VOLUME 33 · NUMBER 6 · FEBRUARY 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cisplatin and Etoposide Versus Carboplatin and Paclitaxel With Concurrent Radiotherapy for Stage III Non–Small-Cell Lung Cancer: An Analysis of Veterans Health Administration Data

Rafael Santana-Davila, Kiran Devisetty, Aniko Szabo, Rodney Sparapani, Carlos Arce-Lara, Elizabeth M. Gore, Amy Moran, Christina D. Williams, Michael J. Kelley, and Jeffrey Whittle

See accompanying editorial on page 532 and article on page 575

Rafael Santana-Davila, University of Washington, Seattle, WA; Kiran Devisetty, Michigan State University, Flint, MI; Aniko Szabo and Rodney Sparapani, Medical College of Wisconsin; Rafael Santana-Davila, Carlos Arce-Lara, Elizabeth M. Gore, Amy Moran, and Jeffrey Whittle, Clement J. Zablocki Veterans Affairs (VA) Medical Center, Milwaukee, WI; and Christina D. Williams and Michael J. Kelley, Durham VA Medical Center, Durham, NC.

Published online ahead of print at www.jco.org on November 24, 2014.

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Rafael Santana-Davila, MD, 825 Eastlake Ave, E Mail-stop G4940, Seattle, WA 98109; e-mail: rafaelsd@u.washington.edu.

0732-183X/15/3306w-567w/$20.00

DOI: 10.1200/JCO.2014.56.2587

ABSTRACT

Purpose
The optimal chemotherapy regimen to use with radiotherapy in stage III non–small-cell lung cancer is unknown. Here, we compare the outcome of patents treated within the Veterans Health Administration with either etoposide-cisplatin (EP) or carboplatin-paclitaxel (CP).

Methods
We identified patients treated with EP and CP with concurrent radiotherapy from 2001 to 2010. Survival rates were compared using Cox proportional hazards regression models with adjustments for confounding provided by propensity score methods and an instrumental variables analysis. Comorbidities and treatment complications were identified through administrative data.

Results
A total of 1,842 patients were included; EP was used in 27% (n = 499). Treatment with EP was not associated with a survival advantage in a Cox proportional hazards model (hazard ratio [HR], 0.97; 95% CI, 0.85 to 1.10), a propensity score matched cohort (HR, 1.07; 95% CI, 0.91 to 1.24), or a propensity score adjusted model (HR, 0.97; 95% CI, 0.85 to 1.10). In an instrumental variables analysis, there was no survival advantage for patients treated in centers where EP was used more than 50% of the time as compared with centers where EP was used in less than 10% of the patients (HR, 1.07; 95% CI, 0.90 to 1.26). Patients treated with EP, compared with patients treated with CP, had more hospitalizations (2.4 *v* 1.7 hospitalizations, respectively; $P < .001$), outpatient visits (17.6 *v* 12.6 visits, respectively; $P < .001$), infectious complications (47.3% *v* 39.4%, respectively; $P = .0022$), acute kidney disease/dehydration (30.5% *v* 21.2%, respectively; $P < .001$), and mucositis/esophagitis (18.6% *v* 14.4%, respectively; $P = .0246$).

Conclusion
After accounting for prognostic variables, patients treated with EP versus CP had similar overall survival, but EP was associated with increased morbidity.

J Clin Oncol 33:567-574. © 2014 by American Society of Clinical Oncology

INTRODUCTION

Nearly one in four patients with non–small-cell lung cancer (NSCLC) has stage III disease at presentation.[1] The outcome of these patients remains poor, with median survival times of only 15.3 to 21.7 months.[2-4] However, approximately 20% of patients achieve durable disease control, arguing for treatment with curative intent in those able to tolerate aggressive therapy.[1,5]

Randomized controlled trials (RCTs) have demonstrated that concurrent chemoradiotherapy improves overall survival (OS) but increases toxicity, compared with sequential chemoradiotherapy.[2,6] Such chemotherapy generally involves a platinum doublet; however, no large RCT directly compares specific combinations in this setting.[2,7] The regimen used in several of the RCTs was etoposide-cisplatin (EP), at systemic doses, adequate to address micrometastatic disease.[2,7-9] Because of the toxicity associated with EP, a competing regimen of dose-reduced weekly carboplatin-paclitaxel (CP) has emerged as an alternative choice.[10]

There is considerable concern that CP, although better tolerated than EP, may be inferior in terms of disease control.[11] To gain insight into the relative efficacy of these regimens, we examined outcomes of patients with newly diagnosed stage III NSCLC using the Department of Veterans Affairs (VA) Central Cancer Registry (VACCR).

METHODS

Patient Selection

Using the VACCR, we identified patients diagnosed with stage III NSCLC (see Appendix, online only, for histologies included) between October 2001 and December 2010. The VACCR stages patients using the contemporaneous International Association for the Study of Lung Cancer/American Joint Committee on Cancer staging classification; thus, version 6 was used through 2009 and version 7 in 2010. We used the VA Decision Support System Pharmacy file to identify chemotherapy drugs received during the 120 days after diagnosis.

We included patients who were classified by the VACCR as receiving radiotherapy as part of primary treatment within 7 days of the start of chemotherapy and received either CP or EP as the chemotherapy backbone. We excluded patients who the VACCR classified as receiving surgery as part of initial treatment or received other anticancer agents in addition to CP or EP as part of their initial treatment. We characterized chemotherapy as induction when it was prescribed as part of the initial 6 weeks of treatment and as consolidation when it was prescribed between weeks 7 and 16. We identified patients who received lung resection using International Classification of Diseases Ninth Revision (ICD-9) or Current Procedural Terminology procedure codes. We augmented the VACCR database with demographic, diagnostic, and laboratory data from several other VA databases. We provide details of this process in the Appendix. The study was approved by the institutional review boards of the Milwaukee and Durham VAs.

Statistical Analysis

The primary outcome was OS, defined by days from VACCR diagnosis until death. We censored OS at 5 years after diagnosis to avoid excessive statistical impact by patients with long survival diagnosed early in the study period. We grouped year of diagnosis into 2001 to 2004, 2005 to 2007, and 2008 to 2010. We used clinical records to obtain baseline values for estimated glomerular filtration rate (eGFR), serum albumin, platelet count, and hemoglobin, as well as weight loss before treatment. We defined anemia as hemoglobin less than 12 g/dL, hypoalbuminemia as serum albumin less than 3.5 g/dL, and chronic kidney disease as eGFR less than 60 mL/min/1.73 m^2.

We used ICD-9 codes from health care encounters during the year preceding diagnosis to calculate a summary burden of comorbidity using the National Cancer Institute (NCI) combined index.[12] ICD-9 codes from encounters during the 4 months after chemotherapy were used to identify adverse effects of treatment.

Outcome Analysis

We tested differences in baseline characteristics between groups using the Pearson χ^2 or t test for categorical and continuous variables, respectively. Survival curves were prepared using the Kaplan-Meier method. We used the following three complementary approaches to adjust our comparison of OS among patients receiving EP and CP for differences in baseline characteristics: a standard Cox proportional hazards model, a propensity score adjustment, and an instrumental variables technique.

