

Trends in cognitive dysfunction following surgery for intracranial tumors

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Abstract

Background: This study was conducted to prospectively assess the cognitive function of patients with intracranial tumors.

Methods: The cognitive status of patients with intracranial tumors were prospectively studied before surgery, and later at 1 and 6 months following surgery, on purposive sampling, using validated post graduate institute (PGI) battery for brain dysfunction (score 0–30) with a higher dysfunction rating score indicating poor cognitive status.

Results: Out of 23 patients enrolled, 20 could complete the study. They had substantial cognitive dysfunction before surgery (score 17.1 ± 9.4). Though there was no significant improvement (16.9 ± 9.0) at 1 month, the score improved significantly (10.3 ± 9.2) at 6 months following surgery ($P = 0.008$). The improvement was relatively subdued in intra-axial, malignant, and radiated tumors. Overall, there was a significant improvement in mental balance ($P = 0.048$), verbal retention of dissimilar pairs ($P = 0.01$), and recognition ($P = 0.01$), while dysfunction persisted in the domains of memory, verbal retention to similar pairs, and visual retention.

Conclusion: Patients with intracranial tumors have substantial cognitive dysfunction, which tend to show significant improvement beyond 6 months following surgery, especially among tumors, which were extra-axial, benign, and nonirradiated.

Key Words: Cognitive dysfunction, intracranial tumor, memory scales, surgery

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INTRODUCTION

Intracranial tumors are one of the common causes of mortality and morbidity worldwide.^[5,16,21] About 60–90% patients with intracranial tumors face cognitive impairments along with some emotional and behavioral changes.^[1,35] Cognitive function, defined as the processes by which sensory input is elaborated, transformed, reduced, stored, recovered, and used,^[27] is known to be altered in patients with intracranial tumors, encompassing memory deficits, confusion, inefficiency in executive functioning, poor attention span or concentration, organizational ability, poor arithmetic or language skills,

lack of mental balance, inability to coordinate various motor activities, inability to learn or process new information, etc.^[1,4,12,35]

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Cognitive dysfunction in these patients can impair the intellectual functions, activities of daily living (ADL), interpersonal relationships, and education and profession of the patients. It may prevent them from fulfilling their familial, professional, and social obligations thus can lead to poor quality of life (QoL) not only in patients,^[34] but also in caregivers.^[25] The importance of identifying and managing the cognitive dysfunction is growing as the survival length and survival rate of these patients are increasing due to innovations in the treatment modalities.

The factors leading to cognitive deficits include paraneoplastic effects such as duration and location of the tumor,^[6,25] brain edema and associated neuroinflammation,^[20] and the impact of treatment modalities like surgery, chemotherapy, radiotherapy, or ventriculo-peritoneal shunt. It is reported that loss of white matter or failure of white matter to develop appropriate for the age can account for cognitive deficits.^[4,8,11,30] Cognitive dysfunction is reported in patients with intracranial tumors irrespective of the treatment modality they have undergone.^[36]

There is lack of evidence on the domains, magnitude, and duration of cognitive dysfunction present in patients with intracranial tumors. Cognitive deficits of these patients are neither monitored nor managed during the follow-up visits. Knowing the trend in cognitive dysfunction is necessary to develop protocols and tools for assessing cognitive function. Identifying the magnitude and type of cognitive dysfunction, may aid in various cognitive behavioral therapies to improve the QoL of patients and caregivers. Appropriate interventions can be developed based on the specific cognitive impairment of the patients. However, there is a paucity of studies on trends in cognitive dysfunction with respect to the treatment provided. With this in mind, this study was undertaken to assess the cognitive function of the patients with intracranial tumors before surgery, later at 1 month and 6 months following surgery.

MATERIALS AND METHODS

A longitudinal study was done to assess the cognitive changes in patients with intracranial tumors. Using purposive sampling, 23 newly diagnosed conscious intracranial tumor patients who were availing treatment from a Tertiary Care Center at Chandigarh and consented to the study were enrolled. Ethical clearance was obtained from the Institute Ethics Committee, and written consent was taken from all study subjects and guardians. All patients who underwent surgical management with or without radiotherapy or chemotherapy were followed up for cognitive assessment. Cognitive status was assessed before surgery, later at 1 month and 6 months following surgery.

