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Jocelyn Chow April 7th, 2022

Characterizing clinical and genomic factors of IDH-wildtype glioblastoma

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Purpose: Glioblastomas (GBMs) are one of the most common types of malignant brain tumor, and are typically associated with poor survival outcomes. Over the past decade, research has stratified GBMs into two categories based on their isocitrate dehydrogenase (IDH) mutational status. IDH-mutations have become a widely accepted marker for better prognosis in GBM. However, approximately 90% of GBMs are marked as IDH-wildtype (IDH-wt). Thus, identification and characterization of the clinical and genomic factors of IDH-wildtype GBM is necessary to analyze their significance for prognostic implications.
Methods: We collected data for 204 patients in the Emory Healthcare system that had a pathological diagnosis of IDH-wt, and had undergone surgical resection. Patient charts were evaluated based on their demographics, surgical outcomes, and pathological reports. Univariate and multivariate analyses were performed on our cohort following data collection.
Results: Overall, clinical factors significant for better prognosis included higher KPS score, fractionated radiation therapy, temozolomide, and avastin treatment. Based on univariate analysis, common IDH-wt GBM mutations such as EGFR amplification and PTEN loss had no significant correlation with overall survival or progression-free survival. Genomic factors that were most significant for better prognosis were 1p/19q co-deletion and chromosome 10q loss. Additional statistical analyses showed that copy neutral loss of heterozygosity (CN-LOH) was a significant prognostic factor for poor overall survival.
Conclusion: Collectively, our results indicate that there are a wide variety of genomic mutations in IDH-wt GBMs, providing a basis for identifying potential chromosomal mutations that may be significant for tumor progression and potential therapeutic effects.

Keywords: isocitrate dehydrogenase mutations, IDH-wildtype, glioblastoma, WHO grade IV glioma, genomic mutations, prognostic factors, overall survival, progression-free survival

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Introduction and Background

Introduction to Gliomas

Gliomas are one of the most common types of brain tumors in the central nervous system (CNS), representing approximately 30% of all brain tumors [1]. These tumors are made from different types of glial cells, and are categorized based on their histologic features, which are analyzed through microscopic examination. Different types of glial cells such as astrocytes, ependymal cells, and oligodendrocytes form into gliomas called astrocytomas, ependymomas, and oligodendrogliomas, respectively, and their classification can help predict how the tumor will behave over time and what treatments are most likely to succeed [2,3].

Histologic features including nuclear atypia, cellularity, mitotic activity, and necrosis are identified by examining the tumor tissue cells and can help organize gliomas into different levels of malignancy based on the World Health Organization (WHO) grade system [2]. These gliomas are graded from I - IV based on their pathological features and their predicted clinical behavior. Grade I gliomas are usually benign and non-infiltrative (i.e pilocytic astrocytomas). Low-grade gliomas (grades II) are generally associated with slow growth and long term survival, while grades III and IV are associated with fast growth, malignancy, and short term survival [4]. Grade IV gliomas are considered the most rapidly growing, invasive, and angiogenic tumors, and are typically called glioblastomas [4].

Recently, studies have shown that integrating genomic findings of gliomas can be an important predictor for prognostic factors and potential treatment therapies [5,6]. This factor is especially true for diffuse infiltrating gliomas, which are characterized by their extensive growth of tumor cells into the neuropil, a dense network of neurons and glial cells in the central nervous system [7]. Diffuse infiltrating gliomas account for more than 80% of primary malignant

gliomas, and are usually difficult to treat due to their heterogeneity [5]. Thus, improving glioma classification has become a significant area of interest, especially for high-grade gliomas.

Specifically, Grade IV astrocytomas, or glioblastoma multiforme (GBM), are known as the most aggressive diffuse infiltrating glioma due to their malignancy and poor prognosis [8]. Patients with GBM typically have a median survival rate of 10-12 months with treatment, and less than 5% of patients survive 5 years following their initial diagnosis [8]. GBM is one of the most common types of malignant brain tumor, accounting for 16% of all primary CNS brain tumors, and 45.2% of malignancy in these tumors [9]. Typical symptoms include seizures, headaches, aphasia, motor weakness, and blurred vision [10]. Based on their regions, frontal lobe lesions are usually associated with motor deficits or personality changes, parietal lobe lesions are frequently associated with sensation loss, temporal lobe lesions are typically associated with seizures, occipital lobe lesions are correlated with vision, and cerebellar lesions are usually involved with coordination problems. Moreover, lesions in the thalamus and brainstem can be associated with all of the above symptoms. The standard forms of treatment for patients with newly diagnosed GBMs include surgical resection, radiotherapy, and chemotherapy [11] (see Figure 1). Studies have shown that maximal resection is the most beneficial for a patient's prognosis compared to biopsy or no surgery [12]. Additionally, patients are normally treated with a combination of radiotherapy and concomitant temozolomide, a type of chemotherapy, followed by cycles of adjuvant chemotherapy to help suppress secondary tumor formation after surgery [13].

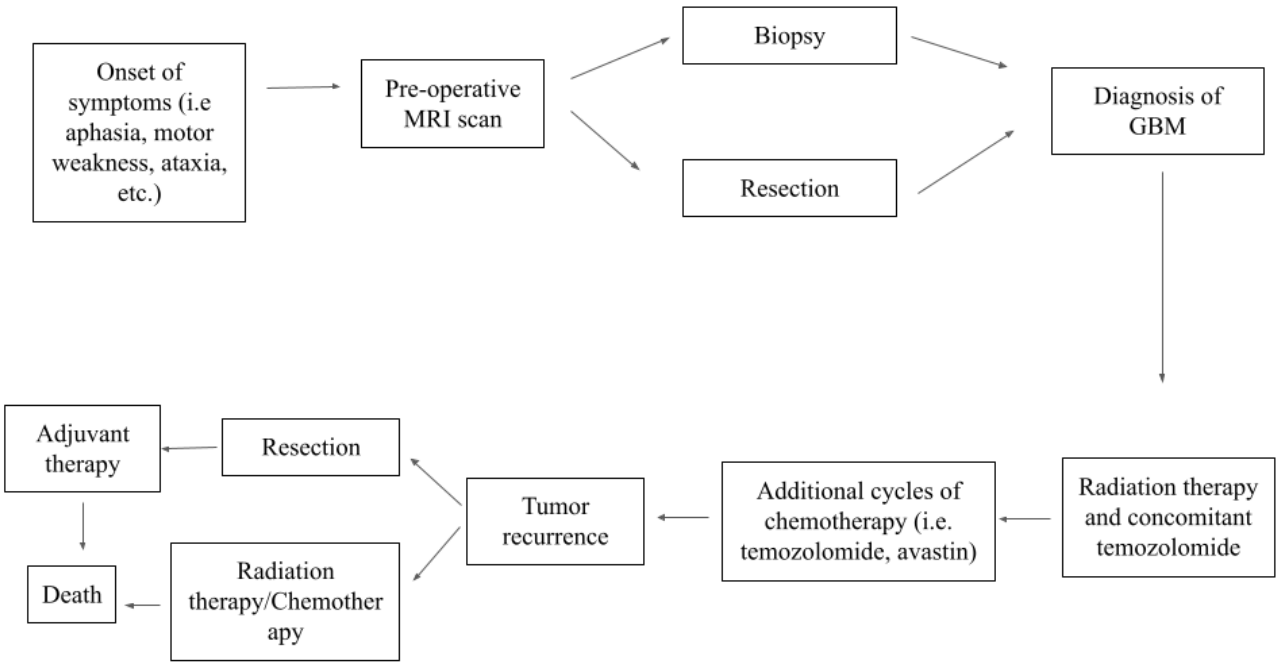


Figure 1. Standard course of treatment for GBM patients following initial onset of symptoms

Although research has shown radiotherapy and chemotherapy to have a statistically significant survival benefit, their efficacy is still somewhat limited due to GBM's resistance to conventional treatment, the spread of malignancy to adjacent brain tissue, and challenges with drug delivery [14-16]. Furthermore, patients' free and overall survival can vary greatly on an individual basis, which makes it difficult to assess treatment options [17]. Previous studies have identified clinical prognostic factors based on age, functional status defined by the Karnofsky Performance Scale (KPS), extent of resection, and use of corticosteroids to help predict the survival of patients [17-20]. Of note, patients with a younger age, higher KPS score, and gross total resection have been associated with better prognosis, while use of corticosteroids has been associated with poorer prognosis [18]. While these clinical factors can characterize GBMs broadly, there is still a paucity surrounding the genomic factors of GBM, and how they are

related to tumorigenesis. Additionally, there is currently no standard care of treatment for GBMs following tumor recurrence [11]. Thus, the ability to identify genetic mutations specific to GBM can allow for further classification of subtypes and can be beneficial for better understanding of the etiology and potential treatment options for GBMs [21-23].

Classification of Glioblastomas

Traditionally, GBMs have been categorized based on their clinical features into either primary or secondary subtypes [24]. GBMs that fall under the primary subtype category are called de novo primary tumors, which means that the first occurrence of brain cancer emerges as Grade IV GBMs at the time of initial diagnosis. Contrastingly, secondary GBMS generally progress from lower grade astrocytomas such as diffuse astrocytomas or anaplastic astrocytomas, and are often less aggressive than primary GBMs [24]. Although these two subtypes are morphologically indistinguishable, they are associated with distinct genetic differences [25]. As a result, researchers have been exploring alternative methods to categorize GBMs that rely more heavily on genetics instead of histopathology [26].

Currently, one of most important forms of distinction between primary vs secondary glioblastomas is using isocitrate dehydrogenase (IDH) mutations, which greatly affect the growth pattern and behavior of GBMs [27, 28]. IDH-wildtype (wt) GBMs are categorized as primary GBMs for their de novo status, and account for around 90% of GBMs, while IDH mutant GBMs are categorized as secondary GBMs [24]. IDH is an enzyme in the Krebs cycle that catalyzes the oxidation reaction of isocitrate into alpha-ketoglutarate, and plays a large role in metabolism, lipid synthesis, and homeostasis [29]. Studies have proposed that when IDH is mutated in the tumor cells, it causes an increase of oxidative metabolism in the Krebs cycle and suppresses reductive glutamine metabolism [30] (see Figure 2). As a result, IDH-mutant cells are thought to

substantially reprogram cellular metabolism, leading to a slower growing glioma that is less aggressive [31]. Comparatively, IDH-wt cells have no major effects on cellular metabolism or tumorigenesis, and thus are more aggressive in nature [32]. IDH mutations have become a significant area of interest due to the fact that IDH mutant GBMs are associated with better prognosis, and longer survival (2-4 years), and IDH-wt GBMs are associated with poor prognosis and shorter survival (9-15 months) [33, 34]. Consequently, the exploration of mutations in genetic coding for IDH enzymes has greatly influenced the process of identification in GBMs, as well as other types of gliomas [35, 36].

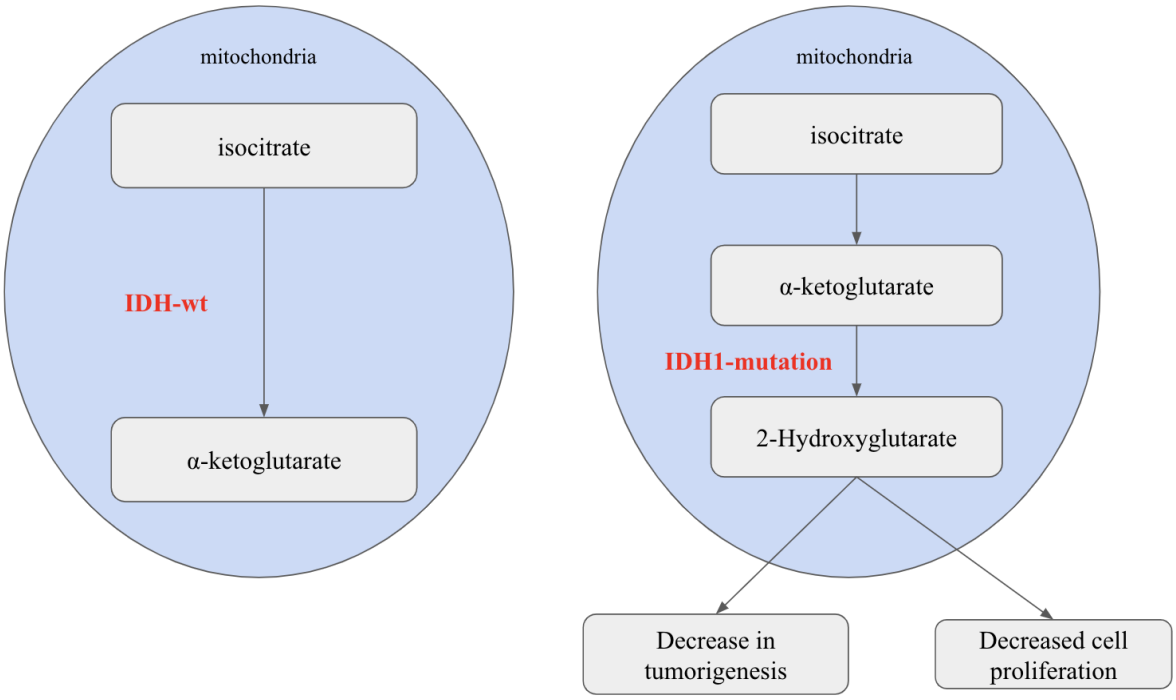


Figure 2. Signaling pathway for IDH-wildtype vs IDH1-mutation in the mitochondria

Other than IDH mutation status, O6-methylguanine-DNA-methyltransferase (MGMT) promoter methylation and telomerase reverse transcriptase (TERT) mutations are the only other known significant prognostic markers associated with GBM patient outcomes [37]. MGMT is an enzyme that repairs damaged O(6)-alkylguanine DNA, and when the gene promoter is

methylated, it represses gene transcription [38]. Studies have identified hypermethylation of the MGMT gene as a key predictive marker of a favorable prognosis in GBM [39]. Patients with a positive result for MGMT-methylation were correlated with a longer overall survival (22.5 months) compared to patients with unmethylated MGMT promoter (14.4 months) [40]. MGMT-promoter methylation has also been correlated with a significant survival benefit in patients treated with radiation therapy plus temozolomide [41, 42]. TERT is a gene located on chromosome 5p and encodes for the enzyme telomerase, which plays an important role in apoptosis, or cell death [43]. TERT gene promoter (pTERT) mutations are an essential feature of tumorigenesis, occurring in approximately 69% of GBMs, and are associated with poorer prognosis of GBM [44]. The classification of GBMs based on these molecular alterations suggests that molecular profiling is beneficial for identifying prognostic factors that can be used for potential treatment options, progression-free survival, and overall survival.

