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Radiosurgery for multiple brain metastases using volumetric modulated arc therapy: a single institutional series

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ABSTRACT

Background: Patients with brain metastases (BM) live longer due to improved diagnosis and oncologic treatments. The association of volumetric modulated arc therapy (VMAT) and image-guided radiation therapy (IGRT) with brain radiosurgery (SRS) allows complex dose distributions and faster treatment delivery to multiple lesions.

Materials and methods: This study is a retrospective analysis of SRS for brain metastasis using VMAT. The primary endpoints were local disease-free survival (LDFS) and overall survival (OS). The secondary outcomes were intracranial disease-free survival (IDFS) and meningeal disease-free survival (MDFS).

Results: The average number of treated lesions was 5.79 (range: 2–20) per treatment in a total of 113 patients. The mean prescribed dose was 18 Gy (range: 12–24 Gy). The median LDFS was 46 months. The LDFS in 6, 12, and 24 months was for 86%, 79%, and 63%, respectively. Moreover, brain progression occurred in 50 patients. The median overall survival was 47 months. The OS in 75%, 69%, and 61% patients was 6, 12, and 24 months, respectively. IDFS was 6 and 24 months in 35% and 14% patients, respectively. The mean MDFS was 62 months; it was 6 and 24 months for 87% and 83% of patients. Acute severe toxicity was relatively rare. During follow-up, the rates of radionecrosis and neurocognitive impairment were low (10%).

Conclusion: The use of VMAT–SRS for multiple BM was feasible, effective, and associated with low treatment-related toxicity rates. Thus, treatment with VMAT is a safe technique to plan to achieve local control without toxicity.

Key words: radiosurgery; volumetric modulated arc therapy; metastasis; radiotherapy

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Introduction

Metastasis is the most common neoplasm of the brain. It has become increasingly frequent due to advances in and increased availability of magnetic resonance imaging (MRI) and contemporary systemic treatments, which have increased patients' survival [1]. Historically, whole-brain radiotherapy (WBRT) has been the standard treatment option for patients with multiple brain metastases (BM). However, WBRT is associated with greater neurocognitive dysfunction than stereotactic radiosur-

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gery (SRS) [2]. Therefore, there is a growing interest in SRS for patients with multiple BM. Prospective randomized clinical trials have demonstrated SRS as an important option to increase local control in patients with BM [3, 4]. Although these results are well established for up to three lesions, there are promising data for patients with 4 to 15 BM [5–7].

The objective of SRS is to deliver a high dose to the lesion while achieving a steep dose gradient outside the treatment volume [8, 9]. This strategy generates different effects in the tumor compared to those in other areas since the higher single dose promotes ablation and necrosis of the irradiated target. Thus, SRS requires small margins, special planning techniques, and equipment to achieve high conformity [8, 10, 11]. The traditional method used for treating multiple BM involves treating each metastatic lesion individually, which makes the procedure complex and time-consuming. It implies that treatment for each lesion needs to be planned using one (or more) isocenter and several non-coplanar arcs with cones, static conformal beams, dynamic arcs with multileaf collimators (MLC), or the Gamma Knife™ (GK) (Elekta, Crawley, UK) shots depending on the available technology [8. 9. 12]. In addition, the potential dose that each lesion receives must be estimated considering spread in the brain. Therefore, the complexity of the planning process and the time spent to treat the patient harboring multiple BM is proportional to the number of targets to be irradiated.

In contrast, in volumetric modulated arc therapy (VMAT), dose distributions are highly conformal to the target volume by varying the dose rate, gantry rotation speed, and MLC aperture shape in one or more arcs dynamically and simultaneously. In this scenario, VMAT technology seems to fill this gap in SRS to treat multiple brain lesions using a single isocenter, enabling shorter treatment time and facilitating the assessment of the dose contribution among multiple targets [13, 14]. Therefore, because the use of VMAT is not very time-consuming and provides dosimetric results equivalent to other treatment methods for brain metastases, image-guided VMAT-SRS plans seem to be a powerful tool for treating multiple BM with a single isocenter [10, 15].

The objective of this study was to analyze the clinical outcomes of patients with multiple BM treated with VMAT-based SRS in a single institution.

Materials and methods

This observational and retrospective study included all consecutive patients who received, VMAT-SRS for multiple BM in a single fraction using a single isocenter between 2012 and 2021 in two different departments of a single institution in Brazil. Treatment was considered for patients with two or more BM. Patients who had previously undergone radiation treatment, SRS, or treatment without the VMAT technique or WBRT were included.

