ABSTRACT

Retrospective Analysis on Differential Effects of Treatment Strategy on Outcome and Survival on Malignant Glioblastoma Multiforme Patients

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Malignant glioblastoma multiforme, or glioma, is one of the most frequent central nervous system tumors in adults, with a dismal prognosis despite aggressive treatment. With median survival less than a year, a multimodal treatment approach has been the standard care for glioma since 2006; this treatment includes a combination of surgical excision, radiotherapy, and temozolomide chemotherapy in order to combat the symptoms and increase median survival time of patients, given race and ethnicity. With this, the purpose of the study was to retrospectively compare data of glioma patients collected at a single institution over a thirty-five year period and compare the differential effects of treatment strategy, race, and tumor grade on outcome and survival. Within the 612 patients included in the final analysis who died during the review period, median overall survival was 8.8 months. Median follow-up time for the 92 survivors included in the analysis was 54 months. The effect of current treatment strategies as per 2006 appeared to have no effect on the longevity of the patients. Interestingly, race and did appeared to have a significant effect in the longevity of glioma patients, specifically in self-identified Hispanic patients and contributed to a higher hazard ratio of death among glioma patients, respectively. Though results slightly varied across univariate and multivariate analyses, the study suggests further exploration of combinatorial treatment methods, further scrutinizing race, ethnicity, and other confounding variables.

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RETROSPECTIVE ANALYSIS ON DIFFERENTIAL EFFECTS OF TREATMENT STRATEGY ON OUTCOME AND SURVIVAL ON MALIGNANT GLIOBLASTOMA MULTIFORME PATIENTS

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TABLE OF CONTENTS

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CHAPTER ONE

Introduction

The term glioblastoma multiforme was historically introduced in 1926 by Percival Bailey and Harvey Cushing, originating from the idea that the tumor is a conglomeration of primitive precursors of glial cells (Ohgaki H et al. 1999), and the highly variable appearance is due to the presence of necrosis, hemorrhage, and cysts (Preusser M et al. 2011).

Physiologically speaking, glioblastoma multiforme (GBM), or Grade IV Astrocytoma (Daumas-Duport C et al. 1988), is the most common and most aggressive malignant primary brain tumor in humans (Bullard DE et al. 1985). Through the etiology of GBM is actually unknown, potential causes include genetic factors, cell phone use, head injury (Weintraub MI 1994), N-nitrous compounds (Scott JN et al. 1998), occupational hazards, electromagnetic field exposure, and race, often more common in whites (Chamberlain MC et al. 1998). This disease, though malignant, is also rare (Russell DS et al. 1998), with 2–3 cases per 100,000 years of life as calculated in Europe and North America (Barnard RO et al.1987). On the other hand, 20% of tumors characterized as glioblastoma (Simpson JR et al. 1999) are more prevalent in men and the elderly than their opposite counterparts (Fisher JL et al. 2007).

Glioblastoma tumors are characterized by fast growth and spread, often equivalent to astrocytoma related cancers (Zulch KJ 1986). These cancers develop from glial cells that then specialize to form astrocytes (Fulci G et al. 2007). Once developed,

such tumors facilitate their own spread, growth, and invasion into normal brain tissue with own blood supply (Liang BC et al. 1991).

GBM usually begins as primary or secondary glioblastoma, an aggressive grade IV tumor (Daumas-Duport C et al. 1988) or a grade II/III tumor that develops into a grade IV for younger patients (Bullard DE et al. 1985). Tumor onset can be diagnosed by an MRI or CT scan, inclusive of, but not limited to, symptoms such as headaches, seizures, vomiting, personality changes, and abnormal vision and speech (Lantos PL et al. 1998).

Thus, begins the treatment process for this disease. The goal of glioblastoma treatment is to retard tumor growth and improve quality of life (Lang FF et al. 1994). Surgery is the first treatment (Ammirati M et al. 1987). This is used to remove as much of the tumor as possible (Rich JN et al. 2004), though high-risk areas prevent removal all of a tumor (Westphal M et al. 2006). Following surgery, radiation is used to kill as many leftover tumor cells as possible (Ciric I et al. 1990) and also slow the growth of tumors (Sanai N et al. 2008). Another viable treatment option is chemotherapy (Bota DA et al. 2007). Temozolomide is the most common chemotherapy drug used for glioblastoma (Farrell CJ et al. 2007) and though it can cause short-term side effects and combined chemotherapeutic treatment are less toxic (Levin VA et al. 1990). A glioblastoma that returns can also be treated with carmustine (or BCNU) in which small wafers of the chemotherapeutic drug are placed in the brain (Ferguson S et al. 2007). All of this put together, combined treatment is actually very common for most people diagnosed with glioblastoma (Lopez KA et al. 2006).

Despite such modest treatment in the past 25 years (Newcomb EW et al. 1998), research on therapies continues to remain palliative and actually has shown to prolong quality survival (Chaichana KL et al. 2014). For example, given that mean survival is inversely correlated with age (Burger PC et al. 1994). Patients with glioblastoma multiformes uniformly die within 3 months without therapy and on the flipside, patients treated with optimal therapy (Burger PC et al. 1994), including surgical resection, radiation therapy, and chemotherapy, have a median survival of approximately 12 months (Chaichana KL et al. 2014). Rarely do patients survive up to 2 years and fewer than 10% of patients survive up to 5 years (Bota DA et al. 2007). Still controversial however is whether the prognosis of patients with secondary glioblastoma is better than or similar to the prognosis of those with primary glioblastoma (Bullard DE et al. 1985). Thus surgery remains standard and stem cell research and further neurological studies are to be conducted in order to really produce a potential cure to such a malignant tumor (Chamberlain MC et al. 1998).

Given the literature review of diagnosis, pathophysiology, and treatment methods, the following study focused on those factors that the literature suggested may be pertinent in glioblastoma outcomes. The purpose and broader scientifically defined question of this particular study, therefore, was to use retrospectively analysis on data of glioma patients collected at a single institution over a thirty-five year period to compare the differential effects of treatment strategy, race and tumor grade on outcome and survival.

CHAPTER TWO

Review of Literature

Gliomas are primary brain tumors that arise within the brain. There are multiple grades of gliomas -- grade II, III and IV, with grade IV being the most malignant (Bullard DE et al. 1985) and are specifically called glioblastoma (Daumas-Duport C et al. 1988). Characteristics of Grade IV tumors include aggressiveness and infiltrative nature, notably spreading into other parts of the brain quickly, without metastasizing outside of the brain (Ferguson S et al. 2007). Further features of glioblastoma multiforme can be separated by category background, signs and symptoms, etiology, pathogenesis, diagnosis, treatment, and prognosis.

