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Disparities in neoadjuvant radiation dosing for treatment of rectal cancer

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A B S T R A C T

Background: Certain patients are less likely to undergo appropriate cancer treatment, worsening their overall cancer survival. The purpose of this investigation was to identify factors associated with inadequate neoadjuvant radiation for rectal cancer.
Methods: The National Cancer Database was queried for patients with locally advanced rectal cancer who received neoadjuvant radiation 2006–2014. Adequate radiation was considered to be 4,500-5,040 cGy. Demographic, hospital and clinical variables were analyzed for association with inadequate radiation.
Results: The study cohort was 34,391 patients; 1,842(5.4%) received inadequate radiation. On multivariate analysis, female gender, older age, other race, government-provided insurance, lower clinical stage and rural location correlated with inadequate radiation.
Conclusions: Women were 50% less likely than men to receive correct neoadjuvant radiation dosing. Other factors including age, race, insurance, clinical stage, geographic location and neoadjuvant chemotherapy were significantly associated with radiation dosing. These factors should be evaluated to determine if they can be modified to improve outcomes.

Summary

On this analysis of the National Cancer Database, women with locally advanced rectal cancer were more likely than men to receive inadequate neoadjuvant radiation. Other factors including age, race, insurance, clinical stage, geographic location and neoadjuvant chemotherapy were significantly associated with receipt of correct preoperative radiation dosing.

Introduction

Appropriate neoadjuvant chemoradiation decreases rates of local recurrence in stage II and III. However, access and implementation of appropriate rectal cancer care may vary based on racial and socioeconomic disparities.[1–6,26] Breakdown in guideline-recommended processes of neoadjuvant and operative treatment can have significant impacts on cancer and survival outcomes.[7]

Socioeconomic status, race, ethnicity, gender and other non-clinical factors have been associated with broad variation in cancer management and survival.[8–12] Patients in areas of lower average income and education rates have higher mortality from cancer, and this inequality gap in survival rates has only widened over time.[10,13] Rectal cancer care follows similar patterns in disparities. Black patients with rectal cancer are more likely than white to undergo inappropriate management such as lack of radiation treatment for locally advanced disease and suffer worse outcomes, including worse overall survival.[1,2] A study of adolescents and young adults with Stage II and III rectal cancer found that Hispanic and black patients were significantly less likely to undergo neoadjuvant chemoradiotherapy when compared with non-Hispanic white patients.[7] Another retrospective study demonstrated that gender and insurance type are associated with receipt of neoadjuvant therapy for patients with locally advanced rectal cancer and linked completion of neoadjuvant therapy to improved survival.[14] These studies are limited in their patient selection, such

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as focus on younger patients alone, or their outcome of interest, concentrating on survival rather than treatment disparity.

In light of these concerns, the aim of this study was to describe treatment disparities in adults undergoing neoadjuvant radiation for locally advanced rectal cancer using data from the 2006–2014 the National Cancer Database. Our hypothesis was that demographic, hospital and clinical factors would demonstrate significant variation based on patient disparities.

Methods

The National Cancer Database (NCDB) is a data repository sponsored by the American College of Surgeons and the American Cancer Society. The NCDB stores data collected from Commission on Cancer-accredited medical centers, and includes information on more than 70% of newly diagnosed cancers in the US. The NCDB was queried for patients 18 years of age and older between 2006 and 2014 with clinical stage II and III rectal cancer who received standard neoadjuvant radiation prior to curative proctectomy.

Standard neoadjuvant radiation dose is 4,500-5,040 cGy (cGy), most commonly administered as 4,500 cGy course with a 540 cGy boost to the tumor bed. Adequate radiation was considered to be between 4,500 and 5,040 cGy (cGy), while inadequate radiation was defined as less than 4,500 cGy. Patients who received more than 5,040 cGy were excluded from analysis. Patients who received exactly 2,500 cGy (n = 253) or 2,000 to 3,000 in 5–10 fractions (n = 116) were considered to be intentionally prescribed short-course radiation and were also excluded.

