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Malignant Gliomas: A Case Study

Bonnie R. Sullivan

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Malignant Gliomas:

A Case Study

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Abstract

Malignant gliomas, of grade III and grade IV malignancy, are incurable neoplasms that arise from cells with several well-characterized genetic profile abnormalities that cause uncontrollable growth and infiltration in the brain. Presenting symptoms of both generalized and focal neurological abnormalities are induced by increased intracranial pressure and focal neuronal dysfunction, respectively. On average, patients experience 3 months or less of clinical history before receiving diagnosis based on multifactorial comparison of clinical and pathological presentation of the tumor. Following diagnosis, maximal safe resection and adjuvant radiotherapy and concurrent chemotherapy typically ensues with subsequent management chemotherapy regimens. Despite aggressive treatment approaches, progression or recurrence is highly typical based on 5-yr survival rates of 5.1% and 27.9% of grade IV glioblastoma multiforme (GBM) and grade III anaplastic astrocytoma (AA), respectively, the two most common malignant gliomas. Severely progressive clinical and functional deterioration in the terminal stage of care may warrant cessation of curative care replaced with maximal palliative care. Brain tumor patients experience the burden of terminal illness as other cancer patients do, but with added neurological-specific impairments that reduce quality of life. Possible causes of death include herniation, tumor progression, and systemic illness, but can be potentially multifactorial. The following manuscript characterizes the pathological mechanisms of oncogenesis and growth, followed by a comprehensive review of the clinical care for brain tumor patients from symptom onset to cause of death. To aid in the clinical applicability of these concepts, a case study of a single patient “WL”, who received a diagnosis of grade III anaplastic astrocytoma following 3 months of visual deterioration, will prompt the clinical review by illustration of disease course and treatment.
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Malignant Gliomas: A Case Study

The purpose of this paper is to describe and illustrate the clinical implications of malignant gliomas*. Although certain protocols regarding diagnosis, initial treatment, and progression are well characterized in the glioma literature, every cancer and patient are unique. Unfortunately, these cases tend to end in devastation, yet understanding the process and the current state of the clinical field improves the appreciation people may have for the patients, their families, and the dedicated medical personnel involved in these cases.

Every cell in the body can suffer mutations of certain vital genes that regulate cell growth, replication, and metabolic functioning to create cancerous tissues that invade and destroy healthy tissue in path of destructive growth having lost the mechanisms to induce healthy apoptosis¹. Malignant cancer of glial cells in the central nervous system have an unfortunate reputation for short prognoses and almost absolute recurrence. Since gliomas do not normally metastasize outside the central nervous system (CNS), the diagnoses are given grades that indicate malignancy tendency rather than staging as with other cancers². Malignant gliomas include both grade III and grade IV variants, which are characterized by infiltrative growth, significant proliferation rates, cellular and nuclear morphology, and necrosis and/or vascular proliferation specific to grade IV tumors². About 12,000 people receive a diagnosis of a grade IV glioblastoma multiforme per year, yet less than 40% of those people are alive 12 months later and less than 9% after 3 years³. These aggressive neoplasms tend to be so devastating because of several highly adapted biomolecular mechanisms to induce angiogenesis and cellular migration at the expense of the healthy, vital tissue of the brain², 4. Essentially, they are incurable and

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* Any claims presented in this manuscript that are not explicitly cited by a source are that of the author as discussion of the literature reviewed. If not cited in the statement, the views of organizations and research groups referenced in this manuscript are not associated with any normative claims made by the author. This manuscript is meant for educational purposes and in no means should represent a complete guide for patients or medical personnel.
debatably treatable, but are still given the best possible medical attention and are being researched thoroughly for more effective treatments. Following oncogenesis and adequate tumor growth to induce symptoms, the clinical journey begins to obtain diagnosis, to estimate prognosis, and to design treatment protocols.

Tumor mass and infiltration can cause brain dysfunction resulting in general or focal symptoms worthy of seeking medical attention\textsuperscript{2,4,5,6}. Some common symptoms such as headache may be less indicative of a brain abnormality than more severe symptoms such as seizure or loss of consciousness, but symptoms usually progress quickly in patients with malignant gliomas regardless of how mild initially present\textsuperscript{5,6}. Patients who receive a diagnosis of GBM typically have short clinical histories of 3 months or less attributed to how rapid infiltration tends to produce obvious symptoms quickly, in opposition to lower grade or slowly infiltrating gliomas\textsuperscript{2,7}.

Radiographic imaging is used to confirm possible tumor presence with magnetic resonance imaging (MRI) used as the gold standard\textsuperscript{2,8,9,10}. However, computer axial topography (CT) is preferably used in emergency medicine for its quick and easy methodology or when the patient is incompatible with MRI methods\textsuperscript{2,8,9,10}. Some tumors are only radiographically confirmed, but histopathology confirmation by biopsy is preferred for diagnosis in terms of thoroughness and for ruling out other possible neoplasms, including meningioma and metastatic carcinoma\textsuperscript{2,3}. Pathology report from biopsy can characterize cell type, cell morphology, nuclear atypia, proliferation index, and presence of necrosis/vascularization\textsuperscript{2}. Tumor resection is preferable at the time of diagnosis if confirmed by cryogenic freeze diagnosis or soon after laboratory confirmation, but may not be possible if located next to eloquent brain areas or located too deeply for safe access\textsuperscript{2,11}. In some cases, diagnosis is clear grade IV status by the
presence of microvascularization and/or necrosis, but more complex cases can arise where pathology report and clinical status contradict themselves as will be illustrated by a case study presented shortly.

Following diagnosis, surgery resection and optional chemotherapy surgical wafer implant usually act as primary therapy followed by adjuvant radiotherapy, concurrent to chemotherapy\textsuperscript{2}. In other cases where surgical debulking is not a treatment option, proceeding with radiotherapy and concurrent chemotherapy is still preferable\textsuperscript{12}. Chemotherapy agents can then be used for management until remission or more likely, progression\textsuperscript{12}. After adequate radiographic evidence for progression indicating treatment failure, chemotherapy protocols must be changed or abandoned\textsuperscript{13}. Recently, tumor treating fields (TTFields) therapy has been approved by the Food & Drug Administration (FDA) for initial and recurrent therapy for GBMs\textsuperscript{14, 15}.

After exhausting treatment options and with severe functional decline, the patient may reach terminal status, which is when palliative care for maximizing quality of life (QoL) should replace all tumor therapies. Significant side effects are noted with all brain cancer therapies and should be implemented in accordance with the patients’ functional and overall health while discussing treatment purposes. Severely increased intracranial pressure by mass effect of the tumor’s growth can cause herniation and lead to respiratory and/or cardiac arrest\textsuperscript{16}. Other causes of death include surgical complications, systemic illness, and more\textsuperscript{16, 17}.

The following report characterizes each step of oncogenesis, tumor growth, diagnosis, tumor treatment, and terminal stage care in clinical detail. To aid in illustration of the clinical and pathological process of malignant gliomas, a case study of a single patient “WL” will be presented prior to the literature review.
Patient WL received a diagnosis of an anaplastic astrocytoma with superior extension into the hypothalamus approximately 3 months after experiencing progressive visual deterioration. With her onset of symptoms, a neuroophthalmologist attempted treating her radiographically confirmed optic chiasmatic lesion and inflammation with corticosteroids. The following month, the tumor tripled in size without response to steroid therapy and WL received a neurooncological consult. Her diagnostic process began, lasting 20 days and ended with a grade III unresectable diagnosis to proceed with radiotherapy and her first round of 8 chemotherapies.

Patient WL responded well to treatment initially, followed by periods of stability, equivocal progression, and finally unequivocal progression on day 300 post-diagnosis. With infiltrative malignancies, equivocal changes in volume or signal represents a large problem with how MRI cannot capture microprogression, which is possibly occurring in such situations. In retrospect, notable progression by appearance of new lesions distal from the primary site, typically along white matter tracts, can confirm the probability that the mild changes represented microprogression, but time is a very valuable thing to waste when making decisions to change or abandon protocols. In WL’s case, distal progression did occur in locations down white matter tracts and confirmed that the minute changes represented microscopic tumor cell migration.

Following synthesis of the new lesions and the clinically confirmed progression, WL changed protocols and continued to do so while her mobility and consciousness declined. Although her functional ability declined quickly, she received chemotherapy until approximately 10 days before expiration. For decreased mental status, WL checked into an emergency hospital and was moved to intensive care unit and intubated for respiratory arrest within 48 hours of arriving. Her last MRI of 10 days prior showed severe cortical, subcortical, and cerebellar
involvement most likely attributing her loss of consciousness and respiratory decline to mass effect of the tumor. Intubation was removed and patient WL expired peacefully 456 days post-diagnosis. The radiographic, functional, and clinical course of patient WL will be described in more detail in Part I – Case Study and in the conclusion section of each subsequent part in the remaining review.
**Part I. Case Study**

As a way of introduction to the discussion of malignant glioma pathology and treatment, a detailed synopsis of a case study of an anaplastic astrocytoma will be presented. Not only will this discussion provide a foundational appreciation for the clinical application of gliomas, but reference to this case will continue throughout the paper for a more illustrative discussion of pathological and treatment-based theory.

**Methods**

With explicit written permission of the family and the patient’s personal representative, complete medical records of the patient were obtained from the primary treatment center designated ‘Hospital 1’ and a separate institution where WL was hospitalized for a short duration, designated ‘Hospital 2’. Records were obtained in compliance with both hospitals’ patient authorization to disclose records requirements by the patient’s personal representative. For confidentiality purposes, the names and details of the patient, medical personnel, and medical institutions will not be disclosed nor any information to identify a single person or place involved. Please contact the author with questions regarding the medical records.

The medical records included reports from outpatient, emergency department, and surgical departments beginning from 20 days pre-diagnosis until 456 days post-diagnosis at the date of expiration. However, symptom onset began approximately 95 days prior to diagnosis, which is described in retrospect by the primary neurooncologist as part of clinical history. For confidentiality purposes and out of respect for the deceased and her family, the patient will be referred to as “WL”.
Quantitative Measures

Karnofsky performance score represents person health and well-being related to impairment by disease and so is an appropriate measure of progression for WL and brain tumor patients\(^2\). Karnofsky scores are reported directly from the primary physician’s notes.

MRI scans are referenced periodically through the case study and images are used to represent location and extent of tumor growth. All MRI scans shown are merely representative of approximate tumor infiltration demonstrated on MRI scans adapted from Harvard of an anonymous healthy patient\(^{20}\). Adobe Illustrator was used to edit areas of infiltration on the scans. Infiltration was quantified into percent scores of infiltration in Table 1 by assessment of the qualitative descriptions provided by the clinical notes where maximum infiltration is the extent found on day 447.

Other functional measures including attention/consciousness and mobility were quantitatively calculated by the author. Attention and consciousness was calculated using clinical notes of behavior to evaluate Glasgow’s chart criteria and converted to percent measures\(^{21}\). Mobility measures were determined by converting qualitative clinical descriptions to percent functions.

Results

WL was a 46 year old woman, who was diagnosed by the tumor review board of Hospital 1, on what will be referred to as day 0, with an anaplastic astrocytoma of the optic chiasm that descended superiorly into the hypothalamus. A detailed look at WL’s visual, neurological, radiological, and general deterioration and the implemented course of treatment will now be presented.
Results: Clinical Description

Over the course of 476 days, 30 and 10 clinical notes were written from Hospital #1 and #2, respectively. Over that time, WL was diagnosed and treated for a malignant brain tumor that affected her vision, mobility and balance, consciousness, and respiratory function. Her disease course has been divided into 7 stages: Pre-symptomatic; Prodromal; Primary Treatment; Response; Disease Stability; Progression; and Terminal.

Pre-diagnosis.

Presymptomatic stage. Prior to symptom onset, WL was a healthy 46 year old female. Her family history was positive for maternal renal cancer, paternal hypertension, and maternal grandfather with Parkinson’s disease. Patient WL quite smoking 10 years prior and had occasional wine. She and other members of her immediate family experienced periodic migraines.

Prodromal stage. Patient WL first noticed deterioration of her vision, predominantly in her left eye, 95 days before an official diagnosis was made. Approximately a month after the initial visual changes, she was evaluated by an ophthalmologist on day -56 who used MRI to diagnose a contrast-enhancing lesion and swollen optic chiasm, predominantly on the left side, (Figure 1). At this date, her vision was 20/20 and 20/400 for her right and left eye, respectively. A treatment course of steroids and a follow-up MRI were scheduled to be completed during the following month. The steroid treatment reportedly stabilized her vision briefly, but did not improve her acuity.
Figure 1. Representation of initial midsagittal (left) and horizontal (right) MRI scans taken on day -56 (scan #1) showing lesion of optic chiasm, predominantly on left.

Comparison of the original and the follow-up scan on day -21 revealed the contrast-enhancing disease to be almost 3x larger and involved the entire chiasm with extension into the optic nerves and left optical tract (Figure 1, Figure 2, Figure 3). Consistent with the radiological progression, her vision was reduced to 20/400 and to only finger movement in her right and left eye, respectively. With functional worsening, no response to corticosteroid therapy, and lesion growth, WL was immediately scheduled to see a neurooncologist for consult.
Figure 2. Representation of midsagittal (left) and horizontal (right) MRI scans taken on day -21 (scan #2) showing enlarged lesion of optic chiasm with extension into the optic nerves and left optic tract.

Figure 3. Composite representation of horizontal MRI scan showing optic chiasm lesion on day -65 (red) with enlargement and extension of the lesion on day -21 (blue).
Given the radiological appearance and contrast enchantment, duration of disease, and rate of progression, the preemptive diagnosis was predicted to be a malignant intrinsic glioma. However, several measures were taken to rule out other possible diagnoses and to confirm and grade the glioma.

Over the next 20 days, WL received an array of diagnostic tests. First, a lumbar puncture was performed to rule out lymphoma on day -16 followed by a biopsy consult, during which the doctor reviewed the previous scans and commented further on the lesions superior ascent into the hypothalamus. Although he agreed the disease was consistent with high grade glioma, he also described other possible, but less likely problems including sarcoid lymphoma and metastatic disease.

Three surgeons performed the stereotaxic biopsy procedure the next day using a left subfrontal and peritoneal craniotomy with left orbital osteotomy technique to be completed with a lumbar drain and a dural graft. A microdissection was noted prior to surgery, but was not performed for inaccessibility. The surgery was tolerated well and WL was put on a regiment of steroids and some medicine for seizure prophylaxis. Over the course of the next two weeks, her case was discussed by the Tumor Board at UW so that an official diagnosis and tumor grade can be made, which will allow for treatment determination and initiation.

**Diagnosis.** As stated before, there are many factors into determining tumor grade. Identification of type of cell, degree of anaplasia, degree of proliferation, and presence of necrosis and/or vascularization are significant contributing factors to a pathological diagnosis by biopsy\(^2\). However, a clinical diagnosis based on radiological and symptomatic evidence are also important to consider and may not actually be consistent with the pathological diagnosis. As with
patient WL, the pathological diagnosis of her biopsy was consistent with low-grade glioma, yet her clinical presentation was much more consistent with high-grade glioma.

Several doctors were involved in reviewing and commenting on her case from neurooncology, neurosurgery, and radiation oncology in addition to consultation of the Tumor Board. The official diagnosis made on day 0 was a grade III anaplastic astrocytoma of the optic chiasm and left hypothalamic region to be treated with concurrent radiotherapy and BCNU chemotherapy. A more detailed description of these types of treatment are presented in Treatment. A higher-grade diagnosis was decided upon in consideration of her significant visual decline and the aggressive behavior of the tumor indicated in the radiologic evidence. A higher grade diagnosis and the corresponding more aggressive treatment plan was implemented in hopes of preserving WL’s vision for as much and as long as possible.

Tumor grade is most often given for relating tumor behavior and presentation to the most probable prognosis so that treatments can be specific and aggressive enough while median survival and quality of life are maximized\(^2\). A more in-depth discussion of tumor grading is presented in part III.

Post-diagnosis.

**Primary treatment.** The primary treatment included radiotherapy, which began the day of diagnosis for 21 days, and concurrent BCNU chemotherapy, which began the day after on day 1 dosed in a single regiment based on body size.

Radiotherapy treatment occurred over the course of day 0 to day 21 with 1.2 Gy fractions bid for a total dose of 64.8 Gy using hyperfractionation without dose escalation. The hyperfractional technique was implemented because of the location of the tumor as a way to limit the dosage delivered and decrease the risk of damage from treatment. However, it was
explained to the patient that there was still a 5% risk that she could lose her vision from the
treatment itself. In addition, she received her first cycle of BCNU chemotherapy at 220mg/m²
for a total dose of 405mg on day 1.

Response. A follow-up consultation was given on day 56, in which she was seen to show
a partial response to treatment. An MRI given on the same day showed decreased size and
enhancement compared to the scans taken on days -21 and 1 (Figure 4). Since day 0, her visual
acuity improved to 20/25 and only finger-counting in the right and left eye, respectively.
However, the right hemifield of the right eye and the right upper quadrant of the left eye were
both completely out. She has also improved at recognizing faces and can read with her right eye
slowly. Side effects possibly related to therapy were noted including some weight gain and
difficulty with short-term memory.

Figure 4. Representation of midsagittal (left) and horizontal (right) MRI scans taken on day 56
(Scan #4) showing reduction of optic chiasm lesion after primary treatment compared to scans #2
and #3, taken on day -21 and day of diagnosis (not pictured), respectively.
Clinical stability. As maintenance therapy, adjuvant chemotherapy of BCNU was prescribed three more times following the initial treatment on days 57, 113, and 161. However, the chemotherapy regiment was abandoned after the follow-up consultation after the 4th round of BCNU on day 203.

A second cycle of BCNU at 220mg/m² for a total dosage of 420mg was scheduled for day 57 in addition to a follow-up appointment and MRI scan on day 112. The follow-up appointment on day 112 showed no radiological progression of the tumor and somewhat improved visual testing (Figure 5). The second cycle of BCNU was not tolerated as well and required an antiemetic. Her visual acuity was 20/20 and 20/800 for the right and left eye, respectively. Similar to the previous visit, her vision in the right upper quadrant of the left eye and the full right hemifield of the right eye were out with additional partial loss in the upper nasal field.

Figure 5. Representation of midsagittal and horizontal MRI scans taken on both day 112 (Scan #5) and 161 (scan #6), showing stability compared to Scan #4, while changes, but not increases in contrast enhancing changes were noted (not pictured).

A third cycle of BCNU was scheduled for day 113 at a 25% reduced dosage of 165mg/m² for a total dose of 320mg. Follow-up on day 161 shows improvement in energy level, but slight
decline in her vision, depth perception, and short term memory. However, MRI shows no progression from the scan taken on day 112 (Figure 5). A fourth BCNU cycle was given on day 161 at the same reduced dosage of 165mg/m² for a total dose of 320mg.

**Disease progression.** On day 203, WL came in for another follow-up consultation, during which there was noted slight clinical and radiological progression of disease. WL described her vision as deteriorating in acuity as well as preservation of the visual fields. She also reported difficulty with balance. Although there was some difficulty in interpretation of the MRI scans, there was increased contrast enhancing volume visible only by coronal sections, which would explain her decreased visual ability (Figure 6).

![Figure 6. Comparison of representation of coronal MRI scans of scan taken on day 151 (left; scan #6) and day 203 (right; scan #7) showing increase in thickness of optic chiasm lesion.](image)

Unfortunately, her platelet count of 85 was too low to schedule another BCNU cycle. Further therapy options were presented to WL for consideration including standard temozolomide or temozolomide with high dose tamoxifen. The options to change the regiment were suggested since the tumor was not continuing to respond as it had done, yet did not
necessarily show unequivocal progression either. However, any further treatment would have to be postponed until WL’s platelet count returned to normal.

Approximately three weeks later, on day 224, WL’s labs improved back to safe levels and she elected to continue with the tamoxifen/temozolomide protocol. Visual acuity had worsened in her right, but not her left eye. Review from the Neuro-Oncology Tumor Board agreed the MRI showed an enlargement in contrast volume, especially in the coronal plane. These findings suggest both clinical and radiological progression of disease.

She began the Tamoxifen/TMZ protocol on day 225 with 60mg/m² per day for 42 days and tapered up on tamoxifen from 40mg bid to 80mg bid. Follow-up on day 245 showed significant decrease in visual ability. WL can no longer read any type of normal print and lost her ability for colors and general focusing. The patient commented on light-headedness at the 80mg tamoxifen level along with loss of balance. Her tamoxifen dosage was decreased to 60mg bid, which she reported as helpful. However, on day 300, issues with her vision, balance, and fatigue persisted.

Comparison of a series MRI scans now show less ambiguous progression. Compared to a scan on day 203 pre-tamoxifen, a scan on day 247 showed increased T1 volume in the chiasm with a separate area in flare signal change in the left lateral wall of the fourth ventricle (Figure 7). However, these changes were not significant enough to be determined as unequivocal progression while it was also too early during the new treatment regimen to imply its failure.
Figure 7. Representation of midsagittal (left), horizontal (middle), and coronal (right) MRI scans (Scan #8) taken on day 247 showing slight increase in volume of chiasm lesion and new signal of lateral wall of fourth ventricle.

A comparison of the day 247 scan to one taken on day 300, eliminates any ambiguity of progression and the protocol is discontinued. On the day 300 scan, disease of the optic chiasm and optic tracts seem stable, but a new subependymal area in the anterior horn of the right lateral ventricle and contrast-enhancing disease in the left deep cerebellar region are evident (Figure 8). Her eye sight has deteriorated further to 20/400 and finger counting only in the right and left eyes, respectively. Her neuro-oncologist planned to explore treatment options for radiosurgery for the lesion of the frontal lobe with concurrent chemotherapy of carboplatin and etoposide.
Figure 8. Representation of sagittal of right hemisphere (left), horizontal (middle), and coronal (right) MRI scans taken on day 300 (Scan #9) showing new involvement of subependymal area of right anterior horn of lateral ventricle and of the left deep cerebellar region while chiasm and 4th ventricle lesions remains stable (not pictured).

Evaluation by two radiation oncologists was implemented on day 306 to discuss radiosurgery and radiotherapy options in regards to her progression. Determining whether or not these new lesions indicated marginal recurrences from tumor spread along with matter tracts or from spread through the cerebrospinal fluid (CSF) was a concern of the radiology staff.

At this point, the radiosurgery therapy would only act as palliative care for the relief of symptoms related to tumor location. With a local procedure, there is an extremely high risk of recurrence and further symptomatic deterioration. Along with concern of treatment and recovery time required, quality of life is a serious consideration when finding the right treatment that will provide more worthwhile time for the patient.

By the Stereotactic Radiosurgery Tumor Board, WL’s case was approved for Gamma Knife Radiation surgery to be performed on day 333 to treat the right frontal periventricular and the left fourth periventricular lesion. However, on day 331, the contrast-enhancing part of the lesions disappeared and the surgery was cancelled. Meanwhile, WL began chemotherapy on day
309 with Gleevec and continued until day 377. Gleevec was opted for against the carboplatin/etoposide combination because of likely reduced toxicity. However, the Gleevec chemotherapeutic agent was only in phase 1 or 2 for the brain tumor setting.

Compared to the scan from day 300, the MRI taken on day 350 showed slight changes in the new areas of the ventricular and cerebellar region, new enhancement in the left thalamus and in the corpus callosum, while the optic chiasm lesions remained stable (Figure 9). Some areas improved in terms of contrast enhancement involvement, but signal changes in surrounding areas of the structures made the improvement equivocal. Her vision and balance was continuing to deteriorate.

Figure 9. Representation of midsagittal (left) and sagittal of left hemisphere (right) MRI scans taken on day 350 (Scan #10) showing new involvement of genu of corpus callosum, left thalamus with increased involvement of periventricular region of the fourth ventricular, most notably of the posterior wall, while the cerebellar and chiasmatic lesion remained stable.

On day 377, another scan revealed expansion of the cerebellar lesion and T1/T2 volume changes bilaterally in the frontal hemispheres, more so on the right than left (Figure 10). Her
vision continued to deteriorate with optic pallor and fine nystagmus in the left eye. Her short
term memory was declining more and she required a cane to walk and support her unsteady gait.
The chemotherapy treatment was switched from the Gleevec to the carboplatin/etoposide
protocol, for which she was able to complete one cycle during days 377-380. She experienced
side effects of severe fatigue and reduced consciousness.

Figure 10. Representation of midsagittal MRI scan taken on day 376 (Scan #11) showing new
bilateral involvement of the frontal lobes and expansion of cerebellar lesion while the chiasmatic,
thalamic, and periventricular lesions remained stable.

On day 392, the patient received an abnormal home blood draw of absolute neutrophil
and platelets, which sent her to the emergency department. The final diagnosis was neutropenia
and she was given an initial dose of G-CSF and received another from her primary neuro-
oncologist on days 393 and 394. During both of those visits, neurological examination showed
poor memory, significant confusion, and orientation to person only.

The patient shortly returned to the emergency department on day 399 following a closed
head injury and treatment for a scalp laceration. The incident occurred during ambulation when
she fell and hit her head against the wall. No significant damage occurred in response to the incident and the wound was anesthetized and stapled.

On day 405, the patient’s deterioration continued and her KFS was lowered to 40. Unfortunately, she was pancytopenic with persistent leukopenia, which did not allow continuation with any chemotherapy treatments. She walked very unsteadily with a mildly wide-based gait and truncal titubation. Her neurological state remained very confused and oriented to person only. To be treated with Compazine, WL had persistent hiccoughs and vomiting for the last two days. Consistent with the coughing, vomiting, and poor gait, her primary neuro-oncologist presumed this could reflect the dipositive disease of the fourth ventricular wall and the cerebellum. Monitoring her condition with laboratory work would determine whether there would be any further treatments. On day 413, her laboratory results improved and she continued with Gleevec at 400mg per day.

**Terminal stage.** Examination on day 447, WL’s scan showed massive progression. The scan revealed massive bilateral involvement of the frontal lobes, left hypothalamus, and of the deep cerebellar region extending entirely around the fourth ventricle into the cerebellar hemispheres (Figure 11). In addition, there was massive edema.
Figure 11. Representation of midsagittal (left) and coronal (right) MRI scans on day 447 (scan #12) showing massive bilateral involvement of frontal lobes, involvement of hypothalamus, and entire periventricular involvement of fourth ventricle expanding out into the cerebellar hemispheres. Stable involvement of the genu of corpus callosum, thalamus, and optic chiasm are represented in comparison to scan #11.

WL was not alert enough to participate in visual acuity testing, hearing, or motor examination. She did not respond to pinprick or deep pain stimulation testing. Although breathing on her own, there were audible snoring, gurgling, and sighing noises. The hiccoughs and vomiting persisted from a previous visit and still required medication. Unfortunately, her KFS lowered to 20. Although discontinuation of therapy and pursuit of hospice care was recommended, the family persisted for continued therapy and she received a prescription for Gleevec for two weeks at 400mg per day.

On day 453, patient WL presented to the emergency room for decreased mental status and was also found to have pneumonia and a urinary tract infection as reported by personnel of the secondary hospital. Upon arrival, a CT brain scan revealed complete effacement of the gray-
white interface, complete loss of foci, and only small lateral ventricles. The ER doctor gave a prognosis of a couple days unless there was some improvement by steroids or other means. Before investigating this further, WL began performing apneustic breathing and was subsequently intubated per the husband’s request rather than following any protocols for avoiding resuscitation, which were not previously decided by the family. WL was then admitted to the ICU with evidence of increased intracranial pressure, associated decreased loss of consciousness, respiratory failure, and pneumonia of the left lower lobe. After the family visited, the intubation was removed and patient WL expired peacefully on day 456.

Results: Progressive Data

Timeline of disease. While there were many clinical visits in between, major events are marked in Figure 12 relating to disease course including onset of symptoms, diagnosis, disease response, stability, disease progression, and terminal stage. Treatment regimens are labeled by color and letter showing initial response and stability followed by serious progression indicated by changes in KPS.

Although initial response was well noted, there was also a period of disease stability. However, MRI tracking showed equivocal changes in disease with possible representation of microprogression by slight signal changes. Over time, the changes turned into unequivocal progression marked by new, distal lesions that continued to expand themselves over time. From that point on, WL no longer responded to any treatments and other functions were being compromised in addition to her vision which consistently remained impaired. The two regimens tried during this time did little to rescue function or performance score with periodic hospitalizations noted indicating severity of disability and toxicity (Figure 12).
Figure 12. Performance and event timeline of patient WL. WL’s Karnofsky Performance Score (KPS) with respect to time with labels for MRI progression (▲), major events (★), and treatment regimen (Z#1).

**Tumor infiltration.** Comparing tumor involvement between the first two scans (red and blue in Figure 13) highlights the initial aggressive infiltration observed predicting the glioma’s overall behavior. Observing the final tumor involvement (yellow in Figure 13) the route of infiltration is well marked from the optic chiasm to the hypothalamus via the optic tract, which provided access to the two routes of infiltration through large white matter tracts: the corpus callosum and cerebellar peduncles.

Superior extension of the tumor to the corpus callosum by involvement of the thalamus and hypothalamus also included the periventricular region of the lateral ventricle to the frontal
lobes. By inferior extension to the cerebellar hemispheres, the glioma first infiltrated through the peduncles to periventricular region of the fourth ventricle into the deep cerebellar region out into the cerebellar hemispheres. By starting out in a subcortical region, the glioma found access to white matter tracts for massive final involvement both superior and inferior to the original lesion.

Figure 13. MRI progression between initial and final scans. Mid-sagittal (left) and horizontal (right) T1-weighted MRI scans of approximate tumor infiltration at 50 days (red) and 20 days (blue) pre-diagnosis; and total tumor infiltration in WL’s last MRI 447 days post-diagnosis (yellow).
### Table 1. Summary table of MRI involvement of patient WL by scan number, date, and quantitative value.

