

# Effectiveness of Chemotherapy for Advanced Lung Cancer in the Elderly: Instrumental Variable and Propensity Analysis

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**Purpose:** To compare the effectiveness of chemotherapy given to elderly patients in routine practice for stage IV non-small-cell lung cancer (NSCLC) with the efficacy observed in randomized trials.

**Patients and Methods:** We used instrumental variable analysis (IVA) and propensity scores (PS) to simulate the conditions of a randomized trial in a retrospective cohort of patients over age 65 from the Surveillance, Epidemiology, and End Results (SEER) tumor registry. Geographic variation in chemotherapy use served as the instrument for the IVA analysis, and propensity scores were calculated with a logistic model based on patient disease and sociodemographic characteristics.

**Results:** Among 6,232 elderly patients, the instrumental variable estimate indicated an increase in median survival of 33 days and an improvement in 1-year survival of 9% attributable to chemotherapy. In a Cox

regression model, chemotherapy administration was associated with a hazard ratio of 0.81 (95% confidence interval, 0.76 to 0.85). When survival was analyzed separately within propensity score quintiles, the hazard ratios were all similar, ranging from 0.78 to 0.85. These results are comparable with those of a large meta-analysis, which found a hazard ratio of 0.87 in the subgroup of patients over age 65.

**Conclusion:** Chemotherapy for stage IV NSCLC seems to have effectiveness for elderly patients and those with comorbid conditions that is similar to the efficacy seen in randomized trials containing mostly younger, highly selected patients. All suitable patients should be given the opportunity to consider palliative chemotherapy for metastatic NSCLC.

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DOES CHEMOTHERAPY for advanced lung cancer improve survival when given to elderly patients outside of a clinical trial setting? The answer to this question has important public health implications. Lung cancer is the leading cause of cancer death in North America. Non-small-cell lung cancer (NSCLC) is the dominant histology, and almost half of those patients present with metastatic (stage IV) disease.<sup>1</sup> Even among patients initially presenting in earlier stages, most will eventually develop metastatic disease. Consequently, the management of metastatic NSCLC will affect over 130,000 Americans diagnosed with lung cancer this year, of whom about half are over age 65.<sup>2</sup>

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Although there is no treatment with curative potential, systemic chemotherapy is often given to NSCLC patients in the hope of temporary disease control, improved quality of life, and a modest increase in survival. In 1995, the Non-small-cell Lung Cancer Collaborative Group (NSCLCCG) reported a meta-analysis of randomized trials using individual patient data. They found that patients with advanced NSCLC who were treated with cisplatin-containing chemotherapy regimens had an increase in median survival of about 6 weeks and a 10% improvement in 1-year survival compared with those managed with supportive care only. However, randomized clinical trials, such as those included in the NSCLCCG meta-analysis, are usually carried out on highly selected patients, in centers of excellence, and under optimal protocol-driven conditions. While a trial may have been well conducted, and thus be internally valid, the results may not be generalizable, or externally valid. Outcomes may be different when other chemotherapeutic regimens are used in a real world setting, in patients who may be older, have less favorable health characteristics, and who may receive doses that must be compromised to avoid toxicity. Consequently, the effectiveness of the intervention in everyday practice may not be as great as the efficacy seen in a clinical trial.<sup>3</sup> Physicians recognize this uncertainty, and have been slow to adopt chemotherapy. Recent reports indicate that just over 20% of elderly patients with advanced lung cancer ever receive chemotherapy.<sup>4</sup>

Although standard statistical methods can adjust nonrandomized observational data to account for observed differ-

