

Peer Review File

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Reviewer A

This study examined treatment and survival differences for locally advanced rectal cancer in Black American, White American (Hispanic and non-Hispanic, and Asian/Pacific Islander (AAPI) patients using the National Cancer Database resource. There were a total of 70,677 patients diagnosed between 2004-2014 that met the study criteria. Comparisons for receipt of treatment was based on clearly defined “standard” or “nonstandard” treatment modalities. The study concludes, as have previous reports, that Black patients were less likely to receive standard treatment modalities and had poorer survival when compared to non-Hispanic White patients. Hispanic and AAPI patients, in contrast, had better survival when compared to non-Hispanic White patients despite a higher percentage for both the Hispanic and AAPI patients receiving the nonstandard treatment modalities.

Specific comments:

-Suggest adding a table of the patient clinical and demographic characteristics by race and ethnicity.

Reply: The table of patient clinical and demographic characteristics has been added to the supplemental data – Table S1.

Changes in text: We added a statement regarding the characteristic table by race to page 6, line 3-4.

-Survival analyses should be presented as overall and rectal cancer specific survival. As the current report appears to only present overall survival.

Reply: The NCDB does not collect cause of death and therefore rectal cancer specific survival is not available. We will add this in our limitations.

Changes in text: We added a statement regarding the lack of rectal cancer specific survival within our discussion on page 10, line 14-16.

-The comment in the discussion section (page 8 line 25-27) regarding the differences in the HR for Stage II and III for White and Black patients receiving standard vs. nonstandard treatment should be qualified, as the difference for Stage II (HR 1.07) was not significant, as indicated in Table 6.

Reply: Thank you for noticing the need for clarification. The 95% CI was added to each hazard ratio.

Changes in text: This was addressed on page 9, lines 23-25.

-Are comorbidities contributing to the differences in treatment and/or outcome?

Reply: A higher Charlson-Deyo Comorbidity index (CCI) was associated with a lower odds of receiving standard treatment and lower survival as noted on page 6/line 12-13 and page 7/line 9, respectively. This was also presented in our multivariable analysis in Table 3 and Table 5, respectively. However, Black race continued to be associated with a lower rate of standard treatment and decreased survival when adjusted for socioeconomic and demographic factors

(including CCI) as discussed on page 7, line 18-19. We discussed the limitation of factors beyond what the NCDB captures on page 10, line 13-14.

Changes in text: N/A.

-The Kaplan-Meier curves on Figures 2 and 3 should have p-values added.

Reply: The p-values are included on the top right aspect of Figure 2 and 3.

Changes in text: The p-values were added to Figure 3 (already present in Figure 2).

Reviewer B

The authors add to existing evidence regarding health disparity of rectal cancer treatment without specifying the reasons or interventions, which is likely limited by the database. The authors first associate Black patients and Hispanic patients with not receiving standard treatment. Not receiving standard treatment is then associated with poor survival. The authors seem to conclude that Black patients have poorer survival due to not receiving standard treatment.

1. It is clear from the presented data that regardless of Black patients having received standard or not standard treatment, they always have poor survival. Regarding lines 17 to 20, how do you know that difference in mortality was due to standard vs. non-standard treatment rather than other factors associated with Black vs. White patients. Additionally throughout the paper, authors should not leap to the conclusion that Black patients have poor survival because they received not standard treatment. There are many other factors.

Reply: The cause of survival disparities between Black and White patients are multifactorial. However, a portion of this disparity may be accounted for by the receipt of standard treatment as discussed in our results under Racial Disparities within Standard and Nonstandard Treatment (page 7, line 12-25). While Black patients continued to have worse survival compared to White patients in both the standard and nonstandard treatment cohorts, the disparity was worse for those who underwent nonstandard treatment—particularly for those with stage III disease. Numerically, this can be seen by the hazard ratio (HR) of 1.10 for Black patients compared to White patients who underwent standard treatment compared to the HR of 1.17 for those undergoing nonstandard treatment. This finding was exacerbated in those with stage III disease where the HR increased from 1.13 in those who received standard treatment to 1.30 in those who received nonstandard treatment. The finding of reduced standard treatment and survival outcomes was significant even after adjusting for demographic, biologic, facility, geographic, and temporal characteristics. While this does not cover all potential confounding factors (as discussed in our limitations – page 10, line 13-14), it demonstrated a widening of survival outcomes with nonstandard treatment. Within our discussion of limitations, we acknowledge that the complex and structurally integrated nature of racial disparities may involve intricate socioeconomic factors and predispositions beyond those stated in our results (page 10, line 17-20). However, receipt of standard treatment is a potentially modifiable factor that may help reduce the survival disparities between White and Black patients.

