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Scientific Article

Stereotactic Radiosurgery for Brain Metastases in Patients With Small Cell Lung Cancer

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Purpose: Treatment of small cell lung cancer (SCLC) with brain metastatic disease has traditionally involved whole brain radiation therapy (WBRT). The role of stereotactic radiosurgery (SRS) is unclear.

Methods and Materials: Our study was a retrospective review of an SRS database evaluating patients with SCLC who received SRS. A total of 70 patients and 337 treated brain metastases (BM) were analyzed. Forty-five patients had previous WBRT. The median number of treated BM was 4 (range, 1-29).

Results: Median survival was 4.9 months (range, 0.70-23.9). The number of treated BM was correlated with survival; patients with fewer BM had improved overall survival ($P < .021$). The number of treated BM was associated with different brain failure rates; 1-year central nervous system control rates were 39.2% for 1 to 2 BM, 27.6% for 3 to 5 BM, and 0% for >5 treated BM. Patients with previous WBRT had worse brain failure rates ($P < .040$). For patients without previous WBRT, the 1-year distant brain failure rate was 48%, and median time to distant failure was 15.3 months.

Conclusions: SRS for SCLC in patients with <5 BM appears to offer acceptable control rates. Patients with >5 BM have high rates of subsequent brain failure and are not ideal candidates for SRS.

Introduction

Small cell lung cancer (SCLC) is characterized by rapid tumor growth and early development of metastases.[1] More than 10% of patients with SCLC have brain metastases (BM) at diagnosis and more than 50% become affected within 2 years.[2]

Prophylactic cranial irradiation (PCI) became a part of standard management for SCLC when a meta-analysis found that PCI reduced risk of BM and improved overall survival by 5%.[3] However, subsequent studies have not found the same benefit for PCI. [4,5]

For patients with BM from non-small cell lung cancer (NSCLC), current treatment options are whole brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS). Trials (which included NSCLC but excluded SCLC) that randomized patients with BM to SRS alone versus WBRT and SRS found equivalent survival with SRS and better neurocognitive outcomes.[6]

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Because of the higher rate of BM with SCLC and the previous long-standing tendency for all SCLC to get PCI, the majority of SCLC with BM are treated with WBRT. There are limited reports regarding the use of SRS in SCLC.[7-9] The primary goal of this study is to provide further data on the use of SRS in SCLC.

Methods and Materials

To evaluate the outcome of BM among SCLC treated with SRS, we used an SRS database. The institutional review board provided approval for data collection. Data were collected from April 2008 to April 2019.

Pathology reports were used to confirm SCLC diagnosis. We retrospectively collected other data, including dates of SCLC diagnosis, BM diagnosis, WBRT (if applicable), SRS, death, BM lesions, central nervous system (CNS) failure, distant brain failure, control of disease outside of CNS at time of SRS, and treatment modalities for primary tumor. Patients were compared using CNS recursive portioning analysis (RPA).

SRS was performed using the Gamma Knife Icon (Elekta, Stockholm, Sweden). After SRS, patients had repeat magnetic resonance imaging with contrast at 6 weeks and then every 3 months. Distant brain failure was defined as a new BM lesion, and local failure was defined as progression of a treated BM lesion. Patients with concern for local recurrence versus radiation necrosis had dynamic imaging (magnetic resonance imaging spectroscopy and perfusion) and were presented in a multidisciplinary tumor board.

Kaplan-Meier with log-rank test was used to compare survival outcomes between variables. An independent *t* test was used to distinguish differences between means of continuous variables, such as number of CNS metastases and karnofsky performance scale score. The χ^2 test was used to test significance between categorical variables, such as stage. Python (Python Software Foundation) was used to conduct all data analysis.

Results

Seventy patients with SCLC and 337 with BM were evaluated. Forty-five had previous WBRT and 25 were treated with SRS alone without previous WBRT. Of those who received previous WBRT, 17 were treated prophylactically. The median age of patients was 62. Thirty-four patients presented with metastases at initial diagnosis of SCLC (Table 1). For those who received WBRT before SRS, WBRT was completed at a median of 8.7 months before SRS.

