Original Article

Glioblastoma

Adjuvant Therapy for Old Age Glioblastoma Patients

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ABSTRACT

Objective: Since the advent of Temozolomide (TMZ), optimum management for elderly patients with newly diagnosed Glioblastoma (GBM) is still elusive. The object of this study was to clarify outcomes of present management.

Study Design: Long term prospective study

Place and Duration of Study: This study was carried out on patients who were treated at the Aseer Central Hospital Abha KSA, Frontier Medical College Abbottabad, Women Medical College Abbottabad and those operated privately between August 2001 and August 2013.

Material and Methods: This is a long term study of 41 consecutive cases involving patients aged 55 years or more with newly diagnosed GBM. The patients' median age was 61 years (range 55-87 years). Twenty nine patients underwent resection and rest underwent biopsy. Patients with deep-seated lesions and multifocal lesions (12 patients= 29.26%) were preferably biopsied than gross total resection. Eighteen patients (43.90%) were treated with chemotherapy (mostly TMZ) with radiation therapy (RT) and Six (14.63%) with RT alone. Three patients (7.31%) received only palliative care after surgery.

Results: New neurological deficits developed in 5 patients (12.19%). Postoperative hemorrhage occurred in 8 patients (19.51%), all of whom underwent biopsy. Chemotherapy complications occurred in 19.51% (Advanced hematological complications in 14.63%).

The overall median values for progression-free survival and overall survival were 4.5 and 6 months respectively. Younger age, single lesion resection and adjuvant treatment were associated with better overall survival. Only adjuvant treatment was significantly associated with prolonged progression-free survival. With combined therapy containing resection, RT, and chemotherapy, the median progression-free survival and overall survival were 7.5 and 11 months, respectively.

Conclusions: The prognosis for GBM worsens with increasing age in elderly patients. When high risk factors are present, resection with adjuvant treatment are associated with prolonged survival but are with associated risks. Advanced age alone should not preclude optimal resection followed by adjuvant radio-chemotherapy.

Key Words: Glioblastoma, Old Patients, Adjuvant Therapy, Overall Survival, Progression Free Survival.

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INTRODUCTION

Glioblastoma (GBM) is the second most common primary brain tumor after meningioma, accounting for 17.6% of all CNS tumors, and it is by far the most common malignant primary brain tumor.[1] The prognosis of GBM remains dismal with median survival of approximately 1 year despite advances in surgery, radiation and chemotherapy.[2] Current standard treatment consists of maximal safe resection followed by RT and concomitant and adjuvant chemotherapy with TMZ(3) (47), which results in a median overall survival of approximately 15 months or longer in appropriately selected patients.[4]

Advanced age has been reported as the most significant unfavorable prognostic factor for patients with GBM.[6] GBM peaks in incidence at 5-74 of age and affects more than 10 per 100,000 people older than 65. (23) In the Pakistani setting an age of 55 is considered to be old, relating to socio-economic standards and health awareness level. Older patients with GBM tend to be offered less aggressive treatment, such as biopsy or even palliative care, for fear of their possible intolerance of standard treatment.

However, the best treatment regimen for these patients is yet to be fully determined. Stupp et al[3] proved the efficacy of TMZ in patients with newly diagnosed GBM, but did not target individuals over the age of 70 years. Therefore, GBM therapy in this population is a difficult decision making resulting in the paucity of evidence. In an attempt to shed light on this situation, we analyzed the outcome in our series of elderly patients with newly diagnosed GBM treated at the Asir central Hospital Abha Saudi Arabia and in Pakistani settings.

MATERIALS AND METHODS

Patients aged 55 or older who underwent surgery in the Department of Neurosurgery Assir Central Hospital Abha, Saudi Arabia, Frontier Medical College Abbottabad, Women Medical College Abbottabad and those operated privately between 2001 and 2013 leading to a new diagnosis of GBM were recruited in this study. Patients with progression from previously diagnosed lower grade glioma were excluded. A total of

41 patients were studied. The patients median age was 61 years (range 56-76 years). Twenty nine patients underwent resection and 12 underwent biopsy. Patients with deep-seated lesions and multifocal lesions) were preferably biopsied than gross total resection. Eighteen patients (43.90%) were treated with chemotherapy (mostly TMZ) with radiation therapy (RT), and six (14.63%) with RT alone. Three patients (7.31%) received only palliative care after surgery.

