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Scientific Article

Time Interval to Initiation of Whole-Brain Radiation Therapy in Patients With Small Cell Lung Cancer With Brain Metastasis

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Abstract

Purpose: Patients with small cell lung cancer (SCLC) who have brain metastases require whole-brain radiation therapy (WBRT). When there is no emergent indication for WBRT, patients may receive systemic therapy first and WBRT afterward. In scenarios when systemic therapy is initiated first, it has not been previously investigated whether delaying WBRT is harmful.

Methods and Materials: The National Cancer Database was queried (2004-2016) for patients with SCLC with brain metastases who received 30 Gy in 10 fractions of WBRT. Patients were divided into groups based on whether they received early WBRT (3-14 days after initiation of chemotherapy) or late WBRT (15-90 days after initiation of chemotherapy). Demographic and clinicopathologic categorical variables were compared between those who had early WBRT (3-14 days) and those who had late WBRT (15-90 days). Factors predictive for late WBRT were determined. Overall survival (OS), which was defined as days from diagnosis to death, was evaluated and variables prognostic for OS were determined.

Results: A total of 1082 patients met selection criteria; 587 (54%) had early WBRT and 495 (46%) received late WBRT. Groups were similarly distributed aside from days from initiating chemotherapy to initiating WBRT ($P < .001$). The early WBRT group had a median of 7 days (interquartile range [IQR], 5-10 days) from initiating chemotherapy to initiating WBRT and the late WBRT group had a median of 34 days (IQR, 21-57 days). On binary logistic regression analysis, a longer time interval between diagnosis and the start of systemic therapy was predictive for later WBRT. Median OS was 8.7 months for early WBRT and 7.5 months for late WBRT (hazard ratio [HR], 1.165; $P = .008$). Early WBRT ($P = .02$), female sex ($P = .045$), and private insurance ($P = .04$) were favorable prognostic factors for OS on multivariable analysis, whereas older age ($P = .006$) was an unfavorable prognostic factor.

Conclusions: Patients with SCLC and brain metastases who received early WBRT were found to have a modest improvement in OS compared with patients who received late WBRT. These findings suggest that early WBRT should be offered to patients who have brain metastases, even in the absence of an indication for emergent WBRT.

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Third-party data: This study was based on the National Cancer Database. The authors do not own these data and hence are not permitted to share them in the original form (only in aggregate form, eg, publications). This data are owned by the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society.

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Introduction

Small cell lung cancer (SCLC) accounts for 14% of all lung cancer diagnoses, with approximately 30,000 new cases per year in the United States.[1,2] SCLC has a predilection for brain metastases, with approximately 10% of SCLC patients presenting with brain metastases at the time of diagnosis.[3] In current practice, patients with SCLC presenting with symptomatic brain metastases are typically managed with steroids and prompt whole-brain radiation therapy (WBRT).[4] Patients with asymptomatic brain metastases at diagnosis have the option of either starting systemic therapy (carboplatin, etoposide, and either atezolizumab or durvalumab) followed later by WBRT or receiving WBRT first followed by systemic therapy.[4] The prognostic outcome of delaying WBRT relative to the start of systemic therapy has not been investigated. The purpose of the present trial was to determine whether there is a clinical effect of delaying WBRT in patients with SCLC.

The current standard systemic therapy regimen for extensive-stage SCLC consists of 4 cycles of cisplatin, etoposide, and either atezolizumab or durvalumab delivered every 3 days with 21-day cycles.[4,5] Therapy is initiated rapidly because of the high proliferative rate displayed by the SCLC histology.[6] Brain metastases are generally considered the limiting factor for survival when present, but the blood-brain barrier limits the penetrance of systemic therapies such as immunotherapy and chemotherapy.[5,7-9] In addition to killing cancer within the brain, brain radiation therapy may impair the integrity of the blood-brain barrier, allowing greater central nervous system (CNS) penetration of systemic therapy.[10] For these reasons, WBRT is universally indicated for brain metastases in these patients. SCLC is very sensitive to chemotherapy and radiation therapy and has variable sensitivity to immunotherapy.[5,11-14] Lastly, all other things being equal, standard principles of radiobiology dictate that earlier radiation therapy is more effective than delaying radiation therapy because delaying radiation therapy leads to a greater population of cancer cells being present and requiring treatment.[15] Therefore, owing to the aforementioned clinical and radiobiologic characteristics, we hypothesized that early initiation of WBRT in this setting would produce favorable outcomes.