In our standard Cox model, we included variables that were associated with OS in univariable analysis with a significance level of $P < .10$. The proportional hazards assumption for each covariate in the final model was tested, and the assumption was appropriate for all. We tested the interaction between chemotherapy regimen and each covariate for significance and found none.

Propensity score analysis adjusts for the bias induced by nonrandom treatment assignment by comparing patients who had a similar likelihood of receiving a treatment but who received different treatments. For this analysis, we used multiple logistic regression to predict the likelihood that a given patient would receive treatment with EP (ie, their propensity score). The model included the following variables, regardless of their individual statistical significance: histology (squamous *v* nonsquamous), stage (IIIA *v* IIIB), weight loss, number of prior hospitalizations, hemoglobin level, platelet count, serum albumin level, age, eGFR, NCI combined index, and geographic region.

We estimated the effect of treatment on survival using the following two approaches: matching and weighting by inverse probability of treatment. Prior work has demonstrated that both approaches allow for the estimation of marginal hazard ratios (HRs) with minimal bias.[13] For the matched-pair analysis, we matched each patient who received EP with one who received CP using exact treatment year category and the logit of the propensity score, using calipers of width equal to 0.2 standard deviations of the logit of the estimated propensity score.[14] To compare the groups, a marginal Cox model was applied using maximum partial likelihood estimates of regression parameters and a robust sandwich covariance matrix.[15,16] The main limitation of this methodology is that it limits the analysis to matched pairs only, thus reducing power. Another frequently used strategy that does not carry this limitation is the use of inverse probability of treatments weights; for this analysis, each observation was first weighted by the inverse probability of receiving the treatment the patients received, based on the propensity score. A Cox proportional hazards model was then fitted with chemotherapy regimen as the only predictor variable. A robust sandwich variance estimator was used to account for the weighted nature of the sample.[17]

Instrumental Variables and Near/Far Analysis

Although propensity scores can address biases caused by observed variables, there may be unknown or unmeasured variables that also affect the choice of treatment and outcomes. Instrumental variable analyses address such unmeasured confounders by using an instrument that is strongly associated with the treatment but is not expected to affect outcomes. The variability among VA medical centers in the use of EP versus CP provided an instrument for our analysis.

We used a novel technique, near/far matching, that unites propensity score matching with classical instrumental variables analysis.[18,19] We identified EP-encouraging centers, in which more than 50% of patients received EP, and EP-discouraging centers, where less than 10% of the patients received EP.

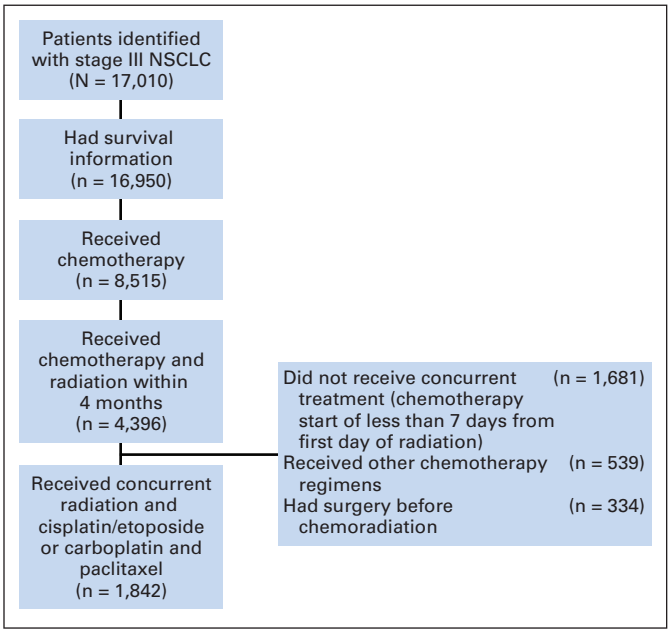

Fig 1. Identification of included and excluded patients with metastatic non–small-cell lung cancer (NSCLC).

We matched an EP-encouraging center to one or more EP-discouraging centers based on overall hospital volume, oncology service volume, and the number of facility oncologists. Using the propensity score obtained in the prior analysis and treatment year, we matched each patient treated in an EP-encouraging center with a patient treated in a matching EP-discouraging center. Thus, the patients were a near match (nearest match) on patient and facility characteristics and a far match (farthest match) based on the instrument. The analysis proceeds as a Cox proportional hazards model with a single predictor variable (encouraged *v* discouraged); matched patient pairs define the strata.[20]

RESULTS

Patient Characteristics

From an initial sample of 17,010 patients with stage III disease, 1,842 patients fulfilled our eligibility criteria (Fig 1). Most of our patients (98%) were men. EP was used in 27% of the patients (n = 499) and CP in 73% (n = 1,343; Table 1). Patients treated with EP, compared with patients treated with CP, were younger (mean age, 61.3 *v* 65.5 years, respectively; $P < .001$) and had higher hemoglobin (mean, 12.9 *v* 12.7 g/dL, respectively; $P < .0378$), higher albumin levels (mean, 3.6 *v* 3.5 g/dL, respectively; $P = .0586$), lower NCI combined index (mean score, 1.1 *v* 1.4, respectively; $P < .001$), and less weight loss (mean, 2.6% *v* 4%, respectively; $P < .001$). In multiple logistic regression analysis, treatment at a later era, younger age, less weight loss, and lower NCI combined index were associated with the decision to use EP (Fig 2).

Patients treated with CP received a median of five cycles (interquartile range, three to six cycles), with 46.8% of patients receiving six or seven cycles. In the EP group, 81.8% of patients received two cycles, and 18.2% received only one cycle. Patients who received CP were more likely to receive consolidation chemotherapy than patients who received EP (67.5% *v* 46.1%, respectively; $P = .0026$). The need for consolidation chemotherapy was put in question after the results of the Hoosier Oncology Group study were presented in 2007.[3] In our

Table 1. Difference in Patient Characteristics Between Patients Treated With EP Versus CP in the Observational Data Set and in Patients Who Were Matched by a Propensity Score

	Observational Data Set (n = 1,842)						Propensity Score–Matched Data Set (n = 762)					
	EP (n = 499)		CP (n = 1,343)				EP (n = 381)		CP (n = 381)			
Characteristic	No. of Patients	%	No. of Patients	%	Standard Difference	*P*	No. of Patients	%	No. of Patients	%	Standard Difference	*P*
Age, years					0.50	< .001					0.06	.3999
Mean	61.3		65.5				62.0		62.4			
SD	7.6		9				7.4		7.9			
Era of diagnosis					0.24	< .001					0	1
2001-2004	129	25.9	477	35.5			94	50	94	50		
2005-2007	194	38.9	393	29.3			152	50	152	50		
2008-2010	176	35.3	473	35.2			135	50	135	50		
Stage IIIB	281	56.3	759	56.5	< 0.01	.9379	189	49.6	204	53.5	0.8	.2769
Histology					0.11	.2112					0.07	.8158
Adenocarcinoma	110	22	252	18.8			82	21.5	85	22.3		
NOS	146	29.3	378	28.1			107	28.1	112	29.5		
Other	3	0.6	15	1.1			3	0.8	5	1.3		
Squamous cell	240	48.1	698	52			189	49.6	179	48.3		
Hemoglobin at baseline, g/dL					0.11	.0378					0.07	.3164
Mean	12.9		12.7				13.0		13.1			
SD	1.8		1.8				1.8		1.7			
Platelets at baseline, $\times 10^9$/L					0.08	.1393					0.03	.7169
Mean	331.2		321.2				324.4		321.1			
SD	124.0		123.3				118.9		126.4			
eGFR at baseline, mL/min					0.16	.0024					0.01	.9721
Mean	87.3		83.7				85.7		85.7			
SD	22.0		23.1				22.1		21.8			
Baseline serum albumin, g/dL					0.11	.0586					0.02	.8084
Mean	3.6		3.5				3.6		3.6			
SD	0.6		0.6				0.6		0.6			
Weight loss, %					0.25	< .001					0.04	.7438
Mean	2.9		4.5				2.9		2.8			
SD	6.3		6.5				6.4		5.8			
NCI combined index > 2	46	9.3	230	17.2	0.24	< .001	39	10.2	30	7.9	0.08	.2559
No. of prior hospitalizations in the year before treatment					0.07	.1601					0.07	.3563
Mean	0.9		0.8				0.9		0.8			
SD	1.0		0.9				1.0		0.9			

