ABCResearch

Arch Basic Clin Res 2023; 5(3): 355-363 · DOI: 10.5152/ABCR.2023.23158

Original Article

Outcomes of Prophylactic Cranial Radiotherapy in Small-Cell Lung Cancer: A Retrospective Analysis

Mustafa Kandaz[1], Alperen Tüysüz[2], Kaan Aydoğdu[1], Mikail Şahin[1], Atalay Balsak[1], Emin Mammadov[1]

[1]Department of Radiation Oncology, Karadeniz Technical University, Faculty of Medicine, Trabzon, Türkiye
[2]Department of Family Medicine, Karadeniz Technical University, Faculty of Medicine, Trabzon, Türkiye

Cite this article as: Kandaz M, Tüysüz A, Aydoğdu K, Şahin M, Balsak A, Mammadov E. Outcomes of prophylactic cranial radiotherapy in small-cell lung cancer: A retrospective analysis. *Arch Basic Clin Res.*, 2023;5(3):355-363.

ORCID iDs of the authors: M.K. 0000-0003-1106-6227, A.T. 0000-0001-6834-6196, K.A. 0009-0008-7524-7709, M.Ş. 0009-0002-0245-2556, A.B. 0009-0005-7459-3165, E.M. 0009-0004-8570-6674.

ABSTRACT

Objective: In this study, a retrospective trial was done to determine the rate of development of brain metastasis in small-cell lung cancer patients treated with concomitant chemoradiotherapy or after chemotherapy chest radiotherapy and then prophylactic cranial radiotherapy and to evaluate the overall survival of the patients and compare it with literature data.

Methods: In this study, patients who were diagnosed with small-cell lung cancer between 2014 and 2022, who received concomitant chemoradiotherapy or thoracic radiotherapy after chemotherapy, whose disease was stable or in remission, without brain metastases, who did not receive cranial radiotherapy before, and who received 25 Gy (2.5 Gy/10) fraction undergoing prophylactic cranial radiotherapy were included. A total of 87 patients were included in this study.

Results: Of the 87 patients, 9 (10%) patients were female and 78 (90%) were male, with a mean age of 62.17 ± 8.33 (range: 41-80) years. The median follow-up was 23 months (range: 5–82 months). Brain metastases developed in 21 (24%) of the patients. The time between thoracic radiotherapy and prophylactic cranial radiotherapy in these patients was 1.92 ± 1.89 (range: 0-7) months. The time between prophylactic cranial radiotherapy and brain metastasis was 8.64 ± 7.3 (range: 2–30) months. The mean overall survival time of all patients was 33.47 ± 5.06 months (confidence interval, 23.66-43.28), and the median overall survival was 18 ± 2.67 (95% confidence interval, 12.74-23.25) months. The 1-, 2-, 3-, and 5-year overall survival rates were 84.7%, 49.2%, 36.3%, and 12.5%, respectively.

Conclusion: Prophylactic cranial radiotherapy is now used to treat both limited and extensive-stage small-cell lung cancer that responds to initial therapy. With combined therapy, the risk of thoracic recurrence is reduced, and as a result, brain metastases become one of the main types of recurrence. Our study demonstrates that prophylactic cranial radiotherapy is a low-risk, safe treatment option for small-cell lung cancer patients to avoid brain metastases. However, additional long-term, large-scale studies are needed to back up these findings and draw firm conclusions.

Keywords: Small-cell lung cancer, prophylactic cranial radiotherapy, brain metastasis

INTRODUCTION

Lung cancer is the second most common cancer and the most common cause of cancer-related death.[1] Non-small-cell lung cancer (NSCLC) is the most common histologic subtype, accounting for approximately 15% of small-cell lung cancer (SCLC).[2] Small-cell lung cancer is the most aggressive form of lung cancer. Although it is a cancer type that responds rapidly to chemotherapy and is sensitive to radiotherapy (RT), the 5-year survival rate is below 10%.[1,2] The central nervous system is a common site of metastasis in SCLC patients. With the use of more effective chemotherapeutic agents and the development of RT techniques, the risk of thoracic recurrence is significantly reduced, and as a result, brain metastasis becomes one of the main types of recurrence. Although treatment outcomes have improved with the addition of prophylactic cranial irradiation (PCI), survival remains poor. Despite advances in combined modality therapy, intracranial relapse remains a common site of relapse and a significant cause of morbidity in these patients.

Corresponding Author: Mustafa Kandaz, **E-mail:** mkandaz61@gmail.com

Received: February 1, 2023
Accepted: March 27, 2023
Publication Date: May 7, 2023

The staging system is different, and the VALSG (Veterans Administration Lung Study Group) classification has been used as a limited and widespread staging for many years.[3] In 30% of the patients, the disease is limited to the thorax (LSCLC), and survival of 15-20 months can be achieved with chemoradiotherapy (CRT)[4] The rate of extensive small-cell lung cancer (ESCLC) is 70%, and the average survival is 8-14 months.[5] It improves both overall survival (OS) and disease-free survival in SCLC in remission with PCI.[6]

At diagnosis, about 20% of patients, that is, 1 in 5 patients have brain metastases. However, other patients also have a risk of developing brain metastases at a rate of 60%-70% and leptomeningeal metastases at a rate of 10%-15% within 2 years.[7] Therefore, PCI has recommended to reduce the rate of brain metastases for both LSCLC and ESCLC stage in SCLC management.[8] The dose taken by the hippocampus is responsible for the neurocognitive dysfunction seen after PCI, and the risk increases in elderly patients (>70 years) and in cases of underlying comorbidity (Alzheimer's disease, etc.). Hippocampus protection can be done to reduce the rate of neurotoxicity.

