Differences in Clinical Trial Patient Attributes and Outcomes According to Enrollment Setting

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ABSTRACT

Purpose

During the last 25 years, National Cancer Institute (NCI) cooperative trial groups have extended trial networks from academic centers to include certain community and Veterans Health Administration (VHA) centers. We compared trial patients' attributes and outcomes by these enrollment settings.

Patients and Methods

Studying 2,708 patients on one of 10 cooperative group, randomized lung trials at 272 institutions, we compared patient attributes by enrollment setting (ie, academic, community, and VHA affiliates). We used adjusted Cox regression to evaluate for survival differences by setting.

Results

Main member institutions enrolled 44% of patients; community affiliates enrolled 44%; and VHAs enrolled 12%. Patient attributes (ie, case-mix) of age, ethnicity, sex, and performance status varied by enrollment setting. After analysis was adjusted for patient case-mix, no mortality differences by enrollment setting were noted.

Conclusion

Although trial patients with primarily advanced-stage lung cancer from nonacademic centers were older and had worse performance statuses than those from academic centers, survival did not differ by enrollment setting after analysis accounted for patient heterogeneity. An answer for whether long-term outcomes for patients at community and VHA centers affiliated with cooperative trial groups are equivalent to those at academic centers when care is delivered through NCI trials requires additional research among patients with longer survival horizons.

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INTRODUCTION

Numerous prior studies have shown that patients treated on clinical trials vary substantially from patients treated in the usual care setting.¹⁻⁵ Among the differences reported include under-representation of ethnic minorities, women, and the elderly. Additional work has shown that some of the misrepresentation of the general population on trials may relate to differences in extent of disease at presentation (ie, fewer early-stage cancers in some ethnic groups compared with others),⁶ medical comorbidity,⁷ performance status,⁸ and logistical factors that uniquely deter enrollment among the elderly.⁹

One approach to better understand the external validity of existing cancer trials is to study multi-institutional trials enrolling patients through settings other than comparatively specialized aca-

ademic centers. Evaluating attributes of patients enrolled on the same trials but in different settings (ie, academic v nonacademic) and evaluating for possible differential patient outcomes according to setting will allow trialists and community oncologists to better understand the generalizability of clinical trial results to the underlying US population with cancer. Moreover, if differences by setting are evident, then differential reporting by trial setting may be useful to clinicians caring for patients outside of academic settings.

With respect to the availability of clinical trials, two National Cancer Institute (NCI) policy initiatives during the last 25 years have extended cooperative group trial networks from exclusively academic centers to include certain community and Veterans Health Administration medical centers. The first initiative, the Community Cancer

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Oncology Program (CCOP), was developed in the early 1980s as explicit effort to reduce barriers to community-dwelling cancer patients' access to NCI-sponsored through, in part, incorporating certain community oncology practices into existing NCI cooperative trial groups.¹⁰ Similarly, the second initiative, the Department of Veterans Affairs and NCI partnership, was initiated in the early 1990s as an explicit effort to improve the access of veterans with cancer to NCI-sponsored trials through, in part, incorporating certain VHA medical centers into existing NCI cooperative trial groups.¹¹ Both of these policy-based initiatives sought to make experimental therapies available to community cancer patients without needing to travel to academic centers.

In this study, we sought to leverage the multi-institutional nature of cooperative group trials to inform whether trial patients' attributes varied by enrollment setting (ie, academic, community, and VHA) and if, after analysis was adjusted for patient attributes (ie, case-mix), there were differences in cancer patients' trial outcomes that were attributable to the type of enrollment setting itself.

PATIENTS AND METHODS

Data Sources

Cancer and Leukemia Group B (CALGB) is an NCI-sponsored cooperative oncology research group that represents a network of more than 3,000 physicians from academic medical centers, community hospitals, and VHA medical centers that share the common goal of decreasing cancer morbidity and mortality through shared therapeutic trials. Among the variables common to all therapeutic trials are registration information, which includes protocol number, patient information (eg, age at enrollment, sex, race), dis-

ease information (eg, tumor stage, patient performance status), treatment information (eg, drugs administered), toxicity information (ie, standard common toxicity criteria), and survival end points. Certain trials collect additional information (eg, socioeconomic status, marital status, employment). The ZIP codes of the patients' residences at the times of enrollment are also available for some trials.

