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Glioblastoma Survival Outcomes at a Tertiary Hospital in Appalachia: Factors Impacting the Survival of Patients Following Implementation of the Stupp Protocol

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Glioblastoma survival outcomes at a tertiary hospital in Appalachia: factors impacting the survival of our patients since implementing the Stupp protocol

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Abstract

Glioblastoma is a fatal brain cancer with low median and yearly survival rates. The standard of care for treating glioblastoma is gross total resection (GTR) coupled with the Stupp protocol, but various factors influence the interventions undertaken and survival achieved. As health disparities exist in rural areas, survival in these areas need to be assessed in order to understand which factors detract from the successes of these standard medical interventions. We retrospectively determined the impact of age of diagnosis, number of lesions, the molecular marker O6-methylguanine methyltransferase (MGMT), extent of surgery, and completion of the Stupp protocol on survival among patients treated at West Virginia University Hospitals. We found that an age of diagnosis under 60 years, having the MGMT gene methylated, having a unifocal tumor, receiving GTR, adhering to the Stupp protocol, and undergoing a treatment course of GTR followed by the Stupp protocol significantly increased survival. Lastly, we compared our findings to a pre-Stupp study done in West Virginia in 1996. This comparison showed that although overall median survival has not increased, all interventions involving GTR have resulted in a significantly higher survival. We conclude that we can serve our patient population by offering GTR to all adult glioblastoma patients when no contraindications exist and ensuring that patients follow the Stupp protocol. After discharge, the Stupp protocol may not be followed/completed for a variety of reasons. In the future, we aim to assess these reasons and analyze other significant interventional and socioeconomic factors which influence survival.

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Keywords

Glioblastoma; Stupp protocol; Appalachia; gross total resection (GTR); West Virginia; median survival; rural areas

Introduction

Glioblastoma, an aggressive glial tumor, is the most prevalent brain tumor in adults and usually occurs in middle-aged patients. On imaging, these tumors appear as contrast enhancing masses, sometimes with a butterfly pattern that can often extend across the corpus callosum. Microscopically, the tumors have central areas of necrosis and hemorrhage surrounded by pseudopalisading cells. Median survival for adults with glioblastoma who undergo appropriate therapy has been reported to be 14.6 months while 2-year survival is 26.5%[27]; patients surviving beyond 36 months are known as long-term survivors. Prognostic indicators of increased survival time are young age, having a single tumor, O^6-methylguanine methyltransferase (MGMT) methylation, gross total resection (GTR) of the presenting lesion, and post-operative completion of the Stupp protocol.

The Stupp protocol calls for the use of 60Gy radiotherapy concurrently with temozolomide (TMZ) over 6 weeks after tumor resection, followed by six 28-day cycles of TMZ alone. The success of this protocol is linked to MGMT methylation as MGMT expression causes tumor resistance to alkylating chemotherapeutic agents such as TMZ and nitrosureas. When this gene is silenced (methylated), the tumor's DNA repair is impaired and chemotherapy becomes more effective, especially when combined with radiation[9]. This observation that the prognostic value of MGMT methylation is dependent on treatment modality builds upon the Stupp findings[27]. MGMT methylation has also been linked to long-term survival[26].

West Virginia, a mostly rural state[5] in the Appalachian region which is medically underserved and economically disadvantaged[3], is known to have many negative health outcome metrics. These include a high overall cancer prevalence relative to the U.S' median[12], as well as a high cancer mortality of 223.9/100000 people and high rates of obesity (35.6%) and diabetes (14.5%)[2]. These statistics earned West Virginia ranks of 48, 47, and 49, relative to other states[2]. Furthermore, West Virginia also rates below the median of the U.S. regarding the social determinants of health such as education and income[2], which have been identified as primary influences driving disparities in cancer morbidity and mortality[11]. These statistics indicate that there are underlying sociodemographic issues that detract from the benefit patients may otherwise experience from a medical intervention.

The Appalachian region's health disparities have impacted the cancer morbidity and mortality for this population. Although cancer rates have declined in the U.S.[25], this decline has been lower in Appalachia[31], with the incidence of cancer being higher in Appalachia than the U.S. in general[29]. It has been shown that although mortality rates have decreased by 22% in the U.S in general from 1990–2001, rural Appalachia has only experienced a decline of 12%[30]. Across the entire U.S, the incidence of cancer was shown to increase only in rural Appalachia between 2007 and 2011[30].

