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Clinical evaluation of simultaneous integrated boost in brain metastasis patients with helical intensity modulated radiotherapy

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► ***Original article***

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ABSTRACT

Background: This study was performed to assess patient survival and treatment toxicity after helical tomotherapy (HT) with simultaneous integrated boost (SIB) radiotherapy (RT) for cancer patients with one to eight brain metastases (BM) who have been treated with or without surgery. ***Materials and Methods***: A total of 48 brain metastasis (BM) patients were included in this retrospective study between April 2015 and December 2016,. The patients were treated with image-guided intensity modulated radiation therapy (IMRT) on the helical tomotherapy (HT) machine. Whole brain HT as 25 Gy and SIB to metastasis sites as 35 Gy was delivered in 10 fractions. The patient were aged between 50 to 80 years old, volume of the BM was between 6 to 75 cc and the number of brain metastasis was between 1 to 8, Karnofsky Performance Score (KPS) ranged between 50-90 and RPA I-III. Surgery was performed to two patients before RT. The maximum patient follow -up time was 20 months. ***Results:*** The primary neurotoxicity observed in patients was grade I- II brain edema related headache and lethargy. In patients who had survived 3- 12 months, KPS improved median score of 20 points and RPA was grade I after six months. Twelve patients had passed away at the end of a 20- month follow-up. ***Conclusion:*** HT utilizing SIB treatment for 1- 8 BM was achieved successfully with no significant toxicity. An improvement of performance status indicators of patients following RT was observed.

Keywords: *Simultaneous integrated boost, brain metastasis, Tomotherapy, radiotherapy.*

INTRODUCTION

Brain metastasis is (BM) a significant clinical problem in cancer management which occurs on 20 to 45% of all cancer patients [1-2]. The primary cancer sites which BM mostly originate from are lung (40-50%) and breast cancer (20-30%) [3]. 20-30% of patients with BM have more than 3 metastases, while 70-80% of patients have 1-3 BM [4]. The median survival has been observed to be 4-7 months with various fractionation and dose regimens of whole brain radiotherapy (WBRT) [5-6].

The treatment of brain metastases is difficult because of the side effects caused by radiotherapy (RT) and chemotherapy (CT). There is still no significant improvement on survival rates despite new treatment schedules [7]. Median survival has been observed to be between 2-13 months in new BM treatment schedules [5-6].

The primary treatment schedule employed for patients with multiple BM is WBRT either with or without steroids. Surgery and/or radiosurgery, either with or without WBRT was employed for patients with between 1 - 4 BM sites. With this local and distant brain failure was observed in a substantial number of patients. Two prospective phase III trials have shown a 1-year local and/or distant brain failure

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rate of 30% - 100% following these treatments [8-9]. A significant positive change in survival and local control rate was observed when a boost RT schedule was applied to metastases sites following WBRT. Casanova *et al*. have shown that >75% 1 year local control rate can be obtained with boost treatment schedules [10].

Multiple retrospective studies have reported more than 4 brain metastases as a negative prognostic factor [11]. WBRT should not be routinely added to radiosurgery or local RT schedules in patients with limited number of metastases [9,12-16]. Stereotactic radiosurgery (SRS) for treating limited number of metastases has been reported with success in multiple studies [12]. Local control rate of metastatic tumors increase when SRS dose is escalated, at the cost of higher toxicity rates [17-20]. Widely accepted SRS dose parameters determined through multiple studies are included in RTOG 95-08 [8].

Selected subgroups of patients who exhibit good performance status, younger age, and absence of extracranial disease, controlled primary tumor and oligometastatic BM might benefit from dose escalation [8, 10, 21]. The aim of treatment should be to maximize long term positive response and obtain better patient performance with minimum toxicity.

RT decreases tumor burden and also increases blood brain permeability, which then subsequently may increase chemotherapy effectiveness due to easier drug uptake as a result of increase in permeability of blood vessels [22].

