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CONTEMPORARY AND EMERGING TREATMENT STRATEGIES FOR GLIOBLASTOMA: INTEGRATION OF SURGICAL, LOCAL, AND MOLECULAR APPROACHES

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ABSTRACT

Glioblastoma is the most common and most aggressive primary malignant tumor of the central nervous system in adults and remains associated with a very poor prognosis despite multimodal treatment. The current standard of care consists of maximal safe surgical resection followed by radiotherapy and temozolomide-based chemotherapy; however, the effectiveness of this strategy is limited by marked tumor heterogeneity, the infiltrative growth pattern, the presence of the blood–brain barrier, and the immunosuppressive tumor microenvironment. The aim of this paper is to review current standards of GBM treatment as well as emerging therapeutic strategies under development. Analysis of the available evidence indicates that novel approaches such as intraoperative 18F-FET PET, intraoperative radiotherapy, local temozolomide delivery using hydrogel-based systems, intranasal drug administration, NanoTherm® therapy, and CAR-T immunotherapy may increase treatment precision, improve local tumor control, and partially overcome the limitations of systemic therapy. However, most of these methods remain investigational or experimental, and their actual impact on overall survival requires further validation. The integration of advanced imaging, local treatment modalities, and molecularly targeted therapies appears to be the most promising direction for future GBM management.

KEYWORDS

GBM, Glioblastoma Multiforme, Neurosurgery, Oncology, PET, Chemotherapy

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1. Introduction

Glioblastoma (GBM, glioblastoma multiforme) is the most common and most aggressive primary tumor of the central nervous system (CNS) in adults (Jassem, Potemski, & Kordek, 2019). Despite the use of standard treatment consisting of maximal safe surgical resection, radiotherapy, and temozolomide-based chemotherapy, prognosis remains poor, with a median survival of approximately 9–12 months (Bigos et al., 2014; Barker et al., 2014; Hegi et al., 2008; Laperriere et al., 2002). The limited effectiveness of therapy results, among other factors, from marked tumor heterogeneity, the presence of the blood–brain barrier, and the immunosuppressive tumor microenvironment. Consequently, novel therapeutic strategies are being intensively developed, including immunotherapy, targeted therapies, genetically engineered approaches, and nanotechnology-based drug delivery systems, with the aim of prolonging survival and improving quality of life. The objective of the present paper is to review current and emerging treatment strategies for GBM.

GBM most commonly develops de novo, and patients diagnosed with glioma typically present with a short clinical history and rapidly progressive focal or generalized neurological symptoms related to increased intracranial pressure, including morning headache, nausea, vomiting, visual disturbances, and cognitive decline. In elderly patients, glioblastoma may manifest as a pseudo-stroke syndrome or a pseudo-psychiatric syndrome, while general symptoms are often subtle.

In the imaging-based diagnosis of CNS tumors, magnetic resonance imaging (MRI) remains the most important modality, with sequences acquired both before and after administration of a gadolinium-based contrast agent. MRI should include T1-weighted and T2-weighted sequences, while T2-FLAIR, diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), and magnetic resonance spectroscopy are also diagnostically relevant. GBMs typically demonstrate an irregular shape, contrast enhancement, surrounding edema, and mass effect (Jassem et al., 2019; Bigos et al., 2014).

2. Methodology

During preparing this review article, numerous scientific publications concerning current and emerging treatment strategies for GBM were analyzed. The literature was identified through a review of databases including Scopus, Google Scholar, and PubMed, as well as selected specialist textbooks in oncology, neurology, and neurosurgery. The included articles and textbooks were primarily drawn from contemporary literature relevant to current standards of diagnosis and treatment, with additional landmark studies incorporated where historically significant.

