Original Article

# Profiling Cognitive Deficits in Intra-Axial and Extra-Axial Tumors Using Addenbrooke's Cognitive Examination as a Screening Tool: An Indian Experience

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## Abstract

**Background:** Tumors of the brain, whether intra- or extra-axial, results in cognitive deficits. The aim of the present study was to profile cognitive deficits using Addenbrooke's Cognitive Examination-Malayalam (ACE-M) as a screen and to determine the sensitivity and specificity of the same. **Methods:** Seventy-four drug naïve patients diagnosed to have brain tumors were assessed for cognitive functioning using ACE-M before surgery. **Results:** Patients with high-grade intra-axial tumors showed a significant association on the cognitive domains of registration (0.04), recall (0.01), and visuospatial functioning (0.02). Gender showed an association between registration (0.02) and verbal fluency (0.02) with females performing better while education was significantly associated with retrograde or remote memory (0.00) with college-educated sample performing better. Significance was assumed at $P < 0.05$. In extra-axial tumors, laterality had a single association with recall (0.02). Males showed a significant cognitive decline on the cognitive domains of attention (0.02), recall (0.05), naming (0.02), and language functions (0.01). College educated group performed better on registration (0.01), recall (0.09), naming (0.00), and visuospatial functioning (0.00). The area under the receiver operating characteristic curve was estimated as 0.75, which indicates fairly good discriminative ability with a cut off of 71/100; sensitivity at 77.3 and specificity fixed at 67. **Conclusions:** ACE-M is capable of bringing out cognitive deficits along with a number of cognitive domains in patients with intra- and extra-axial tumors in the capacity of a screen, with fairly good levels of sensitivity and specificity.

**Keywords:** *Addenbrooke's Cognitive Examination, cognitive deficits, intra- and extra-axial tumors*

## Introduction

Impaired cognition and its ramifications, although ubiquitous in brain tumors, is an under addressed issue in India. This is largely due to the inverse proportion of clinicians and neuropsychologists to the patient volume in a developing country like India. In addition, the dearth of time and resources stops those who are interested in doing anything of significance in this area.

Tumors of the brain, irrespective of whether they are intra- or extra-axial, result in deficits of the executive,[1] visual–spatial,[2-5] linguistic[3,6-8] functions, and behavioral[9] changes. The cognitive alterations resulted from the neoplastic processes are related to the compression, displacement, destruction, or ischemia of intracranial structures, as well as, associated cerebral edema.[10] It is not just the tumor alone that causes the cognitive deficits, but the treatment regimens of surgery, radiation, chemotherapy, and adjunctive medications such as corticosteroids and anticonvulsants which largely contribute to the impairment.[11]

Cognitive function, with higher survival rates and response on brain imaging, is increasingly regarded as an important outcome measure in patients with brain tumors.[12] It has an implication on a number of dimensions ranging from activities of daily living to quality of life and is also an index of recovery as well as relapse. It also points toward illness progression. In addition, the prevalence of neurocognitive dysfunction has implications for decision-making and informed consent.[13] Last but not least, cognitive function profiling has a prognostic value too.[14-16] This has been brought out in a study by Meyers and Hess[14] where recurrent malignant gliomas showed that



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cognitive deterioration may precede radiographic evidence of progression by almost 6 weeks.

Mini Mental Status Examination (MMSE)[17] is one of the widely used instruments in cognitive screening used in brain tumor clinics.[18,19] However, MMSE has poor sensitivity with high ceiling effect as well as poor specificity,[20] and there is little emphasis on executive functions and verbal fluency. MMSE fails in situations where the cognitive impairments are mild, where there are focal lesions,[21] and it cannot pinpoint the cognitive improvements brought about by treatment.[22] The other commonly used cognitive screening tools in brain tumor are Montreal Cognitive Assessment (MoCA), clock drawing test, three item recall, single item memory question, and Addenbrooke's Cognitive Examination (ACE). MoCA has more demanding assessments of executive function, visuospatial function, new learning, attention, and information processing speed,[23] but it has not been translated and adapted to any of the Indian languages.

