Is Patient Travel Distance Associated With Survival on Phase II Clinical Trials in Oncology?

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Background: **Prior research has suggested that patients who travel out of their neighborhood for elective care from specialized medical centers may have better outcomes than local patients with the same illnesses who are treated at the same centers. We hypothesized that this phenomenon, often called "referral bias" or "distance bias," may also be evident in curative-intent cancer trials at specialized cancer centers.** ***Methods:*** **We evaluated associations between overall survival and progression-free survival and the distance from the patient residence to the treating institution for 110 patients treated on one of four phase II curative-intent chemoradiotherapy protocols for locoregionally advanced squamous cell cancer of the head and neck conducted at the University of Chicago over 7 years.** ***Results:*** **Using Cox regression that adjusted for standard patient-level disease and demographic factors and neighborhood-level economic factors, we found a positive association between the distance patients traveled from their residence to the treatment center and survival. Patients who lived more than 15 miles from the treating institution had only one-third the hazard of death of those living closer (hazard ratio [HR] = 0.32, 95% confidence interval [CI] = 0.12 to 0.84). Moreover, with every 10 miles that a patient traveled for care, the hazard of death decreased by 3.2% (HR = 0.97, 95% CI = 0.94 to 0.99). Similar results were obtained for progression-free survival.** ***Conclusion:*** **Results of phase II curative-intent clinical trials in oncology that are conducted at specialized cancer centers may be confounded by patient travel distance, which captures prognostic significance beyond cancer stage, performance status, and wealth. More work is needed to determine what unmeasured factors travel distance is mediating. [J Natl Cancer Inst 2003;95:1370–5]**

Prior observational research suggests that patients who travel out of their neighborhood for elective care from specialized medical centers may have better outcomes than local patients with the same conditions who are treated at the same centers *(1–5).* We hypothesized that this apparent differential treatment effect by patient travel distance, sometimes referred to as "referral bias" or "distance bias," might also be relevant to cancer patients treated on clinical trials at National Cancer Institute (NCI)–designated cancer centers. Results of one study evaluating survival effects of patient travel distance to NCI-designated cancer centers for myeloma care suggested that travel distance is positively associated with survival (i.e., patients who live farther from the center survive longer than patients who live close to it) *(1).* However, the results of this study may have been confounded by incomplete ascertainment of standard demographic and disease factors (e.g., extent of disease, performance status) typically included in clinical trials and by nonuniformity of treatment.

Using phase II clinical trial data from curative-intent cancer protocols conducted at a single specialized cancer center, we tested the hypothesis that cancer patients who travel a distance for their care have a lower hazard of death than patients who live close to the institution, even after adjusting for demographic, disease, and treatment variables.

METHODS

Data Sources

The University of Chicago Medical Center is an NCI-designated cancer center with international prominence in the treatment of head and neck cancer. It is located on the south side of Chicago—an urban and generally low-income area—and cares for patients from the surrounding neighborhood who may have their first point of contact through the Medical Center's emergency department. The University of Chicago Medical Center also cares for head and neck cancer patients, through physician referral and patient self-referral, from neighborhoods outside of its own, including other locations in Illinois, contiguous states, other states, and other countries. For patients of this type, their first point of contact is almost exclusively via a scheduled appointment in the outpatient Head and Neck Oncology Clinic. We analyzed data on both overall survival and progression-free survival from four sequential phase II chemoradiotherapy studies conducted at the University of Chicago from 1993 through 2000 for patients with previously untreated, locoregionally advanced squamous cell cancer of the head and neck. The goals of therapy in each protocol were both eradica-

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tion of disease (i.e., cure) and organ preservation. The results of these studies have been analyzed and reported individually *(6–9)* and have been subsequently analyzed in aggregate with respect to patterns of treatment failures *(10)*.

