Original Research Paper

Volume-9 | Issue-1 | January-2019 | PRINT ISSN - 2249-555X

Neurosurgery

STUDY ON MEDIAN SURVIVAL RATE OF PATIENTS TREATED FOR GLIOBLASTOMA MULTIFORME.

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ABSTRACT

Introduction Glioblastoma multiforme is a primary brain neoplasm, consisting of a phenotypically and genotypically heterogeneous group of tumours. About ninety percent of glioblastoma cases develop de novo from normal glial cells by multistep tumorigenesis (Primary glioblastoma). The remaining10% of gliomas are cases of secondary neoplasm, developing through progression from low-grade tumours (diffuse or anaplasticastrocytomas) which takes about 4–5 years. Secondary glioma is diagnosed mostlyin persons with the mean age 39 years, grows more slowly and has a better prognosis. Management remains palliative and includes surgery, radiotherapy (RT), and chemotherapy. With optimal treatment, patients with GBs have a median survival of less than one year.About 2% of patients survive three years.Previously reported long-term survivors (LTSs) of GB may have been patients who actually harboured other low-grade gliomas .The overall prognosis for GBM has been changed little since the 1980s, despite major improvements in neuroimaging, neurosurgery, radiotherapy, and chemotherapy techniques. This study was planned and conducted to assess the median survival rate in patients with glioblastoma multiforme.

Materials and methods After obtaining institutional ethical committee approval, this study was conducted on patients who underwent surgery for GBM at Institute of Neurosurgery, GGH&MMC, Chennai in the age group of less than 65 years with biopsy reported as glioblastoma multiforme in the supratentorial region. Datas regarding presenting clinical features including clinical signs and symptoms were collected.The pre operative scan& MRI findings were recorded. The surgical treatment details such as date of surgery, intra-op findings like size of the tumour, location of tumour ,type of resection performed(i.e. total, partial or biopsy) were noted.In those patients who underwent radiotherapy and chemotherapy postoperatively, the following parameters like type of radiation, its dose and completeness of cycle, complications, repeat RT if any were observed. Chemotherapy details such as drug, dosage, completeness of cycle and complications were recorded. The performance status of these patients were analysed using Karnofsky and WHO/ ECOG/ Zubrod scoring system.

Results- The median survival rate of GBM patients who got treated in our Institute MMC & GGH during the study period was 14 months. Age group, preop Karnofsky score, type of surgery, adjuvant RT and chemotherapy are the main factors which influence the median survival rate of GBM patients. Patients who underwent total resection and completed full dose of radiation and chemotherapy with preop Karnofsky score more than 80 had longer survival period. Glioblastoma multiforme still has a dismal prognosis and requires further research in other modalities of treatment to improve the median survival period of patients with GBM.

KEYWORDS : Glioblastoma multiforme, median survival rate, Karnofsky performance scale, radiation, chemotherapy, supratentorial brain tumors.

INTRODUCTION

The term glioblastoma multiforme (GBM) was introduced inthe second half of the nineteenth century by Harvey Cushing, while the first operation on a patient suffering from this type of tumour was conducted in Vienna in 1904. Malignant CNS tumours are the third leading cause of cancer related deaths in adults and adolescents aged 15 – 34 years. Glioblastoma multiforme is a primary brain neoplasm, consisting of a phenotypically and genotypically heterogeneous group of tumours.. About ninety percent of glioblastoma cases develop de novo from normal glial cells by multistep tumorigenesis (Primary glioblastoma). The remaining10% of gliomas are cases of secondary neoplasm, developing through progression from low-grade tumours (diffuse or anaplastic astrocytomas) which takes about 4–5 years. Secondary glioma is diagnosed mostly in persons with the mean age 39 years, grows more slowly and has a better prognosis. Glioblastoma multiforme, which develops de novo, grows within3 months [6]. Although the genetic bases, as well as the molecular pathwaysunderlying development of primary and secondary gliomas are different, these two types show no morphological differences. Glioblastoma multiforme (GBM), or grade IV astrocytoma, is the most aggressive of primary tumours of the brain for which no cure is available.Management remains palliative and includes surgery, radiotherapy (RT), and chemotherapy. With optimal treatment, patients with GBs have a median survival of less than one year.About 2% of patients survive three years. Previously reported long-term survivors (LTSs) of GB may have been patients who actually harboured other low-grade gliomas. The overall prognosis for GBM has been changed little since the 1980s, despite major improvements in neuroimaging, neurosurgery, radiotherapy, and chemotherapy techniques. Since GBM is common in our Institute, a study was planned and conducted to assess the median survival rate in patients with glioblastoma multiforme.