ences in case-mix between groups of patients, such methods are unable to account for as yet unknown prognostic features. As a result, a bias could result if the two groups differed in an unmeasured characteristic that affects outcome. Several analytic methods have been developed to try to minimize this bias. Instrumental variable analysis (IVA) is a technique borrowed from econometrics that attempts to simulate a randomized controlled trial when such a trial is not feasible because of cost or entrenched practice patterns. It has already been applied successfully to several other health-related questions.<sup>5-10</sup> The idea behind IVA is to find a variable, the instrument, that is associated with a patient's likelihood of receiving an intervention, but is independent of the outcome of therapy. If the instrument is well chosen, both known and unknown prognostic features can be accounted for in the analysis. For example, in a randomized trial, the process of randomization is the instrument, as it completely determines the treatment received. However, the randomization process itself does not influence outcome; only the actual intervention affects outcome. All other characteristics, both known and unknown, should be evenly distributed between the groups. In an observational study, examples of instruments include the type of physician a patient sees or the region of the country in which the patient lives. Based on our previous work,<sup>4</sup> as well as work by others,<sup>11-13</sup> demonstrating significant unexplained geographic variation in the use of palliative chemotherapy for advanced lung cancer, we have chosen geographic location as an instrument. Because the effectiveness of chemotherapy should be similar no matter where in the country it is given, comparison of the survival of elderly lung cancer patients living in areas of high chemotherapy utilization with those living in areas of low chemotherapy utilization can indicate the effectiveness of the treatment.

Another way to adjust for treatment selection bias is to stratify patients based on propensity score.<sup>14</sup> A propensity score is a measure of the probability that a patient will receive an intervention, which is usually derived from a regression analysis of that patient's sociodemographic and disease characteristics. In this way, the propensity score summarizes these features into a single composite variable. Patients can then be stratified based on this score, and their outcomes compared within strata. Prognostic characteristics should be randomly distributed within each stratum between those who did and did not actually receive the intervention.<sup>15,16</sup>

In this study, we have used instrumental variable analysis to compare regions of high and low chemotherapy utilization, and have created propensity scores for patients based on sociodemographic and disease characteristics in order to stratify patients into cohorts with comparable likelihood of receiving treatment. From these procedures, we have esti-

mated the effectiveness of chemotherapy when applied in the general population of elderly patients, and have compared these effectiveness results to the efficacy observed in randomized trials.

## PATIENTS AND METHODS

### *Data Sources*

We studied patients from the 11 tumor registries participating in the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) program: San Francisco/Oakland, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle/Puget Sound, Utah, Atlanta, San Jose/Monterey, and Los Angeles. These registries collect uniform information on all cancers diagnosed within their geographic regions, capturing about 97% of all incident cases in those areas.<sup>17</sup> The geographic areas covered by SEER contain approximately 14% of the American population,<sup>18</sup> and are demographically fairly representative.<sup>19</sup> Disease-related data collected include the cancer site, stage, histology, date of diagnosis, and date and cause of patient death. The registries also record patient sociodemographic characteristics such as age, sex, and race/ethnicity, and link census data on each patient's census-tract or zip-code of residence, including median and per capita income and wealth, educational levels, and racial mix.

The Health Care Financing Administration (HCFA) Medicare database includes files through 1998 for inpatient and outpatient care, physician and laboratory billings, as well as bills for home health and hospice care. Each patient in the SEER and Medicare databases has a unique case identification number that permits matching and merging of the different files. In this way, cases diagnosed at age 65 and over have been linked between the databases with a 94% match rate.<sup>20</sup>

### *Patient Selection*

To be included in the analysis, patients had to have been diagnosed with stage IV NSCLC between January 1, 1991 and December 31, 1996; Medicare eligible on the basis of age (ie, age 65 or older); and not enrolled in an HMO at any time during that period. Patients were excluded if the dates of diagnosis and death reported in the SEER and Medicare databases differed by more than 2 months or if they survived less than 2 months from the time of diagnosis. To examine the strategy of giving front line chemotherapy and to avoid the bias that patients who live longer may be more likely to receive chemotherapy, patients were considered to have received chemotherapy only if they started treatment within 2 months of diagnosis. We also repeated the analysis using patient selection criteria similar to those usually used in clinical trials, with patients excluded if they had had a myocardial infarction in the year before diagnosis or if they had more than two comorbid conditions. The results of this latter evaluation were similar to the main analysis and are not reported.

### *Identification of Chemotherapy Use*

SEER collects information on initial cancer-directed surgery and radiation, defined as those treatments applied within 4 months of diagnosis. However, the NCI does not release chemotherapy treatment data because outpatient chemotherapy usage may be missed by SEER chart abstractions.<sup>20</sup> Therefore, we identified chemotherapy use from Medicare claims. The International Classification of Disease Version 9 (ICD-9) diagnostic code V58.1 and procedure code 9,925, and the diagnosis related group (DRG) code 410 for chemotherapy administration were used to detect chemotherapy use in the inpatient setting.

