Review

Novel strategies in glioblastoma surgery aim at safe, supra-maximum resection in conjunction with local therapies

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Abstract

The biggest challenge in neuro-oncology is the treatment of glioblastoma, which exhibits poor prognosis and is increasing in incidence in an increasing aging population. Diverse treatment strategies aim at maximum cytoreduction and ensuring good quality of life. We discuss multimodal neuronavigation, supra-maximum tumor resection, and the postoperative treatment gap. Multimodal neuronavigation allows the integration of preoperative anatomic and functional data with intraoperative information. This approach includes functional magnetic resonance imaging (MRI) and diffusion tensor imaging in preplanning and ultrasound, computed tomography (CT), MRI and direct (sub)cortical stimulation during surgery. The practice of awake craniotomy decreases postoperative neurologic deficits, and an extensive supra-maximum resection appears to be feasible, even in eloquent areas of the brain. Intraoperative MRI- and fluorescence-guided surgery assist in achieving this goal of supra-maximum resection and have been the subject of an increasing number of reports. Photodynamic therapy and local chemotherapy are properly positioned to bridge the gap between surgery and chemoradiotherapy. The photosensitizer used in fluorescence-guided surgery persists in the remaining peripheral tumor extensions. Additionally, blinded randomized clinical trials showed firm evidence of extra cytoreduction by local chemotherapy in the tumor cavity. The cutting-edge promise is gene therapy although both the delivery and efficacy of the numerous transgenes remain under investigation. Issues such as the choice of (cell) vector, the choice of therapeutic transgene, the optimal route of administration, and biosafety need to be addressed in a systematic way. In this selective review, we present various evidence and promises to improve survival of glioblastoma patients by supra-maximum cytoreduction via local procedures while minimizing the risk of new neurologic deficit.

Key words Glioma, extensive surgery, photodynamic therapy, local chemotherapy, gene therapy

Glioblastoma multiforme (GBM) has the highest incidence and shortest patient survival of all brain tumors. The incidence of GBM is approximately 3 cases per 100,000 person-years for the general population and 18 cases per 100,000 person-years for individuals over 65 years old[1]. More than 40% of patients are over 65 years of age, and the median survival shortens with increasing age. The prognosis of GBM is among the worst of all human cancers. Even in the modern era, the population-based median survival is only approximately 10 months[2]. The longest survival is achieved in patients who undergo gross total resection followed by radiotherapy and temozolomide (TMZ), but the median survival in this population is still only 20 months.

Strong predictors of beneficial outcomes are not treatment-related but patient-related and cannot be managed, including age, performance score, mental status, and (epi)genetic mutations. The most illustrative example of these patient-related predictors is the silencing of the O-6-methylguanine-DNA methyltransferase gene (*MGMT*) through promoter methylation (*MGMT-p*, coding for a DNA repair protein). These patients with compromised DNA repair benefit most from the current treatments[3]. The most important treatment-related predictor is the extent of surgery: so-called complete resection versus partial resection versus no surgery or biopsy only[2,4-9]. For patients with newly diagnosed GBM, a secure, extensive excision

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associates with better overall survival. Even subtotal resections as low as 78% contribute to a survival benefit[7]. Importantly, approximately 35% of GBM patients are not candidates for (partial) resection of the tumor, mainly due to the involvement of more than one lobe, age over 75 years old, and/or not being married or partnered[2]. GBM is an extended local disease of one organ. It is not a metastatic disease although extracranial metastasis is observed in 0.4% to 0.5% of glioblastoma patients; through 2009, only 88 cases of glioblastoma metastases have been reported[10]. This behavior makes GBM especially suitable for local therapies, including cytoreductive surgery as a first step. It should be recognized, however, that even the ideal supra-maximum (tumor plus margin) surgical resection is unable to eliminate all tumor tissue and, unlike other solid tumors, "clear margins" cannot be achieved in surgery for GBM.

The biggest challenge in neuro-oncology is the treatment of GBM due to its continuing poor prognosis and its increasing incidence in an increasing aging population. In this confined review, we present several treatments that exhibit promises in safely enhancing the extent of surgical resection and to advance (adjuvant) local therapies. Neoadjuvant therapies to reduce the tumor burden prior to resection are uncommon in GBM and are not discussed in this survey. Some of the treatments presented here are not novel but are not in widespread use, whereas others remain experimental or as ideas with a rationale.