We examined data from 10 CALGB phase III clinical trials in lung cancer (Table 1) that enrolled patients during the years 1990 to 2003. The 10 phase III protocols differed in both the types of patients enrolled (particularly by histology and stage of disease) and in types of treatments provided (Table 1).¹²⁻²¹ These trial data included information on patient attributes (ie, age, race, and performance status) and in some cases ZIP code information as well as patient marital status and education. For patients with ZIP code information, we used publicly available data from the 2000 US Census to characterize economic status in patient ZIP code of residence.

Study Cohorts

From all of the phase III CALGB lung cancer trials examined, we selected those that included any patients enrolled at a VHA hospital (10 of the 11 trials). We pooled patients into a parent cohort that consisted of 2,708 trial participants from 272 different treatment centers (48 academic centers, 204 community affiliates, and 20 VHA affiliates) treated on one of the selected 10 phase III lung cancer studies.

We also created to two subsets of the initial cohort; this approach was necessary because of the paucity of female patients enrolling through VHA settings. The first subset involved male patients only from the three settings; there were 1,766 male trial participants from 244 different treatment centers (46 academic, 178 community, and 20 VHA affiliates). The second subset consisted of all male and female patients enrolled at academic and community settings only ($n = 2,369$); they came from 252 different treatment centers (48 academic, 204 community, and 0 VHA affiliates).

Table 1. Cancer and Leukemia Group B Phase III Lung Trials Studied

Study Title and Reference	Study No.	Tumor Histology	Tumor Stage	No. of Patients
Randomized trial of chemotherapy and radiation therapy with or without warfarin for limited-stage small-cell lung cancer: a Cancer and Leukemia Group study ⁴	8534	Small-cell	Limited	116
Cisplatin, vinblastine, and hydrazine sulfate in advanced, non-small-cell lung cancer: a randomized placebo-controlled, double-blind phase III study of the Cancer and Leukemia Group B ⁵	8931	Non-small-cell	IIIB/IV	214
Schedule dependency of 21-day oral versus 3-day intravenous etoposide in combination with intravenous cisplatin in extensive-stage small-cell lung cancer: a randomized phase III study of the Cancer and Leukemia Group B ⁶	9033	Small-cell	Extensive	316
Radiosensitization with carboplatin for patients with unresectable stage III non-small cell lung cancer: a phase III trial of the Cancer and Leukemia Group B and the Eastern Cooperative Oncology Group ⁷	9130	Non-small-cell	III (unresectable)	272
Radiotherapy versus chemotherapy plus radiotherapy in surgically treated IIIA N2 non-small-cell lung cancer ⁸	9134	Non-small-cell	IIIA (unresectable)	55
A phase III trial evaluating the combination of cisplatin, etoposide, and radiation therapy with or without tamoxifen in patients with limited-stage small-cell lung cancer: Cancer and Leukemia Group B study (9235) ⁹	9235	Small-cell	Limited	309
A phase III study of adjuvant chemotherapy after resection for patients with T2N0 stage I non-small-cell carcinoma of the lung ¹⁰	9633	Non-small-cell	IB	311
Single agent versus combination chemotherapy in advanced non-small-cell lung cancer: a Cancer and Leukemia Group B randomized trial of efficacy, quality of life, and cost-effectiveness ¹¹	9730	Non-small-cell	IIIB/IV	562
A randomized phase III study comparing etoposide and cisplatin with etoposide, cisplatin, and paclitaxel in patients with extensive small-cell lung cancer ¹²	9732	Small-cell	Extensive	217
Concurrent carboplatin, paclitaxel, and radiation therapy versus induction carboplatin and paclitaxel followed by concurrent carboplatin and paclitaxel and radiation therapy for patients with unresectable stage III non-small-cell lung cancer ¹³	39801	Non-small-cell	III (unresectable)	336

NOTE. The Table lists details of the 10 studies included in these analyses. Specifically listed are the study title, the CALGB study number, histology and stage requirements, and the numbers of participants on each study. Total number of patients for all 10 studies = 2,708.

