Article published online: 2020-12-28

Review Article

Indian data on central nervous tumors: A summary of published work

Archya Dasgupta, Tejpal Gupta, Rakesh Jalali

Abstract

Tumors of the central nervous system (CNS) constitute approximately 2% of all malignancies. Although relatively rare, the associated morbidity and mortality and the significant proportion of affected young and middle-aged individuals has a major bearing on the death-adjusted life years compared to other malignancies. CNS tumors encompass a very broad spectrum with regards to age, location, histology, and clinical outcomes. Advances in diagnostic imaging, surgical techniques, radiotherapy equipment, and generation of newer chemotherapeutic and targeted agents over the past few years have helped improving treatment outcome. Further insights into the molecular pathways leading to the development of tumors made in the past decade are being incorporated into routine clinical practice. Several focused groups within India have been working on a range of topics related to CNS tumors, and a significant body of work from India, in the recent years, is being increasingly recognized throughout the world. The present article summarizes key published work with particular emphasis on gliomas and medulloblastoma, the two commonly encountered tumors.

Key words: Central nervous system tumor, glioma, Indian data, medulloblastoma

Demographics

The incidence of central nervous system (CNS) tumors in India ranges from 5 to 10 per 100,000 population with an increasing trend and accounts for 2% of malignancies.[1,2] Hospital-based databases capturing CNS malignancies had been analyzed prospectively from registrations in the neuro-oncology clinic of a tertiary care center over a period of 1 year.[3] Astrocytomas (38.7%) were the most common primary tumors with the majority being high-grade gliomas (59.5%). More interestingly during the presentation, the median age of glial tumors was seen to be at least a decade earlier than reported in the Western population, which could be partially explained by the lower life expectancy and a higher proportion of the younger population in India.[3] However, the median age of pediatric tumors such as brainstem glioma, medulloblastoma (MB), and supratentorial primitive neuroectodermal tumors (PNET) was comparable with Western population. Another multi institutional effort involving seven tertiary care hospitals reported the epidemiological profile of 3936 pediatric tumor patients.[4] The most common tumor was astrocytoma (34.7%) followed by MB and supratentorial PNETs (22.4%) and craniopharyngioma. Most of the astrocytic tumors were reported to be low grade commonly pilocytic astrocytoma and subependymal giant cell astrocytoma. This was found to be comparable to data from Western countries or other Asian countries. Similar results were published from a tertiary care center in South India reporting 15 years' experience involving 1043 patients.[5] The five most frequent tumors were astrocytoma (47.3%), MB (11.4%), craniopharyngioma (9.7%), ependymal tumors (4.8%), and nerve sheath tumors (4.1%).

Impact of Pathology and Molecular Biology on Clinical Outcomes: Contributions from India

Adult high-grade glioma

Several novel insights for various aspects of gliomagenesis have been reported by Indian scientists. Some of the key findings include the discovery of protein phosphatase 1 α (PP1A), an enzyme associated with cell cycle, and overexpressed in glioblastoma multiforme (GBM). Expression of PP1A was found to be a strong independent predictor of poor overall survival in p53 positive GBMs.[6] A 10-microRNA (miRNA) expression signature profiling data of 222 GBM patients were tested, seven of which were risky and three protective RNAs.[7] Patients were divided into different groups based on the high- or low-risk scores which differed significantly in terms of both short- and long-term survival. Similarly, 14 genes GBM prognostic signature used weighted gene score can be used as an independent predictor of survival as shown in 123 patients.[8] Interestingly, association was found between

Access this article online
Quick Response Code:
Website: www.sajc.org
DOI: 10.4103/2278-330X.187589

Department of Radiation Oncology, Neuro-Oncology Group, Tata Memorial Hospital, Mumbai, Maharashtra, India
Correspondence to: Dr. Rakesh Jalali,
E-mail: rjalali@tmc.gov.in

How to cite this article: Dasgupta A, Gupta T, Jalali R. Indian data on central nervous tumors: A summary of published work. South Asian J Cancer 2016;5:147-53.

inflammatory/immune response pathways and mesenchymal subgroup in high risk. Team under Chosdol *et al*. used five-hypoxia marker set as predictor for induction of notch pathway signaling which is known to be associated with inferior survival.[9] The present interest lies in understanding the tumor-stroma interactions, the signaling pathways of macrophages/microglial cells with the tumor cells. Recently, the role of macrophage colony-stimulating factor inducing the microglial release of insulin-like growth factor-binding protein 1 leading to angiogenesis has been established.[10] A brain-specific miRNA miR-219-5p has been identified as a novel tumor suppressor in GBM and can be a potential target for epidermal growth factor receptor (EGFR) pathway.[11]

It is possible to differentiate primary (or *de novo*) GBM from secondary GBM (having comparatively protracted survival) based on molecular profiling. Jha *et al*. reported the molecular profile of 75 GBMs with reference to TP53, EGFR, phosphatase and tensin homolog (PTEN), and isocitrate dehydrogenase 1 (IDH1) mutations.[12] For primary GBM, the EGFR amplifications, PTEN mutations were seen in 37.3% and 54.9% of patients, respectively as opposed to 33% and nil in secondary GBMs. In secondary GBMs, the more common mutations were TP53 (66.7%) and IDH1 (44.4%) mutations which were seen in approximately 11% cases with primary GBM. Srividya *et al*. prospectively evaluated 73 adults with newly diagnosed GBM for homozygous 10q23/PTEN deletion which was found to be more frequent in patients more than 45 years of age and associated with inferior outcomes (irrespective of age).[13] For seven long-term survivors of GBM, molecular analysis has revealed EGFR amplifications (4/7), PTEN protein expression (6/7), O^6-methylguanine DNA methyltransferase (MGMT) promoter methylation (5/6), and immunopositivity for p53 (3/7).[14]

