



Survey on Turkish Radiation Oncologists' Approach for Brain Metastases of Small Cell Lung Cancer: A Study from Turkish Radiation Oncology SRS Group (TROD 10-014)

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OBJECTIVE

Prophylactic cranial irradiation (PCI) reduces the risk of intracranial progression and improves overall survival (OS) in small cell lung cancer (SCLC). However, with advances in systemic therapies and improvements in neuroimaging, the OS benefit has been increasingly questioned. Herein, we report the results of a survey study which evaluates the approach of radiation oncologists in patients with SCLC and brain metastases with or without a prior PCI.

METHODS

The online survey was conducted by the Steering Committee of The Turkish Society of Radiation Oncology Stereotactic Surgery (TROD-SRS) subgroup and distributed to the members of TROD-SRS in Türkiye. The survey consisted of two sections including 16 questions.

RESULTS

One hundred and sixty-four respondents completed the questionnaire. While 88% of the respondents preferred SRS in patients with a prior PCI, WBRT came forward in patients without a prior PCI. More than half of the respondents opted for SRS after metastasectomy. The decision to perform SRS in patients with brain metastases of SCLC depend on the presence of a prior PCI, number and volume of metastases, and the availability of SRS. More experienced respondents had a decreased concern for deciding for SRS treatment but these respondents also looked over more factors when deciding for SRS.

CONCLUSION

The results of this survey study indicate that SRS is widely accepted for the management of brain metastasis in patients with SCLC in our country. We anticipate that the utilization of SRS will continue to increase as access to SRS-capable centers.

Keywords: Brain metastasis; small cell lung cancer; stereotactic surgery.

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INTRODUCTION

Small cell lung cancer (SCLC) is an aggressive variant of lung cancer. Despite a high response rate to treatment, it is characterized by early treatment resistance, rapid progression and distant metastasis (DM).[1] Approximately two-thirds of patients with SCLC have DM at the time of diagnosis and the rate of brain metastasis is around 10%.[2,3] The timely and accurate diagnosis of brain metastasis is the most important factor contributing to the prognosis of SCLC.[4] In patients without a brain metastasis, prophylactic cranial irradiation (PCI) has been shown to reduce the rate of intracranial progression and prolong overall survival (OS).[5] Following two pivotal trials, PCI has become the standard of care for patients with at least a stable disease after treatment.[6,7] A meta-analysis also reported that the addition of PCI reduced the frequency of brain metastasis and improved 1-year OS, yet had no effect on long term survival in extensive stage SCLC.[8] On the other hand, this meta-analysis also reported an increased neurotoxicity following PCI.

Recent studies have informed us that neurocognitive functions can be preserved with hippocampal-sparing cranial radiotherapy (RT).[9,10] However, although administered safely, protecting cognitive functions after hippocampal-sparing cranial RT is controversial.[11] In the phase II/III NRG-CC003 study which compares conventional and hippocampus-sparing PCI, although the primary endpoint of less deterioration on the Hopkins Verbal Learning Test-Revised delayed recall test was not achieved, hippocampus-sparing PCI was found to be beneficial for reducing the risk of overall neurocognitive toxicity with similar rates of intracranial recurrence and survival.[12] As systemic therapies for SCLC have evolved, the survival advantage of PCI has been questioned by new strategies that include a close follow-up with brain magnetic resonance imaging (MRI) and early salvage therapy for brain metastasis.[13] A comprehensive multicenter analysis, the FIRE-SCLC study, also provided strong evidence for the use of stereotactic radiosurgery (SRS) for brain metastasis in SCLC, particularly efficient for patients with a single metastasis.[14] The authors emphasized the disadvantages such as a shorter time to central nervous system progression and decreased OS which are similar to SRS-based strategies in other malignancies. The researchers believe these data provide a benchmark for SRS outcomes and support the use of first-line SRS as a treatment option in carefully selected patients with SCLC.

