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Original research article

CyberKnife Stereotactic Radiosurgery in brain metastases: A report from Latin America with literature review

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ABSTRACT

Background and aim: Stereotactic radiosurgery is increasingly being employed for the treatment of brain metastases, both as an adjuvant to surgical resection, and also as a primary treatment modality. The aim of this study is to evaluate overall survival and local control in patients with brain metastases treated with CyberKnife Stereotactic Radiosurgery (CKRS), due to the lack of evidence reported in Latin America.

Materials and methods: We performed a retrospective chart review from October 2011 to January 2017 of 49 patients with 152 brain metastases. Clinical and prognostic factors were further analyzed by independent analysis. Kaplan–Meier curves were constructed for overall survival and local control. The median follow-up period was 12 months (range, 1–37 months).

Results: The median age was 61 years (range, 27–85 years) and Karnofsky performance status >70 in 96% of the patients. The median overall survival rate was 15.5 months (95% confidence interval [CI], 10.23–24.3 months). Overall 3-month, 6-month and 1-year local control rates were 98% (95% CI, 85–99%), 96% (95% CI, 82–99%), and 90% (94% IC, 76–96%), respectively. Local failure (LF) was observed in 6 patients (18 lesions). No late complications, such as radiation necrosis, were observed during the follow-up period.

Conclusions: CKRS achieves excellent overall survival and local control rates with low toxicity in patients with brain metastases.

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1. Background

Brain metastases (BMs) are the most common forms of intracranial tumor, occurring in approximately 20–40% of all cancer patients.[1,2] Causing a significant impact on morbidity and mortality with a median survival of untreated patients being 1–3 months.[3] Treatment options for BMs include surgical resection, whole-brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS).[4]

WBRT has been used for decades as a standard therapy for BMs. Currently, its use is debatable, as although greater distant brain control rates are observed, there is no impact on survival and the effect on patient's cognition and quality of life could overweigh potential benefits.[5] Randomized trials have demonstrated improved local control and quality of life when using SRS alone or in combination with WBRT, particularly in those with a single metastasis regardless of recursive partitioning analysis (RPA) and those with RPA Class 1 with up to three metastases.[5–8]

The CyberKnife system has proven to achieve all the goals of radiosurgery by delivering high, ablative radiation dose with maximal dose fall-off outside the treatment volume with a frameless sub-millimeter accuracy. Although CyberKnife Stereotactic Radiosurgery (CKSRS) for brain metastasis is a common practice, few data exist regarding this technique's efficacy, safety, and optimal patient selection.[9–12]

2. Aim

Stereotactic radiosurgery is increasingly employed for the treatment of brain metastases, both as an adjuvant to surgical resection, and as a primary treatment modality. The aim of this study is to evaluate the local control of disease and overall survival in patients with brain metastases treated with CyberKnife Stereotactic Radiosurgery (CKRS) and review the published data.

3. Materials and methods

3.1. *Study design*

Using a retrospective cohort design, we reviewed 49 patients (corresponding to the authors) with brain metastases of any primary tumor treated with stereotactic radiosurgery at the Christus Muguerza Hospital Alta Especialidad from October 2011 to January 2017. Collected data included gender, age, Karnofsky Performance Scale (KPS), primary site of the tumor, recursive partitioning analysis (RPA) class, number and location of brain metastases, previous local treatment (surgery or WBRT), dosimetry, prognostic index of graded prognostic assessment (GPA) and diagnosis-specific GPA.

3.2. *Radiosurgery characteristics*

All treatments were delivered using the CyberKnife Frameless Radiosurgical System (Accuray, Sunny-vale, CA, USA). A high resolution computed tomogram (CT) was obtained followed by a magnetic resonance imaging (MRI) to fused images for target identification. Dose planning was performed with the Multiplan Software (Accuray Inc., Sunyvale, CA, USA). The gross tumor volume (GTV) was delineated as the edge of contrast enhancement and was considered the same as clinical target volume (CTV). The planning target volume (PTV) was defined as CTV plus a 2 mm margin.

The prescription dose and fractionation were decided following the RTOG 90-05 guidelines and the preference of the treating physician according to radio-sensitivity of the primary tumor, tumor volume, tumor location and distance from critical structures. The treatment volumes were prescribed to a medium 86% isodose line (range 78–90%).

3.3. *Follow-up*

Follow-up, including physical evaluation and gadolinium-enhanced MRI, were performed 3 months after SRS and every 3 to 6 months thereafter until the death or the date of closure of the study (January 2017). Follow up information was available for 42 patients. The median follow-up period was 12 months (range, 1–37 months).

