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Full Length Research Paper

Survival disparities in non-small cell lung cancer patients receiving radiation treatment: An investigation of race and gender

Yogesh Khanal[1], Julie Eaton[2], Janelle Pakish[1], Philemon Yen[1], Renato Martins[3], Laurie Carr[3], Keith Eaton[3] and Shilpen Patel[1]*

[1]Department of Radiation Oncology, University of Washington School of Medicine, 1959 NE Pacific Street, Box 356043, Seattle, WA 98195, U.S.A.
[2]Department of Mathematics, University of Washington, 1959 NE Pacific Street, Box 356043, Seattle, WA 98195, U.S.A.
[3]Department of Medicine Division of Oncology, University of Washington, 1959 NE Pacific Street, Box 356043, Seattle, WA 98195, U.S.A.

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Multiple studies evaluating non-small cell lung cancer disparities reveal male gender and African American race as independent predictors for poorer outcome. This study aims to evaluate the prognostic factors affecting survival of non-small cell lung cancer patients receiving radiation treatment at the University of Washington and to investigate whether race and gender disparities persist at the level of access to radiation treatment. Race, age, stage at presentation, radiation treatment length, and length of time from initial diagnosis to death or last follow-up were recorded and analyzed in a retrospective review of 372 patients receiving radiation treatment from 1994 - 2008. Of a final 372 patients, 306 were Caucasian, 32 African American, 34 Asian American and 134 female, 238 male patients. Cox regression models showed male gender [hazard ratio (HR, 1.34) p-value 0.027] and stage at presentation [stage III: HR, 1.93, p-value .001, stage IV: HR, 2.46, P value < 0.001] were predictors for shorter survival. In these analyses, race had no significant effect on length of survival. These results suggest disparate origins of race and gender inequity in non-small cell lung cancer outcome, highlighting that race differences in lung cancer survival disappear at the level patients have access to radiation treatment. This supports the notion that gender survival differences are likely the result of biologic differences, while racial survival disparities are an issue of healthcare access- however, additional studies are needed to conclusively discern the etiology of these disparities.

Key words: Race, disparity, radiation, lung, cancer.

INTRODUCTION

Although cancer continues to be the leading cause of death in the world, treatment options are improving (Ou et al., 2008). It is important to include all segments of society in these advancements, but this proves to be only an ideal. The unequal distribution of cancer burden is well documented and the American Cancer Society and other institutions have committed themselves to the elimination of cancer disparity - a formidable task. The elimination of disparity is defined as a reduction in cancer incidence and mortality and an increase in cancer survival among socioeconomically disadvantaged people to levels comparable to those in the general population (Ward et al., 2004). As a result, in order to achieve this goal, the complex nature of health disparities must be investigated and as many contributing factors identified as possible. Ideas on the origins of racial health disparities are complex and controversial. Data show overall life expectancy is lower for African Americans than for other racial and ethnic groups in the United States

*Corresponding author. E-mail: shilpenp@u.washington.edu. Tel: 206-598-4100, Fax: 206-598-3786.

(Bodenheimer and Grumbach, 2009).

In fact, infant mortality rates among African Americans are more than double than those for whites. While socioeconomic status appears to be the dominant influence on health status, issues of access to healthcare, cultural barriers, and even racism are also thought to contribute (King and Wheeler, 2007).

Overview of race disparities in cancer

Health disparities in cancer incidence, treatment and survival are tumor specific and diverse in both origin and magnitude. Research of these disparities involves investigating possible biological and lifestyle differences between demographic groups, but also requires an examination of healthcare access, delivery, and the effects of poverty. As an example, breast cancer has been shown to be more aggressive in African American women, thus resulting in poorer survival in comparison to other races (Cunningham and Butler, 2004). Also, some research indicates that differences in tumor size and histological grade in African American women compared to non-Hispanic white women disappeared when controlling for the time-interval since last mammography (Smith-Bindman et al., 2006). Other studies have argued that the “major factor precluding [minority populations] from sharing equally in advances in cancer research is prevailing societal and institutional racism” (Shinagwa, 2000). So in addition to adjusting treatment protocol in response to known biological differences in African American women, issues of health care delivery also need to be addressed in order to effectively remedy breast cancer survival differences. Similar multi-pronged problems result in disparities with regard to other cancers.

In certain types of cancers, such as prostate cancer, race can be used as a prognostic indicator of outcome. Black men have been shown to have more aggressive prostatic tumors, a higher rate of metastasis, and a poorer survival rate than white men (Kim et al., 1995). However, if differences in patient, tumor and treatment factors are controlled, research shows that biological differences between races are unlikely to be responsible for a substantial portion of survival discrepancy with regard to all cancers (Wisnivesky et al., 2005).