For the outpatient files and physician billing claims, HCFA Common Procedure Coding System (HCPCS) codes for chemotherapy administration (Q0083-Q0085, J7150, or J8999-J9999), Current Procedural Terminology (CPT) codes (96400, 96408, 96410, 96412, 96414, and 96545), as well as the relevant revenue center codes (0331, 0332, and 0335) were also used where applicable.

### Definitions of Explanatory Variables

Patients were classified by age at diagnosis (65 to 74, 75 to 84, 85 to 94, and 95 to 104 years) and by race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian, or other). Region-specific socioeconomic quintiles were developed based on the availability of information, according to the following hierarchy: (1) race- and age-specific median household wealth by census tract (86.5% of patients); (2) unadjusted median household income by census tract (9.7%); and (3) median household wealth by census tract or zip code (2.8%). Consequently, almost all patients were classified with census level data, whereas less than 1% were socioeconomically unclassifiable.

We calculated the Charlson comorbidity index<sup>21,22</sup> by examining the ICD-9 diagnostic codes recorded in months 1 to 13 before the diagnosis of lung cancer in each patient, following the method described by Deyo.<sup>23</sup> We also used outpatient and physician bills to identify comorbidities, requiring a diagnosis to appear on at least two occasions separated by at least a month, as described by Klabunde,<sup>24</sup> and applied the Charlson weights to each comorbidity. Cancer-related codes may inadvertently capture some of the initial diagnostic work-up for lung cancer; therefore, the Charlson score was calculated excluding cancer-related diagnoses, again as suggested by Klabunde.<sup>24</sup>

### Propensity Score Analysis

The probability that a patient would receive chemotherapy was calculated with a logistic regression model that incorporated age, sex, race, number of comorbid conditions, socioeconomic status, geographic location, year of diagnosis, and whether the patient was treated in a teaching hospital. As Rubin<sup>14</sup> has shown, subclassification using five or more groups removes approximately 90% of the bias seen in raw comparisons. Consequently, we created five propensity strata and compared survival within each stratum using a Cox proportional hazards model.

### Instrumental Variable Analysis

**Instrument.** Based on our previous demonstration of significant unexplained geographic variation,<sup>4</sup> we divided Health Care Service Areas (HCSA) into quintiles of chemotherapy utilization. HCSAs are groupings of Metropolitan Statistical Areas that represent self-contained regions of medical care delivery that have been identified based on patterns of patient flow in Medicare billing files.<sup>25</sup> HCSAs with fewer than five patients in either cell (chemotherapy, no chemotherapy) were excluded, leaving 38 out of the original 77 HCSAs, which contained 6,232 patients. The HCSAs were then divided into quintiles based on the prevalence of chemotherapy. To assess for bias of the instrument, we incorporated geographic location into a Cox proportional hazards model to see whether it predicted survival independently of chemotherapy use. We also assessed the strength of the instrument through the correlation between geographic location and the likelihood of receiving chemotherapy.<sup>26-28</sup>

**Analytic approach.** We first compared the characteristics of patients who received chemotherapy with those who did not. To estimate the magnitude of selection bias, and to confirm that the two groups

**Table 1. Characteristics of Patients Who Did and Did Not Receive Chemotherapy**

| Variable                | No Chemotherapy | Chemotherapy |
|-------------------------|-----------------|--------------|
| Patients                |                 |              |
| No.                     | 4,220           | 2,012        |
| %                       | 68              | 32           |
| Mean age,*† years       | 73.4            | 71.7         |
| Female,† %              | 43              | 39           |
| Non-white,† %           | 18              | 15           |
| Without comorbidity,† % | 74              | 77           |
| SES quintiles,‡ %       |                 |              |
| 1                       | 23              | 16           |
| 2                       | 21              | 18           |
| 3                       | 19              | 23           |
| 4                       | 19              | 23           |
| 5                       | 19              | 21           |

\*Total no. of patients = 6,232.

† $P < .05$ .