Data were collected retrospectively from the institution's electronic medical records and the radiotherapy management system.

The following clinical factors were analyzed: age, histopathology, features of systemic disease, and previous brain treatments. Regarding irradiation planning, data on the number of lesions as well as maximum and minimum prescribed doses were collected.

Interventions

All patients were treated with frameless image-guided VMAT-SRS and immobilized with thermoplastic masks. For each patient, a computed tomography scan (CT) simulation was performed with 1-mm slice thickness and fused to a T1-weighted contrast enhanced MRI sequence with three-dimensional distortion correction to define the gross tumor volume (GTV). The GTV was expanded to 1 mm to create the planning target volume (PTV). In smaller lesions, larger PTV margins (2 mm) were permitted to minimize uncertainties.

SRS-VMAT plans (single isocenter) for multiple targets were created using up to six arcs and from three to four couch angles — one to two full arcs at 0° and four partial arcs at couch angles around 60° and 300° using both flattening filter-free (FFF) and flat X-rays beams with 6 and 10 MV, depending on the linear particle accelerator (LINAC). The technology used was RapidArc (Varian Medical Systems, Palo Alto CA, USA) created by inverse planning optimization. High-definition (HD) MLC was used for all cases. Treatment was performed in three linear accelerators with a table which moves in six-dimensional couch — two TrueBeam STx (Varian Medical Systems, Palo Alto, CA, USA) and one Novalis Tx (Varian Medical Systems and BrainLab AG, Munich, Germany).

Table 1. Dose constraints

	Volume [cc]	Max point dose [Gy]
Optic pathway	V8 Gy < 0.2 cc	10
Cochlea	–	9
Brainstem	V10 Gy < 0.5 cc	15
Spinal cord and medulla		14

Constraint doses were chosen according to the study by Timmerman et al. showed in Table 1 [16]. Another important parameter to consider was $V_{12} > 8.5$ cm^3 because of the risks of radionecrosis [17].

After a set-up of the patient using a thermoplastic mask, IGRT was performed using either cone-beam CT (CBCT) or the ExacTrac 6D system (BrainLab AG, Munich, Germany), followed by CBCT in different three LINACs. The aim was to hit the multiple targets correctly. However, it is highly desirable to account for both translational and rotational positioning errors; therefore, a 6 degrees of freedom couch was used for positioning for all cases. IGRT images were also recaptured to confirm the correction before dose delivery. Depending on the availability, intrafraction verification was performed using either Align RT (Vision RT Ltd., London, UK) surface-guided radiation therapy (SGRT) system or snap verifications with the ExacTrac 6D system. If motions were detected, the CBCT images were reacquired in between arcs or a pair of X-rays using the ExacTrac 6D system for repositioning.

Outcomes

Local disease-free survival (LDFS) and overall survival (OS) were the primary endpoints. LDFS was defined as the time from the end of SRS to progression of any treated lesion or progression of local treatment. When the patient had more than one SRS course for multiple BM using VMAT, only the first treatment was considered. OS was defined the time from the end of SRS to occurrence of death by any cause. Patients alive without achieving the end point at last follow-up were censored.

The secondary outcomes included intracranial disease-free survival (IDFS) and meningeal disease-free survival (MDFS). IDFS was defined as the time from the end of SRS to any progression in the brain. Disease progression was defined based on MRI. Finally, MDFS was defined as the time from the end of treatment to progression to the leptomeningeal space.

Acute and late toxicities were classified according to CTC 4.0. Toxicity was defined as acute if it occurred from the start of SRS to 3 months after SRS, while it was defined as late if it occurred from any time after 3 months of radiosurgery.

Statistical analysis

Patients were stratified by demographics and pathology characteristics. Data were summarized using frequencies for nominal and ordinal variables. Median and mean were calculated for continuous data. Median [interquartile range (IQR)] follow-up was calculated when appropriate. The median was considered when the interval in the mean was discrepant. Patient characteristics are presented as descriptive statistics.

Categorical data were compared using Fisher's exact test. Statistical significance was defined at $p < 0.05$. OS and LDFS were estimated using the Kaplan-Meier method and compared using the log-rank test. A life table was used to calculate percentage outcomes more accurately for each interval. Some aspects were analyzed according to variables.

Results

A total of 113 patients met all the inclusion criteria. The median follow-up period was 9 months (range: 0–79 months). The patient characteristics are described in Table 2. The median age was 60 years (IQR: 31–91 years). The average number of treated lesions was 5.79 (range: 2–20) per treatment, and 75% patients had no more than seven lesions.