Research has shown that gene expression-based molecular classification can help establish a correlation between certain genomic features of GBMs. One study used unsupervised hierarchical cluster analysis to identify four molecular subtypes of GBMs, the proneural, classical, mesenchymal, and neural subtypes [45]. Associations between IDH mutation, tumor protein 53 (TP53) mutation, and platelet-derived growth factor receptor (PDGFRA) amplification were organized into the proneural subtype, epidermal growth factor receptor (EGFR) amplification and loss of Phosphatase and TENsin homolog deleted on chromosome 10 (PTEN) were organized into the classical subtype, and NF1 mutation and loss of TP53 and cyclin-dependent kinase inhibitor 2A (CDKN2A) were organized into the mesenchymal subtype. The neural subtype had some elevated levels of neural markers, but there were no unique distinguishing molecular features identified. Verhaak et al. found that the classical subtype was

shown to be more responsive towards aggressive treatment than other subtypes, suggesting that molecular classification could help predict future treatment options. However, the correlation between these molecular features of GBM, progression-free survival, and overall survival has not yet been addressed.

Sub-stratification of IDH-wt GBMs

Despite the exploration on the molecular features of GBMs overall, it is important to further characterize the genomic markers of IDH-wt GBMs specifically, due to their heterogeneity, aggressiveness, and short-term survival compared to IDH-mutant GBMs [46, 47]. Some studies have correlated IDH-wt gliomas with several different types of genomic mutations that directly relate to a patient's prognosis [48, 49]. Broadly, genomic alterations with better prognosis of IDH-wt GBM included mutations in PI3K class I genes [50], co-gain of chromosomes 19 and 20 (19+/20+) [51], and decreased expression of several different genes [48]. Some studies have suggested that mutations in TP53 [50], PTEN loss [52], and EGFR amplification may be correlated with worse outcomes in IDH-wt GBM [53]. Furthermore, the combination of certain genomics has also been indicated as beneficial for potential treatment options. For example, hTERT mutation status alone showed no significant correlation with IDH-wt GBM risk [54, 55]. However, when high hTERT expression was combined with MGMT promoter methylation and standard chemoradiotherapy treatment, it allowed for a median overall survival of 17.8 months versus 13.9 months from patients with unmethylated MGMT [56]. These studies show that not only can molecular subtyping be beneficial towards better understanding of IDH-wt GBM progression, but it can also help identify future therapeutic strategies. Due to the molecular heterogeneity and anatomical diversity of IDH-wt GBMS, further studies are necessary to validate these findings. Thus, implementing a large-scale analysis

of genomic factors of IDH-wt GBMs is imperative to properly evaluate prognostic factors and treatment options collectively.

Recently, studies have inferred that copy number variations may play an important role in better characterizing tumor behavior in high grade gliomas [57-59]. Copy number variations (CNVs) are alterations of a single base pair that change the structure of a genome, and commonly results in genetic variation [60]. They have been highly correlated to differential gene expression in multiple types of cancer [61]. Additionally, CNV burden has been associated with tumor recurrence and death in some cancers such as prostate cancer and colerectal cancer [62-63]. There have been some genetic characteristics associated with IDH-wt GBM including a combination of chromosome 7 gains and chromosome 10 losses and chromosome 1p/19q codeletion, but their relevance to prognosis has not been directly evaluated [64, 65]. Thus, the ability to characterize specific copy number variations relevant to prognostic factors of IDH-wt GBMs can help clarify the heterogeneity of this population and identify pertinent genetic mutations for further analysis [66].

Significance of Study

IDH-wt GBMs account for a majority of GBMs and constitute a large portion of primary CNS tumors, making it one of the most common malignant brain tumors, as well as one of the most aggressive [9, 25]. Thus, there is an urgent need to better define treatment options for this diverse population. The efficacy of treatments directed towards IDH-wt GBMs is not well-documented, and there are only a few studies implicating specific genomic factors with the immunological benefits of certain clinical trials [67]. Moreover, research has suggested that genomics play an essential role in the etiology of GBMs [68, 69]. Other types of gliomas, such as IDH-wt anaplastic astrocytomas, often show similar genetic abnormalities to those of

glioblastomas, which may indicate that these gliomas may actually represent early or undersampled glioblastomas rather than anaplastic astrocytomas [51]. Therefore, if the molecular heterogeneity of IDH-wt GBMS can be characterized broadly, it can potentially lead to a better understanding of the signaling pathways involved in this debilitating disease, and how to identify potential treatment options, especially following recurrence [70].

Of note, the genetic factors of IDH-wt GBMS are currently identified by studying tumor tissue obtained from biopsies or surgical resection, which are both invasive techniques [71]. Neuropathologists generally perform a series of molecular tests on genomic DNA isolated from formalin-fixed paraffin-embedded (FFPE) tissue including single-nucleotide polymorphisms SNP Copy Number (SNP-CN) array analysis, Fluorescence in situ hybridization (FISH) tests, and SNaPshot assay to determine the mutational status of multiple genes in brain tumors.

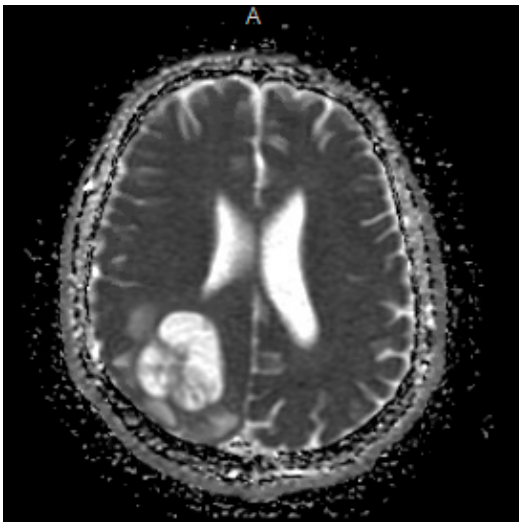
Recently, however, studies have been shown to correlate genomic factors with tumor subtypes based on the magnetic resonance imaging through radiogenomic analysis [72-74]. Not only have these studies found to differentiate between IDH mutant and IDH-wt GBM, but they have also been able to achieve accuracy with moderate to high success ranging from 66%-88% of detectability [75,76]. The use of convoluted neural networks to create machine learning algorithms for MRI is a primarily novel field, with radiological challenges involving the MRI's ability to identify subtle differences within a GBM group. Thus, creating a large-scale database that identifies genomics relevant to IDH-wt GBMs can be beneficial not only for evaluating prognostic factors, but for capturing specificities within IDH-wt GBMs for analysis with MRI in the future.

IDH-wt GBM Study Aims

As a result of the novelty surrounding genomic variables associated with IDH-wt GBM and the recent exploration into MRI machine learning technologies, this thesis has two primary aims. The first aim is to identify and categorize specific genomic variations of IDH-wt GBMs that lead to restricted tumor growth as well as a longer free and overall survival. The second aim is to create a multi-faceted database consisting of genomic, surgical, and clinical data of patients for future radiogenomic analysis.

Clinical Study Presentation of IDH-wt GBM

Here, we present a case study of a patient with a typical IDH-wt GBM that went through the standard treatment of surgical resection followed by radiotherapy and chemotherapy. This was a 57 year old male with no significant past medical history who was sent to the emergency department by an ophthalmologist due to his poor left eye vision. A computerized tomography (CT) scan of his head revealed a right fronto-parietal lesion, and the patient was referred to neurosurgery for outpatient followup. The patient had an MRI that revealed a large enhancing cystic lesion (see Figure 3) which was consistent with a high grade glioma.

A. 

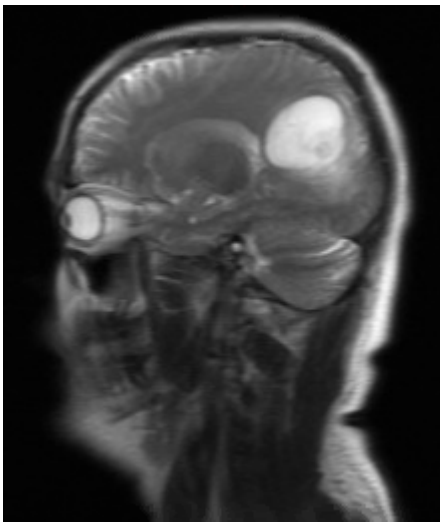
B. 

Figure 3. MRI scans; Figure 3A. axial view and Figure 3B. sagittal view shows the patient's right parietal lobe GBM tumor before surgical operation

Once the mass was identified through imaging, neurosurgery recommended surgical intervention, and the post-surgical risks were discussed including cerebrospinal fluid leak, infection, seizures, stroke, debility, the need for reoperation, and the strong possibility for future radiation therapy and chemotherapy. The patient elected to schedule a surgical resection of his right fronto-parietal glioma, and subsequently underwent a right parietal craniotomy for resection with maximal surgical resection achieved. He also had a Jackson Pratt drain placed, which is used to help prevent the collection of fluid near the incision site after surgery. During his operation, there were no complications that occurred. After his surgery, he was moved to the postoperative recovery unit and was discharged home after 2 days with no postoperative complications and a KPS score of 90. His postoperative MRI showed gross total resection (see Figure 4).

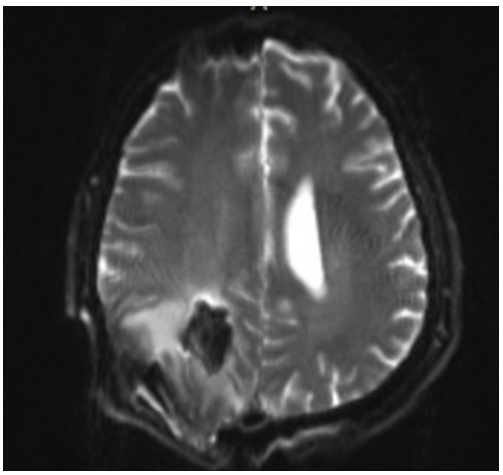
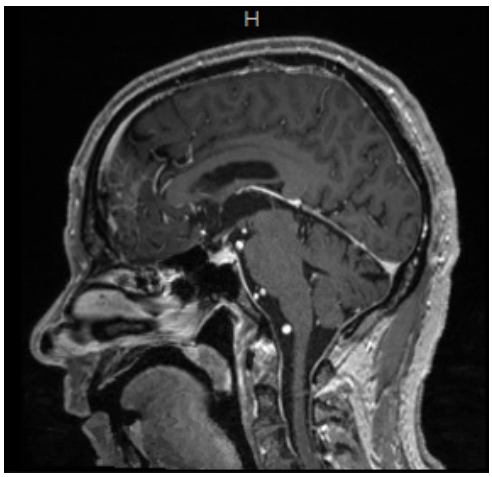
A.  **B.** 

Figure 4. MRI scans; Figure 4A. axial view and Figure 4B. sagittal view shows the patient's right parietal lobe GBM tumor after surgical operation

The anatomical pathology report on the patient reported his lesion as a WHO grade IV IDH-wt GBM. His histology slides showed palisading necrosis, intravascular thrombi and microvascular proliferation. His tumor also had molecular characteristics such as unmethylated MGMT promoter, PTEN loss, and homozygous loss of CDKN2A/B genes, which are common in IDH-wt GBMs and have both been indicated in poor prognosis in gliomas [77, 78].

Following the patient's operation, he started the standard treatment combination of fractionated radiation therapy and temodar. In total, he received 75 Gray (Gy, unit used to measure the total amount of radiation) in 30 fractions over 42 days. The patient tolerated the treatment well, and completed his course without any complications. He then started adjuvant temodar a couple months later to help lower the risk of tumor recurrence [79]. Six months after the patient's gross total resection and therapeutic treatment, his MRI showed signs of increased solid enhancement concerning for tumor progression, so he was started on adjuvant temodar and his steroid dosage was increased. However, the patient's status continued to decline more rapidly during 1 year following his surgery as he started experiencing fatigue and neurocognitive challenges. He passed away two years after his initial diagnosis.

Overall, the patient underwent all the treatment options available at this time for glioblastomas, and remained relatively stable for nearly a year until he started showing more severe signs of neurological deficits. Although he had some genetics associated with poorer prognosis such as PTEN loss and homozygous loss of CDKN2A/B, he also underwent gross total resection, and received both radiation therapy and chemotherapy. Thus, it can be inferred that both clinical and genomic factors are necessary for evaluating GBM survival, and should be studied in correlation to one another.

Methods:

Study design:

This study involves a multi-site retrospective analysis of patients diagnosed with IDH-wt GBMs across Emory University Hospital, Emory University Hospital Midtown, Emory Saint Joseph's Hospital, and Grady Memorial Hospital between 2014 and 2021. Out of a database of over 1000 patients with International Classification of Diseases (ICD) codes relating to GBMs, patients with the IDH-wt GBM diagnosis were identified and screened for analysis. These patients were collected from the CTORE database, a multi-disciplinary, neuro-oncology team focused on collecting patient outcomes for CNS tumors treated at the participating Emory sites. There were 204 eligible patients that were included in our study. Criteria included a diagnosis of IDH-wt GBM, defined as IDH negative status, and extensive pathological workup done. All experimentation was done in compliance with the guidelines set by the institutional review board (IRB) at Emory University under the CNS tumor registry at Emory (CTORE: IRB00117860) to ensure integrity of this project. The study was approved by the institutional review board (IRB) under protocol #00117860 at Emory University, and an informed consent waiver was obtained from the patient.

