Stereotactic Radiosurgery for Brain Metastases in Small Cell Lung Cancer: The Davidoff Cancer Center Experience

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ABSTRACT: **Background:** Prophylactic cranial irradiation (PCI) omission in favor of brain magnetic resonance imaging (MRI) staging and surveillance in the management of small cell lung cancer (SCLC) is controversial yet accepted by some centers. The use of MRI suggests performing stereotactic radiosurgery (SRS) treatment for limited brain metastases. Data regarding SRS efficacy in this setting is limited.

Objectives: To assess intracranial objective response rate (iORR), progression-free survival (iPFS), intracranial failure patterns, overall survival (OS) and time-to-whole-brain radiation therapy (WBRT)/death, whichever occurred first (TTWD) with SRS in SCLC.

Methods: The study comprised 10 consecutive SCLC patients with brain metastases treated with SRS and followed-up at Davidoff Cancer center between Aug 2012 and March 2019. Brain MRI images were reviewed by a neuro-radiology specialist.

Results: iORR was 57% as assessed by response assessment in neuro-oncology brain metastases. Intracranial progression developed in 8 patients. Median iPFS was 4.0 months (95% confidence interval [95%CI] 1.7–7.2). In-site, off-site and combined pattern of intracranial failure was seen in 0, 5, and 3 patients, respectively; median number of new brain lesions following SRS was 4 (range, 1–12). SRS was performed 10 additional times in 6 patients (median number of lesions irradiated per round was 1, range 1–5). WBRT was administered in 3 patients. Median TTWD was 20.9 months (95% CI, 1.9–26.8). Median OS since SRS administration was 23.2 months (95% CI, 4.2–not reached).

Conclusions: MRI surveillance with multiple rounds of SRS may serve a reasonable alternative to PCI or therapeutic WBRT in SCLC.

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KEY WORDS: brain magnetic resonance imaging (MRI), brain metastases, small cell lung cancer (SCLC), prophylactic cranial irradiation (PCI), stereotactic radiosurgery (SRS)

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Small cell lung cancer (SCLC) is a poorly differentiated neuroendocrine tumor, which comprises approximately 15% of all lung cancer cases and occurs mainly in smokers [1]. In 60–70% of patients it presents as a disseminated disease [1]. Despite being sensitive to chemotherapy and radiation SCLC tends to relapse early and the prognosis is poor overall. Median survival ranges are between 14–30 months in limited disease stage and 9–11 months in extensive disease stage, as classified by the Veterans Administration Lung Study Group (VALSG) classification.[2-4]. Overall incidence of brain metastases in SCLC is above 50% [5].

Prophylactic cranial irradiation (PCI) decreases the incidence of brain metastases and may also improve survival [5]. However, most of the studies evaluating the role of PCI in SCLC were conducted in the pre-magnetic resonance imaging (MRI) era and the results may not be applicable to patients staged and followed with brain MRI [6-12]. A prospective Japanese randomized trial, which included only extensive-disease SCLC patients without brain metastases based on MRI brain imaging at the time of enrollment, was discontinued prematurely for futility since overall survival was shorter in patients receiving PCI compared to patients not receiving PCI (11.6 months vs. 13.7 months, hazard ratio [HR] 1.27, 95% confidence interval [95%CI] 0.96–1.68) [13]. Moreover, PCI in contemporary trials has been associated with significant cognitive decline [14].

Based on these results, using brain MRI staging and surveillance instead of PCI became a reasonable strategy that was adopted by some centers both in extensive disease and limited disease SCLC [15]. This strategy suggest that the use of stereotactic radiosurgery (SRS) treatment for limited brain metastases is a viable alternative to whole-brain radiation therapy (WBRT) whether diagnosed during or after initial staging. Most of the data regarding SRS outcomes in SCLC comes from studies evaluating SRS as salvage treatment after PCI or WBRT failure. Data regarding SRS efficacy in the absence of prior PCI or WBRT are limited to small retrospective analyses, mainly conducted in Japan [16-21]. A summary of these studies is shown in Table 1. According to the results of the retrospective