Changes in text: We previously discussed the HR within our discussion on page 8, line 6-9.

Additionally, we discussed the multifactorial nature of the causes of increased incidence and

mortality among Black patients with rectal cancer on page 8, line 13-20. We also added into our discussion that other factors were associated with lower odds of receiving standard treatment, however we chose to focus our study on the disparity for Black patients as poor survival is known in this population (added on page 8, line 26-27 and page 9, line 1-3).

2. Regarding methods, it seems straightforward to group patients to standard treatment but not so straightforward to group patients in the non-standard treatment. How was this done? Were there at least two authors reviewing data? Was there grey area? Could bias been introduced (e.g. poor survival, data entry staff try to group data into non-standard treatment group)? Please include in methods and possibly limitation if there was some subjectivity.

Reply: The data was taken from the NCDB with limitations that include potential coding and clerical areas completed at the facilities (discussed on page 10, line 11). We used a strict definition of standard and nonstandard treatment as described in our methods section (page 4, line 14-23) that depended on the prior coding at the facilities that submitted the data. One gray area was the receipt of short course radiation which would not have been included in our standard treatment group as the patients did not receive concurrent chemoradiation. We discussed this limitation and that only 0.6% of patients were likely to have received this treatment. As the data entry staff did not bin the patients into standard and nonstandard treatment and only reported treatments received (chemo and/or radiation and/or surgery), there would not be a bias or subjectivity toward standard or nonstandard patients as this was defined after the data was entered.

Changes in text: N/A

3. All survival figures should have numbers at risk and censoring notations in the x axis. Figure 2 is especially important to understand the proportions among the groups.

Reply: Figures 2 and 3 were updated to include the number at risk and number censored.

Changes in text: Figure 2a/b and 3a/b have been updated as above.

4. Table 2 is quite confusing. Comparing now to 2014, preop chemo followed by surgery (no RT) and definitive chemo-RT with chemo omitting surgery are becoming an acceptable standard. You may want to include that in the discussion. I wonder if it is possible to do a sensitivity analysis looking at patients who never got surgery, patients who never got radiation, and patients who never got chemotherapy. It might be clearer and cleaner if you present it that way in Table 2 and accompanying text. You may also be able to find factors associated with less likely to get surgery, less likely to get radiation, and less likely to get chemotherapy that could be discussed.

Reply: This study was completed in the context of standard treatment regimens up to 2014. Currently, the omission of surgery and radiation are still investigational and limited to select patients who defer standard treatment or are treated on trial. While it is likely a limited number of patients may have undergone nonstandard regimens on trial, we are unable to parcel out that information and it is known that Black patients have been underrepresented in clinical trials. However, we agree that changes in these practice regimens are important for all patients as potentially omitting these treatments, if proven to be equally efficacious, can allow for less toxicity and morbidity. We have added Table S2 to the supplemental data that shows a

multivariate analysis of likelihood of not receiving surgery, chemo, or radiation. Factors related to a reduced likelihood of surgery, chemo, or radiation were similar to those that were related to a reduced risk of standard treatment and include increasing age, Black race, higher comorbidities, increased distance from the treatment facility, and a zip code in a non-metropolitan location. Between not receiving surgery, chemo, or radiation specifically, patients were less likely to receive surgery with non-private insurances however the likelihood of receiving chemo or radiation varied more depending on the type of non-private insurance.

Changes in text: We added the definition of standard treatment as a caption for Table 2 and noted we defined all other treatment regimens as nonstandard. Table S2 was added into the supplemental data. We added a segment discussing the features related to not undergoing surgery, chemo, or radiation on page 6, lines 15-26 and page 7, line 1-2.

