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Research paper

Outcomes of single brain metastasis treated with gamma knife stereotaxic radiosurgery(GKSR). Our experience on 103 cases☆

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ABSTRACT

Background: Brain metastases (BM) occur in the natural course of malignant tumors in 18–40% of cases. Their management has changed considerably over the past decade thanks to the advent of Gamma knife Stereotactic Radiosurgery (GKSR).
Objective: We report our experience on Single Brain metastasis treated with (GKSR).
Methods: Patients treated by Gamma Knife stereotaxic radiosurgery (GKSR) in our institution between 2009 and 2021 for Single BM were recorded retrospectively.
Results: A total of 103 patients (n = 52; 50.5% females) were included, with a mean age of 56.33 ± 11.33. Breast (n = 39, 37.9%) and lung (n = 36, 35%) were the common original location for the primary tumors. GKSR alone without prior surgery, radiotherapy, or chemotherapy was achieved in 81.5% (n = 84). Thirteen patients (15.1%) progressed in BM volume while finding the appearance of de novo BM in 5 (5.8%) patients. The median percentage of tumor control after radiosurgery treatment was 70% (IQR: 65–78) and only 26.2% (n = 27) of patients had > 80% tumor control and stability over the median follow-up time of 5 (95% CI, 4–6) months. We found only two cases of radionecrosis (1.9%). The median survival time was 5.21 (IQR, 3–8) months. Retreatment, recursive partitioning analysis (RPA) class, and tumor stability influenced the overall survival of BM respectively (Hazard Ratio adjust (HRa)= 5.610,p = 0.045; HRa= 6.133,p = 0.031; HRa= 22.463, p = 0.036).
Conclusion: Stereotaxic Radiosurgery provides good results in terms of Overall survival with fewer neurocognitive disorders.RPA class and tumor control (stability) influenced the overall survival of single BM.

1. Introduction

Brain metastases (BM) occur in the natural course of malignant tumors in 18–40% of cases. They most often affect the posterior cerebral fossa, particularly the cerebellar hemispheres (80%) (Nayak et al., 2012; Trifiletti et al., 2017).

Gamma knife stereotactic radiosurgery (GKSR) is now considered a treatment of choice for the management of patients with a limited number of brain metastases (Patel et al., 2018; Kocher et al., 2014; Mehta et al., 2005; Whole brain radiation, 2022). It is usually offered for small BM (<2 cm3 or between 2 and 5 cm3). Nowadays due to the stages of radiation, large (>10 cm3) brain metastases (BM) could benefit from Stereotactic radiosurgery(SRS) in stages to improve tumor control and reduce radiation damage (Yomo et al., 2012; Serizawa et al., 2005; Higuchi et al., 2009; Ito et al., 2020).

It has been reported previously that patients who received resection and whole-brain irradiation had improved survival when compared with those who received whole-brain irradiation only, suggesting that

Abbreviations: BM, Brain metastasis; GKSR, Gamma Knife stereotactic radiosurgery; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy; RPA, recursive partitioning analysis; HR, Hazard Ratio; HRa, Hazard Ratio adjust.

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radiotherapy plus surgery improves local control and survival (Andrews et al., 2004; Noordijk et al., 1994; Patchell et al., 1990). Besides, SRS was able to achieve the same goals but did not improve the overall survival rate (Fernandez-Vicioso et al., 1997).

However, the management of BM has changed considerably over the past decade, with the availability of specific treatments that further improve the quality of survival and mitigate the side effects of treatment (Arvold et al., 2016). Improvements in systemic therapies are prolonging the survival of patients with brain metastasis (Kohler et al., 2011), but when brain tumors are treated with whole-brain radiation therapies (WBRT) the risk of experiencing major neurocognitive disorders is greater. Thus, to avoid such toxicity issues, GKSR alone has been advocated in patients with a better prognosis and a limited number of metastases (Sneed et al., 1999, 2002). Two randomized studies have revealed that such patients (populations with either one to three or four lesions) receiving SRS alone had similar survival to patients who received WBRT and SRS (Sneed et al., 1999, 2002; Aoyama et al., 2006; Chang et al., 2009).

Also, a series of meta-analyses of randomized controlled trials of WBRT and SRS confirmed that WBRT did not significantly improve overall survival in patients with a limited number of brain metastases (up to four) (Tsao et al., 2012); however, WBRT+SRS allowed significantly better local control and reduced the rate of distant brain metastasis (Tsao et al., 2012). In contrast, patients treated with SRS alone have a higher rate of local recurrence and distant brain metastasis compared with patients treated with WBRT +SRS, However, repeated retreatment with SRS alone allows retreatment of local recurrence and distant brain metastasis with preservation of neurocognitive function (Tsao et al., 2012).

Regarding neurocognitive and performance outcomes, studies have shown a considerable improvement in the preservation of neurocognitive function and performance status in patients treated with SRS alone compared with WBRT and SRS (Chang et al., 2009; Tsao et al., 2012; Aoyama et al., 2007).

We aimed to evaluate the outcomes of single brain metastasis after being managed by a Gamma Knife stereotactic Radiosurgery (GKSR) in our institution. We reviewed the preoperative metastasis characteristics, the primary tumor location whether controlled or not, post-SRS course (clinical and radiological follow-up), and survival data on our monocentric series of patients that had undergone GKSR, with whether the location of the primary tumor was controlled or not, or received before surgery or Radiation for the single BM.

2. Methods

2.1. Ethics statement

The data collected during the study have been stored in a computer file following the law of the Morocco Data Protection, Decree n° 2–09–165 of May 21, 2009. Ethics approval and consent to participate was not applicable: Only projects, questions of a general nature or relating to a trial, experiment or biomedical study relating to human beings examined. Ethics Committee of our institution.

