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ORIGINAL ARTICLE – COLORECTAL CANCER

Variation in the Use of Chemoradiotherapy for Stage II and III Anal Cancer: Analysis of the National Cancer Data Base

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ABSTRACT

Background. Treatment for anal canal cancer has evolved from radical operations to definitive chemoradiotherapy (CRT), which allows for sphincter preservation in most patients.

Objective. The aim of this study was to examine the use of CRT for patients with stage II and III anal cancer, among different patient demographics, geographic regions, and facility types.

Methods. Utilizing the National Cancer Data Base, we examined patients with stage II and III anal canal squamous cell carcinoma from 2003 to 2010. Via univariate analysis, we examined patterns of treatment by patient demographics, tumor characteristics, geographic region, and facility type (academic vs. community). A multivariable logistic regression model was built to evaluate differences in treatment patterns when adjusting by age, sex, race, comorbidities, and stage.

Results. A total of 12,801 patients were analyzed, of which 11,312 (88 %) received CRT. After adjusting for confounders, CRT was less likely to be administered to males [odds ratio (OR) 0.61, 95 % confidence interval (CI) 0.54–0.69], Black patients (OR 0.70, 95 % CI 0.59–0.83), and those with multiple comorbidities (OR 0.60, 95 % CI 0.51–0.72). CRT was not as widely utilized in the West (OR 0.74, 95 % CI 0.59–0.93), and patients treated in academic-based centers were less likely to receive CRT (OR 0.81, 95 % CI 0.72–0.92). Improved median overall survival was observed when CRT was utilized ($p = 0.008$).

Conclusion. When controlling for age, sex, race, comorbidities, and stage, discrepancies in the use of CRT for anal cancer treatment exist between demographic subtypes, geographical regions, and facility types.

With just over 7000 cases per year in the US, anal canal cancer is a relatively uncommon disease when compared with other gastrointestinal malignancies; however, its incidence has been growing considerably.[1,2] Initial treatment of the disease has evolved from radical surgical treatment, including abdominoperineal resection (APR), to a combined chemoradiotherapy (CRT) [modified Nigro protocol] approach that often allows for sphincter preservation.[3,4] Since Nigro's work, CRT has been solidified as the initial treatment of choice.[5–7]

In this study, we examine the use of CRT for the treatment of anal cancer. Current practice guidelines, according to the National Comprehensive Cancer Network (NCCN), recommend definitive CRT as the optimal primary treatment for non-metastatic anal canal squamous cell carcinoma.[8] In an attempt to eliminate bias, we excluded patients with stage IV disease, as well as patients with stage I disease. The standard treatment for those with stage I disease is usually CRT; however, some may have had small foci of disease, found incidentally in a hemorrhoidectomy or polyp specimen, for example, and thus may not have been considered for CRT treatment.[9] We felt that stage I disease would represent too heterogeneous a patient population for analysis. In order to have the most homogenous population to analyze where the initial recommended treatment of choice was clear, we analyzed stage II and III patients only.

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The specific aim of this study was to examine the use of CRT for patients with stage II and III anal cancer among different patient demographic characteristics, geographic regions, and facility types.

