NEUROLOGY INDIA
Publication of the Neurological Society of India

ORIGINAL ARTICLE

Year : 2021 | **Volume** : 69 | **Issue** : 4 | **Page** : 856--860

Glioblastoma with Primitive Neuroectodermal Component Treated with Adjuvant Radiotherapy and Temozolomide: A Pooled Analysis of 23 Patients

Rony Benson[1], Supriya Mallick[1], Suvendu Purkait[2], KP Haresh[1], Subhash Gupta[1], Mehar Chand Sharma[2], Vaishali Suri[2], Dayanand Sharma[1], GK Rath[1],

[1] Department of Radiation Oncology, All India Institute of Medical Sciences, New Delhi, India

[2] Department of Pathology, All India Institute of Medical Sciences, New Delhi, India

Correspondence Address:
Dr. Subhash Gupta
Department of Radiation Oncology, All India Institute of Medical Sciences, New Delhi
India

Abstract

Aim: Glioblastoma (GBM) is one of the most aggressive neoplasms of the central nervous system with dismal survival. In recent years, different variants of GBM have been described in the literature. GBM with areas of neuroectodermal differentiation (GBM-PNET) is a relatively new entity in GBM. Presence of the neuroectodermal component increases the propensity of systemic dissemination as with other intracranial primitive neuroectodermal tumors (PNET). The optimal treatment for these patients remains a controversy, with authors reporting local radiotherapy to craniospinal irradiation and chemotherapy. We intend to analyze the pattern of care for GBM with neuroectodermal component. **Materials and Methods:** We retrieved data of four patients with GBM-PNET treated in our institute; data were also retrieved from published series to derive treatment and outcome results. **Results:** In this series, we report the outcome of a series of four patients of GBM-PNET treated with adjuvant radiotherapy and temozolomide. All but one patient underwent gross total resection of the tumor. Adjuvant hypofractionated radiation with concurrent and adjuvant temozolomide was used in all cases. The median follow-up was 12.9 months in the present series. One patient experienced local recurrence 18 months after the treatment. A review of published literature on GBM-PNET was done; studies with details of patient outcome were used for an independent analysis. Twenty-three patients were identified, and the pooled analysis revealed a median progression free and overall survival of 10 and 25, months respectively. Extent of surgery, local radiation vs. craniospinal irradiation, and age at presentation had no impact on the survival. **Conclusion:** GBM PNET is a new entity with only few cases reported so far. Clinical behavior and treatment outcome of these tumors are not different from conventional GBM. However, these patients are at higher risk of CSF dissemination. Hence, an individualized treatment approach is best suited.

How to cite this article:
Benson R, Mallick S, Purkait S, Haresh K P, Gupta S, Sharma MC, Suri V, Sharma D, Rath G K. Glioblastoma with Primitive Neuroectodermal Component Treated with Adjuvant Radiotherapy and Temozolomide: A Pooled Analysis of 23 Patients.Neurol India 2021;69:856-860

How to cite this URL:
Benson R, Mallick S, Purkait S, Haresh K P, Gupta S, Sharma MC, Suri V, Sharma D, Rath G K. Glioblastoma with Primitive Neuroectodermal Component Treated with Adjuvant Radiotherapy and Temozolomide: A Pooled Analysis of 23 Patients. Neurol India [serial online] 2021 [cited 2021 Sep 23];69:856-860
Available from: https://www.neurologyindia.com/text.asp?2021/69/4/856/323892

Full Text

Glioblastoma (GBM) is the most common primary brain tumor occurring in patients more than 50 years of age.[1] GBM with areas of neuroectodermal differentiation (GBM-PNET) is a rare entity with only few reported cases thus far. Maximal safe surgery is contemplated in all patients. However, adjuvant treatment in such patients varies widely from local radiotherapy to craniospinal irradiation and from concurrent and adjuvant temozolomide alone to platinum-based multiagent chemotherapy. Treatment outcomes of this new entity of GBM also varies across reports. Interestingly, some authors have reported better survival for these patients compared to GBM. Here, we intend to report the outcome of four patients of GBM-PNET treated in a tertiary care centre with hypofractionated simultaneous integrated boost intensity modulated radiotherapy (SIB-IMRT) with concurrent and adjuvant temozolomide. We also performed a systematic review of all published literature on GBM-PNET reporting treatment outcome in these patients, and analyzed the pooled data separately concerning survival and prognostic factors.