2.2. Study population

This retrospective single institutional review of patient data was done at a single academic institution. All patients diagnosed with single brain metastasis and primary tumor between 2009 and 2021 and treated with Lecksell Gama knife stereotactic radiosurgery (GKSR) in the radiosurgery unit of the national center of rehabilitation and neuroscience of Rabat-Morocco were screened for inclusion.

Patients without brain metastasis (BM), BM patients treated only surgically, BM patients lost to follow-up, BM's with clinical and imaging follow-up less than 3 months, and patients with multiple BM were excluded.

The protocol for follow-up at our institution includes an every 3 months assessment after GKSR treatment by MRI.

2.3. Data acquisition and study outcomes

Sociodemographic data (i.e, age, gender), date of management, Karnofsky clinical state, primary tumor type, radiological data (location, size), treatment modality (radiation dose, volume treated), outcomes, and clinical imaging follow-up were extracted retrospectively from the patient's health files.

The primary outcome is to evaluate the outcomes of single brain metastasis after being managed by Radiosurgery Gamma knife. The secondary outcome was to establish if patients receiving chemotherapy or radiotherapy or surgery before GKSR, the volume progression after GKSR, or the type of RPA class influences the Overall Survival.

2.4. Operational definition of terms

Brain metastasis characteristics were recorded from pre-and post-treatment Magnetic resonance imaging (MRI).

A Leksell model G stereotactic frame was attached to the patient's head via four-pin sites by a neurosurgeon and MRI with gadolinium contrast was obtained with the head frame in place (Gamma Knife Surgery, 2021). The MRI was loaded into the GammaPlan system and the tumor was then outlined. Treatment planning focused on maximizing coverage and conformality. Of note, single Brain metastases without cerebral edema, no brain shift, and, KPS $\geqslant$ 70 were treated with GKSR, also, steroids were given systematically at 120 mg/day of methylprednisolone for patients and decreased progressively within two weeks after GKSR. This indication was retained after a concertation meeting between a dedicated neuro-radiologist, neurosurgeon, radiation oncologist, neuro-oncologist, and medical oncologist.

A neurosurgeon, a radiation oncologist, and a medical physicist approved the plan. The dose prescribed depends on the type of treatment, whether single-dose or staging dose. Following GKSR for brain metastases, patients are typically followed with clinical examination and MRI every 3 months, and imaging is reviewed by a dedicated neuro-radiologist, neurosurgeon, radiation oncologist, neuro-oncologist, and medical oncologist, when appropriate. We define local tumor progression as an increase in tumor volume of more than 10% (Snell et al., 2006). In this study, tumors that were unchanged or smaller on follow-up MRI were considered to be locally controlled and stable, also tumor volume was calculated by determining the contours of the tumor on a slice-by-slice. We define the controlled $<$ 50% of the initial volume treated by GKSR, or between 50% and 80%, or $>$ 80%. Of note, the patient who benefited from WBRT, or chemotherapy before GKSR was considered as salvage boost therapy because the single BM wasn't responded to the WBRT or chemotherapy first.

In cases of uncertainty regarding tumor progression (versus, for example, radiation necrosis) MRI perfusion sequences and/or metabolic imaging is used. Radionecrosis was determined on the basis of either MRI/MR perfusion or functional imaging (i.e. positron emission tomography) scan results (Trifiletti et al., 2017). In addition, the indication for retreatment was taken in a concertation meeting between a dedicated neuro-radiologist, neurosurgeon, radiation oncologist, neuro-oncologist, and medical oncologist, and the patient being retreated by GKSR after being treated before by GKSR if the local control was $<$ 50%, or the BM volume was progressed and increased than initial volume, or the appearance of De Novo BM during the follow-u periods, and no important edema or symptomatic edema on MRI, however, the bolus of methylprednisolone 24 h before and the same days of treatment was used.

The recursive partitioning analysis (RPA) (Gaspar et al., 2000) classification was used to study the correlation between the initial clinical status and the outcomes and follow-up results.

2.5. Statistical analysis

Statistical analyses were performed with Excel and SPSS v. 26 (IBM, USA).

Gender, Karnofsky status, type of treatment type of primary tumor, and outcomes were coded as categorical variables. In contrast, age, follow-up time, and events (RPA class, progression, retreatment, alive, death) were coded as continuous variables.

Descriptive statistics were used to present patient characteristics through mean with its standard deviation for normally distributed quantitative variables, median with extremes for non-normally distributed quantitative variables, and proportion as a percentage for qualitative variables.

Kaplan-Meier table life method was used to estimate the overall survival rates, the median, and the interquartile range (IQR) survival time. Mantel-Cox test (log Rank) was employed to assess the equality of survival time in different sub-group of patients. Univariate and multivariate Cox proportional hazard regression models were performed to define independent predictors of survival.

Known predictor variables not statistically significant in univariate analysis were forced to enter the multivariate analysis. Patient characteristics with a Hazard Ratio (HR) > 1 and with an alpha value < 0.05 were defined as independent prognostic factors on overall survival (OS).

3. Results

3.1. Patients characteristics

Among 293 brain metastasis, 103 (35.15%) single brain metastases patients (BM) were included. 170 (58.02%) were excluded because they were multiple brain metastasis, and 20 (6.8%) were lost to follow-up.

A total of 103 patients (50.5% females) were included, with a mean age of 56.33 ± 11.33 (Table 1). Breast (n = 39, 37.9%) and lung (n = 36, 35%) were the common original location for the primary tumors (Fig. 1).

Parietal and cerebellar respectively (n = 12, 30%; n = 12, 30%) were the common location for breast tumor metastasis, cerebellar and occipital for lungs respectively (n = 22,61%; n = 7,19.4%), and other tumors metastasis respectively (n = 5, 21.7%; n = 5, 21.7%) (Fig. 2).