Data collection:

The CTORE team created a REDCap database from a previous study for IDH-mutant GBM that was adapted for IDH-wt GBM data collection. New instruments including a more detailed description of tumor progression data was also created to evaluate potential treatment options following recurrence. All IDH-wt GBMs included demographic, histopathological, clinical, and genomic evaluation. Variables such as gender, age, race, pathology, WHO grade, adjuvant therapy treatments, MGMT methylation status, and other standard microarray analysis

were evaluated and collected in REDCap. Patient data was obtained through the Emory Medical Record (EMR) system by analyzing a series of clinical information including operative notes, discharge summaries, pathology reports, and physician notes from specialties including neurosurgery, radiation oncology, neurology, and hematology/oncology. Pathology results were documented by neuropathologists at Emory and consolidated into an anatomic pathology report. IDH-wt status was confirmed by performing immunohistochemistry on tumor cells. Other genetic factors such as ATRX, P53, and MGMT methylation were also performed in line with the recommended diagnostic criteria for diffuse astrocytic gliomas. Microarray SNP-CN analysis was performed to detect copy number abnormalities for each patient. This test was performed using an oncoscan platform (Thermo Fisher Scientific OncoScan FFPE Assay Kit) [80] to query over 200,000 genetic markers across the human genome. Relevant factors included copy number abnormalities, gene deletion, gene amplification, and copy neutral loss of heterozygosity, which were all documented through REDCap. A Snapshot Cancer mutation panel was also used to assess the mutation status of multiple genes that have been implicated in a variety of cancer types. This test was performed using a PCR-based assay to identify 44 different mutations. Mutations including AKT1, BRAF, EGFR, KRAS, MEK1, NRAS, PIK3CA, and PTEN were detected as the specific point mutations pertinent to the test design [81]. The assistance of other study personnel from CTORE was enlisted for data collection and analysis purposes.

Once all the data was collected within the REDCap database, the last follow up date of the patients was reviewed to see who had not continued their care within the Emory Healthcare system prior to 2022. For patients without a clear follow up status, their contact information from the EMR database was utilized to call the patients' listed phone numbers. The patients were

contacted to assess their survival status, and the relevant information was inputted on REDCap to ensure that the database included the most updated information.

Statistical analysis:

After all the necessary data was collected, descriptive statistics, univariate, and multivariate analysis on JMP, a statistical analysis software program. The primary aims were to evaluate for genomic factors correlated to progression-free survival (PFS), and overall survival (OS). Clinical factors including surgical data, pre-operative complications, radiation therapy, and chemotherapy were also briefly evaluated. Univariate and multivariate analyses were performed using the Cox proportional-hazards model, which is a regression model typically used to investigate the relationship between predictive factors and patient survival, and is commonly used to assess the prognostic impact of glioblastomas [82]. Multivariate analysis was conducted using the backwards selection model. This variable selection method involved removing the least significant variable step by step until no non-significant variables remained. An alpha of 0.2 was used as the cutoff for removal when selecting variables for multivariate analysis. Due to the medical nature of the study, a greater value of alpha was used to minimize the risk of having a false negative, or Type II error, resulting in the assumption that the patient does not have glioblastoma, when they actually do [83]. These tests aimed to determine if there were any significant clinical or genomic markers related to PFS and OS. Hazard ratios (HR) were used to determine the relative risk of the patient populations' survival outcome by comparing the likelihood of an event occurring vs not occurring (i.e. the proportion of having a mutated gene vs wild-type gene) [84]. Once all of the covariates were analyzed, further testing was done on whole chromosomes to see how generalizable our findings could be compared to just one chromosome arm. Additionally, chromosome 7 gain/chromosome 10 loss and co-gain of

chromosome 19 and 20 were analyzed to determine their prognostic significance in relation to previous literature [51, 64]. Kaplan-meier curves were also generated to visualize the clinical course of patients' over time and compare the differences of patient outcome for extent of resection (EOR), PFS and OS. These curves model a non-linear survival probability over time while accounting for censored data (defined as patients with no date of death). Due to the nature of the censored data, this type of curve is able to account for all pertinent patient data without overestimating the survivor probability, thus eliminating the factor of survivor bias. As such, Kaplan-Meier (KM) curves are a useful predictor for visualizing the time it takes for an event of interest to occur (i.e. overall survival) [85].

Results

Descriptive Statistics

We collected clinical and genomic information from 204 patients with a pathological diagnosis of IDH-wt glioblastoma. These patients were evaluated from December 2013 to March 2022. Demographic factors are listed under Table 1. Within our cohort, a majority of the patients were male (57.8%) and Caucasian (81.4%). Additionally, the most common tumor locations were in the frontal (30.4%) and temporal (28.9%) lobes. Table 2 summarizes the treatment data and outcomes of patients. The most frequent type of surgery the patients received were craniotomies for resection (67.2%), with a majority of our patients receiving subtotal resection (45.6%). Additionally, most of the patients' received adjuvant therapy following surgery in the forms of fractionated radiation therapy (41.2%) and temozolomide (50%). 29.4% of patients were listed under the "other" category due to limitations in obtaining follow-up data after surgery. Most of these patients received their adjuvant therapy at an outside hospital or facility,

usually due to their long distance from the Emory Healthcare system as noted in the patients' charts. During the course of patient treatment and follow up, 75 patients had tumor recurrence, and 85 patients died.

Table 3 describes the treatment patients received following tumor progression (n=75). The most significant variables included avastin/bevacizumab given (46.7%) and radiation therapy given (17.3%). Similarly to Table 2, a majority of patients with recurrence that also underwent surgery had sub-total resection (14.6%).

In Table 4, the genomic factors of this study were briefly characterized. At least one genetic mutation was observed in all of the patients. The most frequent mutations included CDK2NA/B deletion (57.8%), PTEN loss (45.1%), and EGFR amplification (36.8%). Additionally, the mean for copy number variations (CNVs) was approximately 16, with a standard deviation of 7.6.

Evaluating Kaplan-meier curves for the patient cohort

To examine the overall survival of our cohort, KM curves were created to provide a comprehensive look at our patient population. Figure 6 demonstrates the overall survival of the patients, where a majority of the patients seem to survive between 1-2 years. The prognostic impact of the extent of resection was also evaluated (Figure 7). KM curves estimates of OS showed biopsy having a significantly shorter survival compared to subtotal resection (STR) and gross total resection (GTR). While there is some overlap between the survival estimates of STR and GTR, cases of GTR are still more significant for survival than STR and biopsy. Figure 8 broadly characterizes progression-free survival in relation to the whole cohort, showing a sharp decline in PFS following the first year.

Clinical Predictors of Overall Survival

Among the 204 patients in our cohort, there were several clinical factors significant for predicting OS in both our univariate and multivariate analysis. Within our univariate analysis (Table 5), age was correlated with poor prognosis for OS with a HR of 1.04 (CI: 1.02-1.06, *P<0.001*). KPS, fractionated radiation, other types of radiation, temozolomide given, avastin, GTR and STR (0.10<HR<0.97, 95% CI, *P<0.05*) were all associated with better prognosis for OS. Comparatively, the multivariate analysis (Table 6) showed again that age (HR=1.02, 95% CI, 1.00-1.05, *P=0.039*) was correlated with a poor prognosis when accounting for the other covariates. Moreover, fractionated radiation, other radiation, avastin given, GTR, and STR (0.08<HR<0.52, 95% CI, *P<0.05*) were also associated with better OS in the multivariate analysis. In the cohort of patients with recurrence (n=75), univariate analysis of OS for adjuvant therapy after recurrence was conducted, and there were no significant factors leading to better or worse outcome (Table 7).

Clinical Predictors of Progression-Free survival

When comparing the univariate analysis for OS and PFS, they both had KPS and GTR (0.51<HR<0.97, 95% CI, *P<0.05*) as a significant factor for a lower chance of recurrence (Table 8). For treatment following recurrence, PFS was not evaluated because PFS mostly aims to look at factors leading up to tumor recurrence.

Genomic Predictors of Overall Survival

The statistical analysis of the genomics was broken down into three sections. The first section evaluated common cancer genetic markers pertinent to the study (Table 9). In this section, 1p/19q co-deletion (HR=0.45, 95% CI, 0.22-0.92, *P=0.03*) was reported as the only significant factor with a better prognosis. No covariates were indicated for poor OS outcome.

Since there was only one significant factor for the univariate analysis of genetic markers for OS, no multivariate analysis was conducted.

The second section evaluated the total number of CNVs gained, CNVs lost, copy neutral loss of heterozygosity (CN-LOH), and mutations in chromosome arm regions. Overall in the univariate analysis (Table 10), CN-LOH was reported as a significant factor of poor OS (HR=1.04, 95% CI, 1.01-1.08, *P=0.014*). Specifically, chromosomes 2p CN-LOH, 2q CN-LOH, 3p CN-LOH, 4p CN-LOH, 4q CN-LOH, 5q CN-LOH, 7q CN-LOH, 12p CN-LOH, 13q CN-LOH, 14q CN-LOH, 18p CN-LOH, and 22q CN-LOH (2.46<HR<4.93, 95% CI, *P<0.05*) were all indicated as significant mutations that were associated with poor prognosis for OS. Additional chromosomal mutations correlated with poor prognosis included 5p loss, 9q gain, 13q loss, 16p loss, 17p loss, 18q gain, and 22q loss (1.61<HR<2.38, 95% CI, *P<0.05*). The only chromosomal mutation that was significant as a predictive factor for better OS was 10q loss (HR=0.52, 95% CI, 0.30-0.92, *P=0.04*). In the multivariate analysis of these biomarkers (Table 11), 10q loss was reported as a significant factor for better prognosis for OS (HR=0.38, 95% CI, 0.20-0.72, *P=0.003*). Interestingly, overall CN-LOH was also recorded as a favorable prognostic factor (HR=0.87, 95% CI, 0.0378-0.97, *P=0.011*). Comparatively, 3p CN-LOH, 5p loss, 5q CN-LOH, 7q CN-LOH, 9q gain, 14q CN-LOH, 16p loss, and 18p loss were all associated with poor prognosis (1.90<HR<11.54, 95% CI, *P<0.05*).

The third section analyzed these biomarkers on a broader scale, looking at whole chromosome gain/loss/CN-LOH to better assess how these genomics could be possibly characterized. Potential prognostic biomarkers stated in previous literature including chromosome 19 gain/20 gain and chromosome 7 gain/10 loss were also evaluated [47, 48]. The univariate analysis (Table 12) reported no significant covariates for better prognosis. However,

whole chromosome CN-LOH in chromosomes 2, 3, 16, 17, and 18 (2.11<HR<5.53, 95% CI, *P<0.05*) were noted as significant factors for poorer OS outcomes. Other whole chromosome mutations correlated with poor prognosis included whole chromosome 9 gain, 12 gain, and 18 loss (1.88<HR<2.11, 95% CI, *P<0.05*). There was no significance indicated in any whole chromosome or chromosome arm combinations of chromosome 19 gain/20 gain and chromosome 7 gain/10 loss in this section. Of note, there were also no whole chromosome mutations for chromosomes 13, 14, and 15. In the multivariate analysis (Table 13), whole chromosomes 9 gain, 12 gain, and 18 CN-LOH (1.85<HR<4.78, 95% CI, *P<0.05*) were highlighted as significant prognosis factors for poor OS outcome.

Genomic Predictors of Progression-Free survival

Similarly to the OS univariate and multivariate analysis, statistical data on PFS was separated into three components including established genetic markers, chromosome arm mutations, and whole chromosome mutations/potential predictors. In the univariate analysis of the first set of mutational markers, there were no pertinent factors identified (Table 14).

In the second category, univariate analysis (Table 15) showed that 1q loss and 10q loss (0.41<HR<0.44, 95% CI, *P<0.05*) were correlated with longer PFS. Contrastingly, 11p loss, 17p loss, 17q loss, and 18q gain (1.77<HR<4.38, 95% CI, *P<0.05*) were associated with short PFS. Multivariate analysis (Table 16) reported parallel results, identifying 1q loss and 10q loss (0.35<HR<0.41, 95% CI, *P<0.05*) as pertinent covariates of longer PFS, and 11p loss, 17p loss, 17q loss, and 18q gain (1.66<HR<3.87, 95% CI, *P<0.05*) as covariates of shorter PFS. Notably, 10q loss was also correlated with better outcome for OS in both univariate and multivariate analyses.

Lastly, for the third category, univariate analysis (Table 17) showed that whole chromosome 1 loss and 7q+/10q- (0.30<HR<0.60, 95% CI, *P<0.05*) was associated with a lower chance of recurrence, and whole chromosome 18 gain (HR=4.19, 95% CI, 1.49-11.81, *P=0.007*) was associated with a greater chance of recurrence. Similarly to the whole chromosomal analysis for OS, there were no whole chromosome mutations for chromosome 13-15. For the multivariate analysis (Table 18), whole chromosome 1 loss and 7q+/10q- (0.22<HR<0.49, 95% CI, *P<0.05*) were significant for longer PFS, and whole chromosome 18 gain (HR=7.00, 95% CI, 2.42-20.30, *P<0.001*) was significant for shorter PFS. *These results are preliminary in nature and additional studies are underway to further qualify our data.*

Discussion

Over the last decade, IDH mutations have become a widely accepted feature for identifying gliomas, and one of the distinct ways to categorize glioblastomas into primary vs secondary GBMs. Clinically, IDH-wt GBMs are known to have a worse prognosis compared to IDH-mutant GBMs, with shorter overall survival times and poorer response to treatment. However, the genomic landscape of IDH-wt GBMs remains relatively uncharacterized. This study explores potential molecular markers of IDH-wt GBMs that can be used for further stratification. Although there have been some mutations commonly correlated with IDH-wt GBMs, their prognostic capabilities are still largely variable due to the heterogeneity of this population. Thus, our study attempts to identify the potential biomarkers of IDH-wt GBMs to see if they may have any implications for patient outcomes.

