Original Study

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Disparities in the Treatment and Outcome of Stage I Non–Small-Cell Lung Cancer in the 21st Century

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Abstract

Racial disparities are historically profound and affect outcomes in early stage non–small-cell lung cancer. We aimed to explore if recent advances in radiotherapy and surgery have improved epidemiological differences in outcomes related to race. African American patients continued to do worse in a contemporary Surveillance, Epidemiology, and End Results data set, because of increased association with T2 disease, older age, squamous histology, male sex, and suboptimal treatment.

Background: African American (AA) individuals are less likely to receive treatment and more likely to die from cancer compared with Caucasian (C) individuals. Recent advancements in surgery and radiation have improved outcomes in early stage non–small-cell lung cancer (ESNSCLC). We studied racial disparities in ESNSCLC in the past decade. **Patients and Methods:** The Surveillance, Epidemiology, and End Results database was used to retrieve data of 62,312 ESNSCLC patients age 60 years and older diagnosed between 2004 and 2012. Patients were divided into racial cohorts: C, AA, American Indian (AI), Asian/Pacific Islander (API), or unknown. Demographics characteristics, therapy, and survival were compared using χ^2 test, Kaplan–Meier method, and Cox multivariate analysis. **Results:** AA and AI individuals were less likely to receive surgery than typical ESNSCLC patients (55.9% and 57.6% vs. 66.7%; $P < .0001$). Two-year overall survival (OS) for C individuals was 70%, for AA 65%, AI 60%, and API 76% ($P < .0001$). Two-year cancer-specific survival (CSS) for C individuals was 79%, AA 76%, AI 73%, and API 84% ($P < .0001$). Median CSS for AI and AA individuals was less than that of typical ESNSCLC patients (49 and 80 months vs. 107 months; $P < .0001$). This difference disappeared in multivariate analysis, accounted by sex, age, treatment, histology, and T stage (all $P < .0001$). **Conclusion:** Despite treatment advancements in the past decade, AA and AI individuals continue to have worse OS and CSS from ESNSCLC. This might be because of the association with more adverse risk factors, including older age, squamous histology, male sex, T2 stage, and tendency to forgo treatment.

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Introduction

As cancer surpasses heart disease as the leading cause of death worldwide, non–small-cell lung cancer (NSCLC) remains the most morbid malignancy in men and women combined, claiming the lives of > 150,000 individuals annually.[1,2] The introduction of new US Preventative Task Force lung cancer screening recommendations combined with an aging population will likely result in earlier detection of this disease.[3,4] At present, one-fourth of patients are diagnosed at an early, potentially curable, stage. Definitive therapy is of the upmost importance in these patients, because > 50% of patients left untreated succumb to their malignancy with poor survival (2%-4% at 5 years).[5] In contrast, patients who are able to

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undergo surgical resection have relative survival rates of 60% at 5 years.[5]

The current literature demonstrates that race, age, and socioeconomic status play a role in the treatment and outcomes for patients with early stage NSCLC (ESNSCLC). One study of 3 major US cities showed that African American (AA) individuals and patients with lower socioeconomic status were less likely to undergo definitive surgical resection compared with Caucasian (C) individuals and patients with higher socioeconomic status. Smith et al reported similar differences among elderly patients in Virginia.[6] Samet et al conducted a study of patients from New Mexico that showed older age and Hispanic ancestry were associated with lower rates of definitive treatment.[7] In fact, a secondary Southwest Oncology Group cohort analysis showed that racial discrepancies in outcomes exist even in patients with equal treatment and follow-up.[8] Population-based analyses before 2000 have corroborated these findings, showing that AA individuals with ESNSCLC have poorer survival compared with other racial subgroups, largely because of lower rates of surgical resection.

