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Chemotherapy for lung cancer: Determinants of guideline adherence and associated patient outcomes

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CHEMOTHERAPY FOR LUNG CANCER: DETERMINANTS OF GUIDELINE ADHERENCE AND ASSOCIATED PATIENT OUTCOMES

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DEDICATION

To my loving wife, Sandra, and to my parents, George and Marie.

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CHAPTER 1. INTRODUCTION

The 2006 Institute of Medicine (IOM) report “From Cancer Patient to Cancer Survivor: Lost in Transition” recommends “health care providers should use systematically developed evidence-based clinical practice guidelines, assessment tools, and screening instruments to help identify and manage late effects of cancer and its treatment.” Without these guidelines, the practices of health care providers will vary widely, leading to inefficiencies in the delivery of care. The report emphasizes the need for evaluating the impact of guidelines in the context of cancer care.

Spending on medical treatment for cancer in the United States accounts for nearly 103 billion dollars annually, with the administering of chemotherapy agents driving the cost of treating advanced stages of the disease. Understanding the extent to which chemotherapy use in practice is consistent with these guidelines as well as the factors associated with inappropriate chemotherapy use has rarely been studied among large populations, mainly because performance status (PS), a key clinical component in assessing chemotherapy appropriateness, is typically missing from claims-based databases. The purpose of PS is to quantify the general well-being of a cancer patient. It is used to determine whether patients can receive chemotherapy, whether dose adjustment is necessary, as a measure for the required intensity of palliative care, and as a quality of life measure in randomized controlled trials.

The goal of this research is to quantify the non-guideline concordant use of chemotherapy within an insured population diagnosed with lung cancer with

documented PS, and to evaluate the factors associated with under- and over-use of chemotherapy within this cohort. By combining data from medical records with those available via an automated tumor registry, medical claims, and Census data, I was able to consider the patients' clinical and socio-demographic characteristics, as well as characteristics of the neighborhoods in which the patients reside.

A key factor in evaluating appropriateness of chemotherapy in lung cancer is the "performance status" (PS) of the patient. PS is a subjective measure used by clinicians to assess functional capacity and the likelihood of adverse events, quality of life, and survival after treatment. Measures of PS are currently not available through automated claims data. This void acts as an impediment in comparative effectiveness research. In chapter 2, I develop a tool to estimate PS using claims-based measures. I used chart abstracted PS (from the medical record) and linked it to automated medical and pharmaceutical claims and tumor registry data.

In chapter 3, I describe the sample of chemotherapy users and nonusers and examine the factors associated with underuse and overuse of chemotherapy. Patients with good PS, for whom chemotherapy treatment is recommended, who did not receive chemotherapy are classified as under-users. Patients with poor PS, who received chemotherapy despite guideline recommendations against its use, are classified as over-users. I use logistic regression to estimate two models. The first model tests non-receipt of chemotherapy among patients with good PS and the second considers the

receipt of chemotherapy among patients with poor PS. In both models, I consider patient-level characteristics including demographic, clinical, socioeconomic, and health care access measures.

In the final chapter, I focus on the outcomes associated with the choice of adherence to guidelines. Specifically, I am evaluating the relationship of over- and under-use with survival. To account for the endogeneity of chemotherapy receipt in estimating outcomes I use a two-stage residual inclusion (2SRI) model. The first stage equation represents a logistic regression for factors associated with receipt of chemotherapy (same equation from chapter 3). For survival, the second stage equation is the Cox proportional hazard model.

CHAPTER 2. USING CLAIMS-BASED MEASURES TO PREDICT PERFORMANCE STATUS IN PATIENTS WITH LUNG CANCER

Performance status (PS) is a good prognostic factor in lung cancer and is used to assess chemotherapy appropriateness. Researchers studying chemotherapy use are often hindered by the unavailability of PS in automated data sources. To my knowledge, no attempts have been made to estimate PS using claims-based measures. The current study explored the ability to estimate PS using routinely available measures.

A cohort of insured patients aged ≥ 50 years who were diagnosed with American Joint Committee on Cancer stage II through IV lung cancer between 2000 and 2007 was identified via a tumor registry (n = 552). PS was abstracted from medical records. Automated medical and pharmaceutical claims from the year preceding diagnosis were linked to tumor registry data. A logistic regression model was fit to estimate good versus poor PS in a random half of the sample. C statistics, sensitivity, specificity, and R^2 were used to compare the predictive ability of models that included demographic factors, comorbidity measures, and claims-based utilization variables. Model fit was evaluated in the other half of the sample.

2.1 Introduction

Since 1997, evidence-based guidelines have recommended the use of chemotherapy for medically fit patients with lung cancer to improve survival, symptoms, and quality of life (1997;2010c;D. G. Pfister *et al.* 2004;2010b). Despite these recommendations, numerous studies (T. J. Smith *et al.* 1995;P. B. Bach *et al.* 1999;C. C. Earle *et al.* 2000;A. L. Potosky *et al.* 2004) have illustrated variability in the receipt of chemotherapy among patients with lung cancer. Nevertheless, the ability to determine the appropriateness of observed treatment variability has been greatly hindered by voids in the clinical information necessary to judge appropriateness.

One key factor in evaluating the appropriateness of chemotherapy is the patient's performance status (PS) (1997;2010b;2010c;D. G. Pfister *et al.* 2004). PS is a subjective composite measure used by clinicians to assess current functional capacity and the likelihood of adverse events, quality of life, and survival after treatment. Measures of PS are currently not available through automated medical claims, tumor registries, or other observational data commonly used to study cancer treatment and its associated outcomes. Thus, the use of such data to address questions regarding chemotherapy has been relatively limited and when undertaken, the inability to consider PS is a noted limitation (A. L. Potosky *et al.* 2004;B. E. Hillner *et al.* 1998;C. J. Bradley *et al.* 2008). The systematic lack of information regarding PS similarly impedes the ability of researchers to use existing automated, observational data for comparative effectiveness research.

This chapter asks two questions. First, how often are measures of a patient's PS documented in his or her detailed medical record? Second, is it possible to accurately estimate a patient's PS using routinely available tumor registry and claims- based measures on that patient's demographics, comorbidities, and prior healthcare utilization? By using a cohort of lung cancer patients diagnosed between 2000 and 2007, the feasibility of using medical record documentation to obtain PS measures was described overall and by patient characteristics. Medical record-documented PS information was then combined with information routinely available in an automated tumor registry as well as medical and pharmaceutical claims data to evaluate the feasibility of estimating PS among lung cancer patients using information routinely available in observational data sources. To my knowledge, this has not previously been attempted among patients with lung or other cancers.

2.2 Materials and Methods

Study Population and Setting

Study patients were those receiving care from a 900-physician member, multispecialty, salaried medical group practice in southeast Michigan. Data available from the medical group's tumor registry were used to identify all patients aged ≥ 50 years who were diagnosed with lung cancer between January 1, 2000 and December 31, 2007. The medical group, which provides care under both fee-for-service and capitated arrangements, staffs 27 primary care clinics

throughout Detroit and the surrounding metropolitan area. Patients eligible for study inclusion were those continuously enrolled in an affiliated health plan (i.e., health maintenance organization) for the 1-year period preceding their date of lung cancer diagnosis. Patients for whom no stage of disease was available at the time of diagnosis or for whom the stage at diagnosis was 0 to I were excluded because chemotherapy was not indicated for patients with stage 0 or I disease during this time period (W. J. Scott *et al.* 2007). The medical group's Institutional Review Board approved all aspects of the study protocol.

PS Measurement

The 2 most commonly used PS systems are the Eastern Cooperative Oncology Group (ECOG) scale and the Karnofsky performance scale (KPS) (S. P. Blagden *et al.* 2003). Although the 2 scales are not identical, they are generally believed to capture the same conceptual domain and conversions are possible between them (Table 1) (G. Buccheri *et al.* 1996). Two trained chart abstractors reviewed inpatient and outpatient nursing and physician notes available within the patient's electronic medical record from 2 months before diagnosis until the first notation of death, disenrollment, initiation of chemotherapy, or 6 months after diagnosis. If available, abstractors documented specific numeric PS and scale (i.e., ECOG or KPS). Patients were assigned a good PS if they had an ECOG score of 0 or 1 or a KPS score of 80 to 100. A poor PS was assigned to patients with an ECOG score of 2 to 5 or a

KPS score of 0 to 70. This was done to be consistent with standards in practice regarding recommendations for chemotherapy use among lung cancer patients during the study period (1997;2010b;2010c;D. G. Pfister *et al.* 2004), as well as with existing research applications (R. C. Lilenbaum *et al.* 2008), With the issuance of the 2009 American Society of Clinical Oncology (ASCO) guidelines, the standard for chemotherapy use changed to include the consideration of use in those patients with an ECOG score of 2 or a KPS score of 60 to 70. Thus, we also presented alternative results for which those patients with these scores were realigned to a good PS.

If no numeric score was documented, abstractors collected medical record documentation of good or poor PS. If no reference to PS was documented in the medical record, notes regarding the patient's functionality (e.g., references to shortness of breath, use of a wheelchair or other personal mobility devices, labor force participation, exercising habits, activities of daily living, or other references to mobility) were recorded and used to estimate PS. Inter-rater reliability between the 2 abstractors was assessed on a random subset of 40 observations. The resulting Cohen κ was 0.88. Among the inter-rater reliability subset (N = 40), in each incident in which the abstracted PS did not match between the 2 abstractors (3 cases), 1 abstractor indicated good or poor whereas the other selected unknown PS. For the final analytical database, these differences were reconciled by choosing good/poor over unknown.

Automated Tumor Registry and Claims Data

Automated tumor registry and claims data were used to obtain patient demographic characteristics, cancer stage, and diagnoses for each patient. Demographic measures included age, gender, and race. The age of the patient (in years) was recorded as of the date of lung cancer diagnosis. Clinical variables examined included stage of disease at the time of diagnosis and the Charlson comorbidity index (M. E. Charlson *et al.* 1987). Cancer stage was reported using the American Joint Committee on Cancer (AJCC) stages II through IV. A dichotomous variable was created to control for AJCC stage IV patients in the regression analysis. The Deyo adaptation of the Charlson comorbidity index and each of its component diagnostic subgroups were constructed using inpatient and outpatient diagnostic information available in the 12-month period preceding diagnosis (R. A. Deyo *et al.* 1992). In addition, claims data provided information regarding prescription drugs dispensed and medical care use within the 12-month period preceding lung cancer diagnosis.

Medical care use measures included those reflective of inpatient stays in a short-stay hospital or skilled nursing facility (SNF); ambulatory care visits; emergency department visits; and use of home health services, same-day surgery, and durable medical equipment (DME). For each person, inpatient use measures included the total number of distinct inpatient stays, the total number of inpatient days, and the average length of an inpatient stay for those with a non-0 number of stays. The number of outpatient visits was recorded, and in the regression analysis a dichotomous variable was created to control for patients

with non-0 outpatient visits. Similar dichotomous variables were constructed to reflect any drug dispensing and any DME use. The emergency department, home health, and same-day surgery use variables measured the counts of visits incurred. We also evaluated the use of a count of the distinct number of medications dispensed during the baseline year, as recommended by Schneeweiss et al (S. Schneeweiss *et al.* 2001). For this measure, medications whose first 8 digits of the American Hospital Formulary Services code were equal were considered to be the same drug (2010a).

Statistical Analysis

Among the cohort of lung cancer patients, we reported the frequency of documented PS in medical records and described the different ways PS was recorded. Systematic differences between patients for whom PS was recorded and patients for whom it was not recorded were examined using 2-sample Student t tests (or Wilcoxon rank sum tests) and chi-square tests, depending on the nature of the characteristic. Similar analyses were conducted to compare unadjusted differences in patient characteristics by good PS versus poor PS. Multivariable logistical regression models were fit to evaluate the feasibility of using routinely available observational data to predict good versus poor PS. Three separate models were estimated, reflective of 3 different levels of the comprehensiveness of observational data routinely available. The first regression model included only those variables typically available via tumor registries (demographics and stage of disease). The second model included those same

variables plus measures of medical care use and diagnoses available in medical claims data. The third model added measures of prescription drug use routinely available via pharmaceutical claims.

For each model, a split-sample cross validation was used to check for model overfitting. C statistics, sensitivity, specificity, and R^2 were used to assess and compare the predictive ability of the different models. Initially, all variables were considered for inclusion. However, the final model in each of the 3 categories was fit using the stepwise elimination method. Pairwise interactions were tested but were not found to enhance model prediction. Likewise, we evaluated the need to account for the non-independence of patients seen by the same physician, but because the intra-class correlation coefficient (ICC) was negligible (ICC = 0.01), we elected not to do so because not doing so enabled us access to additional assessment of model fit. The final models were estimated on the full sample and bootstrapping was used to replicate each final model 1000 times to create 95% confidence intervals around the c and R^2 statistics (B. Efron, G. Gong 83 A.D.).

To examine model discrimination, patients were ranked by their predicted probability of good PS based on each model. Patients were then divided into deciles based on increasing predicted probability of good PS and actual good PS rates were reported among patients in all deciles to suggest how well models separated patients with good PS from those with poor PS (S. Lemeshow, D. W. Hosmer, Jr. 1982). SAS statistical software (version 9.1.3; SAS Institute Inc,

Cary, NC) was used for all analyses. $P < .05$ was considered to be statistically significant.

Table 1. The Eastern Cooperative Oncology Group (ECOG) Performance Status Score (PS) and its Karnofsky PS Equivalent

ECOG Grade	Description	Karnofsky
0	Fully active, able to carry on all pre-disease performance without restriction	100
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)	80-90
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours	60-70
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours	40-50
4	Completely disabled. Cannot carry on any self care; confined to bed or chair	20-30
5	Dead	0-10

2.3 Results

Cohort Characteristics

A total of 552 patients met the criteria for study eligibility. The mean age of the patients at diagnosis was 67.4 years (standard deviation [SD], 9.1 years). Of the patients eligible for the study, 42% were female, whereas the racial distribution was 69% white and 31% black. The AJCC staging distribution was as follows: 9% of patients were diagnosed with stage II disease, 20% with stage IIIA disease, 19% with stage IIIB disease, and 52% with stage IV disease. The average Charlson comorbidity index across the eligible sample was 2.8 (SD, 3.4), whereas the average number of distinct prescription drugs used in the year before diagnosis was 9.3 (SD, 7.1).

