.73 (0.46–1.16)		
Not insured	-	-	Negative CRM	0.54 (0.44–0.66)		
Private	0.73 (0.66–0.8)	<0.001	No resection	0.79 (0.66–0.96)		
Medicaid	0.93 (0.83–1.03)	0.170	Unknown	0.76 (0.64–0.9)		
Medicare	1.39 (1.21–1.6)	<0.001	Surgery			
Other government	0.86 (0.66–1.11)	0.240	No surgery	_		
Unknown	0.67 (0.54–0.82)	<0.001	Excision	0.45 (0.38–0.53)		
Facility type			Partial proctectomy	0.42 (0.39–0.45)		
Community	-	-	Coloanal anastomosis	0.46 (0.4–0.54)		
Comprehensive	0.87 (0.78–0.97)	0.010	Total proctectomy	0.55 (0.5–0.61)		
Academic	0.78 (0.7–0.87)	<0.001	Pelvic exenteration	0.6 (0.51–0.72)		
Integrated	0.77 (0.66–0.9)	0.001	Surgery, NOS	0.54 (0.45–0.65)		
Other	0.79 (0.24–2.59)	0.701	Chemotherapy given			
Median income			No	-		
<\$38,000	-	_	Table 2 (continued)			

Table 2 (continued)

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Table 2 (continued)

Adjusted

Ρ

0.531

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< 0.001

0.345

0.001

0.187

0.001

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< 0.001

< 0.001

< 0.001

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0.722

< 0.001

< 0.001

0.036

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0.158

0.054

0.002

0.003

< 0.001

0.026

0.029

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< 0.001

< 0.001

< 0.001

< 0.001

HR (95% CI)

0.78 (0.35-1.72)

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0.72 (0.65-0.79)

0.86 (0.63-1.18)

0.77 (0.67-0.9)

1.26 (0.89-1.79)

0.65 (0.51-0.84)

-1.78 (1.45–2.18)

2.65 (2.2-3.19)

9.56 (7.96-11.47)

-1.03 (0.86–1.24)

1.77 (1.45-2.16)

2.58 (1.88-3.54)

1.25 (1.01-1.53)

-0.69 (0.41–1.16)

0.58 (0.33-1.01)

0.14 (0.04-0.48)

0.38 (0.2-0.72)

0.44 (0.32-0.6)

0.74 (0.56-0.96)

0.75 (0.59-0.97)

_

0.44 (0.35-0.56)

0.37 (0.33-0.42)

0.4 (0.3-0.52)

0.56 (0.48-0.65)

=			· /		
	Adjusted	1	Multivovice la sustanti		
Multivariable analysis	HR (95% Cl)	Р	wullivariable analysis		
Yes	0.99 (0.89–1.1)	0.836	<7%		
Unknown	0.92 (0.72–1.19)	0.543	Marital status		
Radiation given			Single		
No	-	-	Married		
Yes	0.87 (0.81–0.94)	<0.001	Separated		
SEER: multivariable analysis			Divorced		
Age			Widowed		
<30	-	-	Unknown		
30–39	0.92 (0.75–1.13)	0.438	Stage		
40–44	0.92 (0.75–1.12)	0.392	I		
45+	0.9 (0.74–1.09)	0.285	II		
Sex			Ш		
Male	-	-	IV		
Female	0.87 (0.8–0.95)	0.001	Grade		
Race			I		
White			II		
African American	1.37 (1.22–1.55)	<0.001	Ш		
Year of diagnosis			IV		
2004–2008	-	-	Unknown		
2009–2012	0.94 (0.82–1.07)	0.352	CRM margin status		
Primary payer			0–1 mm		
Not insured	-	-	1.1–2 mm		
Insurance	0.86 (0.71–1.03)	0.102	2.1–5 mm		
Medicaid	1.18 (0.96–1.44)	0.113	5.1–10 mm		
Unknown	0.95 (0.78–1.16)	0.615	>10 mm		
Median income			Negative CRM		
<\$25,000	-	-	No resection		
\$25,000-\$40,000	0.79 (0.6–1.03)	0.079	Unknown		
\$40,001-\$60,000	0.78 (0.6–1.02)	0.073	Surgery		
>\$60,000	0.71 (0.53–0.96)	0.028	No surgery		
Percent No HS degree			Excision		
≥21%	-	_	Partial proctectomy		
13–20.9%	0.92 (0.84–1.02)	0.103	Coloanal anastomosis		
7–12.9%	0.82 (0.71–0.95)	0.008	Total proctectomy		