In this study, our aim is to determine the rate of development of brain metastasis in patients treated with concurrent CRT or thoracic radiotherapy after chemotherapy and evaluate the relationship between PCI and OS in SCLC patients.

METHODS

Patient Selection

In this study, patients who were diagnosed with SCLC between 2014 and 2022 and underwent concurrent CRT or thoracic RT after chemotherapy, patients whose disease was stable or in remission, who did not have brain metastases, who did not receive cranial RT before, and who underwent 25 Gy (2.5 Gy/10 fraction) PCI were included. Institutional ethics committee approval was obtained for this retrospective analysis (Date: January 20, 2023, Project No. 2023-1). Data were obtained through a retrospective analysis of patients' records. Patients' characteristics such as gender (male or female) and age, the concurrent CRT dose, the thorax RT dose, whether brain metastases developed after PCI, and the final status of the patients (alive or dead) were also noted.

MAIN POINTS

- Prophylactic cranial radiotherapy is used to treat both limited and extensive-stage small-cell lung cancer that responds to initial therapy.
- With thoracic chemoradiotherapy, the risk of thoracic recurrence is reduced, and as a result, brain metastases become one of the main sites of recurrence.
- Prophylactic cranial radiotherapy reduces the incidence of brain metastases.

Treatment

Patients are usually placed on their backs during treatment; the trunk is supported, and they are partially immobilized by placing a footboard. More options are allowed when using lateral or oblique beam angles by placing the arms next to the body. Head and neck masks were applied to all patients. Computed tomography (CT) scans were performed on the entire cranium for RT application. Lenses, optic nerves, and brain stem were identified as critical organs. The 3D conformal radiotherapy (3DRT) technique was used. In RT planning, the entire cranium was defined as the clinical tumor volume (CTV). Planned target volume (PTV) was established by giving a 0.5 cm margin to CTV1. The patients received a total dose of 25 Gy in 10 fractions of 2.5 Gy per day. Oral steroids were given to all patients during RT.

Follow-Up

The clinical follow-up of the patients was performed every 3 months for the first 2 years, every 6 months for the next 3 years, and once a year thereafter. Physical examinations, lung CT, and brain MRI examinations were performed at each visit. In addition, cranial MRI was performed in patients with symptoms. The failure pattern was defined as the development of brain metastases after PCI.

Statistical Methods

The obtained data were subjected to statistical analysis by using the Statistical Package for Social Sciences version 23 (IBM SPSS Corp., Armonk, NY,USA) software. Clinical outcome was evaluated according to the development of brain metastases after PCI. The relationship between gender, age, thoracic RT, concomitant chemotherapy use, and metastasis development was analyzed for survival. Survival rates were calculated using the Kaplan–Meier method. The relationships among subgroups were evaluated by using log-rank test. Chi-square test was used to compare the 2 groups. All significant tests and statistical significance were accepted at the calculated *P* value of .05.

RESULTS

Patients Characteristics

A total of 87 SCLC patients were included in the study. Of these patients, 9 (10%) were female and 78 (90%) were male, and the female/male ratio was 1/10. The mean age of the patients was 62.17 ± 8.33 years (range: 41-80), the mean age of women was 59.12 ± 8.18 years (range: 54-75), and the mean age of men was 62.52 ± 8.52

years (range: 41-80). When the patients were divided into decades according to age, we found 7 (8%) patients were in the 5th decade, 27 (31%) were in the 6th decade, 30 (34%) were in the 7th decade, and 23 (27%) were in the 8th decade.

Treatment Characteristics

Forty-six (53%) patients received RT concurrently with chemotherapy. Forty (46%) patients received chemotherapy first, followed by thoracic RT in 30 (34%) of these patients. Eleven (13%) patients did not receive thoracic RT. One (1%) patient did not want to receive chemotherapy; therefore, only thoracic RT (66 Gy/33 fraction) was applied. Thoracic RT was performed in 6 (7%) patients with 30 Gy, 31 (35%) patients with 45 Gy BID (16 (18%) patients with concurrent CRT), 24 (28%) patients with 60 Gy (18 (21%) patients concurrent CRT), and 15 (17%) patients with 66 Gy (12 (14%) patients received concurrent CRT). Average time to PCI with thoracic RT was 1.96 ± 1.65 (range: 0-8) months.