Table 1. Outcomes with upfront stereotactic radiosurgery approach in small cell lung cancer with brain metastases

Study	Number of patients	Local control at 1 year	Off-site intracranial progression at 1 year	Need for additional SRS treatment	Need for WBRT administration	Median neurological survival, months	Median overall survival, months	Symptomatic radionecrosis
Serizawa et al. [16]	34	94.5%	Mean new lesion-free survival 6.9 months	Mean SRS procedures number 1.9, range 1–10	6%	9.0 (mean neurological survival)	9.1 (mean OS)	NR
Yomo et al. [18]	41	86%	44%	44%, median SRS procedures number 1, range 1–5	17%	NR	8.1	5%
Mizuno et al. [19]	24	90%	70%	37.5%	21%	14.5	7.3	0
Jo et al. [20]	12	NR	NR	NR	NR	NR	4.6	NR
Wegner et al. [21]	8	NR	NR	NR	NR	NR	13	NR

NR = not reached, OS = overall survival, SCLC = small cell lung cancer, SRS = stereotactic radiosurgery, WBRT = whole-brain radiation therapy

analysis performed by Ozawa et al. [17], PCI, when MRI surveillance accompanied by SRS is available, has no overall benefit in limited-disease SCLC; however, the study determined inappropriate brain staging, limiting the conclusions (only 60% of patients who did not receive PCI were staged with brain MRI). In our study, we described our experience with SRS as an upfront treatment of brain metastases in SCLC patients who were not treated with PCI or WBRT.

PATIENTS AND METHODS

This study comprised 10 consecutive SCLC patients with brain metastases treated with SRS and followed up at the Davidoff Cancer Center between Aug 2012 and March 2019 who were identified through the institutional database. Patients receiving PCI or WBRT as a primary intervention were excluded from the analysis.

Baseline demographic, clinical, and treatment characteristics were collected. Brain MRI images were reviewed by a neuroradiology specialist (NM). Radiological characteristics of brain lesions including number, size, and localization were determined. Intracranial objective response rate (iORR) and intracranial progression-free survival (iPFS) were assessed using both response assessment criteria for brain metastases (RANO-BM criteria) [22] and modified response evaluation criteria in solid tumors (mRECIST) [23]. These were modified to allow target brain lesions 5 mm or larger in maximum diameter (or at least twice the slice thickness if > 2.5 mm) to be assessed as described by Goldberg et al. [23]. iPFS was calculated from the date of SRS until intracranial disease progression or death. The outcome was censored if a patient was alive without known intracranial progression of disease at the time of last follow-up.

RANO-BM criteria for radiation necrosis definition were used [22]. These criteria included stabilization or shrinkage of a lesion on a follow-up scan, supporting evidence from an advanced imaging modality (e.g., MRI-treatment response assessment maps [MRI-TRAM] or fluorodeoxyglucose positron-emission tomography [FDG-PET]), or clinical judgment of a multidisciplinary team indicating that the radiological changes were due to treatment effect. OS was calculated from the date of SRS until death, and the outcome was censored if a patient was alive at the time of the last follow-up. Intracranial failure patterns following SRS were analyzed. Treatment patterns of intracranial progression were assessed along with the time-to-WBRT or death (TTWD), whichever occurred first. SRS-related toxicity (radiation necrosis) was evaluated.

Institutional review board approval was obtained before the study began, and a waiver for obtaining informed consent from participants was granted.

STATISTICAL ANALYSIS

Categorical variables were presented by numbers and percentiles. Medians and ranges were reported for continuous variables. iPFS, OS, and TTWD were assessed by the Kaplan–Meier method. Time-to-response, iPFS, and OS as well as intracranial failure patterns and treatments delivered upon intracranial progression were also presented in a swimmer plot.

Statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

DEMOGRAPHICS AND CLINICAL PATIENT CHARACTERISTICS

Baseline demographic, clinical, and treatment characteristics are presented in Table 2. Half of the patients were diagnosed with extensive disease. Importantly, only three patients had brain metastases at the time of initial diagnosis. Median time to brain metastases diagnosis was 5.1 months (range 0–17.2). Median number of brain metastases at the first round of SRS was 1 (range 1–11). The majority of brain lesions were small [Figure 1].

