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Radiotherapy related prognostic factors in brain metastasis patients who have undergone whole brain radiotherapy or with local boost and survived more than 6 months

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► ***Original article***

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ABSTRACT

***Background*:** In this study, prognostic features of radiation were investigated in cancer patients with 1-10 brain metastases (BM) who have not under surgery and survived longer than 6 months. ***Materials and Methods*:** This retrospective study included 136 patients have lung, breast, colon cancer and malign melanoma (MM) with 1-10 BM. All patients and data of BM patients who lived longer than 6 months radiotherapy (RT) related factors affecting their survival rates were examined. Patients were given only WBRT (Whole brain Radiotherapy) in 8-20 fractions with a 160-300 cGy / day fraction, or WBRT with local boost RT with an additional daily 300-350 cGy fraction. ***Results*:** When the results were evaluated analysis showed that the having CT, breast cancer, a KPS of 60% or more, daily fraction dose of RT affected survival significantly in all patients. Then subgroub analysis were obtained according to survival rates, number of metastases more than 5 affects life negatively (r=-0.435 and p=0.03) for survival longer than 6 months (SL6m) and survival shorter or equal than 6 months SS6m. The WBRT doses of 3000 cGy with 300 cGy daily fraction size negatively affected life compared to 2500 cGy with 250 cGy (r=-0.280 and p=0.01). ***Conclusion*:** It was determined that KPS > 60 and limiting WBRT doses up to 250 / 2500 cGy daily and total in patients with BM between 1-10 was the important best prognostic factor due to RT for SL6m, which increased patient performance and survival rates.

INTRODUCTION

Usually, when metastases occur in cancer patients, their survival rate decrease significantly. The most common primary focus in patients with brain metastases is lung and breast cancer [1]. It has been reported that 70-80% of these patients have 1-3 metastases and 20-30% more than 3 brain metastases [2]. Median survival is very low that only 2 -15 months with WBRT or with local RT methods [3-5]. The presence of more than 4 brain metastases has been reported as the most important negative prognostic factor [6].

The most common symptom in the BM is headache and the most common clinical sign is hemiparesis. According to the general view, the primary treatment option for patients with multiple BM is WBRT with or without steroids. For patients with 1-4 BM, the surgical and / or radiosurgery methods with or without WBRT can be preferred. In many studies, it has been stated that WBRT does not contribute positively to the results, and local RT methods such as radiosurgery with or without surgery should be performed in patients with 1-4 BM [7-10].

When the dose of Stereotaktic Radio-Surgery (SRS) was increased in the treatment of a limited number of metastases, the expected results could not be obtained as the local control rate increased in the BM because increasing of toxicity [11, 12]. WBRT combined with SRS or surgery has been reported to reduce the incidence of intracranial recurrence, but does not provide an advantage in overall survival over SRS or surgery alone [13]. Adding WBRT to SRS or surgery increases the risk of impaired memory and learning, along with impaired brain function in the first 6 months after treatment [14]. SRS dose parameters are contained in RTOG 95-08 [15]. While fractional RT with 2 to 3 Gy daily fractions is generally recommended for normal brain tissues, higher fraction doses are recommended for metastatic tumors. The reason for this is to prevent toxic effects on normal tissues with RT [16]. SRS is preferred for tumors that can be treated with several fractions in single and small lesions. The local control (LC) ratio in large tumors has been reported to be relatively low with SRS [17]. Different radiobiological advantages of low-dose fraction RT methods and high -dose SRS are known. Low dose daily fractions of RT can reduce tumor load while increasing blood brain permeability. The increasing to effectiveness of chemotherapy concurrently and not increasing

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toxicity are important advantages of low dose RT [18].

Generally, there are studies in the literature that show the effectiveness of SRS / SRT (Stereotactic body Radiotherapy) with WBRT [19, 20]. In recent years, it has been observed that local recurrences can be reduced by giving higher doses to metastatic tumor with advanced IG-IMRT (Image Guided Radiotherapy) and Simultaneous Integrated Boost (SIB) methods concurrent with WBRT. More homogeneous dose distribution and lower toxicity and recurrence rates can be achieved in less time with SIB RT [21-24].

