ACTA ONCOLOGICA
2019, VOL. 58, NO. 4, 491–498
https://doi.org/10.1080/0284186X.2018.1562207

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE



# Stereotactic radiosurgery for brain metastases from newly diagnosed small cell lung cancer: practice patterns and outcomes

Wei Jiang[a,b], Waqar Haque[a], Vivek Verma[c], Brian Butler[a] and Bin S. Teh[a]

[a]Department of Radiation Oncology, Houston Methodist Hospital, Houston, TX, USA; [b]Department of Radiation Oncology, National Cancer Center/Cancer Hospital & Shenzhen Hospital Chinese Academy of Medical Sciences, Shenzhen, China; [c]Department of Radiation Oncology, Allegheny General Hospital, Pittsburgh, PA, USA

**ABSTRACT**

**Background:** Up-front stereotactic radiosurgery (SRS) has been historically thought of as inadequate for brain metastases (BM) from newly diagnosed small cell lung cancer (SCLC). This study evaluates national practice patterns and clinical outcomes for BM from SCLC.

**Material and methods:** The National Cancer Database was queried (2004–2013) for patients with newly diagnosed metastatic SCLC receiving intracranial radiotherapy. Patients were grouped into three categories: upfront SRS, whole-brain radiotherapy (WBRT) alone, or WBRT with boost (SRS or fractionated radiotherapy). Statistics included temporal trend assessment by annual percent change (APC), logistic regression, exploratory Kaplan–Meier overall survival (OS) analysis without and with propensity matching, and Cox proportional hazards modeling.

**Results:** A total of 14,722 patients met selection criteria, of whom 487 (3.3%), 13,657 (92.8%), and 578 (3.9%) received upfront SRS, WBRT and WBRT with boost, respectively. Utilization of SRS showed a slight increasing trend from 2004 to 2013 (2.7–4.3%). In addition to socioeconomic factors, other variables associated with SRS use included diagnosis after 2010, treatment at academic centers, and residing in higher-educated regions. SRS was less often delivered to patients with node-positive disease ($p < .05$). On exploratory analysis, SRS cohort was observed to have a higher overall survival (OS) than WBRT-based groups ($p < .001$), namely in patients without extracranial metastases.

**Conclusions:** Utilization of up-front SRS for SCLC BM has been increasing over time but is driven by socioeconomic disparities. Although there are likely numerous biases associated with the OS findings herein, further research is needed to validate this finding as well as the role of SRS on patients with brain metastases due to SCLC.

**ARTICLE HISTORY**
Received 9 July 2018
Accepted 17 December 2018

## Introduction

Small cell lung cancer (SCLC), which accounts for 12–20% of all lung cancers, is a highly aggressive malignancy with a high likelihood of presenting with metastatic disease at diagnosis [1]. The brain is a common site of metastasis, even after delivering prophylactic cranial irradiation (PCI). Brain metastases (BM) are present in 10–14% of patients with SCLC at the time of initial diagnosis and greater than 50% of patients during the course of their disease [2]. Owing to the radiosensitivity of SCLC, intracranial radiotherapy has played a critical role in the treatment of patients with BM.

Given the diffuse nature of metastatic spread amongst patients with BM due to SCLC, and the high likelihood of clinically occult BM [3], whole brain radiation therapy (WBRT) is the primary treatment option for patients with intracranial metastatic disease. However, intracranial recurrence is still relatively common following WBRT, which also carries the risk of neurocognitive impairment [4,5]. Stereotactic radiosurgery (SRS) is a high-quality local therapy that is increasingly recommended for limited BM from other solid tumors, including non-small cell lung cancer (NSCLC). SRS has also been reported as a promising salvage treatment after WBRT for BM of SCLC [6,7]. Small retrospective case series have also demonstrated that upfront SRS offers favorable outcomes when used for patients with BM due to SCLC, with 1-year local control of 70–80% and median (overall) survival time (MST) of about 8 months [8].

Although controversy exists regarding the optimal treatment for this patient cohort, we hypothesize that the utilization of upfront SRS may be increasing on a national level over recent years. We aimed to utilize the National Cancer Data Base (NCDB) to identify the practice patterns of patients with BM from newly diagnosed SCLC as well as the clinical outcomes associated with various treatment regimens for this patient cohort.

## Methods and material

### *Data source and study population*

This retrospective analysis was conducted using the National Cancer Data Base (NCDB), a joint project of the Commission

CONTACT Bin S. Teh BTeh@houtsonmethodist.org Department of Radiation Oncology, Houston Methodist Hospital, Cancer Center, and Research Institute, Weill Cornell Medical College, 6565 Fannin, Ste DB1-077, Houston, TX 77030, USA

on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The NCDB contains de-identified information from ~70% of newly diagnosed cancers in the US, including treatment details unavailable in the Surveillance, Epidemiology, and End Results (SEER) database [9]. The data used in the study were derived from a de-identified NCDB file (2004–2015). The American College of Surgeons and the CoC have not verified and are neither responsible for the analytic or statistical methodology employed nor the conclusions drawn from these data by the investigators. As all patient information in the NCDB database is de-identified, this study was exempt from institutional review board evaluation.

Patients with newly diagnosed metastatic (stage IV) SCLC treated with intracranial RT were included in this analysis. Information collected included demographic, clinical, and treatment data for each patient. Patients with unknown RT modality and dose or treated with radioactive implants or brachytherapy were excluded from analysis. Patients were divided into three cohorts based on radiation modality delivered. Patient classified as being in the SRS category patients were those treated with upfront SRS. These patients received 'stereotactic radiosurgery, NOS [not otherwise specified]', 'LINAC radiosurgery', or 'gamma knife radiosurgery', or received a daily fraction dose $\geq$6 Gy in no more than 10 fractions as the upfront setting. Subjects receiving an additional boost to initial intracranial radiation which did not meet the aforementioned SRS criteria were designated as receiving WBRT with boost (WBRT + Boost) cohort; all other patients were categorized as WBRT cohort. Importantly, the NCDB only captures the first radiation treatment, so this study was limited to the initial treatment offered to patients and not salvage treatment.

