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Systematic Review and Individual Patient Data Analysis of Uncommon Variants of Glioblastoma: An Analysis of 196 Cases

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Abstract

Objectives: Different variant of GBM has been reported viz. Epithelioid Glioblastoma (GBM-E), Rhabdoid GBM (GBM-R), Small cell GBM (GBM-SC), Giant cell GBM (GBM-GC), GBM with neuro ectodermal differentiation (GBM-PNET) with unknown behavior. **Materials:** We conducted a systematic review and individual patient data analysis of these rare GBM variants. We searched PubMed, google search, and Cochrane library for eligible studies till July 1st 2016 published in English language and collected data regarding age, sex, subtype and treatment received, Progression Free Survival (PFS), Overall Survival (OS). Statistical Package for social sciences (SPSS) v16 software was used for all statistical analysis. **Results:** We retrieved data of 196 patients with rare GBM subtypes. Among these GBM-GC is commonest (51%), followed by GBM-R (19%), GBM-PNET (13%), GBM-SC (9%) and GBM-E (8%). Median age at diagnosis was 38, 40, 43.5, 69.5 and 18 years, respectively. Male: female ratio was 2:1 for GBM-E, and 1:3 for GBM-SC. Maximal safe resection followed by adjuvant local radiation was used for most of the patients. However, 6 patients with GBM-PNET, 3 each of GBM-E, GBM-SC received adjuvant craniospinal radiation. Out of 88 patients who received chemotherapy, 64 received Temozolomide alone or combination chemotherapy containing Temozolomide. Median PFS and OS for the entire cohort were 9 and 16 months. In univariate analysis, patient with a Gross Total Resection had significantly better PFS and OS compared to those with a Sub Total Resection [23 vs. 13 months (p-0.01)]. Median OS for GBM PNET, GBM-GC, GBM-SC, GBM-R and GBM-E were 32, 18.3, 11, 12 and 7.7 months, respectively (P = 0.001). Interestingly, 31.3%, 37.8% of patients with GBM-E, GBM-R had CSF dissemination. **Conclusion:** Overall cohort of rarer GBM variant has equivalent survival compared to GBM not otherwise specified. However, epithelioid and Rhabdoid GBM has worst survival and one third shows CSF dissemination.

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Full Text

Glioblastoma (GBM) is the commonest primary brain tumor occurring in patients more than 50 years of

age.[1],[2] Over the years, different variants of GBM have been reported viz. gliosarcoma, GBM with oligodendroglial differentiation (GBM-O), Epithelioid GBM (GBM-E), Rhabdoid GBM (GBM-R), Small cell GBM (GBM-SC), Giant cell GBM (GBM-GC), GBM with neuro ectodermal differentiation (GBM-PNET).[3],[4],[84],[85] Adjuvant treatment in patients with GBM variants varies widely from local radiotherapy to craniospinal irradiation and from concurrent and adjuvant Temozolomide alone to Platinum based multi agent chemotherapy. Recently, fewer larger series proposed treatment akin to GBM and described equivalent survival for Gliosarcoma and GBM-O.[5],[6],[7] Treatment protocol for the rarer GBM subtypes also varies across reports because of anticipated aggressiveness. Survival outcome has been reported to be not different for these rare GBM subtypes. Interestingly, some of the authors reported a better survival for these patients compared to GBM. But due to rarity, most of the data are derived from case reports or small case series. Here, we intend to present results of systematic review and individual patient data analysis of all published literature on five rare GBM subtypes published in the literature.

Search Method

Three authors (SM, RB, and BP) independently searched PubMed, Google search, and Cochrane library for eligible studies with the following search words: Glioblastoma, Epithelioid GBM, Rhabdoid GBM, Small cell GBM, Giant cell GBM, GBM with neuro ectodermal differentiation, till July 1 2016, published in English language. The details of search strategy in PubMed have been mentioned in supplementary digital content. References from the primary search result also were manually searched for potentially eligible studies.