Locoregional Recurrence and Distant Metastasis

The median follow-up was 23 months (range: 5-82 months). Twenty-one (24%) patients had brain metastases. The time between thoracic RT and PCI in these patients was 1.92 ± 1.89 (range: 0-7) months. The time between PCI and brain metastasis was 8.64 ± 7.3 (range: 2-30) months. Of the patients with brain metastases, 9 (43%) received only thoracic RT, while 12 patients (57%) received concomitant CRT. When the 2 groups were compared with the Chi-square test in terms of the development of brain metastases, no statistically significant difference was found between those who received concurrent CRT and those who received only thoracic RT (P=.910). Of the 21 patients who developed brain metastases, 1 (5%) was female and 20 (95%) were male. When the 2 groups were compared, no statistically significant difference was found (P=.297). Brain metastases were observed in 3 (14%) of the 5th-decade patients, 8 (38%) of the 6th-decade patients, 4 (19%) of the 7th-decade patients, and 6 (29%) of the 8th-decade patients. When the groups were compared, no statistically significant difference was found (P=.911) (Table 1).

In addition, 9 (10%) patients had contralateral lung metastases (time from PCI to lung metastasis was 4.67 ± 3.51 months) (range: 1-8 months), 7 (9%) had liver metastasis (time from PCI to liver metastasis was 7 ± 1 months) (range: 6-8 months), 8 (9%) had bone metastasis (time from PCI to bone metastasis was 5.6 ± 3.91 months) (range: 2-11 months), and 6 (7%) of them had mediastinal lymph node metastasis (time from PCI to lymph nodes metastasis was 8 ± 2.64 months) (range: 6-11 months).

Table 1. Characteristics of Patients with Brain Metastases

		n (%)
Gender	Female	1 (5%)
	Male	20 (95%)
Age(decades)	5	3 (14%)
	6	8 (38%)
	7	4 (19%)
	8	6 (29%)
Treatment	Concomitant chemoradiotherapy	12 (57%)
	Thoracic radiotherapy	9 (43%)

Survival Analysis

The mean OS time of all patients was 33.47 ± 5.06 months (confidence interval [CI], 23.66-43.28) and the median OS was 18 ± 2.67 (95% CI, 12.74-23.25) months. The 1-, 2-, 3-, and 5-year OS rates were 84.7%, 49.2%, 36.3%, and 12.5%, respectively (Figure 1 and Table 2).

The mean OS for female was 35.6 ± 10.23 months (95% CI, 15.54-55.65), and the median OS was 23 ± 10.38 months (95% CI, 5.65-46.35). For female, the 1-, 2-, 3-, and 5-year survival rates were 80%, 80%, 40%, and 40%, respectively. Mean OS for male was 31.77 ± 5.13 months (95% CI, 21.71-41.84), and the median OS was 17 ± 2.5 months (95% CI, 12.09-21.9). For male, the 1-, 2-, 3-, and 5-year survival rates were 63.7%, 31.2%, 27.3%, and 27.3%, respectively. There was no statistically significant difference in survival rates between the 2 groups (P=.160).

The mean age of all patients was 62.17 ± 8.33 (range 41-80) years, and when the patients were divided into decades according to age, in the 5th decade, the mean OS was 21.2 ± 9.16 (95% CI, 3.24-39.15) months and the median OS was 9 ± 1.09 (95% CI, 6.85-11.14) months. The 1-, 2-, 3-, and 5-year survival rates were 40%, 40%, 20%, and 20%, respectively. In the 6th decade, the mean OS was 40.89 ± 9.14 (95% CI, 22.97-58.82) months and the median OS was 26 ± 10.96 (95% CI, 4.51-47.48) months. The 1-, 2-, 3-, and 5-year survival rates were 70.6%, 50.5%, 40.4%, and 40.4%, respectively. In the 7th decade, the mean OS was 25.6 ± 8.7 (95% CI, 8.55-42.66) months and the median OS was 18 ± 5.1 (95% CI, 7.99-28.05) months. The 1-, 2-, 3-, and 5-year survival rates were 58%, 36.2%, 18.1%, and 18.1%, respectively. In the 8th decade, the mean OS was 19.21 ± 1.82 (95% CI, 15.64-22.79) months and the median OS was 18 ± 2.87 (95% CI, 12.37-23.62) months. The 1-, 2-, 3-, and 5-year survival rates were 79%, 32.9%, 32.9%, and 32.9%, respectively. There was no statistically significant difference in survival rates between the 4 groups (P=.573).