### Statistical analyses

Demographic, clinical, and treatment characteristics were compared among the three cohorts using chi-squared tests. Variables were tested for co-linearity and interaction. Univariate and multivariable logistic regression with backward stepwise selection was performed by including variables with variance inflation factors (VIF) <10 to determine characteristics predictive for upfront SRS administration [10]. Temporal trends of different modalities were conducted with graphical assessment and estimated by annual percent change (APC).

Survival analysis was conducted by the Kaplan–Meier method after excluding patients without documented follow-up, and the log-rank test was used for cohort comparisons. Overall survival (OS) was defined as the interval between the date of diagnosis and the date of death or censored at last follow-up. Variables with $p < .2$ on univariate analysis were included in multivariable survival analysis with Cox proportional hazards modeling. Propensity score matching indicative of the likelihood of upfront SRS utilization was performed at a 1:1:1 ratio without replacement using the nearest neighbor method with a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score. All of the clinical, disease, and treatment characteristics recorded in Table 1 were used to general the propensity score used for matching. OS was estimated in the matched sample with the Kaplan–Meier method and log-rank test.

All statistical tests were two-sided, and a value of $p < .05$ was considered statistically significant. Analyses were performed using IBM SPSS, version 24.0 (IBM, Armonk, NY), R version 3.4.3 (www.R-project.org) and Joinpoint Regression Program Version 4.5.0.1, June 2017, National Cancer Institute (http://srab.cancer.gov/joinpoint/).

## Results

### Baseline characteristics

Figure 1 illustrates the inclusion and exclusion criteria for this study. A total of 14,722 patients met the pre-specified selection criteria. Of these patients, 487 (3.3%) received SRS, 13,657 (92.8%) underwent WBRT, and 578 (3.9%) were treated with WBRT + Boost. Table 1 presents baseline demographics and characteristics of patients. Most patients had an advanced T stage (T3–4, 41.2%) and N stage (N2–3, 64.7%). Over half of patients with records regarding the extent of metastatic disease had extracranial metastases. 82.7% of patients received systemic chemotherapy. Most patients in this analysis were white (88.1%), had government insurance (57.2%), and received treatment at non-academic facilities (71.4%). Most notably, the SRS cohort was older ($p = .008$) but had more negative lymph nodal and distant metastases ($p < .001$).

### Trends of preferential SRS utilization

Utilization of upfront SRS for brain metastases from SCLC displayed a statistically insignificant increase from 2004 to 2013 (2.7–4.3%, $p = .08$) (Figure 2(A)), with an APC of 4.17%. WBRT remained the most common therapy for BM from SCLC and constantly between 89 and 93%; however, utilization of WBRT with boost decreased used from 7.8% to 2.6% during this time period ($p < .001$).

Utilization rates of SRS were graphed when stratifying for facility status (Figure 2(B)); education status (Figure 2(C)); and income (Figure 2(D)). While SRS utilization at academic centers displayed no discernible trend, there was a steady increase in its use in non-academic facilities (Figure 2(B)). When determining SRS use while stratifying patients by socioeconomic status, increases in SRS utilization were observed following 2010 in both groups, with a greater rate of SRS use in the higher income group (Figure 2(C)). Patients in lower educated regions had a lower SRS utilization but continually increased when compared to patients in higher educated regions (Figure 2(D)).

### Factors predictive of upfront SRS utilization

On multivariable analysis (Table 2), SRS for newly diagnosed brain metastases from SCLC was more often received by

