Radioinduced effects in patients with brain metastases treated with CyberKnife® platform radiosurgery

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Abstract

The damage associated to stereotactic radiotherapy and radiosurgery is edema and radionecrosis of the brain by magnetic resonance images (MRI), so it is paramount to analyze the factors that contribute to it. **Methods:** This retrospective study included patients with brain metastases that were treated with radiosurgery or stereotactic radiotherapy using CyberKnife® between July 2012 and December 2013, with respect to these criteria: primary disease controlled, functional status KPS >70%, and a maximum of two lesions without mass effect. We analyzed the MRI obtained after their treatment and every three months in order to determine possible changes. **Results:** The most frequent finding was breast cancer Her2/Neu biotype, 83% of the patients with supratentorial location, 33% of patients had received previously whole-brain radiotherapy, and 60% had > 5 cc tumoral volume. The dosimetric parameters included a median of isodose line of 88%, median conformity index of 1.4, median homogeneity index of 1.13 and a median V14Gy of 23 cm³. MRI showed that 83% of the patients developed edema in various grades; of the 17% who reported clinical symptoms none surpassed grade 1 central nervous system toxicity of the Radiation Therapy Oncology Group (RTOG) classification. According to our findings in the analyzed, only V14Gy > 5 cm³ seems to be related to an increase in the edema volume. **Conclusions:** MRI and clinical (minimal) changes were related to the volume of normal brain tissue included in the higher-dose areas of radiation.

Key words: Brain metastases. Radiosurgery. Changes derived from stereotactic radiotherapy/radiosurgery.

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Introduction

Brain metastases are the most common intracranial neoplasm in adults. About 10-30% of patients present with cerebral metastatic disease (BM, brain metastasis), out of which 8-10% are symptomatic¹. In the USA, BM diagnosis has an incidence of 100,000-170,000 cases per year². In Latin America, neoplasms of the central nervous system (CNS) account for 3.2% of mortality, with no specific statistics being determined only for BM. In Mexico, the 2003 national histopathologic report informed 2.18% of CNS neoplasms as a cause of mortality, also with no specification for BM cases³. Most BM originate in primary malignancies such as lung cancer, breast cancer, melanoma, colorectal cancer and, less commonly, lymphoma and renal cancer⁴.

As regards clinical presentation, most patients present with headache, edema and convulsions secondary to the site affected by the metastatic lesion, and edema with cognitive deficit, with paraclinical diagnosis therefore being imperative by means of computed tomography (CT) and magnetic resonance imaging (MRI), with the latter having higher definitive resolution and higher detection of small lesions, in addition to providing better detection of lesions and their components, as well as of perilesional edema at its different sequences and of the hemorrhagic component if there is any; in addition, complementary spectroscopy-provided biochemical information has to be available in order to identify tumor tissue, edema and other non-neoplastic lesions⁵.

In general, survival in case of BM is poor, generally one month without treatment and, with treatment, a prognostic improvement of up to 11-18 months can be obtained with different treatment modalities, adjusted according to the clinical scenario. The best prognostic knowledge and approach is currently achieved with the aid of the Recursive Partitioning Analysis (RPA) and the Radiation Therapy Oncology Group (RTOG) classifications, as well as with the Score Index for Radiosurgery (SIR) and Graded Prognostic Assessment (GPA) scores, which are applied taking into account clinical factors such as the size and number of lesions, patient age and performance status, as well as the status of systemic disease^{6,7}.

The treatment of patients with BM will depend on the number of lesions and patient-related factors such as: age, performance status, neurological deficit, systemic disease control and lesion size. One of the treatment options is surgery, which is used for single, accessible lesions, with patient adequate performance status and for rapid symptom improvement.

Radiotherapy is another treatment modality. It is subdivided into whole brain standard radiation therapy, indicated for tumors in relevant areas with functional status involvement and, currently, there is also radiosurgery available as another therapeutic modality for unresectable lesions, with no mass effect, recurrent lesions after whole brain radiotherapy and residual lesions post-surgical treatment, which is why patients who are candidates to this modality are highly selected^{8,9}.

