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ORIGINAL ARTICLE

Evaluating Current Prognostic Factors for Brain Metastases of Patients with Primary Lung and Breast Cancer Receiving Cranial Radiotherapy - A Single Center Study

Melek Tuğçe YILMAZ, Alper KAHVECİOĞLU, Sezin YÜCE SARI, Melis GÜLTEKİN, Pervin HURMUZ, Faruk ZORLU, Gözde YAZICI

Department of Radiation Oncology, Hacettepe University Faculty of Medicine, Ankara-*Türkiye*

OBJECTIVE

Brain metastases (BM) are a serious cause of morbidity and mortality in patients with solid tumors. Due to improvements in local and systemic therapies, there is a need for novel prognostic factors. Herein, we aimed to evaluate the oncological results and current prognostic factors for BM in patients with breast and lung cancer, receiving cranial radiotherapy (RT).

METHODS

Medical records of 147 patients who were diagnosed with lung or breast cancer and underwent cranial RT at our clinic between 2011 and 2021 were evaluated retrospectively.

RESULTS

The median follow-up was 15 months (3–90 months). Local control rates for irradiated BM were 80% and 76% in patients receiving stereotactic RT and whole brain RT, respectively. Leptomeningeal metastasis (LM) developed in 24 patients (16%) during follow-up and, 87.5% of them had an infratentorial lesion. The 1- and 2-year overall survival (OS) and, intracranial progression-free survival rates were 57% and 36%, 30%, and 17%, respectively. Low- and intermediate-risk BM-velocity (BMV) is associated with better OS. None of the patients experienced severe (≥grade 3) acute toxicity.

CONCLUSION

Primary tumor histology, number, and localization of BM, treatment modality, extracranial disease status, development of radionecrosis, LM during follow-up, and BMV are important prognostic factors on survival in BM of patients diagnosed with lung and breast cancer. In the age of precision medicine, it is more crucial than ever to define and validate novel prognostic factors. Our findings contribute to justifying the addition of radionecrosis and BMV to predictive models.

Keywords: Brain metastasis; brain metastases-velocity; brain metastasis velocity; leptomeningeal metastasis; radionecrosis.

INTRODUCTION

Brain metastases (BM) are the most common intracranial tumors in the adult population and one of the most catastrophic systemic spread patterns of cancer. Approximately, up to 40% of all patients diagnosed with various solid tumors develop BM during their disease period.[1] The incidence of BM has increased in the current era due to elongated survivals with the advent of systemic therapies and modern radiotherapy (RT)

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Dr. Gözde YAZICI
Hacettepe Üniversitesi Tıp Fakültesi,
Radyasyon Onkolojisi Anabilim Dalı,
Ankara-Türkiye
E-mail: yazicig@gmail.com

techniques and the widespread use of magnetic resonance imaging (MRI) which increased the detection of smaller-sized lesions.[2–4] The most common tumors associated with BM are lung (50%) followed by breast (20%) cancer, malignant melanoma (10%), and colorectal carcinoma (5%).[5] Patients with BM generally experience severe neurological symptoms, and the prognosis is poor. Therefore, urgent treatments are required when detected. The primary treatment approaches include surgery, RT, or systemic therapies. For patients with obvious mass effects due to the BM (midline shift and tonsillar herniation), surgery is the preferred option. However, most patients are not suitable for surgery because of the performance status, number and location of BM, and increased risk for surgical morbidity and mortality. Therefore, RT is a mainstay treatment modality for most patients. Stereotactic RT (SRT) and/or whole-brain RT (WBRT) are the options in the first-line or postoperative setting. Depending on the primary tumor histology and genomic profile, initial systemic therapies are another hot-topic option and local therapies could be delayed in some extremely well-selected patients, currently.[6,7]