Anaplastic astrocytomas are associated with higher frequencies of IDH1/IDH2, TP53, and ATRX mutations. Jha *et al*. reported the first series for glioma in Indian patients, and IDH1 mutations were prevalent in 68.8%, 85.7%, and 12.8% of all Grades II, III gliomas, and GBM, respectively.[15] Another series found IDH1 mutations to be 100%, 92.9%, and 12.5% of diffuse astrocytomas, anaplastic astrocytomas, and GBM, respectively.[16] Somasundaram *et al*. established overexpression of achaete-scute complex like 1 in progressive astrocytomas.[17] Similar association was found with inhibition of Notch signaling is associated with transformation to high-grade gliomas. Another study established a 16 gene expression signature using prediction analysis of microarrays for differentiating anaplastic astrocytoma from GBM.[18] Interestingly, epithelial-mesenchymal transition pathway was found to be most differentially regulated pathway in GBM as compared to an anaplastic astrocytoma.

Appropriate radiological evaluation is an integral part of the initial work-up of patients with suspected CNS tumor. Major advances in magnetic resonance imaging (MRI) and functional imaging have led to better anatomical delineation and pathological characterization. Gupta's team attempted to look for the utility of three-dimensional pseudo-continuous arterial spin labeling for grading of gliomas in 64 patients.[19] For the location of gliomas such as brainstem which precludes surgery and histological diagnosis, radiological features coupled with clinical presentation forms the basis of diagnosis, and tailoring treatment. Baseline MRI features and fluorodeoxyglucose positron emission tomography parameters have been used to predict survival of twenty patients with diffuse intrinsic pontine glioma in a prospective study done at Tata Memorial Hospital (TMH).[20] A cumulative radiological prognostic index can be used successfully to stratify into different classes with varied outcomes. Imaging plays an important role to differentiate "pseudoprogression" from true tumor progression. Quite a few studies have been published over the last few years exploring the role of various radioisotopes for functional imaging, and some scored over MRI for detecting recurrences.[21-25]

The standard management of high-grade glioma in the form of maximal safe resection followed by adjuvant radiotherapy (RT) along with concurrent temozolomide (TMZ), followed by 6–12 cycles of adjuvant TMZ has been well established in the last decade or so. Use of intraoperative navigation (with ultrasound or MRI), intraoperative fluorescence, and awake craniotomy with intraoperative functional monitoring is being also increasingly used in the country. Moiyadi *et al*. reported ultrasound as a useful tool in intraoperative localization in CNS tumors.[26] TMZ for radical treatment of newly diagnosed GBM was introduced in 2001 at TMH with first Indian data reported in 2007, which revealed 2 years survival rate of 28%, consistent with the Stupp's results of the landmark European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada study.[27] Similar results in various high-grade gliomas in the Indian population have been summarized in Table 1. In a large audit of 102 adults treated with TMZ for newly diagnosed or recurrent or progressive high-grade gliomas, the incidence of neutropenia and lymphopenia were reported to be 7% and 12%, respectively.[39] Multivariate logistic regression analysis identified female gender, Grade IV histology, baseline total leukocyte count $<7700/mm^3$, and baseline serum creatinine ≥ 1 mg/dl as factors associated with significantly increased risk of clinically significant acute hematologic toxicity.

The role of targeted therapies is yet to be established for newly diagnosed gliomas. Cilengitide is a selective inhibitor of $\alpha v\beta 3$ and $\alpha v\beta 5$ integrin. A multicentric study was undertaken in 25 countries with two institutes from India as participants.[40] For 545 patients with newly diagnosed GBM having methylated MGMT promoter region, random assignment was done to either cilengitide with TMZ chemoradiation or TMZ with RT only. For maintenance, 6 cycles of TMZ were considered with or without cilengitide for 18 months or until disease progression or toxicities warranting stopping the drug. No survival benefits were obtained with cilengitide, and no excessive toxicity was observed. A pure multicentric Indian trial examining the role of nimotuzumab in GBM was carried out as well.[41] For 56 patients with GBM nimotuzumab was used along with standard chemoradiation concurrently and as a part of maintenance therapy every 3-weekly till disease progression or end of study (5 years). At median follow-up of 27.1 months, the median overall survival and progression-free survival were 14.1 months and 9.3 months, respectively and was reasonably well tolerated.

Indian researchers have been also involved in testing novel hypothesis in improving outcomes in GBM. Studies to examine the role of stem cell compartments have been undertaken. Stem

Table 1: Clinical outcomes of high-grade gliomas as reported in Indian population