The average number of inpatient days in the year before diagnosis for the cohort (including those with no inpatient stays) was 2.9 days (SD, 7.5 days), whereas the average number of inpatient stays was 0.5 (SD, 0.8), resulting in an average inpatient length of stay of 5.0 days (SD, 5.2 days). The average number of outpatient visits was 5.7 (SD, 8.5) and the average number of emergency department visits was 0.6 (SD, 1.1) for the same time period. Across the study-eligible sample, 28% recorded any home health use, 3% had same-day surgery, 12% incurred a DME dispensing, and 4% incurred a stay in a rehabilitation facility or SNF. None incurred a hospice stay in the period before the lung cancer diagnosis.

Medical Record Documentation of PS

Of the 552 study eligible patients, PS was recorded in the medical record for 261 cases (47%). Among these, a numeric score was documented in 248 cases (95%), with the ECOG scale most often used (74%). For the remaining 13 patients, although a numeric score was not documented, explicit documentation was found of either good or poor PS.

Among the 291 (53%) patients for whom PS was not recorded, there were 181 for whom there was a sufficient verbal description of the patient's functioning in either the physician's notes, nurse's notes, or a combination of both to enable a determination of either a good or poor PS score. Thus, overall there were 442 patients (80%) for whom PS was determinable in their medical record.

Differences in patient characteristics by PS documentation level are reported in Table 2. The first 2 columns compare those patients for whom medical record documentation could be used to determine PS (known PS) with those for whom medical record documentation was insufficient to determine PS (unknown PS). As shown, patients with unknown PS (n = 110) did not differ significantly from those with a known PS (n = 442) with regard to demographic or clinical characteristics or measures of medical care use.

Among patients with a known PS, the third and fourth columns of Table 2 compare patient characteristics between those who had a documented PS (either numeric or verbal) with those for whom a PS was extrapolated based on notes in the medical record. No significant differences were observed for most measures. However, there were significant differences by gender, diagnosis of

atherosclerotic cardiovascular disease, and the average number of inpatient days.

Patient Factors Associated With PS

Among the 442 patients for whom PS was known, 290 patients (66%) had a good PS using the pre-2009 definition of good and 152 (34%) had a poor PS. This changed to 76% with a good PS and 24% with a poor PS when those with a documented numeric PS of 2 were considered to have good PS, as would be consistent with that in the 2009 ASCO guidelines for the use of chemotherapy. The unadjusted differences in patient characteristics by PS are illustrated in Table 3. Compared with patients with good PS, patients with poor PS were significantly older (69.7 years vs. 66.4 years) and more likely to be male (66% vs. 54%), have stage IV disease (64% vs. 44%), and have a significantly higher Charlson comorbidity index (3.6 vs. 2.4). Consistent with the latter finding, patients with poor PS were significantly more likely to have been diagnosed with several of the individual components of the Charlson comorbidity index when compared with those with good PS. Patients with poor PS also incurred significantly more inpatient days (5.5 days vs. 1.7 days) as well as longer lengths of stay (6.8 days vs. 5.4 days) in the year before diagnosis, and were more likely to have incurred any outpatient visit, home health use, or DME use in the year before diagnosis. Also of note is that patients with poor PS were significantly less likely to have undergone chemotherapy in the year after diagnosis (42% vs. 82%) (data not shown). Similar differences between the groups were found when those

with a PS of 2 were realigned with the good PS group, with 2 exceptions: statistically significant differences in gender and the prevalence of peripheral vascular disease no longer existed.

Predicting Performance Status

Results from the logistical regression models predicting good versus poor PS defined the 2 ways are presented in Table 4. Results are presented for models fit on the full sample and include only significant ($P < .05$) variables per the stepwise regression. In the model that included only tumor registry variables, only age at diagnosis and AJCC stage were selected (Model 1). Diagnosis of chronic pulmonary disease, the number of inpatient stays, any outpatient visits, and the number of emergency department admissions were all added when information from medical claims data were considered (Model 2). One more variable, the number of distinct prescription drugs, was added when information from pharmaceutical claims data was considered (Model 3).

Statistical performance improved with the inclusion of additional explanatory variables (Table 4). Cross-validated C and R^2 values were never more than 0.01 smaller than fitted values. By using a predictive threshold of 0.50, a high sensitivity (0.88 or 0.94, depending on how good PS was defined) was obtained with the best model (Model 3), but with moderate specificity (0.45 or 0.32). Increasing the predictive threshold to 0.70 continued to yield relatively high sensitivity (0.64 or 0.83) and more moderate specificity (0.69 or 0.55), regardless of how good PS is defined.

Table 5 shows the actual and predicted good PS rates for patients within each of the 10 deciles. As measured by the Hosmer-Lemeshow chi-square statistic (S. Lemeshow, D. W. Hosmer, Jr. 1982), all models had good calibration, in which actual and predicted rates within each of the 10 deciles were not significantly different (P = .69, P = .32, and P = .13 for Models 1-3, respectively) when a PS of 2 was defined as poor and likewise not significantly different (P = .92, P = .63, and P = .98 for Models 1-3, respectively) when a PS of 2 was defined as good. Model discrimination was also improved with the inclusion of more explanatory variables.

Table 2. Sample Characteristics, and Prescription Drug and Medical Care Utilization in the Year Prior to Diagnosis of Lung Cancer, by Performance Status (PS) documentation level, (n = 552)

Characteristic	Unknown PS (n =110)	Known PS (n = 442)	Documented PS (n = 261)	Extrapolated PS (n = 181)
Demographic Characteristics				
Average diagnosis age (SD)	66.9 (9.9)	67.5 (8.8)	68.0 (8.6)	66.9 (9.2)
Gender (%)				
Female	45	42	38*	48*
Male	55	58	62	52
Race (%)				
Asian	0	1	1	0
Black	31	30	28	34
White	69	69	71	66
Clinical Characteristics				
AJCC stage (%)				
II	4	11	10	11
IIIA	17	20	19	22
IIIB	24	18	17	20
IV	54	51	54	47
Average Charlson score (SD)	2.7 (3.6)	2.8 (3.3)	2.9 (3.5)	2.7 (3.1)
Atherosclerotic cardiovascular disease (%)	15.4	21.3	24.5*	16.6*
Congestive heart failure (%)	16.4	17.4	18.4	16.0
Ischemic heart disease (%)	8.2	9.3	10.3	7.7
Peripheral vascular disease (%)	11.8	13.4	14.2	12.2
Dementia (%)	0.9	1.1	1.5	0.6
Pelvic ulcer disease (%)	2.7	3.6	3.8	3.3
Rheumatologic disease (%)	5.4	6.3	6.1	6.6
Chronic pulmonary disease (%)	32.7	41.4	41.4	41.4
Liver disease (%)	2.7	1.4	0.8	2.2
Diabetes (%)	19.1	28.3	29.9	26.0
Diabetes with complications (%)	4.6	4.5	4.2	5.0
Paralysis (%)	1.8	0.9	1.1	0.6
AIDS (%)	1.8	1.1	1.1	1.1
Cancer (%)	24.6	29.9	28.0	32.6
Cancer with metastasis (%)	5.4	7.5	8.0	6.6
Renal disease (%)	6.4	5.7	6.1	5.0
Aneurysm (%)	6.4	6.3	7.3	5.0
Gangrene (%)	0.9	0.7	0.8	0.6
Prescription Drug Utilization				
Average no. of dispensings (SD)	8.7 (7.0)	9.4 (7.1)	9.5 (7.1)	9.3 (7.2)
Pct with ≥ 1 dispensing	85	89	91	86
Medical Care Utilization				
Average no. IP days (SD)	2.7 (6.8)	3.0 (7.7)	2.4 (5.1)*	3.9(10.4)*
Average no. IP stays (SD)	0.4 (0.7)	0.5 (0.8)	0.4 (0.7)*	0.6 (0.8)*
Average length of IP stays (SD)	5.8 (5.2)	6.1 (5.2)	6.0 (5.3)	6.1 (5.0)
Average no. of OP visits (SD)	5.9 (8.3)	5.6 (8.6)	5.7 (9.1)	5.5 (7.8)
Pct with ≥ 1 OP visit	75	76	77	76
Average ≥ 1 ED visit (SD)	0.7 (1.0)	0.6 (1.1)	0.7 (1.2)	0.5 (1.0)
Pct with ≥ 1 home health claim	25.4	29.0	31.4	25.4
Pct with ≥ 1 ambulatory surgery claim	2.7	3.2	3.4	2.8
Pct with ≥ 1 rehabilitation/SNF claim	4.6	3.8	5.0	2.2
Pct with ≥ 1 DME claim[3]	10.9	12.0	13.4	9.9

[1] Among all patients (including those with no inpatient stays).
[2] No. of inpatient days divided by no. of inpatient stays – among patients with at least one inpatient stay.
[3] DME included claims for portable oxygen, walkers, canes, wheelchairs, and hospital beds.
[*] Significant difference at 5% level.
Abbreviations: standard deviation (SD); percent (Pct); number (no.); American Joint Committee on Cancer (AJCC); inpatient (IP); outpatient (OP); emergency department (ED); skilled nursing facility (SNF); durable medical equipment (DME).

Table 3. Among Patients with Known Performance Status (PS), Sample Characteristics, and Prescription Drug and Medical Care Utilization in the Year Prior to Diagnosis of Lung Cancer, by PS (n=442)

Characteristic	Pre 2009[1]		Post 2009[2]	
	Good PS (n = 290)	Poor PS (n = 152)	Good PS (n = 336)	Poor PS (n = 106)
Demographic Characteristics				
Average diagnosis age (SD)	66.4 (9.1)*	69.7 (7.9)*	66.8 (8.9)*	70.0 (8.1)*
Gender (%)				
Female	46*	34*	43	38
Male	54	66	57	62
Race (%)				
Asian	1	1	1	0
Black	28	34	28	38
White	71	65	71	62
Clinical Characteristics				
AJCC Stage (%)				
II	13	7	11	9
IIIA	24	13	23	11
IIIB	19	16	19	17
IV	44*	64*	47*	63*
Average Charlson score (SD)	2.4 (3.0)*	3.6 (3.8)*	2.5 (3.1)*	3.9 (3.9)*
Atherosclerotic cardiovascular disease (%)	19.3	25.0	19.9	25.5
Congestive heart failure (%)	12.1*	27.6*	14.3*	27.4*
Ischemic heart disease (%)	6.6*	14.5*	7.7*	14.2*
Peripheral vascular disease (%)	10.3*	19.1*	12.2	17.0
Dementia (%)	0.0*	3.3*	0.0*	4.7*
Pelvic ulcer disease (%)	2.1*	6.6*	2.4*	7.6*
Rheumatologic disease (%)	5.9	7.2	6.3	6.6
Chronic pulmonary disease (%)	34.5*	54.6*	35.4*	60.4*
Liver disease (%)	1.0	2.0	1.0	3.0
Cancer (%)	28.3	32.9	27.7	36.8
Cancer with metastasis (%)	6.6	9.2	6.8	9.4
Diabetes (%)	26.2	32.2	28.0	29.2
Diabetes with complications (%)	3.8	5.9	3.9	6.6
Paralysis (%)	0.3	2.0	0.3	2.8
AIDS (%)	1.0	1.3	0.9	1.9
Renal disease (%)	3.8*	9.2*	3.9*	11.3*
Aneurysm (%)	5.2	8.6	6.2	6.6
Gangrene (%)	0.3	1.3	0.3	1.9
Prescription Drug Utilization				
Average no. of dispensings (SD)	9.0 (7.1)	10.3 (7.2)	9.1 (7.1)	10.5 (7.3)
Pct with ≥ 1 dispensing	87	93	88	92
Medical Care Utilization				
Average no. IP days (SD)[3]	1.7 (3.9)*	5.5 (11.7)*	1.8 (4.1)*	6.8 (13.3)*
Average no. IP stays (SD)	0.3 (0.6)	0.8 (1.0)	0.3 (0.6)	0.9 (1.1)
Average length of IP stays (SD)[4]	5.4 (4.8)	6.8 (5.5)	5.7 (5.1)	6.7 (5.2)
Average no. of OP visits (SD)	6.0 (8.5)	4.9 (8.7)	6.0 (8.6)	4.5 (8.6)

Pct with ≥ 1 OP visit	82*	66*	81*	63*
Average ≥ 1 ED visit (SD)	0.5 (0.9)*	0.8 (1.3)*	0.5 (1.0)*	0.9 (1.3)*
Pct with ≥ 1 home health claim	23.1*	40.1*	24.7*	42.4*
Pct with ≥ 1 ambulatory surgery claim	3.8	2.0	3.6	1.9
Pct with ≥ 1 rehabilitation/SNF claim	3.1	5.3	3.3	5.7
Pct with ≥ 1 DME claim[5]	6.9*	21.7*	8.0*	24.5*

[1] Pre 2009: Good PS = ECOG: 0 – 1; KPS: 80 – 100; Poor PS = ECOG: 2 – 5; KPS: 0 – 70.
[2] Post 2009: Good PS = ECOG: 0 – 2; KPS: 60 – 100; Poor PS = ECOG: 3 – 5; KPS: 0 – 50.
[3] Among all patients (including those with no inpatient stays).
[4] No. of inpatient days divided by no. of inpatient stays – among patients with at least one inpatient stay.
[5] DME included claims for portable oxygen, walkers, canes, wheelchairs, and hospital beds.
* Significant difference at 5% level.
Abbreviations: standard deviation (SD); percent (Pct); number (no.); American Joint Committee on Cancer (AJCC); inpatient (IP); outpatient (OP); emergency department (ED); skilled nursing facility (SNF); durable medical equipment (DME).