Descriptive overview of IDH-wt GBM

The descriptive statistics (Tables 1-4) for this study were collected through our REDCap database under separate instruments for demographic, surgical, and pathological data. These variables were then evaluated statistically using JMP. Our study has shown that many of the descriptive characteristics typically found in IDH-wt GBM are also present in our patient cohort [9,22]. The majority of patients in our study were male and white (Table 1) with a mean age of 63.9, and most of the tumor lesions were located in the frontal and temporal lobe. Additionally, a majority of our patients received surgical intervention, radiation therapy, and chemotherapy, which is the standard form of treatment for GBM patients [12, 13]. Genomically, incidence of GBM was higher in patients with CDK2NA/B deletion, PTEN loss, and EGFR amplification, which is also commonly seen in other studies [48, 52].

When looking at our cohort overall using the KM curve for OS and PFS, we observed survival predictions that closely match other KM curves done for IDH-wt GBMs for OS and PFS [86, 87]. Additionally, the KM curve examining the correlation between extent of resection and OS followed the general trend that maximal extent of resection is beneficial for patient outcomes [12]. Thus, we can infer that our patient population is generally in alignment with the majority of IDH-wt GBM cases evaluated, and follows the typical trend of treatment options available at this time.

Clinical predictors of IDH-wt GBM for overall survival and progression-free survival

We first evaluated the clinical factors of our cohort including general and adjuvant therapy predictors by conducting univariate and multivariate analysis using the relevant variables. For overall survival, the statistically significant factors in the univariate analysis (Table 5) included age, KPS score, radiation therapy, temozolomide, and extent of resection. Additionally, the multivariate analysis for OS (Table 6) showed that fractionated radiation,

avastin, and extent of resection suggests that there may be a relationship between these features. For progression-free survival (Table 8), KPS score and gross total resection were the clinical factors significantly correlated with a longer PFS. These results corresponded to both PFS and OS in the ways that we expected and were all in alignment with previous literature [18], further reinforcing the validity of our cohort in conjunction with other IDH-wt GBM populations.

Additionally, avastin, a common chemotherapy drug, was also listed as a significant factor for better patient outcome for OS. Avastin was also correlated with a lower HR in PFS (HR=0.66, 95% CI, (0.26-1.61, *P=0.348*) and OS after recurrence (Table 7, HR=0.65, 95% CI, 0.38-1.11, *P=0.113*), though our results were not statistically significant in those areas. Despite some areas of uncertainty surrounding the use of avastin (i.e. dosage, duration of treatment), there is data to support that this drug may be beneficial for both PFS and OS, as reported in our study. This notion is further supported by studies reporting that avastin treatment following recurrence can be beneficial for patients [88, 89]. However, these results only report the overall significance of avastin as a chemotherapy drug, and future trials to identify the optimal dosage and length of treatment should be assessed. We collected results regarding these factors in our initial data collection to be analyzed in future experiments. These experiments will evaluate the standardization of avastin and its relevance to biomarkers for patients that would benefit from such treatment.

Other clinical factors such as proton radiation given, clinical trial enrollment, and lomustine given did not produce any particularly significant results. This could be due to the small sample sizes of patients that received such treatments (n=2-8). Since our study is retrospective in nature, there was no methodical way to control for such factors. However, this

information may prove to be useful when examining the correlation between genomic markers and treatment options in the future.

Genomic predictors of IDH-wt GBM

The genomic landscape of this study was evaluated based on their univariate and multivariate analyses for OS and PFS. Variables included in this study were determined based on the genetic tests used by Emory neuropathologist for patients' anatomical pathology reports such as Snapshot mutation panels and Microarray SNP-CN analysis. Additionally, we evaluated genomic markers including 1p19q co-deletion, chromosome 19/20 gain, and chromosome 7 gain/chromosome 10 loss based on previous studies that have cited these mutations as potential molecular markers in GBM [51, 64, 65]. The present research was primarily focused on finding methods to broadly characterize these genomics due to the heterogeneity of the IDH-wt GBM population. Thus, the results reported are preliminary in nature, and should be treated as such.

Characterizing mutational markers for OS and PFS

In the first section for univariate analysis of OS of mutational markers (Table 9), 1p19q co-deletion was reported as the only factor for better patient outcome (n=16). This marker is typically associated with better prognosis in oligodendrogliomas that may be due its a lower acidity compared to intact gliomas [90]. 1p19q co-deletion is also reported to be more common in IDH-mutant GBMs compared to IDH-wildtype GBMs, but has lacked prognosis impact in the past due to the different types of tests and criteria for this biomarker within individual subtypes [91]. Our study suggests that for IDH-wt GBMs specifically, 1p19q co-deletion may result in a better prognosis. Based on the previous literature, this finding may be due to an oligodendroglial component within certain glioblastomas. However, further studies would need to be conducted in order to confirm this feature as a potential biomarker for better patient outcome.

PIK3CA mutation was also previously implicated as a potential prognostic factor for IDH-wt GBMs, as a part of the PI3K class I genes [50]. However, it was not reported to be statistically significant in our findings as a prognostic factor for better or worse outcome in the OS group (n=8, HR=0.97, 95% CI, 0.30-3.08, p=0.956) or for tumor recurrence the PFS group (n=8, HR=1.13, 95% CI, 0.41-3.10, *P=0.810*). Due to the small sample size and p-value of >0.05, we were not able to conclude anything about this finding. However, considering the potential this mutation has for better outcomes, additional validation for this gene may lead to a potential biomarker for IDH-wt GBM in the future.

Contrasting to previous literature on MGMT methylation as a favorable prognostic factor for GBMs [39], our study reported that there was no significance of this mutational marker on our IDH-wt GBM cohort for neither OS nor PFS. We theorize that there may be a few reasons for this finding. There are still some technical challenges with MGMT methylation testing that can lead to an "indeterminate" or "low level" result which may influence the predictive cutoff for what qualifies as an MGMT methylated GBM [92], and affect our interpretation for what counts as a MGMT methylated vs unmethylated result. Additionally, one study found that MGMT methylation in IDH-wt GBM was not associated with any histological features, suggesting that the favorable prognostic value of MGMT methylation may not be due to an inherently less aggressive tumor biology [92]. Together with our findings, these studies infer that although MGMT methylation is usually associated with a better prognosis in GBM patients overall, its genomic status may be variable depending on other factors such as treatment. In order to properly test this theory, further stratification methods within our statistical model would need to be taken to account for different therapeutic options.

Within the univariate analysis of OS and PFS for mutational markers, it is interesting to note that CDK2NA/B deletion, P53 overexpression, EGFR amplification and PTEN loss were not particularly significant for any prognostic factors or tumor recurrence. Although these markers have been implicated for poorer prognosis in other lower grade gliomas [93, 94, 53, 78], there was no clinical significance reported in our study. This contradicts our expectation that these three mutational markers would be associated with poorer prognosis in IDH-wt GBMs. We infer that this result may be due to the high heterogeneity of the GBM population that can reduce the reliability of the results. However, this research still has implications for future genomic analyses. As we continue to stratify for other clinical factors such as comorbidities and treatment options, we theorize that we may be able to further characterize the role of these mutational markers in IDH-wt GBM throughout the course of their treatment.

The role of other mutational markers such as ATRX, BRAF, and KRAS have not been widely studied for IDH-wt GBMs. Additionally, our statistical analyses did not result in any significant results for these specific mutations. Previous literature has shown ATRX and KRAS mutations to be indicated as potential malignancy markers, and BRAF mutations to be associated with improved overall survival in gliomas, but not IDH-wt GBMs specifically [95-97]. Thus, although we cannot rule out the potential of these markers as significant prognosis factors for IDH-wt GBMs, it can also be inferred that they may not be specific markers for this subset of tumors.

Characterizing Microarray data for OS

Overall, the microarray data collected for this study involved identifying chromosomal gains, losses, and CN-LOH for chromosomes 1-23, specifically for chromosome arms p (shorter arm) and q (longer arm). The results were quite variable among the OS and PFS cohort. Within

the univariate analysis for OS, there were several chromosomal mutations reported that were significantly correlated with worse prognosis that had CN-LOH including 2p, 2q, 3p, 4p, 4q, 5q, 7q, 12p, 13q, 14q, 18p, and 22q. Additionally, total CN-LOH was also significant for poorer prognosis for the univariate analysis of OS. Altogether, these results suggest that CN-LOH may hold prognostic value for characterizing IDH-wt GBM, and can be a potential marker for further exploration. CN-LOH describes the event where one of the two homologous chromosomal regions is lost, but there are still two identical copies of the particular region within the genome. Some studies have identified CN-LOH as a significant factor of malignancy primarily in myelodysplastic syndrome, or preleukemia, as well as synchronous colorectal cancer [98, 99]. In correlation with previous literature, our results suggest that CN-LOH may be correlated with unfavorable survival outcomes, and that this specific type of chromosomal mutation may provide some information on different IDH-wt GBM morphologies. Additionally, the multivariate analysis for OS of microarray data reported that CN-LOH of 3p, 5q, 7q, and 14q were all significantly correlated with poorer prognosis as well, indicating that there may be a combination of CN-LOH mutations that could serve as a potential biomarker for IDH-wt GBM. However, due to the small sample sizes for patients with CN-LOH (n=3-15), further studies will need to be conducted to assess the potential impact of this type of chromosomal mutation. Other significant results for poor OS outcomes of microarray data in the univariate analysis included 5p loss, 9q gain, 13q loss, 16p loss, 17p loss, 18q gain, and 22q loss. Some of these mutations have been implicated in previous studies. For example, 17p loss has been indicated as a potential biomarker for poor survival in pediatric medulloblastomas [100]. Additionally, 18q gain has been associated with increased aggression of metastases in prostate cancer [101]. However, these chromosomal mutations have not been widely studied or characterized enough. In the multivariate analysis for

OS, 5p loss, 9q gain, 16p loss, and 18p loss were all significantly correlated with poorer prognosis as well, and may hold some prognostic value in relation to one another. For the purposes of our studies, both significant and insignificant observations should be treated as exploratory findings. As such, further studies that include a genome-wide association study approach may be more beneficial for extricating specific genetic mutations from these chromosome arms that may be more pertinent for prognosis of IDH-wt GBMs.

Most notably, 10q loss was the only significant covariate associated with better prognosis in both the univariate and multivariate analysis of OS for microarray data. There are also a significant number of patients with this mutation (n=176). This finding is contradictory to previous literature which suggests that this chromosomal mutation is usually correlated with poorer prognosis [102]. However, one study noted that when this chromosomal mutation was evaluated in conjunction with age and temozolomide treatment, the effect of the genomic mutation was negated [103]. Thus, this particular chromosome mutation may benefit from further statistical analysis that is stratified for other clinical variables such as treatment effect or age.

Characterizing Microarray data for PFS

In the univariate and multivariate analysis of PFS for the microarray data, there was some overlap with the chromosomal mutations in the OS data. Of note, 17q loss and 18q gain were reported as significant factors correlated with a greater chance of tumor recurrence in the univariate and multivariate analysis. Additionally, 10q loss was also associated with better PFS in this cohort. These mutations were also listed as significant covariates in the multivariate analysis for PFS of microarray data. These correspondent results suggest that 17q loss, 18q gain, and 10q loss may play a role in the tumor progression of IDH-wt GBM, though supplementary

studies will need to be conducted to validate these results and characterize the inherent aggressiveness of tumor biology for these mutations.

Other significant findings for univariate analysis for PFS of the microarray data included associating 11p loss and 17p loss with greater chance of tumor progression and 1q loss with lower chance of tumor progression. 17p loss has been associated with poorer survival for medulloblastoma in previous studies, and may have implications for GBM that have a similar pathway as medulloblastoma [104]. Additionally, 1q loss has been correlated with positive response to chemotherapy treatment in a case report on GBM [105], suggesting that there may be significant implications for treatment options relating to this chromosomal mutation. For the multivariate analysis of PFS for the microarray data, in addition to 17q loss, 18q gain, and 10q loss as listed above, 11p loss and 1q loss were also indicated as significant results for recurrence outcome. Thus, it can be inferred that these mutations may play a role in tumorigenesis to some extent.

Characterizing whole chromosome mutations and potential biomarkers for OS

Similarly to the univariate and multivariate analyses of OS, there were multiple chromosomes with CN-LOH noted as a significant factor for poor prognosis. In the univariate analysis for OS, this included whole chromosome 2 CN-LOH, 3 CN-LOH, 16 CN-LOH, 17 CN-LOH, and 18 CN-LOH. When considering the heterogeneity of the GBM population, the variety of chromosomal CN-LOH between chromosome arms and whole chromosome mutations can suggest that there may be multiple subtypes within the IDH-wt GBM cohort that can be further stratified. However, the novelty of this study and lack of literature supporting these specific CN-LOHs for IDH-wt GBMs indicates that further studies need to be done to validate these findings before they can be used as prognostic factors.

Additional significant findings of the univariate analysis for this group included whole chromosome 9 gain, 12 gain, 16 loss, and 18 loss. When looking at the multivariate analysis, whole chromosome 9 gain, 12 gain, and 18 CN-LOH were all significant factors of poorer prognosis. Specifically, whole chromosome 18-CN-LOH is commonly found in multifocal ileal neuroendocrine tumors [106]. However, there is no literature supporting the prognosis impact of these whole chromosomal mutations for gliomas in general. Although there is not much previous literature to explain our findings, when accounting for the chromosome arm mutation findings in Tables 10 and 11 on the microarray data, it can provide some more specificity for which specific chromosomes may be worth evaluating for further patient outcome, such as chromosome 9 and 18.