The most common primary sites were the lung (40.7%), breast (36.3%), melanoma (7.1%), and colon (4.4%). The most prevalent histology was adenocarcinoma (42.5%), breast cancer (34.5%), melanoma (7.1%), small cell cancer (4.4%), poorly differentiated carcinoid tumors (3.5%), sarcoma (2.7%), and others (6%).

More than two-thirds (72.7%) of the patients had widespread disease. Accordingly, 80.7% patients had received chemotherapy and 48.6% patients had undergone target therapy or immunotherapy before SRS. Considering 43 patients who

Table 2. Patient characteristics

Age [years]	
Mean	61
Number of lesions	
Mean	5.7 (range: 2–20)
2	12.4%
3	14.2%
4	15%
5	16.8%
6	14.2%
7	6.2%
8	4.4%
9	3.5%
≥ 10	13.4%
Maximum dose [Gy]	
Mean	18 (range: 12–24)
Minimum dose [Gy]	
Mean	17 (range: 8–24)
Primary site	
Lung	40.7%
Breast	36.3%
Skin	7.1%
Colon	4.4%
Head and neck	1.8%
Kidney	1.8%
Ovary	1.8%
Endometrium	1.8%
Others	4.5%
Histology	
Adenocarcinoma	42.5%
Invasive breast carcinoma	34.5%
Melanoma	7.1%
Oat cells	4.4%
Poorly differentiated carcinoma	3.5%
Sarcoma	2.7%
Others	5.4%
Systemic disease	72.7%
Previous CNS treatment	39.1%
Previous chemotherapy	80.7%

CNS — central nervous system

received previous CNS treatments to brain metastases: 16 had SRS (however not using single isocenter), 10 had a surgery and 7 WBRT.

The dose prescription varied according to each lesion and PTV diameter, even considering the same courses of treatment. The total number of lesions treated and clinical characteristics were also considered. The prescribed doses varied from 12 Gy to 24 Gy, and the mean dose was of 18 Gy.

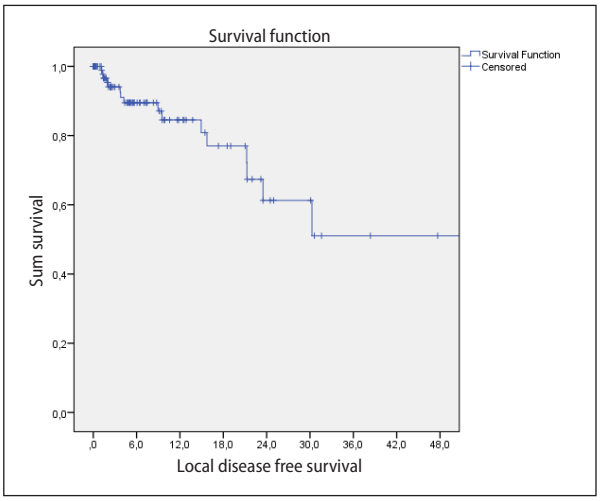

Figure 1. Local disease-free survival

The number of arcs in the treatment varied from 3 to 9, with six arcs planned in 53.1% of the planning.

The median LDFS was 46 months (IC 95% 33.8 - 58.6), being 86% in 6 months, 79% in 12 months and 63% in 24 months, although 16 patients presented local disease (Fig. 1). On univariate analysis, the number of lesions ($p = 0.51$), age ($p = 0.07$), dose ($p = 0.87$), histology ($p = 0.29$), presence of systemic disease ($p = 0.73$), and previous CNS treatment ($p = 0.96$) were not significant variables in terms of LDFS.-

Moreover, brain progression occurred in 50 patients, which was represented by new lesions outside the radiation field. The mean IDFS was 46 months (range: 33–58 months); it was 6 and 24 months in 35% and 14% patients, respectively (Fig. 2). The mean MDFS was 62 months (range: 54–69 months); it was 6 and 24 months in 87% and 83% patients, respectively (Fig. 3). In addition, univariate analyses did not show differences in the following variables in terms of IDFS: number of lesions ($p = 0.37$), systemic disease ($p = 0.9$), or previous treatment of the CNS ($p = 0.98$).

In addition to new lesions in the brain, nine patients had leptomeningeal disease. More than five lesions tended to relapse in the meninges (log rank: 3.7 $p = 0.054$). However, systemic disease ($p = 0.15$), previous CNS treatment ($p = 0.18$), or systemic therapy were not variables that differ in terms of MDFS.