SRS EFFICACY, INTRACRANIAL FAILURE PATTERN

SRS doses ranged from 16 Gray (Gy) to 22.5 Gy. Among patients with measurable (≥ 10 mm) brain metastases by RANO-BM (n=7), iORR was 57%. Among patients with any baseline brain metastases (including lesions < 10 mm, n=10), iORR by mRECIST was 60% [Figure 1].

Median follow-up since SCLC diagnosis was 24.9 months (interquartile range 18.1–33.7). Intracranial progression

Table 2. Baseline demographic, clinical, and treatment characteristics in our study

Characteristic	Value
Age, years median (range)	60 (43–83)
Female	6
Male	4
Smokers, n	10
Histology	
SCLC	9
Mixed SCLC + LCNET	1
Stage, number	
Limited disease	5
Extensive disease	5
Platinum-based chemotherapy, number	9
Chest irradiation, number	7
Chest surgery (lobectomy), number	1
ICPi, number	4
Time to brain metastases diagnosis, month (median range)	5.1 (0–17.2)
Brain metastases at presentation, number	3
Brain metastases (before first round of SRS)	
Number of lesions (median, range)	1 (1–11)
Size of lesions, mm (median, range)	15 (3–22)
Supra-/ infratentorial/ both, number	6/1/3
GPA score (median, range)	1.5 (0.5–4)

GPA = graded prognostic assessment, ICPi = immune check-point inhibitors, LCNET = large cell neuroendocrine carcinoma, SCLC = small cell lung cancer, SRS = stereotactic radiosurgery

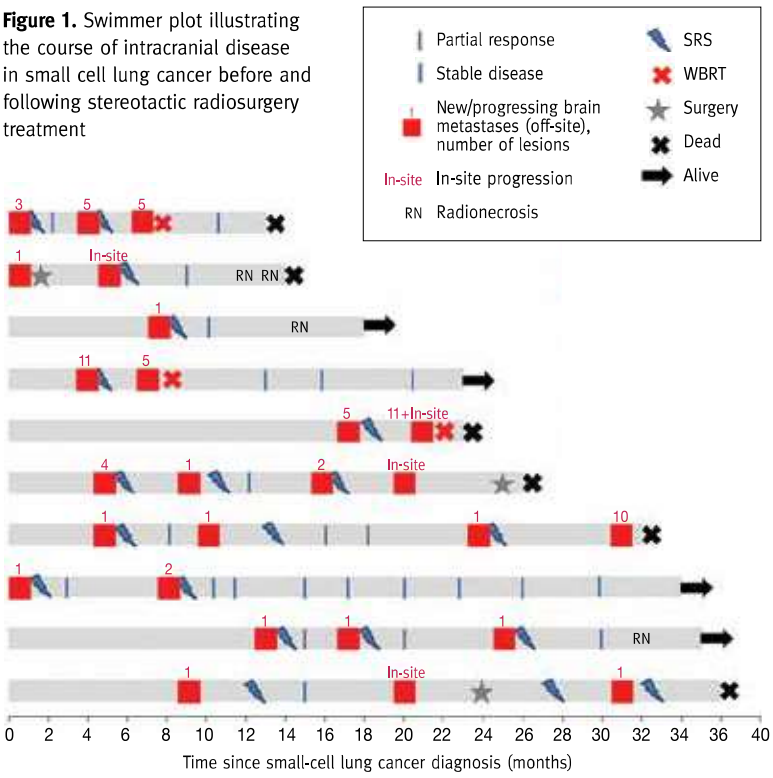


Figure 1. Swimmer plot illustrating the course of intracranial disease in small cell lung cancer before and following stereotactic radiosurgery treatment

SRS = stereotactic radiosurgery, WBRT = whole-brain radiation therapy

developed in eight patients. The median iPFS was 4.0 months (95%CI 1.7–7.2) [Figure 1] in patients with any baseline brain metastases (including lesions < 10 mm, n=10). Following SRS, none of the patients demonstrated isolated in-site progression while off-site and combined pattern of intracranial failure was observed in five and three patients, respectively [Figure 1]. Following SRS, the median number of new brain metastases per disease course was 4 (range 1–12) [Figure 1].