Materials and Methods

We searched our institutional database from January 2008 to December 2015 and retrieved five cases. Central pathological review of these patients confirmed a diagnosis consistent with GBM-PNET in 4 patients; 1 patient was conformed to have GBM only. Demographic features and clinical characteristics, including radiological findings, surgical details, and histopathological features, were recorded in a proforma. In a quest to examine the behavior of these tumors, we retrieved all published reports pertaining to GBM-PNET. We retrieved six full-text articles and one abstract pertaining to the topic with 75 cases. However, individual patients and treatment data was not available for the largest series reported by Perry et al. and Lee et al. Hence, we pooled the survival data of our series of patients with the existing survival outcomes of 19 patients in the literature for a secondary analysis. Survival estimates were calculated using Kaplan–Meier method, and log rank test was used for univariate analysis. The Statistical Package for the Social Sciences version 16.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analysis.

Patient evaluation and treatment

Maximal safe surgery was attempted in all patients after neurological imaging was done. Once the histopathological diagnosis was confirmed as GBM-PNET, patients were subjected to contrast-enhanced magnetic resonance imaging (MRI) of the brain to look for residual disease, and cerebrospinal fluid (CSF) cytology and MRI spine to look for drop metastasis. Adjuvant radiation was delivered within 4–6 weeks of surgery. Radiation therapy was planned by intensity modulated radiotherapy with simultaneous boost (SIB-IMRT) technique. A thermoplastic immobilization cast was used for each patient for treatment position reproducibility. A contrast-enhanced computed tomography (CECT) scan was done in the treatment position for treatment planning. The low risk clinical target volume (CTV 50) included MRI abnormality visible on the T2 fluid-attenuated inversion recovery (FLAIR) sequences of the preoperative MRI with isotropic 1.5-cm margin. The high risk CTV (CTV 60) included a 1.5-cm margin around the T1 contrast enhancing tumor. An isotropic expansion of 5 mm was given around the clinical target volume to generate the planning target volume (PTV). A dose of 60 Gy in 20 fractions and 50 Gy in 20 fractions was prescribed for PTV60 and PTV50, respectively, using simultaneous integrated boost technique. Radiation was planned on the pinnacle treatment planning system. Concurrent temozolomide was prescribed at a dose of 75 mg/m2 daily in empty stomach following antiemetic and proton pump inhibitor (60–90 min before radiation). Temozolomide was continued for 2 weeks after completion of radiotherapy (radiotherapy was completed in 4 weeks). Adjuvant temozolomide was started after a gap of one month. First cycle was given at 150 mg/m2, and depending on the tolerance, was increased to 200 mg/m2 in the next cycle for six cycles repeated every four weeks.

Complete blood count and liver function tests were repeated once a week during radiation and before each cycle of adjuvant chemotherapy. Toxicity was charted according to Radiation Therapy Oncology Group (RTOG) acute toxicity grading criteria. All patients were reviewed after 4–6 weeks of completion of treatment with detailed clinical and neurological examination. Contrast-enhanced brain MRI was performed at 3 months of completion of radiotherapy, and subsequently, after every 3 months.

Results

The patients were treated as a part of an ongoing prospective study comparing hypofractionated SIB-IMRT to conventionally fractionated, 3-dimensional conformal radiotherapy (3D-CRT) in patients with newly diagnosed GBM. Median age at diagnosis was 34 years (range: 23–42). The most common symptom was headache and vomiting seen in three patients followed by seizure in 2 patients. Median duration of symptoms before diagnosis was 9 months (range: 2–15). Two patients had frontal location of tumor, 1 had frontoparietal location, and one patient had temporal lobe lesion. The median Karnofsky performance status (KPS) was 90.

