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NSCLC patient "migration" for treatment: A retrospective analysis of patient characteristics, travel patterns, and survival differences

Danh Pham[a], Shruti Bhandari[a,*], Christina Pinkston[b], Malgorzata Oechsli[c], Goetz Kloecker[a]

[a] Division of Hematology and Medical Oncology, James Graham Brown Cancer Center, University of Louisville, Louisville, KY
[b] Department of Bioinformatics and Biostatistics, School of Public Health and Information Sciences, University of Louisville, Louisville, KY
[c] James Graham Brown Cancer Center, University of Louisville, Louisville, KY

ABSTRACT

Purpose: Every year a significant population exists of those diagnosed with nonsmall cell lung cancer (NSCLC) who do not receive initial treatment upon diagnosis and then "migrate" to additional hospital before ultimately getting treatment. Migration to different hospitals may play a role in the decision to treat or not-to-treat, and we aimed to evaluate the potential factors that lead to treatment.
Methods: A retrospective review of 6212 patients with NSCLC from 29 Kentucky hospital registries from 2012 to 2014 was performed. Variables collected included hospital accreditation status, age at diagnosis, stage, overall survival (OS), and insurance status. Hospital records were matched to Kentucky Cancer Registry records to determine the number of hospitals visited for treatment.
Results: Most patients were treated at their initial hospital (73%). Of the remaining patients, 36% migrated to a different hospital where most received treatment (93%). Migrating to another hospital was associated

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* Correspondence to: Shruti Bhandari, MD, University of Louisville, James Graham Brown Cancer Center, 529 S Jackson St., Louisville, KY 40202.
E-mail address: shruti.bhandari@louisville.edu (S. Bhandari).

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with Stage I-III disease, younger age (66.4 vs 72.2 years), and longer OS (561 vs 157 days). Notably, migration was also associated with private insurance status and missing treatment modalities at the initial hospital. Treatment after migrating was associated with Stage I-II disease, younger age (65.8 vs 72.8 years), and longer OS (595 vs 153 days). After adjusting for confounders, treated migrating patients lived longer than initially treated patients (591 vs 505 days), especially among those with stage III (563 vs 495 days) and IV (379 vs 300 days) disease.

Conclusion: This analysis demonstrates a survival benefit for initially untreated patients with advanced disease who migrate to another hospital for treatment. Migration was associated with having private insurance, thus making it noteworthy of the relationship between NSCLC survival benefit and insurance status.

Introduction

Among the highest in the United States with an adult tobacco use of 29% prevalence, the state of Kentucky also boasts the highest national yearly incidence of all lung and bronchial cancer at 91.4 per 100,000 per year.[1,2] Up to 33% of nonsmall cell lung cancer (NSCLC) diagnoses each year in Kentucky go untreated, far higher than the 19%-24% untreated rate nationally. Furthermore, untreated NSCLC accounts for 55% of all untreated advanced cancers in the US NSCLC is diagnosed at advanced stages (III or IV) in 70% of the cases in the United States and is undoubtedly lethal in the vast majority of patients within 1 year if untreated.[3-5] However, multiple modalities exist for NSCLC treatment that are proven to increase overall survival and significantly developed over the past decade.

Previous studies in the United States have reported on state variation of cancer mortality, which can be contributed by differences in risk and socioeconomic factors as well access to high-quality treatment.[2,6,7] Treatment rates of lung cancer are lower in geographic areas where resources are limited, particularly in rural states such as Kentucky.[8,9] In many different settings, individuals often “migrate” to a different facility than the one they were initially diagnosed before ultimately getting treatment. To date, little is known about factors associated with this “migration” of patients from various institutions and the impact of this migration in lung cancer care and outcomes. Migration to different hospitals may play a role in the decision to treat or not-to-treat, and we aimed to evaluate the potential factors that lead to treatment by investigating factors associated with the migration of patients in a broad sample of Kentucky, USA.

Materials and methods

Patient population and eligibility criteria

As part of the Kentucky Lung Cancer Education Awareness Detection Survival (LEADS) Collaborative, we performed a retrospective cohort study of patients with diagnosed invasive NSCLC from 2012 to 2014 in the state of Kentucky, USA using data from 32 hospital registries across the state. Data collection received an expedited Institutional Review Board approval at the University of Louisville using deidentified Kentucky Cancer Registry (KCR) files not subject to requirement for informed consent.