As whole-brain radiotherapy (WBRT) has been associated with increased neurocognitive toxicity, SRS has become an up-front option for patients with limited brain metastasis with other histologies of lung cancer.[15] On the other hand, the traditional approach for brain metastasis of SCLC is still WBRT.[16] The aim of this study was to design and carry out a survey to evaluate the approach of radiation oncologists in Türkiye in patients with brain metastasis diagnosed with SCLC.

MATERIALS AND METHODS

The survey was developed under the approval and supervision of the executive council of the SRS subgroup of Turkish Society of Radiation Oncology and distributed to the radiation oncologists. The survey was not sent to the members on residency at that time. Participation was voluntary and all responses were collected anonymously. No personal identifying information was obtained. The survey consisted of two sections with a total of 16 questions and took approximately five minutes to complete. The first section included the demographic information and clinical experience of the institution of the respondent. The second part focused on the clinical opportunities, clinical scenarios and treatment options. The survey questionnaire translated to English is provided as Supplementary Appendix 1.

This study was approved by the Ethical Committee of Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, Ankara, Türkiye (approval number 2025-02/31) on Feb 20, 2025 and conducted according to declaration of Helsinki.

Statistical Analysis

The median, mean ($\pm$ standard deviation [SD]), minimum, and maximum values were used as descriptive variables. In assessing normality, the Shapiro Wilk test and the Kolmogorov Smirnow test was used in case the number of data was >30 and ≤ 30 , respectively. The Chi-square test was used for evaluating binary data. If no cell contained a value <5 , the Fisher-Exact Probability Test was used, but if the cells contained a value >5 , the Pearson Chi-square Test was used. For independent groups, Student's t-test or Mann-Whitney U test, as appropriate, was used.

The univariate and multivariate logistic regression analyses were used to measure the relationship between respondent characteristics and treatment preferences for brain metastases in SCLC using odds ratios (OR) and 95% confidence intervals (CI). Independent variables evaluated in the univariate model included

Table 1 Replies of the respondents to questions 2–7 and 11 (n=164)

Questions	n (%)	Questions	n (%)
2) What is the type of institution you currently work in?*		6) What is your preferred approach for patients who develop brain metastases after PCI?	
University Hospital	56 (34)	Surgery	5 (3)
Private Hospital	30 (18)	WBRT	15 (9)
Public Hospital	9 (6)	SRS	144 (88)
Training and Research Hospital	68 (42)	7) What is your preferred treatment approach for patients with SCLC who present with brain metastases and have not received PCI?	
3) How many years have you been practicing as a radiation oncologist? *		WBRT	53 (32)
0–5 years	18 (11)	SRS	42 (26)
6–10 years	23 (14)	WBRT followed by SRS	61 (37)
11–20 years	62 (38)	Surgery followed by cavity-directed SRS	8 (5)
21 years or more	60 (37)	Surgery	0
4) How many SCLC cases do you see per year?		11) What is your preferred approach for a patient who has undergone intracranial metastasectomy?	
1–10	31 (19)	WBRT	37 (23)
11–30	77 (47)	SRS	96 (56)
31–50	37 (23)	WBRT followed by SRS	24 (15)
≥51	19 (11)	Observation / Follow-up	2 (1)
5) Does your institution have the facility and equipment to perform SRS?		Other	5(3)
Yes	151 (92)		
No	13 (8)		

*: One respondent was not included in the analysis as the responses had data entry errors. Not every respondent answered every question. n: Number; PCI: Prophylactic cranial irradiation; SCLC: Small cell lung cancer; SRS: Stereotactic radiosurgery; WBRT: Whole brain radiotherapy.

age, study year, study region, access to treatment-related technologies, treatment center, and the number of patients treated per year. While performing statistical analysis of numerical values, the ROC curve or median/mean values were taken as the absolute points and analyzed separately by grouping. Nonparametric tests were used to analyze Likert-type scale responses. A cross-tabulation was performed to examine the association between prior PCI and years of experience of the respondents, between years of experience and number of cases seen per year, institution type, facility SRS. Statistical analyses were conducted by using Statistical Package for the Social Sciences (SPSS™) version 22.0 (IBM, Armonk, NY, USA). A two-sided statistical test was used in all analyses and a p value of ≤ 0.05 was considered as statistically significant.