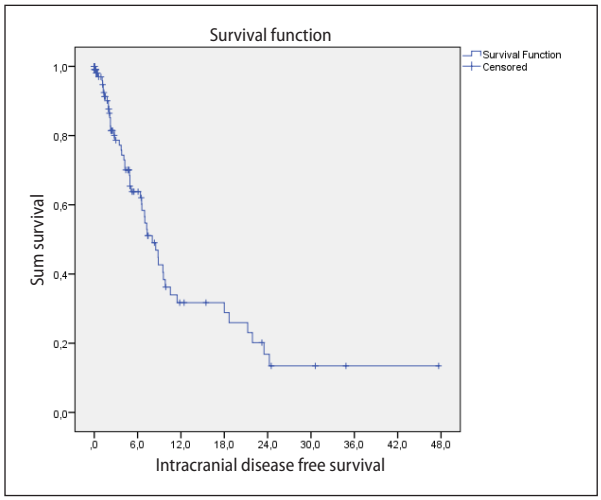

Figure 2. Intracranial disease-free survival

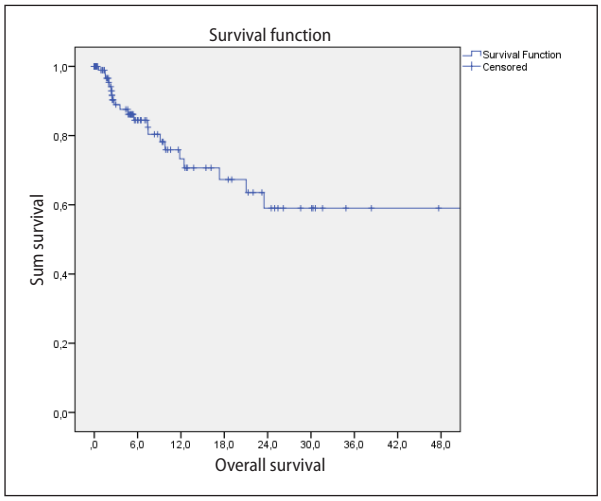

Figure 4. Overall survival

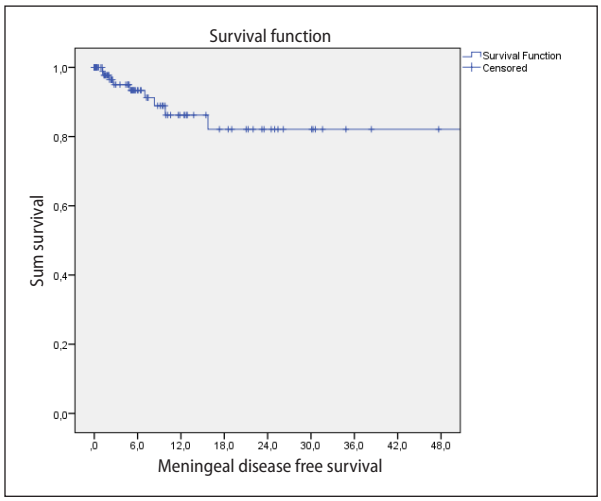

Figure 3. Meningeal disease-free survival

Table 3. Cumulative proportion surviving

	LDFS	MDFS	IDFS	OS
6 months	86%	87%	35%	75%
12 months	79%	83%	35%	69%
24 months	63%	83%	14%	61%

LDFS — local disease-free survival; MDFS — meningeal disease-free survival; IDFS — intracranial disease-free survival; OS — overall survival

Table 4. Analyzes

Log rank (p)	LDFS	MDFS	IDFS	OS
Number of lesions	0.51	0.054	0.37	0.024
Systemic disease	0.73	0.15	0.90	0.17
Previous treatment CNS	0.96	0.18	0.98	0.62

LDFS — local disease-free survival; MDFS — meningeal disease-free survival; IDFS — intracranial disease-free survival; OS — overall survival; CNS — central nervous system

The mean estimated survival was 47 months (95% CI: 38.2–57.4). There were 21 reported deaths in the entire study population. The OS in 75%, 69%, and 61% patients was 6, 12, and 24 months, respectively (Fig. 4). In univariate analysis, age [< 60 years ($p = 0.002$)] and the number of lesions [< 5 lesions ($p = 0.0024$)] were associated with better OS, but dose < 18 Gy was a bad predictor factor of OS considering the maximum dose ($p = 0.007$) and minimum dose ($p = 0.001$). Systemic disease ($p = 0.17$) and previous CNS treatment ($p = 0.62$) were not relevant in terms of OS.