Contrast-enhanced MRI was done in all patients before surgery. The tumor was hypointense on T1 and hyperintense on T2. Three patients had tumor which was contrast enhancing, whereas in 1 patient the tumor was nonenhancing. The median tumor size was 5.2 cm (range: 3.8–6.8 cm). The preoperative diagnosis was high-grade glioma in 3 patients and low-grade glioma in one patient [Figure 1]. All patients underwent surgery in our institute with three patients undergoing gross total excision and one patient undergoing subtotal resection. Histopathological examination revealed a biphasic tumor, which composed of an astrocytic component and an undifferentiated small round cell component. The astrocytic component showed moderate increase in cellularity, marked pleomorphism with many tumor giant cells, increased mitosis, and necrosis suggestive of GBM with PNET-like areas [Figure 2]. Median MIB labeling index was 30 (range: 30–95). Immunohistochemistry of the glial component revealed p53 positivity in three cases. Isocitrate dehydrogenase (IDH-1) was positive in one patient and negative in three patients. The neuronal component showed synaptophysin positivity in all patients. Metastatic work up with CSF cytology and spine screening MRI showed no evidence of drop metastasis in any patient.{Figure 1}{Figure 2}

Adjuvant radiotherapy with concurrent temozolomide (75 mg/m2) was given to all the patients. Conformal radiotherapy at a dose of 60 Gy with intensity modulated radiotherapy by simultaneous integrated boost technique (50 Gy to the low risk PTV and 60 Gy to the high risk PTV) was given to all patients [Figure 3]. The patient and treatment characteristics are summarized in [Table 1]. The median follow-up was 12.9 months. One of the four patients developed local recurrence at 18 months while on follow up. All patients experienced grade III alopecia following radiotherapy and 1 patient developed grade 2 thrombocytopenia during adjuvant temozolomide.{Figure 3}{Table 1}

Twenty-three patients could be included in the pooled analysis. The pooled analysis revealed the median age at diagnosis as 47 years (range: 23–82). Six patients underwent gross total excision whereas 10 patients underwent subtotal excision; others underwent a biopsy or decompression only. Six patients underwent craniospinal irradiation (CSI) whereas 16 patients received focal radiation. All but two patients also received adjuvant temozolomide. The median MIB labeling index was 80 (range: 30–100). Only three patients had documented IDH-1 mutation and all the three patients were alive at the last follow-up. Median follow-up of the cohort was 13 months (range: 2–66). The survival analysis of the cohort revealed a median progression free and overall survival of 10 and 25 months, respectively [Figure 4]. The 2-year progression free survival and overall survival rate 23.4 and 52.1%, respectively. Univariate analysis for the prognostic variables including extent of surgery, local radiation vs. CSI, and age at presentation revealed no significant impact on survival. {Figure 4}

Discussion

GBM is the most common primary brain tumor occurring in patients more than 50 years of age and accounts for approximately 75% of all primary brain tumors in patients more than 60 years of age. Maximal safe surgery followed by adjuvant chemoradiation is the treatment of choice in GBM and produces a median survival of approximately 12–15 months.[1],[2] Different variants of GBM have been described in the literature viz. gliosarcoma, GBM with oligodendroglial component, small cell GBM, etc.[3] In recent years, a new entity of GBM with PNET-like areas has emerged. GBM-PNET is a very rare entity of GBM and only few cases have

been reported in literature so far. Radiologically, it is very difficult to differentiate high-grade gliomas from GBM-PNET, which usually presents with a solid cystic lesion with heterogeneous contrast enhancement. In a small series, Ali et al. reported substantially reduced apparent diffusion coefficient (ADC) values in GBM-PNETs compared to conventional GBM.[4] In the present series also, the preoperative diagnosis was high-grade glioma in 3 patients whereas 1 patient had a preoperative diagnosis of low-grade glioma. These tumors are well-circumscribed and may facilitate surgical excision. However, histopathological examination reveals a biphasic tumor composed of an astrocytic component and undifferentiated small round cell component suggestive of GBM-PNET. The astrocytic areas show nuclear atypia and necrosis, whereas the neuroectodermal foci show high mitotic activity with rosette formation. The glial component usually shows glial fibrillary acid protein (GFAP) positivity, whereas the neuroectodermal foci show positivity for neuronal markers such as synaptophysin and chromogranin. The glial component may show variable positivity to p53, IDH-1, and epithelial growth factor receptor (EGFR). In the present series, 3 out of 4 cases showed p53 mutation, and only 1 showed IDH-1 mutation corroborating the findings of a similar series published by Song et al.[5]

Maximal safe resection is considered optimum for GBM and is advocated for this new entity as well. CSF and systemic spread is rare in GBM, however, it is common in PNETs, which brings into question the optimum adjuvant therapy for GBM-PNET. Systemic metastasis has rarely been reported from a GBM-PNET, however, there are reports of CSF spread in approximately 15–20% of the cases. Thus, evaluation to detect CSF spread such as contrast-enhanced MRI of the spine and CSF cytology should be done in all patients.