Twenty-five patients had SRS without having previous WBRT. The median follow-up for patients without previous WBRT was 5.5 months (range, 2.7-23.9 months), and 12 patients were alive at last follow-up. The median number of treated BM was 3 (range, 1-13 BM). Twelve patients had 1 to 2 BM, 10 patients had 3 to 5 BM, and 3 patients had more than 5 BM. There were no local failures. Eight patients had distant brain failure with a median time to failure of 4.1 months and a 1-year Kaplan-Meier distant brain recurrence-free survival of 52%. For the 12 patients with 1 to 2 BM, there were 5 distant brain failures (median time, 4.9 months). For the 10 patients with 3 to 5 BM, there was 1 failure at 2.9 months. For the 3 patients with more than 5 BM, there were 2 distant failures (median time, 2.8 months; the third patient with more than 5 BM was censored because of death at 56 days).

Forty-five patients had WBRT before SRS. Median number of BM for patients with previous WBRT was 4 (range, 1-29). Fourteen patients with previous WBRT had 1 to 2 BM, 16 patients had 3 to 5 BM, and 15 had more than 5 BM. Twenty-three patients with previous WBRT had subsequent distant brain failure. For the 14 patients with 1 to 2 BM, 3 patients had distant brain failure. For the 16 patients with 3 to 5 BM, 10 patients had distant

Table 1 Patient characteristics

Variable	Data
Sex, no.	
Male	40
Female	30
Age (y)	
Median	62
Range	49-80
CNS metastases at initial SCLC diagnosis, no.	
Yes	34
No	36
Previous chemotherapy, no.	
Yes	47
No	23
Previous WBRT, no.	
Yes	45
No	25
Control of extra-CNS disease, no.	
Yes	29
No	41
RPA class, no.	
1	14
2	47
3	9

Abbreviations: CNS = central nervous system; RPA = recursive portioning analysis; SCLC = small cell lung cancer; WBRT = whole brain radiation therapy.

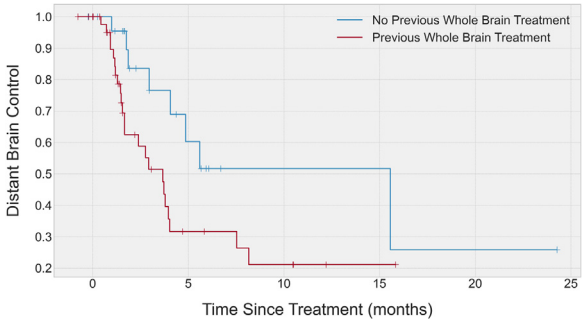

Figure 1 Distant failure rates in patients treated with whole brain radiation therapy and stereotactic radiosurgery versus stereotactic radiosurgery alone ($P < .40$).

failure. For the 15 patients with more than 5 BM, 10 patients had distant failure (the remaining patients were censored because of death). Patients with previous WBRT had a Kaplan-Meier distant brain recurrence-free survival of 22% at 1 year.

There were no differences in survival between patients treated with SRS alone versus SRS with previous WBRT ($P = .282$ for therapeutic, $P = .185$ for prophylaxis). However, for distant brain failure, patients treated with SRS alone had improved distant brain failure compared with patients who had previous WBRT ($P < .040$), as seen in Fig. 1.

Median follow-up for all patients was 3.8 months (range, 0.70-23.9). Median survival was 4.9 months (range, 0.70-23.9). The median number of treated BM was 4 (range, 1-29). Patients with fewer BM had improved overall survival (OS) ($P < .021$; Fig. 2). Patients with 1 to 2 BM had median OS of 9.5 months, patients with 3 to 5 BM had median OS of 4.2 months, and patients with more than 5 BM had median OS of 3.3 months. RPA was also predictive for survival. The median survival time for RPA class 1 was 7.6 months, class 2 was 4.9 months, and class 3 was 3.6 months.

Two patients had local failures. Although local failure and radiation necrosis can be difficult to distinguish, both instances of local failure were felt to be disease

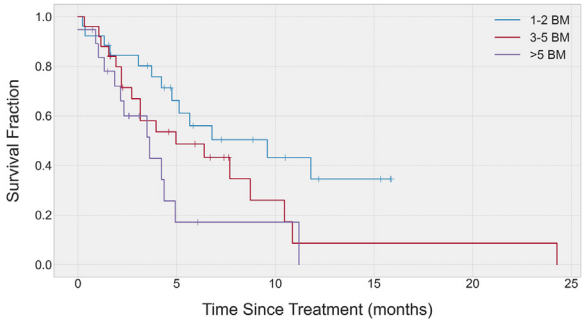

Figure 2 Association between number of central nervous system metastases and survival ($P < .021$).

