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Original Article

Retrospective evaluation of radiotherapy techniques in the management of patients with brain metastasis: A single-center Experience

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Abstract

Introduction: The aim of this study was to evaluate the demographic characteristics and radiotherapy schedules of patients for whom palliative radiotherapy for brain metastasis was administered.

Methods: This was a retrospective study that evaluated the patients who received palliative radiotherapy for brain metastases between January 2011 and December 2019. Patient treatment files and the hospital information management system were used to collect the data.

Results: In this study, 4107 patients who received radiotherapy for any brain tumors were evaluated. Of these, 2910 had metastatic brain tumors. In the metastatic group 1736 (60%) patients were male and 1174 (40%) were female. Primary diagnosis was lung cancer (38%), breast cancer (20%), primary unknown (15%), gastrointestinal cancers (12%), and other cancers (15%). 1643 (52%) patients received whole-brain radiotherapy (WBRT), 535 (18%) received WBRT with stereotactic radiosurgery (SRS) and 706 (29%) received SRS without WBRT for brain metastasis. Radiotherapy data of 26 (1%) patients could not be accessed.

Conclusion: Both WBRT and SRS are good palliative treatment options for brain metastasis. SRS without WBRT can be considered as a treatment option in selected cases.

Introduction

Metastatic brain tumors are the most common types of brain tumors in adults with an incidence of 20%-40% among all cancer types. The most common primary tumors responsible for brain metastases are lung cancer, breast cancer and malignant melanoma.[1,2]

The treatment options for brain metastases are surgery, whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), and systemic therapies. These modalities may be used alone or combined. Many factors such as patient's age, performance status, number of brain metastases, and the extracranial metastases affect the treatment modality choice.[3,4]

Until the 1950s medical supportive care was the only option for patients with multiple brain metastases. Chao et al demonstrated that use of WBRT reliefs the symptoms of 63% of patients with multiple brain metastases. This study was the first step for the use of radiotherapy for brain metastases.[5] Different dose schedules have been used for WBRT (20 Gy/5 fractions, 30 Gy/10 fractions). No significant difference was reported in terms of survival or symptom palliation between these different WBRT schedules.[6]

In recent years questions about the use of WBRT have risen because of late neurological toxicities such as memory loss, emotional dysfunction, and dementia.[7] In recent studies, the role of adjuvant WBRT was assessed. They reported that adjuvant WBRT reduces the intracranial relapse rates but there was no difference in overall survival. WBRT may be added to SRS to increase the local control rates, or SRS may be used alone.[8-10]

The purpose of this study is to review the number of patients, demographic characteristics, radiotherapy techniques (WBRT, SRS, or WBRT+SRS) and treatment doses used for patients with brain metastasis treated in a radiation oncology department.

Methods

This was a retrospective study that evaluated the demographic characteristics and the radiotherapy techniques used for the treatment of patients with brain metastases at a training and research hospital radiation oncology department between January 2011 (the date that we started SRS with Accuray Cyberknife robotic radiosurgery system) and December 2019. All necessary permissions were obtained for this study. Patient treatment files and the hospital information management system of 4107 patients with brain tumors were retrospectively

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reviewed. Patients with primary brain tumors were excluded, only patients with metastatic brain tumors were included in the study. Patients who were younger than 18 years old excluded from the study. Sex, age, primary diagnosis of patients, and radiotherapy techniques were evaluated.

WBRT was administrated by LINAC based conventional radiotherapy devices. SRS was administrated by Accuray Cyberknife robotic radiosurgery system in our clinic. In our department WBRT is preferred in multiple brain metastases whereas WBRT+SRS or SRS is preferred in patients with a limited number (1-5 lesions) of metastases. In WBRT+SRS group WBRT was used as adjuvant treatment after SRS, or SRS was used as a boost dose after WBRT.