In a few studies, the methods only with SRS were compared to WBRT in a narrow and subjective perspective [21, 25]. When the studies in the literature are examined, it is seen that there is a need for articles investigating prognostic factors with a more holistic view. Therefore, it is predicted that a study on patients with BM who lived relatively long could make a better contribution.

As it is known, while the RT target area receives the maximum dose, the dose gradient towards the periphery gradually decreases according to the isodose distribution. One study investigated the isodose sites at distant periphery of target dose which local recurrence and new lesions developed in patients who had only SRS. It was observed that only 1% of relapses occurred at sites receiving doses greater than 7 Gy. When the various isodose levels in which new lesions were developed were examined, it was determined that 66% of the recurrences occurred in the areas receiving less than 1 Gy dose. It was found that only 6% or less of new lesions developed in areas that received doses above ≥4 Gy. This study is very important and gives important clues that the dose of WBRT can be lowered. If the WBRT dose can be reduced, its negative contribution to overall survival may be prevented [26].

It has been shown that limiting the hippocampus mean dose to 9 Gy and the maximum dose to 16 Gy, which is very important in neurocognitive toxicity, causes lower neurocognitive toxicity. Therefore, it may be possible to reduce brain relapses and neurocognitive toxicity even with whole-brain doses as low as 4 Gy with SRS [27]. Therefore, in this study, it is aimed to contribute to the literature in order to reduce the dose of WBRT by examining the BM patients who have lived longer than 6 months and examining the factors related to RT, which has a long life.

In this study, the patients with BM with 1 to 10 brain metastases and who lived longer than 6 months were analyzed retrospectively.

MATERIAL AND METHOD

Study population

This retrospective cohort study included 136 patients who have 1-10 brain metastases. The patients were divided into 2 groups.

Group 1: Patients who have survived longer than 6 months (SL6m) (n=66)

Group 2: Patients who have survived equal or shorter than 6 months (SS6m) (n=70).

Inclusion criteria

The patient have 1-10 brain metastases, ages were 18-87, KPS was 50-90 (Table 1), achieved WBRT with or without local RT and chemotherapy (CT).

Exclusion criteria

Exclusion criteria of study the patients who achieved only local RT (SRS or SBRT) without WBRT, who have received targeted therapy (Except of Herceptin), immunotherapy or metastasectomy and KPS below to 50%.

Patient characteristics were shown in table 1. CT achieved to 94 patients. CT characteristics of patients were shown in table 2. Tumor characteristics were shown in table 3 that patients who survived longer than 6 months (SL6m patients). Tumor characteristics were shown in table 4 that patients who survived longer than 6 months (SS6m patients).

Table 1. Characteristics of all BM patients.

Characters	Patient number	%
Age		
18-50	33	24.26
51-70	69	50.73
71-74	34	25
Gender		
Female	50	37.13
Male	86	63.23
Performance		
Karnofski		
50-60	44	32.35
70-80	74	54.41
90	18	13.23
Achieved CT	94	69.11

Abbreviations: CT: Chemotherapy.

Table 2. CT regimes of all patients (SL6m and SS6m patients).

Characters	Patient number	Median Response rate (%)	Median survival (month)
SL6m Patients			
Achieved CT	53	30	16
Tax+carbo	13	25	9
Gemc+Cisp	8	20	8
Cisp+Etop	7	40	7
5-FU-Oxal	1	30	12
Cyc+Tax	8	35	21
Tax+Hercep	6	40	19
Cape	7	35	17
Other	3	25	9
SS6m Patients			
Achieved CT	41	25	4
Tax+carbo	13	25	4
Gemc+Cisp	8	20	4
Cisp+Etop	7	30	5
5-FU-Oxal	1	25	4
Cyc+Tax	5	30	7
Tax+Hercep	3	35	6
Cape	4	35	7

CT: Chemotherapy, Tax: Taxol, Carbo: Carboplatin, Gemc: Gemcitabine Cisp: Cisplatin, Etop: Etophosid, 5-FU: 5-Fluorouracil, Oxal: Oxaliplatin Cyc: Cyclophosphamide, Hercep: Herceptine, Cape: Capesitabine.