Author	Included patients	Number of patients	Treatment strategy	Median OS[a]	Remarks
Jalali *et al*.[27]	GBM	42	RT[b] + TMZ f/b 6# TMZ	16.4	KPS >80% - better outcomes Grade 3 leucopenia - 2% Grade 3/4 thrombocytopenia - 7% during treatment
Anand *et al*.[28]	HGG	46	RT + TMZ f/b 6# TMZ	15	At 3 m - Grade 3 neurotoxicity (radiologically) seen in 2.7%
Kumar *et al*.[29]	GBM	360	Group 1 (KPS <70) - 30-35 Gy/10-15# Group 2 (KPS ≥70) - 60 Gy/30#	Grade I - 6.33 Grade II - 7.97	Chemotherapy (TMZ/lomustine) in 24.7% only Prognostic factors for survival were: site and location of tumor, dose of RT (<60 vs. 60), and use of chemotherapy
Julka *et al*.[30]	GBM	215	RT + TMZ f/b 6# TMZ	13	Presentation without seizures and 6 cycles of adjuvant TMZ were significant prognostic factors
Gupta *et al*.[31]	Poor prognosis HGG[c]	63	RT (35 Gy/7#) once weekly	7.4	28 of 63 patients completed planned treatment. Performance status and grade affected survival
Singh *et al*.[32]	Gliosarcoma	14[d]	RT + TMZ f/b 6# TMZ	18.5	MGMT promotion in 31.25% of patients not affecting survival
Kumar *et al*.[33]	Gliosarcoma	27	RT + TMZ f/b 6# TMZ	9	Although not statistically significant improved survival for patients receiving TMZ
Goda *et al*.[34]	GBM-O	74	RT + TMZ f/b 6-12# TMZ	23	1p/19q deletion in 33.3% cases Multivariate analysis Completion of minimum 6 cycles of TMZ
Jalali *et al*. (in press)	Pediatric GBM	66	RT + TMZ f/b 6# TMZ	15	Thalamic tumors, incompletely resected tumors, and MIB-1 >25% had poor survival rates
Mallick *et al*.[35]	Pediatric GBM	23	RT + TMZ f/b 6# TMZ	41.9	Use of concurrent and adjuvant TMZ associated with superior OS
Jalali *et al*.[36]	Brainstem Glioma	20	RT + TMZ (54 Gy/30#) f/b maximum 12# TMZ	9.15	Neurological improvement after RT - TMZ had better survival compared to those did not MRI diagnosis of HGG - inferior survival
Moiyadi and Shetty[37]	Recurrent glioma	38	Repeat surgery	Not reported	44% patients showed improvement in preexisting deficits
Anand *et al*.[38]	Recurrent HGG	16	Irradiation with fractionated SRS (30 Gy/5# [median])	9.3	No patient developed radiation necrosis

[a]In months, [b]59-60 Gy in 30-33 # unless otherwise mentioned, [c]KPS ≤70; age 40-78 years, [d]Survival data analyzed. TMZ=Temozolomide, GBM=Glioblastoma, MRI=Magnetic resonance imaging, HGG=High-grade glioma, RT=Radiotherapy, OS=Overall survival, KPS=Karnofsky performance score, f/b=Followed by, MGMT=O^6-methylguanine DNA methyltransferase, SRS=Stereotactic radiosurgery

cells lying in the periventricular region of the lateral ventricles and subgranular layer of the hippocampus are responsible for glioma initiation and progression. It has been reasoned that innate resistance of stem cells to present chemotherapy and radiation may be potential barriers for achieving cure in glioblastoma. Studies carried out in the West to look for the correlation of survival with doses of radiation to the stem cell zone had come out with mixed results. In Indian context for forty patients with supratentorial glioblastoma treated with focal conformal fractionated RT, the doses delivered to the subventricular zone (SVZ) were correlated with survival outcomes.[42] Older age (>50 years), poor recursive partitioning analysis class, and higher than median of mean contralateral SVZ dose were associated with significantly worse progression-free survival and overall survival. In TMH, a Phase II prospective study is undergoing to look for the correlation of dose to SVZ and patterns of failure.

To overcome the limitations of conventional histological classification, a four-point staging and grouping system have been proposed by experts from a tertiary care center accounting for additional features such as tumor location, age, neurological performance score, and adverse biological parameters.[43] Central and institutional review of histology is encouraged since poor agreement with local histological typing have been seen in 34 patients with supratentorial glioblastoma.[44]

Pediatric glioblastoma multiforme

Contrary to their adult counterpart, pediatric GBM, the genetic expression is distinctly different, and a lot of work in their understanding has been pioneered by Indian groups. In a series of 54 pediatric GBM analysis, for expression of p53, EGFR, bcl-2, and retinoblastoma proteins (pRp) was done and correlated with outcomes.[45] Thalamic lesions were predominantly associated with p53 mutations (75% cases) as compared to cerebral lobar (62.2%), followed by brainstem (30%), and absent in cerebellar tumors. EGFR, bcl overexpression, and loss of pRp were seen in 25.9%, 33.3%, and 7.4%, respectively. Mutation of p53 and bcl-2 overexpression was associated with poor prognosis. The AIIMS group in a cohort of thirty patients found PTEN, EGFR mutations to be rare while TP53 mutations were found to be more common as compared to adult glioblastoma.[46] Recent work on methylation profiling in 21 cases of pediatric GBM and mutation analysis revealed H3F3A mutants (in all K27M unlike Western data which had also reported G34 in teenagers) in 36.4% of cases but none of the cases were having IDH1 mutation.[47] A possible role of reactive oxygen species was also demonstrated for pediatric GBMs. The first report of genome-wide profiling of miRNA and small nucleolar RNA in samples from 14 patients with pediatric high-grade gliomas has been carried out by Jha *et al*.[48] On unsupervised hierarchical

clustering, two groups were identified having different survival. The miRNAs unique to pediatric high-grade gliomas were predicted to affect PDGFR and SMAD2/3 pathways as compared to adult GBM.

Owing to the rarity of these tumors, the standard protocol for treatment is yet to be defined, and the difference of opinion exists. In Indian context, a study reported median overall survival of 41.9 months for 23 patients with pediatric glioblastoma treated with similar strategies.[35] Completion of 6 cycles of TMZ as planned was found to be significantly associated with better survival. Jalali *et al*. found the median survival of 15 months with 1 year and 2 years overall survival rates being 62% and 30%, respectively for 66 patients treated with maximal safe resection followed by focal RT with concomitant and adjuvant TMZ (Neuro-Oncology Practice 2015; in press). Molecular analysis revealed p53 mutation and MGMT methylation in 74% and 37%, respectively and did not impact survival. Thalamic location incompletely resected tumors, and tumors with MIB-1 labeling index >25% had poor overall survival rates.