Methods and Materials

Data source and study populations

The National Cancer Database (NCDB) is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. It is a registry of deidentified information from hospital cancer registries for approximately 70% of the US population and includes data on tumor characteristics, patient demographics, and survival. The NCDB is not population based and thus greatly underrepresents rural areas and minority populations. All pertinent cases are reported regularly from centers accredited by the Commission on Cancer and compiled into a unified data set, which is then validated.[16] The data used in the study were derived from a deidentified Participant User File[17] and were therefore exempt from institutional review board oversight.

Patient selection

The NCDB was queried (2004-2016) for all patients with a histologically confirmed diagnosis of stage IV small cell lung carcinoma (261,441 patients). We selected for patients who received WBRT. Because the NCDB does not record whether a patient's brain metastases are symptomatic or asymptomatic, we limited this study to patients who had radiation therapy after initiating the first cycle of systemic therapy to define a cohort that did not require urgent radiation therapy. Because standard extensive stage-SCLC systemic regimens consist of agents administered during the first 3 days of each cycle,[5,18] we used 3 days after initiation of chemotherapy as a cutoff to define a cohort of patients who received radiation therapy after completing administration of the first cycle of chemotherapy. The NCDB does not record the number of chemotherapy cycles or the response to chemotherapy. Because the standard 4 cycles of systemic therapy would terminate at day 84, we excluded patients who did not begin WBRT by day 90. We included only patients who received 30 Gy in 10 fractions to ensure homogeneity in radiation treatment. We subsequently excluded patients who did not survive to day 90 to minimize survivorship bias by ensuring that those who were treated early would have survived long enough that they also could have been treated later.

These restrictions generated a homogeneous population. The early WBRT group was defined as initiating WBRT 37 to 14 days after initiating systemic therapy and the late WBRT group was defined as initiating WBRT 15 to 90 days after initiating systemic therapy. Two weeks (14 days) was chosen as the cutoff for defining early WBRT because we decided it was a reasonable maximum period to allow any practice in the United States to set up logistics for initiating WBRT. These logistical steps include referral to a radiation oncology center, insurance processing, computed tomography simulation, and 3-dimensional conformal radiation therapy planning. A flowchart showing selection of the primary study population is shown in Figure 1.

