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Original Research Article

Racial differences in colorectal cancer survival at a safety net hospital

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ABSTRACT

Background: While racial disparity in colorectal cancer survival have previously been studied, whether this disparity exists in patients with metastatic colorectal cancer receiving care at safety net hospitals (and therefore of similar socioeconomic status) is poorly understood.
Methods: We examined racial differences in survival in a cohort of patients with stage IV colorectal cancer treated at the largest safety net hospital in the New England region, which serves a population with a majority (65%) of non-Caucasian patients. Data was extracted from the hospital's electronic medical record. Survival differences among different racial and ethnic groups were examined graphically using Kaplan-Meier analysis. A univariate cox proportional hazards model and a multivariable adjusted model were generated.
Results: Black patients had significantly lower overall survival compared to White patients, with median overall survival of 1.9 years and 2.5 years respectively. In a multivariate analysis, Black race posed a significant hazard (HR 1.70, CI 1.01–2.90, p = 0.0467) for death. Though response to therapy emerged as a strong predictor of survival (HR = 0.4, CI = 0.2-0.7, p = 0.0021), it was comparable between Blacks and Whites.
Conclusions: Despite presumed equal access to healthcare and socioeconomic status within a safety-net hospital system, our results reinforce findings from previous studies showing lower colorectal cancer survival in Black patients, and also point to the importance of investigating other factors such as genetic and pathologic differences.

1. Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed and third most common cause of cancer mortality in both women and men in the United States (US), with an estimated 134,490 new cases and 49,190 deaths in 2016 [1]. CRC mortality in the US has decreased by about 50% between the years 1975 to 2012, possibly due to increased screening procedures and perhaps better oncological management [2]. However, some reports have indicated a higher reduction in mortality favoring Whites when compared to Blacks [1,3–7]. For example, according to Surveillance, Epidemiology, and End Results (SEER) data from 2008 to 2012, the Black population had the highest CRC incidence and mortality, and most significant decline in mortality was noted in White patients compared to all other racial groups [1].

Biological and molecular risk factors as well as differences in socioeconomic conditions and health care access have been implicated in causing racial CRC mortality disparity [8]. Many factors such as obesity, smoking, diets high in fat and red meat, alcohol use, and low vitamin D may contribute [9–12]. We are now understanding that there may be differences in tumor biology between racial groups; Blacks tend to be diagnosed with CRC at a younger age, present with more proximal, advanced, and aggressive tumors, and are more likely to have KRAS mutations [13–18]. Importantly, healthcare access inequality can lead to suboptimal screening [19], late diagnosis, and underutilization of recommended treatments. Racial differences in fear and mistrust of the healthcare system, and also in health literacy needs to be recognized [20–22].

Many studies on the subject of CRC racial survival disparity reported observations stemming from large database analyses without specific clinical, tumor, socioeconomic or treatment information. Also, a majority of epidemiological research was done in a White-dominant population. Moreover, there is a dearth

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of recent racial disparity studies performed in the era of new biologic agents developed for the treatment of metastatic CRC (bevacizumab, cetuximab and panitumumab). Lastly, as unequal access to healthcare has emerged as a significant contributor to poor survival of Blacks in several studies [18,23], we therefore sought to assess the influence of race on CRC mortality outcomes while minimizing the confounding effect of healthcare access and insurance coverage at an urban, academic safety net hospital consisting of a substantial proportion of Black patients.

2. Methods

This was a retrospective observational cohort study of stage IV CRC patients treated between January 1st 2004 and December 31st 2014 at the Boston University Medical Center (BUMC), the largest safety net hospital in the New England area serving a racially diverse population of patients. During this period, out of a total of 13, 043 patients either diagnosed or treated for solid organ cancers at BUMC, 651 patients had CRC (Table 1). Non-caucasians consisted of almost half (47%) of those cases. Approval from the institutional review board at BUMC was obtained beforehand. About 65% of the patients treated for metastatic CRC during this time period were non-White. Of the 9,849,135 total patient visits to BUMC during this time period, only 1.51% were uninsured visits without any financial assistance. 36.86% of these visits were Medicaid and 13% were charity. Patient data was obtained from our hospital's electronic medical record (EMR).

2.1. Study population and data collection

The study population (n = 147) comprised of patients presenting with stage IV CRC or with initial early stage CRC who later developed stage IV disease. The hospital cancer registry was used to obtain demographic features, date of diagnosis, AJCC staging, primary site of the cancer, and tumor histology. Primary site was categorized into 3 groups; right sided (cecum, ascending colon), left sided (descending colon, sigmoid, rectal) and others (transverse colon and appendix). Chart review was performed using the hospital's EMR system to collect data that was not available through the cancer registry. These included information such as self-identified race, disease burden, mutation status of the tumor, and response to chemotherapy. The primary outcome of interest was overall survival by race. We addressed possible confounding factors known to affect survival, which were: age, gender, Charlson co-morbidity index (CCI), body mass index (BMI), presence of metastasis at the time of presentation, carcino-embryonic-antigen (CEA) level at presentation, primary site and tumor histology. Treatment-related factors were also analyzed, including response to first line treatment.