Radiosurgery is a technique that employs ionizing radiation to treat intracranial targets with sub-millimetric precision and that can offer the same benefit than open surgery but without the risk of comorbidities implied by the surgical procedure. There are different devices for radiosurgery application: Leksell Gamma Knife® (GK, cobalt source with gamma irradiation), radiosurgery with proton beam system and, finally, with linear accelerator (LINAC, based on photon generation). The latter modality can be carried out using a real-time image-guided robotic system without a stereotactic arch, such as the CyberKnife® (CK) system.

According to reports published in the literature, radiosurgery has an effect on brain control in up to 80% of cases and on local control in 80-90%¹⁰⁻¹³. Local control has been assessed as complete and partial response and stable disease control¹⁴. Adverse effects that occur with radiosurgery, assessed in a vast majority with the GK modality, are less frequent than with standard radiotherapy techniques and surgical procedures, but can occur in up to 40% of patients, with a clinical neurological impact in 2-32% of cases.

The most severe adverse effect, which occurs in up to 10% of radiosurgery-treated patients, is radionecrosis with important cognitive deficit. This toxicity can be prematurely identified by MRI in an anatomical study at different T1 sequences with contrast enhancement increase and hypointense center, as well as in T2 in the same form with center or area of hypointensity. Other authors have also proposed calculations with determination of a radionecrosis predictive ratio < 0.3 and perfusion dynamic study with areas of enhancement with hypointense center.

With regard to biochemistry testing with spectrometry in MRI, the relationship of metabolites has been proposed in the form of ratios for the determination of radioinduced effects, such as radionecrosis, with the following patterns: choline/creatine (Cr) = 1.57, choline/*N*-acetyl aspartate (NAA) = 1.31 and NAA/Cr = 1.22 (these patterns suggest neuronal membrane alteration without cellularity increase and with low metabolism); as

suggested by Weybright¹⁵, the profile is complemented with the presence of lipid and lactate elevation as specific data of necrosis and anaerobic metabolism, respectively¹⁶⁻¹⁹.

Other studies, also published, with regard to the use of thallium-210 to differentiate between progression and radionecrosis, propose a better progression diagnosis, of 82.8%, by means of the retention index (late phase/early phase) with a value < 0.775 for radionecrosis and inversely for recurrence. It's important mentioning that there are different reports that agree that there are risk factors that increase the incidence of radioinduced effects, such as radionecrosis in radiosurgery-treated patients, including: incidences of 5 to 10% with biologically effective doses (BED) of 120-150 Gy, respectively, $> 5\text{-}10\text{ cm}^3$ volume, other factors such as associated chemotherapy (methotrexate), low conformity index, advanced age and comorbidities such as diabetes mellitus and small vessel disease^{20,21}.

Other radioinduced changes detected by imaging can occur in up to 25.8% of cases at 1.5-2 years, mostly discordance ratio-assessed changes between T1 and T2²², and being found in T2-weighted sequences with homogeneous enhancement and in T1-contrasted sequences from sixth week and thereafter, associated with vasogenic edema in relation to blood-brain barrier integrity alteration, as well as endothelial changes such as vacuolization, reactive gliosis, hyaline degeneration and demyelination revealed by areas with less hypointensity close to the inflammation area with hyperintensity areas aggregated to the therapeutic target area tissue with regard to vascular hyalinization. From week 12 on, there is larger area of edema surrounding the target area, and at 18 months, there are only small homogeneous and regular enhancement zones left at T2, with regard to gliosis and demyelination, which has an implication with moderate cognitive impairment, as measured by a decrease in the Mini-Mental State Examination score^{23,24}.

In the literature reports, only changes radioinduced by the modality of radiosurgery with GK are addressed, and experience with the CK system modality is still limited in the literature, and it is mainly focused on radionecrosis with regard to a volume smaller than 7 cm^3 with V14, given that this is a recent technological development²⁵. Hence, the purpose of the present study was to assess imaging changes that might be predictive of the development of clinical implications in patients, by evaluating the therapeutic target and non-target tumor tissue, as well as surrounding tissue.

Patients and methods

Treatment with radiosurgery in our country depends on the availability of the required infrastructure to be carried out. The system available at the Institute is the CK system. The research design was observational and retrospective.

The information was collected from the medical records of patients diagnosed with brain metastases from different primary tumors at the Oncology Hospital of the Centro Médico Nacional Siglo XXI, treated with radiosurgery using the CK modality, with patients with or without prior treatment with radiotherapy, any lineage of the primary tumor, with 1-2 metastatic lesions, 18-70 years of age, absence of mass effect, unresectability owing to location, Karnofsky performance status higher than 70%, primary tumor adequate control and BM as only active disease being included.