Background

Glioblastoma multiforme, or GBM, is actually the most common and malignant of the glial tumors (Chamberlain MC et al. 1998). In fact, of 17,000 primary brain tumors potentially diagnosed in the United States, 60% are gliomas (Li J et al. 2011). Also, GBM accounts for approximately 12-15% of intracranial neoplasms and 50-60% of astrocytic tumors GBM (Burger PC et al. 1994). GBM geographical prevalence includes European and North American countries, with approximately 2-3 new cases per 100,000 people per year. This is more common in the United States, Scandinavia, and Israel than in Asia, however (Burger PC et al. 1994), and may reflect differences in genetics, diagnosis, healthcare system, and reporting practices (Brat DJ et al. 2008).

On a smaller, corporal level, GBM, differentiated by neoplastic astrocytes, is a heterogeneous, often differing in location in the central nervous system, age, gender, and growth potential (Vredenburgh JJ et al. 2007), invasiveness, morphological features, tendency for progression, and treatment reaction (Caccamo DV et al. 1997). GBM primarily affects adults and is located preferentially in the cerebral hemispheres, often the frontal and temporal lobes (Chamberlain MC et al. 1998). Much less commonly, GBM can affect the brainstem and the spinal cord, though such pathology is often seen in children (Dohrmann GJ et al. 1976). These tumors may develop from lower-grade astrocytomas or anaplastic astrocytomas, classified as grade II and III, respectively, but, more frequently (Daumas-Duport C et al. 1988), manifest *de novo*, without any evidence of a less malignant precursor lesion (Chamberlain MC et al. 1998), giving rise to various symptoms.

Signs and Symptoms

Although common symptoms of the disease include seizure, nausea, vomiting, headache, memory loss, and hemiparesis, the most prevalent symptoms are progressive memory, personality (Jakola AS et al. 2011), and neurological deficits because GBM primarily affects temporal and frontal lobes (Zulch KJ 1986). Neurologic symptoms and signs can thus be classified as either general or focal. This includes nausea and vomiting, personality changes, and slowing of cognitive function (Barnard RO et al.1987) and hemiparesis, sensory loss, visual loss, aphasia, respectively, thus reflective of the location of the tumor (Greenberg MS 1997). Due to this, more than the pathological properties that characterize GBM, the kind of symptoms produced highly depends on the location of the tumor (Furnari FB et al. 2007). In fact, GBM is

asymptomatic in nature and upon saturation, can start producing symptoms quickly (Watanabe K et al. 2007). Thus, the clinical history of a patient with glioblastoma multiforme (GBM) is usually short, majority of them not surviving past three months (Burger PC et al. 1994), despite truly pinpointed etiology.

Etiology

The etiology of GBM is actually unknown though causes including genetics, cell phone usage, post-head injury (Weintraub MI 1994), N-nitrous compounds (Scott JN et al. 1998), occupational hazards, electromagnetic field exposure, race, often more common in whites, and gender, often more common in males, as data suggests (Chamberlain MC et al. 1998). In terms of dietary intake or lifestyle habits, smoking, consumption of cured meat, or electromagnetic fields, have not been substantially linked with glioblastoma, although alcohol consumption may be a possible risk factor (Keles GE et al. 1999). External causes include ionizing radiation as well as viruses SV40, HHV-6, and cytomegalovirus (Combs SE et al. 2005). In fact, a 2006 study suggested an association of brain tumor incidence and malaria (Barnard RO et al.1987); the anopheles mosquito, the carrier of malaria, may potentially transmit a virus that could cause glioblastoma or its immunosuppression could enhance viral replication (Caccamo DV et al. 1997).

Expansion of other risk factors include male gender, age over 50 years old, ethnicity of either Caucasian or Hispanics, having a low-grade astrocytoma (Waters JD et al. 2013). These low-grade, developing astrocytomas often, given enough time, develop into a higher-grade tumor, or have one of the many genetic disorders associated with them. This leads to an increased incidence of gliomas (Glantz MJ et al. 2000), such

as neurofibromatosis, tuberous sclerosis, Von Hippel-Lindau disease, Li-Fraumeni syndrome, or Turcot syndrome (Daumas-Duport C et al. 1988).

Pathogenesis

In order to better comprehend GBM, its effects and manifestations can be classified as primary or secondary (Kan P et al. 2008).

Primary GBM accounts for at least 60% of cases in adults older than 50 years (Buatti J et al. 2008). These tumors manifest *de novo* and are thereby presented after a short clinical history, usually less than 3 months (Butowsi NA et al. 2006).

On the other hand, secondary GBM accounts for at least 40% and also typically develops in younger patients, as indicated by less than 50 years of age. This is through malignant progression from a low-grade astrocytoma or anaplastic astrocytoma, grade II and III, respectively (Burger PC et al. 1994). Despite both progressing from astrocytoma, the time required for this progression varies considerably, often ranging from 1 to 10 years, with a mean interval of 4-5 years (Batzdorf U et al. 1963). Increasing evidence indicates several differences between primary and secondary glioblastomas, constituting genetic pathways, affected patient characteristics, and response to therapies (Bullard DE et al. 1985). Thus, multiple mutations, in essence, result in the most common astrocytic glioblastoma. Following these mutations is the presence of glioblastoma stem-like cells, metabolism, and ion channels.

Molecular Alterations

Primary or secondary glioblastomas are due to the loss of heterozygosity on chromosome arm 10q, in approximately 60-90% of cases (Bullard DE et al. 1985). Rarely found in other tumors, this loss of heterozygosity at 10q plus 1 or 2 of the additional gene mutations is actually common and a major player in the development of glioblastomas (Greenberg MS 1997).

Also, p53, a tumor suppressor gene, has mutations that were also one of the first genetic alterations identified in astrocytic brain tumors (Bouvier-Labit C et al. 1998). More common in children, the p53 gene appears to be deleted or altered in approximately 25-40% of all GBM (Rich JN et al. 2004) and more commonly in secondary glioblastoma multiformes (Buatti J et al. 2008).

Along with 10q and p53, another mutation occurs in the epidermal growth factor gene (EGFR), a gene of control in cell proliferation (Bruce JN et al. 2000). In this gene, both overexpression of the receptor and disruptive rearrangements causing truncated isoforms are apparent (Ekstrand AJ et al. 1992). Consequently, these mutations lead to a simultaneous loss of chromosome 10 and a concurrent p53 mutation, though the latter is rare (Newcomb EW et al. 1998). With mutations appearing in 40-50% of these tumors (Bullard DE et al. 1985), overexpression or activation mutations in this gene is actually common in primary glioblastoma.

