

Our Radiotherapy Results in Patients with Primary Non-Small Cell Lung Cancer with Brain Metastases

Primeri Küçük Hücreli Dışı Akciğer Kanseri Olan Beyin Metastazlı Hastalarda Radyoterapi Sonuçlarımız

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Özet

Amaç: Akciğer kanseri, dünya çapında en sık görülen kanserdir ve kanser ölümlerinin önde gelen nedenleri arasındadır. Bu çalışmada amaç; beyin metastazları nedeniyle radyoterapi alan, primeri küçük hücreli dışı akciğer kanseri olan hastalarda radyoterapi etkilerini, sağkalımları ve sağkalımı etkileyebilecek faktörleri araştırmaktır.

Gereç ve Yöntemler: Bu çalışmaya primer küçük hücreli dışı akciğer kanserli 99 hasta dâhil edildi. Beyin metastazı olan tüm hastalara radyoterapi uygulandı. Hastalar, beyin metastazı sayısı, beyin metastazı için ameliyat yapıp yapılmadığı, cinsiyet, patoloji ve primer odak evresi, visceral organ tutulumu ve beyin metastazı sonrası ECOG performans durumuna göre gruplara ayrıldı ve gruplar kendi içinde karşılaştırıldı.

Bulgular: Tanı anındaki beyin metastaz sayısına göre sağkalım oranındaki değişim istatistiksel olarak anlamlı bulundu ($p<0.01$). Hastaların tanı anındaki evresine göre sağkalım karşılaştırıldığında istatistiksel olarak anlamlı fark bulundu ($p<0.01$). Benzer şekilde ECOG/PS durumuna göre sağ kalım oranındaki değişim istatistiksel olarak anlamlı bulundu ($p<0.01$). Visceral organ metastazı olan hastalar kendi aralarında yaşayanlar ve yaşamayanlar olarak iki gruba ayrıldığında yaşamayan hasta sayısının yüksek olduğu gözlemlendi ($p<0.001$).

Sonuç: Beyin metastazı gelişmiş hastalarda; yaş, cinsiyet, beyin metastaz sayısı, cerrahi, ECOG/PS, kemoterapi, radyoterapi ve visceral organ metastazının sağkalımı etkileyen faktörler olduğu bulunmuştur.

Anahtar kelimeler: Akciğer kanseri, Beyin metastazı, Küçük hücreli dışı akciğer kanseri, Radyoterapi

Abstract

Objective: Lung cancer is the most common cancer worldwide and is among the leading causes of cancer death. The aim of this study is to examine the survival of patients who received radiotherapy for the brain metastases, whose primary is non-small cell lung cancer, and also determine the factors that are like to affect the survival and to examine the results of radiotherapy in these patients as well.

Materials and Methods: This study included 99 patients with primary non-small cell lung cancer. All patients with brain metastases received radiotherapy. The patients were grouped and compared according to the number of brain metastases, whether surgery was performed for brain metastasis, gender, pathology and stage of the primary focus, visceral organ involvement, and ECOG performance status after brain metastasis developed.

Results: The change in survival rate according to the number of brain metastases at the time of diagnosis was found statistically significant ($p<0.01$). When the stages and survival of the patients at the time of diagnosis were compared, it was statistically significant ($p<0.01$). Similarly, the differences among the ECOG/PS status was also statistically significant ($p<0.01$). When patients with visceral organ metastases were divided into two groups as to groups as dead and alive, it was observed that the number of exitus that most of the patients were lost to their metastatic state ($p<0.001$).

Conclusion: Age, gender, the number of brain metastases the number of brain metastases brain metastasis, surgery, ECOG/PS, chemotherapy, radiotherapy and visceral organ metastasis were found to be factors affecting survival in patients with brain metastases.

Keywords: Brain metastasis, Lung cancer, Non-small cell lung cancer, Radiotherapy

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Geliş tarihi: 05.08.2021

Kabul tarihi: 03.03.2022

DOI: 10.17517/ksutfd.978809

INTRODUCTION

Lung cancer (LC) is the most common cancer worldwide and is among the leading causes of cancer death. Non-small cell LC (NSCLC) is also the most common one among all LCs. It constitutes approximately 85% of LCs and 30% of patients are metastatic at the time of diagnosis (1). Hellman and Weichselbaum (1990) stated that the tumor cell can produce single or limited distant organ metastasis regarding with the biology of the tumor cell (2). Patients are likely to have diverse treatment response depending on the location and number of brain metastases and their performance status. They are treated with local radiotherapy (RT) and surgery (3,4).