More than half of the patients (n = 54; 52.4%) had a BM volume ⩾ of 10 cm3, and most (n = 60;60%) had an RPA class I score (Table 1). GKSR alone without prior surgery, radiotherapy, or chemotherapy was achieved in 81.5% (n = 84) of our cases. Seventeen patients (16.5%) had surgical removal of their Single BM, and 19 patients (18.4%) were treated with chemotherapy or radiotherapy before SRS treatment as boost salvage therapy (Table 1). The primary tumor was controlled in 85.16% of cases (n = 63) (Table 2).

Eighty-seven patients (84.5%) were treated with a median single dose of 20 Gy (IQR:14–29), and 16 patients (15.5%) in two-stage with a median dose of 14 Gy (IQR:10–23) for each staging. Thirteen patients (15.1%) progressed in BM volume while found the appearance of de novo BM was in 5 (5.8%) patients. The median percentage of tumor control after radiosurgery treatment was 70% (IQR: 65–78) and only 26.2% (n = 27) of patients had > 80% tumor control over the median follow-up time of 5 (95%CI, 4–6) months (Table 1).

Eight patients (8.7%) retreated with a mean dose of 22.00 ± 2.131 Gy for a median progression or de novo volume of 8.86 cm3 (IQR:2–20 cm3) over the median follow-up time of 5 (95%CI, 4–6) months (Table 1). Only two cases (1.9%) presented radionecrosis after being treated by radiosurgery as salvage boost treatment because they received before WBRT with no response.

Globally, 7.5% (n = 6) of the patients had died from their BM (neurological causes with neurocognitive disorders), and 92.5% (n = 74) of the patients had died of different neurological causes.

Seven patients still survived with an mRS between 2 and 3 after a mean follow-up time of 5 months (IQR:3–84 months) (Table 1).

There were 45 deaths (56%) over the median follow-up time of 5 (95%CI, 4–6) months. In all patients, the 1-year OS rate was 28.7% (n = 25), the 2-year OS rate was 20.7% (n = 18), and 5-years OS was 17.2% (n = 15)(Fig. 3). The median survival time was 5.21 (IQR, 3–8) months. Survival time was different according to the retreatment of BM (p = 0.04) (Fig. 4).

Table 1
Patient characteristics.

Characteristics	Frequency
Age, years (103)	56.33 ± 11.33
Sex	
Male	51 (49.5)
Female	52 (50.5)
Primary tumor sites(%)	
Breast	39 (37.9)
Lung	36 (35.0)
Other sites	23 (22.3)
Volume of metastasis (cm^3)	10.70 (0.90–92.00)
≤ 5	21 (20.4)
5–10	28 (27.2)
≥ 10	54 (52.4)
Surgery before GKSR	17 (16.5)
Radiotherapy or chemotherapy before GKSR	19 (18.4)
Single Dose SRS (Gy)	20 (14–29)
< 18	19 (18.5)
18 – 24	58 (56.3)
> 24	26 (25.2)
Staging Dose GKSR(Gy)	14 (10–23)
Type of SRS GKSR Dose(%)	
Single Dose	87 (84.5)
2 Stages	16 (15.5)
Volume Progression [86]	13 (15.1)
De novo BM [86]	5 (5.8)
RPA (100)	
Class 1	60 (60.0)
Class 2	35 (35.0)
Class 3	5 (5.0)
Percentage of control [96]	70 [65–78]*
< 50	26 (25.2)
50–80	43 (41.7)
> 80	27 (26.2)
Length of follow-up (months)	5 (3–84)
Retreatment	8 (7.8)
Dose	22.00 ± 2.131
Tumor volume (cm3)	8.86 (2.00–20.00)
Outcomes [87]	
Death	80 (92.0)
Neurological causes (neurocognitives disorders,dying from BM)	6(7.5)
Non-neurological causes	74(92.5)
Alive (mRs between 2 and 3)	7 (8.0)

* Median with its confidence interval at 95%, range: 20–99

3.2. Prognostic factors

On Univariate analysis, the overall survival rate was impacted by retreatment (p = 0.013). Patients who did not undergo retreatment were at a 3.266 (CI 95% 1.282–8.323) risk of dying. Other patient characteristics include prior brain surgery to GKSR (p = 0.295), prior radiotherapy or chemotherapy (p = 0.627), primary tumor type (p = 0.286), RPA classification (p = 0.187), and tumor volume (p = 0.766) did not impact on the OS rate in this cohort (Table2).

On multivariate analysis, patients who did not undergo retreatment (HRa=5.610, 1.042–30.194), presented no stable BM (HRa=22.463 (1.220–413.442), classified RPA Class 2 or 3 (HRa=6.133, 1.183–31.792) were at high risk of dying. Thus, retreatment, RPA class, and tumor stability (control) influenced the overall survival of BM (Fig. 4). The results of the Cox regression analysis are presented in (Table 2).