Table 2. Patient and Trial Composition by Enrollment Setting

Variable	Patient Data by Enrollment (N = 2,708)			P
	Academic (n = 1,181)	Community (n = 1,188)	VHA (n = 339)	
Mean age, years	60.8	61.7	64.4	< .001
% respondents	100	100	100	
Sex, %				< .001
Male	61.5	59.3	98.9	
Female	38.5	40.7	1.2	
% respondents	96.6	98.0	100	.002
Race, %				< .001
White	83.5	89.1	82.6	
Black	12.2	7.7	16.5	
Other	0.9	1.2	0.6	
% respondents	99.6	99.4	100	.351
Hispanic-specific ethnicity, %				
Hispanic or Latino	2.8	1.4	0.3	.007
Non-Hispanic	96.8	98.1	99.7	
% respondents	64.6	62.3	60.5	.158
Family income in ZIP area*, \$				
Median	49,242	48,904	43,953	< .001
Mean No. of patients	763	728	205	
% respondents	64.6	62.3	60.5	.158
Below poverty level in ZIP area*				
%	13.0	11.9	15.2	< .001
Mean No. of patients	763	728	205	
% respondents	100	100	100	NA
WHO performance status, %				< .001
0	37.0	46.0	27.4	
1	53.1	45.8	56.0	
≥ 2	9.9	8.2	16.5	
Year of trial enrollment, %				.029
1990-1994	38.3	38.2	43.7	
1995-1999	35.2	33.2	37.2	
2000-2003	26.5	28.5	19.8	
CALGB study No., %				< .001
8534	4.7	3.7	5.0	
8931	7.6	9.8	2.4	
9033	11.0	11.0	18.0	
9130	9.0	10.1	13.6	
9134	3.0	1.1	1.8	
9235	11.4	11.2	12.4	
9633	11.0	13.3	7.4	
9730	23.8	17.9	20.4	
9732	8.8	8.0	5.3	
39801	10.2	14.2	13.9	

NOTE. This Table describes bivariate associations between our key predictor variable, cooperative group enrollment setting, and other covariates.

Abbreviations: VHA, Veterans Health Administration; NA, not available; CALGB, Cancer and Leukemia Group B.

*In addition, the two variables of mean family income and % below poverty level represent values from only eight of the 10 trials. In CALGB 8534 (n = 116) and CALGB 8931 (n = 214), ZIP code was not collected; therefore, it was not possible to create ZIP code-level socioeconomic status variables. After removing these two trials with wholly missing ZIP data from the denominator, 71% of the remaining eight trials had patient socioeconomic status data. Because this number was not high, however, we excluded these ZIP-level socioeconomic variables from the Cox models reported in Tables 3, 4, and 5.

Outcome Variable, Covariates, and Predictor Variables

Outcome. For each patient, we evaluated time from diagnosis to death as a result of all causes. We censored those patients who had not died at last known follow-up.

Patient attributes. In addition to basic demographic information, we were especially interested in characterizing performance status for all patients by treatment setting. This relates to the importance of performance status in predicting mortality.²² We used the WHO index,²³ which ranges from 0 (full functional status) to 5 (death).

Enrollment Setting

We classified enrolling institutions as academic if the institution was a main member of CALGB. We classified the institution as community if the institution was a non-VHA affiliate and as VHA if the institution was a VHA hospital according to the facility name recorded in the registration data.

Statistical Analyses

To evaluate for differences between characteristics of individuals enrolled at academic, community, and VHA sites, we compared attributes of the trial participants according to enrollment sites using *t* tests for continuous variables and χ^2 tests for categorical variables for all 2,708 patients in the study cohort (Table 2).