Patient, disease and practice variables were derived from NCDB. Patient variables included sex, age, race, and type of insurance as well as Charlson-Deyo score, as a descriptor of comorbidity. Of note, in NCDB, the Charlson-Deyo score is calculated using the patient comorbidity burden, and the patient's cancer is not reflected in the assigned score. NCDB provides proxy variables for individual income and education levels based on zip code information. Socioeconomic status was estimated using information derived from the 2012 American Community Survey, including percent of people living in the patient's area of residence who obtained a high school degree (ranging from <7% to >21%) and median household income (ranging in quartiles from <$38,000 and >$63,000). Patient residence in metropolitan, urban or rural counties, distance from the hospital and national region were used as estimates of physical access to a medical facility.

A practice volume variable was created by stratifying all hospitals into three categories based on number of proctectomies performed during the studied period between 2006 and 2014 (<100, 100–300 and > 300 cases). Academic hospital status was defined by NCDB as a hospital that participates in postgraduate medical education and diagnoses over 500 new cancers per year.

Disease factors evaluated included preoperative disease stage, tumor histotype, grade and size, and receipt of concurrent neoadjuvant chemotherapy.

Statistical analysis

The primary outcome was whether a patient received adequate radiation dosing. Bivariate analyses were performed using Pearson chi square tests for categorical variables and Student's *t*-test for continuous variables.

Associations between receipt of adequate radiation and demographic, socioeconomic, hospital, and clinical factors were evaluated. Patient demographic, hospital and clinical data points were analyzed to identify factors associated with receiving inadequate radiation dosing.

Clinically significant factors and variables statistically significant on bivariate analyses were used in a multivariable logistic regression to assess adjusted relationships to receipt of adequate radiation. Areas under the receiver operating characteristic (ROC) curve were calculated to identify the best fitting iteration of the logistic model. Statistical significance was set at $p < 0.05$. Statistical analysis was performed using StataIC (version 15.1.635).

Results

Between 2006 and 2014, 34,391 patients met inclusion criteria; of those 32,549 (94.6%) patients received adequate long course radiation while 1,842 (5.4%) received less than the appropriate dose.

Bivariate analyses

On bivariate analyses, the patients who received an inadequate dose of neoadjuvant radiation were statistically more likely to be female (6.5% vs. 4.6%), older (mean age 63.2 vs. 60.1 years old), of "other" race and were less likely to have private insurance compared to other types of insurance (Table 1). Differences in percent of high school graduates within the patient's zip code area was not significant, but patients within lower income zip codes were more likely to receive inadequate radiation. Rural patients were more likely than urban-based or metropolitan-based patients to receive inadequate radiation, and patients who travelled a longer distance to the hospital was proportionate more likely to receive inadequate radiation. There were also significant regional variations in regards to levels of inadequate radiation patients received in different parts of the US. Low and moderate volume proctectomy hospitals were more likely than high-volume hospitals to give patient inappropriate radiation treatment. In terms of hospital facility type, patients at community cancer programs were most likely to get inadequate radiation, while those at integrated network cancer programs were least likely.

Patient clinical factors significant in the bivariate analysis were clinical stage and concurrent receipt of neoadjuvant chemotherapy. Compared to clinical stage III, patients with stage II cancer were at higher risk of receiving inadequate radiation. Receipt of concurrent neoadjuvant chemotherapy was correlated with a lower likelihood of inadequate radiation.

Multivariate analysis

On logistic regression, certain demographic, hospital and clinical factors were significantly correlated with inadequate radiation (Table 2). Although absolute numbers were small, women were 1.52 times more likely to receive inadequate radiation ($p < 0.001$). Patients over 60 years old, other race, insurance through Medicare, Medicaid or other government-provided insurance, and clinical stage II were also correlated with inadequate radiation. Compared to New England, patients in East South Central region of the US were more likely to receive inadequate radiation. Rural patients were 1.42 times more likely to be undertreated compared to patients in metropolitan areas ($p = 0.035$). Receipt of concurrent neoadjuvant chemotherapy was a protective factor against receiving inadequate radiation.

Discussion

In this analysis, women were 50% less likely to receive the correct dose of neoadjuvant radiation compared to men when controlling for other demographic, facility and treatment factors. Old age, government-provided insurance, race, and lower stage were other patient and disease-related factors associated with

Table 1
Demographic, clinical and hospital factors and their associations with inadequate radiation dosing on bivariate analyses.