Presurgical Planning and Multimodal Neuronavigation

A common setup for image-guided neurosurgery uses a tracked pointer on a preoperative magnetic resonance imaging (MRI) scan to visualize the tumor and its critical surroundings for guidance during the surgery. This neuronavigation assists in tumor localization and

resection and is a common practice in developed countries although typically only basic anatomic MRI information is uploaded. Multimodal neuronavigation is not in general use. It allows the integration and association of preoperative anatomic and functional data with intraoperative information. Preoperatively, it includes the use of functional MRI and diffusion tensor imaging (DTI) in preplanning. During surgery, this approach includes the use of ultrasound, computed tomography (CT), MRI, and direct (sub)cortical stimulation. The principle behind this approach is to use these modalities simultaneously and allow the intraoperative overlay of both anatomic and functional information to better handle the surgical approach and resection.

Functional MRI measures brain activity by detecting associated changes in blood flow using the hemodynamic response of the blood-oxygen level-dependent (BOLD) signal. This technique relies on the fact that cerebral blood flow and neuronal activation are coupled. Functional MRI is a non-invasive method of brain-mapping to identify regions linked to critical functions (**Figure 1**). Tumors, however, can change the blood flow in ways not related to neural activity. Novel methods that may improve both the spatial and time resolution of functional MRI are being studied using markers, such as temperature, pH, calcium-sensitivity[11]. DTI is a diffusion-weighted MRI that assesses the rate of diffusion of physiologic water and the preferred three-dimensional direction. DTI enables the visualization of white matter tracts (fibertractography) and provides information about the relationship of these tracts to the tumor (**Figure 2**). DTI has provided excellent resolution of the major fiber pathways involved in speech, vision, and motor functions. Recent studies in particular have demonstrated the value of DTI for resections near the optic pathway and radiations[12].

An obvious challenge of functional MRI and DTI is inaccurate image-to-patient mapping as well as brain shifts during surgery, which
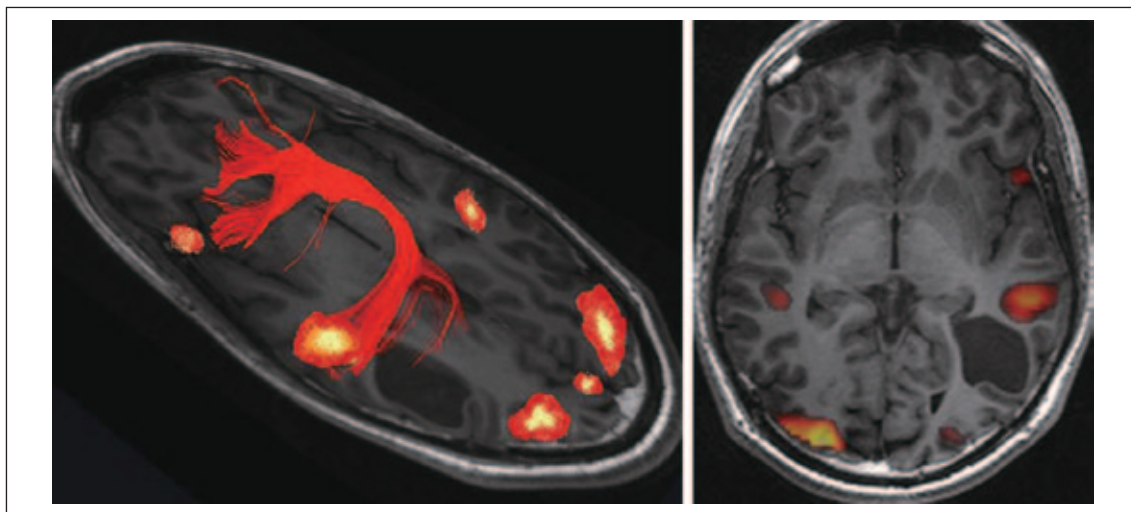