Hospital registries

Twenty-nine of the 32 contacted hospital registries provided patient demographics and tumor characteristics including zip codes, age at diagnosis, stage, overall survival (OS), sex, race, date of diagnosis, date of treatment, treatment type, and insurance status. Accreditation status

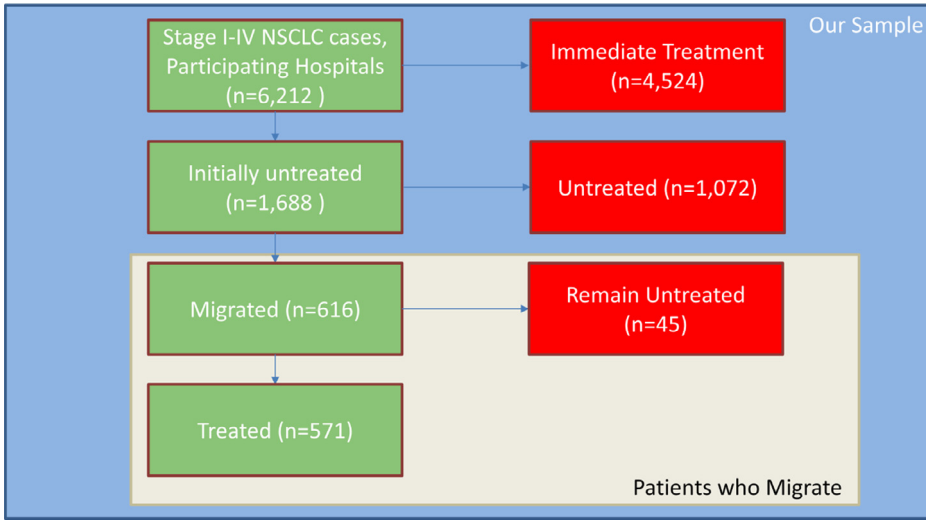

Fig. 1. Flow of NSCLC patient participation in Kentucky from 2012 to 2014. (Color version of figure is available online.)

by the Commission on Cancer (COC) and available treatment modalities was also assessed for each hospital registry.

Kentucky Cancer Registry (KCR)

KCR provided county of residence, age at diagnosis, sex, race/ethnicity, stage, treatment status, insurance status, vital status, date of diagnosis, date of treatment, and date of last contact. Records from hospitals were matched to a KCR record based on the date of diagnosis, date of last contact, vital status, age at diagnosis, sex, and race. In cases of multiple matches, the one with the highest score, or best matched to the data was included. The KCR data was considered the base dataset and all demographic and tumor characteristics were based on the KCR vs the hospital values.

Census American Community Survey (ACS)

County-level socioeconomic variables not available from either the hospital or the KCR, including education, income, and poverty, were obtained from the Census ACS 2015 5-year public use data. Education measured the percentage of the applicable population who completed high school; income measured the median level; and poverty measured the percentage of the population below the US federal poverty line.

Statistical analysis

The flow of patient participation for our sample of Stage 1-4 NSCLC cases is summarized in Figure 1. Although it was not the focus of this analysis, comparison between eligible and ineligible cases was performed (Model 0). Eligible patients drawn from each of the 120 counties in Kentucky were assessed to determine factors associated with immediate treatment (Model 1). Initially untreated patients were assessed to determine factors associated with migration (Model 2). Among migrating patients, factors associated with treatment were identified (Model 3).

Models 1 and 2 were assessed using logistics regression models. The models were adjusted for patient demographics, tumor characteristics, and county-level socioeconomic factors; and clustered by county of residence. Odds ratios (OR) and 95% confidence intervals (CI) were presented from these models.

Model 3 did not have enough power to use the logistic regression models and relied on univariate analyses using *t*-test and X^2-tests to show differences in factors. Model 0 also used univariate analyses to compare patients from the participating hospital registries to those treated elsewhere.

Race/ethnicity was categorized into 3 groups: White, Black and other. Treatment included any combination of surgery, radiation, or chemotherapy. Insurance status collected included uninsured/unknown and insured. Generally, each insurance category – uninsured/unknown, private insurance, Medicare, Medicaid, or Military – was assessed separately with uninsured/unknown insurance as the reference groups.