‡SES = socioeconomic status. Quintiles range from 1 (low) to 5 (high).

were reasonably well matched for prognostic features, we then compared the same characteristics for patients in the high and low utilization areas. In a Cox proportional hazards model with chemotherapy initiation as a time-varying covariate, age, sex, and socioeconomic status were found to be significant predictors of survival. Therefore, the model used in the IVA was adjusted for these factors, with the Charlson comorbidity score forced in as well. The baseline characteristics assumed were those of a 65-year-old white male with median socioeconomic characteristics and no comorbid conditions. The instrumental variable estimate was calculated as the difference between the survival in the highest and lowest geographic quintiles, divided by the difference in the probability of receiving chemotherapy for patients living in those regions, as indicated by the following formula:

$$\text{IV estimate} = \frac{\text{Adjusted Survival}_{\text{Hi}} - \text{Adjusted Survival}_{\text{Lo}}}{P(\text{chemotherapy}|\text{Hi}) - P(\text{chemotherapy}|\text{Lo})}$$

where “Hi” indicates a geographic area with a high rate of chemotherapy utilization and “Lo” indicates an area of low chemotherapy use.

**Bootstrapping.** The precision of the instrumental variable estimate was assessed by bootstrapping. One thousand subsamples of 100% sample size were drawn with replacement from the original population, and the instrumental variable analysis was performed on each subsample. The 5% and 95% percentiles of this analysis were used as the confidence limits.

## RESULTS

Table 1 compares the characteristics of patients who received chemotherapy with those who did not. As expected, there is an indication of possible selection bias, with patients who received chemotherapy being significantly younger, more likely to be white, and of higher socioeconomic status. Table 2 indicates the comorbid conditions of the patient population. As expected, smoking-related comorbidities such as chronic obstructive pulmonary disease and vascular conditions were prominent.

**Table 2. Comorbid Conditions in the Study Population of Patients With Metastatic Non-Small-Cell Lung Cancer**

| Comorbidity                           | Patients Affected (%) |
|---------------------------------------|-----------------------|
| Previous myocardial infarction        | 0.9                   |
| Congestive heart failure              | 3.6                   |
| Peripheral vascular disease           | 2.5                   |
| Cerebro-vascular disease              | 3.2                   |
| Dementia                              | 0.3                   |
| Chronic obstructive pulmonary disease | 14.0                  |
| Rheumatologic disorders               | 1.3                   |
| Peptic ulcer disease                  | 1.0                   |
| Mild liver disorder                   | 0.2                   |
| Severe liver disease                  | 0.0                   |
| Diabetes                              | 6.7                   |
| Diabetic complications                | 0.4                   |
| Paralysis                             | 0.3                   |
| Renal disease                         | 0.4                   |
| AIDS                                  | 0.0                   |

Figure 1 shows the unadjusted Kaplan-Meier survival curves for patients who did and did not receive chemotherapy. The median survival was 30 weeks for patients receiving chemotherapy and 23 weeks for patients receiving supportive care alone, a difference of 7 weeks. The 1-year unadjusted survival was 24% for chemotherapy-treated patients but only 17% for those not receiving treatment. In a Cox proportional hazards model, chemotherapy administration was associated with a hazard ratio (HR) of 0.81 (95% confidence interval [CI], 0.76 to 0.85). Younger age (HR

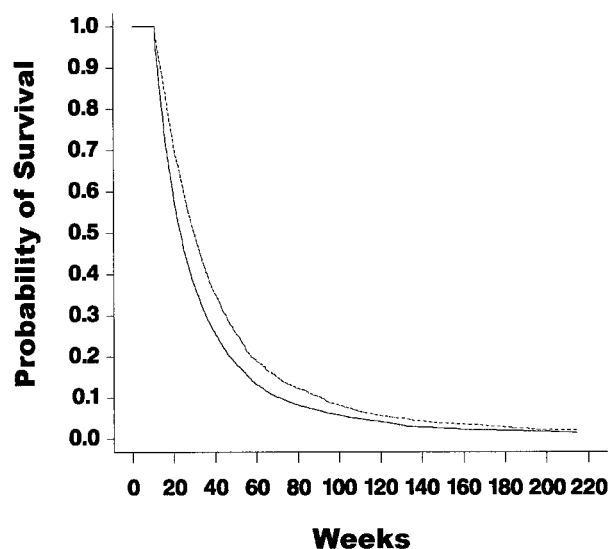


**Fig 1. Kaplan-Meier unadjusted survival curves comparing patients who received chemotherapy (dashed line) with those receiving supportive care only (solid line).**

