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Innovative Surgical Management of Glioma

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1. Introduction

Glioma is one of the most common primary brain tumors accounting for 30 to 40% of all intracranial tumors. Gliomas can be divided into two types based upon histopathalogic diagnosis according to the World Health Organization (WHO) classification, low grade (WHO I and II) and high grade (WHO III and IV). High grade malignant glioblastoma accounts for the majority of diagnoses and carries the worst prognosis. Prognosis with glioma depends on the patient's age and Karnofsky performance score (KPS) as well as the histological grade of the tumor. For the United States in 2010 there were 6.8 new cases of glioblastoma for every 100,000 people[1]. The current standard of care for patients with newly diagnosed high-grade glioma is surgical resection followed by fractionated external beam radiation therapy and systemic chemotherapeutic treatment mostly with temozolomide[2].

The single best therapeutic option in the treatment of glioma is extensive surgical resection, and the extent of resection directly correlates with the greatest survival benefit. Despite our best efforts however, the outcomes for malignant glioblastoma are still very poor with less than 5% of patients surviving five years post diagnosis even with the best current treatment3. In light of these poor results there is significant room for innovation and improvement in the area of surgical management particularly with an objective to increase the extent of surgical resection. Throughout this chapter we will discuss the importance of surgical resection in the treatment of glioma as well as emerging innovative surgical methods and technologies for increasing the extent of resection and improving upon the associated survival benefit. We will also explore adjuvant therapies in glioma management and the important role that surgery plays in maximizing the potential benefit of these adjuvant therapies.

2. Current surgical management of glioma

Three options are available for the surgical management of gliomas. The first option is to refrain from surgery for as long as possible, sometimes referred to as the "wait and see" approach. The second option involves biopsy of the lesion or subtotal resection of surgically accessible areas within the tumor in order to obtain histopathology diagnosis. Biopsy and subtotal resection are often followed by adjuvant therapies (radiation or chemotherapy). The

best surgical option is gross total resection (GTR), usually defined as removal of all areas of contrast enhancement on T1 weighted MRI obtained postoperatively. GTR provides the best surgical treatment and is associated with the best survival rates; however, it also carries the greatest risks of postoperative neurologic deficits and disability.

Current treatment for glioma, particularly high grade lesions, is not curative and the majority of patients experience reoccurrence following initial resection. Reoccurrence is due to the infiltrative nature of these lesions and the inability of current treatment modalities to fully remove and destroy all tumor cells. The rationale behind surgical management of these aggressive lesions is based on the Gompertzian phenomenon. In 1825, the English mathematician Benjamin Gompertz postulated that the biological growth of normal organs and malignancies follows a characteristic curve and that cell number increases with time, but the relative rate of increase falls exponentially as the mass reaches a "plateau phase" of a very slow actual growth[4]. Therapy can induce regression in tumor volume, however, there is always regrowth between cycles of treatment and this "regrowth" will follow the same Gompertzian growth curve. The only escape from Gompertzian phenomenon is complete tumor cell eradication. Therefore, the ultimate goal of surgical therapy in these tumors should be the complete eradication of all abnormal neoplastic cells. With the currently available surgical techniques we are still unable to fully resect most of these tumors. Therefore we need new techniques to improve surgical resection as well as adjuvant therapies to eradicate remaining tumor cells and thereby maximize the survival benefit of surgery.

Low grade gliomas (WHO I and II) are a broad group of tumors that are clinically, histologically and molecularly diverse. WHO grade I tumors comprise the group of pilocytic astrocytoma and subependymal giant cell astrocytoma the more common being pilocytic. Management of WHO grade I glioma consists of gross total resection as the treatment of choice and carries an excellent prognosis. Following resection, 25-year survival rates of 50-94% have been reported[5]. Grade I lesions are the only glioma subtype where gross total resection is considered curative.

WHO grade II gliomas consist of diffuse fibrillary astrocytoma, oligodendrogliomas, and oligoastrocytomas, all of which have similar invasive and malignant potential. Grade II gliomas that are symptomatic and surgically accessible should undergo maximal cytoreductive surgery as the treatment of choice. Predictors of incomplete tumor resection in low grade lesions include tumor involvement of the cortico-spinal tract, large tumor volume, and oligodendroglioma histopathologic type. 5 year survival of up to 95-97% has been reported following gross total resection in these lesions[6]. In 2008, Smith and colleagues reported a large series of 216 patients with biologically aggressive grade II lesions and examined the extent of resection and the effect on overall survival[7]. Patients with at least 90% resection showed 5 and 8 year survivals of 97% and 91% respectively compared to those with less than 90% resection who showed survival rates of 76% and 60% at 5 and 8 years.

For both grade I and grade II tumors, maximal surgical resection is the single best treatment for obtaining increased survival. In cases where there is progressive tumor growth following resection or progressive neurological symptoms in unresectable tumors, adjuvant chemotherapy or radiation treatment may be used.

High grade glioma's (WHO III and IV) consist of anaplastic astrocytoma (Grade III), and glioblastoma (Grade IV). These tumors are malignant and carry a significantly poorer

prognosis than the low grade lesions. The first line therapy for high-grade glioma is cytoreductive surgery with the goal of removing as much abnormal tissue as possible without causing further damage to normal parenchyma. The reduction in tumor volume results in improved survival and quality of life by delaying recurrence and malignant progression.

There are many studies over the past two decades that examine the extent of cytoreductive surgery; gross total resection verses biopsy and subtotal resection in regards to increasing patient survival. Tumor location as well as extent of neurologic deficits plays a large role in the decision making process for surgical management. One retrospective study in 1996 showed significant increased mean survival time of 292 days vs 184 days between a group undergoing cytoreductive surgery and a group undergoing stereotactic biopsy respectively[8]. However quality of life measured by KPS was not significantly different between the two groups.

A prospective study utilizing 60 patients, examined the extent of resection compared to survival. These authors found median survival of 64 weeks for the group who underwent gross total resection compared to 36 weeks for the group undergoing subtotal resection[9]. They concluded that patients undergoing subtotal resection have 6.6 times higher risk of death. Another large prospective of study 645 patients showed that patients undergoing total resection had a median survival of 11.3 months compared to 10.4 months for subtotal resection, both of which were significant increases in survival compared to 6.6 months for patients with biopsy only[10].