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Table 3. Tumor characteristics in patients who survived longer than 6 months (SL6m patients).

Characters	Patient number (%)	Median survival (months)
Primary site of tumor		
Lung	38 (57.57)	10
Breast	21 (31.81)	15
Colon	3 (4.54)	11
M Melanom	4 (6.06)	7
Met number		
1	20	19
2-4	16	10
5-10	30	8
Met volume (ml)		
3-10	8	18
11-25	34	16
26-45	13	12
46-80	11	9
Met other than brain	27	7
Bone	15 (55.55)	8
Lung	4 (14.81)	9
Liver	3 (11.11)	7
Bone+lung	2 7.4	8
Bone+Liver	1 3.7	7
Liver+lung	1 3.7	7
Bone+liver+lung	1 3.7	7

M: Malign, met: Matastasis.

Table 4. Tumor characteristics in patients who survived equal or shorter than 6 months (SS6m patients).

Characters	Patient number (%)	Median survival
Primary		
Lung	44	3
Breast	19	6
Colon	4	4
M Melanom	3	4
Met number		
1	13	6
2-4	27	4
5-10	30	3
Met volume (ml)		
3-10	7	5
11-25	32	3
26-45	18	3
46-80	13	2
Met other than brain	31	
Bone	15	4
Lung	4	3
Liver	3	2
Bone+lung	4	2
Bone+Liver	2	2
Liver+lung	2	2
Bone+liver+lung	1	1

M: Malign, met: Matastasis.

Ethical approve

Ethical approve was taken from Non Interventional Clinical Ethical Board of Bezmialem Vakif University (14/05/2020-6066). This study was prepared in accordance with human rights as stated in Declaration of Helsinki. We also obtained to informed consent from the patients.

Metastasis volume and number

The median metastasis volume was 24 ml and the median metastasis number was 2 in all 136 patients.

Radiotherapy (RT planning)

Treatment planning was achieved LINAC based Linear Accelerator (Varian, (MNT, Health Care and Trade Corporation, Turkey, Bozlu Holding) or TomoTherapy VOLO, HDD (Helical Dynamic Direct) (TomoTherapy, Meditel, Turkey) devices (Table 2). 6 MV beams were used in all plans and patient-specific quality control (DQA) was performed. The patients were fixed with back and thermoplastic head masks. Images were taken in 1-3 mm sections with Computed Tomographic simulation.

Magnetic Resonance (MR) fusion was performed by overlapping perfusion and diffusion MR images taken before treatment and cranial Computerized Tomographic simulation images. Planned Target Volume (PTV) was created by giving a 0 to 3 mm margin to Gross Tumor Volume (GTV) based on the location and volume of the metastatic regions. RT planning isodose distributions in 2 patients with single and 10 metastases are shown in figures 1 and 2. Risky organs (OAR) were safed by contouring to hippocampus, lens, optic nerves, chiazma and brain stem. Patients were performed with 160-300 cGy / day fraction size in 8-20 fractions of WBRT or WBRT with SIB RT which used daily 300-350 cGy fraction size.

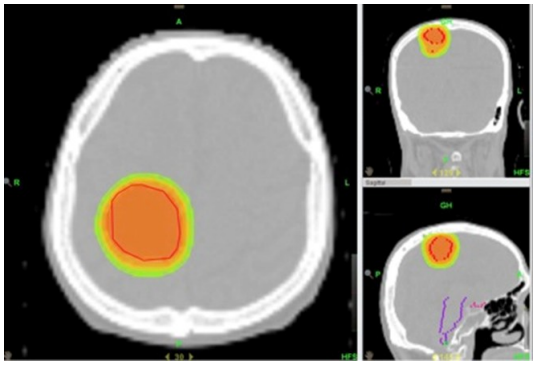

Figure 1. RT planning isodose distribution was shown in patients with single brain metastases.