Modern (ie, post-2000) advancements in surgery and radiotherapy have improved survival rates in ESNSCLC. Video-assisted thoracic surgery and the routine use of positron emission tomography (PET)/computed tomography (CT) for staging have contributed to improved diagnosis, treatment, and survival in NSCLC patients.[9,10] In addition, the safe and effective use of stereotactic body radiotherapy (SBRT) has expanded curative intent to nonsurgical candidates. Although conventional radiotherapy only marginally extends 5-year survival compared with untreated patients, SBRT boasts local control rates of up to 92% and 5-year survival rates of $> 60\%$.[5] In addition, excellent control rates and survival were established in a multi-institutional phase II trial by Timmerman et al in the United States, leading to the adoption of SBRT as the standard of care for inoperable ESNSCLC.[11] In this study, we used a population-based design to determine if racial disparities exist in the treatment and outcome of stage I NSCLC in our cohort and if so, if they have diminished in the past decade considering the increased adoption and availability of advanced treatment options such as SBRT.

Patients and Methods

The Surveillance, Epidemiology, and End Results (SEER) database is a national cancer registry that provides information about demographic and tumor characteristics, treatment, and survival in persons diagnosed with cancer. A case list from the SEER-18 database selecting for all stage I lung and bronchus cancer patients aged 60 and older who were diagnosed between 2002 and 2012 was retrieved. Small-cell histology was excluded. Stage I disease was defined as clinical or pathologic T1-2N0M0 per the American Joint Committee on Cancer (AJCC) Staging Manual, sixth edition. The year 2004 was selected to coincide with the SEER database adoption of the AJCC sixth edition staging and 2012 because it contained the most recent data available through SEER. Treatment was divided into 4 groups: surgery only ("surgery"), radiation only ("radiation"), surgery and radiation ("both"), and no treatment ("observation only"). Patients were divided into 1 of 5 racial cohorts for analysis: C, AA, American Indian (AI), Asian/Pacific Islander (API), or unknown. Chemotherapy regimen, medical comorbidities, radiation modality, and radiation dosing information were not available for analysis.

Differences among demographic characteristics, treatment distribution, and survival were evaluated using χ^2. Overall and cancer-specific survival (CSS) analysis was completed using Kaplan–Meier and Cox multivariate hazard ratio (HR). All P values were chosen to be statistically significant at an α of 5%.

Results

Patient Characteristics

A total of 62,213 met inclusion criteria (Table 1). C individuals comprised most of all cases, followed by AA, API, and AI (86.6%, 8.0%, 5.3%, and 0.3%, respectively; $P < .0001$). In general, the mean age of AA and AI patients was lower than that of C and API patients, although this difference was not statistically significant. Adenocarcinoma constituted most of the histologic subtypes at 53.2%, followed by squamous at 32.4%, and other rare subtypes such as acinar and mucinous carcinoma ($P < .0001$).

Treatment According to Race

Overall, 67% of stage I NSCLC patients underwent surgery, 19% received radiation, 3% received radiation and surgery, and 12% were observed ($P < .0001$; Figure 1A). When stratified according to race, there were clear discrepancies in treatment patterns. AA and AI patients were less likely to receive surgery compared with C and API patients (56% and 58% compared with 67% and 72%; $P < .0001$). In addition, AA patients were more likely to forgo local treatment compared with C patients (18% compared with 11%; $P < .0001$; Figure 1B).

Survival According to Race

Despite a younger age at diagnosis, 2-year OS and CSS were lower for AA and AI patients. The 2-year OS was 70% for C, 65% for AA, 60% for AI, and 76% for API patients ($P < .0001$); 2-year CSS was 79% for C, 76% for AA, 73% for AI, and 84% for API patients ($P < .0001$; Table 2). The median CSS for AI and AA patients was considerably shorter than that of the typical stage I NSCLC patient when not accounting for race (49 months and 80 months respectively, compared with 107 months; $P < .0001$).