Cognitive changes of patients were assessed using PGI battery for brain dysfunction (BBD) which assesses various domains of cognitive functions.^[10] For this study, patients were assessed for 10 domains remote memory, recent memory, mental balance, attention and concentration, delayed recall, immediate recall, verbal retention to similar and dissimilar pairs, visual retention, and recognition.^[10] PGI BBD is a valid and comprehensive tool with a test-retest reliability of up to 0.85 and split half reliability of 0.9.

The raw score of each domain was made into a converted score according to the educational level of the patients. The total dysfunction score was calculated by adding the dysfunction scores of all domains and higher the dysfunction rating score poorer the cognitive status. The total maximum possible score is 30 (3 in each domain).

SPSS 21 (IBM, New York, USA) was utilized for descriptive and inferential statistics. Repeated measures ANOVA was used to compare the dysfunction score at different assessment.

RESULTS

Out of 23 patients with intracranial tumors enrolled, 20 patients were followed up as 2 patients died, and 1 patient was lost to follow-up. As per the sociodemographic data of patients shown in Table 1, the mean age of the patients was 46.1 ± 10.1 years with a range of 29–70 years. Gender difference in patients was not much evident as 52% were male, and 48% were female. The majority of the patients (91%) were married. Furthermore, 48% of them were illiterate, and the employed patients accounted for 30%.

Table 1: Sociodemographic profile of patients (n=23)

Variables	n (%)
Age (years)	
Mean \pm SD	46.13 \pm 10.09
Range	29-70
Gender	
Female	11 (48)
Male	12 (52)
Education	
Illiterate and primary	11 (48)
Elementary to senior secondary	8 (35)
Graduate and above	4 (17)
Marital status	
Married	21 (91)
Unmarried	2 (9)
Occupation	
Unemployed	15 (65)
Employed	7 (30)
Student	1 (4)

SD: Standard deviation

Table 2 reveals the clinical profile of the patients. It was found that 87% of the patients had supratentorial tumors and in 52% of the patients tumor was located on the left side of the brain. Illness onset was <1 month in 61% of the patients. Radiotherapy and chemotherapy, which was started after 2–3 weeks of surgery, were given to 30% and 13% of the patients, respectively. At 1 month assessment of cognitive function, they were on radiotherapy or chemotherapy, but none was receiving the same at 6 months.

Cognitive changes in patients

The cognitive function of the patients was significantly affected as the cognitive dysfunction score was 17.1 ± 9.4 out of 30 before any definite treatment (higher the score higher the dysfunction). There was an only mild nonsignificant improvement in the dysfunction rating score (16.91 ± 9.0) at 1 month of follow-up. There was a significant improvement only in recognition ($P = 0.04$).

There was a significant improvement in cognitive function at 6 months with the dysfunction rating

score decreasing from 17.1 ± 9.4 to 10.3 ± 9.2 ($P = 0.01$) [Figure 1]. Among the domains of cognitive function, there was significant improvement at 6 months in mental balance ($P = 0.048$), verbal retention of dissimilar pairs ($P = 0.01$), and recognition ($P = 0.01$) [Table 3]. While other domains had shown trends toward improvement, recent memory, immediate recall, verbal retention to similar pairs, and visual retention did not change much.

As shown in Figures 2 and 3, cognitive dysfunction score was higher at all points of assessment in patients with intra-axial tumors and malignant tumors as compared to others. Patients who underwent radiotherapy were also found to have consistently higher dysfunction score [Figure 4], compared to those who did not receive radiotherapy. While even patients with infratentorial tumors had some cognitive dysfunction, which remained static, higher dysfunction score in patients with supratentorial tumors showed improvement with treatment [Figure 5].