1.10 for each incremental decade; 95% CI, 1.05 to 1.15) and higher socioeconomic status (HR 0.98 for each increasing quintile; 95% CI, 0.96 to 0.99) were found to be significantly associated with better survival. Female patients also tended to do better (HR 0.89; 95% CI, 0.84 to 0.94), as did those patients treated in a teaching hospital (HR 0.92; 95% CI, 0.88 to 0.97). Race, number of comorbid conditions, year of diagnosis, and geographic location did not significantly predict survival.

### Propensity Score Analysis

As seen in our previous analysis,<sup>4</sup> patients of younger age, male sex, nonblack race, who were treated in a teaching hospital, and who were living in certain geographic regions were significantly more likely to receive chemotherapy. Based on these features, the estimated propensity to receive chemotherapy ranged from 0% to 63%. Figure 2 shows that prognostic characteristics were well balanced within each propensity quintile. When survival was analyzed separately within each propensity score quintile, the hazard ratios for patients receiving chemotherapy compared with those not receiving chemotherapy ranged from 0.78 to 0.85 (Table 3).

### Instrumental Variable Analysis

As designed, the instrument of geographic location significantly predicted the likelihood of receiving chemotherapy, with a partial  $r^2$  of 0.71 (F statistic 7,792), yet it was not independently associated with survival in the Cox regression model. These results support the validity of the instrument. Table 4 compares the characteristics of patients in areas of high chemotherapy utilization with those in areas of low chemotherapy utilization. Here, the two groups are well balanced for most prognostic features, similar to the distribution of factors one might hope for in a randomized trial. There were more nonwhite patients and more patients with comorbidity in the high chemotherapy regions; however, as previously described, these factors did not influence survival. Only 21.2% of the 1,109 patients in the lowest chemotherapy quintile received chemotherapy. The adjusted median survival for this group was 171 days, and 18.9% were alive at 1 year. Thirty-nine percent of the 2,059 patients in the highest chemotherapy quintile received chemotherapy. Their adjusted median survival was 177 days, and the adjusted 1-year survival rate was 20.5%. Consequently, the instrumental variable analysis indicated an increase in median survival of 33 days (95% CI, 14 to 105 days by bootstrapping) for the marginal patients treated with chemotherapy in the high utilization regions. One year survival was increased by 9% (95% CI, 4% to 23%, also by bootstrapping).