3. Results

3.1 Standard Treatment

The cornerstone of treatment is surgical intervention, the extent of which depends, among other factors, on the patient's clinical condition and tumor location; however, complete tumor removal is usually not feasible. The goal of surgery is maximal macroscopic tumor resection while avoiding neurological deficits. In neurosurgery, such procedures are performed using an operating microscope, an ultrasonic aspirator, and neuronavigation. The completeness of resection is assessed by MRI. In some cases, even partial tumor removal may reduce symptoms related to intracranial hypertension. Surgery alone provides an average survival benefit of approximately 4 months; therefore, adjuvant treatment is necessary. In unresectable tumors, stereotactic biopsy is performed to establish the diagnosis required for further therapy (Jassem et al., 2019).

Postoperative radiotherapy (approximately 60 Gy), often combined with temozolomide (TMZ) chemotherapy, is the current standard of care. In patients with glioblastoma, radiotherapy is generally initiated within 2–6 weeks after surgery, most commonly around 3–4 weeks postoperatively, allowing sufficient tissue healing while avoiding excessive delay of treatment. Temozolomide is a central component of GBM management and is administered according to the Stupp regimen (Stupp et al., 2005). During the concomitant phase with radiotherapy, it is given at a dose of 75 mg/m² daily throughout the entire course of irradiation, usually for 6 weeks. After completion of chemoradiotherapy, an approximately 4-week interval is allowed for hematologic recovery. Adjuvant treatment is then initiated, with temozolomide administered in 28-day cycles for 5 consecutive days followed by a 23-day break. In the first cycle, the dose is usually 150 mg/m² and may be increased to 200 mg/m² in subsequent cycles if treatment is well tolerated. Six cycles are considered standard, although in clinical practice treatment may be extended to 12 cycles in selected patients without evidence of disease progression. Such radiochemotherapy significantly improves treatment outcomes, with 5-year survival reaching approximately 10%, compared with 1.9% for radiotherapy alone (Stupp et al., 2005; Weller et al., 2021).

The efficacy of temozolomide is strongly associated with the methylation status of the O6-methylguanine-DNA methyltransferase (MGMT) promoter, which serves as an important predictive factor for treatment response. During therapy, regular monitoring of complete blood count parameters is required because of the risk of myelosuppression, including neutropenia and thrombocytopenia. Furthermore, during the concomitant use of temozolomide and radiotherapy, prophylaxis against opportunistic infections, particularly Pneumocystis jirovecii pneumonia, is recommended (Stupp et al., 2005).

Beyond temozolomide, several other systemic agents have been used in the treatment of glioblastoma, particularly in the recurrent setting. The most important of these are the nitrosoureas, especially lomustine (CCNU) and carmustine (BCNU). Lomustine remains one of the principal therapeutic options for recurrent GBM and is frequently used as a comparator in clinical trials. Carmustine has a more limited role as conventional systemic chemotherapy, but it retains clinical relevance in the form of local biodegradable implants (Gliadel wafers) (Vaz-Salgado et al., 2023; van Opijnen et al., 2023).

Another important agent in recurrent GBM is bevacizumab. Although it is not a classical cytotoxic chemotherapeutic drug, but rather a monoclonal antibody targeting vascular endothelial growth factor (VEGF), it is commonly discussed within the broader context of systemic antitumor therapy for glioblastoma. Clinically, bevacizumab is valued mainly for its ability to reduce peritumoral edema, improve symptom control, decrease corticosteroid requirements, and prolong progression-free survival. However, despite these benefits, available evidence has not demonstrated a clear and consistent improvement in overall survival, which limits its role primarily to selected patients in the recurrent setting.

In recent years, regorafenib has emerged as another relevant option for recurrent GBM (Bruno et al., 2021; Tünbekici et al., 2023). Regorafenib is a multikinase inhibitor rather than a traditional chemotherapeutic agent, but it has gained attention because the phase II REGOMA trial showed a survival advantage over lomustine in patients with relapsed glioblastoma. Subsequent reviews and observational studies have

reinforced its importance and contributed to its inclusion in contemporary treatment discussions and guidelines for recurrence.