During the period in which each study was open to accrual, all newly diagnosed patients who were eligible were offered treatment on that protocol—that is, there were no competing protocols for similar patients. The treatment schedules for the protocols are described in Table 1. Eligibility requirements reflected standard extent-of-disease and general health requirements. Detailed descriptions of both the eligibility criteria and treatment plans can be found in the original reports of the studies *(6–9)*. Although the protocols were all conceptually similar in consisting of aggressive anticancer therapy with five cycles of split-course hyperfractionated concurrent chemoradiotherapy, each protocol also contained unique features that reflected programmatic evolution (i.e., treatment changes) over that period. For example, because of results from the second study, cisplatin was replaced by paclitaxel as a radiation sensitizer in the concurrent chemoradiotherapy regimen for the subsequent studies; because of results from the first three studies, which documented distant relapse, two cycles of induction (i.e., neoadjuvant) chemotherapy were added to the fourth protocol. Survival follow-up of patients on the studies was determined at regular intervals by the same research study nurse during the entire observation period (1993–2001) and consisted primarily of tracking follow-up clinic visits and telephoning patients or their listed emergency contact for those who missed appointments.

Cohort Development

The initial cohort consisted of all patients with stage IVA and IVB *(11)* squamous cell carcinoma of the head and neck treated at the University of Chicago Medical Center on one of four phase II chemoradiotherapy protocols (N = 129) between September 1993 and January 2000. After excluding from our analyses patients with incomplete disease-free survival information (n = 8), incomplete socioeconomic information (n = 10), and incomplete race information (n = 1), we were left with an analytic sample of 110 patients. Excluded patients did not differ from the analytic sample with respect to the key explanatory variable—distance traveled for care. Because no patients were lost to follow-up, there is no possibility of informative censoring of our sample.

Table 1. Treatment schedules for the four phase II protocols in which the patients (N = 110) in the cohort were enrolled*

Protocol	Accrual dates	Schedule	n	Reference
6950	Sept 1993–Oct 1995	CFHX	36	*(6)*
7929	Nov 1995–Feb 1997	TFHX, continuous infusion T	15	*(7)*
8626	Mar 1997–Aug 1998	TFHX, 1-h infusion T	27	*(8)*
9502	Nov 1998–Jan 2000	Induction CbT followed by TFHX	32	*(9)*

*Cb = carboplatin; C = cisplatin, F = fluorouracil; H = hydroxyurea, T = paclitaxel; X = twice-daily (i.e., hyperfractionated) radiotherapy. CFHX and TFHX are combinations of chemotherapy with concurrent radiotherapy (i.e., chemoradiotherapy). These combinations were administered in a week on/week off fashion (i.e., split fractions) over a 10-week period in each protocol. Induction CbT is two cycles of carboplatin and paclitaxel chemotherapy administered prior to concurrent chemoradiotherapy.

Variables

Our key explanatory variable was the distance patients traveled from their residence to the University of Chicago Medical Center for treatment. We used the patient's self-reported address as recorded on the original protocol study forms to determine patient residence. We then calculated the driving miles between the patient's residence and the University of Chicago Medical Center (i.e., 5841 S. Maryland Avenue, Chicago, IL 60637) using an Internet-based mapping engine that relies on commercial mapping data sources. We confirmed accuracy of this distance with a second Internet-based mapping engine that relied on different commercial mapping data sources and found that the distances calculated were similar in all cases.

Variables describing patient age, sex, race, educational level, family income, smoking history, alcohol use history, and Karnofsky performance status (KPS) *(12)* had been collected through patient self-report to research assistants at the time of study enrollment and were therefore available in the original datasets. Variables describing extent of disease (i.e., tumor–node–metastasis [TNM] stage) *(11)* and tumor site had been determined by the original treating physicians and were also available from the original datasets. To adjust our analyses for possible neighborhood effects, which in previous research have been found to be important predictors of cancer survival *(13–15)*, we created a neighborhood-level economic indicator—the median income for each patient's census tract of residence according to 1990 U.S. Census data. Census tract was ascertained through patient address.

To evaluate possible confounding by comorbid illness, we estimated the baseline medical comorbidity for each patient using the Charlson comorbidity score *(16)*. The comorbidity score is a convenient method of quantifying co-occurring medical illness in cancer patients and is often used for risk adjustment. The score, ranging from 0 to 29, consists of a weighted sum of 17 major illnesses (e.g., myocardial infarction, stroke, diabetes, liver disease, dementia, renal disease). The comorbidity score was determined from the list of previous conditions in the "Past Medical History" section of the discharge summaries from the first University of Chicago hospitalization for treatment. Head and neck cancer was not included in the list of possible comorbid illnesses.