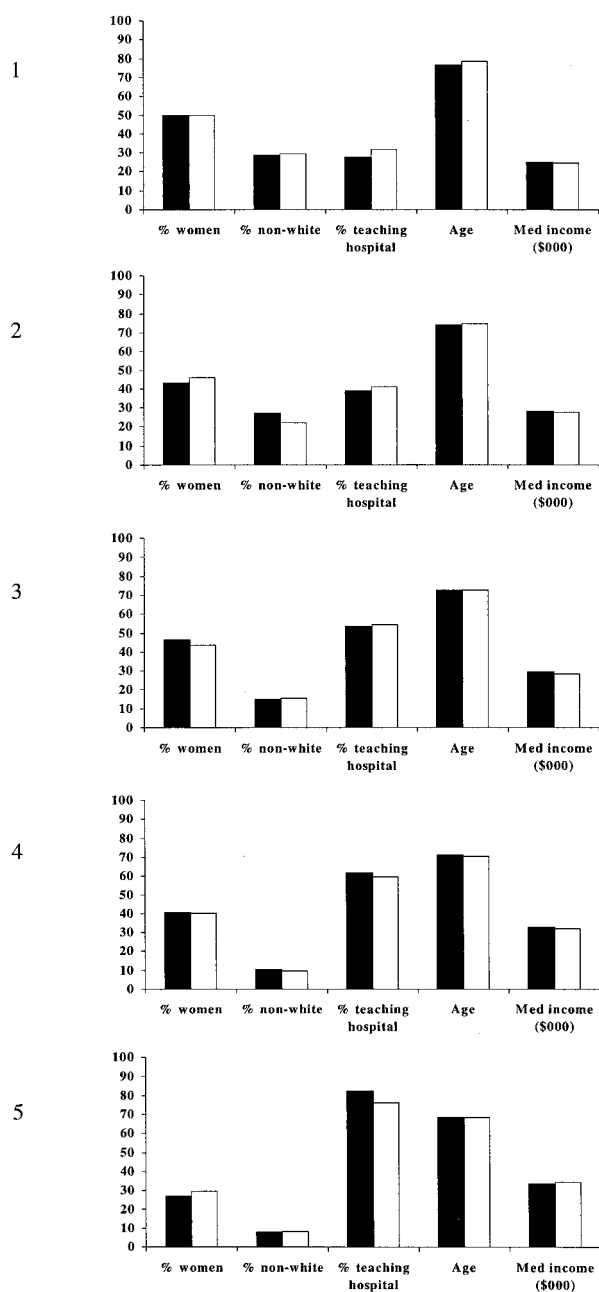


Fig 2. Distribution of explanatory variables between patients receiving chemotherapy (black bars) and those not receiving chemotherapy (white bars) for propensity score quintiles ranging from 1 (least likely to receive chemotherapy) to 5 (most likely to receive chemotherapy).

## DISCUSSION

Published in 1995, the NSCLCCG meta-analysis incorporated individual patient data from 11 trials of chemotherapy in advanced lung cancer.<sup>29</sup> It found a pooled hazard

Table 3. Propensity Score Analysis: Comparison of Survival Across Strata Based on the Propensity to Receive Chemotherapy

| Method                         | Hazard Ratio | 95% CI    |
|--------------------------------|--------------|-----------|
| Cox proportional hazards model | 0.81         | 0.76-0.85 |
| Propensity score               |              |           |
| 1, lowest $P_{\text{chemo}}$   | 0.78         | 0.67-0.91 |
| 2                              | 0.81         | 0.72-0.93 |
| 3                              | 0.85         | 0.76-0.96 |
| 4                              | 0.80         | 0.71-0.90 |
| 5, highest $P_{\text{chemo}}$  | 0.78         | 0.70-0.87 |

ratio of death at 1 year of 0.73 (95% CI, 0.63 to 0.85) for patients treated with cisplatin-containing chemotherapy regimens compared with those managed with supportive care only. The absolute survival benefit at 1 year was 10% (95% CI, 5% to 15%), increasing from 16% to 26%. The gain in median survival was 1.5 months (95% CI, 1 to 2.5 months). Although subgroup analysis was unable to identify groups of patients less likely to benefit from treatment based on age, sex, histology, performance status, or stage of disease (III v IV), 78% of those patients were under 65 years of age, and all trials excluded patients with poor performance status (ECOG > 2, Karnofsky < 50). For the subgroup of patients in that meta-analysis over age 65 with stage IV disease, the hazard ratio was 0.87, although this number is based on only 120 patients (personal communication, L. Stewart). Consequently, it was not clear whether the efficacy seen in these randomized trials could be translated to the elderly patient

Table 4. Instrumental Variable Analysis: Characteristics of Patients in the Lowest  $P_{\text{chemo}}$  Versus the Highest  $P_{\text{chemo}}$  Health Care Service Area Quintiles

| Variable                | Patients                     |                               |
|-------------------------|------------------------------|-------------------------------|
|                         | Low $P_{\text{chemo}}$ HCSEA | High $P_{\text{chemo}}$ HCSEA |
| Patients*               |                              |                               |
| No.                     | 1109                         | 2059                          |
| %                       | 21                           | 39                            |
| Chemotherapy,† %        | 21                           | 39                            |
| Mean age, years         | 72.5                         | 72.7                          |
| Female, %               | 41                           | 40                            |
| Non-white,† %           | 15                           | 19                            |
| Without comorbidity,† % | 78                           | 73                            |
| SES quintiles, %        |                              |                               |
| 1                       | 20                           | 20                            |
| 2                       | 19                           | 20                            |
| 3                       | 20                           | 20                            |
| 4                       | 20                           | 20                            |
| 5                       | 21                           | 20                            |

Abbreviations:  $P_{\text{chemo}}$ , the probability of receiving chemotherapy based on geographic area of residence; SES, socioeconomic status.