Another study found that the stage at which colon cancer is a diagnosed, accounts for more than half of the excess colon cancer mortality in African American versus Caucasian (Mayberry et al., 1995). Other studies have extended this finding to lung cancers as well (Akerley et al., 1993).

Non-small cell lung cancer and race

The present study focuses on non-small cell lung cancer disparity. Prior research has shown poorer survival in males and in African Americans, but has failed to clearly define the origins for these survival disparities (Gadgeel et al., 2001). Bach et al. pointed to differences in treatment in explaining racial differences, showing that African Americans with early stage NSCLC have lower rates of surgical resection (Bach et al., 1999). A study from the Department of Veterans Affairs in Vermont found similar results among late stage lung cancer patients, with a lower rate of prior tumor resection among African American patients, greater frequency of mediastinal lymph node involvement and metastases, and a lower frequency of prior radiation therapy (Akerley et al., 1993).

However, this same study found no differences in intensity of treatment, time to progression, response to treatment, or overall survival among Caucasian versus African American once they entered the prospective study and received uniform treatment. Additional research has shown that when ensuring uniform staging, treatment, and socioeconomic status, overall survival rates for black and white patients with NSCLC were similar (Bryant and Cerfolio, 2008) and socioeconomic status has now been shown to be an independent prognostic factor for poorer outcomes in NSCLC survival (Ou et al., 2008). In effect, past research indicates that differences in lung cancer survival between racial groups are thus unlikely to be a result of genetic or biological causes, but rather an issue of healthcare access.

Non-small cell lung cancer and gender

Past research also indicates poorer survival in males compared to females with respect to non-small cell lung cancer (Cerfolio et al., 2006). Women have been shown to be more susceptible to tobacco carcinogens, but have a lower rate of fatal outcome compared to men with non-small cell lung cancer (JAMA, 2006). These differences are independent of socioeconomic status. Ou et al. (2007) has also shown that male sex is an independent prognostic factor for poorer survival in stage I NSCLC patients.

The present study investigates lung cancer survival disparities, with regard to both gender and race, by investigating survival in patients who received radiation treatment at the University of Washington. By restricting the data pool to non-small cell lung cancer patients with access to radiation treatment at a tertiary hospital, this study is in effect controlling for access to healthcare. Since all patients in the present study are at an equal level of healthcare access, the expectation is that there will be no racial disparity in survival, but a gender disparity in survival will persist due to its non-healthcare access etiology. In addition, stage of presentation of patients will be investigated, and although past research indicates African Americans are more likely to present at

Table 1. Tabulations for NSCLC stages by race.

Stage	I or II (%)	III (%)	IV (%)	Total
Caucasian	49 (16)	142 (46)	115 (38)	306
African American	3 (8)	16 (50)	13 (41)	32
Asian/Pacific Islander	5 (15)	17 (50)	12 (35)	34
Total	57 (15)	175 (47)	140 (38)	372

Table 2. Estimated median survival times in days and stratified by race.

Race	Number of observations	Number of deaths	median survival
Caucasian	306	209	498
African American	32	19	608
Asian/Pacific Islander	34	22	413

a higher stage (Gadgeel et al., 2001), investigating patients at the same level of healthcare access should not show significant differences if issues of access to care are at the root of this disparity. Lastly, any difference between date of diagnosis and start of radiation treatment will be assessed to investigate possible disparities in healthcare access after initial consult at radiation oncology and the actual start of radiation treatment.

MATERIALS AND METHODS

A retrospective review of 372 patients who received radiation treatment for non-small cell lung cancer at the University of Washington from 1994 to 2008 was conducted. Complete cases were those patients who received the entirety of their radiation treatment at the University of Washington, and whose medical records included race, age, gender, stage of presentation, and length of time from initial diagnosis to death or last follow-up.

All patients included in this study were staged, treated, and prescribed radiation doses per treatment guidelines at the time. Treatment planning was undertaken at the University of Washington Medical Center (UWMC) by staff radiation oncologists per specialty standard.

Exposure in this study was defined as a non-small cell lung cancer diagnosis, which was biopsy proven, staged cancer for all patients in the study. End points included date of death or date of last follow-up. Date of death was obtained either directly through patient medical records, or through the social security death index. Patients without a date of death either from their medical chart or through the social security registry were considered to be still alive. For these patients, the date of their last follow-up at the University of Washington was coded and included in the analyses.