Abbreviations: CP, carboplatin-paclitaxel; eGFR, estimated glomerular filtration rate; EP, etoposide-cisplatin; NCI, National Cancer Institute; NOS, not otherwise specified; SD, standard deviation.

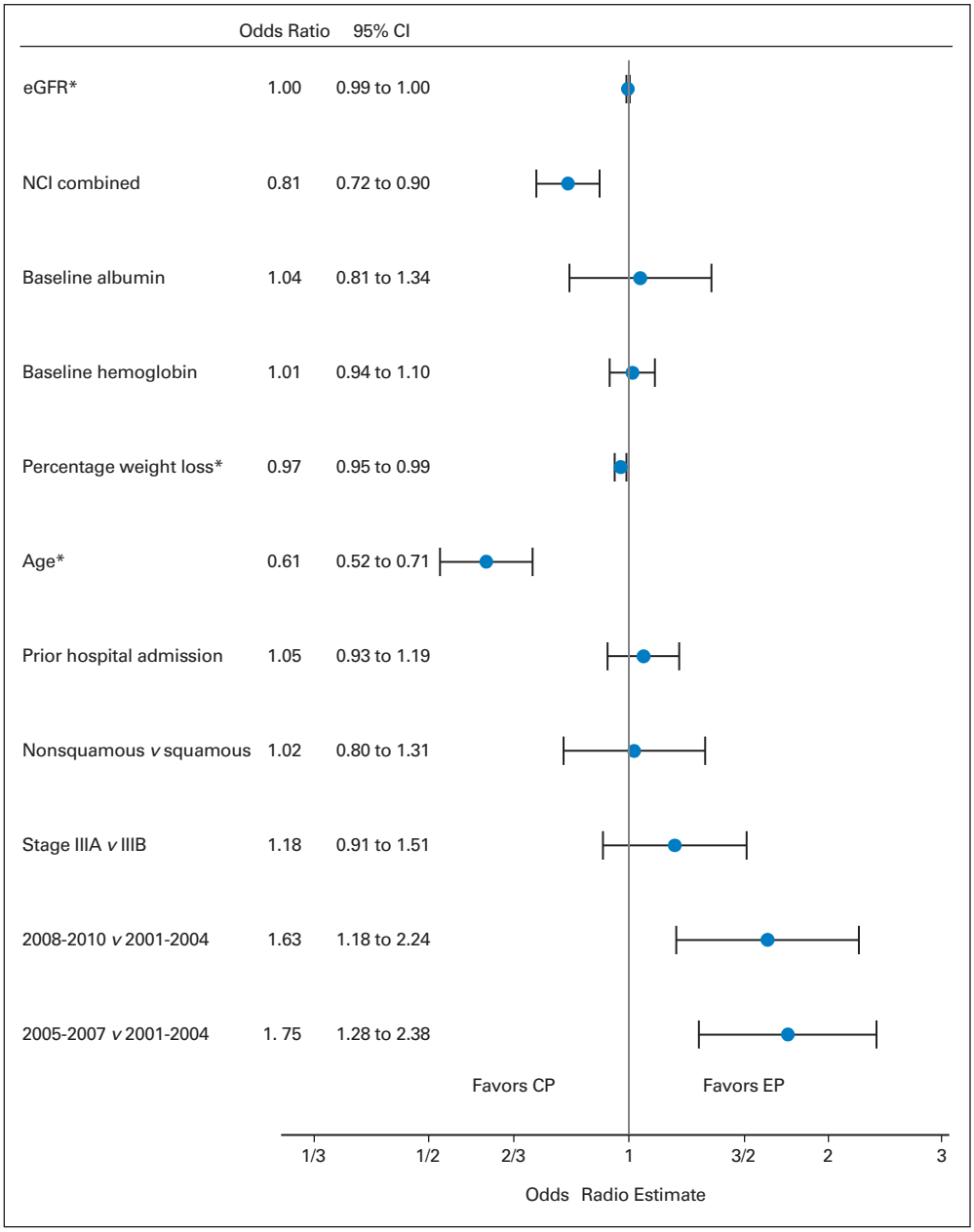

Fig 2. Odds ratio plot. This plot represents characteristics associated with the use of carboplatin-paclitaxel (CP) versus etoposide-cisplatin (EP). eGFR, estimated glomerular filtration rate; NCI, National Cancer Institute. (*) Multiples of 10.

database, before 2007, the rates of consolidation chemotherapy among patients receiving CP were similar to rates among those receiving EP. However, after 2007, the rate of consolidation in the CP group increased from 65.2% to 71.7%, whereas in the EP group, it decreased from 53.6% to 32.4%. Surgical resection after induction chemotherapy was uncommon but was more frequently used in the EP group 7% (n = 35) in contrast to only 2.4% (n = 32) in the CP group.

Survival Outcomes

In an unadjusted two-group analysis, patients treated with EP had a better outcome compared with those treated with CP (median OS, 17.3 *v* 14.6 months, respectively; HR, 0.88; 95% CI, 0.79 to 0.99; $P = .0209$; Fig 3A). In a Cox proportional hazards model, patient age (HR, 1.08; 95% CI, 1.01 to 1.15; $P = .0258$), percentage of weight loss (HR, 1.04; 95% CI, 1.03 to 1.05; $P < .001$), baseline anemia (HR, 1.19; 95% CI, 1.05 to 1.36; $P < .001$), hypoalbuminemia (HR, 1.29; 95% CI, 1.14 to 1.46; $P < .001$), and treatment era were all independently associated with decreased survival, whereas the chemotherapy regimen received was not associated with any survival advantage (HR, 0.97; 95% CI, 0.85 to 1.10; $P = .6327$; Table 2).