Descriptor	Variable	Inadequate dose	Standard dose	p value
Sex n(%)	Male	992(4.6)	20,380(95.4)	<0.001
	Female	850(6.5)	12,169(93.5)	
Age mean (SD)	Years	63.2(13.2)	60.1(12.3)	<0.001
Race/ethnicity n(%)	Non-Hispanic white	1,449(5.5)	24,941(94.5)	0.002
	Non-Hispanic black	128(4.8)	2,561(95.2)	
	Hispanic	74(4.4)	1,617(95.6)	
	Asian/Pacific Islander	50(3.7)	1,299(96.3)	
	Other	141(6.2)	2,131(93.8)	
Insurance n(%)	Private	752(4.3)	16,673(95.7)	<0.001
	Medicare	836(6.8)	11,442(93.2)	
	Medicaid	131(5.9)	2,079(94.1)	
	Other government-provided insurance	23(5.7)	384(94.4)	
	Uninsured	88(5.3)	1,586(94.7)	
Income (Quartiles) n(%)	< $38,000	337(5.7)	5,587(94.3)	0.031
	$38,000-$47,999	479(5.8)	7,810(94.2)	
	$48,000-$62,999	482(5.2)	8,762(94.8)	
	$63,000+	520(4.9)	10,083(95.1)	
Percent No High School Degree n(%)	≥21%	327(5.6)	5,496(94.4)	0.388
	13% - 20	477(5.3)	8,611(94.8)	
	7% - 12.9	613(5.5)	10,575(94.5)	
	<7	401(5.0)	7,580(95.0)	
Living area n(%)	Metro	1,373(5.1)	25,658(94.9)	<0.001
	Urban	358(6.5)	5,186(93.5)	
	Rural	64(7.5)	787(92.5)	
Living area (by distance from hospital) n(%)	≤10 miles	840(5.0)	15,843(95.0)	0.034
	10 to 25 miles	500(5.4)	8,730(94.6)	
	25 to 50 miles	259(5.6)	4,407(94.5)	
	50 to 100 miles	141(6.2)	2,131(93.8)	
	100 to 250 miles	65(6.8)	892(93.2)	
	>250 miles	37(6.4)	546(93.7)	
Facility location n(%)	New England	91(4.6)	1,890(95.4)	<0.001
	Middle Atlantic	236(5.1)	4,354(94.9)	
	South Atlantic	304(4.8)	6,012(95.2)	
	East North Central	338(5.1)	6,360(94.9)	
	East South Central	179(8.2)	1,995(91.8)	
	West North Central	215(6.1)	3,286(93.9)	
	West South Central	140(6.8)	1,923(93.2)	
	Mountain	80(5.5)	1,375(94.5)	
	Pacific	182(4.5)	3,843(95.5)	
Hospital proctectomy resection volume between 2006 and 2014	Low (<100)	578(5.9)	9,287(94.1)	0.017
	Moderate (100–300)	857(5.3)	15,410(94.7)	
	High (>301)	407(4.9)	7,852(95.1)	
Hospital facility type n(%)	Academic/Research Program	553(5.0)	10,532(95.0)	0.001
	Community Cancer Program	205(6.4)	3,000(93.6)	
	Comprehensive Community Cancer Program	843(5.7)	14,030(94.3)	
	Integrated Network Cancer Program	164(4.5)	3,476(95.5)	
Charlson-Deyo Score n(%)	0	1,473(5.4)	26,060(94.6)	0.884
	1	296(5.3)	5,271(94.7)	
	2	73(5.7)	1,218(94.3)	
Histotype n(%)	Adenocarcinoma	1,703(5.3)	30,240(94.7)	0.260
	Mucinous	119(5.5)	2,066(94.5)	
	Signet cell	20(7.6)	243(92.4)	
Clinical Stage n(%)	II	774(5.5)	13,206(94.5)	<0.001
	III	677(4.4)	14,611(95.6)	
Tumor grade	Well-differentiated	127(5.2)	2,307(94.8)	0.848
	Moderately differentiated	1,278(5.5)	21,891(94.5)	
	Poorly differentiated	207(5.5)	3,538(94.5)	
	Undifferentiated, anaplastic	20(6.3)	296(93.7)	
Tumor size	10 mm or less	84(5.3)	1,495(94.7)	0.575
	11–20 mm	206(5.8)	3,351(94.2)	
	21–30 mm	310(5.7)	5,089(94.3)	
	31–40 mm	282(5.4)	4,969(94.6)	
	41 mm or more	584(5.2)	10,591(94.8)	
Received or didn't receive neoadjuvant chemo n(%)	Neoadjuvant chemotherapy	1,424 (5.0)	26,843(95.0)	<0.001
	No neoadjuvant chemotherapy	97(7.5)	1,196(92.5)	