TREATMENT AFTER PROGRESSION

Ten additional rounds of SRS were performed in 6 patients (median number of lesions irradiated per round 1, range 1–5) [Figure 1]. WBRT was administered in three patients, and six patients died [Figure 1]. Median TTWD was 20.9 months (95%CI 1.9–26.8). Median OS since SRS administration was 23.2 months (95%CI 4.2–not reached).

SRS-RELATED TOXICITY

Two patients reported they felt mild general weakness lasting several days after SRS. Three patients developed radionecrosis after SRS (5–7 months after SRS administration), and one of the patients was symptomatic with uncontrolled seizures.

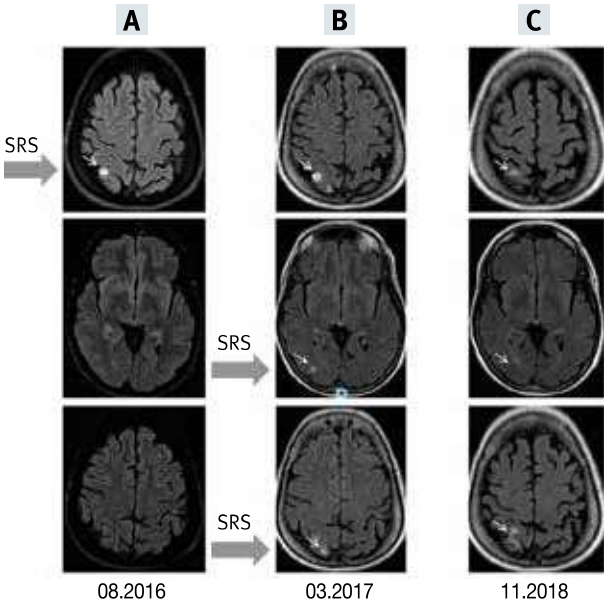
CASE PRESENTATION

A clinical case of a patient treated with several rounds of SRS during the disease course is presented. A 58-year-old female who smoked (100 pack/years) presented with a cough in July 2016 and was diagnosed with a right upper lobe mass and lung, liver, and bone metastases. Computed tomography guided biopsy of a liver metastasis was performed and small-cell lung carcinoma was diagnosed. Brain MRI revealed an 8-mm single brain metastasis in the right parietal lobe [Figure 2]. In July 2016, treatment with cisplatin and etoposide was initiated with a partial response. SRS to the right parietal brain metastasis was performed in August 2016 with significant lesion shrinkage [Figure 2]. In October 2016, treatment with nivolumab/ipilimumab was initiated. In March 2017, the disease progressed with the appearance of two new brain metastases (right occipital metastasis of 7 mm and right parietal metastasis of 5 mm), which were treated with another round of SRS resulting in a partial resolution of both of the metastases in May 2017. At the time of last follow-up (November 2018), a prolonged partial remission was achieved systemically, and there was no active disease in the brain [Figure 2].

DISCUSSION

Our retrospective study illustrates the value of brain MRI surveillance accompanied by SRS in the treatment of SCLC patients. We focused on the disease course before and after SRS administration, and specifically estimated the intracranial response, failure patterns, and timing of new brain metastases development. To

Figure 2. Dynamics of brain metastases following stereotactic radiosurgery administration in a patient with small cell lung cancer in the absence of prior prophylactic cranial irradiation or whole brain radiotherapy
Axial T2-flare MRI sequences in a patient with brain metastases (white arrows) before the first round of SRS **[A]**, 7 months after the first round of SRS and before the second round of SRS **[B]**, and 20 months after the second round of SRS **[C]**



SRS = stereotactic radiosurgery

the best of our knowledge, this is the first report on the efficacy of the approach in a Western population.