OS days were calculated as the number of days from the diagnosis to the date of last contact (death or otherwise). The date of diagnosis was day 1. Differences in least-squares mean OS days were compared using generalized linear models adjusted for age at diagnosis, sex, race, insurance status, and socio-economic factors.

Analyses were completed with SAS v9.4 (SAS Institute, Cary, NC) with a significance level set at $P < 0.05$. Maps were generated using the R package choroplethr.[10]

Results

Demographics of patient population

Twenty-nine of the 32 hospital registries contacted via the LEADS collaborative provided data for 6,212 patients eligible for these analyses. Most participating patients were treated (82%), Caucasian (94.2%), male (55.4%), with advanced disease (Stage III and Stage IV; 66%), and insured (private, Medicaid, and/or Medicare, Military; 91%) (Table 1).

Hospital registry characteristics

Nineteen (66%) and 25 (86%) of the 29 hospital registries were accredited by the COC and had complete treatment modalities available, respectively.

All hospital sites had medical, radiation, and thoracic surgical oncology treatment modalities available, except for 4 hospitals which lacked the surgical treatment modality. The patient population migration pattern between hospital sites is depicted in Figure 2.

Factors associated with initial treatment

Most patients were treated at their initial hospital (73%). Initially treated vs untreated was significantly associated with Stage I-III disease (OR range: 1.23-2.16); insurance status, except Medicaid (OR range: 1.50-2.42); younger age (66.8 vs 70.1 years; +10 years OR: 1.47, 95% CI: 1.37, 1.58); and not missing modality (OR: 0.16, 95% CI: 0.11, 0.23) (Tables 1 and 2). Other factors included race and median income. OS was longer in initially treated patients compared to initially untreated (506 vs 306 days) (Table 1).

Factors associated with migration

Only 36% (n = 616) of the 1,688 initially untreated patients migrated to a different hospital. Migrating to another hospital was associated with Stage I-III disease (OR range: 2.37-5.78),

Table 1
Treatment and self-referral patterns of sample of KY invasive NSCLC patients, 2012-2014.

	Patient referral pattern							
	Initial treatment		Among initially untreated		Among migrating patients			
	Treated N (%)	Untreated N (%)	Migrated % UnTx	Remain untreated N (%)	Treated % UnTx	Untreated N (%)	N (%)	N (%)
Overall (w/% TX)	4524	1688	(33.8)	616	(92.7)	1072	571	45
Stage of disease								
IV	1686 (37.3)	812 (48.1)	(20)	187 (30.4)	(86.6)	625 (58.3)	162 (28.4)	25 (55.6)
III	1127 (24.9)	456 (27)	(35.8)	179 (29.1)	(91.1)	277 (25.8)	163 (28.5)	16 (35.6)
II	296 (6.5)	85 (5)	(60)	52 (8.4)	(98.1)	33 (3.1)	51 (8.9)	1 (2.2)
I	1415 (31.3)	335 (19.8)	(58.2)	198 (32.1)	(98.5)	137 (12.8)	195 (34.2)	3 (6.7)
Race								
White	4275 (94.5)	1578 (93.5)	(33.1)	563 (91.4)	(92.7)	1015 (94.7)	522 (91.4)	41 (91.1)
Other	249 (5.5)	110 (6.5)	(44.6)	53 (8.6)	(92.5)	57 (5.3)	49 (8.6)	3 (6.7)
Sex								
Male	2473 (54.7)	970 (57.5)	(33.7)	359 (58.3)	(91.1)	611 (57)	327 (57.3)	32 (71.1)
Female	2051 (45.3)	718 (42.5)	(34)	257 (41.7)	(94.9)	461 (43)	244 (42.7)	13 (28.9)
Primary payer								
Uninsured/Other	324 (7.2)	129 (7.6)	(39.6)	55 (8.9)	(92.7)	74 (6.9)	51 (8.9)	4 (8.8)
Insured (private)	820 (18.1)	189 (11.2)	(60.3)	114 (18.5)	(100)	75 (7)	114 (20)	0 (0)
Medicaid	397 (8.8)	155 (9.2)	(45.8)	79 (12.8)	(89.9)	76 (7.1)	71 (12.4)	8 (17.8)
Medicare	2888 (63.8)	1195 (70.8)	(27.1)	357 (58)	(90.8)	838 (78.2)	324 (56.7)	33 (73.3)
Military	95 (2.1)	20 (1.2)	(55)	11 (1.8)	(100)	9 (0.8)	11 (1.9)	0 (0)
	Mean (SD/SE)	Mean (SD/SE)		Mean (SD/SE)		Mean (SD/SE)	Mean (SD/SE)	Mean (SD/SE)
Age at diagnosis	66.8 (0.2)	70.1 (0.3)		66.4 (0.5)		72.2 (0.3)	65.8 (0.5)	72.8 (1.6)
Person days	505.7 (6)	305.9 (9.8)		561.3 (13)		156.7 (9.9)	595 (16.9)	153.4 (58.7)
Treatment days	36.3 (1.8)	117.1 (3)		49.3 (8.3)		156.7 (6.3)	40.7 (3.4)	153.4 (11.8)
ACS Census data								
Median income	45049 (161)	44097.7 (265)		43745.1 (424)		44303.8 (324)	43876.4 (425)	42156.6 (1477)
% Completed HS	84.1 (0.1)	83.7 (0.2)		83.5 (0.3)		83.8 (0.2)	83.6 (0.3)	82.4 (1)
% Below poverty	18.7 (0.1)	19.2 (0.2)		19.4 (0.3)		19 (0.2)	19.3 (0.3)	20.3 (0.9)