<table>
<thead>
<tr>
<th>Scan #</th>
<th>Day #</th>
<th>Structures involved</th>
<th>% Infiltration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-56</td>
<td>Optic chiasm – predominance on left</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>-21</td>
<td>Optic chiasm – 3x larger&lt;br&gt;Optic nerves, left optic tract</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>Not described</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>Optic chiasm – reduction</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>112</td>
<td>Optic chiasm – stable</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>161</td>
<td>Optic chiasm – stable</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>203</td>
<td>Optic chiasm – increased thickness</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>247</td>
<td>Optic chiasm – increased volume&lt;br&gt;Left lateral wall of 4&lt;sup&gt;th&lt;/sup&gt; ventricle – new single change</td>
<td>25</td>
</tr>
<tr>
<td>9</td>
<td>300</td>
<td>Optic chiasm – stable&lt;br&gt;Left lateral wall of 4&lt;sup&gt;th&lt;/sup&gt; ventricle – stable&lt;br&gt;Subependymal area of anterior horn of right ventricle - new&lt;br&gt;Left deep cerebellar region – new, contrast-enhancing</td>
<td>45</td>
</tr>
<tr>
<td>10</td>
<td>350</td>
<td>Optic chiasm – stable&lt;br&gt;Periventricular regions – slight increase&lt;br&gt;Deep cerebellar region - stable&lt;br&gt;Corpus callosum, genu – new&lt;br&gt;Left thalamus – new</td>
<td>65</td>
</tr>
<tr>
<td>11</td>
<td>376</td>
<td>Optic chiasm – stable&lt;br&gt;Periventricular regions – stable&lt;br&gt;Deep cerebellar region - increased&lt;br&gt;Corpus callosum, genu – stable&lt;br&gt;Left thalamus – stable&lt;br&gt;Bilateral frontal lobes - new</td>
<td>80</td>
</tr>
<tr>
<td>12</td>
<td>376</td>
<td>Optic chiasm – stable&lt;br&gt;Periventricular regions – 4&lt;sup&gt;th&lt;/sup&gt;: complete involvement&lt;br&gt;Deep cerebellar region – increased&lt;br&gt;Cerebellar hemispheres – new and extensive&lt;br&gt;Corpus callosum, genu – stable&lt;br&gt;Left thalamus – stable&lt;br&gt;Bilateral frontal lobes – increased, extensive&lt;br&gt;Hypothalamus - new</td>
<td>100</td>
</tr>
</tbody>
</table>
Symptomology. The main functional deterioration WL experienced, besides visual, which remained significantly impaired throughout the duration of her disease, were mobility and attention/memory.

Prior to the unequivocal progression found on day 300, KPS and functioning in attention and mobility where stable or unaffected. Following, rapid decline in attention and mobility corresponding with increased tumor involvement of the frontal lobes/hypothalamus and cerebellum, respectively (Figure 14). Functional decline in turn, correlated strongly with KPS decline, indicative of the relationship between well-being and functional capacity (Figure 14).

The patient began weakening and falling, requiring a cane and eventually a wheelchair for assistance. At 50% function, WL was wheelchair bound, but function declined with increased difficulty and inability to perform motor tasks or hold herself up (Table 2). Beyond needing assistance, motor dysfunctions of the upper extremities and ataxia ensued. Additionally, specific cerebellum dysfunction was noted with symptoms of nystagmus, dysmetria, gait, and circumduction of lower extremities were noted most strongly on the side ipsilateral to the primary cerebellar infiltration.

After day 392, WL began experiencing progressive deteriorated in memory and verbal responsiveness (Table 3). Rapid deterioration caused a coma-like state first noted on day 447 where patient WL showed minimal responsiveness to any prompting stimuli, accumulating to loss of response to even painful stimuli shortly before expiration (Table 3).
Figure 14. Symptom deterioration over time. Percent measure with respect to time of tumor involvement (red), of KPS (purple), of mobility (green), and of consciousness (blue).

<table>
<thead>
<tr>
<th>Day #</th>
<th>Percent</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>Without symptoms</td>
</tr>
<tr>
<td>333</td>
<td>90</td>
<td>Gait with mild ataxia, dysmetria, dizziness/loss of balance, assistance during ambulation</td>
</tr>
<tr>
<td>350</td>
<td>80</td>
<td>Increase in falls</td>
</tr>
<tr>
<td>377</td>
<td>70</td>
<td>Unsteady gait, unbalanced/nystagmus/circumduction on left side, assistance with cane</td>
</tr>
<tr>
<td>392</td>
<td>50</td>
<td>Progressively ataxic, wheelchair bound</td>
</tr>
<tr>
<td>393</td>
<td>40</td>
<td>Wheelchair bound, unsteadiness on rapid alternating movements</td>
</tr>
<tr>
<td>399</td>
<td>30</td>
<td>Fell causing head laceration</td>
</tr>
<tr>
<td>405</td>
<td>30</td>
<td>Gait and balance deterioration, moderately ataxic, wheelchair bound</td>
</tr>
<tr>
<td>447</td>
<td>0</td>
<td>Prostrate in wheelchair; non-responsive</td>
</tr>
<tr>
<td>453</td>
<td>0</td>
<td>Non-responsive</td>
</tr>
<tr>
<td>454</td>
<td>0</td>
<td>Non-responsive</td>
</tr>
</tbody>
</table>

Table 2. Qualitative reporting of WL’s mobility function and the corresponding quantified scores.
Table 3. Deterioration of WL’s consciousness over time with score evaluated by Glasgow Coma Scale\textsuperscript{21}.

<table>
<thead>
<tr>
<th>Day #</th>
<th>Score</th>
<th>%</th>
<th>Orientation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4, 5, 6 = 15</td>
<td>100</td>
<td>Conscious</td>
<td>Without symptoms</td>
</tr>
<tr>
<td>333</td>
<td>4, 5, 6 = 15</td>
<td>100</td>
<td></td>
<td>Without symptoms</td>
</tr>
<tr>
<td>350</td>
<td>4, 5, 6 = 15</td>
<td>100</td>
<td></td>
<td>Without symptoms</td>
</tr>
<tr>
<td>377</td>
<td>4, 5, 6 = 15</td>
<td>100</td>
<td></td>
<td>Without symptoms</td>
</tr>
<tr>
<td>392</td>
<td>4, 4, 6 = 14</td>
<td>93</td>
<td>Confused</td>
<td>Confused and disoriented</td>
</tr>
<tr>
<td>393</td>
<td>4, 4, 6 = 14</td>
<td>93</td>
<td></td>
<td>Increasingly confused</td>
</tr>
<tr>
<td>405</td>
<td>4, 3, 6 = 13</td>
<td>87</td>
<td></td>
<td>Oriented only to self, can follow simple commands, very confused</td>
</tr>
<tr>
<td>447</td>
<td>2, 1, 4 = 7</td>
<td>47</td>
<td>Comatose</td>
<td>Non-communicative and nonresponsive to any prompting stimuli</td>
</tr>
<tr>
<td>453</td>
<td>1, 1, 2 = 4</td>
<td>27</td>
<td></td>
<td>Minimal response to pain only</td>
</tr>
<tr>
<td>454</td>
<td>1, 1, 1 = 3</td>
<td>20</td>
<td></td>
<td>none</td>
</tr>
</tbody>
</table>

**Discussion**

WL represents a specific, but relatable clinical case of brain tumor pathology. All of the clinical applications described here will be mentioned in the relevant subsequent sections of the literature review and will also be summarized here for discussing her case as a whole.

First, WL presented with specific and obvious focal neurological symptoms of visual deterioration from her chiasmatic lesion. In only 30 days, the lesion tripled in size and showed extension into the left nerve, bilateral tracts, and left hypothalamus. Per discussion of tumor growth, infiltration usually occurs along white matter tracts and did so here initially\textsuperscript{2}. This increase in size occurred despite the treatment by corticosteroids, changing this neuroophthalmologic problem into a probable neurooncologic problem.

Following, WL quickly received a consult with a neurooncologist who suspected malignant glioma, but continued the diagnostic process for 20 more days to rule out other possible issues and ultimately confirm the suspected pathology by biopsy. Interestingly, the pathology report indicated grade II pathology, proposing a more complicated diagnostic decision.
since clinical behavior of the tumor reflected higher malignancy. Diagnosis is a multifactorial indication of the most likely tumor behavior, prognosis, and response to certain treatments to occur\(^2\). Both grade II and grade III gliomas have a pronounced tendency to recur or progress to grade IV status and may merely represent precursor stages to grade IV\(^2\). Regardless, her tumor was diagnosed with grade III malignancy.

After diagnosis, treatment should start immediately for best results by earliest intervention. Gross total resection by surgery of the tumor is usually primary surgery, but is not always an option depending on location of the tumor for reasons of accessibility or proximity to eloquent or subcortical areas of the brain\(^2,22\). In these cases, partial resection is still recommended, but in cases such as WL, biopsy may be the only option, which is especially true for subcortical structures\(^22\). Following surgery, radiotherapy and concurrent chemotherapy is recommended, which was how WL proceeded\(^12\). WL received hyperfractionated radiotherapy with concurrent BCNU treatment, which were completed on a three and four week cycle, respectively. WL showed marked response to her initial treatments on day 56 and continued on BCNU for management.

Following initial response, WL remained radiographically stable until day 203, then questionable changes on MRI prompted for change in chemotherapy regimen. After one cycle of the new Tamoxifen/TMZ protocol, the changes turned to unequivocal progression status and therapy needed to change. At the time, WL’s labs were not high enough to continue, demonstrating the strong warnings of myelosuppression of many chemotherapy agents. During that time, radiosurgery was an option for one of the new lesions. Yet radiographically, her tumor infiltration continued to change and the operable lesion disappeared, yet the scans still indicated
progression in different areas. The lesions of her cerebellum and hypothalamus had direct effects on her consciousness, balance, and mobility.

WL was declining and was not responding to treatment despite 7 cycles of 4 different variants. With such strong side effects of treatment therapies, continuing treatment can be a universally difficult decision in the terminal phase of brain tumor patients. Patient WL continued with one more cycle of Gleevec, but was admitted a couple weeks later for decreased mental status. During her stay, she was also diagnosed with respiratory and urinary infections. WL was intubated for respiratory distress, which was removed shortly. Her increased intracranial pressure, most likely by mass effect of the tumor, indicates a possible cause of respiratory arrest by brain herniation, which can compromise vital brainstem function.

In the terminal stage, end of life decisions for care are important, but confusing and often undecided in brain tumor patients\textsuperscript{23}. At indication points of unresponsiveness to treatment, significant progression and low well-being score by KPS indication, tumor treatments are removed and palliative care is provided\textsuperscript{23}. This is especially important when regarding the side effects of most tumor treatments and how severe and fatal consequences are possible.

From prodromal to terminal stage by cause of death, the clinical process for diagnosing and treating brain tumors is difficult, yet important to maximize survival and hopefully provide QoL. The following sections will describe generalized pathology, diagnosis, and treatment for malignant gliomas, while relevant sections will reflect back on this case study for illustration of these principles.
Part II. Pathological Mechanisms

This section will cover the topics relevant to the course of pathology of a malignant glioma including oncogenesis, infiltrative behavior, necrogenesis, and pseudopalisading growth.

Glial cells gain their malignant character through genetic mutations that in combination, create unregulated cellular growth and replication. Following, the cells become cancerous tissue by further replication and have characteristic malignant behaviors such as infiltration, migration, microvascularization, and necrosis.

By nature of the topic of pathology, this section is more scientifically described by molecular mechanisms rather than in clinical descriptions. The purpose is to describe the events leading up to clinical manifestation of symptoms by the biological behavior of gliomas. However, beyond symptomatic manifestation and the subsequent treatment, the cells will continue to use these mechanisms to progress, since treatment is not usually curative. By then, symptomatic consequences of tumor infiltration will continue to progress or will create additional dysfunctions over time.
Introduction

Pathological behavior of the tumor corresponds to the initial cancer-cell evolution event up until the formal diagnosis and beyond, as the tumor progresses. This includes both oncogenesis and the pathological mechanisms. The former event begins with the glial cell mutation(s) that induce cancerous behavior in a single glial cell or cell population in the brain with some degree of unregulated growth that eventually form a malignant tumor. The latter event involves cellular behavior mechanisms including growth, cell migration, angiogenesis, and necrogenesis.

Oncogenesis itself most likely will not produce identifiable symptoms, but the pathological mechanisms up to and after onset of symptoms will continue. Depending on the point of infiltration in which induces observable symptoms, tumor growth may be either minimal or extensive at diagnosis. In fact, since malignant gliomas have a tendency to grow incredibly fast, their development abruptly changes certain aspects of the CNS extracellular environment to induce acute, frank neurological symptoms quicker than non-malignant gliomas that slowly infiltrate tissue, giving the CNS time to adapt to any changes. These dramatic changes in the brain will be described here and will provide a basis of why symptoms of malignant gliomas have a rapid, dramatic onset to be described in Diagnosis.

The onset of pathology, specifically the initial cell mutation, is almost impossible to detect given the relatively low initial consequences and the sheer number of glial and other cells in the brain. Each of these ideas will be expanded further, but a brief characterization of the brain and its immune system will serve well to be addressed first to describe certain aspects of the microenvironment around development of malignant gliomas.
CNS Characterization

**Glia.** The brain is a group of highly interconnected neuronal cells that is multidimensionally supported by a system of cells collectively called glial cells. There are many different kinds of glial cells, including astrocytes, oligodendrocytes, microglia, and others less relevant to this discussion.

Astrocytes support the brain through aspects of structure, metabolic support, immune response, CSF production, and other roles in maintaining intracranial homeostasis. Astrocytes specifically act as a web-like form that have a structural functional around neurons and the brain’s vasculature. In addition to maintenance of the BBB and IMS activation, astrocytes also have roles in ion buffering, control of extracellular glutamate levels, energy metabolism and storage, production of a variety of trophic factors, and roles in synaptic transmission. However informative the current studies are, the role of astrocytes in the brain is expected to be more extensive.

Another important type of glial cells in regards to types of malignant gliomas are oligodendrocytes. Malignant oligodendrogliomas are less common than malignant astrocytomas. Oligodendrocytes are cells of myelin sheath that insulate neuronal axons to increase speed and efficiency of action potentials in the cell. Other glial cells in the brain relevant to discussion are those that contribute to the brain’s immune response, most notably the microglia that work in coordination with astrocytes to activate immune response in the CNS and recruit peripheral macrophages to respond.

**The blood-brain barrier.** The BBB is a filtering system of tight junctions between cerebrovascular endothelial cells (CVEs) with a membrane lining 99% of the CNS endothelium. Parts of the hypothalamus, the posterior pituitary, and the circumventricular organs are not protected by the BBB.
physically separating the CNS from the rest of the body\textsuperscript{25, 26}. In addition, supportive pericytes, perivascular macrophages, and astrocyte end feet surround and support the junctions\textsuperscript{26} (Figure 15). Astrocytes have a well-known role in inducing and maintaining gap junction tightness, possibly by producing growth factors, among other proposed mechanisms\textsuperscript{26}. Essentially, only very select, generally small, neutral, lipophilic molecules cross the BBB well while many substances require active transport mechanisms\textsuperscript{25}.

Figure 15. Anatomical view of endothelial junctions of BBB. Adapted from Abbott, Ronnback, and Hansson (2006)\textsuperscript{27}. 

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**CNS immune system.** The CNS is considered an immunologically “privileged” organ by its strongly filtered separation from the peripheral circulatory system, lack of major histocompatibility complex antigens, lack of lymphatic vessels, and slower rejection of grafts compared to the rate of the peripheral system\textsuperscript{25,26}. However, the CNS’s immune mechanisms may just be relatively specialized, but still capable of adequate response in some cases compared to that of the peripheral system\textsuperscript{26}.

The CNS is immunologically specialized by the physical BBB, regular innate immune suppression, antigen draining through sinus and lymphatics, and specialized IMS recruitment of the periphery adaptive immune system (Figure 16)\textsuperscript{26}. The immune system of the CNS relies on several cell types to act as the innate immune system including astrocytes, CVEs, microglial, and CNS specific macrophages\textsuperscript{26}. The CNS innate immune system can become activated and exhibit innate immune defenses by their own actions, but can also recruit the adaptive immune system of the periphery into the CNS by inducing BBB disruption\textsuperscript{26}. Leukocytes and T cells are recruited and increase in number in the CNS, but also have a role in routine immune surveillance of the CNS\textsuperscript{26}. Although astrocytic and microglial activation has benefits for immune or injury response, chronic or unprovoked activation can have severe effects and is not able to handle chronic or massive response needs\textsuperscript{26}. 
GBM patients were found to be immunosuppressive at time of diagnosis by dysfunction of the specialized immune system and possibly influenced by upregulation of TGFβ. Specifically, immunosuppressive mechanisms of the GBM environment somehow results in diminished CD4 cell population, increase in T-regulatory cells, and uncommon inflammation-inducing perivascular cuffing of lymphocytes, which all contribute to the pathological state of the CNS induced by the malignant gliomas.
Oncogenesis

Introduction

Although difficult to observe and truly characterize, oncogenesis of malignant gliomas is theorized to occur by a single or multiple mutations sufficient to cause unregulated growth in a glial cell, leading to formation of a tumor\(^1\),\(^2\). Alternatively, oncogenesis may arise from bipotential precursor cell or neural stem cell to a malignant, somewhat differentiated form\(^2\). This notion is supported by the discovery of brain tumor stem cells with tumorigenic and unlimited growth potential\(^2\).

By genetically profiling tumor cells, several genetic, epigenetic, and expression changes have been correlated with certain aspects of brain tumors, including other co-mutations, malignancy, and response to treatment\(^2\). Of all astrocytic tumors, GBMs have the highest number of genetic alterations, which is most likely indicative of its aggressive nature\(^2\). Using expression profiles, GBMs can be well distinguished from non-malignant pathologies, but may vary largely by specific factors between patients\(^2\). Overall, GBMs tend to overexpress genes coding for growth factor pathways and genes related to cell migration and angiogenesis mechanisms\(^2\).

Notably, genetic profiles show mutation or expression levels at the time of biopsy or autopsy. This does not necessarily provide information of order of mutation occurrence\(^1\),\(^2\). As well, causation cannot be inferred. Table 4 shows genetic and epigenetic changes that, as a percent, are expressed in the GBMs\(^2\). Individual changes may not necessarily be sufficient in themselves to result in a tumor or GBM specifically, in part because of compensation mechanisms by the cells to regulate the effected system well\(^1\),\(^2\). The individual types of changes may contribute to overall unregulated growth, but also may not be necessary in themselves. In
theory, there may be a threshold of genetic and epigenetic changes made in favor of unregulated growth to result in a malignant glioma, but this is beyond the scope of information available. In short, these numbers must be taken in regards to the limits the techniques themselves employ and inferences made should not exceed what the data provides.

Given the numbers shown in Table 4, there are clear differences between the number and types of mutations characterized in primary versus secondary GBMs where secondary GBMs have a confirmed diagnosis of a precursor, less malignant lesion followed by diagnostic confirmation of malignant GBM after recurrence\(^2\). By comparison of primary and secondary GBMs, separate pathogenic pathways may be possibly inferred\(^2\). The mutations regarded by the WHO linked to astrocytomas will be discussed further in regards to expressional or mutational changes and the involved cellular pathways. The mutations linked to primary GBMs are: LOH 10q, epidermal growth factor receptor (EGFR) amplification, P16\(^{\text{INK}4\text{a}}\) deletion, TP53 mutation, and PTEN mutation, ordered in decreasing prevalence in primary GBMs, which constitute 95% of all GBM cases characterized\(^2\).

<table>
<thead>
<tr>
<th>WHO grade II</th>
<th>Astrocytes or precursor/stem cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade astrocytoma</td>
<td>TP53 mutation (59%)</td>
</tr>
<tr>
<td>Clinical History:</td>
<td>↓</td>
</tr>
<tr>
<td>&lt;3mos 68%</td>
<td>&lt;6mos 84%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHO grade III</th>
<th>Astrocytes or precursor/stem cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaplastic astrocytoma</td>
<td>TP53 mutation (53%)</td>
</tr>
<tr>
<td>↓ 5.1 years ↓</td>
<td>↓ 1.9 years ↓</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHO grade IV</th>
<th>Astrocytes or precursor/stem cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary GBM</td>
<td>Primary GBM de novo</td>
</tr>
<tr>
<td>LOH 10q (63%)</td>
<td>LOH 10q (70%)</td>
</tr>
<tr>
<td>EGFR amplification (8%)</td>
<td>EGFR amplification (36%)</td>
</tr>
<tr>
<td>P16(^{\text{INK}4\text{a}}) deletion (65%)</td>
<td>P16(^{\text{INK}4\text{a}}) deletion (31%)</td>
</tr>
<tr>
<td>TP53 mutation (65%)</td>
<td>TP53 mutation (28%)</td>
</tr>
<tr>
<td>PTEN mutation (4%)</td>
<td>PTEN mutation (25%)</td>
</tr>
<tr>
<td>5% of cases</td>
<td>95% of cases</td>
</tr>
</tbody>
</table>

Table 4. Most common genetic and epigenetic changes found in gliomas. Adapted from Louis, Ohgaki, Wiestler, & Cavenee (2007)\(^2\).
LOH 10 Mutation

**Glioblastoma.** LOH of 10 is the most frequent genetic alteration in primary GBMs often with entire copy deletion or one of 3 commonly lost regions\(^2\). The commonality of this deletion suggests the presence of possible tumor suppressive genes including DMBT1 that may have a role in the evolution of chromosomal instability in disease\(^2\). Complete LOH 10 is very rarely seen in low grade tumors, suggesting an additive role contributing to malignancy mechanisms further supported by the associated reduced survival\(^2\). Further, LOH 10 is associated not only with gene expression changes of genes on chromosome 10, but genome wide expression changes implicating important regulatory functions in this chromosomal area\(^2\).

LOH 10q occurs at similar frequencies in both primary and secondary GBMs implicating an association with the general GBM phenotype, yet LOH 10p is seen almost exclusively in primary GBMs\(^2\). LOH 10q typically co-presents with all other genetic alterations described in this section, correlating with disease progression\(^2\). LOH of 10p usually leads to loss of the entire chromosome 10, which is overall very rarely seen in lower grades\(^2\).

**Other LOH loci.** Other LOH trends are seen in GBMs, but with not nearly as high of frequency as that of LOH 10 in either primary or secondary GBMs\(^2\). In addition to 10q, LOH 1p is found at similar frequencies in primary and secondary GBMs implicating a role in both with general GBM phenotype\(^2\). In contrast, LOH19q and LOH22q indicate specific involvement in primary and secondary genotypes by significantly increased frequencies\(^2\).

**Pediatric GBM.** Pediatric GBMs are usually primary, but have different LOH patterns than adult primary GBMs which include +1q, +3q, 16q, -8q, and -17q\(^2\). This notion supports theories of different oncogenesis mechanisms of adult and pediatric GBMs\(^2\).
**Grade III gliomas.** Anaplastic astrocytomas show commonalities with genetic alterations of both high and low grade astrocytomas, supporting the idea that AA may be only a precursor stage to GBM from lower grade tumors\(^2\). Common to lower grade astrocytomas, AAs have a similar frequencies of TP53 (53%), of LOH 17q (50-60%) and of LOH 22q\(^2\). Yet some alterations, including LOH 22q are common in frequency to all grades\(^2\). However, AAs also have significant LOH10q (35-60%) and LOH 19q (46%), more characteristic of GBM genotypes and significantly more frequent than found in low grade AAs\(^2\).

Oligodendrogliomas (OG) can be histologically mistaken for GBMs, but usually identified by its characteristic loss of 1p & 19q chromosomal arms\(^2\). Co-deletion of those arms are associated with favorable OS and PFS within its diagnostic group and may represent the favorable prognoses compared to GBM\(^2\).

Similarly to OG, but to less of an extent, oligodendroastrocytomas (OA) also show LOH 1p/19q (30-50%) and most of those that do not have the astrocytoma-characteristic TP53 mutation (30%), indicating two OA subtypes related more to OG and diffuse astrocytoma (DA) cellular origins, respectively\(^2\). This also implies that this multi-cellular expressing neoplasm does arise from one precursor cell of either astrocytic or oligodendroglial origin\(^2\). Interestingly, OAs arising from the temporal lobe more often represent the TP53/DA subtype than the OG subtype\(^2\). The information implies two genetically distinct subtypes possibly originating from different precursor cells, but this idea is not significantly supported\(^2\).
PI3K/Akt/mTOR (PTEN) Pathway

The PI3K/Akt/mTOR (PTEN) pathway is one that responds to growth factors in a number of ways including increasing glucose intake and stimulating cell proliferation and survival (Figure 17, Figure 18). The biomolecular pathway will first be described followed by ways the process is dysregulated in malignant gliomas by various mutations and changes in protein expression.

Growth factor binding, usually by epidermal growth factor (EGF) or insulin/insulin-like growth factor, to their respective membrane receptors in cells can cause several intracellular mechanisms to occur, stimulating increased nutrient uptake, protein synthesis, lipid synthesis, cell proliferation, and growth. EGFR receptor (EGFR) is a transmembrane receptor that binds the family of extracellular ligands called the epidermal growth factors (EGFs). Binding of these ligands to EGFR transduces an intracellular signal by activation of a second messenger tyrosine kinase that ultimately promotes proliferation. Within this intracellular signal cascade, PI3K, PKB, and mTOR (Akt) also become activated and have downstream effects of increased glucose uptake and inactivation of energy storage mechanisms, essentially stimulating cell proliferation and survival. EGFR can also respond to insulin signals and can activate many other associated mitogen-activated kinases and Ras, which induces transcriptional changes with the ultimate effect of promoting cell division and growth.

An important mediator of this cell growth pathway is the activation of the PTEN gene that inhibits an enzyme in the Akt regulatory cascade by phosphatase activity so as to inhibit cell proliferation. Figure 17 and Figure 18 illustrate these relationships in summarized terms.
Figure 17. Representation of PI3K/Akt/mTOR pathway and role in glucose uptake. Adapted from 31.

Figure 18. Representation of GF pathway including IGFR, PTEN, Akt, and mTOR. Adapted from Feng, Zhang, Levine, & Jine (2005)32.
**General dysregulation.** Activation of this GF-dependent pathway contribute to mechanisms of tumor cell invasion in healthy tissue. In addition to receptor-mediated activation, abnormal activation of the PI3K pathway can also be induced by downstream abnormalities in the PTEN gene and the Ras-dependent pathway by silencing of the NF1 tumor suppressor gene\(^2\). The mitogen/Ras dependent transcriptional process is mediated by GTPase activity transcribed by the Ras gene family, which shows downregulated activity in cancer cells\(^2\). Additionally cancerous mutations in genes coding for the EGFR can cause upregulated, ligand-independent activation of the receptor inducing uncontrolled growth and proliferation mechanisms\(^1\). These mutations are especially well associated with GBM in comparison to other cancers\(^1\).

Another implication of dysfunction of this pathway, notably with the *PTEN* gene and also general abnormal GFR activation, is the well-characterized Warburg effect that induces anaerobic respiration in cancer cells. This mechanism will be described in the *Growth* section, but the stimulation of glycolysis to produce lactate by increasing glucose uptake begins in this pathway and has specific cancer-related metabolism consequences\(^2\).9.

**Mutation trends.**

**EGFR amplification.** Amplification of EGFR is the most frequently amplified gene in GBMs\(^2\). Amplification is observed more frequently in primary (36%) than secondary GBMs (8%) (Table 4)\(^2\). Consequently, amplification of the corresponding gene for EGFR causes overexpression of EGFR in the cell membrane\(^2\). Causality can be assumed here because all GBM cases with EGFR amplification showed EGFR expression, yet only 70-90% of GBM cases with overexpression showed amplification\(^2\). Comparison of these trends implies that expression is part of a multi-system pathway and regulation of other ligands may attribute to the cases where overexpression is observed, but amplification is not\(^2,\)\(^2\)\(^9\).
EGFR in AAs is much less common (<10%), but its amplification does correlate with shorter survival in AAs\textsuperscript{2}. Overall, EGFR amplification has not been consistently found to influence survival\textsuperscript{2}.

Amplification is associated with structural changes resulting in cancerous protein variants that activate the same pathway of EGFR, but at a different step\textsuperscript{2}. The most common EGFR variant observed is called EGFRvIII, which promotes constitutive activation of the growth factor signaling pathways previously mentioned and occurs in 20-50\% of GBM cases that show amplification of EGFR\textsuperscript{3}. The variant results from a non-random in-frame deletion of exons of the EGFR gene\textsuperscript{2}. Because of this variant’s tumor specificity and expression on the extracellular membrane, drug delivery and detection of cancerous cells using antibodies specific to this membrane receptor may be a promising therapeutic target\textsuperscript{2}. However, given the prevalence of expression for this variant, not every case of GBM would respond\textsuperscript{2}. More than that, over 90 genes contribute and/or define its overexpression\textsuperscript{2}. Yet testing of individual GBM biopsies for co-mutation of EGFRvIII and the associated PTEN have helped identify responsive patients to EGFR kinase inhibitor chemotherapies, erlotinib or gefitinib, while the drugs had minimal responses in the overall population\textsuperscript{2}.

**Other loci changes.** Interestingly given the associated EGFR pathways, EGFR amplification shows inverse associations with TP53 and PTEN, but is typically associated with p16\textsuperscript{ink4a} deletions of the Rb pathway\textsuperscript{2}.

PTEN mutations occur in 15-40\% of GBM cases, almost all of which are primary tumors\textsuperscript{2}. In total, 78 possible mutations of different mutation types are responsible for the range of those cases indicating different mechanisms of damage, but that all result in the same dominant phenotype\textsuperscript{2}. 
Amplification of the PI3K enzyme to further exacerbate the pathway occur, but with high variance between studies\(^2\).