MATERIALS AND METHODS

The National Cancer Data Base (NCDB) is derived from hospital registry data from Commission on Cancer-accredited treatment centers. The database captures approximately 70 % of newly diagnosed cancer occurrences within the nation.[10] An even higher number of anal cancer occurrences are captured in the database (over 87 %), making the NCDB a powerful tool to examine this malignancy in particular.[11] Using the NCDB, we examined all patients with *de novo* anal canal squamous cell carcinoma from 2003 to 2010. We excluded all patients with anal margin cancer or other histologic subtypes. Variables of interest were demographics (age, sex, and race), comorbidities, cancer stage, facility type, and geographic region. We also evaluated factors that could possibly affect access to care, including patients residing in an urban versus rural location, miles needed to travel to a treatment center, education level, median income by patient zip code, and patient's insurance status. In the NCDB, comorbidities are defined by the number of components of the Charlson Comorbidity Score (0, 1, or 2 comorbidities).[12] Geographic region is defined as Northeast (CT, MA, ME, NH, RI, VT), Atlantic (NJ, NY, PA), Southeast (DC, DE, FL, GA, MD, NC, SC, VA, WV), Great Lakes (IL, IN, MI, OH, WI), South (AL, KY, MS, TN), Midwest (IA, KS, MN, MO, ND, NE, SD), West (AR, LA, OK, TX), Mountain (AZ, CO, ID, MT, NM, NV, UT, WY), and Pacific (AK, CA, HI, OR, WA). Facility type was defined as community (Community Cancer Program or Comprehensive Community Cancer Program), academic (academic/research program), or other (other specified types of cancer programs). The NCDB classifies patient residence as metro, urban adjacent to metro (we have redefined as 'suburban'), urban not adjacent to metro (we have redefined as 'small town'), and rural. All variables were evaluated by univariable analysis. Those variables with a p value <0.20 were evaluated in a stepwise multivariable logistic regression analysis, and the model was built to evaluate whether differences in patterns of treatment exist when adjusting by age, sex, race, comorbidities, cancer stage, metro/suburban versus small town/rural location, education, facility type, and facility location. A p value <0.2 was chosen in order not to lose any jointly significant but marginally insignificant variables. For those patients who did not receive CRT, we analyzed what treatment, if any, was received. Kaplan–Meier survival curves were constructed to estimate survival in those who received CRT treatment versus those who did not. They were also constructed to compare those who received CRT versus those who did not within the cohort of stage II and stage III patients. We also compared survival of those patients treated in community versus academic programs, as well as those treated in different facility geographic locations. In addition, we examined the use of CRT over the time period of the study to determine if year of treatment played a role. A runs test was performed to determine if there was a statistical difference in the use of CRT between years. Due to the de-identified nature of the data on acquisition, this study is not recognized as human subject research by our Institutional Review Board.

RESULTS

A total of 12,801 patients were analyzed, of which 11,312 (88 %) patients received CRT treatment and 1489 did not (12 %). Univariate analyses of patient characteristics for the two cohorts are listed in Table 1. Patients who received CRT were more likely to be younger (mean age 58.9 vs. 64.6 years; $p < 0.001$), female [7708/11,312 (68 %) vs. 866/1489 (58 %); $p < 0.001$] and White [9895/11,272 (88 %) vs. 1243/1489 (83 %); $p < 0.001$] when compared with those who did not receive CRT. Those with stage III cancers were more likely to receive CRT than those with stage II cancers [4653/5117 (91 %) vs. 6659/7684 (87 %); $p < 0.001$]. On univariate analysis, no statistically significant difference in the use of CRT in community treatment centers was observed when compared with academic treatment centers [7692/8667 (89 %) vs. 3478/3971 (88 %); $p = 0.15$]. There were statistically significant discrepancies in the use of CRT among different facility locations, ranging from 84 % (693/827) in the West to 90 % (2078/2300) in the Great Lakes and 90 % (684/756) in the Northeast. Those who received CRT were more likely to have no Charlson/Deyo medical comorbidities when compared with those who did not receive CRT [9384/11,312 (83 %) vs. 1112/1489 (75 %); $p < 0.001$]. Patients who received CRT were slightly less likely to reside in metro/suburban areas than those who did not receive CRT [10,627/11,312 (94 %) vs. 1401/1489 (95 %); $p = 0.05$]. The two groups had to travel a similar number of miles to treatment centers (20.9 vs. 23.5 miles; $p = 0.49$), resided in zip codes with a similar median income ($p = 0.67$), and had similar rates of graduation with a high-school diploma ($p = 0.15$). The two groups were also similar with regard to those patients who had insurance ($p = 0.65$).

