REGIONAL DISPARITIES IN TREATMENT AND SURVIVAL OF EARLY STAGE NON-SMALL CELL LUNG CANCER

Objectives: Recently, disparities related to ethnicity and rural place of residence for initial treatment and mortality of non-small cell lung cancer (NSCLC) have been reported. As a large proportion of residents in New Mexico are either Hispanic or reside in rural areas, we hypothesized that mortality of patients with early stage NSCLC would be higher in New Mexico compared to other areas of the country.

Methods: We used the Surveillance, Epidemiology, and End Results (SEER) Program registry to compare mortality from Stages 1A–2B NSCLC in New Mexico to other SEER registries between 1988–1997, and determined whether differences were related to demographics, tumor stage, place of residence, ethnicity, or receipt of surgical treatment. Data was collected from nine SEER registries functioning during the entire targeted period of 1988–1997.

Results: Cases in the New Mexico Registry had a greater mortality risk (adjusted HR 1.22, CI 1.12–1.32) compared to cases enrolled in the other SEER registries. This higher risk was related to less cancer-directed surgery in New Mexico SEER patients, and a shift toward greater proportions of elderly and Stage 1B cases in New Mexico. Rural Stage 1B cases also exhibited greater risk than urban cases. Ethnic differences did not contribute to the higher mortality risk observed in New Mexico cases, although rural Hispanics had a higher mortality risk than urban Hispanics.

Conclusions: These findings suggest a regional disparity in treatment and mortality risk for early stage NSCLC in New Mexico compared to the rest of the country. (*Ethn Dis.* 2007;17:358–364)

Key Words: Lung Cancer, Non-Small Cell Lung Cancer, Hispanic, Elderly

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INTRODUCTION

Lung cancer remains the leading cause of cancer death in the United States. Nonsmall cell lung cancer (NSCLC) represents approximately 80% of all new lung cancer cases,¹ although only one third of NSCLC patients present with potentially curable early stage disease. Surgical resection remains the recommended treatment for these patients.^{2–4}

Recently, disparities in initial NSCLC treatment and mortality related to ethnicity, 5-10 age, 10-12 and place of residence at time of diagnosis¹³⁻¹⁶ have been noted in a variety of US population groups. In addition, regional geographic disparities in survival have been noted for several cancers within the United States.⁵ For example, differences in lung cancer mortality between states have been identified.¹⁷ Age-adjusted lung cancer mortality rates vary across regions of the United States, with the Southeast having the highest mortality rates and the Mountain region having the lowest.¹⁸ However, the Mountain region has demonstrated the greatest increases for both sexes over the last few decades.¹⁸

New Mexico, one of the southernmost states of the Mountain region, exhibits unique ethnic and geographic characteristics compared to other areas

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of the country. Hispanics comprise >40% of the state population and a similar proportion of the population is rural. As recent reports correlate these ethnic and residential disparities to increased NSCLC mortality, we hypothesized that NM patients with early stage NSCLC would have increased mortality related to these ethnic and residential disparities compared to other areas of the United States. We used the Surveillance, Epidemiology, and End Results (SEER) Program registry to compare NM to the other SEER registries in the program between the years 1988-1997 with regard to the risk of NSCLC mortality. We determined whether any variations were related to differences in stage at diagnosis, age at diagnosis, sex, place or residence at time of diagnosis (rural vs urban), ethnicity, or receipt of cancer-directed surgery.

MATERIALS AND METHODS

Study Populations and Data Sources

The NCI-sponsored SEER program is a comprehensive source of popula-

tion-based information about cancer in the United States. We drew data for this study from the nine SEER populationbased cancer registries that collected cancer information from their program area during the entire targeted time period of 1988–1997. A comparison to 1990 US census figures indicates that these combined program areas covered approximately 9.3% of the US population.

We obtained our data from the SEER public use data file for 1973-2000. These included patient birth date, age at diagnosis, sex, race, state and county of residence at time of diagnosis, date of cancer diagnosis, cancer site, histological type, extent of disease (EOD: tumor size, extension, lymph node involvement), first course of treatment provided within four months of diagnosis, vital status, date of death when applicable, and active followup time. Cancer site was coded according to International Classification of Diseases for Oncology 2nd edition (ICD-O-2), and included lung and bronchus cancer. In most instances, exact dates were available for birth, diagnosis, and death. When limited to month and year, we assumed the first day of the month. Hispanic ethnicity was included in NM registry files for the entire time period, but was missing from other registries for several years. We based rural/urban designation on patient's county of residence at time of diagnosis, applying 1993 USDA Rural-Urban Continuum codes.¹⁹ Counties with codes 0-3 were designated as urban, 4-9 as Rural.²⁰