**TP53/MDM2/P14\(^{ARF}\) Pathway**

Another process to be referred as the P53 pathway, is activated under cellular stress conditions including hypoxia and DNA damage, apoptosis or senescence, permanent arrest of cell cycle, where the cellular response depends on the extent and duration of stress (Figure 19)\(^1\). Again, the cellular process and relevant genes and proteins will be described in normal function first, followed by mutation trends in malignant gliomas.

The gene TP53 codes for the DNA-binding protein P53 that pauses the cell cycle process until temporary damage can be fixed or, in the event of extensive damage, can signal for apoptosis\(^1,2,29\). The P53 protein inhibits cyclin-dependent kinase (Cdk) complexes required for progression from G1 through S phase and also regulates pro-apoptotic genes (Figure 19)\(^1,29\). Additionally, P53 plays a role in cell differentiation and neovascularization\(^2\).

The MDM2 gene inhibits and promotes the degradation of P53 protein, activated itself by P53 expression as an autoregulatory feedback mechanism (Figure 19)\(^2\). Inhibiting P53 function shows the MDM2 gene’s role in regulating initiation of apoptotic and cell cycle arrest\(^2\). The P14\(^{ARF}\) gene encodes for a protein that inhibits MDM2 transcription, consequently inhibiting MDM2-induced inhibition and degradation of p53\(^2\). In opposition to MDM2 gene, P14\(^{ARF}\) is negatively regulated by P53 and so plays an overall important role in inducing P53 function for cell cycle arrest and apoptosis\(^2\). Figure 19 summarizes this process.

Loss of normal function for any of TP53, MDM2, and P14\(^{ARF}\) can contribute to dysfunction of the initiation of cell cycle arrest and apoptosis when needed\(^2\). Mutations causing
loss of function for P53 are dominant in effect in opposition to Rb genes that control the P16\textsuperscript{ink4a}/Cdk4/Rb1 pathway\textsuperscript{1}.

![Figure 19. Representation of p53 pathway. Adapted from Soussi\textsuperscript{33}](image)

**Mutation trends.** TP53 mutations of all GBMs are overall high, but significantly more so for secondary than primary\textsuperscript{2}. Within the secondary and low-grade populations that show high frequency of TP53 mutations, two separate lesions groups were found indicating different molecular mechanisms for mutation acquisition\textsuperscript{2}. When adjusted for age, TP53 related mutations were not suggestive of prognostic influence\textsuperscript{2}.

Changes of the MDM2 gene can also induce loss of control for this apoptotic pathway\textsuperscript{2}. Amplification was found in 10% of primary GBMs without TP53 mutations and overexpression
>50% GBMs. Overexpression would essentially inhibit and degrade P53 at a rate more than normal resulting in absence of those safety functions in situations that might warrant them.

Alternatively, loss of expression by homozygotic deletion or promoter methylation of the P14\textsuperscript{ARF} gene was found in 76% of patients with no significant difference in primary and secondary groups. Methylation of the gene was found in one-third of low grade astrocytomas indicating its acquisition is progressive with disease course.

**Subtypes.** Giant cell GBM have frequent TP53 mutations (75-90%), possibly attributing to their odd cellular characteristics of large size and multi-nucleations. As stated before about 30% of OA carry mutations for TP53 genes possibly representing an astrocytic origin distinct from other OAs, with a genotype more indicative of OG origin.

**P16\textsuperscript{INK4a}/Cdk4/Rb1 Pathway**

As noted before, P53 has a roll in arresting the cell cycle by indirectly inhibiting Cdk complexes required for completion of the cell cycle. Specifically, this disrupts completion of DNA synthesis in S phase. Similar to downstream activity of P53, the protein coded for by the P16\textsuperscript{INK4a} gene also inhibits a specific Cdk, the Cdk4/cyclin D1 complex, which has normal function of activating the Retinoblastoma-1 (Rb1) protein, coded for by the Rb1 gene, which is a necessary step to activate the genes needed for the G1 to S phase transition (Figure 19).

Loss of expression for either P16\textsuperscript{INK4a} or RB1 and overexpression of Cdk4 or other Cdks can attribute to unregulated cell growth by inability to respond to damage.

**Mutation trends.** Disruption or inactivation of the Rb1/ P16\textsuperscript{INK4a} pathway are common of GBM (40-50%), but only P16\textsuperscript{INK4a} deletion or Rb1 alterations are noted. Rb1 alterations occur either by LOH 13q which includes the Rb1 locus (12% primary GBM, 38% secondary GBM) or by reduced expression from methylation of its promoter (14% primary, 43% secondary) and are
exclusive to grade IV astrocytomas\textsuperscript{2}. Interestingly, this might indicate its role in low-grade evolution to high grade malignancies\textsuperscript{2}. Of malignant gliomas, only 15\% had Cdk4 amplification and were associated with preservation of the P16\textsuperscript{INK4a} gene\textsuperscript{2}.

Of GBMs, EGFR amplification and P16\textsuperscript{INK4a} are often co-presenting\textsuperscript{2}. For the GBM small cell phenotype, co-presence of EGFR amplification, P16\textsuperscript{INK4a} homozygous deletions, PTEN mutations, and LOH 10q are frequent genotypes\textsuperscript{2}. As with other patterns, low P16\textsuperscript{INK4a} deletions in children compared to adult support the notion of different oncogenic mechanisms\textsuperscript{2}.

\textbf{MGMT Promoter}

The O\textsuperscript{6}-methylguanine-DNA methyltransferase (MGMT) is a repair protein that removes abnormally-placed alkyl groups from DNA base pairs than cannot be replicated or transcribed\textsuperscript{2}. The most notable dealkylation activity MGMT is known for removing an alkyl group from the O\textsuperscript{6} position of the DNA guanine base, but may have roles with other alkyl-group mutations\textsuperscript{2,34,35}.

\textit{Mutation trends.} Methylation of promoter CpG islands can cause loss of MGMT expression and is a known genotype of GBM (45-75\%), more so of secondary than primary, that has marked response to temozolomide chemotherapy treatment\textsuperscript{2,34,35}. Decreased expression caused by promoter methylation of other genes including TP53 and P14\textsuperscript{ARF} are common, also more so in secondary than primary GBMs\textsuperscript{2}. This genetic subtype of GBM have relatively pronounced susceptibility to the actions of chemotherapy agent Temozolomide based on the drug’s mechanism and is described in the \textbf{Temozolomide} section

\textbf{Pathological Behavior}

From biopsy, several ways of determining malignancy grade and more importantly its probable response to treatment includes several genetic, molecular, cellular, and macroscopic features. Some features that correlate with different tumor grades include genotypes, gene
expression profile, signaling and apoptosis status, hypoxia presence and extent, and SCLGC presence\(^2\). The features that are most defined in determining the aggressiveness and grade of the tumor at a biological level can be described in terms of varying degrees of infiltrative nature, cellularity, anaplasia, nuclear atypia, and mitotic activity as well as the presence of microvascular proliferation and necrosis. These different classifications are used by pathologists to assign tumor grade and relate to aggressiveness and progress of the tumor\(^2\). This section will describe how those observable qualities change in malignant cancerous cells compared to healthy cells or non-malignant cells. However, their relation to specific tumor grade determination will not be defined here, but in the **Diagnosis** section where grade-specific trends will described in the decision making criteria.

**Malignant Cellular Characteristics**

**Infiltration.** Firstly, substantial growth and infiltration of the cancerous cells is a defining characteristic of malignant gliomas and even the lower grade II diffuse astrocytomas. Essentially, the mass invades tissues with a diffuse nature – an aspect specific to astrocytomas\(^2\). This is usually confirmed and observable through imagery techniques or confirmed through diagnostic surgery\(^2\). The mechanisms behind infiltrative growth and migration will be described in the **Growth** section.

**Cellularity.** In addition, hypercellularity is typically evident with malignant gliomas\(^2\). Physically, this refers to an increase in cell density in an area\(^2\). Low cellularity might indicate early progression of tumor growth, but distinction from a low-grade cancer must show evidence towards future mitotic activity\(^2\). Otherwise, the cancerous cells will most likely not follow pathology of a malignant tumor and is probably indicative of a benign or slow-growing tumor,
instead\textsuperscript{2}. Levels of cellularity must be evaluated by microscopy using tumor tissue extracted during biopsy\textsuperscript{2}.

**Anaplasia.** In addition to increased cellularity, individual cells usually have varying degrees of anaplasia or cell deformities\textsuperscript{2}. The cells can show abnormal, physical defects that may be variable or monotonous in nature\textsuperscript{2}. Especially in GBMs, the cells may have such a high degree of anaplasia their identity might not be determinable, especially at the foci of the tumor\textsuperscript{2}. The extensive heterogeneity of the GBMs poses difficulty in determining cellular nature in some cases\textsuperscript{2}.

**Nuclear atypia.** With increased anaplasia, nuclear morphology becomes more obviously atypical in terms of size, shape, coarsening, and dispersion of chromatin\textsuperscript{2}. As well, increasing nucleolar prominence and number denotes a higher degree of nuclear atypia\textsuperscript{2}. Multinucleated tumor cells or cells with visible abnormal mitoses are also observed\textsuperscript{2}.

**Mitotic activity.** Malignancy denotes active growth of a cell mass and so evidence of abnormally high levels of mitotic activity are, by definition, present in malignant gliomas\textsuperscript{2}. This is an important characteristic of malignant gliomas as indication of their aggressive infiltration behavior, but objective evaluation of the quantity can be difficult to confirm. The genetic pathways dysfunctional in cancerous cells leading to unnecessary replication have been described in the **Oncogenesis** section, which lead to the observable mitotic activity to induce cellular mechanisms of growth and migration to be discussed in the **Growth** section.

Such evidence can be observed by visual confirmation of active mitotic divisions in cells of the mass\textsuperscript{2}. As well, high levels of proteins expressed during the cell cycle can confirm proliferative activity\textsuperscript{2}. In medical practices, tissues extracted from a biopsy can be evaluated microscopically and with immunohistochemistry techniques to observe such types of evidence\textsuperscript{2}.
Usually this is characterized by the Ki-67/MIB-1 proliferative index for growth fraction quantification\(^2\). However, it is important to evaluate this information in context of resection size as well as recognizing the possible heterogeneity of the tumor, especially with grade III and grade IV proliferation determination\(^2\). With stereotactic biopsies, a single mitoses event may suggest significant proliferative activity, but should be verified by immunolabeling\(^2\). As for larger resection specimens, single mitosis events is not as indicative of significant activity\(^2\). This is quantified by a proliferative index, quantified by visual confirmation of mitoses or increased expression of proteins observed in the cell cycle\(^2\).

**Pathological Mechanisms**

The following section will describe malignant glioma cell mechanisms for cellular metabolism, growth, infiltration, hypoxia, microvascular proliferation, and necrosis. Essentially, hypoxia induces the cancerous behaviors of the other mechanisms just listed while the consequences of those mechanisms contribute to furthering the hypoxic environment. Malignant glia tend to upregulate anaerobic glycolysis over the more efficient oxidative phosphorylation, to infiltrate tissue for support, and to induce poorly constructed vascularization leading to necrosis and a pseudopalisading migratory technique. It is difficult to separate those mechanisms in a causative, temporal fashion since they may happen simultaneously and contribute to an overall pathological microenvironment, but they will be described in order of metabolism, growth and spread, microvascularization, necrosis, and pseudopalisading necrosis.

**Glycolytic metabolism.** The Warburg Effect is a mechanism common to cancer cells in which glucose uptake is upregulated to be used for inefficient anaerobic glycolysis used to obtain energy even in the presence of oxygen required for the much more energy-lucrative process of oxidative phosphorylation\(^29\). The preference for anaerobic glycolysis can provide ATP energy at
a much faster rate needed for growth and replication providing a mechanism for rapid growth beyond normal cell need, but also contribute to the hypoxic state of cancer cells^1.

As mentioned before, abnormal GFR activation or loss of the PTEN gene which suppresses the GFR-dependent pathway can cause unregulated growth by overworking this pathway which causes increases in nutrient synthesis and uptake by both direct influence or by transcriptional changes^1,2,29. Specifically, activated Akt can relocalize glucose transporter type 4 (GLUT4) from internal vesicles to the cell membrane to increase glucose uptake, among other mechanisms^29. Increased intracellular glucose levels stimulate glycolysis in metabolically demanding situations such as rapidly proliferating cancer cells^29.

The advantage of using anaerobic glycolysis methods for energy over aerobic oxidative phosphorylation is the ability to produce ATP 100x faster with a tradeoff of forfeiting 96% of glucose energy in the final product lactate rather than CO_2^29. In normal cells, activation of GFR indicating a starved state or a state of high energy demand induced by strenuous exercise are situations where the cell will upregulate glycolysis mechanisms over oxidative phosphorylation^29. Yet cancer cells will use anaerobic glycolysis and homolactic fermentation for energy even in the presence of abundant oxygen^29. Inability to use the oxygen can induce hypoxic-like states in cancer and can contribute to pathology as well as its marked high glucose intake indicated by FDG-PET scans^29.

**Migration and growth.** Growth and replication by genetic dysfunction of the three pathways described in the Oncogenesis section indicate the molecular origins for the upregulation of both of those processes. Following those behaviors supported the abnormal, rapid metabolism described by the Warburg Effect, glial cells exhibit other malignant behaviors such as infiltration and spread. The following is a description of the mechanisms and routes used
MALIGNANT GLIOMAS

in malignant spread. Later, this general migratory response will be described as a specific pseudopalisading migratory response to necrotic areas.

_Mobilizing mechanism_. Although glioma’s infiltrative nature is well known and caused by cell migration, the glioma cell migration mechanism is not yet understood to be different than that of healthy glial cells, adult neural stem cells, and glial progenitor cells. Unfortunately, that means targeting of such molecular processes such as inhibiting the MMPs is largely ineffective.

Essentially, the glial cells must detach from each other onto the extracellular matrix system, causing its subsequent degradation, and then use intracellular reconstructive mechanisms to induce its own directed motility. Mechanisms of invasion are driven by activation of growth-factor dependent pathways, specifically TGF and AKT pathways, in addition to hypoxia-induced HIF-1α activation mechanisms. Enzymes or mechanisms that are known to play a role include matrix metalloproteases (MMPs), intracellular cytoskeletal rearrangements, and targeted chemoattractant migrations.

_Cellular interactions_. Microglia also have a role in not inducing glioma proliferation, but exacerbating it. Microglia have been known to associate with and assist glioma proliferation by a morphologically similar, but functionally distinct activated form from regular microglia.

Correlating to the role of microglia and astrocytes as significant backbones of the CNS innate immune system, activated forms of either cell influences the other by induced activation from responding to secretory proteins released by the other. In a similar responsive relationship, the release of certain factors by astrocytic glioma cells which induce migration and disruption of the extracellular matrix are responded to by microglia, which in turn release metalloproteases that help disrupt extracellular matrices. Other cells including T cells are
thought to play a role in supporting tumor growth more so by supporting astrocytic activity, in this case malignant.

**Routes.** Infiltration by both perivascular spaces and large commissures are typical structural pathways of spread by GBMs. Although migration along perivascular spaces is common, invasion of the vessel lumen does not usually occur. Spread along the corpus callosum into the contralateral hemisphere produces the characteristic, symmetric butterfly pattern of GBMs. Additionally, spread through the internal capsule, fornix, anterior commissure, and optic radiations can occur. Those large commissures will become somewhat enlarged and distorted, but not appear as a focal tumor as only a structure intermediate between multifocal lesions. This invasion mechanism also provides an area to exist and avoid cancer treatments or surgery, attributing to peritumoral recurrence.

**Vascularization causes and consequences.** Both microvascularization and necrosis are indicative of extremely aggressive gliomas. These events are all closely related to the hypoxic cellular state of malignancy glial cells in that hypoxia induces angiogenesis and necrosis, which can consequently further attribute to hypoxia. First, the molecular changes attributing to hypoxia and the cellular response to a state of hypoxia will provide introduction into angiogenesis and necrosis.

**Hypoxia.** Hypoxia is considered a major driving force in malignant glioma angiogenesis, specifically with GBMs. The hypoxic environment of the tumor cells may have a set of multifactorial causes including vascular disruption, weakening, or poor organization and also reduced oxygen diffusion into the cell by the increased metabolic demands of the cell, which contribute to the Warburg effect.
Cells in a hypoxic state have different chemical expression profiles as compensation for the lack of usable oxygen around, which is normally important for vital cell processes such as energy metabolism by oxidative phosphorylation. Upregulation of anaerobic phosphorylation by the Warburg Effect can induce a pseudo-hypoxic state even when oxygen is present since it is not being utilized normally. Since upregulation of anaerobic phosphorylation indicates an abnormal state, transcriptional changes ensue as part of cellular response. Hypoxia induces accumulation of the hypoxia master-regulator hypoxia-inducible factor 1-α (HIF-1α), which activates over 100 hypoxia-regulated genes that promote angiogenesis, vascular permeability, cellular metabolism, apoptosis, and cellular migration\(^2\). Additionally, classic GBM cells upregulate VEGF and interleukin-8, two proangiogenic factors and induce microvascular hyperplasia\(^3\). Perinecrotic palisading cells, pericytes, smooth muscle cells, and perivascular bone marrow derived cells are major components of vascular remodeling to supply the tumor mass and starve the surrounding tissues\(^2\).

**Angiogenesis and microvascular proliferation.** Angiogenesis and subsequent microvascular proliferation can mechanistically occur by three methods: vessel co-option, classical angiogenesis, migration and vasculogenesis\(^2\). Vessel co-option introduces or increases vascularization to the tumor by adoption of pre-existing vessels in the brain by the tumor cells\(^2\). In contrast, classical angiogenesis occurs from endothelial cell proliferation that induces the sprouting of capillaries from the pre-existing vessels to supply blood to the tumor cells\(^2\).

Thirdly, migration and vasculogenesis refers to the process of monopolizing bone marrow-derived cells that support vessel growth from the peripheral blood into the perivascular space next to the tumor\(^2\).
In GBMs, microvascularization is generally of two forms including endothelial proliferation and the more common, glomeruloid microvascular proliferation\textsuperscript{7,37}. The former type of microvascularization forms an environment to support forming vessels with enlarged, proliferating endothelial cells, pericytes, and smooth muscle cells\textsuperscript{7,37}. Extreme angiogenic growths become the larger glomeruloid bodies found in GBMs, a second type of vascular proliferation more common than the endothelial type, with an association of poor prognosis in other cancers\textsuperscript{7,37}. This vascularization supports tumor cell growth away from the hypoxic or necrotic cores, where this large expansion by tumor cells and vascularization can be reasonably well supported by the fluidity of the CNS extracellular matrix\textsuperscript{37}.

**Consequences.** Abnormal vascularization can cause both severe weakening of the BBB leading cerebral edema and the associated symptomology of increased intracranial pressure. At a molecular basis, the mechanisms causing the edema also contribute to further cellular hypoxia\textsuperscript{38}. Quick and aggressive vascular remodeling leaves the network prone to dysfunction such as cerebral hemorrhage\textsuperscript{2}. Another consequence of significant microvascular proliferation is necrosis\textsuperscript{2}. Necrosis of tumor tissue is assumed to be caused by an insufficient blood supply, a direct effect of the induced uncoordinated vascular remodeling, and are thereby ischemic in nature\textsuperscript{2}. Both large areas of necrosis and pseudopalisading necrosis can be observed in the brain of advanced gliomas\textsuperscript{2}.

**Cerebral edema.** Brain edema refers to increased total brain volume by water and/or sodium and can be vasogenic, cytotoxic, or hydrocephalic in origin\textsuperscript{38}. Edema associated with brain tumors is primarily vasogenic where fluid filled with proteins occupies extracellular space as a result of BBB disruption\textsuperscript{38}. BBB disruption can be caused by VEGF- and basic fibroblast growth factor-induced abnormal vascularization, which characteristically do not have tight
endothelial cell junctions, decreasing the BBB integrity\(^3^9\). This in turn causes increased production of the two growth factors, glutamate, leukotrienes, and other proteins that can accumulate to damage the junctions more\(^3^9\). Their presence may also contribute to the edema and vascular permeability by extracellular accumulation\(^3^8,3^9\).

Tumor hypoxia can also be related to treatment resistance by reducing the ability for agents to reach tumor cells\(^3^8\). Vasogenic edema also spreads faster near white matter tracts, possibly by lesser resistance of flow than that occurs in grey matter\(^3^9\). Cerebral edema can also produce generalized symptoms including headache and nausea.

*Necrogenesis.* The necrogenesis process is not fully understood but theorized to be a sequence of small clusters of apoptosis that lead to pseudopalisading necrosis and eventually accumulate into the observable large clusters of necrosis\(^2\). Generally, apoptotic events are low and so areas of necrotic tissue remain rather than normal recycling or ingestion by regulatory glial cells\(^2\).

*Vascular occlusion.* Other theories suggest thrombosis may lead to extensive hypoxia resulting in induced cell migration to form pseudopalisading structures\(^2\). Vascular thrombosis is thought to be a direct result of microvascular proliferation while possibly playing an indirect role in the pathogenesis of ischemic tumor necrosis to be described in the following section\(^2\). Vascular occlusion can occur within the glioma environment thought to be caused by intravascular thrombosis and can lead to necrosis\(^3^7\).

As the BBB becomes dysfunctional in GBM, physical changes include extracellular matrix abnormalities, loss of proteins that regulate gap junction tightness, and physical perforations\(^3^7\). Thrombosis may be activated by dysregulation of pro- and anti-angiogenic factors secreted by the tumor cells and by CNS upregulation to control vascular leakage, respectively\(^3^7\).
Vascular occlusion can also contribute to hypoxia of the tumor and act as a driving force of cell away from the hypoxia and necrosis radially as pseudopalisades.37

Pseudopalisading necrosis. Distinct from larger regions of confluent necrosis, pseudopalisading (PP) necrosis is theorized as part of a temporal evolution of the tumor (Figure 20)². Pseudopalisading necrosis attributes to the necrotic profile as a histological hallmark of GBM secondarily to normal, confluent necrosis². This type of necrosis occurs with equal frequency in primary and secondary GBMs².

Figure 20. Pseudopalisading necrosis found in GBM. Adapted from Wippold, Lammle, Anatelli, Lennerz, and Perry (2006)⁴⁰.

The pseudopalisading cells induce rapid angiogenesis by upregulated secretion of proangiogenic factors together causing the standard pseudopalisading pattern: radial tumor growth of glioma cells around a necrotic center with significant microvascularization surrounding the active migrating hypoxic tumor cells. Areas of pseudopalisading necrosis are generally small, multiple in number, irregular foci of the tumor with varying degrees of
necrosis\textsuperscript{2}. Surrounded by radially oriented, small, dense fusiform glioma cells in a pseudopalisading pattern are foci that are characteristically small, multiple in number, and irregularly shaped or band-like\textsuperscript{2}. Small PP centers are often solely composed of a fine fibrillary network absent of both viable and necrotic glioma cells\textsuperscript{2}. Larger PP centers always contain necrotic centers of glioma tissue\textsuperscript{2}.

As well, PP structures are generally hypoxic in nature and sensibly strongly express HIF-1\(\alpha\) and its transcriptional target, VEGF\textsuperscript{2}. Recall that the hypoxia-induced upregulation of VEGF and other pro-angiogenic factors correlate with vascular proliferation mechanisms\textsuperscript{2}. The pseudopalisading cells upregulate processes and molecular factors to adapt or fix hypoxic environments, which specifically do so by increasing mobility and migration, upregulate glycolysis processes, and induce angiogenesis\textsuperscript{37}.

Interestingly, activation of migration most likely by pseudopalisading features may be associated with a decrease in proliferation rate, indicating that even though growth seems largely uncontrolled, there are metabolic constraints especially in this type of migration mechanism\textsuperscript{2}. Compared to surrounding tumor cells, PP areas have an increase in frequency of apoptotic events and a decrease in frequency of proliferative activity\textsuperscript{2}. Generally, these areas do not attract many phagocytes as part of any immune response initiated in the brain\textsuperscript{2}.

\textbf{Apoptosis.} Although theories of necrogenesis incorporate apoptotic events, overall levels of cell death due to apoptosis are low in malignant gliomas compared to coagulative necrosis and do not correlate with prognosis\textsuperscript{2}.

Apoptosis events occur to a higher extent in pseudopalisading cells around areas of necrosis, which does correlate with an upregulation of certain proteins of the tumor necrosis factor (TNF) family compared to levels in normal tissues\textsuperscript{2}. TNF-related apoptosis-inducing
ligand (TRAIL) induces apoptosis in GBMs by binding to death receptor (DR) 5, ultimately activating caspase-8. In addition, both the fas ligand (FasL) and the fas receptor (FasR), another receptor belonging to the DR family, are upregulated in astrocytomas with highest expression in PP cells and correlate with tumor grade. Interactions between cells expressing either FasL or FasR are thought to contribute to pathology by promoting apoptosis. In both cases, ultimately, the activation of receptors of the DR family through interaction of their respective protein ligands are thought to be responsible for apoptotic events occurring in malignant astrocytomas.

**Discussion**

As with other cancers, mutations associated with gliomas target molecular pathways that regulate growth, replication, and regulation of both processes. Most biochemical pathways are highly regulated at both upstream and downstream points to detect little disruptions in the homeostatic balance of the cell state. Evolution to cancerous status selectively creates dysfunction by over-activating growth mechanisms such as involved with the PI3K/growth factor pathway and inducing loss of function for the cellular mechanisms to inhibit the pathway such as the *PTEN* gene.

Only digging into the surface of the biochemical basis for malignant behavior of glial cells, it is evident how taking advantage of astrocyte’s original cellular interactions and migratory methods enable the cancerous cells to upregulate those processes to assist its need for unlimited growth. With such quick and unorganized vascular reorganization, the cancer cells leave a trail of destruction, typically in a pseudopalisading pattern.

**Discussion of WL**

The only indication of these processes occurring in WL were of the initial biopsy description and of what can be inferred by radiographic evidence. Firstly, the biopsy returned
pathological evidence of non-malignant behavior yet radiographic concurrently showed substantial growth. With biopsy mechanisms, size of sample obtained and area of lesion sampled from, can both influence results by the heterogeneous and radially growing tendencies of malignant gliomas. It is very difficult to infer anything about those factors that may have contributed to lower than expected malignancy behavior observed in cellular form since the surgical reports were not that detailed. However, given the location of the tumor and urgency of symptoms induced, the patient could have just been found very early in the process. Details of what cellular characteristics were described by the pathology report were not given even for reasoning of the grade II malignancy report and so this discussion is very limited.

Although details of cellular or genetic status of the disease were not provided in detail, spread by the tumor can be better inferred based on MRI statuses. Initially, the tumor started on the optic chiasm, which an intermediate spot between four roadways or white matter bundles of the optic nerves and tracts. It was noted how gliomas tend to migrate through white matter tracts and WL’s glioma started in a prime spot for such extension. Extension into the hypothalamus and the nerves and tracts was initially noticed on the second scan, day -21. Further extension did not overpass these structures until the equivocal stage, where a new signal change of the 4th ventricle was noticed. Given the current research, this highly indicates microprogression and migration. This notion is supported by the fact that the next MRI showed unequivocal progression and new, distal lesions that were connected to the original by white matter tracts. Extension along the ventricular walls, most likely on the outer surface given the rarity of migration by circulatory systems, and the cerebellar peduncles provided route for the initial new lesions along the ventricular system and deep cerebellar area, respectively. The peduncles and white matter tracts near the ventricular system, most notably the corpus callosum and internal
capsule, provided prime white matter tract migration opportunities for the glioma cells, which the cells utilized as evidence by the final MRI showing massive involvement the frontal lobes and corpus callosal structures. Essentially, the glioma cells started very low subcortically within the optic chiasm by extension up the hypothalamus and thalamus and diverged between two substantial pathways: rostrally up the ventricular system to the frontal lobe and caudally to the cerebellar through the peduncles and deep cerebellar nuclei out to the hemispheres.

Other aspects of progression including vascularization and necrosis were not mentioned in clinical reports, except by the emergency CT showing severe intracranial pressure and symptomatic evidence of increased intracranial pressure and respiratory arrest. Discussion of this fatal pathology will be described in **Cause of Death** section.

**Conclusion**

The implications of these oncogenic and pathological mechanisms set up the biomolecular basis for why and how patients progress during disease course observable through clinical and radiographic deterioration. Essentially, these processes continue the same except for disturbance by therapeutic intervention. Malignant glioma cells show therapeutic resistance by hiding behind the CNS and in the white matter tracts during surgery and therapy. Some of that behavior makes tracking progression difficult and characteristic peritumoral recurrence.
Part III. Diagnosis

The purpose of the next section is to describe the diagnostic process of malignant gliomas in detail from initial symptoms to diagnostic definitions.

The prodromal stage begins at the onset of tumor-related symptoms that will be listed in detail. The symptom cannot always be pinpointed exactly as many neurological symptoms can be dismissed or only noticed in retrospect unless obviously abnormal and persistent. In fact, there are some case studies that will be briefly mentioned in Cause of Death section where several people died from various tumor-related causes including herniation, mass effect, and/or hemorrhage without knowing of their intracranial glioma because either no symptoms occurred or were not noticeable enough to seek medical attention.

In more typical cases, tumor growth does induce symptoms that require medical attention and initiates the diagnostic process. Upon finding radiographic evidence of a brain tumor, analysis of clinical and pathological features influence the diagnostic assignment of malignancy grade after cellular origin is confirmed. The determination of malignancy and its clinical implications will be the main topic of discussion in this section.

Malignant gliomas include grades III and IV gliomas with multiple variants and subtypes included. Together, glioblastomas and anaplastic astrocytomas are the most common grade IV and III gliomas, respectively, and will be discussed in greatest detail. Glioblastoma is also the most common of malignant brain tumor types and has related variants including Gliomatosis Cerebri and subtypes dependent on cellular patterning. Other grade III gliomas include oligodendrogiomas and oligodendroastrocytomas, which are both less common than AAs.