Table 4. Estimated Logistic Regression Parameters (β) and Standard Errors (SE) and Measures of Model Performance for Alternative Models of Performance Status Predictors

PS (Pre 2009): Good/Poor[1]	Model 1		Model 2		Model 3	
Variable	**β**	**SE**	**β**	**SE**	**β**	**SE**
Intercept	3.97	0.85***	3.65	0.94***	4.55	1.03***
Age in years at diagnosis	-0.04	0.01**	-0.04	0.01**	-0.04	0.01**
AJCC Stage IV	-0.84	0.21***	-0.81	0.23**	-0.84	0.23**
Chronic pulmonary disease			-0.67	0.24**	-0.63	0.24**
Number of Inpatient Stays			-0.58	0.16**	-0.60	0.16**
Any number of outpatient visits			1.05	0.26***	1.19	0.27***
Number of ED visits			-0.22	0.10*	-0.22	0.10*
Any number of DME claim			-0.80	0.35*	-0.81	0.36*
Any prescription drug dispensing					-1.08	0.43*
Model Performance						
C statistic (95% CI)	0.66 (0.61, 0.71)		0.75 (0.71, 0.81)		0.76 (0.72, 0.81)	
R^2 (95% CI)	0.07 (0.03, 0.11)		0.19 (0.13, 0.26)		0.20 (0.15, 0.28)	
Predictive Threshold = 0.50						
Sensitivity (95% CI)	0.88 (0.78, 1.00)		0.90 (0.84, 0.94)		0.88 (0.84, 0.93)	
Specificity (95% CI)	0.20 (0.00, 0.40)		0.43 (0.31, 0.55)		0.45 (0.34, 0.56)	
False positive (95% CI)	0.32 (0.28, 0.37)		0.25 (0.21, 0.29)		0.25 (0.20, 0.29)	
False negative (95% CI)	0.54 (0.29, 0.87)		0.31 (0.24, 0.40)		0.34 (0.25, 0.40)	
Predictive Threshold = 0.60						
Sensitivity (95% CI)	0.72 (0.61, 0.83)		0.79 (0.72, 0.87)		0.79 (0.72, 0.87)	
Specificity (95% CI)	0.43 (0.27, 0.65)		0.53 (0.45, 0.66)		0.55 (0.47, 0.67)	
False positive (95% CI)	0.29 (0.23, 0.33)		0.24 (0.18, 0.27)		0.23 (0.18, 0.26)	
False negative (95% CI)	0.55 (0.46, 0.62)		0.43 (0.34, 0.49)		0.42 (0.34, 0.48)	
Predictive Threshold = 0.70						
Sensitivity (95% CI)	0.49 (0.33, 0.65)		0.61 (0.52, 0.74)		0.64 (0.53, 0.75)	
Specificity (95% CI)	0.75 (0.60, 0.88)		0.69 (0.60, 0.79)		0.69 (0.61, 0.79)	
False positive (95% CI)	0.21 (0.16, 0.26)		0.21 (0.16, 0.25)		0.20 (0.15, 0.25)	
False negative (95% CI)	0.56 (0.51, 0.62)		0.52 (0.44, 0.57)		0.50 (0.43, 0.56)	

PS (Post 2009): Good/Poor[2]	Model 1		Model 2		Model 3	
Variable	**β**	**SE**	**β**	**SE**	**β**	**SE**
Intercept	4.39	0.94***	4.25	1.08***	5.08	1.18***
Age in years at diagnosis	-0.04	0.01***	-0.04	0.02**	-0.04	0.02**
AJCC Stage IV	-0.64	0.23***	-0.55	0.26**	-0.57	0.26**
Chronic pulmonary disease			-0.88	0.27***	-0.83	0.27***
Number of Inpatient Stays			-0.80	0.17***	-0.81	0.17***
Any number of outpatient visits			1.08	0.29***	1.20	0.30***
Number of ED visits			-0.25	0.11**	-0.25	0.11**
Any number of DME claim			-0.60	0.36*	-0.61	0.36*
Any prescription drug dispensing					-0.98	0.50*
Model Performance						
C statistic (95% CI)	0.64 (0.58, 0.70)		0.78 (0.74, 0.84)		0.78 (0.74, 0.85)	
R^2 (95% CI)	0.04 (0.01, 0.08)		0.19 (0.13, 0.28)		0.20 (0.14, 0.28)	
Predictive Threshold = 0.50						
Sensitivity (95% CI)	1.00 (0.98, 1.00)		0.94 (0.91, 0.97)		0.94 (0.91, 0.97)	
Specificity (95% CI)	0.00 (0.00, 0.01)		0.28 (0.19, 0.47)		0.32 (0.21, 0.50)	
False positive (95% CI)	0.24 (0.20, 0.28)		0.19 (0.15, 0.22)		0.19 (0.14, 0.22)	
False negative (95% CI)	1.00 (0.98, 1.00)		0.40 (0.23, 0.48)		0.38 (0.21, 0.46)	
Predictive Threshold = 0.60						
Sensitivity (95% CI)	0.96 (0.87, 1.00)		0.90 (0.86, 0.94)		0.90 (0.86, 0.94)	
Specificity (95% CI)	0.06 (0.00, 0.27)		0.42 (0.29, 0.59)		0.45 (0.32, 0.60)	
False positive (95% CI)	0.24 (0.20, 0.27)		0.17 (0.13, 0.20)		0.16 (0.12, 0.20)	
False negative (95% CI)	0.71 (0.37, 1.00)		0.42 (0.32, 0.52)		0.42 (0.32, 0.51)	
Predictive Threshold = 0.70						
Sensitivity (95% CI)	0.76 (0.62, 0.91)		0.83 (0.78, 0.99)		0.83 (0.76, 0.88)	
Specificity (95% CI)	0.37 (0.13, 0.63)		0.56 (0.22, 0.72)		0.55 (0.46, 0.70)	
False positive (95% CI)	0.21 (0.16, 0.24)		0.14 (0.11, 0.21)		0.15 (0.10, 0.17)	
False negative (95% CI)	0.67 (0.55, 0.78)		0.49 (0.28, 0.58)		0.50 (0.41, 0.57)	

Model 1: Significant (P<0.05) performance status predictors from tumor registries (age at diagnosis and AJCC stage). Model 2: Significant performance status predictors from medical claims (age at diagnosis, diagnosis of COPD, inpatient stays, any outpatient visits, and emergency department visit). Model 3: Significant performance status predictors from tumor registries, medical claims, and pharmacy claims (age at diagnosis, AJCC stage, diagnosis of COPD, inpatient stays, any outpatient visits, emergency department visit, and any prescriptions).
*P<0.05; **P<0.01; ***P<0.0001.
Abbreviations: American Joint Committee on Cancer (AJCC); emergency department (ED); durable medical equipment (DME); chronic pulmonary disease (COPD).

Table 5. Number of Patients with Observed (Predicted) Good Performance Status (PS) by Model and Model Determined Decile

Rank Deciles	Number with Observed (Predicted) Good PS (Pre 2009)		
	Model 1	**Model 2**	**Model 3**
1	23 (21)	10 (9)	8 (8)
2	23 (22)	13 (18)	14 (18)
3	25 (24)	29 (24)	28 (23)
4	26 (27)	29 (27)	27 (27)
5	23 (27)	31 (30)	32 (30)
6	28 (31)	33 (32)	37 (33)
7	26 (29)	34 (34)	31 (36)
8	37 (34)	33 (36)	34 (37)
9	39 (37)	37 (40)	38 (39)
10	40 (38)	41 (40)	41 (39)
P value	0.69	0.32	0.13

Rank Deciles	Number with Observed (Predicted) Good PS (Post 2009)		
	Model 1	**Model 2**	**Model 3**
1	28 (28)	12 (12)	10 (12)
2	29 (30)	22 (24)	24 (24)
3	34 (33)	32 (30)	32 (30)
4	37 (36)	33 (33)	34 (33)
5	32 (34)	38 (36)	36 (36)
6	34 (35)	40 (38)	37 (37)
7	39 (37)	35 (38)	39 (39)
8	42 (42)	42 (40)	39 (40)
9	36 (37)	41 (42)	41 (42)
10	25 (23)	41 (41)	44 (43)
P value	0.92	0.63	0.98

[1] Deciles were created by ranking patients according to increasing predicted likelihood of good performance status on the basis of the explanatory variables in each of the three models.
[2] Pre 2009: Good PS = ECOG: 0 – 1 or KPS: 80 – 100 / Poor PS = ECOG: 2 – 5 or KPS: 0 – 70.
[3] Post 2009: Good PS = ECOG: 0 – 2 or KPS: 60 – 100 / Poor PS = ECOG: 3 – 5 or KPS: 0 – 50.

2.4 Discussion

Among a contemporary cohort of patients with stage II through IV lung cancer, explicit medical record documentation of PS was found less than half the time (47%). Review of nursing and physician notes led PS to be determinable via medical records approximately 80% of the time. Given the central role that PS plays in clinical decision-making among patients with lung cancer, the lack of consistent medical record documentation is troubling. When documented, we found the distribution of PS among the cohort (34% with poor PS [when a PS of 2 was considered as having poor PS]) to be identical to the 34% with poor PS reported by Lilenbaum et al in contemporary clinical studies (R. C. Lilenbaum *et al.* 2008).

It was found that poor PS among lung cancer patients with stage III to IV disease can be predicted reasonably well regardless of whether a PS of 2 is considered good or poor. Furthermore, this was true regardless of the level of comprehensiveness of the data used, but particularly for models that used information routinely available in medical claims data or medical and pharmaceutical claims data combined, in which the c statistics were all >0.70. Although the inclusion of information routinely available in medical claims data marginally improved model fit and predictive accuracy when compared with a model fit using only data available in tumor registries, the inclusion of information from pharmaceutical claims data did not appear to substantively alter model fit, regardless of how good PS is defined.

To my knowledge, this is the first study to use observational data to estimate PS for lung, or any other, cancer patients. As such, these findings represent a significant contribution to the field. These findings are important for the ability to monitor quality of care and the appropriateness of chemotherapy, and the ability to prospectively identify patients who may be appropriate (but not targeted) for clinical trial or palliative care/hospice enrollment without relying on expensive and time-consuming primary data collection methods. Predictive models such as those presented herein that rely on data routinely available within large, observational databases can also be used to augment comparative effectiveness research, including comparisons of different chemotherapy regimens as well as the receipt of chemotherapy versus non-chemotherapy treatment and thereby greatly enhance the capabilities of existing electronic databases such as that available via Surveillance, Epidemiology, and End Results (SEER)-Medicare data.

Although these findings of significant differences in chemotherapy receipt by good versus poor PS add face validity to the accuracy of the PS score abstracted from the medical record, the finding that approximately 42% of patients with medical record-documented poor PS received chemotherapy in the year after diagnosis highlights the importance of attempts such as ours to make documented PS or PS proxies more readily available to those who monitor and study cancer care quality and outcomes. At the time of this study, national clinical practice guidelines for patients with non-small cell lung cancer unequivocally recommended chemotherapy for patients with a PS of 0 or 1 (1997;D. G. Pfister

et al. 2004). These guidelines suggested that chemotherapy might ‘‘possibly’’ be of benefit in patients with a PS of 2, noting that those patients had been excluded from clinical trials. This was in keeping with expert opinions of the time (E. Rodriguez, R. C. Lilenbaum 2008). More recent data have shown survival and quality of life benefits for patients with a PS of 2, although less than with good PS, and the most recent ASCO guidelines are more supportive of chemotherapy for patients with a PS of 2 (C. G. Azzoli *et al.* 2009). Routine chemotherapy among lung cancer patients with a PS ≥ 3 continues to not be recommended by any national professional organization. Chemotherapy use in patients with little chance of benefit and more chance of toxicity may delay discussion about prognosis and dying (A. A. Wright *et al.* 2008), which may lead to further poor quality of care, such as the inappropriate use of mechanical ventilation or delays in referral to hospice, worse surviving caregiver quality of life, and high end-of-life care costs (B. Zhang *et al.* 2009). Without PS proxies, little can be done to use automated data sources to monitor and measure either the underuse or overuse of chemotherapy and its implications on patient and economic outcomes.

The results of the current study should be interpreted in light of the following limitations. First, subjectivity is present in the assignment of PS. Even when assessed by a healthcare professional, PS scales are subjective in nature (K. Kelly 2004) and when estimated by physicians are known to be prone to error (C. Zimmermann *et al.* 2010), usually being overestimated (R. C. Lilenbaum *et al.* 2008). Thus, even if this model were 100% accurate, caution would have to be used in interpreting results dependent on an accurate classification of PS.

Nonetheless, the ability to develop a useful proxy measure of PS from existing observational data will help in the use of existing national data resources such as that available with SEER Medicare data for comparative effectiveness research. Second, these models were developed on a relatively small sample and one that is specific to 1 delivery system. Therefore, not only should care be taken when generalizing findings, but the parsimonious models may exclude important predictors of PS available in observational data. Finally, identifying patients with poor PS by their diagnoses and use of care via claims data poses its own limitations. For example, DME use varies significantly based on differing personal preferences and practices in addition to restrictions on reimbursement by public and private insurers. Although claims for DME offer useful information, they identify only selected people with potentially disabling conditions (L. I. Iezzoni 2003). The same is true of medical diagnoses, many of which are known to be under captured in medical claims data, and prescription drug dispensing, which reflects only those medications prescribed by physicians that the patient elected to fill. Nevertheless, the ability to proxy PS is critical to the ability to use observational data to accurately draw conclusions regarding comparative effectiveness and cancer care quality at a population level if not at the bedside.

Despite these limitations, results from the current study shed new light on the capacity of information routinely available in observational data to identify lung cancer patients with good versus poor PS. This is especially useful for researchers interested in leveraging existing observational databases for comparative effectiveness research. Recent studies have highlighted a likely

overuse of chemotherapy in the treatment of patients with lung cancer as well as aggressive treatment near the end of life (C. C. Earle *et al.* 2004;R. Matsuyama *et al.* 2006;S. E. Harrington, T. J. Smith 2008). Using a predictive model such as the one developed herein with a threshold of 0.70 to proxy a patient as having poor PS would ensure reasonably high specificity (0.69 if a PS of 2 is considered poor) and thereby enable the identification of a population for whom the receipt of chemotherapy appears inadvisable or requiring a more tailored discussion of less benefit and more risk per current guideline recommendations, and for whom early hospice intervention may be warranted. Conversely, using a lower predictive threshold (0.50) and thereby increasing the sensitivity of the predictive model may be useful to health disparities researchers, in whom interest might be in testing a hypothesis centered on under treatment among minority populations. Similarly, choosing a predictive threshold with a high sensitivity could facilitate population identification for observational comparative effectiveness research. The best selection of both a predictive threshold and the allocation of patients with a PS of 2 will ultimately depend on the user's objectives.

PS has long been considered one of the strongest prognostic factors (K. S. Albain *et al.* 1991) and is used today by clinicians to assess the appropriateness of chemotherapy and regimen choice for patients with lung cancer (C. G. Azzoli *et al.* 2009). With the aging population, the number of Americans with functional limitations will increase dramatically, and therefore the urgency to capture and classify information regarding functional status will grow (L. I. Iezzoni, M. S. Greenberg 2003). Furthermore, given the current challenges

faced by the US healthcare system to deliver better and more cost-effective outcomes, the importance of comparative effectiveness studies is likely to only grow. To the best of my knowledge, the results of the current study are the first to provide health services researchers and others with a viable tool with which to predict PS among lung cancer patients using information routinely available in observational data. As such, the value of observational data for comparative effectiveness research and for use by those interested in understanding cancer care quality or targeting specific lung cancer patients for possible inclusion in clinical trials, hospice care, or other interventions is greatly enhanced.

CHAPTER 3. FACTORS ASSOCIATED WITH ADHERENCE TO CHEMOTHERAPY GUIDELINES IN PATIENTS WITH LUNG CANCER

Evidence-based guidelines recommend chemotherapy for medically fit patients with stage II-IV non-small cell lung cancer (NSCLC). Adherence to chemotherapy guidelines has rarely been studied among large populations, mainly because performance status (PS), a key component in assessing chemotherapy appropriateness, is missing from claims-based or other automated datasets. Among a large cohort of patients with known PS, chemotherapy use is described relative to guideline recommendations and patient factors associated with guideline concordant use are identified.