Propensity Score

For the matched analysis, 381 patients treated with EP were identified and matched based on their propensity score and era of treatment with an equal number of patients receiving CP. This analysis eliminated differences in age, hemoglobin, albumin level, percentage of weight loss, and comorbidity scores seen in the larger cohort (Table 1) and revealed no survival advantage for EP (HR, 1.07; 95% CI, 0.91

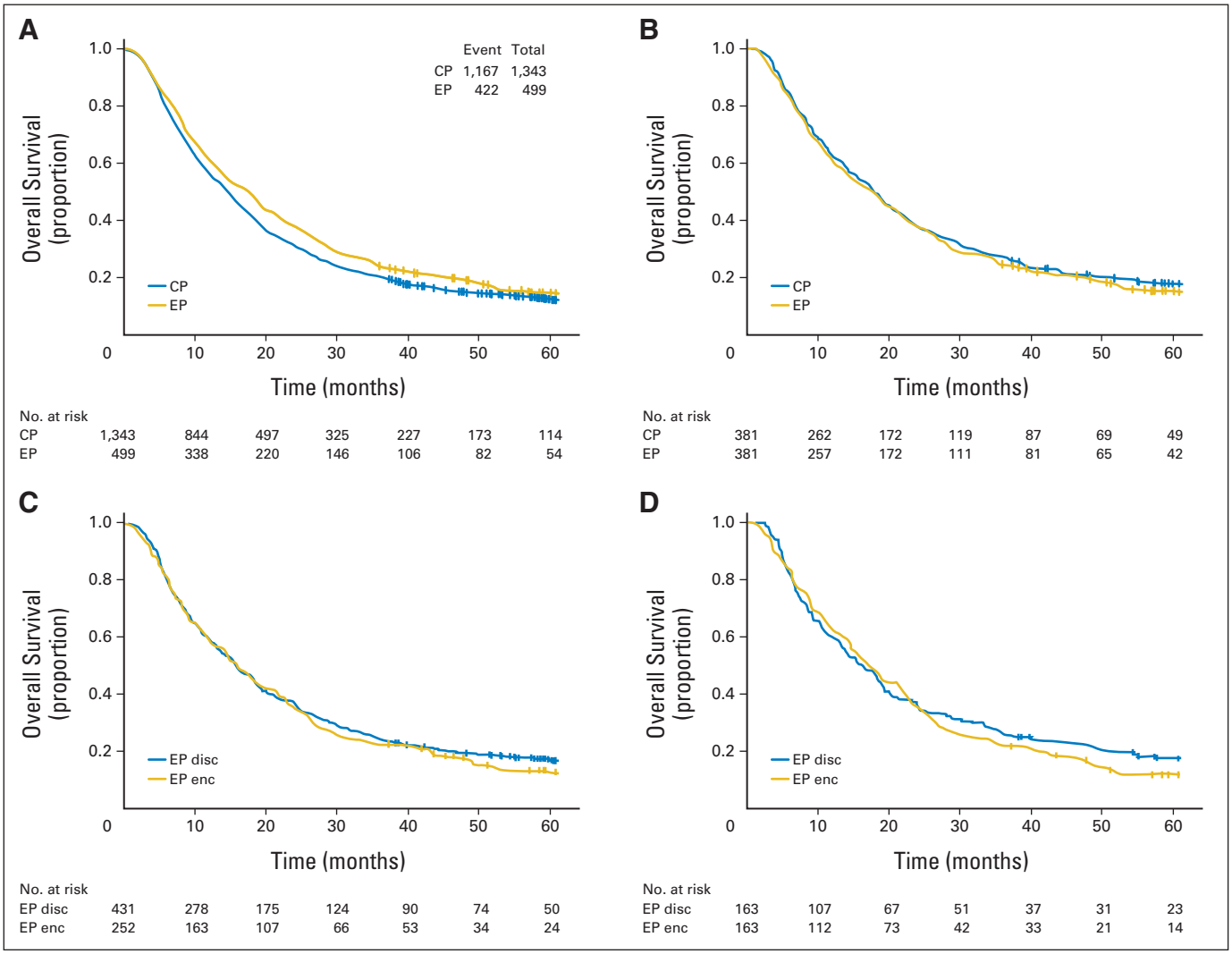

Fig 3. (A) Univariate analysis of overall survival of all patients by treatment with carboplatin-paclitaxel (CP) versus etoposide-cisplatin (EP). (B) Survival of a cohort of patients matched according to their propensity scores by treatment arm. (C) Survival of patients treated at EP-encouraging centers (enc) versus EP-discouraging centers (disc). (D) Survival of the near/far matched cohort.

to 1.24; $P = .4264$; Fig 3C). Subsequently, a Cox proportional hazards model weighted on the inverse propensity for being treated with EP was fitted. This analysis also showed no survival advantage for EP (HR, 0.97; 95% CI, 0.85 to 1.10; $P = .6212$).

Instrumental Variables

In facilities that treated more than 20 patients, there were marked differences between facilities in EP and CP use: eight facilities used EP more than 50% of the time (range, 55% to 81%), whereas 11 centers used EP in fewer than 10% of the cases (range, 0% to 9%). Among these facilities, which were all affiliated with an academic medical center, there were no significant differences in oncologist full-time employment equivalent (median, 2.7 *v* 2.3; $P = .8043$), unique patients seen annually in oncology clinics (median, 1,898 *v* 1,714; $P = .5915$), or overall facility volume (mean, 58,037 *v* 65,151; $P = .5357$).

For the instrumental variable analysis, patients treated at EP-encouraging centers, compared with patients treated at EP-discouraging centers, were younger (mean age, 62.1 *v* 65 years, respectively; $P = .001$) and had higher baseline albumin (mean, 3.8 *v* 3.5 g/dL, respectively; $P = .0032$) and hemoglobin levels (mean, 12.9 *v* 12.6, g/dL, respectively; $P = .0346$; Appendix Table A1, online only). Despite having patients who had better prognostic characteristics, no survival advantage was seen for patients treated in EP-encouraging centers in a univariable analysis (HR, 1.07; 95% CI, 0.90 to 1.26; $P = .4653$; Fig 3C). Furthermore, the near/far analysis, which equilibrated prognostic variables, did not demonstrate a survival advantage for matched patients treated in EP-encouraging centers (HR, 1.03; 95% CI, 0.75 to 1.40; $P = .8736$; Fig 3D).

Toxicity

In the original cohort without adjustments, patients treated with EP had a higher incidence of adverse events during the initial 4 months of treatment compared with patients treated with CP (Table 3). Patients treated with EP, compared with patients treated with CP, had more oncology clinic visits (mean, 17.6 *v* 12.6 visits,

Table 2. Cox Proportional Hazards Model

Variable	No. of Patients	Median Survival (months)	Cox Univariable Analysis			Cox Multivariable Analysis		
			Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P* (n = 1,437)
Chemotherapy regimen					.0209			.6327
Carboplatin and paclitaxel	1,343	14.6	—			—		
Cisplatin and etoposide	499	17.3	0.88	0.79 to 0.98		0.97	0.85 to 1.10	
Baseline hemoglobin, g/dL					< .001			.0064
≥ 12	1,213	17.5	—			—		
< 12	595	10.6	1.42	1.28 to 1.57		1.19	1.05 to 1.36	
Baseline albumin, g/dL					< .001			< .001
≥ 3.5	958	17.7	—			—		
< 3.5	694	10.9	1.49	1.35 to 1.66		1.29	1.14 to 1.46	
Stage					.0014			.1845
IIIA	802	17.3	—			—		
IIIB	1,040	13.7	1.17	1.06 to 1.30		1.08	0.96 to 1.21	
NCI combined index score					.0035			.0503
< 2	1,559	15.4	—			—		
≥ 2	276	12.9	1.22	1.07 to 1.40		1.17	1.00 to 1.37	
Treatment era					< .001			.0281
2001-2004	606	12.8	—			—		
2005-2007	587	15.2	0.84	0.74 to 0.95		0.89	0.77 to 1.02	
2008-2010	649	17.4	0.78	0.69 to 0.88		0.83	0.72 to 0.95	
Age, in 10-year increments	1,842	15.0	1.09	1.03 to 1.15	.0037	1.08	1.01 to 1.15	.0258
% of weight lost in the year before diagnosis	1,622	15.3	1.05	1.04 to 1.06	< .001	1.04	1.03 to 1.05	< .0001

Abbreviation: NCI, National Cancer Institute.

respectively; $P < .001$) and more hospitalizations (mean, 2.4 *v* 1.7 hospitalizations, respectively; $P < .001$).