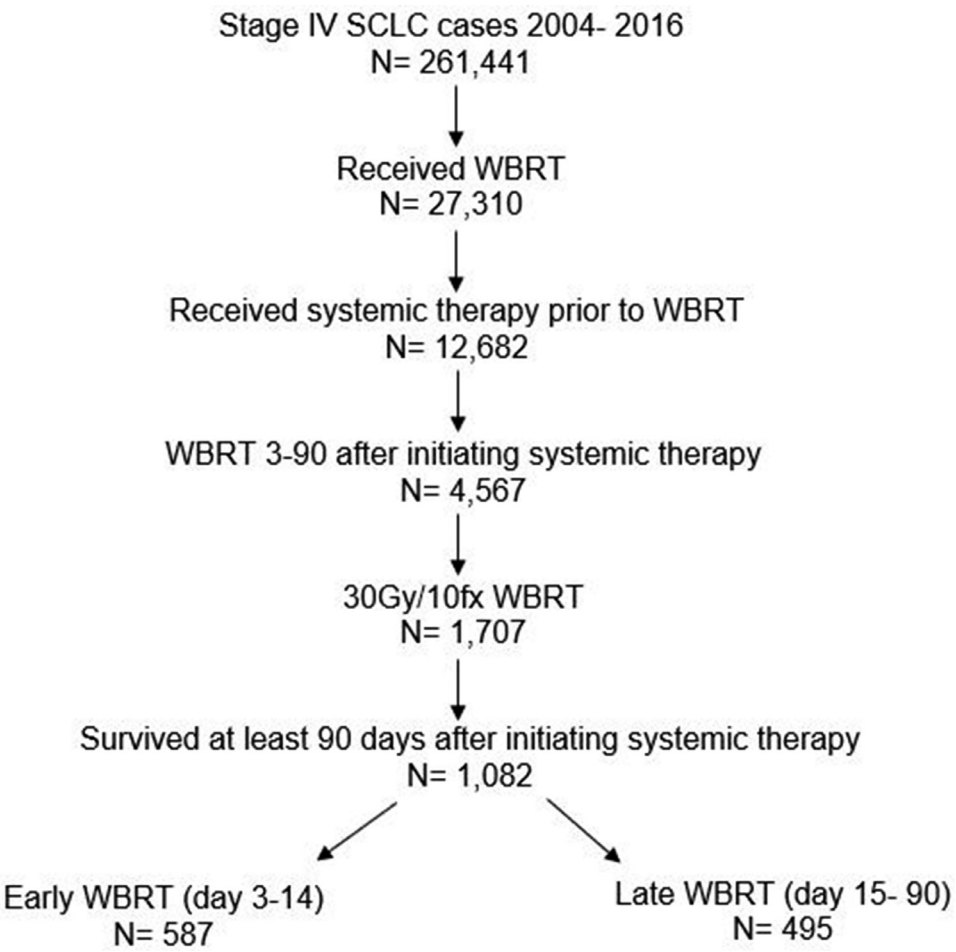

Figure 1 Study design.

Data analysis

Two-sided Pearson χ^2 testing was used to compare categorical frequencies between patients who received early WBRT versus those who received late WBRT. Binary logistic regression analysis determined which factors were predictive for early WBRT. The odds ratio (OR) is reported with the 95% confidence interval (CI) for each variable. Overall survival (OS) was calculated from the date of diagnosis to the date of death from any cause with censoring for the last follow-up. Kaplan-Meier log-rank analysis was used to evaluate OS. Univariable and multivariable Cox proportional hazards regression analysis was used to identify sociodemographic and clinicopathologic factors prognostic for OS. The hazard ratio (HR) is reported with the 95% CI for each variable. Factors with a P value $< .05$ on univariate analysis were included in the multivariate model. Statistical analyses were conducted using R (R Project for Statistical Computing) and SPSS (IBM).

Results

A total of 1082 patients met the selection criteria. The median follow-up was 8 months (interquartile range [IQR], 5-13 months). A total of 587 patients (54%) received WBRT from 3 to 14 days after initiating chemotherapy (early WBRT) and 495 (46%) received WBRT from 15 to 90 days after the initiation of chemotherapy (late WBRT). Overall, the median time from initiating systemic therapy to initiating WBRT was 13 days (IQR, 7-32 days). In the early WBRT group, the median time from initiating systemic therapy to initiating WBRT was 7 days (IQR, 5-10 days). In the late WBRT group, the median time from initiating systemic therapy to initiating WBRT was 34 days (IQR, 21-57 days).

All demographic and clinicopathologic variables were similar between the group that received early WBRT and the group that received late WBRT (Table 1). Overall, the median age was 64 years, 54% of patients were male, 87% of patients were White, and 44% of patients had Medicare insurance, compared with 37% of patients with private insurance. Overall, 46% of patients had T4 disease, 55% had N2 disease, and 60% had a recorded Charlson-Deyo Combined Comorbidity Score of 0. On binary logistic regression analysis (Table 2), the only factor predictive for later WBRT was the time interval between diagnosis and start of systemic therapy (OR, 1.007; 95% CI, 1.001-1.013; $P = .03$).