Grading qualities of grade I and II gliomas, most notably pilocytic astrocytomas and diffuse astrocytomas, will be provided for comparison to the malignant variants.
The information provided here and in general regarding diagnoses is meant to best characterize the presenting cancer, accordingly estimate a prognosis, and treat the cancer given the known behavior of similarly presenting grades and types of cancers. Therefore, pathology and response to treatment are very logically estimated, but not guaranteed. To be demonstrated in the next sections, there are many ways specific cases can be individualized, but general prognoses remain similar and inherently grave.

Finally, a chronological look at WL’s diagnostic procedure will be analyzed and compared to the criteria outlined to provide illustration of the clinical manifestation of a grade III glioma. To be noted, WL’s case represents only one specific case and should not be thought of a standard case since every person and cancer is unique.
Introduction

Diagnosing a malignant brain tumor may take several steps. Generally, GBMs have a short clinical history of less than three months due to the deterioration of affected systems. For example, WL’s onset of symptoms began 95 days or approximately 3 months prior to diagnosis of her malignant glioma and she deteriorated significantly in that pre-diagnostic period. Similarly, patients usually have an initial presentation of symptoms which brings them to the Emergency Room or their primary care clinic, initiating the diagnostic process.

Preliminary diagnostic work focuses on ruling out common causes for common presenting symptoms such as those related to raised intracranial pressure. It is unethical to subject someone to a battery of invasive and expensive procedures as an initial step in the diagnostic process without checking for more reasonable explanations for the presenting symptoms first. Even if the presenting symptoms are highly indicative of a brain tumor, many confirmatory tests should be conducted before attempting a biopsy. Yet after biopsy, there are many factors that contribute to a final diagnosis including malignancy grading, which is the purpose of this discussion.

In the next few sections, the factors that go into making that diagnosis and the purpose of the diagnostic decision. The combination of presenting symptoms, diagnostic procedure, and results are too specific to each case to clearly outline. However, the diagnostic criteria will be described in sufficient detail for general applicability for most malignant glioma cases. Analysis of WL’s diagnostic process will be described to exemplify the steps needed to get from initial presentation of symptoms to a final diagnosis.

For a more realistic understanding of the implications of malignant gliomas in a larger context, incidence rates will be described in relation to other generalized cancers and other brain
tumor malignancies. Additionally, within malignant glioma types, other factors including tumor location will be mentioned.

**Incidence**

Previously, incidence and survival rates were provided in the *Introduction* for glioblastoma and AAs, but there are other grade III tumors to include and many other epidemiological factors worth considering.

The Central Brain Tumor Registry of the United States (CBTRUS) is a non-profit organization that reports comprehensive epidemiological data on brain tumors in the US\(^3\). Their report released in 2015, described all for cancers of the brain and CNS for 2008-2012\(^3\). The following incidence statistics from a report released in 2015 of epidemiological data for the years 2008-2012 are cited here and throughout the paper, sometimes in combination with accepted statistics from the WHO Classification of Tumors of the CNS. It should be noted that the numbers reported are the totals from all registries summed by the CBTRUS, but most reported percentages by individual registers range from the average one reported\(^3\).

*All brain tumors.* Compared to other cancers types, cancers of the CNS and brain were the leading in incidence and the second most common cancer-related cause of mortality in children from ages 0-19 by rates of 5.57 and 0.65 per 100,000 persons, respectively\(^3\). However, CNS/brain cancers were more prevalent in adults 20+ years, but ranked the 7\(^{th}\) incidence rate and 11\(^{th}\) cause of mortality among other cancers by rates of 28.57 and 5.78 per 100,000 persons, respectively\(^3\). For all brain tumors, the highest incidence rates were found in the 85+ age group and lowest in children 0-19 by rates of 83.14 and 5.57 per 100,000 population, respectively\(^3\). The range of incidence rates for all primary malignant tumors was 4.79-8.48 per 100,000 persons after adjustment for age\(^3\).
**Gender.** Females have a higher incidence rate of most brain tumor histologies than men including more than double for meningiomas\textsuperscript{3}. However, men do have higher incidence rates than women in several histologies including glioblastomas, several astrocytic tumor types, tumors of neuroepithelial tissue, and most significantly different in germ cell tumors\textsuperscript{3}. Specifically, GBMs are 1.6x more common in males than females\textsuperscript{3}.

**All gliomas.** Of all brain tumors, gliomas collectively accounted for 27.5\% and 80\% of malignant brain tumors\textsuperscript{3}.

Different parts of the brain are more frequently sites for malignant gliomas than others. The top 3 most common primary sites in the CNS for gliomas are the frontal lobe (25.9\%), the temporal lobe (19.8\%), and other brain (19.4\%)\textsuperscript{3}. The most uncommon primary sites in the CNS for gliomas are the pineal (0.1\%), the meninges (0.1\%) and the cranial nerves (1.2\%)\textsuperscript{3}. Of all gliomas, the majority occur within the four cerebral lobes (60.8\%), which also represent the majority of malignant brain/CNS tumor sites (54.1\%)\textsuperscript{3}. The 5yr survival rates by cortical location differ: frontal (34.3\%), temporal (23.0\%), parietal (19.6\%), and occipital (20.8\%)\textsuperscript{3}. Malignant tumors of the parietal lobe have the lowest ten-year survival rate at 14.3\%\textsuperscript{3}.

**GBM.** Glioblastoma account for 46.1\% of all malignant brain/CNS tumors with an incidence rate of 3.20 per 100,000 population and account for 55.1\% of all gliomas\textsuperscript{3}. However, GBMs are only the third most common tumor type of all non-malignant and malignant tumors (15.1\%) behind the two most common, meningiomas (36.4\%) and pituitary tumors (15.5\%), which both have marked propensity to be of non-malignant nature\textsuperscript{2,3}. The median age for diagnosis of GBM is 64 years old\textsuperscript{3}. For year 2016, CBTRUS estimates 77,670 new primary brain/CNS tumors will be diagnosed including an estimated 12,120 and 1,270 to be diagnosed as GBM and AA, respectively\textsuperscript{3}. 

**Survival rates.** The one, five, and ten year survival rates of GBMs are 37.2%, 5.1%, and 2.6%, respectively\(^3\). AAs survival rates of one, five, and ten years are also lower than most malignant variants by rates of 62.1%, 27.9%, and 19.8%, respectively\(^3\). Of adult age groups, these rates decline with age\(^3\). This is especially extreme when looking at the total malignant tumor one, five, and ten year survival rates at 58.1%, 34.4%, and 28.8%, respectively\(^3\).

**Clinical Methods**

**Imaging Methods**

Several methods exist for radiographically locating a tumor, all with advantages and disadvantages in technique. MRI represents the gold standard for brain tumors while CT scans work as an alternative to MRI and in time-sensitive situations. The descriptions of findings for brain tumors and specific indications for malignant gliomas will be described within the **Diagnostic Profile** section.

**MRI.** MRI is the gold standard for tumor imagery techniques because of its superior resolution quality of soft tissue\(^10, 24\). Magnetic resonance imaging (MRI) uses large magnets to capture the radio waves released by excitation and relaxation of the hydrogen atoms of the body mostly in water and fat corresponding to CSF and white matter of the brain\(^24\).

MRI has remarkable contrast resolution to distinguish differences in similar, but not identical tissues, especially compared to CT results that shows good spatial resolution to differentiate between different structures next to each other\(^10\). Overall, contrast resolution using radio frequencies are better for soft tissue characterization, which proves its superiority in neurooncology use\(^10\). One of the main advantages of MRI over CT lies within the electromagnetic source: harmless radio waves used for MRI and ionizing x-rays for CT\(^10\). While the cancer risk for CT scans is small, effects of ionization are cumulative\(^10\).
Technique. Magnetic resonance imaging (MRI) creates a 3D map of the body by differences in radio signal emissions of soft tissue produced by a large magnetic emitting oscillatory radio-frequencies (RFs) that the body absorbs\textsuperscript{8,10}. More specifically, atoms in tissue can absorb the RF and the emission upon electron relaxation provides a quantifiable signal\textsuperscript{8}. Emission signals are detected by a receiver coil while intensity of that signal are influenced by proton density, T1 reaction time, T2 relaxation time, and flow\textsuperscript{8}. Proton density refers to the concentration of protons in the tissue including those in water, proteins and fats\textsuperscript{8}. T1 and T2 relaxation times refer to the longitudinal and transverse reactions times, respectively\textsuperscript{8}.

T1 weighted images employ shorter pulse sequences by shorter RF periods and shorter echo time based on the single 1\textsuperscript{st} echo signal\textsuperscript{8}. In T1WI, water-based signals are characteristically dark along with air, inflammation solid masses while fat and blood are lighter\textsuperscript{8}. T2 weighted images incorporate the first and second echo in a dual echo method by using a longer RF period\textsuperscript{8}. The dual signals used for T2 contrast the hyperintense proteins deposits against hypointense water based signals and by suppressing the water-based signal, produce Fluid Attenuated Inversion Recovery (FLAIR) images\textsuperscript{8}. T2WI show subacute blood, solid mass, fat, and water-based signals as bright signals, while acute/chronic blood and air appear dark\textsuperscript{8}. FLAIR images show masses, subacute blood, and fat as bright while water-based fluids and acute/chronic blood are dark\textsuperscript{8}. T2/FLAIR images are more sensitive to brain pathologies and should be used prior to T1WI or using contrast agents, such as Gadolinium\textsuperscript{8}. The agent only crosses the BBB if there is disruption and shows as an increased signal on T1 images\textsuperscript{8}.

Limitations. Contrast agents are a contraindication for patients with renal problems\textsuperscript{10}. Other risks or issues associated with MRI include the machine noise, possible peripheral nerve stimulation, and claustrophobia\textsuperscript{10}.
Due to potential shifting of the object or radio-frequency induced heating conducted by metal, MRI use is limited for patients with metallic implants including pacemakers, shell fragments, surgical prosthesis, or aneurysm clips.

Quality of scan produced varies mostly from scan time, which is mostly affected by patient compliance with staying completely still in a very small, loud space. Quality can also be disrupted by movement artifacts produced by the patient even so much as eye movement or arterial brain pulsations. The latter movement can mostly be removed or averaged out over a long scan, but eye movement or any more radical motions cannot.

CT. Computed axial tomography (CT) scans compile a series of x-ray images to create a 3-D representation and is a good secondary option for those excluded from use of MRI imagery for reasons of claustrophobia, implanted devices, or time-sensitivity. For initial presentation and indication of possible brain tumor, CT scans are a quick test and a preferable screening option for primary care or emergency physicians with a strong sensitivity to hemorrhage events. Possible or very obvious tumor presence on CT would most likely warrant MRI scan for better analysis and identification of seizures to indicate histology.

Pathology Sample

Open and closed biopsies can be performed to receive tissue specimen for laboratory testing of histopathology. Both of these techniques will be described in Surgical Techniques, but are at least mentioned here as the possible methods for tissue extraction. Additionally, cryogenic diagnosis during surgery can also provide key tumor identity confirmation during surgery so resection can occur, if appropriate. However, that pathology report is less accurate than laboratory mechanisms.
Symptomology

Introduction

Following the initial oncogenesis event and adequate tumor growth, the prodromal stage begins, in which noticeable symptoms manifest in response to the tumor. Symptoms generally depend both on size and location of the tumor. The onset of any symptoms may be noticed only in retrograde if subtly abnormal. This section first covers the scope of possible symptoms with anatomical explanations of why these symptoms would occur with support from the previous sections regarding tumor infiltration and growth biomolecular mechanisms.

Difficulty in diagnosing a brain tumor given a set of symptoms lies within the nature of the symptoms. Are they severe enough for medical attention? Once provided with medical attention, do the symptoms presented necessarily indicate a brain abnormality? The significant growth rates of high grade tumors have a tendency to produce symptoms of increased intracranial pressure and frank neurological deficits by mass effect compared to the initially unobtrusive, infiltrating lower grade tumors. Frank onset of symptoms may get a patient seen and treated earlier in the process, but at a cost by compromising function that may be irreversible. Glioma localization is related to increasing brain region mass by indication that most gliomas occur in the cortical lobes. Tumors of the frontal or temporal lobes may be focally asymptomatic.

The diagnosis process is extensive and requires many tests than are administered based on relevancy to the symptoms and in priority to rule out as many possible issues quickly. More often than not, most symptoms can be explained with simple issues like a cold or infection and not a rare brain tumor. The symptoms covered in this section are meant to describe common
symptoms that people with brain tumors present, yet many can be explained by other types of pathologies.

The symptoms to be covered in this section are of two main categories: those generally or focally related to tumor presence. General symptoms include those related to raised intracranial pressure and global dysfunction while focal symptoms can include discrete dysfunction and symptoms (Table 5). Overall, brain dysfunction can be caused by mass effect, parenchymal infiltration, and/or tissue destruction\(^4\).

The two categories will be presented include typical cases of generalized and focal symptoms, but there may be overlap between symptomology and cause in some cases. As a specific example, WL’s vision was initially impaired as a presenting symptom and remained impaired along with tumor progression, consistent with the location of her tumor on her optic chiasm. However, visual dysfunction can also occur by other tumor-related causes including papilledema by mass effect\(^2\text{-}^5\). In addition, seizures can technically have either generalized or partial origin, but mostly have partial origins in brain tumors patients and so will be included under focal symptoms\(^43\). Lastly, attributing to the complicated neuroanatomical networking of such functions like memory and personality which can be induced by focal dysfunction, neurologic changes can also be of a generalized origin.
<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>Percentage of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>56</td>
</tr>
<tr>
<td>Memory loss</td>
<td>35</td>
</tr>
<tr>
<td>Cognitive changes</td>
<td>34</td>
</tr>
<tr>
<td>Motor Deficit</td>
<td>33</td>
</tr>
<tr>
<td>Language deficit</td>
<td>32</td>
</tr>
<tr>
<td>Seizures</td>
<td>32</td>
</tr>
<tr>
<td>Personality change</td>
<td>23</td>
</tr>
<tr>
<td>Visual problems</td>
<td>22</td>
</tr>
<tr>
<td>Changes in consciousness</td>
<td>16</td>
</tr>
<tr>
<td>N or V</td>
<td>13</td>
</tr>
<tr>
<td>Sensory deficit</td>
<td>13</td>
</tr>
<tr>
<td>Papilledema</td>
<td>5</td>
</tr>
</tbody>
</table>


**Generalized Symptoms**

Presentation of generalized symptoms are related to tumor size where tumor size alone can induce symptomology, as mass effect. Infiltrating gliomas have a propensity to induce edema, mass effect, vascular bleeding, and hydrocephalus inducing generalization of symptoms. Common symptoms include headache, nausea, vomiting, seizures, and altered mental status.

Edema may produce symptomology by disrupting synaptic transmission or altering neuronal excitability. Those effects can result in headaches, seizures, focal neurological deficits, and drowsiness. The presence of edema presents as an area of low signal on CT and increases T2/FLAIR signals.

In response to vascular bleeding caused by abnormal vascularization typical of GBMs, the brain will swell causing cerebral edema, which can sometimes discontinue the bleeding and cause formation of a hematoma from the extracellular blood circulating, usually in the subdura. Hematomas are normally cleared away by microglial-derived immune activation, but may put pressure or cause vasoconstriction and ultimately ischemic effects on adjacent brain tissues. Hemorrhage events may be amplified in those cases or just cause minimal effects, ultimately
going undetected. However, extensive hemorrhages can occur in GBMs, cause stroke-like symptoms and may produce the first clinical evidence for detection of the tumor.

As the tumor grows, intracranial space is reduced and the pressure inside the skull and against the brain is increased by mass effect, edema, or hemorrhage. Severely increased intracranial pressure can result in loss of consciousness, which requires prompt medical attention. These symptoms can occur from compression of the brain stem. Severe edema and intracranial pressure can lead to herniation as cause of death and will be explained more in that fatal context in the related section.

In general, gastrointestinal symptoms including loss of appetite and nausea and vomiting (N&V) can be caused by general raised intracranial pressure and overall is a more common reported symptom in tumors of the infratentorial space of the posterior fossa.

Headaches are the most common initial symptom experienced and dull tension-type headaches were experienced by the majority of patients with brain tumors (77%)\(^5\). However, the headaches brought on by brain tumors are not exactly the same in behavior as those experienced by people without tumors and may co-present with the other generalized symptoms\(^5\).

Somewhat unfortunately, the milder types of symptoms associated with raised intracranial pressure can be caused by a large number of medical issues and are not sufficient to assume the presence of a brain tumor alone. Depending on severity, persistence, and the patient’s clinical history with these types of symptoms, medical attention may be delayed.

**Venous Thromboembolism (VTE).** Venous thromboembolism (VTE) is a significant pathogenic result of brain tumors and is fatal in patients. Although the onset mechanism is not fully understood, increased expression of tissue factor (TF) and other procoagulants by tumor cells, more so malignant than non-malignant cells, increases the concentration in peripheral
circulation and can activate coagulation, resulting in chronic intravascular coagulation\textsuperscript{39}.

Incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) are reported with more variance\textsuperscript{39}.

**Focal Symptoms**

Along with the previous generalized symptoms, other diverse behavioral symptoms can occur by focal dysfunction related to tumor location and associated peritumoral edema\textsuperscript{4, 5, 6}.

Occurring in 23\% of cases, focal neurological deficits can be caused by mass effect, parenchymal infiltration, and destruction to parts of the brain with specific functions\textsuperscript{4}. Common signs and symptoms per location are listed in Table 6, with less common ones including dermatomal hypoesthesia, neuropsychiatric symptoms, among others\textsuperscript{4}.

Cognitive dysfunction may also be experienced where memory, attention, personality, or language are affected\textsuperscript{5}. Cognitive symptoms may be initially presenting or induced later in the disease progression by tumor or treatment-related effects and may follow a progressive pattern\textsuperscript{5}.

As a presenting symptom, some cognitive symptoms may present similarly to neuropsychiatric disorders and inaccurately diagnosed, delaying correct treatment\textsuperscript{5, 6}.

<table>
<thead>
<tr>
<th>Tumor Location</th>
<th>Signs &amp; Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal lobe</td>
<td>Dementia, personality change, gait disturbance, expressive aphasia, seizure</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>Receptive aphasia, sensory loss, hemianopia, spatial disorientation</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>Complex partial or generalized seizure; behavior change, including symptoms of autism, memory loss, and quadrantanopia</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>Contralateral hemianopia</td>
</tr>
<tr>
<td>Thalamus</td>
<td>Contralateral sensory loss, behavior change, language disorder</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Ataxia, dysmetria, nystagmus</td>
</tr>
<tr>
<td>Brainstem</td>
<td>Cranial nerve dysfunction, ataxia, pupillary abnormalities, nystagmus, hemiparesis, autonomic dysfunction</td>
</tr>
</tbody>
</table>

Table 6. Common focal symptoms experienced by patients with brain tumors by tumor location.

Adapted from Chandana, Movva, Arora, & Singh (2008)\textsuperscript{5}. 
Seizures. Unless the patient has a clinical history with epilepsy, seizures usually receive prompt medical attention and put initial focus on the brain since this type of symptom implies brain abnormality. However, only 1% of those presenting with seizures actually have a brain tumor, but that statistic increases with increasing age. Epileptogenesis in brain tumor patients is thought to be multifactorial and can vary between malignancy grade, extent of hypoxia in tumor microenvironment, and tumor location.

Seizure type. Commonly, seizures are referenced as grand-mal seizures (Table 7). However, Table 7 describes the various types of tumors differentiated by produced behaviors, by epileptic origin, and by localization of activity. In a broader sense, a seizure is a rapid, abnormally strongly coordinated firing of electrical potentials in the brain and so can be instigated by increased neuronal excitability or by dysfunction of the balance in diffuse activating systems of excitability and inhibition of the brain.

Although some types of seizures are very obvious in nature like those with convulsions, others, such as absence seizures, are less overtly symptomatic. Absence seizures are relatively subtle and the patient might not necessarily be aware of its occurrence. In brain tumor patients, the seizures are usually symptomatic and are related to focality of the partial seizure origin. The seizures can be either simple or complex in nature and with or without secondary generalization (Table 7 bolded terms). Tumors located in cortical regions of the frontal, temporal, or parietal lobes have a higher propensity for inducing epileptogenesis while infratentorial and sellar tumors are not associated with seizure activity unless spread to cortical regions.

Epileptogenesis mechanisms. Low grade astrocytomas have a higher frequency of seizures than GBM by 75% compared to 29-49%. A similar trend is found with generally
slower-growing tumors and developmental tumors compared to higher grades\textsuperscript{43}. Definitive mechanisms of epileptogenesis have not been fully accepted, but certain proposed mechanisms correlate stronger with either low or high grade tumors\textsuperscript{43}.

Developmental brain tumors are frequently associated with gross structural abnormalities while low-grade brain tumors tend to isolate brain regions mechanically, both of which show a propensity to induce epileptogenesis\textsuperscript{43}. Morphological changes in tissue related to or causing abnormalities of synaptic vesicles, gap junction transmission, and balances of excitatory-inhibitory neurotransmitter activity, are also related to induced seizure activity\textsuperscript{43}.

In contrast, higher grade astrocytomas are thought to induce seizure activity by consequential effects of hypoxia\textsuperscript{43}. By definition, vasculargenesis and/or necrosis is present in grade IV astrocytomas while grade III tumors have a known propensity to develop these characteristics\textsuperscript{2,43}. Tissue hypoxia is thought to result from inefficient vascular re-organization and increased, unregulated anaerobic metabolism, which can result in tissue necrosis\textsuperscript{43}. Other consequences of tumor and peritumor tissue hypoxia include changes in interstitial pH, cell fluid retention, and glial cell damage\textsuperscript{43}. In turn, these problems increase neuronal excitability and make astrocytes increasingly prone to inward sodium currents, contributing to GBM propensity for seizure activity\textsuperscript{43}.

The relative contribution of either the low-grade/developmental tumor or high grade tumor related mechanisms are not well evaluated, primarily due to the controversial acceptance behind the different theories and the multiplicity in underlying specific factors\textsuperscript{43}. Essentially, each cellular related factor may contribute to the propensity of the nearby tissue to develop seizure activity, yet none seem to be individually absolute regarding causes directly from the presence of the tumor, especially by the heterogeneity of GBMs. However, the best correlation
between underlying mechanisms that may be associated with tumor malignancy behavior, increasing neuronal excitability, and actual seizure activity, is the frequencies reported by patients provided earlier.

**Secondary epileptogenesis.** In a third of cases, secondary epileptogenesis occurs when seizure origin does not correlate with tumor location and is associated with younger age and longer illness duration. Induced cellular consequences by tumor presence that were described previously, is thought to have longer-range influence on other regions of the brain that are possibly more susceptible to seizure activity. This distant influence is thought to be a consequence of a primary epileptic lesion that remained uncontrolled and induced excitability in other regions of the brain. It is recommended to stress early treatment of any primary epileptic lesions found to reduce the chance of secondary, irreversible lesions forming as well.

**Refractory seizures.** Refractory seizures are uncontrolled or untreatable cases of epilepsy thought to be related to nonspecific mechanisms of resistance. This type of disorder is described as comprising of seizures in debilitating frequency and severity so as to significantly impact quality of life uncontrolled by medical interventions. Antiepileptic drugs are not useful in these cases, possibly due to receptor insensitivity. However, various AEDs using different yet still ineffective pharmacological kinetics mechanisms imply the nonspecific mechanisms of resistance mentioned. Such cases are associated with physical or structural lesions of the brain, including tumors. Indirectly, antitumor therapy mechanisms can possibly reduce the frequency and/or severity of refractory seizures.
Table 7. Presentations of different generalized, partial, and other seizure types. Adapted from WebMD\textsuperscript{44}.

\textit{Non-typical focal symptomology.} Additionally, there are atypical presenting cases where unusual or absent symptomology occurs\textsuperscript{4, 6, 7}. Describing these case studies are not to implicate the patient was wrong to not seek attention earlier, but to emphasize how presenting, subtle and usually generalized symptoms may not be significantly alarming.

Odd and unconnected presenting symptoms reported include ulnar neuropathy, vertigo, hearing loss and otalgia, nystagmus, syncope attacks\textsuperscript{4}. A 70 year old female patient did not request medical attention for six months of experiencing vertigo\textsuperscript{4}. Her additional symptoms including a combination of vertigo, hearing loss, otalgia, and nystagmus can all be signs of aging and may have caused the delay in seeking medical attention\textsuperscript{4}. Another patient experienced headaches for six months and did not present to the ER until significant unilateral deficits
occurred and by that time, MRI found multiple malignancies and a hematoma\textsuperscript{4}. Both patients had aggressive deteriorations and diagnoses of GBM, but oddly enough different fates of post-diagnosis expiration after 4mos and full recovery\textsuperscript{4}.

Additionally, neuropsychiatric, subtle or impairing, can also present and remain ignored or misdiagnosed for years\textsuperscript{6}. A report of 8 case studies in which patients with frontal and temporolimbic neoplasms presented with various neuropsychiatric symptoms, representing a less common group of symptomatic presentations\textsuperscript{6}. Focal dysfunction of the frontal lobe can be organized into three groups: presenting dorsolateral syndrome with deficits in executive function; presenting orbitofrontal syndrome with prominent disinhibition; and medial front syndrome with apathy or abulia\textsuperscript{6}. Bilateral involvement of the certain structures was found to more frequently produce the associated focal symptoms than did unilateral involvement\textsuperscript{6}. All of those symptoms can be misinterpreted as depression and in some cases were for 3 years\textsuperscript{6}.

Other case studies with temporolimbic involvement had presentation of auditory/visual hallucinations, mania, and panic attacks that could be mistaken for schizophrenia, bipolar disorder, and anxiety disorder, respectively\textsuperscript{6}. In some of these cases, the patients did not seek medical attention for 3 or even 20 years from symptom onset and some were even admitted to psychiatric hospitals\textsuperscript{6}. From these studies, it was recommended to rule out brain tumors in patients presenting with neuropsychiatric changes occurring over the age of 40, who have additional neurobehavioral or neurologic features, or poor response to psychopharmacological interventions since those situations are not necessarily as common in psychiatric cases\textsuperscript{6}.

**Symptomology Discussion**

The extent to which tumor progression occurs in the prodromal stage before a tumor is found and a diagnosis is made, depends upon many factors. As discussed before, each person and
cancer is unique. Consequently, clinical history and tumor location can greatly influence how quickly medical attention is requested, the tumor is found, a diagnosis is made, and a prognosis is estimated. If a person has a clinical history where headaches are normal and occur often, symptoms related to intracranial pressure may not prompt them to seek medical attention immediately and the cancer may have more time to progress. In another situation, if a tumor is growing in proximity with the temporal lobe, which is usually a relatively quiet area of the brain and does not produce obvious symptoms from pressure, compared to the optic nerve like WL, which had very early and notable consequences in her vision, the former may not be diagnosed as early as the latter.

Apart from describing the trends in presenting symptoms and an overview of how generalized and focal symptoms are caused, those features play a role in tumor progression beyond the prodromal stage. Some symptoms may become more impairing overtime by progressive dysfunction and infiltration of areas while others become rapidly and irreversibly impaired to remain stable over time such as in the case of WL’s vision. In addition, progression of the tumor by migration can induce new symptomology later in the disease course separate from initial symptomology.

**Tumor Presentation Characteristics**

Description of the initial presentation of symptoms and the diagnostic process leading up to finding glial is unique to each patient and cancer. The previous section described common presenting symptoms that may bring someone into the ER because of either the abnormality, persistence, or severity of the symptoms in nature. Through a lengthy series of tests to eliminate other causes, the brain is ultimately examined for causality. Subsequently, disease in the brain may be visually confirmed by radiological techniques, including CT and MRI. Essentially, brain
disease, inflammation, or edema can present similarly radiographically and symptomatically, but have very different causes. For the purposes of this section covering diagnostics, we will assume the disease that is theoretically being imaged and biopsied is that of unregulated cell mass as in a cancerous tumor. The focus of this section will not be to outline the elimination procedure, but what compromises a final diagnosis of malignant glioma in terms of presentation of brain disease. Reaching a final diagnosis is dependent upon a combination of clinical and pathological presentation factors related to the evaluation of a newly discovered brain tumor.

**Clinical Presentation**

Clinical presentation is comprised of symptom progression and radiological behavior. Specific criteria will be outlined in the *Grading* section.

*Symptomatic history.* In the section *Symptoms*, common presenting symptoms were described. The type of symptom, if focally neurological, will aid in locating the tumor to certain part(s) of the brain responsible for the affected system. The deterioration or rate of change for the any of the symptoms may dictate whether or not this should be treated aggressively and immediately. For WL, the biological necessity and quick deterioration of her main affected system, her visual system, prompted a more aggressive approach with the purpose of preventing further, permanent loss of function. Symptom rate of change and severity is definitely taken into consideration in terms of the glioma’s clinical presentation and subsequent diagnosis and treatment.

*Radiological presentation.* Radiological presentation of the disease conveys several types of important information including size and location. Even though most grading criteria is based on pathological report for histological characteristics, it is not always required for diagnostics. In the CBTRUS registry, about 71.3% of tumors had a histologically confirmed diagnosis.
Interestingly, anaplastic oligodendroglioma and oligoastrocytic tumors had the highest rates of malignancy grade completeness (95.0% and 94.6%, respectively)\(^3\).

Initially, brain disease shown radiographically may just indicate a small lesion, easily treated with steroids. However, chronologic persistence and progression of the lesion in size indicates a more serious problem than just inflammation. Many GBMs are so aggressive that when initially imaged, the cancer is already very large and infiltrating\(^2\). Both initial size and progression by scans prior to diagnosis factor in significantly in terms of aggressiveness\(^2\).