Despite significant advances in the treatment of NSCLC, the prognosis would be poor in case of uncontrolled systemic disease. Progression in patients with NSCLC usually results in 20-40% brain metastasis (BM) (5). Currently, surgical resection, RT, stereotactic radiosurgery (SRS) or combined treatment approaches are applied to patients with BM. Davey *et al.* stated that external RT can extend the median survivors of patients with BM up to approximately 4.2 months. In the same study, they stated that the effectiveness of external RT depends on the age of the patient, the number of BM and the location of metastases (6,7). Palliative treatments are recommended for patients with metastatic NSCLC. Metastasis treatments have little contribution to overall survival (OS). Although all treatment modalities are applied to these patients, their survival changes only 8-11 months (8). Survival of patients who are not treated for BM is only 1 month (9). The Radiation Therapy Oncology Group (RTOG); stated that three prognostic factors are important in the survival of patients with BM, age, Karnofsky performance score, and disease extent (10).

Whole brain RT is preferred in many patients with multiple BM. Radiotherapy given to patients who cannot be reached surgically or cannot be operated due to other reasons causes a regression in the neurological symptoms of the patient and provides a better life quality (11,12). After surgical resection or SRS, by whole brain RT application to the patient, an improvement in local control of brain metastasis and decrease in neurological deaths are achieved (13).

Even though local tumor control is achieved in some patients, it is lost due to extra cranial disease. The remaining patients are lost due to cranial disease recurrence (12,13).

The aim of this study is to assess the survival of patients who received RT for the BM, whose primary is NSCLC, and also determine the factors that might be affecting the study.

MATERIALS AND METHODS

This study included 99 patients with primary NSCLC and receiving RT with the diagnosis of BM between April 2016 and August 2019 in Radiation Oncology Department at Adana City Training and Research Hospital. The study was conducted retrospectively. The beginning of the study, ethics committee approval was received from the ethics committee of Cukurova University Faculty of Medicine prior to the study (91/39-4.9.2019).

Radiotherapy

Palliative external RT was given to the whole brain with a total dose of 30 Gy in 10 fractions with intensity-modulated radiotherapy (IMRT) treatment method in 95 (95.9%) patients who had multiple BM and all of whom undergone cranial metastasectomy.

Four (4.1%) inoperable patients who had only one metastasis received palliative external stereotactic radiosurgery (SRS) between 1x15-24 Gy depending on the volume of the tumor.

Symptomatic management

The management of the symptoms was accomplished by the usage of corticosteroids (e.g., dexamethasone or methylprednisolone) and anticonvulsants.

Statistical analysis

Descriptive statistics were expressed as count and percentages for categorical variables and mean and standard deviation for continuous variables. Chi-square test was used to determine the relationship between categorical variables. Kaplan-Meier method was used to determine the mean and median survival time of the patients. Statistical significance level was considered as 5% and SPSS (version: 13) statistical package program was used for all statistical calculations.

RESULTS

Seventy-six (76.7%) male and 23 (23.2%) female patients were included in the study. The mean age (year) of the patients was 61.33 (min: 42- max: 78), mean weight (kg) 63.48 (min: 58- max: 89) and mean height was 164.65 cm (min: 155- max: 176). While RT was given to 21 (21.2%) patients after cranial metastasectomy, 78 (78.7%) patients with the remaining cranial multiple metastases were administered RT after cranial magnetic resonance imaging (MRI). There were 26 (26.2%) patients with a BM number ≤ 5 , and 73 (73.7%) patients with a BM count of >5 . All patients were staged according to "American Joint Committee on Cancer" (AJCC) 7th Edition tumor, nodes, metastasis (TNM) staging system was used (14). Of all patients, 18 (18.1%) patients were stage IIB, 15 (15.1%) patients were stage IIIA, 40 (40.4%) patients were stage IIIB, and 26 (26.2%) patients were stage IV.

According to the performance status of the Eastern Cooperative Oncology Group (ECOG/PS), there were 19 (19.2%) patients with ECOG/PS-2, 59 (59.6%) patients with ECOG/PS-3, 21 (21.2%) patients with ECOG/PS-4. There were 64 (64.64%) patients whose primary pathology was adeno-cancer, 35 (35.36%) patients with squamous cancer (Table 1). Forty seven (47.5%) patients who received RT for BM were given palliative RT with the diagnosis of vena cava superior, while 52 (52.5%) patients were given palliative RT due to bone metastases. The survival of the patients was reported in months. Changes in the hemogram and biochemistry of BM patients with chronic diseases appear in Table 2.