Statistical Analyses

We compared demographic and disease characteristics of those patients who traveled 15 miles or less to the treating center with those of patients who traveled more than 15 miles, the conventional cut point for distinguishing local and distant patients *(17,18)*, using the chi-square test (for categorical variables) and two-sample *t* test (for continuous variables). To evaluate overall survival with respect to both categorical and continuous travel distance and demographic, disease, and treatment variables, we used the Cox proportional hazards model to evaluate covariates singly in relation to the mortality hazard. We then used multivariable Cox regression to estimate the relative mortality hazard according to the distance patients traveled for their care, adjusting for variables that were statistically significant at an alpha level of .10 in the single-variable models as well as other standard demographic and disease variables and vari-

ables in which we had substantive interest. Because we were concerned that economic factors, particularly wealth, might confound an apparent relationship between travel distance and survival, we controlled rigorously for economic status by including covariates for both family income of the individual patient and a neighborhood-level indicator of income (i.e., the median income of the patient's census tract). To account for survival differences related to protocols, we stratified our analyses by protocol to adjust in a maximally flexible manner that had no implicit proportionality assumption.

To evaluate whether differential cancer treatment response could explain differences in overall survival by patient travel distance, we also used the same predictor variables to estimate the impact of patient travel on progression-free survival (i.e., time to cancer progression, to death from cancer, or to death from toxicity of treatment, with death from other causes censored). In both types of survival analysis, travel distance was evaluated both as a dichotomous covariate, using the conventional cut point of 15 miles, and as a continuous variable.

We used the robust method of Lin and Wei *(19)* to calculate the standard errors of parameter estimates for the Cox regressions, which adjusts standard errors appropriately for the lack of independence of observations related to the assigned neighborhood income variable. We assessed the proportionality assumption for all covariates using the method of Grambsch and Therneau *(20)* and found it to hold. Because of the small sample size, no testing for statistical interactions was performed.

All analyses were performed with Stata 7.0 (Stata, College Station, TX). The research was approved by the University of Chicago Institutional Review Board and was conducted in compliance with its requirements.

RESULTS

Cohort Characteristics

Table 2 presents the demographic, disease, and treatment characteristics of the 110 patients studied. Table 3 presents the associations between the distance that patients traveled for cancer care and the other demographic and disease-related variables. Those who traveled more than 15 miles differed from those who traveled 15 miles or less with respect to several demographic factors but few disease factors. On average, patients who traveled more than 15 miles for their cancer care were more often male, white, and college-educated; reported higher family incomes; came from wealthier neighborhoods; and were less likely to report prior heavy alcohol use than those who traveled 15 miles or less. Although the groups were similar with respect to disease factors such as tumor stage, KPS, smoking history, and documented comorbidity burden, more local patients had cancer of the larynx, for which the prognosis is relatively favorable, than patients who had traveled more than 15 miles. Follow-up ascertainment (median follow-up was 40 months for those traveling 15 miles or less and 33 months for those traveling more than 15 miles) was not statistically significantly different between the two groups.

Table 2. Characteristics of cohort (N = 110)

Variable	Value
Age at entry, median y (range)	56.5 (33–81)
Male, proportion (No.)	0.74 (81)
Race, proportion (No.)	
White	0.67 (74)
African American	0.33 (36)
Family income, $; proportion (No.)	
<9999	0.27 (30)
10 000–19 999	0.08 (9)
20 000–29 999	0.15 (16)
30 000–39 999	0.12 (13)
40 000–49 999	0.10 (11)
⩾50 000	0.28 (31)
Census tract income, $; median (range)	33 762 (5261–112 594)
College education, proportion (No.)	0.22 (24)
Distance from residence to center, median miles (range)	20 (0.68–1028.4)
Protocol, proportion (No.)	
6950	0.32 (36)
7929	0.14 (15)
8626	0.25 (28)
9502	0.29 (32)
Head and neck cancer stage, proportion (No.)*	
IVA	0.84 (92)
IVB	0.16 (18)
Tumor site, proportion (No.)	
Oral cavity	0.13 (14)
Oropharynx	0.40 (44)
Hypopharynx	0.09 (10)
Larynx	0.29 (32)
Other	0.09 (10)
Karnofsky performance status, proportion (No.)	
100	0.36 (40)
90	0.32 (36)
80	0.14 (15)
<80	0.18 (19)
Alcohol history, proportion (No.)	
Nondrinker	0.17 (19)
Occasional	0.22 (24)
Moderate	0.16 (18)
Heavy	0.45 (49)
Smoking history, proportion (No.)	
Never smoked	0.06 (7)
Pipe or cigar only	0.05 (5)
Cigarettes, <20 pack-years	0.14 (15)
Cigarettes, 20–40 pack-years	0.41 (45)
Cigarettes, >40 pack-years	0.34 (38)
Charlson comorbidity score, proportion (No.)	
0	0.84 (93)
1	0.12 (13)
2	0.02 (2)
3	0.01 (1)
4	0.01 (1)