We used two Cox regression models to evaluate the effects of enrollment setting on survival. In the first model (ie, model 1 in Tables 3 and 4), we included only enrollment setting and trial number. In the second model (model 2), we added patient case-mix factors (ie, age, ethnicity, performance status) and registration year of the trial as covariates. Because of the small number of Hispanic patients and patients of other races in this cohort, we coded race as white versus nonwhite in our multivariate models. Because of differences in prognosis across the studies, we allowed for different baseline survival functions by stratifying on trial given the differences patient survival according to study. Tests of proportional hazards assumptions demonstrated that it was reasonable to assume other patient factors adjusted the hazard proportionally. In both models, we adjusted standard errors to account for the

Table 3. Hazard of Death After Treatment on CALGB Phase III Lung Trials by Enrollment Site for Male Trial Patients

Variable*	Model 1		Model 2	
	HR	95% CI	HR	95% CI
Enrollment site	1.00	—	1.00	—
Community affiliate	0.95	0.84 to 1.07	0.99	0.87 to 1.12
VHA affiliate	1.17	1.03 to 1.34	1.09	0.96 to 1.24
Age, years			1.00	—
55-59			0.86	0.74 to 0.99
60-64			1.06	0.91 to 1.23
65-69			0.93	0.78 to 1.10
70-74			1.13	0.96 to 1.32
≥ 75			1.30	1.01 to 1.68
Registration year			1.00	—
1995-1999			1.35	0.99 to 1.84
2000-2003			1.44	1.02 to 2.03
Race			1.00	—
Non-white			0.96	0.83 to 1.10
PS			1.00	—
1			1.35	1.21 to 1.49
≥ 2			2.27	1.92 to 2.68

NOTE. Total number of patients = 1,766 in 244 facilities. The median survival of the trial patients was 351 days. Relative hazards of death of community and VA enrollment settings are compared with academic enrollment settings. The analyses were stratified by the 10 treatment trials (ie, CALGB 8534, CALGB 8931, CALGB 9033, CALGB 9130, CALGB 9134, CALGB 9235, CALGB 9633, CALGB 9730, CALGB 9732, and CALGB 39801). Model 1 represents the minimally adjusted model that takes into account only enrollment setting, stratified by the 10 trials. Model 2 extends Model 1 through the addition of patient case-mix factors of age, ethnicity, PS, and registration year.

Abbreviations: CALGB, Cancer and Leukemia Group B; HR, hazard ratio; VHA, Veterans Health Administration; PS, performance status.

*Reference values for each variable are as follows: enrollment site, academic; age, < 55 years; registration year, 1990-1994; ethnicity, white; and PS, 0.

Table 4. Hazard of Death After Treatment on CALGB Phase III Lung Trials by Enrollment Site for Academic and Community Trial Patients

Variable*	Model 1		Model 2	
	HR	95% CI	HR	95% CI
Enrollment site	1.00	—	1.00	—
Community affiliate	0.94	0.86 to 1.04	0.98	0.88 to 1.08
Age, years			1.00	—
55-59			0.93	0.82 to 1.06
60-64			0.91	0.79 to 1.05
65-69			0.91	0.78 to 1.06
70-74			1.15	0.99 to 1.34
≥ 75			1.43	1.18 to 1.72
Sex			1.00	—
Female			0.82	0.75 to 0.90
Registration year			1.00	—
1995-1999			1.22	0.92 to 1.61
2000-2003			1.12	0.83 to 1.50
Race			1.00	—
Non-white			0.98	0.88 to 1.09
PS			1.00	—
1			1.34	1.22 to 1.48
≥ 2			2.23	1.87 to 2.66

NOTE. Total number of patients = 2,369 in 252 facilities. The median survival of the trial patients was 391 days. The Table describes the relative hazards of death of community compared with academic enrollment settings. The analyses were stratified by the 20 treatment trials (ie, CALGB 8534, CALGB 8931, CALGB 9033, CALGB 9130, CALGB 9134, CALGB 9235, CALGB 9633, CALGB 9730, CALGB 9732, and CALGB 39801). Model 1 represents the minimally adjusted model that takes into account only enrollment setting, stratified by the 10 trials. Model 2 extends Model 1 through the addition of patient case-mix factors of age, ethnicity, sex, PS, and registration year.