RESULTS

One hundred and sixty-four respondents completed the survey. The median age of the respondents was 46 years (range: 25–66 years). The other characteristics of the respondents are given in questions 2–5 Table 1. Two responses regarding the demographic informa-

tion from a single respondent were identified as data entry errors attributable to typographical mistakes and were excluded from the final analysis. The majority of the respondents have been working in a university or a research and training hospital and more than half have been working as a radiation oncologist for more than 10 years. Almost half of the respondents treat 11–30 patients with SCLC per year and 92% can apply SRS in their institution. The number of cases seen per year was similar regarding the years of experience and type of institution of the respondents ($p > 0.05$).

When the questions about the clinical practice were evaluated (Table 1), the majority of the respondents were shown to prefer SRS in patients that had undergone a prior PCI. On the other hand, WBRT comes forward, either alone or followed by SRS, in patients without a prior PCI.

In response to the 8th question ‘To what extent do the following factors influence your treatment decision in patients with brain metastases in SCLC?’, the performance status, number of brain metastases, total intracranial tumor volume, a prior PCI and extracranial disease status significantly affected the treatment decision of the respondents (Table 2).

Table 2 Responses to question 8 (To what extent do the following factors influence your treatment decision in patients with brain metastases in SCLC?)

	Never n (%)	Rarely n (%)	Sometimes n (%)	Often n (%)	Always n (%)
Performance status	0	7 (4)	22 (13)	66 (40)	68 (42)
N of brain metastases	3 (2)	7 (4)	19 (12)	67 (41)	66 (40)
Total intracranial tumor volume	3 (2)	10 (6)	23 (14)	68 (42)	59 (36)
Prior PCI irradiation	2 (1)	11 (7)	34 (21)	54 (33)	61 (37)
Extracranial disease status	1 (1)	12 (7)	34 (21)	57 (35)	59 (36)

n: Number, PCI: Prophylactic cranial irradiation; SCLC: Small cell lung cancer.

For the respondents affected by the total number and volume of brain metastases when deciding to perform SRS (questions 9 and 10), the respective median values were 5 (range: 1–20) and 20 cc (range: 2–250 cc).

For the 11th question (Table 1), the majority of the respondents preferred SRS after intracranial metastasectomy, either alone or after WBRT. Thirty-seven (23%) respondents preferred WBRT alone, and only two (1%) respondents opted for observation. For the 12th question, 60% of the respondents had no concerns when deciding to use SRS (Table 3). On the other hand, rapid intracranial progression, lack of scientific evidence and short survival were the main concerns when deciding for SRS treatment in patients with brain metastases of SCLC.

The impact of the type of institution, years of experience, number of cases seen per year and SRS availability in the institution on the respondent's approach for SRS were separately analyzed. The treatment of choice in patients both with and without a prior PCI was not affected by most of the characteristics and experience of the respondents. Nevertheless, 69% of the respondents without SRS in their institution chose WBRT for patients with a prior PCI while 71% with SRS chose to apply SRS either alone or together with WBRT or surgery.

Similarly, while the type of institution, years of experience, and number of SCLC cases seen per year did not have a significant impact, the availability of SRS in their institution significantly affected the respondents while deciding for treatment after intracranial metastasectomy. Despite 62% of the respondents without SRS in their institution preferred

WBRT, 62% of those with SRS stated that they would perform SRS ($p=0.013$).