Higher doses to metastatic sites are needed in order to reduce local recurrences. Boost RT of metastases may be delivered sequentially or simultaneously along with WBRT. SIB RT provides the advantage of achieving a homogeneous dose distribution, shorter treatment time, a reduced recurrence rate and reduced acute, late toxicities [23-28].

This study was performed to assess survival and treatment toxicity rates following helical IMRT (TomoTherapy®) with simultaneous integrated boost for cancer patients with one to eight brain metastases treated with or without surgery.

MATERIALS AND METHODS

Before the study commenced approval was obtained from The Academic Committee of Bezmialem Vakif University Faculty of Medicine, Department of Radiation Oncology with reference number 33/2016 on 10/12/2016 in order to conduct this research. Each patient file was scanned retrospectively and patient selection was conducted according to a set protocol in accordance with committee guidelines. Patient consent was taken prior to treatment.

48 brain metastasis patients were included in this retrospective cohort study between April 2015 and December 2016. The patient's ages were between 50 to 80 years old, with Karnofsky Performance Scorring (KPS) between 50 - 90 (Table 1) and a Recursive Partitioning Analysis (RPA) I-III [29].

Table 1. Patient demographics.

Characters	Number	%
Gender		
Male	28	58,33
Female	20	41,67
Age		
35-49	20	41,67
50-59	8	16,66
60-70	20	41,67
Karnofsky		
>80	12	24,99
60-80	28	58,33
<60	8	16,66
Primary		
Lung	41	85.41
Breast	7	14.59
Number of met		
1	19	0.39
2-3	22	0.45
4-8	7	0.14
Toplam	48	100

Patients were immobilized in the supine position with head and neck thermoplastic masks. Planning computed tomographic (CT) images were acquired through the region of interest using a 3 mm slice thickness. Organ at risks included were the eyes, lens, optic nerves, optic chiasm, hippocampus and brain stem.

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Total brain and metastatic brain lesions were used as the target volumes. Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) and diffusion weighted imaging (DWI) with 1.5 Tesla MR (Avanto, Siemens Healthcare) was performed for treatment planning. MR/CT fusion was performed in order to assist locating metastatic tumour sites. The planning target volume (PTV) margin to the gross target volume (GTV) was determined to be 1 to 3 mm according to metastatic regions and volume.

The contrast-enhanced brain CT simulation was utilized to define the organs at risk and target volumes with coronal and axial contrast-enhanced 64- slice multi-detector computerized tomography (MDCT) (Aquilion, Toshiba Medical Systems, Tokyo). External RT was administered with the TomoTherapy HDA (Helical Direct Dynamic) (TomoTherapy Inc., Madison, WI)

Treatment planning was performed utilizing the TomoTherapy VOLO (TomoTherapy Inc., Madison, WI) treatment planning workstation. A 6 MV beam was used for all patient plans. A field width of 5,054 cm with dynamic jaws, a pitch factor of 0,287 or 0,433 and a modulation factor between 1,8 and 2,5 was utilized in all plans during optimization and dose computation to achieve optimal plans within clinically acceptable treatment time.

HT was applied as 25 Gy to whole brain with a SIB to BM as 35 Gy in 10 fractions was delivered 1 to 8 BM. (figures 1 and 2). Surgery was performed to two patients before RT. The maximum follow-up time was 20 months.

The median hippocampal, lens, optic nerve doses were 7.3 Gy, 2.65 Gy and 24.5 Gy respectively. The median BM GTV was 33.6 cc (ranged 6 – 76 cc), The Median WB-PTV was 1273 cc (ranged 1125–1751cc) (table 2).

Target volume coverage and maximum point dose were assessed as the volume of PTV receiving at least 95% (V95 %) and 107% (V107 %) of the prescribed dose. Dose homogeneity was evaluated quantitatively using the homogeneity index, defined as a ratio of the difference between the dose to 2% volume (D2 %) and 98% volume (D98 %) divided by the mean dose (Dmean) to the PTV expressed as a percentage. The conformation of therapeutic dose volume to the target volume was estimated using the conformity index as defined by Paddick [31].