DISCUSSION

In a large cohort of patients with stage III NSCLC who received concurrent chemoradiotherapy at academically affiliated tertiary care VA hospitals, we found that EP offered no survival advantage over CP and was associated with more toxicity. This finding was consistent across multiple analytic approaches in a database that included a wide range of potential confounders.

After the establishment of concurrent chemoradiotherapy as the standard of care,[2,6] little research has addressed the choice of chemotherapy. Because most of the trials that established this new standard of care used cisplatin-based chemotherapy and because of the theoretical advantage that its initial systemic doses are able to eradicate micrometastatic disease, EP is widely recommended for use.[8,9] However, concerns about toxicity associated with EP have led oncologists to consider alternate regimens, most notably CP.[10,21]

The results of the Cancer and Leukemia Group B 39801 trial cast doubt on the use of CP as chemotherapy because of the low median survival in both arms (12 to 14 months), which was roughly similar to prior sequential chemoradiotherapy arms in RCTs and markedly inferior to that observed in phase III studies using EP.[9,22] In our matched data set, patients treated with CP had an OS of 16.1 months (95% CI, 14 to 18 months; Fig 3). Although we used date of diagnosis, rather than start of treatment, as time zero, this OS is consistent with that seen in clinical trials using EP and better than that seen in the Cancer and Leukemia Group B 39801 trial. This suggests that the lower survival seen in the latter study is not a function of the CP regimen, but rather some characteristic of the population that was enrolled onto that study, because both arms did less well than other studies of similar stage NSCLC.

We are only aware of one published randomized prospective comparison of EP and CP. This was a study of 65 patients by Wang et al,[23] which found that EP had superior OS but similar progression-free survival compared with CP. There are several possible explanations for

Table 3. Morbidity in Patients Treated With EP Versus CP

Outcome*	EP		CP		*P*
	No. of Patients	%	No. of Patients	%	
No. of hospitalizations					< .001
Mean	2.4		1.7		
SD	2.4		1.8		
Outpatient visits					< .001
Mean	17.6		12.6		
SD	11.8		6.7		
At least one encounter for any of the following complications					
Infectious complication	236	47	529	39.4	.0022
Acute kidney injury/dehydration	152	30.5	285	21.2	< .001
Nausea/vomiting	65	13	110	8.2	.0017
Mucositis/esophagitis	93	18.6	193	14.4	.0246
Any of the above	321	64.4	739	55	< .001

Abbreviations: CP, carboplatin-paclitaxel; EP, etoposide-cisplatin; SD, standard deviation.
*Limited to the 4 months after the initiation of chemotherapy.

our contradictory results. Most obviously, the study by Wang et al[23] is small; promising data obtained through small phase II studies frequently are not confirmed when a larger population is studied.[24] Another possibility is that the Chinese population studied by Wang et al[23] has important differences in disease characteristics (eg, frequency of *EGFR* mutations) from our largely white male population. Finally, it could be that our adjustment was unable to eliminate biases that obscured a true benefit of EP.

To our knowledge, the current study is the largest study comparing the survival of patients receiving EP versus CP in this clinical setting. Its main strengths are the richness and robustness of the VA database and the number of patients it contains. We used multiple approaches to address biases that may be introduced by nonrandom assignment of the treatments (EP and CP) being compared. First, we included a wide range of clinically relevant variables in a multiple regression analysis to adjust for differences in the patients who received EP or CP. These variables included change in weight and key baseline laboratory values in addition to the staging, comorbidity, and demographic data.

Second, we used propensity score analysis, a method designed to achieve the same goal of eliminating bias caused by measured patient characteristics that affect both treatment and outcomes. Finally, we used an instrumental variables analysis to overcome bias caused by unmeasured or unknown variables associated with treatment and outcomes. The consistency of our results strengthens our conclusions.

Our study does have other limitations. First, it is not currently possible to establish the dose or duration of radiation treatment in our database. Second, there were other differences in treatment. Notably, patients receiving CP were more likely to receive consolidation chemotherapy. Although studies have not demonstrated a benefit from consolidation[25-27] and its use remains controversial, the lower cumulative dose of chemotherapy in the EP arm might have obscured an advantage for EP. Similarly, our database does not include chemotherapy doses, although our record review (Appendix, online only) confirmed that data regarding which specific drugs were used is accurate. Because we did not collect data prospectively, we cannot comment on the proportion of patients treated as part of a clinical trial or on the initial treatment plan. Similarly, we rely on coded administrative data to identify treatment toxicity; this is a less comprehensive analysis of adverse events than can obtained in prospective trials. Moreover, our database includes only hospitalizations and outpatient visits occurring in the VA system. Thus, we likely underestimate the frequency of visits and adverse events after treatment. However, it is unlikely that this differentially affects patients receiving EP versus CP. We also acknowledge that our VA data set includes mostly older white men; extrapolation beyond this group may be problematic. However, patients treated at the VA for lung cancer have similar outcomes to patients treated in clinical trials[28] as well as in the private sector.[29] Next, although our sample size is comparatively large, it is still possible that a small benefit of EP was missed as a result of insufficient power. Finally, our study compared two specific platinum-based regimens; we cannot comment on the relative efficacy of other combinations, including the use of a platinum agent with vinorelbine or vinca alkaloids.