Table 1 Demographic and clinicopathologic details

Demographic details*	Overall	Early WBRT	Late WBRT	*P* value
Age, median (IQR), y	64 (56-70)	64 (56-70)	64 (56-71)	.67
Sex				
Male	587 (54)	315 (54)	272 (55)	.67
Female	495 (46)	272 (46)	223 (45)	
Race				
White	942 (87)	517 (88)	425 (86)	.37
Black	116 (11)	56 (10)	60 (12)	
Other	24 (3)	14 (2)	10 (2)	
Insurance				
Medicare	476 (44)	268 (46)	208 (42)	.86
Private	395 (37)	209 (36)	186 (38)	
Medicaid	106 (10)	55 (10)	51 (10)	
Other government insurance	38 (4)	21 (4)	17 (3)	
Uninsured	52 (5)	26 (4)	26 (5)	
Facility type				
Academic program	334 (31)	176 (30)	158 (32)	.57
Community cancer program	102 (9)	51 (9)	51 (10)	
Comprehensive cancer program	474 (44)	260 (45)	214 (43)	
Integrated network program	166 (15)	96 (16)	70 (14)	
Clinicopathologic details				
T stage				
T1	83 (10)	42 (9)	41 (11)	.13
T2	221 (27)	127 (28)	94 (25)	
T3	142 (17)	65 (15)	77 (21)	
T4	374 (46)	214 (48)	160 (43)	
N stage				
N0	92 (10)	47 (10)	45 (11)	.58
N1	84 (9)	42 (9)	42 (10)	
N2	498 (55)	262 (54)	236 (56)	
N3	227 (25)	131 (27)	96 (23)	
Time from diagnosis to initiating chemotherapy, median (IQR), d	14 (7- 26)	14 (6- 24)	16 (8- 27)	.26
Time from initiating chemotherapy to initiating WBRT, median (IQR), d	13 (7- 32)	7 (5- 10)	34 (21- 57)	<.001
Time from start of WBRT to end of WBRT, median (IQR), d	14 (12- 15)	14 (12- 15)	14 (12- 15)	.52
Years of diagnosis				
2004-2009	414 (38)	237 (40)	177 (36)	.22
2010-2016	668 (62)	350 (60)	318 (64)	
Charlson-Deyo score				
0	652 (60)	347 (59)	305 (62)	.40
≥1	430 (40)	240 (41)	190 (38)	

Abbreviations: IQR = interquartile range; WBRT = whole-brain radiation therapy.

* Data are presented as the number and percentage of participants unless otherwise indicated.

Median OS was 8.7 months for early WBRT versus 7.5 months for late WBRT (P = .008) (Fig 2). On univariable analysis (Table 3), early WBRT was a favorable prognostic factor for OS (HR, 1.179; 95% CI, 1.043-1.333; P = .009). In addition, female sex (HR, 0.853; 95% CI, 0.755-0.964; P = .01), private insurance (HR, 0.708; 95% CI, 0.617-0.811; P < .001), and Medicaid (HR, 0.767; 95% CI, 0.617-0.953; P = .02;) were favorable prognostic factors, whereas older age (HR, 1.018; 95% CI, 1.012-1.025; P < .001) and days from start to end of WBRT (HR, 0.997; 95% CI, 0.995-1.000; P = .04) were unfavorable prognostic factors. On multivariable analysis (Table 3), early WBRT (HR, 1.165; 95% CI, 1.028-1.320; P = .02), female sex (HR, 0.879; 95% CI, 0.774-0.997; P = .045), and private insurance (HR, 0.839; 95% CI, 1.003-1.021; P = .04) were favorable prognostic factors for OS, whereas older age (HR, 1.012; 95% CI, 1.003-1.021; P < .006) was an unfavorable prognostic factor.

