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Results of low dose helical arch intensive modulated radiotherapy (IMRT) in brain metastases localized in brainstem

Kimia Çepni 1

1SBÜ Başakşehir Çam and Sakura City Hospital Department of Radiation Oncology

Ethical approve: *Tere is no need becausethis is a small retrospective study.*
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Corresponding author: *Kimia Çepni, Başakşehir Çam and Sakura City Hospital Department of Radiation Oncology e-mail: kimiagh@gmail.com*

ABSTRACT
Brainstem localized metastases (BSM) are rare compared to other brain metastases. BSM are associated with a poor prognosis and their management represents a therapeutic challenge.These patients have more complaints, treatment is difficult, and treatment related side effects are more. Radiotherapy (RT) is the primary palliative treatment that can be applied rather than surgery or chemotherapy. Side effects are severe in patients who are treated with high dose RT and the treatment of many patients is left unfinished due to neurological morbidities. We reviewed the literature and the patients' outcomes at our center for those who have metastases localized in brainstem and were treated with conventional fractionation and lower doses than standard.
Keywords*: brainstem metastasis,streotactic radiosurgery BSM RT, BSM SRS*

INTRODUCTION

Brainstem localized metastases (BSM) are rare, occuring with an estimated frequency of 3-7% in patients with central nervous system metastases from systemic malignancies (1).

BSM causes serious neurological complications because these metastases involve critical regions of the brain such as the pons, midbrain, cerebello-pontine angle, medulla and structures adjacent to the brainstem. Surgery and chemotherapy are not the primary treatment modalities of choice. Since the brainstem is located deeply and has many important functions, even biopsy is not recommended. External radiotherapy (RT) is the primary palliative treatment modality for BMS. Since the brainstem (BS) is considered as an organ at risk, this location should be protected in patients undergoing whole brain RT. The presence of metastases in the brainstem leading the entire region to remain within the treated volume of RT, may lead to serious complications. (2-3).

Local control rates with daily low-dose multifractionated external RT, which is applied to avoid increasing complication rates in the treatment of large BSMs, are similar to 3-5 fraction Stereotactic RT (SBRT) or single fraction Stereotactic Radiosurgery (SRS) (4) . The safety of SRT/SRS for brainstem metastases remains an important question given the

proximity to critical structures and the potential for treatment-related toxicity(5).

The rates of acute and chronic toxicity, brain edema and radiation necrosis were found to be lower with multifraction RT than with single-fraction RT methods (4-6). While patients with BSM already have to deal with serious complications caused by the main disease, adding RT to this process causes an increase in complaints. Neurological deficits due to RT may cause further deterioration of the general condition (2-3). Therefore, hypofractionated or multifractionated RT methods may be an option instead of single-fraction, highdose RT techniques for patients whith BSM. In fact, there are no guidelines indicating which dose should be delivered to avoid adverse effects resulting from brainstem injury.

MATERIALS AND METHODS

A total of 19 lesions in 13 patients with brainstem-located metastases treated with Tomotherapy between April 2015 and April 2018 in the Radiation Oncology Department of Bezmialem Vakıf University Faculty of Medicine were retrospectively examined. Patient characteristics are summarized in Table 1.

Table 1. Characteristics of patients with brain metastases located in the brainstem

Patients Characteristics	Number of patients	%
Gender		
Female	5	38.5
Male	8	61.5
Age		
42-60	7	53.8
61-84	6	46.1
Primary cancer site		
Lung	8	61.5
Breast	3	23
Colon	1	7.6
Malign Melanom	1	7.6
ECOG		
1-2	4	30.7
3-4	9	69.2
RPA		
1	1	7.6
2	10	76
3	2	15.3

ECOG: Eastern Cooperative Oncology Group RPA = Recursive Partitioning Analysis, WBRT :whole-brain radiotherapy

The median age was 68 (range, 42-84) years. Eight patients (61.5%) were male and 5 patients (38.5%) were female. The median Eastern Cooperative Oncology Group (ECOG) performance status score was 3 (range 2-3). The median Recursive Partitioning Analysis (RPA) value was 2.