The number of patients who were administrated WBRT, SRS, or SRS+WBRT and doses of WBRT and SRS was evaluated. The changes of radiotherapy technique choice (WBRT+SRS or only SRS) over the years in patients with a limited number of brain metastasis (1-5 metastatic lesions) were also evaluated. SPPS version 22 was used to evaluate the data. Pearson chi-square test was used to evaluate the difference in the number of patients receiving WBRT+SRS or only SRS by years. The total type-1 error level was used as 5% for the statistical significance of possible factors that were statistically significant in the analysis.

Results

A total of 4107 patients received radiotherapy for brain tumors between January 2011 and December 2019. Of all patients, 1410 were treated for primary or benign brain tumors as curative or adjuvant intent and 2910 had metastatic brain tumors. A total of 1736 (60%) of patients were male and 1174 (40%) were female. Median age for patients was 58 (range 20-94). Distribution by primary tumor was determined as lung cancer (38%), breast cancer (20%), primary unknown (15%), gastrointestinal cancers (12%), and other cancers (15%).

A total of 1643 (52%) patients received WBRT, 535 (18%) received WBRT+SRS and 706 (29%) received SRS without WBRT for brain metastases. Radiotherapy data of 26 (1%) patients could not be accessed. In WBRT group 34 patients were re-irradiated with WBRT for progressive symptomatic brain metastases. In SRS without WBRT group 179 patients were irradiated with SRS more than once for more than one lesion.

In patients who received only WBRT, the WBRT doses were 30 Gy/10 fractions in 1412 (86%) and 20 Gy/4 fractions in 231(14%) of 1643 patients.

In WBRT+SRS group WBRT doses were 25 Gy/10 fractions in 144 (27%) and 30 Gy/10 fractions in 391 (73%) of 535 patients. SRS doses were prescribed regarding the tumor size and localization. The suggested SRS doses in literature are 22 Gy in one fraction or 28 Gy in 2 fractions for tumors smaller than 2 cm; 18 Gy in one fraction or 24 Gy in 2 fractions for tumors between 2.1-3 cm; 15 Gy in one fraction or 20 Gy in two fractions for tumors between 3.1-4 cm; 27 Gy in 3 fractions or 25 Gy in 5 fractions for tumors nearby the critical organs like brainstem, optic nerve, and optic chiasm. SRS doses were calculated based on recent SRS studies.[11-13] In SRS, we used one fraction (15-22 Gy) in 51%; two fractions (20-24 Gy) in 15%; three fractions (27 Gy) in 18% and five fractions (25 Gy) in 16% of treatments due to the tumor size and localization. SRS doses were prescribed at the center of the planning target volume (1-2 mm margin to the gross tumor volume) with a minimum 85% of prescribed dose to the surface of the planning target volume.

When the use of WBRT+SRS and SRS without WBRT was evaluated in the patients with the limited number of metastases, it was observed that adding WBRT to SRS decreased over years from 2011 to 2019 except 2012 and 2014. WBRT+SRS rate was 21.6% in 2019 while it was 50% in 2011 ($P < 0.001$). The variation of WBRT+SRS and SRS without WBRT use in patients with a limited number of metastasis by years is summarized in Table 1.

Discussion

Metastatic brain tumors are the most common types of brain tumors in adults with an incidence of 20-40% among all cancer types.[1] In this study, we observed that metastatic brain tumors were 70% of all brain tumors treated in our clinic. These results are compatible with the literature; as the metastatic brain tumors are the most common types of brain tumors.

The primary diagnosis of our patients was lung cancer (38%), breast cancer (20%), primary unknown (15%), gastrointestinal cancers (12%), and other cancers (15%). These results are compatible with the literature.[1]

In patients with multiple metastatic lesions in the brain, the first treatment choice is WBRT. WBRT is an effective treatment modality for the palliation of symptoms. When compared with no treatment, it has a survival advantage. Median overall survival (OS) increases to 3-7 months with WBRT while it is only 1 month with no treatment.[14] The most common dose/fraction schedule is 30 Gy in 10

Table 1. The variation of SRS vs WBRT+SRS by years

	SRS		WBRT+SRS	
	No.	%	No.	%
2011	97	50	97	50
2012	52	40	78	60
2013	67	51.5	63	48.5
2014	53	39.6	81	60.4
2015	69	54.8	57	45.2
2016	61	64.9	33	35.1
2017	73	60.8	47	39.2
2018	118	71.5	47	28.5
2019	116	78.4	32	21.6