**Table 1.** Clinical characteristics of stage IV small cell lung cancer receiving radiation to brain.

| Characteristic | All $n = 14,722$ (%) | SRS $n = 487$ (%) | WBRT $n = 13,657$ (%) | WBRT + Boost $n = 578$ (%) | $p$ Value |
|---|---|---|---|---|---|
| *Clinical characteristics* | | | | | |
| Age | | | | | |
| <50 | 941 (6.4) | 36 (7.4) | 864 (6.3) | 41 (7.1) | .008 |
| 50–69 | 9263 (62.9) | 269 (55.2) | 8624 (63.1) | 370 (64.0) | |
| 70+ | 4518 (30.7) | 182 (37.4) | 4169 (30.5) | 167 (28.9) | |
| Gender | | | | | |
| Male | 7574 (51.4) | 248 (50.9) | 7025 (51.4) | 301 (52.1) | .930 |
| Female | 7148 (48.6) | 239 (49.1) | 6632 (48.6) | 277 (47.9) | |
| Race | | | | | |
| White | 12,963 (88.1) | 426 (87.5) | 12,029 (88.1) | 508 (87.9) | .529 |
| African American | 1160 (7.9) | 34 (7.0) | 1084 (7.9) | 42 (7.3) | |
| Hispanic | 280 (1.9) | 11 (2.3) | 256 (1.9) | 13 (2.2) | |
| Other/not recorded | 319 (2.2) | 16 (3.3) | 288 (2.1) | 15 (2.6) | |
| Charlson Deyo Score | | | | | |
| 0 | 9097 (61.8) | 229 (61.4) | 8431 (61.7) | 367 (63.5) | .826 |
| 1 | 4028 (27.4) | 139 (28.5) | 3735 (27.4) | 154 (26.6) | |
| 2 | 1597 (10.8) | 49 (10.1) | 1491 (10.9) | 47 (9.9) | |
| Facility type | | | | | |
| Academic | 4142 (28.1) | 190 (39.0) | 3812 (27.9) | 140 (24.2) | <.001 |
| Non academic | 10,507 (71.4) | 294 (60.4) | 9780 (71.6) | 140 (74.9) | |
| Unknown | 73 (0.5) | 3 (0.6) | 65 (0.5) | 5 (0.9) | |
| Insurance | | | | | |
| Private | 5038 (34.2) | 174 (35.7) | 4660 (34.1) | 204 (35.3) | .390 |
| Medicaid | 1315 (8.9) | 37 (7.6) | 1218 (8.9) | 60 (10.4) | |
| Medicare | 7111 (48.3) | 239 (49.1) | 6630 (48.3) | 269 (46.5) | |
| Not insured | 718 (4.9) | 15 (3.1) | 675 (4.9) | 28 (4.8) | |
| Other/not recorded | 540 (3.7) | 22 (4.5) | 501 (3.7) | 17 (2.9) | |
| Income | | | | | |
| $63,000 + | 3588 (24.4) | 151 (31.0) | 3312 (24.3) | 125 (21.6) | |
| <$62,999 | 10,806 (73.4) | 319 (65.5) | 10,047 (73.6) | 440 (76.1) | .001 |
| Not recorded | 328 (2.2) | 17 (3.5) | 298 (2.2) | 13 (2.2) | |
| Distance from facility | | | | | |
| <20 miles | 10,438 (70.9) | 332 (68.2) | 9701 (71.0) | 59 (65.6) | .598 |
| ≥20 miles | 3965 (26.9) | 141 (29.0) | 3663 (26.8) | 30 (33.3) | |
| Not recorded | 319 (2.2) | 14 (2.9) | 293 (21) | 12 (21) | |
| Year of diagnosis | | | | | |
| 2004–2007 | 4713 (32.0) | 137 (28.1) | 4312 (31.6) | 264 (45.7) | <.001 |
| 2008–2010 | 4791 (32.5) | 149 (30.6) | 4462 (32.7) | 180 (31.1) | |
| 2011–2013 | 5218 (35.4) | 201 (41.3) | 4883 (35.8) | 134 (23.2) | |
| Percent of zip code without high school education | | | | | |
| ≥29 | 2535 (17.2) | 64 (13.1) | 2376 (17.4) | 95 (16.4) | .002 |
| 20–28.9 | 3828 (26.0) | 105 (21.6) | 3551 (26.0) | 172 (29.8) | |
| 14–19.9 | 3635 (24.7) | 125 (25.7) | 3375 (24.7) | 135 (23.4 | |
| <14 | 4162 (28.3) | 164 (33.7) | 3847 (28.1) | 155 (26.8) | |
| Unknown | 562 (3.8) | 29 (6.0) | 512 (3.7) | 21 (3.6) | |
| *Disease characteristics* | | | | | |
| cT stage | | | | | |
| T1-2 | 5254 (35.7) | 171 (35.1) | 4866 (35.6) | 217 (37.5) | .512 |
| T3-4 | 6120 (41.6) | 196 (40.2) | 5706 (41.8) | 218 (37.7) | |
| T0-Tis | 143 (1.0) | 4 (0.8) | 133 (1.0) | 6 (1.0) | |
| Not reported | 3205 (21.8) | 116 (23.8) | 2952 (21.6) | 137 (23.7) | |
| cN stage | | | | | |
| N0 | 1757 (11.9) | 78 (16.0) | 1580 (11.6) | 99 (17.1) | <.001 |
| N1 | 1220 (8.3) | 34 (7.0) | 1137 (8.3) | 49 (8.5) | |
| N2 | 6737 (45.8) | 212 (43.5) | 6283 (46.0) | 242 (41.9) | |
| N3 | 2787 (18.9) | 79 (16.2) | 2620 (19.2) | 88 (15.2) | |
| Unknown | 2221 (15.1) | 84 (17.2) | 2037 (14.9) | 100 (17.3) | |
| Extracranial metastasis | | | | | <.001 |
| No | 2610 (17.7) | 109 (22.4) | 2411 (17.7) | 90 (15.6) | |
| Yes | 2668 (18.1) | 77 (15.8) | 2525 (18.5) | 66 (11.4) | |
| Not record/unknown | 9444 (64.1) | 301 (61.8) | 8721 (63.9) | 422 (73.0) | |
| *Treatment characteristics* | | | | | |
| Chemotherapy | | | | | |
| No | 2381 (16.2) | 85 (17.5) | 2210 (16.2) | 86 (14.9) | .397 |
| Yes | 12,174 (82.7) | 393 (80.7) | 11,297 (82.7) | 484 (83.7) | |
| Not reported | 167 (1.1) | 9 (1.8) | 150 (1.1) | 8 (1.4) | |

SRS: stereotactic radiosurgery; WBRT: whole brain radiation therapy.

patients treated at academic centers and residing in higher-educated regions ($p < .05$ for both). Tumor characteristics associated with decreased SRS use were the presence of node-positive disease as well as the presence of extracranial metastases. Also, SRS was delivered less often in patients without insurance ($p = .046$), in patients with lower incomes (trend, $p = .089$), and those residing farther from treating facilities (trend, $p = .099$).