Despite these limitations, we believe this study shows that there is considerable equipoise regarding which regimen should be preferred. Given the prevalence of unresectable stage III lung cancer, we believe a phase III randomized control trial should be considered to definitively answer this question. Pending the availability of such data, our results may help guide clinicians and patients trying to decide which chemotherapy regimen to pair with radiotherapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** Kiran Devisetty, Abbott Laboratories, AbbVie **Honoraria:** None **Research Funding:** None **Expert Testimony:** None **Patents, Royalties, and Licenses:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Rafael Santana-Davila, Rodney Sparapani, Jeffrey Whittle
Administrative support: Jeffrey Whittle
Collection and assembly of data: Rafael Santana-Davila, Amy Moran, Jeffrey Whittle
Data analysis and interpretation: Rafael Santana-Davila, Kiran Devisetty, Aniko Szabo, Carlos Arce-Lara, Elizabeth M. Gore, Amy Moran, Christina D. Williams, Michael J. Kelley, Jeffrey Whittle
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Price A: Emerging developments of chemoradiotherapy in stage III NSCLC. Nat Rev Clin Oncol 9:591-598, 2012
2. Curran WJ Jr, Paulus R, Langer CJ, et al: Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: Randomized phase III trial RTOG 9410. J Natl Cancer Inst 103:1452-1460, 2011
3. Hanna N, Neubauer M, Yiannoutsos C, et al: Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: The Hoosier Oncology Group and U.S. Oncology. J Clin Oncol 26:5755-5760, 2008
4. Hoang T, Dahlberg SE, Schiller JH, et al: Randomized phase III study of thoracic radiation in combination with paclitaxel and carboplatin with or without thalidomide in patients with stage III non-small-cell lung cancer: The ECOG 3598 study. J Clin Oncol 30:616-622, 2012
5. Salama JK, Vokes EE: New radiotherapy and chemoradiotherapy approaches for non-small-cell lung cancer. J Clin Oncol 31:1029-1038, 2013
6. Schaake-Koning C, van den Bogaert W, Dalesio O, et al: Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. N Engl J Med 326:524-530, 1992
7. Aupérin A, Le Péchoux C, Rolland E, et al: Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 28:2181-2190, 2010
8. Albain KS,Crowley JJ, Turrisi AT 3rd, et al: Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: A Southwest Oncology Group phase II study, SWOG 9019. J Clin Oncol 20:3454-3460, 2002
9. Gandara DR, Chansky K, Albain KS, et al: Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: Phase II Southwest Oncology Group Study S9504. J Clin Oncol 21:2004-2010, 2003
10. Belani CP, Choy H, Bonomi P, et al: Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: A randomized phase II locally advanced multi-modality protocol. J Clin Oncol 23: 5883-5891, 2005

11. Vokes EE, Herndon JE 2nd, Kelley MJ, et al: Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. J Clin Oncol 25:1698-1704, 2007

12. Klabunde CN, Legler JM, Warren JL, et al: A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal, and lung cancer patients. Ann Epidemiol 17:584-590, 2007

13. Austin PC: The performance of different propensity score methods for estimating marginal hazard ratios. Stat Med 32:2837-2849, 2013

14. Austin PC: Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 10:150-161, 2011

15. Lee EW, Wei LJ, Amato DA, et al: Cox-type regression analysis for large numbers of small groups of correlated failure time observations, in Klein JP, Goel PK (eds): Survival Analysis: State of the Art. Columbus, OH, Springer, 1992, pp 237-247

16. Gayat E, Resche-Rigon M, Mary JY, et al: Propensity score applied to survival data analysis through proportional hazards models: A Monte Carlo study. Pharm Stat 12:222-229, 2012

17. Lin DY, Wei L-J: The robust inference for the Cox proportional hazards model. J Am Stat Assoc 84:1074-1078, 1989

18. Baiocchi M, Small DS, Lorch S, et al: Building a stronger instrument in an observational study of perinatal care for premature infants. J Am Stat Assoc 105:1285-1296, 2010

19. Baiocchi M, Small DS, Yang L, et al: Near/far matching: A study design approach to instrumental variables. Health Serv Outcomes Res Method 12: 237-253, 2012

20. Therneau TM: Modeling Survival Data: Extending the Cox Model. New York, NY, Springer, 2000

21. Akerley W, Herndon JE Jr, Lyss AP, et al: Induction paclitaxel/carboplatin followed by concurrent chemoradiation therapy for unresectable stage III non-small-cell lung cancer: A limited-access study—CALGB 9534. Clin Lung Cancer 7:47-53, 2005

22. Albain KS, Swann RS, Rusch VW, et al: Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: A phase III randomised controlled trial. Lancet 374: 379-386, 2009

23. Wang L, Wu S, Ou G, et al: Randomized phase II study of concurrent cisplatin/etoposide or paclitaxel/carboplatin and thoracic radiotherapy in patients with stage III non-small cell lung cancer. Lung Cancer 77:89-96, 2012

24. Maitland ML, Hudoba C, Snider KL, et al: Analysis of the yield of phase II combination therapy trials in medical oncology. Clin Cancer Res 16:5296-5302, 2010

25. Huber RM, Engel-Riedel W, Kollmeier J, et al: GILT study: Oral vinorelbine (NVBo) and cisplatin (P) with concomitant radiotherapy (RT) followed by either consolidation (C) with NVBo plus P plus best supportive care (BSC) or BSC alone in stage (st) III non-small cell lung cancer (NSCLC): Final results of a phase (ph) III study. J Clin Oncol 30, 2012 (suppl; abstr 7001)

26. Tsujino K, Kurata T, Yamamoto S, et al: Is consolidation chemotherapy after concurrent chemoradiotherapy beneficial for patients with locally advanced non-small-cell lung cancer? A pooled analysis of the literature. J Thorac Oncol 8:1181-1189, 2013

27. Park K, Ahn YC, Ahn JS: A multinational phase III randomized trial with or without consolidation chemotherapy using docetaxel and cisplatin after concurrent chemoradiation in inoperable stage III non-small cell lung cancer (CCheIN). J Clin Oncol 32, 2014 (suppl; abstr 7500)

28. Santana-Davila R, Szabo A, Arce-Lara C, et al: Cisplatin versus carboplatin-based regimens for the treatment of patients with metastatic lung cancer: An analysis of Veterans Health Administration data. J Thorac Oncol 9:702-709, 2014

29. Landrum MB, Keating NL, Lamont EB, et al: Survival of older patients with cancer in the Veterans Health Administration versus fee-for-service Medicare. J Clin Oncol 30:1072-1079, 2012

GLOSSARY TERMS

non–small-cell lung cancer (NSCLC): a type of lung cancer that includes squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma.

Appendix

Potential Confounders

We augmented the Department of Veterans Affairs (VA) Central Cancer Registry database with data regarding laboratory results from the VA Decision Support System laboratory files, weight from the VA Corporate Data Warehouse, and comorbid conditions identified using International Classification of Diseases Ninth Revision (ICD-9) codes from VA Medical SAS inpatient and outpatient encounter files.

Laboratory values. We defined baseline hemoglobin, platelet, creatinine, and albumin levels as the mean of tests obtained within 45 days before and 7 days after initial treatment. We excluded biologically implausible values (hemoglobin $>$ 22 g/dL or $<$ 5 g/dL; albumin $>$ 8 g/dL), which made up less than 0.1% of observations. No implausible values for creatinine or platelets were identified. Plausible hemoglobin, albumin, and platelet levels were identified in 98.2% (n = 1,822), 89.8% (n = 1,666), and 92% (n = 1,878) of eligible patients, respectively. We determined the estimated glomerular filtration rate using the Modification of Diet in Renal Disease equation (Levey AS, et al: Ann Intern Med 145:247-254, 2006); estimated glomerular filtration rate was obtained in 97% of patients (n = 1,801).

Baseline patient characteristics. We defined baseline weight as the median of documented weights obtained between 3 months and 2 years preceding the day chemotherapy started. We calculated change in weight by subtracting the median of weights obtained during the 15 days after the start of treatment from the baseline weight. Weight loss could be calculated in 88% (n = 1,634) of our patients.