Amplification or overexpression, yet again, but this time of a different cell proliferation, the MDM2 gene, constitutes an alternative mechanism. In this mechanism there is an escape from p53-regulated control of cell growth when p53 is bound and its activity obstructed (Bouvier-Labit C et al. 1998). Overexpression of MDM2 is the next

most common gene mutation in GBM, found in 10-15% of patients (Burger PC et al. 1994).

MDM2 gene is followed by PGDF-alpha. Platelet-derived growth factor–alpha (PDGF-alpha) gene also acts as a major mitogen for glial cells, especially in binding to its respective receptor (PDGFR) (Mukundan S et al. 2008). Amplification or overexpression of PDGFR is typical in secondary glioblastomas, often in 60% of the diagnosed patients (Giordana MT et al. 1995).

Another, but not so common gene mutation is of the PTEN gene. This gene involves a tyrosine at 10q23 chromosome (Duerr EM et al. 1998). The PTEN gene usually exists in 20% of glioblastomas, especially in primary glioblastoma multiformes (Bullard DE et al. 1985) and the PTEN gene translation actually produces cellular phosphatase products (Mellinghoff IK). Therefore, mutations to this gene will turn off signaling pathways, consistent with tumor-suppression action (Duerr EM et al. 1998). Usually proliferation precedes this because when phosphatase activity is lost because of genetic mutation, signaling pathways can become activated constitutively and numbers multiply (Reardon DA et al. 2006).

MAC1-E1, MAGE-E1, and NRP/B genes are the genes involved in less frequent, more malignant mutations (Chamberlain MC et al. 1998). MAC1-E1 is a gene that results in gliomas in their most malignant form (Hoffman HJ et al. 1985). MAGE-E1 gene, of the melanoma antigen gene family, results in GBM due to the fact that overexpression is up to 15-fold higher here (Duda DG et al. 2007). NRP/B genes are nuclear-restricted proteins; these protein mutants are more prevalent in glioblastoma cells are expressed in neurons but not in astrocytes (Liang BC et al. 1991).

Additional genetic alterations in primary glioblastomas include p16 deletions and retinoblastoma (RB) gene protein alterations (Bullard DE et al. 1985). Likewise, progression of secondary glioblastomas often includes loss of heterozygote nature at 19q chromosome (50%), RB protein alterations (25%), PTEN mutations (5%), and deleted-in-colorectal-carcinoma gene (DCC) gene loss of expression (50%) (Duerr EM et al. 1998).

Glioblastoma Stem-like Cells

Due to the resistance to treatment methods and expression rates, glioblastomas contain cancer cells with stem-cell like characteristics (Levin VA et al. 1990). The transcription factor Hes3, a biomarker for these cancer stem cells, has been shown to regulate their number when placed in culture (Rich JN et al. 2004).

Metabolism

Changes in other gene expressions result in changes in normal human metabolic process, which once mutated or altered, often result in either primary or secondary GBM (Pompili A et al. 1993). One such gene is the IDH1 gene. The IDH1 gene encodes for the enzyme isocitrate dehydrogenase. This enzyme is found in the citric acid cycle of aerobic metabolism and is frequently mutated in glioblastoma, 5% of primary GBM and more than 80% of secondary GBM (Hartmann C et al. 2010). Upon mutation, IDH1 produces high concentrations of the "oncometabolite" D-2-hydroxyglutarate which deregulates the function of the wild-type IDH1-enzyme (Hegi ME et al. 2005). In this manner, deregulation induces profound changes to the metabolism of IDH1-mutated glioblastoma, (Bruce JN et al. 2000) and increases GBM cell dependence on glutamine or glutamate,

instead of normal glucose, as an energy source (Hulbanni S et al. 1976). Normal, wild-type cells and healthy astrocytes excrete glutamate; IDH1-mutated GBM cells will then migrate, invade, and disperse into healthy parts of the brain where glutamate concentrations are higher (Hartmann C et al. 2010). Thus explains the invasive behavior of these IDH1-mutated glioblastoma and the enhanced metastatic nature of the GBM tumor in the brain (Leibel SA et al. 1994), spreading to higher concentrations disrupts the homeostatic capabilities.

Ion Channels

Furthermore, GBM exhibits numerous alterations in genes that encode for ion channels (Herholz K et al. 1993). These alterations include upregulation of gBK and ClC-3, potassium and chloride channels respectively (Mellinghoff IK). By these upregulation mechanisms, GBM tumor cells actually once again disrupt ion movement over the channels, disrupt the water concentration, and alter osmotic gradient, thereby changing cellular volume very rapidly (Daumas-Duport C et al. 1988). Such effects exacerbate the already extremely aggressive invasive behavior and quick adaptations in cellular volume can facilitate movement through the sinuous extracellular matrix of the brain, thereby spreading the tumor the frontal and temporal lobes (Lesser SA).

Diagnosis

As with many pathological conditions, MRI and CT scans can be used to diagnose glioblastomas (Li J et al. 2011). On an MRI, glioblastomas appear as ring-enhancing lesions (Rich JN et al. 2004) and the appearance is not specific, however, because lesions

such as abscess, metastasis, multiple sclerosis, may have a similar appearance. Thus, definitive diagnosis of a suspected GBM on CT or MRI requires a more stereotactic biopsy or a craniotomy (Fadul C et al. 1988) followed by a tumor resection and pathologic confirmation (Coffey RJ et al. 1988). Biopsy or subtotal tumor resection can result in undergrading of the lesion due to the fact that the tumor grade is based upon the most malignant portion of GBM (Chamberlain MC et al. 1998). Other advanced techniques include using perfusion MRI and MR spectroscopy. Perfusion MRI involves imaging of tumor blood flow and measuring tumor metabolite concentration with MR spectroscopy, thus adding value to standard MRI in diagnosing GBM (Brat DJ et al. 2008). Such is the case because the spectroscopy shows increased relative cerebral blood volume and increased choline peak respectively, but pathology remains standard as in MRI and CT results (Nagashima G et al. 1999).