Oligodendrogliomas

In Indian population, a study reported loss of 1p and/or 19q in 65% of oligodendrogliomas and 66.7% of mixed oligoastrocytomas as compared to nil encountered in pure astrocytomas.[49] Suri *et al*. had reported the molecular profiling of patients with oligodendroglioma for the first time.[50] For 14 pediatric and young adults with age <25 years with oligodendroglioma investigations revealed none of the cases to be having mutations of IDH1 or TP53, and none of the pediatric patients had 1p/19q deletions. In 71% cases, the promoter region of MGMT gene was seen to be methylated. In pediatric oligodendrogliomas, KAA1549-BRAF fusion with activation of aberrant MAPK/ERK pathway similar to pilocytic astrocytomas has been identified recently.[51]

In the latest WHO edition, in 2007, GBM with oligodendroglial component (GBM-O) had been defined as a distinct histomorphological entity. In Indian context, a recently published article reported experience with 57 patients with diagnosis of GBM-O confirmed on histopathological review by the institutional neuropathologist.[34] Patients were treated according to the standard protocols for GBM with maximal safe resection followed by focal RT and TMZ given concomitantly followed by 6 cycles. The results were compared with a cohort of 105 patients with GBM having similar demographic profile and similar treatment strategies. At median follow-up of 16 months, median survival was significantly better for GBM-O as compared to GBM (23 months vs. 14.9 months). Deletion of 1p or 19q was seen in 33% cases, none being co-deleted, and p53 overexpression seen in 44% of the population.

Low-grade glioma

As mentioned earlier for diffuse astrocytomas, IDH1 mutation has been seen to be prevailing in all of 12 patients.[16] It was seen to have a prognostic value for younger age and longer duration for the entire cohort (including high-grade gliomas also) although not patients with GBM. The optimal management strategy had always been a matter of debate among treating oncologists. Post resection or biopsy treatment options include adjuvant radiation with or without chemotherapy. Jalali *et al*. included 47 patients with supratentorial aggressive low-grade glioma selected meticulously based on the predefined high-risk features on preoperative MRI features and/or histomorphology (unpublished data). They were treated with postoperative focal conformal RT (median dose 55.8 Gy) with concurrent and adjuvant TMZ for 6–12 cycles. All patients had either subtotal resection/biopsy or had ≥3 or more Pignatti's adverse factors. For the entire cohort at a mean follow-up of 31 months, 3 years overall survival was 86% while progression-free survival was 80%. For 31 patients having ≥3 Pignatti's factors, 3 years OS, and PFS were 85% and 73%, respectively.

Medulloblastoma

Histologically, it had been possible to identify four distinct categories, classical variant, desmoplastic, large cell/anaplastic, and MB with extensive nodularity. As per international consensus in 2012, four distinct molecular subgroups have been identified in MB with diverse demographic profile and clinical outcomes-wingless (WNT) pathway, Sonic hedgehog (SHH), Group 3, and Group 4 tumors. In Indian cohort reliable classification of 103 MB has been done using a set of 12 protein-coding genes and 9 miRNA evaluated by reverse transcriptase polymerase chain reaction (RT-PCR) with an accuracy of 97% validated in an independent cohort from the pioneer German group.[52] The most common group was found to be SHH unlike that seen in the West where Group 4 is mostly seen. Also in Indian cohort, a higher proportion of patients belonged to WNT pathway (22%) which has been the least common in the Western counterpart. For various age groups, the distributions vary considerably with SHH (65%) and WNT (35%) more commonly seen in adults and SHH (67%) and Group 3 (33%) for children <3 years. Underexpression or overexpression of certain miRNAs have been found to impact outcomes among individual subgroups and can be potentials for targeted therapy.[53-55] A recently published study has recommended a three-tier risk stratification for MB into WNT, SHH, and non WNT/SHH using a panel of IHC markers, RT-PCR for mRNA, miRNA expression, and FISH for MYC amplification.[56]

Certain tumors such as MB, intracranial germ cell tumor, and PNET have high propensity to disseminate through cerebrospinal fluid (CSF) which mandate the imaging of entire neuraxis supplemented by analysis of CSF. Postoperative imaging is required for all cases to assess the extent of resection. A prospective study is being carried out where MRI features are used to predict molecular groups.[57] Initial results have shown encouraging results where the radiological prediction correlates with RT-PCR based molecular classification in over 80% cases for certain subgroups such as SHH-driven tumor.

MBs are treated with maximal safe resection followed by radiation with or without chemotherapy based on risk stratification. The three factors-ages during presentation, presence of metastatic disease, and postsurgical residual disease are used for the conventional risk stratification which categorize to standard- and high-risk disease. The present practice also includes tumors with poor biological behavior like anaplastic histology or Group 3 tumors to be considered as high risk. Craniospinal irradiation (CSI) forms the cornerstone

in the treatment of MB. For average risk patients in the pediatric age group, the standard of care remains CSI to a dose equivalent to 23.4 Gy in 11 fractions followed by boost to the tumor bed up to a dose of 54–55 Gy along with vincristine used concomitantly on weekly basis. This is followed by 6 cycles of vincristine, cyclophosphamide, and cisplatin-based chemotherapy. In adults with standard-risk CSI (35 Gy in 21 fractions) and boost to 54–55 Gy are used without any chemotherapy. For patients with high-risk standard dose CSI (35 Gy) is delivered concurrently with carboplatin for first 15 fractions and the entire posterior fossa is boosted up to 54–55 Gy. Boost is also considered for areas with gross disease. Adjuvant chemotherapy follows same protocol as in standard-risk with reduced dose CSI. Following appropriate treatment, the outcomes are good for MB and 5 years survival rates are beyond 80% in standard-risk disease.