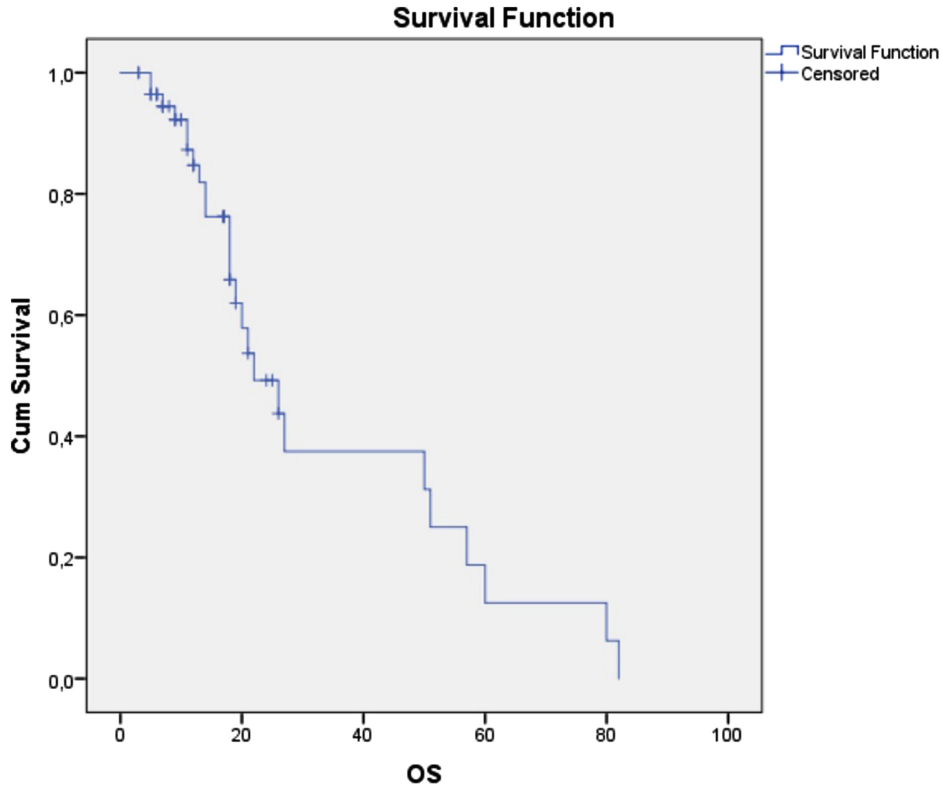

Figure 1. Overall survival.

When the patients were evaluated according to thoracic RT, in those who did not receive RT, the mean OS was 15.74 ± 3.42 months (95% CI, 8.99-22.43) and the median OS was 14 ± 3.14 months (95% CI, 7.84-20.15). The 1- and 2-year survival rates were 64.3% and 21.4%, respectively, and there were no patients who lived for 3 years. In those with RT, the mean OS was 38.75 ± 5.59 months (95% CI, 27.97-49.89) and the median OS was 26 ± 16.08 months (95% CI, 0-57.51). The 1-, 2-, 3-, and 5-year survival rates were 87.5%, 53.3%, 46.6%, and 15.5%, respectively. There was a statistically significant difference when the 2 groups were compared (P=.015).

When the patients were evaluated according to concurrent CRT, in patients treated with RT alone, the mean OS was 18.52 ± 1.76 (95% CI, 15.06-21.99) months and the median OS was 20 ± 1.43 (95% CI, 17.18-22.81) months. The 1- and 2-year survival rates were 73.1% and 27.8%, respectively, and there were no patients who lived for 3 years. In those with concurrent thoracic CRT, the mean OS was 43.05 ± 6.79 months (95% CI, 29.72-56.37) and the median OS was 50 ± 8.66 months (95% CI, 13.41-86.58). The 1-, 2-, 3-, and 5-year survival rates were 95.2%, 63%, 55.1%, and 18.4%, respectively. There was a statistically significant difference when the 2 groups were compared (P=.022).

When the patients were evaluated according to the thoracic RT dose, the mean OS was 15.74 ± 3.42 months (95% CI, 8.99–22.43) and the median OS was 14 ± 3.14 months (95% CI, 7.84-20.15) in those who did not receive thoracic RT. Overall survival at 1 and 2 years was 64.3% and 21.4%, respectively, with no patients surviving 3 years. In 30 Gy thoracic RT areas, the mean OS was 19 months, and the median OS was 19 months. One-year OS was 100%, and there were no patients who survived for 2 years. In 45 Gy BID thoracic RT areas, the mean OS was 39.9 ± 8.46 months (95% CI, 23.31-56.48), and the median OS was 26 ± 22.14 (95% CI, 0-69.4) months. The 1-, 2-, 3-, and 5-year survival rates were 88.9%, 56.4%, 45.1%, and 22.6%, respectively. 60-66 Gy in thoracic RT areas (When applying thoracic RT to the patients, a dose of 60 Gy to 66 Gy was preferred, with an intention of achieving a total lung mean dose <20 Gy and V20<%30-40.), the mean OS was 35.16 ± 6.68 months (95% CI, 22.05-48.26), and the median OS was 22 ± 13.56 months (95% CI, 0-46.61). Overall survival at 1, 2, and 3 years is 81.7%, 49%, and 24.5%, respectively. There were no patients who lived for 5 years. There was no statistically significant difference when the 4 groups were compared (P=.110).

When patients were evaluated according to metastasis status, the mean OS was 39.49 ± 7.07 months (95% CI, 25.62-53.35) and the median OS was 27 ± 24.55 months (95% CI, 0-75.11) in patients without metastasis. The 1-, 2-, 3-, and 5-year survival rates were 92.9%, 55.3%, 39.5%, and 15.8%, respectively. In patients with metastases, the