Study selection

This analysis included published articles describing Epithelioid GBM, Rhabdoid GBM, Small cell GBM, Giant cell GBM, GBM with neuro ectodermal differentiation and treatment. Fully published case reports or case series describing the treatment and outcome were considered eligible. Articles on pathology and genetics alone without report on treatment and clinical outcomes were excluded from the analysis. Three independent authors (SM, RB, and BP) selected the eligible studies and any was solved after discussion with a fourth author (GKR).

Data collection

Three authors independently (SM, RB, and BP) extracted all data from the eligible studies. The following data were collected from each of the study: sex, age, site of disease, histologic subtype, and treatment received, DFS, OS in a predesigned proforma. Analysis was performed on a partial dataset when all relevant information was not available about a particular parameter. In addition, we refrained from including such data where it was not possible to categorically identify it.

Statistical analysis

Data was analysed and categorical variables were summarized by frequency (%) and quantitative variables were summarized by median and range. Progression free survival [PFS] and overall survival [OS] were calculated from the date of diagnosis to the date of documented progression or death respectively. Kaplan Meier method was used for survival analysis. Log rank test was performed to identify the impact of different prognostic variables on DFS and OS, and P value of ≤ 0.05 was taken as significant. Statistical Package for social sciences (SPSS) v16 software was used for all statistical analysis.

Results

We retrieved data of 196 patients with rarer GBM subtypes from 74 publications.[8],[9],[10],[11],[12],[13], [14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29],[30],[31],[32],[33],[34],[35], [36],[37],[38],[39],[40],[41],[42],[43],[44],[45],[46],[47],[48],[49],[50],[51],[52],[53],[54],[55],[56],[57],

[58],[59],[60],[61],[62],[63],[64],[65],[66],[67],[68],[69],[70],[71],[72],[73],[74],[75],[76],[77],[78],[79],[80],[81] Among these, GBM-GC is commonest, accounting for 51%, followed by GBM-R (19%), GBM-PNET (13%), GBM-SC (9%) and GBM-E (8%). Median age of the entire cohort was 42 years (Range: 3.5-92 years). Median age for these variants was 38, 40, 43.5, 69.5 and 18 years respectively. Male: female ratio was 2:1 for GBM-E; 1:3 for GBM-SC. Headache was the commonest presenting complaint in 61.8% patients, followed by hemiparesis in 13.5% and seizure in 11.2% of the patients [Table 1]. 39% patients had tumor in the frontal lobe, and 32% had in the temporal lobe.{Table 1}

Treatment

Surgical details could be retrieved for 157 patients. 58 (36.9%) patients underwent a gross total resection (GTR); 88 (56.1%) underwent a subtotal resection (STR) and 11 (7%) underwent biopsy only. 43.3%; 54.9%; 34.6% patients with GBM-GC; GBM-R; GBM-PNET underwent a GTR. None of the GBM-SC patients underwent a GTR reflecting a highly infiltrative nature of the disease. Adjuvant local radiation following maximal safe resection was given for most of the patients. Radiation details were available for 142 patients. 14 (9.8%) patients did not receive adjuvant radiation mainly because of old age and poor performance status. Adjuvant radiation was used for 128 patients. Out of 128 patients, 10 patients received CSI and two patients received whole brain radiation. Craniospinal radiation was used in 6 patients with GBM-PNET, and 3 each of GBM-E, GBM-SC. Median dose of radiation was 59.4 Gy (Range 20-61.2 Gy). Details of pattern of care for each variant have been shown in [Figure 1]. Chemotherapy details were available in 88 patients. Interestingly, 22 patients did not receive any adjuvant chemotherapy. Temozolomide was the drug used most commonly in 64 (72.7%) cases, either alone or with combination with other drugs. Other chemotherapy drugs used varied widely from Methotrexate, Bevacizumab, Interferon, Ranimustine, Etoposide, Erlotinib and Vorinostat.{Figure 1}

Survival outcome

Median follow-up duration was 12 months (Range: 1-213 months). Median PFS for the entire cohort was 9 months [Range: 6.95-11.04]. Patients underwent a GTR had better survival compared to those with a STR, 12 vs. 7.7 months (p-0.010). Rest of the factors had no significant impact on PFS.