Cancer Stage and Surgical Treatment

Since we focused on clinical diagnosis and treatment, we assigned American Joint Cancer Committee (AJCC) 5th edition²¹ cancer stage to cases. SEER EOD was mapped into AJCC 5 stages using a computerized algorithm that combined TNM definitions,²¹ SEER EOD coding instructions,²² and the SEER Comparative Staging Guide for Cancer.²³ The algorithm yielded 74.1% AJCC V staged cases, comparable to the yield of AJCC III cases by a SEER-developed algorithm. Some cases could not be staged due to unknown tumor size, unknown extent, and/or unknown nodal involvement (41.3%, 12.7%, and 34.8% of unstaged cases, respectively). The percentage of unstaged cases in NM was comparable to the 23.5% unstaged in the other SEER registries. Uniform application of the algorithm assured consistent clinical diagnostic criteria for all 10 years and nine geographic regions of NSCLC cases studied. Surgery treatment was defined according to SEER protocol for first course of treatment, occurring within four months of diagnosis. Patients were classified as having cancer-directed surgery treatment, if the surgery was curative in intent, including local resection, partial resection, segmentectomy, lobectomy, sleeve resection, partial pneumonectomy, and radical pneumonectomy (SEER codes 10-70).

Case Selection

We initially selected all 109,138 patients with microscopically confirmed primary cancer that was anatomically situated in lung or bronchus, was actively followed up, and had invasive NSCLC histology. We applied lung and bronchus cancer histology classifications described by Travis et al,²⁴ excluding cases that had mixed histologies and included small cell as part of the histology, or that were diagnosed with in situ or occult carcinoma. Since during the targeted time period, standards of practice considered only patients with Stages 1A-2B as potential candidates for curative surgical resection, we restricted selection to cases diagnosed with these stages (n=21,144).

Analysis

For all analyses, early stage NSCLC cases were divided into three clinically

relevant stage groups: 1A, 1B, and 2AB. Stages 2A and 2B were combined due to the small number of cases diagnosed with these stages. Cases were also grouped into three age categories: less than 65 years old (<65), 65–74, and 75 years or older (\geq 75). For NM only, ethnicity was assigned by combining race and ethnicity, with resulting categories of Hispanic and non-Hispanic White (NHW) covering 98.1% of cases. We used SAS version 8 for data analysis.

Associations among patient demographic characteristics were assessed with cross-tabulations and Pearson chi square analyses. For survival analyses, survival was calculated in months from time of diagnosis to death or last date of followup. Cases not known to be dead were censored at last date of followup. Cases were followed through December 31, 2000, so that all patients were actively followed for three years or more and 68.9% were followed five years or more. Unadjusted survival curves were constructed with the Kaplan-Meier method and compared using Log-Rank tests. Cox regression was used as a modeling procedure to assess simultaneous effects of registry, age at diagnosis, stage at diagnosis, sex, and rural residence on survival. For some analyses, receipt of cancer-directed surgery was added as a predictor of survival. Multivariate logistic regression was used as a modeling procedure to assess simultaneous effects of the same variables on receipt of cancer-directed surgery for treatment. For analyses restricted to NM patients, race/ethnicity was included as a predictor variable. P values for all tests were 2-sided.

RESULTS

Cases of early stage NSCLC in NM had a significantly greater mortality hazard than cases within the other eight SEER registries (unadjusted HR=1.3, CI 1.2–1.4), P<.0001). Figure 1 shows a Kaplan-Meyer survival curve illustra-

LUNG CANCER TREATMENT DISPARITIES - Crowell et al



Fig 1. K-M survival by stage, NSCLC, 1988–1997. New Mexico vs other registries

ting differences between NM and the other SEER registries by stage, with NM exhibiting lower survival for each stage. Part of these differences may be explained by population characteristics of NSCLC patients within the registries (Table 1). Distribution of cases within each stage was different in NM compared to the other SEER registries with a lower proportion of cases diagnosed at Stage 1A in NM compared to the other registries (28.9% vs 40.3%) and a shift of cases into Stage 1B (58.1% vs 44.8%). In addition, the NM registry contained fewer patients <65 years old than noted in the other registries (31.4% vs 35.4%, respectively). The proportion of male and female cases was similar in NM and the other SEER registries.