Increased survival with resection holds true even for the elderly. A study by Vuorienen, focusing specifically on elderly patients over the age of 65 showed median survival of 5.7 months with open craniotomy and surgical resection compared to 2.8 months with stereotactic biopsy alone for an increased estimated survival time of 2.7 times longer in the resection group[11]. However, this increased survival time is modest in this patient population providing only a 2-3 month survival benefit. The role of aggressive surgical management in the elderly population is still a controversial subject. Chronological age however, is not necessarily the most important factor to consider in deciding to pursue an aggressive surgical course. Rather biological age which takes into account the patients general health and functional level should be used as a guideline.

A recent review article from 2008 examined over thirty published articles from the neurosurgical and neuro-oncologic literature regarding extent of resection and the effects on survival for malignant glioma. Only one study failed to support the idea that extent of surgical resection correlates with an increased survival advantage[12]. These authors recommend that based on the current prospective and retrospective data that for newly diagnosed malignant glioma in adults, maximal cytoreductive surgery should be undertaken provided that postoperative neurological deficits are minimized.

Studies have also been performed in order to quantify exactly what percent of tumor resection is necessary to provide maximal survival benefit. The original landmark study was published in 2001 by Lacroix and colleagues in which they performed a retrospective analysis of 416 patients with glioblastoma treated with surgical resection[13]. Patients who received resection of greater than 98% had a mean survival of 13 months compared to patients receiving resection of less than 98% with mean survival of 8.8 months.

A more recent 2011 retrospective study by Sanai and colleagues also quantified the percent of tumor resection required for maximal survival benefit[14]. 500 patients with gliobastoma were treated with surgical resection followed by standard radiation and chemotherapy. They found a survival benefit with extent of surgical resection of as low as 78%. However, for maximal survival benefit, resection of greater than 95% was observed

Overall, these studies demonstrate that prolonged survival time correlates with the extent of surgical resection. The data also suggests that for high grade lesions, resection of greater than 95% of the tumor volume should be performed in order to provide the maximal survival benefit. In some cases, however, such a high level of resection is unable to be obtained. This is usually due to tumor involvement in areas of eloquent brain tissue (areas involved with speech production, motor function and sensory perception), and is associated with a high risk of postoperative deficits. Maximizing the extent of tumor resection while preserving normal brain function and optimizing quality of life postoperatively represents a major challenge in neurosurgery. Several strategies and innovative techniques have been developed to assist the surgeon in safely resecting tumors located in these eloquent areas, particularly in the areas of neuroimaging, neuronavigation, functional mapping, and photodynamics. Theses new developments provide for greater resection volumes and better survival rates.

3. Neuronavigation

Image guided neuronavigation utilizes the principle of stereotaxis. The brain is considered as a geometric volume which can be divided by three imaginary intersecting spatial planes based on a Cartesian coordinate system. Any point within the brain can be specified by measuring its distance along these three planes. This provides a precise surgical guidance by referencing this coordinate system of the brain with a parallel coordinate system of the three-dimensional image data of the patient that is displayed on a computer-workstation so that the medical images become point-to-point maps of the corresponding actual locations within the brain[15]. Neuronavigation provides intraoperative orientation to the surgeon, helps in planning a precise surgical approach to the targeted lesion and defines the surrounding neurovascular structures. Conventional neuronavigation typically utilizes a preoperative MRI which is registered to the patients skull at the beginning of the procedure and is used throughout the case without any update in imaging or reregistration of the imaging to the corresponding brain tissue. Conventional neuronavigation is readily available at most centers providing neurosurgical care and is not particularly cost prohibitive. (Figure 1)

Intraoperative MRI (iMRI) guided intracranial surgery improves upon the benefits of conventional stereotactic guided neurosurgery by providing a real time updated view of the anatomic relationship between tumor and normal brain structures. During surgical resection utilizing traditional cranial neuronavigation, the brain parenchyma becomes distorted due to changes in tumor volume, edema and volume of cerebrospinal fluid resulting in brain shift, which is not reflected in the preoperatively obtained MRI. This results in less reliability of the stereotactic guidance as the surgery progresses. Intraoperatively obtained MRI allows updating of the images used for neuronavigation as well as updated visualization of the contrast enhancing tissue that remains.