Table 2 Binary logistic regression analysis for factors predicting late WBRT

Variables	OR	95% CI	*P* value
Age, y	1.012	0.995- 1.029	.18
Sex			
Male	1	-	-
Female	0.915	0.708- 1.182	.50
Race			
White	1	-	-
Black	1.291	0.843- 1.979	.24
Other	0.937	0.336- 2.619	.90
Insurance			
Medicare	1	-	-
Private	1.309	0.935- 1.832	.12
Medicaid	1.382	0.831- 2.298	.21
Other government insurance	1.092	0.522- 2.284	.82
Uninsured	1.568	0.815- 3.015	.18
Facility type			
Academic	1	-	-
CCP	1.224	0.764- 1.960	.40
CCCP	1.009	0.747- 1.363	.95
INCP	0.871	0.587- 1.291	.49
T stage			
T1	1	-	-
T2	0.688	0.406- 1.164	.16
T3	1.056	0.602- 1.850	.85
T4	0.727	0.442- 1.197	.21
N stage			
N0	1	-	-
N1	0.940	0.499- 1.771	.85
N2	0.907	0.561- 1.465	.69
N3	0.700	0.4412- 1.188	.19
Days from diagnosis to initiating chemotherapy	1.007	1.001- 1.013	.03
Days from start to end of WBRT	0.994	0.987- 1.000	.054
Years of diagnosis			
2004-2009	1	-	-
2010- 2016	0.994	0.987- 1.000	.054
Charlson-Deyo score			
0	1	-	-
≥1	0.879	0.677- 1.142	.34

Abbreviations: CCP = community cancer program; CCCP = comprehensive community cancer program; CI = confidence interval; INCP = integrated network cancer program; WBRT = whole-brain radiation therapy; OR = odds ratio.

Discussion

In what was, to our knowledge, the largest study to date comparing early WBRT with late WBRT in patients with brain metastases owing to SCLC, the results demonstrated that there was an OS benefit to early WBRT. Despite the OS benefit's being modest, these results imply that WBRT should not be unnecessarily delayed in this patient population.

The question of this study was to assess whether it is safe to delay WBRT in SCLC patients with brain metastases. In this patient population, there is a dilemma regarding the urgency of treating the brain with radiation compared with the urgency of treating the body with systemic therapy. Patients with extensive-stage SCLC without symptomatic metastases may receive systemic therapy as the first line of therapy.[4] Brain metastases are an absolute indication for WBRT, but to our knowledge, the timing of WBRT after initiation of systemic therapy has not been previously investigated as a prognostic factor.

In this study, the only factor that was predictive of later WBRT was the time interval between diagnosis and initiation of systemic therapy. Because both variables represent a delay in receiving treatment, this association may have been owed to other possible underlying social or logistic factors in these patients that resulted in delays. Specifically, some factors that may be related to delays in both systemic therapy and WBRT include workup as an outpatient, insurance details, access to treatment centers