Median OS for the entire cohort was 16.0 months [Range: 1.79-12.47]. In univariate analysis patient with a GTR had significantly better OS compared to those with a STR [23 vs. 13 months (p-0.01)]. Median OS for GBM PNET 32 was found to be months; and those for GBM-GC, GBM-SC, GBM-R and GBM-E were 18.3, 11, 12 and 7.7 months respectively (P = 0.001). Rest of the factors had no significant impact on OS. [Figure 2] depicts the Kaplan Meier survival graph for DFS, OS and impact of survival on DFS and OS.{Figure 2}

Pattern of failure and salvage therapy

The pattern of failure data was available in 35 cases only. Out of these, only 6 cases had local progression of disease. 31.3%, 37.8% patients with GBM-E, GBM-R had CSF dissemination.

Discussion

Glioblastoma (GBM) is the most common primary brain tumor occurring in patients more than 50 years of age and is associated with a dismal prognosis.[1],[2] Different variants of GBM have been described in the literature.[3],[4],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29],[30],[31],[32],[33],[34],[35],[36],[37],[38],[39],[40],[41],[42],[43],[44],[45],[46],[47],[48],[49],[50],[51],[52],[53],[54],[55],[56],[57],[58],[59],[60],[61],[62],[63],[64],[65],[66],[67],[68],[69],[70],[71],[72],[73],[74],[75],[76],[77],[78],[79],[80],[81] Few of these variants viz. GBM-E, GBM-R, GBM-GC has been described earlier and newer variants like GBM-PNET has been described recently.[82],[86],[87],[88],[89] There is little agreement to the clinical behavior and optimum treatment for most of these variants and more aggressive behavior of these variants has been hypothesized compared to classical GBM. Recently, few larger series has described gliosarcoma and GBM-O to have clinical behavior and outcome akin to classical GBM.[5],[90] But, due to rarity no direct comparison between the rarer variants viz. GBM-E, GBM-

R, GBM-GC, GBM-SC is possible.[18],[41]

Among these rare variants, GBM-GC was found to be the commonest followed by GBM-R. GBM-SC was seen in elderly patients with median age of 69 years, whereas GBM-E was seen in younger patients of 2nd decade with median age of 18 years. Hence, the pediatric patients with GBM are more prone to have a GBM-E with aggressive disease. Interestingly, GBM-E was found more frequently in males whereas GBM-SC was predominantly seen in female. This demographic information highlights a possible difference in tumorigenesis of these individual variants and points towards possible difference in clinical behavior as well as outcome. In this individual patient data analysis, maximal safe surgery was found to be contemplated in all patients.[91],[92] Variable fraction of patients underwent a GTR among all these variants except the GBM-SC. None of the GBM-SC patients were amenable for a GTR because of the extreme infiltrative nature of this variant. The present analysis clearly showed significantly better PFS and OS for the patients undergoing a GTR compared to those with a STR.[93],[94] This information again emphasizes the importance of achieving a complete tumor removal for optimizing the survival outcome of these patients.

Adjuvant treatment in such patients has varied widely from local radiotherapy to craniospinal irradiation and from concurrent and adjuvant Temozolomide alone to platinum-based multi agent chemotherapy. This clearly reflects the lack of agreement regarding the clinical behavior of these variants. Adjuvant radiation was not offered to 14 patients due to reasons ranging from old age and poor performance status. Adjuvant craniospinal radiation was used in 10 patients, and 2 of them had leptomeningeal dissemination at diagnosis. The remainder received adjuvant CSI because of anticipated leptomeningeal dissemination and none developed CSF spread. O'Leary et al. recently advocated CSI for GBM PNET to achieve better tumor control.[8],[95] Adjuvant chemotherapy varied widely but Temozolomide was used in about 75% of the patients.[18],[26],[83],[96] This may be because of older cases when Temozolomide was not the standard. However it can also be due to use of more aggressive chemotherapy regimen in a quest of better disease control.