Figure 1. Arcuate fasciculus interconnecting the Broca's and Wernicke's language regions. Cystic lesion in the posterior parietotemporal region of the left hemisphere, closely related to the arcuate fasciculus and Wernicke's area. Functional MRI at a verbal fluency task shows activation in the Broca's area (frontal region) and the Wernicke's area (parietotemporal region). There is also bilateral occipital activation. Because the task is presented visually, so there is additional visual cortex activation. (Courtesy of Dr. Marion Smits, Department of Radiology, Erasmus University Medical Centre, The Netherlands)

Figure 2. Displacement of the cortico-spinal tract. A, tumor in the right primary motor cortex. B, on transverse & coronal color-coded diffusion tensor imaging (DTI) maps, the corticospinal tract is blue. C, transverse & coronal fiber tracking of the corticospinal tract shows medial displacement of the corticospinal tract by the tumor. (Courtesy of Dr. Marion Smits, Department of Radiology, Erasmus University Medical Centre, The Netherlands)
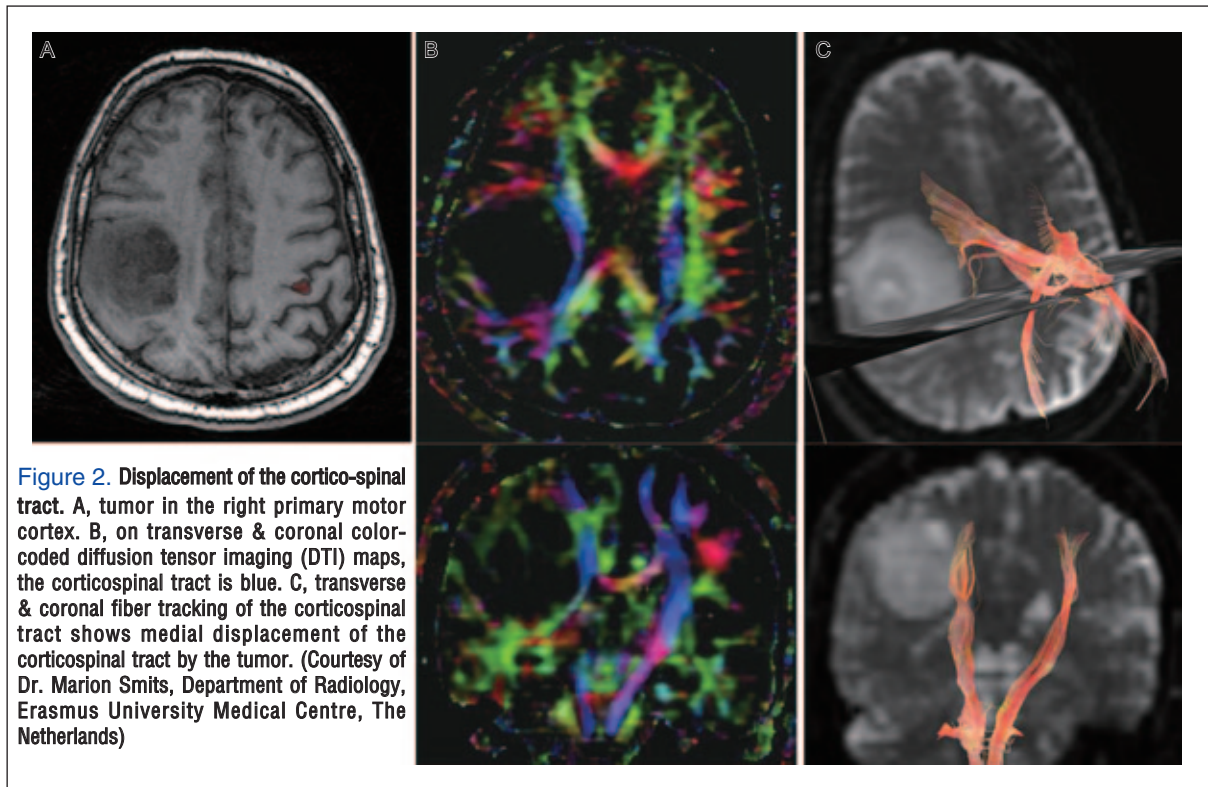
makes adjustments necessary during surgery to maintain accuracy. Some modalities, such as intraoperative MRI, are costly and require major modifications to the operating room. Therefore, intraoperative ultrasound continues to be a pertinent alternative due to its ease of use and economy of cost. The ultrasound signal is typically tracked and superimposed on the preoperative MRI used in a navigation system, allowing the surgeon to assess a misalignment or deformation with respect to the preoperative images. Unfortunately, the comparatively poor image quality of ultrasound allows for the exposure of only a few anatomic structures, such as the tumor, ventricles, and falx. Ongoing research is attempting to improve on corrections for brain shifts through the mapping of preoperative MRI scans to intraoperative ultrasound images. Recent techniques rely on the maximization of gradient orientation alignment in a reduced set of high-confidence locations of interest and apparently allows for fast, accurate, and robust registration[13].