Taken together, these data indicate that while temozolomide remains the backbone of first-line chemotherapy for newly diagnosed GBM, other systemic agents—notably lomustine, carmustine, bevacizumab, and regorafenib—play an important role in salvage treatment and in individualized management of recurrent disease.

3.2 Intraoperative Use of 18F-Fluoroethyltyrosine PET

Positron emission tomography using 18F-fluoroethyltyrosine (18F-FET PET) represents a promising tool supporting treatment planning in glioblastoma. The first attempts to use PET imaging in glioma surgery date back to the early 2000s, when amino acid tracers such as 18F-FET and 11C-methionine were introduced, enabling more accurate delineation of tumor extent. Initially, this method was applied mainly to biopsy and radiotherapy planning, and over time it found application in surgical resection planning using neuronavigation systems (Pauleit et al., 2005).

18F-fluoroethyltyrosine (18F-FET) is a synthetic amino acid analogue transported into tumor cells mainly via the LAT1 transporter (SLC7A5), which is overexpressed in glioblastoma. In contrast to glucose-based tracers, 18F-FET is not incorporated into proteins; rather, its uptake primarily reflects amino acid transport activity associated with increased tumor metabolism and cell proliferation. LAT1 overexpression is linked to activation of signaling pathways such as PI3K/AKT/mTOR, leading to increased amino acid demand and transport into the cell. Importantly, 18F-FET uptake is largely independent of blood–brain barrier integrity, which allows detection of tumor infiltration beyond the regions visible on MRI (Vettermann et al., 2021).

Meta-analyses have demonstrated high diagnostic performance of 18F-FET PET in glioma evaluation, with sensitivity ranging from 84% to 94% and specificity from 81% to 88%, depending on the clinical indication and study population (Dunet et al., 2015). Unlike standard contrast-enhanced MRI, PET enables assessment of tumor metabolic activity, allowing more accurate delineation of true tumor extent, surgical resection margins, differentiation between progression and radiation-induced changes, and optimization of subsequent therapy, including radiotherapy (Law et al., 2019; Grosu et al., 2005). It has been shown that 18F-FET imaging may reveal areas of tumor infiltration not visible on MRI, owing to detection of increased amino acid metabolism characteristic of glioma cells.

Integration of PET and MRI data facilitates improved delineation of tumor boundaries, which may increase surgical radicality while minimizing damage to healthy brain tissue (Law et al., 2019; Galldiks et al., 2017). The resulting images are fused and incorporated into intraoperative neuronavigation systems. Limitations to broader implementation include high cost, limited availability, and the need for close collaboration among a multidisciplinary team including neurosurgeons, nuclear medicine specialists, and radiation oncologists. Further studies are currently underway to assess the efficacy and safety of this technique in GBM treatment.

3.3 Intraoperative Radiotherapy

Intraoperative radiotherapy (IORT) consists of delivering a single high dose of radiation, approximately 10–20 Gy, directly to the postoperative cavity during surgery. This method enables immediate treatment of microscopic tumor remnants while limiting irradiation of healthy tissues. Such an approach shortens the interval before further treatment and reduces the risk of recurrence during the waiting period before conventional radiotherapy, which affects approximately 25% of patients. Available studies indicate improved local control with overall survival comparable to that achieved with standard radiochemotherapy; however, there is no unequivocal evidence of superiority (Combs et al., 2013; Giordano et al., 2019).

The method is particularly used in patients with recurrent glioma who have already received the maximum permissible radiation dose; in such cases, treatment includes repeat surgery followed by intraoperative radiotherapy. IORT remains an experimental method and is currently being investigated in the phase III INTRAGO II clinical trial (ClinicalTrials.gov, 2023).