In addition to information related to size, the location of the tumor can give information relevant to diagnosis related more to type of cancer. Generally, gliomas are infiltrative in nature compared to meningiomas and metastatic melanomas, which both show relatively defined borders radiographically\(^2\). Additionally, the more proximal in location to the meninges, the more difficult it is to infer from radiological imagery whether it may be a meningioma or glioma.

These factors provide important information by radiographic presentation and indicate what type of tumor and how aggressive it is acting, which can aid in a final diagnosis\(^2\).

**Pathological Presentation**

The pathological presentation is the result of biochemical analysis of the biopsied tissue extracted from surgery. Pathology evaluates the cells based on the criteria described in the section called *Tumor biological behavior*, which includes the following subcategories: *infiltrative nature, cellularity, anaplasia, nuclear atypia, mitotic activity, angiogenesis and microvascular proliferation*, and *necrosis*. The biological basis of each of these characteristics were previously defined in their respective sections and will be specifically defined based on tumor grade in the next section, *diagnostic definitions*. 
Cell type. In addition to the evaluation of malignancy of the cell, the type of tumor cell must also be identified to properly categorize the type of tumor\(^2\). Pathology identifies cell type based on shape and expression profiles\(^2\). Difficulty in diagnosing some tumors occurs with multiple or unclear cell identification in the tumor\(^2\). One example occurs with tumors of mixed glial components such as those with a significant amount of cells with identifiable astrocyte and oligodendrocyte phenotypes, which are diagnosed as oligodendrogliomas\(^2\). Oligodendrogliomas make up 1.8% of all gliomas registered by the Central Brain Tumor Registry of US as reported by WHO\(^2\).

Additionally, some tumor cells have such a high degree of anaplasia that its original identity cannot be determined\(^2\). Oligodendroglial cells and astrocytes are similar enough that increased anaplasia may significantly blur the line for a differential diagnosis\(^2\). Such a high level of anaplasia usually correlates with significant genomic instability usually coinciding with other aggressive features found in GBMs\(^2\).

Metaplasia refers to the reversible acquisition of morphological features of another type of differentiated cell different from its original differentiated identity\(^2\). This reflects a high degree of genomic instability and is most frequently observed as a pre-neoplastic lesion of epithelial tissues\(^2\). This phenomenon may explain the mixed and indistinguishable tumor cell situations described previously\(^2\).

**Diagnostic Definitions**

In this section, two main types of astrocytomas will be discussed based on malignancy: malignant and non-malignant. Malignant astrocytomas will be further divided for specific discussion of grade IV and grade III. As the classic stage IV astrocytoma, glioblastomas will be discussed first. Understandably, most of the literature of malignant gliomas is based upon GBMs
since they have a significantly higher prevalence rate than all other types of malignant gliomas\(^3\). From there, a discussion of the other main type of malignant astrocytoma, the classic grade III astrocytoma called an anaplastic astrocytoma, will follow and be compared to the previous outlined profile of the corresponding grade IV astrocytoma. Finally, a combined discussion of grade I/II non-malignant gliomas will follow to emphasize what and why specific characteristics correspond with higher malignancy.

Each of the three gliomas discussed, grade IV, grade III, and combined grade I/II, will be discussed in a similar manner. First, the specific defining requirements of each diagnosis will be stated. This part is meant to emphasize what is required and prioritized when evaluating the profile of a newly-discovered astrocytoma in a clinical setting. Following, an in-depth look at other contributing factors to grade determination will provide a holistic clinical profile of how each type of astrocytoma presents in terms of all the characteristics of astrocytomas described before. The following will be the characteristics described: radiographic, macroscopic, and microscopic appearance with relevant subsections and attributes. Lastly, a brief summary of the subtypes of each category will conclude each discussion and an overall summary is presented in Table 8.

**Grading Purpose**

When reading through this section, one should bear in mind the purpose and meaning of tumor grading. Grading is a way to characterize the presenting clinical and pathological features to estimate subsequent pathology and prognosis based on collections of features that are found in tumors at diagnosis that indicate it might be curable or will cause death within a certain amount of time\(^2\). There is technically no grade III or grade IV disease that are two distinct species and may even be merely different stages of the same entity\(^2\). Yet, certain features distinguish the two
subtypes into groups with different average prognoses and different responses to certain treatments. Even within these marked groups, other prognostic factors influence overall prognosis as well. This includes clinical features, radiological features, treatment course, and genetic alterations. For the purpose of this section, diagnostic criteria will be outlined in a way to emphasize differentiation of the tumor profile from that of a higher grade.

**Malignant Grade IV (GBM)**

Of all astrocytomas, grade IV is the most common and most aggressive tumor with a 5-year survival rate of 5.1%. Commonly referred to as ‘glioblastoma multiforme’, the second term refers to the high variability of tumor histopathology. As such, Subtypes addresses this variability in which 3 of 8 subtypes will be defined to describe cellular trends that have been known to occur within GBM diagnoses and within a single tumor. However, co-occurrence or absence of any of these subtypes does not change the diagnosis, yet some subtypes correlate with better or worse prognoses than the other grade IV non-subtype equivalents. The diagnostic profile will describe features that are commonly observed in GBMs regardless of the presence or absence of subtypes.

**Diagnostic requirements.** By definition, diagnosis of a grade IV tumor occurs if and only if there is pathological confirmation of angiogenesis and microvascular proliferation and/or necrosis. Accordingly, grade I, II, and III diagnoses are invalid if either or both features are present regardless of other features such as a low proliferative index. However, given the pathway description of how cell proliferation, microvascular proliferation, and necrosis are related, it is unlikely to have the latter two features without noticeable and high cell proliferative indexes. Along with the evaluation of necrosis and microvascular proliferation, other biological
features are typically present in grade IV tumors, which will be discussed in the ‘diagnostic profile’.

**Diagnostic profile.**

*Radiographic appearance.* GBM presentation usually presents by a hyperdense ring with a hypodense core on non-contrasted CT\(^9\). Accompanying cerebral vasogenic edema will appear surrounding the mass along subcortical white matter tracts (Figure 21)\(^9\). Mass effect can produce sulcal effacement, a midline shift, compression of the ventricles, and various types of herniation\(^9\). Abnormal vessel structure is a key component of the GBM tumor morphology and contributes to the presence of the radiographic contrast-enhancing ring mentioned previously\(^2\).

![Figure 21. MRI T1-post contrast (left) and T2 Flair (right) of GBM, demonstrating tumor enhancement and surrounding edema, respectively. Adapted and retrieved from Yanagihari & Wang (2014)\(^{15}\).](image)

**Macroscopy.** At time of diagnosis, tumor area may be quite large despite short clinical history of typically three months\(^2\). Specifically, the tumor will most often occupy a significant
amount of a lobe, usually unilaterally, with poor delineation, clear intraparenchymal infiltration, and areas of necrosis representing non-viable tumor tissue.2

Generally, glioblastomas predominately occur in the subcortical white matter of the cerebral hemispheres. One study reported by the WHO found occurrence in each of the four cerebral lobes in descending order as the following: temporal (31%), parietal (24%), frontal (23%), and occipital (16%). In addition, midbrain, intraventricular, brain stem, and cerebellum/spinal cord tumor sites are relatively less common than subcortical sites and were listed in ascending order of rarity. Rarely, the tumor may present superior to the cerebrum and within the meningeal layers, which may be misjudged as a possible metastatic carcinoma or meningioma.

Often, spread to adjacent cortex and ultimately through the corpus callosum into the contralateral hemisphere occurs (Figure 22). As well, spread between fronto-temporal regions is typical. These trends correlate well with the known preference glioma cells exhibit for migratory mechanisms through white matter tracts. Typically, tumor growth is unilateral, but can infiltrate the contralateral hemisphere through rapid growth along white matter structures such as the corpus callosum or the fornices. This mechanism of tumor spread is more common than migration through the CSF. Both types of spread employ different cellular mechanisms as well as correspond with different prognoses.
Corresponding to the highly infiltrating nature of GBMs, the tumor typically appears poorly delineated from viable neuronal tissue with yellow-ish centers of necrosis and peripheral grey tumor tissue of hypercellular viable tumor tissue (Figure 23)\(^2\). The circumferential hypercellular tissue corresponds to the contrast-enhancing ring usually seen radiographically\(^2\). Multifocal tumors may appear from long-distance infiltration, but a subset of GBMs are true multifocal cancers arising from separate oncogenic events\(^2\). Although rare (2.3%), true multifocal GBMs can only be confirmed if they occur infratentorially or supratentorially, far from
structures that may support spread through the CNS such as the ventricular system or commissures\(^2\).

Figure 23. Extensive infiltration by frontal lobe GBM with visible viable tumor, necrosis, and hemorrhage. Adapted from International Agency for Research on Cancer\(^46\).

Areas of necrosis may generally appear superficial and surrounded by the peripheral hypercellular area or actually more medial and inferior towards the midbrain\(^2\). However, areas of necrosis may not necessarily always be surrounded by viable tumor tissue\(^2\). Physically, the area of necrosis will appear as a yellow or white granular coagulum (Figure 23)\(^2\). Central necrosis may occupy up to 80% total tumor mass as a result of directed blood supply to the viable tumor tissue with reasonable ongoing mechanisms of proliferation\(^2\). Poor delineation of necrotic, viable tumor, and healthy neuronal tissue represent the infiltrating nature of not only astrocytomas, but
of normal astrocytes as well\textsuperscript{2}. Radiographically, this will show up as a non-enhancing core\textsuperscript{2}. Their ubiquitous nature is complemented by the aggressive and severe genetic mutations of tumor cells, allowing for rapid spread faster than the process of cellular tumor stages, resulting in an expanse of cells in different stages of proliferation and cell death\textsuperscript{2}.

In connection with such a vast network of tumor cells with varying degrees of blood supply and proliferative potential, other tissue features such as foci indicative of hemorrhages as well as microscopic cysts can be present\textsuperscript{2}. Vascular proliferation is ubiquitous within the lesion with high density levels around necrotic foci and the peripheral hypercellular area of infiltration\textsuperscript{2}. Tumor appearance may include red and brown foci representing newer and older hematomas, respectively, resultant from brain hemorrhages induced by abnormal vascularization\textsuperscript{2}.

In addition to hemorrhage evidence, microscopic cysts may also contribute to the macroscopic appearance of the tumor and are significantly different from those typically associated with grade II diffuse astrocytomas which are usually well-delineated retention cysts\textsuperscript{2}. Cysts associated with GBMs usually contain turbid fluid indicative of liquefied tumor tissue, contrasting to retention cysts that usually form from secretory glandular fluids\textsuperscript{2}.

**Microscopy.** As indicated by the nomenclature *multiforme*, tissue patterns may vary substantially from tumor to tumor that receive GBM diagnosis\textsuperscript{2}. Correlating diagnosis with tumor appearance is largely dependent on the following features and their distribution within tumor tissue: presence of secondary structures, cellularity, and microscopic evidence of vascularization\textsuperscript{2}. Additionally, cellular proliferation can be quantitatively assessed by measuring the proliferation index or by observing mitoses\textsuperscript{2}.

Distribution of these features vary on a case to case basis, but the general patterns will be described\textsuperscript{2}. Many factors contribute to this variable tissue pattern including region of
oncogenesis, variable, but usually poor cell differentiation, and extensive infiltrating mechanisms\(^2\).

*Secondary structures.* Secondary structures are very common in GBMs and generally represent the accumulation of tumor cells against tissue borders and the migratory capacity of the tumor itself\(^2\). Typically, accumulation will occur in the subpial zone of the cortex, the subependymal region about neurons, the perifocal zone of edema, and the surrounding myelinated pathways or blood vessels\(^2\). Presence of any type of secondary structure against this border is usually indicative of chosen pathways for tumor spread leading to multifocal intracranial tumors\(^2\).

*Cellularity.* GBMs are remarkable as a neoplasm for its heterogeneity within the diagnostic category and even within single patient tumors\(^2\). The neoplasms may be made up of both obviously undifferentiated and differentiated cell populations\(^2\). Changes in morphology within tumors can be abrupt or continuous and the presence of additional morphologies may represent new tumor formations\(^2\). GBMs may have any or all of the following cellular morphisms: small cell; oligodendroglial components; multinucleated giant cells; gemistocytes with displaced nuclei to the cell periphery; granular cells; lipidized cells with foamy cytoplasms; and perivascular lymphocyte cuffing\(^2\). If any of those specialized cells dominate the tumor, it may receive a diagnostic GBM subtype component\(^2\). In that respect, both small cell and giant cell GBM subtypes are reasonably known and have some characteristic genotype trends, previously mentioned\(^2\). Tumors can be highly pleomorphic representing growth effects of unstable or undifferentiated progenitor cells\(^2\).

*Microvascular proliferation and necrosis.* Microscopically, both necrotic glioma cells and faded images of large, dilated necrotic tumor vessels, a consequence of the ischemic nature
of the affected area, can be found within the central area of necrosis (Figure 24). Occasionally, preserved tumor vessels and viable tumor cell coronas will be seen within necrotic areas of GBMs.

Figure 24. Necrosis of GBM histopathology located in upper right corner surrounded by palisading tumor cells and microvascular proliferation. Adapted and retrieved from Agamanolis (2016).47

**Cellular proliferation.** Proliferative activity is definitionally present with a growth fraction of 15-20% determined by the Ki-67/MIB-1 index. Detectable mitoses are almost always present with atypical mitoses characteristic. However, growth fractions and visual mitotic activity can vary widely between tumor cases as well as regionally within the same tumor. Typically, small, undifferentiated fusiform cells show high proliferative activity compared to
neoplastic gemistocytes\textsuperscript{2}. However, the WHO does not formally recognize any association between proliferative index and clinical outcome\textsuperscript{2}.

**Subtypes.**

**Small cell GBM.** Small cell GBMs appear as densely packed, highly monotonous groups of cells\textsuperscript{2}.

**Giant cell GBM.** Giant cell glioblastomas appear as large multi-nucleated cells and a subtype of GBM (5\% all GBMs) distinct by obvious giant cell histology, some genetic mutation trends, always de novo origin, large necrosis without pseudopalisading pattern, and heavy lipidization (Figure 25)\textsuperscript{2}. However, GC-GBMs are common to classic GBMs by similar proliferation rates, short clinical histories, and poor prognoses\textsuperscript{2}.

![Figure 25. Histological view of giant cell glioblastoma subtype showing extreme anaplasia. Adapted and retrieved from Agamanolis (2016)\textsuperscript{47}.](image-url)
**Gliomatosis cerebri.** A specific and rare form of GBM is called gliomatosis cerebri that by its diagnostic definition occupies at least three cerebral lobes and commonly further extension into the deep grey matter, brain stem, cerebellum, and spinal cord\(^2\). The glioma usually displays an astrocytic glial phenotype, but other variants are not uncommon\(^2\).

**Malignant Grade III (AA)**

Anaplastic astrocytomas (AA) are the most common form of grade III astrocytomas with others including anaplastic oligodendrogliomas and others unspecified\(^2, 3\). Every year, 1,200 AAs are diagnosed while the other subtypes are diagnosed less often\(^3\). AAs are very diffuse and infiltrating in its malignant nature\(^2\). The tumor may be primary or secondary in nature as can occur with GBMs\(^2\). However, there is an inherent tendency to progress to GBM character within an average of 2 years\(^2\).

**Diagnostic requirements.** Grade III tumors show an increased degree of cellularity, nuclear atypia, and proliferative activity from that of grade II criteria typically around 5-10%\(^2\). Specific features will be outlined in the *diagnostic profile*. By definition, microvascular proliferation and necrosis are both absent\(^2\).

**Diagnostic profile.**

**Macroscopy.** With a pronounced tendency to invade proximal brain structures, infiltration usually results in marked enlargement of those structures rather than absolute tissue destruction as is more typical in grade IV tumors\(^2\). However, grade III tumors have a pronounced tendency for infiltrating other tissue, significant from grade II tumors\(^2\).

Other typical features include areas of granularity, opacity, and soft consistency\(^2\). Pronounced increased cellularity compared to that of grade II tumors allows for a more grossly
obvious tumor mass\textsuperscript{2}. In addition, AAs do not typically have cystic components found in either grade IV or II tumors\textsuperscript{2}.

\textit{Microscopy.}

\textit{Cellularity.} As mentioned previously in terms of macroscopic changes, increased regional cellularity as compared to grade II tumors is typical (Figure 26)\textsuperscript{2}. However, pronounced hypercellularity is not necessary for diagnosis in case of high mitotic activity\textsuperscript{2}. Features of anaplasia correspond to those described in the GBM diagnostic profile, usually to a lesser severity\textsuperscript{2}.

\textit{Nuclear Atypia.} Generally, with increasing anaplasia, nuclear atypia becomes more pronounced\textsuperscript{2}. Nuclear atypia is a typical component of AAs (Figure 26)\textsuperscript{2}. Specifically, nuclear morphology has increasing variations in nuclear size, shape, coarsening, and dispersion of chromatin as well as an increasing nucleolar prominence and number\textsuperscript{2}. Although not characteristic of AAs, both abnormal mitoses and multinucleated tumor cells are observed\textsuperscript{2}.

Figure 26. Histological view of anaplastic astrocytoma with nuclear atypia and increased cellularity. Adapted and retrieved from UWL dosimetry (2012)\textsuperscript{48}. 

\textsuperscript{2}MALIGNANT GLIOMAS
Cellular proliferation. Depending on resection size, single or multiple mitoses may be sufficient evidence for increased proliferation\(^2\). Growth fraction is usually 5-10% as characterized by the Ki-67/MIB-1 index\(^2\). However, overlap with grade IV or II index range is still compatible with a grade III diagnosis in light of other diagnostic criterion\(^2\).

Subtypes.

**Anaplastic oligodendroglioma.** Anaplastic oligodendrogliomas (AOG) are diffuse, infiltrating neoplasms morphologically indicative of oligodendroglial origin with malignancy characteristics similar to grade III anaplastic astrocytoma\(^2\). Oligodendrogliomas of both grade II and grade III variants have a common characteristics co-deletion of 1p & 19q that is unique\(^2\).

**Anaplastic oligoastrocytomas.** Although macroscopically indistinguishable from AAs or AOGs, histopathology indicates these neoplasms have distinct cells expressing astrocytic and oligodendroglioma origins with either a diffuse or biphasic patterning\(^2\).

**Non-Malignant Astrocytoma Grade I/II (pilocytic and diffuse astrocytomas)**

Pilocytic and diffuse astrocytomas are the most recognized non-malignant astrocytomas of grades I and II, respectively\(^2\). Including other subtypes, approximately 1,000 and 1,700 gliomas of grades I and II, respectively, are diagnosed each year\(^3\). Grade I and II gliomas generally have low or non-existent proliferative activity and have much better prognoses than those of higher grade\(^2\). With relatively circumscribed borders and cystic nature, grade I tumors may generally be cured by resection alone, which contrasts to diffusely infiltrating grade II tumors that generally recur, sometimes with a higher grade of malignancy\(^2\).

Pilocytic astrocytomas are relatively circumscribed, often cystic, and occur in children and young adults (Figure 27)\(^2\). They also have a tendency to show a biphasic histological pattern of compacted bipolar cells and loose-textured multipolar cells\(^2\). In comparison, diffuse
Astrocytomas are more infiltrating in nature, have higher degrees of cellular differentiation, and have a tendency for malignant progression on recurrence for either anaplastic astrocytoma or glioblastoma characterization. The following discussion will be based on diagnostic criteria as recognized by the WHO of tumors of the CNS for grade II diffuse astrocytomas (DA), which are the more common variant of the two.

Figure 27. Pontine pilocytic astrocytoma with typical cystic component. Adapted and retrieved from Agamanolis (2016)47.

**Diagnostic requirements.** These neoplasms must have low proliferative indices, low anaplasia qualities, if any, and show reasonable circumscribed (grade I) or slight infiltration (grade II)2. By definition, both microvascular proliferation and necrosis are incompatible with any grade II diagnosis2.
Diagnostic profile.

Radiographic appearance. In CT scans, DAs present as ill-defined, homogenous masses of low density without contrast enhancement. Calcification, cystic changes, and lower degrees of enhancement may be present at time of diagnosis.

As for MRI scans, T-1 weighted images show hypodensity while T-2 weighted images show hyperdensity (Figure 28). Both scans may show areas of enlargement indicating areas correlated initial tumor growth. Gadolinium enhancement is uncommon in DA, but may indicate progression to higher malignancies.

Macroscopy. As a result of the slower infiltrative nature of the tumor, anatomical boundaries are extensive and may cause enlargement and distortion of invaded structures, typically of the frontal cortex and along myelinated pathways (Figure 29). Although contralateral growth is observed, it is especially particular in frontal lobe tumors. Accordingly, DAs are most often found supratentorially in the frontal and temporal lobes.
Figure 29. Macroscopic view of left thalamic grade II astrocytoma demonstrating enlargement and distortion of structures with midline deviation. Adapted from Agamanolis (2016).

In addition to neuroimaging evidence for cystic profiles, they are also confirmed macroscopically\(^2\). If cystic features are present, there are commonly multiple of different sizes appearing focally spongy\(^2\). Numerous and proximal cystic features may provide a gelatinous appearance\(^2\). Occasionally, a single, large cyst may dominate and those with smooth-wall features are most compatible with the gemistocytic subtype\(^2\). These cysts contrast in both membrane and intracellular appearances compared to those that occasionally appear in GBMs that were previously described\(^2\). Most significantly, the two differ on membrane delineation and cystic contents\(^2\).
Other macroscopic features observed include granular areas, zones of firmness or softening, focal calcification, or a diffuse grittiness profile. Local lesions may be present in either gray or white matter.

**Microscopy.** Generally, DAs are composed of well-differentiated astrocytes, usually of specific subtypes outlined in the next section, composed against a loosely structured tumor matrix often cystic in nature (Figure 30). Neoplastic astrocytes in non-malignant gliomas are generally difficult to distinguish individually from normal or reactive cells (Figure 30). Most apparently, diffuse astrocytoma cells are usually increased in size and number, have minor degrees of anaplasia, and have a very monotonous morphology, in opposition to its reactive cellular counterpart. Specifically, the neoplastic astrocytes differ from normal astrocytic nuclear features of an oval-to-elongated nucleus, intermediately sized chromatin masses, and a distinctive nucleolus. Reactive astrocytes usually show enlarged nuclei, an eccentric nucleus, and cytoplasm that extends into fine processes. Reactive astrocytes usually vary greatly in those features, such as presence of enlarged nuclei or varying amounts of cytoplasm, corresponding to different stages of reactivity. In addition, DA backgrounds usually show normal density or at least increased number of cellular process, yet reactive cells usually show a somewhat rarefied background. As a result, conclusions may point toward injury-related reactions.
Figure 30. Histological view of gemistocytic astrocytoma, similar in appearance to reactive astrocytes. Adapted from Agamanolis (2016).

*Nuclear atypia.* Occasional nuclear atypia is typically observed\(^2\). Histological characterization of nuclear features via H&E staining is vital in recognition of neoplastic astrocytes\(^2\). Specifically, the nuclei may be enlarged, cigar-shape, or irregularly hyperchromatic\(^2\).

*Cellular proliferation.* Generally, mitotic activity is absent, but if present, may still indicate lower-grade astrocytoma\(^2\). As determined by the Ki-67/MIB-1 labeling index, the growth fraction is usually less than 4% with a mean of 2.5%\(^2\).

**Subtypes.**

*Fibrillary astrocytoma.* Fibrillary astrocytomas are the most common histological subtype of DAs\(^2\). Specific characteristics include the presence of intermediate fibers formed by
the neoplastic cell processes, domination of histological profile by microcysts, and other features outlined in the general DA discussion. Occasional presence of gemistocytic neoplastic cells may be observed, but refer Gemistocytic astrocytoma for the differential diagnosis criterion of that subtype.

**Gemistocytic astrocytoma.** This subtype is characterized specifically by an obvious, yet usually variable, presence of gemistocytic neoplastic astrocytes. By differential diagnosis, the cellular fraction of gemistocytic neoplasms should be at least 20%, with a mean of 35%. Specifically, the histological profile should be dominated by plump, glassy, eosinophilic cell bodies of angular shape and tumor cells with stout cellular processes that form a coarse fibrillary network. This subtype is especially prone to malignant progression to higher grade tumor recurrence.
Table 8. Diagnostic summary of non-malignant (combined grade I & II), malignant grade III, and malignant grade IV astrocytomas.
Prognosis

Significant prognosis factors recognized by the WHO for tumors of the CNS are age, presence and extent of necrosis, extent of surgical resection, and LOH 10\(^2\). Not many predictive factors are consistently and significantly associated with prognosis for GBMs, but the four mentioned will be expanded upon in terms of their positive or negative predictive factor\(^2\). Other factors or biomarkers that have not been consistently confirmed in their role by clinical trials are not mentioned in this paper. Lastly, YKL-40 (chitinase-3-like-1) is mentioned as a somewhat promising biomarker.

**Age.** Both the time of survival and time of symptom-free months correspond negatively with age at diagnosis\(^2\). The relationship is generally linear\(^2\). However, karnofsky score is largely determinant in older populations with a positive linear relationship to time of survival and of symptom-free\(^2\).

**Necrosis.** Generally, the presence and increasing extent of necrosis is associated with poorer prognosis\(^2\).

**Extent of surgical resection.** In terms of treatment, extent of surgical resection is the most significant predictive factor\(^2\). Concurrent treatment of radiotherapy and chemotherapy for patients had generally better prognoses, but the relationship was not significant to groups that received only one type\(^2\).

**LOH 10.** The most common genetic alteration, LOH 10, was the only one consistently shown to be a predictive factor and to be formally recognized by the WHO\(^2\). Unfortunately, LOH 10 is associated with reduced survival\(^2\).

**YKL-40.** YKL-40 is a secreted protein of unknown function that has been linked to overexpression in GBMs and is predictive of certain aspects of treatment response and
prognosis\textsuperscript{2}. The protein is associated with LOH 10q genotype, poorer radiation response, and reduced overall survival\textsuperscript{2}. As a biomarker, one use of detection in serum corresponds with monitoring patients for recurrent tumor growth\textsuperscript{2}. The protein is typically coexpressed with matrix metalloproteinase-9 (MMP-9), which play a role in astrocytic migration by extracellular reorganization and degradation\textsuperscript{2,18,19,36}.

**Other.** Specific to AAs, EGFR-amplified genotypes have significantly shorter survival rates\textsuperscript{2}.

**Discussion**

Presenting symptoms for brain tumors range greatly from generalized headaches, memory loss, and personality changes to focal sensory disruption, seizures, and motor issues. Unfortunately, symptoms can also be absent for a significant amount of time or even the entire disease course. Symptomology, both type and severity, can greatly influence the time point in which the patient will seek medical advice and in when the medical personnel will look for and find a brain tumor. Although presenting symptomology can range in number and type, progression of disease can cause new symptoms to arise and increase the original in severity. In essence, symptomology can be defined in relation to the diagnostic process, but is truly a progressive part of the disease and will most likely continue to change, increase, or persist throughout disease. In fact, symptomology in the terminal stage has similarities to other terminal cancers, but is also greatly affected by the debilitating neurologic-specific symptoms brain tumor patients must endure\textsuperscript{17,23}.

Diagnosis of brain tumors is a significant multi-factorial decision that pulls from a variety of analysis techniques including radiographic, clinical, macroscopic, and pathological presentations. Radiographic presentation was mainly based on the features of contrast-
enhancement found on MRI\(^2\). Additionally, if multiple scans are taken prior to diagnosis, progressive behavior can be inferred over time. Symptomology also influences diagnosis such as if the particular function affected is eloquent and vital in daily function or if the behavior induced is severe and aggressive treatment is preferred to preserve function. However, those assertions are only situationally involved in the process. Macroscopic presentation provides information of vascularity and necrosis, which are the most important aspects of GBM diagnosis. In opposition, grade I pilocytic tumors are relatively well circumscribed and may be a reasonable macroscopic feature to note\(^2\).

Lastly, pathology report can affirm cellular identity, which is most important to confirm the glioma identity or subtype, and cellular profile, which is most important differentiating between grade III and grade I/II tumors. Since grades I-III by definition do not show the vascularization or necrosis of which defines grade IV status, differences in cellular integrity and proliferation are the most notable differences. Although not always necessary for diagnosing tumors, histological grades are useful for predicting biological behavior, prognoses, and the best course of treatment.

Beyond the implications of profiling the tumor, diagnosis determines treatment protocols and provides important information in retrospective clinical studies to assess treatment efficacy or diagnostic accuracy.

**Discussion of WL**

**Symptomology.** During the prodromal stage, WL complained entirely of focal symptoms related to loss of visual acuity. Since her symptoms were very easily related neurologically, her first MRI was done early in the diagnostic process. Unfortunately, neuro-oncological consultation was delayed for an attempt to reduce the lesion and inflammation by corticosteroids
while the tumor grew substantially within that time, tripling in size. The diagnostic process then took another month to rule out other possible causes including lymphoma and other metastatic diseases and to perform a biopsy. Although the problem was pinpointed rather quickly, the process in itself took three months from symptom onset, which is valuable time to the patient and important for early intervention.

WL’s symptomology continued only with her vision until the point when unequivocal progression was confirmed (day 300). From there, the lesions of her cerebellum, hypothalamus, and frontal lobe all most likely contributed focally toward dysfunction in gait, balance, attention, and memory. Cerebellar dysfunction was very focally related to progression of that brain region by her observed and progressive deterioration of gait, nystagmus, dysdiadochokinesia, and others. Both tumor spread and functional decline were rapid and closely linked after the tumor began progressing.