In the historical recursive partitioning analysis (RPA), age, Karnofsky performance status (KPS), and extent of extracranial disease are important prognostic factors for patients with BM.[8] However, these factors are inadequate in determining the prognosis of patients with different tumor types and molecular genomic profiles in the current era. Consequently, the diagnosis-specific graded prognostic assessment (GPA) has been developed.[9] In addition to classification according to primary cancer in GPA, the histological subtypes for breast cancer and the presence of a driver mutation for lung cancer were added to the prognostic index. Furthermore, in the 2022 update, the presence of programmed death ligand-1(PDL-1) was also included in the prognostic scoring.[10] Apart from these well-defined prognostic factors, BM-velocity (BMV), another recently defined prognostic factor is defined for patients treated with initial SRT.[11,12]

In our retrospective study, we aimed to evaluate the oncological outcomes and current prognostic factors for lung and breast cancer patients receiving cranial RT for BM.

MATERIALS AND METHODS

Patient Population

Medical records of the patients with BM of primary lung or breast cancer who received cranial RT (WBRT and/or SRT) in our department were retrospectively analyzed. Patients who had follow-up MRI at least 3 months after the initial RT were included in the analyses. Patients with a history of another malignancy, previous cranial RT, who did not have follow-up MRI, did not complete the intended treatment, and patients with leptomeningeal metastasis (LM) were excluded from the study. The study was conducted in compliance with the principles of the Helsinki Declaration and institutional ethics board approval was obtained (2023/08–22).

RT

In our clinic, WBRT and SRT decisions are taken by considering factors such as the number/volume of metastases, the age of the patient, the histology of the primary tumor, the extracranial disease status, and the patient's performance. Roughly, SRT is often used in cases with 4 or less metastases, and WBRT is typically used in cases with more than 4 metastases.

All patients underwent simulation computed tomography (sim-CT) in a supine position with a thermoplastic mask for appropriate immobilization. For patients who received WBRT, clinical target volume (CTV) was delineated as the whole brain parenchyma down to the level of the second cervical vertebra. The planning target volume (PTV) was delineated as CTV+1 cm. Varian Clinac DHX High-Performance Linear Accelerator was used for treatment delivery. For patients who received SRT, gross tumor volume (GTV) was delineated by fusion of sim-CT and planning MRI, which was performed a maximum of 1 week before the first fraction of RT. For intact metastasis, the whole contrast-enhanced lesion was delineated as GTV. For resected metastasis, the whole resection cavity ± residual lesion was delineated as GTV. CTV was not delineated and the PTV was delineated as GTV+1.25 cm. Accuray Cyberknife® was used for treatment delivery. For patients with symptomatic BM, 4×4 mg of dexamethasone and 20 mg of rabeprazole were prescribed, and all patients who received SRT were intravenously premedicated with 8 mg of dexamethasone, and 20 mg of rabeprazole before the first fraction of treatment.

Statistics

Statistical Package for the Social Sciences version 23.0 (IBM, Armonk, NY, USA) was used for all statistical analyses. All time-related events were defined as from the completion of RT to the last follow-up, death, or recurrence, whichever came first. Kaplan–Meier estimates were used for survival analysis and log-rank tests for comparison. Age, histology, status of extracranial disease, localization and number of BM, RT technique, presence of surgery, presence of LM, and radionecro-

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sis were defined as covariates for survival. For patients who received initial SRT, BMV was calculated by dividing the newly emerging BM number after initial SRT by the follow-up period (years). A $p<0.05$ was considered statistically significant. The Cox proportional hazards model was used for multivariate analyses. The potentially significant covariates following univariate analyses with significant contributions to the survival estimation ($p<0.1$) were preserved in the final multivariate model. Hazard ratios with a 95% confidence interval (CI) were reported.