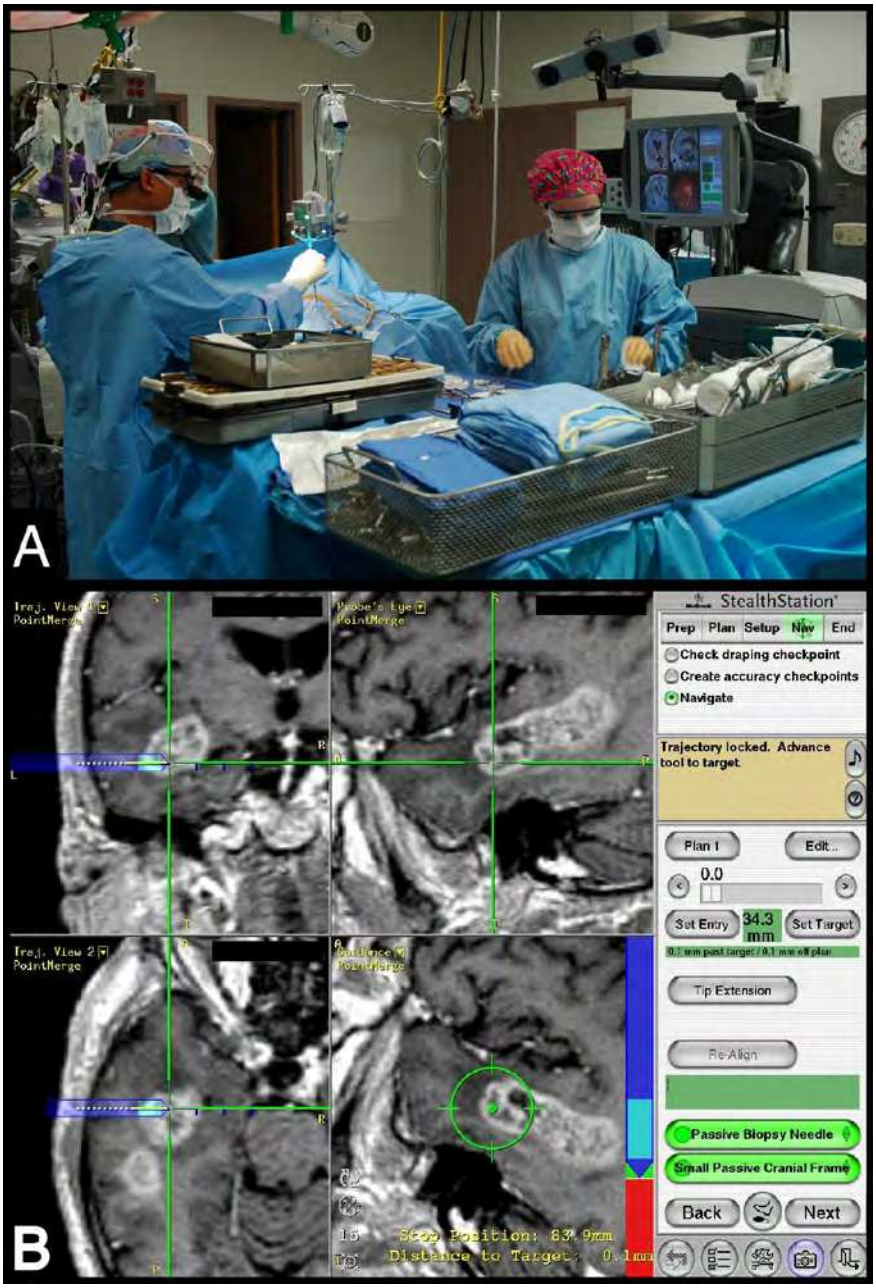

Fig. 1. Neuronavigation. Operating room setup with patient positioned and neuronavigational stereotactic equipment (A). Neuronavigational MRI for stereotactic guided biopsy showing a temporal lobe glioma in three planes.

Over the past decade several studies have looked at iMRI guided resection vs conventional neuronavigation in patients with glioma. In 2000, Wirtz and colleagues examined 68 cases of high grade glioma resected with iMRI[16]. Of the 68 cases, 27% of showed GTR on the first iMRI scan and 66% percent underwent continued resection. Median survival was 13.3 months for GTR vs 9.2 months for subtotal resection.

In 2005, Hisrschberg and colleagues examined the use of iMRI in 32 patients with glioblastoma compared to a matched control group of 32 patients using conventional neuronavigation. They found a mean survival time of 14.5 months in the iMRI group vs 12.1 months in the control group. They also saw a significant increase in length of surgical time with iMRI 5.1 hours vs 3.4 with conventional navigation. They also reported postoperative functional performance results, which were not significantly different between the two groups. Neurologic improvement was seen in 16% of patients, 55% showed no change, and 19% showed some worsening of symptoms.

In 2010, Senft and colleagues reported on 41 patients with glioblastoma, 10 of whom underwent resection with iMRI and 31 who received resection by conventional means[17]. GTR was seen in all 10 iMRI cases and 19 of the conventional group. Median survival was 88 weeks for the iMRI group and 68 weeks for the conventional group. Median survival in regards to the extent of resection was 74 weeks for the 29 patients who obtained GTR vs 46 weeks for the 12 patients who obtained subtotal resection.

A recent 2011 review article of 12 studies from the current literature examined the benefits of iMRI vs conventional stereotactic surgery for glioblastoma. The authors concluded that iMRI guided surgery is more effective that conventional neuronavigational surgery in increasing the extent of resection and prolonging survival in patients with glioblastoma[18]. However there are currently no randomized trials with validated endpoints that demonstrate the additional value of iMRI guided surgery. Intraoperative MRI is currently of limited availability, adds significant expense and prolongs surgical time. Therefore, the decision to use this modality should be made judiciously on a case by case basis.

These systems are not perfect and continued improvements are needed. Advances in real time surgical imaging are important to reduce the neuronavigational inaccuracies due to brain shift as well as to provide a clearer more accurate representation of the tumor margins throughout the case. Currently these systems still rely heavily on a rigid fixation of the patient's head and a registration landmark. Movement of the patient's head, pin slippage, and loss of registration can drastically limit the utility of these surgical tools and more robust technologies are needed. Despite these limitations, the use of improved neuroimaging and newer methods of neuronavigation can significantly improve the extent of resection and thereby increase the survival rates for patients with glioma.

4. Functional mapping

Functional mapping is another tool that is changing the surgical management of glioma therapy. These new techniques allow the protection of eloquent areas of the brain while permitting the extent of surgical resection to be maximized. With this technology, lesions that were previously thought to be inoperable due to location are now often resectable. One such procedure is awake craniotomy. Intraoperative direct electrostimulation under awake

anesthesia is the best technique to locate eloquent domains as well as to distinguish functional area from nonfunctional area. In 2008, Duffau and colleagues, reported the largest experience with cortical and subcortical mapping of gliomas affecting the language area[19]. They performed resection using awake craniotomy and direct electrical stimulation in 115 patients. 98% of patients improved or returned to their preoperative baseline following resection guided by direct electrostimulation. Awake craniotomy however presents several challenges in regards to anesthesia, patient comfort and anxiety as well as prolongation of operative time.

Functional magnetic resonance imaging (fMRI) is another improving technology that shows promise for increasing the extent of surgical resection while minimizing neurological deficits by providing functional mapping with the use of newly developed imaging modalities. The use of functional magnetic resonance imaging (fMRI) allows information regarding the location of specific brain functions such as speech, motor function, and sensory perception to be mapped to three-dimensional reconstructed MRI images. Blood oxygen level dependent (BOLD) fMRI is one of the most commonly used forms of fMRI. BOLD fMRI provides functional information based on cerebral hemodynamic responses by measuring changes in the ratio of blood oxyhemoglobin and deoxyhemoglobin during the presentation of a various stimuli to the patient. This data can then be used to map task-driven regional cortical activity in patients to noninvasively locate the brains essential eloquent areas and guide surgical planning. (Figure 2)

In 2010, Talacchi and colleges retrospectively examined the use of preoperative fMRI and neuronavigation compared to traditional intraoperative neurostimulation in 171 patients[20]. They found that preoperative fMRI provided equivalent rate of GTR when compared to the invasive neurostimulation 71% vs 73%c compared to 40% in resections not utilizing either modality. Similar findings have been demonstrated by additional authors[21,22]. Together these studies support fMRI as a viable alternative to awake craniotomy and functional neurostimulation with the benefit of reduced operative time as well as elimination of the challenges associated with awake craniotomy.

