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Predictors and impact of second-line chemotherapy for advanced non-small cell lung cancer in the United States: real-world considerations for maintenance therapy

David E. Gerber, MD^{1,2}, Drew W. Rasco, MD^{1,2}, Phat Le¹, Jingsheng Yan, PhD³, Jonathan E. Dowell, MD^{4,1,2}, and Yang Xie, PhD³

¹ Department of Internal Medicine, Harold C. Simmons Cancer Center, University of Texas Southwestern Medical Center, Dallas, Texas

² Division of Hematology-Oncology, Harold C. Simmons Cancer Center, University of Texas Southwestern Medical Center, Dallas, Texas

³ Department of Clinical Sciences, Harold C. Simmons Cancer Center, University of Texas Southwestern Medical Center, Dallas, Texas

⁴ Veterans Affairs North Texas Health Care System, Dallas, Texas

Abstract

Introduction—Recent clinical trials incorporating maintenance chemotherapy into the initial treatment of advanced non-small cell lung cancer (NSCLC) have highlighted the benefits of exposing patients to second-line therapies. We therefore determined the predictors and impact of second-line chemotherapy administration in a contemporary, diverse NSCLC population.

Methods—We performed a retrospective analysis of consecutive patients diagnosed with stage IV NSCLC from 2000 to 2007 at clinical facilities associated with the University of Texas Southwestern Medical Center. Demographic, disease, treatment, and outcome data were obtained from hospital tumor registries. The association between these variables was assessed using univariate analysis and multivariate logistic regression.

Results—A total of 406 patients in this cohort received first-line chemotherapy and were included in the analysis. Mean age was 59 years, 28% were women, and 59% were white. Among these patients, 197 (49%) received second-line chemotherapy. Among those patients who had not progressed after 4–6 cycles of first-line chemotherapy, 67% received second-line chemotherapy. Receipt of second-line chemotherapy was significantly associated with patient insurance type ($P=0.007$), number of cycles of first-line chemotherapy ($P<0.001$), and receipt of pre-chemotherapy palliative radiation therapy ($P=0.005$), but was not associated with patient age, gender, race, histology, or year of diagnosis. In a multivariate model, second-line chemotherapy administration remained associated with insurance type ($P=0.003$), number of cycles of first-line chemotherapy ($P<0.001$), and receipt of pre-chemotherapy palliative radiation therapy ($P=0.008$). The number of cycles of first-line chemotherapy and administration of second-line chemotherapy were associated with overall survival in both univariate and multivariate analyses.

Conclusions—In this unselected, contemporary and diverse cohort of patients with advanced NSCLC, 67% of individuals whose disease had not progressed after 4–6 cycles of first-line

chemotherapy eventually received second-line chemotherapy. Markers of socioeconomic status, symptom burden, and response to and tolerance of first-line chemotherapy were associated with receipt of second-line chemotherapy. These factors may assist in the selection of patients most likely to benefit from maintenance chemotherapy.

INTRODUCTION

The role of second-line chemotherapy for advanced non-small cell lung cancer (NSCLC) has been highlighted by a number of recent clinical trials examining the role of “maintenance” therapy.^{1–6} Traditionally, patients with responsive or stable disease after four to six cycles of first-line platinum doublet chemotherapy have been monitored clinically and radiographically off therapy, with second-line chemotherapy initiated upon disease progression. Currently, three agents—docetaxel, pemetrexed, and erlotinib—are approved for this indication in the United States.^{7–9} With maintenance therapy, patients receive subsequent treatment immediately after completing first-line chemotherapy, either with a new agent (“switch maintenance”)^{2,4–5,10} or with an agent given during first-line therapy (“continuation maintenance”).^{1,5} Across studies, maintenance chemotherapy has been associated with prolongation of progression-free survival. Some trials have also demonstrated improvement in overall survival.^{2,10}

Clinical trials of maintenance chemotherapy have been noteworthy for widely varying rates of second-line chemotherapy administration. Among patients randomized to observation after completion of first-line treatment, anywhere from 17–82% of patients received second-line therapy upon disease progression; 3–63% of patients received the same agent given in the maintenance arm.^{1,4–5} These discrepancies have confounded the interpretation of study results. It is not clear if maintenance chemotherapy provides a benefit because of its timing, or because it exposes more patients to additional, potentially effective therapies. That is, if there were a means to predict which patients would be fit to receive second-line therapy at the time of progression, it might not be necessary to offer these individuals maintenance regimens.