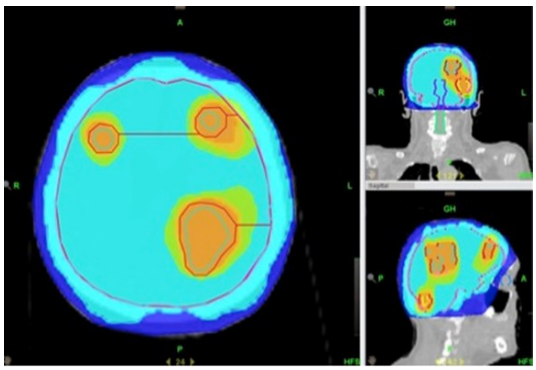

Figure 2. RT planning isodose distribution was shown in patients with 10 brain metastases.

Target volumes

The target volume was defined as the volume of PTV that received at least 95% and 105% of the prescribed dose.

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Homogeneity (HI) and conformity index (CI)

The dose homogeneity value (HI) was defined by dividing the difference between 2% volume (D2%) and 98% volume (D98%) into the average dose (Dmean), and therapeutic-target volume suitability and Conformity Index (CI) were determined by the Paddick suitability index [28, 29].

The homogeneity index (HI) was determined as median 0.31 and CI median 0.98.

RT doses of organ at risk (OAR)

In all patients, median hippocampal, lens and optic nerve doses were 12.2 Gy, 9.5 Gy and 36.3 Gy, respectively in all patients. The median GTV of the BM volume was 44.7 ml (1 - 82 ml), the median WB-PTV was 1271 ml (1114-1762 ml) in all patients.

In SL6m patients, median hippocampal, lens and optic nerve doses were 7.6 Gy, 3.5 Gy and 25.3 Gy, respectively in patients who surviving longer than 6 months (SL6m). The median GTV of the BM volume was 49 ml (1 - 78 ml), the median WB-PTV was 1320 ml (1114-1650 ml) in SL6m patients.

In SS6m patients, median hippocampal, lens and optic nerve doses were 9.7 Gy, 5.5 Gy and 35.3 Gy, respectively in patients who survived equal or shorter than 6 months (SS6m). The median GTV of the BM volume was 44 ml (3 - 82 ml), the median WB -PTV was 1340 ml (1150-1762 ml) in SS6m patients.

Patient following, patients were evaluated by comparing clinical evaluation with 2 months interval by MR perfusion and diffusion imaging and their performance and prognostic status.

Statistical analysis

The results were evaluated by Cox proportional hazards regression analysis. For statistical analysis, we used Instat Statistical Package Program (Instat Graphad Software v5.0, San Diego, CA, USA). Subgroub analysis were obtained with Man Witney U test. Statistically significant of P value was considered as $P < 0.05$.

RESULTS

Response rate in all patients, the total response rate was detected to 72.05% (98 patients) that 22.05% (30 patients) had complete and 50% (68 patients) partial response in all 136 patients. While 23 patients (18.91%) remained stationary, 15 patient (7.35%) had progression. according to the results of MR taken 2 months later.

Response rate of SL6m patients, the total response rate was detected to 72.72% (48 patients) that 25.75% (17 patients) had complete and 46.96% (31 patients) partial response in 66 patients of those SL6m. While 14 patients (21.21%) remained stationary, 5 patient (7.57%) had progression in the SL6m.

Response rate of SS6m patients, the total response rate of the patients was 71.42% (50 patients), 20% (14 patients) had complete, and 51.42% (36 patients) partial response. 11 patient (15.71%) remained stationary and 9 patient (12.85%) had progressive disease in SS6m (70 patients).

Radiotherapy characteristics and survival rates, radiotherapy characteristics and survival rates in patients for SL6m shown to table 5. Radiotherapy characteristics and survival rates in patients for SS6m shown to table 6.

Table 5. Radiotherapy characteristics and survival rates in patients for survived more than 6 months (SL6m).