Table 2. Patient Characteristics and Survival Analysis

	n (%)	Mean (95% CI)	Median (95% CI)	1 Year (%)	2 Years (%)	3 Years (%)	5 Years (%)	*P*
All	87	33.47 ± 5.06 23.66-43.28	18 ± 2.67 12.74-23.25	84.7	49.2	36.3	12.5	
Gender	9 (10%)	35.6 ± 10.23 15.54-55.65	23 ± 10.38 5.65-46.35	80	80	40	40	.160
Female								
Male	78 (90%)	31.77 ± 5.13 21.71-41.84	17 ± 2.5 12.09-21.9	63.7	31.2	27.3	27.3	
Decade	7 (8%)	21.2 ± 9.16 3.24-39.15	9 ± 1.09 6.85-11.14	40	20	20	20	.573
5								
6	27 (31%)	40.89 ± 9.14 22.97-58.82	26 ± 10.96 4.51-47.48	70.6	50.5	40.4	40.4	
7	30 (34%)	25.6 ± 8.7 8.55-42.66	18 ± 5.1 7.99-28.05	58	36.2	18.1	18.1	
8	23 (27%)	19.21 ± 1.82 15.64-22.79	18 ± 2.87 12.37-23.62	79	32.9	32.9	32.9	
Thoracic radiotherapy	11 (13%)	15.74 ± 3.42 8.99-22.43	14 ± 3.14 7.84-20.15	64.3	21.4	0	0	**.015**
None								
Yes	76 (87%)	38.75 ± 5.59 27.97-49.89	26 ± 16.08 0-57.51	87.5	53.3	46.6	15.5	
Concurrent chemotherapy	41 (47%)	18.52 ± 1.76 15.06-21.99	20± 1.43 17.18-22.81	73.1	27.8	0	0	**.022**
None								
Yes	46 (53%)	43.05 ± 6.79 29.72-56.37	50 ± 8.66 13.41-86.58	95.2	63	55.1	18.4	
Radiotherapy	11 (13%)	15.74 ± 3.42 8.99-22.43	14 ± 3.14 7.84-20.15	64.3	21.4	0	0	.110
None								
30 Gy	6 (7%)	19	19	100	0	0	0	
45 Gy (BID)	31 (35%)	39.9 ± 8.46 23.31-56.48	26 ± 22.14 0-69.4	88.9	56.4	45.1	22.6	
60-66 Gy	39 (45%)	35.16 ± 6.68 22.05-48.26	22 ± 13.56 0-46.61	81.7	49	24.5	0	
Metastasis	36 (41%)	39.49 ± 7.07 25.62-53.35	27 ± 24.55 0-75.11	92.9	55.3	39.5	15.8	**.006**
None								
Yes	51 (59%)	14.02 ± 1.33 11.39-16.06	12 ± 2.78 6.54-17.45	48.3	12.5	0	0	
Metastasis site	21 (24%)	24.88 ± 3.52 17.97-31.78	27 ± 6.11 15.01-38.98	77.9	43.6	10.9	0	.127
Brain								
Lung	9 (10%)	23 ± 1.99 19.54-27.36	24 ± 2.35 19.38-28.61	83.3	31.3	0	0	
Liver	7 (9%)	17 ± 2.42 12.6-21.39	19 ± 4.02 10.7-27.29	80	0	0	0	
Lymph nodes	6 (7%)	19.5 ± 3.71 12.22-26.77	18 ± 4.58 9.01-26.96	75	37.5	0	0	
Bone	8 (9%)	15.2 ± 3.3 8.71-21.66	17 ± 7.66 1.97-32.03	60	20	0	0	

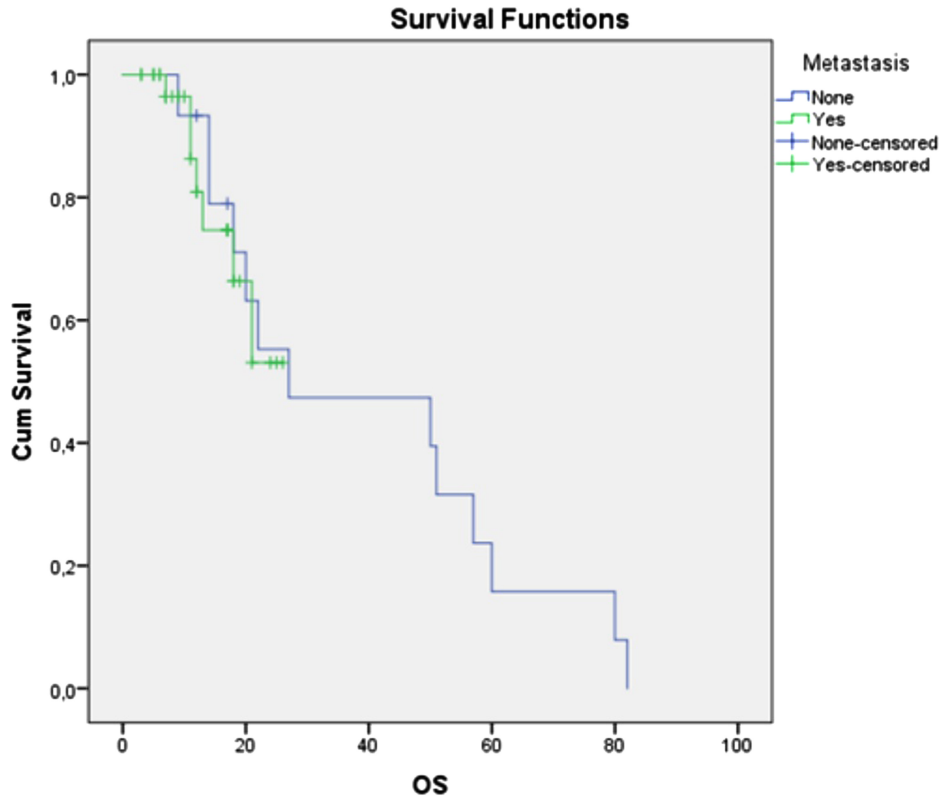

Figure 2. Overall survival according to metastasis.