Outside the controlled environment of a clinical trial, little is known about administration of second-line chemotherapy. Large administrative databases do not routinely record this information. A recently published study from South Korea reported that 86% of patients received second-line treatment.¹¹ This unusually high rate exceeds those of prospective, randomized maintenance chemotherapy trials and may reflect the young age and good performance status of the patient population. Indeed, multiple lung cancer studies have demonstrated substantial differences in treatment effects and overall prognosis between East Asian and western populations.^{12–16} To provide further insight into this issue, we examined the predictors and impact of second-line chemotherapy administration at a large North American medical center providing care to a diverse patient population within three different hospital systems.

METHODS

Study setting

The study cohort was captured from clinical facilities associated with the University of Texas Southwestern Medical Center (UT Southwestern), including Parkland Health and Hospital System (PHHS), University Hospital (which includes the freestanding Harold C. Simmons Cancer Center), and the Dallas Veterans Affairs (VA) Medical Center. PHHS consists of a 968-bed public hospital and outpatient clinics that provide health care to predominantly indigent and uninsured residents of Dallas County. Dallas County is the ninth most populous county in the United States, with an estimated 2.4 million residents, of whom

39 percent are Hispanic, 35 percent are white, and 21 percent are African-American.¹⁷ University Hospital (415 beds) is the principal medical and surgical referral hospital for UT Southwestern. The Dallas VA, a 289-bed hospital and outpatient clinics, serves as the principal tertiary care center for military veterans in a 40-county region of Northern Texas and Southern Oklahoma. It provides full medical, radiation, and surgical oncology services.

Data extraction

This study was approved by the UT Southwestern and the Veterans Affairs North Texas Health Care System Institutional Review Boards. We identified patients diagnosed with stage IV NSCLC between January 1, 2000, and December 31, 2007, in the UT Southwestern, Parkland Health and Hospital System, and Dallas VA tumor registries. Additional information was obtained through electronic and paper medical records. The tumor registries identify cases through review of pathology records, clinic schedules, and hospital admission and discharge records. Certified tumor registrars extract data directly from medical records according to standards established by the American College of Surgeons Commission on Cancer, Surveillance Epidemiology and End Results (SEER)/National Cancer Institute (NCI) and the National Program of Cancer Registries (NPCR). Multiple data fields are collected per patient, including demographics, cancer diagnosis and stage, treatment, and follow-up. After initial cancer diagnosis and treatment, the tumor registries contact patients and their medical providers every six months for follow-up data. These data are then reported to the Texas State Cancer Registry and to the Commission on Cancer's National Cancer Database.

We limited our study period to the years 2000–2007 for the following reasons: (1) randomized clinical trial data supporting the use of second-line chemotherapy for advanced NSCLC was first published in 2000⁷; (2) adequate data were first recorded by UT Southwestern-associated tumor registries in 2000; (3) maintenance chemotherapy for advanced NSCLC was not incorporated into clinical practice during this period; and (4) the 2007 cutoff provides sufficient follow-up time for survival outcomes. We included only those patients who received platinum-based doublet chemotherapy as first-line treatment, as a survival benefit of second-line or maintenance chemotherapy has not been demonstrated for patients treated with single-agent first-line regimens.

Recording and Definition of Variables

For each patient, the following demographic data were recorded: age, gender, race/ethnicity, and insurance type. Race/ethnicity was categorized as white (non-Hispanic), Hispanic, African-American, or other. Insurance type was recorded as one of the following: no insurance, Medicaid (a federal/state health care program for low-income families), Medicare (a federal health care program for individuals age 65 years and older), VA, and private. The designation “no insurance” primarily includes individuals ultimately treated through a Dallas County public health plan that provides patients access to all standard diagnostic and treatment modalities. Disease variables recorded included tumor histology, date of diagnosis, and date of death or last known follow-up. Histology was categorized as adenocarcinoma, squamous cell carcinoma, or other. Overall survival was defined as the interval between date of diagnosis and date of death.