Abbreviations: CALGB, Cancer and Leukemia Group B; HR, hazard ratio; VHA, Veterans Health Administration; PS, performance status.

*Reference values for each variable are as follows: enrollment site, academic; age, < 55 years; sex, male; registration year, 1990-1994; ethnicity, white; and PS, 0.

clustering of patients within enrollment centers. Because all 10 trials were negative (ie, treatment arms were equivalent with respect to survival), we did not control for treatment arm.

We also performed sensitivity analyses to determine if the effect of trial setting on patient survival differed for the two curative intent trials, an adjuvant chemotherapy trial for stage Ib non-small-cell lung cancer (CALGB 9633) and a chemoradiotherapy trial for limited-stage small-cell lung cancer (CALGB 9235).

Each of the original 10 CALGB treatment trials were approved by the local institutional review board of the enrolling institutions, and each patient willingly provided informed consent to the trial. Additionally, the planned analyses were approved by the CALGB Executive Committee and deemed permissible from a human patient standpoint by the Dana-Farber/Harvard Cancer Center institutional review board.

RESULTS

Attributes of Trial Participants by Enrollment Setting

Among the 2,708 patients in the 10 clinical trials, patients enrolled at academic facilities were, on average, younger compared with clinical trial patients enrolled at nonacademic facilities (Table 2). Clinical trial patients enrolled at community facilities were more often women and had superior performance statuses compared with those enrolled through academic and VHA settings. Overall, patients enrolled at VHA centers were older, nearly always men, more often

black, and had worse performance statuses at the time of enrollment compared with academic and community enrollees. Specifically patients at VHAs were substantially less likely to have a performance status of less than 2, which is the critical cut point for treatment of elderly patients who have advanced lung cancer with chemotherapy. The proportion of individuals with performance status less than 2 was 83.4% in the VHA compared with 90.1% in academic center and 91.8% in community centers. Patients enrolled at VHA centers were more likely to live in relatively lower-income and higher-poverty regions compared with patients enrolled on trials at non-VHA facilities. Of note, 37 of the 2,708 patients, or 1%, were enrolled at six CALGB sites in Canada. The mean follow-up time for those 12% (ie, 326 of 2,708) of patients who had not died varied by enrolling institution, as 5.6 years for academic centers, 4.9 years for community centers, and 5.6 years for VHA centers ($P = .03$).

Enrollment Setting and Trial Participants' Outcomes: Male Cohort

Among patients in the male cohort, described in Table 3, patient attributes were associated with enrollment setting in a similar manner to that observed in the entire cohort. In the model that included only enrollment setting, patients at VHA facilities had a higher hazard of death (hazard ratio [HR], 1.17; 95% CI, 1.03 to 1.34) compared with patients enrolled at academic facilities (Table 3; $P = .02$). After analysis adjusted for patient age, ethnicity, performance status, and year of enrollment, however, the hazard of death for patients treated at a VHA versus an academic center decreased from 1.17 to 1.09 (95% CI, 0.96 to 1.24; $P = .19$) and was no longer statistically significant.

Enrollment Center Type and Trial Participants' Outcomes: Academic/Community Cohort

Among the patients in the academic/community cohort, patient attributes again were associated with enrollment setting similar to that observed in the parent cohort. Similar to the analyses in the male-only cohort, the results of the partially and fully adjusted Cox regression analyses (Table 4) show that survival is not significantly different in community settings compared with academic settings in either model.

Sensitivity Analysis for Patients in Trials With Curative Intent

Enrollment setting was not associated with survival outcomes when patients from the two curative-intent trials, CALGB 9235 and 9633, were combined and analyzed in manner similar to the main Cox models described in the Methods (Table 5). Both the community and VHA setting had a small increase in hazard of death compared with the academic setting; these differences were not statistically significant.