A patient specific quality assurance (DQA) was performed for every treatment plan. Each DQA plan was prepared on the planning workstation and transferred via the network to the treatment unit. Octavius II phantom and Octavius 729 detector were used for each patient QA. 3%/3 mm percentage difference/ distance to agreement was the accepted tolerance criteria used during assessment.

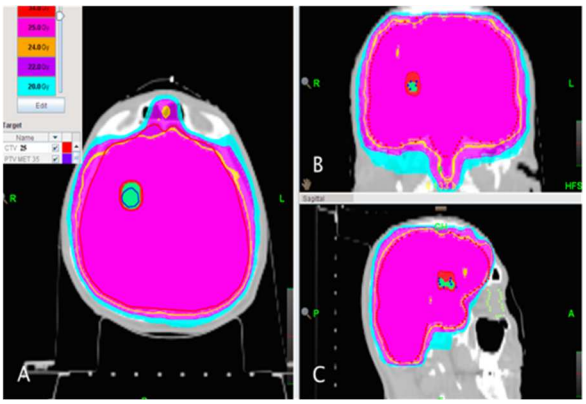


Figure1. SIB dose distribution of a patient with a single BM lesion A: Horisontal section image, B: Coronal section image, C: Sagittal section image

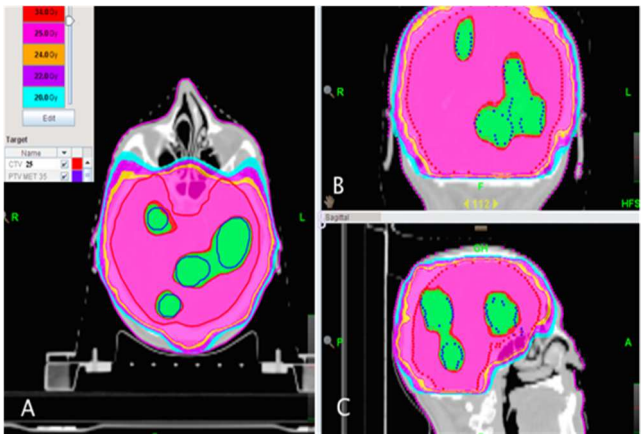


Figure2. SIB dose distribution of a patient with 8 BM lesions A: Horisontal section image, B: Coronal section image, C: Sagittal section image

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Table 2. Dose, HI, CI, Hippocampus dose and PTV volume for WB and BM sites.

RT Characters	Dose Median Gy	HI Median	CI Median	Hippocampus dose (Gy)	RT volume Median (ml)
Whole Brain	25	0,3	0,99	5.2	1273
Met region	35	0,3	0,99	7.3	45

The patients follow up evaluations included MR perfusion and diffusion imaging, KPS and RPA scoring which were repeated with 2 months interval.

The primary end-points of this study was patient performance and secondary end point was survival.

Statistical analysis was performed using the SPSS 11.0 software (SPSS Inc., IL, Chicago, USA). Quantitative and qualitative variables were determined as mean, median and percentage values. Kaplan Meirer Method was used for survival analyses and curves.

RESULTS

The total response rate of patients was 68.7% (33 patients), complete response was observed in 11 (22.9%) and partial response in 22 patients (45.8%). 10 patients remain stationary (20.8%) and disease progression was observed in five patients (10.4%) for during first 6 months. 12 patients (25%) were dead at the end of the 20-month follow-up. The median disease free (DFS) and overall survival (OS) was 6 and 8 months respectively for the 12 dead patients.

The median Homogeneity Index (HI) (The uniformity of dose distribution in the target volume) was 0.3 [30, 31]. The medican Conformity Index (CI) was 0.99 (The ratio between the references isodose (V_{RI}) and target volume (TV) ($CI = V_{RI}/TV$) (table 2).