In the diagnosis of GBM, however, it is important to distinguish primary from secondary glioblastoma. These tumors either are spontaneous or are consecutive derivatives from a lower-grade glioma, respectively (Shapiro WR et al. 1989). Primary glioblastomas have a worse prognosis; having had different tumor biology responses to therapy (Fine HA et al. 1993), primary GBM requires a more critical evaluation to determine prognosis and therapy (Burger PC et al. 1994) while over 80% of secondary glioblastoma carries a mutation in IDH1, this mutation is rare in primary glioblastoma (8%) (Quang TS et al. 2004). Since histopathologically both primary and secondary GBMs are very similar, making distinction more reliable, IDH1 mutations and other biomarkers may become a useful tool to distinguish primary and secondary glioblastomas in the future (Walker MD et al. 1978). More techniques are being used now to

differentiate primary and secondary GBMs according to the set of unique mutations more prevalent in each, respectively (Shapiro WR et al. 1989).

Treatment

The treatment of glioblastomas remains difficult in that no contemporary treatments are curative but GBM has a controlling of pathological condition mode of treatment (Bota DA et al. 2007). Despite high stakes and overall high mortality rates, recent work leading to an understanding of the molecular mechanisms and gene mutations combined with clinical trials are leading to promising and tailored therapeutic approaches (Ohgaki H et al. 1999). Multiple challenges remain, however, including, but not limited to, tumor heterogeneity, isolateral location, and rapid, aggressive relapse (Avgeropoulos, N. G et al. 1999). Therefore, the treatment still remains palliative and encompasses an amalgamation of surgery, radiotherapy, and chemotherapy (Stupp R et al. 2009).

Upon initial diagnosis of GBM, physicians usually recommend the standard treatment, consisting of maximal surgical resection, radiotherapy, and chemotherapy (Friedman HS et al. 2000), but in concordance with the characteristics of the patient (Burger PC et al. 1994). For example, elderly patients usually receive a less aggressive therapy, employing radiation or chemotherapy alone (Friedman HS et al. 2000). In fact, data suggests that elderly patients with glioblastoma who underwent radiotherapy alone had improved overall cancer-specific survival (Chaichana KL et al. 2014) compared with those who did not undergo radiotherapy treatment (Stupp R et al. 2009). Recent evidence also hints that in such patients (Burger PC et al. 1994), chemotherapy treatment with

temozolomide drug is associated with longer survival than standard radiotherapy (Friedman HS et al. 2000). In general, for patients over the age of 70, chemotherapy or hypo-fractionated radiotherapy is associated with prolonged survival than treatment with standard fractionated radiotherapy (Brem H et al. 1995). The improvement in survival with temozolomide is actually better in patients with MGMT methylation (Chaichana KL et al. 2014). All in all, the treatment packages depend on the type of mutation or metabolism interruption that resulted in the particular GBM (Butowski NA et al. 2006), in addition to patient characteristics.

Furthering radiation treatment, a study by Stupp reported the final results of a phase III trial for patients with glioblastoma (Stupp R et al. 2009). These patients were treated with adjuvant temozolomide and radiation with a median follow-up of more than 5 years (Cloughesy TF et al. 2008). The study had previously reported improved median and 2-year survival when temozolomide was added to radiation therapy in glioblastoma (Combs SE et al. 2005). However, soon statistics showed that in the combined therapy group (ie, temozolomide and radiation), survival continued to exceed that of radiation alone throughout the 5-year follow-up ($p< 0.0001$) (Combs SE et al. 2005). Thus, several supportive studies show that survival of patients who received temozolomide and radiotherapy for GBM is superior to radiotherapy alone (Dropcho EJ et al. 1996) alone across all clinical prognostic subgroups (Stupp R et al. 2009).

In general, for patients with GBM, median time to recurrence after standard therapy is 6.9 months (Burger PC et al. 1994). For recurrent GBM, however, surgery, another treatment strategy, is appropriate in selected patients, once again depending on the characteristics of the patients and the recurrence of the disease as well as various

radio-therapeutic, chemotherapeutic, biologic, or experimental therapies that may have already been employed (Ciric I et al. 1990).

Compared to just surgery alone and according to combinatorial therapy, radiation therapy with surgery or surgery with chemotherapy (Ciric I et al. 1990) has been shown to prolong survival in patients with GBM (Bota DA et al. 2007). The addition of radiotherapy to surgery has been shown to increase survival from 3-4 months to 7-12 months (Stupp R et al. 2009).

Further proof of the effectiveness of the treatment is signified by dose-response curves (Avergeropoulos, N. G. et al. 1999). With doses usually administered 5 days per week in doses of 1.8-2.0 cGy (Darefsky AS), dose response relationships for GBM demonstrate that a radiation dose at most 4500 cGy results in an approximate survival of 13 weeks in comparison to 42 of 6000 cGy (Chaichana KL et al. 2014).

Thus, it follows that GBM responsiveness to radiotherapy varies (Westphal M et al. 2006). In many instances, radiotherapy can induce remission, characterized by stability, neurological deficit regression, or diminution in the size of tumor mass (Mamelak AN et al. 2006). Unfortunately, any period of response is short-lived because the tumor typically recurs, resulting in further deterioration.

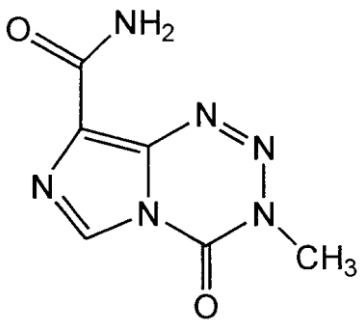
A form of radiation known as interstitial brachytherapy is of limited use and is rarely used. By implantation of radioactive seeds, with rapid fall-off of radiation in surrounding tissue, a large dose of radiation is delivered to the tumor volume, (Nigro HM et al. 1989). In order for this treatment method to be successful, the tumor must be unilaterally smaller than 5 cm in diameter (Avergeropoulos, N. G. et al. 1999). For example, in one study, patients had a significantly better median survival (2 mo) when

treated with interstitial brachytherapy compared with those treated with the conventional external radiation therapy. Following interstitial brachytherapy, however, less than half of patients require another surgery for removal of tissue damaged by radiation necrosis (Burger PC et al. 1994).

Radiosensitizers are also another form of treatment (Avergeropoulos, N. G. et al. 1999). Radiosensitizers such as chemotherapeutic agents, molecular agents, and antiangiogenic agents may augment the palliative nature of radiotherapy (Duda DG et al. 2007). Though radiotherapy for recurrent GBM is controversial, some studies have suggested a benefit to radiosurgery or fractionated re-irradiation (Stupp R et al. 2009).