AIM OF THE STUDY

The aim of this study is to find out the median survival rate of patients treated for glioblastoma multiforme in our institute and to find out the effectiveness of multimodality approach in the survival rate of GBM patients and also to compare the effectiveness of surgery alone with surgery and radiotherapy and chemotherapy and to further determine other clinical parameters affecting median survival rate of patients with GBM and the effectiveness of various prognostic performance score in the survival rate of GBM patients.

MATERIALS AND METHODS

After obtaining institutional ethical committee approval, this study was conducted on 70 patients who underwent surgery for GBM at Institute of Neurosurgery, GGH&MMC, Chennai during the period between January 2011 and December 2012 and whose biopsy was reported as glioblastoma multiforme (GBM) in the age group less than 65 years. Patients with glioblastoma multiforme in infratentorial or spinal cord site and patients associated with any other systemic malignancy or with other life threatening illnesses and over 65 years were excluded from the study.The patient demographic data and relevant past medical and family history were collected. Data regarding presenting clinical features including clinical signs and symptoms were collected.The pre operative scan& MRI findings were recorded.The surgical treatment details and in patients who underwent radiotherapy and chemotherapy postoperatively, the details of the radiation therapy and chemotherapy details were recorded. The performance status of these patients were analysed using Karnofsky and WHO/ ECOG/ Zubrod scoring system.The information collected regarding all the selected cases were recorded in a Master Chart and data analysis was done.

DISCUSSION

Glioblastoma is the most common and most malignant primary tumour of the brain. It is associated with one of the worst 5 year survival period among all human malignancy. In spite of multimodal aggressive

treatment comprising surgical removal, focal radiotherapy and systemic chemotherapy, the median survival period after diagnosis is in the range of 12 months (Smith and Jenkins,).With a population-based studies conducted by Ohgaki et al had observed shorter median survival period. Only a small fraction of glioblastoma patients survive for more than 36 months.

This study was carried out with the aim of finding the median survival rate of patients treated for GBM at this institute.

AGE AND SEX CHARACTERISTICS :-

The mean age at diagnosis in this study group is 49.8yrs(male 49.68yrs; female 51 yrs and the median is 54 years. Majority of the study population falls in the age group of 40-60 years which is comparable with study done by DietmarKrex et al. which showed the study population of glioblastoma had 55 patients (male 28; female 27) with a median age at diagnosis of 51 years (range 21–72 years),which is similar to this study. Vittori et al study showed the median age in their study was 57 years (24 patients were male and 19 female.) Similarly the median age was 54 yrs in the study conducted by Michael el al.which are all similar to this study.

SYMPTOMATOLOGY

In this study the most common symptom is headache which is seen in about 87% of patients followed by the neurological deficit (57%) and seizures (54%). The others were being vomiting (40%), dementia (25%), personality changes (17%), visual loss (7%) and loss of consciousness (3%) being the least.In Chang et al study the clinical symptomology was as follows ,headache(56%) followed by memory loss(35%), cognitive changes(34%) motor deficit(33%) , language deficit (32%), seizures(32%) , personality changes(23%),visual problems (22%), changes in consciousness (16%) vomiting (13%), which is somewhat similar to this study.

LATERALISATION OF TUMOR

In this study, the tumour most commonly lateralizes to the right in about 71% of patients and to left in 29% of patients which is in contrast with the study conducted by Vittori et al who stated that the tumour commonly lateralized to left in 23 patients and to right in 17 patients and to midline in 3 patients in their study.

LOCATION OF TUMOUR

In this study the anatomic location of glioma was not regular, with the number of tumours substantially higher for the frontal(36%) and temporal lobes(35%) than for other lobes parietal(20%),occipital(8%) which is consistent with the results obtained from the study done by Vittori et al and Suvi larjavaara et al. In Vittori et al study,frontal and temporal lobes accounted for 40% and 26% of GBM patients, the others being parietal (16%), occipital (6%).a small number of patients had GBM in brain stem and corpus callosum also.In Suvi Larjavaara et al study GBM most commonly located in the frontal lobe which accounted for 40% followed by temporal lobe 29%, parietal lobe 14% and occipital lobe 3%.which is similar to this study.