In addition to the development of new drugs, which could supposedly improve prognosis after development of malignant tumors, chemotherapy, immunotherapy, or target therapy did not differ in terms of LDFS, MDFS, IDFS, or OS. The results are summarized in Table 3 and analyses are described in Table 4.

Acute severe toxicity was relatively rare. Only 9.3% had adverse symptoms, and most of them were minor. Grade 2 CNS-related acute toxicity was reported in 17 patients. Grade 3 CNS-related acute toxicity requiring hospitalization due to seizures occurred in only three patients. No events of radiodermatitis or mucositis were observed in any patient.

During follow-up, the rates of radionecrosis on MRI and occurrence of neurocognitive deficits were clinically relevant. No deaths related to

Table 5. Toxicity

CNS	87.6%
Headache	4 patients
Seizure	3 patients
Nausea	4 patients
Vertigo	3 patients
Skin	0%
Radionecrosis	14.7%
Neurocognitive dysfunction	11.9%

the treatment were noted. The toxicities are summarized in Table 5.

The median of the volume that received 12 Gy (V_{12}) was 12 cc, although the standard deviation was 17.5 cc. The mean unit monitor was 7652 UM (range: 3710–15832).

Discussion

Development of the VMAT technique has allowed for the treatment of multiple brain metastases in a single isocenter [18]. Therefore, the VMAT technique enables dose distribution using a single safe and effective plan considering patient selection [19, 20]. Our results showed that VMAT–SRS for multiple brain metastases was effective and maintained a good LDFS (6 months in 86% patients). The treatment could also be considered safe as acute and chronic toxicities rates were low.

It is previously known that in SRS for multiple lesions, a major drawback is the increase in radiation dose to the healthy brain. Therefore, the dose coverage may be limited to respect healthy brain constraints and can become more difficult to avoid due to the overlap of the PTV for each target. In our cohort, the number of lesions were 2–20 (mean: five lesions). The most prevalent number of lesions was 5 (16.8%) and the accumulated percentage was 72.6%, considering two to six lesions. The number of lesions was not a significant predictor of clinical outcomes. In a study by Hughes et al., initial SRS was performed on patients with five to 15 brain metastases [6]. Comparing one to ten lesions, cases with only one lesion had better results than cases with more than one lesion. However, there was no difference in outcomes between cases with two to five lesions and those with six to ten lesions as well as in cases with four or more lesions and those with only four lesions ($p = 0.91$) [5]. Freedom from intracranial progression was observed at 6.3 months [21].

The isodoses described in the literature ranged from 12 Gy to 25 Gy, which was comparable with the maximum doses prescribed in our institution, which varied from 12 to 24 Gy because for the same treatment, it was possible to simultaneously prescribe different doses according to lesion size and proximity of the organs at risk (OAR). In most cases, low doses were prescribed to cavities (after surgery) or large lesions. Lau et al. used a median dose of 20 Gy for a median of three BM. They also reported a mean dose to the normal brain of 4.2 Gy, a median V_{12} of 38.0 cm^3, and a median $V_{4.5}$ to the normal brain of 350.5 cm^3. No discernible relationship between dose to the normal brain and toxicity was observed [22]. Fiorentino et al. prescribed a dose of 15 Gy and up in a single fraction or using hypofractionated treatments (five fractions) [23].

Considering single-isocenter VMAT plans for multiple metastases seems to be equivalent in plan quality. Retrospective analyses concluded that multiple non-coplanar arc VMAT provides accurate and high quality radiosurgery while delivering low doses to the healthy brain and high dose conformity to the target as well as allows for time optimization [24]. The volumes of healthy brain receiving at least 50% of the dose prescription were the lowest for the same arc configuration of VMAT compared to DCAT [25]. Conformity index (CI) and coverage quality were superior or equivalent for VMAT plans compared to conventional planning [24]. The mean MU decreased by 42%, and the treatment time was reduced by 49%. However, the volume receiving 5 Gy 46% was larger for VMAT. Most studies evaluated dosimetric features in SRS for multiple brain metastasis using VMAT techniques. However, it is uncertain if dosimetric results translate in clinical outcomes.