A multivariable model for the likelihood of receiving CRT is presented in Table 2. In stepwise logistic regression, high-school diploma was eliminated from the model ($p = 0.88$). In multivariable modeling, age was not a

TABLE 1 Univariate analyses of patient characteristics comparing those who received chemoradiotherapy treatment with those who did not

	CRT ($N = 11,312$)	No CRT ($N = 1489$)	P value
Age, years [mean (IQR)]	58.9 (50–68)	64.6 (52–79)	<0.0001[a]
Sex			
Male	3604 (85)	623 (15)	<0.0001[b]
Female	7708 (90)	866 (10)	
Race			
White	9895 (89)	1243 (11)	
Black	1115 (85)	202 (15)	
Other	262 (86)	44 (14)	<0.0001[b]
Stage			
II	6659 (87)	1025 (13)	
III	4653 (91)	464 (9)	<0.0001[b]
Facility type			
Community	7692 (89)	975 (11)	
Academic	3478 (88)	493 (12)	
Other	142 (87)	21 (13)	0.150[b]
Facility location			
Northeast	684 (90)	72 (10)	
Atlantic	1609 (89)	207 (11)	
Southeast	2417 (87)	356 (13)	
Great Lakes	2078 (90)	222 (10)	
South	754 (88)	106 (12)	
Midwest	897 (89)	111 (11)	
West	693 (84)	134 (16)	
Mountain	474 (87)	72 (13)	
Pacific	1706 (89)	209 (11)	<0.0001[b]
No. of comorbidities			
None	9384 (89)	1112 (11)	<0.0001[b]
One	1261 (85)	221 (15)	
More than one	667 (81)	156 (19)	
Patient's residence			
Metro/suburban	10,629 (88)	1410 (12)	0.05[b]
Small town/rural	683 (90)	79 (10)	
Travel miles to treatment center [mean (IQR)]	20.9 (3.5–17.9)	23.5 (3.3–17.9)	0.492[a]
No high-school diploma			
29 % or more	2011 (87)	300 (13)	0.153[b]
20–28.9 %	2831 (89)	353 (11)	
14–19.9 %	2709 (89)	349 (11)	
Less than 14 %	3761 (89)	487 (11)	
Insurance status			
Yes	10,574 (88)	1397 (12)	0.651[b]
No	738 (89)	92 (11)	
Median income			
Less than $30,000	1712 (88)	239 (12)	0.666[b]
$30,000–$35,000	2284 (88)	311 (12)	
$35,000–$45,999	3302 (89)	424 (11)	
$46,000+	4014 (89)	515 (11)	

Data are expressed as n (%) unless otherwise specified

CRT chemoradiotherapy, *IQR* interquartile range

[a] Welch two-sample t-test

[b] Chi square test

TABLE 2 Multivariable model for the likelihood of receiving chemoradiotherapy treatment

Variable	OR (95 % CI)
Age, years (reference = 50)	0.90 (0.77–1.06)
69	
Sex (reference = female)	0.61 (0.54–0.69)
Male	
Race (reference = white)	0.70 (0.59–0.83)
Black	0.73 (0.52–1.03)
Other	
Stage (reference = stage II)	1.50 (1.33–1.69)
Stage III	
Facility location (reference = Southeast)	1.54 (1.17–2.04)
Northeast	1.23 (1.02–1.49)
Atlantic	1.45 (1.21–1.74)
Great Lakes	0.97 (0.77–1.24)
South	1.06 (0.83–1.34)
Midwest	0.74 (0.59–0.93)
West	0.84 (0.63–1.12)
Mountain	1.20 (0.99–1.45)
Pacific	
Patient residence (reference = metro/suburban)	1.31 (0.98–1.77)
Small town/rural	
Facility type (reference = community)	0.81 (0.72–0.92)
Academic	0.78 (0.48–1.26)
Other	
Number of comorbidities (reference = no comorbidities)	0.60 (0.51–0.72)
Two or more comorbidities	

OR odds ratio, *CI* confidence interval

predictor for receiving CRT [odds ratio (OR) 0.90, 95 % confidence interval (CI) 0.77–1.06]. Males were less likely than females to receive CRT (OR 0.61, 95 % CI 0.54–0.69), and Black patients were less likely to receive CRT (OR 0.70, 95 % CI 0.59–0.83) than White patients. Patients with stage III disease had increased odds of receiving CRT than those with stage II disease (OR 1.50, 95 % CI 1.33–1.69), while those patients with two or more comorbidities were much less likely to receive CRT (OR 0.60, 95 % CI 0.51–0.72).