Distribution of patients with BM according to their survival status is given in Table 3. The survival rate in male patients was found 17.1%, while it was 30.4% in

female patients. Although the survival rate was approximately 13% higher in female patients, the difference was not statistically significant.

Similarly, the survival rate was found to be 23.8% in patients with surgery, while it was 17.9% in patients without surgery.

On the other hand, when survival and BM number were compared; the survival rate was found 38.5% in patients with a BM number ≤ 5 while it was 13.7% in patients with a BM number >5 . In patients with a BM number of >5 , a difference of approximately 25% was found between the two groups, and it was statistically significant ($p < 0.01$).

The change in survival rate according to the stage at the time of diagnosis was also found to be statistically significant ($p < 0.01$). While 55.6% survival was observed in patients with stage IIB at the time of diagnosis, this rate decreased to 20% in patients with stage IIIA and 17.5% in patients with stage IIIB. When observing the patients with stage IV, the survival rate was found 0%.

Similarly, the change in survival rate according to ECOG/PS status was found to be statistically significant ($p < 0.01$). While survival was 52.6% in patients with ECOG/PS 2, this rate decreased to 16.9% in patients with ECOG/PS 3 and was 0% in patients with ECOG/PS 4.

When the pathology diagnosis and survival of the patients were compared, it was not found statistically significant ($p = 0.792$).

Visceral organ metastasis was a statistically significant characteristic for patient survival as it has found that most of the patients were lost (dead) ($p < 0.01$).

Patients who were undergone cranial metastasectomy had higher mortality rate. Their low survival rate was statistically significant ($p < 0.01$).

Median survival was 34 ± 1.65 months (95% CI: 30.78-37.23) while the mean survival time of patients diagnosed with BM after primary diagnosis (disease-free survival) was 32.24 ± 1.08 months (95% CI: 30.12-34.36). Graph showing the survival of patients diagnosed with BM after LC diagnosis.

Median survival was 40 ± 0.54 months (95% CI: 38.98-41.05), while the mean survival time of patients diagnosed with BM after primary diagnosis was 36.46 ± 1.21 months (95% CI: 34.08-38.84). The mean survival time of patients diagnosed with BM after primary diagnosis was 7.930 ± 0.07 months (95% CI: 7.79-8.07).

Table 1. Descriptive statistics for characteristics of patients with BM

	n (%)
Gender	
Male	76 (76.7)
Female	23 (23.2)
Number of brain metastasis	
≤ 5	26 (26.2)
$5 >$	73 (73.7)
Initial stage at diagnosis	
Stage IIB	18 (18.1)
Stage IIIA	15 (15.1)
Stage IIIB	40 (40.4)
Stage IV	26 (26.2)
ECOG/PS	
2	19 (19.2)
3	59 (59.6)
4	21 (21.2)
Pathology	
Adenocarcinoma	64 (64.64)
Squamous Cell Carcinoma	35 (35.36)
Mode of surgery	
Cranial metastasectomy	21 (21.2)
Mode of radiologic diagnosis	
MRI	99 (100)

ECOG/PS: Eastern Cooperative Oncology Group Performance Status

MRI: Magnetic resonance imaging

BM: Brain Metastases

Table 2. Descriptive statistics of hemogram and biochemical properties of patients with BM

	Mean	SD	Minimum	Maximum
Basophil(μ l)	10.913	1.121	8.0	13.7
LY(μ l)	0.056	0.051	0.00	0.20
LY%	1.221	0.538	0.60	3.60
NE(μ l)	13.559	7.392	2.2	26.8
NE%	8.0278	7.001	2.80	28.30
PLT(μ l)	66.071	14.289	54.2	92.2
WBC(μ l)	266.621	74.947	141	433
HCT%	10.279	5.240	4.50	30.70
Urea(mg/dL)	36.312	3.863	29.0	42.7
K (mmol/L)	29.904	7.783	20.71	53.72
Na (mmol/L)	4.224	0.568	3.56	4.92
ALT (U/L)	137.815	2.868	132.0	142.0
LDH (U/L)	46.953	41.949	8.2	123.6
AST (U/L)	247.11	90.587	190	562
Alkaline phosphatase(u/L)	48.645	31.806	9.8	96.3
Ca(mg/dL)	195.011	154.433	12	494
Creatinine(mg/dL)	8.698	0.655	6.9	9.9
Basophil(μ l)	0.612	0.072	0.50	0.72