RESULTS

Patient, Tumor, and Treatment Characteristics

Patient, tumor, and treatment characteristics are presented in Table 1. The median age was 60 years (range, 23–80 years). Fifty-two percent of the patients were male, and 48% were female. Of patients with lung cancer, 93% of them had non-small cell lung cancer (NSCLC), and the remaining 7% had SCLC. None of the patients with NSCLC had a driver mutation (epidermal growth factor receptor, anaplastic lymphoma kinase, proto-oncogene tyrosine-protein kinase ROS, etc.). Of patients with breast cancer, 80% of them had a luminal subtype, and 20% of them had a triple negative subtype. Forty-two percent of patients had more than five BM, and 33% had solitary BM. Eighty-two percent of patients received RT alone, remaining 18% of patients had initial surgery followed by postoperative RT. Of patients who received postoperative RT, 48% received WBRT, while the remaining 52% received SRT and of patients who received postoperative WBRT, number of BM was >5 in 60% and <2 in 18% of the patients. Of patients who received RT alone, 57% of them received WBRT, while the remaining 43% received SRT. Median BMV was 0.7 (range, 0–25). The median WBRT dose was 30 Gy (range, 25–30 Gy) in 10 to 12 fractions and the median SRT dose was 24 Gy (range, 15–35 Gy) in one to five fractions.

Table 1 Patient, tumor and treatment characteristics

Characteristics	n	%
Primary tumor		
Lung	104	71
Breast	43	29
Status of extracranial disease		
Controlled	64	44
Uncontrolled	83	56
Number of BM		
1	49	33
2–3	27	18
4–5	9	7
>5	62	42
Localization of BM		
Supratentorial	64	44
Infratentorial	24	16
Both	59	40
Treatment		
Surgery and PORT	27	18
RT	120	82
BMV*		
<4	53	80.3
4–13	11	16.7
>13	2	3

*: For patients received initial SRT. BM: Brain metastasis; PORT: Postoperative radiotherapy; RT: Radiotherapy; BMV: BM-velocity; SRT: Stereotactic radiotherapy

Treatment Outcomes

In the first MRI assessment after RT, 28% of patients achieved a complete response, 67% had a partial response, 2% had stable lesions and 3% had progression on treated tumor volume. The median follow-up period was 15 months (range, 3–90 months). During the follow-up, intracranial failure was observed in 82 patients (56%). Intracranial failure was observed as the progression of previously irradiated lesions in 19 patients (23%), newly emerging lesions in 49 patients (60%), and both previously irradiated and newly emerging lesions in 14 patients (17%). Local control (LC) rates for irradiated BM were 80% and 76% in patients receiving SRT and WBRT, respectively.

The 1- and 2-year overall survival (OS) rates were 57% and 36%, and intracranial progression-free survival (ICPFS) rates were 30% and 17%, respectively. During the follow-up period, the development of the LM rate was 16%. In patients with BMs initially located at the supratentorial- and infratentorial regions, the development rates of LM were 4% (n=3) and 17% (n=4), respectively. For patients who had BMs initially located at both supra- and infratentorial locations, the development rate of LM was 29% (n=17) (Fig. 1).

Prognostic Factors

The results of the univariate analysis is presented in Table 2. Patients with primary breast cancer had better 2-year OS (55% vs. 27%, p=0.04) and ICPFS (26% vs. 12.5%, p=0.02) compared to patients with primary lung cancer. The median OS of patients with isolated supratentorial BM was 17 months (SE: 2.3, 95% CI: 12.8–22.1) and patients with infratentorial metastasis had a median 13 months (SE: 1.4, 95% CI: 10.1–15.9).