After adjusting for these confounding variables, CRT treatment was not as widely utilized in the West region (OR 0.74, 95 % CI 0.59–0.93). Patients treated in academic-based cancer programs were less likely to receive CRT when compared with community-based cancer programs (OR 0.81, 95 % CI 0.72–0.92).

When examining facility types within each region, the region with the highest percentage of academic centers is the Atlantic, with 49 %, while the region with the lowest percentage of academic centers is the Mountain region, with 21 %. Of the 1489 patients who did not receive CRT,

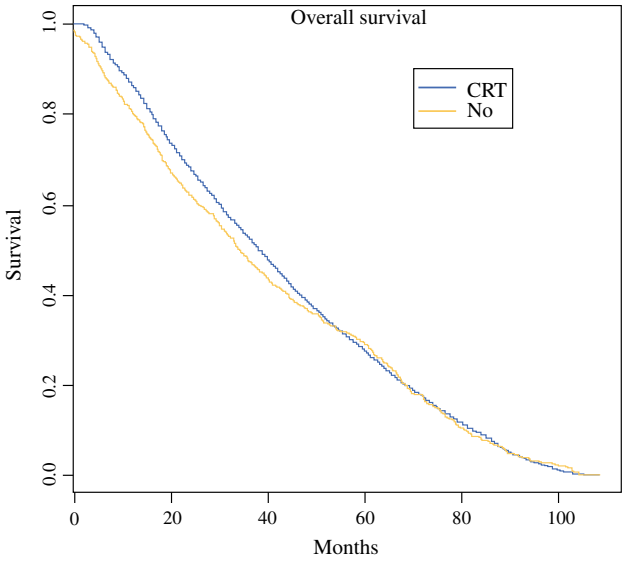

FIG. 1 Kaplan–Meier OS curve, grouped by CRT. The median OS for patients who received CRT was 38.3 months (95 % CI 37.5–39.3) compared with 34.0 months (95 % CI 31.9–37.0) for those who did not (log-rank test *p*-value = 0.008). *OS* overall survival, *CRT* chemoradiotherapy, *CI* confidence interval

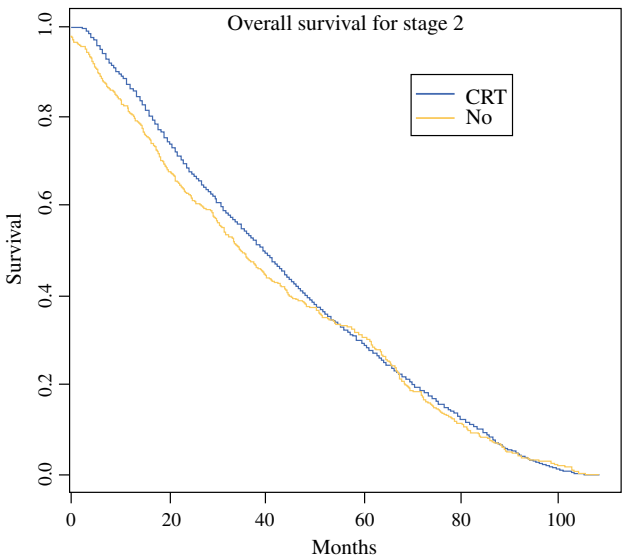

FIG. 2 Kaplan–Meier OS curve for stage 2, grouped by CRT. The median OS for patients who received CRT was 39.7 months (95 % CI 38.8–40.9) compared with 35.1 months (95 % CI 32.4–38.6) for those who did not (log-rank test *p* value = 0.023). *OS* overall survival, *CRT* chemoradiotherapy, *CI* confidence interval

586 (39 %) received radiation alone and 232 (16 %) received chemotherapy alone; 671 (45 %) received neither chemotherapy nor radiation treatment. Of these, 429 received surgical treatment. Overall, 328 patients received local excision or tumor destruction alone, while 95 patients underwent APR as their definitive treatment and 6 patients had an unspecified surgical procedure.