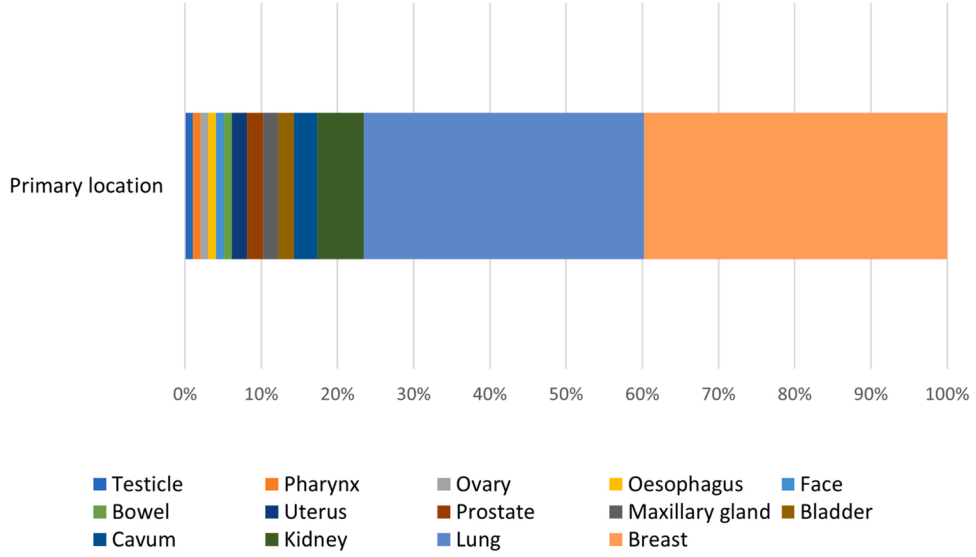

Fig. 1. Primary tumor location in the overall population.

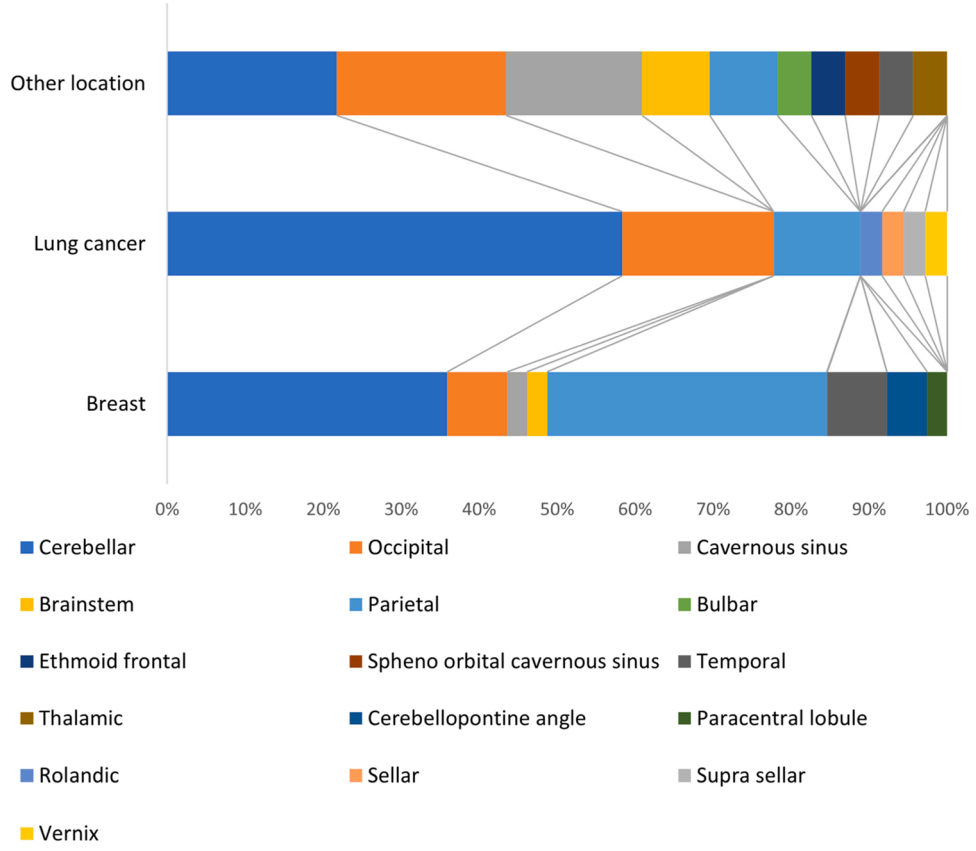

Fig. 2. Location of Brain metastasis according to their original location.

4. Discussion

In this current study, we found that the breast and lungs were the common locations for primary tumors. The primary tumors were locally controlled before GKSR for the single BM in 85.16% (n = 63) of cases. Fifty-four patients (52.4%) had a BM volume ⩾ of 10 cm3, and 60% of the patient were classified as RPA class I.

GKSR alone without prior surgery, radiotherapy, or chemotherapy was achieved in 81.5% (n = 84) of our cases. The single dose of GKSR was the most option (84.5%). Patients presented instability by progression in BM volume after treatment in 15.1% of cases, while the appearance of de novo BM was in 5 (5.8%) patients. The median percentage of tumor control after radiosurgery treatment was 70% (IQR: 65–78) and only 26.2% (n = 27) of patients had > 80% tumor control over the median follow-up time of 5 (95%CI, 4–6) months. Globally, 7.5% (n = 6) of the patients had died of neurological causes and 92.5% (n = 74) of the patients had died of different neurological causes. Seven patients still survived with an mRS between 2 and 3 after a mean follow-

Table 2
Univariate and Multivariate analysis.