The primary toxicity observed was grade I-II acute neurotoxicity (brain edema related headache and increased paresia and lethargy. Grade I neurotoxicity was shown in 58, 3% patients and grade II in 11 (22.9%) patients. % 25 of patient experienced grade I-II skin toxicity. KPS scores were improved median 20% and RPA improved grade I after the 12 months. The median follow-up time was 12 months (1-20 months) and the 1-year local control rate was 68.7% (figure 3). The 20 months OS was observed to be 75% in these patients.

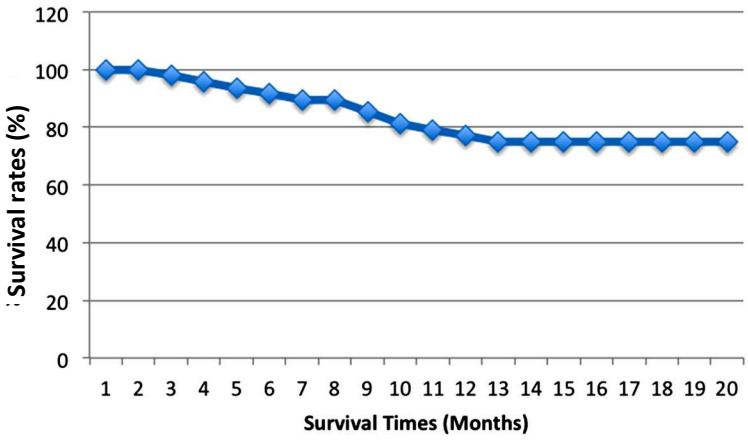


Figure 3. Patient Survival curve over 20 months follow up.

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DISCUSSION

Most common primary tumor location of brain metastases are lung, breast and gastrointestinal cancers [33, 34]. Treatment schedules for single BM are surgical resection, radiosurgery, stereotactic radiosurgery, stereotactic radiotherapy, WBRT with or without chemotherapy. Surgical resection should be applied when neurologic symptoms occur or local mass and cerebral edema is present for single or several metastases [35]. WBRT can be used for multiple brain metastases. WBRT shouldn't be used or RT doses must be decreased for single metastases cases due to significant acute and chronic neurotoxicity observed [36, 37]. Cesium-131 and iodine-125 seed intracranial brachytherapy and MR-guided laser interstitial thermal therapy (LITT) are other alternative therapies that could be used for BM treatment [38-40].

The recommended prescribed radiation dose is 20 to 32,5 Gy to whole-brain and 30 to 48 Gy to the gross metastatic lesion, with 1 to 5 mm margin to the metastatic lesion for BM. 1-year intracranial control rate was observed to be 67% to >75% in various studies [10, 23, 25]. Some studies showed that 11% to 33% complete remission in metastatic lesions with WBRT and SIB can be obtained [25]. The response to RT was observed to be most prominent during the first month [25]. Mean hippocampal dose limit is 8-13 Gy in most studies [27-29].

In our study, the primary tumor location of brain metastases are 85.4% lung and 14.5% breast. In this study, unlike other studies in the literature, 1-8 metastatic lesions were treated with SIB with IMRT and HT without increasing toxicity [10, 23, 25, 31, 36, 37].

We observed 22.9% complete, 45% partial response rate and 75% 20 months OS while using a lower dose rate compared to other studies. The 1 year local brain control rate is 68.7% and is similar with other studies [25, 41, 42]. The toxicity rates are lower than other studies because RT doses are lower. The hippocampus dose is median 7.3 Gy which is important for the quality of life of patients and is lower than other studies [27-29].

Randomized new prospective studies should be done for the treatment of 4 or more brain metastases by lowering the WBRT and local dose for lower toxicity and a better quality of life for patients.

CONCLUSION

The SIB treatment for brain metastases while utilizing TomoTherapy HDA was achieved delivering of 35 Gy in 10 fractions to one to eight BM with no significant toxicity. The performance status was observed to improve post treatment of BM patients while utilizing the treatment regimen outlined in this study.

***Conflicts of interest*:** *Declared none.*

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