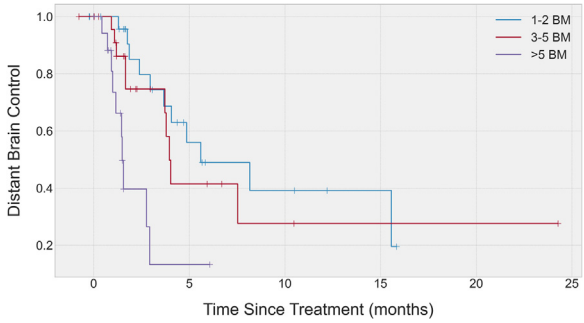

Figure 3 Association between number of treated central nervous system metastases and central nervous system failure rates ($P < .005$).

progression as opposed to radiation necrosis. Both patients with local failure were treated with both WBRT and SRS.

The number of treated BM was associated with different brain failure rates. One-year CNS control rate was 39.2% for 1 to 2 BM, 27.6% for 3 to 5 BM, and 0% for more than 5 treated BM ($P < .005$; Fig. 3). The median time to failure was 5.5 months for 1 to 2 metastases, 3.9 months for 3 to 5 metastases, and 1.5 for more than 5 BM. Systemic disease control was not associated with difference in brain control.

Discussion

SCLC is an aggressive cancer with a high rate of BM.[2] Because of the high BM rates it was standard for patients without BM to be offered PCI and patients with BM to have treatment with WBRT. However, more recent data have called into question the value of PCI[4,5] for patients without BM, and for patients who have BM the treatment options have begun to include SRS.[7-9]

We found that SRS for BM from SCLC is potentially effective in patients with 5 or fewer BM. For patients with more than 5 BM, we found that the incidence of subsequent brain failure is high (we had no patients with more than 5 BM have long-term distant free survival and a median time to subsequent failure of only 45 days) and feel that SRS is not an ideal treatment option for patients with more than 5 BM. However, in patients with 5 or fewer brain metastatic lesions, we found SRS to be safe and effective, with a 1-year control rate of 52% for patients without previous radiation.

Our control rates for fewer than 5 BM are slightly lower compared with NSCLC[10] and are similar to the limited data available for SCLC. Yomo and Hayashi[11] reported a 12-month control rate of 53% (median number of BM on this study was 2). A meta-analysis by Viani et al[12] reported a 12-month control rate of 59% with SRS. A multicenter study by Rusthoven et al[13] reported a 12-month control rate of 58%. Similar to other studies, we

also confirmed the association between the number of BM and OS.

This study has the same limitations shared by all the studies on this topic. Because the patients are not randomized there can be biases that affect the results. Although attempts were made to control for as many variables as possible, variables such as patient frailty, social support, and degree of neurologic symptoms are very difficult to control for. We were also not able to calculate BM volume, which can be an important variable. Another limitation is not being able to control for immunotherapy. Atezolizumab is being used in the first-line setting for extensive stage SCLC and appears to have intracranial penetration.[14] Our data are valuable despite these flaws. Our results contribute to the growing information regarding SRS for SCLC BM as being a potential treatment option. Treating SCLC BM with SRS rather than WBRT would reduce treatment toxicity and is logistically easier for patients and caregivers.[7,15,16]

We feel our data are especially valuable in helping better select the patient population that would have the best outcomes with SRS. We found that patients with more than 5 BM have very high distant brain failure rates, and our recommendation for these patients is WBRT. We also found that previous WBRT was not associated with improvement in control rates. This finding is hard to interpret as patients with SCLC treated with WBRT alone were not included in our SRS database. Also, it is possible that patients who have failed WBRT have worse biology that even salvage SRS cannot overcome.

Conclusion

We found that SRS alone may be a viable option for patients with SCLC with 5 or fewer BM but that patients with more than 5 BM are better treated with WBRT.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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