COMPLICATIONS OF RADIOCHEMOTHERAPY

In this study post radiotherapy complications observed were somnolence (57%), dermatitis in 21%, serous otitis media14%, radiation induced necrosis 8%. Complications of chemotherapy in this study were nausea and vomiting, thrombocytopenia and anaemia.In Vittori et al study, the observed radiotherapy complications were, lethargy50%, loss of hair 30% and serous otitis media 10%.And most of the patients had nausea and vomiting. Radiation induced necrosis was found in 5% and Fits occurred in 2% of patients. Chemotherapy complications were thrombocytopenia 20%, neutropenia and anaemia 9%, transaminase elevation in 24%, nausea and vomiting 31%.which is somewhat similar to this study.

Factors influencing survival rate :-

Age:-

Younger the age group, longer the survival period which is seen in this study. The median survival period is longer for age <20 yrs (22mths) followed by 20-40yrs (16mths) and 11 months for patients in the age group of 40-60yrs. Similar results had been obtained in many other studies as shown by Brandes Et al in their study observed that the median survival rate was 16.4 months in the patients with age between 30-60yrs and they declared age as an independent prognostic factor affecting survival period. Vittori et al observed that patients with age less than 61 yrs had a longer survival period and DietmarKrex et al have shown that younger age at the time of diagnosis was an important parameter associated with longer survival.

Preop Karnofsky Performance Score

Higher the preop karnofsky score higher the survival period. In this study those patients with a score of 90 had a survival period of 31 months while those patients with score of 20 had a survival period of 3 months. KPS is one of the most important prognostic factors for malignant gliomas. In the RTOG-ECOG trial, the 18-month survival period for patients with a KPS of 70 was 34% compared with 10%-13% for those with a KPS of less than 70 by Vittori et al. Lamborn et al identified four risk groups. The two lower-risk groups included patients younger than age 40 years, young patients with tumour in the frontal lobe being the lowest risk group, patients with a KPS >70, subtotal or total resection, and between ages 40 and 65 years constitutes intermediate-risk group. The highest-risk group included patients older than age 65 years and patients between ages 40 and 65 yrs with either KPS <80 or patient underwent biopsy only but subgroup analyses indicated that inclusion of adjuvant chemotherapy provides an increase in survival, even though that improvement tends to be minimal for patients older than 65 years, for patients older than 40 years whose KPS less than 80, and for those treated with brachytherapy.In a multivariate regression models which accounting for preoperative KPS score, age, extent of resection, radiation therapy, temozolomide therapy were independently associated with prolonged survival.

ECOG / ZUBROD Score

Analysing the preop Zubrod score, lower the score, higher the survival period. In this study those patients with a score of 1 had a survival period of 31 months while those patients with score of 4 had a survival of 2.5 months which is consistent with the results obtained from many studies.

Surgery and adjuvant therapy

In this study the median survival of patients who received chemo radiotherapy is 22 months compared with 14 months in patients with radiation alone, whereas the survival period decreases to 5 months in patients who bypassed chemo radiation. Stupp et al conducted a large randomized phase III clinical trial which showed a significantly increased overall survival in patients who received complete dose of radiotherapy and chemotherapy compared to patients who got treated with radiation alone. It could be increased from 12.1 to 14.6 month. Moreover, several studies suggested that gross or subtotal tumour resection is better than biopsy alone.In this study, without chemo radiation, patients who underwent total resection had median survival rate of 8 months, partial resection had 5 months and who underwent biopsy alone had Median survival period only 2 months which is similar to many studies. Parisi et al (27) study showed that the combination of RT and TMZ improves long term survival in glioblastoma patients which is evidenced in this study also.In this study it is observed that

- Patients who underwent total excision followed by full dose radiation and complete chemotherapy having long survival period than who underwent partial excision/ biopsy with RT and chemotherapy.
- Patients who underwent surgery whatever its type (total excision / partial/ biopsy) and completed RT and chemotherapy having long survival period than who underwent surgery alone.