*American Joint Commission on Cancer Staging *(11)*.

Overall Survival After Study Enrollment

By modeling time to death with single-variable Cox proportional hazards models, we found that patient age, income, smoking history, KPS, and protocol therapy were each predictors of survival at an alpha level of .10. Patient age and income were evaluated both as linear terms and as quadratic terms to allow for any nonlinearity of association. The single-variable Cox model with patient travel distance revealed that, with each 10 miles a patient traveled for care, the hazard of death decreased by 3.0% (hazard ratio [HR] = 0.97, 95% confidence interval [CI] = 0.95 to 0.99).

By modeling time to death with a multivariable Cox proportional hazards model that included patient age, race, family income, neighborhood income, tumor stage, larynx site, smoking

Table 3. Characteristics of cohort (N = 110) according to distance traveled from residence to treating institution*

Variable	Distance traveled ⩽15 miles (n = 43)	Distance traveled >15 miles (n = 67)	*P*
Sociodemographic factors			
Age, mean y	54.3	56.5	.254
Female, proportion	0.33	0.22	.237
White, proportion	0.23	0.91	<.001
Family income, mean $	17 325	38 731	<.001
Median neighborhood income, mean $	22 474	45 292	<.001
College graduate, proportion	0.07	0.31	.003
Disease factors			
Stage IVB, proportion	0.14	0.18	.584
Larynx site, proportion	0.42	0.21	.018
Karnofsky performance status, mean	87	89	.665
Cigarette pack-years smoked, mean	31.6	30.4	.726
Heavy alcohol consumption, proportion	0.53	0.39	.133
Charlson comorbidity score, mean	0.23	0.21	.844

*P values from chi-square test (for categorical variables) and two-sample t test (for continuous variables).

history, and KPS and that was stratified by protocol (Table 4), we found that patients who lived more than 15 miles from the treating institution had only one-third the hazard of death of those who lived closer (HR = 0.32, 95% CI = 0.12 to 0.84) (Table 4). Other factors that were statistically significantly associated with survival were age, race, family income, smoking history, and tumor stage. Compared with white patients, African American patients had only one-third the hazard of death (HR = 0.30, 95% CI = 0.10 to 0.89). With each $1000 increase in annual family income, the hazard of death decreased by 3.6% (HR = 0.97, 95% CI = 0.94 to 0.99). With each additional pack-year of cigarette smoking, the hazard of death increased 4.0% (HR = 1.04, 95% CI = 1.01 to 1.07). Compared with patients with stage IVA disease, patients with stage IVB disease had three times the hazard of death (HR = 3.07, 95% CI = 1.26 to 7.46). We used the model's predicted values to plot graphically the association of travel distance and survival (Fig. 1). This graph shows the estimated baseline survival functions for patients with a particular covariate profile according to whether they lived within 15 miles or more than 15 miles from the treating institution.