We recorded the following treatment variables: receipt of palliative radiotherapy prior to initiation of first-line chemotherapy (and site irradiated), number of cycles of first-line chemotherapy, disease status at end of first-line chemotherapy, and receipt of second-line chemotherapy. For patients who received at least four cycles of first-line chemotherapy, post-treatment disease status was characterized as progressive or non-progressive according to the overall radiographic and clinical impression in the medical record. We did not review

imaging studies or employ formal scales, such as those of the World Health Organization (WHO) or Response Evaluation Criteria in Solid Tumors (RECIST) for this determination.

Statistical analysis

Descriptive statistics (medians/means for continuous variables and percentages for discrete variables) were generated for baseline demographic and clinical characteristics. Both univariate and multivariate logistic regression models were used to explore the association between demographic, disease, treatment characteristics, and receipt of second-line chemotherapy. In these analyses, age was dichotomized as < 65 years and ≥ 65 years; year of diagnosis was dichotomized as 2000–2003 and 2004–2007; race/ethnicity was characterized as white (non-Hispanic) or other. In the multivariate model, we included age, gender, race/ethnicity, insurance type, number of cycles of first-line chemotherapy, and pre-chemotherapy palliative radiation therapy. We analyzed the association between demographic, disease and treatment characteristics, receipt of second-line chemotherapy, and overall survival using univariate and multivariate Cox regression. Age, gender, race/ethnicity, insurance type, number of cycles of first-line chemotherapy, pre-chemotherapy palliative radiation therapy, and administration of second-line chemotherapy were included in the multivariate model. All reported *P* values are two-sided.

All statistical analyses were performed using SAS 9.2 Service Pack 4 for Windows (SAS Institute Inc., Cary, NC).

RESULTS

Study population

From the tumor registries, we identified a total of 472 patients who received first-line chemotherapy. Of these patients, 66 received single-agent first-line therapy (39 received a cytotoxic agent; 27 received an epidermal growth factor receptor [EGFR] tyrosine kinase inhibitor) and were excluded from the analysis. Within the remaining cohort of 406 patients, 186 (46%) were from Parkland Health and Hospital System, 153 (38%) were from the Dallas VA, and 67 (16%) were from University Hospital. Mean age was 59 years, 28% were women, and 59% were white. Additional patient characteristics are listed in Table 1. Median follow-up was 9.4 months.

Specific years of diagnosis were as follows: 2000 (32 patients), 2001 (48), 2002 (53), 2003 (50), 2004 (60), 2005 (48), 2006 (63), 2007 (52). Of the 132 patients listed as “other” histology, 3 had large cell and 129 had NSCLC not otherwise specified. Among the 121 patients who received pre-chemotherapy palliative radiation therapy, the following sites were irradiated: brain (65 patients), lung (23 patients), bone (18 patients), brain and lung (9 patients), brain and bone (5 patients), lung and bone (1 patient).

Second-line therapy administration

Overall, 197 of 406 patients (49%) received second-line chemotherapy. Of the 142 patients with non-progressive disease after 4–6 cycles of first-line chemotherapy, 95 (67%) received second-line chemotherapy. For 149 patients (76%), second-line chemotherapy was a cytotoxic agent. Forty-eight patients (24%) received an EGFR tyrosine kinase inhibitor as second-line therapy.

In univariate analysis, insurance type, number of cycles of first-line chemotherapy, and pre-chemotherapy palliative radiation therapy were significantly associated with receipt of second-line chemotherapy (see Table 2). In multivariate analysis, the following variables remained significantly associated with second-line chemotherapy administration: insurance

type ($P=0.003$), number of cycles of first-line chemotherapy (OR for < 4 cycles 0.24; 95% CI, 0.16–0.38; $P<0.001$), and receipt of pre-chemotherapy palliative radiation therapy (OR 0.51; 95% CI, 0.31–0.84; $P=0.008$).