Table 2 (continued)

Table 2 (continued)

Table 2 (continued)

Table 2 (continued)

Multiveriable analysis	Adjusted	
	HR (95% CI)	Р
Pelvic exenteration	0.7 (0.53–0.91)	0.009
Surgery, NOS	0.6 (0.41–0.87)	0.008
Chemotherapy given		
No	_	-
Yes	1.06 (0.91–1.23)	0.461
Radiation given		
No	-	-
Yes	0.89 (0.81–0.99)	0.035

Cancer-specific survival

For the SEER cohort, after propensity score matching, the 5- and 10-year CSS was 66.2% and 56.8% respectively. White race had improved CSS compared to African Americans before (HR 1.5, 95% CI: 1.4–1.7, P<0.001) and after propensity score matching (HR 1.2, 95% CI: 1.1–1.4, P=0.005). However, when stratified by stage at diagnosis, only stage III patients demonstrated a difference in CSS (HR 1.5, 95% CI: 1.2–1.9, P=0.002). The estimated 10-year CSS for stage III rectal cancer among whites compared to African Americans was 57.7% vs. 49.9% (P=0.002) respectively. There were no statistically significant differences between whites and African Americans in CSS among stage I, II, or IV patients (*Figure S2*).

Discussion

With over 20,000 young rectal cancer patients assessed, this is one of the largest, contemporary cohort analyses evaluating trends in incidence and outcome disparities over time. While the overall incidence of rectal cancer among young patients is rising, our analysis demonstrates that this is driven predominantly by young white patients, with an APC of approximately 3%. In addition, there appears to be a significant increase in stage III and IV rectal cancer among young white patients with APC of 5.4% and 3.8%, respectively, while there is significant increase in stage III rectal cancer among African Americans. Despite the disparity of increasing incidence of rectal cancer among young white patients, young African American patients have worse outcomes in both the NCDB and SEER databases. Moreover, we implemented robust statistical techniques with PS-matching and IPTW-adjustment to mitigate indication bias between white and African American patients. This revealed that young stage III rectal cancer patients have disparate outcomes in terms of OS for both NCDB/SEER cohorts as well as CSS for the SEER cohort. This combined data analysis further contributes to the growing body of literature that identifies increasing incidence of rectal cancer among young patients.

In addition to race and stage, there were a number of other patient and treatment characteristics that portended worse overall survival, many of which are possibly surrogates for overall socioeconomic status and performance status. Specifically, Medicare (which for the cohort analyzed would only be available to patients receiving social security disability insurance or who have end-stage renal disease or amyotrophic lateral sclerosis), CDCC index, and median income <\$48,000 were all associated with worse OS, even on IPTW-adjusted MVA. Moreover, patients that did not receive surgery and those with close/positive CRM margins (0–1 mm) had worse outcomes.

Recently, Virostko *et al.* published an NCDB analysis of trends in age of CRC from 2004–2015 (24). They noted younger patients were more likely to have stage III/IV disease compared to older patients (52% *vs.* 40%). Notably, this study is unable to capture true epidemiologic metrics as the NCDB does not collect population data. Crosbie *et al.* evaluated SEER and New Jersey State Cancer Registry and identified an increase in rectal cancer incidence among young patients in both cohorts (25). While both of these studies provide important insight into the trends and incidence of CRC among young patients, neither evaluated outcome disparities.

African Americans are reported to have increased incidence of CRC and worse OS compared to whites (26). Indeed, Rahman *et al.* reported on increased CRC incidence among young minorities and worse OS among African Americans compared to whites (5-year OS 56% *vs.* 66%, P<0.0001) (27). However, this study reported on raw survival outcomes and provided point-estimates at 1- and 5-year. Holowatyj published a SEER analysis comparing racial/ethnic survival disparities among young patients with CRC (28). They also identified an improvement in both OS and CSS among young white compared to African American patients. In contrast, Kolarich *et al.* analyzed the NCDB (2004 to 2014) and noted that African American young rectal cancer patients had worse OS on univariate analysis, but not on multivariable analysis (HR 1.1, 95%

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Figure 3 Overall survival for young rectal cancer patients, stratified by stage, in NCDB (A,C,E,G) and SEER 18 (B,D,F,H), after propensity score matching with inverse probability of treatment weighting.

CI: 0.8–1.5) (29). Nevertheless, covariate adjustment via Cox proportional hazards modeling yields HRs that are estimates of a conditional effect, and do not necessarily reflect marginal effects at the population level (30).