DISCUSSION

Our findings suggest that the types of patients who enroll on NCI cooperative group clinical trials at nonacademic medical centers (ie, community and VHA medical centers) differ from patients who enroll on the same trials at academic medical centers. Patients who were enrolled at academic centers were younger and resided in more affluent neighborhoods compared with patients who were enrolled through nonacademic settings. Given growing ethical concerns regarding access in experimental research^{3-5,8,24,25} and related practical

Table 5. Hazard of Death After Treatment on Two Curative Intent Protocols, CALGB 9235 and 9633, in Male Trial Patients

Variable*	Model for CALGB 9235 and 9633 Combined (N = 373)	
	HR	95% CI
Enrollment site†	1.00	—
Community affiliate (n = 161)	1.06	0.80 to 1.39
VHA affiliate (n = 65)	1.22	0.91 to 1.62
Age, years	1.00	—
55-59	1.00	0.65 to 1.52
60-64	1.13	0.76 to 1.69
65-69	1.27	0.84 to 1.93
70-74	1.65	1.06 to 2.56
≥ 75	1.50	0.85 to 1.93
Registration year	1.00	—
1995-1999	1.37	1.02 to 1.85
2000-2003	2.04	1.22 to 3.40
Race	1.00	—
Non-white	0.96	0.62 to 1.46
PS	1.00	—
1	1.28	0.99 to 1.66
≥ 2	2.20	1.34 to 3.63

NOTE. The median patient survival of patients treated on CALGB 9235 (n = 173) was 571 days and for those treated on 9633 (n = 200) was 2,053 days. When patients on these trials were combined, the median patient survival was 1,038 days. The Table describes the relative hazard of death associated with community and VHA enrollment settings compared with academic enrollment settings for patients enrolled in one of the two curative-intent studies. Results were adjusted for patient case-mix factors of age, ethnicity, PS, and registration year and stratified by study.

Abbreviations: CALGB, Cancer and Leukemia Group B; HR, hazard ratio; VHA, Veterans Health Administration; PS, performance status.

*Reference values for each variable are as follows: enrollment site, academic; age, < 55 years; registration year, 1990-1994; ethnicity, white; and PS, 0.

†No. of patients at academic enrollment site = 147.

concerns regarding the generalizability of clinical trial results to the underlying population of Americans with disease,^{1,26-30} these findings suggest that certain nonacademic trial settings may introduce into cooperative trial cohorts important heterogeneity with respect to patient demographics and performance status and, thus, may be associated with both greater access to research and greater generalizability of results.

Additionally, and no less important, we found that, after accounting for differences in patient case-mix between the academic, community, and VHA settings studied, the enrollment setting itself did not appear overall to affect trial patient survival. This suggests that the apparent trend toward inferior outcomes associated with receipt of trial therapy at a VHA versus an academic center described in the unadjusted analyses were spurious and were the result of confounding by patient factors (ie, patient case-mix), perhaps most importantly age and performance status.

These findings have important implications for both clinical research and health care policy. With respect to clinical cancer research, the literature on whether enrollment setting confounds patient outcomes on clinical trials is scant³¹⁻³³ despite its importance to interpretation of multicenter cancer trials.³⁴⁻³⁷ With respect to health care policy, the lack of difference in outcomes by enrollment setting also may indicate that select community and VHA treatment centers may provide a similar level of cancer care as academic centers when deliv-

ered through an NCI cooperative group clinical trial. Thus, the NCI policy-driven CCOP and VHA initiatives have been successful in providing community-dwelling patients with cancer access to the same high-quality, cutting-edge cancer trials available at academic centers without the need to travel to primarily urban academic centers. It also suggests that the survival outcomes provided by these nonacademic centers in the setting of an NCI clinical trial may be equivalent to those provided by the specialized cancer centers.