Treatment with the CK system: Each patient diagnosed with BM had an assessment MRI study performed prior to the radiosurgery treatment; subsequently, for the treatment, a simulation study was performed consisting of a plain CT scan with 2.5-mm sections and a MRI with 1-mm sections, with tridimensional reconstruction in T13D-weighted sequence contrasted with gadolinium (Gadovist®, gadobutrol at 0.1 mmol/kg with intravenous administration), in order to obtain a fusion of both studies to subsequently develop the plan. The dose was established after the volume of the tumor target was assessed at the physician's judgment, at 15-24 Gy.

Radioinduced effects follow-up was carried out with a 3-tesla resonator (Philips®). The first control study was performed once 8 weeks had elapsed since the treatment, by means of an anatomical study with contrasted sequences weighted at T1, T2, axial FLAIR, sagittal and coronal FLAIR; as well as dynamic study, diffusion and biochemical study, which was performed at the radiologist physician's judgment according to the need to assess the treatment response (complete, partial, progression, necrosis).

The biochemical study with spectroscopy was carried out with the monovoxel technique and with multivoxel in case of suspected progression. The reviews of the studies were made at 8-week intervals; in the first study, treatment response and radioinduced effects such as toxicity, both edema and radionecrosis, were assessed. Treatment response evaluation was performed according to the following definition: complete response (no evidence of tumor lesion or 95% tumor volume reduction), partial response (25-94% lesion

reduction), stable disease (lesion decrease lower than 25%) and progression (lesion volume increase). In addition, in the case of tumor progression, the presence of brain failure was also assessed.

Initially, the presence of baseline edema was assessed, with more emphasis in patients with previous whole brain treatment within an interval of 6-13 months. With regard to corticoid therapy, it was given prior to the radiosurgery management.

Peritumoral edema was assessed based on the radiologist physician interpretation prior and after radiosurgery treatment, and was classified in three different grades (0 = no edema, 1 = presence of mild edema, 2 = presence of moderate edema and 3 = presence of severe edema) (Fig. 1).

Radionecrosis evaluation was carried out by assessing the changes at different plain and contrasted sequences by anatomical, dynamical and biochemical MRI with complementary spectroscopy, and in case of doubt about radionecrosis or progression, single-photon emission tomography study with thallium 201 was contemplated.

Data analysis

Statistical analysis was carried out with the GraphPad Prism Version 6.0 statistical package (Trial®) using descriptive statistics. With regard to radioinduced changes on therapeutic target tissue and non-neoplastic surrounding tissue, the distribution was plotted. To determine the association of factors with the presence of radioinduced effects, Spearman's correlation coefficient was used.

Results

BM-diagnosed patients treated with radiosurgery at the Centro Médico Nacional Siglo XXI Oncology Hospital during this study were 15, in a period encompassed between June 2012 and December 2013; three patients were excluded from the study for not being able to carry out an adequate imaging follow-up. Patient characteristics are shown in table 1.

Local control was achieved in 91.7% of patients, with a median progression-free period of 8 months (Fig. 1).

First of all, it is important mentioning that, just owing to the presence of BM lesions, 91.7% of patients had grade 1 and 2 perilesional edema. Radioinduced effects on non-tumor or surrounding tissue found in this study were edema and radionecrosis, which were characterized by complementary anatomical, dynamical

and biochemical MRI. After treatment, 25% of patients had edema symptoms, and treatment with steroids was therefore administered, with only one patient requiring treatment with anticonvulsants.

The presence of post-treatment edema was documented by MRI in 100% of patients, at different grades (Fig. 2), with predominance of grade 2 in 50% of patients and grade 3 in 33%, but only 16.7% of these patients had RTOG classification grade 1-related CNS symptoms²⁶.

Follow-up for longer than 6 months was achieved in 33% of patients, with similar behavior being found at 24 weeks, with radioinduced edema persistence, but no patient had related symptoms at that period. With regard to treatment-associated factors that might intervene with different post-treatment edema grades, the therapeutic target volume, the prescribed dose, as well as BED and V14GY were assessed, with statistical analysis finding a tendency towards a correlation with $BED > 100$ and $V14Gy > 5 \text{ cm}^3$ (as observed in table 2).

