ORIGINAL ARTICLE

Neurocognitive Functions after Stereotactic Radiosurgery- An Analysis with Mini-Mental State Examination (MMSE)

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Abstract

Background: Throughout the past decade, the research on neuro-oncology has increased awareness regarding the significance of cognitive functions as an outcome in different treatment modalities for patients with a primary brain tumor but only limited studies have explored the subject of the likelihood of cognitive dysfunction in patients undergoing stereotactic radiosurgery/stereotactic radiotherapy (SRS/SRT). This modern radiation delivery technique allows high-dose delivery to the target and minimum dose to the brain/critical organs resulting in better tumor control and perhaps an improvement in Neurocognitive functions (NCF).

Objective: To explore the effect of stereotactic radiosurgery/stereotactic radiotherapy on neurocognitive functions (NCF) in various brain tumors.

Methods: A prospective observational study was conducted at Neurospinal and Cancer Care Institute (NCCI), Karachi. A total of 100 patients who had undergone multisession stereotactic radiosurgery /stereotactic radiotherapy were selected after taking their written informed consent by employing a convenient sampling technique. The type of tumor was classified and identified on a radiological and histological basis. Neurocognitive function evaluation was carried out through Mini-Mental State Examination (MMSE) score questionnaire provided to patients at baseline (pre-radiosurgery SRS/SRT), and 6 months after treatment (post-radiosurgery SRS/SRT).

Results: The mean age of patients was 37.38±15.03 years and the majority (49%) belonged to the 27-44 years age group. The majority of them were males whereas the most common pathology found was glioma (31%). Moreover, both overall and in patients having prior surgery, the comparison of different MMSE score levels showed that there was a significant increase in patients with normal score levels and a significant decrease in patients with mild and moderate score levels after treatment (P=0.006 and P=0.046 respectively) at post-treatment time.

Conclusion: Stereotactic radiosurgery results in the improvement of neurocognitive functions. Previously known radiation-related impairment of NCF should be re-explored in light of modern radiosurgery/radiotherapy techniques with larger studies.

Keywords: *Neurocognitive function, stereotactic surgery, mini-mental state examination, brain tumors, radiotherapy.*

INTRODUCTION

Globally, tumors of the brain cause significant mortality and morbidity, with an overall incidence of 4-5 cases per 100,000 population annually. In Pakistan, approximately 150,000 fresh cases of malignancies are annually diagnosed, with a mortality rate of 60-80% [1]. The popularity of radiosurgery and precision radiation therapy in brain tumor management has increased with the recent advancement in modern radiotherapy equipment and the latest immobilization devices [2-3]. The term “Stereotactic radiosurgery-(SRS)”, was coined and defined by Lars Leksell as “the delivery of an ablative dose of ionizing radiation to the precise or focused target with stereotactic localization to elicit a specific radiobiologic response and causing its destruction, avoiding concomitant harm to the adjacent normal tissues” [4]. Conventionally, this is conducted in a single session with a fixed frame. Later many neurologic societies mutually decided to describe SRS in a way that contains both traditional single-dose SRS, and multi-dose (Multisession) SRS up to 5 doses (2-5 doses) [3]. A high dose of radiation results in single or double-stranded DNA breaks and initiates cellular and immune responses in the body soon after the exposure. A few examples are apoptosis, anti-angiogenesis, and initiation of immune responses.

“Stereotactic Radiotherapy (SRT)” refers to the delivery of targeted, precision radiation therapy by stereotactic localization of the target with more than 5 fractions as a standard long course of radiotherapy.

Throughout the past decade, research on neuro-oncology has increased awareness regarding the significance of cognitive function as a consequence of different treatment modalities for patients with a primary brain tumor [5]. Patients with brain tumors face several challenges causing mental and neurocognitive changes [6, 7]. In such patients, cognitive problems can be provoked by normal brain compression directly or indirectly or by reactive edema. Furthermore, the parenchymal glial tumor invasion right away into regions of the functional brain or indirectly through discontinuation of structures can additionally promote neurocognitive deficits [8-10].