Bello *et al.*[14] proposed several strategies to reduce the problem of brain shift. In addition to repeated landmark checks during surgery to improve clinical navigation accuracy, they advise limiting the craniotomy size to the minimum necessary to expose the tumor area and a narrow portion of the surrounding brain. Furthermore, resection should be performed in a manner that safeguards the accuracy of neuronavigation. In cases of frontal tumors located near the cortico-spinal tract, resection began from the inferior-posterior border of the tumor (**Figure 3**). Subsequently, the remaining anterior part of the tumor was resected. Similarly, in cases of parietal tumors, resection

began from the anterior border (**Figure 1**). However, even when these suggestions are followed, the risk of brain shift remains substantial, and the accuracy of the information provided by the neuronavigation system remains inadequate. In such cases, intraoperative mapping would be most beneficial.

Preoperative anatomic and functional imaging offers the opportunity to quickly identify the neurons and fibers associated with motor or language functions when used in combination with intraoperative data, such as (sub)cortical mapping. The clinical relevance of this combined approach comes from the fact that it further enhances surgical safety by maintaining a very high rate of functional preservation while striving for supra-maximum resection.

Supra-maximum Resection

Awake craniotomies (asleep-awake anesthesia) are not novel although this approach is not yet widely used for routine glioma surgery[15-17]. The routine of awake craniotomy may decrease postoperative neurologic deficits and allow for the extensive resection of tumor even in precarious areas of the brain. The patient's verbal help is used for continuous clinical neurologic testing to detect early deficits in the sensory motor, language, or visual domains during tumor removal. Indeed, knowledge that the patient's neurologic function remains intact imbues the surgeon with the confidence to continue, resulting in a more extensive excision. Naturally, surgeons who use awake craniotomies far away from risky areas of the brain
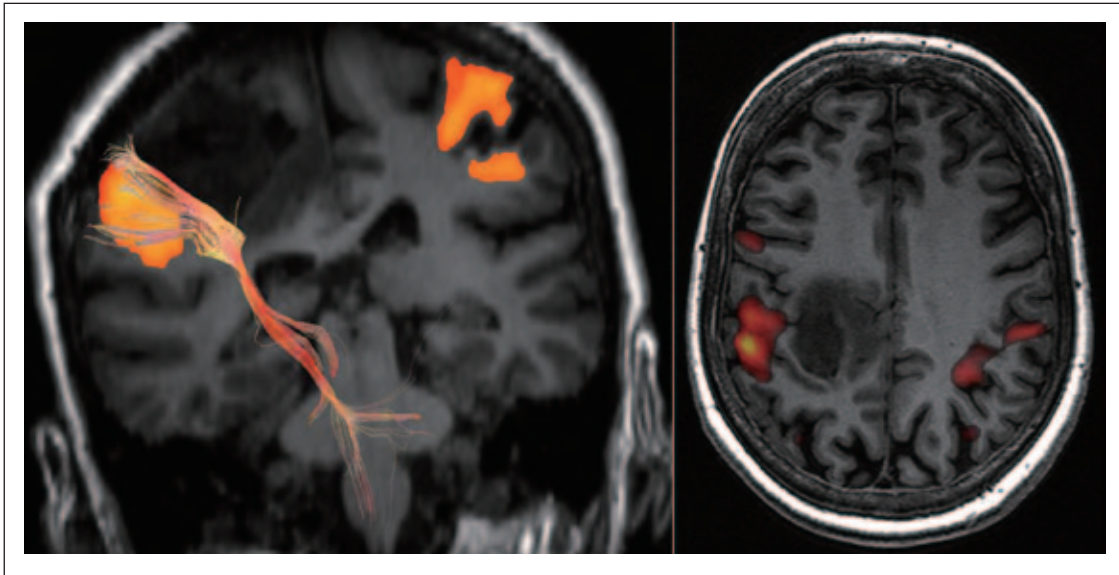
Figure 3. **Location of the displaced corticospinal tract. Tumor located in the primary motor cortex, which is displaced inferiorly (functional MRI at fingertapping with both hands), and there is displacement of the corticospinal tract. (Courtesy of Dr. Marion Smits, Department of Radiology, Erasmus University Medical Centre, The Netherlands)**