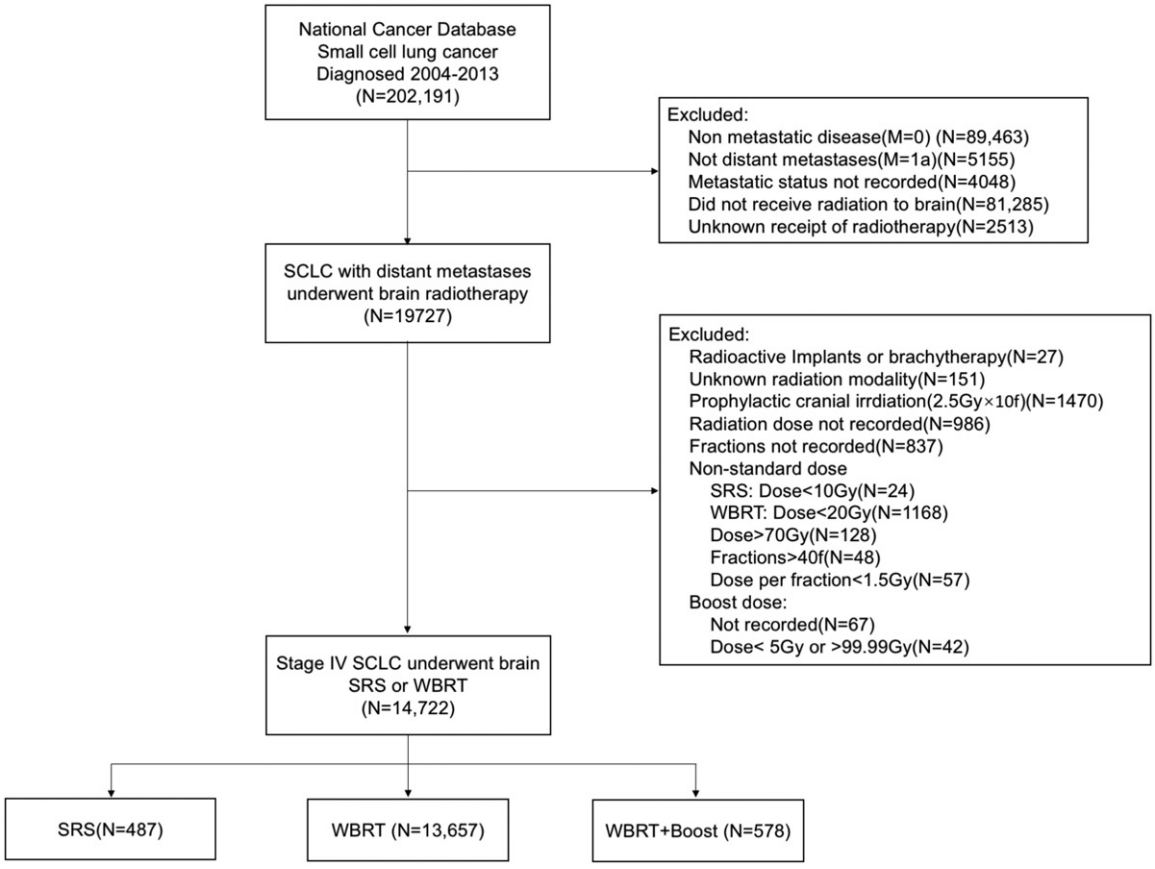


**Figure 1.** Patients' selection diagram. SCLC: small cell lung cancer; SRS: stereotactic radiosurgery; WBRT: whole brain radiation therapy.

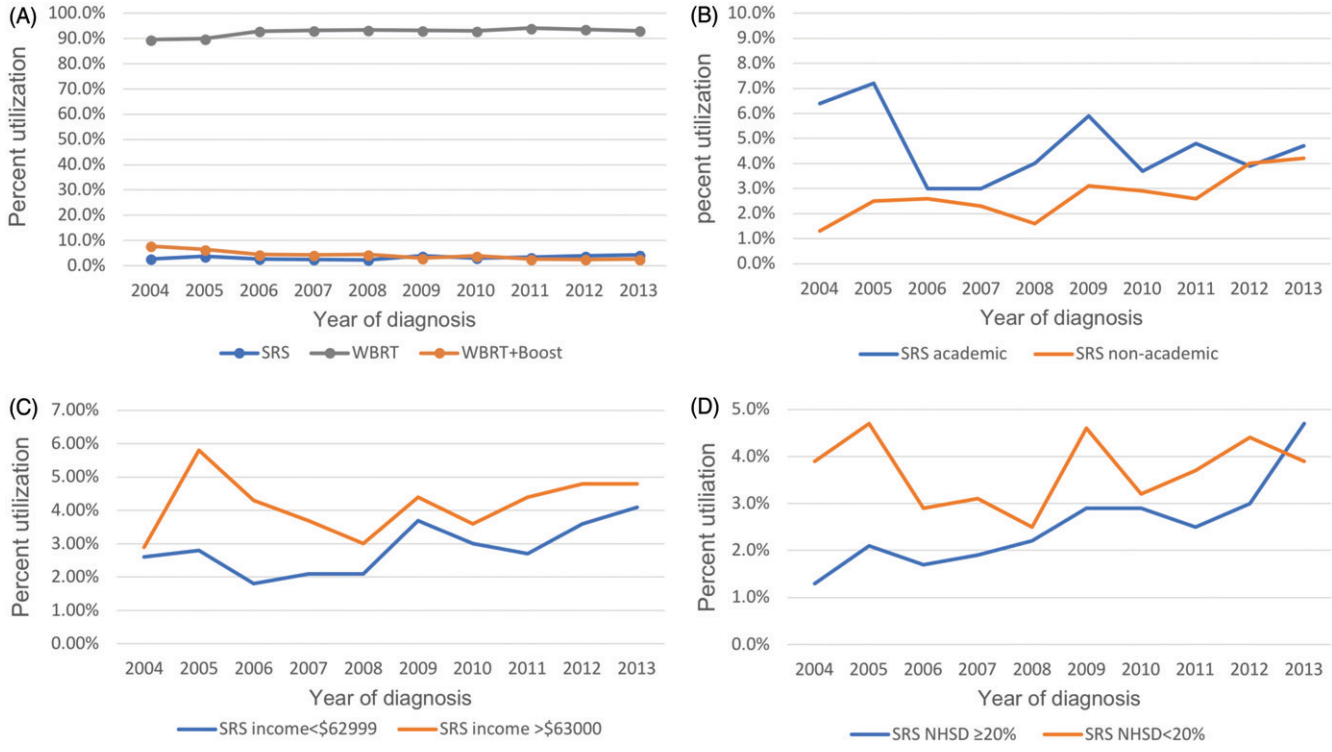


**Figure 2.** Temporal trends of radiotherapy modalities for brain metastases from small cell lung cancer. (A) All patients; (B) patients stratified by facility status; (C) patients stratified by income status; (D) patients stratified by education status. SRS: stereotactic radiosurgery; WBRT: whole brain radiation therapy; NHSD: no high school diploma.