Multivariate Analysis

This difference in CSS remained significant in multivariate analysis for certain races (Table 3). AI patients continued to have the worst survival (HR, 1.33; $P = .0194$) whereas API patients had the best survival (HR, 0.80; $P < .0001$). The difference in survival between AA and C patients became insignificant (HR, 0.98) in multivariate analysis when using C as a reference value. Other variables significantly correlated with survival included sex (using female as reference; male HR, 1.28), age (unit relative risk, 1.02), treatment (using observation only as reference; surgery HR, 0.18; radiation HR, 0.51; surgery and radiation HR, 0.36), histology (using squamous as a reference; adenocarcinoma HR, 0.74; epithelial not otherwise specified HR, 1.03; acinar HR, 0.55; cystic/mucinous/serous HR, 0.84; and complex epithelial HR, 1.04), and T stage (using T1 as reference; T2 HR, 1.71; all $P < .0001$).

Discussion

Eliminating cancer-related disparities is fundamental to recent American Cancer Society challenge goals.[12] Population-based

Table 1 Patient Characteristics

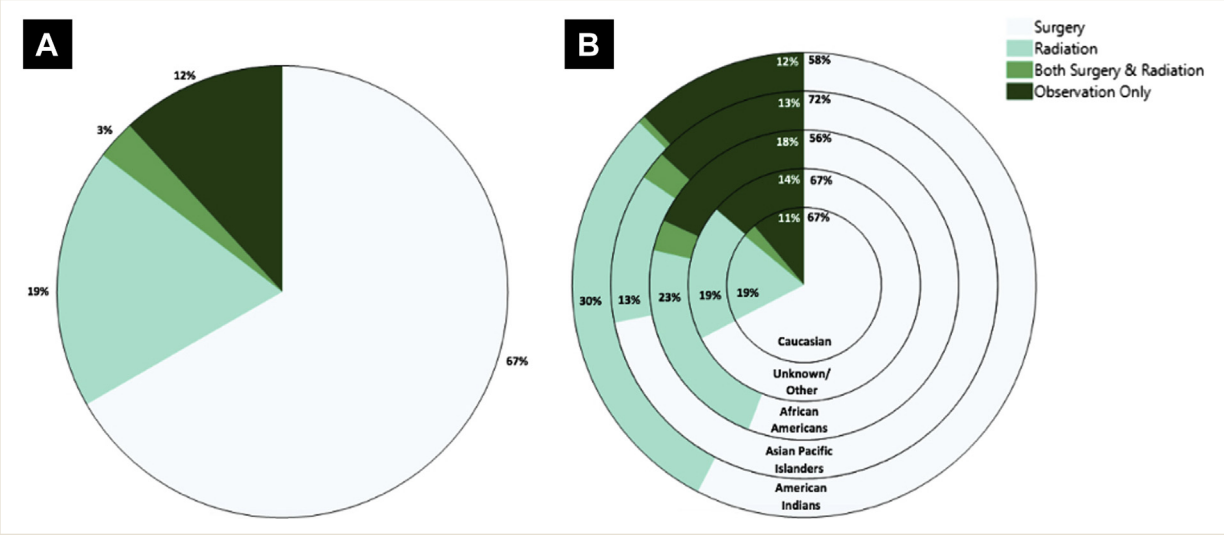
	Caucasian		African American		American Indian		Asian Pacific Islander		Unknown/Other	
	n	%	n	%	n	%	n	%	n	%
Overall	53,872	86.6	4947	8.0	198	0.3	3101	5.0	95	0.2
Age, y										
60-69	18,321	34.0	2254	45.6	90	45.5	1028	33.2	42	44.2
70-79	23,576	43.8	1918	38.8	76	38.4	1366	44.1	36	37.9
≥80	11,975	22.2	775	15.7	32	16.2	707	22.8	17	17.9
Sex										
Male	26,495	49.2	2610	52.8	102	51.5	1596	51.5	52	54.7
Female	27,377	50.8	2337	47.2	96	48.5	1505	48.5	43	45.3
Histology										
Adenocarcinoma	28,380	52.7	2459	49.7	88	44.4	2125	68.5	48	50.5
Squamous	17,723	32.9	1755	35.5	75	37.8	605	19.5	28	29.5
Other	7769	14.4	733	14.8	35	17.7	371	12.0	19	0.2