The number of SCLC cases seen per year significantly affected the responses to many questions. While 53% of the respondents that see >30 patients per year reported that performance status was important, 35%

Table 3 Responses to question 12 (What are your concerns regarding the use of SRS in patients with SCLC with brain metastases? You may select more than one option)

	n (%)
Rapid intracranial progression	83 (51)
Lack of sufficient evidence	46 (28)
Short survival	38 (23)
High cost	5 (3)
Limited access to SRS technology	13 (8)
I have no concerns	65 (40)

n: Number; SCLC: Small cell lung cancer.

of the respondents that see ≤ 30 patients considered it less important ($p=0.006$). Likewise, 51% of the respondents that see >30 patients per year thought that previous PCI was important for their treatment decision compared to 31% of the respondents that see ≤ 30 patients per year ($p=0.024$). The presence of extracranial disease also significantly affected the the respondents while deciding for treatment. Forty-two percent of more experienced respondents thought that it was important whereas 33% of the less experienced respondents thought so ($p=0.008$).

None of the characteristics significantly affected the treatment decision regarding the number or volume of brain metastases.

Nevertheless, as the number of SCLC patients seen per year increased, the concerns about performing SRS decreased and even disappeared in some respondents. While 34% of the respondents that see fewer cases had no concerns, the respective rate for the respondents that see more patients was 50% ($p=0.074$). The fear of rapid progression and short survival were significantly affected by the number of cases seen per year ($p=0.018$ and $p=0.028$, respectively). The respondents that see fewer patients per year were more concerned about short survival while the concerns decreased as the

number of patients seen per year increased. The concern for rapid progression was significantly increased in the respondents that see ≤ 30 patients per year ($p=0.048$). Similarly, the concern for a short survival was also increased when patients seen per year was ≤ 30 ($p=0.033$). There was a statistically significant difference between the respondents with and without SRS in their institution in terms of concerns for the lack of evidence. While no respondents without SRS had concerns about the lack of evidence, the respective rate for those with SRS was 31% ($p=0.02$). The distribution of concerns for the lack of evidence was similar across different institution types and years of experience.

DISCUSSION

This survey among Turkish radiation oncologists shows that the decision to perform SRS in patients with brain metastases of SCLC depends on the presence of a prior PCI, number and volume of metastases, and the availability of SRS. The majority of the respondents were experienced for treating SCLC patients with brain metastases which came with a decreased concern for deciding for SRS treatment. On the other hand, this survey is evidence that the more experienced the radiation oncologist is, the more complex the decision for SRS is. The performance status of the patient, prior PCI and extracranial disease were the most important factors while deciding for SRS.

Brain metastasis is frequently encountered in patients with SCLC and the management is often complicated. Cranial prophylaxis is recommended in patients without a brain metastasis. However, as cranial prophylaxis is known to negatively affect the neurocognitive functions, omitting prophylaxis and treating the metastasis with SRS once it develops is a frequently discussed option. Current approach is to perform WBRT for brain metastases of SCLC in patients without a prior PCI. Contemporary guidelines acknowledge SRS as an option in selected patients while adding WBRT to SRS is generally not recommended due to the absence of a demonstrated survival benefit and the risk of increased neurocognitive toxicity.[17] Similarly, there were also significant variations among the respondents in our survey. Whole brain RT, WBRT+SRS and SRS was preferred in patients with brain metastases without a prior PCI was 32%, 37%, and 26%, respectively.

In patients with a prior PCI, the optimal management strategy remains less clear due to limited prospective data.[14] Retrospective series have reported

acceptable local control and survival outcomes with SRS for intracranial relapse after PCI, supporting its role as a reasonable salvage treatment option in selected patients.[18] Current guidelines also emphasize an individualized decision-making and often favor SRS when feasible rather than re-irradiation with WBRT.[17] Consistent with these observations, in our survey the majority of the respondents (88%) preferred SRS for the management of brain metastases in patients with a prior PCI.