mean OS was 14.02 ± 1.33 months (95% CI, 11.39-16.06) and the median OS was 12 ± 2.78 months (95% CI, 6.54-17.45). The 1- and 2-year survival rates were 48.3% and 12.5%, respectively, and there were no patients who lived for 3 years. There was a statistically significant difference when the 2 groups were compared (P=.006) (Figure 2). In patients with brain metastases, the mean OS was 24.88 ± 3.52 months (95% CI, 17.97-31.78) and the median OS was 27 ± 6.11 months (95% CI, 15.01-38.98). The 1-, 2-, and 3-year survival rates were 77.9%, 43.6%, and 10.9%, respectively, and there were no patients who lived for 5 years. In patients with lung metastases, the mean OS was 23 ± 1.99 months (95% CI, 19.54-27.36) and the median OS was 24 ± 2.35 months (95% CI, 19.38-28.61). The 1- and 2-year survival rates were 83.3% and 31.3%, respectively, and there were no patients who lived for 3 years. In patients with liver metastases, the mean OS was 17 ± 2.42 months (95% CI, 12.6-21.39) and the median OS was 19 ± 4.02 months (95% CI, 10.7-27.29). The 1-year survival rates were 80%, and there were no patients who lived for 2 years. In patients with lymph node metastases, the mean OS was 19.5 ± 3.71 months (95% CI, 12.22-26.77) and the median OS was 18 ± 4.58 months (95% CI, 9.01-26.96). The 1- and 2-year survival rates were 75% and 37.5%, respectively, and there were no patients who lived for 3 years. In patients with bone metastases, the mean OS was 15.2 ± 3.3 months (95% CI, 8.71-21.66) and the median OS was 17 ± 7.66 months (95% CI, 1.97-32.03). The 1- and 2-year survival rates were 60% and 20%, respectively, and there were no patients who lived for 3 years. There was no statistically significant difference when the 5 groups were compared (P=.127) (Figure 3).

DISCUSSION

Small-cell lung cancer accounts for 15%-20% of all lung cancers, although its incidence is decreasing. At the time of diagnosis, about 1 in 3 patients have limited-stage disease, and others have extensive-stage disease. Although its incidence increases with age, it is most common cancer in males aged 50-70 years and typically in heavy smoker men, either currently or in the past.[9] In our study, the female-to-male ratio was found as 1/9. This can be explained by the fact that women smoke less than men in the region where we conducted the study. The mean age of the patients was 63 years, similar to the published data in the literature.

In the study of Aupérin et al,[6] although the rates of OS were found to be higher in women than in men, they could not provide a hypothesis to explain this (performance status, extent of disease at baseline, and type of induction therapy). However, in terms of OS, PCI was less effective in women than in men. In our study, OS was 35 months in women and 31 months in men, and there was no statistical significance.

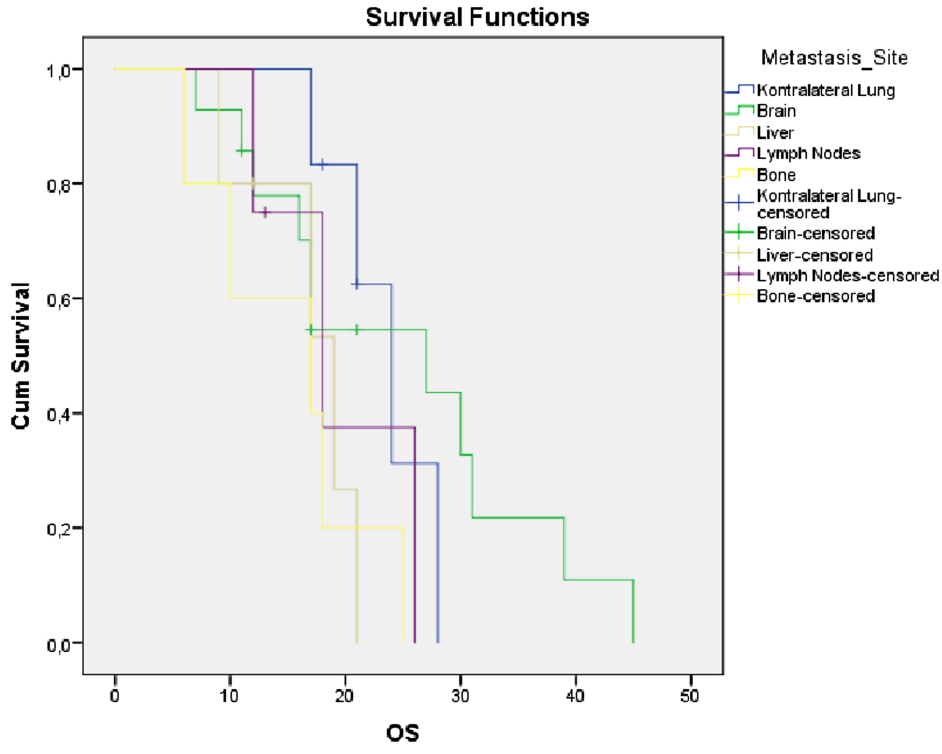

Figure 3. Overall survival by metastasis site.