3.4 Local Delivery of Temozolomide

A research team from Jagiellonian University has developed a biodegradable hydrogel-based system for local temozolomide delivery in the treatment of gliomas after surgical resection. The system is based on cross-linked hydrophilic polymers, including gelatin methacryloyl (GelMA), chitosan, and hyaluronic acid, enabling TMZ encapsulation and controlled release within the tumor environment. Physicochemical characterization demonstrated appropriate mechanical properties, swelling capacity, and structural stability of the hydrogel, supporting its intraoperative implantation into the postoperative cavity (Krajcer et al., 2025).

Release kinetics studies indicate a profile dependent on both diffusion and degradation of the polymer matrix, allowing maintenance of therapeutic TMZ concentrations at the target site over an extended period. By modifying polymer composition and the type of TMZ derivative, release profiles ranging from rapid to sustained can be achieved. Faster release may be advantageous in the presence of substantial residual tumor burden, whereas slower release may support prolonged prevention of recurrence.

Under in vitro conditions, the system demonstrated significant cytotoxicity against glioma cells together with good biocompatibility. The use of a local drug delivery system allows circumvention of the blood–brain barrier and reduction of systemic exposure (Krajcer et al., 2025; van Tellingen et al., 2015; Upadhyayula et al., 2017).

These findings suggest that implantable hydrogels may represent an effective platform for local chemotherapy in GBM; however, further validation in in vivo models and clinical trials is required. Important challenges include temozolomide stability in aqueous environments and precise control of drug release under in vivo conditions. Despite promising results obtained in in vitro and in vivo models, including inhibition of tumor growth and increased apoptosis of cancer cells, clinical data confirming efficacy in patients are still lacking. Initial phase I clinical studies are currently in preparation (Krajcer et al., 2025).

The concept of local drug delivery is not new, as illustrated by carmustine wafers (Gliadel wafers), which are not part of standard first-line treatment for glioblastoma but are approved for use in selected cases (Westphal et al., 2003). They are used mainly in patients with recurrent GBM who remain in good general condition and are candidates for maximal tumor resection. The product is placed intraoperatively into the postoperative cavity, usually in a number of up to eight wafers, enabling local drug delivery directly to the area from which the tumor has been removed.

These wafers are biodegradable polymer carriers (polifeprosan 20) that undergo gradual hydrolytic degradation after implantation, resulting in controlled release of carmustine over several weeks. This allows high drug concentrations to be achieved locally while limiting systemic exposure (Zhang et al., 2014).

Carmustine is an alkylating cytotoxic agent that penetrates tumor cells and causes DNA damage by forming cross-links, mainly within guanine residues, thereby inhibiting DNA replication and inducing apoptosis. Local administration allows the blood–brain barrier to be bypassed, representing a significant advantage over systemic therapy. Despite documented efficacy, the clinical benefit of this method remains limited, which accounts for its selective use in clinical practice. These limitations have prompted the search for novel local drug delivery systems based on more advanced carriers. In this context, hydrogel systems for local temozolomide delivery may constitute a promising alternative, offering greater control of drug release kinetics and the potential to deliver multiple therapeutic agents, which may ultimately improve treatment efficacy (Bastiancich, Danhier & Préat, 2016).

Intranasal administration of temozolomide represents a promising therapeutic strategy enabling direct transport of the drug to the central nervous system while bypassing the blood–brain barrier. Owing to the mucoadhesive properties of the carrier, the drug may act longer and more effectively. This mechanism is based on transport along the olfactory and trigeminal nerves, which may increase drug bioavailability in brain tissue while reducing systemic adverse effects (Lochhead & Thorne, 2012).

In a preclinical study in rats, intranasal administration of temozolomide resulted in a significant prolongation of survival (approximately 31 days vs. 20 days in the control group), corresponding to an improvement of around 50%, as well as marked inhibition of tumor growth compared with systemic administration (Li et al., 2014). Despite these promising preclinical findings, the method remains experimental and requires further clinical investigation.

