Role of Race in Survival among Patients Who Refuse the Recommended Surgery for Early Stage Non-Small Cell Lung Cancer: A Seer Cohort Study

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Abstract

Introduction: Blacks are more likely than whites to refuse potentially curative surgery for early stage non-small cell lung cancer (NSCLC). We sought to compare survival among blacks and whites in this population, as patients who refuse the surgery are expected to be different from others. Also, racial differences are known to exist in the end-of-life care preferences.

Methods: Surveillance, Epidemiology, and End Results (SEER) database was used to create a cohort of 970 patients diagnosed with stage I and II NSCLC between 1988 and 2002 who refused surgery. The outcome was overall and lung cancer-specific survival, while race was the key predictor variable. Kaplan-Meier survival analysis was performed to estimate crude survival differences. Potential confounders were adjusted for in Cox-proportional regression analysis.

Results: A majority (78%) was white and 11% were blacks. In the crude analysis of all-cause mortality, blacks tended to have lower mortality than whites (p-value 0.075). In the adjusted model, blacks had 19% lower risk of mortality than whites (HR 0.81, 95% C.I. 0.67, 0.99, p-value 0.045). There were no differences in cancer-specific mortality in either crude or adjusted analysis. Females, individuals who receive radiotherapy and those with higher education in a county had lower risk of overall and cancer-specific mortality.

Conclusions: Among patients who refused surgery for early stage NSCLC, blacks have a lower risk of all-cause mortality than whites, but there are no differences in the cancer-specific mortality. This should be interpreted with caution due to lack of chemotherapy data and information on quality of life.

Keywords: Early stage non-small cell lung cancer; Refuse surgery; Survival; Race

Introduction

Lung cancer is the leading cause of cancer mortality in both males and females. After a consistent increase, the mortality started to decline from early 1990s, with the highest rate of decline noticed in the past few years [1]. However, crude racial differences in lung cancer mortality, which could be traced back to 1960s, [2] still continue to exist. [3] Although 5-year relative survival increased by 35% from 1975 to 2002 (12% to 16.2%) in all races combined, yet it increased only marginally from 11.6% to 12.5% in blacks [4].

Blacks are less likely than whites to receive the potentially curable recommended surgical treatment for early stage (stage I-II) non-small cell lung cancer (NSCLC) [5-10]. However, surprisingly, there are no significant racial differences in mortality once potential confounders are adjusted for [11-14]. In our previous paper, we demonstrated that blacks are more likely than whites to refuse the recommended surgery [37]. Patients who refuse the potentially life-saving surgery are expected to be different from rest of the population, especially in terms of their faith and beliefs about the medical practices and possibly their end-of-life care preferences [38]. Racial differences are known to exist in these areas. For instance, in general, blacks have greater distrust in medical system and false perceptions about diagnosis, treatments and prognosis[15-19]. Also, blacks are more likely than whites to pursue aggressive life-sustaining therapies and less likely to enroll for hospice care [20-23]. All of these issues may impact survival once a patient refuses the surgery. Therefore, we hypothesized that there will be racial differences in the survival among patients who refuse the recommended surgical treatment. We specifically aimed to compare the overall survival as well as lung cancer-specific survival among blacks and whites for early stage NSCLC who refused the surgery for early stage NSCLC.

Materials and Methods

This study and data are the extension of our previous study [37] which determined the influence of race and health disparities on refusal of recommended potentially curative surgery.

Data

This cohort study utilized the Surveillance, Epidemiology, and End Results (SEER) database which cover geographic areas representing about 28% of the U.S. population, about 25% of whites and 26% of blacks. SEER-17 November 2009 Submission (1973-2007 varying) database was obtained using the SEER*Stat software [24].

Inclusion/Exclusion criteria

We included all patients who were diagnosed with malignant neoplasm of lung and bronchus with early stage (stage I and II) NSCLC histology between 1988 and 2002 and who refused the recommended surgery. This time period was chosen to allow uniformity of data coding throughout the study period. Also, as the database contained...
information on patients until 2007, we used 2002 as our cut-off point to allow five years of observation on patients diagnosed in 2002. NSCLC histology was identified using ICD-O-3 coding (8000-8040, 8046-9989). American Joint Committee on Cancer Staging (AJCC) stage 3rd edition (1988+) was used to identify patients with stage I and II. No specific age limit was set for inclusion criteria; however patients with unknown age were excluded.