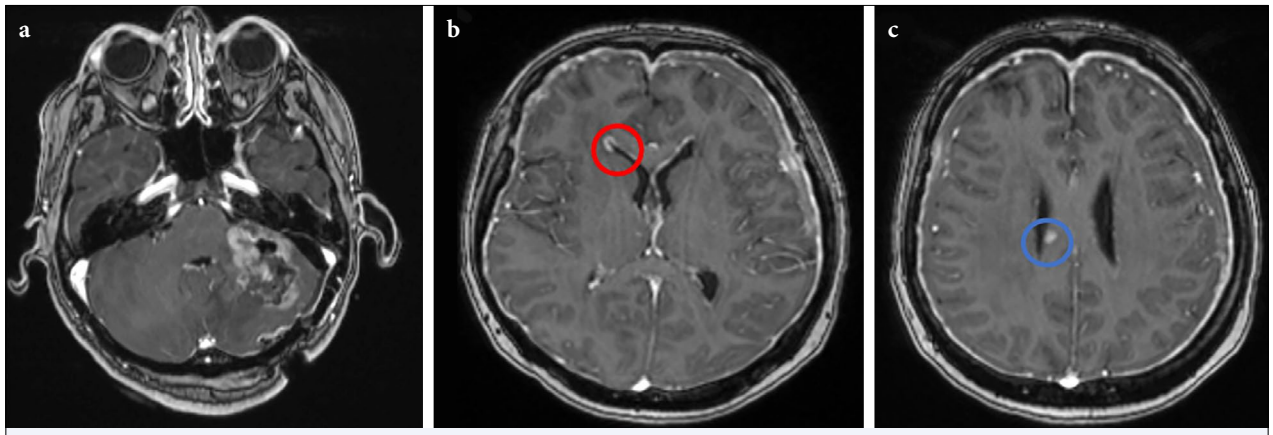

Fig. 1. Magnetic resonance image of isolated infratentorial metastasis (a) Pre-operative MRI scan, (b, c) Post-operative/post-SRS MRI scan showing epandymal seeding and leptomeningeal metastasis).
MRI: Magnetic resonance imaging; SRS: Stereotactic radiosurgery.

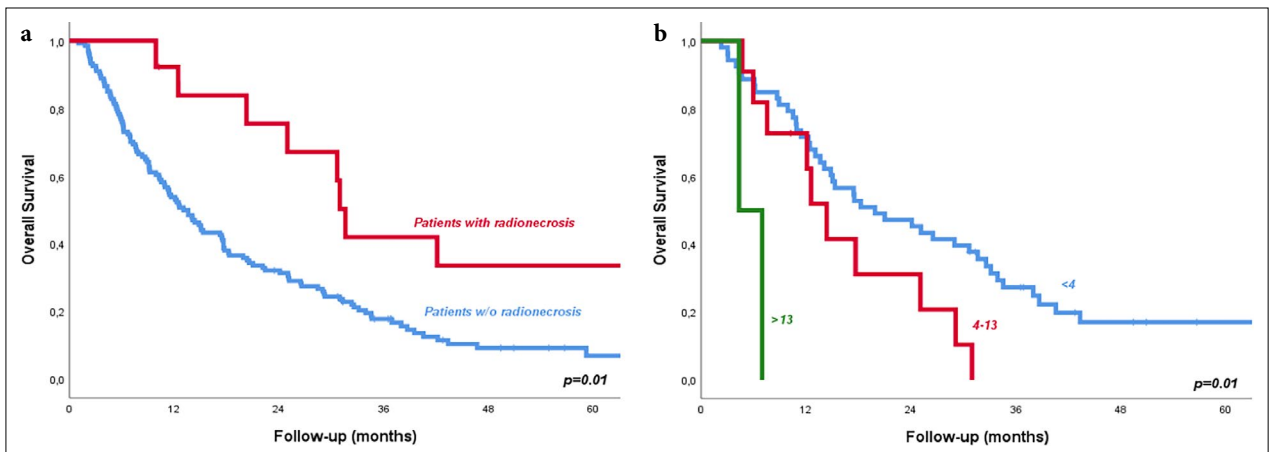

Fig. 2. Kaplan-Meier survival curves for overall survival (a) OS curves for radionecrosis, (b) OS curves for brain metastasis velocity.