Insured patients, ages 50+, diagnosed with stage II-IV NSCLC between 2000-2007 were identified via tumor registry (n=406). Chart abstracted PS, automated medical claims, Census tract information, and travel distance were linked to tumor registry data. Chemotherapy was appropriate for patients with PS 0-2. Multivariate logit models were fit to evaluate patient characteristics associated with chemotherapy over- and under-use per guideline recommendations.

Overall compliance with chemotherapy guidelines was 71%. Significant ($p<0.05$) predictors of chemotherapy underuse (19%) included increasing age (odds ratio [OR], 1.09), higher income (OR, 1.02), diagnosed before 2003 (OR, 2.05), and vehicle access (OR, 6.96) in the patient's neighborhood. Significant predictors of chemotherapy overuse (10%) included decreasing age (OR, 0.92),

diagnosed after 2003 (OR, 3.24), and higher income (OR, 1.05) in the patient's neighborhood.

Among NSCLC patients 29% do not receive guideline recommended chemotherapy treatment, missing opportunities for cure or receiving chemotherapy with more risk of harm than benefit, thereby likely foregoing beneficial palliation. Care concordant with guidelines is influenced by age, and economic considerations, such as income, and transportation barriers.

3.1 Introduction

Evidence-based treatment guidelines recommend the use of chemotherapy for medically fit patients with unresectable or stage IV non-small cell lung cancer (NSCLC) to improve survival, symptoms, and quality of life (1997;2010b;D. G. Pfister *et al.* 2004;2010c). Despite these recommendations, studies in the past decade have documented variability in the receipt of chemotherapy among patients with NSCLC (T. J. Smith *et al.* 1995;P. B. Bach *et al.* 1999;C. C. Earle *et al.* 2000;A. L. Potosky *et al.* 2004). Understanding the extent to which chemotherapy use in practice is consistent with these guidelines, as well as the factors associated with inappropriate chemotherapy use has rarely been studied among large populations, mainly because performance status (PS), a key clinical component in assessing chemotherapy appropriateness, is typically missing from claims-based databases.

Determining whether care meets professional standards is important in lung cancer care. Adherence to evidence-based guidelines has been used to

assess the quality of health care for a wide range of conditions (M. A. Schuster *et al.* 2005), so it is natural to ask how often lung cancer care agrees with guideline recommended care. Previous studies suggest that chemotherapy is sometimes overused at the end of life, with 20% (C. C. Earle *et al.* 2004) to 43% (J. R. Murillo, Jr., J. Koeller 2006) or more of lung cancer patients receiving chemotherapy within just a few weeks of a patient's death. Yet, lung cancer patients who use hospice for at least one day – thus avoiding chemotherapy during their stay in hospice, and getting appropriate symptom management – have been shown to live significantly longer than lung cancer patients who never use hospice.(S. R. Connor *et al.* 2007) Recent studies show that at 2 months before their death, half of the doctors of lung cancer patients have not even mentioned hospice options (H. A. Huskamp *et al.* 2009), and the average hospice length of stay is only 4 days (J. S. Temel *et al.* 2010). At the same time, an underuse of curative surgery, combined chemotherapy and radiation (P. B. Bach *et al.* 1999;T. J. Smith *et al.* 1995) and palliative chemotherapy may unnecessarily increase the symptom burden and the death rate from this disease.

The issue of guideline adherence has been more comprehensively examined in breast cancer research where a number of studies have demonstrated improvement in survival when patients were treated according to clinical practice guidelines (A. Olivotto *et al.* 1997;N. Hebert-Croteau *et al.* 2004;T. L. Lash *et al.* 2000;T. L. Lash *et al.* 2005). Several breast cancer studies have found that increased age, comorbidity, black race, lower educational

attainment, and advanced disease stage are associated with receipt of nonstandard treatment regimens (usually underuse or use of reduced doses), which in turn contributes to less favorable outcomes (J. J. Griggs *et al.* 2007;N. A. Bickell *et al.* 2006;D. Hershman *et al.* 2005;N. A. Bickell *et al.* 2009;N. Krieger 1992). Furthermore, a conceptual model that explains the underuse of effective therapy in breast cancer has been proposed, where therapy underuse is explained by the interaction of patient, physician, and system factors, each of which exists within a health care system and an individual's community (N. A. Bickell 2002).

The purpose of this research is to quantify the extent of adherence to evidence-based guidelines for use of chemotherapy among an insured population diagnosed with NSCLC between 2000 and 2007 with medical record documented PS, and to evaluate the factors associated with both the under- and over-use of chemotherapy within this cohort. By combining data from patients' medical records with those available via an automated tumor registry, medical claims, and Census data, this study is able to consider the patients' clinical and socio-demographic characteristics, as well as the characteristics of the neighborhood in which they reside and how they are associated with use consistent with guidelines.

Studies of chemotherapy use for NSCLC in the past have neglected PS, a clinically important measure in the assessment of appropriateness of chemotherapy. The present study contributes to the literature by explicitly accounting for a patient's PS. In so doing, it is able to accurately quantify the

extent and nature of deviations from treatment guidelines, and to quantify the patient characteristics associated with both under- and overuse of chemotherapy.

3.2 Methods

Study Population and Setting

Study patients were those receiving care from a 900-physician member, multispecialty, salaried medical group practice in southeast Michigan. Data available from the medical group's tumor registry were used to identify all patients aged ≥ 50 years who were diagnosed with NSCLC between January 1, 2000 and December 31, 2007. The medical group, which provides care under both fee-for-service and capitated arrangements, staffs 27 primary care clinics throughout Detroit and the surrounding metropolitan area. Patients eligible for study inclusion were those continuously enrolled in an affiliated health plan (ie, health maintenance organization) for the 1-year period preceding their date of lung cancer diagnosis. Patients for whom no stage of disease was available or for whom the stage at diagnosis was 0 or I were excluded. The latter were excluded because chemotherapy was not indicated for patients with stage 0 or I disease during this time period (W. J. Scott *et al.* 2007). Patients who died within one month of their diagnosis were also excluded from the study. The medical group's Institutional Review Board approved all aspects of the study protocol.

Primary Outcome of Interest

Per the American Society of Clinical Oncology (ASCO) clinical practice guidelines issued in 2009 (C. G. Azzoli *et al.* 2009), chemotherapy was recommended for patients with good PS (i.e., PS= 0-2) and not recommended for patients with poor PS (i.e., PS=3-4). Earlier ASCO guidelines had recommended

chemotherapy for patients with PS 0-1 only.(1997) In model estimations I include patients with PS=2 in the good PS group. Alternative models that instead include PS 2 patients in the poor PS group were also estimated, and are included in Appendix A. Throughout, instances in which patients with good PS did not receive chemotherapy were classified as “underuse,” while instances in which patients with poor PS received chemotherapy were classified as “overuse.”

Two trained chart abstractors reviewed inpatient and outpatient nursing and physician notes available within the patient’s electronic medical record from 2 months before diagnosis until the first notation of death, disenrollment, initiation of chemotherapy, or 6 months after diagnosis to obtain PS. Abstractors documented specific numeric PS, if available, or an estimated PS based on medical notes. In the latter case, notes regarding the patient’s functionality (e.g., references to shortness of breath, use of a wheelchair or other personal mobility devices, labor force participation, exercising habits, activities of daily living, or other references to mobility) were recorded and used to estimate PS. Inter-rater reliability between the 2 abstractors was assessed on a random subset of 40 observations and the resulting Cohen κ was 0.88.

Automated Tumor Registry and Claims Data

Automated tumor registry and claims data were accessed to obtain patient demographic characteristics, date of cancer diagnosis, stage at diagnosis, and comorbidities in the 12-month period preceding diagnosis for each patient. Patient demographics included age, gender, and race. The age of the patient (in

years) was recorded as of the date of lung cancer diagnosis. Clinical measures for each patient included stage of disease at the time of diagnosis and the Charlson comorbidity index (M. E. Charlson *et al.* 1987). Cancer stage was reported using the American Joint Committee on Cancer (AJCC) stages II through IV. The Deyo adaptation of the Charlson comorbidity index and each of its component diagnostic subgroups were constructed using inpatient and outpatient diagnostic information available in the 12-month period preceding diagnosis (R. A. Deyo *et al.* 1992).

Socioeconomic Data

Socioeconomic information, including education level, median household income, and vehicles per household were obtained from the 2000 US Census. Using patients' residential street address, Census tract level data were used to characterize the socioeconomic profile of each patient's neighborhood of residence. MapPoint (2010; Microsoft Corporation, Redmond, WA) was used to calculate the travel distance between each patient's home and the nearest chemotherapy facility that was affiliated with the group practice.

Statistical Analysis

Patients were assigned into 4 distinct groups: patients with good PS who received chemotherapy; patients with good PS who did not receive chemotherapy; patients with poor PS who received chemotherapy; and patients with poor PS who did not receive chemotherapy. Systematic unadjusted

differences between patients receiving chemotherapy and those who did not receive chemotherapy, within the good PS and poor PS groups (patients in the first two groups and patients in the latter two groups) were examined, using 2-sample Student *t* tests (or Wilcoxon rank sum tests) and chi-square tests, depending on the nature of the characteristic. Two multivariate logistic regression models were fit to evaluate the factors associated with receipt of chemotherapy, given the patient's PS. The first model estimated chemotherapy receipt among patients with good PS (i.e., evaluated factors associated with chemotherapy under use) while the second model estimated chemotherapy receipt among patients with poor PS (i.e. evaluated factors associated with chemotherapy overuse). Both models controlled for patient age at diagnosis, gender, race, and comorbidities as well as the college graduation rate, median household income, and vehicle access in their neighborhood, distance to nearest chemotherapy facility, and year of diagnosis.

SAS statistical software (version 9.1.3; SAS Institute Inc, Cary, NC) was used for all analyses. $P < .05$ was considered to be statistically significant.

3.3 Results

Cohort Characteristics

A total of 406 patients met the criteria for study eligibility. Overall sample characteristics are reported in Table 6. The mean age of the cohort was 67.4 years (standard deviation [SD], 8.9 years). Just under half (41%) were female, whereas the racial distribution was 69% white, 29% black, and 2% of other races.

The AJCC staging distribution was as follows: 11% of patients were diagnosed with stage II disease, 41% were diagnosed with stage IIII disease, and 48% were diagnosed with stage IV disease. The average Charlson comorbidity index across the sample was 1.3 (SD, 1.6).

At the Census tract level, the mean college graduation rate for the cohort was 6.9% (SD, 5.6), the median household income (in 2000) was $49,200 (SD, 21,900), and 12.2% (SD, 19.0) of residents lived in households that had no vehicles. The average travel distance of patients to the nearest chemotherapy facility was 10.8 miles (SD, 11.7).

Across the sample, 13% of patients received no anti-cancer treatment for their lung cancer, 1% received surgery only, 16% received radiation therapy only, 13% received chemotherapy only, 5% received a combination of surgery and chemotherapy but no radiation, 44% received radiation and chemotherapy but no surgery, and 8% received all three modes of treatment.

Table 6. Overall Sample Characteristics, Lung Cancer Patients with Stages II-IV (n = 406)

Demographic Characteristics	
Average age at diagnosis (SD)	67.4 (8.9)
Gender (%)	
Female	41
Male	59
Race (%)	
Black	29
White	69
Other	2
Clinical Characteristics	
AJCC stage (%)	
II	11
III	41
IV	48
Average Charlson comorbidity index (SD)	1.3 (1.6)
Socioeconomic Characteristics	
Pct with college degree (SD)	6.9 (5.6)
Median household income in $1000s (SD)	49.2(21.9)
Access to Treatment	
Pct without vehicle (SD)	12.2(19.0)
Distance (miles) to chemotherapy facility (SD)	10.8(11.7)
Treatment(s) Received	
No treatment (%)	13
Surgery only (%)	1
Radiation therapy only (%)	16
Chemotherapy only (%)	13
Surgery + radiation therapy (%)	0
Surgery + chemotherapy (%)	5
Radiation + chemotherapy (%)	44
Surgery + radiation + chemotherapy (%)	8

Chemotherapy Receipt by Performance Status

Table 7 reports chemotherapy receipt by stage and PS. Overall, 77 patients (19%) with good PS did not receive chemotherapy, while 39 patients (10%) with poor PS received chemotherapy. Among patients diagnosed with stage II disease, 9 (20%) with good PS did not receive chemotherapy and 6 (14%) with poor PS received it. Among those diagnosed with stage III disease, 31 (19%) with good PS did not receive chemotherapy and 9 (5%) with poor PS received it. Among those diagnosed with stage IV disease, 37 (19%) with good PS did not receive chemotherapy and 24 (12%) with poor PS received it.

Table 8 reports the unadjusted differences in cohort characteristics between patients receiving chemotherapy and those not receiving it, across 2 groups: patients with good PS and poor PS. Among patients with good PS, there were significant differences between those receiving chemotherapy and those not receiving it by age at diagnosis, the patient's Charlson comorbidity index, and the vehicle ownership rate in the patient's neighborhood. Among patients with poor PS, there were significant differences between those receiving chemotherapy and those not receiving it by age and median household income in the patient's neighborhood.