Adjuvant radiation volume has been an area lacking consensus among various centers, with volume ranging from craniospinal irradiation to local radiotherapy. There is consensus that patients with CSF positivity need to be treated with craniospinal irradiation. The toxicity associated with craniospinal irradiation may be of concern when considering CSI in patients with CSF negative disease. In the largest series by Perry et al., 17 patients received local radiotherapy whereas 1 patient received craniospinal irradiation.[6] Another series from O'Leary et al. reported the feasibility of craniospinal irradiation along with concurrent temozolomide in these patients with survival not different from focally treated GBM.[7]

Chemotherapy regimen also varies widely with some series using platinum-based chemotherapy, as in PNET, while others using temozolomide-based chemotherapy alone, as in GBM. One series by Lee et al. used a combination of temozolomide and platinum chemotherapy and found it to be a feasible option.[8] In our series, we used local radiotherapy along with concurrent and maintenance temozolomide.

Median survival of these patients ranged from 9 to 10 months according to the published literature. Some authors have reported the outcome in patients with GBM-PNET to be better than that of the GBM patients. Our pooled analysis revealed a median progression free survival and overall survival of 10 and 25 months, respectively. The well-circumscribed nature of the disease may facilitate better surgical resection and confer better survival. In addition, these tumors may harbor more IDH-1 mutation or MGMT methylation. A summary of various case series, their adjuvant treatment approach, and survival outcomes is summarized in [Table 2].[5],[6],[7],[8],[9],[10],[11]{Table 2}

Conclusion

Based on the current available evidence, it is difficult for us to conclude what regimen of chemotherapy and what volume of irradiation is ideal among these patients. The adjuvant treatment needs to be individualized considering the good outcome in patients treated with adjuvant local radiation and concurrent temozolomide, with or without platinum-based chemotherapy. The survival outcome in these patients may be slightly better in patients with GBM-PNET than in patients with GBM.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, *et al*. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomized phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009;10:459-66.

2 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.

3 Mallick S, Gandhi AK, Sharma DN, Gupta S, Haresh KP, Rath GK. Pediatric gliosarcoma treated with adjuvant radiotherapy and temozolomide. Childs Nerv Syst 2015;31:2341-4.

4 Ali S, Joseph NM, Perry A, Barajas RF Jr, Cha S. Apparent diffusion coefficient in glioblastoma with PNET-like components, a GBM variant. J Neurooncol 2014;119:353-60.

5 Song X, Andrew Allen R, Terence Dunn S, Fung KM, Farmer P, Gandhi S, *et al*. Glioblastoma with PNET-like components has a higher frequency of isocitrate dehydrogenase 1 (IDH1) mutation and likely a better prognosis than primary Glioblastoma. Int J Clin Exp Pathol 2011;4:651-60.

6 Perry A, Miller CR, Gujrati M, Scheithauer BW, Zambrano SC, Jost SC, *et al*. Malignant gliomas with primitive neuroectodermal tumor-like components: A clinicopathologic and genetic study of 53 cases. Brain Pathol 2009;19:81-90.

7 O'Leary B, Mandeville HC, Fersht N, Solda F, Mycroft J, Zacharoulis S, *et al*. Craniospinal irradiation with concomitant and adjuvant temozolomide-a feasibility assessment of toxicity in patients with glioblastoma with a PNET component. J Neurooncol 2016;127:295-302.

8 Lee APS, Brewer J, Back M, Wheeler H. Combination therapy for glioblastoma multiforme with primitive neuroectodermal tumor components: Case series. J Clin Oncol 2012;30:e12507.

9 Kaplan KJ, Perry A. Gliosarcoma with primitive neuroectodermal differentiation: Case report and review of the literature. J Neurooncol 2007;83:313-8.

