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Review

Stereotactic Radiosurgery (SRS) experience on brain metastases: A 3-year retrospective study at King Abdulaziz University Hospital

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ABSTRACT

Objectives: Stereotactic radiosurgery (SRS), a non-invasive surgical procedure had been utilized for treatment of patients with brain metastases. This study aims to determine the survival, local control of brain metastases and treatment outcome to SRS-treated patients based on radiological imaging.
Methods: The MRI scans of SRS-treated patients with brain metastases (n = 24) from the Radiology Department of King Abdulaziz University from January 2016 to September 2019 were examined. The data was analyzed using descriptive statistics and Chi-square test.
Results: Out of 24 patients, most had brain metastases (95.8%, n = 23) with mean interval development (after primary site) of 21.88 ± 25.2 months. Radiological imaging revealed tumor characteristics of smallest (n = 11) and biggest lesions (n = 24) of patients to be 0.98 ± 0.7 and 2.23 ± 0.9, respectively and number of lesion to be 4–5 lesions (n = 3), 3 lesions (n = 6), 2 lesions (n = 4) and 1 lesion (n = 11). After SRS treatment, findings showed 17.6% (n = 3) no recurrence among the patients. Those with recurrences have decrease in lesion enhancement (11.8%, n = 2), decrease in size (29.4%, n = 5) and decrease in both enhancement and size (29.4%). Overall survival obtained was 16.7% (n = 2) at 313.83 ± 376.0 days (n = 23) survival period. Chi-square test showed that radiological findings were significantly associated with tumor recurrence ($p = 0.010$), having SRS-treated patients with recurrences (n = 12) to experience significant decrease ($p = 0.010$) in tumor enhancement, size, and both enhancement and size.
Conclusion: A significant decrease in tumor size and enhancement was observed in SRS-treated patients, suggesting SRS treatment to have associated benefit with prolonged survival duration.

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1. Introduction

Stereotactic radiosurgery (SRS) is a non-surgical radiation therapy that is precisely-targeted treatment intended for tumors that are difficult to remove and functional abnormalities of the brain (Harris and Das, 2020). This can be performed using Proton Beam, Gamma Knife or Linac frame-based technique to ensure precise and focused delivery of high-dose radiation to target intracranial lesions which helps to preserve healthy tissue and allow a much higher dose application in only a single or few treatment sessions (RadiologyInfo.org; Harris and Das, 2020). This technique can be done in four phases, (1) placement of the head frame, (2) imaging of the tumor location, (3) computerized dose planning and lastly, (4) radiation delivery (RadiologyInfo.org). SRS can be applied before or after Whole Brain Radiotherapy (WBRT) and had been widely utilized in handling patients with brain metastases (Suh, 2010; Baschnagel et al., 2013; Lippitz et al., 2014).

The mortality and morbidity of patients having metastatic cancer are significantly attributed to acquiring brain metastases (Liu et al., 2019). The incidence of brain metastases can reach more up to 65% in the period of the disease trajectory, considering the type of primary tumor (Lassman and DeAngelis, 2003; Bilger et al., 2017; Tsao et al., 2018). For unselected patients with varying tumor types, such incidence is estimated to fall between 8% and 10% (Taillibert and Le Rhun, 2015; Liu et al., 2019). Alarmingly, the median survival of patients with brain metastases is estimated to only last for 4 months relative to the time they were diagnosed (Fonkem et al., 2012; Tazi et al., 2015). For untreated patients, the projected median survival rates are only weeks (Raizer et al., 2008; Suh, 2010) or 51 days (Langley et al., 2013; Lippitz et al., 2014).

Subjecting patients with limited numbers of brain metastases ($\leq$4) to SRS alone have less negative impact for their survival, and that at least delays potential neurocognitive effects and other acute toxicities (alopecia, serous otitis media, and hearing loss) (Aoyama et al., 2006; Baschnagel et al., 2013). In comparison to resection, SRS is considered less invasive and more cost-effective option for treatment (Minniti et al., 2011). Another advantage is that SRS was linked with short term stay in hospital, and less frequent and shorter steroid administration (Muacevic et al., 2008; Lippitz et al., 2014). In terms of quality of life, one study showed that SRS-treated patients experienced lower risk of declination in learning and memory function by 4 months (Chang et al., 2009; Lippitz et al., 2014). Survival advantages associated with the use of SRS have been reported by various studies (Kocher et al., 2011; Minniti et al., 2011).

These potentials mentioned above relative to SRS treatment and natural rarity of such cases posed an opportunity of story and knowledge worthy to be shared. This study was investigated with the intention of contributing to the entire SRS treatment experience and outcome of patients with brain metastases. Also, information derived on this study can be used in the development of meta-analysis on SRS treatment to brain metastases for the entire Saudi Arabia and perhaps globally in the near future.