**Variables**

The primary outcome of interest was overall as well as lung cancer-specific survival. The survival time was defined as the number of months from the date of diagnosis to one of the following - date of death, date last known to be alive, or follow-up cutoff date. Overall survival was coded as alive or dead, while lung cancer-specific survival was coded as ‘alive or died of other causes’ or ‘died of lung cancer’. The information on mortality is collected and maintained by the National Center for Health Statistics (NCHS) [25] and is incorporated within the SEER database, accessible through the SEER*stat software [26]. The key predictor variable was race, which was categorized as white, black, and others (including American Indians/Alaskan Natives, Asians/Pacific Islanders, all other races and unknown). Although we included the “other” category in the race variable, this was not included in our primary hypothesis because of the lack of clinical information gained from a merged race category. Based on prognostic implications, some covariates which were included in the analysis are (1) age - categorized as < 50 years, 50-64 years, 65-79 years and 80 and above years, (2) gender, (3) marital status - categorized as married or not married (single/ never married/ separated/ divorced/widowed), (4) year of diagnosis (continuous variable from 1988 to 2002) (5) radiation therapy (performed, not performed or refused), (6) geographic region (as per the U.S. Census Bureau [27], categorized as North-East, West, Mid-West and South). (7) proxy measures (county level data) of socio-economic status (SES) such as education (percentage less than high school education), percentage of people with English language difficulties and if they lived in a metropolitan or a non-metropolitan county to roughly estimate the proximity and availability of health care. The county level continuous variables (percentage less than high school education, percentage of people with English language difficulties) were both categorized into quartiles. The classification of metropolitan vs. non-metropolitan counties was based on the “SEER Rural-Urban Continuum Code” [28]. As education and income are highly correlated, income was not included in the model.

Analysis was conducted using STATA/SE 11.1 for windows [29]. Two separate analyses were carried out – (1) for all-cause mortality and (2) for lung-cancer specific mortality. In both the analyses, Kaplan-Meier survivor curves were created for the comparison of crude survival among different races and the log-rank tests were used to test for the statistical equivalence of the curves. The decision to use log-rank test in contrast to one of its test variations was made a-priori, because we did not find a need to apply differential weights at any specific failure time. To determine the differences between blacks and whites, Bonferroni corrected alpha-level of 0.017 (0.05/3) was used as cut-off significance. Bonferroni alpha correction was applied because the Kaplan-Meier analysis contained three race groups, while we wanted to detect differences only between blacks and whites. Kaplan-Meier survivor functions were used to estimate one, three and five -years ‘all-cause’ as well as ‘lung cancer-specific’ survival probabilities across different races.

To estimate the hazard ratios across different races while controlling for potential confounders, the most parsimonious Cox-Proportional Hazard Model was created based on the p-value significance cutoff point of 0.05. To account for the random-effects of county, first a shared-frailty Cox model was created. However, the likelihood ratio test for the estimated frailty variance (\(\hat{\theta}\)) was borderline significant (p-value 0.070), signifying that the correlation because of the random-level county effect in our model may be ignored. Nevertheless, to account for possible correlations within individuals from a same county, adjustment was performed by clustering on different counties in the Cox model. The functional forms of the continuous variables (year of diagnosis, high school education and language difficulty) were identified using Martingale residuals and the Lowess smoother curves. No significant interactions of the covariates with race were found based on the likelihood ratio test with a p-value significance cutoff point of 0.05. None of the covariates was found to violate the proportional hazard assumptions, which were tested using a graphical technique (Log-Log plot) and an analytical technique (Grambsch and Therneau’s method). The Goodness-of-Fit was assessed using the Cox-Snell residual method and the Harrell’s c concordance statistic was used to determine the predictive power of the fitted Cox Models.

**Results**

The dataset contained information on 970 individuals from 192 counties. One person with unknown race was excluded from the analysis. The majority (78%) was white while 11% were black. There were roughly similar number of males and females, a majority was between the age group 65-79 (53%), about 40% were married and 87% lived in a metropolitan county. More blacks (47%) received radiation therapy as compared to whites (41%), but the differences were not significant (Pearson chi-square p-value 0.38) [Table 1]. On an average, about 20% of patients had less than high school education (standard deviation 7.5, range 5.6 - 50.6%) and fewer than 7% were categorized as having ‘language isolation’ (standard deviation 5, range 0 - 17.3%).

The overall median survival (95% C.I) was 17 (16-19) months in whites, 19 (15-29) months in blacks and 21 (16-27) months in individuals of ‘other’ race. All-cause as well as lung cancer-specific survival probabilities over 1, 3 and 5 years are depicted in Table 2.

**Model 1: All-cause mortality**

Out of a total of 969 observations, 11 events occurred on or before the start date. Of the remaining 958 eligible observations, 903 events occurred while 55 were censored (about 5% whites and 8% blacks). The total follow-up time was 24,456 person-months. During the follow-up period, 488/750 (65%) whites and 78/110 (70.9%) blacks were alive at one year; 169/750 (22.5%) whites and 32/110 (29.1%) blacks at three years, and 67/750 (8.9%) whites and 11/110 (10%) blacks were alive at five years.

Kaplan-Meier survivor curves for different races are depicted in Figure 1. Blacks appeared to have better overall survival compared to whites. The Log-rank test showed that although the overall differences in survival among different races were significant (p-value 0.047), but those between blacks and whites were not (p-value 0.075).