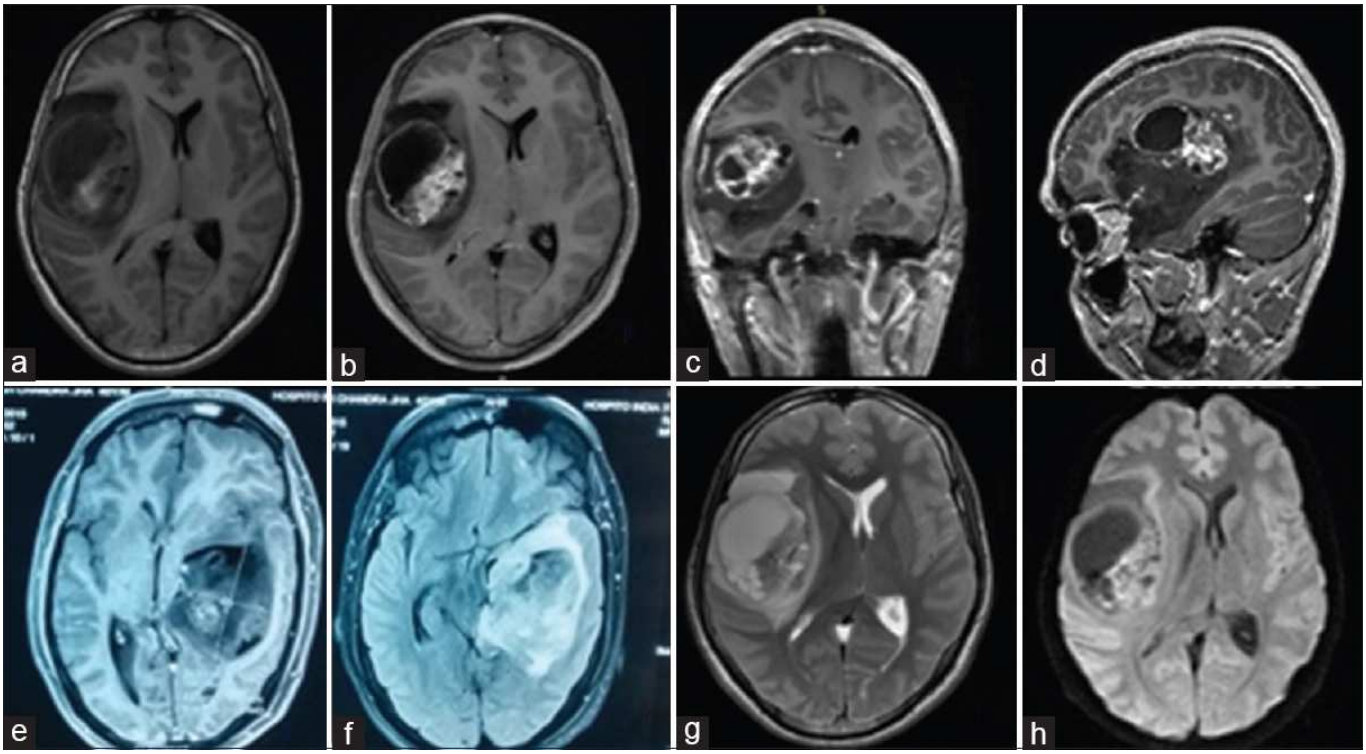
10 Kandemir NO, Bahadir B, Gul S, Karadayi N, Ozdamar SO. Glioblastoma with primitive neuroectodermal tumor like features: Case report. Turk Neurosurg 2009;19:260-4.

11 Chu A, Bourgeois DJ, Prasad D. A responsive yet persistently recurrent GBM with PNET features. Appl Rad Oncol 2015;4:28-30.