When reanalyzed using a proportional hazards model with covariates including stage, age, sex, and place of residence at time of diagnosis, the hazard ratio for NM remained significantly higher compared to the other SEER registries (Table 2). When stratified by stage, the hazard ratio in NM was similar to the other SEER registries for Stage 1A but differed significantly across registries for both Stages 1B and 2AB. When stratified by age, the risk of mortality for cases <65 years old was similar for NM and the other SEER registries, but was higher in NM than the other registries for patients \geq 65 years old. Women in NM, as well as the other SEER registries, exhibited a lower hazard ratio compared to men (data not shown). However, women in NM exhibited a higher mortality risk than women in the other registries. A similar difference was noted across registries for men.

There was a large disparity between the proportion of rural cases in NM (41.1%) compared to the other SEER registries (12.1%; Table 1). Both rural and urban patients in NM had a higher mortality risk compared to rural and

urban cases in the other SEER registries (Table 2). There was no difference in overall mortality hazard in rural compared to urban residences in NM (HR=1.12, 95% CI 0.95-1.31), or when stratified by age or sex. However, rural cases of Stage 1B NSCLC in NM exhibited an increased mortality hazard compared to urban patients of similar stage (HR=1.27; 95% CI 1.03-1.51), a difference not seen for Stages 1A or 2AB. This difference was maintained even when receipt of cancer-directed surgery was added to the model as another covariate (HR= 1.26, 95% CI 1.01-1.56), indicating the disparity was not related to surgery.

Disparities in NSCLC treatment and survival between Hispanics and other ethnic groups have been previously described.⁶⁻¹¹ Because of the lack of identifying data for Hispanics in the national SEER program in the earlier years of the period evaluated in this study, we were unable to make this comparison for the other SEER registries. However, this information has been collected by the NM SEER since its inception in 1973. We found no differences in survival between Hispanics and NHW within the NM SEER (HR= 1.1, 95% CI 0.89-1.36), although rural Hispanics had a higher mortality hazard than urban Hispanics (HR = 1.51, 95% CI 1.00-2.28),a difference not seen in NHW (HR=1.06, CI 0.87-1.26). There was no difference between rural and urban Hispanics related to age, stage at diagnosis, or sex.

Surgical resection was the method for curative treatment of early stage NSCLC during the years covered in this study. As shown in Table 1, the proportion of cases who received cancerdirected surgery was significantly less in NM for all early stage NSCLC. The multivariate odds of receiving cancerdirected surgery for early stage NSCLC in NM was about half of the other SEER registries (Table 3). This difference was consistent when stratified by

	New Mexico $(N = 872)$		Other SEER Registries* $(N=20,278)$		
Characteristic	N	(%)	N	(%)	P value
Stage (AJCC 5)					
1A	252	(28.9)	8,577	(40.3)	
1B	507	(58.1)	9,074	(44.8)	< 0.0001**
2AB	113	(13.0)	2,627	(13.0)	
Sex					
Male	478	(54.8)	11,577	(57.1)	0.1840^{3}
Female	394	(45.2)	8,701	(42.9)	
Age (years)					
< 65	274	(31.4)	7,172	(35.4)	
65–74	377	(43.2)	8,456	(41.7)	0.0432**
≥ 75	221	(25.3)	4,650	(22.9)	
Place of residence‡					
Rural	358	(41.1)	2,460	(12.1)	< 0.0001†
Urban	514	(58.9)	17,818	(87.9)	
Ethnicity					
Hispanic	152	(17.4)	Not available		
Non-Hispanic White	720	(82.6)	Not available		—
Cancer-directed surgery					
Yes	617	(70.8)	17,095	(84.8)	< 0.0001†
No	255	(29.2)	3,183	(15.7)	

Table 1. Population characteristics of early stage NSCLC (1988–1997)

* Other registries include the San Francisco/Oakland Metropolitan Statistical Area (MSA), Connecticut, Detroit MSA, Hawaii, Iowa, Seattle/Puget Sound, Utah, and Atlanta MSA.

** From Pearson chi square analysis, df = 2.

 \dagger From Pearson chi square analysis, df = 1.

‡ Definition of rural vs urban nature of the county of residence at time of diagnosis as designated by 1993 USDA Rural-Urban Continuum codes, with codes 0-3 as Urban and 4-9 as Rural.