Variables	N (%)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*p*	HRa (95% CI)	*p*
Sex					
Female	45 (56.96)	Reference		Reference	
Male	34 (43.04)	1.148 (0.717–1.838)	0.565	0.836 (0.287–2.434)	0.742
Age (years)					
< 50	23 (29.11)	Reference		Reference	
50–65	37 (46.84)	0.853 (0.493–1.476)	0.570	1.180 (0.523–2.611)	0.690
≥ 65	19 (24.05)	0.941 (0.496–1.784)	0.851	0.199 (0.044–0.895)	0.035
Primary tumor location					
Breast	34 (43.03)	Reference		Reference	
Lung	23 (31. 08)	1.217 (0.692–2.142)	0.495	1.534 (0.418–5.631)	0.519
Other locations	17 (21.51)	1.648 (0.887–3.062)	0.114	2.239 (0.798–6.286)	0.126
Primary controlled					
Yes	63 (85.16)	Reference		Reference	
No	11 (14.84)	1.241(0.632–2.437)	0.531	0.235(0.048–1.144)	0.073
Surgery before GKSR					
Yes	14 (17.72)	Reference		Reference	
No	65 (82.28)	1.413 (0.740–2.699)	0.259	1.263 (0.450–3.541)	0.658
Radiotherapy or chemotherapy before GKSR					
Yes	15 (18.99)	Reference		Reference	
No	64 (81.01)	0.885 (0.481–1.554)	0.627	1.006 (0.403–2.513)	0.990
Volume-staged GKSR					
No	68 (86.07)	Reference		Reference	
Yes	11 (13.93)	0.599 (0.296–1.213)	0.154	0.335 (0.110–1.021)	0.057
Tumor volume					
< 5	15 (18.98)	Reference		Reference	
5–10	23 (29.11)	1.203 (0.603–2.398)	0.600	1.274 (0.462–3.513)	0.640
≥ 10	41 (51.90)	0.989 (0.531–1.843)	0.972	0.919 (0.367–2.298)	0.856
Retreatment					
Yes	08 (10.13)	Reference		Reference	
No	71 (89.87)	3.266 (1.282–8.323)	**0.013**	5.610 (1.042–30.194)	**0.045**
Progression					
No	54 (80.60)	Reference		Reference	
Yes	13 (19.40)	0.421 (0.207–0.858)	0.017	14.882 (0.966–229.224)	0.054
Stability					
Yes	54 (80.60)	Reference		Reference	
No	13 (19.40)	0.384 (0.183–0.810)	0.012	22.463 (1.220–413.442)	**0.036**
Percentage of control					
> 80	24 (32.80)	Reference		Reference	
50–80	31 (42.50)	1.429 (0.759–2.692)	0.269	1.761 (0.710–4.364)	0.222
< 50	18 (24.70)	0.803 (0.449–1.435)	0.459	1.143 (0.525–2.486)	0.737
RPA Class					
Class 1	47 (61.84)	Reference		Reference	
Class 2 or 3	29 (38.16)	1.326 (0.814–2.160)	0.257	6.133 (1.183–31.792)	**0.031**

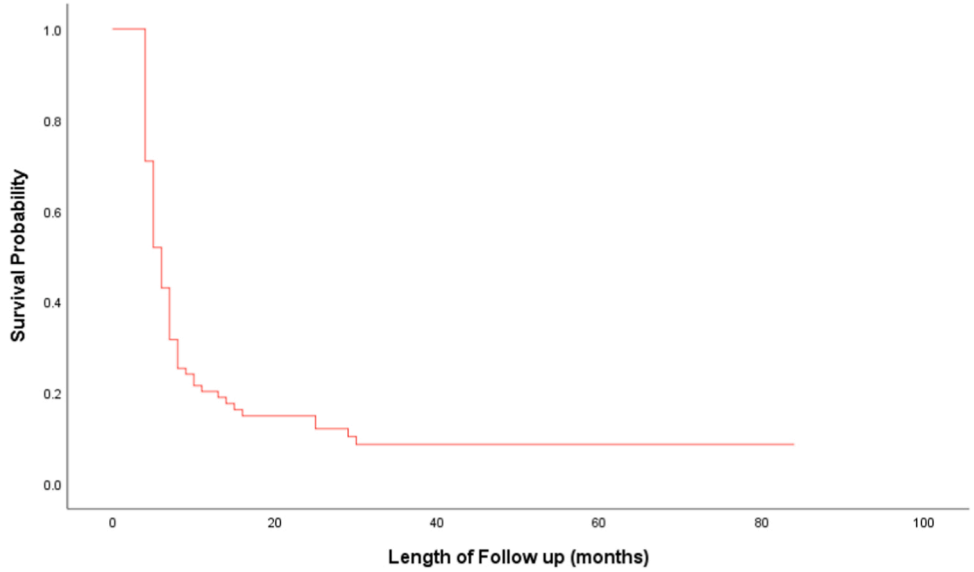

Fig. 3. Overall Free Survival progression Kaplan Meir after Stereotactic Radiosurgery for Brain metastasis.