**Table 2.** Multivariable analysis of predictor for upfront SRS use for SCLC brain metastases.

| Characteristics | Odds ratio | 95% Confidence interval | *p* Value |
|---|---|---|---|
| Age | | | |
| <50 | 1 (reference) | | |
| 50–69 | 0.746 | 0.519–1.074 | .115 |
| 70+ | 1.037 | 0.713–1.509 | .848 |
| Gender | | | |
| Male | 1 (reference) | | |
| Female | 1.019 | 0.849–1.223 | .840 |
| Race | | | |
| White | 1 (reference) | | |
| African American | 0.947 | 0.654–1.372 | .775 |
| Hispanic | 1.381 | 0.740–2.576 | .311 |
| Other/not recorded | 1.402 | 0.834–2.358 | .203 |
| Charlson Deyo Score | | | |
| 0 | 1 (reference) | | |
| 1 | 1.087 | 0.883–1.337 | .432 |
| 2 | 0.947 | 0.694–1.292 | .730 |
| Facility type | | | |
| Academic | 1 (reference) | | |
| Non-academic | 0.617 | 0.511–0.744 | <.001 |
| Not recorded | 0.703 | 0.210–2.350 | .567 |
| Insurance | | | |
| Private | 1 (reference) | | |
| Medicaid | 0.811 | 0.562–1.172 | .265 |
| Medicare | 0.855 | 0.678–1.077 | .184 |
| Not insured | 0.575 | 0.334–0.990 | .046 |
| Other/not recorded | 1.126 | 0.712–1.783 | .612 |
| Income | | | |
| $63,000 + | 1 (reference) | | |
| <$62,999 | 0.809 | 0.633–1.033 | .089 |
| Not recorded | 6.638 | 1.413–28.703 | .016 |
| Distance from facility | | | |
| <20 miles | 1 (reference) | | |
| ≥20 miles | 1.194 | 0.967–1.473 | .099 |
| Not recorded | 0.134 | 0.030–0.593 | .008 |
| Year of diagnosis | | | |
| 2004–2007 | 1 (reference) | | |
| 2008–2010 | 1.148 | 0.897–1.469 | .272 |
| 2011–2013 | 1.534 | 1.147–2.051 | .004 |
| Percent of zip code without high school education | | | |
| ≥29 | 1 (reference) | | |
| 20–28.9 | 1.099 | 0.801–1.508 | .558 |
| 14–19.9 | 1.349 | 0.988–1.842 | .059 |
| <14 | 1.429 | 1.019–2.004 | .038 |
| Unknown | 1.998 | 1.050–3.800 | .035 |
| cT stage | 1.032 | 0.834–1.276 | .773 |
| T1–2 | 1 (reference) | | |
| T3–4 | 0.801 | 0.291–2.202 | .667 |
| T0–Tis | 1.032 | 0.834–1.276 | .773 |
| Not recorded | 1.063 | 0.811–1.393 | .660 |
| cN stage | | | |
| N0 | 1 (reference) | | |
| N1 | 0.641 | 0.424–0.968 | .034 |
| N2 | 0.742 | 0.567–0.970 | .029 |
| N3 | 0.669 | 0.484–0.925 | .015 |
| Unknown | 0.931 | 0.675–1.284 | .662 |
| Extracranial metastasis | | | |
| No | 1 (reference) | | |
| Yes | 0.709 | 0.525–0.958 | .025 |
| Not record/unknown | 0.965 | 0.731–1.274 | .801 |
| Chemotherapy | | | |
| No | 1 (reference) | | |
| Yes | 0.992 | 0.775–1.269 | .949 |
| Not recorded | 1.517 | 0.745–3.091 | .251 |

SRS: stereotactic radiosurgery; SCLC: small cell lung cancer.

### *Survival outcomes*

Owing to the numerous biases associated with survival analyses in a retrospective, heterogeneous population, OS analysis was conducted in an exploratory manner. At a median follow-up of 54.8 months, the median OS of all patients was 8.1 months. When evaluating outcomes for all patients, OS of the SRS, WBRT, and WBRT + Boost cohorts, respectively, were 10.02 versus 8.02 versus 9.3 months ($p < .001$, Figure 3(A)). Following propensity matching, the OS differences remained statistically significant, and favored the SRS arm ($p = .001$, Figure 3(B)).

Predictors of OS on multivariable analysis are depicted in Table 3. Based on the multivariable model, intracranial SRS, early T and N stage, absence of extracranial metastases, receipt of chemotherapy, younger age, female gender, white race, fewer comorbidities, non-governmental insurance, socioeconomic status, diagnosis after 2010, and residing farther from the treating facility were independently predictive of improved OS.

Survival outcomes were evaluated when stratifying by extracranial metastasis, and, as shown in Figure 3(C) and (D), SRS was associated with a significant OS advantage in patients with brain-only metastases ($p = .011$) but not in patients with extracranial metastases ($p = .977$).

## Discussion

SCLC is often excluded from large studies of SRS for BM owing to the high rate of 'distant brain failure' [11]. This study of a large, contemporary national database shows that WBRT is the most common treatment choice used for BM in this patient population. The utilization of SRS for these patients showed a slight increase trend over the study period from 2.7% in 2004 to 4.2% in 2013, with several socioeconomic factors impacting its use.