Median PFS and OS for the entire cohort were found to be 9 and 16 months, which are well comparable to classical GBM or Gliosarcoma cohorts. Median OS for GBM PNET 32 months; GBM-GC 18.3 months; GBM-SC 11 months; GBM-R 12 months; and GBM-E 7.7 months ($P = 0.001$). This difference in survival again strengthens the hypothesis of differential origin or tumorigenesis of these individual variants. The most interesting point of the present analysis was the striking difference in the pattern of failure. Among the patients with available information, 31.3% and 37.8% patients with GBM-E and GBM-R, respectively, had CSF dissemination. This extremely high rate of CSF dissemination in GBM-E and GBM-R has also been reported in different series.[18] This survival data along with the pattern of failure emphasize to look beyond the basic pathological factors directs to adopt more aggressive treatment strategy. MRI screening of the entire neuro-axis and CSF cytology should be a part of the workup for GBM-R and GBM-E and patients with CSF positive and M1 disease should be treated with a craniospinal radiation. [Table 2] depicts the differences in these rare GBM variants. [Figure 3] depicts a possible treatment algorithm of these rare GBM variants.{Table 2}{Figure 3}

This analysis has few limitations which are mainly because of lack of all necessary information about the demography, treatment and outcome of individual patients. However, it is difficult to expect and extract all possible information from all individual case reports as these are reported during a prolonged period of time. In addition, the diagnostic and treatment criteria also changes with such duration. However, point should be made that these are rare tumors and direct comparison is hardly possible with in limited time frame. In addition the results reflect the nature of the disease and the clinical behavior of the overall cohort corroborates with the overall outcome of GBM.

Conclusion

Overall cohort of rarer GBM variant has equivalent survival compared to GBM not otherwise specified. However, epithelioid and Rhabdoid GBM has worst survival and one third shows CSF dissemination. Treatment protocols for these two variants should be more aggressive. Molecular characterization and formulation of uniform diagnostic guideline should help to treat these tumors better.

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Conflicts of interest

There are no conflicts of interest.

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Figure 1: Pattern of care among the GBM subtypes

