Neurosurgical Clinical Trials for Glioblastoma

Subjects: Oncology

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Standard neurosurgery for cerebral glioma requires maximal safe tumor resection. For low-grade tumors (WHO Grade II–III), maximal safe resection of the tumor confers an improved outcome without compromising functional outcomes. In the case of glioblastoma, the location of the bulk of the tumor relative to eloquent brain areas dictates the safest and most effective surgical approach.

Keywords: glioblastoma ; brain mapping ; immunotherapy ; radiotherapy ; tissue-treating fields ; blood-brain barrier opening ; temozolomide

1. Efforts to Improve the Completeness of Tumor Resection

1.1. Cortical and Subcortical Electrical Stimulation Mapping

A consensus agreement was reached among authors in the neurosurgical literature that more extensive tumor resection improves glioblastoma life expectancy. Two separate studies from the UCSF and MD Anderson Cancer Center reported that MRI-visible glioblastoma resection needed to reach a threshold of at least 78%, preferably greater (98 to 100%), to provide a relevant survival benefit (**Table 1**) [1][2]. (There is abundant evidence supporting maximal safe resection in non-eloquent brain regions. Neurosurgeons have recently advocated for the supramaximal resection of a glioma when feasible to improve overall survival further. Several groups advocate resecting a substantial margin beyond the contrast-enhancing rim for non-eloquent-location high-grade gliomas (~1–2 cm). In a series of reports on this subject, supramaximal resection resulted in patient survival of 20.9–30.7 months [3][4][5]. However, supramaximal resection is impossible in all patients because a bulk tumor invades into the adjacent eloquent cortical and subcortical structures. The survival advantage of the complete resection of MRI-visible tumors in glioblastoma was reported to be 2.9 months in one study and 6.4 months in another [1][6]. The survival advantage of complete tumor resection is much longer in lower-grade gliomas than in glioblastoma (**Table 1**).

Table 1. Prognostic impact of extent of resection.

Brain Tumor Type and WHO Grade	Invasive	Complete Resection Possible	Life Expectancy (Months) Biopsy	Life Expectancy (Months) MR Incomplete Resection	Life Expectancy (Months) MR Complete Resection	Survival Advantage (Months) with MR Complete Resection Compared to Incomplete Resection
I Neuronal DNET Ganglioglioma Pilocytic astrocytoma	No	Yes; if outside eloquent structures	Prolonged	Prolonged	Prolonged	Uncertain: residual tumors require additional surgery
II Low-grade astrocytoma and oligodendroglioma	Yes	No		61	90.5	29.5
III Anaplastic astrocytoma and oligodendroglioma	Yes	No		64.9	75.2	10.3
IV Glioblastoma multiforme	Yes	No	9.4 †	11.3	14.2 15.8 †	2.9 6.4 [6]

1.2. Assessment of the Extent of Tumor Resection in the Intraoperative MRI Suite

Another surgical adjunct to enhance the extent of tumor resection is intraoperative MRI. A randomized trial of patients with a high-grade glioma confirmed that patients with a complete tumor resection had a longer PFS than patients with a residual tumor (median 226 [162–290] vs. 98 days [92–104], $p = 0.003$). This finding highlights the prognostic significance of complete tumor resection. Although a significantly higher proportion of patients in the intraoperative MRI group had a gross total resection (96% vs. 68%, $p = 0.023$), progression-free survival showed only a trend toward significance ($p = 0.083$). The patients most likely to benefit from intraoperative MRI were the 28% of patients in the iMRI group who would not have received a gross total resection in the microsurgery group. The other 68% percent of patients in either group had a gross total resection or would not be expected to have different outcomes in terms of progression-free survival [7]. Cortical mapping can also be performed in the intraoperative MRI suite for tumors near eloquent regions. After initial tumor resection, MRI scans are performed, and if residual is detected in a surgically accessible area, more tumor is subsequently removed. Therefore, at most, two intraoperative MRI scanning sessions, one after the initial resection and one after the subsequent resection of the residual MRI-visible tumor, are required to confirm tumor resection from non-eloquent regions [8]. Over the last decade, iMRI has become a mainstay of surgical neuro-oncology and has directly impacted onco-functional outcomes for glioma patients [9].

1.3. Use of Fluorescent Labeling and Resection of Fluorescent Labeled Tumor Tissue

Another surgical adjunct to increase the volume of malignant glioma resection is oral 5-aminolevulinic acid (5-ALA). 5-ALA penetrates the blood–brain barrier of the MRI-enhancing tumor volume and highlights the extent of the tumor intraoperatively. 5-ALA is a natural precursor molecule in heme synthesis that is selectively converted to fluorescent porphyrins in malignant or highly metabolic tissue. In a randomized controlled multicenter phase III trial by Stummer and colleagues, the rate of gross total resection was 65% in the 5-ALA group compared to 36% in the white-light microscopy alone group [10]. The gross total resection rate of 65% was slightly less than in the microsurgery control group in the intraoperative MRI study of Senft et al. in 2011 [7]. After surgery, temporary neurologic deficits occurred more frequently after 5-ALA use, consistent with more extensive resections, but, longer term, the 5-ALA group had improved progression-free survival at six months (PFS6), better function, and less need for repeat surgical resection [11].