Diffusion tensor imaging (DTI) is an additional form of functional magnetic resonance imaging used to delineate white matter anatomy. DTI is based upon the principle that water preferentially diffuses along the long axis of white matter tracts and the degree and direction of water diffusion can be measured. Tractography uses algorithms to process this data and to reconstruct three-dimensional maps representing subcortical fiber tracts[23]. Tractography can be used in surgical planning to show the relationship between white matter tracts and tumor. It can reveal whether tracts are displaced, disrupted, or infiltrated by tumor. (Figure 3)

In 2007, Wu and colleges reported a large prospective randomized controlled trial of 238 patients with gliomas[24]. A randomized study group of 118 patients underwent resection with DTI tractography and neuronavigation while a control group of 120 patients underwent resection with neuronavigation alone. They found a significant increase in the ability to achieve GTR with the use of DTI tractography with 74.4 % of patients in the study group achieving GTR compared to 33.3% of patients in the control group. This translated into an increased mean survival time 21.2 months in the study group compared to 14.0 months mean survival in the control group. They also found better outcomes with DTI

tractography with motor strength deterioration occurring in 15.3% of patients in the study group compared to 32.8% in the control group. Improved outcome was also demonstrated in 6 month Karnofsky Performace Scale scores with a mean score of 77 for study group patients and 53 for the control group. When combined, fMRI, neuronavigation, and DTI allows precise surgical resection of the maximal tumor volume while sparing intact fiber tracts as well as eloquent areas of the brain. This results increased patient survival and improved functional outcomes.

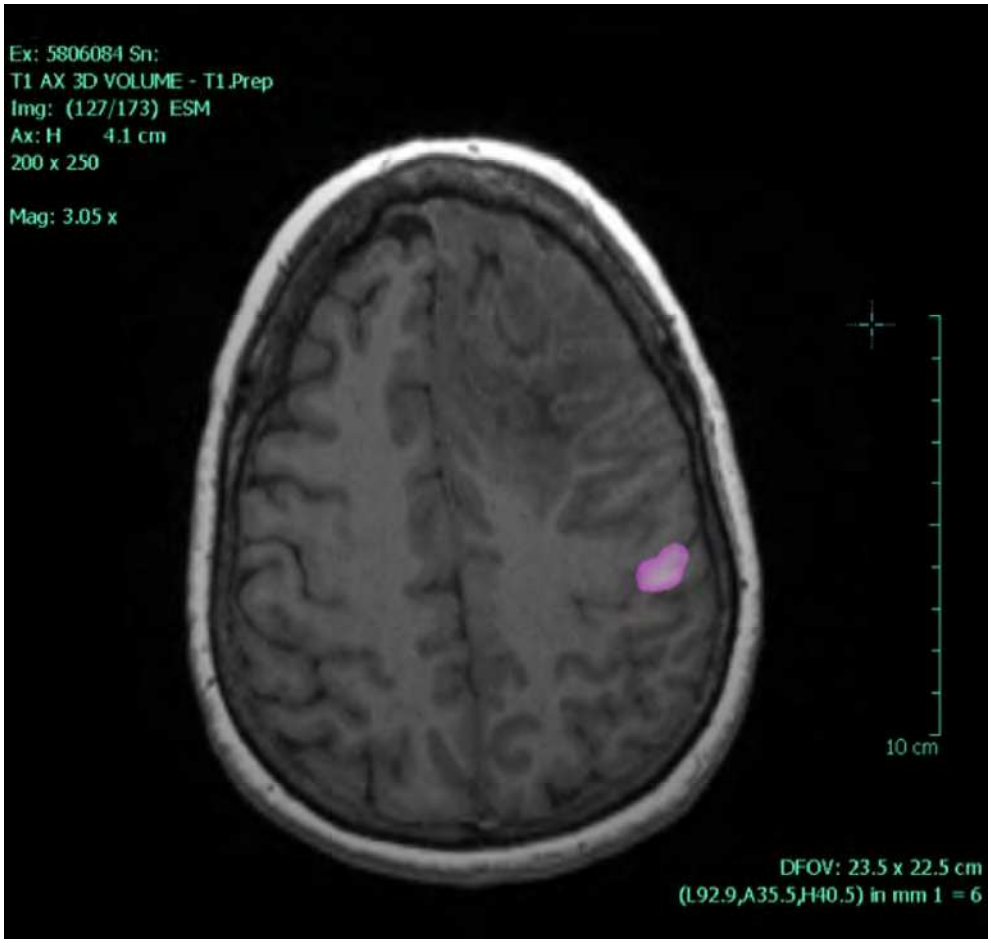

Fig. 2. Functional MRI. MRI generated from BOLD data in a patient with large frontal lobe glioma showing areas of activation during a sentence completion task.

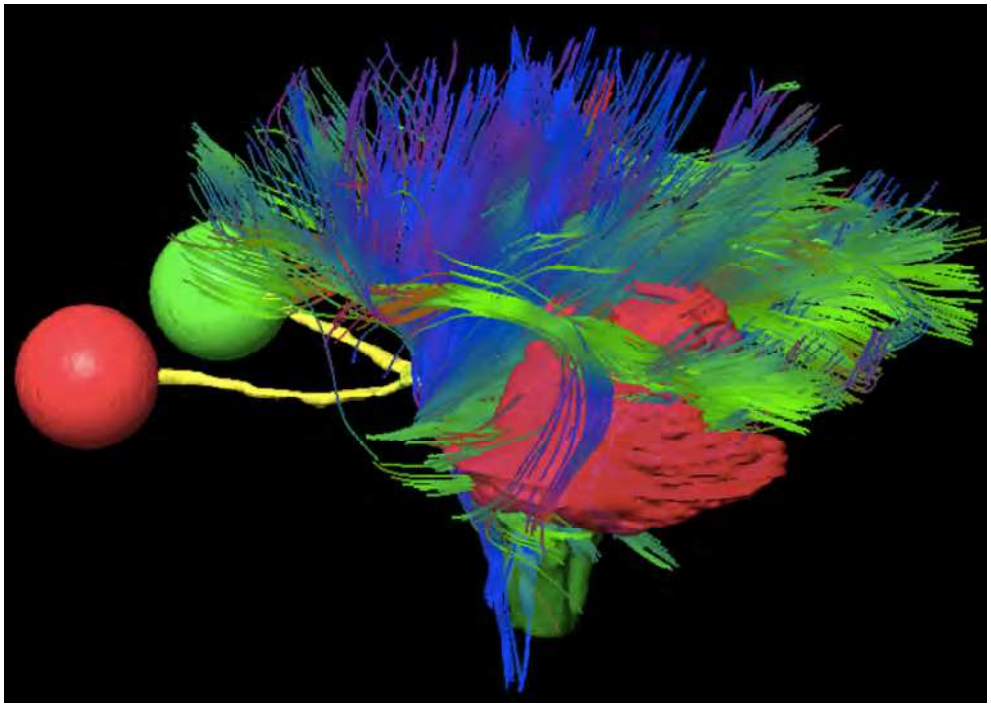

Fig. 3. Tractography. 3-Dimensional reconstruction showing fiber tracts generated from DTI MRI sequence in a patient with large glioblastoma multiforme.