A relatively large series with 365 patients of MB aged <18 years treated over a period of 25 years reported 5-year and 10-year progression-free survival rate was 73 and 41% for average-risk disease while for high-risk disease rate it was 34%.[58] However, inferior survival rates were reported from a center in South India, with adult populations performing comparatively better.[59] However, the recent reports have been encouraging where for 25 patients with average risk MB treated prospectively with hyperfractionated RT (HFRT), 3 years overall survival was observed to be 83.2% with preserved cognitive function.[60] The survival has been considerably different among various molecular subgroups and first Indian data reported from Tata Memorial Centre with WNT tumors performing the best while Group 3 associated with worst outcomes.[52] The use of HFRT for 20 patients without upfront platinum-based chemotherapy resulted in preserved hearing in a large proportion of patients in the audible speech range.[61]

Other brain tumors

Three tertiary care centers from India involving 95 cases of CNS germ cell tumors found germinoma to be the most common histopathological subtype and pineal region to be the most common location (unpublished observation). At 5 years, the event-free survival was 72.1%. Age <10 years, pineal location and germinoma/teratoma histology were associated with significantly favorable outcome. For 15 patients with intracranial atypical teratoid rhabdoid tumor had been 10 months.[62] On univariate analysis extent of surgery, CSI and MIB-1 labeling index were found to be significant predictors of overall survival. A retrospective audit of 15 patients with nonpineal supratentorial PNET revealed the estimated event-free survival to be 4.12 years for a median follow-up of 22.6 months.[63] For 17 patients with pinealoblastoma, the 2 years actuarial overall survival have been reported to be 85.6%.[64] Leptomeningeal spread at diagnosis was seen in 4 patients during presentation and age more than 8 years, and no metastasis were significant predictors for better relapse-free survival. For 44 patients with primary CNS lymphoma treated at TMH, overall survival was found to be 83% (ASNO 2013) treated with high-dose methotrexate and RT.

The functional, neurocognitive, and neuroendocrine evaluation was done prospectively for 71 patients with residual or recurrent craniopharyngioma.[65] At a mean follow-up of 36 months (range 6–98 months), 63 patients were controlled with a 5-year OS of 95.6% and 5-year PFS of 92.3%. Mean Barthel's index (BI) score at baseline, 2 years, and 4 years were 95.0, 100, and 100, respectively. Pre-RT BI score was significantly lower in visually challenged (P = 0.007), low KPS score, poor neurological function status (NPS), and in patients with severe hydrocephalus (P = 0.031). Loewenstein Occupational Therapy Cognitive Assessment scores showed improvement in visuomotor/thinking and maintained in orientation, spatial perception, thinking, and attention concentration domains. At baseline, 73% patients had hormone deficiency in at least one axis. Pre-RT BI score was significantly lower in visually challenged, low KPS score, poor NPS, and severe hydrocephalus.

Neurocognition and Quality of Life

Improving survival outcomes with newer treatment strategies have increased the concern regarding the quality of life (QOL) which can be affected by any of the treated modalities or by the tumor itself. Several questionnaires and tools exist to assess the functional and psychological status of patients with brain tumor encompassing different domains. For 38 young adults and pediatric patient with low-grade brain tumor prospectively treated with high-precession conformal RT, activities of daily living have been evaluated using Barthel's battery.[66] Postsurgery patients were having lower than normal scores, and at 2 and 3 years follow-up post-RT, no further decline was observed. Post-RT maximum improvement was seen in ambulation-related domains. Visually challenged patients were found to have significant improvement in scores. Two large series investigating functional/psychological impairments and QOL scores in adults with primary brain tumor reported certain factors such as performance score, nature of tumor (benign vs. malignant), location of tumor (cerebral vs. cerebellar), status of education to impact them significantly.[67,68] Interestingly, it has been found that younger age (<15 years) and radiation dose to left temporal lobes affect adversely neuropsychological outcomes for patients treated with RT.[69]

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Nair M, Varghese C, Swaminathan R. Cancer: Current Scenario, Intervention Strategies and Projections for 2015. NCMH Background Papers; 2015.
2. Yeole BB. Trends in the brain cancer incidence in India. Asian Pac J Cancer Prev 2008;9:267-70.
3. Jalali R, Datta D. Prospective analysis of incidence of central nervous tumors presenting in a tertiary cancer hospital from India. J Neurooncol 2008;87:111-4.
4. Jain A, Sharma MC, Suri V, Kale SS, Mahapatra AK, Tatke M, *et al.* Spectrum of pediatric brain tumors in India: A multi-institutional study. Neurol India 2011;59:208-11.
5. Asirvatham JR, Deepti AN, Chyne R, Prasad MS, Chacko AG, Rajshekhar V, *et al.* Pediatric tumors of the central nervous system: A retrospective study of 1,043 cases from a tertiary care center in South India. Childs Nerv Syst 2011;27:1257-63.
6. Shastry AH, Thota B, Srividya MR, Arivazhagan A, Santosh V. Nuclear protein phosphatase 1 α (PP1A) expression is associated with poor prognosis in p53 expressing glioblastomas. Pathol Oncol Res 2016;22:287-92.
7. Srinivasan S, Patric IR, Somasundaram K. A ten-microRNA expression signature predicts survival in glioblastoma. PLoS One 2011;6:e17438.
8. Arimappamagan A, Somasundaram K, Thennarasu K, Peddagangannagari S, Srinivasan H, Shailaja BC, *et al.* A fourteen gene GBM prognostic signature