3.5 Intraoperative NanoTherm Therapy

NanoTherm® therapy is an innovative antitumor treatment based on the introduction of Superparamagnetic Iron Oxide Nanoparticles (SPIONs) into the tumor, which, under the influence of an alternating magnetic field, induce localized hyperthermia within the tumor bed. The mechanism of action relies on the superparamagnetic properties of the nanoparticles, which generate thermal energy when exposed to an alternating magnetic field. These nanoparticles selectively damage cancer cells and increase their sensitivity to radiotherapy and chemotherapy. The particles remain at the site of administration and are considered safe for healthy tissues (Maier-Hauff et al., 2011; Grzegorzewski et al., 2025).

The therapeutic procedure consists of several stages. In the first stage, during neurosurgery or via stereotactic administration, nanoparticles are introduced into the tumor or postoperative cavity. After a recovery period, the patient undergoes a series of hyperthermia sessions, usually repeated several times at intervals of a few days. Each session consists of exposure to an alternating magnetic field for a defined period, enabling controlled heating of the region containing nanoparticles. As a result of energy loss associated with Néel and Brownian relaxation, a local temperature increase is achieved, usually within the range of 42–45°C. Elevated temperature leads to cellular structural damage, protein denaturation, and destabilization of cell membranes, ultimately inducing apoptosis and necrosis of tumor cells (Pulvirenti et al., 2022). In addition, hyperthermia increases blood flow and vascular permeability, which may improve drug penetration and sensitize tumor cells to radiotherapy by inhibiting DNA repair mechanisms. NanoTherm therapy is often combined with radiotherapy, allowing a synergistic effect to be achieved.

In a clinical study involving 66 patients, the use of magnetic hyperthermia combined with radiotherapy in recurrent glioblastoma resulted in prolonged overall survival, with a median of approximately 13.4 months from diagnosis of recurrence and approximately 6.2 months from initiation of therapy. Treatment included an average of 6–8 hyperthermia sessions lasting about 60 minutes each at temperatures of 42–45°C. The therapy was well tolerated, with the most common adverse events including local inflammatory reactions, symptoms related to tissue heating, and cerebral edema (Maier-Hauff et al., 2011; Chrzanowska et al., 2025).

Although this therapy does not provide a cure, it may prolong survival and improve quality of life. The method is used in the treatment of glioblastoma, particularly in recurrent disease, where standard treatment options are limited. NanoTherm is currently the only clinically approved nanoparticle-based therapy for glioblastoma (Grzegorzewski et al., 2025). It has CE certification in the European Union, and in Poland it is available in Lublin, where clinical studies evaluating its efficacy are being conducted.

3.6 CAR-T

Chimeric antigen receptor T-cell (CAR-T) therapy represents one of the most advanced immunotherapeutic strategies currently being developed for cancer treatment. The production process begins with leukapheresis and isolation of autologous T lymphocytes, which are then activated and genetically modified, most commonly using lentiviral or retroviral vectors, to express a chimeric antigen receptor. Following ex vivo expansion and quality control, the cells are administered to the patient either intravenously or, in the case of central nervous system tumors, locoregionally.

In glioblastoma, the selection of an appropriate target antigen remains a major challenge. Among the best-characterized targets are Interleukin-13 Receptor α2 (IL13Rα2) and Epidermal Growth Factor Receptor variant III (EGFRvIII). IL13Rα2 is overexpressed in a substantial proportion of GBMs and is associated with an aggressive tumor phenotype, while showing relatively limited expression in healthy tissues. IL13Rα2 is a membrane protein located on the cell surface. It binds interleukin-13 (IL-13), a cytokine involved in immune regulation. In contrast to the “classical” IL13Rα1 receptor, IL13Rα2 does not mediate typical immune signaling and often functions as a decoy receptor. EGFRvIII, in turn, is a tumor-specific, constitutively active variant of the EGFR receptor generated by deletion of exons 2–7 and unable to bind the EGF ligand. EGFRvIII continuously activates signaling pathways such as phosphoinositide 3-kinase/serine/threonine kinase (PI3K/AKT) and mitogen-activated protein kinase (MAPK), thereby increasing proliferation and inhibiting apoptosis in tumor cells. This EGFR variant is characterized by high specificity but also by substantial heterogeneity of expression. In practice, this reflects a fundamental trade-off between target specificity and target stability.