Table 2: Clinical profile of the patients (n=23)

Variables	n (%)
Tumor location	
Supratentorial	20 (87)
Infratentorial	3 (13)
Tumor side	
Right	7 (30)
Left	12 (52)
Middle	4 (18)
Duration of illness at first visit	
<1 month	14 (61)
>1 month	9 (39)
Radiotherapy received	7 (30)
Chemotherapy received	3 (13)

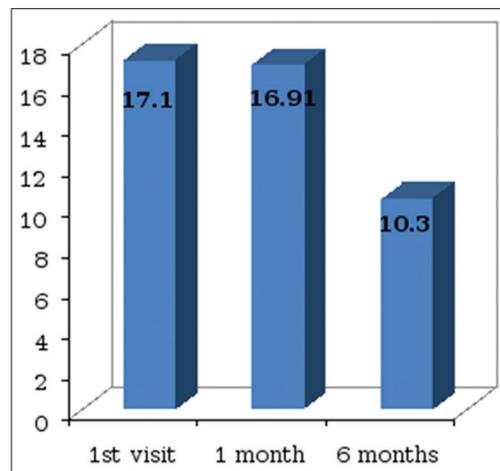


Figure 1: Cognitive dysfunction score of the patients (P = 0.008)

Table 3: Domain-specific cognitive dysfunction score of the patients

Cognitive function	Dysfunction rating score			P	
	First visit	1 month	6 months	First visit versus 1 month	First visit versus 6 months
Remote memory	1.2±1.28	1.14±1.39	0.85±1.38	1	0.25
Recent memory	0.8±1.15	0.33±0.85	0.5±1.1	0.14	0.37
Mental balance	2.15±1.31	2.05±1.24	1.35±1.46	0.6	0.048*
Attention and concentration	2±1.38	2.1±1.14	1.6±1.54	0.8	0.24
Delayed recall	2.1±1.29	2.24±1.04	1.85±1.46	0.65	0.41
Immediate recall	0.95±1.36	1.33±1.46	0.95±1.39	0.41	1
Verbal retention to similar pairs	1.8±1.28	2.05±1.12	1.65±1.46	0.26	0.64
Verbal retention to dissimilar pairs	2.6±0.94	2.29±1.19	1.8±1.32	0.22	0.009*
Visual retention	1.9±1.44	2.2±1.29	1.75±1.51	0.39	0.659
Recognition	1.6±1.39	1.19±1.44	0.7±1.3	0.038*	0.014*
Total dysfunction rating score	17.1±9.36	16.91±8.98	10.3±9.24	0.71	0.008*