will report the lowest deficits.

Additionally, direct intraoperative awake mapping is the "gold standard" for safe surgery in critical functional areas[16,18,19]. (Sub)cortical bipolar stimulation depolarizes a very focal area, which in turn evokes certain responses in motor, language, or visual function. Originating from the techniques developed in epilepsy surgery, large exposures of the cortex and the marking of "positive" functional sites was the rule until recently. In recent years, a "negative sites" strategy (no clinical effect at stimulation) is used in glioma surgery[18]. The advantage is less extensive mapping and smaller exposure with less brain shift. However, negative mapping does not guarantee safe surgery, although safe surgery may be more problematic in low-grade glioma than in GBM. High-grade gliomas usually dislocate the tracts, whereas low-grade gliomas might infiltrate them[14].

If the critical tissues that should be spared were identified, then supra-maximum resection could be feasible in GBM and could be even safer than in low-grade glioma. The rate of neurologic deficits will depend on how willing the surgeon is to approach the edge between the tumor and functional tissue. Given that the risks should be in balance with survival benefits, a high-risk strategy appears less appropriate for GBM because the patient have little time to recover. The exceptions might be the neurologically and mentally intact younger patients in whom survival might be significantly protracted.

Cytoreduction is limited by the difficulty in distinguishing glioma infiltration from the normal brain during surgery and concerns over causing neurologic deficits. Achieving supra-maximum resection is challenging when using only conventional white light microsurgical techniques; MRI-verified gross total resections are only achieved in 23% to 50% of all high-grade glioma resections[6,8,20].

Gross total resections might be achieved by better tumor localizing techniques as well as by better visualization and identification techniques. Intraoperative MRI has gained an evidence base with reports of increased complete resection rates and improved survival[21,22]. Unfortunately, as stated earlier, the expense of intraoperative MRI is severely high.

The proof of principle for better tumor visualization by fluorescence guidance was convincingly demonstrated in a large, multicenter phase III randomized controlled trial of 270 patients with high-grade glioma, 88% of whom had GBM[23]. After the oral administration of the pro-drug 5-amino-levulinic acid (5-ALA), the fluorescent molecule protoporphyrin IX (PpIX) accumulates in high-grade glioma, allowing the neurosurgeon to more easily detect and resect the tumor. In 65% of cases, a gross total resection was achieved compared with a 36% gross total resection rate when using conventional white light. Moreover, a survival benefit of 5 months was observed after gross total resection.

Intraoperative fluorescence imaging, especially near-infrared fluorescence imaging, has the potential to revolutionize neurosurgery by providing high sensitivity and real-time imaging guidance to surgeons to define glioma margins[20,24]. PpIX fluorescence has been suggested to be better for defining tumor extent than gadolinium enhancement in intraoperative MRI. In a novel application, PpIX-positive coordinates were recorded intraoperatively and were used to correct MRIs for brain shift[25].

In fluorescence-guided surgery using 5-ALA, the photosensitizer PpIX is still available in the remaining peripheral tumor extensions after the gross total resection; therefore, photodynamic therapy (PDT) is possible. PDT is a two-stage therapy that makes use of nontoxic light-sensitive drugs that become toxic to targeted (malignant) cells

when they are exposed to light. The application of light results in the production of free oxygen radicals (Type I PDT, caused through electron abstraction or transfer from a substrate molecule) and singlet oxygen (Type II PDT). PDT is recognized as a valuable treatment option for localized cancers, e.g., cancers that have not spread far from where they started and are easily accessible, such as cancers of the skin, mouth, or gastrointestinal tract[26,27]. The major difference between different types of photosensitizers is the part of the cell that they target. Unlike radiotherapy, where the damage targets the cell DNA, most photosensitizers target other cell structures. For example, 5-ALA has been found to localize in the mitochondria, other photosensitizers exhibit high affinity for endothelial cells, and so on. Because local light application is necessary for the toxic effect, PDT can be directed, thereby making it an accurate and safe procedure. PDT exhibits dual-selectivity; the sensitizer accumulates more or less selectively in the tumor, and light irradiation is applied selectively to the tumor[26,28].