inappropriate radiation dosing. Certain hospital and treatment factors were protective, including location within certain regions, metropolitan area designation and concurrent receipt of neoadjuvant chemotherapy. While age, race, socioeconomic status, hospital type and location, cancer treatment volume and regional variation have previously been linked with disparities in rectal cancer treatment and outcomes,[1,8,11,13] the association of female gender has not been explored. Additionally, our study focused on adults of all ages and examined radiation treatment disparities using a larger and more recent NCDB dataset.

Examples of race, ethnicity and socioeconomic disparities in rectal cancer care delivery processes and outcomes have been

Table 2
Multivariate logistic regression demonstrating associations with receipt of inadequate radiation.

	Odds Ratio	95% Confidence Interval		P value
Gender				
Male (Ref)	1	*	*	*
Female	1.52	1.35	1.71	**<0.001**
Age over 60 years old	1.23	1.05	1.44	**0.012**
Race/ethnicity				
Non-Hispanic white (Ref)	1	*	*	*
Non-Hispanic black	0.98	0.87	1.11	0.742
Hispanic	0.95	0.85	1.05	0.288
Asian/Pacific Islander	0.94	0.86	1.03	0.176
Other	1.07	1.02	1.12	**0.005**
Insurance				
Private (Ref)	1	*	*	*
Medicare	1.38	1.17	1.63	**<0.001**
Medicaid	1.42	1.11	1.83	**0.005**
Other government-provided	1.63	1.01	2.63	**0.046**
Uninsured	1.25	0.93	1.67	0.144
Income				
< $38,000 (Ref)	1	*	*	*
$38,000-$47,999	1.11	0.92	1.35	0.262
$48,000-$62,999	1.2	0.98	1.45	0.072
$63,000+	1.13	0.92	1.38	0.26
Great circle group over 100 miles (distance from hospital)	0.76	0.56	1.02	0.064
Geographic Region				
New England (Ref)	1	*	*	*
Middle Atlantic	1.07	0.78	1.47	0.673
South Atlantic	1.07	0.78	1.46	0.669
East North Central	1.06	0.78	1.43	0.708
East South Central	1.51	1.07	2.13	**0.021**
West North Central	1.26	0.91	1.73	0.165
West South Central	1.42	1	2.03	0.052
Mountain	1.14	0.78	1.68	0.499
Pacific	0.99	0.71	1.37	0.93
Area designation				
Metro (Ref)	1	*	*	*
Urban	1.14	0.96	1.35	0.126
Rural	1.42	1.02	1.97	**0.035**
Hospital type				
Academic/Research Program (Ref)	1	*	*	*
Community Cancer Program	1.18	0.92	1.53	0.199
Comprehensive Cancer Program	1.13	0.97	1.32	0.12
Integrated Network Cancer Program	1.06	0.85	1.32	0.603
Hospital proctectomy resection volume between 2006 and 2014				
<100	1	*	*	*
100–300	0.86	0.73	1.02	0.078
>301	0.93	0.75	1.14	0.462
Clinical stage				
II	1.21	1.07	1.37	**0.002**
III (Ref)	1	*	*	*
Receipt of neoadjuvant chemotherapy	0.65	0.51	0.84	**0.001**

evaluated in the literature. Morris et al. described disparities along racial lines with black patients more likely to be diagnosed a later stage of disease and less likely to receive neoadjuvant therapy and sphincter-sparing procedures.[1] Likewise, in an analysis of the Surveillance, Epidemiology and End Results (SEER) database, Martinez et al. noted that Hispanic white patients were significantly less likely to receive neoadjuvant radiation compared to non-Hispanic white patients.[15] An NCDB study of young adults and adolescents with locally advanced rectal cancer also demonstrated black and Hispanic patients were less likely to receive neoadjuvant chemoradiation, along with uninsured patients and those treated at community cancer centers.[7] Other socioeconomic factors previously linked with inadequate rectal cancer care include income, insurance type, and education level.[16–18] Similar to these findings, our study demonstrated that inadequate radiation was associated with demographic and socioeconomic variables including age, race, insurance and living area population density.