A pre-Stupp study by Jubilirer in 1996 at Charleston Area Medical Center (CAMC) in West Virginia found that a younger age at diagnosis (<40) and radiotherapy (albeit of varying doses) were the best predictors of survival in 138 patients[16], a result which has been verified by other studies[8,18]. However, due to both tumor (e.g. location) and patient characteristics such as comorbidities, this approach is not always practical. The impact on survival of implementing the Stupp protocol in an Appalachian hospital is unknown but could be important in standardizing and optimizing treatment practices and delivery of care in West Virginia and Appalachia in general, especially in light of the state's poor health metrics. We analyzed data from 243 glioblastoma patients from 2009-present to determine patient demographics and survival, tumor characteristics, and courses of treatment. We then used multivariate analyses to determine which combination of these factors yielded the greatest survival in our patients. As our institution serves a mostly rural population with its own health disparities, we hypothesized that our population would show an overall median survival less than that shown by Stupp et al[27] but that the reported indicators of increased survival will also serve as good prognostic indicators in out patient population. This research serves as a springboard for finding deficiencies in glioblastoma care and identifying ways to ameliorate those deficiencies in economically disadvantaged rural communities.

Methods

Study Approval

This retrospective cohort study was approved by the WVU Office of Research Integrity and Compliance.

Study Design

The information for this study was gleaned from West Virginia University Hospital's (WVUH) electronic medical record as well as other hospitals' records when needed. Our data came from 243 living and deceased patients and consisted of 96 females (39.5%) and 147 males (60.5%) ranging between the ages of 20–88 at diagnosis. Only newly diagnosed cases with a definitive pathologic diagnosis of glioblastoma were included. These diagnoses were made by a neuro-pathologist who was at our institution for the entire period we reviewed in this study. Most resections done at our institution (89%) were done by four surgeons, whose techniques were tailored largely to the tumor's location. Although all surgeries used pre-operative imaging, post-operative imaging was not done in all cases. One surgeon frequently used fluorescein staining during his procedures.

Procedure

Demographical information collected included name; date of birth; age at diagnosis; and survival from diagnosis until death, or present if they were still alive. Patient identifying information was used only for the purpose of collating information. Overall survival was calculated from the diagnosis of glioblastoma, even if lower grade tumors were present before this diagnosis. The prognostic factors we looked at individually as independent variables were:

- age (below 60 years, 60 years and above)

- MGMT gene methylation status (positive, negative)
- number of tumors at presentation (unifocal, multifocal)
- surgical intervention (GTR, subtotal resection (STR), or biopsy)
- completion of the Stupp protocol (full, incomplete, none)

The determination of GTR versus STR was made using Brainlab software to calculate tumor volumes before and after surgery. Using this software, our criteria for GTR was a resection of 98% or greater while STR was defined as being below 98% of the tumor volume, based on one of the earlier papers that evaluated a threshold for a beneficial extent of resection and found that removing ≥98% of the tumor had the greatest effect on increasing survival[17]. We calculated survival due to the surgical intervention from the date of the initial resection/biopsy. In cases where a biopsy preceded a resection by less than two months, we counted the resection as the intervention as patients may have received a biopsy to assess the need for – and extent of – resection. In all analyses that involve a surgical intervention, the denominator we used was the total number of patients that received any surgical intervention.

Due to clinical patient considerations, we considered a complete dose of radiation as being 54-63Gy. 13 patients died before chemoradiation was discussed or begun and were excluded from our study. As radiation could start at various time points after a resection/biopsy and last for various periods, the survival data for assessing the effect of completion of the Stupp protocol were corrected to start from the mid-point of the course of concurrent chemoradiation.

In order to reflect the impact of the standard clinical management of glioblastoma, we then sought to discover the survival impact of undergoing the standard course of treatment. For this, we considered the surgical intervention they underwent and their completion of the Stupp protocol. In doing so, we derived the following groups:

- GTR with completion of the Stupp protocol
- STR with completion of the Stupp protocol
- Biopsy

Lastly, in order to assess how the impact of implementing the Stupp protocol in West Virginia, we compared our results to those of Jubilirer (1996), taking care to compare the groups in his study to equivalent groups in ours that reflect the standard of care.