1.4. Improving Extent of Resection of Gliomas Using Intraoperative Raman Histology

Over the last five years, Raman Histology has been proposed as an important surgical adjunct to improve the extent of the resection of gliomas by identifying tumor infiltration in situ. Raman Histology is capable of rapidly generating histological images of specimens in a label-free manner by detecting molecular vibrations of scattered light. Using this stimulated Raman scattering approach, multicolor images are generated that are comparable to conventional Hematoxylin and Eosin staining [12][13]. As such, serial tumor sampling around the tumor margin is feasible and can permit rapid intraoperative tumor diagnoses [14][15][16]. Similar techniques are also being developed using a hand-held device capable of delineating glioma Raman spectra intraoperatively [17][18]. Overall, these techniques may facilitate the detection of glioma infiltration and, ultimately, improve outcomes for patients by improving the extent of resection.

2. Efforts to Prevent Neurological Deficits Resulting from Tumor Resection

Protecting quality of life and onco-functional status is critical for patients with malignant gliomas [19][20][21]. The decision to opt for aggressive surgical resection must be counterbalanced by the risks of diminishing the patient's neuropsychological and functional status. McGirt and colleagues highlighted the effect of a surgically-induced neurologic deficit on survival after surgical treatment of glioblastoma. McGirt et al. retrospectively reviewed 306 consecutive patients, 18 to 70 years of age, with newly diagnosed glioblastoma and good performance documented by Karnofsky performance scores (80–100). Although the 89% of patients who were deficit free after surgery had a 12.8-month median survival, the 5% of patients with a new language deficit had a 9.6-month median survival, and the 6% of patients with a new motor deficit had a 9.0-month median survival. After glioblastoma surgery, a permanent neurological deficit shortened survival by 3 to 4 months and reduced quality of life [22].

Mapping techniques identify eloquent cortex and subcortical tracts involved in expressive and receptive language, motor function, and tactile sensation that are avoided to prevent a neurological deficit. Resections with less than a 1 cm margin from these eloquent cortical areas risk temporary or permanent neurological deficits, with temporary deficits from procedural edema and permanent deficits due to microvascular disruption and resection margin infarcts.

3. Less Invasive Glioblastoma Surgical Treatments

Laser Interstitial Thermal Therapy

For some deep-seated inoperable glioblastomas, tailored surgical approaches to minimize adjacent white matter disruption while maximizing cytoreduction should be considered. Over the past several years, laser interstitial thermal therapy (LITT) has been popularized for gliomas. Using stereotactic navigation through a 3 mm incision, a laser catheter can be inserted into a target lesion, which can then be coagulated with real-time MR thermography. Although restricted to smaller lesions (<2.4 cm), LITT is particularly suited for treating deep, surgically inaccessible tumors [23][24]. Initial experiences using LITT for gliomas suggest that adequate cytoreduction (>70%) can improve overall survival. Overall survival in newly diagnosed glioblastomas was reported as between 14–24 months in some series. Survival increased more in patients with smaller lesions and there was a greater extent of ablation [25][26][27]. For patients with deep lesions who would otherwise receive a biopsy without tumor resection, LITT can provide cytoreduction that facilitates subsequent chemoradiation. Clinical studies also suggest that LITT may incite or potentiate a local immune response and transiently open the blood–brain barrier to systemic immune cells [25][28][29]. Since the LITT incision is tiny and blood flaps are unnecessary, chemoradiation can be started within 7–10 days of LITT, allowing patients receiving LITT to be treated sooner after the cytoreduction procedure than patients undergoing conventional resections through much larger surgical openings.

4. Non-Surgical Glioblastoma Treatments

4.1. Tumor-Treating Electric Fields

Tumor-treating electric fields disrupt cancer cell division. A randomized trial in GBM patients previously treated with chemoradiotherapy showed that patients treated with the tumor-treating fields (TTFs) and temozolomide (TMZ) had a median progression-free survival of 7.1 months compared to 4.0 months with TMZ alone (p = 0.001). Median survival was 20.5 months in the TMZ plus tumor-treating fields and 15.6 months in the TMZ alone group (p = 0.004). There was a 43% incidence of mild to moderate skin reactions and a 2% incidence of severe skin reactions (medical device site reactions beneath the transducer arrays) in patients treated with tumor-treating fields plus temozolomide [30].