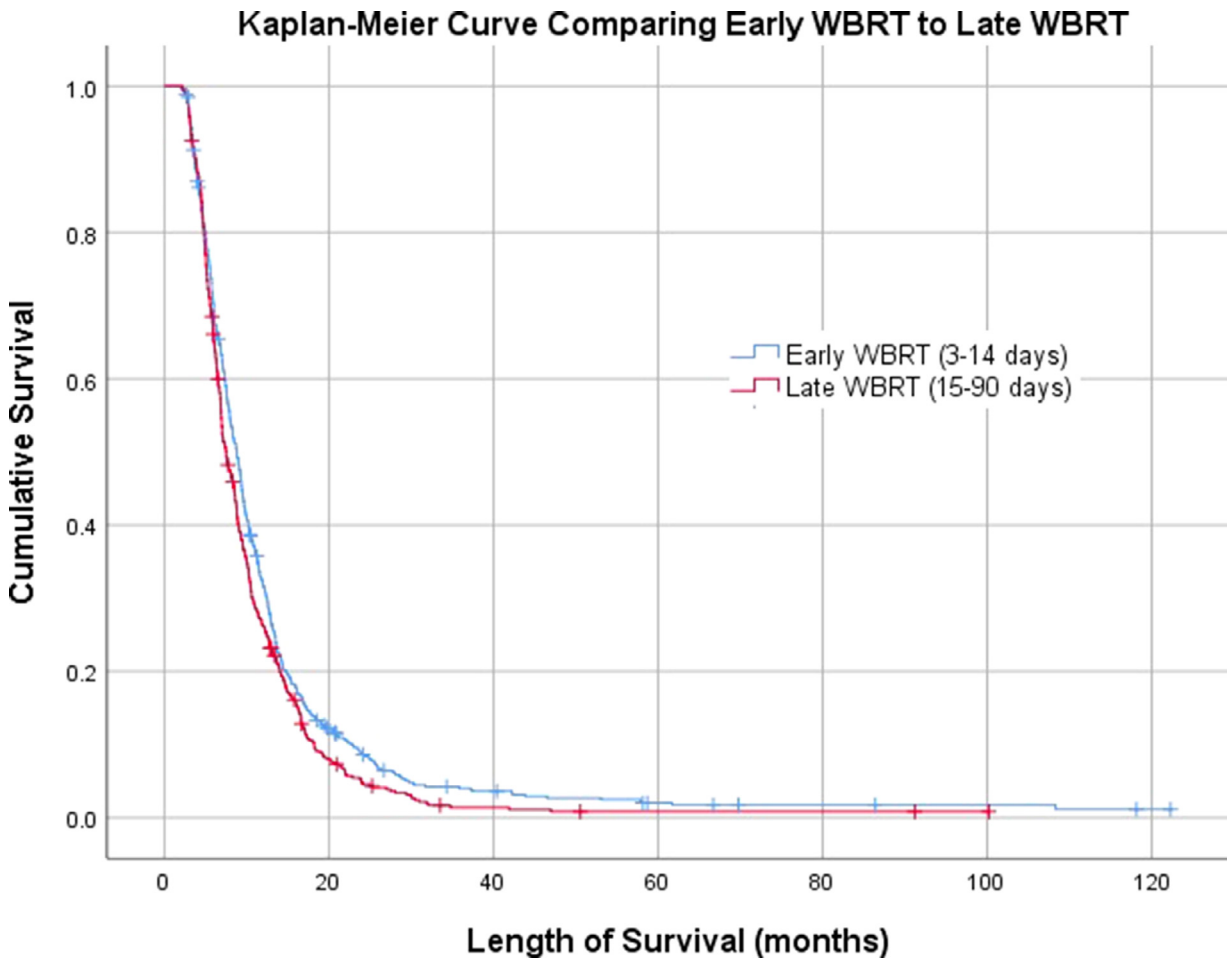

Figure 2 Kaplan-Meier curve.

in certain regions of the country, motivation for treatment, and social support.

The median time from initiation of chemotherapy to initiation of radiation therapy was 13 days, suggesting that in general, radiation therapy began early. Factors that might be responsible for a delay in WBRT include poor performance status, poor tolerance of systemic therapy, and an overall high burden of disease. The improvement in overall survival associated with earlier radiation therapy was relatively small in absolute terms—1.2 months—which may be explained by the terminal nature of this disease and the poor survival in general for patients with brain metastases.[7] However, this is similar to the absolute benefit of 2 months found with the addition of immunotherapy to chemotherapy in patients with extensive-stage SCLC.[5] The relative survival benefit was 14%, which better highlights the significance of these findings and constitutes a meaningful prolongation induced by earlier WBRT. Because brain metastases are the limiting factor for survival in these patients, we suspect that earlier WBRT improved survival because radiation therapy is more effective when tumor size is smaller compared with when tumor size is larger.

Older age was found to be a negative prognostic factor for overall survival as expected. Female sex was a positive prognostic factor for OS, which is consistent with the results of most SCLC trials.[19] Private insurance, compared with coverage with Medicare, was a positive prognostic factor for OS even after accounting for age on multivariable analysis. This may be owed to better availability of medical care, earlier workup and management such as earlier magnetic resonance imaging of the brain, and better palliative treatment options related to end-of-life care. The number of total days between the start and end of the radiation therapy course trended toward prognostic significance. This is supported by multiple studies of different aggressive malignancies, suggesting that extended treatment breaks during the course of radiation therapy lead to worse OS.[20-24] Comorbidities, as measured by the Charlson-Deyo Combined Comorbidity Score, were not prognostic for overall survival; this was expected, because brain metastases are the limiting factor for survival in these patients, rather than any comorbidity they may have.