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Neurocognitive functioning, with esteem to the outcomes of tumor and its treatment on the normal brain, is a valuable outcome measure for brain tumor patients, since neurocognitive deficits, even slight, may harmfully disturb the health-associated quality of life, the professional recovery, interactive relations, and routine events [11].

Conventional examination of the neurocognitive system is time taking and may exhaust the brain tumor patients, thus incorrect outcomes. Less time-taking options, *i.e.* the Mini-Mental State Examination (MMSE), might miscalculate the fraction of patients with a definite decline in cognitive function, and essential but little variations in cognition can be overlooked. Nevertheless, the MMSE seems to be susceptible enough to identify cognitive deficits related to the progression of the tumor. [12] In adults, the Mini-Mental State Examination (MMSE), established in 1975, is a standardized tool for the assessment of mental status, taking only 5-10 minutes to process, and is feasible to utilize frequently and consistently [13].

Limited studies have explored the problem of the likelihood of cognitive problems in patients who underwent radiosurgery [14]. Literature indicates that primary tumors of the brain and their management are frequently related to neurocognitive deficits; however, this knowledge remains inadequate. This study, therefore, intends to assess the neurocognitive functional impairment after stereotactic radiosurgery/ stereotactic radiotherapy of various brain tumors.

MATERIALS AND METHODS

It was a prospective observational study conducted at Neurospinal and Cancer Care Institute (NCCI), Karachi. A total of 100 patients who had undergone multisession stereotactic radiosurgery/stereotactic radiotherapy were selected between June 2009 and May 2011 after taking their written informed consent by employing a convenient sampling technique. The main study outcome was depending upon stereotactic radiosurgery that will improve neurocognitive function in patients undergoing the procedure. The patients who were unable to cooperate were excluded from the study. The Median Follow-up time was 12 months (range: 6-30 months). All patients were alive at the time of follow-up.

The type of tumor was classified and identified on a radiological and histological basis. Brain tumors were managed by multisession stereotactic radiosurgery/ stereotactic radiotherapy with the support of a modern linear accelerator (Synergy-S, ELEKTA-Crawley UK). The neurocognitive function (NCF) evaluation was done through Mini-Mental State Examination (MMSE) score questionnaire provided to patients at baseline (pre-radiosurgery) and 6 months after treatment (post-radiosurgery). MMSE contained 11 questions in 5 fields of condition assessment, attention, writing, calculation, language, and memory. The maximum possible score was 30 and a score lower than 23 was indicative of a cognitive disorder [13]. The MMSE score was classified into normal, mild, moderate, and severe with corresponding scores of 25-30, 21-24, 10-20, and <10 respectively. MMSE score was determined for the whole group of patients as well as the group who underwent prior surgery.

Data analysis was done through SPSS, 24.0. For continuous variables, summary statistics included mean and standard deviation whereas for categorical variables, percentages and frequencies were generated. ANOVA was applied to see differences before (pre-radiosurgery) and after treatment (post-radiosurgery) in terms of the severity of MMSE scores. The p-value of <0.05 was considered statistically significant.

RESULTS

The mean age of patients was 37.38±15.03 years and the majority (49%) belonged to the 27-44 years age group (**Table 1**). 60% of them were males whereas the most common pathology found was low-grade glioma (31%) (**Fig. 1**). In 77% of the cases, five fractions of radiotherapy were used. The median prescription isodose line was

Table 1: Descriptive Statistics of Patients (n=100).

Variable	Frequency (%) / Mean ± S.D. / Median (IQR)
Gender	
Male	60 (60%)
Female	40 (40%)
Age (years)	37.38±15.03
Age Groups (years)	
9-26	22 (22%)
27-44	49 (49%)
45-62	20 (20%)
62-80	9 (9%)
No. of Fractions	
Five	77 (77%)
Twenty-Five	23 (23%)
Prescription Isodose Line (%)	90 (65-100)
Mean Planning Target Volume (cm^3)	55.80 (4.2-200)
Mean Dose for Five Fractions (Gy)	30.19±7.14
Mean Dose for Twenty-Five Fractions (Gy)	46.42±10.74