Table 7. Chemotherapy Receipt by Performance Status (PS), (N = 406)

		Chemotherapy Received?	
		Yes	No
All Cases, (N = 406)			
ECOG PS	0-1	213(52%)	63 (16%)
	2	30 (7%)	14 (3%)
	3-4	39 (10%)	47 (12%)
Stage II, (N = 44)			
ECOG PS	0-1	25 (57%)	9 (20%)
	2	1 (2%)	0 (0%)
	3-4	6 (14%)	3 (7%)
Stage III, (N = 165)			
ECOG PS	0-1	99 (60%)	25 (15%)
	2	8 (5%)	6 (4%)
	3-4	9 (5%)	18 (11%)
Stage IV, (N = 197)			
ECOG PS	0-1	89 (45%)	29 (15%)
	2	21 (11%)	8 (4%)
	3-4	24 (12%)	26 (13%)

Table 8. Sample Characteristics, by Performance Status (PS) and Choice of Chemotherapy Receipt or Non-Receipt, for Lung Cancer Stages II-IV (n = 406)

	Good PS[1] (n = 320)		Poor PS[2] (n = 86)	
	Chemo (n = 243)	No Chemo (n = 77)	Chemo (n = 39)	No Chemo (n = 47)
Demographic Characteristics				
Average age at diagnosis (SD)	65.5 (8.5)[3]	71.4 (8.9)[3]	66.9 (9.0)[4]	71.1 (7.5)[4]
Gender (%)				
Female	41	47	36	36
Male	59	53	64	64
Race (%)				
Black	26	30	31	36
White	72	66	69	58
Other	2	4	0	6
Clinical Characteristics				
AJCC stage (%)				
II	11	12	15	6
III	44	42	23	39
IV	45	48	62	55
Average Charlson comorbidity index (SD)	1.0 (1.4)[3]	1.4 (1.5)[3]	1.9 (2.0)	2.3 (2.3)
Socioeconomic Characteristics				
Pct with college degree (SD)	7.1 (6.0)	6.1 (4.9)	6.7 (5.9)	6.9(4.4)
Median household income in $1000s (SD)	50.4(22.2)	47.6(19.8)	52.4(27.8)[4]	42.7(16.6)[4]
Access to Treatment				
Pct without vehicle (SD)	10.0(15.1)[3]	15.9(21.8)[3]	12.8(17.7)	16.3(29.3)
Distance (miles) to chemotherapy facility (SD)	11.3(13.6)	10.6 (8.7)	9.5 (8.0)	9.6 (6.4)
Treatment(s) Received				
No treatment (%)	-	42	-	45
Surgery only (%)	-	5	-	2
Radiation therapy only (%)	-	52	-	53
Chemotherapy only (%)	17	-	31	-
Surgery + radiation therapy (%)	-	1	-	-
Surgery + chemotherapy (%)	8	-	-	-
Radiation + chemotherapy (%)	62	-	64	-
Surgery + radiation + chemotherapy (%)	13	-	5	-

[1] Good PS: ECOG 0-2
[2] Poor PS: ECOG>2
[3] Among patients with good PS, significant difference by chemotherapy receipt/non-receipt, at 5% level
[4] Among patients with poor PS, significant difference by chemotherapy receipt/non-receipt, at 5% level

Factors Associated with the Non-Receipt of Chemotherapy among Patients with Good Performance Status

Results from the multivariable logistic regression model for factors associated with the non-receipt of chemotherapy among patients with good PS are presented in Table 9. As indicated in the model, patients who are significantly less likely to receive chemotherapy when the PS is good include older patients, patients residing in neighborhoods with higher median household income, and those living in neighborhoods with a higher percentage of households without any vehicle. At the same time, patients who are more likely to receive chemotherapy when their PS is good include patients residing in neighborhoods with a higher percentage of college graduates and patients diagnosed in 2003 or later. Factors that were not significant in this model included gender, race, comorbidities, and distance to nearest chemotherapy facility.

Factors Associated with the Receipt of Chemotherapy among Patients with Poor Performance Status

Table 10 reports the results of the logistic regression model for chemotherapy receipt among patients with poor PS. Factors that were associated with significantly higher odds of chemotherapy receipt when PS is poor include median household income and being diagnosed in 2003 or later. Older patients and those who lived in neighborhoods with a higher percentage of college graduates are less likely to receive chemotherapy when they have poor

PS. Factors that were not significant in this model included gender, race, comorbidities, vehicle access, and distance to nearest chemotherapy facility.

Table 9. Factors Associated with Non-Receipt of Chemotherapy among Patients with Good Performance Status (PS), for Lung Cancer Stages II-IV (N = 320)

Performance Status = Good[1]	**Odds of Under Use (95% CI)**	***P* Value**
Patient Demographics		
Age at diagnosis (years)	1.09 (1.05-1.13)	<0.01
Gender = female	1.35 (0.77-2.37)	0.29
Race = white	0.75 (0.36-1.58)	0.46
Clinical Characteristics		
Charlson comorbidity index	1.16 (0.96-1.39)	0.13
Socioeconomic Characteristics		
College degree	0.93 (0.86-1.00)	0.07
Median income ($1000s)	1.02 (1.00-1.04)	0.05
Access to Treatment		
Pct without vehicle	6.96(1.00-49.34)	0.05
Distance to chemo facility	1.00 (0.99-1.03)	0.50
Guidelines		
Year of diagnosis < 2003	2.05 (1.17-3.62)	0.01
Model Performance		
Pseudo-R^2		0.13
C-statistic		0.74

[1] Good PS: ECOG 0-2

Table 10. Factors Associated with Receipt of Chemotherapy among Patients with Poor Performance Status (PS), for Lung Cancer Stages II-IV (N = 86)

Performance Status = Poor[1]	Odds of Over Use (95% CI)	*P* Value
Patient Demographics		
Age at diagnosis (years)	0.92 (0.86-0.98)	0.01
Gender = female	0.87 (0.32-2.38)	0.79
Race = white	0.83 (0.24-2.85)	0.77
Clinical Characteristics		
Charlson comorbidity index	1.01 (0.78-1.32)	0.92
Socioeconomic Characteristics		
College degree	0.89 (0.78-1.02)	0.08
Median income ($1000s)	1.05 (1.01-1.10)	0.02
Access to Treatment		
Pct without vehicle	3.41(0.25-46.81)	0.36
Distance to chemo facility	0.97 (0.90-1.04)	0.38
Guidelines		
Year of diagnosis ≥ 2003	3.24 (1.07-9.85)	0.04
Model Performance		
Pseudo-R^2		0.19
C-statistic		0.75

[1] Poor PS: ECOG>2

3.4 Discussion

Using a large cohort of patients with lung cancer for whom PS is known, this study found the overall adherence to evidence-based guidelines for chemotherapy treatment to be 71%. Among those whose care was non-concordant with guideline recommendations, 19% did not receive chemotherapy when it was indicated and 10% received chemotherapy when it was not recommended. This study recorded a higher adherence rate than a previous lung cancer study that used population-based Medicare data and did not control for PS (A. L. Potosky *et al.* 2004). This study finds that older patients are less likely to use chemotherapy, regardless of their PS. That is, among patients with good PS, older patients are less likely to receive recommended chemotherapy, and among patients with poor PS, they are also less likely to receive chemotherapy. While the latter likely implies high quality care, the former does not. Variations in the receipt of chemotherapy by age are consistent with findings from a previous study (A. L. Potosky *et al.* 2004). Whether this is a result of patient preferences or barriers, physician bias, or a combination of these is not known.

The higher the median household income in the patient's neighborhood of residence the more likely they are to be out of compliance in both directions, both "overusing" and "underusing" chemotherapy. As with the findings of differences in chemotherapy use by patient age, this study is not able to determine the extent to which observed utilization is a result of patient preferences or barriers, physician bias or a combination of these.

Unlike other studies that analyzed Medicare claims data, this research considered a rarely studied managed care cohort that included younger patients as well as older ones. Another notable difference is that this study found no racial differences were found in the receipt of chemotherapy (either underuse or overuse). This difference may be attributable to two factors. First, the study population consisted of patients who received their care through a managed care plan, whereas previous studies have focused mainly on seniors with traditional Medicare (i.e., Parts A and B), not enrolled in a Medicare managed care plan (i.e., Part C). Research suggests that managed care plans reduce health care disparities, at least for broadly defined measures of access to care (A. I. Balsa *et al.* 2007). Second, unlike prior studies (P. B. Bach *et al.* 1999;A. L. Potosky *et al.* 2004;T. J. Smith *et al.* 1995), this one was able to control for a patient's PS as well as several socioeconomic characteristics at the census tract level, i.e., education, income, and car ownership. It may not be race, per se, that leads to previously documented treatment disparities, but rather PS and socioeconomic characteristics, both of which are highly correlated with race.

Finally, among the urban/suburban population studied here, travel distance was not found to be associated with recommended chemotherapy treatment. Instead, the study found that if fewer households in a patient's neighborhood had access to a car, this travel barrier was associated with underuse of chemotherapy relative to guideline recommendations. This finding implies that even among a non-rural population, the presence of transportation barriers is an important predictor of the underuse of chemotherapy among

patients with good PS. Thus, despite the health system in which this study was conducted having multiple and geographically dispersed clinics that offer chemotherapy treatment, these findings suggest that patients without access to a car may have difficulty reaching a clinic, even when there is a clinic a relatively short distance from their home.

The results of the current study should be interpreted in light of the following limitations. First, these findings are based on a cohort of insured cancer patients, and adherence rates as well as the factors associated with them may differ among an uninsured population. Similarly, models were developed on a sample of patients receiving their care from one delivery system located in a large urban area. Therefore, care should be taken when generalizing findings to other delivery settings and locales. Likewise, models may exclude important factors associated with chemotherapy receipt including provider characteristics and variations across health systems and geographical regions. However, the average age and other characteristics of this cohort are similar to the whole U.S. Finally, this study was not intended to assess appropriateness of specific chemotherapy regimens, and further, it is not known whether chemotherapy was given with good intent in lieu of hospice for palliative reasons to those with poor PS, and if there was any subsequent impact on symptom burden or hospitalizations for side effects.

In summary, about 71% of patients in an insured population received chemotherapy concordant with guideline recommendations based on performance status, but 29% did not. There will be over 222,000 people

diagnosed in the U.S. with lung cancer in 2011 (American Cancer Society 2010). Given the effectiveness of modern chemotherapy for palliation and prolonged survival, 19% of patients almost certainly did not live as long or as well as they might have with chemotherapy, and about 10% of patients received chemotherapy that had little chance of benefit and excess risk of toxicity including hospitalizations, excess cost, and delay of entry into hospice.

CHAPTER 4. ADHERENCE TO CHEMOTHERAPY GUIDELINES AND SURVIVAL AMONG PATIENTS WITH LUNG CANCER

Evidence-based guidelines recommend chemotherapy for medically fit patients with stage II-IV non-small cell lung cancer (NSCLC). The relationship between adherence to chemotherapy guidelines and overall survival is not known. Insured patients, ages 50+, diagnosed with stage II-IV NSCLC between 2000-2007 were identified via tumor registry (n=406). Chart abstracted Performance Status (PS), automated medical claims, and Census tract information were linked to tumor registry data. Chemotherapy was appropriate for patients with PS 0-2. Kaplan Meier estimates were used to describe survival differences by PS and choice of chemotherapy. Multivariate Cox logistic regression analysis was used to determine the factors associated with treatment outcome.

Guideline adherent use of chemotherapy reduced risk of dying (hazard ratio [HR], 0.64). Other factors associated with survival among good PS patients ($p<0.05$) include surgery (HR, 0.33), female gender (HR, 0.66), and stage IV disease (HR, 2.19). Overuse of chemotherapy also reduced risk of dying (HR, 0.04). Among poor PS patients, stage IV diagnosis was also associated with higher risk of death (HR, 1.90). Chemotherapy has positive effects on survival for both good and poor PS patients. In the poor PS group, the relationship between chemotherapy and survival may be affected by other unobservable factors.

4.1 Introduction

Lung cancer is the second most common cancer diagnosed in the United States and is the leading cause of cancer-related deaths, with an estimated 222,520 new cases and 157,300 deaths in 2010. The economic cost of lung cancer is high, with an estimated cost of $10 billion per year.(American Cancer Society 2010) Non-small cell lung cancer (NSCLC) makes up approximately 85% of lung cancer cases in the United States. Because of the incidence, severity, and rising costs, it is becoming increasingly important to deliver consistent, high-quality, cost-effective care for NSCLC.

Evidence-based treatment guidelines recommend the use of chemotherapy for medically fit patients with unresectable or stage IV NSCLC to improve survival, symptoms, and quality of life (1997;2010b;2010c;D. G. Pfister *et al.* 2004). Despite these recommendations, studies in the past decade have documented variability in the receipt of chemotherapy among patients with NSCLC (P. B. Bach *et al.* 1999;C. C. Earle *et al.* 2000;A. L. Potosky *et al.* 2004;T. J. Smith *et al.* 1995).

Due to improvements in surgical techniques and combined therapies, survival for lung cancer patients has improved in the last 2 decades. Despite these advancements, the 1-year relative survival for lung cancer is just over 40%, while the 5-year survival for NSCLC remains at 17%. Although overall survival is documented by stage, gender, and other clinical and demographic characteristics in studies that have demonstrated significant benefits of chemotherapy (S. D. Ramsey *et al.* 2004;2008), the relationship between adherence to chemotherapy

guidelines and survival is not known. This is largely due to the fact that measures of PS, a key factor in evaluating the appropriateness of chemotherapy, are currently not available though automated medical claims, tumor registries, or other observational data commonly used to study cancer treatment and its associated outcomes.

The purpose of this research is to examine survival of insured patients diagnosed with NSCLC in relation to adherence to chemotherapy guidelines, controlling for other patient clinical and socio-demographic characteristics. By combining data from medical records with those available via an automated tumor registry, medical claims, Census data, and chart-abstracted PS, this study is able to consider the patients' clinical and socio-demographic characteristics as well as adherence to chemotherapy guidelines in measuring effects on survival.

4.2 Methods

Study Population and Setting

Study patients were those receiving care from a 900-physician member, multispecialty, salaried medical group practice in southeast Michigan. Data available from the medical group's tumor registry were used to identify all patients aged ≥ 50 years who were diagnosed with NSCLC between January 1, 2000 and December 31, 2007. The medical group, which provides care under both fee-for-service and capitated arrangements, staffs 27 primary care clinics throughout Detroit and the surrounding metropolitan area. Patients eligible for study inclusion were those continuously enrolled in an affiliated health plan (ie,

health maintenance organization) for the 1-year period preceding their date of lung cancer diagnosis. Patients for whom no stage of disease was available or for whom the stage at diagnosis was 0 or I were excluded. The latter were excluded because chemotherapy was not indicated for patients with stage 0 or I disease during this time period (W. J. Scott *et al.* 2007). Patients who died within one month of their diagnosis were also excluded. The medical group's Institutional Review Board approved all aspects of the study protocol.

Performance Status (PS) and Guideline Adherence

Instances in which patients with good PS did not receive chemotherapy were classified as "underuse," while instances in which patients with poor PS received chemotherapy were classified as "overuse." Per the American Society of Clinical Oncology (ASCO) clinical practice guidelines issued in 2009 (C. G. Azzoli *et al.* 2009), chemotherapy was recommended for patients with good PS (i.e., PS= 0-2) and not recommended for patients with poor PS (i.e., PS=3-4). Earlier ASCO guidelines had recommended chemotherapy for patients with PS=0-1 only.(1997) The baseline models included patients with PS=0-2 in the good PS group. Alternative models that considered PS=2 patients with the poor PS group were also evaluated. Two trained chart abstractors reviewed inpatient and outpatient nursing and physician notes available within the patient's electronic medical record from 2 months before diagnosis until the first notation of death, disenrollment, initiation of chemotherapy, or 6 months after diagnosis to obtain PS. Abstractors recorded the PS documented closet to the diagnosis date.