Chemotherapy is another treatment. Several studies have suggested adjuvant chemotherapy has provided benefit to more than 25% of patients, although, the optimal chemotherapeutic regimen for GBM is not well defined at present (Bota DA et al. 2007). Meta-analyses of adjuvant chemotherapy show that in fact there is a 6-10% increase in 1-year survival rate (Chaichana KL et al. 2014). Carmustine (BCNU) and cis -platinum (cisplatin) are two chemotherapeutic drugs that have been the primary agents used against gliomas (Chamberlain MC et al. 1998). According to statistics, all agents in use have no greater than a 30-40% response rate, and most fall into the range of 10-20% (Duda DG et al. 2007).

Temozolomide, another chemotherapeutic drug, is an orally active alkylating agent used for persons newly diagnosed with GBM and often in combination with chemotherapy, radiation, and surgery (Bota DA et al. 2007). Temozolomide, seen on the right, was approved by



the FDA in March 2005 and is shown to tolerate GBM and provide a survival benefit due to its metabolic activity in penetrating the blood brain barrier (FDA. Avastin Approval History). According to data, adjuvant and concomitant temozolomide with radiation was associated with significant improvements in median progression-free survival over surgery or radiation alone (6.9 vs 5 mo), overall survival (14.6 vs 12.1 mo), and the likelihood of being alive in 2 years (26% vs 10% and 10%) (Chaichana KL et al. 2014).

Nitrosoureas and BCNU (carmustine)-polymer wafers (Gliadel), another set of drugs, were approved by the FDA in 2002 (FDA. Avastin Approval History). Though Gliadel wafers show only a modest increase in median survival over placebo (13.8 vs. 11.6 months), they are used by some for initial treatment (Avergeropoulos, N. G. et al. 1999) and have also been used in the largest phase III trial (Chaichana KL et al. 2014). These wafers are associated with increased rates of cerebrospinal fluid leak and intracranial pressure after prolonged edema and mass effect (Brem H et al. 1995).

Gene therapy may also be employed. Gene therapy is usually used to treat MGMT (Piroth MD et al. 2011). In approximately 45% of GBM cases, methylation of MGMT promoter results in an epigenetic silencing of the gene (Pompili A et al. 1993), thereby decreasing the tumor cell's capacity for DNA repair and consequently increasing susceptibility to temozolomide (Bullard DE et al. 1985). When comparing patients with and without MGMT promoter methylation, patients were treated with temozolomide (Olson JJ et al. 2014), the groups had median survivals of 21.7 versus 12.7 months, and 2-year survival rates of 46% versus 13.8%, respectively (Chaichana KL et al. 2014). Though temozolomide is currently a first-line agent in the treatment of GBM,

unfavorable MGMT methylation status could help select patients appropriate for future investigations (Burger PC et al. 1994).

Consequently, for the treatment of glioblastomas, University of California at San Francisco data indicates that surgery followed by radiation therapy leads to 1-, 3-, and 5-year survival rates of 44%, 6%, and 0%, respectively (Barker FG et al. 1996). Comparatively, surgery followed by radiation and chemotherapy, using nitrosourea-based regimens and drugs, resulted in 1-, 3-, and 5-year survival rates of 46%, 18%, and 18%, respectively (Bota DA et al. 2007).

As with any treatment procedure, however, there are problems. With chemotherapeutic agents use for brain tumors, a major problem is the fact that the blood-brain barrier effectively excludes many agents from the central nervous system (Coffey RJ et al. 1988). For this reason, novel methods of intracranial drug delivery are being developed to deliver higher concentrations of chemotherapeutic agents to the tumor cells while at the same time avoiding the adverse systemic effects (Lang FF et al. 1994).

Benefits of the treatments are limited by the adverse effects of such medications and thus provide only modest benefits. Pressure-driven infusion of chemotherapeutic agents through an intracranial catheter, also known as convection-enhanced delivery (CED), has the advantage of delivering drugs along a pressure gradient rather than by simple diffusion (Mellinghoff IK). Chemotherapy for recurrent glioblastoma multiforme provides modest, if any, benefit, and several classes of agents are used (Bota DA et al. 2007) as exemplified by carmustine wafers that increased 6-month survival from 36% to 56% over placebo in one randomized study of 222 patients, despite significant

association between the treatment group and serious intracranial infections (Brem H et al. 1995).

Furthermore, genotyping of brain tumors may have applications in stratifying patients for clinical trials of various therapies (Burger PC et al. 1994). For example, bevacizumab, an anti-angiogenic agent was approved by the U.S. Food and Drug Administration for recurrent glioblastoma in May 2009 (Cloughesy TF et al. 2008). When amalgamated with irinotecan, bevacizumab improved 6-month survival in recurrent glioma patients to 46% though previously only 21% in patients treated with temozolomide alone (Butowski NA et al. 2006). This bevacizumab and irinotecan combination for recurrent GBM has been shown to improve survival over bevacizumab or temozolomide alone (Chaichana KL et al. 2014).

Continuously, a small fraction of glioblastomas responds to gefitinib or erlotinib (tyrosine kinase inhibitors) (Chi AS et al. 2007). The simultaneous presence in glioblastoma cells of mutant EGFR (EGFRviii) and PTEN gene pathways was associated with responsiveness to tyrosine kinase inhibitors. Other targets include PDGFR, VEGFR, mTOR, farnesyltransferase, and PI3K (CloughesyTF).

Other therapy modalities under investigation include gene therapy, cell vaccines, chlorotoxins, and radiolabeled drugs (Duda DG et al. 2007).

Prognosis

Individual prediction of clinical outcome has remained an elusive goal, despite extensive clinical trials. This is because GBM is very malignant and median survival exists even with optimal treatment (Chaichana KL et al. 2014). For instance, in a series of

279 patients receiving radiation and chemotherapy (Barker FG et al. 1996), only about 2% survived longer than 3 years, thus, signifying the need for further treatment experimentations (Butowski NA et al. 2006).

Patient survival actually depends on a plethora of clinical parameters and especially the condition of the GBM (Chaichana KL et al. 2014). Younger age, higher Karnofsky ability of patients with cancer to perform daily tasks, radiotherapy, and chemotherapy all correlate with improved outcome (Bota DA et al. 2007). According to the Radiation Therapy Oncology Group (RTOG) GBM database (Barker FG et al. 1996), clinical evidence even suggests that a greater extent of resection favors longer survival (Devaux BC et al. 1993).