Characterizing whole chromosome mutations and potential biomarkers for PFS

When comparing the microarray data for PFS (Tables 15, 16) with the whole chromosome mutations data (Tables 17, 18), there is overlap involving whole chromosome 1 loss and 18 gain. Specifically, whole chromosome 1 loss is associated with better outcome for PFS and whole chromosome 18 gain is associated with poorer outcome for PFS. Similarly to the results and literature for the previous microarray data, these results may suggest that these particular chromosomes are significant for tumor recurrence. Since 1q loss is associated with longer PFS and 1p/19q co-deletion has been correlated with better survival outcomes, the finding that whole chromosome 1 loss is significant for longer PFS may suggest that this chromosomal mutation has significant benefit for tumor suppression. However, due to the lack of literature available on the effects of whole chromosome 1 loss in the setting of cancer, further studies are necessary to validate this finding. Additionally, the marker for chromosome 7q gain/10q loss was associated with longer PFS in our findings. Contrastingly, the 7/10 signature has been previously

implicated in studies with IDH-wt astrocytoma as a marker for shorter PFS that can lead to a higher malignancy grade [107]. Although our results are contradictory to the previous literature, the relevance of this marker to GBM literature suggests that this biomarker has potential implications for further stratification of IDH-wt GBM. Thus, further studies correlating this marker to IDH-wt GBM survival outcomes are necessary to determine its relevance to tumor progression. Lastly, the significance of whole chromosome 18 gain has not been previously evaluated in the literature. However, in general, whole chromosome gains have been frequently observed as a genomic abnormality in tumors and is common in lympho-haematopoietic and embryonic neoplasms [108]. This outcome suggests that this mutation may be relevant to tumorigenesis, and can be evaluated in future experiments to clearly assess its prognostic impact. Whole chromosome 1 loss, 18 gain, and 7q gain/10q loss were also evaluated in the multivariate analyses and reported significant results, thus inferring that further statistical analyses with other clinical factors such as adjuvant therapy treatment may be relevant for assessing the effects of these genomic mutations on IDH-wt GBMs.

Ethical guidelines for the Study

This study is heavily focused on identifying the genomics related to IDH-wt GBMs, and utilizes information from a variety of genetic tests consolidated into an anatomical pathology report within patients' medical records. Due to the recent developments in research for genetic testing, it is necessary to address the legal and ethical implications of this study to minimize and justify the social impact that it may have. Some studies have brought up the concern for genetic discrimination, and how predictive genetic testing may decrease an individuals' rights related to healthcare insurance and employment [109]. Additional arguments have been brought up regarding privacy issues and disposition towards fetal and embryonic genetic screening [110].

Thus, limiting privacy risk was a primary goal to maintain the responsible conduct of research (RCR) of this study. In order to maintain patient confidentiality, the following steps were taken so that the disclosure of protected health information (PHI) would result in no more than minimal privacy risk to the participant:

- All data were stored behind the Emory firewall and in compliance with Emory's Data Security Policy
- Data were only accessible by researchers of the study that are CITI trained and approved by IRB
- Patient identifiers were not disclosed beyond study personnel except as required by law, or for authorized oversight of the study
- All data will be eradicated after the project is complete

To mitigate the risk of genetic discrimination, we also abide by the Genetic Information Nondiscrimination Act (GINA) which was created in 2008, and prevents employers and other third parties from requiring anyone entering a contract from disclosing genetic testing information [111].

All efforts were taken towards this study to protect patient confidentiality and promote inclusivity. Moreover, all experimentation was done in compliance with the guidelines set by the institutional review board (IRB) at Emory University under the CNS tumor registry at Emory (CTORE: IRB00117860) to ensure integrity of this project.

Limitations

There were some limitations of our current study. First, the retrospective nature of our study prevented us from evaluating some patients throughout the entire course of their treatment, which may affect the accuracy of the survival outcomes in the data collected. Although we tried

to account for this by calling patients for follow-up and censoring the data of these patients during our statistical analysis, our results may be limited due to poor follow-up with patients. Moreover, our single-institutional study collected patients using the data available to use through Emory, which may result in a convenience bias relative to the patient population within the Emory community. Thus, further studies including a stricter exclusion criteria for patient follow-up and randomized studies on a multi-institutional level can be done to optimize findings for IDH-wt GBM patients.

Additionally, the techniques we used to observe the genomic markers in our data is partially limited due to the current technological landscape available to us. Although the majority of mutational markers were most likely accounted for, we cannot say with certainty that all genomic mutations were detected through our testing methods. As technology advances, future studies that involve more precise techniques can more accurately identify specific genomic mutations that may be pertinent for survival outcomes of IDH-wt GBM patients.

Conclusion

Overall, our study demonstrates that there are multiple chromosomal mutations that may hold prognostic significance for IDH-wt GBM. For the mutational markers such as 1p/19q co-deletion and MGMT methylation, further studies are necessary to assess their relative patient outcomes to treatment options (i.e. extent of resection, radiation therapy, chemotherapy). For the microarray data, CN-LOH and 10q loss seem to be heavily correlated with our patient cohort, and may need to be further investigated to evaluate their significance as genomic markers. Additionally, some of the biomarkers indicated in this study were also pertinent in other gliomas such as oligodendrogliomas. This research has several implications that will require future

experimentation. Most notably, our comprehensive database on REDCap includes other clinical factors besides survival such as comorbidities, age, and treatment options that can all be evaluated with our current dataset. By further stratifying our data for potential confounding variables, we may be able to better understand the significance of our findings. Additionally, our database includes information on IDH-mutant GBMs with the same set of data collected that could be used in a comparative study to evaluate the OS and PFS of these two cohorts against each other. Finally, we hope to utilize the findings in our database for encoding purposes that can be used in conjunction with MRI to create a neural network that may potentially evaluate genomic factors such as IDH mutation from an imaging standpoint rather than a pathological standpoint.

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Figures and Tables

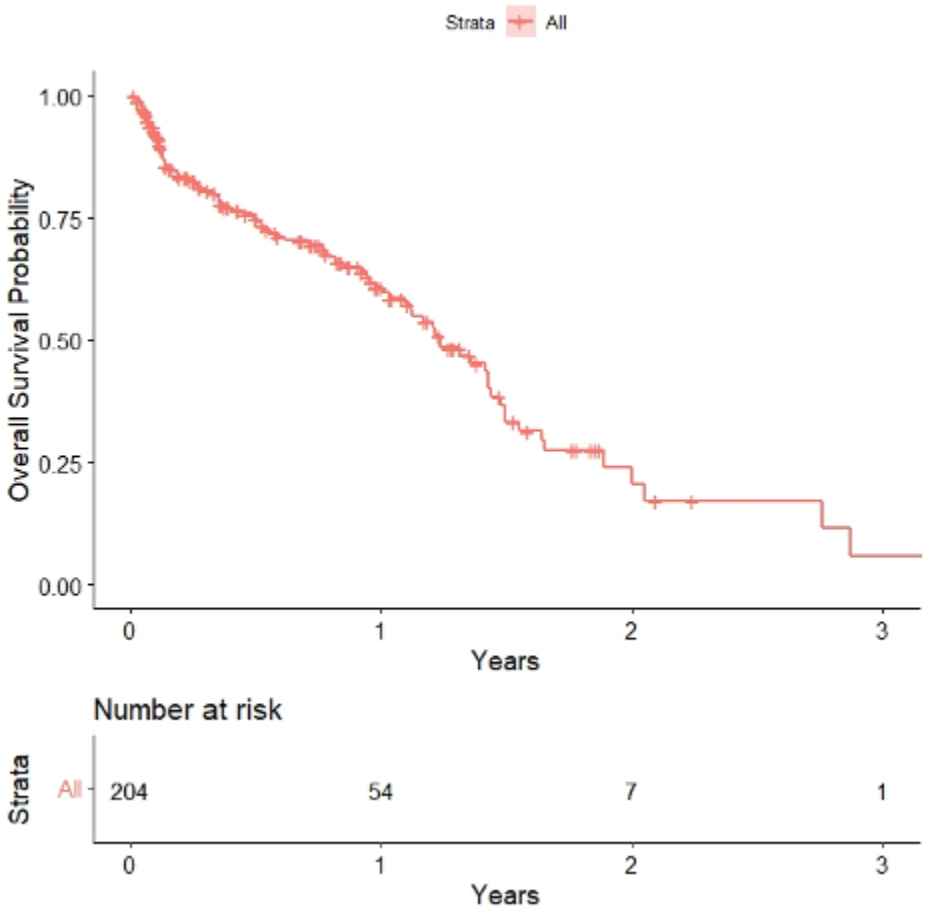

Figure 5. Kaplan-Meier Survival Curve of Study Cohort Overall Survival with Risk Table

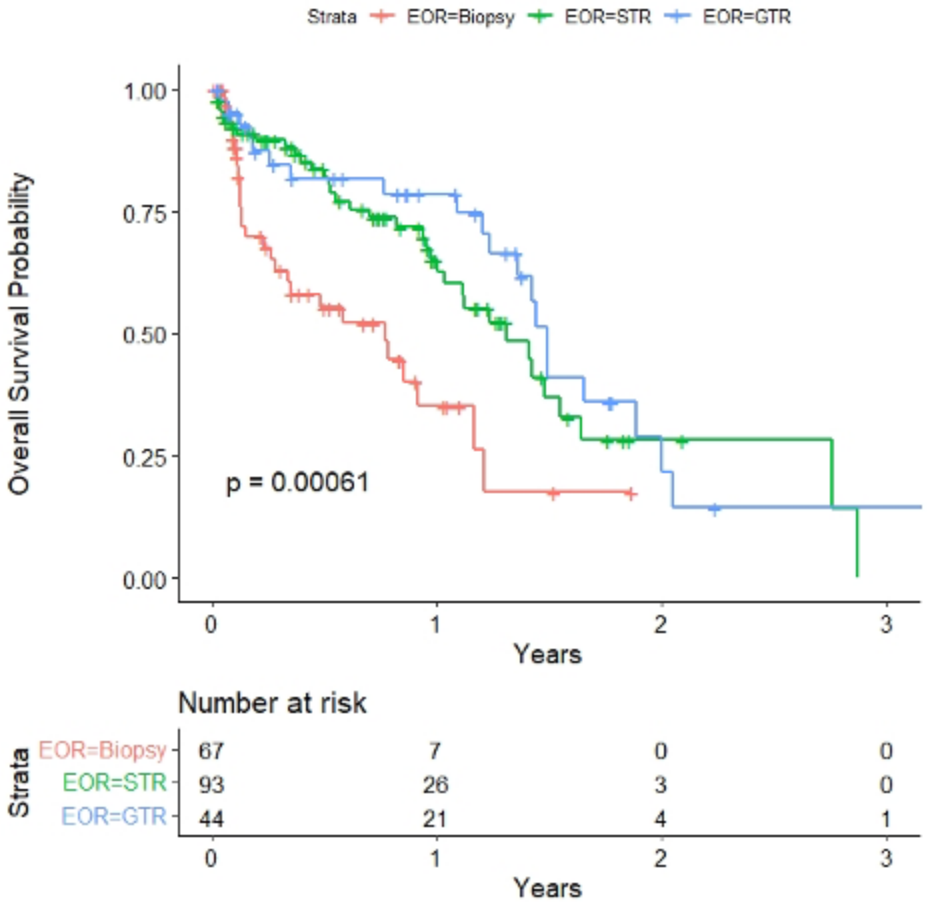

Figure 6. Kaplan-Meier Survival Curve of Extent of Resection Predicting Overall Survival with Risk Table

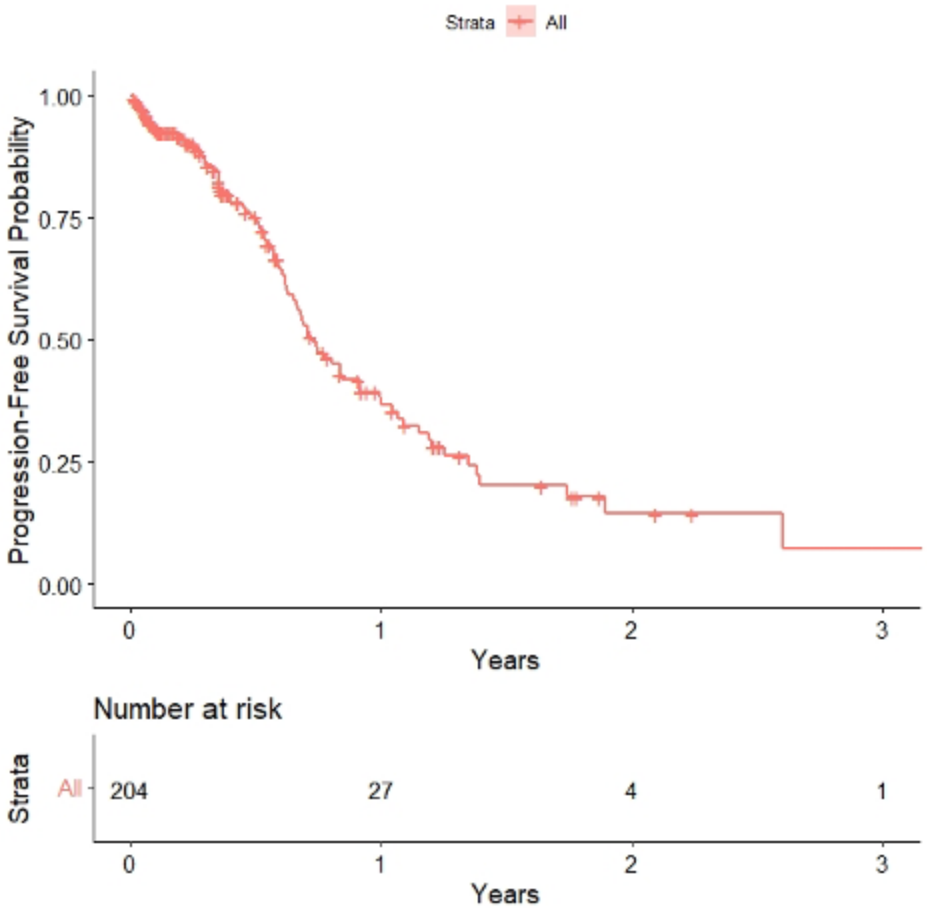

Figure 7. Kaplan-Meier Survival Curve of Study Cohort Progression-Free Survival with Risk Table

Table 1. Demographic Descriptive Statistics		
Variable	**Level**	**N (%) = 204**
Age	Mean (SD)	63.9(11.8)
Sex	Male	118(57.8)
	Female	86(42.2)

Race	White	166(81.4)
	African American	20(9.8)
	Latino	0
	Asian	5(2.5)
	Other	1(0.5)
Preoperative KPS	Mean(SD)	68.4(14.8)
Tumor Locations	Frontal	62(30.4)
	Parietal	43(21.1)
	Temporal	59(28.9)
	Occipital	12(5.9)
	Insula	1(0.5)
	Thalamus/Basal Ganglia	16(7.8)
	Cerebellum	9(4.4)
	Brainstem	2(1.0)