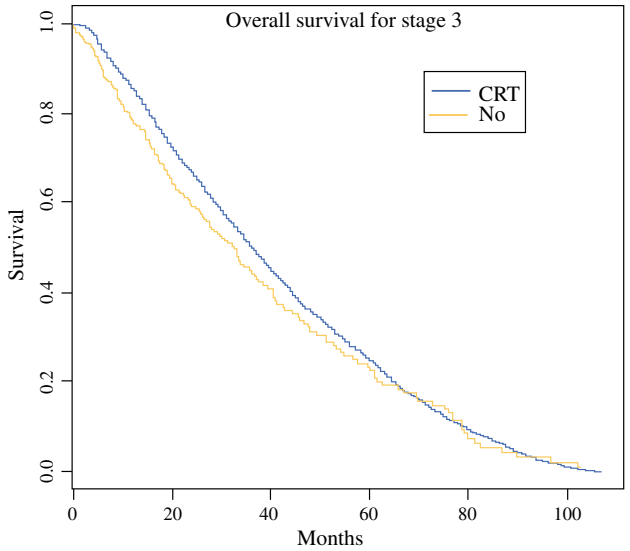

FIG. 3 Kaplan–Meier OS curve for stage 3, grouped by CRT. The median OS for patients who received CRT was 36.3 months (95 % CI 35.0–37.6) compared with 32.6 months (95 % CI 27.5–37.5) for those who did not (log-rank test p value = 0.023). *OS* overall survival, *CRT* chemoradiotherapy, *CI* confidence interval

Kaplan–Meier overall survival (OS) curves comparing those who received CRT with those who did not are depicted in Fig. 1. Median OS for those who received CRT was 38.3 months (95 % CI 37.5–39.3) versus 34.0 months (95 % CI 31.9–37.0) for those who did not receive CRT ($p = 0.008$). Kaplan–Meier curves for OS comparing those who received CRT with those who did not within stages II and III are depicted in Figs. 2 and 3, respectively. CRT was associated with improved OS within the cohort of stage II patients [median OS 39.7 months (95 % CI 38.8–40.9) vs. 35.1 months (95 % CI 32.4–38.6); $p = 0.02$], and was also associated with improved OS within the cohort of stage III patients [median OS 36.3 months (95 % CI 35.0–37.6) vs. 32.6 months (95 % CI 27.5, 37.5); $p = 0.02$]. A small but statistically significant difference in OS was seen when comparing patients by facility type [community vs. academic centers; 38.5 months (95 % CI 37.7–39.6) vs. 37.4 months (95 % CI 35.8–39.2), respectively; $p = 0.03$]. In addition, a noted difference in OS was observed when comparing geographical locations of treatment centers, ranging from 41.6 months (95 % CI 37.4–44.6) in the Northeast to 34.9 months (95 % CI 32.0–37.5) in the Midwest ($p = 0.001$).

When examining the use of CRT over the study period, a range of 87–91 % was observed; the lowest use was in 2009 and the highest use was in 2007. On runs test, no statistical difference was noted between years of the study and the use of CRT ($p = 0.13$).

DISCUSSION

Although anal canal squamous cell carcinoma is a rare disease, its prevalence is rising dramatically,[2] which has been largely attributed to the prevalence of the human papilloma virus (HPV).[13,14] To date, no literature has examined practice patterns or potential treatment disparities in the anal cancer patient population.

In this study, using the NCDB, we have determined that approximately 12 % of patients with stage II or III anal canal cancer do not receive CRT treatment. There is an association between demographic features and the number of comorbidities with receipt of CRT. When controlling for age, sex, race, comorbidities, and stage, discrepancies exist between geographical regions and facility types in the use of CRT as definitive anal cancer treatment. Patients who received CRT had an increased median OS when compared with those who did not.

After examining over 12,000 cases of anal cancer from 2003 to 2010, we determined that 88 % of patients received CRT. This is a significant improvement from the just over 60 % of patients receiving radiation treatment in a study of the Surveillance, Epidemiology and End Results (SEER) database from 1973 to 200[8,15] which could be due to advances in treatment protocols and more defined treatment in more recent years.[16–19]

In this study, males were much less likely to receive CRT for their anal cancer than females (85 vs. 90 %). This decreased probability of receiving CRT in males held true when controlling for confounders in multivariable analysis, the reasons for which are unknown. A potential variable is that the most common cancer in men is prostate cancer, which is often treated with pelvic radiation.[2] Patients with a prior history of pelvic radiation may not be candidates for further radiation to treat their anal cancer due to concerns regarding treatment toxicity. Another contributing factor may be HIV-positive status, which is known to be more common in men.[20] This disease, along with a low CD4 count, could result in a patient becoming more ill and unable to tolerate standard CRT regimens.