2. Methods

2.1. Study design and subjects

This retrospective study was carried out among patients (31–67 year old) with brain metastases at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia. The radiological brain imaging records by 3 Tesla MRI, from 2016 to 2019 was examined after securing informed consent from King Abdulaziz University ethical committee at College of Medicine.

2.2. Data gathered

This study collected information on the profile of the patients both demographic and clinical symptoms. To determine the tumor characteristics before and after undergoing Stereotactic Radiosurgery (SRS), radiological findings based on imaging available at the Radiology Department in KAUH were collected for examination. To describe the effectivity of the treatment and survival of the patients, information on follow-up check-ups was scrutinized. All data gathering was carried out by two investigators and was reviewed by two reviewers.

2.3. Statistical analyses

In this study 24 patients were utilized to calculate for the sample size, considering expected frequency and confidence interval of

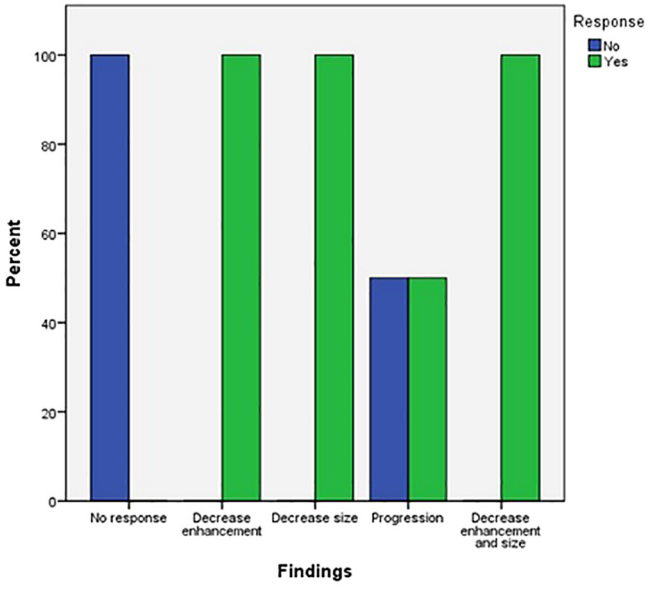

Fig. 1. Distribution of patients with and without tumor recurrences against radiological findings (N = 16).

Table 1
Demographic characteristics of the studied population (N = 24).

Demographics	N	Min	Max	Mean	SD
Age	24	31	67	47.7	9.5
		Count	**%**		
Total		24	100.0		
Gender	Male	8	33.3		
	Female	16	66.7		
1ry brain	1ry brain	1	4.2		
	Mets	23	95.8		
Primary site other than brain	Lungs	7	29.2		
	Breast	13	54.2		
	Colon	1	4.2		
	Cervix	1	4.2		
	Melanoma	1	4.2		
	GBM	1	4.2		

Table 2
Symptoms of brain metastases in the studied patients (n = 24).

Variables	N	Min	Max	Mean	SD
Interval of developing brain metastases after primary (months)	24	0	93	21.88	25.2
		Count	**%**		
Total		24	100.0		
ECOG*	0	1	4.2		
	1	20	83.3		
	2	3	12.5		
Seizures	No	17	70.8		
	Yes	7	29.2		
Motor insult	No	8	33.3		
	Yes	16	66.7		
Headache	No	9	37.5		
	Yes	15	62.5		
Anti-convulsive	No	17	70.8		
	Yes	7	29.2		
Vomiting	No	12	50.0		
	Yes	12	50.0		

* ECOG – Eastern cooperative oncology group.

95%. The collected data was analyzed using IBM SPSS version 23 (IBM Corp., Armonk, New York). A simple descriptive statistic was used to define the characteristics of the study variables through a form of counts and percentages for the categorical and nominal variables, while continuous variables were presented by mean and standard deviations. To establish a relationship between categorical variables, this study used Chi-square test. Lastly, a conventional p-value <0.05 was the criteria used to reject the null hypothesis (see Fig. 1).

3. Results

3.1. Patients and clinical characteristics

In this retrospective study, the study population (N = 24) revealed an average patient age of 47.7 ± 9.5 (min = 31, max = 67), having majority of them to be female (66.7%, n = 16), had brain metastases (95.8%, n = 23), and breast (54.2%, n = 13) and lungs (29.2%, n = 7) as the primary site of tumor occurrence aside from the brain (Table 1). As shown in Table 2, the mean interval (in months) of developing brain metastases after the occurrence at the primary site was found to be 21.8 ± 25.2 (min = 0, max = 93). Mostly of the patients were eastern cooperative oncology group 1-classified (ECOG-1) (83.3%, n = 20), were not anti-convulsive (70.8%, n = 17), and had no seizures (70.8%, n = 17). Roughly two-thirds experienced motor insult (66.7%, n = 16), and headache (62.5%, n = 15). Equal number of participants reported to have and have not vomited.