The significant predictors which were incorporated in the final Cox Proportional hazards model, clustered by county, include race, gender, radiation therapy, year of diagnosis and education. Blacks had 19% lower risk (HR 0.81, 95% C.I. 0.67, 0.99, p-value 0.045) and the individuals of ‘other’ race had 17% lower risk (H.R. 0.83, 95% C.I. 0.69, 0.99, p-value 0.048) as compared to whites. Females had 22% lower risk as compared to males (HR 0.77, 95% C.I. 0.69, 0.88, p-value <0.001). As expected, not receiving radiation therapy was associated with an
increased risk (HR 1.33, 95% C.I. 1.16, 1.54, p-value <0.001) compared to those who underwent radiation therapy. With every year increase from 1988, the risk decreased by 3% (HR 0.97, 95% C.I. 0.96, 0.99, p-value <0.001). The risk also increased as the percentage of individuals with less than high-school education in a county increased [Table 3].

The Cox-Snell residual method suggested the final model fits the data very well [Figure 3a]. The Harrell’s c concordance statistic was 0.5722, which suggests that the predictive ability of the model was 57%.

Model 2: Lung cancer-specific mortality

Out of a total of 969 observations, 11 events occurred on or before the start date. Of the remaining 958 eligible observations, 710 events occurred while 248 were censored (about 26% whites and 28% blacks). The total follow-up time was 24,456 person-months.

Kaplan-Meier survival curves for different races are depicted in Figure 2. The Log-rank test showed that there were no overall differences in the survival among different races (p-value 0.1813).

Race was not found to be a significant predictor in the Cox Proportional Hazards model clustered by county; however, it was
Figure 2: Crude lung cancer-specific survival estimation using Kaplan-Meier survival curves.

**Discussion**

It is known that there are no racial differences in survival in patients with early stage NSCLC once potential confounders are adjusted for in the analysis [9-12,14,30]. We demonstrate that among patients who refused the recommended surgery for early stage NSCLC, blacks have a lower overall risk of mortality than whites, but there are no differences in the cancer-specific mortality. We specifically concentrated on people who refused the recommended surgery because the individuals who refuse to seek potentially life-saving recommended surgery are expected to be different from those who do not undergo surgery due to contraindications and from those who undergo the surgery. As such this specific group of individuals forms a unique population which warranted further attention. We believed there may be racial differences in survival within this population because of the known differences in the end-of-life care choices among different races. For instance, among patients with advanced cancers, blacks are less likely to enroll for hospice care, blacks have about 70% higher odds of revoking hospice to pursue life-prolonging therapies as compared to whites [33]. On the other hand, data also suggest that terminally ill lung cancer patients who are cared for by hospice may actually have longer survival than those not under hospice care [34].

The fact that we did not find racial differences in the lung cancer-specific survival undermines the fatal course of the illness without treatment regardless of the end-of-life care choices. Further, the differences in median overall survival between blacks (19 months) and whites (17 months) found in our study may not be clinically meaningful without the understanding of quality of life which could be determined in our study.

We recognize several limitations of our study. First, as this is a...
cohort study involving secondary data analysis, potential information bias due to misclassification of race, age and other variables in the database could not be excluded. Also, bias introduced from potential coding errors inherent in the SEER database cannot be ruled out. For instance, error in coding “surgery refused” to “unknown” category or “not recommended” may cause study results to deviate in either direction. However, given a fairly large sample as well as national database, we hope that such errors are minimal, although certainly possible. Second, we used “proxy measures” of the SES variables which were linked to county, because SEER does not contain individual level data for these. Third, our study was not able to control for several other prognostic factors such as the use of adjuvant chemotherapy (which improves survival in early stage NSCLC as compared to no chemotherapy [37]), history of smoking, co-morbidity index, psychological distress, psychiatric disorders, functional status, access to health care, health insurance, cultural barriers, social/family support, information on spirituality and beliefs and hospice utilization [35]. It may not be imprudent for our study to assume fair homogeneity in terms of performance status and co-morbidities in our patient population as these are the patients who were recommended surgical treatment and lung cancer surgery mandates good performance status and absence of significant co-morbidities. Also, access to health care may be approximated by using metropolitan vs. non-metropolitan residence status. Some of this information could be obtained from the SEER-linked Medicare database; however that would restrict the study population to patients over the age of 65 and also to a population that has somewhat better prognosis compared to those with Medicaid and no insurance [36]. Last but certainly not least, although overall sample size is fairly large, yet proportion of black patients is relatively small compared to whites. This is, however, representative of US population in general and also a reflection of the rarity of event being studied.

**Conclusion**

Although blacks are more likely than whites to refuse the recommended surgery for early stage NSCLC, yet among patients who refused the surgery, there is no differences in the lung cancer-specific mortality. This reflects the uniformly fatal course of the disease once the potentially life-saving treatment is refused, and racial factor alone does not impact survival. This should be strongly emphasized by physicians during their conversation about treatment choices. Blacks do have a lower risk of all-cause mortality than whites, which may be a reflection of aggressive end-of-life care choices preferred by blacks compared to whites. However, our findings should be interpreted with caution due to the unavailability of chemotherapy as well as end-of-life care data in our study. Future studies also should incorporate data on hospice use and quality of life measures.

**Acknowledgement**

I wish to thank Anhassios Angiris, MD, Charity G. Moore, PhD, MSPH, Kevin Kraemer, MD, MSc., Gordon Wood, MD and (Joyce) Chung-Chou H. Chang, PhD for their support in writing and editing of this manuscript.

**References**