*P<0.05

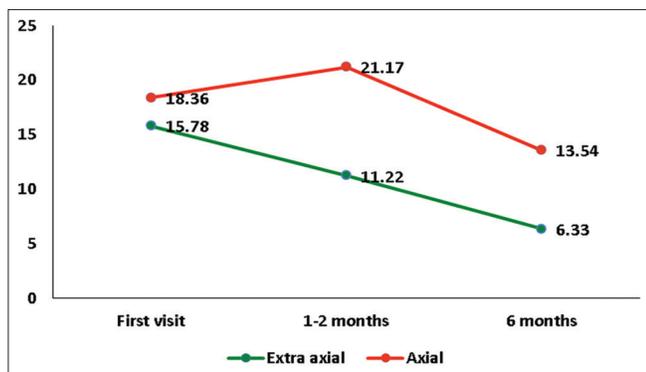


Figure 2: Cognitive dysfunction: Extra-axial versus axial tumors

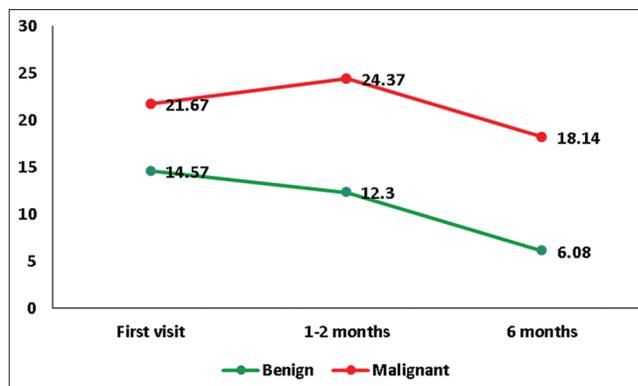


Figure 3: Cognitive dysfunction: Benign versus malignant tumors

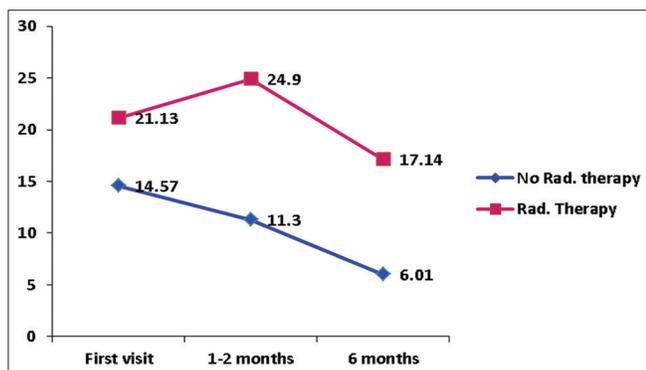


Figure 4: Cognitive dysfunction: Patients received radiotherapy versus no radiotherapy

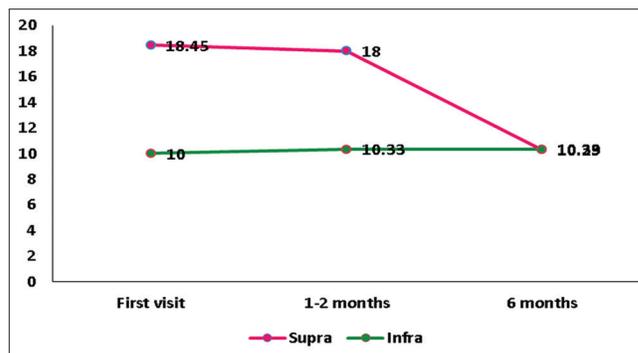


Figure 5: Cognitive status: Supratentorial versus infratentorial tumors

DISCUSSION

Cognitive dysfunction in patients with intracranial tumors is well evident in literature.^[14,17,19,32,37] However, there is paucity on a prospective analysis of cognitive dysfunction in these patients with respect to surgery. This study focused on trends in cognitive function from before surgery until 6 months after surgery.

There are many domains of cognitive function. There is no conclusive evidence on the particular domain being affected due to the difference in the cognitive tools used in various studies. In this study, most affected by all domains on first assessment was verbal retention to dissimilar pairs, an indicator of new learning. Other domains highly affected were a mental balance, attention, concentration, and delayed recall. The domains least affected were a recent memory and immediate recall. Cognitive deficits reported in literature include deficits in working memory, cognitive control, cognitive processing speed, visual searching, planning foresight, general attention,^[14] executive function, language,^[32] concentration performance intelligent quotient, verbal intelligent quotient, and visuoconstruction.^[8,14,23,26,30,32]

Cognitive deficits are reported in these patients before any definitive treatment, at 3 months postradiotherapy,^[17] and even at 5 years of follow-up.^[29] Cognitive decline in

some domains among patients receiving radiation therapy was reported by Prabhu *et al.* in 2014 at 1, 2, 3, and 5 years.^[31] However, Arreguín González *et al.* reported in a case report that cognitive functions such as attention, language, memory, praxis, thought, calculation, and executive function which were impaired before surgery were improved 3 months after surgery, but not after 1 week of surgery.^[2] Cognitive improvements at 3 months postoperatively are also reported by Koizumi *et al.* in 2014 in patients suffering from meningioma and have associated it with recovered neuronal viability as evidenced by single-photon emission computed tomography.^[18] In this study, at 1 month follow-up after the surgery, the cognitive function remained same without much improvement. However, there was a significant improvement in recognition, and mild improvement was shown in domains of recent memory, and verbal retention to dissimilar pairs. Even 1 month could be too early for regaining the cognitive function which was disturbed due to the paraneoplastic or treatment effect.