Survival analysis

In univariate analysis, overall survival was associated with age (for ≥ 65 years, HR for death 0.76; 95% CI, 0.61–0.95; $P=0.02$), number of cycles of first-line chemotherapy (for < 4 cycles, HR for death 3.50; 95% CI, 2.82–4.34; $P<0.001$), and administration of second-line chemotherapy (if second-line chemotherapy received, HR for death 0.41; 95% CI, 0.34–0.51; $P<0.001$). Overall survival was not associated with gender, race/ethnicity, insurance type, or receipt of pre-chemotherapy palliative radiation therapy. In multivariate analysis, gender, number of cycles of first-line chemotherapy, and receipt of second-line chemotherapy were associated with overall survival (see Table 3 and Figure 1). For patients receiving fewer than 4 cycles of first-line chemotherapy, median survival was 164 days (95% CI, 146–185 days) compared to 495 days (95% CI, 431–522 days) for patients receiving 4 or more cycles. Overall, median survival was 185 days (95% CI, 159–206 days) for patients who did not receive second-line chemotherapy, versus 472 days (95% CI, 419–522 days) for those who did receive second-line treatment. When both variables were considered, median overall survival was as follows: fewer than 4 cycles of first-line chemotherapy without second-line therapy (128 days; 95% CI, 117–146 days), fewer than 4 cycles of first-line chemotherapy with second-line therapy (274 days; 95% CI, 231–353 days), 4 or more cycles of first-line chemotherapy without second-line therapy (329 days; 95% CI, 274–382 days), 4 or more cycles of first-line chemotherapy with second-line therapy (537 days; 95% CI, 503–601 days).

DISCUSSION

The recent wave of clinical trials examining the role of maintenance chemotherapy for advanced NSCLC has again placed a spotlight on the benefits of second-line chemotherapy for this disease. Somewhat unexpectedly, these studies have revealed widely varying rates of second-line chemotherapy administration. In some studies, the likelihood of patients randomized to observation after first-line chemotherapy receiving chemotherapy at the time of progression is below 20%,¹ raising the possibility that broader use of second-line therapies could mitigate some of the benefit attributed to a maintenance approach. The study of immediate (i.e., maintenance) or delayed docetaxel following 4 cycles of first-line therapy provides a prime example of this scenario; overall survival for patients who received immediate docetaxel and for the two-thirds of patients randomized to delayed docetaxel who ultimately received the assigned treatment was identical.⁴

The current study, which employs a contemporary, diverse, and unselected population, offers further insight into the real-world experience of second-line NSCLC treatment. In this cohort, 67% of individuals who had not progressed after receiving 4 cycles of first-line chemotherapy (i.e., those patients considered candidates for maintenance chemotherapy) ultimately received second-line treatment. While this rate itself is noteworthy for matching those reported in numerous maintenance therapy clinical trials,^{2,4,10} it must also be placed into context. Our population likely includes many individuals who, either due to performance status, adherence to medical care, or comorbidities, would not be candidates for clinical trials. This study also examines second-line chemotherapy patterns among the larger population of all patients with advanced NSCLC receiving first-line treatment. Compared to the maintenance chemotherapy-eligible cohort, patients who—either because of disease progression, intolerable toxicities, or non-adherence—did not receive 4 cycles of first-line chemotherapy were substantially less likely to receive second-line chemotherapy (OR 0.26).

This and earlier studies raise numerous questions. Why is there such variation in rates of second-line chemotherapy administration? What are the reasons patients do not receive second-line therapy? Why does the rate of second-line chemotherapy use in our series of unselected patients treated in a relatively uncontrolled setting match or exceed that of several prospective, randomized clinical trials? While there are no precise explanations, features of these clinical trials may have contributed to these observations. One study—in which disease progression was cited as the predominant reason why one-third of patients in the non-maintenance arm did not receive second-line chemotherapy—employed a relatively long (three-month) inter-scan interval in the non-maintenance arm, during which symptomatic progression and associated clinical decline may have hindered administration of second-line therapy.⁴ Another study—conducted in over 80 centers in 20 countries, throughout which second-line practice patterns could vary considerably—left the administration and selection of post-progression treatment to the discretion of the investigator rather than mandating second-line therapy for patients in the non-maintenance arm.¹⁰ A third study included a high proportion of patients with poor performance status (>80% ECOG 2).¹

We found the following variables to be associated with receipt of second-line chemotherapy: insurance type, number of cycles of first-line chemotherapy, and receipt of palliative radiation therapy prior to first-line chemotherapy administration. In a previous study of a similar patient cohort, we found that older patients with advanced NSCLC were less likely to receive *first-line* chemotherapy,¹⁸ presumably because older individuals tend to be more frail and have more medical comorbidities. It seems logical that age would not be associated with receipt of *second-line* chemotherapy in the same population because those older patients not fit for chemotherapy have already been selected out of the present study cohort. These observations echo those of a subset analysis of the phase III trial of second-line pemetrexed versus docetaxel, in which elderly patient participation was similar to rates observed in the first-line setting.¹⁹ By contrast, we found insurance type to predict receipt of both first-line¹⁸ and second-line treatment. While reasons for this ongoing association throughout the entire disease course are not evident from either study, it seems possible that insurance type—a surrogate marker of socioeconomic status—could be associated not only with performance status and comorbidities, but also with treatment preferences and adherence to medical care, factors that continue to impact populations well beyond first-line chemotherapy. Year of diagnosis was not associated with second-line chemotherapy administration, although we had expected to see an increase after 2004, when results of phase III trials of second-line erlotinib and pemetrexed, as well as second-line docetaxel quality of life data, were presented.^{8–9,20}