Evidence of biological activity of CAR-T therapy in GBM has been provided by early-phase clinical studies. In one such study, locoregional administration of CAR-T cells directed against IL13Rα2 resulted in regression of tumor lesions and induction of an inflammatory response within the central nervous system (Brown et al., 2016). Another independent study confirmed the ability of intravenously administered

EGFRvIII-directed CAR-T cells to migrate to the tumor and exert selective pressure leading to loss of expression of the target antigen. At the same time, increased immunosuppressive signaling was observed, including upregulation of Programmed Death-Ligand 1 (PD-L1) and indoleamine 2,3-dioxygenase 1 (IDO1) (O'Rourke et al., 2017). Taken together, these findings indicate that CAR-T cells are functionally active in GBM, but their efficacy is limited by adaptive tumor escape mechanisms.

The major limitations of CAR-T therapy in GBM include:

- antigen heterogeneity and the associated escape of tumor clones lacking the target antigen,
- the strongly immunosuppressive tumor microenvironment leading to functional exhaustion of T lymphocytes,
- limited penetration of effector cells due to the blood–brain barrier,
- insufficient durability of therapeutic response.

These issues mean that monovalent CAR-T constructs targeting a single antigen have limited efficacy in solid tumors.

At present, CAR-T therapy in GBM remains experimental and has not become a standard treatment. Nevertheless, strategies aimed at overcoming the limitations of first-generation approaches are being intensively developed, including multi-antigen constructs (dual or tandem CARs), locoregional delivery approaches, and combination therapies with immune checkpoint inhibitors. In particular, constructs capable of recognizing more than one antigen simultaneously, such as IL13Rα2 and EGFR, are intended to reduce antigen escape and improve therapeutic efficacy.

4. Discussion

The treatment modalities presented in this review reflect the current direction of GBM therapy development, namely a shift away from exclusively standard surgical and radiochemotherapeutic management toward more personalized, local, and biologically targeted strategies. The common goal of these approaches is to improve local disease control, prolong survival, and reduce the impact of the blood–brain barrier and tumor heterogeneity on treatment efficacy. At the same time, analysis of the available data indicates that most of these methods remain in clinical development or at the experimental stage, and their role in everyday clinical practice has not yet been definitively established (tab.1).

In the case of intraoperative 18F-FET PET, the principal benefit appears to be improved precision of surgical treatment and subsequent therapeutic planning. The method is not directly therapeutic; rather, it enhances the identification of metabolically active tumor areas that may not be visible on conventional MRI. From a clinical standpoint, this is important because extent of resection remains one of the most relevant prognostic factors in GBM. Available studies suggest that integration of PET with neuronavigation may improve assessment of true tumor infiltration and reduce the risk of incomplete resection. At the same time, this method is primarily supportive and diagnostic rather than therapeutic. Its value depends on the availability of appropriate infrastructure, team expertise, and the feasibility of integrating metabolic imaging into the surgical workflow.

Intraoperative radiotherapy, by contrast, represents an attempt to immediately treat microscopic residual disease during surgery. Its main advantage is shortening the interval between resection and adjuvant therapy, while concentrating the radiation dose in the postoperative cavity with relative sparing of healthy tissues. From the perspective of GBM biology, this is justified because the tumor is characterized by rapid local recurrence, often developing even before initiation of standard postoperative radiotherapy. Existing studies suggest improved local control, although there is no clear evidence of a significant advantage in terms of overall survival. This indicates that IORT may be a valuable adjunct, particularly in patients with recurrence or in situations where re-irradiation options are limited, but at present it cannot be regarded as a breakthrough method or as equivalent to standard radiochemotherapy.