Statistical analysis

With survival as an endpoint, we calculated median survival, with standard error (SE) and 95% confidence intervals (CI) using the formulas below, for the above prognostic factors. The standard error formula was adjusted for the use of median values by multiplying by 1.253. A Moods test in XLSTAT (Addinsoft) with multiple pairwise comparisons set to give exact p-values was used to evaluate for significance among the medians of the groups into which the prognostic factors were divided. Pairwise testing was used as the groups under each prognostic factor (or combination of) carry their own clinical weight. α was set at 0.05

for all these conditions. Kaplan-Meier curves were also made in XLSTAT for the groups of each prognostic factor. These curves were used to compare the number of patients alive after 1 year. We used a log rank test to evaluate for significance among the curves.

In comparing our date to that of Jubelirer's, we calculated the percentage of people who had undergone a specific intervention by setting the denominator to be the number of patients that had received any surgical intervention (including a biopsy). Lastly, we calculated the 95% CI for the groups in our data that were equivalent to his.

$$\text{CI lower limit}$$
$$\frac{n}{2} - \frac{1.96\sqrt{n}}{2}\text{ th ranked value}$$
$$\text{CI upper limit}$$
$$1 + \frac{n}{2} + \frac{1.96\sqrt{n}}{2}\text{th ranked value}$$

Results

Age and survival

The majority of our patients were above 60 years old when initially diagnosed (Table 1) with the median age at diagnosis in our patient population being 63.5 years (Table 2). Our patient population had a median survival of 7 months (SE ± 1.3) with 18 people who had survived longer than 36 months (long-term survivors), most of whom were under 60 years at the time of diagnosis (see tables). The group of patients who were below 60 years at diagnosis had a higher median survival of 14 months (SE ± 2.5; 95% CI: 11–18); the group of patients above 60 years at the time of diagnosis had a median survival of 4 months (SE ± 1.2; 95% CI: 3–5) (Figure 1). A Moods test showed that these results were significantly different ($p<0.0001$).

The 1-year survival in the group of patients who were below 60 at the time of diagnosis was 55% while that in the group of patients above 60 at the time of diagnosis was 21% (Figure 2). A log-rank test showed that the survival distribution of these groups over time were significantly different ($p<0.0001$).

Tumor characteristics and survival

The molecular marker tested most frequently was MGMT, albeit tested in less than 50% of initial cases – the gene was found to be methylated (MGMT+) in 37% of patients tested. We found that the MGMT+ group had a median survival of 14 months (SE ± 3.0; 95% CI: 8–22) while that of the MGMT- group was 7 months (SE ± 2.4; 95% CI: 4–11) (Figure 1). A Moods test showed that these values were significantly different ($p=0.021$). The MGMT+ group had a 1-year survival of 49% while the MGMT- group had a 1-year survival of 29% (Figure 2). A log-rank test showed that the survival distribution of these groups over time were not significantly different ($p=0.069$).

Most of our patients had unifocal tumors at presentation, mostly in the frontal lobe. Most multifocal tumors also involved the frontal lobe. The groups with unifocal tumors at

presentation had a median survival of 8.5 months (SE ± 1.5; 95% CI: 6–10) while this was 4 months (SE ± 2.4; 95% CI: 2–9) in the group with multifocal tumors (Figure 1). A Mood's test showed that these values were significantly different (p=0.010). The group with a unifocal tumor at presentation had a 1-year survival of 36% while the group with multifocal tumors showed a 1-year survival of 24% (Figure 2). A log-rank test showed that the survival distribution of these groups over time were significantly different (p=0.023).

Individual interventions and survival

Most of our patients received a resection at WVUH as part of their treatment, with 41 patients having both a biopsy and a resection – in such cases, the biopsy was used to determine a diagnosis and/or assess the need for resection. Of all patients that had a resection, 50 were scheduled for a re-resection either due to incomplete resection or recurrence (Table 1). Here, we only include results for those patients whose pre- and post-operative scans we had, from which we were able to assess an accurate extent of resection.