Despite treatment research and combined measures, prognosis shows that survival is minimal for patients with p53, EGFR, or MDM2 mutations; long-term survivors, defined as those who survive longer than 2 years, is also rare (Bouvier-Labit C et al. 1998). However, long-term benefits do exist for those who receive surgery (Butowski NA et al. 2006), radiotherapy, and temozolomide chemotherapy. Still much remains unknown about why some patients survive longer with GBM and others do not (Stupp R et al. 2009). Younger age increases survival in GBM, as is 98%+ resection and use of temozolomide chemotherapy (Chaichana KL et al. 2014). A recent study also confirms that younger age is associated with a much better prognosis, with a small, effective portion of patients under 50 years obtaining a certain cure (Devaux BC et al. 1993), measured to be when a population's risk of death equals that of the normal population, often 10 years in GBM (Barker FG et al. 1996).

Clearly, new approaches for the management of GBM are necessary. Enrollment of patients into clinical trials will generate new information regarding therapies (Butowski NA et al. 2006) and novel approaches, such as the use of gene therapy and immunotherapy, as well as improved methods for the delivery provide hope for the future (Caccamo DV et al. 1997).

CHAPTER THREE

Methodology

A database was created following approval by the IRB, institutional review board. Using ICD 9 codes, all adult patients over 18 years of age with a new diagnosis of glioblastoma multiforme between 1976 and 2011 were identified. Demographic information including age, race, and gender were extracted from the electronic medical record. Clinical information including grade of tumor, treatment year, and survival time from diagnosis or time of last contact were extracted as well. Adults over age 18 with at least 1 year follow-up, as well as astrocytoma cancer patients were also included in the analysis.

Statistical Analysis

Variables of interest included age group (60 years of age served as the cutoff), treatment year group (prior to and following 2006), race, and tumor grade. Overall survival and risk of death were compared dichotomously by these four factors using univariate and multivariate Cox proportional hazards regression models. SAS 9.2 software (SAS Institute INC, Cary, NC) was used for data analysis; a p-value of less than 0.05 indicates statistical significance.

CHAPTER FOUR

Results, Analysis, and Conclusion

Nine hundred sixty five patients diagnosed with brain tumor were initially considered in the analysis, but those lost to follow-up or under the age of 18 were excluded. Within the six hundred twelve patients included in the final analysis who died during the review period, median overall survival was approximately 8.8 months (95% CI, 7.7-10.0 months). Median follow-up time for the 92 survivors included in the analysis was 54 months. According to the univariate analysis, patients diagnosed with high grade gliomas lived for shorter length of time compared to patients with low grade gliomas ($p = 0.0001$). The effect of current treatment strategies indicated by the cutoff at year 2006 appeared to have no effect on the longevity of the patients. Interestingly, race did appear to have a significant effect in the longevity of glioma patients, specifically in patients of self-identified Hispanic origin who had a significantly higher median survival time compared with Caucasians ($p<0.037$). Additionally, age also contributed to a higher hazard ratio (HR) of death among glioma patients ($p<0.0001$) (Table 2).

In the multivariate analysis, all other variables were held constant to determine whether these risk factors were independent of each other (Table 3). Low grade gliomas had a significantly lower risk of death than high grade ($p < 0.0002$). In this analysis, treatment after 2006 showed significantly lowered mortality risk compared with the time period before 2005 (0.646, $p < 0.0001$). Patients older than 60 years and above had higher

risk of death than younger patients (2.377, $p<0.0001$). On the other hand, race was not seen to be an independent risk factor for survival.

Table 1. Descriptive Statistics according to Survival Status

		Deceased	Alive
Grade			
	Low	100 (19.38%)	38
	High	416 (80.62%)	54
Year Group			
	2005 and earlier	397 (76.94%)	61
	2006 and after	119 (23.06%)	31
Race			
	Black	21 (4.07%)	6 (6.52%)
	Hispanic	23 (4.46%)	7 (7.61%)
	Other/Unknown	10 (1.94%)	4 (4.35%)
	White	462 (89.53%)	75
Age, mean (SD)		63 (14)	43 (15)
	<60	186 (36.05%)	78
	≥60	330 (63.95%)	14

Table 2. Univariate Survival Analysis

	Median Survival (95% CI)			HR (95% CI)			P-value
Grade							
Low	15.80	10.05	24.54		1.000		
High	7.98	7.03	9.17	1.768	1.418	2.204	**<.0001**
Year Group							
1976-2005	8.97	7.89	10.02		1.000		
2006-2011	7.90	5.68	14.32	0.907	0.739	1.114	0.3531
Race							0.0525*
Black	15.87	9.17	25.43	0.677	0.437	1.049	0.0808
Hispanic	16.82	8.12	37.06	0.641	0.422	0.975	0.0378
Other/Unknown	12.67	2.60		0.743	0.397	1.391	0.3536
White	8.18	7.16	9.63		1.000		
Age							
<60	18.96	15.77	22.18		1.000		
≥60	5.16	4.50	5.95	3.054	2.531	3.685	**<.0001**

*Overall significance of Race

Univariate analysis shows that higher grade and higher age affect the survival in a negative way. In addition, Hispanic race has better survival than white.

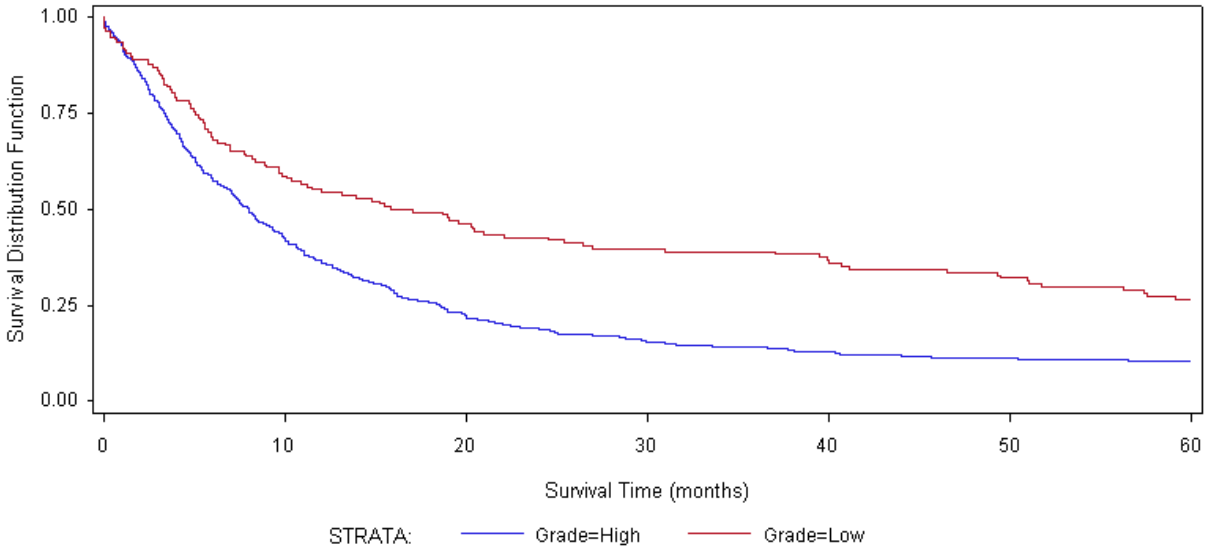
Table 3. Multivariable Survival Analysis