The overall cognitive function at 6 months following surgery was significantly improved ($P = 0.008$). Though there was an improvement of cognitive function in all domains at 6 months, mental balance, verbal retention of dissimilar pairs and recognition have shown significant improvement [Table 3]. There was a consistent

improvement in all these 3 domains from the baseline to 1 month and then to 6 months. Even though the overall cognitive function was significantly improved at 6 months, dysfunction persisted in few of the cognitive domain such as recent memory, verbal retention, and visual retention. The improvement in cognitive status following surgery is likely due to improved perfusion in the adjacent areas.^[7]

The cognitive deficits identified in this study before initiation of radiotherapy, chemotherapy, or surgery explains the influence of tumor and its pathological process on cognitive deficits. It is reported that patients with frontal glioma exhibit more cognitive deficits due to the damage in the frontal lobe.^[25] Even though the influence of tumor location on cognitive dysfunction was not analyzed in this study, it remained inferior in patients with axial tumors as compared to patients with extra-axial tumors.

Cognitive function was found to be better in patients with benign tumor and poor in patients who underwent radiotherapy at all points of assessment. The majority of the patients who received radiotherapy had a malignant tumor. The aggressive nature of the tumor along with radiotherapy can result in higher cognitive dysfunction. A mild deterioration in cognitive function at 1 month observed in patients of the malignant tumor could be due to the transient neurotoxic effect of radiation.^[11,31] There could be the negative impact of radiation-induced inflammation on hippocampal neurogenesis as shown in animal models.^[33] Even though reduced brain volume in patients who are undergoing cranial irradiation is reported by many authors, Horská *et al.* in 2010 reported that the reduced vermis volume was not responsible for cognitive deficits and highlighted the importance of considering the influence of brain malignancy and preradiation treatment on cognitive deficits.^[15] Radiation therapy also produces leukoencephalopathy, radiation necrosis, and dementia.^[35] Armstrong *et al.* in 2002 have reported reduced toxic effects with current radiation therapy techniques.^[1] Increased severity of cognitive dysfunction is reported in patients who received radiotherapy along with chemotherapy.^[22,38] It is reported having cognitive dysfunction like memory loss, decreased information processing speed, and reduced attention in patients who received chemotherapy for a brain tumor.^[24] Though the influence of chemotherapy on cognitive dysfunction is not studied much, Fliessbach *et al.* in 2005 reported that methotrexate-based chemotherapy did not produce gross cognitive deficits in patients with lymphoma at 1 year of follow-up.^[13] However, he observed that cognitive deficits were retained when patients had a residual tumor.

Cognitive dysfunction leads to difficulties in performing cognitive tasks, contribute to functional disability, and behavioral changes and thus, makes the individual

handicapped.^[30] Patient's ability to perform ADL is directly related to the cognitive function.^[39] Caregivers of patients with cognitive deficits are reported providing more assistance with ADL than those without cognitive deficits.^[28] Cognitive deficits in these patients are a good predictor of poor QoL not only in patients,^[3] but also in family caregivers.

This study is limited because of small sample size. Multicenter studies of larger sample size are needed to identify the significant relationship of various factors described in this study. A long-term follow-up of cognitive function will aid in cognitive rehabilitation which can be individualized for the patients with and without improvement in the cognitive function. As the cognitive dysfunction was found persisting even at 6 months, monitoring cognitive task, and developing appropriate management strategies are important to equip these patients in their personal, as well as social life. The neuro-oncology team must facilitate this to improve QoL for patients and their caregivers. Socioeconomic barriers are reported to result in irregular follow-up visits and poor outcome among neurosurgical patients.^[9] Guiding the patients and caregivers to overcome such barriers could also improve the rate of follow-up. Present findings can aid in exploring more about cognitive aspect of these patients.

CONCLUSION

Patients with intracranial tumors have substantial cognitive dysfunction before any definite treatment. However, there was a significant improvement in cognitive function at 6 months following surgery with deficits persisting in some domains. One of the long-term goals for the neuro-oncology team must be to reduce the cognitive sequelae of these tumors with improvement in treatment modalities.

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Conflicts of interest

There are no conflicts of interest.

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