The group that received GTR had the longest median survival of 15 months (SE ± 6.6; 95% CI: 12–24). The group that received STR had a median survival of 10 months (SE ± 7.8; 95% CI: 3–15) while the group that received a biopsy had a median survival of 3 months (SE ± 0.8; 95% CI: 2–4) (Figure 1). A Moods test showed a significant difference in survival between only the groups that received GTR and biopsy (p<0.0001). The group that received GTR had the highest 1-year survival of 64%. The 1-year survival with the group that received STR was 41%, while that for the group with a biopsy was 10% (Figure 2). A log-rank test showed that the survival distribution of these groups over time were significantly different (p<0.0001).

Among the patients for whom we had definitive information, most of those who underwent radiation completed treatment as per the Stupp protocol. The group that completed the Stupp protocol had a median survival of 16 months (SE ± 3.3; 95% CI: 13–20), the group that did not undergo this treatment had a median survival of 3 months (SE ± 2.4; 95% CI: 1–5), while the group that did not complete this treatment had a median survival of 2 months (SE ± 0.6; 95% CI: 1–3) (Figure 1). A Moods test showed that the result for the group that completed the Stupp protocol differed significantly from both the group that did not undergo (p=0.0004) or not complete this treatment (p<0.0001). The group that completed the Stupp protocol had a 1-year survival of 66%. The group that did not undergo this treatment had a 1-year survival of 12%, while the group that did not complete this treatment had a 1-year survival of 0% (Figure 2). A log-rank test showed that the survival distribution of these groups over time were significantly different (p<0.0001).

Treatment course and survival

The group that had received GTR with completion of the Stupp protocol showed the greatest median survival of 23.5 months (SE ± 7.1; 95% CI: 13–34) and 1-year survival of 87%. The group that received STR with completion of the Stupp protocol had a median survival of 14 months (SE and 95% CI could not be calculated) with a 1-year survival of 63% (see figures). A Moods test showed a significant difference in median survival between those that received GTR and completed the Stupp protocol and those that received a biopsy (p<0.0001). A log-

rank test showed that the survival distribution of these groups over time were significantly different ($p<0.0001$).

Comparison to previous West Virginia study

We compared the treatment groups in the Jubilirer 1996 study to equivalent groups in ours. Overall median survival, survival with STR, and survival with STR and radiation therapy (RT; for which the equivalent in our study is completion of the Stupp protocol) were similar between our studies. The percentage of patients receiving GTR alone, GTR and RT, STR alone, and STR and RT were all decreased in our study. Lastly, the survival with GTR, survival with GTR and RT, percentage receiving biopsy, percentage receiving RT, and 1st and 2nd year survival were all increased in our study (Table 2). For the purposes of this table, biopsies were only considered when comparing surgical interventions and were not part of the comparison for the treatment courses. Survival with the treatment courses and percentage receiving RT are given as a percentage of all patients that received resection.

Discussion

As age, MGMT gene methylation, tumor burden, extent of resection, and the Stupp protocol have all been linked to survival in other studies, we performed this study to determine the impact these prognostic factors have on our patient population as a way of assessing the outcome of glioblastoma care provided by our institution within the context of being in a state with poor health metrics and outcomes. Our principal finding was that glioblastoma survival is influenced by patient, tumor, and treatment factors.

We found that an increased age at the time of diagnosis corresponded with decreased survival (see figures). The low overall median survival of our patient population may be explained by the fact that the majority of them were above 60 years at the time of diagnosis (Table 1). Our finding of a low median and 1-year survival in the elderly group corroborates other studies which also find a low median survival of 4–6 months in this population, sometimes even with standard treatment[14,21]. In such cases, attention shifts towards maintaining a good quality of life. It is, however, noted that these patients still face many morbidities[13].

As it determines the patient's responsiveness to treatment with TMZ, we surveyed the survival of patients with MGMT methylation. Our findings that MGMT methylation increased survival (see figures) are in line with other studies that have found MGMT methylation to be a strong prognostic factor[10,15] although this is not universal[20]. Other markers such as epidermal growth factor receptor[6], alkylpurine-DNA-N-glycosylase [1], isocitrate dehydrogenase 1[24], alpha thalassemia/mental retardation syndrome X-linked [7], and p53[23] may be tested and have independent and dependent prognostic implications, but none of these helps determine a treatment modality.