Median survival period

In this study the median survival period for 70 patients is 14 months. Only 3 (4%) patients survived for three years or longer.A population based outcome data over a twenty years period from the Alberta Brain Tumour registry stated that, out of 689 glioblastoma patients, only 2% survived three years or longer, and of these 15 patients only 4 were still alive at the time of the report. The study done by Mirimanoff et al showed that the median survival period for the total group was 13.6 months and the 2- yearssurvival rate was 24.4%. Three patients survived for more than 3 years after diagnosis and 8 patients were in their second year at the time of their study analysis.(23) From the study done by post-Stupp cohort , it was observed that the median survival period was 15.3 months, with 1 year and 2 years survival rate of 65.7% and 19%, respectively.Increased patient age , higher ZUBROD score had a significant negative impact. In this study older age groups, low pre op Karnofsky score, high ZUBROD score had less

survival period which is similar to the above studies.

RESULTS AND CONCLUSION

The median survival rate of GBM patients who got treated in our Institute MMC & GGH during the study period was 14 months. Age group, preop Karnofsky score, type of surgery, adjuvant RT and chemotherapy are the main factors which influence the median survival rate of GBM patients. Patients who underwent total resection and completed full dose of radiation and chemotherapy with preop Karnofsky score more than 80 had longer survival period. Glioblastoma multiforme still has a dismal prognosis and requires further research in other modalities of treatment to improve the median survival period of patients with GBM.

OBSERVATIONS AND TABLES

FIGURE 1 - KAPLAN MEIER SURVIVAL FUNCTIONS WITH PREOP KPS

The relation between pre op KPS score and survival period was depicted in following chart x-axis indicates months, y-axis indicates percentage of patients surviving at a particular time and with different color code for each KPS score.

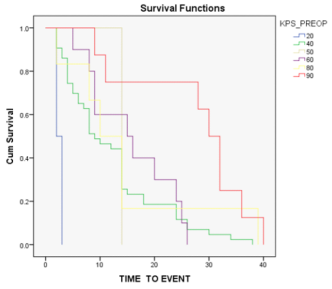

FIGURE 2-KAPLAN MEIER GRAPH COMPARING PREOP ZUBROD AND THE MEDIAN SURVIVAL RATE

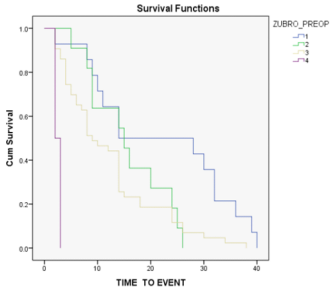

FIG 3. KAPLAN MEIER GRAPH COMPARING TYPE OF SURGICAL RESECTION AND MEDIAN SURVIVAL RATE

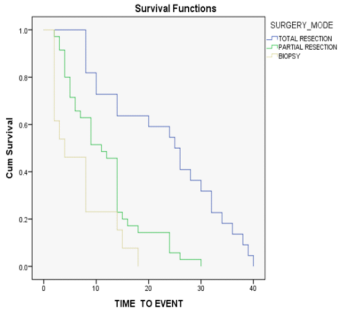

TABLE-1: RELATION BETWEEN TYPE OF SURGERY AND MEDIAN SURVIVAL

TYPE OF SURGERY	NO. OF PATIENTS	MEDIAN SURVIVAL RATE		
		SURGERY	SURGERY+ RT	SURGERY+ RT+ CHEMO
Total	22	8mths	23mths	30mths
Partial	35	5mths	14mths	14mths
Biopsy	13	2mths	_	14mths

TABLE 2 RELATION BETWEEN TREATMENT MODALITY AND MEDIAN SURVIVAL RATE

TREATMENT MODALITY	NO. OF PATIENTS	MEDIAN SURVIVAL RATE
Surgery alone	22	5mths
Surgery +RT	7	14mths
Surgery +RT+Chemo	41	22mths

TABLE 3 MEDIAN SURVIVAL RATE IN VARIOUS AGE GROUP OF GBM PATIENTS

AGE	NO. OF PATIENTS	MEDIAN SURVIVAL PERIOD
<20 YRS	3(4%)	22mths
20-40 YRS	8(11%)	16mths
40-60YRS	47(68%)	11mths
>60 YRS	12(17%)	9mths

TABLE 4 GROSS SURVIVAL PERIOD OF PATIENTS

SURVIVAL PERIOD	NO. OF PATIENTS	%
<6mnths	19	27%
6-12mnths	16	23%
12-18mnths	16	23%
18-24mnths	5	7%
24-36mnths	11	16%
>36mths	3	4%

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