5. Florescence guided resection

Another problem arises in surgery when dealing with the infiltrating malignant cells present at the tumor margins. These cells often lie outside the area of enhancement on neuroimaging and intraoperatively appear grossly and microscopically indistinguishable from normal brain tissue. These areas of infiltrating cells contribute to reoccurrence and negatively effect long-term tumor control if not resected.

Fluorescence image guided surgical resection (FIGS) is another innovative surgical technique which uses fluorescence intraoperatively to enhance the visualization of abnormal tumor cells intraoperatively and allow for maximal extent of resection. 5-Aminolevulinic acid (ALA) is injected systemically prior to surgery. High grade gliomas and other metabolically active tumors take up ALA at a rapid rate. After gross resection of the visible tumor, a specially filtered blue light can illuminate the areas of high uptake within the cavity allowing selective resection of the residual areas[25].

In 2000, Stummer and colleagues reported an initial study of the efficacy of FIGS which demonstrated FIGS to be quite specific (only 0.4 % of fluorescent biopsy sites did not contain tumor cells) and quite sensitive (81.6% of fluorescent biopsy sites contained tumor cells)[26]. In 2006 this same author reported a multicenter phase III trial comparing FIGS to placebo and found 64% complete surgical excision with fluorescence guided resection compared to 38%

complete excision in the placebo group[27]. In 2007 Stepp and colleagues reported similar findings with GTR in 65% of patients undergoing FIGS compared to 36% in placebo group[28]. They also demonstrated improved 6 month progression free survival in 41% of patients in the study group vs 21% in the control group.

Despite the positive initial results with FIGS, there are several limitations of this modality. The blue light used to illuminate 5-ALA has a depth of penetration of only a few millimeters and is easily obscured by blood products. Also 5-ALA has minimal uptake in tumors that have minimal contrast enhancement or that do not enhance at all, such as low grade glioma[29,30]. Advances in florescence guidance, particularly in its use for resection of these low grade, non-enhancing lesions are needed. As this technology continues to progress it will allow for greater extent of resection and increased survival in patients with glioma.

6. Photodynamic treatment

Photodynamic treatment (PDT) is another novel surgical method for the treatment of malignant glioblastoma. It utilizes the selective uptake of a photosensitizer by the individual tumor cells followed by irradiation of the tumor with light of a specific wavelength during surgery, which activates the photosensitizer to destroy the tumor cells selectively via oxidative reactions. Many different photosensitisers have been studied with the most promising being haematoporphyrin derivative (HPD). One of the greatest benefits with PDT is that it is a localized treatment, which lacks the systemic side effects associated with chemotherapy and radiation. The major side effect associated with PTD is cerebral edema in the irradiated area which can usually be managed with steroids.

In 2005, Stylli and colleagues reported one of the largest series of PDT for high grade glioma in 136 patients[31]. They utilized HPD administered IV preoperatively followed by irradiation with laser light during surgery. Median survival time following treatment for the 78 patients with glioblastoma was 14.3 months and median survival for the patients with anaplastic astrocytoma was 76.5 months. The same authors have also reported a review of the literature examining 10 studies, which show similar results although with fewer numbers of patients[32]. They conclude that PDT shows potential as a novel adjuvant therapy for glioma treatment along with chemotherapy and radiation therapy. However, further controlled clinical trials are needed to standardize HPD dosage as well as type and dose of light irradiation.

7. Radiation therapy

Following surgical resection, radiation therapy (RT) is considered the next step in the treatment of glioma. The principal goal of RT is to destroy residual tumor cells that were not removed with surgery, therefore preventing or postponing tumor reoccurrence. RT is most affective on smaller lesions and is therefore an adjuvant therapy in addition to surgical resection. Resection of maximal tumor bulk results in smaller residual volumes which are more responsive to RT and thereby increase the efficacy of RT. Historically, conventional radiation therapy using external beam radiation has been the main modality of radiotherapy used for glioma. Due to the risk of radiation induced injury to normal brain tissue, conventional radiation therapy is fractionated and the total dose is delivered over several treatments. Standard therapy usually consists of a total radiation dose in the range of 50–60 Gy administered over 20-30 fractions each with a dose of 1.8–2.0 Gy [33].

Novel methods of administering radiation therapy are also being developed. Following optimal surgical resection, image guided stereotactic radiosurgery (SRS) is now being evaluated for treatment these lesions. This new modality utilizes a single high doses of radiation specifically targeted to a well-defined lesions using detailed neuroimaging. This allows delivery of focused radiation to the tumor with a much lower dose to adjacent non-targeted tissue which results in reduced side effects compared with traditional methods.

For low grade gliomas, adjuvant RT following resection has failed to show a survival benefit. In cases of disease progression or inoperable lesions with neurologic symptoms, delayed RT appears to provide the same survival advantage as postoperative RT[34]. For newly diagnosed high grade gliomas studies have demonstrated that SRS does not provide a significant survival advantage over conventional radiotherapy[35,36]. The use of SRS has also been explored as a treatment for recurrent high grade lesions. A recent article by Romanelli and colleagues reviewed 17 retrospective studies examining the role of SRS in the treatment of recurrent high grade glioma. This review demonstrated that SRS is associated with prolonged survival in patients with recurrent GBM with median survival times ranging from 7.5 to 30 months[37]. SRS has been shown to have no significant advantage as a first line radiation therapy for glioma and the results for recurrent glioma are inconclusive, therefore further study on the role of SRS in glioma treatment is needed.