NEUROLOGY INDIA
Publication of the Neurological Society of India

Close

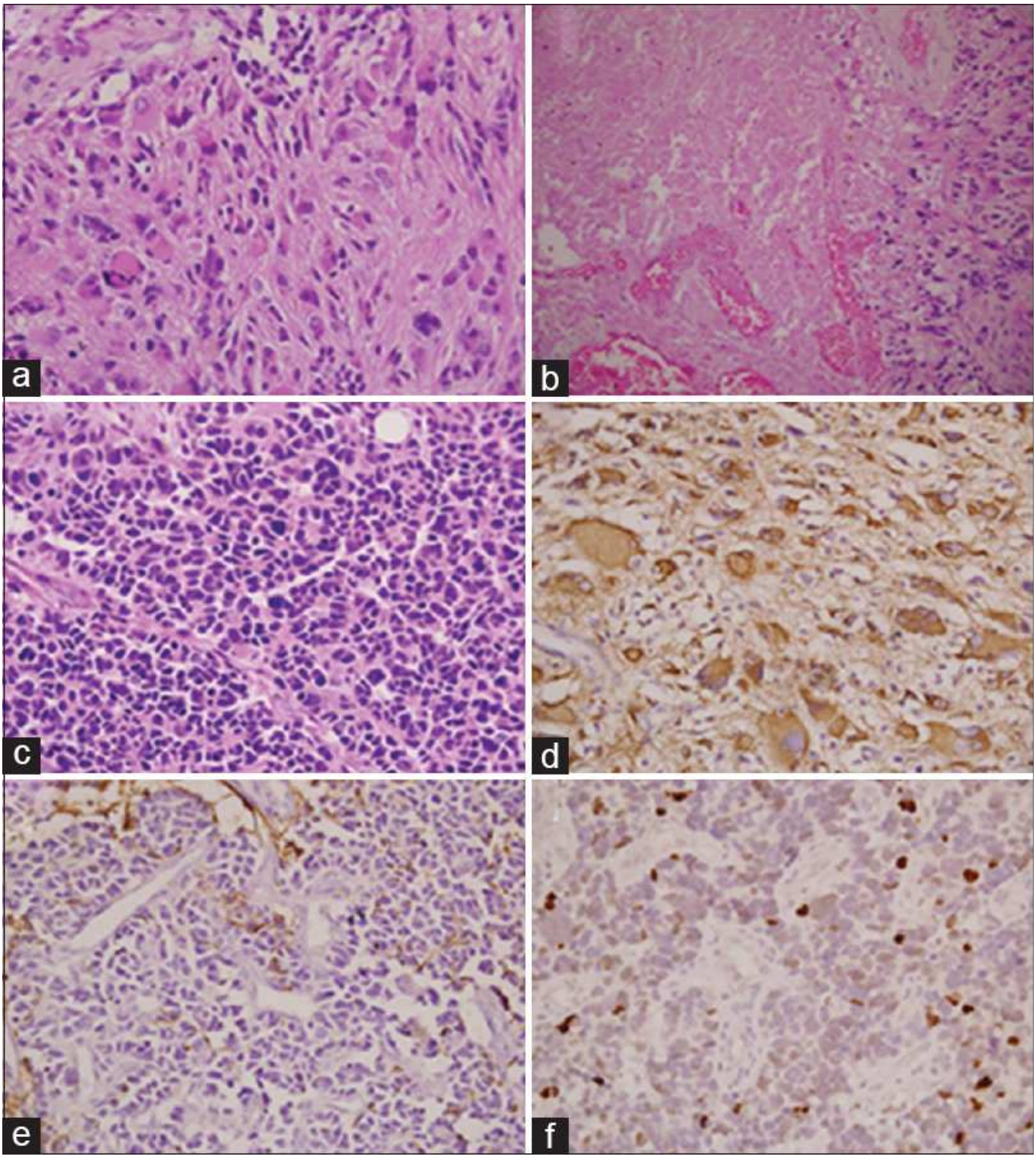
Figure 1: Contrast-enhanced magnetic resonance imaging of a patient of GBM with areas of neuroectodermal differentiation (a) T1 axial noncontrast image (b-e) axial, coronal, and sagittal T1 postcontrast image showing heterogeneously contrast-enhancing mass with cystic component with mass effect and midline shift; (f and g) axial T2 FLAIR image; (h) axial diffusion-weighted image