Our clinical outcomes were similar to those reported in the literature; however, most data were correlated with dosimetry. Our cohort demonstrated local control at 1 year in 79% patients, and 1-year OS in 69% patients. Some retrospective studies in the literature described local control at 1 year and 2 years in 99% and 95.1% patients, respectively. Although some studies showed variable numbers, they had non-significant differences

[23, 26]. Even when the treatment involved more than one fraction, most studies reported an OS of 9 to 30.5 months and local control in 62.5–88% patients [19, 20].

There are no prospective randomized phase III trials comparing VMAT to other techniques for upfront SRS treatment. The evidence is based on few results, with preliminary follow-up and only a few patients included.

The VMAT technique seems to be dosimetrically safe in providing the clinical effectiveness necessary to assure the supposed advantages of concomitant treatments. Comparing the IMRT sliding window and VMAT (one to two arcs) in SRS or SBRT, technical aspects were considered similar in terms of dosimetric conformity, sparing OAR, and homogeneity among the three techniques. The mean beam confirmed that time was reduced by 73%, and that MU was reduced by 43%. Additional treatment time increased the probability of intra-fractional errors [27]. A study by Andrews et al. compared outcomes using GK against LINAC for patients treated with SRS for BM and found that there was no difference [3]. In contrast, Shafie et al. compared dosimetrically VMAT and CyberKnife (CK) for treating five or more lesions. The gradient dose outside the target was steeper for CK ($p < 0.001$). Estimated treatment time was shorter for VMAT (13.7 minutes) than for CK (130 minutes) ($p < 0.001$) [28]. LINAC, GK, and CK were dosimetrically compared in 10 patients with two or more large lesions (median: 18.31 cm^3). GK and CK plans had 20% less normal brain volumes receiving 12 Gy or 20 Gy, although the mean bean times of GK and CK were 64 minutes and 31 minutes, respectively, compared to 4 minutes in LINAC [29]. In areas distant from the treatment target, the estimated dose received by the brain was approximately 2.60–6.69 Gy [30].

In addition, as the number of isocenters increases, the normal brain isodoses volumes decrease up to 15%, considering a single lesion [18]. Radionecrosis occurred in 1.4% (grade 2) and 0.9% (grade 3) patients [21]. Trifiletti et al. also described a low number of toxicity of grades 3–4 (7.4%), even in the presence of brainstem metastases [31]. Another study described the rate of radionecrosis grades 3 to 5 to be 25% for deeply located tumors and 1.9% for non-deep metastases. Although the analysis of late toxicity or marked worsening in cognition has been poorly reported, the fact that there were no serious neurocognitive worsening events shows that doses received by the healthy brain were not compromised by the nature of this treatment [19, 20]. In most analyses, severe adverse events, such as grade 3 or 4 toxicities, were not described. There were no neurological deaths attributable to the treatment in both studies. Acute and late toxicities were acceptable. The rate of late toxicities were comparable to that reported in the literature wherein radionecrosis and neurocognitive impairments were each found in approximately 3% subjects.

Similarly, other approaches have been developed with an aim to conserve neurocognitive function. The use of memantine at 24 weeks during and after WBRT was found to contribute to cognitive preservation. The combination of the hippocampus avoidance technique concomitant with memantine preserves cognitive function and patient-reported symptoms, maintaining the same OS and PFS [32].

There are limitations to our study. First, this study was a retrospective analysis. However, since our study was a single-institute study, there was more uniform conduct among the team dose prescription and criteria selection were similar. Prospective and randomized trials should compare among the techniques mentioned in this study. Second, despite studies on oligometastases, including multiple primary sites, it is well-established that histology association with systemic therapy could provide different outcomes. Third, the number of lesions seems less important than the volume of treatment because the former is related to the amount of normal brain tissue. Fourth, systemic therapy has improved in the last few years, making an increase in OS possible. However, there is a disparity in the availability of immunotherapy and target therapy among patients.

Considering treatment time, coverage quality, and conformity, single-isocenter VMAT seems to be advantageous for the treatment of multiple brain metastases. A short treatment time guarantees more comfort to the patient and a lesser probability of movement while the dose is being delivered. In addition, the VMAT technique allows for sophisticated planning and can make use of other technologies, such as some types of IGRT, including OSMS, cone beam, ExacTrac, and others.

In conclusion, the use of the VMAT technique in SRS for multiple brain metastases was feasible

and effective using a single isocenter. The technique showed a low occurrence of treatment-related toxicity and acceptable clinical outcomes comparable to other techniques described in the literature.

Conflict of interest

None declared.

Funding

None declared.

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