Prognostic factors play an important role in treatment decisions in patients with brain metastases of SCLC. A study have consistently shown that several clinical variables including performance status, the number of brain metastases, total intracranial tumor volume, prior PCI and the presence or last status of extracranial disease play an important role in determining both survival outcomes and optimal treatment strategies.[19] However, increasing evidence from retrospective series has suggested that upfront SRS may be a reasonable alternative in carefully selected patients with a limited number of metastases, demonstrating comparable overall survival but higher rates of distant intracranial failure requiring close follow up via imaging and potential salvage therapy.[16] In our survey, the performance status, number of brain metastases, total intracranial tumor volume, a prior PCI and extracranial disease status significantly affected the treatment decision of the respondents.

Current evidence suggests that SRS may be considered in carefully selected patients with a limited number of lesions and low cumulative intracranial tumor volume.[20] Clinicians are increasingly considering both the number of lesions and the cumulative intracranial tumor volume when determining the eligibility for focal therapy.[21] In a study by Aizer et al.,[22] the neurological mortality rates were lower when SRS was used compared to WBRT in patients with 1–10 brain metastases of SCLC. Furthermore, the authors reported a salvage brain RT rate of 22% during the follow-up period after SRS which is very low. On the other hand, the rate of a new brain metastasis was high after SRS. However, in this study, brain metastases were detected early with regular MRI follow-ups after SRS. Salvage SRS yielded disease control in most patients, reducing the need for an additional WBRT. These findings support the benefit of SRS in this patient population. In our survey, respondents influenced by both the number and total volume of brain metastases indicated a median threshold of 5 metastases and a median total intracranial tumor volume of 20 cc.

In a multi-institutional evaluation of SRS for brain metastases, the availability of SRS was found to be the strongest prognostic factor and more effective than the other clinical eligibility factors.[23] In our study, the most important factor determining the approach to treat a brain metastasis in the non-PCI group was having the availability of SRS.

In cases where surgical resection of brain metastases is performed, postoperative irradiation is generally recommended to reduce the risk of local recurrence.[24] Stereotactic radiosurgery directed to the surgical cavity has emerged as a potential alternative to WBRT, particularly because it may achieve comparable local control while minimizing neurocognitive toxicity associated with WBRT. The results of our survey demonstrated that Turkish radiation oncologists predominantly preferred postoperative SRS following brain metastasectomy in patients with SCLC. Furthermore, the availability of SRS was highly influential in the treatment selection for patients after metastasectomy.

In a survey conducted among the United States-based radiation oncologists, the number of brain metastasis was the most important factor followed by the performance status, cognitive function, and response to prior treatment when deciding for the RT technique.[25] Also, in an analysis conducted among European radiation oncologists and medical oncologists, WBRT followed by chemotherapy was the most frequently recommended treatment method for symptomatic patients with brain metastases of SCLC. On the other hand, some experts preferred SRS in patients with a limited number of metastases. Significant differences were observed in the clinical decision-making process among the European experts regarding the first-line treatment for patients with SCLC and brain metastases in that analysis.[26] In our survey, 23% of the respondents hesitated to perform SRS due to concerns of short survival in patients with SCLC. Also, the respondents that treat a higher number of patients per year were mostly affected by the performance status. We also observed that the respondents with a more extensive clinical experience assigned a greater significance to prior PCI.

This study has several limitations. The survey does not reflect the evolving treatment paradigms in the era of immunotherapy, nor does it address modern neurocognitive protection strategies such as memantine use or hippocampal avoidance techniques. Furthermore, current approaches integrating SRS with contemporary systemic treatments have not been evaluated. Howev-

er, the results provide valuable insights into common approaches to managing brain metastasis in patients with SCLC. Future research that reflect modern clinical practices, particularly the integration of immunotherapy, neurocognitive protective RT strategies, and the increasing role of SRS in the management of brain metastasis from SCLC is warranted.