If no specific PS was documented, they estimated PS based on medical notes. In the latter case, notes regarding the patient's functionality (e.g., references to shortness of breath, use of a wheelchair or other personal mobility devices, labor force participation, exercising habits, activities of daily living, or other references to mobility) were recorded and used to estimate PS. Inter-rater reliability between the 2 abstractors was assessed on a random subset of 40 observations and the resulting Cohen κ was 0.88.

Automated Tumor Registry and Claims Data

Automated tumor registry and claims data were accessed to obtain patient demographic characteristics, date of cancer diagnosis, stage at diagnosis, and comorbidities in the 12-month period preceding diagnosis for each patient. Patient demographics included age, gender, and race. The age of the patient (in years) was recorded as of the date of lung cancer diagnosis. Clinical measures for each patient included stage of disease at the time of diagnosis and the Charlson comorbidity index (M. E. Charlson *et al.* 1987). Cancer stage was reported using the American Joint Committee on Cancer (AJCC) stages II through IV. The Deyo adaptation of the Charlson comorbidity index and each of its component diagnostic subgroups were constructed using inpatient and outpatient diagnostic information available in the 12-month period preceding diagnosis (R. A. Deyo *et al.* 1992). The date of death was obtained from the tumor registry.

Claims data were also used to identify treatment types, including receipt of chemotherapy, surgery, and/or radiation therapy. Because NSCLC has a very high short-term mortality rate, initial treatment (chemotherapy, surgery, or radiation therapy) was defined by administrative claims codes for these treatments appearing within 1 week before, to 3 months after the date of diagnosis.

Socioeconomic Data

Socioeconomic information included education level and median household income. These were obtained from the 2000 US Census using the patients' residential street address. Census tract level data were used to characterize the socioeconomic profile of each patient's neighborhood of residence.

Statistical Analysis

Patients were assigned into 4 distinct groups: patients with good PS who received chemotherapy; patients with good PS who did not receive chemotherapy; patients with poor PS who received chemotherapy; and patients with poor PS who did not receive chemotherapy. Systematic unadjusted differences between patients receiving chemotherapy and those who did not receive chemotherapy, within the good PS and poor PS groups (patients in the first two groups and patients in the latter two groups) were examined, using 2-

sample Student *t* test (or Wilcoxon rank sum tests) and chi-square tests, depending on the nature of the characteristic.

For survival analyses, conventional two-stage instrumental variable methods may produce biased estimates in nonlinear models, and two-stage least squares regression fails to account for time to death and disregards censoring. Therefore, the two-stage residual inclusion (2SRI) method was used to account for the endogeneity of chemotherapy receipt in estimating outcomes. Terza et al (J. V. Terza *et al.* 2008). showed that 2SRI estimation is consistent across a variety of nonlinear models, including survival models. In the first stage, logistic equations were used to evaluate the factors associated with receipt (or non-receipt) of chemotherapy (*Y*). Two distinct models were used for the good PS and the poor PS groups, as described in chapter 3:

$$P(Y_g=1|X) = \exp(Z)/[1+\exp(Z)] \quad \text{for: PS=good}$$

$$\text{and} \quad P(Y_p=1|X) = \exp(Z)/[1+\exp(Z)] \quad \text{for: PS=poor}$$

where $Z = \beta_0 + X_1\beta_1 + X_2\beta_2 + X_3\beta_3 + X_4\beta_4 + X_5\beta_5 + e$ with each patient having demographic covariates (X_1), clinical characteristics (X_2), socioeconomic characteristics (X_3), access to treatment (X_4), and year of diagnosis (X_5). The residuals were calculated by subtracting the predicted likelihood of receiving chemotherapy from the actual value of the treatment received. Two variables, vehicle ownership and the year of diagnosis dummy variable (before/after 2003), were identified as instrumental variables in these equations. The first stage

residuals were included as additional covariates in the second stage, Cox proportional hazards equations, along with the endogenous treatment variables and other relevant covariates.

Survival Analysis

The objective of the survival analysis was to compare survival for patients, stratified by PS and receipt of chemotherapy. Patients were initially grouped by good vs. poor PS. After stratifying patients by chemotherapy receipt, Kaplan Meier survival curves were created. The Kaplan-Meier estimator KM(t) describes the probability that the time-to-death T exceeds any given value t. It is plotted as a function of t over the range of times of interest and is a decreasing curve with value 1 at time of diagnosis and other values given by:

$$KM(t) = \prod_{i\,:s_i<t} (1 - r_{si}),$$

where $\{s_1, s_2, \ldots\}$ are the observed death times and r_s is the estimated hazard or risk of death at time s, among all patients at risk of death at time s.

Cox proportional hazards regression analysis was used to evaluate the impact of chemotherapy use by PS group, after adjusting for other relevant clinical and socio-demographic characteristics and for the possible endogeneity of chemotherapy using residuals from the first-stage logit equations. The Cox regression is the most common regression approach used in time-to-event problems, and describes the dependence of risk at any time t on the covariates in the model (D. R. Cox 1972). It is semi-parametric in that no assumptions are made about how the hazard rates vary with time; however, the hazards for

different covariate values are assumed to be proportional with a ratio that is constant over time. Two multivariate Cox regressions were fit to evaluate survival given the patient's PS:

$$h_g(t|X) = h(t)\exp(X_e\beta_e + X_o\beta_o + \hat{X}_u\beta_u) + e^{2SRI} \qquad \text{for: PS=good}$$

$$\text{and} \quad h_p(t|X) = h(t)\exp(X_e\beta_e + X_o\beta_o + \hat{X}_u\beta_u) + e^{2SRI} \qquad \text{for: PS=poor}$$

where X_e is the endogenous regressor (receipt or non-receipt of chemotherapy) and X_o is a vector of observable exogenous covariates. In the 2 equations above, e^{2SRI} is the regression error term and $\hat{X}_u$ is the residual from the first-stage model.

The first model estimated survival among patients with good PS (where non-receipt of chemotherapy was considered under use) while the second model estimated survival among patients with poor PS (where receipt of chemotherapy was considered over use). Both models controlled for the receipt of initial surgery and radiation therapy, patient age and AJCC stage at time of diagnosis, gender, race, comorbidities, as well as the college graduation rate and median household income in their neighborhood.

SAS statistical software (version 9.1.3; SAS Institute Inc, Cary, NC) was used for all analyses. $P < .05$ was considered to be statistically significant.

4.3 Results

Cohort Characteristics

A total of 406 patients met the criteria for study eligibility. Table 11 shows the patient characteristics by PS. The mean age of the cohort was 66.9 years (standard deviation [SD], 8.9 years) for patients with good PS, compared with 69.2 years (SD, 8.4) for those with poor PS. Just under half (42%) of good PS patients were female versus 36% of poor PS patients, whereas the racial distribution for good PS patients was 71% white, 27% black, and 2% of other races, compared with 63% white, 34% black, and 3% other races for poor PS patients. The AJCC staging distribution was as follows: for good PS, 11% of patients were diagnosed with stage II disease, 43% were diagnosed with stage IIII disease, and 46% were diagnosed with stage IV disease; for poor PS, 11% of patients were diagnosed in stage II, 31% in stage III, and 58% in stage IV. The average Charlson comorbidity index across the sample was 1.1 (SD, 1.4) for good PS patients and 2.1 (SD, 2.1) for poor PS patients. Of all patients with good PS, 63.4% died by the end of the study period and the mean survival was 20.2 months (SD, 21.4). Poor PS patients experienced significantly poorer survival with 84.9% dying by the end of the study period and a mean survival of 10.5 months (SD, 16.1).

Table 11. Overall Sample Characteristics and Survival, Lung Cancer Patients with Stages II-IV, by Performance Status (PS) (n = 406)

Demographic Characteristics	**Good PS N = 320**	**Poor PS N = 86**
Average age at diagnosis (SD)	66.9 (8.9)	69.2 (8.4)
Gender (%)		
Female	42	36
Male	58	64
Race (%)		
Black	27	34
White	71	63
Other	2	3
Clinical Characteristics		
AJCC stage (%)		
II	11	11
III	43	31
IV	46	58
Average Charlson comorbidity index (SD)	1.1 (1.4)	2.1 (2.1)
Socioeconomic Characteristics		
Pct with college degree (SD)	6.9 (5.8)	6.8 (5.1)
Median household income in $1000s (SD)	49.7(21.7)	47.1(22.8)
Treatment(s) Received		
No treatment (%)	8	28
Surgery only (%)	1	1
Radiation therapy only (%)	10	31
Chemotherapy only (%)	15	11
Surgery + radiation therapy (%)	1	0
Surgery + chemotherapy (%)	6	0
Radiation + chemotherapy (%)	50	27
Surgery + radiation + chemotherapy (%)	9	2
Survival		
Mean survival time in months (SD)	20.2(21.4)	10.5(16.1)
Died by end of study period (%)	63.4	84.9

Chemotherapy Receipt by Performance Status

Table 12 reports the unadjusted differences in cohort characteristics between patients receiving chemotherapy and those not receiving it, across 2 groups: patients with good PS and patients with poor PS. Among patients with good PS, there were significant differences between those receiving chemotherapy and those not receiving it by age at diagnosis, and the patient's Charlson comorbidity index. Among patients with poor PS, there were significant differences between those receiving chemotherapy and those not receiving it by age and median household income in the patient's neighborhood. Among the good PS group, patients who received chemotherapy had significantly greater survival; the mean survival time was 21.7 months (SD, 20.6) for patients who received chemotherapy versus 15.6 months (SD, 23.0) for those who did not, while 61.7% of patients in this group who received chemotherapy died by the end of the study period compared with 68.8% of those without chemotherapy. Similarly, significant survival differences were recorded among the poor PS group; patients with chemotherapy had a mean survival time of 13.6 months (SD, 19.1) compared with 7.9 months (SD, 12.8) for those without chemotherapy, and 84.6% of those receiving chemotherapy in this group died by the end of the study period compared with 85.1% of those not receiving chemotherapy.

Table 12. Sample Characteristics and Survival, by Performance Status (PS) and Choice of Chemotherapy Receipt or Non-Receipt, for Lung Cancer Stages II-IV (n = 406)

	Good PS[1] (n = 320)		Poor PS[2] (n = 86)	
	Chemo (n = 243)	**No Chemo (n = 77)**	**Chemo (n = 39)**	**No Chemo (n = 47)**
Demographic Characteristics				
Average age at diagnosis (SD)	65.5 (8.5)[3]	71.4 (8.9)[3]	66.9 (9.0)[4]	71.1 (7.5)[4]
Gender (%)				
Female	41	47	36	36
Male	59	53	64	64
Race (%)				
Black	26	30	31	36
White	72	66	69	58
Other	2	4	0	6
Clinical Characteristics				
AJCC stage (%)				
II	11	12	15	6
III	44	42	23	39
IV	45	48	62	55
Average Charlson comorbidity index (SD)	1.0 (1.4)[3]	1.4 (1.5)[3]	1.9 (2.0)	2.3 (2.3)
Socioeconomic Characteristics				
Pct with college degree (SD)	7.1 (6.0)	6.1 (4.9)	6.7 (5.9)	6.9 (4.4)
Median household income in $1000s (SD)	50.4(22.2)	47.6(19.8)	52.4(27.8)[4]	42.7(16.6)[4]
Treatment(s) Received				
No treatment (%)	-	42	-	45
Surgery only (%)	-	5	-	2
Radiation therapy only (%)	-	52	-	53
Chemotherapy only (%)	17	-	31	-
Surgery + radiation therapy (%)	-	1	-	-
Surgery + chemotherapy (%)	8	-	-	-
Radiation + chemotherapy (%)	62	-	64	-
Surgery + radiation + chemotherapy (%)	13	-	5	-
Survival				
Mean survival time in months (SD)	21.7(20.6)	15.6(23.0)	13.6(19.1)	7.9(12.8)
Died by end of study period (%)	61.7	68.8	84.6	85.1

[1] Good PS: ECOG 0-2
[2] Poor PS: ECOG >2
[3] Among patients with good PS, significant difference by chemotherapy receipt/non-receipt, at 5% level
[4] Among patients with poor PS, significant difference by chemotherapy receipt/non-receipt, at 5% level

Survival

To better understand the factors associated with improved survival, univariate and multivariate analyses were performed using patient characteristics. The 2SRI analysis found that the residual from the first equation, explaining factors associated with chemotherapy receipt, was not a significant regressor in the second equation (survival model). Since the receipt of chemotherapy was not found to be endogenous in the good PS two-stage model, these preliminary findings are shown in the appendix, but excluded from final results.

Overall median survival was longer for patients who received chemotherapy in both the good and poor PS groups. Survival for patients who received chemotherapy, regardless of PS, was superior to that of patients who did not receive chemotherapy (Figure 1).

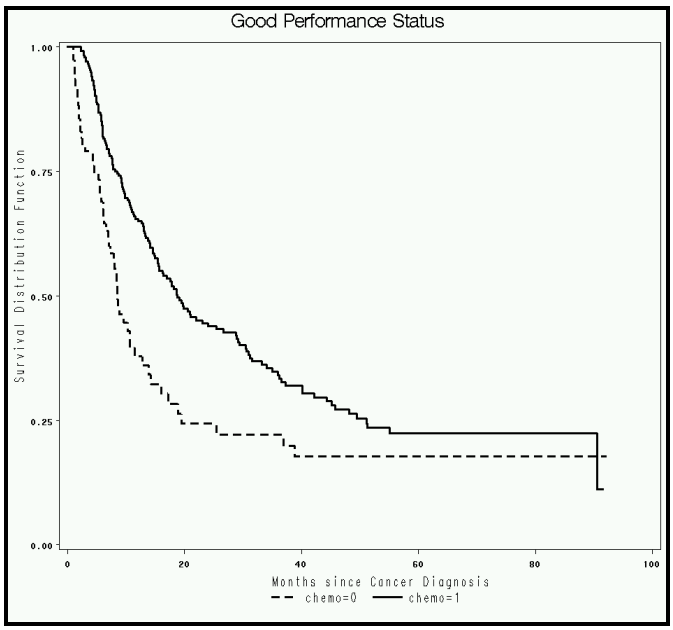
Table 13 lists the adjusted hazard ratios for the good PS group. The sample is stratified by receipt of chemotherapy. Among patients with good PS, the multivariate Cox regression analysis found that stage IV diagnosis (hazard ratio [HR], 2.19) was significantly associated with a higher risk of dying, whereas the receipt of chemotherapy (HR, 0.64), surgery (HR, 0.33), and female gender (HR, 0.66) were all significantly associated with a lower risk of dying. The residual from the first-stage equation was not significantly associated with the dependent variable and was dropped from this table, but included in the appendix. This suggested that there was no evidence of endogeneity for chemotherapy in the good PS model.