The uncontrolled extracranial disease was also an important parameter for OS, consistent with the literature (p=0.004). Patients in whom two treatment modalities were applied together had better 2-year OS (63% vs. 30%, p=0.006) and ICPS (37% vs. 12%, p=0.001) compared to patients who received cranial RT for intact BM. The number of BM was also an important factor for OS. Patients with solitary BM had better 2-year OS (54% vs. 21%, p=0.001) and ICPFS (27% vs. 11%, p=0.003), compared to patients with >1 BM. The absence of LM during follow-up is associated with better 2-year OS (38% vs. 25%, p=0.04) compared to the presence of LM. The presence of radionecrosis on MRI affected OS drastically, and the median OS of patients who had radionecrosis was 31.6 months (SE: 0.8, 95 CI: 30–33.2) and median OS for absent radionecrosis was 13 months (SE:1.5, 95% CI: 10–16) (Fig. 2).

BMV was calculated in patients who received SRT as the initial treatment approach. Patients were classified into low-, intermediate-, and high-risk groups based on the number of new metastases per year: 4, 4–13, and >13.[12] The median OS for patients who had <4 metastases per year was 19.8 months (SE: 5.1, 95% CI: 9.8–29.9), for patients who had 4–13 metastasis was 14.3 months (SE:1.6, 95% CI: 11–17.6) and for >13 metastasis was 4.3 months (Fig. 2).

Results of the multivariate Cox proportional hazards model are presented in Table 3. Having a breast primary, solitary BM, controlled extracranial disease, presence of radionecrosis, and absence of LM were found to be statistically significant positive prognostic factors for OS. For ICPFS, breast primary, solitary BM, and resected BM were statistically significant positive prognostic factors.

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Table 2 Univariate analysis for overall survival and intracranial progression-free survival

Covariates	2-y OS	p	2-y ICPFS	p
Age				
<60 years	38	0.8	17	0.66
≥60 years	35		15	
Histology				
Lung cancer	27	0.063	12.5	0.02
Breast cancer	55		26	
Extracranial disease status				
Controlled	45	0.01	18	0.31
Uncontrolled	28		15	
BM localization				
Isolated supratentorial	41	0.03	22	0.2
Infratentorial	31		12	
BM number				
1	54	0.001	27	0.003
≥2	27		11	
Treatment approach				
RT alone	30	0.006	12	0.001
Surgery and PORT	63		37	
RT technique				
WBRT	30	0.07	16	0.6
SRT	43		17	
Radionecrosis*				
Present	75	0.01	17	0.3
Absent	32		15	
Development of LM*				
Present	25	0.04	4	0.1
Absent	38		19	
BMV**				
<4	47	0.001	N/A	N/A
4–13	31			
>13	0			

*: During follow-up period; **: For patients received initial SRT. OS: Overall survival; ICPFS: Intracranial progression free survival; BM: Brain metastasis; RT: Radiotherapy; PORT: Postoperative radiotherapy; WBRT: Whole brain radiotherapy; SRT: Stereotactic radiotherapy; LM: Leptomeningeal metastasis; BMV: Brain metastasis velocity; N/A: Not available

Toxicity

None of the patients experienced severe (≥grade 3) acute toxicity. The most common mild acute toxicities were headache, nausea, vomiting, and focal alopecia. During the follow-up period, the only ≥grade 3 late toxicity was radiation necrosis and it was observed in 13 patients (9%). In one patient (7%), radionecrosis developed 6 months after SRT (24 Gy in 1 fraction). The remaining 12 patients (93%) received reirradiation due to intracranial failure during their follow-up (WBRT and/or SRT). For patients with symptomatic radionecrosis, medical treatments such as steroids were initiated.