We have also demonstrated that Black patients are less likely to undergo CRT for their anal cancer than White patients (85 vs. 89 %). Racial disparities in cancer treatment and survival have been described with other malignancies. When examining rectal cancer patients, Kim et al. also demonstrated differences in CRT administration, depending on patient race.[21] Furthermore, multiple studies have demonstrated survival disparities in colorectal cancer and anal cancer among Black patients.[15,22–24] Many studies attribute these differences to socioeconomic and insurance disparities; however, in our study, this racial disparity was independent of those factors. As race is not a biological

construct, these and our observations should be brought to the attention of future treating providers.

Several studies of rectal cancer patients have demonstrated a correlation of lower income and socioeconomic status with poorer cancer outcomes and treatment disparities.[21,22] However, in our study, patient income, insurance status, residence in a rural versus metropolitan area, and distance traveled to the treatment center did not play a role in whether or not patients received CRT treatment.

In our study, we were not surprised to find that those patients with comorbid medical conditions were less likely to receive CRT. CRT for anal cancer is a difficult treatment to tolerate, with multiple severe early and late toxicities that an otherwise medically frail individual may not be able to endure. Toxicities include debilitating skin dermatitis, proctitis, and anal and vaginal stenosis. Doyen et al. found that over 30 % of patients suffer from severe toxicities.[25] Furthermore, patients who have completed anal cancer treatment and survived for multiple years have been shown to have other less-recognized side effects, such as poor incontinence and fecal urgency.[26] With this knowledge of potential treatment toxicities, it is likely that clinicians did not recommend treatment to otherwise frail individuals. We could not examine the type of radiation treatment utilized throughout the years of the study. With widespread use of modern radiation methods, such as intensity-modulated radiation therapy (IMRT) that has more favorable side effect profiles, we may start to see more prevalent treatment in those with comorbidities.[27]

We identified statistically significant differences in the use of CRT throughout different geographical regions on univariable as well as multivariable analysis. The reasons for this are unclear but are most likely multifactorial. There may be cultural differences in the goals of certain patient populations and physicians. The percentage of academic centers within a treatment region did not seem to correlate with practice patterns, but facility type in itself did. Although not statistically different on univariable analysis, on multivariable analysis we found that patients treated at academic centers were less likely to have CRT treatment. The reasons for this are not entirely evident. It is possible that more complex, medically fragile patients are referred to academic centers, and may not be candidates for standard treatment protocols. They may instead require specialized care pathways due to other comorbidities or prior treatments.

When examining OS, those patients who received CRT had improved survival when compared with those who did not receive standard treatment. This survival advantage was also present within the cohort of patients with stage II and stage III disease. Despite those treated at academic centers being less likely to receive CRT on multivariable analysis, OS only differed by approximately 1 month compared with patients treated in community centers, which suggests that those who did not receive CRT at academic centers were most likely chosen appropriately. A survival discrepancy between different treatment facility locations was observed; however, these survival differences did not exactly correlate with the discrepancies in CRT use in each location, suggesting that other unmeasured variables also play a role.

This study was limited in its retrospective nature, and we were limited to examining variables that were available in the dataset. Notably, HIV status and CD4 count are not reported during the years of this study. Furthermore, we do not know the reasons patients did or did not undergo CRT, and the database does not specify which chemotherapy regimen was utilized.

CONCLUSIONS

On multivariable analysis in this study, male sex, Black race, stage II disease, multiple medical comorbidities, regional location, and treatment center type were all risk factors for not receiving CRT. It is unclear whether those who did not receive standard treatment were not offered the therapy by their clinicians, refused the therapy, or were not candidates for the therapy; however, those who received CRT treatment had an improved OS. This study supports establishing protocolization of treatment guidelines for anal cancer in order to improve patient survival.

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