studies up to 2002 showed that efforts to mitigate racial discrepancies were largely unsuccessful,[13] although recent data suggest that the disparity gap has narrowed for lung cancer as a whole.[14,15] Unfortunately, despite advancements in diagnosis and management that allow for more convenient therapy of ESNSCLC (minimally invasive thoracic surgery and SBRT), our data demonstrate that treatment and outcome discrepancies persist. Although some statistical differences in survival were on the basis of risk factors in more aggressive disease (such as older age, squamous histology, higher T stage, and male sex), the inability to receive definitive therapy for some racial groups remained an independent risk factor. Previous studies using older national data (before 2002) showed that AA patients are less likely to receive surgical resection than C patients.[16-20] The fact that 12% of patients with potentially curable disease (on the basis of our more contemporary patient population) do not receive definitive therapy is a significant concern.

Unfortunately, no simple solution for minimizing racial disparities in the treatment of ESNSCLC exists. Instead, multiple social, cultural, and economic factors likely influence an individual patient's course along the cancer care continuum (Figure 2).[21,22] Previous studies have reported evidence to support the idea that multiple medical risk factors contribute to the poor survival seen in some racial groups. For example, a SEER−Medicare analysis of colorectal cancer patients showed that racial disparities decreased significantly after adjusting for comorbidities, indicating that these populations might be worse surgical candidates and therefore might not be eligible for the traditionally recommended definitive therapy.[23] If this is the case for ESNSCLC patients as well, outcomes for these populations might continue to improve, because SBRT offers favorable survival outcomes to patients who are deemed inoperable because of medical comorbidities. In fact, the convenience and noninvasive nature of SBRT might attract patients who previously chose to undergo observation only. One comorbidity that we could not include in our analysis was tobacco use, which is associated with higher rates of pulmonary complications, surgical site infection, and 30-day mortality after surgery. In addition, smoking has been shown to increase side effects and decrease treatment effectiveness for surgery and radiation. Although rates of smoking appear to be declining overall, AA individuals appear to have the highest smoking rates.[24]

There is a longstanding epidemiological association between socioeconomic deprivation and race; this is a factor that is challenging to account for using SEER.[21] Previous studies have noted that socioeconomic status also influences lung cancer incidence and mortality.[25-27] Lower socioeconomic status invariably exposes patients to issues related to access to care, including inadequate insurance status and decreased proximity to comprehensive medical centers. Previous studies have noted racial disparities in lung cancer staging with PET/CT as well as the timeliness of definitive care.[28,29] Patients who are unable to practice optimal prevention and screening measures are more likely to present with advanced disease. Socioeconomic status can also result in misperceptions about the risk of lung cancer, the benefits of surgical resection, and lung cancer mortality.[30-32] More difficult to quantify is effect of race and/or socioeconomic status on patient−physician relationships. AA lung cancer patients have been observed to have lower levels of trust in their physicians as well as poorer physician−patient communication

Figure 1 Distribution of Treatment According to Race for Early-Stage NSCLC Patients Diagnosed Between 2004 and 2011. (A) Distribution of Treatment for All Patients Assessed in the Study. (B) Caucasian and Asian Pacific Islander Patients Had Similar Distributions of Treatment. However, African American and American Indian Cohorts Were Less Likely to Receive Surgery and More Likely to Forgo Treatment Entirely



Abbreviation: NSCLC = non–small-cell lung cancer.

compared with white patients.[33,34] Poor trust and communication might also explain why AA individuals are still hesitant to participate in ongoing trials, which limits their access to the best care moving forward.[35]

Investigative efforts have also been to examine the cultural factors that might play a role in treatment choice and survival. Some studies show that AA and AI populations align culturally with fatalism, the belief that all events are predetermined.[36] An acceptance of the inevitability of mortality might hinder their desire to seek out interventional care for a cancer diagnosis. Supporting this notion are data showing that even if access to health care is available, AI individuals have lower rates of medical management, suggesting a cultural barrier to treatment.[37] Regardless of whether these differences are the consequence of medical mistrust or inherent cultural differences, these data, along with our findings, show that many intangible factors are significant potential impediments to eliminating the health disparities facing vulnerable populations. To combat this, physicians must be proactive in overcoming challenges that are not always obvious.