In contrast to the above SEER and NCDB analyses, the strength of the current study is the combined analysis of both databases and the ability to estimate marginal HR via propensity score matching and inverse probability of treatment weighting. Importantly, the incidence trends in the SEER 9 and SEER 18 registries were validated in the non-population based NCDB cohort. Furthermore, after adjusting for confounding factors, all baseline characteristics were similar among both cohorts, thus allowing for adjusted univariate and doubly robust multivariable analyses to further understand the impact of race on OS and CSS. These robust statistical analyses identified young African American patients to have worse OS (doubly robust HR 1.4, 95% CI: 1.2--1.6, P<0.001) compared to young white patients. These findings were further validated using the NCDB database, in which the doubly robust HR was 1.2 (95% CI: 1.1-1.3), P<0.001. Another strength of the current study is a focused analysis on rectal cancer as these tumors have very different treatment approaches and outcomes.

There are multiple hypotheses that attempt to explain the underlying force responsible for the striking increase in rectal cancer incidence among young patients. Recently, Liu et al. reported on the association of obesity and earlyonset CRC using The Nurses Health Study II. They found that for every 5-point increase in BMI, there was an associated 20% increase in CRC (31). Notably, obesity in the US has increased significantly from 1980 to 2000 and 2003 to 2004 (32). Indeed, a recent report of the National Health and Nutrition Examination Survey identified ageadjusted prevalence of obesity of 36.5% and 40.8% for men and women, respectively (33). Unfortunately, neither the NCDB or SEER databases record information on height, weight, or BMI. Metabolic syndrome and insulin resistance, both of which are highly correlated with obesity, also seem to be associated with an increase in CRC incidence (34). Likewise, poor nutrition (35) and a sedentary lifestyle (36) have also been associated with increased incidence of CRC. Recently, Willauer et al. showed that the molecular background of tumors are different in adults vs. young patients (37). Moreover, tumors were molecularly distinct among subsets of young adults.

SEER and NCDB data have a tremendous quality control mechanism. Nevertheless, the data are dependent on precise coding as well as reporting, and are at risk for reporting bias. Furthermore, despite attempts to control for confounding variables, there are likely multiple unmeasured and unknown confounders that cannot be adequately controlled for. For instance, family history of cancer, BMI, diet, genetics and comorbid medical conditions are not recorded and, therefore, cannot be used to adjust for confounding. As reported, age-adjusted obesity is more prevalent among African Americans compared to whites for all ages (48% *vs.* 37%), 20–39 years old (43% *vs.* 32%), 40–59 years old (54% *vs.* 41%), and 60+ years old (47% *vs.* 40%) (33). Nevertheless, this study is one of the largest studies to date, and to our knowledge, the only combined SEER/NCDB cohort analysis demonstrating consistent outcomes in both databases.

Conclusions

The current study adds to the growing body of literature demonstrating an alarming increase in incidence of rectal cancer among young patients. Moreover, the incidence appears to be increasing particularly among young white patients and driven by stage III disease. After controlling for confounding variables, we identified outcome disparities among young African American patients with stage III rectal cancer, compared to matched white patients. The etiology of this disparity remains to be characterized but may relate to observed trends in nutrition and obesity however other risk factors can play a role. Further research into the link between obesity and rectal cancer is greatly needed and may further inform a risk-adapted screening program.

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Footnote

Reporting Checklist: The authors present the study in accordance with the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/jgo-20-197

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi. org/10.21037/jgo-20-197). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

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to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The SEER/NCDB registries provide deidentified data. Consequently, this study does not require Institutional Review Board (IRB) review or approval.

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Supplementary



Figure S1 Age-adjusted annual percent change of incidence in young rectal cancer using the SEER 18 registry for white (A) and African American (B) patients, stratified by stage at diagnosis.



Figure S2 Cancer-specific survival for young rectal cancer patients in SEER 18, stratified by stage I (A), II (B), III (C), and IV (D) after propensity score matching with inverse probability of treatment weighting.