Studies have found ACE[24] to be a more sensitive test of cognitive dysfunction than the MMSE, revealing significant baseline cognitive impairment in tumors.[22] ACE-revised (ACE-R) is an extended cognitive screening tool that incorporates the Mini-Mental State Examination (MMSE).[25] Although it is not as comprehensive as a detailed neuropsychological battery, or a substitute, ACE can point out the deficits across a number of cognitive domains. ACE has shown promising diagnostic performance and could be administered at primary care level[26] which can extract significant performance/nonperformance indicators across several cognitive domains. Moreover, ACE is already translated and adapted to Malayalam, a regional Indian language. Hence, ACE-Malayalam (ACE-M) was used as the cognitive screening tool in this study and an attempt to find out the sensitivity and specificity of the tool in the present sample were made.

## Methods

### Design and sample

The study had a prospective, cross-sectional design.

The sample comprised 74 patients diagnosed to have brain tumors, before surgical intervention. Patients were seen after the diagnosis was made and they were assessed for cognitive functioning using ACE. Informed patient consent was obtained and the study was approved by Institutional Ethics Committee.

Patients selected were ≥18 years of age, and were not undergoing any adjuvant therapies. Only literate patients with no sensory impairment were included in the study. Patients with gross cognitive deficits with poor comprehensive abilities, major mental illnesses, who are on anticonvulsants and corticosteroids and those with aphasias were excluded from the study.

### Material

The ACE-R is an extended cognitive screening tool that incorporates the Mini-Mental State Examination (MMSE). ACE-M, which was translated and adapted to Malayalam[27] was administered to the patients who met the inclusion or exclusion criteria. The cognitive domains assessed using ACE-M is tabulated in Table 1.

### Statistical analysis

All the analyses were performed using IBM SPSS version 20. Descriptive statistics were found. For comparison between groups Mann–Whitney *U*-test for nonnormal variables and independent sample *t*-test for normally distributed variables were used. Significance was assumed at $P < 0.05$.

## Results

The sample was split into those with intra-axial tumors ($n = 46$) and extra-axial tumors ($n = 23$). The two groups were analyzed for association of cognitive deficits with tumor variables of grade and laterality as assessed by ACE-M. Patient variables of education and gender were also analyzed for association with cognitive deficits [Table 2].

In line with the WHO Grading System, the tumors were classified into the high- and low-grade. Patients

**Table 1: Cognitive domains as assessed by Addenbrooke's Cognitive Examination - Malayalam**

| Variables |
|---|
| Orientation |
| Attention |
| Registration |
| Recall |
| Remote memory |
| Verbal fluency |
| Naming |
| Language |
| Visuospatial |

**Table 2: Patient socio-demographic details**

| | Number of patients (%) |
|---|---|
| Gender | |
| Male | 43 (58) |
| Female | 31 (42) |
| Education | |
| School educated | 40 (54) |
| College educated | 34 (46) |
| Tumor grade | |
| High-grade | 27 (41) |
| Low-grade | 39 (59) |
| Laterality | |
| Right | 46 (66) |
| Left | 24 (34) |
| Intra-axial tumors | 46 (67) |
| Extra-axial tumors | 23 (33) |

with high-grade intra-axial tumors showed a significant association on the cognitive domains of registration (0.04), recall (0.01), and visuospatial functioning (0.02). A significant association is also found between the tumor grade and ACE-M score (0.004) as well as with MMSE score (0.018), with high-grade intra-axial tumors more cognitive deficits than the low-grade intra-axial tumors [Table 3].

Association of gradable extra-axial tumors with cognitive domains could not be analyzed due to inadequate number of high-grade tumors under this category.

No significance was found on laterality in patients with intra-axial tumors.

Interestingly enough, laterality in patients with extra-axial tumors had a single association with recall (0.02) [Table 4].

Patient variables of gender and education showed associations with cognitive variables, but differently on intra- and extra-axial tumors. In intra-axial tumor sample gender showed an association between registration (0.02) and verbal fluency (0.02) with females performing better, while education was significantly associated with retrograde or remote memory (0.00) with college-educated sample putting in a better performance [Table 5].