identifies association of immune response pathway and mesenchymal subtype with high risk group. PLoS One 2013;8:e62042.
9. Irshad K, Mohapatra SK, Srivastava C, Garg H, Mishra S, Dikshit B, *et al.* A combined gene signature of hypoxia and notch pathway in human glioblastoma and its prognostic relevance. PLoS One 2015; 10:e0118201.
10. Nijaguna MB, Patil V, Urbach S, Shwetha SD, Sravani K, Hegde AS, *et al.* Glioblastoma-derived macrophage colony-stimulating factor (MCSF) induces microglial release of insulin-like growth factor-binding protein 1 (IGFBP1) to promote angiogenesis. J Biol Chem 2015;290:23401-15.
11. Rao SA, Arimappamagan A, Pandey P, Santosh V, Hegde AS, Chandramouli BA, *et al.* miR-219-5p inhibits receptor tyrosine kinase pathway by targeting EGFR in glioblastoma. PLoS One 2013;8:e63164.
12. Jha P, Suri V, Singh G, Jha P, Purkait S, Pathak P, *et al.* Characterization of molecular genetic alterations in GBMs highlights a distinctive molecular profile in young adults. Diagn Mol Pathol 2011;20:225-32.
13. Srividya MR, Thota B, Shailaja BC, Arivazhagan A, Thennarasu K, Chandramouli BA, *et al.* Homozygous 10q23/PTEN deletion and its impact on outcome in glioblastoma: A prospective translational study on a uniformly treated cohort of adult patients. Neuropathology 2011;31:376-83.
14. Das P, Puri T, Jha P, Pathak P, Joshi N, Suri V, *et al.* A clinicopathological and molecular analysis of glioblastoma multiforme with long-term survival. J Clin Neurosci 2011; 18:66-70.
15. Jha P, Suri V, Sharma V, Singh G, Sharma MC, Pathak P, *et al.* IDH1 mutations in gliomas: First series from a tertiary care centre in India with comprehensive review of literature. Exp Mol Pathol 2011;91:385-93.
16. Thota B, Shukla SK, Srividya MR, Shwetha SD, Arivazhagan A, Thennarasu K, *et al.* IDH1 mutations in diffusely infiltrating astrocytomas: Grade specificity, association with protein expression, and clinical relevance. Am J Clin Pathol 2012; 138: 177-84.
17. Somasundaram K, Reddy SP, Vinnakota K, Britto R, Subbarayan M, Nambiar S, *et al.* Upregulation of ASCL1 and inhibition of Notch signaling pathway characterize progressive astrocytoma. Oncogene 2005;24:7073-83.
18. Rao SA, Srinivasan S, Patric IR, Hegde AS, Chandramouli BA, Arimappamagan A, *et al.* A 16-gene signature distinguishes anaplastic astrocytoma from glioblastoma. PLoS One 2014;9:e85200.
19. Roy B, Awasthi R, Bindal A, Sahoo P, Kumar R, Behari S, *et al*. Comparative evaluation of 3-dimensional pseudocontinuous arterial spin labeling with dynamic contrast-enhanced perfusion magnetic resonance imaging in grading of human glioma. J Comput Assist Tomogr 2013;37:321-6.
20. Goda JS, Dutta D, Raut N, Juvekar SL, Purandare N, Rangarajan V, *et al.* Can multiparametric MRI and FDG-PET predict outcome in diffuse brainstem glioma? A report from a prospective phase-II study. Pediatr Neurosurg 2013;49:274-81.
21. Santra A, Sharma P, Kumar R, Bal C, Kumar A, Julka PK, *et al.* Comparison of glucoheptonate single photon emission computed tomography and contrast-enhanced MRI in detection of recurrent glioma. Nucl Med Commun 2011;32:206-11.
22. Santra A, Kumar R, Sharma P, Bal C, Julka PK, Malhotra A. Detection of recurrence in glioma: A comparative prospective study between Tc-99m GHA SPECT and F-18 FDG PET/CT. Clin Nucl Med 2011;36:650-5.
23. Santra A, Kumar R, Sharma P, Bal C, Kumar A, Julka PK, *et al.* F-18 FDG PET-CT in patients with recurrent glioma: Comparison with contrast enhanced MRI. Eur J Radiol 2012;81:508-13.
24. Karunanithi S, Sharma P, Kumar A, Gupta DK, Khangembam BC, Ballal S, *et al.* Can (18)F-FDOPA PET/CT predict survival in patients with suspected recurrent glioma? A prospective study. Eur J Radiol 2014;83:219-25.
25. Khangembam BC, Karunanithi S, Sharma P, Kc SS, Kumar R, Julka PK, *et al.* Perfusion-metabolism coupling in recurrent gliomas: A prospective validation study with 13N-ammonia and 18F-fluorodeoxyglucose PET/CT. Neuroradiology 2014;56:893-902.
26. Moiyadi AV, Shetty PM, Mahajan A, Udare A, Sridhar E. Usefulness of three-dimensional navigable intraoperative ultrasound in resection of brain tumors with a special emphasis on malignant gliomas. Acta Neurochir (Wien) 2013; 155:2217-25.
27. Jalali R, Basu A, Gupta T, Munshi A, Menon H, Sarin R, *et al.* Encouraging experience of concomitant temozolomide with radiotherapy followed by adjuvant temozolomide in newly diagnosed glioblastoma multiforme: Single institution experience. Br J Neurosurg 2007;21:583-7.
28. Anand AK, Chaudhory AR, Aggarwal HN, Sachdeva PK, Negi PS, Sinha SN, *et al.* Survival outcome and neurotoxicity in patients of high-grade gliomas treated with conformal radiation and temozolamide. J Cancer Res Ther 2012;8:50-6.