Hb: Hemoglobin, LY: Lymphocyte, LY%: Lymphocyte percent, NE: Neutrophil, NE%: Neutrophil percent, PLT: Platelets, WBC: White blood cells, HCT: Hematocrit, K: Serum Potassium level, Na: Serum Sodium level, ALT: Alanine transaminase, LDH: Lactate dehydrogenase, AST: Aspartat Transaminase, Ca: Calcium

Table 3. Distribution of patients with BM according to their status

	Alive n (%)	Dead n (%)	p
Sex			
Male	13 (17.1)	63 (82.9)	0.163
Female	7 (30.4)	16 (69.6)	
Metastasectomy			
Yes	5 (23.8)	16 (76.2)	0.563
No	14 (17.9)	64 (82.1)	
Number of brain metastasis			
≤ 5	10 (38.5)	16 (61.5)	0.007
$5 >$	10 (13.7)	63 (86.3)	
Initial stage at diagnosis			
Stage IIB	10 (55.6)	8 (44.4)	0.001
Stage IIIA	3 (20)	12 (80)	
Stage IIIB	7 (17.5)	33 (82.5)	
Stage IV	0 (0)	26 (100)	
ECOG/PS			
2	10 (52.6)	9 (47.4)	0.001
3	10 (16.9)	49 (83.1)	
4	0 (0)	21 (100)	
Pathology			
Adeno	15 (23.4)	49 (76.6)	0.792
Squamous	8 (22.9)	27 (77.1)	
Visceral organ metastasis	4 (8.9)	41 (91.1)	0.001
Cranial metastasectomy	5 (23.8)	16 (76.2)	0.001

ECOG/PS: Eastern Cooperative Oncology Group Performance Status

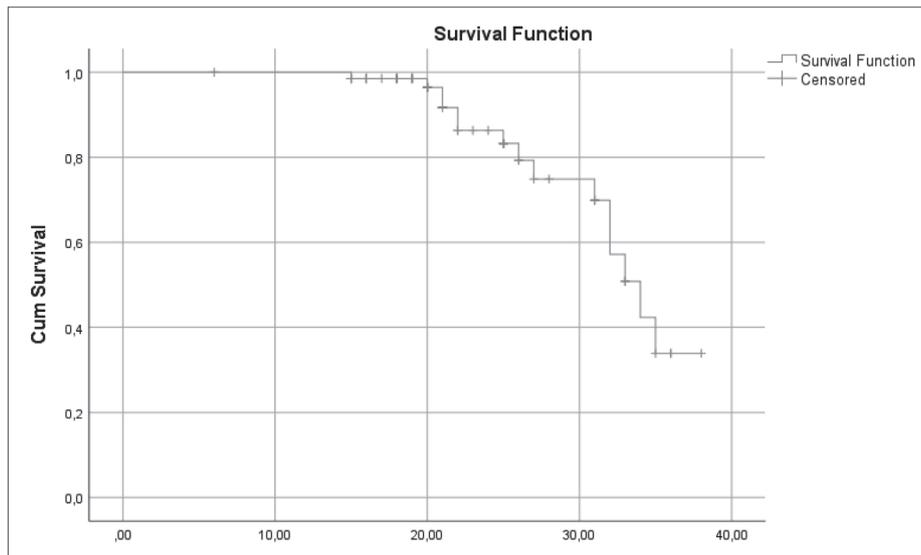


Figure 1. Cumulative disease free survival of patients following LC diagnosis in patients with brain metastasis (additional information is shown in the discussion)