In extra-axial tumors, a lot more associations with cognitive variables were found on gender and education than in intra-axial tumors. Males showed a significant cognitive decline on the cognitive domains of attention (0.02), recall (0.05), naming (0.02), and language functions (0.01). College educated group performed better on registration (0.01), recall (0.09), naming (0.00), and visuospatial functioning (0.00) receiver operating characteristic (ROC) curve was used to estimate the sensitivity and specificity of ACE-M. The area under the ROC curve was estimated as 0.75, which indicates fairly good discriminative ability. A cut off of 71/100 was computed with sensitivity at 77.3 and specificity fixed at 67 [Figure 1].

**Table 3: Association of tumor grade in intra-axial tumors with cognitive domains**

| Cognitive variables | Mean (SD) | | *P* |
|---|---|---|---|
| | High-grade (*n*=24) | Low grade (*n*=22) | |
| Orientation | 9.04 (1.33) | 9.59 (0.73) | 0.139 |
| Attention | 4.08 (1.28) | 4.41 (1.10) | 0.309 |
| Registration | 14.04 (4.35) | 16.55 (5.45) | 0.048 |
| Recall | 3.21 (2.95) | 5.36 (2.92) | 0.016 |
| Remote memory | 3.29 (1.12) | 3.50 (0.80) | 0.648 |
| Verbal fluency | 8.79 (3.02) | 10.23 (3.15) | 0.084 |
| Naming | 9.67 (2.82) | 10.36 (2.98) | 0.226 |
| Language | 14.71 (1.52) | 15.27 (1.42) | 0.110 |
| Visuospatial | 2.13 (1.60) | 3.18 (1.53) | 0.028 |
| ACE score | 67.88 (12.54) | 78.05 (11.61) | 0.004 |
| MMSE | 24.96 (2.91) | 26.95 (2.28) | 0.018 |

*P*<0.05. ACE – Addenbrooke's Cognitive Examination; MMSE – Mini Mental Status Examination; SD – Standard deviation

**Table 4: Association of laterality with cognitive domains in extra axial tumors**

| Cognitive domains | Mean (SD) | | *P* |
|---|---|---|---|
| | Right (*n*=10) | Left (*n*=12) | |
| Orientation | 8.70 (1.703) | 7.67 (2.839) | 0.525 |
| Attention | 3.90 (1.595) | 3.67 (1.775) | 0.860 |
| Registration | 15.20 (5.203) | 14.00 (6.928) | 0.620 |
| Recall | 4.50 (2.121) | 2.42 (1.832) | 0.028 |
| Remote memory | 3.30 (0.949) | 2.67 (1.557) | 0.397 |
| Verbal fluency | 9.30 (2.163) | 7.83 (3.664) | 0.245 |
| Naming | 10.30 (1.889) | 9.33 (3.525) | 0.710 |
| Language | 14.70 (1.767) | 13.75 (4.245) | 0.942 |
| Visuospatial | 2.10 (2.079) | 2.17 (1.946) | 0.946 |
| ACE score | 73.40 (16.728) | 62.58 (21.673) | 0.262 |
| MMSE | 25.70 (3.498) | 22.67 (7.414) | 0.332 |

*P*<0.05. ACE – Addenbrooke's Cognitive Examination-Malayalam; MMSE – Mini-Mental Status Examination; SD – Standard deviation

## Discussion

Neuropsychological literature chronicles plenty of studies carried out on cognitive deficits in tumors, but the account of studies which explored cognition specifically in the discrete categories of intra- and extra-axial tumors is scarce. While it is no doubt that comprehensive neuropsychological batteries can bring about an in-depth description of cognitive status, what would be viable in a busy center would be a screening test which can leave pointers to almost all the areas of cognition. In the hands of a competent neuropsychologist, ACE can be used to quickly assess the cognitive status on different domains. The discussion below testifies clearly that cognitive deficits are brought out by ACE-M.