CONCLUSION

Due to the concerns about the rapid recurrence rate in other brain regions, 37% of the respondents participating in our study preferred adding SRS to WBRT in patients without a prior PCI. However, in patients with a prior PCI, the most preferred technique was SRS/SRT presumably to avoid toxicity. Our findings are consistent with the literature. The concern of a rapid progression increases as the number of metastatic lesions increases. As the experience of the respondents increases, they are more likely to choose SRS/SRT alone. While the respondents are justified in their concerns about the rapid appearance of a new brain metastasis, the less toxic and less time-consuming technique of SRS/SRT can become increasingly available in patients with a good performance and an opportunity to undergo regular MRI checkups.

Ethics Committee Approval: The study was approved by the Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Ethics Committee (no: 2025-02/31, date: 20/02/2025).

Informed Consent: Informed consent was not needed for this study.

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Dear Colleague,

First of all, we would like to thank you for participating in this survey.

By taking part in this study, you will share your institution's approach to the management of patients with brain metastases from small cell lung cancer.

Through this nationwide survey conducted across Turkey, we aim to obtain an overall perspective on current clinical practices for the treatment of these patients.

All information collected will be used solely for research purposes. No personal data will be shared, and the results of the survey will be presented anonymously.

Thank you for your valuable contribution.

1. How old are you?

_____ years

2. What is the type of institution you currently work in?
(Please select one)

☐ University Hospital

☐ Training and Research Hospital

☐ Private Hospital

☐ Public (State) Hospital

3. How many years have you been practicing as a radiation oncologist?

☐ 0–5 years

☐ 6–10 years

☐ 11–20 years

☐ 21 years or more

4. How many small cell lung cancer (SCLC) cases do you see per year?

☐ 1–10

☐ 11–30

☐ 31–50

☐ ≥ 51

5. Does your institution have the facility and equipment to perform stereotactic radiosurgery (SRS)?

(Please select one)

☐ Yes

☐ No

6. What is your preferred approach for patients who develop brain metastases after prophylactic cranial irradiation (PCI)?

(Please select one)

☐ Surgery

☐ Whole-brain radiotherapy (WBRT)

☐ Stereotactic radiosurgery (SRS)

7. What is your preferred treatment approach for patients with SCLC who present with brain metastases and have not received PCI?

(Please select one)

☐ Whole-brain radiotherapy (WBRT)

☐ Stereotactic radiosurgery (SRS)

☐ WBRT followed by SRS

☐ Surgery

☐ Surgery followed by cavity-directed SRS

8. To what extent do the following factors influence your treatment decision in patients with brain metastases in SCLC?

	Never	Rarely	Sometimes	Often	Definitely
Performance status	☐	☐	☐	☐	☐
Number of brain metastases	☐	☐	☐	☐	☐
Total intracranial tumor volume	☐	☐	☐	☐	☐
Prior prophylactic cranial irradiation (PCI)	☐	☐	☐	☐	☐
Extracranial disease status	☐	☐	☐	☐	☐

9. If the number of brain metastases influences your decision to perform SRS, what is the maximum number of metastases for which you would consider SRS?

_____ metastases

10. If the total intracranial tumor volume influences your decision to perform SRS, what is the maximum total tumor volume (in cc) for which you would consider SRS?

_____ cc

11. What is your preferred approach for a patient who has undergone intracranial metastasectomy? (*Please select one*)

☐ Whole-brain radiotherapy (WBRT)

☐ Stereotactic radiosurgery (SRS)

☐ WBRT followed by SRS

☐ Observation / Follow-up

☐ Other: _____

12. What are your concerns regarding the use of SRS in patients with SCLC with brain metastases? (*You may select more than one option*)

☐ Rapid intracranial progression

☐ Lack of sufficient evidence

☐ Short overall survival

☐ High cost

☐ Limited access to SRS technology

☐ I have no concerns

☐ Other: _____