Table 2. Surgical and Outcome Descriptive Statistics

Variable	**Level**	**N (%) = 204**
Type of Surgery	Stereotactic Biopsy	57(27.9)
	Open Biopsy	8(3.9)
	Craniotomy for Resection	137(67.2)
	Radiosurgery	2(1.0)
Postoperative KPS	Mean(SD)	78.1(18.6)

Extent of Resection	Gross-Total Resection	44 (21.5)
	Subtotal Resection	93 (45.6)
	Biopsy	67(32.8)
Radiation	Fractionated	84(41.2)
	SRS	1(0.5)
	Other	60(29.4)
	No Radiation Given	35(17.2)
Chemotherapy given	Temozolomide	102(50.0)
	Avastin/Bevacizumab	23(11.3)
	Lomustine	2(0.9)
	Other	2(0.9)
Tumor Recurrence	Progression noted	75 (36.8)
Length of Progression free survival	Median (IQR)	215 (123-305.5)
Patient Status	Death	85 (41.7)

Table 3. Recurrence Descriptive Statistics

Variable	**Level**	**N (%) = 75**
Extent of Resection after recurrence	Gross-Total Resection	1 (1.3)
	Subtotal Resection	11(14.6)
	Biopsy	1 (1.3)

Radiation Necrosis	Identified	8 (10.7)
Radiation therapy given after recurrence		13 (17.3)
Chemotherapy given after recurrence	Temozolomide	16 (21.3)
	Avastin/Bevacizumab	35 (46.7)
	Lomustine	6 (8.0)
	Other	1(1.3)

Table 4. Genomic Descriptive Statistics

Variable	**Level**	**N (%) = 204**
1p19q status	Co-deleted	16(7.8)
ATRX	Deleted	6(2.9)
CDK2NA/B	Deleted	118(57.8)
MGMT	Methylated	58(28.4)
P53	Overexpressed	59(28.9)
AKT1	Mutated	0
BRAF	Mutated	4(2.0)
EGFR	Amplified	75(36.8)
KRAS	Mutated	3(1.4)
MEK1	Mutated	0
NRAS	Mutated	0
PIK3CA	Mutated	8(3.9)
PTEN	Loss	92(45.1)

Copy Number Variations Gained	Median(IQR)	6(3-8)
Copy Number Variations Lost	Median(IQR)	9(6-12)
Copy Neutral Loss of Heterozygosity	Median(IQR)	1(0-2)
Total Copy Number Variations	Mean(SD)	16.6(7.6)

Table 5. Univariate Association with Overall Survival for General and Adjuvant Therapy Predictors

		Survival (yrs)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**
Age		204	1.04(1.02-1.06)	**<0.001**
Preoperative KPS		204	0.97(0.96-0.99)	**<0.001**
Postoperative KPS		204	0.96(0.94-0.97)	**<0.001**
Radiation	Fractionated	84	0.10(0.05-0.19)	**<0.001**
	SRS	1	0.15(0.02-1.21)	0.075
	Other	60	0.11(0.05-0.22)	**<0.001**
	No Radiation Given	35	-	-
Proton Radiation Given		7	1.16(0.41-3.24)	0.779
Enrolled in Clinical		8	0.67(0.25-1.85)	0.442

Trial				
Temozolomide Given		102	0.36(0.23-0.58)	**<0.001**
Bevacizumab Given		23	0.32(0.15-0.68)	**0.003**
Lomustine Given		2	1.06(0.15-7.67)	0.954
Other Chemotherapy Given		2	2.98e-8(0-Inf)	0.995
Extent of Resection	Gross-Total Resection	44	0.36(0.20-0.65)	**0.001**
	Subtotal Resection	93	0.45(0.27-0.74)	**0.002**
	Biopsy	67	-	-

Table 6. Multivariate Association with Overall Survival for General and Adjuvant Therapy Predictors

		Survival (yrs)		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**
Age		204	1.02(1.00-1.05)	**0.039**
Radiation	Fractionated	84	0.10(0.05-0.19)	**<0.001**
	SRS	1	0.14(0.02-1.16)	0.069
	Other	60	0.08(0.04-0.18)	**<0.001**
	No Radiation Given	35	-	-

Bevacizumab Given		23	0.44(0.20-0.97)	**0.041**
Extent of Resection	Gross-Total Resection	44	0.42(0.22-0.82)	**0.011**
	Subtotal Resection	93	0.52(0.30-0.90)	**0.02**
	Biopsy	67	-	-

Table 7. Univariate Association of Overall Survival with Adjuvant Therapy After Recurrence

	Survival (yrs)		

Covariate	**N**	**Hazard Ratio (95% CI)**	**HR P-value**
Radiation After Recurrence	13	0.91(0.41-2.01)	0.812
Chemotherapy After Recurrence	44	0.81(0.42-1.59)	0.548
Clinical Trial After Recurrence	5	1.02(0.35-2.95)	0.966
Temozolomide After Recurrence	16	1.97(0.85-4.57)	0.115
Avastin After Recurrence	35	0.65(0.38-1.11)	0.113
Lomustine After Recurrence	6	0.82(0.30-2.26)	0.704

Table 8. Univariate Association with Progression-Free Survival for General and Adjuvant Therapy Predictors

		Progression-Free Survival (yrs)

Covariate	Level	N	Hazard Ratio (95% CI)	HR P-value
Age		204	1.01(0.99-1.03)	0.254
Preoperative KPS		204	0.99(0.98-1.01)	0.373
Postoperative KPS		204	0.97(0.96-0.99)	**<.001**
Radiation	Fractionated	84	1.10(0.38-3.16)	0.858
	SRS	1	6.87(0.75-62.89)	0.088
	Other	60	0.48(0.15-1.52)	0.212
	No Radiation Given	35	-	-
Proton Radiation Given		7	0.71(0.26-1.97)	0.517
Enrolled in Clinical Trial		8	0.65(0.26-1.61)	0.348
Temozolomide Given		102	1.79(0.98-3.29)	0.059
Bevacizumab Given		23	0.66(0.37-1.17)	0.154
Lomustine Given		2	0.95(0.13-6.85)	0.959
Other Chemotherapy Given		2	0.27(0.04-2.05)	0.206
Extent of Resection	Gross-Total Resection	44	0.51(0.26-0.98)	**0.043**
	Sub-Total Resection	93	1.00(0.59-1.70)	0.992
	Biopsy	67	-	-

Table 9. Univariate Association with Overall Survival of Pathology Reported Mutational Markers				
		Survival (yrs)		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**
1p19q	Co-deleted	16	0.45(0.22-0.92)	**0.03**
	Not Co-deleted	165	-	-
ATRX	Deleted	6	0.42(0.13-1.37)	0.151
	Retained	150	-	-
CDK2NA/B	Deleted	118	1.05(0.32-3.42)	0.936
	Wild-Type	5	-	-
MGMT	Methylated	58	1.08(0.64-1.81)	0.772
	Unmethylated	110	-	-
P53	Overexpressed	59	1.21(0.70-2.10)	0.502
	Not Overexpressed	101	-	-
BRAF	Positive	4	0.18(0.02-1.36)	0.097
	Negative	200		-
EGFR	Amplified	75	0.75(0.48-1.18)	0.214
	Not Amplified	129	-	-
KRAS	Positive	3	1.21(0.29-4.93)	0.795
	Negative	201	-	-

PIK3CA	Positive	8	0.97(0.30-3.08)	0.956
	Negative	196	-	-
PTEN Loss	Positive	92	1.001(0.65-1.54)	0.996
	Negative	112	-	-

Table 10. Univariate Association with Overall Survival for Microarray Data

		Survival (yrs)		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**
Copy Number Variations Gained		204	1.00(0.97-1.04)	0.759
Copy Number Variations Lost		204	1.03(1.00-1.07)	0.071
Copy Neutral Loss of Heterozygosity		204	1.04(1.01-1.08)	**0.014**
Total Copy Number Variations		204	1.02(0.99-1.05)	0.146
Multiple Mutations on a Single Chromosome		186	1.99(0.80-5.00)	0.141
1p	Gain	31	0.88(0.48-1.58)	0.659
	Loss	81	1.14(0.74-1.75)	0.567
	CN-LOH	11	1.42(0.65-3.09)	0.376
1q	Gain	51	1.13(0.71-1.82)	0.606
	Loss	32	0.62(0.34-1.15)	0.128
	CN-LOH	5	1.48(0.54-4.05)	0.449

2p	Gain	25	1.10(0.61-1.98)	0.755
	Loss	25	1.64(0.90-3.00)	0.105
	CN-LOH	6	3.20(1.28-7.98)	**0.013**
2q	Gain	21	1.11(0.57-2.17)	0.75
	Loss	45	0.93(0.55-1.55)	0.775
	CN-LOH	3	4.63(1.43-14.95)	**0.011**
3p	Gain	31	1.60(0.91-2.81)	0.101
	Loss	25	1.28(0.69-2.36)	0.435
	CN-LOH	6	3.78(1.52-9.41)	**0.004**
3q	Gain	47	1.15(0.67-1.96)	0.62
	Loss	44	1.07(0.66-1.76)	0.774
	CN-LOH	6	2.46(0.99-6.11)	0.053
4p	Gain	11	0.99(0.45-2.19)	0.984
	Loss	32	1.21(0.68-2.15)	0.523
	CN-LOH	7	2.56(1.03-6.36)	**0.043**
4q	Gain	45	0.96(0.56-1.66)	0.89
	Loss	41	1.16(0.69-1.97)	0.572
	CN-LOH	8	2.64(1.14-6.10)	**0.023**
5p	Gain	19	0.89(0.42-1.86)	0.749
	Loss	21	2.02(1.13-3.60)	**0.017**

	CN-LOH	4	1.46(0.46-4.65)	0.526
5q	Gain	15	0.87(0.40-1.92)	0.737
	Loss	29	1.07(0.60-1.89)	0.831
	CN-LOH	6	3.70(1.33-10.27)	**0.012**
6p	Gain	13	1.70(0.84-3.42)	0.137
	Loss	50	1.29(0.78-2.12)	0.318
	CN-LOH	10	0.98(0.40-2.44)	0.969
6q	Gain	12	1.48(0.67-3.23)	0.331
	Loss	71	0.94(0.59-1.49)	0.79
	CN-LOH	10	0.91(0.36-2.25)	0.83
7p	Gain	171	1.21(0.67-2.19)	0.53
	Loss	8	0.81(0.26-2.58)	0.726
	CN-LOH	16	0.99(0.40-2.46)	0.978
7q	Gain	152	0.87(0.54-1.40)	0.557
	Loss	7	1.10(0.44-2.73)	0.84
	CN-LOH	15	2.22(1.06-4.64)	**0.034**
8p	Gain	12	1.17(0.56-2.47)	0.675
	Loss	34	1.24(0.69-2.21)	0.471
	CN-LOH	6	0.58(0.14-2.35)	0.442
8q	Gain	20	1.07(0.55-2.08)	0.841

	Loss	30	0.80(0.44-1.45)	0.462
	CN-LOH	6	0.64(0.16-2.64)	0.542
9p	Gain	25	1.57(0.91-2.72)	0.106
	Loss	151	0.99(0.61-1.60)	0.961
	CN-LOH	23	1.00(0.54-1.86)	0.994
9q	Gain	24	1.75(1.03-2.99)	**0.04**
	Loss	37	1.09(0.64-1.85)	0.764
	CN-LOH	6	0.29(0.04-2.07)	0.216
10p	Gain	8	1.17(0.47-2.90)	0.732
	Loss	173	1.07(0.59-1.94)	0.82
	CN-LOH	23	1.42(0.81-2.50)	0.219
10q	Gain	5	0.75(0.10-5.39)	0.771
	Loss	176	0.52(0.30-0.92)	**0.024**
	CN-LOH	24	1.43(0.83-2.48)	0.199
11p	Gain	13	0.90(0.43-1.89)	0.79
	Loss	43	1.20(0.72-2.01)	0.488
	CN-LOH	7	1.74(0.70-4.34)	0.232
11q	Gain	18	1.48(0.78-2081)	0.228
	Loss	50	1.21(0.74-1.99)	0.442
	CN-LOH	7	1.62(0.65-4.03)	0.299

12p	Gain	24	1.73(0.95-3.15)	**0.073**
	Loss	31	0.89(0.50-1.58)	0.682
	CN-LOH	4	3.06(0.95-9.81)	0.06
12q	Gain	48	1.58(0.96-2.61)	0.075
	Loss	53	0.78(0.46-1.29)	0.33
	CN-LOH	3	1.95(0.61-6.19)	0.26
13p	Gain	0	-	-
	Loss	0	-	-
	CN-LOH	0	-	-
13q	Gain	16	0.72(0.33-1.58)	0.412
	Loss	89	1.75(1.13-2.72)	**0.012**
	CN-LOH	10	2.78(1.27-6.06)	**0.01**
14p	Gain	0	-	-
	Loss	0	-	-
	CN-LOH	0	-	-
14q	Gain	9	1.96(0.85-4.50)	0.115
	Loss	83	1.41(0.91-2.20)	0.124
	CN -LOH	13	2.58(1.28-5.20)	**0.008**
15p	Gain	0	-	-
	Loss	0	-	-
	CN-LOH	0	-	-
15q	Gain	9	1.28(0.58-2.85)	0.541

	Loss	54	1.40(0.87-2.23)	0.163
	CN-LOH	9	1.45(0.67-3.16)	0.345
16p	Gain	14	0.88(0.40-1.92)	0.741
	Loss	38	1.73(1.07-2.80)	**0.026**
	CN-LOH	6	1.95(0.78-4.89)	0.153
16q	Gain	10	1.12(0.48-2.59)	0.796
	Loss	47	1.39(0.87-2.23)	0.169
	CN-LOH	8	2.11(0.85-5.26)	0.108
17p	Gain	19	1.07(0.51-2.22)	0.866
	Loss	40	1.72(1.01-2.92)	**0.047**
	CN-LOH	25	1.98(1.13-3.49)	**0.018**
17q	Gain	32	0.86(0.47-1.56)	0.616
	Loss	40	1.17(0.68-1.99)	0.573
	CN-LOH	21	1.90(0.97-3.72)	0.061
18p	Gain	14	1.41(0.68-2.92)	0.361
	Loss	30	1.61(0.90-2.89)	0.108
	CN-LOH	6	4.92(1.75-13.80)	**0.002**
18q	Gain	13	2.38(1.14-4.97)	**0.021**
	Loss	30	1.32(0.73-2.40)	0.361
	CN-LOH	9	2.01(0.81-5.02)	0.135