ACS, American Community Survey (2015, 5-year); HS, high school; N, number; NSCLC, nonsmall cell lung cancer; SD, standard deviation; SE, standard error; TX, treated.

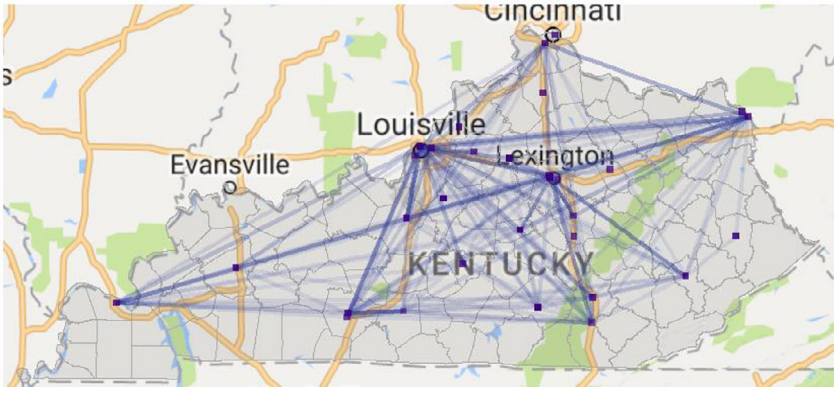

Fig. 2. Migration pattern between hospital systems in State of Kentucky. The darkness of the lines indicating the greater number of hospital systems being visited. (Color version of figure is available online.)

Table 2
Odds ratios and 95% confidence intervals for initial treatment and migration, respectively.

	Initial treatment			Migration		
Characteristic	OR	(95% CI)	*P*-value	OR	(95% CI)	*P*-value
Missing modality	**0.16**	**(0.11, 0.23)**	**<0.001**	**3.39**	**(2.1, 5.47)**	**<0.001**
Age, 10 years younger	**1.47**	**(1.37, 1.58)**	**<0.001**	**1.59**	**(1.4, 1.81)**	**<0.001**
Insurance Status (None/Unknown is the Reference)						
Insured (private)	**1.74**	**(1.33, 2.27)**	**<0.001**	**2.19**	**(1.33, 3.6)**	**0.002**
Medicaid	0.97	(0.73, 1.28)	0.81	1.27	(0.76, 2.11)	0.36
Medicare (including supplements)	**1.50**	**(1.17, 1.91)**	**0.001**	0.98	(0.63, 1.54)	0.94
Military	**2.42**	**(1.42, 4.14)**	**0.001**	2.19	(0.78, 6.14)	0.14
Stage (Stage IV is the reference)						
Stage I	**2.16**	**(1.86, 2.51)**	**<0.001**	**5.78**	**(4.31, 7.76)**	**<0.001**
Stage II	**1.70**	**(1.31, 2.21)**	**<0.001**	**5.16**	**(3.16, 8.43)**	**<0.001**
Stage III	**1.23**	**(1.07, 1.42)**	**0.004**	**2.37**	**(1.81, 3.09)**	**<0.001**
White	**1.38**	**(1.08, 1.76)**	**0.01**	0.71	(0.46, 1.1)	0.12
Male Gender	0.92	(0.82, 1.04)	0.18	1.10	(0.88, 1.38)	0.40
+$1K median income	**1.02**	**(1, 1.03)**	**0.02**	1.00	(0.97, 1.03)	0.89
More %HS graduates	0.96	(0.8, 1.16)	0.67	0.80	(0.55, 1.15)	0.22
Less %poverty	0.93	(0.74, 1.16)	0.51	1.35	(0.84, 2.16)	0.22