Characters	Patient number	%	Median survival (months)
Fr number x dose (cGy)			
7-10x250/350 SIB	32	51.42	14
8-15x160 WB	6	8.57	16
10x300 WB	6	8.57	8
12x250/350 SIB	22	31.42	10
Tomo IG IMRT	59	84.28	16
Linac IMRT	11	15.71	14

Fr: Fraction, SIB: Simultaneous Integrated Boost, Tomo: Tomotherapy WB: Whole brain.

Table 6. Radiotherapy characteristics and survival rates in patients for survived equal or shorter than 6 months (SS6m).

Characters	Patient number	%	Median survival (months)
Fr number x dose (cGy)			
8-10x250/350 SIB	18	25.71	6
10x300 WB	33	47.14	3
12x250/350 SIB	19	27.14	4
Tomo IG IMRT	23	32.85	5
Linac IMRT	43	61.42	4

Fr: Fraction, SIB: Simultaneous Integrated Boost, Tomo: Tomotherapy WB: Whole brain.

After 36 months of follow-up

Survival, 6 patients (9.06%) in SL6m and 0% in SS6m still lived. Median overall survival (OS) and median recurrence free survival (RFS) was 14 and 12 months in patients of SL6m. Median overall survival (OS) and median recurrence free survival (RFS) was 4 and 2 months in patients of SS6m. Median overall survival (OS) and median recurrence free survival (RFS) was 7 and 5 months in all patients. Median follow-up was 14 months in all patients, the shortest 7 months and the longest 36 months.

Median survival was 15 months in patients with metastatic tumor number 1, and 5 months in the presence of 5-10 metastases in all patients. The isodose distributions of RT planning of patients with metastatic number 1 and 10 shown to figure 1 and 2.

In SL6m patients, the median survival was 19 months in patients with metastatic tumor number 1, and 8 months in the presence of 5-10 metastases. Median survival was 19 months in patients who received taxol and herceptin, and 7 months in patients who received cisplatin and etoposide. Median survival was 10 and 15 months in patients who have primary tumor of lung and breast cancer

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respectively. The patients had metastatic tumor volume under 20 ml lived for median 17 months.

In SS6m patients, the median survival was 6 months in patients with metastatic tumor number 1, and 2 months in the presence of 5-10 metastases. Median survival was 6 months in patients who received taxol and herceptin, and 4 months in patients who received cisplatin and etoposide. Median survival was 3 and 5 months in patients who have primary tumor of lung and breast cancer respectively. The median survival was 5 months in patients with metastatic tumor volume 20 ml or below. In patients with metastases in 2 or 3 different organs other than the brain, the median life is 2 and 1 months, respectively.

Survival rates and Kaplan Meier graphic are shown in figure 3 for SL6m, SS6m and all patients.

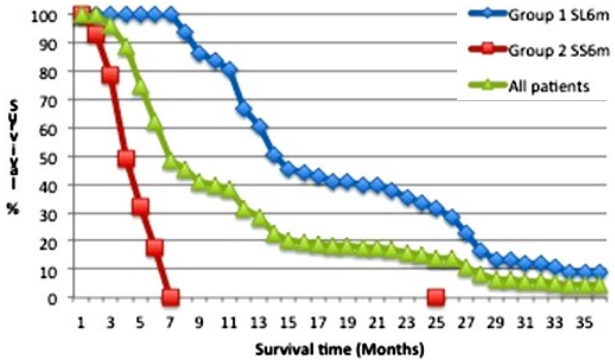

Figure 3. Survival rates and Kaplan Meirer graphic for Group 1 (SL6m), group 2 (SS6m) and all patients.

Toxicity

In SL6m patients, grade I neurotoxicity was seen in 55.71% (39 patients) and grade II in 40% patients (28 patients), grade III in 4.28% patients (3 patients). At the 36-month follow-up, the KPS scores improved by 20% and the RPA grade by 1 degree.