Various strategies are conceivable in PDT. Before closing, illumination of the resection cavity with the appropriate light is a straightforward option. The debate about improved efficacy by light fractionation is ongoing. So-called metronomic PDT involves prolonging the (low-dose) illumination by one or more light distributors in the tumor cavity and guiding them subcutaneously for intermittent PDT in the immediate postoperative days. One novel approach will be the use of an implantable telemetric light delivery and monitoring system for metronomic PDT[29]. It is likely that the oral 5-ALA will need to be administered multiple times during such a prolonged treatment. Further novel intraoperative fluorescence imaging systems and probes, including fluorescein sodium, dye-containing nanoparticles, and targeted nano-probes, are being researched to improve the specificity and selectivity of intraoperative fluorescence[28].

The Immediate Postoperative Hiatus and Local Treatments

Given that GBM is typically localized in one lobe, seldom metastasizes, and exhibits local recurrence, the disease is a proper candidate for local treatments. Notably, the only double-blinded trials ever conducted on GBM studied the effect of carmustine wafers implanted in the resection cavity[30-32]. These three studies reported a significant increase in survival after the local application of the impregnated polymer wafers during surgery. The largest study involved 240 patients with glioma, 86% of whom had GBM, and reported a median survival increase of 2.3 months[32]. This result is consistent with the current standard based on the non-blinded trial on conventional radiotherapy and a concomitant adjuvant TMZ regime[33]. The latter involved 573 patients with glioma, 79% of whom had GBM, and reported a median survival increase of 2.5 months. Both carmustine and TMZ are non-specific alkylating drugs. TMZ is administered during radiotherapy and for 6 months thereafter. The carmustine wafer lasts only 2 to 3 weeks[34]. The proof of principle for the efficacy of drug diffusion with locally high concentration is

evident. Obviously, the extra cytoreduction by local chemotherapy is well suited to bridge the unavoidable treatment gap between surgery and radiotherapy in these quickly dividing tumor cells. Remarkably, randomized trials combining local chemotherapy wafers implanted at time of resection with standard radiotherapy and a concomitant TMZ regime have never been performed. This multimodal approach has been evaluated in a retrospective analysis and a phase II study as reported on only in congress abstracts of 2006 and 2008[35,36]. The presented survival rate for patients with newly diagnosed malignant gliomas treated by this multimodal approach is 21 months, compared with 15 months for those treated by chemoradiotherapy alone[33]. This difference suggests the expected additive effect of local chemotherapy. Several other agents with activity against malignant tumors of the central nervous system are being evaluated in (preclinical) studies via local implants and gels, including taxanes, cyclophosphamide, adriamycin, and irinotecan[37,38]. Nonetheless, in routine surgery, the immediate postoperative period largely remains a therapeutic hiatus.

Another local approach is convection-enhanced delivery of (biological) agents through low-flow microinfusion. This approach was explored in several trials, typically in combination with targeted (immuno)toxins or gene therapy, both of which are experimental therapies. Here, the challenge is to evenly distribute the toxic agent and cover the (remnant) tumor area. Back flow along the microcatheters, the infusion rate, variable tissue pressure, routes, and areas of less resistance are all matters that must be better understood before widespread use[39]. Principally, the use of real-time imaging to follow the drug (e.g., by the co-infusion of a suitable tracer or more directly by stable labeling) appears to be necessary but is not currently possible. After this challenge is surmounted, the heterogeneity problem of target expression and the potency of the drug must be resolved. An comprehensive survey of local treatments in malignant glioma was recently reported[37].