At BUMC, KRAS and BRAF mutation testing was included in the standard evaluation of patients with CRC from 7/18/2008 onwards.

Table 1
Total solid tumor cases treated at BUMC between 2004 and 2014.

Primary site	Blacks	Whites	Others	Total
Brain	17 (14%)	98 (81%)	6 (5%)	121
Ovary	43 (32%)	75 (56%)	17 (12%)	135
Pancreas	96 (32%)	182 (62%)	18 (6%)	296
Colorectal	261 (40%)	343 (53%)	47 (7%)	651
Stomach	121 (40%)	154 (50%)	30 (10%)	305
Lung	443 (27%)	1099 (68%)	88 (5%)	1630
Liver/Intrahepatic Bile Duct	85 (30%)	143 (51%)	52 (19%)	280
Bladder	84 (27%)	210 (66%)	23 (7%)	317
Kidney/Renal Pelvis	144 (32%)	271 (59%)	41 (9%)	456
Other Sites	2905(33%)	5391 (61%)	556 (6%)	8852
TOTAL CASES	4199 (32%)	7966 (61%)	878 (7%)	13043

Microsatellite instability (MSI) testing also was part of our standard pathologic evaluation from 2007 onwards. KRAS analysis was performed via PCR in which PCR products were cycle sequenced with ABI BigDye® 3.1 cycle sequencing kit. Capillary-electrophoresis was performed on Genetic Analyzer 3130 and analyzed with sequencing analysis software 5.3.1. As for BRAF analysis, AS0-PCR was performed in duplicate with different DNA concentrations. PCR products were run in a 3% agarose gel and mutation status were compared and assayed with a positive and negative control. MSI testing was performed by immunohistochemical staining for 4 proteins in tissue sample: MLH1, MSH2, MSH6, and PMS2. MSI-PCR was performed with fluorescent labeled primers of BAT25 (6FAM-blue), BAT26 (NED-black), D5S346-APC (HEX-green), D2S123 (FMA) and D17S250 (HEX). PCR products were capillary-electrophoresed on ABI Genetic Analyzer 3130 and analyzed with GeneMapper4.0 software. The EGFR inhibitor cetuximab was first approved for treatment of metastatic CRC in 2004. This recommendation was updated in 2009, as it was found not to be effective in patients with KRAS mutant tumors [24,25]. In 2012, the US Food and Drug Administration (FDA) granted approval for cetuximab to be used in combination with chemotherapy for first-line treatment of KRAS wild-type (WT) metastatic CRC. The FDA concurrently approved the Therascreen® KRAS RGQ PCR Kit, establishing testing of tumor tissue for KRAS mutations as a standard of care. More than 75% of our patients were tested for KRAS even when it was not the standard of care at the time. Bevacizumab, approved in 2004 for first-line metastatic CRC treatment was also approved for second-line use in 2006. CEA testing was done at diagnosis and at regular intervals to assess for response to treatment or disease progression. It was performed using the Abbot Architect CEA Assay by Chemiluminescent Microparticle Immunoassay (CMIA), a modified and advanced form of ELISA.

Chemotherapy regimens have evolved over time and were incorporated as part of the standard of care at BUMC upon their FDA approval. We grouped first line chemotherapy regimens into three classes based on the combination of chemotherapeutic agents and biologics. Regimen I is defined as a regimen containing fluoropyrimidine based doublet plus a biologic agent (bevacizumab or EGFR inhibitor). Regimen II is defined as fluoropyrimidine based doublet without a biologic agent, and Regimen III included all other combinations.

The response to therapy was categorized based on standard AJCC criteria and grouped as complete response, partial response and stable disease [26]. Response to 1st line chemotherapy was categorized as response (complete or partial response or stable disease) versus no response (as progressive disease).

2.2. Statistical analysis

Summary statistics are presented for all study variables including the mean +/− SD for continuous variables and N (%) for categorical variables. Comparisons were done using ANOVA and Chi-squared tests as appropriate. The median and range are reported for survival time. Kaplan-Meier survival curves by race are also presented. For the primary outcome of survival, each demographic and clinical predictor was first examined in a univariate cox proportional hazards model with hazard ratios and 95% confidence intervals reported. Any predictor significant in the univariate model at the $p < 0.1$ level was considered a potential confounder and was included, along with race, in a multivariable adjusted model. A similar approach was used for the outcome of response to first line treatment with logistic regression as the modeling method and odds ratios reported. In adjusted analyses, $p < 0.05$ was considered statistically significant. Analyses were performed using Matlab 2016a (Mathworks Inc.) and SAS v9.4.