Radionecrosis was found to be present in 25% of patients by means of spectroscopy, but no case had data consistent with symptomatic radionecrosis. It is important to highlight that, in two radionecrosis cases, the patients had previously received treatment with whole brain radiotherapy with hypofractionated scheme of 20 Gy in 10 fractions and 30 GY in 10 fractions, 10 and 12 months prior, respectively.

Spectroscopy assessment by biochemical MRI with monovoxel and multivoxel techniques was performed in two patients specifically to assess for tumor persistence and radionecrosis, thus enabling the determination of tumor tissue being present or only edema and radionecrosis changes, as shown in the following cases (Fig. 3).

Discussion

Radiosurgery in the treatment of BM is a palliative treatment option suggested in international guidelines. In the present study, treatment was found to have been carried out in 66.7% of patients as a single modality and in 33.3% after whole brain radiotherapy. The literature has reported 80-90% local control with radiosurgery with radioinduced effects' minimal toxicities, such as edema and radionecrosis in up to 20-40%, with the majority of this percentage being described as asymptomatic in different series with different systems, such as GK or LINAC^{5,10,11}; in the case of the present study, local control of 91.7% was found with the CK system.

Figure 1. Actuarial analysis for progression-free control of patients with radiosurgery treatment.

Figure 2. Images of post-treatment radioinduced effect with T2-weighted and FLAIR sequences. Image **A** corresponds to grade 1 (mild) edema; grade 2 (moderate) edema is observed in image **B**, and in image **C**, grade 3 (severe). In no case was there post-treatment absence of edema.

Radioinduced effects in this study were edema and radionecrosis. Edema as a radioinduced effect was present in 100% of patients, but only 16.7% had symptoms with CNS mild toxicity according to RTOG classification. Edema persisted until week 24 with subsequent gradual reduction, with no clinical impact.

In the assessment of edema as the most common radioinduced effect, a correlation between dose, tumor volume and therapeutic target surrounding tissue volume was observed; in this study, a correlation with $> 5,000 \text{ mm}^3$ volume, BED $> 100 \text{ Gy}$ and V14Gy could be appreciated, but with no statistical significance, probably owing to the nature of the study and to the small number of studied patients.

As previously commented, the edema effect with radiosurgery or with CK could probably be explained by the oxidative stress-mediated damage to the cerebral vascular endothelium, as well as intercellular adhesion molecule 1, E-selectin, interleukin-1 and tumor necrosis factor α expression, which occurs as an acute and subacute effect for up to six months, as described in the study by Chiang et al.²³.

Additionally, in the present study, edema was found in patients beyond six months, with no radionecrosis events being observed in those patients, which may suggest that a single dose could be associated with an early response in some patients, and might explain that the degree of edema is unable to induce apoptosis or

Table 1. Analyzed patients characteristics

Patient characteristics	No. (%)
Gender	M = 2 (16.7), median = 10 (83.3)
Age (years)	27-78 (median = 49)
Primary cancer (histology)	
Breast cancer (luminal [1], Her2/Neu [2], triple negative)	4 (33.4)
Melanoma*	1 (8.3)
Soft tissue sarcoma*	1 (8.3)
Renal cancer*	1 (8.3)
Endometrial cancer*	2 (16.7)
Lung cancer (papillary, adenocarcinoma)*	2 (16.7)
Ovarian cancer*	1 (8.3)
Comorbidity	
Arterial hypertension	2 (16.7)
Diabetes mellitus	1 (8.3)
Other	3 (25)
None	6 (50)
Previous whole brain treatments	
Yes	4 (33.3)
No	8 (66.7)
Number of lesions	
One lesion	10 (83.3)
Two lesions	2 (16.7)
Tumor lesion location	
Supratentorial	11 (91.6)
Infratentorial ^E	1 (8.3)
Tumor volume (mm ³)	
< 5,000	5 (41.7)
> 5,000	7 (58.3)
Prescribed dose	
15 Gy	1 (8.3)
18 Gy	6 (50)
24 Gy*	5 (41.6)
BED	
< 100	8 (66.7)
> 100	4 (33.3)
Isodose curve	76-96% (median = 88)
Conformity index	1.19-1.82 (median = 1.40)
Homogeneity index	1.09-1.32 (median = 1.13)
Maximum point dose (Gy)	
Target tissue (tumor)	18-27 Gy (median = 21.73)
Surrounding tissue (non-tumor)	9-27 Gy (median = 20.8)
V14Gy	median = 23 (4.7-38.6)
< 5 cm ³	5
> 5 cm ³	7