In addition to externally administered sources of radiation therapy, interstitial brachytherapy is another form of radiation therapy used to treat glioma, which refers to surgical placement of the radioactive source a short distance from or within the tumor being treated. Brachytherapy was developed due to the observation that 80% of malignant gliomas reoccur within 2cm of the initial tumor site following resection. By placing the radioactive source directly in the tumor or tumor bed, continuous high dose radiation increases damage to nearby proliferating tumor cells located at the margin with a rapid fall off in the dose delivered to normal cells which are located farther from the source.

There are multiple surgical methods for delivering the radiation source to the tumor. During surgery, temporary implants can be placed which provide a source of radiation for a specified duration and are then removed at a later time, however this usually requires multiple procedures. To avoid multiple procedures, small radioactive seed have been developed which are surgically implanted and are left permanently to gradually decay over a period of weeks to months to a state of zero radiation emission. Another novel approach uses a surgically implanted catheter system with an expandable balloon reservoir implanted at the site of resection and a catheter connecting to a subcutaneous access port. A radioactive solution can then be injected percutaneously into the implanted reservoir and retrieved at a later time. The most commonly radiation sources used for glioma brachytherapy are iodine-125 and iridium-192.

Brachytherapy is usually reserved for cases of high grade gliomas which have shown reoccurrence since several studies have shown no significant survival benefit for brachytherapy in newly diagnosed glioma[38,39]. One large randomized study by Selker and colleagues with 270 patients examined the use of interstitial brachytherapy in newly diagnosed high grade glioma[40]. Patients were randomized to two groups, one receiving resection, external beam radiation, and chemotherapy with the other group receiving resection, external beam radiation, chemotherapy, and ^{125}I permanent interstitial

brachytherapy. They found no statistical difference in the median survival time between the two groups for newly diagnosed high grade glioma.

The results for brachytherapy in the case of recurrent high grade glioma appear to show improved survival[41–43]. One large study with 95 patients by Gabayan and colleagues examined the use of the GliaSite Radiation Therapy System in the treatment of recurrent high grade glioma. This system utilizes ^{125}I administered via a surgically implanted balloon catheter system. All patient were initially treated with resection followed by external beam radiation. Following reoccurrence, patients underwent maximal surgical debulking followed by implantation of an expandable balloon catheter system. Radioactive solution was then administered between 2-6 weeks following the debulking procedure. Patient undergoing this treatment showed median survival of 36.3 weeks from the time of the debulking surgery with a 1 year survival of 31.1%. Although no control group was used in this study, survival times were compared to matched patients from another published study matched for age, KPS, and surgical management. These control patients showed a median survival of 23 weeks following resection for reoccurrence. The results from the brachytherapy group compare favorably with the control group. Further studies including randomized trials are still needed but brachytherapy appears to show promise as adjuvant therapy in recurrent glioma.

8. Chemotherapy

In addition to surgical resection and radiation therapy the other mainstay of treatment for malignant glioma is chemotherapeutics. Chemotherapy is another adjuvant therapy to be utilized along with surgical resection. As with radiation therapy, chemotherapy is more effective in treating smaller tumor volumes and therefore maximizing the extent of surgical resection is important in order to provide a more favorable response to chemotherapy[44]. Two main classes of drugs are currently used, alkylating agents (carmusitine, temozolomide) and antiangiogenic agents (bevacizumab).

9. Blood brain barrier

The blood brain barrier (BBB) presents difficulty in the chemotherapuetic treatment of gliomas as many agents that are effective for the treatment of systemic disease are unable to cross the BBB. There have been several developments designed to open the BBB and provide direct treatment of the central nervous system. Initial therapies to open the BBB made use of small lipophilic molecule drugs administered systemically for increased permeation across the BBB. This approach was limited by drug binding to plasma protein as well as extravasation of the drug back across the BBB into the systemic circulation. Other early treatments used osmotic modification of the BBB with agents such as mannitol given intra-arterially to disrupt the BBB followed by the chemotherapeutic agent of choice. The effectiveness of these early methods were limited due to the transient elevation of drug concentration within the brain tissues and short drug half–life which did not allow for accumulation of the drug at a therapeutic concentration. Over the past decade, several innovative surgical methods of opening the BBB have been developed to provide longer acting and direct treatment to the tumor cells.

10. Implantable polymers

One advancement has come in the area of surgically implantable polymers, which are infused with chemotherapeutic agents. These polymers are then placed into the surgical cavity following resection to provide direct application of the chemotherapeutic agent to the tumor bed over a prolonged period of time as the polymer degrades and releases the agent.

The most widely studied therapy of this nature utilizes a polyanhydride wafer embedded with carmustine (gliadel wafers). Gliadel is currently the only interstitial chemotherapy treatment approved for use with malignant glioma. Wafers can be implanted at the time of initial surgery or reserved for episodes of reoccurrence. Several trials have demonstrated increased survival following the use of implantable wafers. For initial tumor treatment, increased survival has been shown of 13.9 months compared to 11.6 months in non-treatment group. Wafer usage for treatment of tumor reoccurrence provided increased survival of 31 weeks compared to 23 weeks in non-treated patients[45–47].

Overall, these studies show a 35% risk reduction of death with the use of gliadel, with a median survival of 14 months, which is a 2.5 month improvement over placebo. 1 year survival is approximately 10% better with use of gliadel[48]. Care must be taken with the use of this therapy as side effects of necrosis, cerebral edema, and seizure are common but can be controlled with steroid and antiepliptic therapy.

Use of gliadel can also exclude from further clinical trials and newer treatments. It can cause confounding effects on another trial because all of these are so new. Improvement of surgical resection can eliminate these problems.

11. Nanoparticles

Another novel approach still in the early phases of development is the use of surgically implantable nanoparticles to deliver chemotherapeutic agents. Small spherical particles 7 to 10 nanometers in size comprised of polymers or liposomes are non-covalently attached to slow sustained release formulations of chemotherapeutic drugs for delivery. These nanoparticles are small enough to cross the blood brain tumor barrier (BBTB) and transmit drug directly into individual tumor cells[49].