		NCD	B baseline o	haracteri	stics			NCDB b	aseline cha	aracteristic	cs IPTW	
Characteristics	White (N=	=15.608)	African A	merican			White (N:	=15.617)	African A	merican		
onalaotonotios		_10,000/	(N=2,	218)	_ P	SMD			(N=2,	189)	P	SMD
	Count	%	Count	%			Count	(%)	Count	(%)		
Age, years					0.88						0.08	
<30	714	4.6	109	4.9		0.016	721	4.6	95	4.4		0.012
30–39	3,032	19.4	427	19.3		0.004	3,036	19.4	470	21.5		0.051
40-44	4,135	26.5	578	26.1		0.01	4,133	26.5	591	27		0.012
45+	7.721	49.5	1.103	49.8		0.005	7.721	49.5	1.030	47.1		0.047
Sov	,,,,,	1010	1,100	10.0	0.00	0.000	.,	10.0	1,000		0.78	0.011
Sex		FT 4	1 00 1	0	0.09	0.000	0.000	50.0	4 005	50 5	0.78	0.000
Male	8,908	57.1	1,224	55.2		0.038	8,869	56.8	1,235	56.5		0.006
Female	6,694	42.9	993	44.8		0.038	6,742	43.2	951	43.5		0.006
Year of diagnosis					0.09						0.52	
2004–2008	8,150	52.2	1,115	50.3		0.039	8,122	52	1,154	52.8		0.015
2009–2012	7,452	47.8	1,102	49.7		0.039	7,489	48	1,033	47.2		0.015
Charlson/Deyo Score					<0.001						0.68	
0	14,147	90.7	1,936	87.3		0.107	14,080	90.2	1,960	89.6		0.019
1	1 255	8	224	10.1		0 072	1.305	84	192	8.8		0.015
0.	000	1.0	<i>22</i> 7	0.0		0.072	0.00	1.4	05	1.6		0.010
2+	200	1.3	57	2.0		0.094	220	1.4	35	1.0		0.012
Primary payer					<0.001						0.72	
Not insured	1,127	7.2	273	12.3		0.172	1,236	7.9	186	8.5		0.022
Private	11,800	75.6	1,234	55.7		0.43	11,400	73	1,569	71.8		0.028
Medicaid	1,603	10.3	463	20.9		0.296	1,819	11.7	265	12.1		0.014
Medicare	569	3.6	141	6.4		0.125	619	4	84	3.8		0.006
Other government	192	1.2	45	2		0.063	212	1.4	36	1.6		0.022
Unknown	311	2	61	2.8		0.05	325	2.1	47	2.2		0.005
Eacility type	011	_	0.	2.0	~0.001	0100	010				0.07	0.000
	4 4 7 0	7 -	450	0.0	<u>_0.00</u> 1	0.000	1 10 1	7 -	450	7 4	0.07	0.040
Community	1,1/6	1.5	152	6.9		0.026	1,164	1.5	156	7.1		0.012
Comprehensive	5,378	34.5	604	27.2		0.157	5,247	33.6	750	34.3		0.015
Academic	4,446	28.5	779	35.1		0.143	4,561	29.2	581	26.6		0.059
Integrated	840	5.4	145	6.5		0.049	869	5.6	134	6.1		0.023
Other	3,762	24.1	537	24.2		0.003	3,771	24.2	566	25.9		0.04
Median income					<0.001						0.9	
<\$38,000	2,311	14.8	891	40.2		0.593	2,813	18	401	18.4		0.009
\$38 000-\$47 999	3 726	23.9	523	23.6		0.007	3 721	23.8	515	23.5		0.007
\$48,000 \$62,000	4 250	27.0	447	20.0		0.101	4 109	26.0	570	20.0		0.010
\$40,000-\$62,999	4,350	27.9	447	20.2		0.101	4,190	20.9	570	20		0.019
\$63,000+	5,208	33.4	354	16.0		0.412	4,870	31.2	700	32		0.017
Unknown	7	0.1	2	0.1		0.017	8	0.1	1	0.1		0.004
Percent no HS degree					<0.001						0.01	
≥21%	2,564	16.4	759	34.2		0.418	2,932	18.8	471	21.6		0.069
13–20.9%	4,026	25.8	770	34.7		0.195	4,189	26.8	553	25.3		0.035
7–12.9%	5,174	33.2	477	21.5		0.264	4,945	31.7	654	29.9		0.039