Of the 19 lesions treated with tomotherapy, 12 (63.1%) were located in the pons, 4 (21%) in the medulla, and 3 (15.7%) in the midbrain. Localization of

brain metastases in brainstem are summarized in Table 2.

Table 2. Localization in BMs located in the brainstem

Tumor location	Patients n.	%
Midbrain	2	15 .3
Pons	9	69.2
Medulla	2	15.3
Total	13	100

Patients n=Patients number

In 8 of the patients (61.5%), the primary cancer site was the lung, breast in 3 (23%) and malignant melanoma in 2. (15.3%).

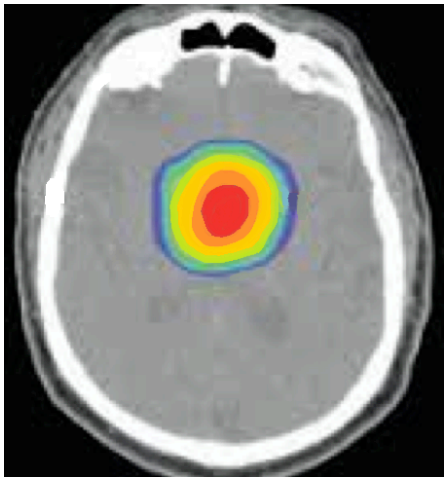

Figure 1. SIB RT was applied to the metastasis areas with a 350 cGy/ fraction

Radiotherapy: All patients received whole brain RT and Simultaneous Integrated Boost RT (SIB RT) for metastatic lesions. Whole brain RT (WBRT) was implemented using a Tomotherapy device. Adjunct to whole brain RT, SIB RT was added to the treatment plan.

With Helical Arc (HA) IMRT a total of 25 Gy in 250 cGy/fraction was applied to the planned tumor volume (PTV) without any margin to the gross tumor volume (GTV) and a total of 35 Gy external SIB RT was applied to the metastasis areas with a 350 cGy/ fraction (Figure 1).

After SIB IMRT with Tomotherapy HA, the first follow-up was performed with Magnetic Resonance Imaging (MRI) 2-3 months after the end of treatment.

Local failure was considered, if there was an increase in metastasis volumes.

Tumor progression or radiation necrosis were differentiated by using spectrometry, perfusion and diffusion MRI.

Symptomatic failure was defined as worsening of neurological symptoms or the emergence of new neurological symptoms due to the brainstem lesion after SIB IMRT. Symptoms due to lesions other than metastasis in the brainstem were excluded.

RT toxicity was graded according to the Radiation Oncology Toxicity Criteria of RTOG.

RESULTS

A total of 19 BSM lesions in 13 patients were treated with SIB IMRT. The median follow-up was 11 (6-36) months. The median tumor diameter was 12 mm (5.0-45) mm.

Eleven patients had other intracranial metastases during brainstem

radiotherapy, and additional SRS/SBRT was performed 2-34 months later in 3 patients due to new BMS lesions and in 2 patients (in 3 foci) due to new BMS or local recurrence.

BSM local progression or recurrence was observed in only 3 (15.7%) of 19 lesions for which MRI data could be monitored. Local whole brain control rates at 6 , 12 and 36 months were 69.2%, 61.5%, and 53.8%, and the 6 ,12 and 36 month local BSM control rates were found to be 92.4, 84.7, and 84.7%, respectively.

In 3 patients who had 4-8 metastases in the brain simultaneously with BSM, complaints of headache, somnolence and decreased appetite during RT were evaluated as grade 1-2 acute toxicity and patients' complaints improved with corticosteroids.

In the first 6 months after RT, edema in the RT area and a decrease in performance score were detected in 2 of the patients who initially had acute toxicity. No Grade 3 neurological toxicity was observed.