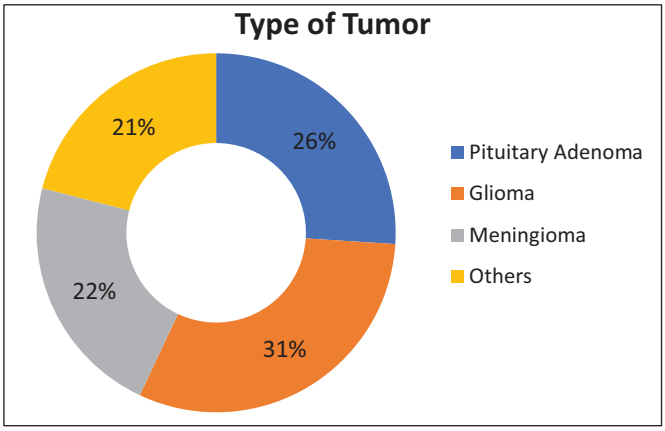

Fig. (1): Distribution of Tumor Type (n=100).

90% (range: 65-100%) whereas the median planning target volume was 55.80 cm^3 (range:4.2-200 cm^3). The overall mean dose for five fractions was 30.19±7.24 Gy (**Fig. 2**) whereas that for twenty-five fractions of radiotherapy was 46.42±10.74 Gy (**Fig. 3**). No patient received chemotherapy during illness.

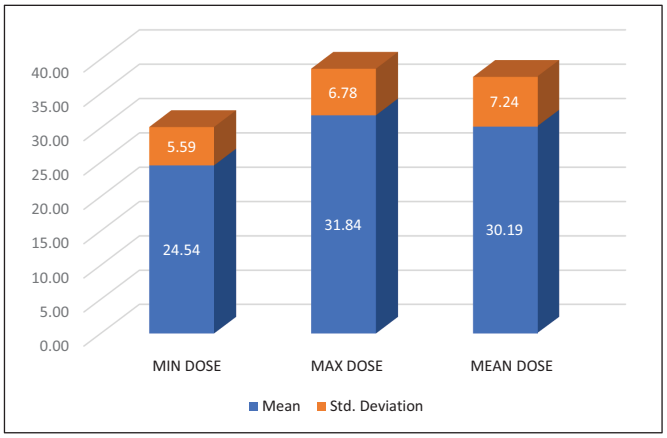

Fig. (2): Distribution of five fractions in Grays (Gy) (n=100).

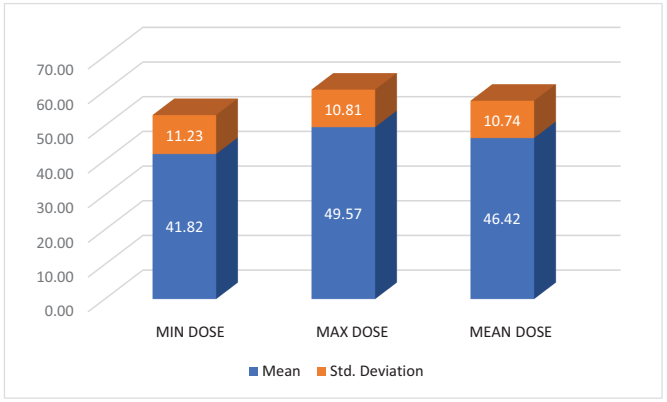

Fig. (3): Distribution of twenty-five fractions in Grays (Gy) (n=100).

At baseline, overall 23% of patients had normal MMSE scores before treatment (pre-radiosurgery SRS/SRT), while the cumulative increase in this percentage was 52% after treatment (post-radiosurgery SRS/SRT). Similarly, for mild and moderate cases, the cumulative rise of score levels was 48% from 27%, and 24% from 12% respectively was observed. For the severe score level, the number was reduced to 5% from 9%. Moreover, the comparison of different MMSE score levels showed that there was a significant increase in patients with normal score levels and a significant decrease in patients with mild and moderate score levels after treatment (post-radiosurgery SRS/SRT) (P=0.006) at 6 months (**Table 2, Fig. 4**).