Data was organized in Microsoft access, and statistical analyses were performed using The R project for statistical computing. To investigate disparities in stage of presentation, chi-squared tests were used to examine the significance of differences in the proportions of each stage between racial groups. A Cox proportional hazards model was used to evaluate survival, and included the following variables: age, race, gender and stage of presentation. A linear regression model adjusting for those same variables was used to investigate lag time from diagnosis to treatment.

This study was approved by the Institutional Review Board at the University of Washington.

RESULTS

Of a total 372 patients, 306 were Caucasian, 32 were African American, and 34 were Asian/Pacific Islander. Among all patients, 57 presented with stage 1 or 2 NSCLC, 175 at stage 3 and 140 at stage 4. These results are summarized in Table 1. No significant differences were found in the stage of presentation between Caucasians, African Americans and Asian/Pacific Islanders (P value < 0.89).

Using the Kaplan Meier technique, median survival after diagnosis was estimated for Caucasians, African Americans, and Asian/Pacific Islanders at 498, 608, 413 days respectively. These results, along with the number of deaths observed in each racial category are summarized in Table 2. Cox regression models revealed male gender [hazard ratio (HR, 1.34) P value < 0.027] and stage of cancer [stage III: HR, 1.93, P value < 0.001, stage IV: HR, 2.46, P value < 0.001] to be significant predictors of survival. Other variables in the Cox model such as age and race were not significant. Tables 3, 4 and 5 summarize the results of the survival analyses.

Lastly, an ANOVA test of the covariates from linear regression models was performed to determine which variables in the model account for a significant amount of variation of the time between diagnosis and treatment. In other words, the ANOVA test hoped to determine which variables in the logistic regression model significantly predicted a longer or shorter lag time from diagnosis to treatment. None of the variables in the model, which included race, stage, age, and gender, proved significant (Table 6).

DISCUSSION

Poorer survival was associated with gender but not race in the study population. These results are consistent with previous research on survival disparities of non-small cell lung cancer patients. By isolating a patient population at

Table 3. Summary of Cox regression coefficient.

	Coefficient β	Standard error of β	P value	Hazards ratio
Stage III	0.66	0.20	0.001	1.93
Stage IV	0.90	0.21	< 0.001	2.46
Age	0.019	0.005	0.009	1.01
Gender = male	0.30	0.13	0.027	1.34
Race = African American	- 0.11	0.24	0.65	0.905
Race = Asian/Pacific Islander	- 0.0112	0.23	0.96	0.99

Table 4. Estimated median survival time in days and stratified by stage.

Stage	Number of observations	Number of deaths	Median survival
I or II	57	31	1107
III	175	119	450
IV	140	100	371

Table 5. Estimated median survival time in days and stratified by gender.

	Number of observations	Number of deaths	Median survival
Female	134	88	686
Male	238	162	418

Table 6. ANOVA decomposition of days to start treatment adjusted by stage, age and gender.

Covariate	Degrees of freedom	Sum of squares	Mean square error	F-value	P value
Stage	2	34.66	17.33	7.48	< 0.001
Age	1	0.22	0.22	0.09	0.76
Gender	1	6.27	6.27	2.71	0.10
Race	2	4.73	2.36	1.02	0.36
Residuals	365	848.43	2.32		
Total	371	893.35			

a common level of healthcare access, it is possible to further investigate whether certain disparities are a result of a lack of access to healthcare. Akerly et al. (1993) was able to isolate a patient population at a similar level of access by designing a prospective study of patients who after a certain point all received treatment for their non-small cell lung cancer at the VA hospital system. The present study shows a similar result to Akerly et al. (1993) with no racial survivability difference among patients with access to radiation treatment at a tertiary hospital.

In addition, this study found that African American patients were no more likely than white patients to present with advanced stage disease. Akerly et al. (1993) used patients who all had advanced stage disease and was able to show greater rates of metastases among African American patients. However, in this study, since any patient that received the entirety of their radiation treatment at a University of Washington hospital was included, patients encompassed both early and late stage lung cancers at presentation - and no significant differences were found among black and white patients. All patients in our study had access to, and were able to complete a full course of treatment at the University of Washington. Thus, finding no difference in stage of presentation between racial groups indicates that healthcare access could be at the root of this disparity.

The analysis of time elapsed between diagnosis and treatment was performed in hopes of further investigating possible treatment differences between the races, but none were found. This provides further evidence of equal healthcare access between racial groups in this study, as an increased lag time between diagnosis and initiation of treatment in one racial group versus another could result

from disparate access to healthcare.