Patients with high-grade intra-axial tumors have deficits on registration, immediate recall, and visuospatial perception,

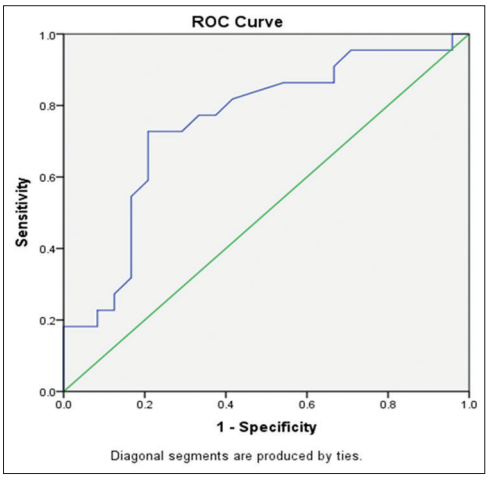


**Figure 1: Addenbrooke's cognitive examination-Malayalam receiver operating characteristic curve for determination of sensitivity and specificity**

**Table 5: Association of gender and education with cognitive domains**

| Cognitive domains | Intra-axial tumors | | | | | | Extra axial tumors | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Gender, mean (SD) | | | Education, mean (SD) | | | Gender, mean (SD) | | | Education, mean (SD) | | |
| | Male | Female | *P* | School | College | *P* | Male | Female | *P* | School | College | *P* |
| Orientation | 9.14 (1.30) | 9.59 (0.62) | 0.43 | 9.33 (1.20) | 9.27 (1.03) | 0.63 | 8.42 (1.38) | 7.82 (3.12) | 0.79 | 7.57 (2.74) | 9.00 (1.22) | 0.25 |
| Attention | 4.17 (1.14) | 4.35 (1.32) | 0.34 | 4.42 (0.97) | 4.05 (1.40) | 0.54 | 4.58 (0.79) | 3.00 (1.95) | 0.02 | 3.36 (1.91) | 4.56 (0.73) | 0.13 |
| Registration | 14.17 (4.56) | 17.06 (5.36) | 0.02 | 14.63 (5.02) | 15.91 (5.03) | 0.40 | 14.58 (5.04) | 14.73 (7.11) | 0.85 | 12.14 (6.02) | 18.56 (3.32) | 0.01 |
| Recall | 3.79 (3.17) | 5.00 (2.92) | 0.19 | 4.08 (2.92) | 4.41 (3.35) | 0.87 | 4.17 (2.29) | 2.45 (1.63) | 0.05 | 2.64 (1.65) | 4.44 (2.46) | 0.09 |
| Remote memory | 3.31 (1.17) | 3.53 (0.80) | 0.58 | 2.96 (1.16) | 3.86 (0.35) | 0.001 | 3.50 (0.52) | 2.36 (1.63) | 0.11 | 2.71 (1.44) | 3.33 (1.00) | 0.26 |
| Verbal fluency | 8.69 (3.02) | 10.82 (2.92) | 0.02 | 8.79 (2.86) | 10.23 (3.31) | 0.07 | 8.83 (2.59) | 8.09 (3.53) | 0.64 | 7.71 (2.67) | 9.67 (3.32) | 0.12 |
| Naming | 9.93 (2.84) | 10.12 (3.06) | 0.92 | 9.75 (3.34) | 10.27 (2.35) | 0.97 | 11.25 (0.75) | 8.36 (3.53) | 0.02 | 8.71 (3.12) | 11.67 (0.71) | 0.001 |
| Language | 14.83 (1.56) | 15.24 (1.35) | 0.32 | 14.75 (1.70) | 15.23 (1.19) | 0.33 | 15.58 (0.90) | 12.73 (4.20) | 0.01 | 13.29 (3.91) | 15.67 (0.50) | 0.10 |
| Visuospatial | 2.55 (1.57) | 2.76 (1.79) | 0.56 | 2.54 (1.74) | 2.73 (1.55) | 0.80 | 2.67 (1.44) | 1.64 (2.29) | 0.19 | 1.14 (1.56) | 3.78 (1.20) | 0.001 |
| ACE score | 70.34 (13.79) | 76.82 (10.78) | 0.13 | 71.50 (12.73) | 74.09 (13.50) | 0.63 | 73.92 (11.4) | 61.27 (24.59) | 0.26 | 61.14 (21.48) | 78.33 (9.86) | 0.03 |
| MMSE | 25.45 (2.84) | 26.71 (2.59) | 0.16 | 26.17 (2.62) | 25.64 (3.00) | 0.45 | 26.25 (1.66) | 21.73 (7.86) | 0.51 | 22.43 (7.06) | 26.67 (1.58) | 0.32 |

*P*<0.05. ACE – Addenbrooke's Cognitive Examination; MMSE – Mini Mental Status Examination; SD – Standard deviation

and constructive abilities. Registration in ACE-M denotes the sensory element in cognition and comprehension. This domain also points to the ability of learning. Deficits in the immediate recall or short-term memory have a lot to do with the poor comprehension and learning ability. When assessed, what became apparent was the inability to learn and retain new information, to integrate this into the existing knowledge base and to generalize what had been learnt to new situations,[28] which resulted in poor memory and difficulty with new learning.