Treatment Era

The cohort was divided into three treatment eras based on date of diagnosis (2001 to 2003, 2004 to 2007, and 2008 to 2010).

Record Review

Two of the authors (A.M. and R.S.-D.) reviewed the electronic records of a random sample of 158 patients (8.5%) to confirm that chemotherapy was administered concurrently with radiotherapy and that the chemotherapy regimen was correctly classified as etoposide-cisplatin (EP) or carboplatin-paclitaxel (CP). Both were confirmed in all patients.

Chemotherapy. The Decision Support System pharmacy records were used to obtain chemotherapy information. We defined induction chemotherapy as that prescribed in the first 6 weeks after the initiation of treatment and consolidation as that administered after 6 weeks and until 16 weeks after initiation of treatment. During the induction phase, for patients treated with CP, all chemotherapy drugs identified every 7 days were counted as a cycle. For patients treated with EP, all chemotherapy drugs identified every 19 days were counted as a cycle. For the consolidation phase in both groups, cycles were identified as all drugs administered every 19 days.

Surgery. Receipt of surgery was identified by looking at diagnostic and procedure codes in both the outpatient and inpatient fee basis and MedSAS files. We used ICD-9 Clinical Modification codes (32.09, 32.10, 32.50, 32.60, 32.40, 32.29, and 32.90) and Current Procedural Terminology codes (32440, 32442, 32445, 32480, 32482, 32484, 32486, 32500, and 32999).

Comorbidities

We measured comorbidities using ICD-9 diagnosis and procedure codes from inpatient and outpatient encounters occurring between 13 months and 1 month before non–small-cell lung cancer diagnosis. We applied the Deyo algorithm for generating the Charlson comorbidity index from administrative data. We then excluded cancer diagnoses and applied the lung cancer–specific weights developed by Klabunde et al (Klabunde CN, et al: J Clin Epidemiol 53:1258-1267, 2000)[12] to obtain the National Cancer Institute combined index. We identified VA hospitalizations during the year before the start of treatment, because prior hospitalizations are known to predict future hospitalizations and death (Anderson G, et al: JAMA 263:967-972, 1990). We used the 2009 Area Resource File to identify area-level surrogates for socioeconomic status (ie, proportion of adults with high school education, median household income, urban/rural status).

Outcomes

We obtained data regarding date of death from the VA's vital status file updated in February of 2014. This is created by combining mortality data from various VA databases and the Social Security Administration and provides data quality similar to that available from the National Death Index for veterans who use the VA for health care (Sohn MW, et al: Popul Health Metr 4:2, 2006).

We summarized the number of VA hospitalizations and outpatient visits during the 4 months after the start of treatment. We identified complications commonly associated with chemotherapy using the ICD-9 diagnosis codes associated with these encounters. When available, previously defined coding algorithms were applied; for other complications, we developed algorithms based on appropriate coding documents. Complications were categorized as infection or neutropenia; acute kidney injury or dehydration; nausea or vomiting; hemorrhage; or mucositis/esophagitis. We did not attempt to grade the severity of these complications, but note that they were significant enough to be coded.

Complications of Treatment

Hospital encounters and outpatients records were used to obtain coding information to identify complications from treatment that occurred within 4 months of the start of treatment. Infections or neutropenic complications were defined as having an inpatient or outpatient visit with a primary or secondary diagnosis of neutropenia (ICD-9 Clinical Modification 288.0), fever (780.6), or a list of

infections previously used by other authors (Weycker D, et al: BMC Health Serv Res 13:60, 2013). Acute kidney disease or dehydration was defined as having a primary or secondary diagnosis of dehydration (276.5), hypernatremia (276.0), acute kidney failure (584.0), or renal failure, unspecified (586.0). Nausea/vomiting complications were identified with diagnosis for nausea and vomiting (787.0) or persisting vomiting (536.2). Hemorrhage was defined as having ICD-9 codes for extracranial hemorrhages (ie, GI, genitourinary, retroperitoneal) or primary and secondary diagnoses of intracranial hemorrhage, including intracerebral, subarachnoid, or subdural hemorrhages, as done by Fang et al (Fang MC, et al: J Am Coll Cardiol 58:395-401, 2011).

Facilities

We used 2012 VA Physician Workforce and Support Staff Data from the VA Office of Productivity, Efficiency, and Staffing to identify academic affiliation, number of oncologist full-time employment equivalents, and the number of unique patients seen at the facility, both overall and in oncology clinics.

Histologies

Histologies are listed in Appendix Table A2.

Table A1. Differences in Patient Characteristics Between Centers Where the Majority of Patients Were Treated With EP (EP-encouraging centers) and Centers Where EP Was Used in Less Than 10% of Patients (EP-discouraging centers)

	Comparing All Patients						Near/Far Match Analysis					
	EP-Encouraging Center (n = 252)		EP-Discouraging Center (n = 431)				EP-Encouraging Center (n = 163)		EP-Discouraging Center (n = 163)			
Characteristic	No. of Patients	%	No. of Patients	%	Standard Difference	*P*	No. of Patients	%	No. of Patients	%	Standard Difference	*P*
Treatment					1.83	< .001					1.82	< .001
EP	173	68.7	16	3.7			107	65.6	3	1.8		
CP	79	31.3	415	96.3			56	34.4	160	98.2		
Treatment era					0.17	.0964					0	1
2001-2004	95	38.9	149	61.1			61	50	61	50		
2005-2007	92	40.2	137	59.8			60	50	60	50		
2008-2010	65	30.9	145	69.1			42	50	42	50		
Age, years					0.31	< .001					0.02	.7250
Mean	62.1		65				64.5		64.2			
SD	8.8		8.8				8.5		7.8			
Stage IIIB	140	55.6	64.9	8.8	0.06	.4576	89	54.6	102	62.6	0.17	.1438
Histology					0.28	.0065					0.04	.0210
Adenocarcinoma	54	21.4	69	16			32	19.6	24	14.7		
NOS	92	36.5	123	28.5			64	39.3	46	28.2		
Other	1	0.4	6	1.4			0	0.0	2	1.2		
Squamous	105	41.7	233	54.1			67	41.1	91	55.8		
Hemoglobin, g/dL					0.17	.0346						.3293
Mean	12.9		12.6				12.9		12.7		0.11	
SD	1.8		1.7				1.8		1.6			
eGFR, mL/min					0.13	.1094						.3779
Mean	87.5		84.4				84.3		86.6		0.10	
SD	23.9		24.4				23.8		24.3			
Albumin, g/dL					0.25	.0032						.0029
Mean	3.7		3.5				3.8		3.6		0.33	
SD	0.6		0.6				0.5		0.6			
Weight loss, %					0.12	.1740						.7829
Mean	3.5		4.2				3.9		4.1		0.03	
SD	6.5		6.7				6.2		5.7			
Modified NCI score > 2	28	11.2	66	15.3	0.12	.1259	21	12.9	19	11.7	0.04	.7357

Abbreviations: CP, carboplatin-paclitaxel; eGFR, estimated glomerular filtration rate; EP, etoposide-cisplatin; NCI, National Cancer Institute; NOS, not otherwise specified; SD, standard deviation.