29. Kumar N, Kumar P, Angurana SL, Khosla D, Mukherjee KK, Aggarwal R, *et al.* Evaluation of outcome and prognostic factors in patients of glioblastoma multiforme: A single institution experience. J Neurosci Rural Pract 2013;4 Suppl 1:S46-55.
30. Julka PK, Sharma DN, Mallick S, Gandhi AK, Joshi N, Rath GK. Postoperative treatment of glioblastoma multiforme with radiation therapy plus concomitant and adjuvant temozolomide: A mono-institutional experience of 215 patients. J Cancer Res Ther 2013;9:381-6.
31. Gupta T, Dutta D, Trivedi S, Upasani M, Jalali R, Sarin R. Assessment of compliance to treatment and efficacy of a resource-sparing hypofractionated radiotherapy regimen in patients with poor-prognosis high-grade gliomas. J Cancer Res Ther 2010;6:272-7.
32. Singh G, Mallick S, Sharma V, Joshi N, Purkait S, Jha P, *et al.* A study of clinico-pathological parameters and O6-methylguanine DNA methyltransferase (MGMT) promoter methylation status in the prognostication of gliosarcoma. Neuropathology 2012;32:534-42.
33. Kumar N, Bhattacharyya T, Chanchalani K, Shalunke P, Radotra BD, Yadav BS. Impact of changing trends of treatment on outcome of cerebral gliosarcoma: A tertiary care centre experience. South Asian J Cancer 2015;4:15-7.
34. Goda JS, Lewis S, Agarwal A, Epari S, Churi S, Padmavati A, *et al.* Impact of oligodendroglial component in glioblastoma (GBM-O): Is the outcome favourable than glioblastoma? Clin Neurol Neurosurg 2015; 135:46-53.
35. Mallick S, Gandhi AK, Joshi NP, Kumar A, Puri T, Sharma DN, *et al.* Outcomes of pediatric glioblastoma treated with adjuvant chemoradiation with temozolomide and correlation with prognostic factors. Indian J Med Paediatr Oncol 2015;36:99-104.
36. Jalali R, Raut N, Arora B, Gupta T, Dutta D, Munshi A, *et al.* Prospective evaluation of radiotherapy with concurrent and adjuvant temozolomide in children with newly diagnosed diffuse intrinsic pontine glioma. Int J Radiat Oncol Biol Phys 2010;77:113-8.
37. Moiyadi AV, Shetty PM. Surgery for recurrent malignant gliomas: Feasibility and perioperative outcomes. Neurol India 2012;60:185-90.
38. Anand AK, Kumar P, Patir R, Vaishya S, Bansal AK, Chaudhoory AR, *et al.* Fractionated stereotactic radiosurgery with volumetric modulated arc therapy (Rapid Arc) for reradiation in recurrent high grade gliomas. J Cancer Res Ther 2014; 10:97-102.
39. Gupta T, Mohanty S, Moiyadi A, Jalali R. Factors predicting temozolomide induced clinically significant acute hematologic toxicity in patients with high-grade gliomas: A clinical audit. Clin Neurol Neurosurg 2013; 115: 1814-9.
40. Stupp R, Hegi ME, Gorlia T, Erridge SC, Perry J, Hong YK, *et al.* Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): A multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2014; 15: 1100-8.
41. Jalali R, Julka PK, Anand AK, Bhavsar D, Singhal N, Naik R, *et al*. An open label, prospective, multicentric study to evaluate the safety and efficacy of BIOMAb-EGFR™ (Nimotuzumab) as induction and maintenance therapy in combination with radiotherapy plus temozolomide (Concomitant & Adjuvant) in Indian patients with glioblastoma multiforme. Neuro Oncology 2011; 13;iii57.
42. Gupta T, Nair V, Paul SN, Kannan S, Moiyadi A, Epari S, *et al.* Can irradiation of potential cancer stem-cell niche in the subventricular zone influence survival in patients with newly diagnosed glioblastoma? J Neurooncol 2012; 109: 195-203.
43. Gupta T, Sarin R, Jalali R, Sharma S, Kurkure P, Goel A. A pragmatic clinicopathobiological grouping/staging system for gliomas: Proposal of the Indian TNM subcommittee on brain tumors. Neurol India 2009;57:247-51.
44. Gupta T, Nair V, Epari S, Pietsch T, Jalali R. Concordance between local, institutional, and central pathology review in glioblastoma: Implications for research and practice: A pilot study. Neurol India 2012;60:61-5.
45. Ganigi PM, Santosh V, Anandh B, Chandramouli BA, Sastry Kolluri VR. Expression of p53, EGFR, pRb and bcl-2 proteins in pediatric glioblastoma multiforme: A study of 54 patients. Pediatr Neurosurg 2005;41:292-9.
46. Suri V, Das P, Pathak P, Jain A, Sharma MC, Borkar SA, *et al.* Pediatric glioblastomas: A histopathological and molecular genetic study. Neuro Oncol 2009; 11:274-80.
47. Jha P, Pia Patric IR, Shukla S, Pathak P, Pal J, Sharma V, *et al.* Genome-wide methylation profiling identifies an essential role of reactive oxygen species in pediatric glioblastoma multiforme and validates a methylome specific for H3 histone family 3A with absence of G-CIMP/isocitrate dehydrogenase 1 mutation. Neuro Oncol 2014; 16: 1607-17.
48. Jha P, Agrawal R, Pathak P, Kumar A, Purkait S, Mallik S, *et al.* Genome-wide small noncoding RNA profiling of pediatric high-grade gliomas reveals deregulation of several miRNAs, identifies downregulation of snoRNA