WBRT is the major strategy, but intracranial control remains a concern even at the expense of neurocognitive impairment [4]. Consequently, the role of SRS in these patients is increasingly being explored and some retrospective studies have suggested a benefit with the use of SRS [8, 12]. The increased utilization of SRS after 2010 is probably related to the improvement of SRS technology, which was reported in one study to be the strongest predictor of SRS use for BM [13]. National Comprehensive Cancer Network (NCCN) guidelines have recommended SRS for patients with limited BM from NSCLC as well as other solid tumors since 2011 [14].

The management of brain metastases also depends on extracranial disease status. This database analysis demonstrated that upfront SRS was less likely delivered to patients with extracranial metastases, consistent with national guidelines for most histologies [15]. Additionally, SRS is also preferred in patients with stable systemic disease or reasonable systemic treatment according to these guidelines. However, in our study, SRS held no OS benefit in patients with extracranial metastases; it is thus possible that the benefit of SRS may be limited to patients with well-controlled systemic disease. NSCLC patients have also been reported to have a worse OS with synchronous metastases and N positive disease than N0, suggesting aggressive treatment likely helps less for extensive disease [16]. Unfortunately, the response to first-line chemotherapy and stability of extracranial disease could not be accessed from this database, which is also an

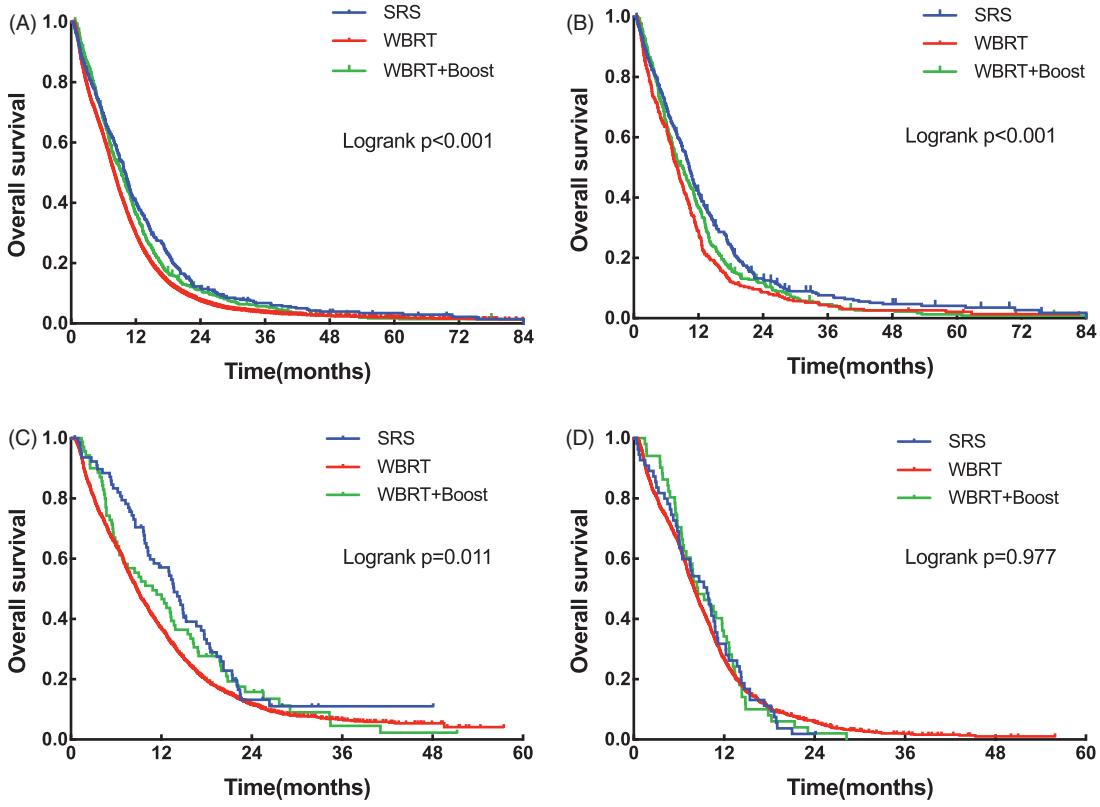


**Figure 3.** Kaplan–Meier overall survival curve of small cell patients with brain metastases treated with three radiotherapy modalities. (A) All patients; (B) propensity-matched population; (C) patients without extracranial metastases; (D) patients with extracranial metastases. SRS: stereotactic radiosurgery; WBRT: whole brain radiation therapy.

important limitation for this study. Further studies are needed to identify the optimal SCLC patients who would benefit from the use of SRS.

We also identified socioeconomic factors associated with preferential use of SRS: residence in higher-educated regions, household income, and the type of medical insurance. Similar factors have also been to predict for the use of SRS for brain metastasis from other histologies [17,18].

The increased use of SRS in academic facilities may be attributable to several factors. The advantages of academic settings such as greater multimodality co-ordination, regular follow-up imaging for early detection, and technical capabilities, may have contributed to the increased adoption of SRS. A survey on recommendations for SRS to BM displayed a greater degree of support for SRS planning among the providers at academic centers [19]. Also, academic institutions may offer more effective salvage therapies (or clinical trials), leading to the longer observed OS for patients at academic facilities and perhaps thus a greater detection of intracranial recurrences for which salvage SRS may have been used. Additionally, the utilization of SRS at non-academic institutions has been increasing. This is potentially related to SRS modifications based on an existing linear-accelerator which may have led to the increased ability for smaller non-academic facilities to deliver SRS [20]. To date, unsystematic comparisons showed equivalent survival and local progression-free survival between the two different techniques of Gamma knife or Linac-based SRS, encouraging the increased uptake of SRS for SCLC BMs [21].