**Diagnosis.** Although each diagnostic profile and definition seemed straightforward, with neoplasms that have such well-known heterogeneity, there are many situations where the pathological report may be difficult to summarize into a diagnosis or it may not be in agreement with the clinical presentation, as in the case of WL. Although specifics were not provided, WL’s pathology report indicated grade II pathology. Yet, radiographic presentation indicated significant and fast infiltration. It seemed the decision to treat WL’s tumor as grade III came from reasoning of caution and wanting to preserve the eloquence of the optic area, especially since surgical resection was not used. Besides providing a prognosis, malignancy grade decides the initial and subsequent courses of treatment including eligibility for clinical trials. The reasoning provided within the clinic notes mostly referenced the radiographic presentation and best use of an aggressive treatment protocol to preserve optic function for as long as possible.
Conclusion

Diagnosis confirms the tumors identity and provides cellular indication of malignancy factor. However, the measurements and comparison between pathology report and clinical behavior do not provide a fool-proof formula for determining malignancy grade. Even more than that, the grades represent well-defined, but not distinct groups. Meaning the grading groups have exceptions and other subtypes even within themselves and do not necessarily share all qualities, such as proliferative index, genetic profile, or cellular composition. Despite variance in these factors and qualities, the protocols for treatment are pretty consistent albeit response variance between patients and overall debatable efficacy. However, the unique properties that define individual patients and their tumors influence the response to treatment.
Part IV. Treatment

The current standard treatment practice begins with maximal tumor resection, followed by radiotherapy and concomitant and adjuvant chemotherapy. An initial treatment regimen is followed by reassessment and revision of chemotherapeutic agents. Progress during reassessment is evaluated by imaging techniques, patient symptom report, and clinical evaluation. Bloodwork to monitor platelet count, immune status, and other aspects can dictate whether further treatment is safe for the patient. The following sections describe the purpose, mechanisms, and efficacy of both FDA approved treatments and progressive treatments still in trial status.

Overall, treatment begins with maximal safe resection followed by radiotherapy and concurrent chemotherapy and finally management, chemotherapy. However, these options may vary from person to person depending on factors such as karnofsky score, age, clinical history, co-morbidities, or histological subtype. Clinical management of the disease and treatment plan requires tracking disease progression to judge the response and efficacy of the current protocol. The definitions and techniques for assessing progression will be discussed.

Besides treatment for the cancer, an overview of palliative medications common to brain tumor patients will be presented. Palliative care may be helpful to the patient while receiving therapies targeted at the tumor for managing comorbidities or complications from treatment. With refractory or aggressively recurrent disease, the tumor may progress beyond a point of rescue and reach terminal stage where only palliative care should be implemented. An overview of complications and of causes of death during the terminal stage will be described to conclude this section.

The purpose of describing treatment here are to provide the available and used options within treatment for malignant gliomas. However, since malignant gliomas are largely incurable
and have strong tendencies for poor treatment response, perfect and absolute protocols do not exist in the literature. Clinical cancer organizations such as the European Society for Medical Oncology (ESMO) describe recommendations for treatment and provide qualitative grades on which those recommendations have clinical study support. Essentially, clinical studies seek to prove one regiment or combination of treatment modalities over another increases OS or PFS, which are the classic clinical end points to indicate treatment efficacy. The recommendations provided then describe the number, the methodological strength, and the benefit the available studies have shown. Some of those conclusions will be cited in this paper for a general approach to malignant glioma treatment and guiding discussion.

The majority of this section will describe treatment purpose, theory, and technique and without asserting efficacy and describing specific clinical protocols other than for exemplary purposes. The descriptions here are not meant to recommend any protocols, but to describe the available treatments. Some specific protocols will be mentioned to only exemplify how and to what magnitude the treatment may be used such as with chemotherapy dosage or TTFields usage. Indications of preference or efficacy of one type of treatment over another will be described when relevant, but are not comprehensive in citing all clinical study evidence besides recommendation conclusions by cancer organizations and so will be minimal.
Introduction

Although there is considerable overlap with treatment regiments for anaplastic astrocytomomas and glioblastomas, certain factors such as age, Karnofsky performance score, and tumor histology guide overall treatment pathway. Specific selection of options within treatment types are up to the discretion of the physician based on factors including those specific to the patient including treatment history and comorbidities and those specific to the tumor including location, extent of infiltration, genetic subtype, or histological variant.

For good surgical candidates, maximal resection surgery is the preferred primary treatment, but should be replaced by biopsy if resection is not determined safe\textsuperscript{12}. Following primary surgical intervention, adjuvant therapy regimens must be decided and depend on genetic subtypes, age, and KPS\textsuperscript{12}. For the standard treatment of GBMs, neoadjuvant temozolomide (TMZ)/RT protocol is recommended followed by maintenance TMZ\textsuperscript{12}. Those with genetically confirmed MGMT promoter methylation are the most responsive to TMZ therapies\textsuperscript{12}. For grade III tumors, standard treatment includes only radiotherapy (RT), but treatment with adjuvant PCV chemotherapy is mentioned somewhat favorably, especially in those with co-deletion status of 1p19q\textsuperscript{12}. Deviations from the protocols mentioned occur with poor KPS status and/or old age where generally the number of treatment modalities are reduced and in the case of radiotherapy, hypofractionation is preferred over standard\textsuperscript{12}.

Measures of Treatment Efficacy

Even though specific recommendations will not be given, the theory behind determining treatment efficacy in clinical studies will be described. Essentially, proving one drug or a regimen is superior to another requires statistical evidence that the therapy will cause a measurable benefit or clinical end point such as extending overall survival.
Desirable benefits include increasing overall survival (OS), progression-free survival (PFS), objective response rate (ORR), or quality of life (QoL). The two most commonly reported main clinical end measures include OS and PFS, with OS historically marked as the gold standard for clinical studies. However, in the patient’s disease duration, multiple regiments may be attempted and may cause confounding results in reporting OS alone. Similar confounding factors of treatment and disease history may affect radiographic and PFS measures. Multiple end points may make analysis more difficult, but may help avoid statistical errors in determining overall efficacy of certain treatments.

Both overall and progression free survival time begins with either diagnosis or trial initiation and ends with death for overall or confirmed ‘progressive disease’ criteria. Given that the start point can vary, clear disease stage criteria should be defined in different trials such as newly diagnosed, refractory, and recurrent, but may produce confounds anyway and limit direct trial comparison. Given those confounding factors and noticeable issues with reproducibility in clinical trials, specific progression criteria has been defined by several groups as an attempt to reduce variability in methodology across trials and make direct comparisons easier and less time consuming.

Additionally, QoL will be discussed in its value as a measure relating to the effect of the treatment on the patient more so than the tumor and the treatment’s efficacy as a neoplastic agent. Other clinical targets include time to progression and objective response rate (ORR).

**Overall survival.** Overall survival is an objective measure of time from either diagnosis or clinical trial initiation to death. As stated previously, it is the golden standard clinical end point, but has some drawbacks in application and unavoidable confounds. These are best discussed in context of PFS and are outlined in the next section.
**Progression-free survival.** Progression free survival calculates the time between diagnosis or the start of a clinical trial to defined disease progression. Compared to OS, PFS usually occurs earlier, shortening the overall trial length and requiring less resources for follow-up\(^{51}\). Quicker results would allow for earlier assessment of the treatment\(^{51}\). Additionally, PFS may have more significant clinical value to the patient as an endpoint\(^{51}\). As noted before, PFS also reduces confounds produced by multiple, uncontrolled regiments the patient might experience, which is important in cases of treatment-related COD. Statistically, the PFS measure has higher statistical power and indicated increased sensitivity for treatment efficacy\(^{51}\). The criteria to measure progress and so calculate PFS also have clinical implications when assessing efficacy of treatment in a single patient and to determine whether to continue or abandon the regimen. The criteria to evaluate this will be described in the **Progression** section.

Although PFS exemplifies known benefits, the measurement is still subject to its weaknesses of multiple progression criteria guidelines and the subjective relationship between radiological progression, clinical benefit, and QoL\(^{51}\). With progression as the determined end point, there is issue with the difference in time between the start of actual progression and the time it was captured by radiographic imagery\(^{50,51,52}\). Differences in trial requirements for time between MRIs may produce variability between trials besides the general confound of having to estimate progression as the first time it is captured by scan.

A large meta-analysis found strong correlation between PFS and OS in GBM clinical trials, implicating the former’s possible surrogacy for the latter’s\(^{51}\). However, this relationship is not true of all cancer types and should not be a generalized substitution\(^{51}\).
**Quality of life.** Quality of life (QoL) reports the patient’s well-being and life-satisfaction by physical, emotion, and social domains\(^53\). Interestingly, QoL may actually have prognosis value and improvement may be associated with increased OS\(^53\).

Several QoL measurement tools are used, but the most notable seem to be the more general health-related quality of life (HRQOL) assessment and the brain-tumor specific Functional Assessment of Cancer Therapy-Br (FACT-Br) and Brain Cancer Module-20 (BCM-20)\(^53, 54\).

Quality of life of patients is slightly more complicated in patients with brain tumors because of tumor-related neuropsychiatric complications and treatment-related neurotoxicity\(^53, 54\). Compared to controls, malignant glioma patients score lower in all measurable categories related to QoL and have more problems symptomatically and socially related to QoL\(^53\). Between grade III and IV malignancies, specific QoL responses may not differ, but overall, patient perceived rating of QoL may be higher in grade III\(^53\). However, this may be related more to progression status\(^53\).

Currently, there are limited treatment protocols for increasing QoL among brain tumor patients besides those targeted at symptom relief, which are not well-defined to begin with\(^53\). However, just measuring QoL regularly may show benefit of physician-patient communication and QoL\(^54\).

With such significant side effects and toxicities associated with tumor-related treatments, QoL should be emphasized more in clinical trials and the impact communicated with the patient. While QoL is mentioned sparingly in the clinical and protocol literature, it does not seem to carry the same weight as other clinical measures. Given that QoL is less indicative of treatment efficacy than PFS or OS besides indication of symptom relief, it is understandable that QoL may
be less of a priority if treatment can provide long term benefits with temporary sacrifice of QoL. However, with malignant gliomas and their incredible mortality rate, the actuality of that benefit occurring may not be experienced. Subjection to various treatment regimens sound worthwhile when favorable OS and/or PFS scores of even a few months are produced from a clinical standpoint, but could actually be unnecessarily prolonging life. The ethical implications of trading OS for QoL is incredibly difficult to address, quantify, or use to change treatment goals, but is discussed here to emphasize its use in the literature and distinguish its measure from other clinical endpoints.

**Surgical Resection**

Extent of surgical resection has been mostly consistently shown to positively influence overall survival time, but can lead to complications such as new deficits, to recovery time that delays treatment with other agents, and to controversially not improving quality of life\textsuperscript{12}. Although those negative consequences of surgery resection are possible, the benefits in terms of survival are well documented\textsuperscript{12}. However, due to gliomas’ infiltrative and motile nature, surgical resection is not used for curative purposes\textsuperscript{12}. The most important goals of surgery are to provide tissue for pathology to confirm clinical diagnoses, reduce interstitial pressure caused by the tumor’s volume, increase survival, decreased the need for corticosteroids, and accompany adjuvant therapies, possibly improving efficacy of agents to reach the tissue\textsuperscript{12}.

There are several guiding principles in which the surgical protocol should adhere to while taking into account patient-specific factors including age, KPS, proximity to eloquent brain regions, ability to reduce volume-related interstitial pressure, resectability of the tumor, and history of previous surgeries\textsuperscript{12,22}. The guiding principles for surgical approach include maximizing resection, minimizing surgical morbidity, and providing sufficient tissue for accurate
biopsies\textsuperscript{12, 22}. The importance of the latter principle is well illustrated by the cellular characteristics previously described obtained from biopsy. Without providing an adequate amount of tissue, the biopsy may not represent the holistic cellular state of the tumor, which can be difficult with especially heterogeneous tumor subtypes\textsuperscript{2}.

Maximum surgical resection has been correlated with increased overall survival\textsuperscript{2, 12}. However, it is argued that surgery does not lead to any greater deficits than those induced by the tumor yet may contribute negative surgical side effects\textsuperscript{22}. Partial resections increase morbidity risk by supposedly 40\% with doubtful overall benefits\textsuperscript{22}. Due to tumor infiltrative nature, healthy tissue may be present within gross tumor area and resection may be avoidably devastating, yet there are methods to avoid this\textsuperscript{22}. Additionally, extent of resection is less strongly prognostic than age, KPS, and histology\textsuperscript{22}. Although maximal tumor resection is still recommended, the opposing recommendations or complications should be noted.

Types of surgical techniques will be described subsequently followed by brain tumor-specific postoperative protocols.

**Protocol**

As the first step in an outlined treatment regiment, surgery is used for both treatment itself and as a diagnostic confirmation, which usually helps plan adjuvant treatment therapies\textsuperscript{12}. In accordance with the diagnostic profile subtypes to be identified in the pathology report, tissue extraction by surgical intervention may help specialized treatment plans and define clinical trial information relating genetic factors to prognostic results\textsuperscript{12}. Essentially, this step and the results of the surgery are very informative regarding prognosis and further treatment plans. For initial surgery, stereotactic biopsy, open biopsy, subtotal resection, and gross total resection are the main surgical options\textsuperscript{12, 22}. 
Maximum tumor resection should be performed as the primary treatment for suspected malignant glioma to the extent deemed safe by neurosurgical consultation\textsuperscript{12,22}. Additionally, if gross resection is not feasible or too risky, the other three mentioned surgical techniques for biopsy or partial resection should be performed, if only for diagnosis\textsuperscript{12}. Lastly, if intraoperative frozen cryosection diagnosis is used as a method for quick, less reliable diagnosis of malignant glioma, BCNU surgical wafers may be placed for primary chemotherapy\textsuperscript{12}.

**Tumor resection.** To access the tumor, the surgeon must perform a craniotomy by standard or intraoperative techniques\textsuperscript{9}. The former technique uses craniometrics and requires larger incisions and skull fragments to be removed\textsuperscript{9}. Intraoperative navigation technology allows more efficient localization of the tumor, precise and minimal incision, and reduces total duration of operation\textsuperscript{9}.

In cases where the tumor is located near or below eloquent areas, an awake craniotomy may be of value to map out the extent of those areas to avoid resection or plan trajectory around\textsuperscript{9}. The patient is sedated before and after the mapping takes place since participation is required for demonstrating certain functions\textsuperscript{9}. While the patient is awake, a neurologist will assist the neurosurgeon with both electrically stimulating and mapping the region\textsuperscript{9}. For obvious reasons, the patient must be a qualified candidate for such a procedure, which may include confirming the patient has no disruptive psychiatric or cognitive disorders\textsuperscript{9}. Recent inventions that maximize resectability and accuracy include neuronavigation, functional mapping, intraoperative fluorescent dyes, and intraoperative MRI (iMRI)\textsuperscript{9}.

The primary and non-argued goal of resection should be to alleviate mass effect and to provide diagnosis, but extent of resection is a more controversial goal yet has significant support and research\textsuperscript{9}. As described before, total gross tumor resection improves overall survival
compared to subtotal resection. Additionally, gross tumor resection is found to be especially effective in OS of patients with good KPS\textsuperscript{12}. Given those extensive data analyses, maximal resection is rightfully preferred when safe.

*Open biopsy.* When a craniotomy is performed to either resect the tumor or for another procedure where a tumor is identified, tissue can be extract for biopsy or part of the resected tumor can be saved for this purpose\textsuperscript{9}. An open biopsy refers to the exposed surgical technique of craniotomy in opposition to biopsy by creation of a burr hole in stereotactic biopsies\textsuperscript{9}.

*Stereotactic biopsy.* It is clear there are benefits of removing maximal tumor mass to deter spread and alleviate interstitial pressure of the tumor\textsuperscript{12}. However, that type of surgery is limited by several factors. Tumor location may cause increased risk if the surrounding tissue is involved in vital behaviors such as expression, communication, or sensory processing (Table 9)\textsuperscript{12}. Tumor resection may not be appropriate in such cases and in others if the location is inaccessible or near midbrain (Table 9)\textsuperscript{12}. Surgical resection loses its purpose if side effect damage causes deficits that ultimately lower quality of life more so than it would without surgery. That idea is especially important when focusing on resection’s non-curative nature. Additionally, total resection becomes less beneficial when tumors have minimal mass effect or the patient is not expected to tolerate the surgery well by responses to general anesthesia and surgical recovery\textsuperscript{12}. In these cases, rather than tumor resection, stereotactic biopsy may be more appropriate\textsuperscript{12}.
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<tr>
<th>Grade I: noneloquent area</th>
<th>Grade II: near eloquent area</th>
<th>Grade III: eloquent area</th>
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<tr>
<td>Frontal or temporal pole</td>
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<td>Motor/sensory cortex</td>
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<td>Right parieto-occipital</td>
<td>Near calcarine fissure</td>
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<td>Cerebellar hemispheres</td>
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Table 9. Eloquency rating of different brain areas. Adapted from Brell, Ibanez, Caral, & Ferrer (2000).11

Stereotactic biopsy has considerable benefits including bypassing the issues described previously that cause difficulty with resection surgeries. Biopsy is the only way to confirm clinical diagnoses, which is beneficial in terms of legal requirements from insurance for further treatment, more accurate treatment and prognosis estimates, and eligibility for clinical trial treatments.

**Technique.** Stereotaxis surgery uses MRI/CT and computer navigational analysis for precise location targeting to direct surgery. The head is marked and stabilized by a metal frame with localization using Cartesian coordinates. However, this technique was more recently replaced by small fiducial markers placed on the scalp referred to as the guided frameless stereotactic neuronavigation system technique. Biopsies that do not use the standard, more accurate stereotactic methods are merely referred to as needle biopsies.

In surgery, the patient is first induced followed by placement of the navigational system and fiducial markers. A quarter-sized incision is made into the skull and once the dura is cut, the stereotactic biopsy needle is inserted and guided by the neuronavigation system. Tissue extraction is made for cryogenic and full pathological biopsies. This technique can reach far subcortical tissues when resection is not safe and in some cases, can be treated as an outpatient.
procedure\textsuperscript{11}. The stereotactic navigation allows for smoother insertion through healthy tissue with minimal risk\textsuperscript{11}.

Risks for this procedure include the following at 1\% risk or less: intracranial hemorrhage, infection, and repeat biopsy from insufficient tissue extraction\textsuperscript{11}.

**Risks**

With general surgery and specifically brain tumor surgery, there are associated risks that may not frequently occur, but are still possible and should be noted\textsuperscript{55}. General surgical risks include infection, bleeding, blood clots, pneumonia, and blood pressure instability\textsuperscript{55}. Risks specific to brain tumor surgery include seizures, weakness, balance/coordination difficulties, memory/cognitive deficits, CSF leakage, meningitis, brain swelling, stroke, excess fluid in the brain, coma, and death\textsuperscript{55}.

Overall complication with biopsy and partial/subtotal/gross total resection ranges 21-31.9\% including neurological, regional, systemic, and mortality results\textsuperscript{22}. Neurological complications are typically the most frequent of complications ranging 10.6-26\% and in one study, included most frequently sensory and motor dysfunction and less frequently vegetative status\textsuperscript{22}. Overall, KPS changes usually improved (81.5\%) yet some worsened (18.5\%) and is still a possible complication\textsuperscript{22}. Regional complications occur by 7-16\% of patients and in one study, were most frequently in form of postoperative epilepsy and CSF leakage\textsuperscript{22}. Systemic complications were less frequently than others occurring within 4.5-8.2\% patients and in one study, included pneumonia and urinary infection\textsuperscript{22}. Mortality rate range significantly and interestingly were either low 0.7-3\%, moderate 18.5-22.3\%, or high with one study at 41.1\% all for GBM patient groups\textsuperscript{22}. 
Certain factors have been found to increase occurrence rates for the above complications. Neurological complications were associated with infratentorial tumor location and previous radiotherapy\textsuperscript{22}. Interestingly, surgical intervention of eloquent brain areas were not associated with increased risk of neurological complications, but may represent the result of a less-aggressive resection technique\textsuperscript{22}. Previous radiotherapy was also a risk factor for regional complications possibly related to the known side effects of radiotherapy with wound healing\textsuperscript{22}. Systemic complications were higher in older patients over 60 years and those with pathological antecedents\textsuperscript{22}. No factors were found related to mortality rate\textsuperscript{22}.

**Radiotherapy**

Fractionated external beam radiation therapy (EBRT) is the standard recommendation following surgical intervention\textsuperscript{12}. Several EBRT techniques can be used for treatment while standard fractionation up to 60Gy in 1.8-2.0Gy fractions is most typical\textsuperscript{12}. Depending on certain risk factors, hyperfractionation or hypofractionation may be employed\textsuperscript{12,56}. Additionally, extent of tumor infiltration or lesion number may favor whole brain radiation therapy (WBRT), however, involved field radiation therapy (IFRT) is more typically used to reduce the associated delayed increase of toxicity with WBRT when the lesion(s) are mostly localized\textsuperscript{56}. Increased dosage techniques including hyperfractionation, brachytherapy, fractionated stereotactic radiotherapy (FRST), and stereotactic radiosurgery (SRS) are mostly well tolerated, but did not improve OS or QoL\textsuperscript{56}.

Radiation administration acts to destroy tumor cells by damaging DNA\textsuperscript{57}. Cells with DNA damage lose their ability to reproduce and such arrest of the cell cycle may induce apoptosis\textsuperscript{29,57}. Malignant tumors may shrink somewhat gradually within a couple months in response to treatment whereas non-malignant tumors may take up to 2 years\textsuperscript{57}. 
Techniques

Radiotherapy is divided between external and internal beam techniques where the radiation is performed externally from the body and internal administration of radioactive substances, respectively\(^57\).

**External beam RT.** Although there are several techniques for EBRT, emphasis will be placed on overall EBRT procedure and fractionation schedule\(^57\). Techniques such as intensity-modulated radiation therapy (IMRT) and 3D conformal radiation therapy (CRT) maximize precision targeting by computer mapping of the tumor and surrounding health tissue\(^57\). Radiation is produced using a linear accelerator (LINAC) in the form of high-energy x-rays or photons created and targeted specifically to each unique tumor\(^57\). The LINAC has several safety measures to ensure quality control and safe protection of the staff who are continually around the procedure\(^57\).

The entire treatment is planned and monitored intently by an expert team that includes a radiation oncologist who prescribes the treatment volume and dosage; a radiation dosimetrist and a medical physicist who both determine delivery method and duration of accelerator to provide the dose; and a radiation therapist who operates the LINAC and administers the treatments\(^57\).

**Whole brain vs. focal brain RT.** In some cases where spread is significantly diffuse or where there are multiple lesions, whole brain radiation therapy (WBRT) may be appropriated\(^56, 57\). However, the more precise involved field radiation therapy (IFRT) technique is better used to maximize dose delivered to the tumor, to minimize dosage to healthy tissue, and to avoid the increased delayed neurotoxicity associated with WBRT\(^56, 57\). Even with WBRT, peritumoral recurrence still occurred and so IFRT can target the actual tumor with higher delivered dosage while targeting the primary neighboring recurrence areas without subjecting the entire brain to
targeted radiation\textsuperscript{56}. Even though OS is the same between techniques, there are marked advantages for IFRT in most cases\textsuperscript{56}.

**Procedure.** Prior to treatment, simulation and planning must occur to physically prepare the patient for the treatment and to prepare the treatment dose and specificity for the patient’s tumor, respectively\textsuperscript{57}. Simulation involves defining the treatment position of the patient, ways to optimize the ability of the patient to stay in precise position, and permanent or near-permanent markers to direct therapy on the skin or in the tumor by seed-form\textsuperscript{57}.

Planning follows simulation by the dosimetrist, radiation physicist, and radiation oncologist using very precise computer analysis to determine dosage and orientation based on tumor specific characteristics mapped by radiographic images\textsuperscript{57}. Tumor size and shape varies between T1 MRI, T2 MRI, and CNI MRS where T1 images are too small and T2 images include more and less than compared to the histologically validated CNI-MRS measure\textsuperscript{56}. Expansion by 2-3cm to include probably peritumoral microscopic infiltration\textsuperscript{16}. Additionally, increasing accuracy of this stage and minimizing dosage to surrounding healthy tissue can be done by making use of the IMRT or 3D-CRT techniques\textsuperscript{57}.

Following successful simulation and planning, treatment begins and usually continues once a day for the full 20 sessions\textsuperscript{57}. Once positioned exactly as done in the simulation procedure, accuracy of set up is confirmed by radiography imagery and treatment can occur\textsuperscript{57}. Each session may take up to an hour with positioning the patient taking the majority of time while actual treatment may take only several minutes\textsuperscript{57}. Duration of treatment varies between some techniques and dosage schedule\textsuperscript{57}. Follow-up evaluations will be scheduled once treatment is completed to track toxicity, which has a delayed effect after initiation of treatment\textsuperscript{57}. 
**Fractionation schedule.** Administration of EBRT can be of standard protocol, hypofractionation in which less total radiation is administered at higher doses with shorter overall treatment, and hyperfractionation, which delivers more total radiation over the same period of time by larger fractions. The standard protocol is usually administered, but in certain cases, the latter two may be more appropriate. In all fractionation schedules, the involved field is usually reduced for the last treatment to boost radiation target in the tumor.

The standard dosage for EBRT is 60Gy in 1.8-2.0Gy fractions or 59.4Gy in 1.8Gy fractions as stated previously. However, for grade III astrocytomas or for gliomatosis, the dosage may be changed to either 55.8Gy in 1.8Gy fractions or 57Gy in 1.9 fractions.

Hypofractionation adjusts the dosage size for reduced total radiation in larger session quantities resulting in reduced number of therapy exposures to be completed within 2-4 weeks. This technique, which reduces the overall treatment time, is used for patients with significant negative prognostic factors and was found especially effective in older patients with GBM. An example of a typical hypofractionation regimen is 40Gy in 15 fractions total, but can vary.

Hyperfractionation is administered by an increased number of reduced dosages from standard for a higher total radiation dose to be delivered within the same time period. The purpose of this schedule is for possible increased efficacy and supposed avoidance of toxicity associated with larger doses, yet no advantage has been demonstrated for this technique.

**Surgical radiation therapy.** Stereotactic radiosurgery (SRS) involves stereotactic technique to hold and target specific lesions as an alternative to WBRT or to boost its effect as adjuvant radiotherapy. SRS is done in one therapy session whereas stereotaxic radiotherapy (SRT) is fractionated between multiple sessions when the lesion is located next to eloquent brain areas to decrease single-dose toxicity and side effects. Since multiple radiation exposures
are then required, SRT may use a mask of thermoplastic material to replace the stereotactic frame for added protection the face and head\textsuperscript{58}. The SRS procedure are generally limited to lesions with maximum 3.0cm diameter, with exceptions, and to 4 lesions per treatment session\textsuperscript{58}.

**Procedure.** Using stereotactic techniques, a single dose of radiation is administered using either a Gamma Knife machine or LINAC administering gamma rays or photons, respectively\textsuperscript{58}. Both types use stereotactic frames to guide and secure head placement with sterile pins as well as use radiographic and computer guidance for tumor location\textsuperscript{58}. However, gamma knife can treat lesions 5-40mm whereas LINAC method can treat lesions only up to 35mm\textsuperscript{58}.

Eligibility criteria for this therapy are strict enough that clear correlation between favorable outcome and treatment intervention is not known for certain\textsuperscript{56}.

One complication that is treatment specific is pin-site bleeding\textsuperscript{58}. Other complications common to either radiotherapy or surgical intervention are infection, peritumoral edema, seizures, and radiation necrosis\textsuperscript{58}.

**Internal radiation therapy.** Internal radiation therapy or brachytherapy places radioactive material inside or next to the tumor on a temporary or permanent timescale\textsuperscript{57}. The encapsulated agents used in these processes include: iodine, palladium, cesium, and iridium\textsuperscript{57}. Computer mapping or radiographic imagery can help guide and confirm placement\textsuperscript{57}.

Most side effects specific to this type of radiation are related to administration technique by irritation, tenderness, or swelling\textsuperscript{57}. Anesthesia may be used to accompany administration of delivery device and so the related side effects apply\textsuperscript{57}. Long term side effects are possible\textsuperscript{57}.

**Temporary brachytherapy.** Temporary brachytherapy is completed by implantation of a delivery device, including a catheter, a needle, or an applicator, through which radiation is
delivered by a remote-afterloading machine to control dosage\textsuperscript{57}. Treatment can last 10-20 minutes or 20-50 hours for high-dose rate and low-dose rate protocols, respectively\textsuperscript{57}.

**Permanent brachytherapy.** Permanent brachytherapy or seed implantation administers radioactive seeds into the tumor tissue that deliver treatment at device-dependently controlled intervals\textsuperscript{57}. These seeds’ total dosage is finite and decays quickly overtime, but may be detectable long-term\textsuperscript{57}. Care should be taken with subsequent interaction with women or children and concurrent interaction should not occur\textsuperscript{57}. Seed implantation is hypothetically effective because of the increased local dosage for better targeting and for prevention of recurrence, the lower dose rate to be tolerated by healthy tissue with an overall higher dose to be delivered, and the seed design that allows rapid decrease in dosage outside the targeted area\textsuperscript{56}. However, no significant and reproducible benefit has been established compared to IFRT protocol\textsuperscript{56}.

**Recurrent cases.** Re-irridation may be an option for cases with favorable response factors, including good KPS and small recurrent tumor size\textsuperscript{12}.

**Other therapies.** Controversial treatments include particle therapy in which the photon radiation is replaced with subatomic particles, but are linked with RT-induced morbidity\textsuperscript{16, 56}. Experimental radiosensitizers including hypoxic cell sensitizers and halogenated pyrimidines have been attempted to increase tumor cell susceptibility to radiation effects, but no clear benefits have been demonstrated\textsuperscript{56}.

**Risks**

White matter changes caused by radiotherapy techniques can be physically observed on MRI and CT imaging where extent and frequency were positively correlated with increasing radiation dosage\textsuperscript{56}. These changes correlate well with the observed longer term side effects of radiotherapy including radiation-induced necrosis, dementia, and higher-cognitive deficits\textsuperscript{56}.
Theoretical desirable results occur from increasing dosage to prevent recurrence, but must be balanced with the toxic properties of radiation that produces the dangerous and ultimately lethal destruction of white matter in healthy tissue by radiation-induced necrosis. These toxic effects may be consequential enough to be responsible for the 60 Gy dosage ceiling in terms of long-time survival\textsuperscript{56}.