3.4. *Statistical methods*

Overall Survival (OS) rate was the primary endpoint, secondary endpoints included Local Control (LC) and Distant Brain Control (DBC). Data analysis was performed using STATA version 14.2 (StataCorp LCC, TX, USA). LC was defined as a stabilization or reduction of the tumor and "contrast enhancement" on MRI, and DBC as the absence of new brain metastases or leptomeningeal disease outside the radiosurgical target volume. Kaplan–Meier rates for OS were calculated from the date of CKSRS to the date of patient's last follow up clinic visit or death. Patients who received salvage treatment with new SRS or WBRT where followed up for survival and toxicity.

Patients were classified according to the GPA and diagnosis-specific GPA. The log-rank test was used for univariate analysis to assess predictive factors associated with OS. Estimated hazard ratios (HRs) were calculated. A P value <0.05 was considered statistically significant. Statistical test was based on a 2-sided significance level. The following clinical factors were investigated for their association with OS: age, gender, Karnofsky, GPA Score, RPA Class, number of metastases, extracranial disease, prior WBRT and tumor volume.

4. Results

4.1. *Patient characteristics*

Forty-nine patients with 152 brain metastases were identified, with a median age of 61 years (range, 27–85 years) and Karnofsky performance status >70 in 96%. The most frequent primary tumor type was the lung cancer (48%) followed by the breast cancer (12%) and melanoma (10%). Patient's characteristics are summarized in Table 1 and diagnosis-specific GPA in Table 2.

Fifteen patients had received prior local treatment including WBRT, surgery or both. Nine patients had received surgery as a primary treatment, of which 5 patients received adjuvant SRS to the resection cavity and 4 patients as salvage therapy

Table 1 – Patients characteristics.

Characteristics	No. patients (%)	Median (range)
No. patients	49	(152 BMs)
Male	29 (59)	
Female	20 (41)	
Age (years)		61 (27–85)
KPS		90 (60–100)
RPA		
I	10 (20)	
II	37 (76)	
III	2 (4)	
Primary site		
NSCLC	22 (46)	
SCLC	1 (2)	
Breast	6 (12)	
Melanoma	5 (10)	
Thyroid	3 (6)	
Colon	2 (4)	
RCC	2 (4)	
Bladder	2 (4)	
Others	6 (12)	
Prior WBRT	6 (12)	
Prior surgery	7 (14)	
Prior WBRT and surgery	2 (4)	
SRS alone	34 (69)	

KPS: Karnofsky performance status; RPA: recursive partitioning assessment; NSCLC: Non-Small Cell Lung Cancer; SCLC: Small Cell Lung Cancer; RCC: renal cell carcinoma; WBRT: whole brain radiotherapy.

Table 2 – No. patients by diagnosis specific-GPA.

Primary tumor	0–1.0	1.5–2.0	2.5–3.0	3.5–4.0	No. total
NSCLC	7	5	9	1	22
SCLC	0	1	0	0	1
Breast	0	1	3	2	6
Melanoma	1	1	1	2	5
RCC	1	1	0	0	2
GI cancer	0	3	1	0	4
Others	2	4	2	1	9
Total	11	16	16	6	49

NSCLC: Non-Small Cell Lung Cancer; SCLC: Small Cell Lung Cancer; RCC: renal cell carcinoma; GI: gastrointestinal.

to local recurrence; median duration between surgery and SRS was 32 days (range, 24–45 days) and 11 months (range, 5–26 months), respectively.

The treatments were delivered in 81% of cases in a single fraction, 15% in three fractions, 3% in five fractions and only one patient received four fractions. In patients receiving multifraction treatments, the interfraction interval was 24 h. Patients received 8 mg dexamethasone immediately after each fraction. Treatment characteristics are summarized in Table 3.

4.2. *Overall survival*

The median overall survival rate was 15.5 months (95% confidence interval [CI], 10.23–24.3 months). By the end of follow-up, 25 of 49 patients had died. Overall 3-month, 6-month and 1-year survival rates were 89%, 84% and 62%, respectively. The median survival times for RPA classes 1, 2 and 3 were 24 (95% CI, 6.4–24 months), 15 (95% CI, 9.7–22 months) and 3 (95% IC, 2.46–6.4 months) months, respectively (*P* value = 0.44) (Fig. 1A and B).

Table 3 – Treatment characteristics.