On visuospatial perception and constructive abilities to this group exhibits significant deficits, which could mean that there is significant impairment in the frontoparietal cortex. Deficits on this domain imply difficulty with visual processing as well as with executive functions translated into impaired ability in mental imagery and navigation, distance and depth perception, and visuospatial construction.

Patients with low-grade intra-axial tumors scored better on the ACE-M scale as well as on MMSE. This is very much in line with the previous findings of a greater cognitive decline in high-grade tumors.[29] Although significant symptom burden is associated with low-grade tumors also, the cognitive status when compared with high-grade tumors[30] is much more intact. High-grade tumors such as glioblastomas and astrocytomas tend to infiltrate and displace or "crowd" normal tissue, thereby disrupting brain function[31] including cognition. A study by Miotto *et al*.[10] clearly brings out the difference in cognitive functions in high-grade and low-grade tumors, further lending credibility to the present finding. No literature is available on a comparison of cognition between intra-axial and extra-axial tumors, and the same could not be carried out in this study because of poor numbers in the high-grade extra-axial tumors.

Although laterality is one of the determinants of cognitive function,[32-34] in this study, only patients with extra-axial tumors on the right side exhibited an association with laterality and short-term memory. The slow growing extra-axial tumors with their compressive effects are likely to interfere with the transmission of information from short into long-term memory.[35] Reports of greater interconnection between the limbic system and right hemisphere,[36-38] which are closely associated with processing and storage of memories[39,40] than the left hemisphere explains this finding.

In both intra- and extra-axial tumors, females showed better performance on all language measures including reading writing, naming, and verbal fluency. While naming and language functions of reading and writing were better performed by female patients with extra-axial lesion, those with intra-axial tumors performed better than males on verbal fluency. Sex differences in cognitive abilities have long been hypothesized with women performing better on

tasks involving receptive and productive language[41] and in spite of the presence of an intra-axial lesion, it could be assumed that the temporo-frontal areas are functionally more intact than that of males.

In intra-axial lesions, education has a significant association with remote or retrograde memory, with college educated group performing better than the school educated group. Retrograde memory items largely check the explicit memory comprising facts and general knowledge, and as expected people with higher levels of education performed better than their school educated counterparts. In extra-axial lesion group, education had a significant association with registration, recall, and naming. They also showed a significant association with the overall ACE-M score. Education is one of the determinants of cognitive reserve,[42,43] and irrespective of the nature of the tumor, helps in preserving the cognitive functions more or less.

Although the study has been successful in profiling the cognitive deficits in intra- and extra-axial tumors using ACE as the only and primary tool, it is not without its limitations. A bigger sample size would have yielded more meaningful results which then can be reiterated and generalized. Inadequate numbers of high-grade tumors within the extra-axial category, which prevented any meaningful statistical analysis from being carried out is a major limitation. The item of clock drawing test has been classified under visuospatial function. If the scores on this and verbal fluency subtest were brought under the domain of executive function, then that will enable the tester to have a total and complete idea of the cognitive status. Whether ACE-M can reliably bring out the influence of various treatment modalities and can bring out the efficacy of cognitive remediation, at least in a clinic set up remains to be explored. For ACE-M to be used as a screen in tumor patients, especially since the tool is already translated and adapted to Malayalam, and considering its ease of administration and sensitivity, population-based norms need to be developed.

## Conclusions

ACE-M is capable of bringing out cognitive deficits along with a number of cognitive domains in patients with intra- and extra-axial tumors. It can be used to successfully profile the cognitive deficits in tumor patients in the capacity of a screen. The tool also shows fairly good levels of sensitivity and specificity.

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### Conflicts of interest

There are no conflicts of interest.

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