With regard to local temozolomide delivery, hydrogel-based systems are of particular interest, as they fit within the broader trend of local drug administration directly into the postoperative cavity. Interpretation of the available data indicates that the greatest potential of this method lies in achieving high local drug concentrations while limiting systemic toxicity and partially bypassing the blood–brain barrier. This is a significant advantage over systemic treatment, especially in GBM, where effective penetration of infiltrating tumor cells remains a major therapeutic challenge. On the other hand, the current evidence is largely preclinical, and efficacy observed in vitro or in animal models does not necessarily translate directly into clinical benefit in humans. In this context, experience with carmustine wafers shows that the concept of local drug delivery is

biologically rational, but its actual clinical advantage may be limited. Hydrogel-based temozolomide systems appear technologically more flexible than Gliadel, but they still require clinical validation.

Intranasal temozolomide administration represents a somewhat different developmental direction, focused not on intraoperative local treatment but on an alternative route of drug delivery to the central nervous system. Preclinical findings are promising and suggest improved brain bioavailability and survival benefit in animal models; however, at present this method should be regarded as an interesting translational concept rather than a clinically established solution. Compared with hydrogels, intranasal delivery is less invasive but potentially less precise in controlling local drug concentrations within the postoperative cavity.

NanoTherm® therapy occupies an intermediate position between local therapy and combination treatment. Reports of prolonged survival after recurrence are clinically relevant, although it must be emphasized that the available data derive mainly from studies conducted in selected patient populations. An important advantage of NanoTherm is that it is one of the few nanomedicine-based technologies to have reached the level of actual clinical use. Compared with local drug delivery systems, this method does not rely on the direct cytotoxic effect of a chemical agent, but rather on physical modulation of the tumor environment, which represents a distinct and potentially complementary therapeutic value.

Against the background of local and intraoperative methods, CAR-T therapy stands out as a systemic-biological, molecularly targeted approach with the potential to actively eliminate tumor cells beyond the macroscopic tumor mass. Studies employing CAR-T cells directed against IL13Rα2 and EGFRvIII confirm that cellular immunotherapy is biologically active in GBM; however, its efficacy is constrained by the fundamental biological features of this malignancy, namely antigen heterogeneity, the immunosuppressive tumor microenvironment, and limited durability of response. Compared with the other methods discussed, CAR-T has the greatest potential for treating residual disease and diffuse infiltrative tumor cells at the microscopic level, but it is also associated with the highest degree of biological, technological, and logistical complexity. Whereas 18F-FET PET improves delineation of tumor margins, IORT reduces the risk of residual microscopic disease within the cavity, and hydrogels or NanoTherm exert local effects, CAR-T attempts to overcome a problem not fully addressed by the other modalities: the presence of dispersed infiltrating tumor cells beyond the area of resection.

When comparing the strategies discussed, it becomes clear that they differ primarily in their therapeutic point of action. 18F-FET PET acts at the diagnostic and treatment-planning stage by increasing precision. IORT and local drug delivery systems act mainly at the level of the postoperative cavity, which is the site of highest local recurrence risk. NanoTherm is also locally focused, but it employs a physical mechanism and often acts synergistically with radiotherapy. CAR-T, in contrast, targets molecular features of tumor cells and may extend beyond the area of the macroscopic lesion.

A second important comparison concerns the degree of clinical maturity. Among the methods described, the highest level of practical implementation currently applies to PET-supported imaging tools in selected centers, carmustine wafers in specific indications, and NanoTherm under narrowly defined clinical conditions. IORT, TMZ hydrogels, and CAR-T remain more experimental, despite promising biological rationale.

A third dimension of comparison is the ability to overcome the limitations of classical GBM therapy. Local methods are best suited to addressing the blood–brain barrier and the high risk of local recurrence, but they are less effective against diffuse microscopic infiltration. CAR-T, by contrast, may theoretically better address disseminated tumor cells, yet it encounters resistance arising from immunosuppression and antigen variability. This means that the methods discussed should not be viewed solely as competing strategies, but rather as potentially complementary elements of combination therapy.