However, there are important caveats to our work regarding survival outcomes that are related to the patients with cancer whom we studied. Because advanced-stage lung cancer has a short survival horizon (ie, median survivals of < 1 year during these study years) and because nearly half of our sample had such advanced cancer, it may be that our cohorts' survivals were simply too short to allow evaluation of what may be comparatively subtle effects of enrollment setting on survival. Because of small sample sizes, our sensitivity analysis in patients who were treated on two curative-intent protocols is not sufficiently powered to provide definitive evidence regarding the relationship between enrollment setting and survival in these patients.

A related issue is our inability to account for differences in subsequent anticancer treatments in patients. Although information about subsequent therapies are now routinely collected in clinical trials, these data were not collected by CALGB at the time these studies were performed (ie, starting in 1990), primarily because there were no efficacious second-line chemotherapy regimens for non-small-cell lung cancer. It was not until May 2000 (a date before which 75% of patients with non-small-cell lung cancer in our cohort had been treated) that Shepherd et al³⁸ first reported that second-line chemotherapy was superior to best supportive care in clinical trial patients with non-small-cell lung cancer who had failed platinum-based doublet therapies. Because most patients were enrolled before May 2000, second-line chemotherapy was unlikely to be a factor for most patients in our study but could confound survival results of those patients enrolled after May 2000, who may have received subsequent chemotherapy. That is, unobserved differential treatment with second-line therapy at the center level could bias in our estimates of the hazards of death associated with each center type.

A mechanistic issue is whether VHA associations with academic medical centers, via shared physicians and/or equipment, could in part explain the lack of difference in overall survival between the trial VHA and academic centers. All VHAs must necessarily have an academic affiliate to become a member of the CALGB. However, this academic affiliate need not be, and often are not, in close physical proximity to the VHA. On the basis of contact with individuals within the VHA and CALGB, we estimate that approximately 50% of VHAs were physically located near academic centers and that approximately 50% of those shared with the academic center some type of cancer-related medical faculty (ie, medical oncologist, thoracic surgeon, radiation oncologist) for a portion of the week or month. These estimates clearly are limited by memory, given that we spoke with current staff and that the first trial analyzed opened to accrual nearly 20 years ago. However, even if academic oncologists who spend part of a day per week or month at a few VHAs were the sole mechanism driving the overall equivalence of patient clinical trial outcomes by enrollment venue, this would not diminish the importance of our findings. Instead, it would highlight the VHA's ability to evaluate its clinical needs, meet them successfully through forging academic affiliations, and advance clinical oncology through both providing veterans access

to clinical trials and introducing important patient heterogeneity into those trials, which would make results more generalizable to the rest of the country.

An additional limitation is that substantial socioeconomic patient and area-level status information was missing. For example, patient-level socioeconomic status variables of marital status and education were missing for greater than 50% of patients on the 10 trials. Although the missing data is largely due to secular changes of CALGB data collection practices within the observation period, some of the variables that are incomplete are established predictors of survival, even on clinical trials^{39,40}; therefore, their absence may limit our models. For example, the fact that we could not observe patient-level socioeconomic factors, a potentially important source of confounding,^{41,42} could potentially bias our estimates of treatment center associations with patient survival. This concern is most salient for the VHA center estimates, given the established lower socioeconomic status of veteran compared with nonveteran populations. This discrepancy could lead to spuriously inflated hazards for the VHA setting.⁴³

In conclusion, our research demonstrates important differences in trial patient case-mix across academic, community, and VHA enrollment settings in cooperative group trials. These findings suggest that nonacademic trial venues may introduce into clinical trial cohorts important heterogeneity with respect to demographics and performance status and, thus, may be associated with both greater access in research and greater generalizability of results. Additionally, overall we did not find differences in patient survival attributable to the type of enrollment setting among our cohorts, which consisted primarily of patients with advanced stages of lung cancer. This suggests that cancer care delivered outside of academic centers may be similar to that of academic centers when it is delivered through an NCI cooperative

group clinical trial. However, additional research is needed to evaluate longer-term outcomes among larger numbers of patients enrolled on curative-intent trials and/or trials for malignancies with longer survival horizons.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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