$P < 0.001$

SRS: stereotactic radiosurgery, WBRT : whole-brain radiotherapy.

fractions. Different dose-fractionation schedules have been investigated in recent studies.[6,15] No difference was observed in terms of local relapse time or palliation of symptoms.[6] Only in a study by Hindo et al, 10 Gy in a single fraction to the whole brain was reported as so toxic. Two of the patients in this study died after 48 hours from WBRT.[15] The most common schedule we use in our department is 30 Gy in 10 fractions (86% of all WBRT patients). This schedule is well tolerated and good in symptom relief.

In 2004 results of Radiation Therapy Oncology Group (RTOG) 9508 were reported. In this study patients with 1-3 brain metastases were randomized to WBRT or WBRT followed by SRS arms. A survival advantage was observed in WBRT+SRS group for single brain metastasis (median survival time for WBRT+SRS group 6.5 months and 4.9 months for WBRT group; $P=0.03$). In this study, WBRT+SRS was also suggested as the standard treatment for patients with single unresectable brain metastasis.[16]

In EORTC 22952-26001 trial the role of adjuvant WBRT after SRS or surgery was assessed. Three hundred fifty-nine patients with 1-3 brain metastases were treated with complete surgery or SRS and randomized to WBRT or observation arms. WBRT reduced the 2-year relapse rates both at initial sites (surgery: 59% to 27%, $P<0.001$; SRS: 31% to 19%, $P=0.04$) and at new sites (surgery: 42% to 23%, $P=0.008$; SRS: 48% to 33%, $P=0.02$). Overall survival was similar in WBRT and observation arms.[9] In the secondary analysis of EORTC 22952-26001 no survival benefit was observed with WBRT.[17]

As a result of these studies, SRS without WBRT could be considered as a treatment option for patients with a limited number of brain metastases. In this study, we observed that in a selected patient group, SRS without WBRT had been increased by years, except for the years 2012 and 2014. But from 2014 to 2019 SRS without WBRT had been increased year by year. There may be many reasons such as doctors' choice, tumor and patients' characteristics why WBRT+SRS increased in 2012 and 2014 compared to previous years. In 2011, 50% of patients were treated with WBRT + SRS and 50% of them were treated with SRS without WBRT. in 2019 , 21.6% of patients were treated with WBRT +SRS while 78.4% of them were treated with SRS without WBRT ($P<0.001$). We think that the ratio of 21.6% WBRT+SRS in 2019 is still high because SRS without WBRT is recommended for the treatment of limited number of brain metastases.[18] This study is a retrospective study and we could not access all the data such as patients' performance status, the status of extra cranial metastases, the location and the size of tumors that may affect the decision of doctors about adding WBRT to SRS.

Conclusion

Both WBRT and SRS are efficient treatment modalities for metastatic brain tumors. Results obtained from our study show that SRS has started to be preferred to WBRT in selected patients over the years. This overlaps with the treatment approaches are suggested in the literature.

For the treatment of brain metastases in centers capable of performing specific treatments SRS must be common and accessible as well as WBRT.

Experience and specific treatment devices related to the use of SRS are increasing day by day in our country. In this study we presented radiotherapy techniques that we used for the treatment of metastatic brain tumors. We aim to design common studies with other radiation oncology centers in which treatment results can be evaluated with a large number of patients.

Study Highlights

What is current knowledge?

- Metastatic tumors are the most common brain tumors
- Radiotherapy is the mainstay of the treatment
- WBRT and SRS are both the radiotherapy options

What is new here?

- Only SRS may be considered in selected patient group

Conflict of Interest

None.

Ethical Approval

This retrospective study was approved by the Medical Specialty Training Board of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (Approval ID:26.11.2019/83).

Authors' contributions

FG: methodology, data preparation, writing, supervision. YGA: investigation, writing-reviewing and editing

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