Alternative models that considered patients with PS=2 under the poor PS group are presented in Appendix B. The major difference compared with the baseline models is that chemotherapy was not significantly associated with a lower risk of death for patients with good PS, when PS 2 patients are excluded from this group.

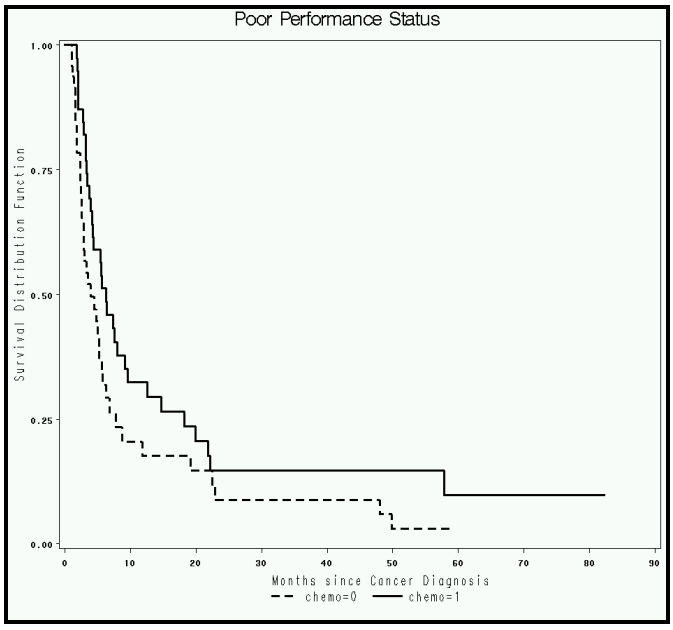
Among patients with poor PS (table 14), the multivariate Cox regression found that stage IV diagnosis (HR, 1.90) was associated with a higher risk of dying, whereas the receipt of chemotherapy (HR, 0.04) was associated with a lower risk of dying. Female gender (HR, 0.61) and living in a neighborhood with a higher rate of college graduates (HR, 0.93) were associated with a lower risk of dying. However, these associations were not significant at $P < 0.05$. There is also evidence of an association between the residual from the first-stage equation and the risk of dying ($P = 0.06$), suggesting that unobservable disturbances from the first stage equation are associated with the dependent variable in the poor PS Cox model.

Figure 1. Kaplan-Meier Curves by Chemotherapy Receipt for Patients with Good Performance Status (PS)[1] (A; N = 320) and Poor PS[2] (B; N = 86)

A



B



[1] Good PS: ECOG 0-2
[2] Poor PS: ECOG >2

Table 13. Multivariate Cox Proportional Hazards Model of Survival for Good Performance Status (PS) Patients Diagnosed With Stage II-IV Lung Cancer between 2000 and 2007 (N = 320)

Performance Status = Good[1]	**Parameter**	**Hazard Ratio**	***P* Value**
Treatment Received			
Chemotherapy	-0.45	0.64	0.01
Surgery	-1.12	0.33	<.01
Radiation	0.18	1.20	0.30
Patient Demographics			
Age at diagnosis (years)	0.01	1.01	0.20
Gender = female	-0.41	0.66	<.01
Race = white	0.29	1.34	0.12
Clinical Characteristics			
Stage IV at diagnosis	0.78	2.19	<.01
Charlson comorbidity index	0.02	1.02	0.75
Socioeconomic Characteristics			
College degree	0.01	1.01	0.56
Median income ($1000s)	-0.01	0.99	0.07
Model Characteristics			
Likelihood ratio, $\chi^2(10)$	94.0		
Probability > χ^2	0.00		

[1] Good PS: ECOG 0-2

Table 14. Multivariate Cox Proportional Hazards Model of Survival for Poor Performance Status (PS) Patients Diagnosed With Stage II-IV Lung Cancer between 2000 and 2007 (N = 86)

Performance Status = Poor[1]	**Parameter**	**Hazard Ratio**	***P* Value**
Treatment Received			
Chemotherapy	-3.20	0.04	0.03
Surgery	-15.33	0.00	0.98
Radiation	0.29	1.34	0.30
Patient Demographics			
Age at diagnosis (years)	-0.04	0.96	0.09
Gender = female	-0.50	0.61	0.06
Race = white	-0.32	0.73	0.33
Clinical Characteristics			
Stage IV at diagnosis	0.64	1.90	0.02
Charlson comorbidity index	0.08	1.08	0.14
Socioeconomic Characteristics			
College degree	-0.08	0.93	0.07
Median income ($1000s)	0.02	1.02	0.16
First Stage Residual	1.20	3.31	0.06
Model Characteristics			
Likelihood ratio, $\chi^2(10)$	37.4		
Probability > χ^2	0.00		

[1] Poor PS: ECOG >2

4.4 Discussion

To my knowledge, this is the first study that examines the impact of guideline recommended (and non-recommended) chemotherapy on survival of lung cancer patients in a large cohort of managed care enrollees. There are several findings to note from this study. First, all else equal, insured patients with good PS who receive chemotherapy have significantly higher survival compared with those with no chemotherapy. Second, similar patients with poor PS who receive chemotherapy also have significantly higher survival compared with those who do not receive chemotherapy. The two-stage model used to explain this relationship suggests that other unobservable factors associated with the receipt of chemotherapy in poor PS patients may have a positive impact on survival. Further, by considering the alternative models that used the pre-2009 guidelines in defining chemotherapy appropriateness, it seems that chemotherapy may be especially beneficial for PS 2 patients. This finding explains why the guidelines were revised to recommend chemotherapy for this group of patients.

These conclusions should be interpreted in the light of several important limitations. First, these findings are based on a cohort of insured cancer patients, and survival rates as well as adherence rates may differ among an uninsured population. Similarly, models were developed on a sample of patients receiving their care from one delivery system located in a large urban area. Therefore, care should be taken when generalizing findings to other delivery settings and locales.

Furthermore, models may exclude important factors associated with survival including variations across health systems and geographical regions.

Second, some patients who were prescribed chemotherapy but did not live long enough to receive treatment would be counted as having not received chemotherapy. If survival after diagnosis predicts chemotherapy use, this could bias survival in favor of those who received chemotherapy.

Finally, it is not known whether chemotherapy was given with good intent in lieu of hospice for palliative reasons to those with poor PS, and if there was any subsequent impact on symptom burden or hospitalizations for side effects.

CHAPTER 5. CONCLUSION

Performance status is widely recognized as a predictor for treatment appropriateness and reducing chemotherapy to patients with poor PS has been recommended as one way to increase health care quality and reduce costs (T. J. Smith, B. E. Hillner 2011). This is the first study to use observational data to estimate PS for lung, or any other, cancer patients. Despite good predictability of PS using this model, a predicted version will always be second-best to having the actual PS data. Tumor registries should include PS as a required field in order to assess quality of care.

Using the first large cohort of patients with lung cancer for whom PS is known, this study found the overall adherence to evidence-based guidelines for chemotherapy treatment to be 71%. Among those whose care was non-concordant with guideline recommendations, 19% did not receive chemotherapy when it was indicated and 10% received chemotherapy when it was not recommended. This study recorded a higher adherence rate than previous lung cancer studies that used population-based Medicare data and did not control for PS (P. B. Bach *et al.* 1999;C. C. Earle *et al.* 2000;T. J. Smith *et al.* 1995;A. L. Potosky *et al.* 2004) and found that older patients are less likely to use chemotherapy, regardless of their PS.

The higher the median household income in the patient's neighborhood of residence the more likely they are to be out of compliance in both directions, both "overusing" and "underusing" chemotherapy. Unlike other studies that analyzed Medicare claims data, this study considered a rarely studied managed care

cohort that included younger patients as well as older ones, although the median age of 67 was close to the US median age at diagnosis of 71 (National Cancer Institute 2010). Another notable difference of this study is that it found no racial differences in the receipt of chemotherapy (either underuse or overuse), which suggests that disparities may be attributable to other factors. Among the urban/suburban population studied here, this study did not find travel distance to be associated with recommended chemotherapy treatment. Instead, it was found that if fewer households in a patient's neighborhood had access to a car, this travel barrier was associated with underuse of chemotherapy relative to guideline recommendations. This finding suggests that patients without access to a car may have difficulty reaching a clinic, even when there is a clinic a relatively short distance from their home. This suggests a helpful question to ask on intake screening: "Will you have difficulty getting to your next appointment?"

Finally, this is the first study that examines the impact of guideline recommended chemotherapy on survival of lung cancer patients in a large cohort of managed care enrollees. The study found that regardless of PS, patients who received chemotherapy had significantly higher survival compared with those who did not receive chemotherapy, although the model suggests that other unobservable factors associated with the receipt of chemotherapy in poor PS patients may have a positive impact on survival.

This study is not without its limitations. First, subjectivity is present in the assignment of PS. It is documented that PS scales are subjective in nature, and when estimated by physicians they are known to be prone to error, usually being

overestimated. Second, the study relies on a relatively small sample that is specific to one health care delivery system, located in a large urban area. The findings of this study may not be generalized, especially to non-urban populations. Third, the models in this study may exclude relevant measures, including provider characteristics and variations across health systems and geographic areas. Also, these findings are based on an insured cohort of lung cancer patients, and may be different among the uninsured. Finally, this study was not intended to assess specific chemotherapy regimens. Therefore it is not known whether chemotherapy was given with good intent in lieu of hospice for palliative reasons to those with poor PS.

Given the limitations of the current study, several ideas for future research emerge. First, the analysis could be expanded to include multiple health systems, with a larger cohort of patients and geographic variations. The advantage of having a larger, more diverse cohort to study will allow for the examination of more factors, including provider characteristics and health system variations, and allow for the study of treatment costs. A priority in the study of costs would be to define a treatment episode for lung cancer patients and measure per episode costs. Once the treatment episode is defined, cost effectiveness analysis could be performed using survival and cost resulting from lung cancer treatment.

APPENDIX

Appendix A. Factors Associated with Non-Receipt of Chemotherapy among Patients with Good Performance Status (PS) (N = 276) and Receipt of Chemotherapy among Patients with Poor PS (N = 130)

Performance Status = Good[1]	**Odds of Under Use (95% CI)**	***P* Value**
Patient Demographics		
Age at diagnosis (years)	1.10 (1.06-1.14)	<0.01
Gender = female	1.37 (0.74-2.54)	0.31
Race = white	0.71 (0.31-1.64)	0.43
Clinical Characteristics		
Charlson comorbidity index	1.20 (0.97-1.49)	0.10
Socioeconomic Characteristics		
College degree	0.96 (0.88-1.04)	0.35
Median income ($1000s)	1.02 (1.00-1.05)	0.09
Access to Treatment		
Pct without vehicle	5.12(0.55-47.79)	0.15
Distance to chemo facility	1.00 (0.98-1.03)	0.56
Guidelines		
Year of diagnosis < 2003	2.29 (1.22-4.32)	0.01
Model Performance		
Pseudo-R^2		0.14
C-statistic		0.75
Performance Status = Poor[2]	**Odds of Over Use (95% CI)**	***P* Value**
Patient Demographics		
Age at diagnosis (years)	0.93 (0.89-0.98)	0.01
Gender = female	0.78 (0.35-1.74)	0.54
Race = white	0.94 (0.38-2.35)	0.90
Clinical Characteristics		
Charlson comorbidity index	0.99 (0.81-1.20)	0.91
Socioeconomic Characteristics		
College degree	1.00 (0.90-1.10)	0.91
Median income ($1000s)	1.03 (1.00-1.06)	0.09
Access to Treatment		
Pct without vehicle	0.91(0.11-7.56)	0.93
Distance to chemo facility	0.98(0.93-1.03)	0.40
Guidelines		
Year of diagnosis ≥ 2003	2.59(1.12-6.00)	0.03
Model Performance		
Pseudo-R^2		0.13
C-statistic		0.71

[1] Good PS: ECOG 0-2
[2] Poor PS: ECOG>2

Appendix B. Two-Stage Residual Inclusion Method: Multivariate Cox Proportional Hazards Models with Residuals from Chemotherapy Receipt Logit Regression, (N = 320)

Performance Status = Good[1]	**Parameter**	**Hazard Ratio**	***P* Value**
Treatment Received			
Chemotherapy	-1.54	0.21	0.15
Surgery	-1.12	0.33	<.01
Radiation	0.19	1.21	0.29
Patient Demographics			
Age at diagnosis (years)	-0.00	1.00	0.91
Gender = female	-0.48	0.62	<.01
Race = white	0.38	1.46	0.06
Clinical Characteristics			
Stage IV at diagnosis	0.79	2.20	<.01
Charlson comorbidity index	0.02	1.00	0.97
Socioeconomic Characteristics			
College degree	-0.00	1.02	0.38
Median income ($1000s)	-0.02	0.99	0.04
Residual	0.47	1.60	0.30
Model Characteristics			
Likelihood ratio, $\chi^2(10)$	95.0		
Probability > χ^2	0.00		

[1] Good PS: ECOG 0-2

Appendix C. Alternative Models with Pre-2009 Definition of Performance Status (PS): Multivariate Cox Proportional Hazards Model of Survival for Patients Diagnosed With Stage II-IV Lung Cancer between 2000 and 2007

Performance Status = Good[1]	Parameter	Hazard Ratio	*P* Value
Treatment Received			
Chemotherapy	-0.34	0.71	0.09
Surgery	-1.15	0.32	<.01
Radiation	0.21	1.24	0.28
Patient Demographics			
Age at diagnosis (years)	0.01	1.01	0.34
Gender = female	-0.39	0.67	0.02
Race = white	0.49	1.63	0.02
Clinical Characteristics			
Stage IV at diagnosis	0.74	2.09	<.01
Charlson comorbidity index	0.09	1.09	0.18
Socioeconomic Characteristics			
College degree	0.02	1.02	0.40
Median income ($1000s)	-0.01	0.99	0.03
Model Characteristics			
Likelihood ratio, $\chi^2(10)$	78.0	N=276	
Probability > χ^2	0.00		

Performance Status = Poor[2]	Parameter	Hazard Ratio	*P* Value
Treatment Received			
Chemotherapy	-2.84	0.06	0.04
Surgery	-2.48	0.08	0.02
Radiation	0.18	1.20	0.40
Patient Demographics			
Age at diagnosis (years)	-0.01	0.98	0.38
Gender = female	-0.55	0.58	0.01
Race = white	-0.27	0.76	0.29
Clinical Characteristics			
Stage IV at diagnosis	0.60	1.83	0.01
Charlson comorbidity index	0.01	1.01	0.83
Socioeconomic Characteristics			
College degree	-0.02	0.98	0.50
Median income ($1000s)	0.01	1.01	0.22
Residual	0.96	2.62	0.10
Model Characteristics			
Likelihood ratio, $\chi^2(10)$	41.3	N=130	
Probability > χ^2	0.00		

[1] Good PS: ECOG 0-1
[2] Poor PS: ECOG >1

REFERENCES

1. "Clinical practice guidelines for the treatment of unresectable non-small-cell lung cancer. Adopted on May 16, 1997 by the American Society of Clinical Oncology." *J Clin Oncol.*, August 1997, *15* (8), 2996-3018.