NEUROLOGY INDIA
Publication of the Neurological Society of India

Close

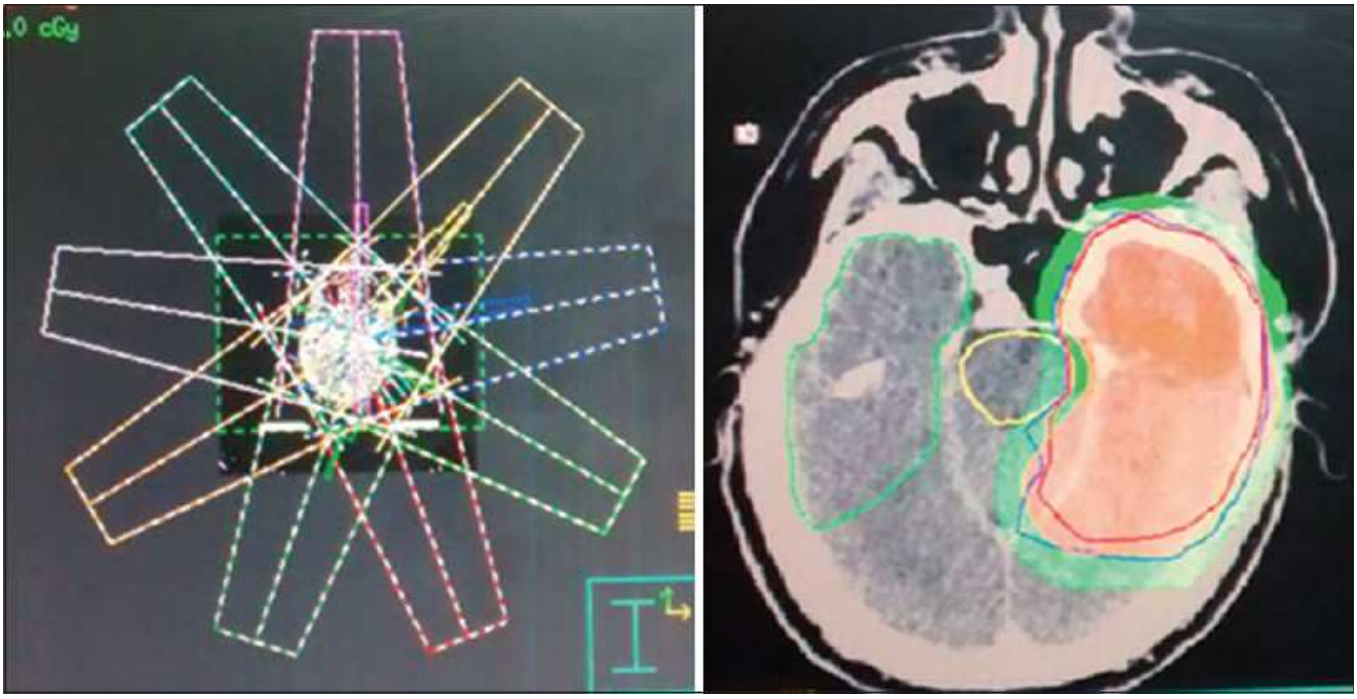
Figure 2: Photomicrographs showing a biphasic tumour comprising of astrocytic and primitive neuroectodermal components. The astrocytic areas showing oval to spindle cells, gemistocytes, and areas of necrosis with psedopallisading of cells (a and b, H and E ×400); Primitive neuroectodremal component is composed of small round to oval cells with hyperchromatic nuclei anf increase mitises (c, H and E ×400). Glial component is immunopositive for GFAP (d) but primitive neuroectodremal component is negative (e) and it is focally immunipositive for Neu N (f, ×400 each)



NEUROLOGY INDIA
Publication of the Neurological Society of India

Close

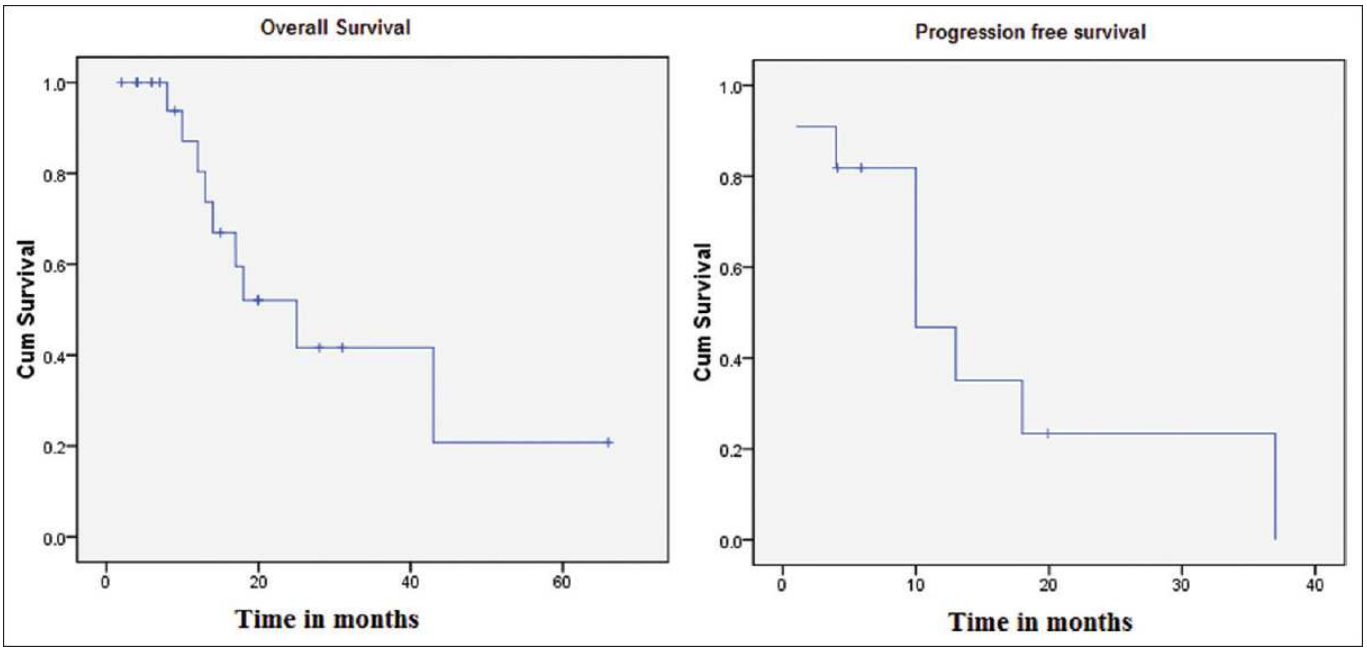
Figure 3: A 9-field dynamic intensity modulated radiotherapy plan for a patient of GBM with neuroectodermal differentiation