3.2. Tumor metastases characteristics

Prior to treatment, radiological assessment was conducted to characterize the metastases. Records used in the study discovered that all patients were subjected to MRI modality and 75.0% (n = 18) had specifically underwent MRI spectroscopy to further described the lesion. As shown in Table 3, on the average (in cm) the smallest lesion was 0.98 ± 0.7 (min = 0.2, max = 2.3) and this was observed to 11 (46%) patients. On the other hand the biggest lesion size (in cm) identified was of 2.23 ± 0.9 (min = 0.7, max = 3.6) and this was observed to all the 24 patients. In terms on the number of lesions, out of the 24 patients, only 3 (12.5%) had 4–5 lesions, 6 (25%) had 3 lesions, 4 (16.7%) had 2 lesions and 11 (45.8%) had only 1 lesion (Table 3).

3.3. Clinical implementation of treatment

In this particular study, records have shown that out of the 24 patients, only 12.5% (n = 3) had brain resection procedure. In terms of Whole Brain Radiation Treatment (WBRT), only 62.5% (n = 15) had records indicating experience on WBRT. Also, based on records, the WBRT dose provided to patients were 20 Gy (33.3%, n = 8) or 30 Gy radiation (25.0%, n = 6). There was no information regarding the amount of radiation applied during WBRT to the remaining 41% (n = 7%) of the patients (Table 3).

In terms on Stereotactic Radiosurgery (SRS), records revealed that SRS was only administered to 15 patients (62.5%). No information on SRS treatment that indicates to the remaining 9 patients

Table 3
Radiological findings and follow up status of the studied patients (N = 24).

Variables	N	Min	Max	Mean	SD
Biggest lesion size	24	0.7	3.6	2.23	0.9
Smallest size	11	0.2	2.3	0.98	0.7
		Count	**%**		
Total		24	100.0		
MRI	Yes	24	100.0		
MRI spectroscopy	No	18	75.0		
	Yes	6	25.0		
Radiology findings	1 lesion	11	45.8		
	2 lesions	4	16.7		
	3 lesions	6	25.0		
	More than 3 and less than 5	3	12.5		
Biopsy	No	24	100.0		
Resection	No	21	87.5		
	Yes, Partial	3	12.5		
Whole brain radiation	No	9	37.5		
	Yes	15	62.5		
Whole brain radiation dose	No Report	10	41.7		
	20 Gy	8	33.3		
	30 Gy	6	25.0		
Whole brain examination	Before SRS*	12	80.0		
	After SRS	3	20.0		
	Missing	9			
Headache	No	10	41.7		
	Yes	14	58.3		
Response	No	5	29.4		
	Yes	12	70.6		
	Missing	7			
Findings	No response	3	17.6		
	Decrease enhancement	2	11.8		
	Decrease size	5	29.4		
	Progression	2	11.8		
	Decrease enhancement and size	5	29.4		
	Missing	7			
Date of death	2014	1	9.1		
	2015	1	9.1		
	2016	2	18.2		
	2017	2	18.2		
	2018	5	45.5		
	Missing	13			
Mortality	Dead	10	83.3		
	Alive	2	16.7		
	Missing	12			
Variables	**N**	**Min**	**Max**	**Mean**	**SD**
Survival Date** (days)	23	0	1595	313.83	376.0

* SRS – stereotactic radiosurgery.
** Survival Date = Last date of follow up − Date of SRS.

(37.5%). However, records used in this study also provided no information indicating the SRS dose administered to the patients. Whole brain examination before and after SRS treatment was also identified. Out of these 15 patients, 12 (80%) had their brain examined before SRS and only 3 (20%) had their brain examined after SRS treatment (Table 3).

3.4. Treatment outcomes

Records indicated that patients were followed two (2) weeks post radiation treatment and then every two (2) months. As shown in Table 3, this study has found that some patients have experienced headache (70.6%) after following complete treatment. Records examined also revealed no recurrence to 17.6% (n = 3) of the patients while 82.4% have recurrence and 11.8% (n = 2) had progression after radiation treatment. Among those that have recurrence, 11.8% (n = 2) were noticed to have decreased enhancement in lesion formation, 29.4% (n = 5) were observed to have decreased on lesion size. In addition, records also revealed that 29.4% (n = 5) have decreased both on lesion enhancement and size combined (Table 3).

Like any other treatment implementation, one interesting outcome to know is the impact on survival of the patient. Records analyzed in this particular study have discovered 83.3% (n = 10) mortality of patients and only 16.7% (n = 2) remained alive (Table 3). However, the exact reason for the death of these patients was not indicated in the records investigated. Nonetheless, also shown in Table 3, the mean survival period obtained by the patients treated was 313.83 83 ± 376.0 days (min = 0, max = 1,595). The survival period described in this study was defined as the last date of follow up subtracted by the date of SRS, of patients (n = 23).