Nanoparticles can be administered intravascularly or directly into the brain via a surgically implanted catheter. Delivery of nanoparticles via surgically implanted catheter has the benefit of greater volume of distribution directly to the brain tissue compared with diffusion alone[50]. Development of these nanoparticle systems for treatment of malignant brain tumors is currently in the animal model phase and no human studies are currently available. Rat models of glioblastoma have shown increased survival using doxorubicin bonded to cyanoacrylate nanoparticles for delivery to tumor cells. The drug transport across the BBB by nanoparticles appears to be due to a receptor-mediated interaction with the brain capillary endothelial cells, which is facilitated by certain plasma apolipoproteins adsorbed by nanoparticles in the blood. Nanoparticle uptake appears selective to tumor cells in these models as the animals did not manifest signs of neurotoicity[51].

In addition to drug delivery, nanoparticles are being investigated for use in neuroimaging. Current imaging techniques have a maximum resolution of 1 mm. Nanoparticles could

improve the resolution by a factor of ten or more, allowing detection of smaller tumors and more precise surgical resection. Several nanoparticle-based contrast materials have been used to enhance MRI imaging. One iron oxide nanoparticle currently under study has shown an innocuous toxicity profile as well as sustained retention in mouse tumors[52]. These fluorescent nanoparticles improved the contrast between the tumor tissue and the normal tissue in both MRI and optical imaging, which can be used during surgery to see the tumor boundary more precisely.

Another promising role of nanoparticle in the treatment of glioma involves hyperthermia treatment. The heating of cancerous tissues between 41 and 45°C, has been shown to improve the efficacy of cancer therapy when used in conjunction with chemotherapy and radiation[52]. Magnetic nanocomposites based on iron oxide can be used as implantable biomaterials for thermal cancer therapy applications at the time of surgery. These implanted particles can then be remotely heated by exposure to an external alternating magnetic field.

In 2011, Maier-Hauff and colleagues reported a trial of magnetic nanoparticle thermotherapy in conjunction with radiation treatments in 59 patients with recurrent glioblastoma[53]. Magnetic fluid was instilled within the tumor site using a neuronavigational procedure comparable to a brain needle biopsy and an external magnetic field was then applied for multiple treatments. Patients undergoing this procedure showed a mean survival time of 13.4 months after the first re-occurrence. Thermotherapy using magnetic nanoparticles in conjunction with a reduced radiation dose is safe and effective and leads to longer overall survival compared with conventional therapies in the treatment of recurrent GBM.

12. Immunotherapies

Using the body's own immune system to fight glioma, immunotherapy, is a new field which has seen significant advancements over the past decade. There are two categories of immunotherapy for glioma that are currently undergoing clinical research. Passive immunotherapy involves the activation of cytotoxic effector cells ex vivo and thee transfer of these activated cells back into the patient's body. Active immunotherapy, on the other hand, uses an exogenous trigger which causes activation of endogenous effector cells within the patients own body to target tumor cells. Active immunotherapy is generally employed in the tumor vaccine model. Surgery plays a large role in these therapies, as sizeable volumes of tumor tissue must be surgically obtained in order to construct the immunotherapeutic agents. Also several of these therapies utilize direct delivery of these agents into the brain during surgery.

Current clinical trials utilizing passive immunotherapy focus on the activation of effector cytotoxic T lymphocytes, natural killer cells, or lymphokine activated killer cells sensitized to glioma-associated antigens. Once such trial for glioblastoma treatment uses donor cytotoxic T lymphoyctes which are sensitized ex vivo to recognize patient human leukocyte antigen (HLA) groups expressed on the surface of glioma cells but not on normal neurons or glia. After surgical resection, the sensitized CTL cells are placed in the resection cavity as well as surgical placement of an intraparanchemal catheter and reservoir system to allow future delivery of CTL cells. An initial pilot study with this model showed significant survival benefit in 3 of 6 patients with 2 patients surviving >15 years since beginning immunotherapy[54].

Treatments using active immunotherapy via cell-based and peptide vaccines are also under study. Cells from glioma tumors are thought to be poor antigen-presenting cells because they often secrete immunosuppressive cytokines as well as growth factors such as transforming growth factor and vascular endothelial growth factor which can have a negative effect on T cell and natural killer cell activity. Tumor vaccines are designed to augment tumor-specific cellular immunity and enhance low-level immunity by stimulating the production of higher-avidity T cells specific to a tumor[55].

Chang and colleagues published results from one vaccine based phase II clinical trial in 2011. 16 patients with glioblastoma (8 newly diagnosed, 8 recurrent) underwent craniotomy for maximal cytoreduction followed by standard external beam radiation therapy in the newly diagnosed patients. Tumor cells obtained from the surgical resection were cultured in the laboratory and combined with autologous dendritic cells to produce vaccine. The vaccine was administered to patients via subcutaneous injection over lymph nodes for a total of 10 treatments over a 6 month period. Median survival and 5 year survival was 381 days and 12.5% for the newly diagnosed group, 966 days and 25% for the recurrent group compared to 380 days mean survival and 0% five years survival for a 16 patient age and sex matched historical control group.

Although most published results are from preliminary studies with small numbers of patients, immunotherapy for the treatment of glioma is a promising area currently undergoing multiple phase II and phase III trials for FDA approval[54]. Once the basic efficacy of these initial studies have been verified as a plausible modality for the treatment of glioma, randomized and controlled clinical trials can be undertaken to further explore the full potential of this therapy.

13. Gene therapy

Gene therapy is another novel modality used in the treatment of glioma, which focuses on the delivery of apoptotic genes at the time of surgical intervention and implantation in the surgical cavity. One of the most effective methods of in vivo gene delivery is the use of viral vectors as gene carriers. Retroviruses, adenovirus, and herpes simplex virus-1 (HSV-1) are all currently undergoing trials as vectors for viral brain tumor therapy Replication competent retroviruses have been shown to have infection rates of 97% with specificity for tumor cells without significant effects on non-tumor cells[56]. Adenovirus and HSV-1 are used in both replication competent and replication defective forms and have shown high transgenic capacity and persistent gene expression[57].

In 2003, Germano and colleagues reported a series of 11 patients with high grade glioma treated with gene therapy using adenovirus as a viral vector[57]. Adenovirus was used to transfer the herpes simplex-thymidine kinase gene into malignant glioma cells. This gene then phosphorylates ganciclovir, a non-cytotoxic nucleotide analog, into a compound that halts the transcription of DNA in dividing cells. Since normal brain cells are not rapidly dividing they are not affected. At the time of surgery, following gross total resection, the viral solution was injected directly into the tumor bed. This was followed by administration of ganciclovir systemically over 7 days. Of the 11 patients 10 had a survival of > 52 weeks following treatment. This survival time was associated with maintaining quality of life. 8 patients maintained a KPS of greater than 70 after 3 months and 5 patients 6 months after treatment.