19p	Gain	73	0.82(0.53-1.28)	0.388
	Loss	19	1.16(0.56-2.41)	0.692
	CN-LOH	12	1.21(0.58-2.52)	0.608
19q	Gain	66	0.83(0.52-1.31)	0.42
	Loss	40	1.32(0.76-2.29)	0.33
	CN-LOH	14	1.24(0.62-2.50)	0.541
20p	Gain	60	0.88(0.56-1.38)	0.58
	Loss	20	0.83(0.38-1.80)	0.637
	CN-LOH	7	1.83(0.79-4.22)	0.156
20q	Gain	67	0.92(0.59-1.44)	0.724
	Loss	14	1.24(0.54-2.85)	0.616
	CN-LOH	6	2.35(0.95-5.85)	0.065
21p	Gain	0	-	-
	Loss	0	-	-
	CN-LOH	0	-	-
21q	Gain	13	1.02(0.37-2.80)	0.973
	Loss	20	1.74(0.91-3.30)	0.092
	CN-LOH	4	3.57(0.86-14.77)	0.079
22p	Gain	0	-	-
	Loss	0	-	-
	CN-LOH	0	-	-

22q	Gain	15	0.79(0.37-1.73)	0.561
	Loss	85	1.61(1.04-2.47)	**0.032**
	CN-LOH	13	2.22(1.11-4.46)	**0.025**
23p	Gain	0	-	-
	Loss	0	-	-
	CN-LOH	0	-	-
23q	Gain	0	-	-
	Loss	0	-	-
	CN-LOH	0	-	-

Table 11. Multivariate Association with Overall Survival for Microarray Data

		Survival (yrs)		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**
CN-LOH		204	0.87(0.78-0.97)	**0.011**
3p	CN-LOH	6	11.54(1.10-121.35)	**0.042**
5p	Loss	21	2.79(1.51-5.19)	**0.001**
5q	CN-LOH	6	4.87(1.05-22.56)	**0.043**
7q	CN-LOH	15	2.72(1.01-7.33)	**0.048**

9q	Gain	24	2.43(1.39-4.22)	**0.002**
10q	Loss	176	0.38(0.20-0.72)	**0.003**
14q	CN-LOH	13	3.03(1.21-7.61)	**0.018**
16p	Loss	38	1.68(1.00-2.84)	0.052
18p	Loss	30	1.90(1.00-3.60)	**0.05**

Table 12. Univariate Association with Overall Survival for Whole Chromosome Mutations from Microarray Data

		Survival (yrs)		

Covariate	**Level**	**N(% of 204)**	**Hazard Ratio (95% CI)**	**HR P-value**
1	Whole Chromosome Gain	20(9.8)	0.66(0.30-1.43)	0.291
	Whole Chromosome Loss	18(8.8)	0.73(0.35-1.52)	0.401
	Whole Chromosome Loss of Heterozygosity	3(1.5)	1.89(0.59-6.03)	0.28
2	Whole Chromosome Gain	15(7.4)	1.04(0.50-2.17)	0.921
	Whole Chromosome Loss	12(5.9)	1.29(0.56-2.98)	0.55

	Whole Chromosome Loss of Heterozygosity	3(1.5)	4.66(1.44-15.06)	**0.01**
3	Whole Chromosome Gain	23(11.3)	1.51(0.77-2.95)	0.227
	Whole Chromosome Loss	13(6.4)	1.44(0.66-3.13)	0.36
	Whole Chromosome Loss of Heterozygosity	4(2.0)	3.02(1.10-8.29)	**0.032**
4	Whole Chromosome Gain	7(3.4)	1.49(0.59-3.77)	0.397
	Whole Chromosome Loss	18(8.8)	1.19(0.57-2.47)	0.644
	Whole Chromosome Loss of Heterozygosity	5(2.5)	2.16(0.79-5.93)	0.135
5	Whole Chromosome Gain	10(4.9)	0.84(0.33-2.13)	0.712
	Whole Chromosome Loss	9(4.4)	1.44(0.58-3.57)	0.435
	Whole Chromosome Loss of Heterozygosity	3(1.5)	3.00(0.72-12.4)	0.13
6	Whole Chromosome Gain	5(2.5)	1.84(0.72-4.68)	0.202
	Whole Chromosome Loss	37(18.1)	1.03(0.58-1.83)	0.93
	Whole Chromosome Loss of Heterozygosity	8(3.9)	0.64(0.20-2.04)	0.453
7	Whole Chromosome Gain	147(72.1)	0.84(0.53-1.33)	0.447
	Whole Chromosome Loss	3(1.5)	0.91(0.22-3.73)	0.899
	Whole Chromosome	10(4.9)	1.64(0.66-4.06)	0.29

	Loss of Heterozygosity			
8	Whole Chromosome Gain	9(4.4)	1.17(0.50-2.75)	0.724
	Whole Chromosome Loss	19(9.3)	0.91(0.42-1.98)	0.808
	Whole Chromosome Loss of Heterozygosity	5(2.5)	0.69(0.17-2.83)	0.607
9	Whole Chromosome Gain	15(7.4)	1.88(1.04-3.42)	**0.038**
	Whole Chromosome Loss	34(16.7)	1.02(0.58-1.79)	0.942
	Whole Chromosome Loss of Heterozygosity	6(2.9)	0.29(0.04-2.08)	0.217
10	Whole Chromosome Gain	3(1.5)	1.08(0.15-7.79)	0.94
	Whole Chromosome Loss	160(78.4)	0.91(0.55-1.53)	0.732
	Whole Chromosome Loss of Heterozygosity	23(11.3)	1.43(0.81-2.51)	0.213
11	Whole Chromosome Gain	7(3.4)	1.44(0.61-3.36)	0.404
	Whole Chromosome Loss	34(16.7)	1.05(0.59-1.86)	0.881
	Whole Chromosome Loss of Heterozygosity	6(2.9)	1.80(0.72-4.45)	0.209
12	Whole Chromosome Gain	15(7.4)	2.26(1.16-4.40)	**0.016**
	Whole Chromosome Loss	20(9.8)	0.78(0.39-1.58)	0.493
	Whole Chromosome Loss of Heterozygosity	2(1.0)	4.08(0.99-16.85)	0.052

13	Whole Chromosome Gain	0	-	-
	Whole Chromosome Loss	0	-	-
	Whole Chromosome Loss of Heterozygosity	0	-	-
14	Whole Chromosome Gain	0	-	-
	Whole Chromosome Loss	0	-	-
	Whole Chromosome Loss of Heterozygosity	0	-	-
15	Whole Chromosome Gain	0	-	-
	Whole Chromosome Loss	0	-	-
	Whole Chromosome Loss of Heterozygosity	0	-	-
16	Whole Chromosome Gain	6(2.9)	1.20(0.43-3.36)	0.724
	Whole Chromosome Loss	24(11.8)	1.73(1.00-3.00)	**0.049**
	Whole Chromosome Loss of Heterozygosity	4(2.0)	4.49(1.39-14.48)	**0.012**
17	Whole Chromosome Gain	15(7.4)	1.01(0.44-2.34)	0.975
	Whole Chromosome Loss	26(12.7)	1.42(0.77-2.63)	0.267
	Whole Chromosome Loss of Heterozygosity	16(7.8)	2.11(1.05-4.26)	**0.036**
18	Whole Chromosome Gain	8(3.9)	2.17(0.88-5.38)	0.094

	Whole Chromosome Loss	17(8.3)	2.11(1.05-4.27)	**0.037**
	Whole Chromosome Loss of Heterozygosity	5(2.5)	5.53(1.98-15.49)	**0.001**
19	Whole Chromosome Gain	62(30.4)	0.89(0.56-1.41)	0.627
	Whole Chromosome Loss	16(7.8)	0.98(0.42-2.25)	0.958
	Whole Chromosome Loss of Heterozygosity	11(5.4)	1.36(0.65-2.82)	0.417
20	Whole Chromosome Gain	55(27.0)	0.94(0.59-1.49)	0.786
	Whole Chromosome Loss	10(4.9)	1.17(0.47-2.89)	0.74
	Whole Chromosome Loss of Heterozygosity	5(2.5)	2.02(0.74-5.55)	0.172
21	Whole Chromosome Gain	0	-	-
	Whole Chromosome Loss	0	-	-
	Whole Chromosome Loss of Heterozygosity	0	-	-
22	Whole Chromosome Gain	0	-	-
	Whole Chromosome Loss	0	-	-
	Whole Chromosome Loss of Heterozygosity	0	-	-
23	Whole Chromosome Gain	0	-	-
	Whole Chromosome Loss	0	-	-

	Whole Chromosome Loss of Heterozygosity	0	-	-
19 + / 20 +	19p/20p	45(22.1)	0.84(0.51-1.38)	0.494
	19p/20q	46(22.5)	0.96(0.59-1.55)	0.856
	19q/20p	42(20.6)	0.83(0.49-1.41)	0.485
	19q/20q	44(21.6)	0.92(0.55-1.53)	0.75
7 + / 10 -	7p/10p	153(75.0)	0.99(0.60-1.64)	0.978
	7p/10q	151(74.0)	0.90(0.56-1.46)	0.676
	7q/10p	135(66.2)	0.78(0.50-1.22)	0.281
	7q/10q	140(68.6)	0.77(0.49-1.20)	0.247

Table 13. Multivariate Association with Overall Survival for Whole Chromosome Mutations from Microarray Data

		Survival (yrs)		

Covariate	**Level**	**N(% of 204)**	**Hazard Ratio (95% CI)**	**HR P-value**
9	Whole Chromosome Gain	15(7.4)	1.85(1.01-3.39)	**0.045**
12	Whole Chromosome Gain	15(7.4)	2.17(1.10-4.25)	**0.025**

16	Whole Chromosome Loss	24(11.8)	1.72(0.97-3.03)	0.063
18	Whole Chromosome Loss	17(8.3)	1.96(0.94-4.07)	0.071
	Whole Chromosome Loss of Heterozygosity	5(2.5)	4.78(1.67-13.63)	**0.003**

Table 14. Univariate Association with Progression-Free Survival of Pathology Reported Mutational Markers

		Progression-Free Survival (yrs)		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**
1p19q	Co-deleted	16	0.52(0.24-1.15)	0.109
	Not Co-deleted	165	-	-
ATRX	Deleted	6	2.56e7(0-Inf)	0.996
	Retained	150	-	-
CDK2NA/B	Deleted	118	0.47(0.11-1.94)	0.295
	Wild-Type	5	-	-
MGMT	Methylated	58	1.30(0.78-2.14)	0.313
	Unmethylated	110	-	-
P53	Overexpressed	59	0.92(0.55-1.54)	0.746
	Not Overexpressed	101	-	-
BRAF	Positive	4	3.06e-8(0-Inf)	0.994

	Negative	200	-	-
EGFR	Amplified	75	0.71(0.46-1.11)	0.134
	Not Amplified	129	-	-
KRAS	Positive	3	3.92e-8(0-Inf)	0.996
	Negative	201	-	-
PIK3CA	Positive	8	1.13(0.41-3.10)	0.81
	Negative	196	-	-
PTEN Loss	Positive	92	0.86(0.55-1.33)	0.488
	Negative	112	-	-

Table 15. Univariate Association with Progression-Free Survival for Microarray Data

		Progression-Free Survival (yrs)		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**
Copy Number Variations Gained		204	0.99(0.95-1.03)	0.472
Copy Number Variations Lost		204	1.03(0.99-1.07)	0.149
Copy Neutral Loss of Heterozygosity		204	1.02(0.98-1.07)	0.298
Total Copy Number Variations		204	1.01(0.98-1.03)	0.669
Multiple Mutations on a Single Chromosome		186	1.19(0.54-2.63)	0.662

1p	Gain	31	1.00(0.58-1.73)	1
	Loss	81	1.00(0.65-1.56)	0.987
	CN-LOH	11	1.12(0.48-2.57)	0.797
1q	Gain	51	0.71(0.42-1.21)	0.207
	Loss	32	0.44(0.23-0.86)	**0.016**
	CN-LOH	5	0.86(0.21-3.51)	0.833
2p	Gain	25	0.67(0.33-1.35)	0.261
	Loss	25	1.48(0.80-2.75)	0.215
	CN-LOH	6	3.95e-8(0-Inf)	0.996
2q	Gain	21	0.75(0.34-1.64)	0.472
	Loss	45	0.88(0.53-1.47)	0.627
	CN-LOH	3	2.99e-7(0-Inf)	0.995
3p	Gain	31	0.99(0.51-1.92)	0.966
	Loss	25	0.92(0.44-1.90)	0.815
	CN-LOH	6	0.77(0.11-5.57)	0.797
3q	Gain	47	0.82(0.46-1.46)	0.491
	Loss	44	0.79(0.47-1.33)	0.377
	CN-LOH	6	0.92(0.22-3.76)	0.904
4p	Gain	11	0.61(0.24-1.54)	0.297
	Loss	32	0.95(0.51-1.75)	0.858

	CN-LOH	7	0.92(0.22-3.75)	0.904
4q	Gain	45	0.84(0.48-1.47)	0.539
	Loss	41	1.01(0.58-1.45)	0.981
	CN-LOH	8	0.82(0.20-3.35)	0.781
5p	Gain	19	1.19(0.59-2.38)	0.633
	Loss	21	1.13(0.54-2.53)	0.746
	CN-LOH	4	0.71(0.10-5.15)	0.738
5q	Gain	15	0.69(0.28-1.73)	0.433
	Loss	29	0.92(0.50-1.70)	0.786
	CN-LOH	6	0.88(0.12-6.40)	0.902
6p	Gain	13	0.57(0.21-1.59)	0.284
	Loss	50	1.25(0.75-2.08)	0.385
	CN-LOH	10	0.90(0.36-2.25)	0.827
6q	Gain	12	1.13(0.48-2.65)	0.774
	Loss	71	1.31(0.83-2.04)	0.243
	CN-LOH	10	0.81(0.32-2.00)	0.642
7p	Gain	171	1.04(0.59-1.86)	0.885
	Loss	8	1.28(0.52-3.16)	0.595
	CN-LOH	16	1.58(0.72-3.46)	0.255
7q	Gain	152	0.66(0.41-1.05)	0.08