Our use of pre-chemotherapy palliative radiation therapy as a predictive variable also merits comment. We selected this unconventional metric as a potential marker of disease burden and severity. It represents a diverse group of patients, including those with brain metastases; clinically significant hemoptysis or airway compromise; and refractory pain, neurologic sequelae, or skeletal instability from bony metastases. It is possible that these patients represent a population at subsequent risk for a more symptomatic, complex clinical course. It follows that these patients are substantially less likely to receive second-line chemotherapy (OR 0.53 in this study). It seems less likely that pre-chemotherapy palliative radiation therapy itself—either via the delay in initiation of systemic therapy or through radiation-associated toxicities—accounts for the reduced rate of second-line chemotherapy administration.

Both the number of cycles of first-line chemotherapy and the receipt of second-line chemotherapy were independently associated with overall survival. While no conclusions about the effect of these treatment factors on clinical endpoints can be drawn from this

observational, non-randomized trial, these findings may provide insight into overall outcomes. We selected a cut-off of 4 cycles of first-line chemotherapy because this number implies clinical effect (as radiographic studies assessing response to therapy are typically performed every 2 cycles), acceptable toxicity profile, and patient adherence to treatment. Among patients who ultimately received second-line chemotherapy, median survival was 17.9 months for those who received 4 or more cycles of first-line chemotherapy, compared to 8.7 months for those who received fewer than 4 cycles of first-line chemotherapy. These findings echo those of earlier studies, in which response to first-line chemotherapy was an independent predictor of receipt of second-line chemotherapy¹¹ and overall survival.²¹

Limitations of this study include its retrospective nature, its single academic center setting, and relatively small sample size. Despite the retrospective design, disease and treatment follow-up data were available until patient death for over 95% of the cohort. Due to the geographical setting and variety of UT Southwestern-affiliated clinical facilities, our patient cohort is racially and socioeconomically diverse. Nonetheless, certain patient populations, such as East Asians, are under-represented. Furthermore, the physicians caring for these individuals are predominantly academic thoracic oncologists, who may be more likely to employ second-line chemotherapy than are other practitioners. That stated, the ability of these physicians to deliver second-line chemotherapy to two-thirds of this largely socioeconomically challenged cohort suggests that it may be feasible in most other U.S. settings as well. Finally, reasons why second-line chemotherapy was not administered were not available.

In conclusion, in this unselected, diverse cohort of patients with advanced NSCLC, approximately 50% of patients who received first-line chemotherapy eventually received second-line chemotherapy. Limiting the analysis to those individuals whose disease did not progress after 4–6 cycles of first-line chemotherapy—the population eligible for maintenance chemotherapy—the rate rises to 67%, a figure that meets or exceeds those of numerous recent clinical trials. Markers of socioeconomic status, symptom burden, and response to and tolerance of first-line chemotherapy were associated with receipt of second-line chemotherapy. Maintenance chemotherapy trials have highlighted critical economic and quality of life issues. The cost per life-year gained from maintenance pemetrexed exceeds \$120,000.²² While approved maintenance agents such as pemetrexed and erlotinib are generally well tolerated, there is clearly a subset of patients who maintain prolonged disease control after first-line chemotherapy with no subsequent treatment—and who then successfully receive second-line therapy at the time of progression. It follows that identifying those patients least likely to receive second-line chemotherapy might guide the selective use of maintenance chemotherapy, thereby limiting both costs and toxicities. Based on the findings in the present study, socioeconomically disadvantaged patients and patients with greater symptom burden—manifest by the need for pre-chemotherapy palliative radiation therapy—may represent such a target population.