cluster HBII-52 and delineates H3F3A and TP53 mutant-specific miRNAs and snoRNAs. Int J Cancer 2015;137:2343-53.
49. Shukla B, Agarwal S, Suri V, Pathak P, Sharma MC, Gupta D, *et al.* Assessment of 1p/19q status by fluorescence *in situ* hybridization assay: A comparative study in oligodendroglial, mixed oligoastrocytic and astrocytic tumors. Neurol India 2009;57:559-66.
50. Suri V, Jha P, Agarwal S, Pathak P, Sharma MC, Sharma V, *et al.* Molecular profile of oligodendrogliomas in young patients. Neuro Oncol 2011;13:1099-106.
51. Kumar A, Pathak P, Purkait S, Faruq M, Jha P, Mallick S, *et al.* Oncogenic KIAA1549-BRAF fusion with activation of the MAPK/ERK pathway in pediatric oligodendrogliomas. Cancer Genet 2015;208:91-5.
52. Kunder R, Jalali R, Sridhar E, Moiyadi A, Goel N, Goel A, *et al.* Real-time PCR assay based on the differential expression of microRNAs and protein-coding genes for molecular classification of formalin-fixed paraffin embedded medulloblastomas. Neuro Oncol 2013;15:1644-51.
53. Gokhale A, Kunder R, Goel A, Sarin R, Moiyadi A, Shenoy A, *et al.* Distinctive microRNA signature of medulloblastomas associated with the WNT signaling pathway. J Cancer Res Ther 2010;6:521-9.
54. Yogi K, Sridhar E, Goel N, Jalali R, Goel A, Moiyadi A, *et al.* MiR-148a, a microRNA upregulated in the WNT subgroup tumors, inhibits invasion and tumorigenic potential of medulloblastoma cells by targeting neuropilin 1. Oncoscience 2015;2:334-48.
55. Panwalkar P, Moiyadi A, Goel A, Shetty P, Goel N, Sridhar E, *et al.* MiR-206, a cerebellum enriched miRNA is downregulated in all medulloblastoma subgroups and its overexpression is necessary for growth inhibition of medulloblastoma cells. J Mol Neurosci 2015;56:673-80.
56. Kaur K, Kakkar A, Kumar A, Mallick S, Julka PK, Gupta D, *et al.* Integrating molecular subclassification of medulloblastomas into routine clinical practice: A simplified approach. Brain Pathol 2016;26:334-43.
57. Dasgupta A, Gupta T, Pungavkar S, Shirsat N, Mahajan A, Janu A, *et al.* Combined clinical parameters with specific MRI features yield highly accurate prediction of medulloblastoma subtypes: Data from 72 patients in a blinded study. Neuro Oncology 2016;18:iii104-iii105.
58. Muzumdar D, Deshpande A, Kumar R, Sharma A, Goel N, Dange N, *et al.* Medulloblastoma in childhood-King Edward Memorial hospital surgical experience and review: Comparative analysis of the case series of 365 patients. J Pediatr Neurosci 2011;6 Suppl 1:S78-85.
59. Menon G, Krishnakumar K, Nair S. Adult medulloblastoma: Clinical profile and treatment results of 18 patients. J Clin Neurosci 2008;15:122-6.
60. Gupta T, Jalali R, Goswami S, Nair V, Moiyadi A, Epari S, *et al.* Early clinical outcomes demonstrate preserved cognitive function in children with average-risk medulloblastoma when treated with hyperfractionated radiation therapy. Int J Radiat Oncol Biol Phys 2012;83:1534-40.
61. Gupta T, Mohanty S, Kannan S, Jalali R. Prospective longitudinal assessment of sensorineural hearing loss with hyperfractionated radiation therapy alone in patients with average-risk medulloblastoma. Neurooncol Pract 2014;1:86-93.
62. Biswas A, Julka PK, Bakhshi S, Suri A, Rath GK. Intracranial atypical teratoid rhabdoid tumor: Current management and a single institute experience of 15 patients from North India. Acta Neurochir (Wien) 2015;157:589-96.
63. Biswas A, Mallick S, Purkait S, Roy S, Sarkar C, Bakhshi S, *et al.* Treatment outcome and patterns of failure in patients of non-pineal supratentorial primitive neuroectodermal tumor: Review of literature and clinical experience form a regional cancer center in North India. Acta Neurochir (Wien) 2015;157:1251-66.
64. Biswas A, Mallick S, Purkait S, Gandhi A, Sarkar C, Singh M, *et al.* Treatment outcome and patterns of failure in patients of pinealoblastoma: Review of literature and clinical experience from a regional cancer centre in North India. Childs Nerv Syst 2015;31:1291-304.
65. Jalali R, Gupta T, Goswami S, Golambade N, Shah N, Sarin R. Detailed Neuropsychological, Activity of Daily Living and Endocrine Function Assessment in Children with Craniopharyngioma Treated with High Precision Focal Radiotherapy: Data from a Prospective Trial. ISPNO; 2011.
66. Jalali R, Dutta D, Kamble R, Gupta T, Munshi A, Sarin R, *et al.* Prospective assessment of activities of daily living using modified Barthel's index in children and young adults with low-grade gliomas treated with stereotactic conformal radiotherapy. J Neurooncol 2008;90:321-8.
67. Dutta D, Vanere P, Gupta T, Munshi A, Jalali R. Factors influencing activities of daily living using FIM-FAM scoring system before starting adjuvant treatment in patients with brain tumors: Results from a prospective study. J Neurooncol 2009;94:103-10.
68. Budrukkar A, Jalali R, Dutta D, Sarin R, Devlekar R, Parab S, *et al.* Prospective assessment of quality of life in adult patients with primary brain tumors in routine neurooncology practice. J Neurooncol 2009;95:413-9.
69. Jalali R, Mallick I, Dutta D, Goswami S, Gupta T, Munshi A, *et al.* Factors influencing neurocognitive outcomes in young patients with benign and low-grade brain tumors treated with stereotactic conformal radiotherapy. Int J Radiat Oncol Biol Phys 2010;77:974-9.