RESULTS

Patients Data is presented in Table 1. Twenty nine patients (70.73%) presented with focal deficits including cognitive dysfunction (37%) and motor deficit (33%). Nineteen patients (46.34%) experienced seizures before surgery. Seven patients (17.07%) presented with headache and vomiting with or without decreased level of consciousness. Intra-tumoral bleeding was noted at time of presentation in 4 patients (9.75%). Associated medical conditions were common, including cancer in 6 patients (14.63%), coronary artery disease in 5 patients (12.19%), and hypertension in 14 patients(34.14%). The median maximum tumor diameter was 38 mm (range 23-76). Lesions were located most frequently in the Temporal lobe (31%). Multifocal lesions defined as multiple separate enhancing lesions with or without connection when visualized on fluid-attenuated inversion recovery sequences of MRI, were frequently seen (29%).

Surgical outcome: For most patients undergoing resection or open biopsy and for all patients undergoing frameless stereotactic biopsy, MRI or CT scan was obtained prior to surgery for stereotactic purposes. The images were transferred into Neuro-navigation system, a facility only available in Saudi Arabia, and were used during craniotomy as well as tumor resection or biopsy. For patients undergoing frame-based stereotactic biopsy, MRI or CT scan was obtained after frame placement under general anesthesia.

Table No.1:Location of the Glioblastoma in Our series

Location	No. of Patients
Frontal	12
Temporal	15
Parietal	8
Occipital	4
basal ganglia & thalamus	2
corpus callosum	2
Cerebellum	8
deep lesion	6
Bilateral Lesion	13
Multifocal Lesion	9
Eloquent Lesion	7
	23

Table No.2: Patients Data

Variable	Total (n=41)	Group	
		Resection (n=29)	Biopsy (n=12)
Age (yrs)			
Mean	64.1±5.3	64.3±5.5	65.8±5.1
Range	55-87	55-87	55-86
Sex			
Male	25	15	10
Female	16	09	07
Preop focal deficit	28	18	10
Preop Sz	33	12	07
Increased ICP Syndrome tumor size (mm)	16	07	09
Mean	44.9±17.0	46.6.1±11.5	41.1±16.4
Range	15-74	18-72	16-71

Table No.3: Patients in Treatment Groups

	Total (n-41)	Treatment Group	
		Resection (n-29)	Biopsy (n -12)
adjuvant treatment			
chemo & RT	21	18	03
RT alone	11	08	03
chemo alone	01	0	01
palliative	08	03	05

Table No.4: Complications during our Study

Type of Complication	Total (n=37)	Treatment Group	
		Resection (n = 25)	Biopsy (n = 12)
any complication	17	11	6
hematological complication	8	7	1
systemic complication†	8	6	2
dermatological complication	3	1	2
psychiatric	1	0	1

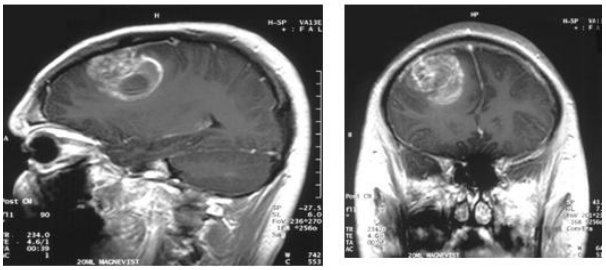

Figure No.1: Right Frontal Glioblastoma with mass effect

Target and trajectory for stereotactic biopsy were determined using the software program. The patients with pacemakers underwent CT scan instead of MRI.

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Twenty nine (70.73%) patients underwent resection and 12 patients (29.27%) underwent biopsy. The resection group included 5 patients who had previously undergoing biopsy for diagnostic purposes prior to resection. There were no statistically significant differences between the biopsy and resection groups regarding age, sex, morbidities, or tumor size. Resection group presented more frequently with increased ICP and had a higher dexamethazone dose than the biopsy group.

Lesions were located more often in the temporal lobe in the resection group and less often in the parietal lobe, the basal ganglia, and the corpus callosum (Deep Lesion) in the biopsy group.

Surgical complications were divided into 3 groups as suggested by the Glioma Outcome Project . The overall complication rate was 24.8%. Neurological complications were seen in 17 patients (41.46%).