Ongoing initiatives and improvements in medicine give hope for eliminating these racial and socioeconomic disparities. For example, an analysis of the NLST (National Lung Cancer Screening Trial) showed that the reduction in lung cancer-specific mortality caused by screening was more pronounced in black individuals than white individuals, although black NLST participants had more features associated with socioeconomic disadvantages, such as unmarried status and lower education levels.[38] In addition, the analysis showed that all-cause mortality was significantly reduced by CT screening in black patients, but not white patients.[38] Although this is very encouraging news, the most patients (90%) in the NLST were white and there are concerns that the screening guidelines in the trial do not adequately reflect the risks of lung cancer among AA and Hispanic individuals.[38,39] In addition, in recent years the Affordable Care Act has increased the number of individuals with health

Table 2 Overall and Cancer-Specific Survival According to Race for Early-Stage NSCLC Patients Diagnosed Between 2004 and 2011

	Number in Cohort (%)	Mean Age, y	Overall		Cancer-Specific	
			Median Survival, mo ($P < .0001$)	2 Year Survival, % ($P < .0001$)	Median Survival, mo ($P < .0001$)	2-Year Survival, % ($P < .0001$)
Caucasian	53,872 (86.6)	73	51	70	>96	79
African American	4947 (8.0)	71	42	65	80	76
American Indian	198 (0.3)	71	40	60	49	73
Asian Pacific Islander	3101 (5.0)	73	68	76	>96	84

Abbreviation: NSCLC = non–small-cell lung cancer.

Table 3 Multivariate Cancer-Specific Survival Analysis for Early-Stage NSCLC Patients Diagnosed Between 2004 and 2011

Variable	Descriptor	HR	Test Statistic
Sex	Male	1.28	P < .0001
	Female	REF	—
T Stage	T1	REF	—
	T2	1.71	P < .0001
Treatment	Surgery	0.18	P < .0001
	Radiation	0.51	P < .0001
	Both	0.36	P < .0001
	Neither	REF	—
Age	Unit Increase (≥60)	1.02	P < .0001
Race	Caucasian	REF	—
	African American	0.98	P = .3847
	American Indian	1.33	P = .0194
	Asian Pacific Islander	0.80	P < .0001
Histology	Adenocarcinoma	0.74	P < .0001
	Squamous	REF	—
	Epithelial not otherwise specified	1.03	P = .2079
	Acinar	0.55	P < .0001
	Cystic/mucinous/serous	0.84	P = .0040
	Complex epithelial	1.04	P = .4345

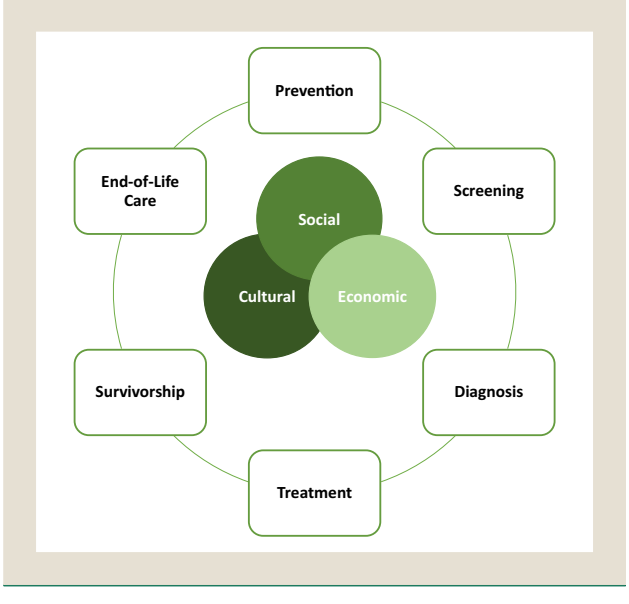
Abbreviations: HR = hazard ratio; NSCLC = non–small-cell lung cancer; REF = reference.