DISCUSSION

In this study, we have assessed the efficacy of SIB IMRT for the treatment of metastases located in the brainstem and determined rates of local control and intracranial control .

For best local control, surgery should be considered a good option as it shows more efficacy on lesions that may determine the prognosis (7-8). However, a surgical approach to the brainstem is risky for lesions located in contact with the fourth ventricle. Chemotherapy, except temozolomide, has poor results because the blood–brain barrier does not allow transit of molecules inside the parenchyma (9). Therefore, radiation therapy plays an important role in the treatment strategy for brainstem lesions. Initially, whole-brain radiation therapy has been used as standart therapy, then in combination with radiosurgery (10).

In the first study on brainstem metastases by Huang et al. in 1999, all patients were newly diagnosed and had applied fractionated radiotherapy (30 Gy with 1.8 to 3-Gy fractions) before radiosurgery (11). Increasingly, radiosurgery has been performed up front.

Several studies have evaluated the use of Gamma Knife (GK) SRS for the management of BSMs. In 2016, findings of a multicenter study demonstrated the effectiveness of GK SRS (4-12).

The results of a retrospective review demonstrate that the outcome following linac-SRS for metastases affecting the brainstem is equivalent to that following GKS (1).

Other studies have shown that SRS is an effective treatment in patients with brainstem metastases. In these studies, it was claimed that WBRT was more toxic than SRS (13). However, the WBRT doses applied were higher than doses we used in this study. Furthermore, risky areas such as the hippocampus were not protected.

Some studies have warned that protocols should not include SRS in regions such as the brainstem or the midbrain, pons and medulla oblongata. SRS administered with a single high-dose fraction may exceed tolerance doses of brainstem even at the margin of the lesion (5-14). Exposure of the brainstem to more than 12 Gy at volumes as low as 0.1 cm^3 can produce adverse radiation imaging effects (ARIE) and new neurological deficits. The tolerance of the brainstem to radiosurgery is related to patient age, lesion volume, and pathology (5).

In BSM patients, the dose received by the lesion is very important to reduce the

dose and toxicity of normal tissues. Reviewing the literature, although it has been reported in some small series that SRS doses of at least 15-20 Gy (7/) increase local control, lower tumor margin doses such as 12 Gy have been recommended to avoid increasing toxicity (10-15). The radiosurgery technology used is also important in terms of both local control and toxicity.

Danie.A et al. found in their study the median survival to be 5.6 months, with 1-year and 2 year survival rates of 32.7% and 16.7%, respectively (16). In this study, for patients who had previously received WBRT, the median time between WBRT and recurrence was 4.5 months. It has been reported that 84% of patients who developed grade 3 or higher toxicity received WBRT at some point in their treatment before brainstem SRS. Toxicity was significantly less in patients with an interval of more than 4.5 months between WBRT and SRS (P <.001). Severe toxicity was not seen in brainstem metastases smaller than 0.1 mL or in those receiving a margin dose of less than 12 Gy (16).

In our study after SIB IMRT, we found local whole brain control rates at 6 , 12 and 36 months to be 69.2%, 61.5%, and 53.8%, respecitvely, and the 6 ,12 and 36 month local BSM control rates to be 92.4%, 84.7%, and 84.7%, respectively. In other studies in which patients were treated with SRS, local control rates were found to be 92% at 6 months and 88% at 1 year (1). These results are compatible with our study.

In our study 3 patients' complaints of headache, somnolence and decreased appetite during RT were evaluated as grade 1 acute toxicity and patients' complaints improved with corticosteroids. In the first 6 months after RT, edema in the RT area and a decrease in performance score were detected in 2 of the patients who initially had acute toxicity. No Grade 3 neurological toxicity was observed. Reviewing the literature, no high grade-toxicity or new neurological deficits were observed, only headache and nausea that resolved with a short course of steroids. This is in accordance with several other studies that have demonstrated complication rates in the range of 0-10% (17).

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