younger age (66.4 vs 72.2 years; +10 years OR: 1.59, 95% CI: 1.40, 1.81), and longer OS (561 vs 157 days) (Tables 1 and 2). Notably, migration was also associated with private insurance status (OR: 2.19, 95% CI: 1.33, 1.60), and missing treatment modalities (OR: 3.39, 95% CI: 2.10, 5.47) at the initial hospital. Socioeconomic status measured by poverty level, median income, and education level was not significantly associated with migration (Table 2).

Factors associated with treatment after migration

Stage I-II disease, younger age (65.8 vs 72.8 years), and longer OS (595 vs 153 days) were all associated with treatment after migration (Table 1). After adjusting for confounders, treated migrating patients lived longer than initially treated patients (591 vs 505 days, $P < 0.001$), especially among those with Stage III (563 vs 495 days, $P = 0.02$), or Stage IV (379 vs 300 days, $P = 0.002$) disease (Table 3). Benefits are noted through 3 years postdiagnosis, with the overwhelming benefit seen early for those treated after migration in both stages Stage III (<8 months) and Stage IV (<16 months) (Fig 3).

Table 3
Average overall survival days among treated patients.

Stage of disease	Treated initially (n = 4524)	Treated with migration (n = 571)	*P*-value
Stage I	723.4	743.8	0.44
Stage II	673.0	766.3	0.08
Stage III	**495.2**	**563.2**	**0.02**
Stage IV	**299.7**	**379.3**	**0.002**
All stages, combined	**505.4**	**590.9**	**<0.001**

Least-square means adjusted for age, gender, race, insurance status, Census ACS variables (median income, %HS grad, %below poverty).

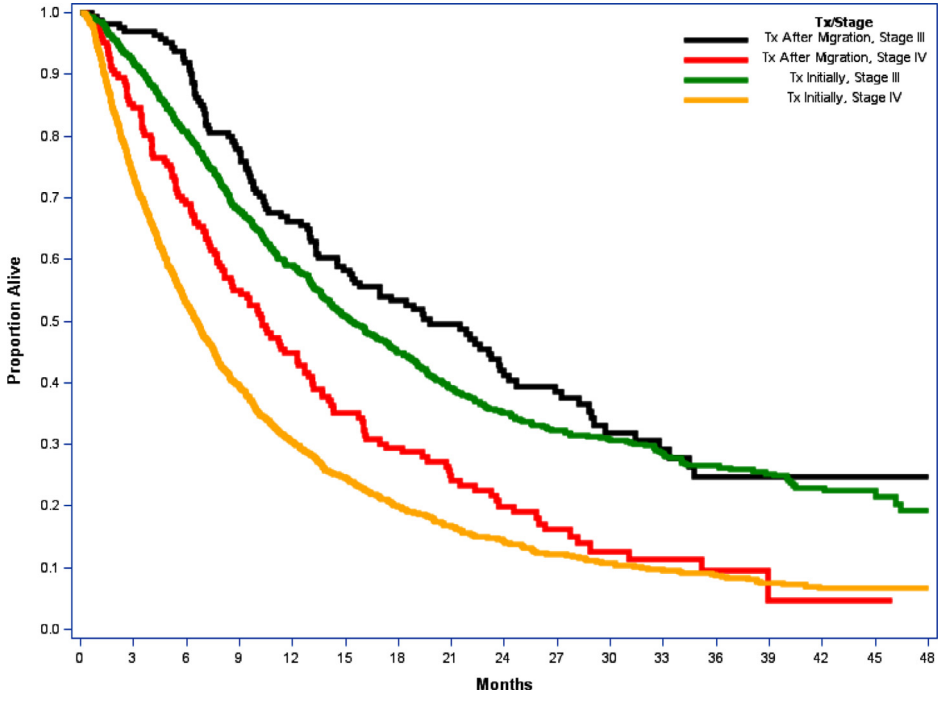

Fig. 3. Kaplan-Meier survival curves for those treated initially and after migration. (Tx, Treatment) (Color version of figure is available online.)