3.5. Association of radiological findings to recurrence of tumor

To determine the effectivity of the treatment employed, analysis on the association of radiological findings with respect to recurrence of tumor formation after SRS among the studied patients was conducted (Table 4). Analysis of the results showed that all radiological findings were significantly associated with tumor recurrence ($p = 0.010$) according to Chi-square test. Specifically, out of 16 patients evaluated for recurrence based on radiological findings,

Table 4
Association of radiological findings with respect to recurrence of tumor formation after SRS among the studied patients.

Variables		Total	Response		p-Value
			No	Yes	
Total		16	4	12	–
Findings	No response	3	3(100.0%)	0(0.0%)	0.010[a]
	Decrease enhancement	2	0(0.0%)	2(100.0%)	
	Decrease size	5	0(0.0%)	5(100.0%)	
	Progression	2	1(50.0%)	1(50.0%)	
	Decrease enhancement and size	4	0(0.0%)	4(100.0%)	

[a] Significant using Chi-Square Test @<0.05 level.

one with and without tumor recurrence experienced significant progression. Interestingly, all patients with recurrences (n = 12) after SRS treatment had significant decrease ($p = 0.010$) in tumor enhancement (n = 2) decrease in tumor size (n = 5), and decreased in tumor enhancement and size combined (n = 4).

4. Discussion

In this retrospective study, the survival, local control and treatment outcome of Stereotactic Radiosurgery (SRS)-treated patients with brain metastases was assessed using records on radiological imaging. After the follow up, findings showed no recurrence rate of 17.6% among SRS-treated patients whereas for the 82.4% with recurrence rate, roughly one-third of them had decrease enhancement in lesion formation, decrease in lesion size and decrease in lesion enhancement and size combined. This outcome however was contrary to the recurrence rate conducted by Aoyama et al. (2006) on a similar study of SRS-treated patients with brain tumor. Aoyama et al. (2006) found a four times higher 12-month recurrence rate of 76.4%. Similar result was observed in the study of Minniti et al. (2011) wherein the SRS-treated patients with cerebral metastases experienced a higher 1-year brain tumor recurrence rate of approximately 50%.

The survival rate of patients in this study was determined to be 16.7% at the last day of follow up, with the overall survival period of 314 days (~10.5 months). This result was almost similar to the results of Knisely et al. (2012) on a restospective study to SRS-treated patients with melanoma brain metastases. Knisely et al. (2012) found a 2-year survival rate of 19.7%. These results however were found to be low in contrast to the results of Bilger et al. (2017), Tazi et al. (2015) and Minniti et al. (2011). Bilger et al. (2017) using Kaplan-Meier method found a roughly two times higher 1-year estimated survival rate of 35.6% on the patients studied. Minniti et al. (2011) reported SRS-treated patients to have 58% 1-year survival rate, a rate close to the retrospective study of Tazi et al. (2015) wherein patients with metastatic melanoma who received SRS and ipilimumab treatment experienced 3-year survival rate of 50%. Moreover, in 2018, Saki et al. reported a case of a 42-year-old man treated with Gamma Knife-frame SRS technique, having total of 98 brain metastases to have survive for nearly five years relative to his initial treatment – a survival period not commonly available and far better in published works.

Results of radiological findings showed that out of 16 patients evaluated for recurrence based on MRI scans, one with and without tumor recurrence experienced significant progression. This result is relatively lower compared to the report of Bilger et al. (2017) in which 40 SRS-treated patients (87%) had progressive disease. Additionally, in the present study, all patients with recurrences after SRS treatment had significant ($p = 0.010$) decrease either in tumor enhancement, tumor size, and both tumor enhancement and size combined. Survival advantages associated with the use of SRS for patients with single or multiple metastases have been already reported by various studies like Kocher et al. (2011), Minniti et al. (2011) and Tazi et al. (2015).

This study had its own limitations. Small sample size was used, making it hard to conduct multivariate analysis about factors associated with worse outcomes. Further studies carried out in large population size are recommended to evaluate the validity of result on a regional or national level. Also, further retrospective studies on SRS in combination with other treatments are suggested to open opportunities for more possible improvement of survival in patients suffering from brain metastases.

Overall, a significant decrease in tumor size and enhancement was observed in SRS-treated patients with tumor recurrences, suggesting SRS treatment to have associated benefit with survival duration.

Ethical statement

The study was approved by the Unit of Biomedical Ethics at College of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia. Informed consent was taken from the participants, following the Declaration of Helsinki guidelines.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: 'This research did not receive any specific grant from any public, commercial or non-profit sectors funding agencies. Thus, the authors declare no competing financial interests or personal relations that could have appeared to influence the work reported in this paper.

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