In our series, only a minority of the patients (30%, which is similar to 25% reported in the literature [24]) had brain metastases at presentation, and median time to diagnosis of brain metastases (5.1 months, range 0–17.2) was in accordance with the previously reported 7.8 months (0.3–149) [18] and 11.3 months [20]. Since the time to intracranial progression was long in our study and in other studies as well, it will be reasonable to postpone the radiation treatment. Active brain MRI surveillance allowed the majority of lesions to be diagnosed when they were small, asymptomatic, and limited in number so they did not have a negative effect on quality of life and favored treatment with SRS.

Importantly, SRS achieved excellent local control (70%), which is slightly lower than 86–94.5% observed in previous series with a different duration of follow-up [16,18,19]. The results probably reflect the small size and longer follow-up in our cohort. The majority of intracranial progression cases were off-site, which is in concordance with reported data on the distant brain metastases rate in the range of 45–70% during the first year following SRS administration [18,19].

Based on our observations, the multi-focal nature of the intracranial disease in SCLC should be carefully examined. For example the median number of brain metastases per disease course following the SRS administration in our series was only four (range 1–12), which does not justify WBRT. Indeed, 60% of patients in our cohort (and 37.5–44% in the literature [16-20]) required additional treatment with SRS, as opposed to only 30% (and 6–21% in previously reported series [16-20]) who were treated with WBRT.

Intracranial PFS was relatively short. However, introduction of active brain MRI surveillance resulted in earlier detection, smaller and fewer new lesions allowing SRS to be performed whenever intracranial progression was observed and delaying WBRT or making WBRT unnecessary.

The rate of symptomatic radionecrosis in our cohort was unexpectedly high, which might be explained by the long follow-up. Moreover, we observed a surprisingly long median overall survival, which might be attributed to immune checkpoint inhibitor administration in 40% of patients in our series. This treatment might have central nervous system activity as well as systemic activity [23,25].

LIMITATIONS

Our study has several limitations that should be acknowledged. The conclusions study are limited by the small number of patients in the analysis, especially patients with a limited disease stage since the effect of not administering PCI to limited-disease stage patients is largely unknown. Furthermore, the retrospective nature of the analysis may have introduced selection bias (e.g., patients diagnosed with multiple brain metastases were more likely to be treated with WBRT instead of SRS at the time of brain metastases diagnosis). Due to the retrospective study design, MRI scans at predefined time points were unavailable, which lessened the accuracy of the radiological assessment. The decision regarding the SRS vs. WBRT at the time of intracranial progression was not pre-specified, and therefore, might vary among different physicians. There was no comparison group so we could not assess the survival impact or the quality-of-life impact the SRS approach.

STRENGTHS

The radiological review was performed by an expert in the field of neuroradiology (NM), which is necessary in a study on intracranial response and failure patterns assessment. Also, the duration of follow-up in our series was long enough to observe the whole course of the disease.

CONCLUSIONS

Based on the pattern and timing of intracranial failure in our study along with the lack of the survival benefit observed in a different study [13], brain MRI surveillance combined with multiple rounds of SRS in cases of limited brain metastases

development may serve a viable alternative to PCI or therapeutic WBRT in SCLC. Further prospective data on active surveillance accompanied by SRS in SCLC is urgently needed. This finding is especially true since the introduction of immune-check-point inhibitors into the treatment algorithm of SCLC. The ENCEPHALON trial (https://clinicaltrials.gov/ct2/show/NCT03297788) investigating local control, survival, and neurocognitive effects of SRS vs. WBRT in extensive-stage SCLC with up to 10 brain metastases is currently ongoing. The cost efficacy of the proposed treatment strategy warrants further evaluation as well.

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"Truth does not change according to our ability to stomach it"

Flannery O'Connor (1925–1964), writer

"A true and worthy ideal frees and uplifts a people; a false ideal imprisons and lowers"

W.E.B. Du Bois (1868–1963), American sociologist, historian, civil rights activist, and author