The neurological complication rate did not differ significantly between the resection group and the biopsy group. Regional complications affected 13 patients (31.70%) including hemorrhage in 6 patients (14.63%). All hemorrhagic events occurred in the biopsy group. Systemic complications occurred in 7 patients (17.07%), including thrombo-embolic events in 4 patients (9.7%).

The perioperative mortality (death within 30 days of surgery) rate was 9.7% (3 patients undergoing biopsy and one from resection group).

Outcomes for Adjuvant Treatment: Five patients (12.08%) received palliative care only without any active tumor treatment. All remaining received RT with a completion rate of 100%. The median radiation dose delivered was 51.0 Gy (range 10.0-68.0 Gy). More patients in the biopsy group received only palliative care postoperatively than the resection group of patients with hematological complications (myelosuppression), 2 required dose reduction and 3 needed to discontinue chemotherapy. One of those patients receiving TMZ required platelets. Systemic complications occurred in 6 patients Frontal ,Temporal ,corpus callosum Eloquent Lesion and included deep venous thrombosis (3 patients) and pulmonary embolism (1 patient), complications included rash, stomatitis, and depression. Among 64 patients who received RT, 8 patients (19.5%) were not able to complete the prescribed treatment. Five patients experienced clinical deterioration during RT.

Significant differences were noted between patients receiving palliative care and patients receiving adjuvant treatment Patients receiving RT alone were older than those receiving RT and chemotherapy, were more likely to have presented with increased ICP (39% vs 15%), and had a higher mean Dexamethazone dose.

Progression Free Survival (PFs) and overall survival

Median PFS, calculate from date of surgery, was 4.5 months. Factors significantly associated with poor PFS included deep lesion, multifocal lesions biopsy only, new persistent postoperative focal deficit, and palliative care (that is lack of adjuvant treatment) The median PFS for patients undergoing adjuvant treatment was 5.5 months, whereas that for patients who had palliative care only was 0.5 months. Patients receiving chemotherapy along with RT had achieved significantly longer PFS compared with those with RT alone.

The median Overall Survival differed strikingly among the age groups: 1. Months for patients younger than 70 years, but merely 4.5 months for patients aged over 70 years. Favorable survival effects of resection and adjuvant treatment in this study mainly result from relatively younger patients (< 65 years) among our elderly patient adjuvant treatment lived substantially longer if they had undergone resection compared with biopsy (median OS 11.5 months vs 6.5 months). With maximal safe resection followed by the combination of RT and chemotherapy, which is the standard treatment for unselected GBM patients, the median PFS and OS among our elderly patients with GBM were 8 months and 12.5 months, respectively. When limited to patients who were 70 years of age or older, they were 6 months and 10.0 months, respectively.

DISCUSSION

Gross total (safe) surgical resection followed by adjuvant treatment including RT and chemotherapy with TMZ has become the standard of care for patients with newly diagnosed GBM since the landmark study from Stupp and colleagues[3,21].

But patients older than 70 years were excluded from this study which is relatively common.[8,17] In clinical practice, physicians and surgeons are frequently reluctant to offer aggressive treatment to elderly patients because of concerns that it may not be tolerated due to advanced age, co-morbidities and an underlying propensity to complications. Therefore, although the age-adjusted incidence of GBM is greatest among patients older than 65 years, the best treatment strategy for these patients is not as well defined as in younger patients, the very reason this study was carried out.

Impact of Resection versus Biopsy on Survival in Elderly Patients have been performed evaluating the impact of the prospective studies9,25 have been more definitive, demonstrating an association Sanai et al,[10,14] and between resection and survival specially in younger patient impact of extent of resection (determined with or without computer-assisted volumetric assessment) on survival and concluded that the majority supported extent of resection as a prognostic factor for prolonged survival. Some authors ha reported increased extent of GBM resection and prolonged PFS in patients undergoing fluorescence-guided surgery using 5-aminolevulnic acid (5-ALA) in a prospective, randomized controlled trial"[12,20] Older patients are often believed to take longer to recover from an aggressive

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surgery and carry a higher risk of peri-operative complications. Thus, biopsy is often resection for these patients.[13,1] A retrospective study from the independent predictor of survival and was associated with favorable OS among patients along with age and performance status.[14,13] However, this benefit was only evident for patients who went on to receive adjuvant treatment (median survival for resection vs biopsy: 11.5 vs 6.5 months).