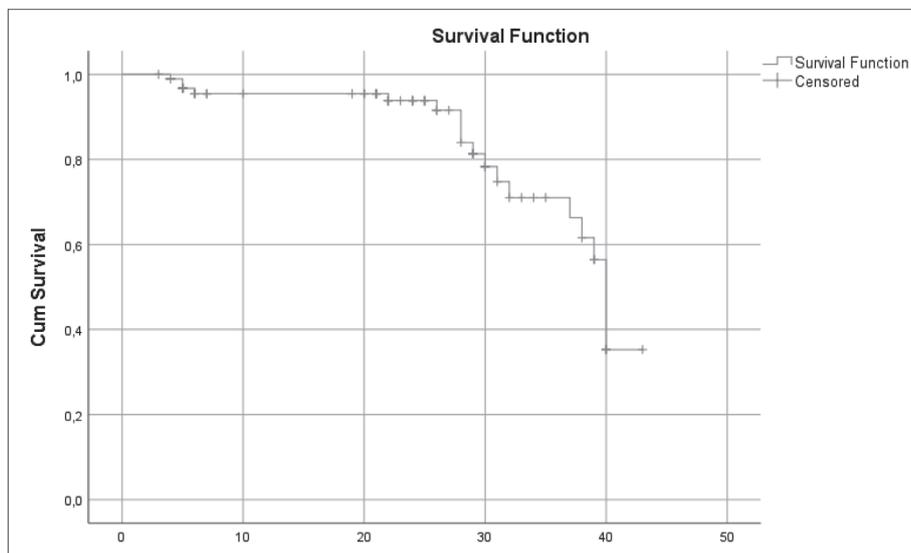


Figure 2. Cumulative survival of patients diagnosed with brain metastasis after Lung Cancer diagnosis (additional information is shown in the discussion)

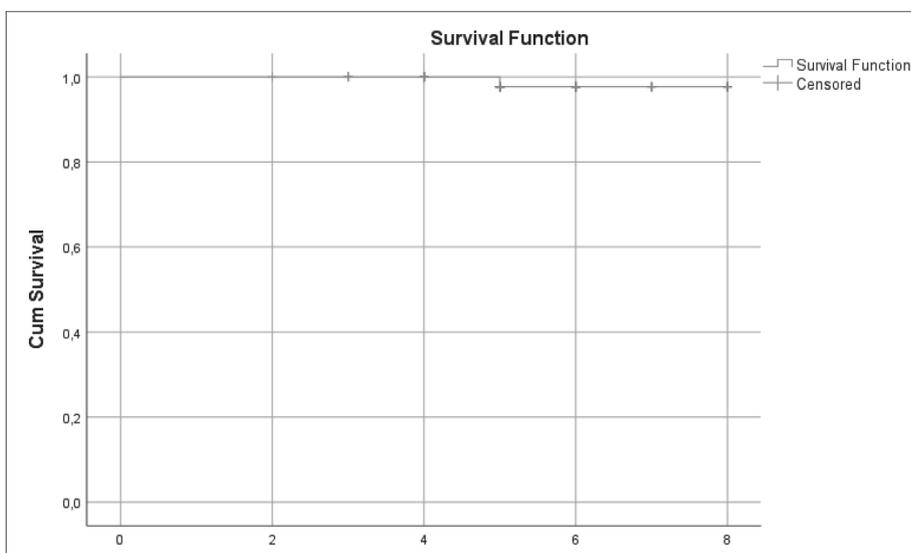


Figure 3. Cumulative survival of patients following brain metastasis diagnosis (additional information is shown in the discussion)

DISCUSSION

LC is the most common cancer worldwide, and it is also the most common cause of cancer-related death (15). Every year over 1 million new LC diagnoses are made and over one million patients die from LC. The BM is the most common cause of death in NSCLC (16). In our study, the general characteristics of the patients, the stage of the primary at the time of diagnosis and the ECOG/PS at the time of the diagnosis of BM. It can be stated that male LC patients are more common than female LC patients. As reported in the previous studies on LC in our country (17,18), the result of this study indicated that the incidence of getting LC was higher in men.

Adenocancer pathology is the most common in LC (19), and adeno cancer pathology was also more common in patients who were included in our study (Table 1). In the study conducted by Yin J *et al.*, the mean age of the patients was 61.8. In our study the average age of the patients was found 61.33 years (42-78) (20). MRI gives us the best information regarding the localization, number of metastases in patients with BM and whether they can undergo surgery (21,22). In our study, all patients were diagnosed with BM by MRI.

In the study conducted by Dong K *et al.*, it was reported that the survivors of female and male patients receiving RT from the BM were close to each other (23). Rotta JM *et al.* showed that male patients with BM live less than ($p < 0.01$) female patients (24). In our study, it is also observed that male patients with BM live less than female patients.

Tumor excision performed to BM provides local control of cancer and increases progression-free survival. In addition, it can be effective on the symptoms and course of the disease. Patchel *et al.* reported that BM patients had an average survival of 16 months after surgery, and that patient who received RT alone had a survival of 6 months (24). In the same study, it was shown that adjuvant RT reduces the local recurrence of patients and increases their quality of life. In our study, operated patients live approximately 5% longer than those who do not (24). After several studies combining resection of a single BM with RT, evaluating the role of surgery, adjuvant RT has become the standard (25-29). When the survivors of the surgical group and the non-surgical group were compared, there was no statistically significant result in our study. We attributed this to small sample size of the groups.