Since multifocality may influence the risk of undergoing GTR, we looked at the survival of patients with using this variable. Most (81%) of patients presented with unifocal tumors. When patients presented with multifocal tumors, the approach used was to target the resection to the larger tumors evident on imaging and attempt to remove easily accessible

nodules within their vicinity. We found an increased median survival in patients with unifocal tumors on presentation (see figures), which may be due to anatomic difficulties in achieving GTR or due to a different biological behavior of these tumors.

Resection clearly improved survival over biopsy (see figures). When performed as the sole intervention, a biopsy was done when the patient was elderly and likely to face further morbidity as a result of the surgery or when the tumor was in a deep location that made resection dangerous. For our analyses, we considered any resection ≥ 98% to be GTR. GTR significantly increases survival over STR as there is a decreased chance of recurrence; indeed, most of our recurrences were in patients who had initial subtotal resections. Unfortunately, GTR is not possible when the chance of injury to eloquent areas is high. Our findings support many studies that have found GTR to be a strong prognostic factor[18,22]. These studies also suggest that resection of the surrounding FLAIR (fluid attenuated infusion recovery) signal may also be beneficial.

Completion of the recommended Stupp protocol improved survival (see figures). It is important to note the Stupp protocol calls for the use of concurrent TMZ with 54-63Gy radiation AND six cycles of post-radiation TMZ; the group that did not complete their therapy consisted of those who did not adhere to both requirements. Radiation doses prescribed by the neuro-onclogist depended on age and need for aggressive treatment. Reasons for not completing the Stupp protocol or forgoing it altogether include a decision to go into palliative care, lack of insurance, worsening morbidity, and an assessment by the neuro-oncologist that radiation would provide no benefit. Again, here, treatment is focused on enhancing quality of life.

In agreement with the literature, the highest survival in our patient population was seen in the group that received GTR and adhered to the Stupp protocol (see figures). Predictably, the group that underwent STR and adhered to the Stupp protocol had a lower survival. Both figures suggest that GTR and the Stupp protocol greatly augment each other.

Our comparison with Julbilirer's study[16] shows that the standard management for glioblastoma – GTR with completion of the Stupp protocol – has indeed improved median survival in West Virginia (Table 2). This comparison further highlights that *overall* median survival has indeed not increased, even with the implementation of the Stupp protocol, use of new modalities, research, and advents in technology. As the interventions involving GTR resulted in increased survival in our patients, the lack of an increased overall survival may be due to the large number of biopsies we perform as the sole intervention. A possible reason for the prevalence of biopsies among our patients may be a reasonable reluctance to subject the elderly and those that present with low Karnofsky Performance Scale (KPS) scores to resection, a trend that is also present at other institutions[21]. However, a study by Marina et al found that conventional therapy[19] – or at least STR[28] – does improve survival and functional outcomes in elderly patients.

We discovered that the three factors that yielded a median survival at or above the reported value of 14.6 months were receiving GTR (regardless of post-surgical interventions), adhering to the Stupp protocol (regardless of surgical intervention) and undergoing a

treatment course of GTR followed by the Stupp protocol. Our results highlight the fact that multiple conditions/interventions differently influence the survival of a patient with glioblastoma and that survival has to be considered by the neurosurgeon using such a multifactorial stance. Currently, with a median survival of 7 months, we acknowledge that there are deficiencies in care (patient and disease factors notwithstanding) even with standard interventions being available, which may well stem from outside the hospital setting. We may increase the survival in our patient population by having discussions through which patients understand the disease process and treatments available and in which we advocate (when safe) for the best treatment course – GTR followed by full concurrent chemoradiation and post-radiation TMZ. We will also work with patients and other members of the healthcare team to ensure both that patients have access to – and follow up with – appropriate and timely aspects of standard care.