The newest frontier of cutting-edge local treatment is gene therapy, the transfer of genetic materials into tumor cells for therapeutic purposes[40]. However, gene therapy is similarly hindered by the problems of proper delivery and agent effectiveness that plague other approaches. In the context of gene therapy, several methods of delivery have been explored. Simple mechanical application is a commonly used strategy in several trials on GBM. It is straightforward but not very sophisticated. Multiple injections into the (remnant) tumor have an intrinsic distribution flaw to an even greater degree than low-flow micro-infusion. Synthetic vehicles, such as liposomes or nanoparticles, and viral transfer methods have emerged as more promising application techniques[41,42]. Several "intelligent" polymeric nanoparticles that dissolve, swell, or collapse in response to an internal stimulus (e.g., pH, glucose, reduction potential, and lysosomal enzymes) or external stimulus (e.g., temperature, magnetic field, ultrasound, and light) have been engineered to achieve improved drug release at the target site (spatial control) and/or at the right time (temporal control). Drug release in response to multiple stimuli, such as pH/temperature, pH/redox, pH/magnetic

field, temperature/pH/magnetic, and pH/redox/magnetic, is another novel approach. Programmable site-specific drug delivery methods are in the proof-of-principle phase, but such treatments may find application in targeted therapy, e.g., in acidic or hypoxic tumor tissue. Another possibility is the use of nanoparticles responsive to external stimuli, which could provide spatial, temporal, and dose control of drug release by an on/off switch.

In vivo gene transfer makes use of non-replicating viral vectors and conditionally replicating oncolytic viruses. Generally, the viral genome has been genetically modified to make it replication-incompetent and non-pathogenic as well as to make the insertion of a transgene possible. Oncolytic viruses act selectively by self-replication in specific tumor cells, causing cell lysis, as well as by amplifying therapeutic genes. Numerous viral vectors have been tested, typically replication-deficient adenoviruses and retrovirus. Oncolytic viruses have also been tested, including conditionally replicating adenovirus, herpes simplex virus, retrovirus, poliovirus, Newcastle disease virus, and measles virus. The transduction efficiency is higher with replication-competent viruses than with replication-deficient viruses.

Using various vectors, the gene therapy approaches for the treatment of malignant gliomas include pro-drug activation/suicide gene therapy, anti-angiogenic gene therapy, immunomodulatory therapy, correction of gene defects, inhibition of tumor invasion, apoptosis induction, gene therapy to enhance chemotherapy and radiotherapy, and antisense and RNA interference-based strategies, as was recently reviewed[37,42]. Gene therapy using viral vectors has been explored in several clinical GBM treatment trials with disappointing outcomes. Failure is attributed to difficulties in achieving the uniform distribution of viral vectors in the tumor and in the sufficient transduction of GBM cells. The development of real-time imaging to visualize the gene transfer may address this problem.

A novel treatment frontier is to use different types of autologous cell vectors, including neural stem cells, multi-potent stromal cells, hematopoietic progenitor cells, and skin-derived stem cells, as vehicles for transgenes[43,44]. Implanting or injecting stem and progenitor cells that have been genetically modified to produce antitumor substances has several advantages over viral vector-mediated gene delivery. In contrast to viral vectors, stem cells are tumor-tropic and exhibit little tropism for normal neural cells (non-neurotropic). However, the immune system may neutralize non-autologous vector cells, and autologous cell vectors will not be available at the time of the first surgery. Given that gene delivery specific to the tumor cells appears feasible, the most significant treatment approach has yet to be realized. Theoretically, stem cell–mediated delivery of oncolytic viruses has the best potential to target and eliminate tumor cells selectively. However, the common same issues of the choice of cell vector, the choice of therapeutic transgene, the optimal route of administration, and biosafety need to be addressed in a systematic way. An extensive review is provided by Bexell *et al*.[45]. Currently, only preclinical studies have been performed[44].

Conclusions

Given the number of new agents, delivery variables, and all possible combinations, testing in classical clinical trials for the most powerful modality will be impractical. Screening through unconventional phase II trials in the framework of a working-party seems desirable[46]. Further testing can occur only in the event of an overwhelming survival benefit in a phase II trial. Overall, gene therapy has the potential to exhibit therapeutic improvements in well-designed clinical studies. To date, in addition to surgical cytoreduction, only carmustine wafers in three double-blinded controlled trials have met the common standard for local intracerebral therapies; true advancements await clinical evidence.

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