Being male was associated with a 1.34-fold greater risk of death compared to female patients. Recent research has shown somewhat similar results, with men maintaining a 20% increased risk compared to women following a diagnosis of NSCLC (Visbal et al., 2004). This same study found that survival for men with NSCLC stage Ia was similar to that of women with stage Ib NSCLC, and that men with stage IIa had outcomes similar to women with stage IIb. Essentially men with a given NSCLC stage had survival equivalent to women with the next stage of NSCLC.

Current research indicates a genetic predisposition to NSCLC (Visbal et al., 2004; Nakamura et al., 2000; Sellers et al., 1992) Cellular and immunological markers have been shown to not only vary with NSCLC stage, but also with patient demographic characteristics such as age and gender as well. Differing immunological markers not only suggest varying biological response to NSCLC between men and women, which could be the basis of differential survival, but it also has important treatment potential as well (Nakamura et al., 2000).

It logically follows that those patients who experience worse outcomes primarily as a result of their lack of healthcare access would not be included in the study population, as they would be less likely to have ongoing access to an academic hospital in order to complete their full course of radiation treatment. Gender was found to be an independent prognostic factor in NSCLC outcome independent of healthcare access. However, isolating a patient population at an equal level of healthcare access eliminated known racial differences in survival. The results of this study indicate that healthcare access may be an important confounding factor in disparate outcomes in NSCLC.

A limitation of our study is the small number of African American patients. Given the small number of African Americans (n = 32), a sensitivity analysis was performed to investigate the size of a hazard ratio detectable given a power of 0.8. In this study, given the proportion of Caucasians to African Americans, it would be possible to detect a hazards ratio of 1.77 with 0.8 power, but nothing smaller. In terms of median survival, the median survival for African Americans needed to have been 1.77*498 = 881 days or greater or 281 days or less than Caucasian patients to detect a difference. As an example of prior research results in racial survival differences, Gadgeel et al. (2001) found that African Americans in comparison to whites with local stage NSCLC in the Detroit metro area were at a 1.24 relative risk of death, $P < 0.0001$ (Gadgeel et al., 2001). It is worth noting that our study found a slight non-significant survival advantage among African American patients, HR 0.905. It is thus possible only to say that our results are trending toward no racial differences in survival. Further studies, with more robust power would allow for more definitive conclusions.

Of note, the small number of African American subjects included in this study may reflect the larger issue of disparate access. Our study's inclusion criteria of cases from 1994 to 2008 reflected only those patients that completed their entire course of radiation therapy at the University of Washington Medical Center (UWMC). It is possible that the small number of African American patients that did complete their entire radiation course at UWMC simply reflects the barriers to accessing radiation therapy at a tertiary care facility among members of their racial group. However, further studies are needed to make this conclusion definitively.

Another potential limitation of this study is the length of time this study spans, 1994 to 2008. There has been great changes in radiation techniques and treatment modality in these fourteen years. However, there were no differences between genders or races, in time period from which they were treated. Nonetheless, it is feasible that non-significant differences in the date of each case may have altered results. Also, though we did include patient prognostic factors such as stage of cancer and age of patient into our Cox model, other patient prognostic factors such as nutrition, co-morbid medical conditions were not coded and thus not included in our calculation. It is possible that these other prognostic factors could have accounted for some of the survival differences seen between male and female patients. Further investigation will be needed to characterize the root of gender differences in our study.

The implications of the present study's results are important to consider when assessing the problems of healthcare in the United States. The trend of the present study's findings shed light on the arguably serious issues of disparate healthcare access among certain segments of our society. It is well known that regions in the nation with higher health care spending do not have better outcomes (Fisher, 2003) and issues of healthcare access may very well be a significant contributing factor for this discrepancy.

Studies in the past have suggested institutionalized racism, including cultural barriers between physicians and patients, as a reason for racial disparities in health (King and Wheeler, 2007). It is well known that neighborhoods that have high proportions of African American or Latino residents have far fewer physicians practicing (Komaromy, 2006). In addition, it is possible that unconscious forms of discrimination may continue to enter interactions between patients and their caregivers and influence access to care for minorities (Van Ryn, 2002). However, the trends of the present study's findings do not support this, as survival was equal when access among patients was equal. Further research is necessary to pinpoint the exact biological etiology of the gender disparity in non-small cell lung cancer survival. With regard to the racial disparity of lung cancer outcome, further research into the specific nature of disparate access to healthcare among African Americans is urgently necessary in order to effectively combat this

problem.

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