*One patient was managed with a 24-Gy scheme in 3 fractions. ^EOnly one case had localization of high-risk for radioinduced effects with infratentorial lesion location close to the brainstem. No.: number; M: male; F: female; mm³: cubic millimeters; Gy: Grey (unit of radiation absorbed in a body); BED: biologically effective dose; V14Gy: volume of non-tumor tissue receiving 14 Gy of the prescribed dose.

necrosis, as assessed and referred in the study by Sharp et al.²⁷, and probably time should be also considered,

as previously mentioned in the literature, even when there is no previous history of related edema.

Figure 3. **A:** gadolinium-enhanced T1-weighted axial sequence with parietal lobe lesion presence prior to radiosurgery treatment. **B:** post-treatment diffusion sequence with reduction of initial lesion but heterogeneous. **C:** FLAIR-weighted axial sequence with non-circumscribed residual tumor and edema being observed, and assessment with multivoxel spectroscopy technique (**D**) was therefore performed eight weeks post-treatment, where tumor residual was still observed to be 33%, taking into account metabolite ratios such as choline/NAA = 3.7 and choline/Cr = 4.69, as well as data consistent with necrosis by elevation of the lipid curve within the tumor lesion. **E:** presence of non-tumor surrounding tissue with fluid peak elevation consistent with tissue necrosis. Cr: creatinine; NAA: N-acetyl aspartate.

In this study, radionecrosis was found to be present in 25% of patients, and it was relevant to observe the presence of radionecrosis in non-tumor surrounding tissue in one patient since the first eight weeks post-treatment, which is why it's important mentioning that, in this

case, the patient had the following factors: tumor volume > 5,000 mm³, BED = 54 Gy and V14Gy = 38.6 cm³; in addition, the patient had a history of systemic arterial hypertension as a comorbidity. Probably these factors suggest an influence on this early radioinduced effect.

Table 2. Radio-induced edema effect in relation to treatment and patient factors

	Volume < 5000	Volume > 5000	BED < 100	Bed > 100	v14Gy < 5 cm ³	v14Gy > 5 cm ³	Whole brain radiotherapy
R (95% CI)	0.8839	0.7201	0.096	0.4125	0.3227	0.1800	0.5774
p-value	0.1000	0.1429	0.142	0.2000	0.4000	0.1429	0.5000
Significant (alpha = 0.05)	No	No	No	No	No	No	No

Gy = Grey; CI: confidence interval.

Therefore, it is important questioning that early presence of non-tumor surrounding tissue radionecrosis is probably due to exposure with BED doses > 50 Gy, as some authors have already proposed, claiming that doses > 50 Gy increase the induction of lethal damage in normal and tumor tissues. Recently, it has even been suggested that radiosurgery can induce an abscopal effect mediated by immune system cells and that it could also be the cause of larger edema and radionecrosis effect^{28,29}.

In this study, an association of edema and radionecrosis radioinduced effects with factors such as treatment volume, dose, comorbidities and history of previous exposure to ionizing radiation was observed. As regards the influence of other factors, such as chemotherapy treatments and comorbidities such as diabetes mellitus, only a tendency was observed, although in other reports they have been associated with factors that can increase morbidity such as edema and radioinfection³⁰.

However, although in the present study it is only suggested that the V14Gy and BED > 100 factors might be influencing on the presence of edema, there are other recent studies associating V14Gy > 5 cm³ as a predictor of edema and radionecrosis in radiosurgery³¹.

At patient follow-up review cutoff point, 33.3% of them were found to have progression by brain failure (one patient in this group was already receiving whole brain treatment); 8.3% had only systemic progression, and the rest of patients (58.4%) remained stable.

Conclusions

Radiosurgery with the CK system is a safe palliative treatment modality with acceptable local control. Owing to the methodological nature and limitations of the study, post-treatment edema is suggested to have a tendency to correlate with factors such as BED > 100 and V14Gy > 5 cm³. The presence of radionecrosis had

no clinical significance, and it also appears to be associated with total dose, V14Gy > 5 cm³ and comorbidities such as systemic arterial hypertension.

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