Our study had several limitations inherent to studies from large databases [22–31]. First, there is a lack of disease-specific information in the NCDB, including a number of intracranial metastases, size, and location. The number of brain metastases is a very important factor for SRS adoption in other histologies [23], and patients receiving therapeutic WBRT are likely to have greater intracranial disease, that may confound the association we observed and may have led to a selection bias regarding the SRS cohort. Second, the absence of information regarding local and regional control make it difficult to determine the advantage of SRS in this disease with disseminated nature, and even the survival benefit should be interpreted with great caution without the information of salvage therapy. Third, there is no information on performance status, which is not the same as Charlson score. It is a key predictor of survival of BMs [24], also validated in SCLC patients [25], and an important indicator for treatment choice in BMs disease [26]. Fourth, though the NCDB does specify the location treated with radiation, it does not specify the volume within the volume that is treated. Therefore, patients having received radiation therapy to the brain and not meeting the criteria for SRS were coded as having received WBRT, it is possible that some of these patients may have received partial brain radiation. Fourth, the frequency and modality of post-therapy imaging is a critical factor that can influence the perceived "success" of SRS for SCLC BMs. Last, the generalizability is limited due to the omission of patients from non-CoC accredited facilities and rigorous selection in this analysis.

**Table 3.** Multivariable analysis of prognostic factors of overall survival for SCLC patients with brain metastases.

| Characteristic | HR | 95% CI | *p* Value |
|---|---|---|---|
| Modality | | | |
| SRS | 1 (reference) | | |
| WBRT | 1.334 | 1.204–1.478 | <.001 |
| WBRT + Boost | 1.152 | 1.009–1.317 | .037 |
| Age | | | |
| <50 | 1 (reference) | | |
| 50–69 | 1.022 | 0.947–1.102 | .576 |
| 70+ | 1.290 | 1.184–1.406 | <.001 |
| Gender | | | |
| Male | 1 (reference) | | |
| Female | 0.875 | 0.845–0.907 | <.001 |
| Race | | | |
| White | 1 (reference) | | |
| African American | 0.915 | 0.855–0.979 | .010 |
| Hispanic | 0.765 | 0.665–0.881 | <.001 |
| Other/not recorded | 0.842 | 0.742–0.956 | .008 |
| Charlson Deyo Score | | | |
| 0 | 1 (reference) | | |
| 1 | 1.138 | 1.092–1.186 | <.001 |
| 2 | 1.225 | 1.154–1.299 | <.001 |
| Facility Type | | | |
| Academic | 1 (reference) | | |
| Non-academic | 1.039 | 0.998–1.082 | .065 |
| Not recorded | 0.780 | 0.596–1.021 | .071 |
| Insurance | | | |
| Private | 1 (reference) | | |
| Medicaid | 1.176 | 1.097–1.260 | <.001 |
| Medicare | 1.197 | 1.144–1.253 | <.001 |
| Not insured | 1.159 | 1.061–1.267 | .001 |
| Other/not recorded | 1.122 | 1.016–1.238 | .022 |
| Income | | | |
| $63,000 + | 1 (reference) | | |
| <$62,999 | 1.065 | 1.020–1.112 | .004 |
| Not recorded | 2.690 | 1.293–5.599 | .008 |
| Distance from facility | | | |
| <20 miles | 1 (reference) | | |
| >20 miles | 0.954 | 0.915–0.995 | .028 |
| Not recorded | 0.472 | 0.225–0.990 | .047 |
| Year of diagnosis | | | |
| 2004–2007 | 1 (reference) | | |
| 2008–2010 | 0.958 | 0.917–1.001 | .056 |
| 2011–2013 | 0.899 | 0.846–0.956 | .001 |
| Percent of zip code without high school education | | | |
| ≥29 | 1 (reference) | | |
| 20–28.9 | 0.984 | 0.930–1.041 | .576 |
| 14–19.9 | 1.020 | 0.962–1.081 | .505 |
| <14 | 1.007 | 0.943–1.074 | .840 |
| Not recorded | 0.982 | 0.840–1.148 | .818 |
| cT stage | | | |
| T1–2 | 1 (reference) | | |
| T3–4 | 1.098 | 1.053–1.144 | <.001 |
| T0–Tis | 0.596 | 0.492–0.721 | <.001 |
| Tx | 1.015 | 0.962–1.072 | .557 |
| cN stage | | | |
| N0 | 1 (reference) | | |
| N1 | 1.051 | 0.968–1.140 | .238 |
| N2 | 1.217 | 1.146–1.293 | <.001 |
| N3 | 1.291 | 1.205–1.383 | <.001 |
| Nx | 1.102 | 1.022–1.189 | .011 |
| Extracranial metastasis | | | |
| No | 1 (reference) | | |
| Yes | 1.307 | 1.223–1.397 | <.001 |
| Not record/unknown | 1.133 | 1.064–1.206 | <.001 |
| Chemotherapy | | | |
| No | 1 (reference) | | |
| Yes | 0.380 | 0.361–0.400 | <.001 |
| Not reported | 0.499 | 0.417–0.598 | <.001 |

SCLC: small cell lung cancer; SRS: stereotactic radiosurgery; WBRT: whole brain radiation therapy; HR: hazard ratio; CI: confidence interval.

Additionally, the rationale for the selection of radiation treatment modality is missing from the present study, as this information is not present in the NCDB. Nevertheless, prospective trials of SRS for SCLC BM are underway, and the authors eagerly await the results of such trials (NCT0329778) addressing this issue.

## Conclusion

This NCDB analysis demonstrates that utilization of upfront SRS for BM from newly-diagnosed SCLC has been increasing over time. Socioeconomic disparities exist with regards to SRS utilization. The use of SRS was associated with improved OS, largely in patients without extracranial metastases, though this could be due to selection bias. Further research is required to further elucidate the role of SRS in BMs due to SCLC and the patients most likely to benefit from its use.

## Disclosure statement

The authors report no conflicts of interest.