Of thirty-seven patients (37%) who had undergone prior surgery, 24% had normal MMSE scores before treatment (pre-radiosurgery SRS/SRT), whereas the cumulative increase in this percentage was 54 % after treatment (post-radiosurgery SRS/SRT). Similarly, for mild, moderate, and severe score levels, the respective

Table 2: Mini-Mental State Examination Score (MMSE Score) for all the cases (n=100).

Variable	Before Treatment (Pre-Radiosurgery-SRS/SRT)		After Treatment (6 months) (Post-Radiosurgery-SRS/SRT)		P-Value
	Frequency	Percent (%)	Frequency	Percent (%)	
Normal	23	23	52	52	**0.006**
Mild	48	48	27	27	
Moderate	24	24	12	12	
Severe	5	5	9	9	
Total	**100**	**100**	**100**	**100**	

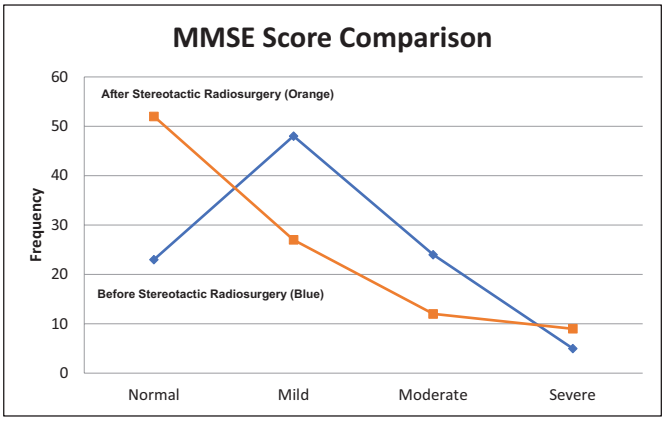

Fig. (4): Comparison of Mini-Mental State Examination (MMSE) Score for all the cases (n=100).

levels were improved to 51% from 27%, 18.9% from 16.2%, and 5.4% from 2.7%. Moreover, the comparison of different MMSE score levels showed that there was a significant increase in patients with normal score levels and a significant decrease in patients with mild and moderate score levels after treatment (post-radiosurgery SRS/SRT) (P=0.046) at 6 months (**Table 3**).

DISCUSSION

This study represents the long-term effects of stereotactic radiosurgery/stereotactic radiotherapy on the neurocognitive functions of patients with various brain tumors. Many factors were considered responsible for the deterioration of NCF during the illness. Primarily, disease presence or progression of the disease is the main factor affecting NCF, others include surgery, chemotherapy, and radiotherapy.

Table 3: Mini-Mental State Examination Score (MMSE Score) for patients Having prior surgery (n=100).

Variable	Before Treatment (Pre-Radiosurgery-SRS/SRT)		After Treatment (6 months) (Post-Radiosurgery-SRS/SRT)		P-Value
	Frequency	Percent (%)	Frequency	Percent (%)	
Normal	9	24.3	20	54.1	0.046
Mild	19	51.4	10	27.0	
Moderate	7	18.9	6	16.2	
Severe	2	5.4	1	2.7	
Total	**37**	**100.0**	**37**	**100.0**	

Prior studies have shown that the patients with brain tumors who were managed by surgery had high cognitive and mental problems in contrast to those who were not treated with surgery [15, 16]. Some potential neuropsychological research in patients with breast cancer has also shown that a considerable category of patients has declined cognitive function followed by chemotherapy, and incidence was usually between 20-60% [17-19]. Few other studies further revealed that patients show post-chemotherapy changes concerning memory and learning speed of processing the information and decision-making performance [20-22]. It has also been identified that a variety of delayed adverse effects on cognitive function may occur including deficits in inattention, the ability to learn, working memory, and executive function at one end to disabling dementia at another end [23].

Similarly, radiotherapy in brain tumors is considered to be the offender behind the cognitive impairment of such patients. Tallet *et al.* showed that neurocognitive functions as assessed by MMSE were impaired after "whole brain radiotherapy" in the following year but appeared strongly related to uncontrolled brain metastases. MMSE has some disadvantages such as difficulty in the identification of mild cognitive impairment, and difficulty in the recording of changes in patients with severe dementia. Additionally, education, age, the socioeconomic and cultural background may influence biases in the scores of MMSE [24]. Aoyama *et al.* reported that control of brain tumors is the key factor for stabilizing neurocognitive functions rather than the type of therapy [25, 26].