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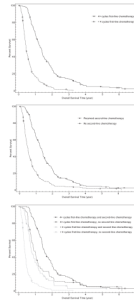


FIGURE 1. Overall survival curves of patients categorized by number of cycles of first-line chemotherapy (Fig. 1a), receipt of second-line chemotherapy (Fig. 1b), and both the number of cycles of first-line chemotherapy and receipt of second-line chemotherapy (Fig. 1c).

TABLE 1

Baseline patient characteristics

Characteristic	Mean (\pm SD) or number (%)
Total number	406
Age (y)	59.1 \pm 10.6
Gender	
Male	294(72.4)
Female	112 (27.6)
Race/ethnicity	
Non-Hispanic white	238(58.6)
African-American	127(31.3)
Hispanic	32(7.9)
Other	9(2.2)
Insurance type	
Private insurance	91(22.9)
No insurance	85(21.4)
Medicaid	20(5.0)
Medicare	47(11.8)
VA	154(38.8)
Year of diagnosis	
2000–2003	182(44.8)
2004–2007	224(55.2)
Histology	
Adenocarcinoma	168(41.4)
Squamous cell	106(26.1)
Other	132(32.5)
Number of cycles of first-line chemotherapy	
1–3	202 (49.8)
\geq 4	204 (50.2)
Non-progressor after \geq 4 cycles of first-line chemotherapy	
Yes	141(34.7)
No	59(14.5)
Not applicable	206 (50.7)
Pre-chemotherapy palliative radiation therapy	
Yes	121(30.0)
No	283(70.0)

SD, Standard Deviation

TABLE 2

Association Between Baseline Characteristics and Administration of Second-Line Chemotherapy (Univariate Analysis)

Characteristic	Number (%) Receiving Second-Line Chemotherapy	OR(95% CI) for Receiving Second-Line Chemotherapy	Overall P Value
Age			
< 65 y	137/287(47.7)	Reference	0.73
≥ 65 y	59/119(49.6)	1.08(0.70–1.65)	
Gender			
Male	139/294(47.3)	Reference	0.51
Female	57/112(50.9)	1.16(0.75–1.79)	
Race/ethnicity			
Non-Hispanic white	116/238(48.7)	Reference	0.82
Other	80/168(47.6)	0.96(0.64–1.42)	
Insurance type			
Private insurance	55/91(60.4)	Reference	0.007
No insurance	37/85(43.5)	0.51(0.28–0.92)	
Medicaid	7/20(35.0)	0.35 (0.13–0.97)	
Medicare	29/47(61.7)	1.06(0.51–2.17)	
VA	63/154(40.9)	0.45(0.27–0.77)	
Year of diagnosis			
2000–2003	82/182(45.1)	0.79(0.53–1.17)	0.24
2004–2007	114/224(50.9)	Reference	
Histology			
Adenocarcinoma	88/168(52.4)	Reference	0.37
Squamous cell	47/106(44.3)	0.72(0.44–1.18)	
Other	61/132(46.2)	0.78(0.50–1.23)	
No. cycles of first-line chemotherapy			
1–3	64/202(32.0)	0.26(0.17–0.40)	<0.001
≥4	131/204(64.2)	Reference	
Pre-chemotherapy palliative radiation therapy			
Yes	45/121(37.2)	0.53(0.34–0.82)	0.005
No	149/283(52.7)	Reference	

CI, Confidence Interval; OR, Odds Ratio

TABLE 3

Association Between Demographics, Treatment Characteristics, and Overall Survival (Multivariate Analysis)

Characteristic	HR (95% CI) for Death	Overall P Value
Age		
< 65 y	Reference	0.14
≥ 65 y	0.82(0.63–1.07)	
Gender		
Male	Reference	0.03
Female	0.75(0.57–0.97)	
Race/ethnicity		
Non-Hispanic white	Reference	0.25
Other	0.87(0.70–1.10)	
Insurance type		
Private insurance	Reference	
No insurance	1.17(0.85–1.60)	0.46
Medicaid	1.38(0.83–2.30)	
Medicare	1.40(0.93–2.09)	
VA	1.13(0.82–1.55)	
Number of cycles of first-line chemotherapy		
1–3	3.16(2.52–3.96)	<0.001
≥4	Reference	
Pre-chemotherapy palliative radiation therapy		
Yes	0.83(0.65–1.05)	0.13
No	Reference	
Receipt of second-line chemotherapy		
Yes	0.46(0.37–0.58)	<0.001
No	Reference	

CI, Confidence Interval