## ORCID

Wei Jiang http://orcid.org/0000-0002-9079-0792
Vivek Verma http://orcid.org/0000-0002-5863-6023

## References

[1] Noone AM, Howlader N, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2015, National Cancer Institute [cited 2018 Apr 16]. Available from: https://seer.cancer.gov/csr/1975_2015/.
[2] Arriagada R, Le Chevalier T, Borie F, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. J Natl Cancer Inst. 1995;87:183–190.
[3] Baumert BG, Rutten I, Dehing-Oberije C, et al. A pathology-based substrate for target definition in radiosurgery of brain metastases. Int J Radiat Oncol Biol Phys. 2006;66:187–194.
[4] Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18:663–671.
[5] Bernhardt D, Adeberg S, Bozorgmehr F, et al. Outcome and prognostic factors in patients with brain metastases from small-cell lung cancer treated with whole brain radiotherapy. J Neurooncol. 2017;134:205–212.
[6] Nakazaki K, Higuchi Y, Nagano O, et al. Efficacy and limitations of salvage gamma knife radiosurgery for brain metastases of small-cell lung cancer after whole-brain radiotherapy. Acta Neurochir. 2013;155:107–113.
[7] Harris S, Chan MD, Lovato JF, et al. Gamma knife stereotactic radiosurgery as salvage therapy after failure of whole-brain radiotherapy in patients with small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2012;83:e53–e59.
[8] Yomo S, Hayashi M. Is stereotactic radiosurgery a rational treatment option for brain metastases from small cell lung cancer? A retrospective analysis of 70 consecutive patients. BMC Cancer. 2015;15:95.
[9] Bilimoria KY, Stewart AK, Winchester DP, et al. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. Ann Surg Oncol. 2008;15:683–690.
[10] Dormann CF, Elith J, Bacher S, et al. Collinearity: a review of methods to deal with it and a simulation study evaluating their performance. Ecography. 2013;36:27–46.

[11] Kann BH, Park HS, Johnson SB, et al. Radiosurgery for brain metastases: changing practice patterns and disparities in the United States. J Natl Compr Canc Netw. 2017;15:1494–1502.
[12] Serizawa T, Ono J, Ichi T, et al. Gamma knife radiosurgery for metastatic brain tumors from lung cancer: a comparison between small cell and non-small cell carcinoma. J Neurosurg. 2002;97: 484–488.
[13] Hodgson DC, Charpentier AM, Cigsar C, et al. A multi-institutional study of factors influencing the use of stereotactic radiosurgery for brain metastases. Int J Radiat Oncol Biol Phys. 2013;85: 335–340.
[14] National Comprehensive Cancer Network. Non-Small Cell Lung Cancer. 2011. Available from https://www.nccn.org/professionals/physician_gls/default.aspx.
[15] National Comprehensive Cancer Network. Central Nervous System Cancers. Version 1, 2018. [cited March 20, 2018.] Available from: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf.
[16] Ashworth AB, Senan S, Palma DA, et al. An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. Clin Lung Cancer. 2014;15:346–355.
[17] Haque W, Verma V, Butler EB, et al. Utilization of stereotactic radiosurgery for renal cell carcinoma brain metastases. Clin Genitourin Cancer. 2018;16:e935–e943.
[18] Park HS, Wang EH, Rutter CE, et al. Changing practice patterns of Gamma Knife versus linear accelerator-based stereotactic radiosurgery for brain metastases in the US. J Neurosurg. 2016;124: 1018–1024.
[19] Sandler KA, Shaverdian N, Cook RR, et al. Treatment trends for patients with brain metastases: Does practice reflect the data? Cancer 2017;123:2274–2282.
[20] Niranjan A, Maitz AH, Lunsford A, et al. Radiosurgery techniques and current devices. Prog Neurol Surg. 2007;20:50–67.
[21] Alongi F, Fiorentino A, Mancosu P, et al. Stereotactic radiosurgery for intracranial metastases: linac-based and gamma-dedicated unit approach. Expert Rev Anticancer Ther. 2016;16:731–740.
[22] Haque W, Verma V, Hatch S, et al. Omission of chemotherapy for low-grade, luminal A N1 breast cancer: Patterns of care and clinical outcomes. Breast 2018;41:67–73.
[23] Haque W, Verma V, Hatch S, et al. Response rates and pathologic complete response by breast cancer molecular subtype following neoadjuvant chemotherapy. Breast Cancer Res Treat 2018;170:559–567.
[24] Haque W, Verma V, Butler EB, et al. Omission of radiotherapy in elderly women with early stage metaplastic breast cancer. Breast 2018;38:154–159.
[25] Haque W, Verma V, Naik N, et al. Metaplastic Breast Cancer: Practice Patterns, Outcomes, and the Role of Radiotherapy. Ann Surg Oncol 2018;25:928–936.
[26] Haque W, Verma V, Butler EB, et al. Chemotherapy versus chemoradiation for node-positive bladder cancer: practice patterns and outcomes from the National Cancer Data Base. Bladder Cancer 2017;3:283–291.
[27] Haque W, Verma V, Bernicker E, et al. Management of pathologic node-positive disease following initial surgery for clinical T1-2 N0 esophageal cancer: patterns of care and outcomes from the national cancer data base. Acta Oncol 2018;57:782–789.
[28] Haque W, Lewis GD, Verma V, et al. The role of adjuvant chemotherapy in locally advanced bladder cancer. Acta Oncol 2018;57:509–515.
[29] Haque W, Verma V, Butler EB, et al. National practice patterns and outcomes for T4b urothelial cancer of the bladder. Clin Genitourin Cancer 2018;16:42–49.e1.
[30] Haque W, Verma V, Butler EB, et al. Radical cystectomy versus chemoradiation for musle-invasive bladder cancer: impact of treatment facility and sociodemographics. Anticancer Res 2017;37:5603–5608.
[31] Haque W, Verma V, Butler EB, et al. Radiation dose in neoadjuvant chemoradiation therapy for esophageal cancer: patterns of care and outcomes from the National Cancer Data Base. J Gastrointest Oncol 2018;9:80–89.