After SCLC was found to be chemo- and radiosensitive in the 1960s, approximately 25% of the benefit was found with concurrent CRT in the 1980s. In a meta-analysis of 13 studies and 2140 patients, Pignon et al[9,10] found that chemotherapy and thoracic RT improved 3-year OS by 5.4% compared to chemotherapy alone (14.3% vs. 8.9%). In our study, OS was 15 months in those who did not receive thoracic RT, while it was 38 months in those who received thoracic RT. In addition, in the meta-analysis of Pijls-Johannesma 11 et al in controlled randomized studies, it was shown that survival was improved with the early addition of thoracic RT to chemotherapy. In the light of this information, the recommended treatment in LSCLC is 1 or 2 cycles of concurrent thoracic RT and a total of 4 cycles of chemotherapy.[9,12] Consolidative thoracic RT (recommended dose: 30 Gy/10 fraction) is recommended for those who respond to treatment after a total of 6 cycles of chemotherapy (cisplatin and etoposide) in ESCLC.[13] In our study, OS was 43 months versus 18 months, which was statistically significant ($P=.022$) in those who received chemotherapy and RT concurrently.

Many studies have been conducted showing the relationship between thoracic RT dose and survival. Turrisi et al[14] compared 45 Gy BID with 45 Gy/1.8 Gy in 1999 and found reduced local failure in the twice-daily arm (52% vs. 36%) and found to increase 5-year OS (26 vs. 16%) compared to the once-daily arm. 45 Gy BID was compared with 70 Gy of conventional RT in the CALGB 30610[15] study and 66 Gy in the CONVERT[16] study, and it was shown that high doses did not improve survival. In our study, although 45 Gy BID did not show a statistically significant difference in OS, an improvement of 35 months versus 39 months was observed.

Although 10%-20% of brain metastases are seen at the first diagnosis, there is a 60%-70% risk of developing brain metastases in the next 2 years, and Hirsch[17] et al in 1970 suggested that microscopic metastases in the brain were not affected by chemotherapy because of the blood–brain barrier and hypothesized that brain metastases could be prevented by PCI. As a result of these assumptions, several clinical studies have been conducted to evaluate the role of PCI. In these first trials, a decrease in the rate of brain metastases was observed, but no difference in survival was found.[18] In conclusion, PCI has been accepted as standard of care in the treatment of LSCLC since the 1990s, with a complete response to systemic therapy,[6] and after the phase 3 study of Slotman et al[20] since 2007. However, there is a 10%-30% risk of developing brain metastases after PCI.[20,21], In patients with brain metastases, the treatment option is best limited to supportive therapy or palliative cranial reirradiation, and surgery has no place.[6,22] Stereotaxic radiosurgery, on the other hand, is controversial because of the risk of multiple brain metastases and diffuse recurrence in SCLC, unlike the approach in brain metastases

of other solid tumors.[20,21] In our study, 11 (13%) of the patients underwent PCI after systemic treatment without thoracic RT. About 76 (87%) patients underwent PCI after thoracic RT. In our study, 24% of brain metastases developed, which is consistent with the literature.

Different dose schedules have been used in PCI: 20 Gy in 5-8 fractions, 24 Gy in 12 fractions, 25 Gy in 10 fractions, 30 Gy in 10-12 fractions, or 36-40 Gy in 18-20 fractions.[20,23] The biologically equivalent doses for these programs range from 25 to 39 Gy. Wolfson et al[22] compared 25 Gy with 36 Gy PCI. Because of the increased risk of developing chronic neurotoxicity in 36 Gy study patients, the 25 Gy PCI dose remains the standard of care for patients with SCLC. Le Péchoux et al[24] discovered that patients who received 25 Gy instead of 36 Gy had significantly lower chronic neurotoxicity (60% vs. 85%, $P=.02$, respectively). Hippocampus-sparing RT has become a priority in recent years to reduce neurocognitive toxicity. Gondi et al[25] showed that the hippocampal protective RT method for whole-brain irradiation due to brain metastases improved memory maintenance and quality of life. In our study, 25 Gy PCI was applied to all patients.

It is possible that advances in RT devices and techniques may reduce PCI toxicity. Changing the dose and schedule of PCI can clearly reduce potential morbidity. In addition, emerging approaches such as hippocampal protection and the use of protective agents (e.g., memantine) may also improve the therapeutic index.

Our study has several limitations. First, it is a retrospective study conducted in a single center. Therefore, the results should be interpreted with caution. Second, the limited sample size makes it difficult to obtain statistical significance in subgroup analysis, thus limiting the power of the study. Finally, we did not analyze quality of life or neurocognitive impairment. Comparative studies are needed to find the effectiveness of PCI. However, since PCI is a standard practice, such a study does not seem possible in our clinic.

Prophylactic cranial RT is now used to treat both limited and extensive-stage SCLC that responds to initial therapy. With combined therapy, the risk of thoracic recurrence is reduced, and as a result, brain metastases become one of the main sites of recurrence. Prophylactic cranial RT both reduces the incidence of brain metastases and increases survival. However, larger studies are needed to evaluate its contribution to survival in SCLC patients. Our study demonstrates that PCI is a low-risk, safe treatment option for SCLC patients to avoid brain metastases. However, additional long-term, large-scale studies are needed to back up these findings and draw firm conclusions.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee (Date: January 20, 2023, Number: 2023-1).