In SS6 patients, neurotoxicity was observed to grade I in 7.57% (5 patients), grade II 62.12% (41 patients), and grade III in 30.3% (20 patients). KPS scores decreased to median 20% and RPA grade 1 respectively.

Primary neurotoxicity was observed in all 136 patients that 31.61% patients (43 patients) had grade I and 50.73% grade II (69 patients), and 17.6% (24 patients) had grade III neurotoxicity. In all patients, median survival was 7 months and 36 months survival was 6.1% (9 patient), KPS scores increased to median 10% and RPA grade 1.

Statistical analysis

When the results were evaluated Cox proportional hazards regression analysis showed that the having CT, breast cancer, a KPS of 60% or more, daily 250 cGy fraction and up to total 2500 cGy dose of RT affected survival significantly in all patients (p=0.05, 0.04, 0.04 and 0.01 respectively). Then subgroub analysis were obtained according to survival rates. Man Witney U test showed that the number of metastases more than 5 affects life negatively (r = -0.435 and p = 0.03) between SL6m and SS6m. The WBRT doses of 3000 cGy with 300 cGy daily fraction size negatively affected life compared to 2500 cGy with 250 cGy (r = -0.280 and p = 0.01).

DISCUSSION

In studies on WBRT, methods with a daily fraction of 300 cGy were generally preferred. The aim here is to complete a palliative treatment in a short time. Many patients leave RT after 1-2 fractions, as their performance is already low due to the fact that they are metastatic. For this reason, studies can be carried out on methods with lower dose fractions. Therefore, the prognostic features of RT were investigated in this study.

Low doses of radiation can increase immune cells by modulating the stromal microenvironment. The brain is a privileged organ capable of harboring many different immune responses. While treatments such as high-dose SRS have advantageous effects on the brain, low-dose RT methods also have advantages [30].

Due to the high toxicity of WBRT, only SRS or SBRT can be successfully performed up to 4 brain metastases, but when more than 4 metastases are present, WBRT should be performed due to the presence of a large number of possible micro metastases [31-33]. When studies conducted in patients with 2-10 BM were examined, there was no difference between patients treated with WBRT and / or local RT [32]. It is known that local control and survival rate are increased with SRS and SBRT, which are generally administered with high dose single fraction [34, 35]. Median survival was only 2-15.2 months with local treatment or with WBRT [3-5, 31, 36]. The most important factor limiting local treatments in patients with more than 4 metastases is that the duration of treatment is prolonged because they can be in different isocenter. Another disadvantage is that the total brain dose can be increased by increasing the toxicity with high dose local treatments. Volumetric or helical arc radiation treatments can be used with image guidance to shorten the time and decrease the toxicity. With advanced devices with applications such as Helical arc, RT can be performed simultaneously, even to a large number of lesions, without increasing treatment time and toxicity. In a study that RT with VMAT (Volumetric modulation arc therapy) for multiple lesions in the brain, VMAT was shown to be equal to gamma knife radiosurgery for the dose distribution [25, 28, 37, 38].

Since survival rates are low when only local treatments are performed, WBRT can be added with an appropriate fraction to increase survival rates. There are some studies in the literature similar to our study. Aoyama and a study of his group reported that mental function was impaired in patients who received a total of 30 Gy WBRT with a daily 300 cGy

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fraction [31]. BM volume was found to be affect brain function more than the number of metastatic lesions [39].

In our study, survival rates were high in patients with low metastasis volume and number. In the joint study of 23 gamma knife centers, median overall survival was found to be 12 months in patients treated with radiosurgery. While the incidence of new lesions in 1 metastasis was 36% in 12 months, this rate was found as 54% in patients with 2-4 lesions and 64% in patients with 5-10 lesions. The risk of developing new lesions was similar to that of patients with 1 metastasis. There was no significant difference between 2-4 and 5-10 lesions in terms of the risk of developing new lesions. Similar results were obtained in terms of leptomeningeal spread risk. When these data are analyzed, it is stated that only up to 10 lesions, local RT may be sufficient [37, 40, 41].