Table A2. Histologies Included in the Study

Histology/Behavior Code	Histology Description	Histology/Behavior Description
8000/0	Neoplasm	Neoplasm, benign
8000/1	Neoplasm	Neoplasm, uncertain whether benign or malignant
8000/3	Neoplasm	Neoplasm, malignant
8001/3	Neoplasm	Tumor cells, malignant
8002/3	Neoplasm	Malignant tumor, small-cell type
8003/3	Neoplasm	Malignant tumor, giant-cell type
8004/3	Neoplasm	Malignant tumor, spindle cell type
8010/2	Carcinoma, NOS	Carcinoma in situ, NOS
8010/3	Carcinoma, NOS	Carcinoma, NOS
8011/3	Carcinoma, NOS	Epithelioma, malignant
8012/3	Carcinoma, NOS	Large-cell carcinoma, NOS
8013/3	Carcinoma, NOS	Large-cell neuroendocrine carcinoma
8014/3	Carcinoma, NOS	Large-cell carcinoma with rhabdoid phenotype
8020/3	Carcinoma, undifferentiated NOS	Carcinoma, undifferentiated type, NOS
8021/3	Carcinoma, undifferentiated NOS	Carcinoma, anaplastic type, NOS
8022/3	Carcinoma, undifferentiated NOS	Pleomorphic carcinoma
8030/3	Giant- and spindle cell carcinoma	Giant-cell and spindle cell carcinoma
8031/3	Giant- and spindle cell carcinoma	Giant-cell carcinoma
8032/3	Giant- and spindle cell carcinoma	Spindle cell carcinoma
8033/3	Giant- and spindle cell carcinoma	Pseudosarcomatous carcinoma
8041/3	Small-cell carcinoma, NOS	Small-cell carcinoma, NOS
8042/3	Small-cell carcinoma, NOS	Oat cell carcinoma
8043/3	Small-cell carcinoma, NOS	Small-cell carcinoma, fusiform cell
8044/3	Small-cell carcinoma, NOS	Small-cell carcinoma, intermediate cell
8045/3	Small-cell carcinoma, NOS	Combined small-cell carcinoma
8046/2	Non–small-cell carcinoma, in situ	Non–small-cell carcinoma, in situ
8046/3	Non–small-cell carcinoma, NOS	Non–small-cell carcinoma
8050/2	Papillary carcinoma, NOS	Papillary carcinoma in situ
8050/3	Papillary carcinoma, NOS	Papillary carcinoma, NOS
8052/2	Papillary carcinoma, NOS	Papillary squamous cell carcinoma, noninvasive
8052/3	Papillary carcinoma, NOS	Papillary squamous cell carcinoma
8070/2	Squamous cell carcinoma, NOS	Squamous cell carcinoma in situ, NOS
8070/3	Squamous cell carcinoma, NOS	Squamous cell carcinoma, NOS
8071/3	Squamous cell carcinoma, NOS	Squamous cell carcinoma, keratinizing, NOS
8072/3	Squamous cell carcinoma, NOS	Squamous cell carcinoma, large cell, nonkeratinizing
8073/2	Squamous cell carcinoma, CIS	Squamous cell carcinoma, CIS
8073/3	Squamous cell carcinoma, NOS	Squamous cell carcinoma, small cell, nonkeratinizing
8074/3	Squamous cell carcinoma, NOS	Squamous cell carcinoma, spindle cell
8075/3	Squamous cell carcinoma, NOS	Squamous cell carcinoma, adenoid
8076/2	Squamous cell carcinoma, NOS	Squamous cell carcinoma in situ with questionable stromal invasion
8076/3	Squamous cell carcinoma, NOS	Squamous cell carcinoma, microinvasive
8078/3	Squamous cell carcinoma, NOS	Squamous cell carcinoma with horn formation
8140/2	Adenocarcinoma, NOS	Adenocarcinoma in situ
8140/3	Adenocarcinoma, NOS	Adenocarcinoma, NOS
8141/3	Adenocarcinoma, NOS	Scirrhous adenocarcinoma
8144/3	Adenocarcinoma, NOS	Adenocarcinoma, intestinal type
8147/3	Adenocarcinoma, NOS	Basal cell adenocarcinoma
8200/3	Adenoid cystic and cribriform carcinoma	Adenoid cystic carcinoma
8230/3	Solid carcinoma, NOS	Solid carcinoma, NOS
8231/3	Solid carcinoma, NOS	Carcinoma simplex
8250/2	Bronchioloalveolar adenocarcinoma in situ	Bronchioloalveolar adenocarcinoma in situ
8250/3	Bronchioloalveolar adenocarcinoma	Bronchioloalveolar adenocarcinoma
8251/3	Bronchioloalveolar adenocarcinoma	Alveolar adenocarcinoma
8252/2	Bronchioloalveolar adenocarcinoma in situ	Bronchioloalveolar adenocarcinoma in situ
8252/3	Bronchioloalveolar adenocarcinoma	Bronchioloalveolar carcinoma, nonmucinous
8253/3	Bronchioloalveolar adenocarcinoma	Bronchioloalveolar carcinoma, mucinous
8254/3	Bronchioloalveolar adenocarcinoma	Bronchioloalveolar carcinoma, mixed mucinous and nonmucinous
8255/3	Bronchioloalveolar adenocarcinoma	Adenocarcinoma with mixed subtypes
8260/3	Papillary adenocarcinoma, NOS	Papillary adenocarcinoma, NOS
8263/3	Papillary adenocarcinoma, NOS	Adenocarcinoma in tubulovillous adenoma

(continued on following page)

Table A2. Histologies Included in the Study (continued)

Histology/Behavior Code	Histology Description	Histology/Behavior Description
8310/3	Clear cell adenocarcinoma, NOS	Clear cell adenocarcinoma, NOS
8320/3	Granular cell carcinoma	Granular cell carcinoma
8323/3	Granular cell carcinoma	Mixed cell adenocarcinoma
8430/3	Mucoepidermoid carcinoma	Mucoepidermoid carcinoma
8430/3	Mucoepidermoid carcinoma	Mucoepidermoid carcinoma
8480/3	Mucinous adenocarcinoma	Mucinous adenocarcinoma
8481/3	Mucinous adenocarcinoma	Mucin-producing adenocarcinoma
8490/3	Signet ring cell carcinoma	Signet ring cell carcinoma
8550/3	Acinar cell carcinoma	Acinar cell carcinoma
8560/3	Adenosquamous carcinoma	Adenosquamous carcinoma
8572/3	Adenocarcinoma with metaplasia	Adenocarcinoma with spindle cell metaplasia
8574/3	Adenocarcinoma with metaplasia	Adenocarcinoma with neuroendocrine differentiation
8575/3	Adenocarcinoma with metaplasia	Metaplastic carcinoma, NOS
8576/3	Adenocarcinoma with metaplasia	Hepatoid adenocarcinoma
8803/3	Sarcoma, NOS	Small-cell sarcoma
8940/3	Mixed tumor, malignant, NOS	Mixed tumor, malignant, NOS
8980/3	Carcinosarcoma, NOS	Carcinosarcoma, NOS
9015/3	Adenocarcinofibroma	Mucinous adenocarcinofibroma

Abbreviations: CIS, carcinoma in situ; NOS, not otherwise specified.