\*Total no. of patients = 3,168.

† $P < .05$ .

with comorbid conditions who commonly presents in the real world clinic.

Our results indicate that chemotherapy given in the nontrial setting is effective for elderly patients with stage IV NSCLC, with a modest magnitude of benefit consistent with that observed in randomized trials. To our knowledge, this is the first study to use instrumental variable analysis and propensity scores to examine the outcomes of chemotherapy for advanced lung cancer in routine practice. The bootstrap analysis indicated some lack of precision in the instrumental variable estimates, most likely because of the small sample size used to compare the highest and lowest quintiles of chemotherapy use. However, the findings using this observational method were remarkably similar to the results reported in the meta-analysis of randomized trials. The change we observed in median survival of 33 days is consistent with the 6 weeks noted in the NSCLCCG study, and the 9% change in survival at 1 year is similar to the 10% reported by that group. As is expected when treatments are brought into routine practice, these effectiveness differences are less than the efficacy differences seen in clinical trials. Yet this loss of benefit is very small. We selected patients to be similar to those seen in randomized trials by restricting analysis to those with a minimum of 2 months survival. Still, patients in our study were older, and did not have to meet the rigid selection criteria of a prospective trial. Furthermore, treatment consisted of a variety of chemotherapy regimens given without protocol guidance as to administration and dose modifications.

A very important finding of this study was that patients with less propensity for treatment appear to realize the same benefits when they receive chemotherapy as those with greater propensity. Stratification of patients based on their propensity to receive chemotherapy did not affect the hazard ratios obtained by receiving chemotherapy. This suggests two possibilities: either physicians are accurately able to select out those patients from each stratum who are going to benefit from chemotherapy, or the effectiveness of chemotherapy may not be restricted only to those patients who, with their physicians, most commonly decide to receive treatment. However, the findings of the instrumental variable analysis, that the additional marginal patients who receive chemotherapy solely on the basis of where they live also derive benefit from treatment, indicates that the latter explanation is true: the relative survival benefits of chemotherapy may be able to be realized by many patients who are

not currently treated, at least up to the 39% who were treated in the high utilization areas.

Our application of the instrumental variable technique was only possible because we had previously demonstrated significant unexplained practice variation based on nonmedical factors, including geographical location. It is a necessary condition that, like the coin toss of a randomized trial, a good instrument should not be a known prognostic factor for the outcome of interest. We found that despite large differences in the rates of chemotherapy use across geographic regions, the prognostic features of patients in high and low utilization areas were remarkably similar. This similarity, coupled with the fact that geographic region did not independently predict survival once chemotherapy use had been controlled for, indicates that geographic location may be a relatively unbiased instrument in this situation. Whether location is such can never be proven absolutely, however.<sup>30</sup>

Chemotherapy for advanced lung cancer has been controversial, especially for elderly patients. This analysis suggests that the results of randomized clinical trials in lung cancer can be transferred to the real world setting. Elderly patients treated with chemotherapy outside of a clinical trial appear to receive modest survival benefits from treatment similar in magnitude to the benefits experienced by younger, highly selected patients reported in clinical trials. Furthermore, patients who are usually not treated seem to derive the same benefits from chemotherapy as those with greater propensity to receive chemotherapy. Most do not receive it, though. This may be appropriate if it is truly the preference of those patients. However, Raby et al<sup>31</sup> found that only 20% of Canadian physicians surveyed thought that treating advanced NSCLC with chemotherapy was worthwhile. Furthermore, Crook et al<sup>32</sup> in Great Britain found an age bias when they reported that only 11% of clinicians would recommend chemotherapy for advanced lung cancer patients, increasing to 26% if the patient was less than 50 years of age. Our analysis indicates that such bias cannot be defended unless based on patient preferences and that all appropriate patients should be given the option of receiving chemotherapy in addition to supportive care.

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