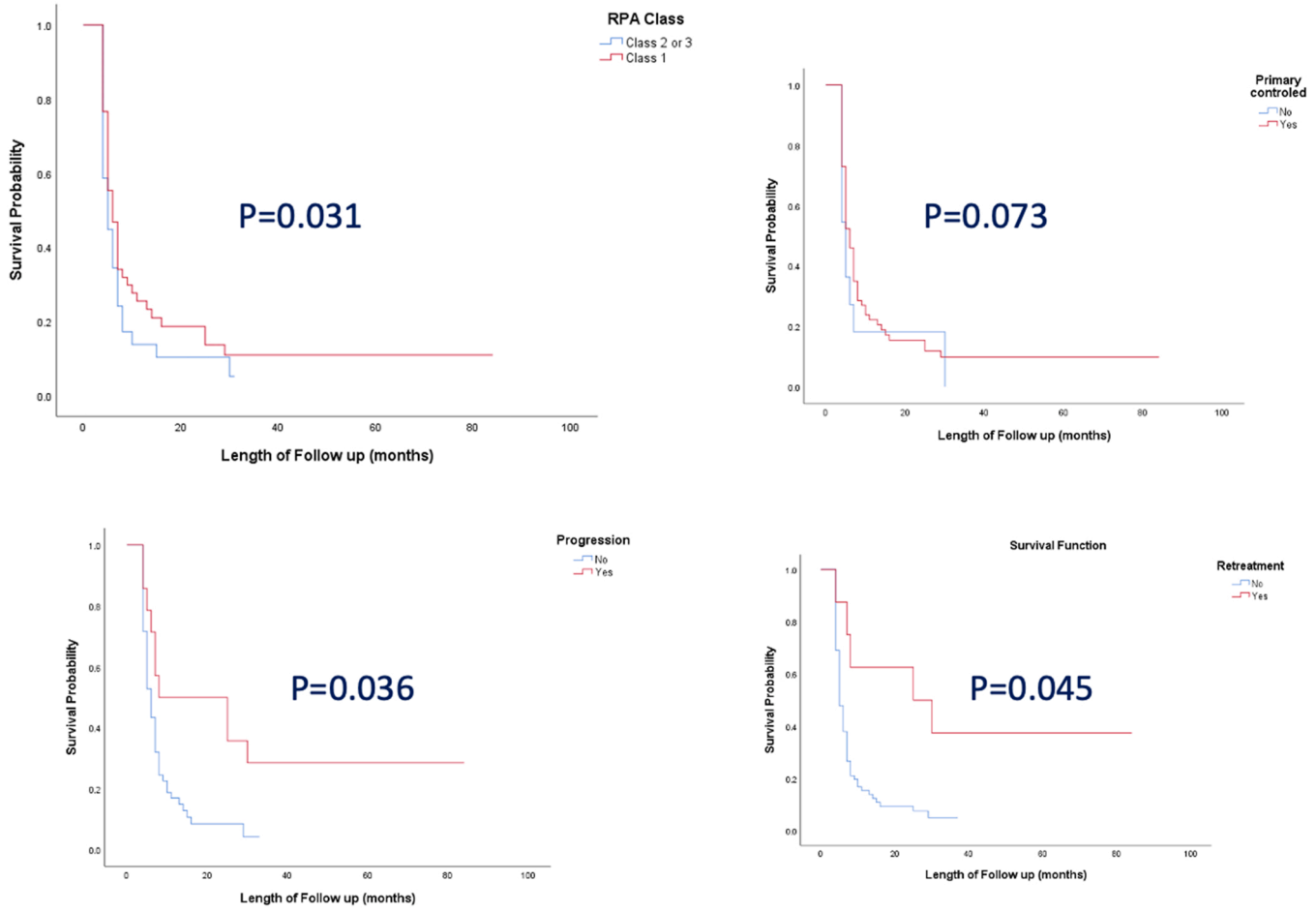

Fig. 4. Survival Time according to the recursive partitioning analysis(RPA) class primarily controlled, progression, and Brain metastasis retreatment.

up time of 5 months (IQR:3–84 months). The median survival time was 5.21 (IQR, 3–8) months. Retreatment, RPA class, and tumor stability influenced the overall survival of BM respectively.

BM from the breast and gastrointestinal are common in the cerebellum (breast BM: OR 2.161, probability 32.4%, CI 23.3–43.0%, $p = 0.006$; gastrointestinal BM: OR 2.117, probability 31.9%, CI 21.3–44.9%, $p = 0.016$) and were rarely found in the frontal lobes (breast BM: OR 0.487, probability 19.4%, CI 14.5–25.6, $p < 0.001$; gastrointestinal cancer: OR 0.572, probability 22.1%, CI 15.2–31.0%, $p = 0.025$) (Schroeder et al., 2020). In our series, BM from breast tumor are common in parietal and cerebellar lobes respectively ($n = 12$, 30%; $n = 12$, 30%), and BM from the lung are commonly located in cerebellar and occipital lobes respectively ($n = 22$,61%; $n = 7$,19.4%), the other sites primary location such as gastrointestinal were rare in our series ($n = 3$,3.06%)(Figure1).

Authors suggested a single (marginal) dose of 20 Gy as a reasonable choice that balances the effect on local control or partial remission after SRS against the risk of late side effects such as radionecrosis, and Higher doses (22–25 Gy) may be used for smaller (< 1 cm) lesions, while a dose reduction to 18 Gy may be necessary for lesions greater than 2.5–3 cm (Kohler et al., 2011). Authors reported 6.2% of radiation necrosis on MRI during follow-up with dizziness as the most common neurologic symptom (Schüttrumpf et al., 2014).

In our series, only two cases (1.9%) presented radionecrosis after being treated by radiosurgery as salvage boost treatment after previous WBRT,87 patients (84.5%) were treated with a median single dose of 20 Gy (IQR:14–29), we respected the literature guidelines and our results are in perfect adequation with the literature results. Besides, 16 patients (15.5%) were treated in two-stage with a median dose of 14 Gy (IQR:10–23) for each stage. Staged SRS requires adaptive planning during each stage of the irradiation period for improved tumor control and reduced radiation damage (Ito et al., 2020). Two-session Gamma Knife radiosurgical treatment for large brain metastases with a Median tumor volume of 17.8 cm^3 (range 10.0–53.3 cm^3) represents a safe treatment modality allowing neurological palliation in the short to medium term, with acceptable tumor control rates and low morbidity (Yomo et al., 2012).

One multi-institutional review reported that the median survival times for patients treated with SRS alone initially vs. SRS + WBRT were 14.0 vs. 15.2 months for RPA Class 1 patients, 8.2 vs. 7.0 months for Class 2, and 5.3 vs. 5.5 months for Class 3, respectively. With adjustment by RPA class, there was no survival difference comparing SRS alone initially to RS + up-front WBRT ($p = 0.33$, hazard ratio = 1.09) (Sneed et al., 2002). Thus our results are not far from their results and confirmed that GKSR is an effective option for the management of single brain metastases with the same results in terms of overall survival as other options such as WBRT alone or WBRT+SRS or Surgery+WBRT, we performed GKSR alone in 81.5% ($n = 84$) of our cases. Besides, compared with SRS alone, the use of WBRT plus SRS did not improve survival for patients with single brain metastases, but intracranial relapse occurred considerably more frequently in those who did not receive WBRT (Aoyama et al., 2006).