Unique challenges that patients in West Virginia and the rest of rural Appalachia face in attaining optimal care for glioblastoma may include low health literacy[4], sparse distribution of tertiary care centers, resigned attitudes to terminal illness, and lack of social and family support. In a future study, we will identify sociodemographic factors (cultural views, income, education, insurance et al) which negatively affect survival with glioblastoma among patients in West Virginia. Some limitations of this study stem from its retrospective nature that covers patients over a period of 7 years. Firstly, we have added many treatment tools since the earliest diagnosis were recorded, which was in 2009. We also have also not accounted for advances in training and management protocols and changes in personnel that have occurred since then. Secondly, our molecular marker analysis is limited to MGMT as other markers were not routinely tested for in the earlier part of this study; until the WHO 2016 classification made isocitrate dehydrogenase testing routine, we only ordered this test when necessary for diagnosis. We now order IDH and MGMT testing routinely, as well as newer clinically relevant markers when appropriate, but the number of these newer markers is too low for to allow analysis.

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Abbreviations used

MGMT	O^6-methylguanine methyltransferase
GTR	gross total resection
TMZ	temozolomide
CAMC	Charleston Area Medical Center
WVUH	West Virginia University Hospital
STR	subtotal resection
SE	standard error of the median

CI	confidence interval
FLAIR	fluid attenuated inversion recovery

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Highlights

1. An age of diagnosis under 60 years, having the MGMT gene methylated, having a unifocal tumor, receiving gross total resection (GTR), adhering to the Stupp protocol, and undergoing a treatment course of GTR followed by the Stupp protocol significantly increased survival among patients in West Virginia
2. Despite much advances in glioblastoma management, median survival of patients in West Virginia has not increased since 1996. However, all interventions involving GTR have significantly enhanced survival since then. The fact that median survival has not increased warrants further investigation.

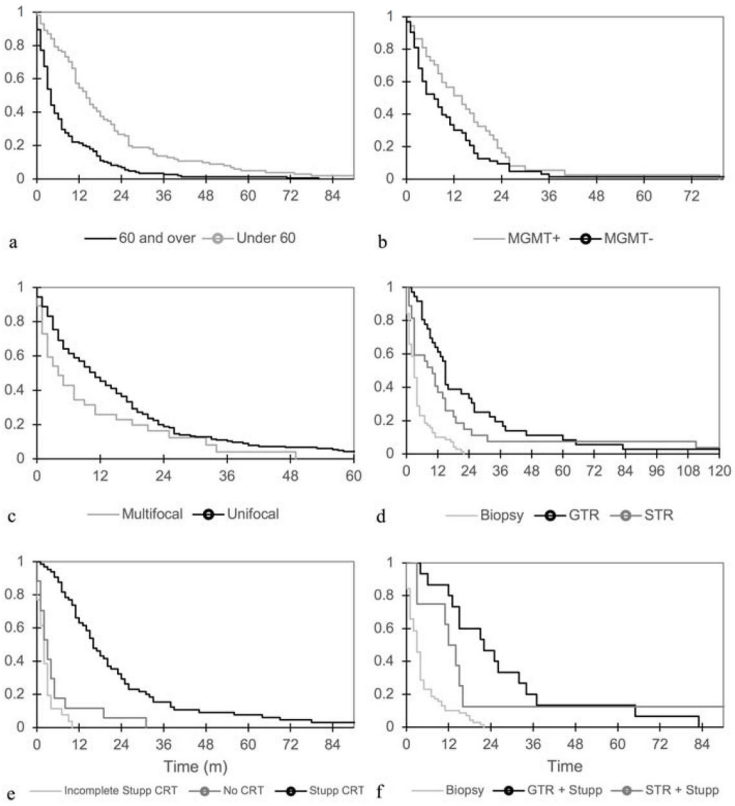

Figure 1.

Bar graphs showing median survival in months, with SE, according to prognostic indicators of survival: a) age at diagnosis; b) MGMT methylation status; c) number of lesions; d) surgical intervention; e) completion of the Stupp protocol; f) treatment course