In one of the studies, it was established that the global health-associated quality of life and cognitive scores were considerably enhanced in patients receiving stereotactic radiosurgery as compared to whole-brain radiotherapy [27]. Lippitz *et al.* reported a progressive influence on the cognitive status and health-related quality of life in the patients treated by stereotactic radiosurgery as matched to whole-brain radiotherapy [28, 29]. The Quality of life was also analyzed as part of the prospective randomized investigation that displayed statistically important enhancement in clinical performance after reducing the dose of steroids with fractionated radiosurgery [30].

The treatment with Gamma knife for brain metastases recognized that the life quality parameters remained constant or enhanced in the absence of tumor progression [31]. The average duration of decline in MMSE Score was substantially reduced in SRS alone as compared to the SRS used with WBRT [32] The significance of WBRT has been reduced due to its adverse effects on neurocognition. Nevertheless, SRS was established as the supportive therapy for WBRT in patients having limited brain metastases [33].

However, a similar trend was observed in MMSE scores in this study *i.e.* the majority of the patients had significant improvement in NCF as assessed by MMSE after stereotactic radiosurgery where most of the mild and moderately impaired NCF were converted to normal. Comparable results were found in the patients who had undergone surgery before radiosurgery. A slight rise was seen overall in severe impairment cases, *i.e.*, from 5% before SRS to 9% after SRS, which was thought to be related to tumor progression as also reported by Tallet *et al.* earlier [24].

The characteristics of stereotactic radiosurgery such as better dose delivery, better conformity, and better selectivity increase the tumor control rates and reduces the normal brain doses that result in limiting radiation-related cognitive impairments. On the other hand, better tumor control with stereotactic radiosurgery also results in the improvement of preexisting poor cognitive functions. Moreover, a reduction in radiotherapy volumes (GTV, CTV, PTV) and remarkable sparing of organs at risk (OAR), immobilization devices, modern treatment planning systems, and use of modern radiotherapy techniques like IMRT/VMAT resulted in a significant decrease in overall doses to the brain and critical organs. Therefore, NCF impairment secondary to radiation must be explored with currently available radiotherapy/ radiosurgery delivery techniques and available modern equipment.

The scope of this study was limited to 6 months of follow-up and given objectives were achieved. Further long-term assessment of NCF/overall survival in this group of patients for 5-10 years intervals may be a valuable option. Any future study in this regard may emphasize detailed types of tumors and categories depending on more specific locations of tumors. Although this study sampled an extensive range of patients treated with stereotactic radiosurgery/stereotactic radiotherapy, it is acknowledged that study results might not be free from observer bias. Reflecting on the effects of radiation and to what range they are consistent with other scoring systems of cognitive functions would be informative and valuable to standardize the effects of radiation therapy on cognitive functions.

CONCLUSION

Stereotactic radiosurgery results in the improvement of neurocognitive functions. The uncertainties about the potential neurotoxicity of radiation should be moderated by the consideration that it significantly delays the time to tumor progression, which in turn interrupts the cognitive deterioration related to tumor advancement. Previously known radiation-related impairment of NCF should be re-explored in light of modern radiosurgery/ radiotherapy techniques with larger studies.

ETHICAL APPROVAL

Ethical approval was taken from the institutional ethical review committee. All procedures performed in studies involving human participants were in accordance with

the ethical standards of the institutional and/or national research committee and with the Helsinki declaration.

CONSENT OF PUBLICATION

We undersigned, give our consent for the publication of identifiable details within the text to be published in the above journal and article.

AVAILABILITY OF DATA

The data will be provided on request.

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CONFLICT OF INTEREST

We confirm that no author/co-author(s) have any personal or business interest in or potential gain from any of the organizations or projects.

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AUTHOR'S CONTRIBUTION

Azhar Rashid (concept, data collection, literature review, discussion), Binish Essani (data collection, literature review, and analysis), Muhammad Ali Memon (data collection, interpretation, discussion), Abdul Sattar M Hashim (analysis, discussion, review).

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