On other hand, studies have shown a considerable improvement in the preservation of neurocognitive function and performance status in patients treated with SRS alone compared with WBRT and SRS (Andrews et al., 2004; Noordijk et al., 1994; Patchell et al., 1990). Also, the authors reported 21% of local control failure between 1 and 13 months after two-session GKS (median 6.2 months) with a local control rate was

85% and 61% at 6 and 12 months, respectively (Yomo et al., 2012).

The overall survival rate after GKS in their series was 63% and 45% at 6 and 12 months, respectively with a Median survival time of 11.9 months (95% CI, 4.67–15.63 months), and the rate of prevention of neurological death after GKS was 90% and 78% at 6 and 12 months, respectively (Yomo et al., 2012). In our series, the 1-year OS rate was 28.7% (n = 25), the 2-year OS rate was 20.7% (n = 18), and 5-years OS was 17.2% (n = 15)and 92.5% (n = 74) of our patients had died of extra neurological causes. Our results are not so far from the literature results.

However, patients treated with SRS alone experience an increase in recurrence or metastases elsewhere in the brain, and retreatment with repeated SRS or WBRT results in overall survival compared to initial treatment with WBRT and SRS (Fernandez-Vicioso et al., 1997). Indeed in our series,8 patients (8.7%) retreated for a volume progression or de novo volume BM, and the retreatment, the RPA class, and tumor stability influenced the overall survival of single brain metastases respectively (HRa=5.610,p = 0.045; HRa=6.133,p = 0.031; HRa=22.463, p = 0.036), and only 7.5% (n = 6) of the patients had died of neurological causes with neurocognitive disorders.

Of note, In our series, the primary tumor location or its controlled, tumor volume prior to treatment, percentage of tumor control volume after GKSR, Radiotherapy, or chemotherapy prior to SRS, and Surgery prior to GKSR, didn't influence the overall survival respectively (HA=1.53,p = 0.51; HA=1.2,p = 0.64; HA=1.7,p = 0.22; HA=1.00, p = 0.99; HA=1.26,p = 0.65).

Thus SRS alone should be considered a routine treatment option due to favorable control of the brain tumor volume, favorable neurocognitive outcomes, less risk of late side effects of radiation, and not adversely affecting the patient's performance status (Chang et al., 2009; Tsao et al., 2012; Aoyama et al., 2007).

4.1. Limitations

Despite the relatively large sample size for single brain metastasis, our study presents several shortcomings, most inherent to its retrospective design and pattern for data acquisition. In turn, we acknowledge that our results must be considered with caution as they are subject to confounding by indication, and memory biases, and have limited external validity.

Nonetheless, our study presents a large sample of single brain metastases that all the patients who have been treated by the same neurosurgical and neuro-oncological,neuro-radiological, technician radiological team, which may have limited the heterogeneity of the groups and the impact of the GKSR technique on OS.

5. Conclusion

Our study confirmed the feasibility of this treatment option for single-brain metastasis again. Brain metastasis was common in the Breast and lungs, its control locally does not allow for improving the overall survival rate. RPA class and tumor stability influenced the overall survival of BM. Globally, the outcomes of brain metastasis are poor, and GKRS allows to achieve less death from neurological disorders.

Importance of the Study

A small number of centers practice GKSR in Africa, due to the scarcity of radiosurgery skills and equipment. Our center is a rare one of center in Africa that practices radiosurgery. Our study confirmed the feasibility of this treatment option for single-brain metastasis again. This should encourage the other colleagues to take into consideration GKSR for BM management and do their best to have the skills and the equipment for the wellness of their patients.

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CRediT authorship contribution statement

Nourou Dine Adeniran Bankole: Conceptualization, Methodology, Data curation, data analysis, Writing – original draft, Writing – review & editing. **Adyl Melhaoui:** patient management, Data curation, Validation, Supervision, Writing – review & editing. **Yasser Arkha:** Patient management, Validation. Writing – review & editing. **Semmar Afaf:** Validation, Writing – review & editing. **Khalid Bouyakhlef**: Patient management, Writing – review & editing. **Mohamed Jiddane:** Writing – review & editing. **Abdelsalam El Khamlichi:** Conceptualization, Patient management, Supervision, Data curation, Validation, Writing – review & editing, Supervision.

Conflicts of Interest

The authors do not have any conflicting interests in this case report or any financial resources.

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References

Nayak, L., Lee, E.Q., Wen, P.Y., 2012. Epidemiology of brain metastases. Curr. Oncol. Rep. févr 14 (1), 48–54.

Trifiletti, D.M., Hill, C., Cohen-Inbar, O., Xu, Z., Sheehan, J.P., 2017. Stereotactic radiosurgery for small brain metastases and implications regarding management with systemic therapy alone, 1 sept J. Neurooncol 134 (2), 289–296.

Patel, A., Mohammadi, H., Dong, T., Shiue, K.R.Y., Frye, D., Le, Y., et al., 2018. Brainstem metastases treated with Gamma Knife stereotactic radiosurgery: the Indiana University Health experience. CNS Oncol. janv 7 (1), 15–23.

Kocher, M., Wittig, A., Piroth, M.D., Treuer, H., Seegenschmiedt, H., Ruge, M., et al., 2014. Stereotactic radiosurgery for treatment of brain metastases, 1 juin Strahl. Onkol. 190 (6), 521–532.

Mehta, M.P., Tsao, M.N., Whelan, T.J., Morris, D.E., Hayman, J.A., Flickinger, J.C., et al., 2005. The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for brain metastases, 1 sept Int J. Radiat. Oncol. Biol. Phys. 63 (1), 37–46.

Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial - The Lancet [Internet]. [cité 25 juill 2022]. Disponible sur: https://www.thelancet.com/journals/lancet/article/PIIS0140–6736(04)16250–8/fulltext.

Yomo, S., Hayashi, M., Nicholson, C., 2012. A prospective pilot study of two-session Gamma Knife surgery for large metastatic brain tumors, 1 août J. Neurooncol. 109 (1), 159–165.

Serizawa, T., Saeki, N., Higuchi, Y., Ono, J., Iuchi, T., Nagano, O., et al., 2005. Gamma knife surgery for brain metastases: indications for and limitations of a local treatment protocol, 1 juill Acta Neurochir. (Wien.) 147 (7), 721–726.

Higuchi, Y., Serizawa, T., Nagano, O., Matsuda, S., Ono, J., Sato, M., et al., 2009. Three-Staged Stereotactic Radiotherapy Without Whole Brain Irradiation for Large Metastatic Brain Tumors, 1 août Int J. Radiat. Oncol. Biol. Phys. 74 (5), 1543–1548.

Ito, D., Aoyagi, K., Nagano, O., Serizawa, T., Iwadate, Y., Higuchi, Y., 2020. Comparison of two-stage Gamma Knife radiosurgery outcomes for large brain metastases among primary cancers (mars). J. Neurooncol. 147 (1), 237–246.

Andrews, D.W., Scott, C.B., Sperduto, P.W., Flanders, A.E., Gaspar, L.E., Schell, M.C., et al., 2004. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial, 22 mai Lancet 363 (9422), 1665–1672.

Noordijk, E.M., Vecht, C.J., Haaxma-Reiche, H., Padberg, G.W., Voormolen, J.H., Hoekstra, F.H., et al., 1994. The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age, 1 juill Int J. Radiat. Oncol. Biol. Phys. 29 (4), 711–717.

Patchell, R.A., Tibbs, P.A., Walsh, J.W., Dempsey, R.J., Maruyama, Y., Kryscio, R.J., et al., 1990. A randomized trial of surgery in the treatment of single metastases to the brain, 22 févr N. Engl. J. Med. 322 (8), 494–500.

Fernandez-Vicioso, E., Suh, J.H., Kupelian, P.A., Sohn, J.W., Barnett, G.H., 1997. Analysis of prognostic factors for patients with single brain metastasis treated with stereotactic radiosurgery. Radiat. Oncol. Invest. 5 (1), 31–37.

Arvold, N.D., Lee, E.Q., Mehta, M.P., Margolin, K., Alexander, B.M., Lin, N.U., et al., 2016. Updates in the management of brain metastases (août). Neuro-Oncol. 18 (8), 1043–1065.

Kohler, B.A., Ward, E., McCarthy, B.J., Schymura, M.J., Ries, L.A.G., Eheman, C., et al., 2011. Annual report to the nation on the status of cancer, 1975–2007, featuring tumors of the brain and other nervous system, 4 mai JNCI J. Natl. Cancer Inst. 103 (9), 714–736.

Sneed, P.K., Lamborn, K.R., Forstner, J.M., McDermott, M.W., Chang, S., Park, E., et al., 1999. Radiosurgery for brain metastases: is whole brain radiotherapy necessary?, 1 févr Int J. Radiat. Oncol. Biol. Phys. 43 (3), 549–558.

Sneed, P.K., Suh, J.H., Goetsch, S.J., Sanghavi, S.N., Chappell, R., Buatti, J.M., et al., 2002. A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases, 1 juill Int J. Radiat. Oncol. Biol. Phys. 53 (3), 519–526.

Aoyama, H., Shirato, H., Tago, M., Nakagawa, K., Toyoda, T., Hatano, K., et al., 2006. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial, 7 juin JAMA 295 (21), 2483–2491.

Chang, E.L., Wefel, J.S., Hess, K.R., Allen, P.K., Lang, F.F., Kornguth, D.G., et al., 2009. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial (nov). Lancet Oncol. 10 (11), 1037–1044.

Tsao, M., Xu, W., Sahgal, A., 2012. A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases, 1 mai Cancer 118 (9), 2486–2493.

Aoyama, H., Tago, M., Kato, N., Toyoda, T., Kenjyo, M., Hirota, S., et al., 2007. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone, 1 août Int J. Radiat. Oncol. Biol. Phys. 68 (5), 1388–1395.

Gamma Knife Surgery | Radiosurgery Treatment Process | Elekta [Internet]. 2021 [cité 16 août 2022]. Disponible sur: https://www.elekta.com/patients/gamma-knife-treatment/.

Snell, J.W., Sheehan, J., Stroila, M., Steiner, L., 2006. Assessment of imaging studies used with radiosurgery: a volumetric algorithm and an estimation of its error: Technical note, 1 janv J. Neurosurg. 104 (1), 157–162.

Gaspar, L.E., Scott, C., Murray, K., Curran, W., 2000. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases, 1 juill Int J. Radiat. Oncol. Biol. Phys. 47 (4), 1001–1006.

Schroeder, T., Bittrich, P., Kuhne, J.F., Noebel, C., Leischner, H., Fiehler, J., et al., 2020. Mapping distribution of brain metastases: does the primary tumor matter?, 1 mars J. Neurooncol. 147 (1), 229–235.

Schüttrumpf, L.H., Niyazi, M., Nachbichler, S.B., Manapov, F., Jansen, N., Siefert, A., et al., 2014. Prognostic factors for survival and radiation necrosis after stereotactic radiosurgery alone or in combination with whole brain radiation therapy for 1–3 cerebral metastases, 2 mai Radiat. Oncol. 9 (1), 105.