2. "Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials." *J.Clin.Oncol.*, October 2008, *26* (28), 4617-4625.

3. *AHFS Drug Information*. Bethesda, MD: American Society of Health-System Pharmacists, 2010a.

4. National Cancer Institute: Physician Data Query Cancer Information Summaries. National Cancer Institute . 3-10-2010b. 5-11-2010b.
Ref Type: Electronic Citation

5. National Comprehensive Cancer Network and American Cancer Society: Lung Cancer: Treatment Guidelines for Patients. Version 1, December 2001. National Comprehensive Cancer Network . 3-5-2010c.
Ref Type: Electronic Citation

6. Albain, K. S., Crowley, J. J., LeBlanc, M., Livingston, R. B. "Survival determinants in extensive-stage non-small-cell lung cancer: the Southwest Oncology Group experience." *J Clin Oncol.*, September 1991, *9* (9), 1618-1626.

7. American Cancer Society. Cancer Facts and Figures 2010. 2010. Atlanta, GA.

   Ref Type: Report

8. Azzoli, C. G., Baker S Jr, Temin, S., Pao, W., Aliff, T., Brahmer, J., Johnson, D. H., Laskin, J. L., Masters, G., Milton, D. *et al.* "American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer." *J Clin Oncol.*, December 2009, *27* (36), 6251-6266.

9. Bach, P. B., Cramer, L. D., Warren, J. L., Begg, C. B. "Racial differences in the treatment of early-stage lung cancer." *N.Engl.J Med*, October 1999, *341* (16), 1198-1205.

10. Balsa, A. I., Cao, Z., McGuire, T. G. "Does managed health care reduce health care disparities between minorities and Whites?" *J.Health Econ.*, January 2007, *26* (1), 101-121.

11. Bickell, N. A. "Race, ethnicity, and disparities in breast cancer: victories and challenges." *Womens.Health.Issues.*, September 2002, *12* (5), 238-251.

12. Bickell, N. A., Wang, J. J., Oluwole, S., Schrag, D., Godfrey, H., Hiotis, K., Mendez, J., Guth, A. A. "Missed opportunities: racial disparities in adjuvant breast cancer treatment." *J.Clin.Oncol.*, March 2006, *24* (9), 1357-1362.

13. Bickell, N. A., Weidmann, J., Fei, K., Lin, J. J., Leventhal, H. "Underuse of breast cancer adjuvant treatment: patient knowledge, beliefs, and medical mistrust." *J.Clin.Oncol.*, November 2009, *27* (31), 5160-5167.

14. Blagden, S. P., Charman, S. C., Sharples, L. D., Magee, L. R., Gilligan, D. "Performance status score: do patients and their oncologists agree?" *Br.J Cancer*, September 2003, *89* (6), 1022-1027.

15. Bradley, C. J., Dahman, B., Given, C. W. "Treatment and survival differences in older Medicare patients with lung cancer as compared with those who are dually eligible for Medicare and Medicaid." *J Clin Oncol.*, November 2008, *26* (31), 5067-5073.

16. Buccheri, G., Ferrigno, D., Tamburini, M. "Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution." *Eur.J Cancer*, June 1996, *32A* (7), 1135-1141.

17. Charlson, M. E., Pompei, P., Ales, K. L., MacKenzie, C. R. "A new method of classifying prognostic comorbidity in longitudinal studies: development and validation." *J Chronic.Dis.*, 1987, *40* (5), 373-383.

18. Connor, S. R., Pyenson, B., Fitch, K., Spence, C., Iwasaki, K. "Comparing hospice and nonhospice patient survival among patients who die within a three-year window." *J.Pain.Symptom.Manage.*, March 2007, *33* (3), 238-246.

19. Cox, D. R. "Regression Models and Life-Tables." *Journal of the Royal Statistical Society*, 1972, *34* (2), 187-220.

20. Deyo, R. A., Cherkin, D. C., Ciol, M. A. "Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases." *J Clin Epidemiol.*, June 1992, *45* (6), 613-619.

21. Earle, C. C., Neville, B. A., Landrum, M. B., Ayanian, J. Z., Block, S. D., Weeks, J. C. "Trends in the aggressiveness of cancer care near the end of life." *J Clin Oncol.*, January 2004, *22* (2), 315-321.

22. Earle, C. C., Venditti, L. N., Neumann, P. J., Gelber, R. D., Weinstein, M. C., Potosky, A. L., Weeks, J. C. "Who gets chemotherapy for metastatic lung cancer?" *Chest*, May 2000, *117* (5), 1239-1246.

23. Efron, B., Gong, G. "A leisurely look at the bootstrap, the jackknife, and cross-validation." *The American Statistician*, February 83 A.D., *37* (1), 36-48.

24. Griggs, J. J., Culakova, E., Sorbero, M. E., Poniewierski, M. S., Wolff, D. A., Crawford, J., Dale, D. C., Lyman, G. H. "Social and racial differences in selection of breast cancer adjuvant chemotherapy regimens." *J.Clin.Oncol.*, June 2007, *25* (18), 2522-2527.

25. Harrington, S. E., Smith, T. J. "The role of chemotherapy at the end of life: "when is enough, enough?"." *JAMA*, June 2008, *299* (22), 2667-2678.

26. Hebert-Croteau, N., Brisson, J., Latreille, J., Rivard, M., Abdelaziz, N., Martin, G. "Compliance with consensus recommendations for systemic therapy is associated with improved survival of women with node-negative breast cancer." *J.Clin.Oncol.*, September 2004, *22* (18), 3685-3693.

27. Hershman, D., McBride, R., Jacobson, J. S., Lamerato, L., Roberts, K., Grann, V. R., Neugut, A. I. "Racial disparities in treatment and survival among women with early-stage breast cancer." *J.Clin.Oncol.*, September 2005, *23* (27), 6639-6646.

28. Hillner, B. E., McDonald, M. K., Desch, C. E., Smith, T. J., Penberthy, L. T., Retchin, S. M. "A comparison of patterns of care of nonsmall cell lung carcinoma patients in a younger and Medigap commercially insured cohort." *Cancer*, November 1998, *83* (9), 1930-1937.

29. Huskamp, H. A., Keating, N. L., Malin, J. L., Zaslavsky, A. M., Weeks, J. C., Earle, C. C., Teno, J. M., Virnig, B. A., Kahn, K. L., He, Y. *et al.* "Discussions with physicians about hospice among patients with metastatic lung cancer." *Arch.Intern Med*, May 2009, *169* (10), 954-962.

30. Iezzoni, L. I. "Risk adjustment for studying health care outcomes of people with disabilities," Iezzoni, L. I., *Risk Adjustment for Measuring Health Care Outcomes*. Ann Arbor: Health Administration Press, 2003, 363-382.

31. Iezzoni, L. I., Greenberg, M. S. "Capturing and classifying functional status information in administrative databases." *Health Care Financ.Rev*, 2003, *24* (3), 61-76.

32. Kelly, K. "Challenges in defining and identifying patients with non-small cell lung cancer and poor performance status." *Semin.Oncol.*, December 2004, *31* (6 Suppl 11), 3-7.

33. Krieger, N. "Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology." *Am.J.Public.Health.*, May 1992, *82* (5), 703-710.

34. Lash, T. L., Clough-Gorr, K., Silliman, R. A. "Reduced rates of cancer-related worries and mortality associated with guideline surveillance after breast cancer therapy." *Breast.Cancer Res.Treat.*, January 2005, *89* (1), 61-67.

35. Lash, T. L., Silliman, R. A., Guadagnoli, E., Mor, V. "The effect of less than definitive care on breast carcinoma recurrence and mortality." *Cancer*, October 2000, *89* (8), 1739-1747.

36. Lemeshow, S., Hosmer, D. W., Jr. "A review of goodness of fit statistics for use in the development of logistic regression models." *Am J Epidemiol.*, January 1982, *115* (1), 92-106.

37. Lilenbaum, R. C., Cashy, J., Hensing, T. A., Young, S., Cella, D. "Prevalence of poor performance status in lung cancer patients: implications for research." *J Thorac.Oncol.*, February 2008, *3* (2), 125-129.

38. Matsuyama, R., Reddy, S., Smith, T. J. "Why do patients choose chemotherapy near the end of life? A review of the perspective of those facing death from cancer." *J Clin Oncol.*, July 2006, *24* (21), 3490-3496.

39. Murillo, J. R., Jr., Koeller, J. "Chemotherapy given near the end of life by community oncologists for advanced non-small cell lung cancer." *Oncologist.*, November 2006, *11* (10), 1095-1099.

40. National Cancer Institute. *SEER Cancer Statistics Review, 1975-2007*. Altekruse SF, Kosary CL Krapcho M Neyman N Aminou R Waldron W Ruhl J Howlader N Tatalovich Z Cho H Mariotto A Eisner MP Lewis DR Cronin K Chen HS Feuer EJ Stinchcomb DG Edwards BK. 2010. Bethesda, MD, http://seer.cancer.gov/csr/1975_2007/, based on November 2009 SEER data submission, posted to the SEER web site. Ref Type: Report

41. Olivotto, A., Coldman, A. J., Hislop, T. G., Trevisan, C. H., Kula, J., Goel, V., Sawka, C. "Compliance with practice guidelines for node-negative breast cancer." *J.Clin.Oncol.*, January 1997, *15* (1), 216-222.

42. Pfister, D. G., Johnson, D. H., Azzoli, C. G., Sause, W., Smith, T. J., Baker S Jr, Olak, J., Stover, D., Strawn, J. R., Turrisi, A. T. *et al.* "American

Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003." *J Clin Oncol.*, January 2004, *22* (2), 330-353.

43. Potosky, A. L., Saxman, S., Wallace, R. B., Lynch, C. F. "Population variations in the initial treatment of non-small-cell lung cancer." *J Clin Oncol.*, August 2004, *22* (16), 3261-3268.

44. Ramsey, S. D., Howlader, N., Etzioni, R. D., Donato, B. "Chemotherapy use, outcomes, and costs for older persons with advanced non-small-cell lung cancer: evidence from surveillance, epidemiology and end results-Medicare." *J.Clin.Oncol.*, December 2004, *22* (24), 4971-4978.

45. Rodriguez, E., Lilenbaum, R. C. "New treatment strategies in patients with advanced non-small-cell lung cancer and performance status 2." *Clin.Lung Cancer*, November 2008, *9* (6), 326-330.

46. Schneeweiss, S., Seeger, J. D., Maclure, M., Wang, P. S., Avorn, J., Glynn, R. J. "Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data." *Am.J.Epidemiol.*, November 2001, *154* (9), 854-864.

47. Schuster, M. A., McGlynn, E. A., Brook, R. H. "How good is the quality of health care in the United States? 1998." *Milbank Q.*, 2005, *83* (4), 843-895.

48. Scott, W. J., Howington, J., Feigenberg, S., Movsas, B., Pisters, K. "Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd edition)." *Chest*, September 2007, *132* (3 Suppl), 234S-242S.

49. Smith, T. J. and Hillner, B. E. Bending the cost curve in cancer. N.Engl.J Med . 2011.
Ref Type: In Press

50. Smith, T. J., Penberthy, L., Desch, C. E., Whittemore, M., Newschaffer, C., Hillner, B. E., McClish, D., Retchin, S. M. "Differences in initial treatment patterns and outcomes of lung cancer in the elderly." *Lung Cancer*, December 1995, *13* (3), 235-252.

51. Temel, J. S., Greer, J. A., Muzikansky, A., Gallagher, E. R., Admane, S., Jackson, V. A., Dahlin, C. M., Blinderman, C. D., Jacobsen, J., Pirl, W. F. *et al.* "Early palliative care for patients with metastatic non-small-cell lung cancer." *N.Engl.J.Med*, August 2010, *363* (8), 733-742.

52. Terza, J. V., Basu, A., Rathouz, P. J. "Two-stage residual inclusion estimation: addressing endogeneity in health econometric modeling." *J.Health Econ.*, May 2008, *27* (3), 531-543.

53. Wright, A. A., Zhang, B., Ray, A., Mack, J. W., Trice, E., Balboni, T., Mitchell, S. L., Jackson, V. A., Block, S. D., Maciejewski, P. K. *et al.* "Associations between end-of-life discussions, patient mental health,

medical care near death, and caregiver bereavement adjustment." *JAMA.*, October 2008, *300* (14), 1665-1673.

54. Zhang, B., Wright, A. A., Huskamp, H. A., Nilsson, M. E., Maciejewski, M. L., Earle, C. C., Block, S. D., Maciejewski, P. K., Prigerson, H. G. "Health care costs in the last week of life: associations with end-of-life conversations." *Arch.Intern.Med.*, March 2009, *169* (5), 480-488.

55. Zimmermann, C., Burman, D., Bandukwala, S., Seccareccia, D., Kaya, E., Bryson, J., Rodin, G., Lo, C. "Nurse and physician inter-rater agreement of three performance status measures in palliative care outpatients." *Support.Care Cancer*, May 2010, *18* (5), 609-616.

ABSTRACT

CHEMOTHERAPY FOR LUNG CANCER: DETERMINANTS OF GUIDELINE ADHERENCE AND ASSOCIATED PATIENT OUTCOMES

by

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Evidence-based guidelines recommend chemotherapy for medically fit patients with stage II-IV non-small cell lung cancer (NSCLC). Adherence to chemotherapy guidelines has rarely been studied among large populations, mainly because performance status (PS), a key component in assessing chemotherapy appropriateness, is missing from claims-based datasets. Among a large cohort of patients with known PS, this dissertation describes chemotherapy use relative to guideline recommendations and identifies patient factors and outcomes associated with guideline concordant use. Among these patients 29% do not receive guideline recommended chemotherapy treatment, missing opportunities for cure or receiving chemotherapy with more risk of harm than benefit, thereby likely foregoing beneficial palliation. Care concordant with

guidelines is influenced by age, and economic considerations, such as income, and transportation barriers. Guideline adherent use of chemotherapy reduced risk of dying. Overuse of chemotherapy also reduced risk of dying. Among poor PS patients, stage IV diagnosis was also associated with survival. Chemotherapy has positive effects on survival for both good and poor PS patients. In the poor PS group, the relationship between chemotherapy and survival is affected by other unobservable factors.

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