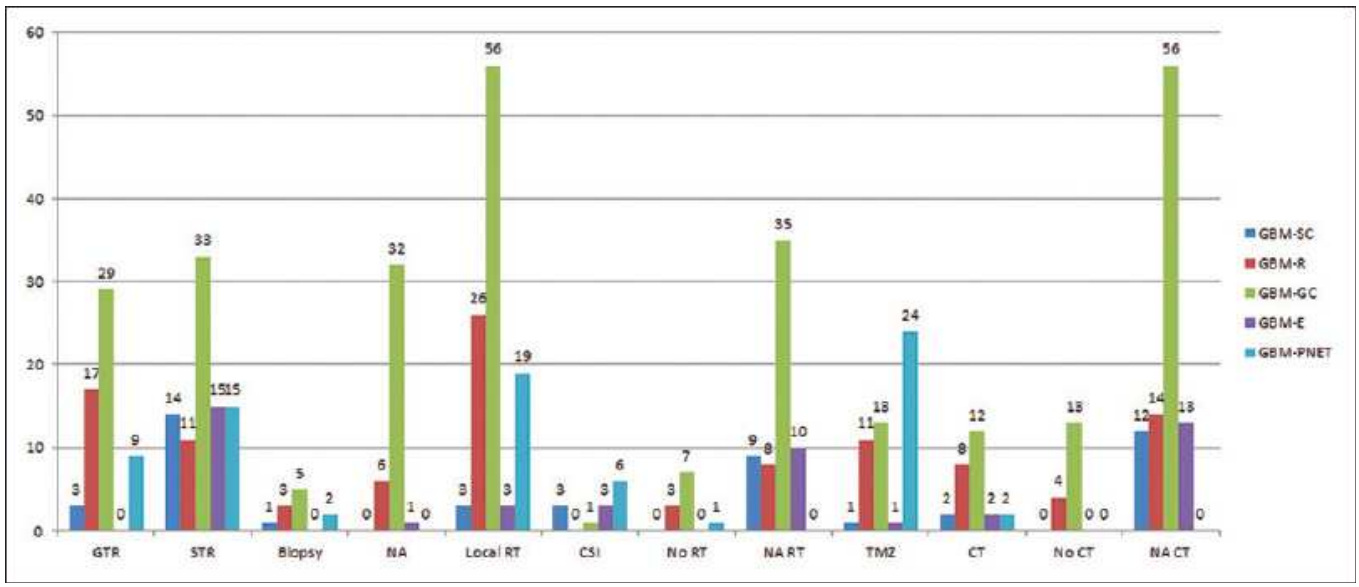

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Figure 2: Kaplan Meier survival graph of DFS, OS and impact of surgery of DFS, OS