Discussion

Among the variables most correlated with treatment migration were stage of disease and missing the surgical treatment modality. In particular, there was a high likelihood of migration in early stage NSCLC, demonstrated with stage I (OR 5.78) and II (OR 5.16) disease; and when the initial hospital site lacked the surgical treatment modality (OR 3.39). However, only 4 out of the 29 hospital registries lacked a surgical treatment modality. These hospitals were smaller volume sites and their patients did not account for a substantial number of the patients who were treated after migration (136 out of 1093, or 12%). The remainder of patients who migrated even from facilities with all 3 treatment modalities available suggests the likely desire to seek higher levels of care regardless. Overall, it appears that patients with early stage disease are migrating to treatment centers with multidisciplinary availability which suggests the need for migration when curative treatment is intended.

Regarding the differing rates of advanced NSCLC (stage III and IV) overall survival with migration, there are few explanations. Mokdad et al extensively described NSCLC survival differences through the potential combination of risk factor profile, lack of awareness in the population and health care clinicians, and poor access to adequate health care.[11] Results of our study suggest the interplay of patients with advanced NSCLC who simply seek treatment at a separate site of diagnosis to have an increased survival benefit. This seemed to be the case because patients were more likely to be treated at a migrating site vs their initial site of diagnosis (93% vs 73% treatment rate) and thus prolonging overall survival. Thoracic surgery alone does not appear to be the driving force for migration and survival, since the benefit is seen only advanced stages. It otherwise remains unclear why patients migrating with advanced disease would result in prolonged survival other than inherent selection bias of migrating individuals having better performance statuses with greater inherent ability to travel potentially long distances. These patients may be more physically fit at baseline and live to have a greater benefit from treatment. As a result, migrating patients with advanced disease appear to have the luxury of postponing immediate treatment in order to seek the appropriate care.

Moreover, the disparities in insurance status is clearly apparent from our analysis as only private insurance status was significantly associated with treatment migration, whereas other socioeconomic factors including poverty level, median income, and education were not. While previous studies have accounted for the survival disparities of the insured population,[12-15] their source of insurance now provides additional insight into the sub-groups benefitting from cancer care. Ellis L et al recently reported that improved cancer survival was almost exclusively limited to patients with private or Medicare insurance vs other forms of public insurance. The authors postulated that having proper health insurance that covers cancer healthcare includes prevention, diagnosis, and lastly treatment, which all play a role in cancer survival.[16] In regards to the multidisciplinary therapeutics required for NSCLC treatment, public insurance such as state-based Medicaid may not be equally accepted by all treating providers across the state, which may enable those with private insurance to access care at various referral sites of high quality care.[17,18] The relationship of insurance status and survival benefit will undoubtedly continue to be a topic of debate given the continued changes made to the Patient Protection and Affordable Care Act via its subsidized private health insurance as well as expansion of Medicaid.[19]

Limitations

There are several limitations to our analysis. Our analysis only accounts for initial treatment. Patients were excluded from further analysis once they received treatment at their initial site, and the study does not account for subsequent treatments at different institutions upon disease progression. The study additionally cannot distinguish whether the inciting factor for patient migration is via healthcare provider or self-initiated. We are also unable to account for migration outside our participating registries, such as neighboring states or hospital systems. However, cases of migrating out-of-state are expected to represent a small minority of patients due to state-based payment sources for treatment. The data notably is restricted to initial diagnosis from 2012 to 2014 and prior to the development of immunotherapy in the first line setting for NSCLC. This treatment is believed to be more readily administered at higher level-of-care institutions, which may contribute to further migration.

Conclusion

This analysis demonstrates a survival benefit for initially untreated patients who migrate to another hospital. This migration is significantly associated with stage, missing treatment modalities at diagnosis site, and insurance status which suggests that patients intending to seek better care will frequently migrate. They are more likely to receive treatment and live longer if they

are insured, particularly with private insurance. Considering the current landscape of changing healthcare policy, it is notable that insurance status plays such a significant role in enabling lung cancer patients to find effective treatment. Data past 2014 will be useful to determine if trends persist, especially with newer treatment modalities such as immunotherapy approved to treat advanced NSCLC in the first-line setting.

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