NEUROLOGY INDIA
Publication of the Neurological Society of India

Close

Figure 4: Kaplan–Meier survival estimate progression free survival and overall survival in the pooled cohort



NEUROLOGY INDIA
Publication of the Neurological Society of India

Close

Table 1: Summary of patient characteristics and immunohistochemistry findings and treatment outcome of patients treated with simultaneous integrated boost intensity modulated radiotherapy (SIB-IMRT) along with temozolomide (TMZ)

Patient No	Age (Years)	Gender	Location of the tumor	p53	Isocitrate Dehydrogenase	Synaptophysin	Surgery	Adjuvant treatment	Follow up (months)/Status
1	40	Male	Frontoparietal	Positive	Negative	Positive	Gross total excision	SIB-IMRT + TMZ	20.0/Alive
2	42	Male	Temporal	Positive	Negative	Positive	Gross total excision	SIB-IMRT + TMZ	5.9/Alive
3	23	Female	Frontal	Positive	Positive	Positive	Subtotal excision	SIB-IMRT + TMZ	19.9/Alive
4	28	Male	Frontal	Negative	Negative	Positive	Gross total excision	SIB-IMRT + TMZ	4.1/Alive

NEUROLOGY INDIA
Publication of the Neurological Society of India

Table 2: Summary of adjuvant treatment and survival outcome patients of glioblastoma with neuroectodermal differentiation from various published case series

Trial	Adjuvant Radiotherapy	Adjuvant Chemotherapy	Survival Outcome
Perry *et al.*, 2009 *n*=53[6]	Local radiotherapy - 17 Craniospinal irradiation - 1 Concurrent chemotherapy - 14	Glioma-like chemotherapy - 16 Platinum-based - 3	Median survival - 9.1 months Cerebrospinal fluid (CSF) dissemination - 21%
Song *et al.*, 2011 *n*=10[5]	Local radiotherapy (RT) - 9	Temozolomide (10)	Median survival - 10 months (2-31 months) CSF dissemination - 20%
O'Leary *et al.*, 2016 *n*=6[7]	Craniospinal irradiation	Temozolomide	Temozolomide with craniospinal irradiation is feasible with acceptable toxicity
Lee *et al.*, 2012 *n*=3[8]	Local radiotherapy with temozolomide and xarboplatin	Ifosphamide + Carboplatin + Etoposide for 3 cycles followed by temozolomide for 6-36 months	1 local progression at 32 months 2 disease free at 36 and 56 months
Kaplan *et al.*, 2007 *n*=1[9]	Local RT	NA	Local progression - 10 months
Kandemir *et al.*, 2009 *n*=1[10]	Local RT	NA	Alive at 9 months
Chu *et al.*, 2015 *n*=1[11]	Local RT 59.4 Gy à 17Gy boost	Temozolomide	Local progression - 1 month Survival - 28 months
Present Series *n*=4	Local RT (Hypofractionated simultaneous integrated boost intensity modulated radiotherapy)	Temozolomide	3 patients did not have any recurrence on last follow-up while one patient had local recurrence at 18 months