In patients with BM, the number of metastases is also very important. Nieder *et al.* divided the BM number into two groups as 1-3, 4 and above. When these

two groups of patients were compared, they showed that patients with BM of 4 or more lived a median of 3.6 months, while patients with BM of 1-3 lived a median of 4.2 months (30). In the study conducted by Rotta JM *et al.*, it was shown that patients with multiple BM lived 16.85 months, and patients with a single BM lived 16.76 months. However, in this study, no statistically significant difference was found between the two groups of patients in terms of survival (25). He ZY *et al.*, divided the patients into two groups according to the number of BM and gave RT together with chemotherapy (CT). They found that patients with a BM number of 3 lived 18 months and patients with a BM number > 3 lived 12.5 months ($p < 0.05$) (31). In our study, it was observed that the survivors of patients with a BM number of 5 were 25% better than patients with a BM number of > 5 , which was statistically significant ($p < 0.01$).

Ji *et al.* followed the development of BM in NSCLC stage IIIA-stage IIIB patients. The data they obtained from their study were parallel to our study. The risk of developing BM increases due to the increase in the stages of the patients at the time of diagnosis (32). In our study, when the stages of the patients at the time of diagnosis were compared with the survival of the BM patients, it was found statistically significant.

Doi *et al.* stated that patients with BM with LC showed better survival than those with 0-1 according to the Eastern Cooperative Oncology Group performance status (ECOG/PS) (33). In our study, it is seen that the survivors of the patients with poor performance are also poor according to the ECOG/PS examined before RT. In parallel with this, statistically significant results were obtained when ECOG/PS and survival were compared.

In previous studies, no connection was found between the pathologies of patients with LC and BM (34-36). In our study, there was no statistically significant result between the primary pathologies of the patients and BM.

The prognosis and survival of BM patients with visceral organ metastasis is poor. Since resistance to CT develops in these patients during the treatment period, primary tumors grow in size (37,38). Distant organ metastasis is shown as the cause of death in many cancer patients (39,40).

Gandara DR *et al.* found the median disease-free survival of patients with LC and BM as 16 months and their survival as 26 months (41). In our study, the average disease-free survival time was 32.24 months, while the average survival time was 36.4 months. In previous studies, it was reported that the survival of patients who received

RT for the BM could only be 4.2 months (6,7). Ali et al. found the Median overall survival of these patients as 7.8 months (42). In our study, it was found that patients with BM lived an average of 7.9 months. BM is common in patients with LC. neurological symptoms as their initial complaints, their primary diagnosis is LC (1,5).

Due to the insufficient number of patients treated with SRS in our study, the analysis of survival and other parameters could not be examined separately in this group of patients.

In patients with developed BM; age, gender, BM number, surgery, ECOG/PS, CT, RT, and visceral organ metastasis are the factors affecting survival. Although we evaluated these factors in our study, we could not reach the results we wanted in some groups due to the limited number of BM patients.

CONCLUSION

Treatment decision should be made depending on the number, size and location of metastases in BM patients with LC. The number and location of metastases, and the patient's performance status determines the radiation treatment modality. Surgery or SRS treatment should be preferred depending on the location and number of metastases in patients with BM. In BM patients with very short survival, personalized treatments should be given to increase the quality of life and survival of the patient.

Treatment modalities should be chosen according to the number, size, and location of metastases in LC patients with BM. The number and location of BM, and the patient's performance status are the key factors for applying RT treatment. Surgery or SRS treatment are the treatment modalities which can be performed for the LC patients with BM. In BM patients with short survival, personalized treatment modalities should be performed to increase the quality of life of the patients.

In the patients who underwent EBRT treatment to BM, we obtained OS similar to the previous studies in the literature. The number of BM, the stage of primary disease, the presence of visceral organ metastases with BM, and ECOG performance status are the major factors that affect OS of these patients. The survival of the patients who underwent whole brain RT treatment were also found similar to the previous studies in the literature (Table 1,2,3-Figure 1,2,3).

Conflict of Interest and Financial Status: The authors of the current paper declare no conflict of interest.

Ethical Approval: Ethical approval for this study was obtained from the Ethics Committee Cukurova University Faculty of Medicine. We started the study

after the approval of the Ethics Committee (Date 04.9.2019, Decision number: 39).

Research Contribution Rate Statement Summary: Writing – original draft, review & editing, Conceptualization:FK. Conceptualization: SM, AA, MES,TÇ. Formal analysis:SK.

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