<7%	3.838	24.6	211	9.5		0.409	3.545	22.7	508	23.3		0.013
l Irban status	0,000	2.110		0.0	~0.001	01100	0,010			2010	0 10	0.010
Metro	10 501	20.6	1 006	00	<0.001	0.069	10 770	01.0	1 000	00.4	0.15	0.041
	12,001	0.0	1,990	90		0.200	12,773	01.0	1,023	63.4		0.041
Urban (20,000+)	974	6.2	83	3.7		0.115	925	5.9	115	5.2		0.03
Urban (2,500–19,999)	1,434	9.2	92	4.1		0.203	1,336	8.6	163	7.5		0.04
Rural	308	2	20	0.9		0.09	287	1.8	37	1.7		0.01
Unknown	305	2	26	1.2		0.063	290	1.9	48	2.2		0.025
Stage					0.007						0.83	
I	4,310	27.6	642	29		0.03	4,334	27.8	614	28.1		0.007
Ш	3 206	20.5	458	20.7		0.003	3 218	20.6	457	20.9		0.007
	5 155	20.0	657	20.6		0.072	5,090	20.0	710	20.0		0.005
111 117	0,001	10.0	400	23.0		0.075	0,000	10	000	10.0		0.005
IV	2,931	18.8	460	20.7		0.049	2,970	19	398	18.2		0.021
Grade					<0.001						0.16	
I	1,335	8.6	234	10.6		0.068	1,371	8.8	178	8.2		0.022
II	9,451	60.6	1,166	52.5		0.162	9,304	59.6	1,320	60.4		0.016
III	2,207	14.1	317	14.3		0.004	2,220	14.2	341	15.6		0.039
IV	174	1.1	24	1.1		0.003	174	1.1	25	1.1		0.002
Unknown	2,435	15.6	477	21.5		0.152	2,543	16.3	322	14.7		0.043
CRM margin status					<0.001						0.77	
0–1 mm	674	4.3	70	32	•	0.061	651	42	93	42		0.004
110mm	014	ч.U	10	0.2		0.001	001	т. <u>с</u>	04	 		0.004
1.1-2 mm	214	1.4	10	U./		0.064	201	1.3	24	1.1		0.02
2.1–5 mm	234	1.5	19	0.9		0.06	222	1.4	34	1.6		0.012
5.1–10 mm	108	0.7	11	0.5		0.026	105	0.7	19	0.9		0.024
>10 mm	185	1.2	14	0.6		0.058	175	1.1	28	1.3		0.015
Negative CRM	2,090	13.4	272	12.3		0.034	2,068	13.2	283	12.9		0.01
No resection	1,169	7.5	227	10.2		0.097	1,229	7.9	189	8.6		0.027
Unknown	10,928	70	1,588	71.6		0.035	10,960	70.2	1,517	69.4		0.018
Surgerv	.,	-	,		<0 001		- ,=		,		0 79	
No surger	0 5 40	16.0	E00	04	-0.00 I	0.100	0 707	17.0	200	17 -	5.13	0.004
	∠,549	10.3	532	24		0.192	2,707	17.3	383	17.5		0.004
Excision	1,367	8.8	316	14.3		0.173	1,472	9.4	197	9		0.015
Partial proctectomy	7,310	46.9	799	36		0.221	7,102	45.5	979	44.8		0.015
Coloanal anastomosis	931	6	112	5.1		0.04	912	5.8	122	5.6		0.011
Total proctectomy	2,692	17.3	339	15.3		0.053	2,655	17	403	18.4		0.037
Pelvic exenteration	350	2.2	59	2.7		0.027	357	2.3	49	2.2		0.005
	102	26	60	 07		0 000	406	26	55	 2 5		0.006
Chomotherance of the	-100	2.0	50	۲.1	-0.004	0.000	400	۲.0	JJ	2.0	0.04	0.000
onemounerapy given	0.44	10 5		05 -	<i>ر</i> 0.001	0.4.1-	0.00-	00 -		00.5	0.01	0.00-
No	3,111	19.9	575	25.9		0.143	3,229	20.7	444	20.3		0.009
Yes	12,269	78.6	1,600	72.2		0.151	12,148	77.8	1,706	78		0.005
Unknown	222	1.4	42	1.9		0.037	234	1.5	36	1.7		0.013
Radiation given					<0.001						0.31	
No	5,024	32.2	853	38.5		0.132	5,140	32.9	696	31.8		0.023
Yes	10,582	67.8	1,364	61.5		0.132	10,471	67.1	1,490	68.2		0.023