There are numerous limitations to this study. The retrospective nature of the study precludes establishing

Table 3 Univariate and multivariate cox regression analyses of OS

	Univariate analysis			Multivariate analysis		
Variables	HR	95% CI	*P* value	HR	95% CI	*P* value
Age, y	1.018	1.012- 1.025	<.001	1.012	1.003- 1.021	.006
Sex						
Male	1	-	-	1	-	-
Female	0.853	0.755- 0.964	.01	0.879	0.774- 0.997	.045
Race						
White	1	-	-	-	-	-
Black	0.921	0.757- 1.121	0.41	-	-	-
Other	1.022	0.632- 1.653	0.93	-	-	-
Insurance						
Medicare	1	-	-	1	-	-
Private	0.708	0.617- 0.811	< 0.001	0.839	0.710- 0.991	0.04
Medicaid	0.767	0.617- 0.953	0.02	0.897	0.701-1.149	0.39
Other government insurance	0.657	0.659- 1.300	0.66	-	-	-
Uninsured	0.462	0.662- 1.206	0.46	-	-	-
Facility type						
Academic	1	-	-	-	-	-
CCP	0.946	0.753- 1.188	0.63	-	-	-
CCCP	1.073	0.930- 1.239	0.34	-	-	-
INCP	1.132	0.935- 1.371	0.20	-	-	-
T stage						
T1	1	-	-	-	-	-
T2	0.963	0.735- 1.261	0.78	-	-	-
T3	1.023	0.766- 1.364	0.88	-	-	-
T4	1.031	0.799- 1.330	0.81	-	-	-
N stage						
N0	1	-	-	-	-	-
N1	0.837	0.604- 1.160	0.29	-	-	-
N2	1.074	0.840- 1.375	0.57	-	-	-
N3	1.010	0.771- 1.322	0.94	-	-	-
Days from diagnosis to initiating chemotherapy	0.999	0.996- 1.001	0.29	-	-	
Days from initiating chemotherapy to initiating WBRT (continuous)	1.003	1.000- 1.005	0.04	-	-	—
Days from initiating chemotherapy to initiating WBRT						
3-14	1	-	-	1	-	-
≥15	1.179	1.043- 1.333	0.009	1.165	1.028- 1.320	0.02
Days from start to end of WBRT	0.997	0.995- 1.000	0.04	0.998	0.995- 1.000	0.06
Years of diagnosis						
2004-2009	1	-	-	-	-	-
2010- 2016	0.945	0.834- 1.071	0.37	-	-	-
Charlson-Deyo score						
0	1	-	-	-	-	-
≥1	1.105	0.975- 1.251	0.12	-	-	-

Abbreviations: CCP = community cancer program; CCCP = comprehensive community cancer program; CI = confidence interval; HR = hazard ratio; INCP = integrated network cancer program; WBRT = whole-brain radiation therapy.

causal relationships. The abundance of missing data in the NCDB led to exclusion of a large majority of cases. Although detailed radiation therapy data were available (ie, dose, fractions, and administration interval), the lack of detailed systemic therapy data further limited the study. For example, we did not know the regimen of systemic therapy administered, the number of cycles administered, when the cycles were administered, the patients' response to systemic therapy, or steroid use. We also did not know which patients received immunotherapy as part of their systemic therapy course; however, because the data included patients diagnosed until 2016, we assumed there was minimal immunotherapy use. In addition, we did not know the reason for the delay of

radiation therapy, the number or volume of brain metastases, or whether the brain metastases were symptomatic. Finally, it was not possible to determine at which point during the treatment course patients developed brain metastases. It is possible that patients receiving later WBRT were diagnosed with brain metastases at a later time, and this was the reason for the late initiation of WBRT. Despite these limitations, a strength of this trial is the time course of radiation therapy with respect to both diagnosis and initiation of chemotherapy.

For patients with SCLC who had brain metastases, this study's data showed that those who received WBRT within the first 2 weeks of starting systemic therapy had improved overall survival compared with patients who received WBRT between 2 weeks and 90 days after initiation of systemic therapy. These findings suggest that WBRT should not be delayed in patients with SCLC with brain metastases at diagnosis, assuming they are healthy enough at presentation to survive the standard systemic therapy course.

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