Characteristics	Number (%)	Median (range)
Brain metastases	152	
Brain metastases/patient[a]		
1	26	
2	12	
3	6	
4	2	
5	2	
6	2	
>7	6	
Location of lesions		
Frontal lobe	27 (18)	
Parietal lobe	49 (32)	
Temporal lobe	21 (14)	
Occipital lobe	24 (16)	
Cerebellum	29 (19)	
Others	2 (1)	
Tumor volume (cc)		6.71 (0.036–49.68)
Fraction (No. lesion)/dose (Gy)		
1 (126)		20 (13–24)
3 (22)		22 (18–27)
4 (1)		23.5 (–)
5 (3)		26 (22.5–30)

[a] 3 patients received multiple courses of radiosurgery.

Results of univariate analyses are shown in Table 4, no factor was found to be a statistically significant predictor of OS, so we did not perform a multivariate analysis.

4.3. *Local control and distant brain control*

The median overall local control for all patients was 7.4 months (95% CI, 0.43–12.57 months). Overall 3-month, 6-month and 1-year local control rates were 98% (95% CI, 85–99%), 96% (95% CI, 82–99%), and 90% (94% IC, 76–96%), respectively. Local failure (LF) was observed in 6 patients (18 lesions). A sub-analysis of patients stratified by dose (≤20 Gy and >20 Gy) demonstrated a median local control of 6.9 months (95%, 6.9–24.8) and 7.3 months (95% CI, 4.3–12.56), respectively (*P*-value = 0.5214) (Fig. 1C).

New metastases outside the radiosurgical target volume were observed in 12 patients in 43.6 weeks of median follow-up. Among them, 3 patients (10 lesions) were treated by salvage CKSRS, out of whom 2 failed locally and died. The remaining patient had local and distant brain control after the second CKSRS. The median time between radiosurgery and the detection of new intracranial lesion was 6.6 months (range, 1–15 months). The other 9 patients received salvage WBRT (4 patients) and palliative treatment (5 patients).

We evaluated a total of 1113 person-months for DBC and we observed 11 events of failure, which was not enough to evaluate the median time to event. Hence, the 25th percentile of distant brain control was 24.8 months. Although no factor was statistically significant for predicting DBC, the number of brain metastases at the time of SRS showed a trend for decreased distant brain control rate from 24.8 months (≤3 lesions) to 9.8 months (>3 lesions). (Fig. 1D).