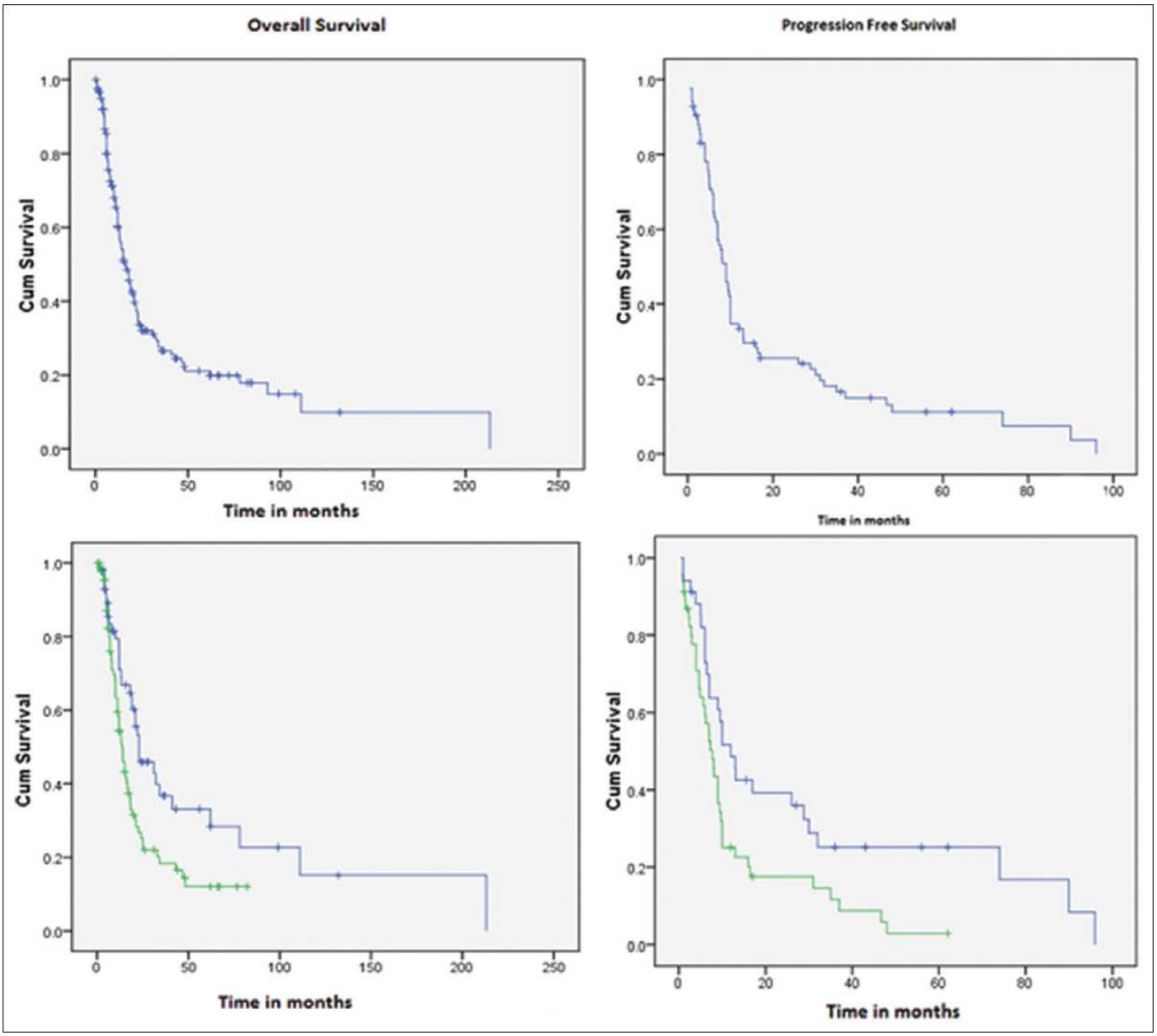

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Figure 3: A treatment algorithm of these rare GBM variants