Table 3 Multivariate analysis for overall survival and intracranial progression free survival

	HR	95% CI	p
2y-OS			
Primary tumor type (Lung vs. breast)	0.6	0.4–0.9	0.03
BM number (1 vs. >1)	2.08	1.1–3.6	0.009
Radionecrosis (present vs. absent)	2.4	1.2–5	0.014
LM (present vs. absent)	0.5	0.3–0.8	0.013
2y-ICPFS			
Primary tumor type (Lung vs. breast)	0.6	0.4–0.9	0.03
BM number (1 vs. >1)	1.6	1–2.3	0.017

HR: Hazard ratio; CI: Confidence interval; OS: Overall survival; BM: Brain metastasis; LM: Leptomeningeal metastasis; ICPFS: Intracranial progression free survival

DISCUSSION

In this retrospective single-center study, we observed that primary tumor type, number of BM, resection status, and extracranial disease status are important prognostic factors for survival in patients with BM of primary lung or breast cancer, which are consistent with the literature. In addition, the presence of radionecrosis during follow-up and isolated supratentorial localization are also important positive prognostic factors for survival. Most of the patients with LM had BM in the infratentorial fossa. For patients treated with initial SRT, low-risk BMV (<4) is associated with better survival, compared to intermediate and high risk.

RT is a cornerstone treatment approach in patients with BM. WBRT is recommended for patients ineligible for surgery and/or SRT.[2,13] For patients with poor performance status, WBRT does not improve OS compared to the best supportive care.[14] However, the decision of the treatment should be tailored for each patient, especially in the modern era, as the prognosis shows a wide diversity. The most common recommended WBRT dose is 30 Gy in 10 fractions and, dose escalation to 37.5 Gy in 15 fractions does not provides any survival benefit and, also increases toxicity.[15] In our study, the median WBRT dose was 30 Gy in 10 fractions for patients with both intact and/or resected BM, which is consistent with the literature. Due to the modern non-invasive treatment techniques such as SRT, the role of surgery is only limited to well-selected patients and is reserved for the presence of life-threatening symptoms (tonsillar herniation and midline shift), large and relatively few BM in a resectable brain location. In three trials examining the role of surgery followed by WBRT, two of them showed a survival benefit with surgery compared to WBRT alone.[16–18]

All of these three trials included patients with solitary BM. In addition, for patients with resected solitary BM, the addition of WBRT to surgery also improves local and distant brain control.[19] These historical trials did not contain modern treatment techniques such as SRT. SRT provides similar OS and has less toxic effect on neurocognitive functions than WBRT, for patients with a limited number of BM.[20–22] In our study, 27 patients (18%) received postoperative RT (WBRT 48%, SRT 52%) and 2-years OS and ICPFS were significantly higher in patients with resected BM. As the surgery was only limited to a small portion of patients with favorable prognostic factors, this positive effect might be related to the other prognostic features in patients with resected BM. We also consider that the high rates of postoperative WBRT in our study are due to the large number of BM in patients treated with surgery (18%<2, 60%>5 BM). In the current American Society for Radiation Oncology guideline, postoperative SRT is strongly recommended over WBRT for patients with a limited number of BM to preserve neurocognitive functions and patient-reported quality of life.[6]

Several important prognostic factors were defined in the literature for BM. These prognostic factors are crucial in the optimal treatment decision in BM patients as they enable us to predict patients' survival. In the RPA classification, which is the oldest classification we have, median survivals for class I, II, and III by assessing age, KPS, and extracranial disease status were are 7.1, 4.2, and 2.3 months, respectively.[8] The diagnosis-specific GPA which takes many different factors into account has been developed as mentioned before.[9] According to the GPA, performance score, age, presence of extracranial metastases, number of BM, epidermal growth factor receptor mutation, ALK gene fusion status, PDL-1 positivity are important prognostic factors for lung, and performance score, age, presence of extracranial metastases, number of BM, and histological subtype (basal, luminal A, human epidermal growth factor receptor-2 or luminal B) are for breast cancer.[3,10] In our study, age was not a prognostic factor for survival but controlled extracranial disease is associated with better OS.