Table S1 NCDB baseline characteristics before and after propensity score matching and inverse probability of treatment weighting, stratified by race

	SEER baseline characteristics				SEER baseline characteristics IPTW				ics IPTW			
Characteristics	White (N=5 437) African American					White (N	J=5,436)	African	American			
	Count		(N=7	/07)	_ P	SMD	Count		(N=	=705)	_ P	SMD
	Count	90	Count	90	0.04		Count	90	Count	%	0.76	
Age, years	007	1 1	97	2.0	0.04	0.027	000	12	20	11	0.70	0.01
<00	1.062	10.5	124	10		0.027	1 060	4.5	150	4.1		0.01
30-39	1,002	19.5	134	19		0.015	1,060	19.5	150	21.1		0.04
40-44	1,442	26.5	196	27.7		0.027	1,449	26.7	187	26.4		0.00
45+	2,696	49.6	350	49.5		0.002	2,693	49.5	342	48.4		0.02
Sex					0.84						0.12	
Male	3,154	58	413	58.4		0.008	3,160	58.1	433	61.2		0.06
Female	2,283	42	294	41.6		0.008	2,276	41.9	275	38.8		0.06
Year of diagnosis					0.007						0.24	
2004–2008	2,870	52.8	411	58.1		0.108	2,900	53.4	361	51		0.04
2009–2012	2,567	47.2	296	41.9		0.108	2,535	46.6	347	49		0.04
Primary payer					< 0.001						0.89	
No insurance	246	4.5	67	9.5		0.195	276	5.1	35	4.9		0.00
Insurance	2,961	54.5	270	38.2		0.331	2,859	52.6	372	52.5		0.00
Medicaid	516	9.5	122	17.3		0.23	565	10.4	80	11.3		0.03
Unknown	1,714	31.5	248	35.1		0.075	1,736	31.9	221	31.3		0.01
Median income					<0.001						0.99	
<\$25,000	123	2.3	13	1.8		0.03	120	2.2	16	2.3		0.00
\$25,000-\$40,000	1,249	23	218	30.8		0.178	1,297	23.9	168	23.7		0.004
\$40,001-\$60,000	3 360	61 8	394	55.7		0.124	3 321	61 1	432	61		0.00
>\$60,000	705	13	82	11 6		0 0/12	607	12.8	92	12		0.00
Percent no US doares	, 05	10	52	11.0	0 000	0.042	001	12.0	JL	10	0.04	0.00
	0.044	07 F	007	10 1	0.002	0.10	0 070	20.0	000	40.0	0.24	0.05
≥21%	2,041	37.5	307	43.4		0.12	2,078	38.2	290	40.9		0.05
13-20.9%	2,536	46.6	317	44.8		0.036	2,523	46.4	316	44.6		0.03
7–12.9%	840	15.4	83	11.7		0.108	817	15	102	14.5		0.01
<7%	20	0.4	0	0		0.086	18	0.3	0	0		0.08
Percent below poverty					<0.001						0.89	
>25%	145	2.7	28	4		0.072	153	2.8	21	2.9		0.00
15–25%	1,631	30	309	43.7		0.287	1,715	31.6	231	32.6		0.02
10–14.9%	1,559	28.7	183	25.9		0.063	1,541	28.3	192	27.1		0.02
<10%	2,102	38.7	187	26.4		0.263	2,027	37.3	265	37.4		0.00
Marital status	-				<0.001						0.99	