Table 2. Mortality hazard ratio¹ for early stage NSCLC in New Mexico vs other SEER registries²

	HR* (95% CI)	P value
Overall NM vs other	1.22 (1.12–1.32)	< .0001
Stratified by stage (AJCC 5)		
1A	1.10 (0.93-1.29)	.2442
1B	1.21 (1.09–1.35)	.0004
2AB	1.45 (1.19–1.77)	.0003
Stratified by age (years)		
< 65	1.12 (0.96-1.32)	.1349
65–74	1.23 (1.09-1.39)	.0008
≥ 75	1.28 (1.10–1.49)	.0009
Stratified by sex		
Male	1.24 (1.12-1.38)	< .0001
Female	1.18 (1.04–1.34)	.0105
Stratified by place of residence		
Rural	1.27 (1.12-1.45)	.0003
Urban	1.18 (1.07–1.32)	.0012

* From a multivariate Cox proportional hazards model that included all non-stratified predictor variables: SEER registry, AJCC 5 stage at diagnosis, age at diagnosis, sex, and place of residence at diagnosis.

** Cases from SEER9 registries, 1988–1997.

stage, age, sex, or rural residence. A separate hazard analysis showed that when patients received cancer-directed surgery, there was no difference in multivariate hazard between NM and the other registries (HR= 1.0; 95% CI 0.9-1.1). However, patients who did not receive cancer-directed surgery in NM had a higher hazard than patients in the other registries (HR= 1.4; 95% CI 1.2–1.5). The inverse relationship between age and odds of having cancerdirected surgery was similar in NM to the other SEER registries (increasing odds of getting surgery for younger age at diagnosis), and there were no differences in regard to place of residence. In a separate multivariate analysis, we added ethnicity to the predictors of surgery for NM cases and found that the odds of Hispanics receiving surgery was similar to NHW (HR = 0.84, 95% CI 0.56 - 1.27).

DISCUSSION

Disparities in lung cancer outcomes have been associated with lower rates of initial cancer treatment7,8,10 certain ethnic backgrounds,7,8-10 age,11,12 and rural place of residence.^{13–16} Lower rates of cancer-directed surgery for early-stage NSCLC has been identified as an important cause of poorer lung cancer outcomes in African Americans and Hispanics.^{7,8} A previous study in NM suggested that Hispanic ancestry was associated with lower rates of potentially curative surgery.²⁵ Although we found that patients in NM had lower rates of cancer-directed surgery compared to patients in other SEER registries, this disparity was not associated with Hispanic background. In fact, this treatment disparity appeared to affect all early stage NSCLC cases in the NM SEER regardless of stage, age group, sex, place of residence, or ethnicity. The estimated per capita number of thoracic and general surgeons in the state in the year 2001 was

Table 3. Odds^{*} of receiving cancer-directed surgery for early-stage NSCLC in New Mexico vs other SEER registries^{**}

	OR* (95% CI)	P value
Overall NM vs other	0.46 (0.39-0.54)	< .0001
Stratified by stage (AJCC 5)		
1A	0.37 (0.26-0.51)	< .0001
1B	0.48 (0.39-0.59)	< .0001
2AB	0.51 (0.34-0.77)	.0012
Stratified by age (years)		
< 65	0.60 (0.42-0.87)	.0064
65–74	0.46 (0.36-0.59)	< .0001
≥ 75	0.37 (0.28-0.50)	< .0001
Stratified by sex		
Male	0.45 (0.37-0.56)	< .0001
Female	0.46 (0.36-0.60)	< .0001
Stratified by place of residence		
Rural	0.40 (0.31-0.53)	< .0001
Urban	0.50 (0.40–0.61)	< .0001

* From a multivariate logistic regression model including all non-stratified predictor variables: SEER registry, stage at diagnosis, age at diagnosis (years), sex, and place of residence at diagnosis.

** Cases from SEER9 registries, 1988-1997.

about half the national average (.87 vs $1.79/100,000^{26}$), suggesting that differences in access to appropriate surgeons and centers to provide these surgeries may be a factor for less cancer-directed surgery for NM NSCLC patients.

Other factors also contribute to increased early stage NSCLC mortality risk noted in our study. Lower rates of cancer-directed surgery have been well-documented in elderly patients compared to younger NSCLC patients.^{10,25} However, patients >65 years of age had a higher mortality risk in NM compared to the other SEER registries, even when controlled for stage, place of residence,

Although we found that patients in NM had lower rates of cancer-directed surgery compared patients in other SEER registries, this disparity was not associated with Hispanic background.

and rates of cancer-directed surgery. We also identified a higher proportion of Stage 1B cases of NSCLC in NM than were noted in the other SEER registries. This within-stage shift has important prognostic implications, as Stage 1B NSCLC has a significantly lower 5-year survival compared to Stage 1A cancers.²⁷ Explanations for this shift are uncertain, but could be related to factors such as delayed access to medical care or presenting to a provider only when symptoms occur.^{14–16,28} More study is needed to evaluate possible reasons for the differences in the ratio of Stage 1A:1B tumors between NM and the other SEER registries.