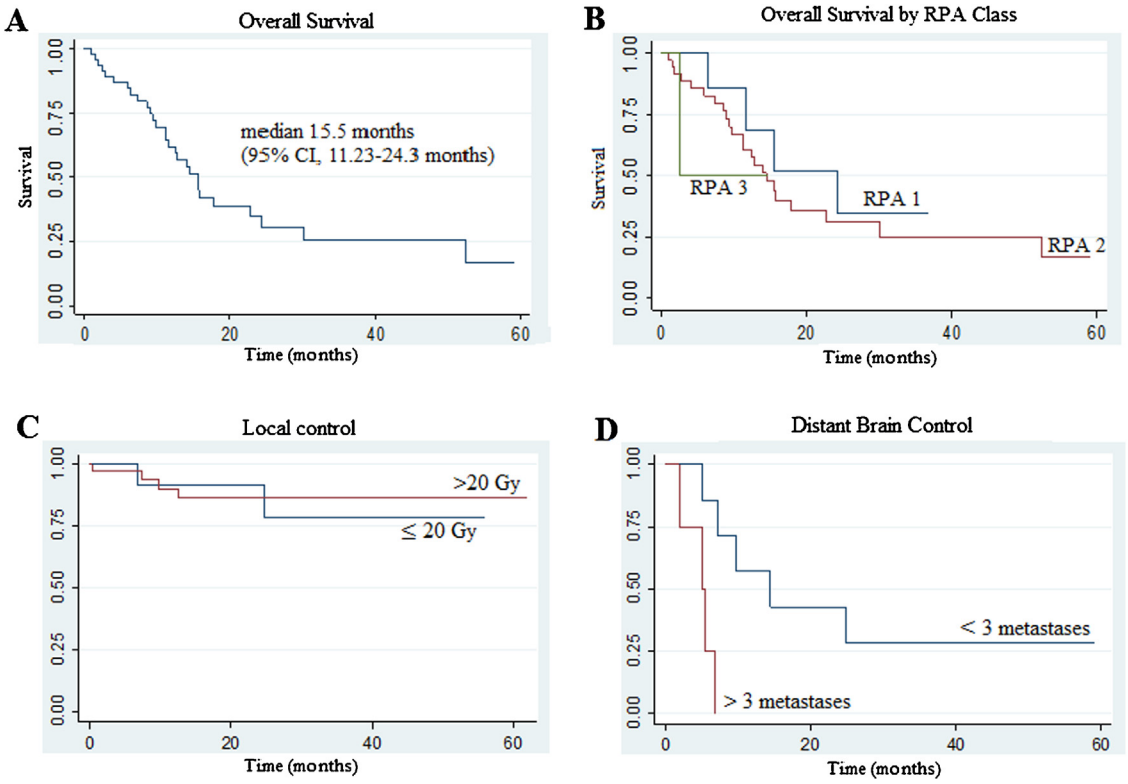

Fig. 1 – Outcomes. (A) Kaplan–Meier analysis of overall survival after CyberKnife Stereotactic Radiosurgery. (B) Survival rates by recursive partitioning analysis (RPA) class. (C) Local control rates by average dose and (D) distant brain control by number of metastases at the time of treatment.

Table 4 – Univariate and multivariate analysis of factors associated with overall survival.

Characteristic		Univariate *P*-value[a]	Univariate	
			Hazard ratio	[95% conf. interval]
Age	>70 years old	0.4022	0.7	0.31–1.61
Sex	Male	0.8393		
Karfnosky	>70	0.6757	0.73	0.17–3.17
GPA Score	1.5–2.5	0.4313	1.65	0.47–5.79
	3.0–4.0	0.2654	1.44	0.75–2.79
RPA class	Classes 2 and 3	0.4422	1.51	0.52–4.40
Number of lesions	>3	0.4823	0.72	0.29–1.79
ESD	Yes	0.0658	2.28	0.92–5.66
Dose average	>20 Gy	0.6338	1.22	0.53–2.79
Prior WBRT	Yes	0.5679	0.76	0.28–1.99
Average volume	>3000 mm^3	0.6284	1.2	0.57–2.55

[a] log-rank test.
ESD: Extracranial Systemic Disease; GPA: graded prognostic assessment; RPA: recursive partitioning assessment; WBRT: whole brain radiotherapy.

4.4. *Toxicity*

None of the patients had grade 3 or higher toxicity according to the Radiation Therapy Oncology Group criteria. No late complications, such as radiation necrosis, was observed during the follow-up period.

5. Discussion

SRS has become a standard treatment modality for single and multiple brain metastases allowing to perform multicenter protocols and investigate whether this technique should partly or wholly replace surgery or other forms of irradiation.

Table 5 – Review of reports of CyberKnife Stereotactic Radiosurgery for brain metastases.

Author (year)	*n* Patients	*n* BMs	Dose, Gy (fractionation)	Local control (time)	Overall survival
Shimamoto[27] (2002)	48	77	9-oct (not referred)	80% (6 m)	Not referred
Nishizaki[9] (2006)	71	148	7.8–30.1 (1–3 fx)	83%	56 weeks
Soltys[30] (2008)	72	76 (cavities)	15–30 (1–5 fx)	86% (crude)	15.1 months
Hara[10] (2009)	62	145	14–24 (1 fx)	87% (12 m)	8.3 months
Wang[12] (2009)	40	68	18–36 (1–5 fx)	94.10% (3 m)	97.50% (3 m)
Wowra[28] (2009)	63	63	17–22 (1 fx)	95.20% (12 m)	Not referred
Muacevic[11] (2010)	333	783	17–22 (1 fx)	95% (12 m)	12.2 months
Choi[31] (2012)	97	152 (BM + cavities)	15–27 (1–5 fx)	91.70% (12 m)	15.6 months
Inoue[32] (2013)	145	159	27–30 (3 fx)	95.80% (7 m)	Not referred
Tamari[33] (2015)	67	109	18–36 (1–3 fx)	83.30% (12 m)	13.1 months
Borzillo[34] (2015)	116	178	oct-25 (1–5 fx)	[a]	[a]
Shultz[18] (2015)	95	652 (BM + cavities)	16–30 (1–5 fx)	95% (12 m)	18 months
Current study	49	152	13–30 (1–5 fx)	90% (12 m)	15.5 months

[a] Local control rate and overall survival classified by Specific Diagnosis GPA Score.