Oncolytic viruses are also currently being used for clinical trials. These virus replicate selectively within tumor cells and can lead to increased intratumoral viral titers and cell death[58]. In 2004, Harrow and colleges used a modified herpes simplex virus with an affinity for glioblastoma cells which replicates only in rapidly diving cells causing cell lysis while sparing normal terminally differentiated cells. Twelve patients, 6 with newly diagnosed glioblastoma and 6 with recurrent glioblastoma, underwent craniotomy and surgical resection. Following resection during the same surgical procedure they were injected with the modified herpes virus at 8-10 sights adjacent to the tumor bed. Four patients, 2 newly diagnosed and 2 with recurrent disease showed survival of greater than 15 months following treatment.

Viral vectors, although promising, do have several limitations. Viral vectors suffer from low levels of gene incorporation due to limited diffusion into the brain parenchyma as well as low transfection rates of some cell types. Formation of antigenicity to vectors and introduced gene products causes additional difficulties. Also the use of retroviruses that incorporate genes into the host chromosome can result in insertional mutagenesis and propensity to form new tumors. The use of genetically modified cells to deliver gene therapy to the CNS may avoid some of these limitations. The use of stem cells is one area of research being used to avoid these limitations seen with traditional gene therapy.

Neural stem cells (NSC) are self-renewing multipotent cells found in the fetal brain within the ventricular zone, midbrain and spinal cord. These cells have the ability to repopulate a degenerated CNS region and can migrate toward pathologically altered tissues, including stroke, trauma and tumors. Genetic changes in NSCs may result in tumorigenesis by activation of oncogenes and/or inactivation of tumor suppressor genes.

Within brain tumors, a population of cells known brain tumor stem cells (BTSC) have been found. They are resistant to current treatments and capable of maintaining and propagating these tumors[59]. BTSCs are thought to arise from aberrant NSCs or from mature cells that have undergone mutation and dedifferentiation. BTSCs are similar to normal stem cells with regards to self-renewal, capacity, multi-potentiality, tumorigenicity as well as migratory capability. Transformation of these neural stem cells and their progenitor cells may therefore lead to the formation of BTSCs and eventually malignancy[60]. Gene therapies focusing on preventing the malignant transformation of

NSCs into BTSCs as well as the use of normal stem cells as a method of targeted delivery of therapeutic agents to glioma cells are currently under investigation.

Genetic modification of NSCs to secrete anti-tumor agents allows targeted delivery as well as provides a high level of active compounds at the local site of neoplasm. These types of therapies are still in the early stages and have not been evaluated in human glioma patients, however there are studies which have shown good results using animal models. One model using neural stem cells modified to produce high quantities of interleukin-4 in vivo was examined in Spraque-Dawley rats[61]. They implanted the modified NSCs into the brain tissue of rats affected with malignant gliobastoma and found a long term survival of 50% compared to control animals.

Another rat study used immortalized neural progenitor stem cells to express a eukaryotic catalytic enzyme that converts the nontoxic compound 5-flourocytosine into the highly toxic

drug 5-flourouracil[62]. These stem cells were then implanted in rats with induced glioblastoma and the animals were subsequently treated with the nontoxic compound. After 10 days, the animals treated with the modified NSCs showed significant 50% decrease in tumoral mass compared to a control group. After histopathological examination of the treated tissue, they also found high levels of the toxic 5-flourouracil drug in adjacent tissue demonstrating in vivo conversion of the nontoxic compound to the toxic drug with therapeutic benefit.

Neural stem cells are also being used as vehicles for the tracking and suppression of glioblastoma. These methods exploit the tendency of NSCs to preferentially migrate towards brain tumors. This allows NSCs to be labeled and used as diagnostic imaging tools to identify extent of tumor invasion. One such animal model used NSCs modified to express the firefly luciferase gene[63]. These cells were then implanted into the contralateral brain parenchyma as well as injected into the ventricles of mice with intracranial gliomas. Over a period of 3 weeks, serial bioluminescence imaging was performed, which showed migration of the implanted cell across the corpus callosum with a maximal density at the site of the tumors. A subsequent study using the same model but with the addition of an apoptosis-promoting gene to the NSCs was performed to evaluate the therapeutic possibilities of this model. NSCs were modified not only to express the luciferase gene but also the tumor necrosis factor related apoptosis inducing ligand S-TRAIL. The transformed NSCs were then stereotactically implanted into the left frontal lobe of mice and glioma cells were stereotactically injected into the right frontal lobe of the same animals. Serial imaging was again performed which initially showed increased tumor volumes at the site of glioma injection as well as migration of the NSCs towards the tumor areas. After 16 days however there was a considerable decrease in tumor growth and a significant reduction in tumor cells on quantitative analysis compared to control animals. They also found expression of the S-TRAIL gene product at the tumor site on histopathological examination. These studies demonstrate the promising role that stem cells can play in the treatment of glioma.

14. Conclusion

Surgical resection remains the single most important primary treatment in the management of patients with glioma and extent of surgical resection directly correlates with increased patient survival. In this chapter we reviewed several innovative technologies and surgical methods for increasing the extent of resection as well as several adjuvant therapies and the important role that surgery plays in maximizing the potential benefit of these therapies in the treatment of glioma. As our ability to increase the extent of resection improves and new innovative technologies are perfected, we will continue to see improvements in long term survival in patients affected with glioma.

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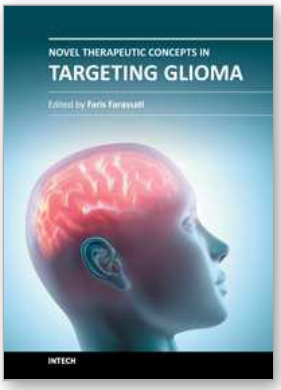

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Novel Therapeutic Concepts for Targeting Glioma offers a comprehensive collection of current information and the upcoming possibilities for designing new therapies for Glioma by an array of experts ranging from Cell Biologists to Oncologists and Neurosurgeons. A variety of topics cover therapeutic strategies based on Cell Signaling, Gene Therapy, Drug Therapy and Surgical methods providing the reader with a unique opportunity to expand and advance his knowledge of the field.

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