BMV is a recently defined prognostic factor for patients treated with initial SRT.[11,12] It is calculated by dividing the newly emerging BM number after the initial SRT by the follow-up period (years). Precision medicine has led to the development of numerous models to find the best possible treatment modality, but none of these models took into consideration the number of BM at the time of failure.[23–25] BMV is a unique prognostic factor in this regard, which enables it to function as a sort of indicator of tumor aggressiveness. In our study, we have validated BMV as a prognostic marker in our series of patients with breast and lung cancer patients with BMV <4 had 2 times higher OS compared to ≥4, and high-risk patients' median survival was 4 months, which is consistent with the recent literature. The fact that the patients with low and intermediate risk in our study had better survival compared to the literature may be due to the good prognostic histology of our patients. However, high-risk patients' survival is similar to the literature and it can be interpreted as patients with high-risk BMV having a poor prognosis independent of histology, and the most appropriate treatment in these patients may be the best supportive care.

Supratentorial region is the most common location of BM. However, the prognostic value of BM localization on survival is controversial in the literature. There are some studies considering the infratentorial location as a negative prognostic factor, most probably due to the increased risk of development of LM.[26,27] In our study, patients with isolated supratentorial BM had better OS, compared to patients with infratentorial BM. In addition, LM developed in 16% of the patients during follow-up, and 87.5% of them had infratentorial BM and, 12.5% of them had isolated supratentorial BM. The risk of LM development depending on the BM localization may be beneficial when deciding of the RT technique (e.g., posterior fossa RT, WBRT, or SRT). However, prospective randomized trials are needed to determine the optimal approach for patients with infratentorial BM.

Radionecrosis is a rare late complication of cranial RT and the rates that have been reported in the literature are between 0 and 20%, depending on the RT technique, size of irradiated BM, fraction number, etc. [6] Data on whether radionecrosis can be prognostic on survival and local control are controversial. In their cohort of 149 patients, Martens et al.[28] demonstrated that radionecrosis is a poor predictor of survival after SRS. Patients with necrosis had a median survival of 5.4 months, whereas patients without tumor necrosis had a median survival of 7.2 months. In contrast, Huang et al.[29] found that improved local control was linked with a higher MRI zone percentage representing necrosis in patients who had received gamma-knife. In our study, although re-irradiation was applied due to the intracranial failure in 93% of the patients who developed radionecrosis, they had better 2-year OS compared to the patients without radionecrosis. This may be associated with radionecrosis as a good prognostic factor, but also, the fact that these patients received re-irradiation may be the reason for their good prognosis.

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Limitations of the Study

Although our study validates novel prognostic factors such as BMV and radionecrosis for patients with BM treated with cranial RT, it also has some limitations. First of all, retrospective design limits our knowledge of RT technique, RT timing, and performance scores. A major limitation of our study is lack of the details on systemic therapies, which affect the oncological outcomes. However, all of the patients in the current study were treated with cytotoxic chemotherapies due to the lack of driver mutations, and possible positive prognostic effects of targeted therapies on survival were disposed of.

CONCLUSION

For patients with BM of primary lung or breast cancer, several prognostic factors were defined. Breast cancer histology rather than lung cancer, solitary BM and supratentorial localization of BM, surgery before RT, controlled extracranial disease, and development of radionecrosis are important positive prognostic factors. For patients with infratentorial BM, the risk of developing LM during follow-up is high and should be kept in mind when deciding on the RT technique. In addition, BMV is another current prognostic factor and low and intermediate risk groups are associated with increased OS in patients treated with initial SRT. Our study provides evidence to support the assertion of radionecrosis and BMV to prognostic models. Defining and validating novel prognostic factors is more important than ever in the era of precision medicine.

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Conflict of Interest: All authors declared no conflict of interest.

Ethics Committee Approval: The study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (no: 2023/08-22, date: 02/05/2023).

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