	Loss	7	0.85(0.31-2.33)	0.753
	CN-LOH	15	1.92(0.83-4.44)	0.13
8p	Gain	12	0.61(0.24-1.53)	0.288
	Loss	34	1.36(0.78-2.39)	0.28
	CN-LOH	6	1.67(0.61-4.59)	0.323
8q	Gain	20	0.74(0.33-1.65)	0.464
	Loss	30	0.77(0.42-1.43)	0.407
	CN-LOH	6	1.73(0.54-5.50)	0.356
9p	Gain	25	0.66(0.34-1.28)	0.217
	Loss	151	1.25(0.73—2.13)	0.418
	CN-LOH	23	0.83(0.43-1.57)	0.558
9q	Gain	24	0.73(0.37-1.42)	0.348
	Loss	37	1.05(0.60-1.84)	0.872
	CN-LOH	6	0.48(0.12-1.99)	0.315
10p	Gain	8	0.69(0.25-1.88)	0.465
	Loss	173	1.24(0.66-2.36)	0.502
	CN-LOH	23	1.22(0.66-2.27)	0.522
10q	Gain	5	1.35(0.33-5.51)	0.677
	Loss	176	0.41(0.23-0.74)	**0.003**
	CN-LOH	24	1.24(0.68-2.25)	0.481

11p	Gain	13	0.81(0.39-1.69)	0.572
	Loss	43	1.77(1.09-2.88)	**0.021**
	CN-LOH	7	0.93(0.29-2.97)	0.907
11q	Gain	18	0.97(0.48-1.96)	0.932
	Loss	50	1.06(0.64-1.74)	0.828
	CN-LOH	7	0.87(0.27-2.78)	0.817
12p	Gain	24	1.45(0.74-2.82)	0.279
	Loss	31	1.04(0.58-1.85)	0.903
	CN-LOH	4	0.94(0.13-6.78)	0.947
12q	Gain	48	0.64(0.33-1.25)	0.192
	Loss	53	0.75(0.45-1.25)	0.27
	CN-LOH	3	1.70(0.23-12.36)	0.6
13p	Gain	0	-	-
	Loss	0	-	-
	CN-LOH	0	-	-
13q	Gain	16	0.69(0.31-1.51)	0.351
	Loss	89	1.28(0.81-2.00)	0.288
	CN-LOH	10	1.11(0.35-3.52)	0.862
14p	Gain	0	-	-
	Loss	0	-	-
	CN-LOH	0	-	-

14q	Gain	9	0.90(0.28-2.86)	0.861
	Loss	83	1.26(0.81-1.97)	0.3
	CN-LOH	13	1.81(0.66-5.00)	0.251
15p	Gain	0	-	-
	Loss	0	-	-
	CN-LOH	0	-	-
15q	Gain	9	0.96(0.39-2.39)	0.93
	Loss	54	1.55(0.97-2.47)	0.065
	CN-LOH	9	1.47(0.64-3.40)	0.364
16p	Gain	14	1.21(0.60-2.47)	0.593
	Loss	38	1.39(0.83-2.34)	0.213
	CN-LOH	6	1.17(0.29-4.78)	0.829
16q	Gain	10	0.83(0.33-2.10)	0.698
	Loss	47	1.02(0.61-1.70)	0.95
	CN-LOH	8	2.01(0.73-5.57)	0.178
17p	Gain	19	1.53(0.80-2.92)	0.194
	Loss	40	2.36(1.41-3.95)	**0.001**
	CN-LOH	25	1.35(0.67-2.71)	0.399
17q	Gain	32	1.33(0.77-2.30)	0.31
	Loss	40	2.23(1.34-3.71)	**0.002**
	CN-LOH	21	0.86(0.35-2.13)	0.745

18p	Gain	14	1.29(0.60-2.81)	0.516
	Loss	30	1.64(0.92-2.93)	0.096
	CN-LOH	6	1.39(0.19-10.18)	0.743
18q	Gain	13	4.38(1.93-9.96)	**<0.001**
	Loss	30	0.92(0.48-1.79)	0.814
	CN-LOH	9	1.76(0.64-4.87)	0.274
19p	Gain	73	1.14(0.74-1.75)	0.566
	Loss	19	0.99(0.45-2.15)	0.978
	CN-LOH	12	1.31(0.63-2.74)	0.468
19q	Gain	66	1.26(0.81-1.95)	0.307
	Loss	40	1.65(0.98-2.76)	0.058
	CN-LOH	14	1.33(0.66-2.69)	0.42
20p	Gain	60	0.83(0.53-1.30)	0.405
	Loss	20	1.27(0.66-2.47)	0.477
	CN-LOH	7	2.26(0.91-5.63)	0.08
20q	Gain	67	0.73(0.47-1.16)	0.181
	Loss	14	0.94(0.38-2.34)	0.897
	CN-LOH	6	1.44(0.45-4.60)	0.534
21p	Gain	0	-	-
	Loss	0	-	-
	CN-LOH	0	-	-

21q	Gain	13	1.16(0.47-2.88)	0.745
	Loss	20	1.37(0.68-2.75)	0.367
	CN-LOH	4	1.90(0.26-13.81)	0.527
22p	Gain	0	-	-
	Loss	0	-	-
	CN-LOH	0	-	-
22q	Gain	15	1.12(0.55-2.25)	0.759
	Loss	85	1.40(0.91-2.17)	0.129
	CN-LOH	13	2.17(0.94-5.04)	0.07
23p	Gain	0	-	-
	Loss	0	-	-
	CN-LOH	0	-	-
23q	Gain	0	-	-
	Loss	0	-	-
	CN-LOH	0	-	-

.

Table 16. Multivariate Association with Progression-Free Survival for Microarray Data

		Progression-Free Survival (yrs)		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**

1q	Loss	32	0.41(0.21-0.81)	**0.009**
10q	Loss	176	0.35(0.19-0.65)	**<0.001**
11p	Loss	43	1.66(1.00-2.73)	**0.049**
17q	Loss	40	2.35(1.39-3.97)	**0.001**
18q	Gain	13	3.87(1.66-9.04)	**0.002**
22q	CN-LOH	13	2.20(0.94-5.17)	0.07

Table 17. Univariate Association with Progression-Free Survival for Whole Chromosome Mutations from Microarray Data

		Progression-Free Survival (yrs)		
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Covariate	**Level**	**N(% of 204)**	**Hazard Ratio (95% CI)**	**HR P-value**
1	Whole Chromosome Gain	20(9.8)	0.70(0.35-1.40)	0.314
	Whole Chromosome Loss	18(8.8)	0.30(0.11-0.82)	**0.018**
	Whole Chromosome Loss of Heterozygosity	3(1.5)	0.48(0.07-3.46)	0.466
2	Whole Chromosome Gain	15(7.4)	0.73(0.31-1.69)	0.459
	Whole Chromosome Loss	12(5.9)	1.17(0.51-2.69)	0.718
	Whole Chromosome	3(1.5)	2.99e-7(0-Inf)	0.995

	Loss of Heterozygosity			
3	Whole Chromosome Gain	23(11.3)	0.96(0.44-2.10)	0.91
	Whole Chromosome Loss	13(6.4)	1.55(0.62-3.86)	0.351
	Whole Chromosome Loss of Heterozygosity	4(2.0)	0.78(0.11-5.64)	0.806
4	Whole Chromosome Gain	7(3.4)	0.76(0.23-2.52)	0.658
	Whole Chromosome Loss	18(8.8)	0.84(0.36-1.93)	0.674
	Whole Chromosome Loss of Heterozygosity	5(2.5)	0.97(0.24-3.96)	0.964
5	Whole Chromosome Gain	10(4.9)	0.74(0.27-2.04)	0.565
	Whole Chromosome Loss	9(4.4)	1.24(0.45-3.41)	0.671
	Whole Chromosome Loss of Heterozygosity	3(1.5)	2.99e-7(0-Inf)	0.995
6	Whole Chromosome Gain	5(2.5)	0.91(0.27-3.04)	0.883
	Whole Chromosome Loss	37(18.1)	1.25(0.72-2.17)	0.422
	Whole Chromosome Loss of Heterozygosity	8(3.9)	0.80(0.29-2.21)	0.668
7	Whole Chromosome Gain	147(72.1)	0.69(0.44-1.09)	0.111
	Whole Chromosome Loss	3(1.5)	1.36(0.43-4.34)	0.6
	Whole Chromosome Loss of Heterozygosity	10(4.9)	1.81(0.73-4.50)	0.203

8	Whole Chromosome Gain	9(4.4)	0.49(0.15-1.59)	0.232
	Whole Chromosome Loss	19(9.3)	1.05(0.51-2.19)	0.89
	Whole Chromosome Loss of Heterozygosity	5(2.5)	1.83(0.58-5.85)	0.306
9	Whole Chromosome Gain	15(7.4)	0.58(0.25-1.34)	0.2
	Whole Chromosome Loss	34(16.7)	1.12(0.63-1.99)	0.706
	Whole Chromosome Loss of Heterozygosity	6(2.9)	0.48(0.12-1.99)	0.315
10	Whole Chromosome Gain	3(1.5)	1.62(0.40-6.63)	0.501
	Whole Chromosome Loss	160(78.4)	0.81(0.49-1.34)	0.413
	Whole Chromosome Loss of Heterozygosity	23(11.3)	1.22(0.66-2.27)	0.522
11	Whole Chromosome Gain	7(3.4)	0.78(0.28-2.20)	0.637
	Whole Chromosome Loss	34(16.7)	1.46(0.86-2.50)	0.163
	Whole Chromosome Loss of Heterozygosity	6(2.9)	0.95(0.30-3.03)	0.933
12	Whole Chromosome Gain	15(7.4)	0.98(0.36-2.69)	0.969
	Whole Chromosome Loss	20(9.8)	0.70(0.33-1.45)	0.334
	Whole Chromosome Loss of Heterozygosity	2(1.0)	3.00e-7(0-Inf)	0.995

13	Whole Chromosome Gain	0	-	-
	Whole Chromosome Loss	0	-	-
	Whole Chromosome Loss of Heterozygosity	0	-	-
14	Whole Chromosome Gain	0	-	-
	Whole Chromosome Loss	0	-	-
	Whole Chromosome Loss of Heterozygosity	0	-	-
15	Whole Chromosome Gain	0	-	-
	Whole Chromosome Loss	0	-	-
	Whole Chromosome Loss of Heterozygosity	0	-	-
16	Whole Chromosome Gain	6(2.9)	1.14(0.40-3.25)	0.802
	Whole Chromosome Loss	24(11.8)	1.01(0.52-1.97)	0.972
	Whole Chromosome Loss of Heterozygosity	4(2.0)	1.60(0.22-11.65)	0.641
17	Whole Chromosome Gain	15(7.4)	1.19(0.54-2.61)	0.671
	Whole Chromosome Loss	26(12.7)	1.59(0.86-2.94)	0.143
	Whole Chromosome Loss of Heterozygosity	16(7.8)	0.81(0.30-2.22)	0.683
18	Whole Chromosome Gain	8(3.9)	4.19(1.49-11.81)	**0.007**

	Whole Chromosome Loss	17(8.3)	1.17(0.47-2.91)	0.739
	Whole Chromosome Loss of Heterozygosity	5(2.5)	1.6(0.21-11.39)	0.659
19	Whole Chromosome Gain	62(30.4)	1.26(0.81-1.96)	0.312
	Whole Chromosome Loss	16(7.8)	0.76(0.31-1.89)	0.56
	Whole Chromosome Loss of Heterozygosity	11(5.4)	1.19(0.54-2.60)	0.663
20	Whole Chromosome Gain	55(27.0)	0.76(0.47-1.21)	0.245
	Whole Chromosome Loss	10(4.9)	0.81(0.29-2.23)	0.683
	Whole Chromosome Loss of Heterozygosity	5(2.5)	1.50(0.47-4.79)	0.492
21	Whole Chromosome Gain	0	-	-
	Whole Chromosome Loss	0	-	-
	Whole Chromosome Loss of Heterozygosity	0	-	-
22	Whole Chromosome Gain	0	-	-
	Whole Chromosome Loss	0	-	-
	Whole Chromosome Loss of Heterozygosity	0	-	-
23	Whole Chromosome Gain	0	-	-
	Whole Chromosome Loss	0	-	-

	Whole Chromosome Loss of Heterozygosity	0	-	-
19 + / 20 +	19p/20p	45(22.1)	0.96(0.60-1.54)	0.858
	19p/20q	46(22.5)	0.82(0.50-1.35)	0.432
	19q/20p	42(20.6)	1.09(0.67-1.77)	0.722
	19q/20q	44(21.6)	0.90(0.55-1.48)	0.676
7 + / 10 -	7p/10p	153(75.0)	0.98(0.59-1.64)	0.947
	7p/10q	151(74.0)	0.82(0.51-1.33)	0.43
	7q/10p	135(66.2)	0.72(0.46-1.12)	0.148
	7q/10q	140(68.6)	0.60(0.38-0.93)	**0.023**

Table 18. Multivariate Association with Progression-Free Survival for Whole Chromosome Mutations from Microarray Data

		Progression-Free Survival (yrs)		

Covariate	**Level**	**N(% of 204)**	**Hazard Ratio (95% CI)**	**HR P-value**
1	Whole Chromosome Loss	18(8.8)	0.22(0.08-0.62)	**0.004**
18	Whole Chromosome Gain	8(3.9)	7.00(2.42-20.30)	**<0.001**
7 Gain / 10 Loss	7q/10q	140(68.6)	0.49(0.31-0.77)	**0.002**