Single	1 256	23.1	202	41 3		0 397	1 370	25.2	178	25.1	0.00	0.00
Married	3 205	60.9	201	41.0		0.4	2 1 9 2	59.5	/10	50		0.00
	3,303	00.0	291	41.2		0.4	3,103	1.0	410	33		0.01
Separated	78	1.4	21	3		0.105	86	1.6	10	1.4		0.01
Divorced	536	9.9	72	10.2		0.011	538	9.9	69	9.8		0.00
Widowed	55	1	3	0.4		0.07	51	0.9	7	1.0		0.00
Unknown	207	3.8	28	4		0.008	207	3.8	25	3.6		0.01
Stage					0.02						0.78	
I	1,291	23.7	154	21.8		0.047	1,277	23.5	154	21.8		0.04
II	1,014	18.6	134	19		0.008	1,016	18.7	136	19.3		0.01
III	1,934	35.6	227	32.1		0.073	1,912	35.2	253	35.7		0.01
IV	1,198	22	192	27.2		0.119	1,231	22.6	165	23.3		0.01
Grade					0.59						0.93	
I	388	7.1	60	8.5		0.05	396	7.3	47	6.7		0.02
II	3,428	63	438	62		0.023	3,420	62.9	455	64.2		0.02
Ш	870	16	105	14.9		0.032	863	15.9	107	15		0.02
IV	84	1.5	10	14		0.011	83	1.5	12	16		0.00
Linknown	667	12.3	94	13.3		0.031	674	12 /	88	12 /		0.00
CRM margin status	501	.2.0	U-T	10.0	0 001	0.001	577	. 2.7	00	12.7	0.06	0.00
0_1 mm	0 ∩1	2 7	05	9 F	0.001	0 000	201	2 7	00	Л	0.20	0.04
	201	J.1	25	3.5		0.009	201	J.1	28	4		0.01
1.1-2 mm	62	1.1	2	0.3		U.102	5/	1	4	0.6		0.04
2.1–5 mm	70	1.3	5	0.7		0.058	67	1.2	11	1.5		0.02
5.1–10 mm	47	0.9	1	0.1		0.102	42	0.8	4	0.6		0.02
>10 mm	96	1.8	4	0.6		0.112	89	1.6	20	2.9		0.08
Negative CRM	599	11	58	8.2		0.096	581	10.7	68	9.6		0.03
No resection	493	9.1	71	10		0.033	500	9.2	72	10.1		0.03
Unknown	3,869	71.2	541	76.5		0.122	3,900	71.7	501	70.7		0.02
Surgery					<0.001						0.93	
No surgery	963	17.7	173	24.5		0.166	1,006	18.5	136	19.3		0.01
Excision	400	7.4	60	8.5		0.042	407	7.5	52	7.3		0.00
Partial proctectomy	2.766	50.9	304	43		0.158	2.716	50	347	48 9		0 02
Coloanal anastomosio	207	2 Q	02 204	<i>3</i> 3		0 03	2002	27	29	л		0.02
	207	174	110	16.0		0.00	200	47	100	4		0.01
iotal proctectomy	928	17.1	119	16.8		0.006	926	1/	122	17.2		0.00
Pelvic exenteration	106	1.9	17	2.4		0.031	108	2	11	1.6		0.03
Surgery, NOS	67	1.2	11	1.6		0.028	69	1.3	12	1.7		0.03
Chemotherapy given					0.62						0.98	
No/unknown	1,140	21	154	21.8		0.02	1,146	21.1	149	21		0.00
Yes	4,297	79	553	78.2		0.02	4,290	78.9	559	79		0.00
Radiation given					0.67						0.63	
No/unknown	1,718	31.6	229	32.4		0.017	1,723	31.7	218	30.8		0.01
Yes	3.719	68.4	478	67.6		0.017	3.713	68.3	490	69.2		0.010
	.,											