20-32.5 Gy WBRT and 30-48 Gy RT to local BM regions were recommended as to the brain RT regions. 1 year intracranial metastasis control rate in BM patients up to 4 metastases varies between 67% and 75% according to the method applied [23, 42, 43]. It has been reported that when WBRT and SIB are administered together, the response rates increase and 11% to 33% complete remission can be achieved [23].

In this study, the results were same as other similar studies in the literature since the total response rate of 72.05% in all patients [23, 44, 45]. Patients in SS6m and had a WBRT dose of up to 25-36 Gy had a total response rate of 71.42% that similar to SL6m patients which total response rate of 72.72%. While median survival time of all patients was 7 months, median survival was 14 months in patients in SL6m and 4 months in SS6. The 3-year survival was 9.06% in SL6m and 0% in SS6m.

In statistical analyzes, 300 cGy fraction dose of WBRT is negative contribution of survival as significantly. In the SL6m, the patients survival was median 17 months that metastatic tumor volume under 20 ml. But in the SS6m patients, the median survival was found to be 5 months in those with metastatic tumor volume 20 ml or below indicate that even if the metastatic volume is low, the WBRT and daily fraction dose may affect the result negatively if it is over 2.5 / 25 Gy.

In statistical analysis, demonstrated to negative contribution of metastasis number to the result. In SL6m patients, the median survival was 19 months in patients with metastatic tumor number 1, and 8 months in the presence of 5-10 metastases.

In the SL6m, 40% grade II and 4.28% grade III acute neurotoxicity was observed as the primary toxicity lower than SS6m that have 62.12% grad II and 30.3% grad III neurotoxicity. The median survival and median disease free survival were 14 and 12 months, and 36 months survival rate was 13.3% and 0%, respectively, in the SL6m and SS6 patients. In this study, since the rate of total response in patients with total brain dose and daily fraction size are high in SS6 patients which up to 2500-3600 cGy and 250-300 cGy, the median survival is 4 months due to increased toxicity and is lower or higher than some studies in the literature [3-5, 23, 29, 42, 43, 46, 47]. The fact that 56% of patients had primary tumor focus on the lung also affected the results negatively.

Since SL6m patients with 1-10 metastatic lesions were treated with using a lower doses, also with applied new technologic IMRT, HA and SIB techniques were obtained lower toxicity than in the literature [23, 29, 42, 43, 46, 47]. The median hippocampus dose is 7.6 Gy in SL6m. which important for quality of life and is lower than other studies. The average hippocampal dose in most studies is 8-13 Gy [48-50]. Lowering the dose of WBRT and lowering the dose of hippocampus is one of the most important factors reducing neurotoxicity. The survival advantage obtained in the group that received a maximum of 2500 cGy RT with 250 cGy fraction in this study may also be due to the decrease in the median hippocampus dose.

It was observed that the increase of WBRT doses in patients with a low performance and high metastasis number affected the results negatively because contribute higher toxicity related to decreasing quality of life and survival time. In patients with metastases in 2 or 3 different organs other than the brain, the median life is 2 and 1 months, respectively, and follow-up with supportive treatment may be a better approach in these patients.

The advanced technological volumetric arc and TomoTherapy HAD IG IMRT methods and up to 250 cGy fraction size, 25-30 Gy WBRT and additional SIB treatment can be applied as a good modality in 1-10 focused BM in order not to increase the toxicity. Larger randomized studies should be conducted on this subject.

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***Ethical Statement*:** Ethical approval was obtained from Bezmialem Vakif University, Non Interventional Clinical Ethical Board (Date and number of Ethical approve is 14/05/2020-6066).

***Author contributions*:** Conceived and designed the analysis: Kiziltan HS, Coban G, Mayadagli A. Collected the data: Kiziltan HS, Altinok P, Tekce E, Mayadagli A. Contributed data or analysis tools: Kiziltan HS, Coban G, Altinok P, Tekce E, Mayadagli A. Performed the analysis: Kiziltan HS. Wrote the paper: Kiziltan HS, Coban G.

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