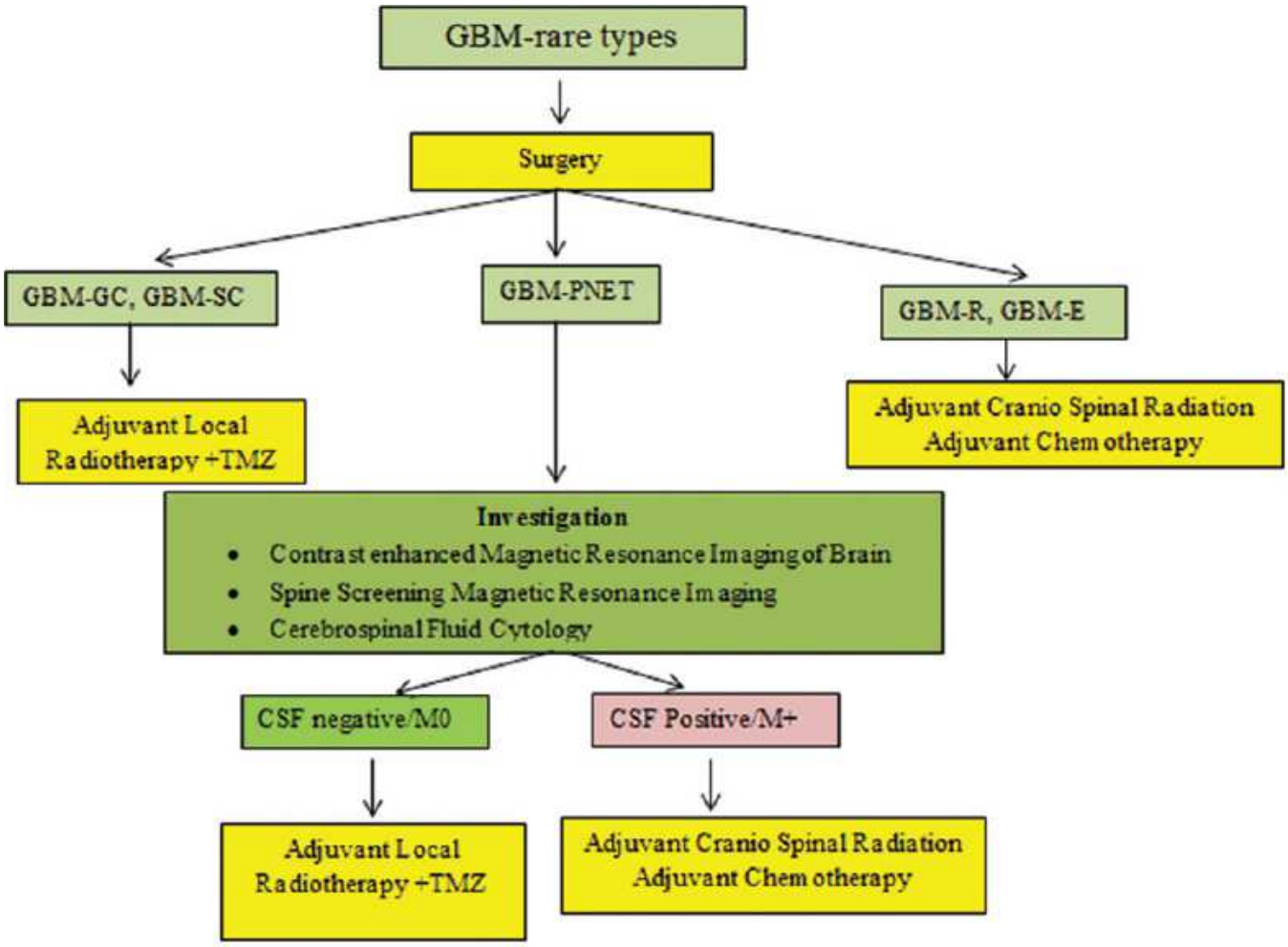

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Table 1: Demographic features and patterns of care in patients with different rarer GBM subtypes

Patient characteristics	Number of patients [Percentage]/[Range]
Age	Median- 42 (Range 3.5-92)
Sex	Male-98
n=169	Female -71
	Male: female ratio of 1.4:1
Presenting Symptoms	Headache-61.8%
	Seizure-11.2%
n=89	Hemiparesis-13.5%
	Others-13.5%
MIB labelling Index	Median- 7 (Range 1-30)
Surgery	Gross total or near total resection - 58 (36.9%)
n=157	Subtotal resection or debulking -88 (56.1%)
	Biopsy -11 (7%)
Radiation	Adjuvant Radiation-128 (65.3%)
	No Adjuvant Radiation-14 (7.1%)
	Information NA-55 (28.1%)
Radiation Volume	Cranio spinal radiation-10 (7.8%)
n=128	Local radiation-65 (50.8%)
	Whole brain radiation-2 (1.6%)
	Details not available-51 (39.8%)
Chemotherapy	Used-88 (44.9%)
n=196	Not Used-22 (11.2%)
	Information NA-86 (43.9%)

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Table 2: Describes the differences in these rare GBM variants

	Gliosarcoma (5)	GBM-PNET (13%)	GBM-SC (9%)	GBM-GC (51%)	GBM-R (19%)	GBM-E (8%)
Age (Median)	45	43.5 (17-82)	69.5 (23-92)	38 (1.9-76)	40 (12-79)	18 (3.5-69)
Gender (Male: Female)	3:1		1:3.5	1:1	1:1.4	2:1
Radiology/ Nature	Intense peripheral or irregular ring enhancement, calcification	ring-enhancing Reduced ADC	Multifocal, infiltrative	Demarcated	well-circumscribed and enhancing mass	Sharply demarcated
Molecular changes	MGMT-31.25%, IDH1, p53, PTEN	N-myc,C-myc,IDH1 Loss chromosome 10q	EGFR,EGFRvIII,PTEN	P53, PTEN, MDM2; Mean survival: 18, 33, 79, 93, 105, ICD-0 9441/3 Loss chromosome: 10	BRAF V600E mutation CDKN2A/ 2B deletion, and EGFR/ MET copy number gain	P53, p21, EGFR BRAF: p.V600E mutation-50% H3F3A p.K27M mutation
Pattern of failure	Local		Local Leptomeningeal-5%	Local Leptomeningeal-5%	Local Leptomeningeal- 31.3%	Local Leptomeningeal-37.8%
Survival						
Median OS	16.7 months	32 months	11 months	18.3 months	12 months	7.7 months