Table 1. Comparative analysis of GBM treatment strategies (own study)

Strategy	Therapeutic point of action	Mechanism of action	Clinical maturity	Strengths	Limitations
18F-FET PET	Diagnostic and treatment-planning stage	Amino acid positron emission tomography based on LAT1-mediated tracer uptake	Implemented in selected centers	Improved tumor delineation and support for maximal safe resection	No direct therapeutic effect and limited availability
Intraoperative radiotherapy (IORT)	Postoperative cavity	Single high-dose localized irradiation delivered during surgery	Experimental / clinical trials	Immediate treatment of residual tumor cells and reduced delay to radiotherapy	Limited penetration depth and no clear overall survival advantage
Local drug delivery systems	Postoperative cavity	Controlled local chemotherapy release, including biodegradable implants and hydrogel systems	Carmustine wafers approved in selected indications; temozolomide hydrogels experimental	Bypasses the blood–brain barrier and enables high local drug concentration	Limited effect on diffuse microscopic infiltration and variable clinical benefit
NanoTherm® therapy	Local tumor or postoperative cavity	Magnetic nanoparticle-induced hyperthermia, often combined with radiotherapy	CE-marked and used in selected European centers	Localized effect and synergy with radiotherapy	Requires specialized equipment and remains available only in selected centers
Chimeric antigen receptor T-cell (CAR-T) therapy	Molecular and systemic tumor targeting	Antigen-specific T-cell-mediated cytotoxicity directed against tumor-associated targets such as IL13Rα2 or EGFRvIII	Experimental / early-phase clinical trials	Potential to target disseminated tumor cells beyond the macroscopic lesion	Antigen heterogeneity, immune escape, immunosuppression, and limited durability of response

5. Conclusions

Overall analysis indicates that none of the discussed methods alone resolves all therapeutic challenges associated with glioblastoma. In the near future, the greatest clinical value is likely to lie in combined strategies involving more precise metabolic imaging with 18F-FET PET, maximal safe surgical resection, local treatment of the postoperative cavity (IORT, hydrogel-based systems, hyperthermia), and selectively applied biological therapies such as CAR-T. The integration of diagnostic, local, and molecular approaches appears to be the most rational direction for the future development of GBM treatment.

From a practical perspective, 18F-FET PET and IORT may be regarded as tools that enhance the effectiveness of local treatment; hydrogels and other local drug delivery systems as attempts to improve pharmacotherapy after resection; NanoTherm as an example of a clinically implemented technology supporting treatment of recurrence; and CAR-T as the most advanced, though still experimental, attempt at immunologically targeted elimination of glioma cells. Their common denominator is the effort to improve outcomes in a malignancy that, despite technological progress, remains one of the greatest challenges in modern neuro-oncology.

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List of abbreviations:
GBM - glioblastoma multiforme
18F-FET PET - fluorine-18 fluoroethyl-L-tyrosine positron emission tomography
CNS - central nervous system
MRI - magnetic resonance imaging
DWI - diffusion-weighted imaging
PWI - perfusion-weighted imaging
TMZ - temozolomide
MGMT - O6-methylguanine-DNA methyltransferase
CCNU - lomustine
BCNU - carmustine
VEGF - vascular endothelial growth factor
IORT - intraoperative radiotherapy
GelMA - gelatin methacryloyl

SPIONs - superparamagnetic iron oxide nanoparticles
CAR-T - chimeric antigen receptor T-cell
IL13Rα2 - interleukin-13 receptor α2
EGFRvIII - epidermal growth factor receptor variant III
IL-13 - interleukin-13
PI3K/AKT - phosphoinositide 3-kinase/serine/threonine kinase
MAPK - mitogen-activated protein kinase
PD-L1 - programmed death-ligand 1
IDO1 - indoleamine 2,3-dioxygenase 1
BBB - blood-brain barrier

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