Radiation necrosis occurs by poor radiation-affected tissue clearance mechanisms of damage tissue and can cause further brain swelling\textsuperscript{56}. Treatment includes increased glucocorticoids, hyperbaric oxygen, or surgical removal of necrotic tissue\textsuperscript{56}.

In addition to consequences of radiotherapy related to overall survival, certain common acute side effects may impact quality of life measures as well\textsuperscript{56}. The four most common side effects are temporary alopecia, skin irritation or erythema, fatigue, and edema\textsuperscript{56,57}. These and other side effects may occur with delay from treatment around 2-3 weeks after initial therapy\textsuperscript{57}. Other side effects include serous otitis media and hearing problems, nausea, vomiting, loss of appetite, memory or speech problems, and headaches\textsuperscript{56,57}. Radiotherapy may also reduce wound healing ability because of skin changes, diminished microcirculation, and loss of epithelial cells\textsuperscript{22}.

Even with the benefits of maximal safe radiation of 60 Gy, if the patient does not tolerate the therapy well the ‘extra’ months may not be pleasant\textsuperscript{56}. This balance, as opposed to the dosage balance previously mentioned, plays on a slightly more qualitative, ethical aspect of treatment rather than objective biological factors. The protocol for hypofractionation, is recommended as most appropriate in situations where the patient has a shorter than average life expectancy due to negative prognostic factors such as old age and low Karnofsky score\textsuperscript{56}. However, these prognostic factors may cause poorer reaction to any radiotherapy, reducing QoL. In addition, an
important concern with the use of hypofractionation is increased radiation-induced morbidity\textsuperscript{56}. In fact, the patient may not live any longer than without the therapy and might suffer from the acute side effects to diminish QoL. Interestingly, use of hypofractionation in this patient group also has a recommended limit to exclude patients that may be bed-ridden or cognitively impaired\textsuperscript{56}. Adding such normative claims to these protocols are difficult when comparing OS to QoL without some type of conversion factor or description.

**Chemotherapy**

**Purpose**

Stemming from the discussion of genetic mutations and abnormalities, the basis of chemotherapy works to target dysfunctional proteins or signaling, metabolic, and proliferation pathways\textsuperscript{2}. With the purpose of blocking cancerous growth and invasion, chemotherapy agents target primary, responsive areas of certain processes to effectively stop or destroy the mutated cells to prevent progression and spread to other brain regions\textsuperscript{2}.

**Mechanism**

Due to the low permeability of the BBB and high tumor interstitial pressure, drug delivery through the vascular system is generally poor unless aided by certain mechanisms that disrupt or bypass the barrier\textsuperscript{2}. In addition to poor results with delivery techniques, which provide a physical barrier the cancer can utilize for protection, the cancer itself displays therapeutic resistance to chemical and radiological therapies possibly due to high genomic instability where mutations arise that may increase drug-resisting capabilities or properties to any one agent\textsuperscript{2}. In combination with gliomas’ invasive tendencies, holistic targeting of the entire cancerous cell population is very difficult and coarse\textsuperscript{2}.
In non-stem-cell like tumor cells, the retention of DNA repair mechanisms may be directly responsible to reducing the effectiveness of the drug at a cellular level past drug delivery barriers. Populations of neural stem-cell-like glioma cells (SCLGCs) have been identified with distinct resistance mechanisms from non-stem-cell like tumor cells, which may result in or be responsible for the observed increased heterozygosity of tumor cell populations in malignant gliomas.

In compliance with the discussion in the Oncogenesis section about how signaling pathway regulation may be very extensive and alternative methods can compensate for dysfunctional parts, arises the theory of redundant signaling pathway abnormalities. This theory describes the complex problem therapeutic agents encounter where targeting a single, specific, small-molecule signaling pathway will most likely not be effective at shutting down the malignant behavior of glioma cells with multiple dysfunctional pathways in a network. Since genetic mutation profiles of the malignant glioma population are not exact or universal and individual mutations show a contributive, but not required role in GBM, targeting a single aspect of either pathways that regulate expression of certain genes such as TP53 or pathways involving upstream markers are not enough to compensate for other contributing mutations and dysfunctional pathways. The pathways relating to the mutations listed in Table 4 are more complex than described in this text and have many regulating mechanisms that intertwine other metabolic pathways creating a dynamic metabolic network that should be appreciated on a holistic level as well as attenuating the specialized pathways. This is the basis of the theory described. For example, small molecule inhibitors such as gefitinib that inhibit the EGF tyrosine kinase have had poor clinical results, yet testing individual biopsies may identify patients responsive to specific inhibitors providing, a regiment of agents with better prognoses to work in
a logical combination\textsuperscript{2}. Using agents with targets common to GBMs should be focused in such a manner to reduce toxicity and drug load, yet comprehensively target dysfunctional small-molecules with complementation\textsuperscript{2}.

Building off the idea to use multiple molecular targets, identification of glioma subtypes utilizes biopsy tissue profiles and further analysis to prioritize certain cellular targets\textsuperscript{2}. This profile using recursive petition analysis to form classes is based on information including genetic abnormalities, gene expression, signaling and apoptosis pathway status, hypoxia, SCLGC composition, and NDA repair protein levels and distribution\textsuperscript{2}. From the classification information comes correlative conclusions about therapeutic pairings and effectiveness based on survival rates of specific classifications\textsuperscript{2}. For example, universal benefit between classes of total gross tumor resection was demonstrated, while certain classes were also shown to have better overall survival\textsuperscript{2}.

Several chemotherapy agents will be discussed by those recommended in the literature, those with FDA indication for brain tumor treatment, and those otherwise mentioned in the literature. A summary of these agents is presented in Table 10.
<table>
<thead>
<tr>
<th>Name</th>
<th>Other Names</th>
<th>Chemical Effect</th>
<th>Use</th>
<th>FDA Indication (boxed warning)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carmustine Wafer</strong></td>
<td>Gliadel® wafer, BCNU-W</td>
<td>DNA and RNA alkylation; cytotoxicity</td>
<td>Surgical implant: 8 wafers as an adjunct to surgery and/or radiation</td>
<td>New high-grade glioma; recurrent GBM; (no)</td>
</tr>
<tr>
<td><strong>Carmustine – IV</strong></td>
<td>BiCNU®, BCNU</td>
<td>DNA and RNA alkylation; cytotoxicity</td>
<td>IV: 150-200mg/m² every 6 weeks</td>
<td>Single or combo agent for gliomas (YES)</td>
</tr>
<tr>
<td><strong>Temozolomide</strong></td>
<td>TMZ, Temodar®, Temodal</td>
<td>DNA alkylation; cytotoxicity</td>
<td>IV or po: 75 mg/m² concomitant w/ RT; 150 mg/m² as single agent; on 5-28 schedule</td>
<td>New &amp; maintenance for GBM; refractory AA; (no)</td>
</tr>
<tr>
<td><strong>Procarbazine</strong></td>
<td>Matulane®</td>
<td>Inhibition of protein, RNA, DNA synthesis; hydrogen peroxide damage</td>
<td>IV or po: 100mg/m² daily for 2 weeks</td>
<td>None (YES)</td>
</tr>
<tr>
<td><strong>Lomustine</strong></td>
<td>CeeNU®, Gleostine®, CCNU</td>
<td>DNA and RNA alkylation</td>
<td>Po: 130mg/m² once every 6 weeks</td>
<td>Primary &amp; metastatic brain tumors (YES)</td>
</tr>
<tr>
<td><strong>Vincristine</strong></td>
<td>Marqibo®</td>
<td>Inhibition of microtubule formation; cell cycle arrest</td>
<td>IV only: various schedules</td>
<td>Neuroblastomas only (YES)</td>
</tr>
<tr>
<td><strong>Bevacizumab</strong></td>
<td>Avastin®</td>
<td>VEGF antagonist; anti-angiogenic agent</td>
<td>IV: 10 mg/kg every 2 weeks</td>
<td>Refractory GBM; (YES)</td>
</tr>
<tr>
<td><strong>Cyclophosphamide</strong></td>
<td>Neosar®, Cytoxan®</td>
<td>DNA cross-linking</td>
<td>IP: various schedules</td>
<td>Neuroblastoma &amp; retinoblastoma (no)</td>
</tr>
<tr>
<td><strong>Carboplatin</strong></td>
<td>Paraplatin®</td>
<td>DNA cross-linking</td>
<td>IV: 360mg/m² as single agent or in combination on 1-28 schedule</td>
<td>None (YES)</td>
</tr>
<tr>
<td><strong>Irinotecan</strong></td>
<td>Camptosar®, Onivyde™</td>
<td>Inhibition of topoisomerase-I</td>
<td>IV infusion: various doses/schedules as mono or combined agent</td>
<td>None (YES)</td>
</tr>
<tr>
<td><strong>Etoposide</strong></td>
<td>Toposar®, Vepesid®</td>
<td>Inhibition of topoisomerase-II; DNA damage by free radicals</td>
<td>IV or po: 100-250mg/m² on 5-28 schedule</td>
<td>None (YES)</td>
</tr>
<tr>
<td><strong>Tamoxifen citrate</strong></td>
<td>Nolvadex®, Soltamox®</td>
<td>Antiestrogenic by competitive binding of tissues</td>
<td>Po: 20-40mg daily</td>
<td>None (YES)</td>
</tr>
<tr>
<td><strong>Imatinib mesylate</strong></td>
<td>Gleevec®</td>
<td>Small molecule protein-kinase inhibitor</td>
<td>IV or po: various schedules</td>
<td>None (no)</td>
</tr>
</tbody>
</table>

Table 10. Summary of chemotherapy agents discussed including associated names, antineoplastic mechanism, dosage schedule, FDA recommendations for brain tumors, and FDA black boxed warnings.
Types

**Literature recommended.**

*Carmustine.* Carmustine is a nitrosourea derivative that exhibits anti-angiogenic properties by inhibiting DNA, RNA, and protein synthesis through DNA modifications including alkylation† and possibly DNA cross-linking and carbamylation⁵⁹. This chemotherapy agent can be administered intravenously as adjuvant therapy, but can also be used as a primary treatment in the form of a Gliadel wafer placed in the surgical cavity at the time of initial operation¹²,⁵⁹,⁶⁰,⁶¹. Although the wafer shows benefit in patient groups, carmustine has known drug interactions and subsequent increased toxicity when used in conjunction with other chemotherapy agents⁶¹. Additional certain clinical trials provide exclusion criteria on whether or not the therapy has been previously used⁶¹.

Both modalities will be discussed, however, it is important to note that the wafer has been FDA approved as primary and recurrent treatment adjunct to surgery and/or RT, yet adjuvant BCNU chemotherapy is recommended to be used as a second-line option to TMZ as adjuvant chemotherapy protocol⁶⁰,⁶¹.

*Gliadel wafer implant.* The carmustine implant has been shown to provide increase OS benefits for both primary and recurrent clinical studies and is approved by the FDA for both treatment protocols in high-grade gliomas¹²,⁶⁰. In addition to carmustine, polifeporson is embedded in the implant wafer, which is a biodegradable copolymer that degrades by the aqueous intracranial environment, releasing carmustine into the cavity⁶⁰.

During surgery and following maximum resection, up to 8 wafers (7.7mg individual, up to 61.6mg total) may be placed in the surgical cavity with slight overlapping, if necessary⁶⁰. The

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† DNA and RNA damage by alkylation is the only FDA approved mechanism, but other properties have been proposed.
wafer is generally biodegradable, but wafer remnants have been detected as long as 232 days post-implantation. Warnings indicated by the FDA include seizures, intracranial hypertension, impaired neurosurgical wound healing, meningitis, wafer migration, and embryo-fetal toxicity. In newly diagnosed patients, cerebral edema, asthenia, N&V, constipating, wound healing abnormalities, and depression are the most common adverse reactions. However, in recurrent patients, the most common adverse reactions are urinary tract infection, wound healing abnormalities, and fever.

_Carmustine by injection._ In reference to the chemical’s short half-life, degradation of carmustine occurs quickly while the degradation products react rapidly with DNA and nucleoproteins. Despite carmustine’s nonspecificity to cancerous cells only, the rapidly proliferating cancer cells with angiogenic activity are most susceptible. Kinetically, carmustine enters the CSF within 30 minutes of administration and persists within the body up to 72 hours post-administration. Crossing of the BBB by carmustine and the related CCNU and PCNU has been characterized and attributed to the chemical’s low molecular weight and lipid-solubility.

Carmustine can be used as a single agent or in combination with other approved agents for malignant astrocytomas. Given the drug’s side effect, blood counts, pulmonary, liver, and renal tests should be monitored. Dosage is 150-200mg/m² every six weeks, but should be lowered in patients using the drug in combination with other agents or have low bone marrow reserve.

Carmustine for injection has a strict FDA boxed warning about bone marrow suppression and pulmonary toxicity, both of which have cumulative effects. Bone marrow suppression leading by thrombocytopenia and leukopenia are the most common and severe side effects of the
drug and can possibly lead to bleeding or infection\textsuperscript{61}. Pulmonary toxicity can also be delayed by years post-treatment and can result in death\textsuperscript{61}. Pulmonary, hematologic, gastrointestinal, hepatotoxicity, nephrotoxicity, ocular toxicity, and local soft tissue toxicity are possible\textsuperscript{61}. Other symptoms reported are neuroretinitis, chest pain, headache, allergic reaction, hypotension, and tachycardia\textsuperscript{61}.

\textbf{Temozolomide.} Temozolomide (TMZ) is the standard of care for GBMs and may have some benefit for grade III tumor treatment\textsuperscript{12}. Temozolomide is an alkylating agent that damages DNA and causes cell arrest\textsuperscript{34}. Mechanistically, TMZ may be administered by IV or taken orally and will spontaneously, nonenzymatically convert to its active form MTIC in a pH-dependent reaction\textsuperscript{34, 35}. TMZ has a couple associated methylation sites while the sites’ roles in antitumor activity is controversial\textsuperscript{34}. However, given the increased responsiveness of the hypermethylated MGMT subtype, TMZ’s methylation site of the O\textsuperscript{6} position of guanine has the most indicated role in antitumor activity\textsuperscript{34, 35}. Following these methylation events in which the abnormal DNA base cannot be bases paired, nicks in the DNA accumulate and may inhibit the replication process initiation, resulting in apoptosis\textsuperscript{34}.

Hypermethylation of the MGMT (O\textsuperscript{6}-methylguanine-DNA methyltransferase) resulting in low expression levels is a genetic subtype of malignant gliomas associated with enhanced chemosenstivity to TMZ and so adjuvant TMZ is highly recommended for this subtype\textsuperscript{12, 34}. The MGMT promoter codes for a DNA enzyme that can cause cellular resistance to DNA-alkylating drugs and so the hypermethylated/reduced expression subgroup, typically found in oligodendroglomas, show significantly increased response to agents such as TMZ\textsuperscript{12}. Since hypermethylation decreases expression levels of the MGMT repair protein that would otherwise
fix the methylation alteration made by TMZ, the subtype’s marked susceptibility seems logical with the provided evidence\textsuperscript{34}.

FDA approval is indicated for newly diagnosed GBM first concomitant with RT and then as needed for maintenance therapy and for refractory AA patients, specifically who have experienced progression while treating with nitrosoureas and/or procarbazine\textsuperscript{35}. When post-RT or without RT, TMZ dosage is 150-200mg/m\textsuperscript{2} qd on for days 1-5 of a 28 day cycle\textsuperscript{35}. However, the dosage is reduced during RT therapy\textsuperscript{35}. Dosage may be adjusted if abnormal nadir neutrophil and platelet counts were found in the previous cycle or before initiation of the next cycle\textsuperscript{35}.

TMZ is administered orally, crosses the BBB well and is not dependent on hepatic conversion\textsuperscript{34}. Overall, TMZ is associated with only mild-moderate toxicity and stage 1 and 2 clinical trials included leukopenia, lymphocytopenia, neutropenia, and thrombocytopenia with response rates of 13-21\%\textsuperscript{34}. The toxicity is dose-dependent and was reported to be manageable\textsuperscript{34}. Additionally, in older patient groups, combined RT/TMZ adjuvant treatment plans may be beneficial, but in especially older patients who have increased susceptibility to radiation-induced toxicity, TMZ may be administered alone\textsuperscript{12}.

Side effects include alopecia, N&V, headaches, fatigue, anorexia, constipation, convulsions, rash, hemiparesis, and others\textsuperscript{8, 35}. Administration of TMZ increases the risk for pneumocystis pneumonia and so requires concurrent prophylaxis treatment against\textsuperscript{35}. Myelosuppression, hepatotoxicity, myelodysplastic syndrome, and secondary malignancies including myeloid leukemia have been reported\textsuperscript{35}. The most common hematological abnormalities were lymphopenia, thrombocytopenia, neutropenia, and leukopenia\textsuperscript{35}.

\textsuperscript{8} Other side effects include diarrhea, asthenia, fever, dizziness, abnormal coordination, viral infection, amnesia, and insomnia\textsuperscript{35}.
Specific increased toxicity by drug interaction between Gliadel wafer implants and TMZ have been noted\textsuperscript{35}. However, the timing of administration of TMZ after implantation may be safe, but does not seem to be clearly defined\textsuperscript{35}.

**PCV.** The PCV regimen includes administration of Procarbazine, CCNU, and Vincristine agents.

*Procarbazine.* Procarbazine hydrochloride is a hydrazine derivative with antineoplastic activity by generally unknown mechanisms, but indicated inhibition of protein, RNA, and DNA synthesis\textsuperscript{62}. Possible mechanisms include inhibition of t-RNA synthesis by inhibiting normal transmethylation enzymes with downstream effects of interrupting protein and consequent RNA/DNA synthesis\textsuperscript{62}. Activation of the drug involves formation of hydrogen peroxide, which may damage residual proteins bound to DNA\textsuperscript{62}.

Procarbazine has indicated use for stage III and IV Hodgkin’s disease as a combination therapy and is used in the “MOPP: nitrogen mustard, vincristine, procarbazine, prednisone” regimen\textsuperscript{62}. Procarbazine crosses the BBB well for overall equilibration between the plasma and CSF\textsuperscript{62}. It is recommended to begin therapy with a tapering up of dosage and/or to maintain the full recommended dosage of 100mg/m\textsuperscript{2} daily for 14 days\textsuperscript{62}. It is recommended to wait at least one month before using procarbazine if previous radio or chemotherapies with associated marrow suppressant activity were used\textsuperscript{62}.

Although the FDA provides a black box warning for this compound, it is only to strongly recommend to receive administration of the compound in an adequate and experienced facility by a physician as with other potent neoplastic agents\textsuperscript{62}. Other precautions include CNS symptoms of paresthesia, neuropathies, or confusion; delayed leukopenia; thrombocytopenia; hypersensitivity; stomatitis; diarrhea; and hemorrhage or bleeding\textsuperscript{62}. Adverse reasons of nearly
every system in the body are possible and should be reviewed prior to use. The most common issues are leukopenia, anemia, thrombopenia, and N&V.

*Lomustine.* Lomustine is another antineoplastic nitrosourea compound and related to BCNU with similar alkylation activity of DNA and RNA. Additionally, inhibitory function of enzymatic processes by carbomylation activity of proteins is another cited mechanism. Like BCNU, lomustine can cross the BBB well. Intended use of lomustine includes both primary and metastatic brain tumors following surgical and/or radiotherapy treatments and as a combination therapy for Hodgkin’s lymphoma. The dosage recommendation is 130mg/m² orally once every six weeks.

The FDA provided a black box warning of possible delayed, dose-related, cumulative, and possibly fatal myelosuppression with severe thrombocytopenia. It is strongly recommended to monitor blood counts, to not give more frequently than once every six weeks and to not exceeding the single dose recommendation. Other precautions of use include pulmonary toxicity, secondary malignancies, hepatotoxicity, nephrotoxicity, and embryo-fetal toxicity. The most common adverse reactions include delayed myelosuppression, N&V, stomatitis, and alopecia.

*Vincristine.* Vincristine is an antineoplastic agent, in which the mechanisms of action are not fully understood, but thought to relate to inhibition of microtubule formation in the mitotic spindle inducing cell cycle arrest.

Vincristine is administered by intravenous route only and can be fatal with other uses including intrathecal. Unfortunately for some uses including one intended use in neuroblastomas, the drug does not enter the CNS well. Other intended uses include acute leukemia, Hodgkin’s disease, rhabdomyosarcoma, and others. For treatment of leukemia,
vincristine may be used as a monotherapy, but is advised to be used in combination with other antineoplastic agents especially for treatment of the other cancers listed\textsuperscript{64}.

The FDA boxed warning includes the importance of proper technique as leakage to surrounding tissue can cause irritation and cellulitis\textsuperscript{64}. Additionally, the box warns against fatally administering the drug in any method besides intravenous\textsuperscript{64}. Other side effects include hypersensitivity, gastrointestinal issues, polyuria, hyper- and hypotension, neuromuscular dysfunction and impairment, localized pain, convulsions, optic atrophy with blindness, endocrine syndromes, alopecia, fever, headache, and more\textsuperscript{64}. Some drug interactions are known and it is advised not to take vincristine while receiving radiotherapy or at least to use precaution\textsuperscript{64}.

**Other FDA indicated therapies.** With recurrence or progression after first-line adjuvant agents have been attempted, second-line chemotherapy agents may be recommended when response to current therapy regiments ceases or reverses disease extent\textsuperscript{12}. These agents include only bevacizumab and cyclophosphamide, while platinum-based agents, irinotecan, etoposide, tamoxifen, and imatinib are periodically mentioned in the literature, but do not have current FDA indication for brain cancer treatment.

**Bevacizumab.** Bevacizumab is an anti-angiogenic agent and is known to bind and inhibit the function of VEGF, which normally causes endothelial cell proliferation and angiogenesis by interaction with its receptor\textsuperscript{65}.

The intended use of Bevacizumab is for GBM as second-line therapy as a single agent\textsuperscript{65}. Bevacizumab is administered by intravenous infusion only and not push or bolus, by the recommended dosage of 10mg/kg every 2 weeks\textsuperscript{65}. Although certain experiment combination regiments have been tried, the FDA describes intended use as a monotherapy and recognizes that no data showing improvement in tumor-related symptoms or OS have been demonstrated\textsuperscript{65}. 
The FDA provided a boxed warning for possible gastrointestinal perforation, wound healing abnormalities, and hemorrhage\textsuperscript{65}. For these issues, treatment should be discontinued and clinical history should be consulted for prescription decision\textsuperscript{65}. The most common side effects reported include epistaxis, headache, hypertension, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain, and exfoliative dermatitis\textsuperscript{65}. Other possible side effects include perforations or fistulas, arterial and venous thromboembolic events, posterior reversible encephalopathy syndrome, proteinuria, infusion reactions, embryo-fetal toxicity, and ovarian failure\textsuperscript{65}.

\textit{Cyclophosphamide}. Cyclophosphamide is an alkylating antineoplastic agent with intended use for refractory nephrotic syndrome pediatric patients and in several malignant diseases including neuroblastoma and retinoblastoma, but no gliomas\textsuperscript{66}. For malignant diseases, the treatment can be administered intravenously or taken orally with various dosing spread out over a couple days or on weekly or daily scheduling\textsuperscript{66}. Cyclophosphamide is more frequently used in combination with other neoplastic agents, but is still effective as a monotherapy\textsuperscript{66}.

Cyclophosphamide is chemically related to the nitrogen mustard and although not fully understood, its antineoplastic function is thought to involve cross-linking of DNA\textsuperscript{66}. The drug requires biotransformation to its active metabolites by the liver\textsuperscript{66}.

Severe side effects include possible myelosuppression, immunosuppression, urinary tract and renal toxicity, cardiotoxicity, pulmonary toxicity, secondary malignancies, veno-occlusive liver disease, and embryo-fetal toxicity\textsuperscript{66}. Most common adverse reactions reported are neutropenia, febrile neutropenia, fever, alopecia, N&V, and diarrhea\textsuperscript{66}.

\textbf{Other agents}. The next agents do not have any FDA indication for brain tumor or glioma treatment, but have been mentioned in the literature periodically.
**Carboplatin.** Carboplatin is a chemotherapy agent of the platinum-based variety, which includes cisplatin\textsuperscript{67, 68}. Both have a cell-cycle nonspecific mechanism that primarily produces interstrand DNA cross-links\textsuperscript{68}.

Carboplatin is administered by IV injection of 360mg/m\textsuperscript{2} on day 1 of 28 day cycles and can be combined in therapy with cyclophosphamide at a reduced dose of 300mg/m\textsuperscript{2} on the same schedule for 6 cycles\textsuperscript{68}. However, the FDA prescribing information only indicates the drug’s use for treatment of ovarian carcinoma; treatment for brain tumors is not mentioned\textsuperscript{68}. Cisplatin is indicated for testicular, ovarian, and bladder cancers only\textsuperscript{67}.

The FDA specifically warns against possible dose-related bone marrow suppression, anemia, vomiting, and anaphylaxis by marked warning label\textsuperscript{68}. Possible toxicities include hematologic, gastrointestinal, neurologic, nephrotic, and hepatic\textsuperscript{68}. Additionally, abnormal electrolyte changes, injection site reactions, pain, asthenia and less frequently, alopecia, cardiovascular events, respiratory events, genitourinary events, mucosal events, malaise, anorexia, hypertension, dehydration, and stomatitis have been reported\textsuperscript{68}.

**Irinotecan.** Irinotecan is a topoisomerase inhibitor chemotherapy agent for newly diagnosed, recurrent, or progressed metastatic carcinomas with no indication of use for gliomas\textsuperscript{69}. Binding of irinotecan and its metabolite to topoisomerase II, which normally relieves torsional strain in DNA by inducing single-stranded breaks, impairs its ability to fix the breaks\textsuperscript{69}. This results in probable and unfixable double strand DNA breakage\textsuperscript{69}.

Administration can be used as combination or mono therapy used on 3 of 30 day schedules and 4 of 36 days schedules with individual intravenously administered dosages of 125-350mg/m\textsuperscript{2} on those respective days, depending on the regimen\textsuperscript{69}. 
Severe boxed warning of diarrhea and myelosuppression can occur. Other precautions of use include cholinergic reactions, neutropenia, hypersensitivity, renal impairment and failure, pulmonary toxicity, and embryo-fetal toxicity. The most commonly reported reactions include N&V, abdominal pain, diarrhea, anorexia, neutropenia, pain fever, alopecia, constipation, and more.

_Etoposide_. With intended use for refractory testicular tumors and small cell lung cancer, etoposide has been seen to cause cell cycle arrest in low concentrations and cell lysis at high concentrations. By interaction of DNA topoisomerase II and by inducing free radicals, etoposide promotes DNA strand breakage without interfering with microtubular assembly. Dosage schedules vary, but generally follow distribution of 100-250mg/m² over 5 days to be repeated on a 3-4 week interval.

A boxed warning about administration supervision and possible severe myelosuppression resulting in infection or bleeding was presented. Adverse reactions include hematologic toxicity, gastrointestinal toxicity, hypotension, anaphylactic reactions, alopecia, and numerous other toxicities including hepatic toxicity. The most common side effects reported were leukopenia, thrombocytopenia, anemia, N&V, anorexia, alopecia.

_Tamoxifen citrate_. Tamoxifen citrate is a nonsteroidal agent with antiestrogenic and antineoplastic activities. The drug’s antiestrogenic function works by competitive binding for tissue targets. Its intended use does not include brain cancer, but treatment of breast cancer and ductal carcinoma. For breast cancer treatment, recommended daily doses were 20-40mg. The FDA indicates a boxed warning towards certain female populations including those at risk for breast cancer for severe or fatal side effects of use including stroke, pulmonary emboli, and uterine malignancies. However, in women who already have been diagnosed with breast
cancer, the warning includes that the benefits of tamoxifen do outweigh the risks. Other risks include hyperglycemia, other cancers, severe liver abnormalities, ocular disturbances, and fetal harm.

*Imatinib mesylate.* Imatinib is a small molecule protein-kinase inhibitor. Specifically, Imatinib inhibits abnormal kinases implicated in chronic myeloid leukemia pathology and others involved in platelet-derived growth factor and stem cell factor pathways. Ultimate effects are inhibiting proliferation and inducing apoptosis in cells that have mutated kinases of those varieties. The FDA does not indicate any use for brain tumor therapy. Dosage depends on the intended use and ranges from 100-800mg/day.

Warnings of using Imatinib include possible edema, severe fluid retention, cytopenias, severe congestive heart failure, severe and fatal hepatotoxicity, grade 3 hemorrhages, gastrointestinal perforations, cardiogenic shock, hypothyroidism, fetal harm, growth retardation in children, among others. The most common reactions were edema, N&V, muscle cramps and pain, diarrhea, rash, fatigue, and abdominal pain. There are some known drug interactions to be aware of.

**Conclusion**

Preference for the standard chemoradiotherapy combination is well documented even if not every study recapitulates the benefit.

Some agents used for treatment are not explicitly approved for brain tumor patients by the FDA and many come with severe black-boxed warnings. Unfortunately, all anti-neoplastic agents come with significant side effects by their non-exclusive cellular targeting. Specific side effects were given for each drug, but most commonly hepatic, gastro, and cardio toxicities are noted.
**Tumor Treating Fields (TTFields) Therapy**

**Purpose**

Cellular components can interact with induced alternating electrical fields with a range of effects dependent on frequency\(^7\). Low frequencies (<1 kHz) can stimulate membrane depolarization and bone growth, which diminishes with increasing frequency for frequencies >10 kHz\(^7\). In contrast, higher frequencies (>1000 kHz or >1MHz) have significant thermal inducing effects on tissues\(^7\). Fields in the intermediate range between these two groups do not significantly display those affects\(^7\). Instead, the primary non-neutral effect\(^**\) of the 100 kHz – 1MHz\(^††\) range, referred to as Tumor Treating Fields (TTFields), is disruption of the cell cycle by interference of formation of the mitotic spindle microtubules and destruction of cells undergoing cleavage\(^7\). In these stages, the intracellular ac fields are non-uniform cumulating in dipole charge orientation towards the cleavage furrow in the range of 100-1000kHz whereas non-dividing cells have uniform ac field distributions with no net dipole\(^7\). Induced alternating electrical fields of that range disrupt cell cycle events that require that specific orientation of microtubules and preventing subsequent step of the cell cycle\(^7\). These properties establish the theory of TTFields therapy, which selectively target rapidly replicating neoplastic tumor cells with limited adverse effects\(^7\).