4.2. Immunotherapy and Virotherapy

Immunotherapy using immune checkpoint inhibitors is FDA-approved for treating metastatic melanoma and other cancers. Thus far, clinical trials of immune checkpoint inhibitors in patients with GBM have been unsuccessful. However, there is enthusiasm about developing immunotherapy for GBM because of the limited effectiveness of the current standard therapy of surgical resection of the primary tumor mass and chemoradiation of the residual tumor. Immunotherapy depends on the established capacity of activated lymphocytes to freely enter and exit the central nervous system (CNS) through the blood–brain barrier. Immune checkpoint inhibitors suppress the immune activation of tumors. Checkpoint inhibitors include cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death 1 (PD-1). Ipilimumab, a monoclonal antibody against CTLA-4, received FDA approval in 2011 to treat metastatic melanoma. Nivolumab and pembrolizumab are monoclonal antibodies inhibiting the PD1 receptor that received FDA approval in 2014, and also for the treatment of malignant melanoma. The Phase III trial of nivolumab versus bevacizumab (anti-vascular endothelial growth factor A (anti-VEGF-A) humanized monoclonal antibody) in 369 randomized patients with glioblastoma at first recurrence following standard radiation and temozolomide therapy demonstrated a higher objective response with bevacizumab (23.1%) than with nivolumab (7.8%). The 12-month overall survival (OS) was 42% in both groups [31].

Other efforts to improve outcomes for glioblastoma have relied on viral-based gene therapy and oncolytic virotherapy. Initial studies focusing on viral-based gene therapy have relied on replication-defective adenoviral vectors, which did not demonstrate significant tumor transduction beyond the injection site [32]. However, with the advent of replication-competent viruses, virotherapy may adapt to the evolving tumor microenvironment. Newer generation viral-based gene therapies used replication-competent retroviruses (Maloney murine leukemia virus) and herpes simplex virus to transduce host cancer cells [33][34]. Prodrug activating viral-based gene therapy facilitates tumor selective viral transduction and introduces a “suicide” transgene that converts a non-toxic prodrug into a intracellular chemotherapeutic. The recent Toca511 Phase III clinical trial evaluated the efficacy of a retroviral-mediated gene therapy for recurrent glioblastoma and did not reach its study endpoints [35]. However, there was a significant survival benefit in IDH-mutant and anaplastic astrocytoma. Therefore, selecting the proper patient/subgroup for gene therapy trials remains essential.

4.3. Methods to Improve the Delivery of Therapeutic Agents to Glioblastoma

Clinical trials have tested methods enhancing the delivery of hydrophilic, high molecular weight compounds to brain tumors. These methods include convection-enhanced delivery, blood–brain barrier opening, chemotherapeutic modifications and conjugations that improve the transport of the active antitumor moiety, and osmotic or receptor-mediated opening of the blood–brain barrier [36][37][38][39][40]. Still, the new agents remain less effective than systemic chemotherapy using the hydrophobic agent temozolomide (**Table 2**).

Table 2. Comparison of methods to deliver therapeutic agents to glioblastoma.

	Convection-Enhanced Delivery	BBB Opening	Systemic Chemotherapy
Drug delivery into brain tissue or lesion	**During tissue infusion**	**During the opening of the BBB**	**Limited by the intact BBB**
MW of therapeutic agent	**Large or small**	**Large or small**	**Small**
Brain–Blood Concentration	**>100 × systemic concentration**	**≤1 × systemic concentration**	**<1 × systemic concentration**
Hydrophilic compounds	**Enters CNS**	**Enters CNS**	**<<<1 × systemic concentration**
Hydrophobic compounds	**Enters CNS**	**Enters CNS**	**<1 × systemic concentration**
Distribution of Compound within CNS	**Volume spreads radially from the infusion site**	**The volume of distribution rests in the arterial distributions injected with mannitol**	**Entire CNS**
The volume of the brain that can be treated	**Large (4–8 cm^3)**	**Large (4–8 cm^3)**	**Large (entire brain)**

4.4. A Better Understanding of Tumor Components, Therapeutic Susceptibilities, and Mechanisms of Therapeutic Benefit May Lead to Improved Therapeutic Strategies for Glioblastoma

Cancer is a cellular disease whose cure requires the lethal treatment of every tumor cell. Substantially prolonged survival in glioblastoma depends on preventing tumor recurrence by eradicating tumor cells in the primary tumor mass and the surrounding and distant brain regions. Conventional surgery and chemoradiation of glioblastoma effectively slow the growth of the tumor by eradicating the fastest dividing tumor cells that create the central mass of the tumor. Chemoradiation targets the fastest dividing cells most amenable to DNA damage, which cannot be repaired between rapid cell divisions. These therapies leave slower-dividing tumor clones to maintain glioblastoma growth. If this theory is correct, the present glioblastoma treatment essentially lengthens survival by eradicating the most rapidly dividing tumor clones. Life expectancy increases after the first wave of therapy because the glioblastoma growth rate falls when slower-dividing tumor clones drive it. If a tumor cure is presently unattainable and radio- and chemotherapy extend life by eliminating the fastest-growing tumor cell clones, therapies that slow the tumor cell cycle through non-DNA toxic treatments may be logical choices for treating recurrent glioblastoma. Future therapies may slow tumor growth by changing the tumor environment, providing time and a more conducive milieu for treatments such as immunotherapy to eradicate glioblastoma.

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