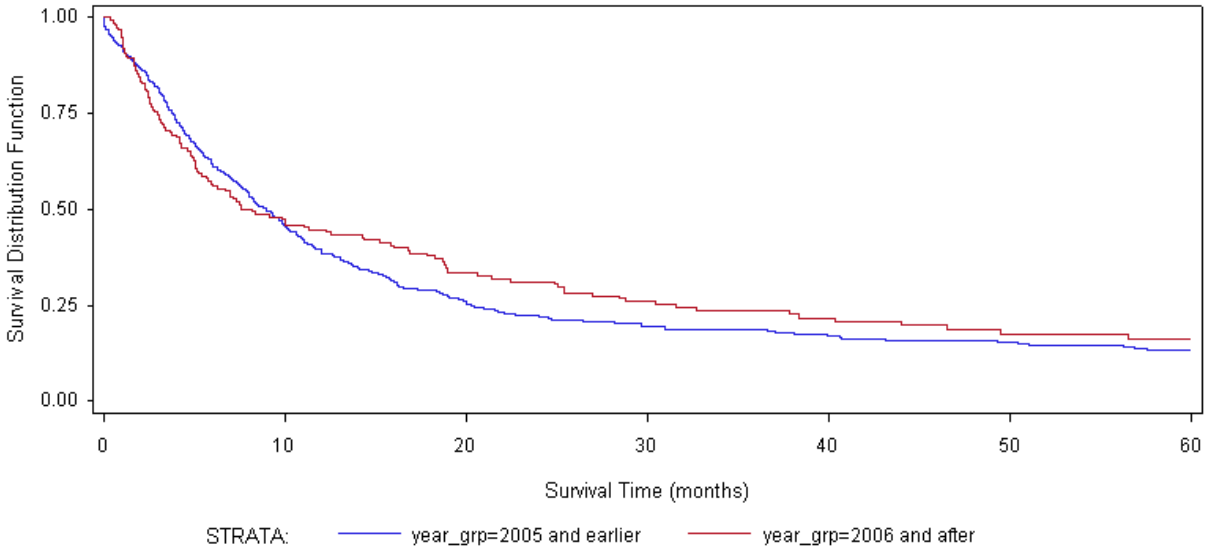
		HR (95% CI)		P-value
Grade				
Low		1.000		
High	1.542	1.229	1.936	**0.0002**
Year Group				
1976-2005		1.000		
2006-2011	0.797	0.646	0.983	**0.0344**
Race				0.5029*
Black	0.780	0.503	1.209	0.2657
Hispanic	0.816	0.535	1.245	0.3453
Other/Unknown	0.815	0.434	1.531	0.5244
White		1.000		
Age				
<60		1.000		
≥60	2.877	2.377	3.482	**<0.0001**