Possible toxicities have been identified based on the electrical theory behind this treatment, but have not been documented\(^7\). For example, the fields might stimulate abnormal neurological and cardiac activity, which could result in seizures and heart attacks, respectively\(^7\). However, any stimulatory effect the alternating electrical fields diminishes significantly at

\(^**\) Other recognized, but generally non-consequential biological effects include the pearl chain effect or microscopic particle alignment and cell rotation\(^7\).

\(^††\) Although this entire range is of the intermediate TTFields definition, 100-300 kHz is the range for cancer therapy treatments, primarily to reduce temperature effects while still effectively disrupting neoplastic cell cycles\(^7\).
>10kHz and the treatment protocol of this therapy uses frequencies ranges of 100-300kHz depending on targeted cell types and properties\textsuperscript{73}. This trend is theorized to occur due to electrochemical properties of cell membranes\textsuperscript{73}. Another concern is broader damage to the body in cells with natural high turnover rates, specifically with bone marrow cells and small intestine mucosal cells\textsuperscript{73}. However, no damage has been reported in animal models and patients undergoing therapy did not have a significant amount of adverse effects of all body systems\textsuperscript{14, 73}. The two cell types mentioned before are thought to be protected by factors related to the surrounding tissues and slower replication cycles in the mucosal cells relative to neoplastic cells\textsuperscript{73}.

The FDA approved the TTFields therapy for primary and recurrent treatments in 2015 and 2011, respectively\textsuperscript{74}.

**Protocol**

The Optune treatment includes components to maintain portability of the device and most importantly, the active devices, which are an electric field generator (Optune device) and INE insulated transducer arrays\textsuperscript{14}. Powered by portable lithium batteries, the Optune device generates TTFields to the transducer arrays placed on the scalp to reach the neoplastic cells in the brain\textsuperscript{14}. When using the device, patients are responsible for charging batteries, keeping scalp completely shaved, and proper set up to allow for maximal use and results\textsuperscript{15}. Patients to use the device less than the recommended 18 hours per day had an overall survival 3mos less than those that followed protocol\textsuperscript{15}. The recommended therapy term is a minimum of four weeks and disrupting or ending the treatment early can result in decreased response to treatment, continued tumor growth, and reappearance of symptoms in 1-2 weeks\textsuperscript{14}. This minimum treatment period was found using a model based on growth kinetics of a malignant tumor and reflects the time needed
for tumor stabilization\textsuperscript{14}. Maintenance of the system is relatively straightforward and settings do not need to be adjusted. For treatment of GBMs, the settings are maintained at a frequency of 200 kHz and an intensity of 0.7V/cm\textsuperscript{14}.

Depending on whether or not there is progressive disease of >25\% or new lesions, the protocol will follow that of newly diagnosed or recurrent regiments\textsuperscript{14}. These protocols differ mostly by simultaneous use with TMZ in newly diagnosed cases whereas Optune is used as a monotherapy in recurrent cases\textsuperscript{14}. Specific inclusion and exclusion criteria also differ between groups\textsuperscript{14}. For newly diagnosed GBMs, the therapy is used in tandem with maintenance TMZ therapy and must be at least 4 weeks post-surgery and at least 4 weeks, but not more than 7 weeks post-radiotherapy+TMZ\textsuperscript{14}. For recurrent GBMs, the patient uses TTFIELDS therapy without other treatments and must have documented disease progression, must not be eligible for further radiotherapy or resection procedures, and must not be within 4 weeks of prior surgery, chemotherapy, or radiation therapy\textsuperscript{14}. Both protocols have limits on significant co-morbidities and both require Karnofsky scores equal to or above 70\textsuperscript{14}.

The only side effect reported linked directly to the use of Optune was scalp irritation from the transducers, which should be treated with hydrocortisone creams and are generally mild to moderate in nature unless untreated\textsuperscript{14}.

**Conclusion**

Although the TTFIELDS therapy is newly approved for GBM treatment, the results seem to be promising with limited risks, as of now. For the limited benefit of other treatment modalities, new therapy techniques, especially those without severe and common toxicities, should be welcomed.
Other Medications

Brain tumor patients incur many complications and side effects that require palliative medications that do not target the tumor, but symptoms less directly related. Treatable problems and medications include: cerebral edema and corticosteroids; seizures and antiepileptic drugs; endocrine disorders and checking for treatment-induced toxicities; psychiatric disorders and psychopharmalogical drugs; venous thromboembolisms or risks and anticoagulant medications; and various allied services.\textsuperscript{16, 17, 23}

Reassessment

Purpose

Given the well-documented progressive tendencies of the cancer albeit aggressive treatment modalities, reassessment is important to evaluate response to treatment and possible toxicities or side effects. Radionecrosis and pseudoprogression should be monitored as possibilities in addition to monitoring current therapies. Even if the tumor is not progressing, reassessment based on tolerance of the drug’s side effects is important for the patient and their QoL.

After therapy begins or into the process, the tumor can completely or partially respond, remiss, remain stable, or progress.\textsuperscript{50} Criteria is in place to categorize these stages and are important for determining efficacy of treatment. If remaining stable, new therapies with more promising results could be attempted by switching protocols. If the tumor is progressing, the current treatment is not helping, if not instigating growth itself, and should be discontinued. Alternatively, if the disease is responding, partially or completely, continuing treatment may be valuable, while remission may allow cessation of treatment altogether. These steps after determining progression status are up to the discretion of the doctor in agreement with the
patient. However, the point of defining progression and reassessing the protocol provides a way to evaluate and determine next steps.

**Microscopic Infiltration**

Attributing to difficulty in treating or assessing progression of gliomas further, infiltration is thought to extend 2cm beyond radiographic evidence of disease and usually not localized to one venous access point\(^\text{16}\). As previously mentioned untraceable microscopic infiltration extent of the malignant glial cells is significant\(^\text{16}\). Neurological deterioration is known to occur without significant mass effects and can be attributed to this microscopic spread\(^\text{16}\). Symptoms of deterioration include increased risk of aspiration, deep venous thrombosis, and pulmonary embolism\(^\text{16}\).

Autopsy reports of gliomas show more than half may exhibit contiguous spread with only 3% showing CSF seeding only, while 25% patients exhibit both types of spread\(^\text{16}\). Additionally, multifocal GBM, possibly representing independent tumors or undetected spread by CSF, have an incidence of 0.9-17% of patients\(^\text{16}\).

**Pseudoprogression**

Extent and distribution of contrast enhancement, edema, and mass effect demonstrated on MRI or CT scans are more directly related to BBB function and therapy effects while less directly indicative of tumor size or progression known as the problem of “pseudoprogression”\(^\text{75}\). Difficulty in distinguishing tumor progression and BBB dysfunction exacerbated possibly by surgery, RT, and corticosteroid use stems from interpretation of qualities of MRI radiography including contrast enhancement, T2-weighted abnormalities, and mass effect\(^\text{75}\).

Radiotherapy is associated with BBB dysfunction and corticosteroid use may be recommended\(^\text{46, 57}\). With increased corticosteroid use, tracking of progression by MRI may be
worse than actual progression usually within the 3 months post-RT treatment\textsuperscript{56, 57}. Within this window, extent of mass effect and brain edema may indicate under- and overdosing of corticosteroids\textsuperscript{56, 57}. Following this window, MRI progression evidence can be related more reliably to tumor recurrence\textsuperscript{56, 57}.

Although limited in consistency, use of MR spectroscopy, MR perfusion, or PET can be used to better distinguish those progression-mimicking features, also known as pseudoprogression, but is not absolute enough to discontinue therapies\textsuperscript{75}. Reoperation may be the best solution for treating radionecrosis, but is more difficult when viable tumor contributes to the heterogeneous mass with radionecrosis\textsuperscript{75}. Distinguishing radionecrosis from progression or recurrence is also limited in application for that issue\textsuperscript{75}. Unfortunately, steroid use is also limited by providing only temporary relief\textsuperscript{75}.

**Disease Progression**

Macdonald criteria (MC) was the most frequently used assessment response guidelines for GBM, but has recently been challenged by new protocols\textsuperscript{50}. Other guidelines include the Levin criteria, the World Health Organization (WHO) oncology response criteria, and the response evaluation criteria in solid tumors (RECIST), which were all either not as effective or not specific to brain tumors\textsuperscript{50}. The MC classified progression trends into 4 groups: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD)\textsuperscript{50}.

Recently identified issues with quantification of certain components of contrast-enhancing and non-contrast-enhancing guidelines and definitive criteria for duration between scans all call for further refinement of the MC\textsuperscript{50}. Non-contrasting infiltration and vascularized components, contrast-enhancing pseudoprogression, baseline scan, and event-related scan guidelines are not provided or adequate enough to account for these important or recently
recognized problems\textsuperscript{50}. Recently, modified response criteria implemented in two case studies, a 2006 BRAIN study and the phase 3 AVAglio study of 2009, prompted the Response Assessment in Neuro-oncology (RANO) working group to publish an updated criteria guideline\textsuperscript{13,50}. Further clinical confirmation of its applicability and reproducibility are needed and subsequent revisions are expected\textsuperscript{50}. 

<table>
<thead>
<tr>
<th>Criteria</th>
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<tr>
<td><strong>CR</strong></td>
<td>Requires all of the following:</td>
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<td>-- complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks;</td>
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<td></td>
<td>--no new lesions;</td>
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<td></td>
<td>--<strong>no corticosteroids</strong>; and</td>
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<td>--stable or improved clinically</td>
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<td></td>
<td>--<strong>stable or improved nonenhancing (T2/FLAIR) lesions</strong>;</td>
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<td>--<em>patients must be off corticosteroids (or on physiologic replacement doses only)</em>;</td>
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<td></td>
<td>--<strong>Note: Patients with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.</strong></td>
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<td><strong>PR</strong></td>
<td>Requires all of the following:</td>
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<td>--≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks;</td>
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<td>--no new lesions;</td>
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<td>--<strong>stable or reduced corticosteroid dose</strong>; and</td>
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<td></td>
<td>--stable or improved clinically</td>
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<td></td>
<td>--<strong>no progression of nonmeasurable disease</strong>;</td>
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<tr>
<td></td>
<td>--<strong>stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan</strong>;</td>
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<td>--<strong>the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan</strong>;</td>
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<td>--<strong>Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.</strong></td>
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<td><strong>SD</strong></td>
<td>Requires all of the following:</td>
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<td>--does not qualify for complete response, partial response, or progression;</td>
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<td></td>
<td>--and <strong>stable clinically</strong></td>
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<td></td>
<td>--<strong>stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan.</strong></td>
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<td>--<strong>In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.</strong></td>
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<tr>
<td><strong>PD</strong></td>
<td>Defined by any of the following:</td>
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<td>--≥ 25% increase in <strong>sum of the products of perpendicular diameters of enhancing lesions</strong>;</td>
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<td>--any new lesion; or</td>
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<td>--<strong>clinical deterioration</strong></td>
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≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids*;  
-- significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy* not caused by comorbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects);  
-- clear clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose;  
-- failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

Table 11. Comparison of progression criteria for complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) between MC (top row) and RANO criteria (bottom row). **Bold statements:** revised MC in RANO criteria; *italicized statements:* added in RANO criteria; **crossed statements:** original statements in MC not included in RANO criteria.

Adapted from Wen et al. (2010).  

The RANO criteria seems to be generally well-received as it addresses many important concerns, but still faces some problems. Specificity in defining or providing techniques for complex geometric tumor shapes or requirements for enhancement thickness were not well defined. Criteria for nonenhancing lesions might not have been defined at the same level of detail between groups and may represent a gap in application. Many AAs do not enhance and so provides difficulty with that subgroup as well as the heterogeneous nature of GBM tumors. Lastly, RANO proposed at 12 week cutoff for pseudoprogression risk, but may not be long enough.

Progression is a detailed analysis of radiographic interpretation and tracking in conjunction with KPS defined clinical stability by MC and RANO criteria. However, the process can be complex and certain scenarios can leave room for errors in reproducibility. The criteria can always be improved in conjunction of evolving radiographic and analytical...
technologies, but has made considerable strides with each significant renewal or modification\textsuperscript{13, 50, 52}. Given the RANO criteria’s infancy and MC’s reputation, but lack of certain important features that RANO includes, both are presented for definitive purposes (Table 11). The purpose of this section and its applicability in the rest of the report are to describe the general state of progression criteria and its applicability in context of its limitations.

**Recurrence**

By radiographic monitoring, evidence of recurrence can hopefully be caught early and has approved treatment options depending on number or spread of recurrent lesions. Re-resection or reirriddiation are sometimes appropriate protocols, but controversially effective\textsuperscript{12}. Generally, some benefits in using chemotherapy agents in patients who did not receive antineoplastic agents prior to recurrence are noted\textsuperscript{12}. Otherwise, the protocol for determining course treatment is not as specific or directed as that for newly diagnosed cases\textsuperscript{12}.

**Terminal Stage**

Specific recommendations for supportive care of patients with brain tumors is not explicitly focused on in the relevant literature, but instead must be deduced from larger study groups including those of general cancer patients, general neurological disease patients, and general palliative care groups. As such, there is not a general protocol or comprehensive review of end of life problems for brain tumor patients. However, several recent studies have provided information to better characterize the symptoms experienced by and support provided to brain tumor patients in the end of life stage.

**Purpose of Care**

With the terminal stage of disease where tumor progression continues and treatment options have been exhausted without response, continuation of treatment may do more harm than
good and maximizing quality of life should be the main goal. End of life care in general should find a balance between alleviating symptom burden, postponing avoidable fatal complications, avoiding burdensome or painful prolongation of life, and supporting the patient and family in a psycho-social manner\textsuperscript{16,23}.

Any treatment within this stage should be weighted in terms of clinical benefit to possible complication burden with consent from the patient when applicable. Protocols of other palliative or prophylaxis medications specific to brain tumor patients are not always available, but should be considered within the context of specific neurological deterioration associated with brain tumors and specific to the patient’s condition. Prophylaxis of well-known causes of death (COD) including steroid treatment or tumor debulking may be palliative options to prevent painful unnecessary death, but not at the cost of quality of life. Since these protocols are so subjective and patient-specific, it is very difficult to describe general approaches, but should be planned with care and with informed consultation with the patient or family when possible for the overall goal of maximizing quality of life in the short remaining time the patient may have\textsuperscript{16,17,23}.

**Final stages**

Comparison of symptoms, medication, diagnostics, and procedures implemented in the last 10 weeks of life, divided into 3 phases, of 29 GBM patients was described by Oberndorfer et al. (2008). Symptoms of decreased vigilance, fever, and dysphagia increased significantly from phase 1 and 2 to phase 3 and were the most common symptoms recorded in phase 3\textsuperscript{17}. Other symptoms that increased across phases 1-3 were seizures, vomiting and skin problems, pneumonia, and urinary infection, in order of decreasing frequency in phase 3\textsuperscript{17}. Pain, headache, and edema\textsuperscript{‡‡} peaked in phase 2 following a decrease in frequency in phase 3\textsuperscript{17}.

\begin{footnotesize}\‡‡ Symptoms clinically suspected brain edema\textsuperscript{17}.\end{footnotesize}
In regards to pharmacological interventions, use of AEDs, psychopharmacological drugs, NSAIDs, opioids, heparin, gastric protection, intravenous fluids, oxygen insufflation, and antiemetics increased across the three phases\textsuperscript{17}. More than 2/3 of the patients used IV fluids and opioids, heparin and gastric protections, NSAIDs, and AEDs, during phase 3, in order of decreasing frequency\textsuperscript{17}. Total diagnostic procedures and consultations peaked during phase 2 with blood tests being the most frequently used procedure in all three phases\textsuperscript{17}. Medical interventions of venflon, urinary catheter, and air bed were the most commonly utilized measures taken in phase 3 in at least 2/3 of the patients, listed in decreasing order of frequency\textsuperscript{17}. Lastly, the cause of death was determined to be 62\% tumor progression, 21\% pneumonia, 14\% respiratory distress, and 3\% treatment complication\textsuperscript{17}.

**Advanced Directives**

A living will or advanced directive provides the patient and their family to legally instate their preferred wishes in the case of extreme measures, which includes decisions that may prolong or reduce life\textsuperscript{23}. Living wills can be made at any point during someone’s life, but can become especially important when given a diagnosis of any type of disease with known association in cognitive deterioration, such as with most neurological disorders.

Specific to patients with brain tumors, these decision include withdrawal of supportive treatment or pharmacological agents, withholding nutrition in vegetative patients, and palliative sedation\textsuperscript{23}. Specific decisions may solve one possibly fatal problem, but induce other complications. For example, parenteral feeding does not alter survival, but may increase fluid secretion and retention of the body and in the brain, respectively\textsuperscript{23}. Other decisions may require approval of controversial sedative drugs to alleviate suffering until death, which can be ethically controversial\textsuperscript{23}. Yet other decisions may require approval for cessation of supportive treatments,
such as with down tapering of steroids. Generally, these decisions are regarded as extreme measures to replace a function needed for life, alleviate suffering by intervention, or cessation certain treatments.

These interventions are usually done following explanation or consultation to the family. However, it is suggested patient or family involvement in the decision making process is rare. In specific regards to the patient’s consent or involvement in the decision making, there is pressure for early action due to the overall cognitive decline and the observed rapid deterioration in later stages. Up to 40% of patients are unaware of their prognosis, however, a study by Pace et al. (2009) asserted that not all patients wish to be aware of their prognosis. Their recommendation is to tailor the extent and delivery communication to the patient’s and families’ coping methods. It is not clear whether that is meant for the entire duration of treatment or only in the terminal phase. In the same study, only 6% of patients declared early directives for end of life treatment. It was also determined the majority of patients were not competent enough to make any decisions in the last month of their life. In respect to the patient and their family, early education and discussion of these options are recommended and should be pursued through other counselors from the primary.

**Types of Care**

**Palliative care.** Generally, symptomology, pharmacological interventions, and procedural interventions increase towards the end of patient life. However, protocols for induced sedation are controversial among general palliative care specialists, pain treatment and extent are controversial for brain tumor patients, opioid treatment for respiratory distress is not described for brain tumor patients, only cancer patients in general, and treatment using steroids and AEDs are not described specifically for the terminal phase of brain tumor patients.
Comparisons from the terminal phase medical treatments and interventions described to the general cancer, palliative care, and neurological disease groups show overlap in experiences with specificity in terms of seizures, progressive neurological deficits, symptoms from brain edema, headache, personality changes, and restlessness for brain tumor patients. As such, protocols designed for and based on the general groups may not fit the needs of most terminal brain tumor patients. For example, with a significant frequency of reported dysphagia in brain tumor patients requires alternative delivery of pharmacological agents than oral administration such as intramuscular or intravenous delivery. Possibly, changing administration route early may prevent exacerbation of dysphagia and related pain if oral administration provokes this symptom or causes avoidable choking. Earlier switches may reduce the number of complications occurring in the more fragile states if switching requires change in medication. Those ideas are merely speculations, but, with proper research by more comprehensive retrospective studies of the terminal stage of brain tumor patients, may prove to be substantial claims and patients may benefit when these types of complications are better understood specific to brain tumor patients.

Ultimately, the actual protocol used for individual patients are determined by the patient’s management team. However, treatment designs may benefit greatly from accessible information regarding dosage and side effects for patients with brain tumor specific complications or concomitant symptoms by clinical research. Specifically, prophylactic treatment for brain tumor specific symptoms such as seizures, headache, and restlessness may be possible targeted research topics.

**Basic needs.** Other services or protocols may have to be adjusted from normal in response to certain symptomatic complications a patient may be experiencing. Fulfilling basic needs such as nutrition and hydration may be given less specific attention when describing
Palliative care of patients in comparison to the symptomatic relief care described previously. However, for the sake of describing end of life care in full, common adjustments needed to be made for brain tumor patients will be described.

One of the most prominent and significantly interfering complication among brain tumor patients is dysphagia^{23}. This interferes with such activities such as medication administration as mentioned previously, and in terms of its relation to basic needs, nutrition and hydration^{23}.

**Cause of Death**

Although many complications may be present in brain tumor patients in the terminal stage, certain issues are attributed to cause of death more so than others. Although CODs of GBM patients was previously thought to be primarily herniation or treatment complications, but may not actually be that straightforward^{16}. Postmortem autopsies have purpose for defining accuracy of diagnosis in retrospect, topographic patterns of tumor growth, and most likely primary CODs and subsequent relation of those principles to the efficacy of aggressive treatments using patient and treatment factors^{16}.

In Oberndorfer et al. (2008), more than half were attributed to tumor progression, one-fifth to pneumonia, followed by respiratory distress, and minimal treatment complication^{17}. A previous study of GBM patients at University of Washington medical center analyzed COD slightly more specifically with different overarching COD categories. Potential CODs were herniation; postoperative death defined as death within 30 days of surgical intervention secondary to complications including cerebral edema, cerebral hemorrhage, or systemic complications; severe systemic illness including pneumonia, sepsis, pulmonary embolus, and myocardial infarction; tumor infiltration of the brainstem; and widespread gliosis caused by neutron irradiation toxicity^{16}. Of the total 117 patients, CODs of 8 patients who did not have
evidence of herniation could not be identified while 50% of total patients had indication of multiple CODs\textsuperscript{16}. With the cases of multiple possible CODs, some causes may be interlinked or merely potential in nature\textsuperscript{16}.

Herniation is a significant potential COD, but evidence does not always indicate the event as the primary cause\textsuperscript{16}. Herniation is noted with occurrence of axial, transtentorial, subfalcine, or tonsillar herniation as a result of tumor mass effect\textsuperscript{16}. More than half the patients had postmortem evidence of herniation, further divided into three populations in decreasing frequency: evidence for brainstem distortion, no brainstem abnormalities, and Duret’s hemorrhage\textsuperscript{16}. Patients without ante mortem diagnosis and patients treated with neutron irradiation were positive and negative predictors of herniation, respectively\textsuperscript{16}. Less than half of those with herniation evidence did not have other potential CODs associated\textsuperscript{16}. A hypothetical example provided by the UWMC study where respiratory failure secondary to pneumonia can cause evidence of herniation, in which the difficulty lies within postmortem interpretation of these multiple signs of potential CODs\textsuperscript{16}.

Brainstem damage can be considered a significant potential COD and was found in 38% of patients in the UWMC study\textsuperscript{16}. Damage includes Duret’s hemorrhage and nuclear molding\textsuperscript{16}. Although herniation usually results in brainstem damage, more patients had evidence of herniation than brainstem damage and so does not seem necessary in response\textsuperscript{16}. In fact, a hypothetical case where this could occur would be compensation by intracranial shift from herniation enough to avoid brainstem damage\textsuperscript{16}. Additionally, tumor invasion of the brainstem was found in 15% of patients, 2/3 herniated and 1/3 not herniated\textsuperscript{16}.

Given the incidence of possible herniation COD and significant presence of other complications, treatment should generally try to both attempt mass effect reduction and attenuation to the other CODs listed\textsuperscript{16}. 
Discussion

Initial surgical resection is followed by radiotherapy concurrent with chemotherapy, TMZ for GBM and PCV or TMZ for AAs. Maintenance chemotherapy can continue while monitoring progression, toxicities, radionecrosis, and pseudoprogression. Upon refractory or recurrent cases, changing chemotherapy protocol, reirradiation, or reoperation may be deemed appropriate. Palliative care measurements treating common complications such as seizures, VTE, fatigue, endocrine disorders, and others should be done as needed and primarily during the terminal stage in which palliative cares and basic needs are the priorities.

Discussion of WL

Treatment. Without possibility of resection, WL received her biopsy by stereotaxic technique and began primary radiotherapy and chemotherapy after recovering. Monitoring progression occurred before each protocol began or continued to validate the next move. Also, radiation followed up several weeks after treatment to check on her status and most likely delayed radionecrosis. A summarized list of her treatments and therapeutic interventions are listed in Table 12.
The initial radiotherapy and BCNU protocol induced response by MRI and some functional relief. The disease remained stable for some time then equivocal changes, possibly indicating microprogression, marked by signal changes, which turned into volume changes of the lesion and progression was determined. However, the progressive volume changed after already switching from the BCNU protocol to Tamoxifen/TMZ, so the course was finished. Shortly after on day 300, progression continued and new lesions were found in distal locations indicating overall progression and failure of the Tamoxifen/TMZ protocol. The third protocol of Gleevec began, but progression continued and another regimen was elected for, since Gleevec was only in phase 1-2 setting for brain cancer treatment at the time. The carboplatin/etoposide protocol began, but WL was soon admitted to the hospital with abnormal labs to be treated with CSF injections. Although the repercussions were not serious, her labs were too low to continue chemotherapy and functional decline was apparent.
**Terminal stage.** Unfortunately, the tumor was massively progressed, WL was not responding to therapies, and functional decline was significant. At this point, the primary neurooncologist mentions hospice care considerations, indicating terminal stage status, but the family persisted for continued treatment and her last round of Gleevec was given. Approximately 6 days later, before even finishing the Gleevec protocol, WL was hospitalized for decreased mental status and was also found to have pneumonia and a urinary tract infection as well. Severe increased intracranial pressure was found by CT scan, accounting for the decreased mental status and her subsequent respiratory failure intervened by intubation. The infiltration around the fourth ventricle and cerebellum possibly seemed significant enough to cause herniation and brainstem compression by increased intracranial pressure.

Lack of advanced directives and end of life care plans may have made this period more difficult for the family and the patient, although she was likely to have not been aware enough to comprehend this issue. Brain tumor treatment is well marked by surgical treatment, radiotherapy, and chemotherapy, but supplemented by a lack of characterization of the terminal stage complications, treatments, and CODs. Even though the patient is terminal at this point, providing QoL and care are equally, if not more, important than previously, since these are usually the last moments of life the patient and family have.

**Conclusion**

In general, treatment should be intervened as early as possible in disease course since these neoplasms’ prognoses are marked in months and the tumor may be far progressed by the time symptoms present. Unfortunately, even the best of care is not usually successful in the long term since the 5-yr survival rates are 27.9% and 5.1% for AAs and GBMs, respectively\(^3\). However, QoL should be maximized whenever possible when determining treatment.
aggressiveness and possible side effects, especially in the elder population and those with low KPS statuses.

Generalized issues such as fatigue, pain, and systemic illnesses persist in the terminal stage accompanied by progressive, neurologic-specific complications. Causes of death include herniation, post-op complications, systemic illness, brainstem infiltration, and gliosis. During the terminal stage, palliative care should be implemented to reduce these complications or act to prevent the known possible causes of death. However, prolonging death is controversial in this stage of disease progression. Discussing advanced directives and preference for end of life care is important early in the disease course before awareness or memory fails. Also, preparing for this difficult time should be done with counseling resources beyond the clinical support of the primary. Essentially, this entire process relies on diverse specialties for both treatment and care, which are important from the start to the end of this course.
Part V. Conclusion

The main purpose of this review and case study report was to clinically characterize the process of handling cases of malignant gliomas from start to finish. Malignant brain tumors have some of the poorest prognoses, responses to therapy, and substantial burden by neurologic-specific symptomology and deterioration. Treatment and management of malignant gliomas is difficult and somewhat unpromising in the long term.

The tumor itself is evolving and growing with multimodal techniques for inducing vascularization and migration, even before the patient is aware. Symptomology is both lifesaving to get a patient into the clinic and burdensome as a progressive problem throughout disease course to usually increase in severity and in number. Diagnosis, treatment, and management follow to help the patient through what may only be short time longer. The disease is well known to be fatal by direct or indirect means despite aggressive treatments.

Throughout the manuscript, the clinical disease course of patient WL has been well described and analyzed in retrospect of the decisions of a team of clinicians. This case report supplemented the literature review in an invaluable illustration of how these protocols are implemented in real patients over the entirety of the journey. However, this one case was specialized and reporting of more unique and classic examples would supplement this manuscript well in future renditions. Additionally, application and analysis was somewhat stinted by the lack of supporting materials included in the clinic notes including actual MRI scans and reports, lab reports, and others. The information presented was based on clinic notes, which were summarized based on the presenting evidence. However, the summaries were valuable in many ways including how the primary physician described their thought process even though details were not always enclosed.
WL’s tumor behavior well characterized the typical invasiveness, spread mechanisms, and massive growth of malignant gliomas. The most noted unique characteristics to her case were the symptomology, the initial lesion location and subsequent access to white matter migratory tracts, and the unresectability. These features are implied to vary strongly from patient to patient, but were notable features that determined much of the clinical reporting. The educational purposes of including this report provided great benefits in protocol illustration and disease characterization that could not have been provided easily with other mechanisms.

Although meant to be comprehensive, this manuscript focused on current protocols, yet many experimental therapies are under development or have been in controversial practice previously. For example, tumor-targeting immunotherapies are hopeful therapies that may reduce non-specific toxicities associated with current chemotherapies and provide better tumor uptake. Additionally, the manuscript focused on current and accepted understandings of tumor biology, but increasingly in-depth biochemical mechanisms are most likely presented elsewhere in the literature. Although sufficient for introductory purposes into the clinical field of neurooncology, better and more specific clinical practices of the protocols presented and further case study analysis will improve the appreciation and understanding of the topics presented.
References