insurance. Although it is difficult to gauge the long-term effects of this policy at this time, one proposed benefit is that more patients might be able to undergo routine screening and definitive treatment. However, the longevity of this policy is unclear, because current legislative proposals have suggested eliminating the individual mandate, removing guarantees of coverage for preexisting conditions, and making significant cuts to Medicaid funding. These changes might result in many losing access to quality, affordable, health insurance. As these legislative battles unfold, the future of American health care and the resulting consequences on populations with poor rates of survival in ESNSCLC are yet to be determined. Efforts moving forward should seek to close racial disparities by improving the multiple biologic and social factors that cause worse survival in certain races. One possibility is the inclusion of lung cancer screening and treatment education programs in at-risk communities.

Dedicated study is also required to explain the poorly understood biologic differences in lung cancer between races. Epidermal growth factor receptor-mutant adenocarcinoma is more likely to occur in Asian patients, which holds prognostic and predictive value because of the availability of multiple targeted agents.[40,41] Although systemic therapy is not first-line treatment in early stage disease, these treatments might have been considered at the time of future recurrence or if local treatment was refused. In addition, our data show that AA individuals have higher rates of squamous cancer, for which targeted therapies are not available. Furthermore, although studies have established survival benefit with immunotherapy in advanced stage disease, its role in early stage disease is less clear.[42]

Our study has several limitations. First, we must acknowledge the retrospective nature of this study and all of the inherent associated biases. In addition, there are also limitations related to the weaknesses of the SEER database. Chemotherapy or systemic therapy use is not recorded in SEER, so it is unknown if this might contribute to some of the differences in treatment or survival. For example, patients who were classified under "observation only" might not have been surgical/radiation candidates and might have received

Figure 2 Factors Influencing Disparities Observed in Cancer Care. A Visual Representation of the Social, Cultural, and Economic Influences Underlying the Cancer Care Continuum, From Prevention to End of Life Care



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systemic therapy as a means of treatment. Recent staging is not available and conclusions about associations with race are made on the basis of the AJCC sixth edition. In addition, the SEER database does not code for quality of life, progression-free survival, or event-free survival, factors that are important in judging the choice or quality of treatment modality. Many variables are not completely coded ("blank" or "unknown"); however, if > 80% of cases did not code for a specific variable, we did not report significance. Finally, we must acknowledge the possibility of incorrectly coded information in the SEER database, which has been previously discussed with regard to breast cancer.[43]

Conclusion

Previous studies have documented a historical difference in the treatment and survival of patients with ESNSCLC across racial/ethnic groups. The source of these differences is complex, involving multiple social, economic, and cultural factors. As a result, national efforts and goals have been developed and implemented with the aim of mitigating these differences. Although there have been encouraging trends in reducing health care disparities in the management of lung cancer as a whole, our population-based study is the first, to our knowledge, to report that for ESNSCLC, racial disparities in management and survival outcomes persist.

Clinical Practice Points

- Racial disparities are historically profound and affect outcomes in early stage NSCLC.
- We aimed to explore if recent advances in radiotherapy and surgery have improved epidemiological differences in outcomes related to race.
- African American patients continued to do worse in a contemporary SEER data set, because of increased association with T2 disease, squamous histology, older age, male sex, and suboptimal treatment.
- Multiple socioeconomic issues affect survival outcomes and likelihood to seek care; this must be taken into account when treating patients.

Disclosure

The authors have stated that they have no conflicts of interest.

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