Another area of investigation in rectal cancer has been treatment and outcome variation in different hospitals and regional areas of the US. A seminal NCDB analysis by Monson et al. demonstrated that hospital type, location and number of annual rectal cancer resections were significantly associated with use of implementation of neoadjuvant chemoradiation in adherence to National Comprehensive Cancer Network (NCCN) clinical practice guidelines for stage II and III disease.[18] In our study, regional location was a significant factor that affected receipt of appropriate neoadjuvant radiation on adjusted analyses.

It is uncertain why women were more likely to receive inadequate radiation dosing compared to men. Although the overall percentage of under-treated patients was small, the trend of women receiving inadequate radiation dosing was large and strongly significant. Patient gender has been previously shown to affect surgeon treatment risk estimation in lung cancer, and could potentially have a similar effect in this case.[19] Prior studies noted that women are at higher risk of not receiving neoadjuvant therapy, but did not address the potential underlying reasons for inadequate dosing.[7,14] Lee et al. demonstrated that young men are more likely to undergo neoadjuvant radiation than young women, but did not discuss the potential causes for this disparity.[7] Similarly, Freischlag and Sun et al. showed that women are at higher risk of receiving an incomplete neoadjuvant radiation course, but implied that this may because some patients do not complete full dosing without exploring the potential for pre-determined under-treatment.[14]

There is ample data demonstrating that women are persistently under-treated in a variety of healthcare settings. Gender disparities have been demonstrated in the treatment and outcomes of women with a wide range of diagnoses including cardiovascular disease,[20] diabetes[21] and colorectal cancer.[9] In a retrospective cohort analysis of a large insurance claims database, Leeds et al. demonstrated that women were less likely to receive surgery and biologics for treatment of ulcerative colitis, and more likely to undergo rescue therapy and receive corticosteroids.[22]

This study was conducted using the NCDB, and is thus limited by its retrospective nature, the selection of variables recorded in the database and missing data. Evaluation of adequate neoadjuvant radiation dosing would benefit from more information regarding tumor location within the rectum (high vs. low), whether or not there was concern for threatened margin and reasons for premature cessation of therapy. Adequate doses of radiation may also not have been achievable due to intolerance, complications of the primary tumor, disease progression through treatment or prior radiation given for other pelvic malignancy. There's also no information on type and number of neoadjuvant chemotherapy cycles nor specifics regarding radiotherapy technique. Although data granularity is a concern, significant trends with large effect sizes were identified, which should be further evaluated prospectively. Additionally, despite its limitations, the NCDB encompasses approximately 70% of cancers diagnosed in the US and is likely representative of care delivered at Committee on Cancer-accredited hospitals where this data is collected. Lastly, the ideal dose of radiation may still be unclear; approaches to neoadjuvant therapy are evolving and variable based on protocols from different groups, including the watch and wait approach, total neoadjuvant therapy, and the Mercury trial among others.[23–25]

The NCDB does not explain why patients may undergo cessation of radiation, nor specifies the pre-planned dose regimen. It's unclear whether women are more likely to stop treatment, potentially in the setting of side effects, or if radiation oncologists decide on different treatment doses for women compared to men. Further investigation should be directed towards elucidating whether the disparity in receipt of neoadjuvant radiation is patient-driven in the setting of a worse side effect profile or provider-driven, for example due to differences in body habitus.

Conclusions

Demographic, socioeconomic and clinical factors including gender, age, insurance type, clinical stage and receiving neoadjuvant chemotherapy, as well as hospital location were significantly associated with radiation dosing in this analysis. In particular, female sex was strongly associated with neoadjuvant radiation under-treatment. It is unclear if any of these associations are causative, and whether systemic issues, physician bias or patient preference contribute to the difference in received radiation dose. However, these factors should be individually evaluated to determine if they can be modified as patients who receive inadequate doses of neoadjuvant radiation experience worse outcomes.

Author contributions

All authors have read and complied with author guidelines.

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Declaration of competing interest

Dr. Stein has been a speaker for Merck and has received a grant from 11 Health. Dr. Dietz has been a speaker and teacher for Ethicon. Drs. Ofshteyn, Bingmer, Dorth and Steinhagen have no conflicts of interest or financial ties to disclose.

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