While not the major reason for differences in early stage NSCLC survival between NM and the other SEER registries, rural residence did appear to affect outcomes of particular subgroups. Rural Hispanics exhibited poorer survival than urban Hispanics, a disparity not seen in NHW and was not due to differences in cancer-directed surgery. Moreover, it did not affect the overall similarity in survival between Hispanics and NHW when all NM cases were considered. Also, rural patients with Stage 1B tumors had poorer survival compared to their urban counterparts. The reason for this disparity is not clear, since the odds of surgery were similar for rural vs urban Stage 1B tumors and the proportion of rural vs urban cases within each stage was similar.

Explanations for lower cancer survival in rural areas often focus on difficulties accessing appropriate health care providers and facilities.¹³⁻¹⁶ New Mexico is a large, predominantly rural state, ranking 45th in population density in the US³¹ with more than 95% of the counties in the state designated as medically underserved or areas with shortages of healthcare professionals^{29,30} Distance and travel time are likely barriers to appropriate health care and may be a significant consideration for many patients with lung cancer.¹³⁻¹⁶ In NM, rural providers believe that their patients have less access to healthcare facilities than non-rural providers.³¹

Although recent studies suggest Hispanics with all stages of lung cancer^{5,10} as well as Stage 1 NSCLC⁸ exhibit poorer survival compared to NHW, we did not find any difference in survival from early stage NSCLC between Hispanics and NHW in NM. Differences between these studies and our results may in part be explained by the fact that we did not observe a decreased rate of cancer-directed surgery in Hispanics compared to NHW in NM, as has been noted in prior studies of Hispanic populations.^{8,10} However, any such disparities in NM may be overshadowed by the low rate of cancerdirected surgery for all early-stage NSCLC in the state, which is similar to the rate noted for Hispanics in other studies.¹⁰

Several potential limitations of our study should be noted. The SEER program may underestimate overall prevalence and mortality for tobaccorelated cancers due to the over-representation of areas with traditionally lower smoking prevalence.³² However, accuracy of diagnosis and mortality data in SEER has been confirmed³² and SEER data concerning cancer-related surgery is similar to Medicare³³ and the National Cancer Data Base program of the American College of Surgeons and American Cancer Society.34 Additionally, eliminating cases with unknown AJCC 5 stage from our analyses may have introduced bias if the distribution of unstaged cases drew more from some early stages than others. However, in our sample, the distribution of unknown cases was similar across registries (NM 26.6%, other SEER registries 25.0%), sex (female 24.6%, male 25.2%), rural residence (rural 25.9%, urban 24.8%), ethnicity (Hispanic 26.0%, NHW 25.3%), and receipt of surgery (surgery 25.6%, no surgery 23.3%).

As the nationwide SEER registry does not include comorbidity or socioeconomic measurements, we could not directly evaluate the effects of these potential variables. Comorbidities have a significant negative influence on lung cancer outcomes.35 The fact that NM cases not receiving cancer-directed surgery had a lower survival rate compared to similarly untreated patients in the other registries may suggest a higher rate of comordid conditions for cases in NM. However, comorbidities did not appear to influence decreased rates of cancer-directed surgery in African Americans⁷ and Hispanics⁸ in other recent studies. Lower socioeconomic status has been linked to outcomes in lung cancer^{7,9,11,35,36} and there is a generally high rate of poverty throughout NM.37 Further study is needed to determine the relationships between the higher mortality risk in the state and socioeconomic parameters within the state and between New Mexico and the other SEER registries.

In summary, Stage 1A–2B NSCLC cases enrolled in the NM SEER Registry between 1988 and 1997 had a higher mortality risk compared to cases in the other SEER registries active during that

period. This increased risk was related to less cancer-directed surgery in NM SEER patients, a shift toward greater proportions of Stage 1B patients, patients older than 65 years of age, and rural place of residence for Hispanics and Stage 1B patients. Ethnicity or sex differences did not appear to contribute to the greater risk observed in NM cases. These findings suggest a regional disparity in early stage NSCLC outcomes in NM compared to the rest of the country.

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LUNG CANCER TREATMENT DISPARITIES - Crowell et al

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- Design concept of study: Crowell, Goetz, Wiggins, Magana
- Acquisition of data: Crowell, Goetz, Wiggins, Magana
- Data analysis and interpretation: Crowell, Goetz, Wiggins

Manuscript draft: Crowell, Wiggins

Statistical expertise: Goetz Acquisition of funding: Crowell, Wiggins

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