Informed Consent: Consent was obtained from the hospital management for the data obtained from the patient records. Because our study was retrospective, ethics committee approval is sufficient, informed consent is not required.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.K., A.T., K.A., M.S., A.B., E.M.; Design – M.K., A.T., K.A., M.S., A.B., E.M.; Supervision – M.K., A.T., K.A., M.S., A.B., E.M.; Resources – M.K., A.T., K.A., M.S., A.B., E.M.; Materials – M.K., A.T., K.A., M.S., A.B., E.M.; Data Collection and/or Processing – M.K., A.T., K.A., M.S., A.B., E.M.; Analysis and/or Interpretation – M.K., A.T., K.A., M.S., A.B., E.M.; Literature Search – M.K., A.T., K.A., M.S., A.B., E.M.; Writing Manuscript – M.K., A.T., K.A., M.S., A.B., E.M.; Critical Review – M.K., A.T., K.A., M.S., A.B., E.M.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Torre LA, Siegel RL, Jemal A. Lung cancer statistics. *Adv Exp Med Biol*. 2016;893:1-19. [CrossRef]
2. Gazdar AF, Bunn PA, Minna JD. Small-cell lung cancer: what we know, what we need to know and the path forward. *Nat Rev Cancer*. 2017;17(12):765. [CrossRef]
3. Zelen M. Keynote address on biostatistics and data retrieval. *Cancer Chemother Rep 3*. 1973;4(2):31-42.
4. Chen J, Jiang R, Garces YI, et al. Prognostic factors for limited-stage small cell lung cancer: a study of 284 patients. *Lung Cancer*. 2010;67(2):221-226. [CrossRef]
5. Horn L, Mansfield AS, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med*. 2018;379(23):2220-2229. [CrossRef]
6. Aupérin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med*. 1999;341(7):476-484. [CrossRef]
7. Tsui DCC, Camidge DR, Rusthoven CG. Managing central nervous system spread of lung cancer: the state of the art. *J Clin Oncol*. 2022;40(6):642-660. [CrossRef]
8. 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(5):663-671. [CrossRef]
9. van Meerbeeck JP, Fennell DA, De Ruysscher DK. Small-cell lung cancer. *Lancet*. 2011;378(9804):1741-1755. [CrossRef]
10. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med*. 1992;3;327(23):1618-24.

11. Pijls-Johannesma M, De Ruysscher DK, Vansteenkiste J, Kester A, Rutten I, Lambin P. Timing of chest radiotherapy in patients with limited stage small cell lung cancer: a systematic review and meta-analysis of randomised controlled trials. *Cancer Treat Rev*. 2007;33(5):461-473. [CrossRef]
12. Bogart JA, Waqar SN, Mix MD. Radiation and systemic therapy for limited-stage small-cell lung cancer. *J Clin Oncol*. 2022;40(6):661-670. [CrossRef]
13. Slotman BJ, Tinteren HV, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet. 2015;3: 385(9962):36-42.
14. Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med*. 1999;28:340(4):265-271.
15. Bogart J, Wang X, Masters G, et al. High-dose once-daily thoracic radiotherapy in limited-stage small-cell lung cancer: CALGB 30610 (alliance)/RTOG 0538. *J Clin Oncol*. 2023;9:JCO2201359. [CrossRef]
16. Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. *Lancet Oncol*. 2017;18(8):1116-1125. [CrossRef]
17. Hirsch FR, Paulson OB, Hansen HH, Vraa-Jensen J. Intracranial metastases in small cell carcinoma of the lung: correlation of clinical and autopsy findings. *Cancer*. 1982;50(11): 2433-2437. [CrossRef]
18. Rittberg R, Banerji S, Kim JO, Rathod S, Dawe DE. Treatment and prevention of brain metastases in small cell lung cancer. *Am J Clin Oncol*. 2021;44(12):629-638. [CrossRef]
19. Kristiansen PEG, Kristensen CA. The role of prophylactic cranial irradiation in the management of small cell lung cancer. *Cancer Treat Rev*. 1993;19(1):3-16. [CrossRef]
20. Slotman BJ, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med*. 2007;357(7):664-672. [CrossRef]
21. Bernhardt D, Bozorgmehr F, Adeberg S, et al. Outcome in patients with small cell lung cancer re-irradiated for brain metastases after prior prophylactic cranial irradiation. *Lung Cancer*. 2016;101:76-81. [CrossRef]
22. Wolfson AH, Bae K, Komaki R, et al. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2011;81(1):77-84. [CrossRef]
23. Prophylactic Cranial Irradiation Overview Collaborative Group. Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission. *Cochrane Database Syst Rev*. 2000;(4):CD002805. [CrossRef]
24. Le Péchoux C, Dunant A, Senan S, et al. Prophylactic cranial irradiation (PCI) collaborative group. Standard dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. *Lancet Oncol*. 2009;10(5):467-474. [CrossRef]
25. Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol*. 2014;32(34):3810-3816. [CrossRef]