Table S2 SEER baseline characteristics before and after	r propensity score	matching and inverse	e probability of treatmen	nt weighting, stratified by race
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Griaracteristics	HR (95% CI)	Р	HR (95% CI)	Р
Age			2	
<30	-	-		
30–39	0.82 (0.71–0.94)	0.004	0.73 (0.6–0.89)	0.002
40–44	0.78 (0.69–0.9)	<0.001	0.69 (0.57–0.84)	<0.001
45+	0.77 (0.67–0.87)	<0.001	0.69 (0.57–0.82)	<0.001
Sex	(, <u> </u>			
Male	_	_		
Female		-	0 01 /0 75 0 00	20.004
remale	u. <i>r (</i> (u. <i>r</i> 3–0.81)	<0.001	U.81 (U.75–U.88)	<0.001
Kace				
White	-	-		
African American	1.15 (1.06–1.25)	0.001	1.26 (1.12–1.42)	<0.001
Year of diagnosis				
2004–2008	-	-		
2009–2012	1 (0.94–1.07)	0.953	0.99 (0.91–1.08)	0.908
Charlson/Deyo Score				
0	-	_		
1	1.08 (0.98–1.19)	0.118	0.59 (0.5–0.71)	<0.001
2+	1.67 (1.38–2.03)	<0.001	1.38 (1.13–1.69)	0.001
Primary paver	(1.00 2.00)		0.7 (0.58-0.84)	~0.001
Not incured			0.7 (0.00-0.04)	<u>\0.001</u>
		-		
Private	0.51 (0.47–0.56)	<0.001		
Medicaid	1.07 (0.96–1.19)	0.217	0.85 (0.65–1.1)	0.215
Medicare	1.16 (1.01–1.33)	0.04	0.81 (0.63–1.05)	0.109
Other government	0.6 (0.46–0.78)	<0.001	0.68 (0.52–0.91)	0.008
Unknown	0.67 (0.55–0.83)	<0.001		
Facility type				
Community	_	_	0.84 (0.77–0.92)	<0.001
Comprehensive	0.82 (0.74–0.91)	<0.001	0.66 (0.58–0.76)	<0.001
Academic	0.8 (0.72_0.0)	<0.001	0.82 (0.37_1 21)	0.626
Integrated	0.0 (0.72-0.9)	<0.001	0.02 (0.37-1.01)	0.020
Integrated	U.76 (U.65–U.88)	<0.001		
Other	0.91 (0.81–1.01)	0.085		
Median income			0.9 (0.71–1.14)	0.378
<\$38,000	-	-	0.82 (0.65–1.04)	0.098
\$38,000-\$47,999	0.92 (0.85–1)	0.038	0.71 (0.56–0.9)	0.004
\$48,000-\$62,999	0.77 (0.71–0.84)	<0.001		
\$63,000+	0.61 (0.56–0.66)	<0.001		
Unknown	1.58 (0.6–4.15)	0.352	0.57 (0.52–0.62)	<0.001
Percent no HS dearee			0.8 (0.58–1.09)	0.158
≥21%	_	_	0.74 (0.64–0.85)	<0.001
/~ 13_20.9%		0.001		0.001
10-20.370	0.00 (0.02-0.95)	0.001	1.13 (0.1-CO.U)	0.308
1-12.9%	0.72 (0.67-0.78)	<0.001	0.57 (0.45–0.73)	<0.001
<7%	0.58 (0.53–0.64)	<0.001		
Urban status				
Metro	-	-	1.88 (1.56–2.26)	<0.001
Urban (20,000+)	1.18 (1.05–1.32)	0.005	2.67 (2.27–3.13)	<0.001
Urban (2,500–19,999)	1.14 (1.03–1.25)	0.009	15.07 (12.9–17.59)	<0.001
Rural	1.24 (1.03–1.5)	0.024		
Unknown	0.74 (0.59–0.94)	0.013		
Stage			1.15 (0.96–1.38)	0.138
-	_	_	2.38 (1.96-2.89)	<0.001
Ш	2 7 (2 28_2 0E)	<u>~0 001</u>	3 05 /2 22_1 17	~0.001
	2 06 (2 44 4 00)	-0.001	106(160)	<0.001
111 N /	3.00 (3.44-4.33)	<0.001	1.90 (1.0–2.4)	<0.001
IV	19.58 (17.52–21.88)	<0.001		
Grade				
1	-	-	0.8 (0.47–1.34)	0.389
II	1.31 (1.16–1.48)	<0.001	0.53 (0.3–0.91)	0.022
III	2.87 (2.52–3.27)	<0.001	0.15 (0.04–0.5)	0.002
IV	3.31 (2.62–4.19)	<0.001	0.26 (0.14–0.5)	<0.001
Unknown	1.81 (1.59–2.07)	<0.001	0.33 (0.24–0.45)	<0.001
CRM margin status			2.63 (2.05–3.37)	<0.001
0–1 mm	_	_	0.9 (0.71–1 13)	0.355
1 1–2 mm	0 28 10 31_0 73V	0.001	0.0 (0.1 1110)	0.000
0.1 5 mm	0.40 (0.31-0.73)	0.001		
∠.ı−o mm	0.52 (0.35-0.77)	0.001		
5.1–10 mm	0.23 (0.11–0.51)	<0.001	0.12 (0.09–0.15)	<0.001
>10 mm	0.46 (0.29–0.73)	0.001	0.17 (0.15–0.18)	<0.001
Negative CRM	0.38 (0.3–0.46)	<0.001	0.17 (0.13–0.22)	<0.001
No resection	2.72 (2.28–3.24)	<0.001	0.27 (0.24–0.3)	<0.001
Unknown	0.84 (0.71–0.98)	0.032	0.4 (0.31–0.52)	<0.001
Surgery			0.27 (0.19–0.39)	<0.001
No surgery	_	_		
Excision	0.1 (0.09-0.12)	<0.001		
Partial proctectomy	0 10 /0 18_0 011	~0.001	2 17 (1 02_2 16)	~0.001
		~0.001	L.II (I.JZ-Z.40)	<u>\0.001</u>
Coloanal anastomosis	0.2 (0.18–0.24)	<0.001		
Total proctectomy	0.28 (0.25–0.3)	<0.001		
Pelvic exenteration	0.38 (0.32–0.45)	<0.001	0.87 (0.8–0.95)	0.002
Surgery, NOS	0.28 (0.23–0.33)	<0.001		
Chemotherapy given				
No	_	_		
Yes	2.42 (2.2-2.65)	<0.001		
Unknown	1 85 (1 44-2 27)	<0.001		
Badiation given	1.00 (1.44-2.07)	~0.001		
	-	-		
Voc	0.8 (0.75-0.85)	<0.001		

Table S3	Propensity score matched,	, inverse probability	of treatment weighted	univariate overall surviva	l analysis in the NC	CDN and SEER registries
			0			U