Surgical Complications in Elderly Patients: High complication rates in elderly patients like new neurological deficits are associated with decreased survival, not just decreased quality of life."[15,16] Our overall complication rate of 24.8% for elderly patients compares favorably to other authors and true for patients undergoing resection in our series. The overall complication rate in these patients was 18.9%. By comparison, patients with newly diagnosed malignant glioma undergoing first craniotomy in the Glioma Outcome project had an overall complication rate of 24.2% including 8.1% permanent neurological worsening, 10% regional complications, 9.2% systemic complications, and 1.5% mortality.

Similarly, Sawaya et al reported their experience at MD Anderson Cancer Center with 400 craniotomies for intra-axial tumors (206 gliomas, 194 metastases). The overall complication rate was 32% (including 8.5% permanent neurological worsening, 7% regional complications, 7.8% systemic complications and 1.7% mortality) those undergoing resection (30.8% vs. 18.9%) although the difference did not reach statistical significance. complication rates for stereotactic biopsy in our series of elderly patients with GBM are higher than those reported in large unselected mortality rates range from 0.6% to 2.8%.[3,9,16,25]

Impact of Adjuvant Treatment on Survival in Elderly Patients: Radiation therapy has an established role in GBM therapy. RT has a significant survival benefit and appears to hold true for elderly patients.[13,14,15,17] Superiority of an abbreviated RT course (40 Gy in 15 fractions over 3 weeks) in elderly patients has been successfully proved by a prospective randomized clinical trial by Roa and colleagues.[18]

Like RT, chemotherapy has an established role in GBM treatment. For many years nitrosoureas such as BCNU or lomustine (CCNU) were the mainstay of chemotherapy for GBM patients and 2 meta-analyses consistently confirmed their efficacy for longer survival.[19,10] However, the benefits of nitrosoureas for old patients was questioned (similar to RT) especially given the higher incidence chemotherapy-related neurotoxcity and myelosuppression in this population. The changed the standard of care for patients with newly paper by Stupp et al changed the standard of care for the patients with newly diagnosed GBM by demonstrating increased survival for patients receiving RT with concurrent TMZ followed by adjuvant TMZ compared with RT alone (median survival 14.6 months vs 12.1 months), excluding 70 plus patients. Some recent papers have reported favorable survival for elderly patients with GBM receiving RT and TMZ, such as 10.6 months with the Stupp regimen for 2 patients aged 70 or older or 11 months with adjuvant RT and reduced dose of TMZ.[9,21]

Adjuvant Treatment Toxicity in Elderly Patients: Adjuvant treatment including RT and TMZ was feasible for elderly patients and was allocated with a modest complication rate.[4,5,6,9,11,12,24,25]

Most of the major complications did not seem to be directly associated with RT except for an infarct of the ipsilateral corona radiata 2 years after RT for a temporal tumor. In addition to resection and adjuvant treatment, other factors reported to favorably influence survival in unselected GBM patients include young age, good performance status, good mental status, seizure presentation, frontal lesion, superficial 3.1780.11) Younger single lesion, and the absence of postoperative complications age has consistently been one of the strongest favorable prognostic factors across many studies. It is interesting that our data suggest that this holds true even among the elderly population (age-65 years). Several hypotheses have been proposed to explain the poor clinical outcome of GBM in older patients, including the presence of comorbidities, resistance to cancer therapy, genetic aberrations, different histology, neurodegeneration and age discrimination.[2,4,19, 22,23,26]

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CONCLUSION

This study demonstrates that aggressive treatment with resection and adjuvant treatment is associated with significantly longer survival for patients 65 years of age or older with newly diagnosed GBM. This finding must be interpreted with caution given that this study not randomized and patient biopsy and/or palliative care were significantly different (had tumors in deeper, more eloquent locations poorer performance status, increased dexamethasone dose) from those receiving resection and or adjuvant treatment. Nevertheless, resection and adjuvant treatment remained significant prognostic factors in a multivariate analysis and were generally well tolerated in this group of elderly patients. Although advanced age is an independent unfavorable factor, this alone should not disqualify patients from being treated with optimal tumor resection followed by.

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