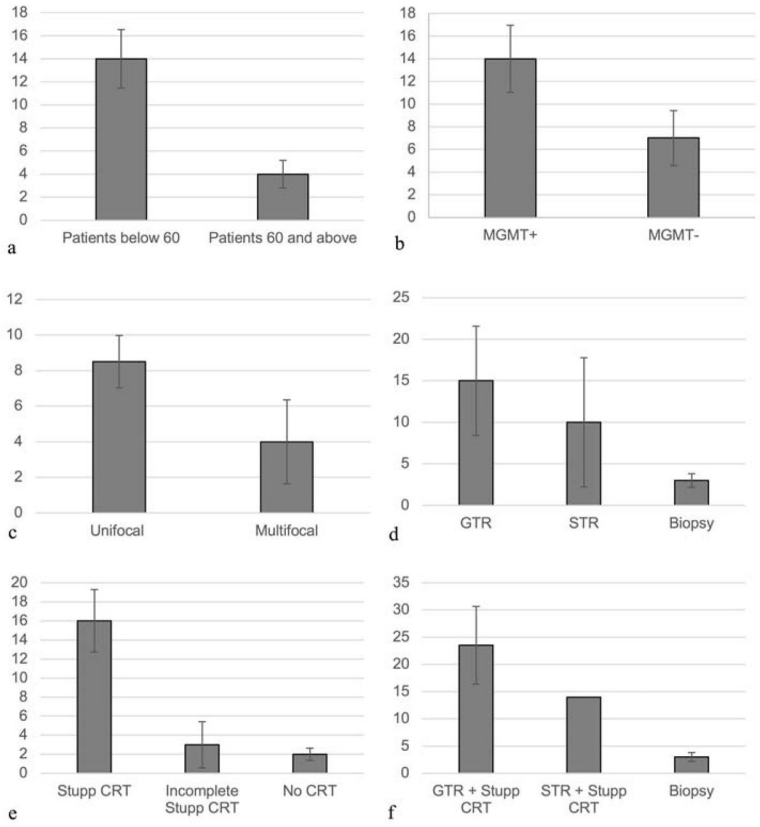

Figure 2.

Kaplan Meier curves of cumulative probability of survival over time according to: a) age at diagnosis; b) MGMT methylation status; c) number of lesions; d) surgical intervention; e) completion of the Stupp protocol; f) treatment course

Table 1

Demographic, treatment, and survival information of patients treated for glioblastoma. CRT = chemoradiation, GTR = gross total resection, STR = subtotal resection

	Number of patients	Percentage of patients	Number of long- term survivors
Gender			
Male	147	60.5	
Female	96	39.5	
Age at diagnosis			
20–59	98	40.3	14
≥60	145	59.7	4
Surgical technique used[a]			
Biopsy alone	70	52.6	0
STR	27	20.3	2
GTR	36	27.1	7
Re-resection	50/125	40.0	
Completion of the Stupp protocol[b]			
Full	67	60.4	10
Incomplete	26	23.4	0
None	18	16.2	0
Survival (m)			
<1	17	7.0	
1–12	143	58.8	
13–24	46	18.9	
25–36	19	7.8	
37–48	6	2.5	
>48	12	4.9	

[a] some patients did not have post-operative imaging and thus could not be definitely classified as having received STR or GTR

[b] adherence to the Stupp protocol could not be determined for some patients treated at other institutions

Table 2

Summary of interventions and outcomes between our current study and Jubilirer's 1996 study at CAMC. "RT" should be taken to mean "Stupp protocol" in the context of WVUH. CAMC: Charleston Area Medical Center, CI: Confidence interval, GTR: Gross total resection, RT: radiation therapy, STR: Subtotal resection, WVUH: West Virginia University Hospitals

	WVUH	CAMC
Number of patients	243	138
Median age at diagnosis (range)	63 (20–88)	59 (21–87)
Percentage of females	39.5	42
Overall median survival (95% CI)	7 (6–10)	7
Percentage receiving GTR	27.1	29
Survival with GTR (95% CI)	15 (10–25)	4 (2–6)
Percentage receiving GTR and RT	11.2	23.9
Survival with GTR and RT (95% CI)	23.5 (12–37)	12 (10–13)
Percentage receiving STR	20.3	26.1
Survival with STR (95% CI)	10 (3–15)	3 (1–7)
Percentage receiving STR and RT	6.0	18.8
Survival with STR and RT (95% CI)	14 (3–16)	10 (7–14)
Percentage receiving biopsy	52.6	2.2
Percentage receiving RT	73	42.7
1-year survival (%)	36.6	29
2-year survival (%)	15.4	3