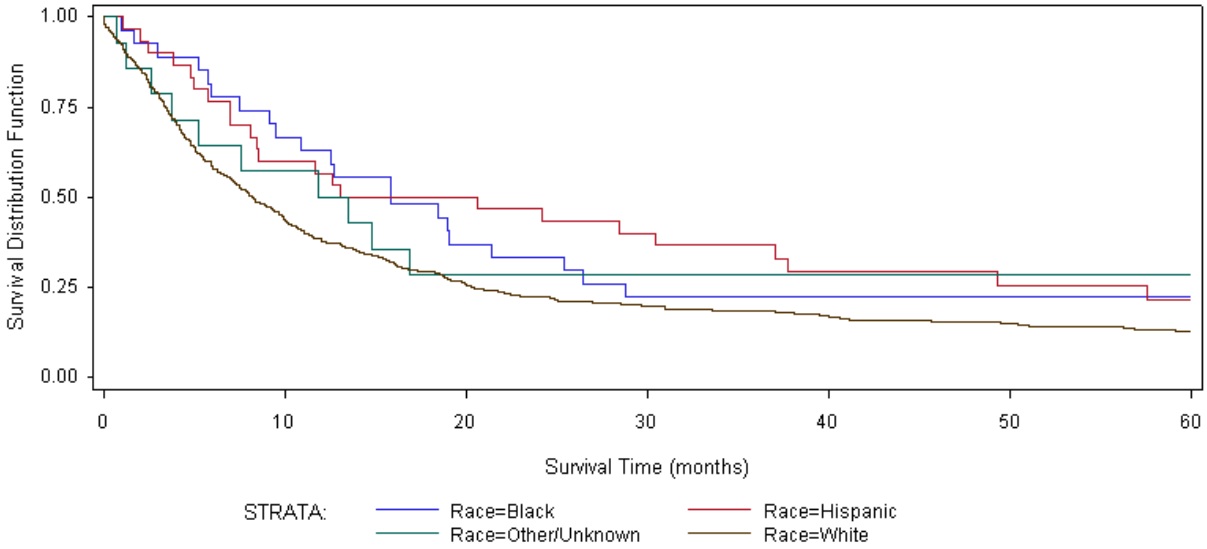
*Overall significance of Race

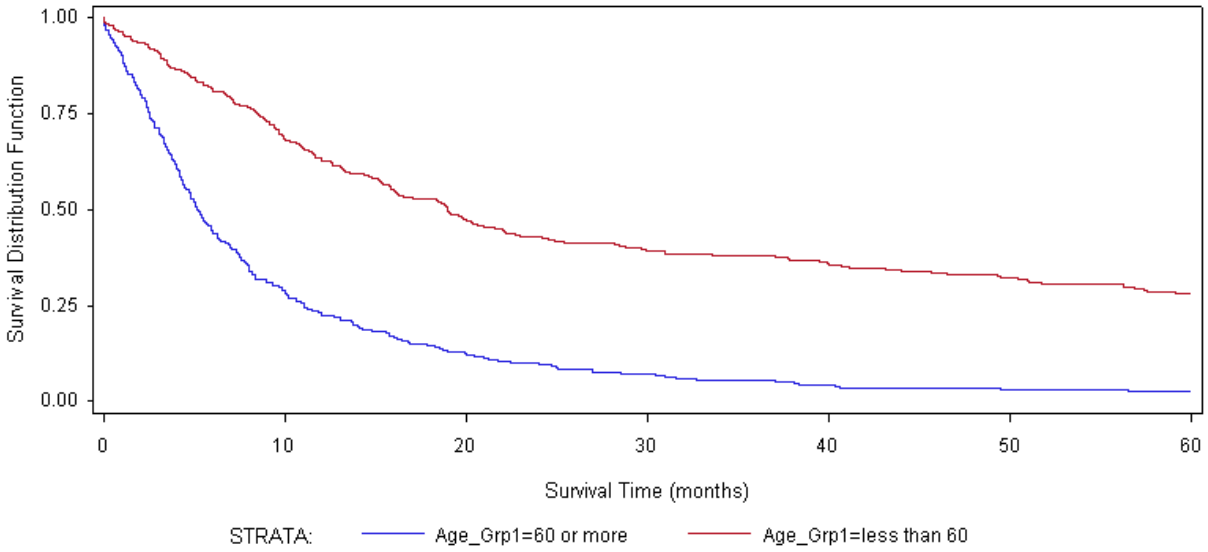
Result of multivariate analysis shows that higher grade and higher age negatively affect the hazard ratio negatively. On the other hand, year group 2006 and later affect hazard ratio in a positive way.

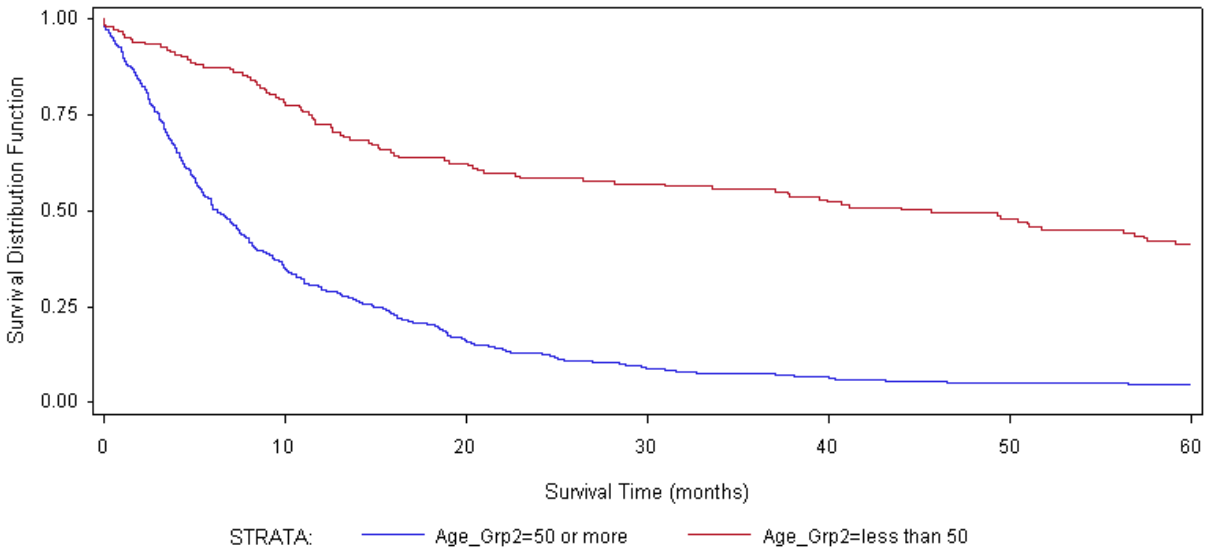
Figure 1. Kaplan-Meier Survival Curves






1.00
0.75
0.50
0.25
0.00
Survival Distribution Function
0
10
20
30
40
50
60
Survival Time (months)
STRATA:
Race=Black
Race=Hispanic
Race=Other/Unknown
Race=White


1.00
0.75
0.50
0.25
0.00
Survival Distribution Function
0
10
20
30
40
50
60
Survival Time (months)
STRATA:
Age_Grp1=60 or more
Age_Grp1=less than 60


1.00
0.75
0.50
0.25
0.00
Survival Distribution Function
0
10
20
30
40
50
60
Survival Time (months)
STRATA:
Age_Grp2=50 or more
Age_Grp2=less than 50

As analysis shows, in the year 2006, the standard treatment of GBM changed dramatically with adoption of a multimodal treatment strategy consisting of surgical resection, radiation therapy and temozolomide. Past studies have implicated that surgery has a beneficial effect on survival time in glioma patient. Additionally, incorporation of total resection has been reported to significantly lengthen the survival time when compared with biopsy only. Controlling for other factors, including age, race and grade of the tumors, there was a significant improvement in survival after 2006 in analysis as well. This result suggests that treating the tumors alone with temozolomide without tumor resection and radiotherapy is less beneficial than the combined approach with surgery, radiation, and temozolomide chemotherapy.

Further analysis of this study shows that high grade tumors had a significantly increased hazard ratio and decreased median survival time of GBM patients. High grade tumors are more aggressive and fast growing, spread rapidly locally and lethal in a shorter period of time.

Also observed was age did have a significant negative impact as indicated by increase in hazard ratio and decrease in survival. This observation is supported by other studies (Scott et al. 1998). Scott and colleagues observed similar observation in the prognostic outcome of GBM treatment (Scott et al. 1998). In this retrospective study the researcher compare the outcome of treatment in the age group 70 and above with the younger age group. Several putative reasons can explain these findings. As seen by this study also, isocitrate dehydrogenase (IDH) mutant tumors are associated with relatively better treatment outcome across gliomas. The occurrence of IDH mutant gliomas drastically decreases after 60 years of age and such an observation may explain at least

partially the poor prognosis of the elderly patients even after treatment. Elderly populations may have compromised bodily functions ranging from hepatic, renal, and immunological. Interestingly, the standard treatment with temozolomide in elderly population also needs to be evaluated as it has been reported that the benefit of using temozolomide chemotherapy decreases in elderly population.

The analysis of outcomes in different ethnic groups also suggests new areas for further research, especially in concurrence to central Texas demographics. The observation of decreased median survival time in Caucasian population with significantly increased survival in Hispanics in univariate analysis, for example, has not been reported previously. Though this did not reach significance in the multivariate analysis, because the study was not powered to explore this finding, further controlled studies are needed.

Thus, given these statistical analyses of age, gender, race, and prognosis, clearly further research needs to be conducted to evaluate surgery, radiotherapy, and chemotherapy treatments. Further questions of demography, geography, and universality can aide in a more controlled evaluation of such GBM trends.

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