5. Regarding table 1, it seems like every demographic is statistically significant in the two groups. Nothing is the same. How do you know that you have all the factors? Are there other confounding factors between the two groups you have not considered? I think you have two inherently different two groups despite they all come from the same database.

Reply: It is possible the patient populations that receive standard treatment versus nonstandard treatment are inherently different as multiple factors weigh into the decision of standard versus nonstandard treatment and may not be captured in the NCDB. However, subgroup analysis within the standard and nonstandard treatment cohorts continued to show a difference in survival outcomes between Black and White patients. This shows there is an inherent difference between the Black and White population that extends beyond the treatment received. However, the hazard ratio decreased from 1.17 in the nonstandard group compared to 1.10 in the standard treatment group which supports the rationale that receipt of standard treatment may improve the survival disparity between Black and White patients, and even more so in those with stage III disease. We believe establishing awareness of modifiable factors contributing to racial disparities is essential to ameliorate the survival outcome differences.

Changes in text: In our discussion, (page 8/line 13-15) we added that the cause of CRC incidence and mortality in Black patients are multifactorial and involve complexities beyond merely treatment regimens, which supports our finding of continued survival discrepancies between Black and White patients undergoing standard treatment. A portion of this concerning disparity can be accounted for by the limited access to preventative, screening, and treatment resources associated with low socioeconomic environments. Further investigation is essential but one potentially modifiable factor is the receipt of standard treatment, which is supported in our study as Black patients had a lower risk of mortality when compared to White patients in the standard treatment group compared to the nonstandard treatment group—particularly for those with stage III disease. We also highlighted on page 10/line 13-14 that our results may be biased by additional confounding and unobserved patient and facility characteristics not encompassed within the NCDB.

6. Because the database has such a large sample size, even small differences will be statistically significant. The discussion should also comment on size of the odds ratio with some of the factors (age, insurance, education, race) over others, since most of them are statistically significant.

Reply: We added other independently associated demographic and socioeconomic factors for the receipt of standard treatment into the discussion. However, we chose to continue emphasizing the disparity due to race as it was also an independent factor (with an odds ratio of 0.75) and an important factor to further evaluate the disparities in survival between Black and White patients. Additionally, the hazard ratio for mortality in Black compared to White patients reduced from 1.17 to 1.10 in the nonstandard to standard treatment groups (with an even larger reduction for those with stage III disease). This 7% higher probability of death for Black (in comparison to White) patients receiving nonstandard treatment compared to standard treatment is clinically significant as ameliorating the risk of death for Black patients should be a priority.

Changes in text: We added the additional information on other odds ratios for receipt of standard treatment on page 8/line 26-27 and page 9/line 1-3.

Reviewer C

The paper looks into a very important topic. Specifically, it explores the use of standard treatment across racial groups in locally advanced rectal cancer and the impact on survival. The study concluded that the receipt of standard treatment is lower in Black and Hispanic White patients compared to non-Hispanic White patients and nonstandard treatment is significantly associated with worse survival.

The paper is very well written overall. The methodology and statistical analyses are appropriate. The tables and figures are easy to read.

I do have the following question: Equal access to standard treatment is undeniably critical and will likely improve the racial disparities in rectal cancer outcomes. Could you please discuss the finding that the 5- and 10-year long survival are dramatically lower even among Black patients who received the standard of care? I understand that the difference is less pronounced compared to those who received non-standard treatment, however it is extremely concerning.

Reply: We agree that this finding is very concerning and have placed in our introduction and discussion that the causes for increased mortality in Black patients are likely multifactorial and complex – related to limited access to preventative, screening, and treatment resources which leads to a higher prevalence of both cancer and advanced disease. However, these characteristics make receipt of standard of care treatment even more important for Black patients as advanced disease will be more likely to require standard/updated treatment regimens. Additionally, while disparities still exist in the standard treatment cohort between White and Black patients, there was narrowing of the disparity from a hazard ratio of 1.17 to 1.10 (and even further for those with stage III disease).

Changes in text: We clarified this point on page 8, line 13-20.

Once again, I would like to congratulate the authors for this very well written paper.