Table 4. Multivariable Cox regression model of overall survival (N = 110)*

Variable	Hazard ratio	95% confidence interval
Patient residence, distance in miles from treating institution		
⩽15	1.00	Referent
>15	0.32	0.12 to 0.84
Age		
Age	1.01	0.99 to 1.05
Age × Age	1.01	1.01 to 1.01
Race		
White	1.00	Referent
African American	0.30	0.10 to 0.89
Economic measures		
Family income (per $1000 increment)	0.96	0.94 to 0.99
Family income × family income (per $1000 increment)	1.00	0.99 to 1.00
Median neighborhood income (per $1000 increment)	1.02	0.99 to 1.04
Tumor stage		
IVA	1.00	Referent
IVB	3.07	1.26 to 7.46
Larynx primary tumor site	0.70	0.36 to 1.35
History of cigarette smoking (per pack-year)	1.04	1.01 to 1.07
Karnofsky performance status		
100	1.00	Referent
<100	1.98	0.97 to 4.05

*Analysis was stratified by treatment protocol. The linear age variable is centered at 58 years, and the family income variable is centered at $25 000. The variable × variable terms are the respective centered linear variable squared.

We also evaluated the relationship between travel distance and survival, treating travel distance as a continuous, rather than a categorical, variable. After adjusting for the previously mentioned variables (i.e., patient age, race, family income, neighborhood income, tumor stage, larynx site, smoking history, KPS, and protocol), the hazard of death decreased by 3.2% (HR = 0.97, 95% CI = 0.94 to 0.99) with each 10 miles the patient traveled for treatment.

Progression-Free Survival After Study Enrollment

To evaluate the possible contribution of differential cancer treatment effects as an explanation for the effect of travel distance on overall survival, we estimated the impact of patient travel on progression-free survival using the same predictor variables as in the analysis of overall survival. The resulting multivariable Cox proportional hazards model, which adjusted for patient age, race, family income, neighborhood income, tumor stage, larynx site, smoking history, and KPS and was stratified by protocol, estimated that those patients who lived more than 15 miles from the treating institution had only one-third the hazard of recurrent disease than those who lived closer (HR = 0.30, 95% CI = 0.10 to 0.89). Similarly, when travel distance

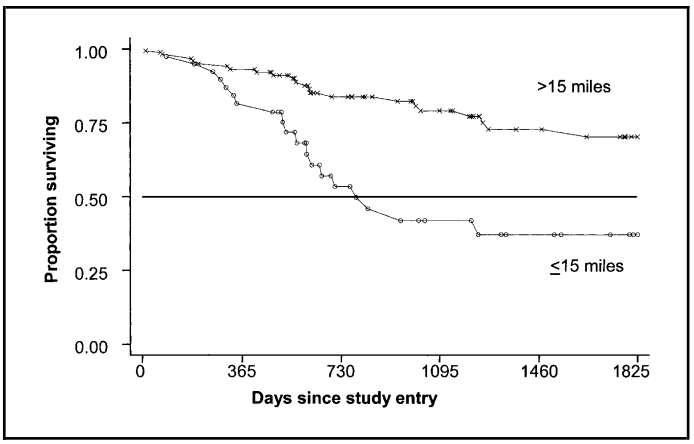

Fig. 1. Graphic representation of expected survival differences according to travel distance. We used the multivariable Cox proportional hazards model to estimate the expected survival function for a fixed covariate profile (i.e., a 58-year-old white patient with stage IVA larynx cancer, Karnofsky performance status of less than 100, median family income, median neighborhood income, 30 pack-years of cigarette smoking, treated on protocol 6950), stratifying the analysis by travel distance. **Upper line** shows the expected survival pattern for patients with this covariate profile who traveled greater than 15 miles from their home to participate in a curative-intent phase II clinical trial; the lower line (**points marked with circles**) shows the expected survival pattern for those patients traveling less than or equal to 15 miles. **Horizontal line** represents the median survival.

was treated as a continuous variable, a Cox model that adjusted for the same variables revealed that the hazard of recurrent disease decreased by 4.4% (HR = 0.96, 95% CI = 0.91 to 1.00) with each 10 miles the patient traveled for care.

Discussion

We found that, beyond standard malignancy-related and nonmalignancy-related factors commonly included in analyses of clinical trial results in oncology, a social factor—the physical distance patients traveled from their homes to the treating institution—predicted survival following curative phase II chemoradiotherapy studies at an NCI-designated cancer center. The association of travel distance with both overall and progression-free survival suggests a component of differential treatment effect associated with travel distance, rather than simply excess unmeasured comorbidity varying by travel distance. Moreover, the magnitude of the hazard reduction was substantial, such that a distance of 10 miles was apparently associated with as much of a decrease in risk as a pack-year of cigarette smoking was associated with an increase in risk.