Survival benefits using SRS alone have shown mixed results, with many trials failing to demonstrate an increase survival rate when compared to SRS plus WBRT,[6,13–15] whereas Chang et al.[16] suggests an advantage for SRS alone. WBRT independently compromises neurocognition and quality of life (QOL) outcomes, and some authors postulate that the decline of QOL can affect negatively the survival result.[16,17] Deferral of WBRT by using SRS alone or even multiple courses of SRS for distant brain failure yields high local control, low toxicity and favorable duration of overall and neurologic survival.[18]

In the absence of a difference in overall survival and less cognitive deterioration, we selected a group of patients to receive CKSRS to newly diagnosed BMs and salvage treatment after WBRT or surgery. Our results demonstrated great OS rates (median 15.5 months), despite the low number of patients and despite the fact that 41% of our cases can be considered unfavorable patients (size >4 cm and >3 BMs). In our univariate analysis to assess the impact of prognostic factors in OS, such as age, Karfnosky, RPA Class, GPA Score, number of brain metastases and extension of systemic disease, among others, with no factor found to be statistically significant, probably due to the small size of the sample. However, several studies have shown that survival may be independent of the number of metastases and RPA; furthermore, systemic disease and histology may play a larger role in determining survival.[19–21]

Local control outcomes using SRS for a single brain metastasis have shown to be roughly equivalent to surgical resection. Madawala et al. reported their result comparing radiosurgery alone or postoperative radiosurgery for 1–3 metastases, concluding that the overall local tumor control rate was similar in both groups (87% and 90% respectively) and that the SRS dose was an important factor for tumor control rate in the SRS-alone group.[22] The evidence-based guideline state that either surgery or radiosurgery may be considered and selected in patients with more than one lesion who may be treated with radiosurgery alone.[23] Our 90% 1-year local control rate using SRS alone confirms that this technique provides excellent results for BMs patients. In an early study by Shimamoto et al., CKSRS showed to be an effective technique for BMs and recommended a dose of at least 24 Gy to achieve complete response.[24] During our study we escalated the dose from 18–20 Gy to 24 Gy in 1 fraction in lesions less than 3 cm, and fractionated scheme in patients with lesions greater than 3 cm depending on the irradiated brain volume. We performed a sub-analysis to evaluate the difference in local control outcomes in patients receiving more than 20 Gy than those receiving 20 Gy or less, showing an insignificant difference between the results (7.3 and 6.9 months, respectively).

The number of lesions and the tumor size that can be effectively treated with SRS alone is not well defined. A recent large study (JLGK0901) of 1194 patients suggest that overall survival and distant brain failure using SRS alone in patients with 5–10 is non-inferior to that in patients with 2–4 BMs, constituting a suitable alternative for patients with up to ten brain metastases.[25] In a meta-analysis performed by Sahgal, concluded that the initial omission of WBRT in patients <50 years old with multiple brain metastases did not adversely impact distant brain relapse rates.[26] We observed that patients presenting less than 3 metastases had a favorable survival and lower risk of distant brain failure than patients with 4 or more metastases, although this results did

not achieve statistical significance due to the limited sample size.

Nishizaki et al. evaluated the role of CKSRS for multiple or large size brain metastases, concluding that in an unfavorable patient population the results of survival and tumor local control rates were comparable to those of other published series and that this technique provides the advantage of allowing fractionated treatments for multiple or large-size tumors.[9] More recently, a series of reports have found that CKSRS provided excellent local control rates for radioresistant lesions (e.g., melanoma and renal cell) and may allow WBRT to be omitted in the initial treatment regimen.[10–12,27,28]

The majority of the series reported of SRS performed using the GammaKnife or LINAC system.[29] However, the CyberKnife design coupled with real-time imaging have improved accurate target localization and dose delivery for brain tumors allowing higher biologically effective dose delivery without increased incidence of toxicity. A review of published studies on CyberKnife radiosurgery for brain metastases are summarized in Table 5. Our report is an addition to the previously reported series of the use of CKSRS in brain metastases and, to our knowledge, the first report in Latin America.

This study is not free of limitations. The sample size and restricted follow-up limited the statistical power of our study. As we collected data from hospital records, there is a chance of selection bias. Despite multivariable adjustment, unmeasured confounding is likely to exist and further studies, including a bigger sample size, should be performed to allow adjustment for other confounders such as histologic subtype, GPA and other prognostic factors.

6. Conclusion

CKSRS is an effective, noninvasive, frameless, therapy in the management of brain metastases. This technique provided excellent overall survival and local control rates with low toxicity. Despite the not inconsiderable number of lesions treated with CKSRS, the number of patients is still too small to make an optimal feedback. This data encourage us to enroll patients for this treatment when appropriate.

Conflict of interest

None declared.

Financial disclosure

None declared.

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