These results have direct clinical implications and broad epidemiologic implications. First, our study formally documents something clinical researchers in oncology have long appreciated. That is, on average, those patients who are able and willing to 1) research therapeutic options (or have agents who will do so for them) and 2) find and expend the resources necessary to then receive those therapies seem to fare better than those patients who end up at the closest place for care, even if their diseases and treatments are apparently the same. Our results suggest that further work is needed to better characterize which individual (e.g., better overall health, greater unmeasured wealth, personality traits, greater compliance) and social [e.g., social capital *(21),* social networks] factors travel distance is mediating. Such a discriminative tool might be used to ultimately improve the outcomes of patients deficient in some of these factors through clinic-level interventions.

More broadly, our results suggest that, separate from actual drug effects, patient selection has the potential to influence the pathway to new drug development. Because results of phase II studies inform the design of the phase III studies that ultimately lead to decisions about new drug approval by the U.S. Food and Drug Administration, selection bias in the phase II setting could lead to bias in recommendations for which drugs should advance to phase III evaluation. Although phase III randomization would remove phase II selection bias from the treatment effect, resources for the phase III studies may be consumed, and potentially active agents may be passed over at the phase II level, as a consequence of patient selection. That is, the same drug might be associated with different survival outcomes, depending on the heterogeneity of the population studied. This phenomenon may, at least in part, explain the attenuation of treatment effects that is sometimes observed when chemotherapy regimens are moved from phase II to phase III settings *(22–30),* and it may hold relevance for comparisons of phase II results between those specialized cancer centers with and without emergency departments (i.e., portals by which local patients may gain access to clinics that offer trials). Thus, these results, if verified in other groups and clinical settings, suggest an important area for greater research: the division of patient travel distance into its more root prognostic elements.

In addition, this work contributes to the existing experimental oncology literature in two ways. First, it documents the extent to which local and referred patients can differ with respect to demographic and socioeconomic features, with the referred patients in our sample being wealthier and better educated than the local patients. Second, it measures the impact of certain health factors that are separate from malignancy on survival in locoregionally advanced head and neck cancer. That is, we have shown a very strong negative association between smoking and survival. Given the etiologic pathway to this malignancy [i.e., the importance of tobacco smoke exposure *(31)*], this association is expected, but, to our knowledge, the magnitude had not previously been estimated for head and neck cancer patients treated on clinical trials. Similarly, the large positive association between wealth and survival that we report is expected, given the substantial previous research in medicine in general and in the subspecialty of oncology *(32–34)* but, to our knowledge, the association had not been reported in clinical trials in head and neck cancer in which both disease extent and therapies were uniform.

Finally, our findings regarding the association of race with overall survival are inconsistent with the many well-documented reports of race-related disparities in cancer outcome *(35–37)* and thus deserve further mention. We showed that when treatment was standardized and health factors, social resources, and neighborhood effects were rigorously accounted for, African American patients may actually have had better survival outcomes than white patients in the phase II trials included in our study. This finding suggests that the racial disparities observed in other clinical oncology settings may actually be a proxy for unmeasured or unreported disparities in quality of medical care, in underlying patient health, and/or in patient social resources. That is, our results do not support a biologic explanation for the race-related differences that have been seen in cancer outcome between African Americans and whites.

There are several limitations to our study. Given the location of the University of Chicago Medical Center in an urban area and its wide regional and distant referral patterns for head and neck cancer, our results may not apply to treatment centers that are located in less urban areas and/or have different referral patterns. We also cannot exclude the possibility that patients with poor prognoses might have moved closer to the University of Chicago for care before their first medical encounter, thus creating a spurious association between travel distance and outcome.

We conclude that results of single-institution phase II clinical trials in oncology at specialized cancer centers may be sensitive to a social factor—the distance that cancer patients travel for experimental curative-intent treatment. Because travel distance appears to capture prognostic significance beyond disease stage, performance status, and wealth, it may confound the apparent relationship between a given therapy and survival on such nonrandomized trials. More work is needed to determine what unmeasured factors travel distance may be mediating.

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NOTES

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